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Studies on the sequential multi-component coupling/Diels–Alder cycloaddition reaction

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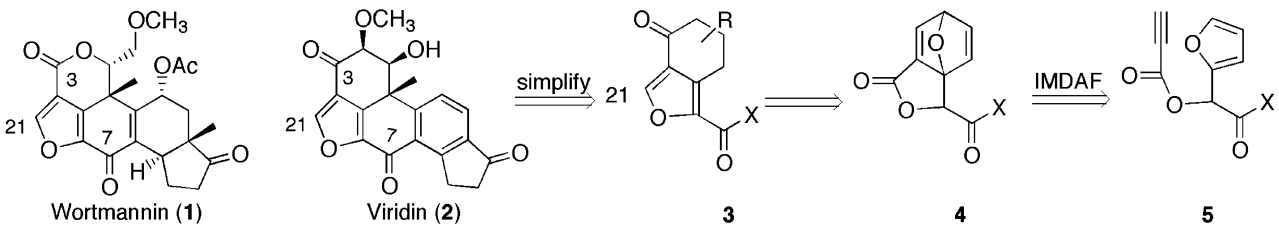
Abstract—The synthesis of highly functionalized oxabicyclo[2.2.1]heptadiene derivatives through the sequential use of an Ugi or Passerini multi-component coupling reaction followed by an intramolecular acetylene/furan Diels–Alder reaction was investigated. The nature of the heteroatom in the tether was determined to play a critical role.

Wortmannin (**1**) and viridin (**2**) are highly oxygenated furanosteroids isolated from fungal sources.[1] These compounds have received considerable attention because they function as potent inhibitors of the signaling enzyme phosphatidylinositol-3-kinase (PI-3K).[2] Excessive activity of PI-3K has been associated with certain types of cancer, prompting the development of potent and specific inhibitors.[3] It is proposed[4] that **1** and **2** inhibit PI-3K by covalent modification of the active site. This occurs through addition of the ε-amino group of lysine 802 to the C21 position followed by elimination of the furan oxygen. Although typically a nucleophile, the furan is rendered electrophilic at C21 by virtue of the carbonyl groups at C3 and C7, while furan opening is promoted by relief of ring strain. Although these compounds are potent inhibitors of PI-3K, they are not completely selective, inhibiting other kinases such as mTOR[5] and DNA-dependent kinase.[6]

We have an ongoing interest in synthesizing simplified analogs of these compounds to study their biological function. The design of these simplified analogs (generalized in structure **3**) (Scheme 1) is based on the hypothesis that the annulated furan in this structure contains the required features to covalently modify the enzyme. These simplified analogs retain the furan moiety, deactivated at C21 by two carbonyl groups. The E-ring is also retained to incorporate strain in the furan and provide additional sites for modification. A strategy for the synthesis of these analogs was devised that would maintain a high degree of synthetic flexibility. It was envisioned that derivatives of **3** could arise from an oxabicyclo derivative **4** prepared from **5** by an intramolecular Diels–Alder reaction of furan (IMDAF)[7] with a pendant alkyne. Placement of an amide function as the C7 carbonyl unit permits the direct and flexible preparation of **5** through a Passerini multi-component coupling reaction (MCR).[8]

Paulvannan[9] has described an Ugi MCR reaction followed by an IMDAF with an olefinic dienophile to construct combinatorial scaffolds. This was recently used by Schreiber[10] in an approach to natural product-



Scheme 1. Design of simplified viridin analogs.

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like libraries. However, there was no information available on the use of acetylenic dienophiles or the assembly of the cycloaddition precursors through a Passerini MCR.

We initially chose to study the sequential Ugi/IMDAF sequence using acetylenic dienophiles. Ugi condensation of 2-furaldehyde **6**, acetylenic acids **7**, isonitriles **8** and amines **9** proved very efficient for the generation of acetylenic amides **10a–f** in high yield (Scheme 2).

Conversion to the oxabicyclo[2.2.1]heptadiene derivatives was initially studied under Lewis acid catalysis. Surprisingly, treatment with Me_2AlCl, reported[11] to be effective for IMDAF reactions, failed to deliver any of the cycloadducts, returning either starting material or extensive decomposition of the Ugi product. However, it was observed that when the Ugi products were allowed to stand at room temperature, they would partially convert to the corresponding cycloadduct. A complete conversion to the adducts **11a–e**[12] could be effected smoothly under thermal conditions in less than 24 h. The terminal acetylene **10f** decomposed under the reaction conditions (Table 1).

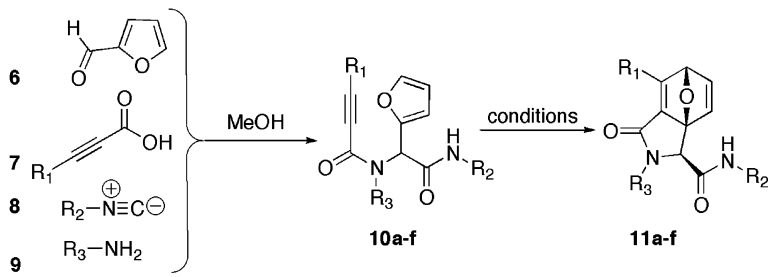
The reactions were highly diastereoselective with less than 10% of any other isomers detected in the crude product. The minor isomers were easily removed upon purification of the cycloadduct. The relative orientation of the carboxamide sidechain could not be assigned by NMR methods. Fortunately, an X-ray crystal structure of adduct **11c** (Fig. 1) revealed that the major diastereomer possessed the *exo*-oriented sidechain. The stereochemistry of the other adducts was assigned by analogy.

While exploring the use of Lewis acids to catalyze the Diels–Alder reaction, an unusual cascade process was observed. Upon exposure to catalytic $Yb(OTf)_3$ in 1,4-dioxane at high temperatures, the Ugi products **10a–e** were cleanly converted to the isoindolinones **13a–e** (Scheme 3) in high yield.

One possibility for the formation of these novel phenolic derivatives involves initial conversion to the Diels–Alder adducts **11a–e**. Lewis acid promoted opening of the oxo-bridge and elimination would give the unsaturated amides **12a–e**, which would be expected to tautomerize to the phenols **13a–e**. This process represents a direct synthesis of highly substituted isoindolinones in two operations from simple starting materials (Table 2).

With the successful demonstration that acetylenic dienophiles were effective with Ugi based substrates, a series of IMDAF precursors were assembled through a Passerini MCR process. Addition of the three reagents to a solution of dichloromethane gave high yields of the Passerini products **14a–e** (Scheme 4).

However, attempts to convert the Passerini products to the oxabicyclo derivatives failed under thermal conditions. The starting materials were recovered unchanged after heating to 250°C, except with **14e** that underwent extensive decomposition. Surprisingly, the Lewis acid-catalyzed reaction that had failed with the acetylenic amide series proved highly effective with the acetylenic esters. Treatment of the furans with Me_2AlCl[11] delivered the Diels–Alder adducts **15a–d** in good yields, except with the terminal acetylene **14e**. As before, the



Scheme 2. Synthesis of bicyclic lactams.

Table 1. Sequential Ugi/IMDAF studies

Entry (MCR)[a]	R1	R2	R3	MCR yield (%)	Entry (IMDAF)[b]	IMDAF yield[c] (%)
10a	Me	Bn	Bn	88	**11a**	74
10b	Ph[d]	Bn	*t*Bu	74	**11b**	81
10c	Me	*t*Bu	*t*Bu	N/A[e]	**11c**	81
10d	Me	Bn	*t*Bu	92	**11d**	78
10e	Ph	Bn	Bn	89	**11e**	80
10f	H	Bn	*t*Bu	84	**11f**	Dec.

[a] Reactions were run at a concentration of 0.6 M in MeOH at rt.
[b] A 0.02 M solution of the furan in toluene was heat at 200°C in a sealed tube.
[c] Yields reported are for a pure diastereomer.
[d] MCRs with phenyl propiolic acid were run in the dark to limit alkyne dimerization.
[e] Cyclized spontaneously upon standing at rt.

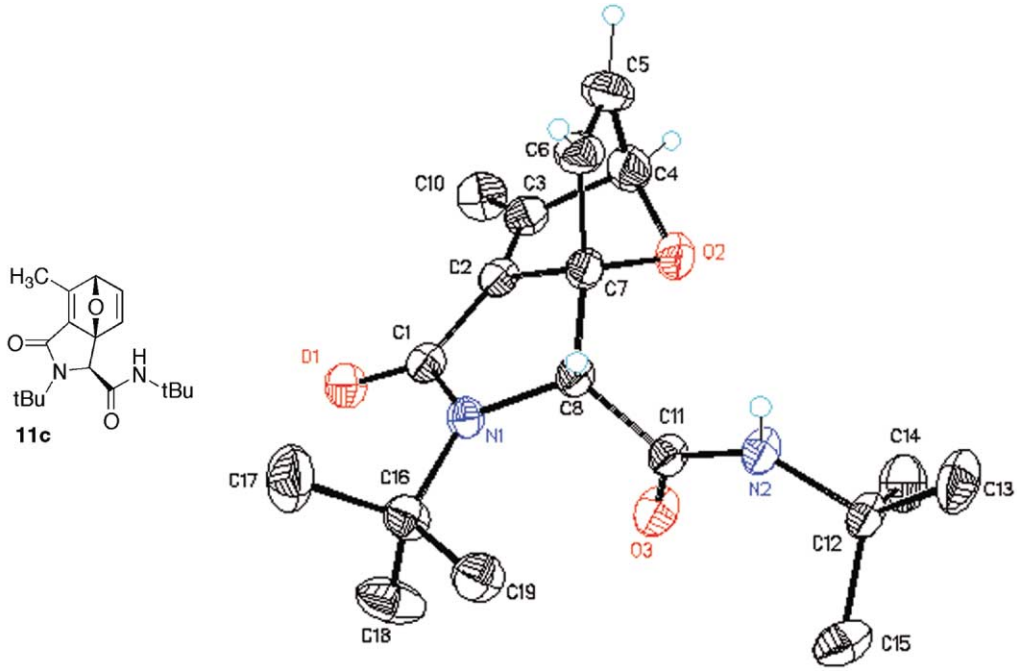
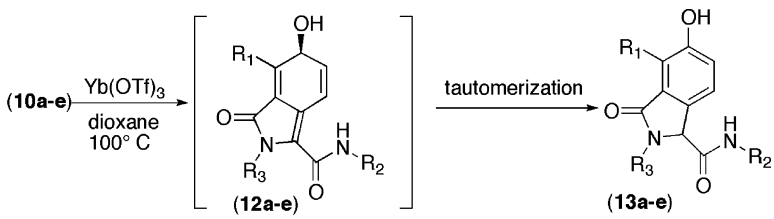


Fig. 1. X-Ray structure of cycloadduct **11c**.

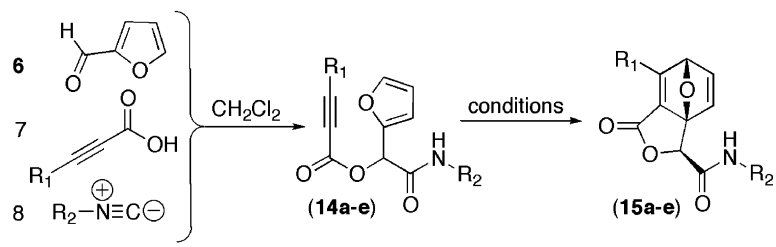


Scheme 3. Two-step synthesis of isoindolinones.

Table 2. Synthesis of isoindolinones

Entry (MCR)	R1	R2	R3	Entry (phenol)[a]	Yield (%)
10a	Me	Bn	Bn	**13a**	80
10b	Ph	Bn	*t*Bu	**13b**	77
10d	Me	Bn	*t*Bu	**13d**	81
10e	Ph	Bn	Bn	**13e**	91
10f	H	Bn	*t*Bu	**13f**	Dec.

[a] Reactions conditions: 0.02 M substrate in 1,4-dioxane, 20 mol% $Yb(OTf)_3$, heated at 100°C in a sealed tube.



Scheme 4. Synthesis of bicyclic lactones.

reactions were highly selective, the stereochemistry of the cycloadducts provisionally assigned based on the X-ray structure of bridged bicycle **11c**. Unfortunately, attempts to directly convert the Passerini products to isobenzofuranones under ytterbium catalysis have not been successful (Table 3).

Table 3. Sequential Passerini/IMDAF studies

Entry (MCR)[a]	R1	R2	MCR yield (%)	Entry (IMDAF)[b]	IMDAF yield[c] (%)
14a	Me	Bn	86	**15a**	77
14b	Ph[d]	*t*Bu	79	**15b**	72
14c	Ph[d]	*t*Bu	69	**15c**	68
14d	Me	*t*Bu	82	**15d**	72
14e	H	Bn	79	**15e**	Dec.

[a] Reactions were run at a concentration of 0.2 M in CH_2Cl_2 at rt.
[b] A 0.2 M solution of the furan in CH_2Cl_2 was treated with Me_2AlCl at −78°C to rt.
[c] Yields reported are for a pure diastereomer.
[d] All MCRs with phenyl propiolic acid were run in the dark to limit alkyne dimerization.

This striking difference in reactivity is quite interesting considering the small change from nitrogen to oxygen in the tether. This difference in reactivity may reflect the difference in conformation between an ester and amide sidechain or in the stability of the cycloadducts. Moreover, it was observed that the IMDAF derivatives from the Passerini reaction were much less stable than those derived from the Ugi products. The lactones quickly undergo retro Diels–Alder reaction at elevated temperatures while the lactams are completely stable. This may explain the failure to effect IMDAF reaction under thermal conditions with the acetylenic esters. An even greater instability of the lactones was observed in the presence of acid. For example, a solution of the cycloadduct **15a** prepared in commercial $CDCl_3$ showed reversion to the starting furan within hours at rt while solutions in C_6D_6 are stable for at least one week. Protic acids have been reported to promote retro-IMDAF reactions of oxabicyclo[2.2.1]heptadiene derivatives[13] to regenerate furan starting materials. In sharp contrast, the lactam derivatives do not show any propensity to undergo cycloreversion upon exposure to acidic conditions. Despite the structural similarities present in these two families of oxabicyclo[2.2.1]-heptadiene derivatives, their reactivities and stabilities are quite different.

The sequential use of MCRs and cycloadditions can lead to structurally complex materials in short sequences. Utilizing Passerini and Ugi reactions in tandem with an IMDAF led to annulated oxabicyclo[2.2.1]heptadiene derivatives that are amenable to further elaboration. Studies on the conversion of the Passerini derivatives to analogs of viridin is currently under investigation.

Acknowledgements

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