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Studies on the Diels–Alder reaction of annulated furans: application to the synthesis of substituted phenanthrenes

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Abstract—In an attempt to utilize the synthetic power of the furan nucleus in the synthesis of complex natural products, we have developed an entry into annulated furan intermediates that involves an electrochemical annulation protocol. An approach to the eunicellin diterpenes based on this methodology required the use of an intermolecular Diels–Alder reaction on an annulated furan. Although well known for simple furans, there is a paucity of related examples on annulated furans. To examine the feasibility of such an approach to these diterpenes, we have studied this key cycloaddition reaction. Our studies indicate that the process can be hampered by a facile retro-Diels–Alder that is highly dependent on the dienophile employed.

Over the past several years, we have developed an electrochemical protocol that generates annulated furans in a high-yielding and stereoselective manner.[1–3] The use of furan in the annulation has several strategic implications in that the aromatic moiety is easily transformed to several other structural types through ring-opening or cycloaddition reactions. We recently formulated an approach to the eunicellin diterpenes such as eleutherobin (**1**) and sarcodictyn (**2**) based on the ability to assemble and then exploit an annulated furan intermediate.

This approach to the eunicellin skeleton would involve an early electrochemical[4] furan annulation onto cryptone[5] to produce the tricyclic intermediate **3**. Elaboration of the furan through a subsequent Diels–Alder reaction would produce the phenathrene skeleton **4**. Unraveling of the eunicellin skeleton would take place through a sequential reductive opening/oxidative cleavage reaction to produce **6** (Scheme 1).[6] Key to the success of this approach is the ability to carry out the Diels–Alder reaction on an annulated furan such as **3**. Although simple furans have frequently been used in Diels–Alder chemistry,[7] the use of annulated furans has remained virtually unexplored[8] and prompted us to examine the feasibility of such reactions. In this letter, we describe studies on the scope of the intermolecular Diels–Alder reaction of these annulated furan systems.

Our studies commenced with the previously described furan **7**,[2] readily available through the electrochemical annulation of cyclohexenone. A series of typical dienophiles was examined both under thermal and Lewis acid-catalyzed conditions (Table 1).

The thermal addition of highly reactive dienophiles such as maleic anhydride and *N*-methyl maleimide proceeded well and produced good to excellent yields of the corresponding cycloadducts **8** and **9**. The lower yield of the anhydride adduct was associated with hydrolytic instability of the adduct rather than a less efficient Diels–Alder reaction. DMAD added in excellent yield to give adduct **10** at room temperature. These reactions proceeded in a highly diastereoselective manner, producing a single adduct where the dienophile had added in the *endo*-mode from the convex face of the *cis*-decalin system.[9] In contrast, attempts to add less reactive dienophiles such as MVK, acrolein, acrylonitrile or methacrylate were disappointing, typically returning

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Keywords: Eleuthosides; Annulated furan; Diels–Alder.

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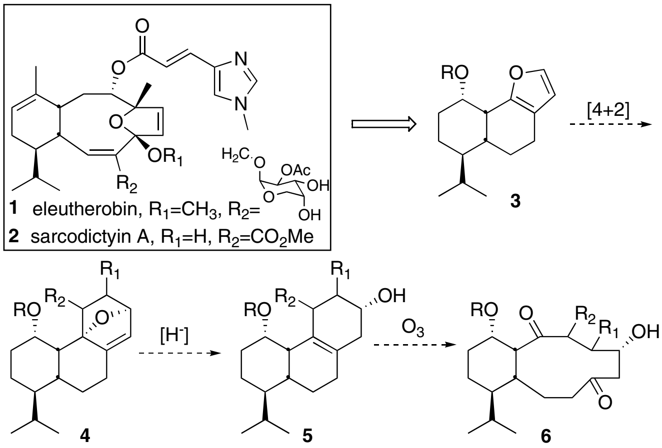
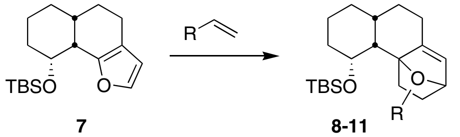


Scheme 1. Approach to the eunicellins.

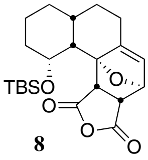
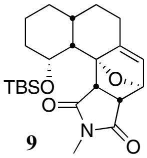
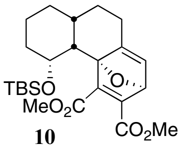
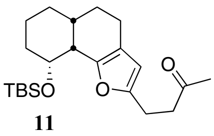
only unreacted starting material. Attempts to promote these reactions with Lewis acids (ZnI_2, BF_3OEt_2, $HfCl_4$[10]) were also unsuccessful with only products of conjugate addition (e.g., **11**) being produced with MVK. Although limited to highly reactive dienophiles, we were encouraged to construct a system more relevant to the eunicellins (Scheme 2).

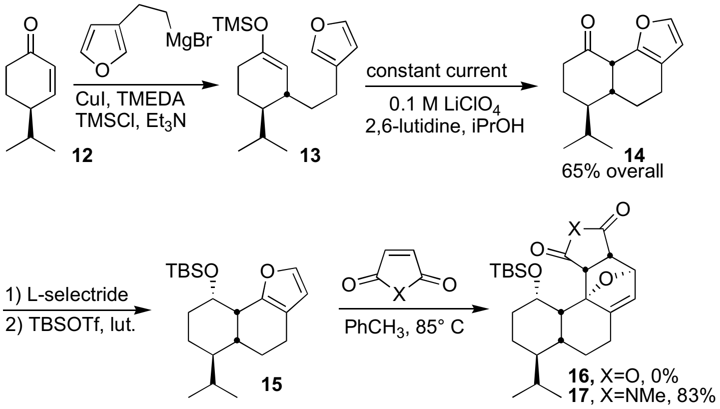
Application of the two-step annulation protocol to cryptone **12** produced the tricyclic ketone **14** in 65% yield for

Table 1. Diels–Alder reactions of an annulated furan



7 **8-11**

Dienophile	Conditions	Product	Yield (%)
Maleic anhydride	85 °C, $PhCH_3$	 **8**	63
N-Methyl maleimide	85 °C, $PhCH_3$	 **9**	91
Dimethylacetylene dicarboxylate	25 °C, Neat	 **10**	93
Methyl vinyl ketone	120 °C, $PhCH_3$	No reaction	N/A
Methacrylate	120 °C, $PhCH_3$	No reaction	N/A
Methyl vinyl ketone	$HfCl_4$, 0 °C, DCM	 **11**	88
Methacrylate	$HfCl_4$, 0 °C, DCM	Decomposition	N/A



Scheme 2.

two steps. Addition of the cuprate occurred with greater than 10:1 selectivity with respect to the isopropyl group and produced a single diastereomer during the cyclization. Subsequent reduction/protection of the ketone gave annulated furan **15** for the key cycloaddition reaction. Surprisingly, attempted condensation with maleic anhydride failed to produce any of the desired adduct **16**. A variety of attempts were made to force the reaction although only starting material was recovered. Attempts to add DMAD also failed although *N*-methylmaleimide added with similar efficiency as the model furan producing **17**. Traces of adduct **16** could be observed but quickly decomposed. A successful cycloaddition with maleic anhydride was finally realized using the Grieco et al. protocol[11] whereby the reaction was performed in 5 M lithium perchlorate (Scheme 3).

Stirring the furan **15** and maleic anhydride at room temperature in a concentrated lithium perchlorate solution led to the production of **16**, a highly unstable adduct. Upon standing at room temperature, **16** underwent thermal cycloreversion to return **15**, which accounted for the failure of the thermal reactions described previously. Careful work-up of the cycloaddition reaction below ambient temperature followed by immediate exposure to super-hydride gave the lactone **18** in 44% overall yield. Reduction of the anhydride had occurred in accordance with attack from the least hindered trajectory[12] to produce a single regioisomer whose structure was determined through X-ray crystallographic analysis (Fig. 1).

The structure of **18** provided a great deal of insight into the instability of **16**. The X-ray structure showed that in the solid state that the molecule adopted a conformation that placed both the isopropyl group and siloxy groups in a diaxial relationship. Molecular modeling[13] also showed that this conformation was preferred in **16** by 3–4 kcal/mol over the alternative conformation that placed these two groups in a diequatorial relationship. Relative to the stable adduct **8**, this adduct is highly destabilized by the presence of the large isopropyl group in an axial position that promotes the retro-Diels–Alder process. Apparently, the ease at which the adducts of **15** decompose through the cycloreversion process is heavily dependent on the leaving dienophile. The impact of the dienophile on the stability of simple furan adducts has been studied by DiMare and co-workers who calculated that the maleimide adduct was approximately 3 kcal/mol more stable than the maleic anhydride adduct.[14]

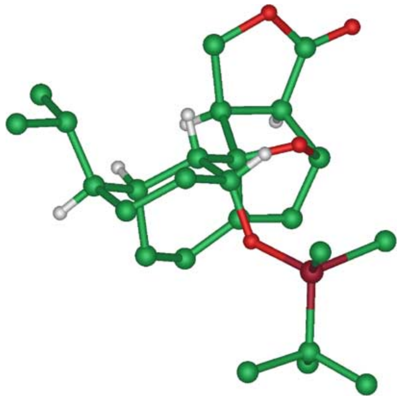
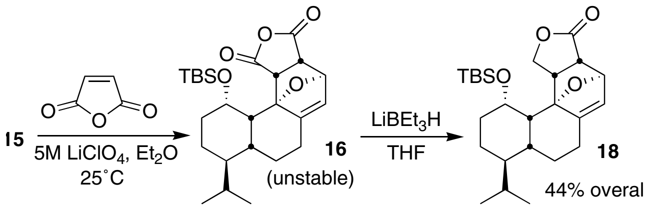


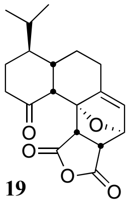
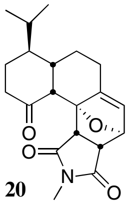
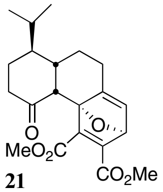
Figure 1. X-ray structure of adduct **18**.



Scheme 3.

In an attempt to alleviate some of the destabilizing interactions in these adducts, similar Diels–Alder reactions were examined with the ketone **14** where retaining the ketone in the oxidized state eliminated the unfavourable diaxial interactions experienced by the silyloxy group. Previous experience suggested that compounds related to **14** were somewhat unstable as they are prone to undergo oxidation at the activated position between the furan and the ketone. Accordingly, attempted thermal addition of any dienophiles to ketone **14** produced only trace amounts of product. Recourse to milder conditions proved more reliable for these systems (Table 2).

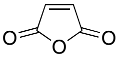
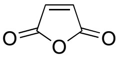
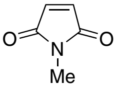
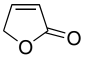
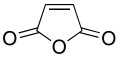
Table 2. Diels–Alder reactions of ketone **14**

Dieneophile	Conditions	Product	Yield (%)
Maleic anhydride	5 M $LiClO_4$, Et_2O, 25 °C	 **19**	25
N-Methylmaleimide	5 M $LiClO_4$, Et_2O, 25 °C	 **20**	84
DMAD	Neat, 25 °C	 **21**	88

Cyclocondensation of ketone **14** with maleic anhydride in concentrated lithium perchlorate gave low yields of the corresponding adduct **19** as the retro-Diels–Alder was still problematic. Under similar conditions the maleimide added smoothly to produce **20** in high yield. As with furan **7**, exposure to neat DMAD at ambient temperature produced the oxabicyclohexadiene adduct **21** in very good yield. Although removing the steric problem associated with the siloxy group improved the thermal stability of the adducts, the bulky isopropyl group is clearly a major destabilizing influence. A thermal stability study of some key adducts clearly demonstrated that the nature of the departing dienophile is a major influence on the cycloreversion reaction (Table 3).

Utilizing variable temperature NMR, the stability of the adducts towards cycloreversion was studied. Whereas the maleic anhydride adduct **8** that lacked the isopropyl group was stable at 100 °C, the presence of this group lowered that temperature to approximately 20 °C. However, the corresponding lactone **18** and imide adducts **17** showed much better thermal stability.

Table 3. Thermal stability of representative adducts

Entry	Adduct	Dienophile	Stable at (°C)
1	**8**		100
2	**16**		20
3	**17**		80
4	**18**		50
5	**19**		30

Despite the utility of simple furans as dienes in Diels–Alder reactions, significantly less is known about related reactions on annulated congeners. These studies show that although these reactions can be very useful, the products are highly susceptible to cycloreversion reactions. A key finding of this work is that the particular dienophile employed can have a significant impact on the reaction. These differences in adduct stability can dramatically impact the ability to use annulated furans in cycloaddition chemistry. Coupled with our methodology for constructing annulated furans, this process represents a rapid entry into highly substituted phenathrene systems and currently forms the basis for an approach to the eunicellin diterpenes.

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