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Synthetic Studies Towards Batrachotoxin 1. A Furan-based Intramolecular Diels-Alder Route To Construct The A-D Ring System

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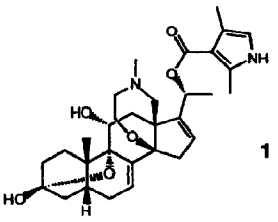
Abstract: A stereoselective intramolecular Diels-Alder reaction has been developed using annelated furans to produce functionalized steroidal nuclei, which can serve as advanced intermediates in the synthesis of batrachotoxin.

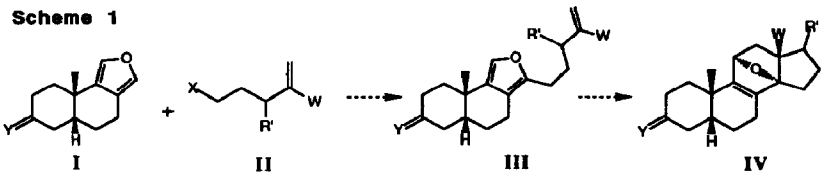
The intramolecular Diels-Alder reaction has repeatedly been demonstrated to be a potent and broadly applicable transformation in organic synthesis.[1] Indeed, during our contemplation of a synthetic strategy of batrachotoxin (**1**),[2,3] a steroidal alkaloid isolated from frogs of the genus *Phyllobates*[4] and known to exhibit remarkable biological activity,[5] we recognized the possibility that an intramolecular Diels-Alder process might allow us to construct the A-D[6] ring system of **1** in a convergent manner. In essence, we envisioned first



1 : Batrachotoxin

to couple a furan-annelated A-B ring with a suitable alkene-bearing portion, cf. **I**+**II**→**III**, and then to construct the C-D ring *via* an intramolecular Diels-Alder reaction, cf. **III**→**IV**. The intramolecular Diels-Alder strategy has, in fact, been successfully executed in the steroid field,[7] but this plan differs significantly from any previously reported steroid synthesis.

Scheme 1

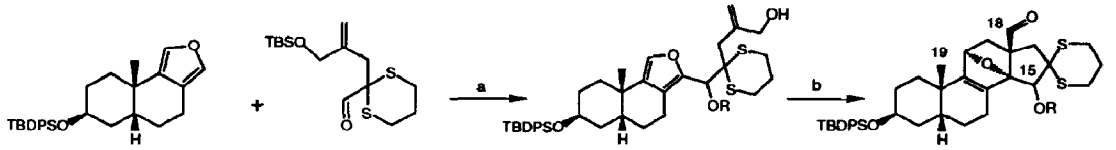


I **II** **III** **IV**

There are several concerns regarding the proposed intramolecular Diels-Alder reaction. First, the facial selectivity of the cyclization is crucial for our purposes. The development of a quaternary carbon center with the proper stereochemistry is often troublesome and, for this case, the stereochemical course of the cyclization should be determined by remote chiral centers. Nevertheless, we felt that the convex face in the *cis*-decalin system would facilitate a desired β-attack onto the furan. Second, an inspection of the related examples known in the literature[8] revealed that the proposed cyclization might have an equilibrium disfavored for the product; in order to shift the equilibrium to the product side, geminal substituents might be required to be appended on the acyclic portion. Third,

to the best of our knowledge, no successful example is recorded for a furan-based intramolecular Diels-Alder reaction involving the alkene with this degree of substitution. Using three relevant substrates, we addressed these issues[9] and demonstrated the feasibility of this approach to batrachotoxin.

The coupling of furan **2**[10] with aldehyde **3**[11] was realized by using anion chemistry (Scheme 2). It is worth noting that, under the specified conditions,[12] the regioselectivity of the anion formation on **2** and subsequent C-C bond formation with **3**, was approximately 5:1. The furfuryl alcohol **4** thus obtained was a 1.1:1 mixture of the two possible diastereomers, which were separated[13] and subjected to the following reactions separately. The unstable enal was generated *in situ* and allowed to stand in a dilute solution (ca. 1.0 mM) at room temperature. In the event, we found that each epimer could undergo a high-yielding, selective Diels-Alder reaction (Table 1).



2 **3** **4** **5**

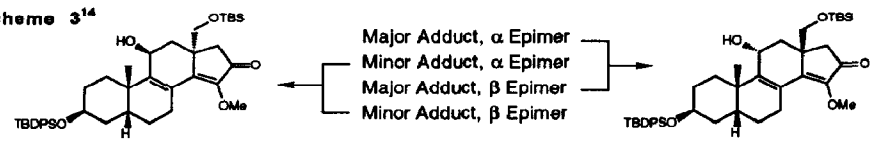
Scheme 2. Reagents and Reaction Conditions: a. 1. **2**, *s*-BuLi, THF, -78 °C, followed by addition of **3** then HPLC separation. 2. NaH, RX, THF. 3. TBAF, THF. b. 1. MnO_2, CH_2Cl_2. 2. See Table 1.

Table 1

substrates	solvent	R	time	temp	product ratio (major : minor : SM)
C.15 α-isomer	hexanes	Me	36 h	25 °C	8.0 : 1.0 : 1.0
	MeCN	Me	48 h	0 °C	0.8 : 0.3 : 1.0
	hexanes	Bn	36 h	25 °C	8.7 : 1.3 : 1.0
	MeCN	Bn	40 h	25 °C	5.1 : 2.9 : 1.0
C.15 β-isomer	hexanes	Me	20 h	25 °C	1.2 : 0.9 : 1.0
	MeCN	Me	20 h	25 °C	10 : 2.0 : 1.0
	hexanes	Bn	20 h	25 °C	0.8 : 0.4 : 1.0
	MeCN	Bn	48 h	0 °C	7.5 : 2.9 : 1.0

Of some interest is the substantial solvent effect observed, which is reversed with respect to the stereoisomers at the furfurylic position. The structure of the products were determined on the basis of two pieces of evidence. First, the two series of adducts were correlated by chemical means[14] (Scheme 3), which revealed that the facial selectivity was the same in both cases, and not controlled by the C.15 stereocenter but by the A-B ring moiety. Second, with this information, a series of nOe studies allowed us to assign their stereochemistry unambiguously; in particular, a clear interaction between the C.18 aldehyde and the C.19 methyl group was detected for the major diastereomers of **5** but not for the minor diastereomers of **5**.

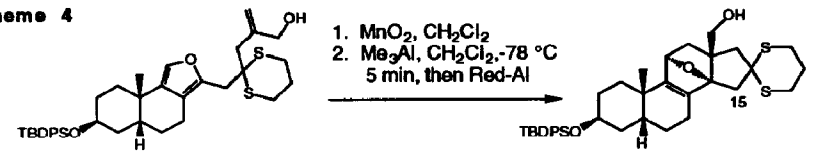
Scheme 3[14]



Having demonstrated the feasibility of the proposed intramolecular Diels-Alder reaction in **4**, we sought to determine the suitability of a substrate lacking the C.15 substituent, because this variant apparently offered some synthetic advantages. Thus, **4** was converted to **6**,[15] which was then exposed to the established sequence of

reactions. Here the rate of the reaction was increased, but the facial selectivity decreased. In fact, the retro Diels-Alder process was so facile that isolation of the pure product by silica gel chromatography was impossible. Nevertheless, these limitations were overcome by utilizing a Lewis acid (Me_3Al, 1.0 equiv.) at -78 °C for 5 min, followed by trapping the labile aldehyde using Red-Al (Scheme 4). Thus, an efficient (80% isolated yield based on the allylic alcohol), stereoselective (the selectivity = 8:1, favoring the desired diastereomer) cyclization could also be attained with this substrate.

Scheme 4



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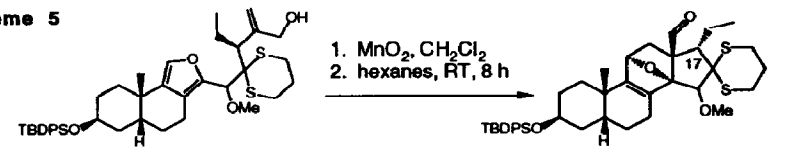
Furthermore, the effect of the inclusion of an alkyl group at C.17[16,17] was found to be quite dramatic (Scheme 5). With an ethyl substituent at C.17, a superb cycloaddition was obtained, giving the desired adduct almost exclusively (20:1, either methoxy epimer) under mild conditions. As batrachotoxin contains such an alkyl group, this result is of particular relevance to our designs.

Scheme 5



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In conclusion, a method of constructing a highly functionalized steroid framework has been achieved. Our route is convergent, which allows for the rapid installation of substituents at some of the more inaccessible positions on this nucleus. Also, the ability to obtain a quaternary carbon originating in the dienophile significantly extends the scope of the furan-based intramolecular Diels-Alder reaction.

Acknowledgment. Financial support from the National Institutes of Health (NS 12108) is gratefully acknowledged. T.J.G. thanks Eli Lilly Company for a predoctoral fellowship.

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6. The standard steroid numbering and ring lettering system are used throughout this paper.

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9. Through examining a series of simple model systems, we found that: (1) the quaternary center in the product did, indeed, inhibit the reaction and geminal substitution at C.16 did not overcome this effect and (2) an electron withdrawing group at C.18 induced a rapid, reversible cyclization but was not sufficient synthetically (poor equilibrium constant and low selectivity).

10. The racemic furan **2** was synthesized from the known ethylene glycol monoketal (McMurry, J. E. *J. Am. Chem. Soc.*, **1968**, *90*, 6821) of the Wieland-Miescher ketone in 6 steps: (1) Li, NH_3, THF, -78 °C, (2) TBDPSCl, imid., DMF, (3) cat H_2SO_4, aq. THF, (4) NaH, HCO_2Et, THF, (5) *n*-BuSH, *p*-TsOH, PhH, reflux, and (6) NaH, Me_3SI, DMSO-THF; $HgCl_2$, pentane. A modified Garst-Spencer sequence was used to construct the furan ring; the 3-β configuration was necessary for the success of this method.

11. The aldehyde **3** was synthesized according to the following sequence: TBS protected methallyl alcohol was brominated allylically (*p*-ClPhSeBr, CH_2Cl_2, -78 °C; O_3, -78 °C; 2,6-lutidine, RT, 8 h), coupled with 2-formyl-1,3-dithiane (NaH, DMF, 0 °C, 20 min), and the resultant mixture (*O*-and *C*-alkylation) was heated (toluene, reflux, 12h).

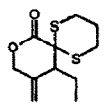
12. No other lithiation condition examined provided any degree of selectivity.

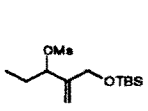
13. Separation was accomplished by using a DuPont Zorbax column (hexanes/*t*-BuOMe). The stereochemistry was assigned through nOe studies on the cyclized products.

14. This was achieved in 4 steps: (1) $NaBH_4$, MeOH, (2) TBS-Cl, imidazole, DMF, (3) aq. $Hg(ClO_4)_2$, $CaCO_3$, and (4) NaOMe, MeOH.

15. Where R=Ac and the primary alcohol is protected as the TBS ether, the condition, 1 eq. Et_3SiOTf, 6:1 CH_2Cl_2:Et_3SiH, -78 °C, 6 min, was used, followed by TBAF induced desilylation.

16. The substrate **8** was synthesized by coupling the racemic lactone **10** with the furan **2**, followed by (1) LAH, THF, 0 °C, (2) TBS-Cl, imidazole, CH_2Cl_2, (3) NaH, MeI, THF, (4) TBAF, THF. **10** was synthesized by coupling 2-cyano-2-lithio-1,3-dithiane with the mesylate **11** (selectively giving S_N2 over S_N2' substitution) followed by (1) HF-py, MeCN and (2) CSA, PhH, reflux, 6 h.

10 

11 

17. All four diastereomers were readily separable; the stereochemistry was assigned through nOe studies on the cyclized products. The α-isomers cyclized well, but with poor selectivity.

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