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COMMUNICATION

The clerodane ring system: investigating the viability of a direct Diels–Alder approach†

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A direct synthetic approach to the spiro-γ-lactone clerodane ring system has been investigated. This work builds on that of Jung and highlights the inherent difficulties associated with the otherwise obvious Diels–Alder approach.

Clerodane natural products[1] are a prolific family of biologically active diterpenes numbering over a thousand. This series of natural products has received comparatively little synthetic attention.[2] For example, only 4 total syntheses of clerodanes containing the spiro-γ-lactone moiety, a structural feature found in a large number of all clerodane natural products isolated so far, have been reported (*i.e.* teucvin **1**,[3] 12-*epi*-teucvin **2**,[3] teuscorolide **3**,[4] montanin A **4**[4]) (Fig. 1). Considering this apparent lack of synthetic attention and the potential biological properties the clerodane systems offer[5] the authors have independently pursued total syntheses in this area, with Ley achieving the total synthesis of ajugarin **5**[6] and Williams exploring an ambitious 6π-electrocyclisation as a general route.[7] During these pursuits both groups postulated that access to the spiro-γ-lactone sub-class might be more successful through the direct application of a Diels–Alder (DA) reaction on densely functionalised systems. Although Diels–Alder approaches to these molecules have been utilised previously[2–6,8] they were applied in the early stages of the various synthetic strategies. We, however, proposed a late stage DA reaction in which most of the required functionality is delivered from a very advanced intermediate.

In fact we are not the first to propose such a strategy; Jung reported[9] that diene **8** and the phenyl allenic spiro-γ-lactone **9** react to give **10** as a mixture of diastereomers. This method was not further elaborated, presumably due to difficulties in accessing the corresponding furano allenic spiro-γ-lactone (Scheme 1). Based on this premise we herein report studies in attempting to develop an advanced intermediate based on the DA chemistry, poised to access a number of clerodane natural products containing the furanospiro-γ-lactone moiety (*i.e.* montanin B **6**[10] and teucrin A **7**[11]) (Fig. 1).

The approach to our desired target (**12**), although not grossly dissimilar to that of Jung, has two significantly different challenges: 1) the questionable stability of the *cis*-furanospiro-γ-lactone **11** in terms of both access and reaction survival; and 2) the

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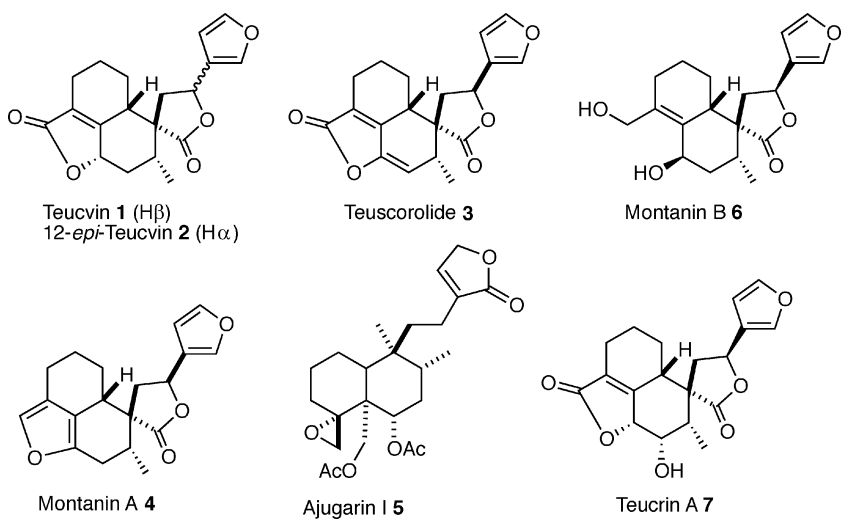
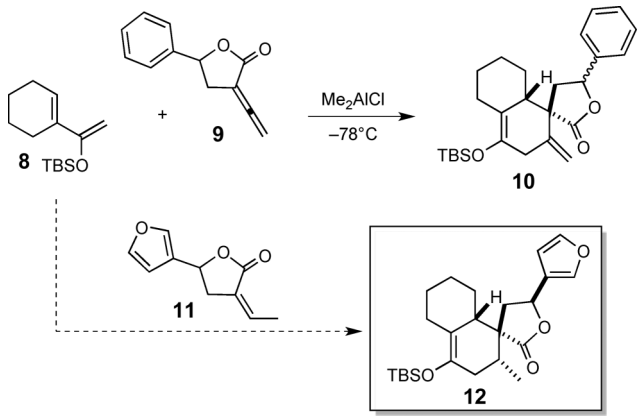


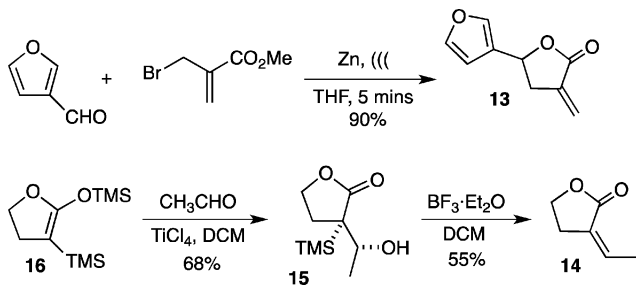
Fig. 1



Scheme 1

change in both electronic and steric demand of **11** compared to allenic lactone **9** (Scheme 1). With this in mind the initial objective was to test the viability of the Diels–Alder reaction with two model dienophiles (*i.e.* **13** and **14**), which would also give an indication with respect to the availability and stability of **11**.

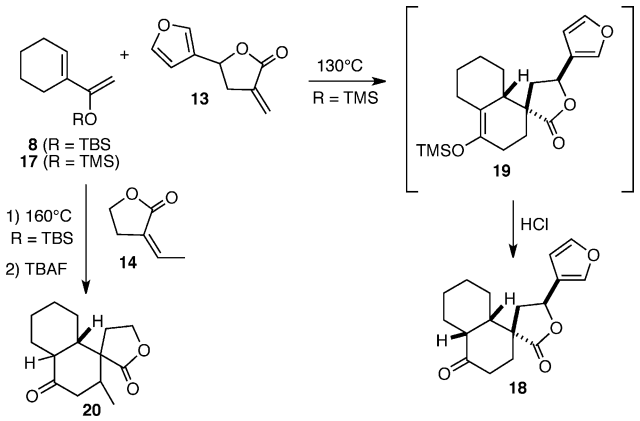
Compound **13** was rapidly obtained in 90% yield *via* sonication of methyl α-methylacrylate with 3-furaldehyde in the presence of zinc,[12] whereas compound **14** was accessed utilising the work of Yamamoto[13] *via anti*-elimination of aldol product **15** derived from **16** (Scheme 2).



Scheme 2

Diels–Alder reactions with diene (**8**) and the corresponding TMS derivative **17** involving both dienophiles **13** and **14** were next investigated (Scheme 3). Surprisingly, attempts to drive the reaction between **13** and **17** using Lewis acids completed failed, even though stability studies involving the exposure of **13** to a variety of Lewis acids at low and room temperature suggested acceptable stability. It was not until heating at 130 °C in a presilylated glass pressure vessel was adduct **18** obtained in 31% yield (*via* treatment of **19** with hydrochloric acid). Fortuitously **18** was attained as the sole *cis*-decalin diastereomer as observed by X-ray crystal structure analysis (Fig. 2). All attempts to enhance the yield of the DA reaction using ultra high pressure and higher temperature conditions were unsuccessful.

With the knowledge that **13** is sufficiently stable and undergoes the DA reaction with excellent stereochemical control, together with the observation that the trisubstituted system **14** also undergoes reaction (albeit with limited stereocontrol), a synthesis of *cis*-furanospiro-γ-lactone **11** was sought. Unfortunately the method used for **13** was not applicable to **11** as supported by Loffler.[14] Thus the method used for **14** was explored in two



Scheme 3

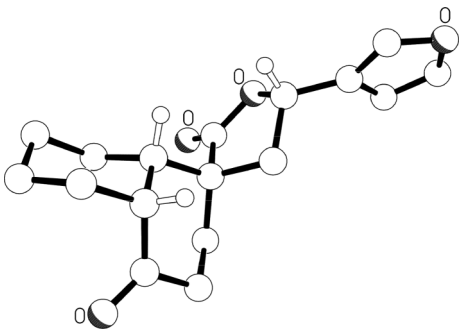
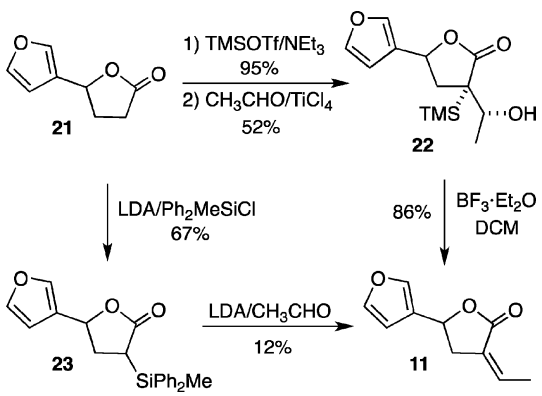


Fig. 2 The molecular structure of **18**.

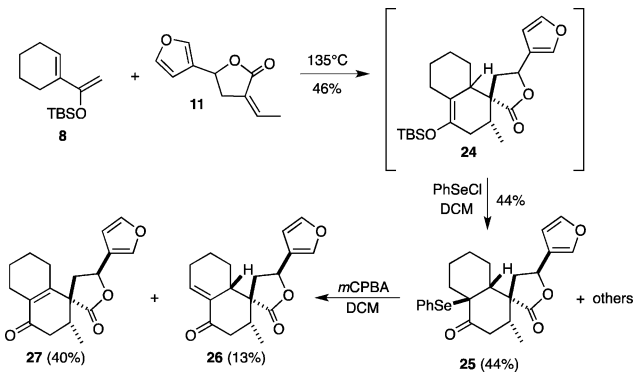
separate variations starting from lactone **21**,[15] obtained from 3-bromopropionic acid and 3-furaldehyde in 41% yield (Scheme 4). Pleasingly, following the Yamamoto route lactone **21** was converted into **22** and subjected to elimination giving **11** in 42% yield over three steps. In an attempt to limit steps and increase yield, lactone **21** was silylated (*i.e.* **23**) and subjected to a Peterson type olefination, which unfortunately did not lead to an improvement in overall yield (Scheme 4). Again, like lactone **13**, it was a pleasant surprise to observe that the *cis*-furanospiro-γ-lactone **11** was not as sensitive as first anticipated.



Scheme 4

Having successfully obtained **11** in workable quantities the key DA reaction with diene **8** could now be probed. Again, reaction in the presence of Lewis acids returned starting material. Heating, however, at 135 °C in a presilylated glass pressure vessel for

90 h produced **24** in 46% yield as a mixture of 3 inseparable diastereomers in a ratio of 6 : 3 : 1 (GC). Desilylation (protolysis) did not improve the stereochemical outcome, however, treatment of the mixture (*i.e.* **24**) with phenylselenyl chloride afforded pure **25** as the major compound. Unfortunately, elimination using a variety of oxidation–elimination protocols consistently gave a 1 : 3 ratio of enones **26** and **27**, with the desired advanced intermediate **26** being obtained in only 13% yield (Scheme 5).



Scheme 5

We believe the presence of the additional methyl group in alkylidene lactone **11** is responsible for the loss of stereocontrol of the Diels–Alder reaction compared to the unsubstituted alkylidene lactone **13**. In the reaction of **13** with diene **8** the initial direction of approach will be controlled by the stereochemistry of the furan substitution. The dienophile will then approach with the lactone carbonyl interacting with the diene in an *endo* approach, maximizing orbital overlap between the carbonyl of the lactone and the diene. The initial approach for **11** will also be determined by the furan orientation. However, in this case if an *endo* approach is considered the additional methyl group will be brought into close proximity to the silyl group of the diene (Fig. 3). Therefore the favoured *endo* approach of the lactone will be offset by the increased steric interaction, leading to loss of stereocontrol.

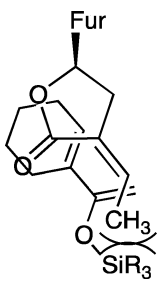


Fig. 3

In conclusion, this body of work advances the seminal studies of Jung demonstrating an advanced intermediate (*i.e.* **26**) containing most of the functionality required for the spiro-γ-lactone clerodane ring system can be obtained *via* a direct Diels–Alder approach. The likelihood of this approach being viable is, however, questionable due to issues associated with stereocontrol most likely arising from the methyl substituent contained with dienophile **11**. Finally, rapid access to the clerodane system remains elusive, requiring new innovative strategies to facilitate syntheses in an acceptable number of steps.

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