

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

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Received 17th March 2011, Accepted 27th April 2011

DOI: 10.1039/c1ob05422h

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 products¹ 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**) (Fig. 1). Considering this apparent lack of synthetic attention and the potential biological properties the clerodane systems offer⁵

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 6 π -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 reported⁹ 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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† Electronic supplementary information (ESI) available. CCDC reference numbers 814882. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob05422h

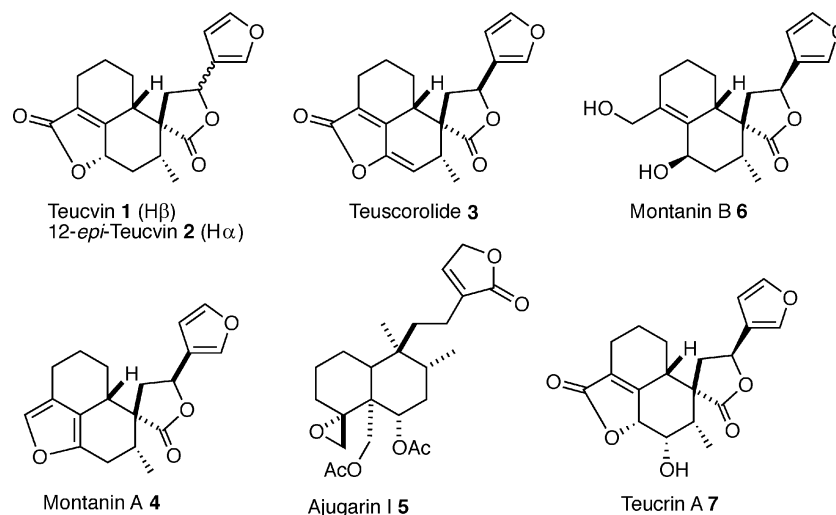
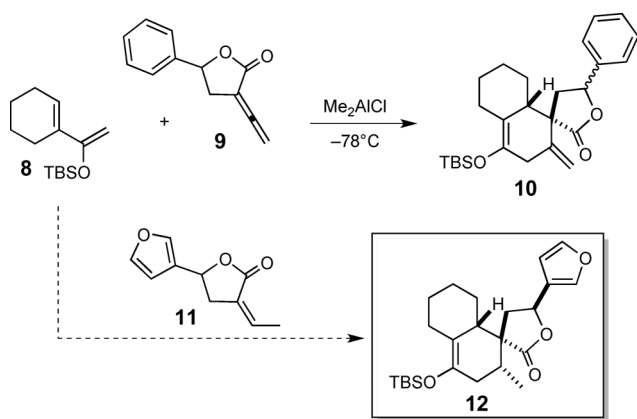


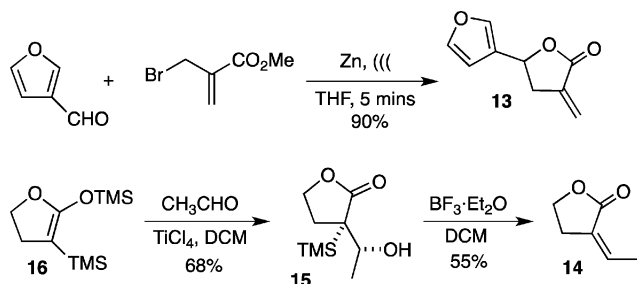
Fig. 1



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**.

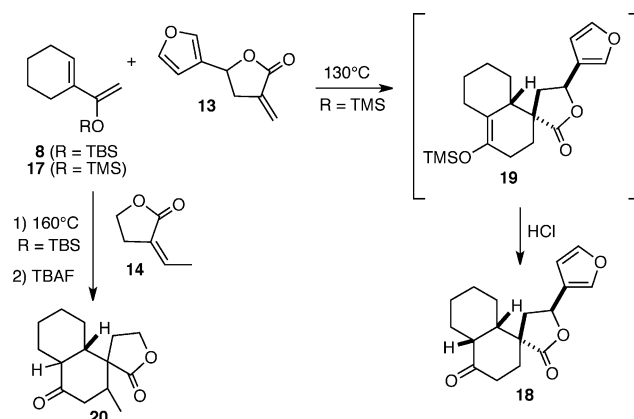
Compound **13** was rapidly obtained in 90% yield *via* sonication of methyl α -methylacrylate with 3-furaldehyde in the presence of zinc,¹² whereas compound **14** was accessed utilising the work of Yamamoto¹³ *via anti*-elimination of aldol product **15** derived from **16** (Scheme 2).



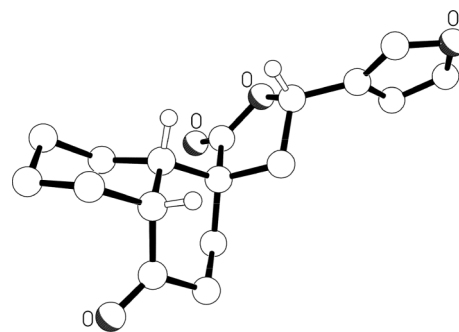
Scheme 2

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.

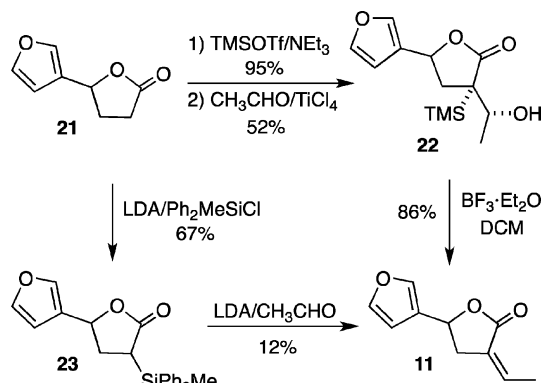
With the knowledge that **13** is sufficiently stable and undergoes the DA reaction with excellent stereochemical control, together with the observation that the trisubstituted system **14** also undergoes reaction (albeit with limited stereocontrol), a synthesis of *cis*-furanospiro- γ -lactone **11**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



Scheme 3

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

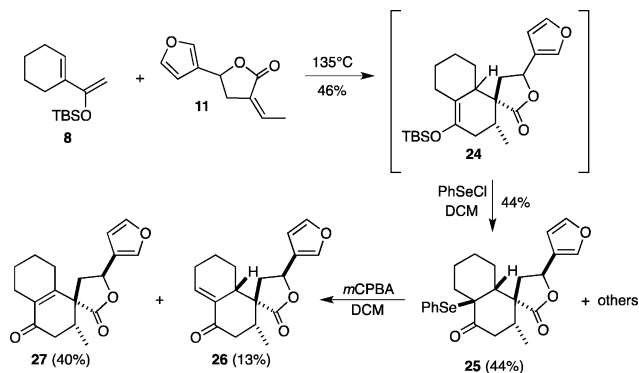
separate variations starting from lactone **21**,¹⁵ obtained from 3-bromopropionic acid and 3-furaldehyde in 41% yield (Scheme 4). Pleasingly, following the Yamamoto route lactone **21** was converted into **22** and subjected to elimination giving **11** in 42% yield over three steps. In an attempt 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 phenylselenenyl 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 alkyldiene lactone **11** is responsible for the loss of stereocontrol of the Diels–Alder reaction compared to the unsubstituted alkyldiene 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.

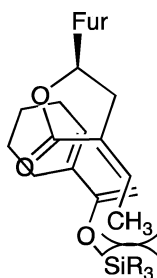


Fig. 3

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.

Acknowledgements

The authors thank the EPSRC (UK), Imperial College London, the University of Cambridge and The University of Queensland for financial support. Special thanks to Dr Andrew J. P. White (Chemical Crystallography Laboratory, Department of Chemistry, Imperial College London, UK) for assistance with X-ray crystal data.

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