

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

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A direct synthetic approach to the spiro- $\gamma$ -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<sup>1</sup> are a prolific family of biologically active diterpenes numbering over a thousand. This series of natural products has received comparatively little synthetic attention.<sup>2</sup> For example, only 4 total syntheses of clerodanes containing the spiro- $\gamma$ -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**,<sup>3</sup> 12-*epi*-teucvin **2**,<sup>3</sup> teuscorolide **3**,<sup>4</sup> montanin A **4**) (Fig. 1). Considering this apparent lack of synthetic attention and the potential biological properties the clerodane systems offer<sup>5</sup>

the authors have independently pursued total syntheses in this area, with Ley achieving the total synthesis of ajugarin **5**<sup>6</sup> and Williams exploring an ambitious 6 $\pi$ -electrocyclisation as a general route.<sup>7</sup> During these pursuits both groups postulated that access to the spiro- $\gamma$ -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<sup>2–6,8</sup> 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<sup>9</sup> that diene **8** and the phenyl allenic spiro- $\gamma$ -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- $\gamma$ -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- $\gamma$ -lactone moiety (*i.e.* montanin B **6**<sup>10</sup> and teucrin A **7**<sup>11</sup>) (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- $\gamma$ -lactone **11** in terms of both access and reaction survival; and 2) the

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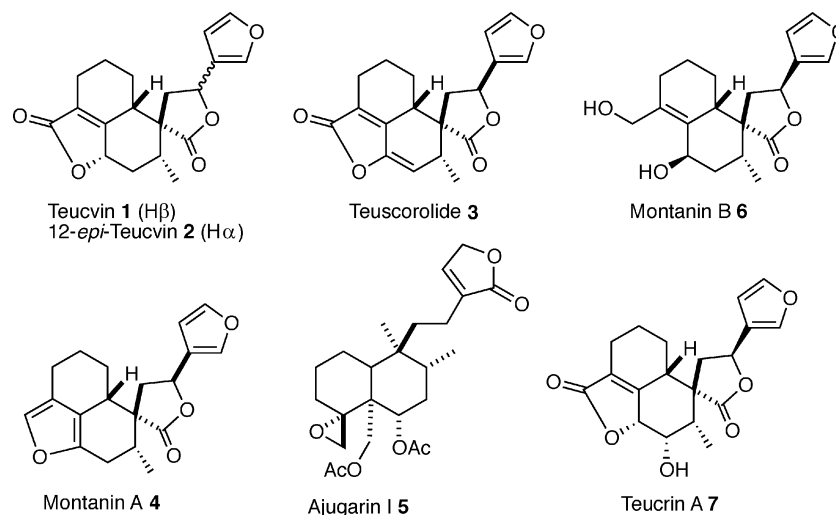
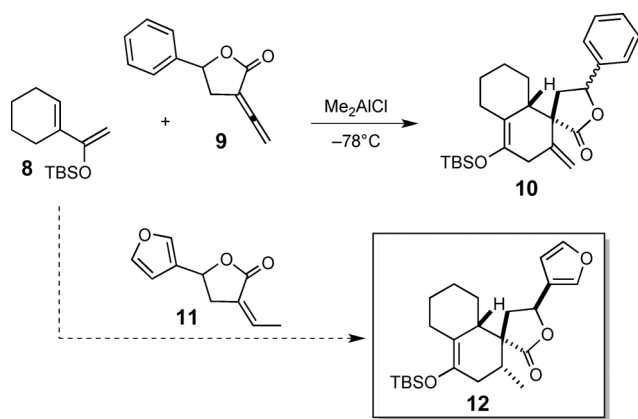


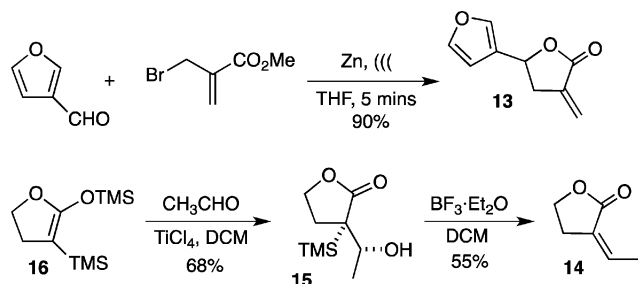
Fig. 1



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**.

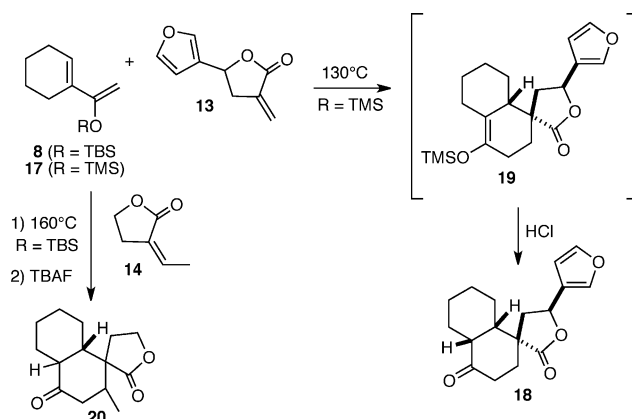
Compound **13** was rapidly obtained in 90% yield *via* sonication of methyl  $\alpha$ -methylacrylate with 3-furaldehyde in the presence of zinc,<sup>12</sup> whereas compound **14** was accessed utilising the work of Yamamoto<sup>13</sup> *via anti*-elimination of aldol product **15** derived from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



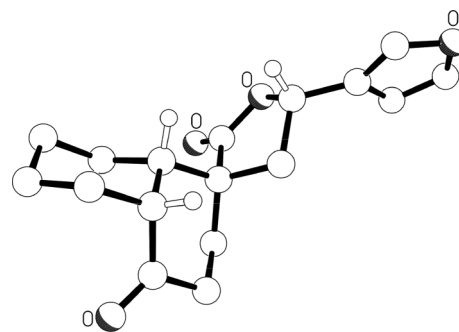
Scheme 2

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.

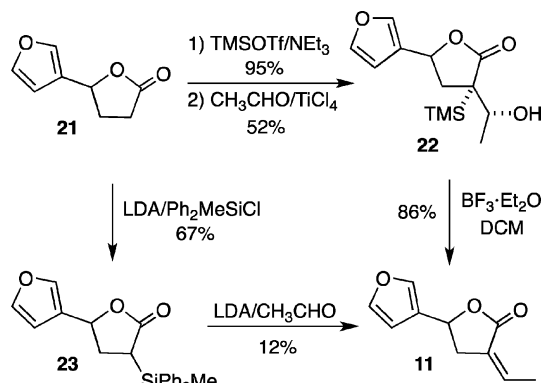
With the knowledge that **13** is sufficiently stable and undergoes the DA reaction with excellent stereochemical control, together with the observation that the trisubstituted system **14** also undergoes reaction (albeit with limited stereocontrol), a synthesis of *cis*-furanospiro- $\gamma$ -lactone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



Scheme 3

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

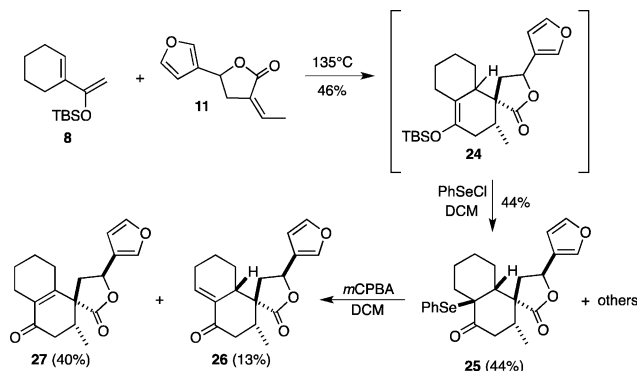
separate variations starting from lactone **21**,<sup>15</sup> obtained from 3-bromopropionic acid and 3-furaldehyde in 41% yield (Scheme 4). Pleasingly, following the Yamamoto route lactone **21** was converted into **22** and subjected to elimination giving **11** in 42% yield over three steps. In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

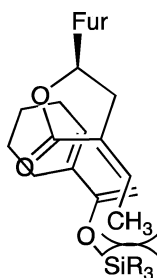


Fig. 3

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- $\gamma$ -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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## References

- (a) A. T. Merritt and S. V. Ley, *Nat. Prod. Rep.*, 1992, **9**, 243–287; (b) J. R. Hanson, *Nat. Prod. Rep.*, 2002, **19**, 125; (c) J. R. Hanson, *Nat. Prod. Rep.*, 2005, **22**, 594.
- (a) T. Tokoroyama, *Synthesis*, 2000, **5**, 611–633; (b) A. S. Sarma, *J. Sci. Ind. Res.*, 1987, **46**, 492.
- H.-J. Liu, J.-L. Zhu, I.-C. Chen, R. Jankowska, Y. Han and K.-S. Shia, *Angew. Chem., Int. Ed.*, 2003, **42**, 1851–1853.
- I.-C. Chen, Y.-K. Wu, H.-J. Liu and J.-L. Zhu, *Chem. Commun.*, 2008, 4720.
- See for example, M. S. J. Simmons, W. M. Blaney, S. V. Ley, G. Savona, M. Bruno and B. Rodriguez, *Phytochemistry*, 1989, **28**, 1069.
- (a) S. V. Ley, N. S. Simpkins and A. J. Whittle, *J. Chem. Soc., Chem. Commun.*, 1983, 503; (b) P. S. Jones, S. V. Ley, N. S. Simpkins and A. J. Whittle, *Tetrahedron*, 1986, **42**, 6519; (c) S. V. Ley, “Synthesis of Insect Antifeedants” in *Pesticide Science and Biotechnology*. Ed. R. Greenhalgh and T. R. Roberts, Blackwell Scientific Publications (Oxford) 1987, ISBN: 0-632-01618-3, p25–34.
- R. H. Pouwer, H. Schill, C. M. Williams and P. V. Bernhardt, *Eur. J. Org. Chem.*, 2007, 4699.
- See for example, (a) T. Tokoroyama, R. Kanazawa, S. Yamamoto, T. Kamikawa, H. Suenaga and M. Miyabe, *Bull. Chem. Soc. Jpn.*, 1990, **63**, 1720; (b) T. W. Ly, J.-H. Liao, K.-S. Shia and H.-J. Liu, *Synthesis*, 2004, **2**, 271; (c) C.-H. Lai, Y. L. Shen and C.-C. Liao, *Synlett*, 1997, 1351; (d) T. Tokoroyama, K. Matsuo and T. Kubota, *Tetrahedron*, 1978, **34**, 1907; (e) T. Tokoroyama, K. Matsuo, H. Kotsuki and R. Kanazawa, *Tetrahedron*, 1980, **36**, 3377.
- M. E. Jung, C. N. Zimmerman, G. T. Lowen and S. I. Khan, *Tetrahedron Lett.*, 1993, **34**, 4453. See also, (a) M. E. Jung and C. N. Zimmerman, *J. Am. Chem. Soc.*, 1991, **113**, 7813; (b) M. E. Jung, J. Cordova and M. Murakami, *Org. Lett.*, 2009, **11**, 3882.
- P. Malakov, G. Papanov and N. Mollov, *Tetrahedron Lett.*, 1978, 2025.
- G. Savona, M. C. Garcia-Alvarez and B. Rodriguez, *Phytochemistry*, 1982, **21**, 721.
- Tin and indium can also be used instead of zinc, see (a) K. Uneyama, K. Ueda and S. Torii, *Chem. Lett.*, 1986, 1201; (b) P. K. Choudhury, F. Foubelo and M. Yus, *Tetrahedron*, 1999, **55**, 10779.
- K. Yamamoto, Y. Tomo and S. Suzuki, *Tetrahedron Lett.*, 1980, **21**, 2661.
- A. Löffler, R. Pratt, J. Pucknat, G. Gelbard and A. S. Dreiding, *Chimia*, 1969, **23**, 413.
- L. T. Burkha, T. M. Harris and B. J. Wilson, *J. Org. Chem.*, 1974, **39**, 2212.