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On the Diels–Alder reactions and the Lewis acid induced rearrangements of 6-fumaryl 1,3,8-nonatrienes

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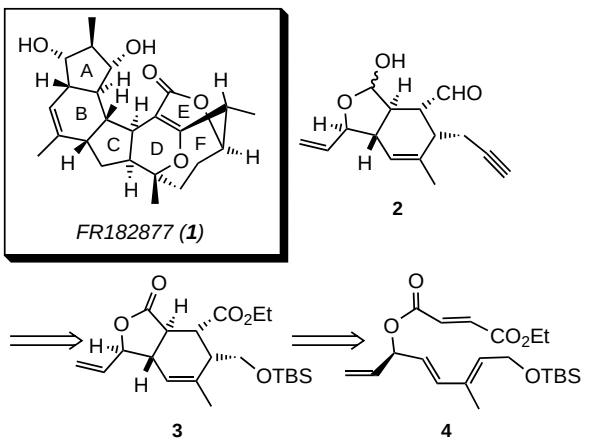
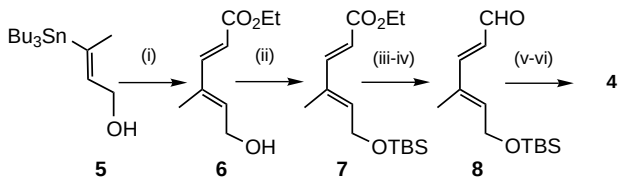
Abstract—6-Fumaryl 1,3,8-nonatrienes substituted at the *C*5 position by a vinyl group were found to undergo competing tandem sigmatropic rearrangement/Diels–Alder cyclisation when heated under standard Diels–Alder cyclisation conditions. This rearrangement became the exclusive pathway when the reactions were performed in the presence of a Lewis acid.

As part of our studies towards the total synthesis of FR182877[1,2] **1** and related compounds, we have investigated the potential use of an intramolecular Diels–Alder cyclisation to install the B-ring with appropriate functionality to allow the synthesis of the A- and C-rings via a simultaneous two-directional reductive annulation strategy. Such a route would provide functionality on the C-ring suitable to expedite its union with a DEF-ring precursor unit. To this end our initial target was **2** (Scheme 1) which we reasoned could be synthesised from **4** by way of an intramolecular Diels–Alder cyclisation reaction, followed by functional group manipulations.



Scheme 1.

Compound **4** was synthesised in six steps from known Stille coupling precursors (Scheme 2).[3,4] Protection of the hydroxyl group of **6** as a TBS ether followed by reduction of the ester and re-oxidation to the aldehyde furnished **8**, which was converted into **4** by the addition of vinyl magnesium bromide and subsequent esterification with monoethyl fumaryl chloride.



Scheme 2. *Reagents and conditions*: (i) $EtO_2CCH{=}CHI$, $(MeCN)_2PdCl_2$, DMF, 84%; (ii) TBSCl, imidazole, DMF, 100%; (iii) DIBAL-H, CH_2Cl_2, −78°C–rt, 95%; (iv) Swern oxidation, 75%; (v) vinyl magnesiumbromide, THF, rt, 99%; (vi) $EtO_2CCH{=}CHCOCl$, py, CH_2Cl_2, 0°C, 100%.

If **4** were to undergo an intramolecular Diels–Alder cyclisation four possible products could be formed (Fig. 1). These products result from both *exo*- and *endo*-cyclisation and cyclisation onto either of the α or β faces of the diene unit. The stereochemistry required for our synthesis would necessitate *exo*-cyclisation from the α-face of the diene unit (i.e. the *exo-trans* compound[5] **3**). We predicted that this would be the case due to a minimisation of steric interactions between the *exo*-cyclic vinyl group and *H*3 and *H*8 in the transition

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state. Indeed, MM2 calculations indicated that α-attack would be preferred by approx. 1.32 kcal mol^{-1}. While we were engaged in these studies a report by Sherburn et al. appeared detailing both computational[6] and synthetic studies[7] on a similar system which indicated that our predictions were correct.

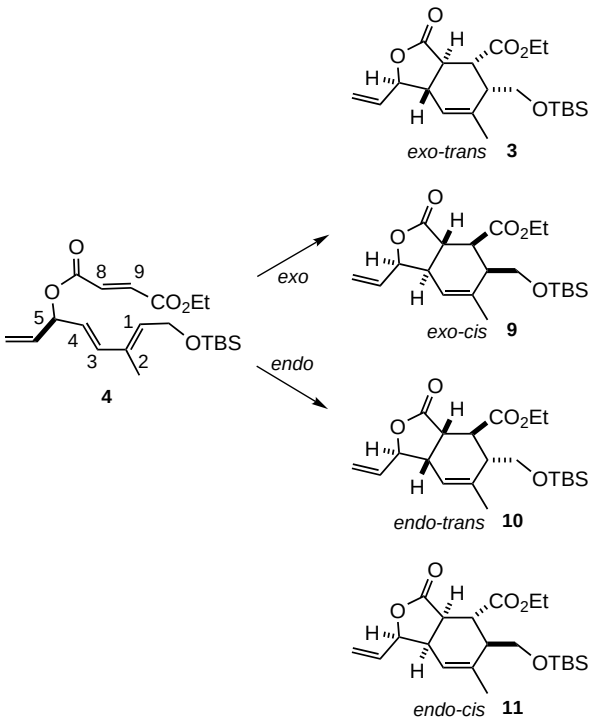

Figure 1.

While the crude 6-fumaryl 1,3,8-nonatriene **4** was a black oil, its ^1H NMR showed it to be a single compound and its TLC showed only one spot (R_f= 0.79; 1:2 EtOAc–petroleum ether). Decolourisation of **4** could only be achieved through filtration via a plug of silica gel. This, however, caused decomposition of **4**, generating three additional compounds. Due to the decomposition it was decided to effect the Diels–Alder cyclisation on the crude material. To this end **4** was heated in toluene in the presence of butylated hydroxytoluene (BHT) to 110°C, under the conditions reported by Sherburn,[7] to generate five new products. The five products were identified as **3** 39%, **9** 7%, **12** and **13** 6% and **14** 11% (Fig. 2).[8] Gratifyingly, the major Diels–Alder adduct was the desired **3** with the other *exo*-isomer **9** appearing in small quantities. As far as we could detect (by 400 MHz ^1H NMR) neither of the *endo*-isomers were formed. Surprisingly, significant quantities of rearranged products **12**, **13** and **14** were isolated. Compounds **12** and **13** were isolated as a mixture, inseparable by flash column chromatography. The major component **12** was finally isolated after extensive HPLC separations.[9] Unfortunately, useful quantities of **13** could not be isolated in this manner. We postulate that **12** is formed by the thermal [3,3] sigmatropic transposition of the fumarate group to the terminal double bond, thus allowing the formation of a conjugated triene, which rapidly undergoes Diels–Alder cyclisation. By this reasoning **14** must be formed by sequential [3,3] sigmatropic transpositions of the fumarate group down the chain in the opposite direction to form the other conjugated triene. Interestingly, when **14** was re-submitted to the Diels–Alder conditions no further rearrangements or cyclisations took place. Rearrangements of this type are not unprecedented. Eberle reported a similar observation while studying the Diels–Alder cyclisations of monoethyl-fumarates of 1-phenyl-2,4-hexadien-1-ol and related compounds.[10]

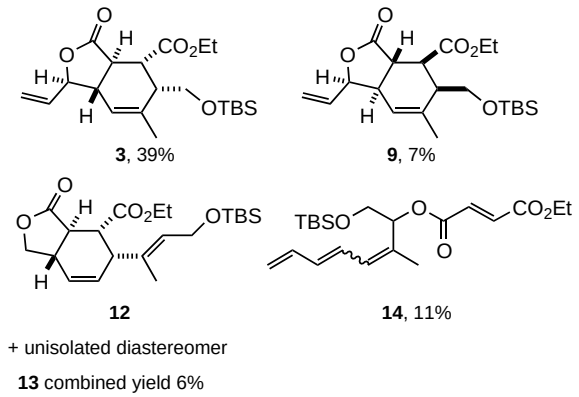

Figure 2.

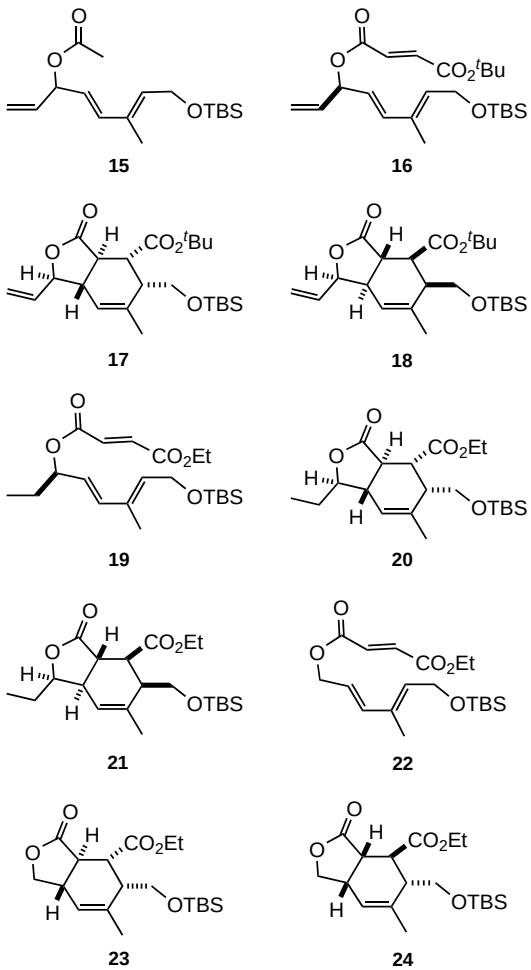

Figure 3.

Having identified the compounds of the thermal Diels–Alder reaction we were now in a position to recognise the major two products of the silica gel promoted decomposition of **4** as **3** and **14**, showing that the rearrangement is very facile. Interestingly, when the Diels–Alder cyclisation was attempted using Et_2AlCl catalysis, **12** and **13** were the only detectable products by 400 MHz ^1H NMR analysis and were isolated in a combined 41% yield. To date we have been unable to obtain any quantity of uncontaminated **13**, so its structure has not been determined.

Intrigued by this result we sought to determine the structural requirements for the [3,3] sigmatropic rearrangements. Contrary to the observations of Eberle,[10] we did *not* detect any rearrangement products when acetate **15** (Fig. 3) was heated in toluene in the presence of BHT to 110°C. Similarly, when **15** was treated with Et_2AlCl no rearrangement occurred. When the mono *tert*-butyl fumarate[11] **16** was used instead of **4** only the appropriate *exo-trans* **17** 17% and *exo-cis* **18** 4% products of Diels–Alder cyclisation were detected and isolated, albeit in low yield and overall conversion. Similarly, when the diene bearing an ethyl group at the *C*5 position **19** instead of a vinyl group was heated in toluene in the presence of BHT to 110°C, the only products were of Diels–Alder cyclisation, namely the *exo-trans* **20** 45% and *exo-cis* **21** 7%. Rearrangement also failed to occur when the unsubstituted diene **22** was heated under our standard conditions. In this case the *exo*-product **23** was formed as the major isomer with only trace amounts of the *endo*-product **24** being detected.

It would seem from these studies (and the earlier work of Eberle) that the Diels–Alder cyclisations of 6-fumaryl 1,3,8-nonatrienes bearing pendant unsaturation are far from straightforward. Diels–Alder cyclisations compete with a very facile [3,3] sigmatropic rearrangement. As compounds **19** and **22** do not rearrange, the driving force for the rearrangement is undoubtedly the formation of a conjugated triene system. The resultant triene may or may not then undergo Diels–Alder cyclisation. In the case of **12**, the precursor triene has no difficulty in adopting the required *S-cis* conformation of the diene component, and so Diels–Alder cyclisation can occur. However, in the case of **14**, if one assumes sequential [3,3] sigmatropic rearrangements proceeding via chair-like transition states, then this would generate triene **14** with the double bond geometries shown in Fig. 4. In this case the adoption of the *S-cis* conformation needed for Diels–Alder cyclisation would be disfavoured due to the steric interaction of the H and Me groups indicated, and hence the rate of any subsequent cyclisation reaction slowed. The *tert*-butyl compound **16** may not rearrange due to the bulky nature of the *tert*-butyl group and due to the fact that some other decompositional pathway competes with rearrangement and Diels–Alder cyclisation. This is noticeable by the greatly reduced yield of recognisable products from the reaction of **16**.

It seems that the fumaryl group, more than the other esters studied is especially prone to these rearrangements. Although the relative rates of rearrangement of different esters appears to be dependent upon the nature of the conjugated system generated: the greater the conjugation the more facile the rearrangement process.

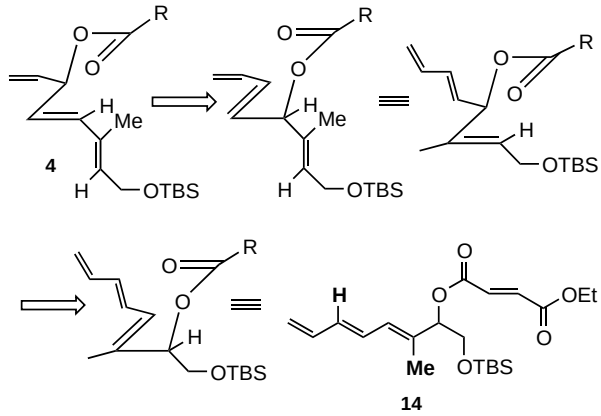

Figure 4.

In summary, we have shown that 6-fumaryl 1,3,8-nonatrienes substituted at the *C*5 position by an unsaturated unit undergo rearrangements which compete with the 'desired' Diels–Alder cyclisation. In some cases this process is so facile that it completely dominates the reactivity of these systems. This observation will be of interest to those seeking to use these 6-fumaryl 1,3,8-nonatrienes in synthesis.

Acknowledgements

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References

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2. Two other groups have reported their efforts towards a synthesis of FR182877: (a) Vanderwal, C. D.; Vosburg, D. A.; Weiler, S.; Sorensen, E. J. *Org. Lett*. **1999**, *1*, 645; (b) Armstrong, A.; Goldberg, F. W.; Sandham, D. A. *Tetrahedron Lett*. **2001**, *42*, 4585.
3. Vinyl stannane see: Betzer, J.-F.; Delaloge, F.; Muller, B.; Pancrazi, A.; Prunet, J. *J. Org. Chem*. **1997**, *62*, 7768.
4. Vinyl iodide see: (a) Zoller, T.; Uguen, D. *Tetrahedron Lett*. **1998**, *39*, 6719; (b) Takeuchi, R.; Tanabe, K.; Tanaka, S. *J. Org. Chem*. **2000**, *65*, 1558.
5. The nomenclature *exo-trans* refers to the product of *exo* Diels–Alder cyclisation where the protons at *C*4 and *C*5 are *trans* to each other. Likewise the *exo-cis* product

refers to the product of *exo* cyclisation where the protons at *C*4 and *C*5 have the *cis* relationship. This terminology has also been applied to the products of *endo* Diels–Alder cyclisation. We believe that the use of this nomenclature makes the structures of the products instantly recognisable: a feature that cannot often be said of the Seebach *like* and *unlike* terminology.

6. (a) Lilly, M. J.; Paddon-Row, M. N.; Sherburn, M. S.; Turner, C. I. *Chem. Commun.* **2000**, 2213; (b) Paddon-Row, M. N.; Sherburn, M. S. *Chem. Commun.* **2000**, 2215.
7. Turner, C. I.; Williamson, R. M.; Paddon-Row, M. N.; Sherburn, M. S. *J. Org. Chem.* **2001**, *66*, 3963.
8. All yields refer to the isolated yields of single compounds (by ^{1}H NMR, 400 MHz and ^{13}C NMR, 100 MHz spectroscopy) which have been purified by silica gel chromatography.
9. Separated by HPLC on a chiralpak AD column; 5% EtOH/heptane, flow rate 1.0 ml min^{-1}. Retention time for **12** of 9.06 min.
10. Eberle, M. K.; Weber, H.-P. *J. Org. Chem.* **1988**, *53*, 321.
11. Mono *tert*-butyl fumarate was not commercially available, so it was prepared as follows. Powdered maleic anhydride (5.00 g, 50.99 mmol) was added to a solution of potassium *tert*-butoxide (5.78 g, 51.50 mmol) in THF (100 ml) at 0°C and stirred for 3 h. At this time the mixture was diluted with EtOAc, water and the aqueous layer acidified with 1 M HCl until pH 2. The aqueous layer was then extracted with EtOAc until no further colour was taken into the organic phase. The combined organics were then washed with brine, dried ($MgSO_4$) and evaporated to yield a residue which was filtered via a plug of Celite to give the mono ester as an E/Z mixture (5.04 g, 57%).

A portion of this mixture (100 mg, 0.581 mmol) was added to a solution of potassium *tert*-butoxide (66 mg, 0.587 mmol) in THF (15 ml) at 0°C and stirred for 3 h. At this time the mixture was diluted with EtOAc, water and the aqueous layer acidified with 1 M HCl until pH 2. The aqueous layer was then extracted with EtOAc until no further colour was taken into the organic phase. The combined organics were then washed with brine, dried ($MgSO_4$) and evaporated to yield the mono *tert*-butyl ester of fumaric acid as a white solid (86 mg, 86%). δ_H (400 MHz, $CDCl_3$) 6.88 (1H, d, $J=15.8$ Hz), 6.67 (1H, d, $J=15.8$ Hz) and 1.52 (9H, s).

Attempts were made to combine these steps into a single-pot procedure, but the best results were always obtained using the two-step sequence detailed above.