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LETTERS

Intramolecular Diels–Alder Reactions of Tethered Homo- and Heterotrienes. Synthesis of Substituted Cyclohexenes and Six-Membered Heterocycles

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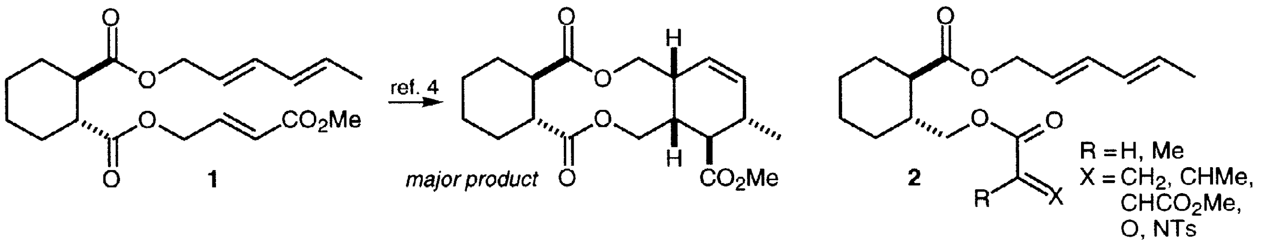
Abstract: Intramolecular Diels–Alder reactions of a number of diester-tethered trienes are reported. All-carbon trienes **5**, **7** and **13** show little or no selectivity for trans-fused products. Heterotrienes **21** and **25** exhibit good to excellent cis-selectivity, with low to good selectivity for one of the two cis-fused isomers. © 1998 Elsevier Science Ltd. All rights reserved.

For some time we[2] and others[3] have been investigating tethered intramolecular Diels–Alder (IMDA) reactions, in which the temporary, covalent connection of the diene to the dienophile confers many of the synthetic advantages of intramolecularity on [4+2] cycloaddition processes which are intermolecular overall. Latterly, our work in this area has been focused on the formation of medium rings using this strategy. We have found that incorporation of two ester linkages in the tether, as in **1** gives rise to relatively unreactive substrates; these undergo Diels–Alder reactions whose stereoselectivity arises from the constrained conformation of the trans-1,2-cyclohexanedicarboxylate linker.[4] We now report on the development of IMDA reactions of related trienes **2**, in which one of the ester groupings has been reversed, and demonstrate the availability from a common intermediate of several homo- and hetero-IMDA substrates of this type.



In order to develop a divergent approach to the preparation of IMDA trienes **2**, our first target was the alcohol **4**; we anticipated being able to effect reaction of **4** with a variety of acylating agents to give a range of substrates. An adaptation of the procedure of Zwanenburg and co-workers was used.[5] Thus, reaction of trans-1,2-cyclohexanedicarboxylic anhydride with *E*,*E*-2,4-hexadienol and diisopropylamine in the presence of DMAP in dichloromethane gave the corresponding half-ester as the diisopropylammonium salt, which was treated in situ with isobutyl chloroformate to give the mixed carboxylic–carbonic anhydride **3**. After removal of diisopropylammonium chloride by simple filtration, the filtrate was treated with sodium borohydride in water at -10°C to yield **4** in 69% yield over the three-step, two-pot sequence (Scheme 1).[6]

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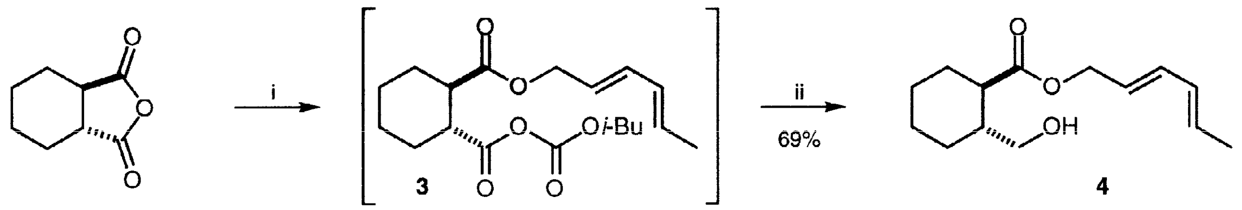
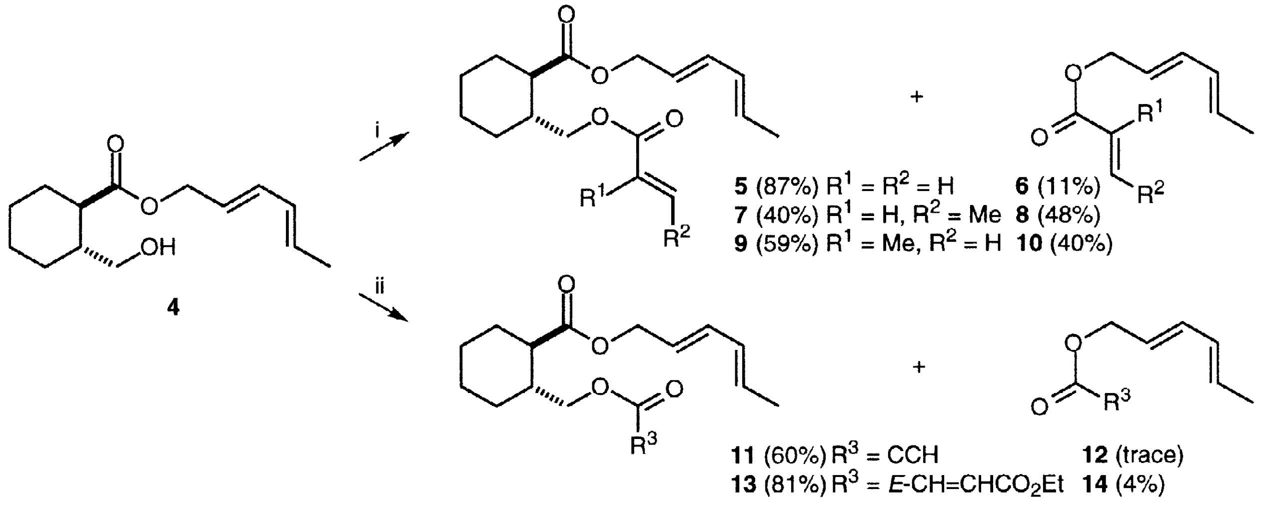


Reagents and conditions: (i) *E*,*E*-2,4-hexadienol (1 equiv), *i*-Pr_2NH (1.1 equiv), CH_2Cl_2, reflux, 2 h; cool to -10°C, then add *i*-BuOCOCl, -10°C→rt, 1 h, then filter; (ii) cool filtrate to -20°C, add $NaBH_4$ (1.4 equiv), H_2O.

Scheme 1

Compound **4** was found to be unstable; nevertheless, reaction with a variety of acyl donors provided the desired IMDA substrates, with formation of the hexadienyl esters **6**, **8**, **10**, **12** and **14** resulting from acylation of the 2,4-hexadienol decomposition product of **4** occurring to varying extents.[7] The syntheses of the tethered IMDA substrates **5**, **7**, **9**, **11** and **13** are depicted in Scheme 2.

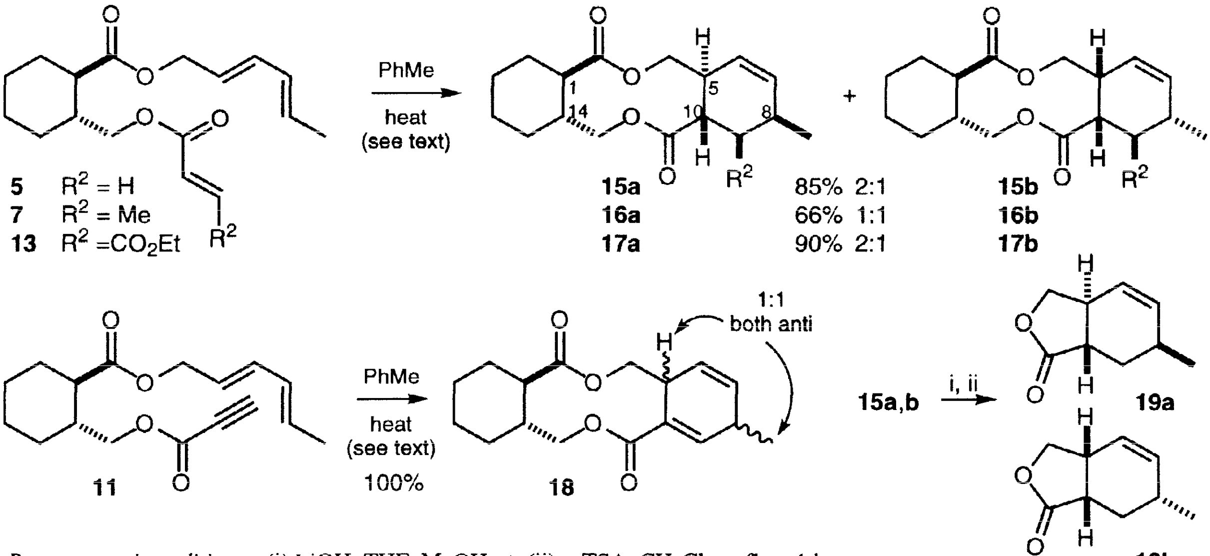


Reagents and conditions: (i) $R^2CH{=}CR^1COCl$, Et_3N (Py for **7**), CH_2Cl_2, rt; (ii) R^3CO_2H, DCC, DMAP, CH_2Cl_2, rt.

Scheme 2

Heating of a solution of the acryloyl triene **5** at 170°C overnight resulted in complete consumption of starting material and the formation in 85% yield of a 2:1 mixture of two inseparable cycloadducts **15**, as measured by integration of the ^1H nmr spectrum of the unpurified product. Treatment of this material with LiOH, followed by acid gave two lactones **19**; the major isomer **19a** showed two large couplings to H-1, characteristic of the trans-ring junction, from which was inferred the identity of the major cycloadduct as **15a**. As expected, the analogous crotonyl triene **7** reacted more sluggishly, giving a 1:1 mixture of cycloadducts in 66% yield; by analogy, these were assigned as having structures **16a,b**. The methacryloyl derivative **9** was inert under the more forcing conditions used for IMDA reaction of **7**. IMDA Reaction of propiolate **11** gave the two possible cycloadducts **18** non-selectively; substrate **11** showed reactivity comparable to that of acrylate **5**. Substrate **13**, possessing the fumarate dienophile was the most reactive of those studied, undergoing complete cycloaddition after heating in toluene overnight at 80°C. Two major products **17a,b** were formed in a 2:1 ratio; assignments followed from the observation of a 2% n.O.e. between C-8 CH_3 group and H-10 in **17a**, and from single-crystal X-ray analysis[8] of **17b** (Scheme 3, Figure 1).

Two principal trends emerged from the IMDA reactions depicted in Scheme 3. Firstly, the present substrates, in which one of the ester groups in the tether has been reversed, are considerably more reactive than the triene **1** studied in our earlier work.[4] We speculate that this is because of the greater flexibility of the alkyl C–O bond in the tether compared to the acyl C–O linkage present in the previous dicarboxylate-tethered substrates, allowing closer mutual approach of the diene and dienophile. Secondly, where stereoselectivity is observed, the predominant cycloadducts are trans-fused; these arise from the preferred adoption of the previously less favoured "outside" conformation of the diene. In all of our previous work involving sorbyl alcohol-derived



Reagents and conditions: (i) LiOH, THF–MeOH, rt; (ii) *p*-TSA, CH_2Cl_2, reflux, 1 h.

Scheme 3

dienes, cis-fused compounds arising from "inside" conformations were the largely predominant or sole products. Nevertheless, in the present work the topicity of reaction of the dienophile with respect to the tethering group in the major products is the same as that observed for **1**.

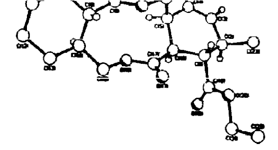
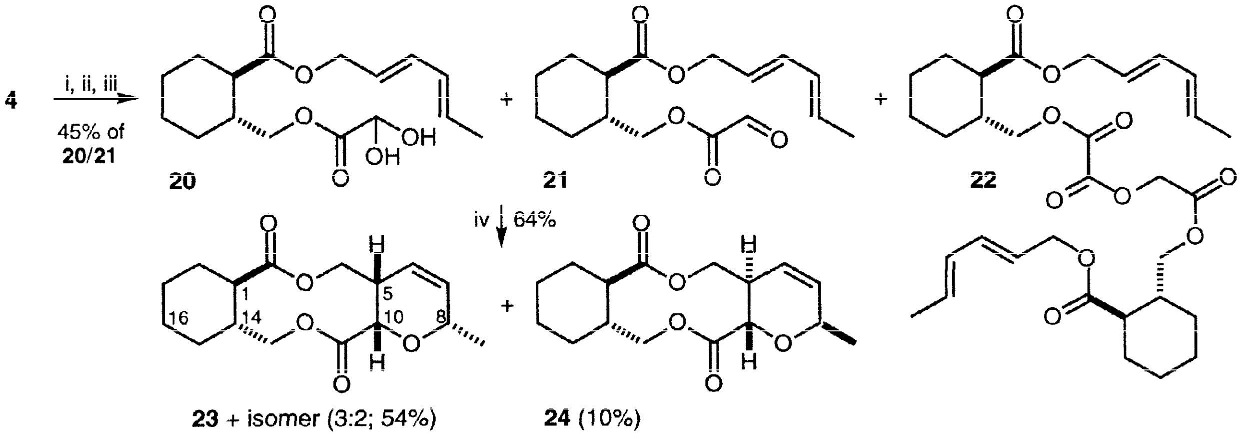


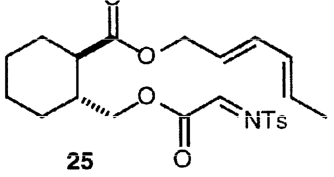
Figure 1
X-Ray structure of **17b**

Given the relatively high reactivity of **5** and **13**, and the ready accessibility of **4**, we were keen to extend the study to include trienes possessing heterodienophiles. To this end, **4** was acylated with 2-(*tert*-butyldiphenylsilyloxy)acetic acid^9 in the presence of DCC–DMAP. Desilylation gave the corresponding alcohol, which was oxidised using Dess–Martin periodinane. The product aldehyde **21** existed as an equilibrium mixture containing predominantly the hydrate **20**; the presence of **21** was confirmed by its conversion into **13** on Wittig reaction with ethoxycarbonylmethylenetriphenylphosphorane. The modest yield obtained in the final oxidation step was largely a result of competitive formation of the oxalate **22**, presumably through nucleophilic interception of **21** by unconsumed starting material, followed by oxidation. Heating of the glyoxalate **20/21** in toluene at 150°C for 24 h gave in 64% yield a 5:1 mixture of cis- and trans-fused cycloadducts, as shown by H5–H10 J-values of 3 and 9.5 Hz respectively. Again, structures **23** and **24** were assigned to respectively the major cis-, and the sole trans-fused products on the basis of the dienophile topicity observed in all previous cycloadditions of this type (Scheme 4).



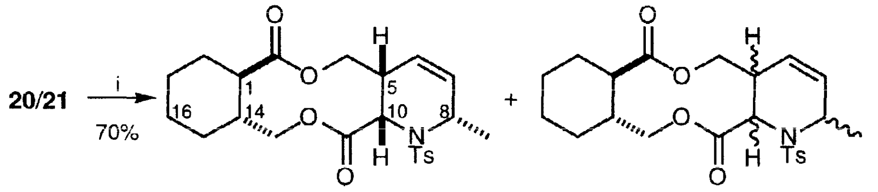
Reagents and conditions: (i) $TBDPSOCH_2CO_2H$, DCC, DMAP, CH_2Cl_2, rt; (ii) TBAF, THF, rt; (iii) Dess–Martin periodinane, CH_2Cl_2, reflux (68% **20/21** + 21% **22**); (iv) PhMe, 150°C, 24 h.

Scheme 4



25

Finally, we looked at tethered hetero-IMDA reactions of activated imines. Heating of a mixture of **20/21** with tosyl isocyanate[10] effected in situ [2+2] cycloaddition, extrusion of CO_2 to give **25** and hetero-IMDA reaction, giving as the major compound in 60% isolated yield the cis-fused piperidine **26**.[11] Again, ^1H nmr spectroscopy allowed its identification as a cis-fused compound, and the structure **26** was unambiguously assigned by X-ray crystallography (Figure 2).[8] The remaining material comprised largely the other cis-fused isomer **27**, with small amounts of the trans-fused compounds **28** and **29** formed also. Thus, IMDA reaction of the *N*-tosylimine derivative **25** showed not only enhanced cis-selectivity (> 20:1) with respect to the parent oxygen analogue **21**, but a marked preference (ca. 8:1) for one of the cis-fused products over the other (Scheme 5).



26 (60%)

27-29: 1 cis + 2 trans (5:1:1; 10%)

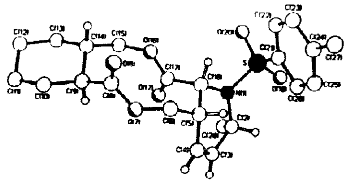


Figure 2
X-Ray structure of **26**

Reagents and conditions: (i) TsNCO (2.5 equiv), PhMe, 125°C, 16 h.

Scheme 5

In summary, we have demonstrated that whilst all-carbon trienes possessing a 'reversed' ester tether show low or zero selectivity for the trans-fused products, heterodienophilic substrates tethered in the same way undergo cis-selective IMDA reactions; the nitrogen-containing heterotriene **25** gives the tricyclic piperidine **26** in a synthetically useful yield. To our knowledge, this represents the first example of a medium ring-forming tethered hetero-Diels–Alder reaction. We are currently looking at IMDA reactions of compounds analogous to **21** and **25** possessing acylnitroso dienophilic units, as part of an approach to five-membered nitrogen heterocycles. The results of these studies will be reported in due course.

ACKNOWLEDGEMENTS

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REFERENCES AND NOTES

1. This work was carried out at Imperial College during February–November 1997 as part of an exchange programme between the Departments of Chemistry at the University of Cape Town and Imperial College.
2. For a leading reference, see: Ainsworth, P. J.; Craig, D.; White, A. J. P.; Williams, D. J. *Tetrahedron* **1996**, *52*, 8937-8946.
3. For reviews of silicon-tethered reactions, see: Bols, M.; Skrydstrup, T. *Chem. Rev.* **1995**, *95*, 1253-1277; Fensterbank, L.; Malacria, M.; Sieburth, S. McN. *Synthesis* **1997**, 813-854.
4. Craig, D.; Ford, M. J.; Stones, J. A. *Tetrahedron Lett.* **1997**, *38*, 515-518.
5. Nefkens, G. H. L.; Thuring, J. W. J. F.; Zwanenburg, B. *Synthesis* **1997**, 290-292.
6. All yields reported herein refer to isolated, pure materials which had ^1H and ^{13}C nmr, ir, and elemental combustion analysis and/or high-resolution ms characteristics in accord with the proposed structures.
7. Yields of trienes were maximised when freshly-prepared **4** was used in the acylation reactions.
8. We thank Professor David J. Williams and Dr Andrew J. P. White for the X-ray structure determinations.
9. 2-(*tert*-Butyldiphenylsilyloxy)acetic acid was prepared by disilylation of glycolic acid (2 equiv TBDPSCl, Et_3N, CH_2Cl_2, reflux) followed by saponification of the silyl ester (KOH, MeOH, 20°C).
10. Hamley, P.; Holmes, A. B.; Kee, A.; Ladduwahetty, T.; Smith, D. F. *Synlett* **1991**, 29-30.
11. Spectroscopic data for **26**: ν_{max} 1736 cm^{-1}; δ_H (500 MHz, $CDCl_3$) *inter alia* 7.68 (2H, d, J 8.5 Hz, *meta*-C_6H_4), 7.29 (2H, d, J 8.5 Hz, *ortho*-C_6H_4), 5.76 (1H, dt, J 10.5, 2.5 Hz, H-7), 5.70 (1H, dt, J 10.5, 2.5 Hz, H-6), 4.97 (1H, dd, J 12.0, 3.0 Hz, H-4), 4.58 (1H, d, J 5.5 Hz, H-10), 4.52 (1H, t, J 11.5 Hz, H-13), 4.44 (1H, 1H, m, H-8), 3.85 (1H, dd, J 12.0, 2.5 Hz, H-4), 3.60 (1H, dd, J 11.5, 4.5 Hz, H-13), 2.40 (3H, s, $CH_3C_6H_4$), 2.25 (1H, m, H-5), 2.10 (1H, m, H-14), 2.00 (1H, td, J 11.0, 3.5 Hz, H-1), 1.60 (3H, d, J 6.5 Hz, C-8 CH_3); *m/z* (CI) (Found: $[M+NH_4]^+$, 465.2059. $C_{23}H_{29}NO_6S$ requires $[M+NH_4]^+$, 465.2059).