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Domino pericyclic reactions of acyclic conjugated (*E*,*Z*,*E*,*E*)-tetraenes

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Abstract—Acyclic conjugated (*E*,*Z*,*E*,*E*)-tetraenes, upon thermolysis, undergo a domino pericyclic process involving 6π electrocyclisation of the (*E*,*Z*,*E*)-triene moiety to give the corresponding *cis*-disubstituted 5-vinyl-1,3-cyclohexadienes, followed by an intramolecular Diels–Alder reaction with the vinyl side chain to give tricyclo[3.2.1.0^{2,7}]oct-3-enes.

Upon thermolysis, acyclic conjugated (*E*,*Z*,*Z*,*E*)-tetraenes typically undergo a conrotatory 8π electrocyclisation to a cyclooctatriene, often followed by a disrotatory 6π electrocyclisation to a bicyclo[4.2.0]octadiene (Path A, Fig. 1).[1] Such periselectivity for Woodward–Hoffmann processes which involve the longest part of the conjugated system is not absolute, but is dependent upon the reaction conditions and the polyene substitution. Thus, the same (*E*,*Z*,*Z*,*E*)-tetraene can also be viewed as an (*E*,*Z*,*Z*)-triene conjugated to an (*E*)-alkene, and as such is capable of undergoing a disrotatory 6π electrocyclisation to a 5-vinyl-1,3-cyclohexadiene,[2,3] followed by an intramolecular Diels–Alder (IMDA) reaction to give a tricyclo[3.2.1.0^{2,7}]oct-3-ene,[4] as has been reported[3a] (Path B, Fig. 1). Isomerisation of one of the inner *Z* olefinic bonds of the (*E*,*Z*,*Z*,*E*)-tetraene to the *E* configuration should preclude adoption of a conformation suitable for 8π electrocyclisation, forcing the alternative 6π process to prevail (Fig. 1). We examine here the occurrence of pericyclic reactions in such acyclic conjugated (*E*,*Z*,*E*,*E*)-tetraenes (cf. Figs. 1 and 3).

We have previously shown that a stereochemically related (*E*,*Z*,*E*,*Z*)-tetraene, that is, the 7*E*,9*Z*,11*E*,13*Z*-hexadeca-7,9,11,13-tetraene shown in Figure 2,

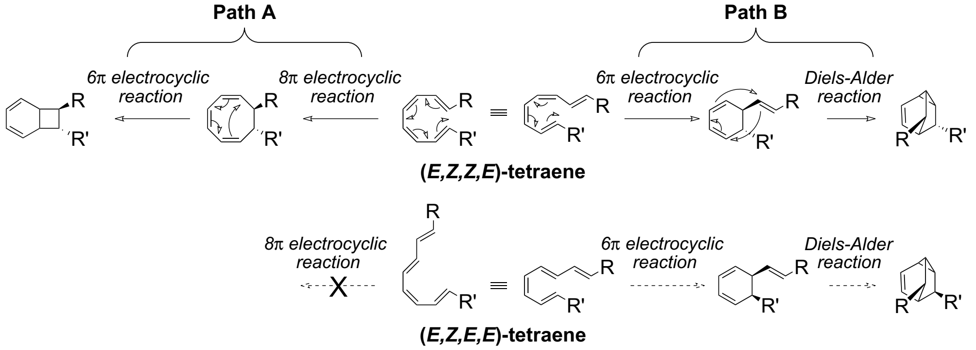

Figure 1. Pericyclic reaction pathways of (*E*,*Z*,*Z*,*E*)- and (*E*,*Z*,*E*,*E*)-tetraenes (solid arrows show established pathways, dashed arrows show potential pathways).

Keywords: Electrocyclic reaction; Intramolecular Diels–Alder reaction; Tetraenes; Polyenes.

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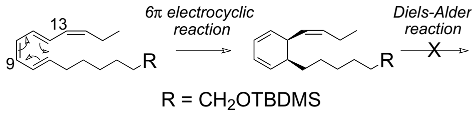


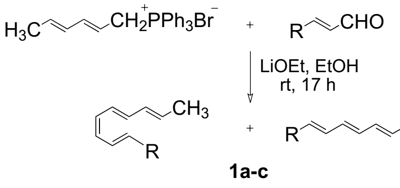
Figure 2. 6π Electrocyclisation of an (*E*,*Z*,*E*,*Z*)-tetraene.

undergoes thermal electrocyclisation to a 5,6-*cis*-disubstituted cyclohexadiene.[5] This process provides a biomimetic precedent for the possible involvement of ‘electrocyclase’ enzymes in the biosynthesis of certain *o*-dialkyl-substituted benzenoid microbial products which lack oxygen functionality on or adjacent to the aromatic ring. In this case the electrocyclisation is centred about the 9*Z*-olefinic bond, the flanking 7*E* and 11*E* bonds undergoing disrotatory thermal motion as predicted by Woodward and Hoffmann.[1] The conjugated 13*Z*-bond here plays only a spectator role, with steric hindrance by its *Z*-substituents preventing its IMDA reaction with the cyclohexadiene moiety to form a tricyclo[3.2.1.0^{2,7}]oct-3-ene.

The present (*E*,*Z*,*E*,*E*)-systems **1a**–**c** (Fig. 3) would be expected to yield the 5,6-*cis*-disubstituted cyclohexadienes **2a**–**c**. These cyclohexadienes, however, carry at last one vinyl substituent with an *E*-, not *Z*, configuration, and it was unclear whether this *E*-olefin would undergo an IMDA reaction. While precedents for such an intramolecular cycloaddition of a pendant 5*E*-olefin in 5,6-*cis*-disubstituted cyclohexadienes exist,[3c,d] the examples are unrelated to the present systems **2a**–**c**. Molecular modelling studies indicate that the enthalpy of activation for the IMDA reaction of cyclohexadiene **2b**, depicted in Figure 3, is almost twice that for the 6π electrocyclisation by which it is formed.[6]

Polyenes **1a**–**c** were prepared by Wittig reactions between (2*E*,4*E*)-hexa-2,4-dienyltriphenylphosphonium bromide and sorbic aldehyde, crotonaldehyde and cinnamaldehyde and obtained as 1:1 mixtures of (*Z*/*E*)-stereoisomers about the new double bond (Table 1).[7,8] Immediately prior to thermolysis, the polyenes were chromatographed to remove any polymer formed during storage. This gave rise to altered (*Z*/*E*)-isomer ratios compared to freshly prepared material (cf. Tables 1 and 2).

Table 1. Preparation of polyenes **1a**–**c** by Wittig reactions

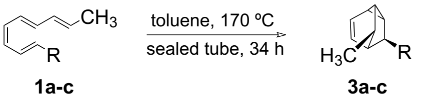


Entry	R	Product[a]	Yield[b] (%)
1	(*E*)-CH=CHMe	**1a**	79
2	Me	**1b**	49
3	Ph	**1c**	80

[a] Polyenes **1a**–**c** were obtained as 1:1 mixtures of (*Z*/*E*)-isomers about the new double bond.

[b] Isolated yields.

Table 2. Thermolysis of polyenes **1a**–**c** to tricyclo[3.2.1.0^{2,7}]oct-3-enes **3a**–**c**



Entry	R	*Z*/*E* Ratio[a]	Product	Yield[b] (%)
1	(*E*)-CH=CHMe	70:30	**3a**	60[c] (51)[d]
2	Me	67:33	**3b**	87[c] (15)[d]
3	Ph	>98:2	**3c**	17[c] (16)[d]

[a] Refers to the (*Z*/*E*)-ratio of the newly formed double bond.

[b] Yields are corrected for the amount of (all-*E*)-isomer present in the starting material.

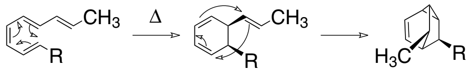
[c] Yields based on analytical GC.

[d] Isolated yields, which are low due to the high volatility of the compounds.

(*E*,*E*,*Z*,*E*,*E*)-Pentaene **1a** was the first polyene to be thermolysed, since symmetry properties should distinguish the expected product, the *cis*-disubstituted cyclohexadiene **2a**, from the alternative *trans*-disubstituted isomer. Thus, a dilute solution of pentaene **1a** {containing 30% of the (all-*E*)-stereoisomer[9]} was heated in a sealed tube at 170 °C for 34 h.[7] Analysis by GC revealed that essentially all the starting material had reacted to form one major compound,[10] in 60% yield when corrected for the initial presence of the (all-*E*)-stereoisomer, the remainder of the starting material presumably polymerising into non-volatile material not observable by GC (Table 2).

EI-MS confirmed, as expected, that the major product was isomeric with the starting material (**1a**). NMR spectroscopy, however, revealed the presence of only two double bonds and therefore the product was tricyclic. Thus, the most likely explanation is that the acyclic (*E*,*E*,*Z*,*E*,*E*)-pentaene **1a** upon heating does indeed undergo disrotatory 6π electrocyclisation of its central (*E*,*Z*,*E*)-triene moiety to give the corresponding *cis*-5,6-disubstituted 1,3-cyclohexadiene **2a**,[1a] followed by an IMDA reaction[3,4] involving one of its (*E*)-prop-1-enyl side chains to give the *endo*,*exo*-6,8-disubstituted tricyclo[3.2.1.0^{2,7}]oct-3-ene **3a** (cf. Figs. 3 and 4). The alternative conrotatory 6π electrocyclisation of pentaene **1a** would produce the corresponding *trans*-5,6-disubstituted cyclohexadiene, whereupon an IMDA reaction would then form the analogous *exo*,*exo*-isomer (not shown). The Woodward–Hoffmann rules predict the former reaction sequence.[1a]

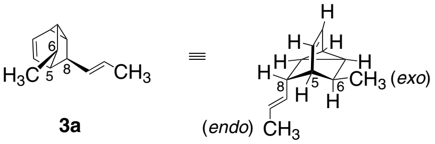
The proposed *endo*,*exo*-6,8-disubstituted tricyclo-[3.2.1.0^{2,7}]oct-3-ene structure of the tricyclic diene **3a** was supported by ^{1}H NMR spectroscopy, including selective homonuclear decoupling and ^{1}H,^{1}H-correlation spectroscopy (COSY). In particular, designation of the propenyl substituent as *endo* is based on the COSY contour map where the signal belonging to the bridgehead proton 5-H shows no correlation whatsoever to the signal for the allylic proton 8-H (cf. Fig. 4). This



1a-c **2a-c** **3a-c**

a: R = (*E*)-CH=CHMe; **b:** R = Me; **c:** R = Ph

Figure 3. Pericyclic reactions of (*E*,*Z*,*E*,*E*)-tetraenes.



3a

Figure 4. Structure of the *endo*,*exo*-6,8-disubstituted tricyclo[3.2.1.$0^{2,7}$]-oct-3-ene (**3a**).

lack of vicinal coupling between 5-H and 8-H is characteristic for these compounds when 8-H is oriented *exo*,[3a,11] and is consistent with a measured dihedral angle between these protons of 81°, obtained from the minimised structure computed using molecular mechanics.[12]

As it was now apparent that an IMDA could occur in these *cis*-disubstituted cyclohexadienes carrying an *E*-olefin substituent, (*E*,*Z*,*E*,*E*)-decatetraene **1b** was examined next, on the premise that the *endo*,*exo*-isomer of the expected thermal product, tricyclooctene **3b**, could be easily distinguished from the symmetrical *exo*,*exo*-isomer, lending further support to the proposed pericyclic cascade. Thus, a dilute solution of tetraene **1b** {containing 33% of the (all-*E*)-isomer[13]} was heated at 170 °C for 34 h[7] and analysed by GC, which revealed that most of the starting material had reacted to form one major compound[14] in 87% yield when corrected for the initial presence of the (all-*E*)-isomer in the starting material (Table 2). The product of the reaction was confirmed by a combination of MS and NMR spectroscopy as *endo*,*exo*-6,8-dimethyltricyclo[3.2.1.$0^{2,7}$]oct-3-ene **3b**.[8]

Finally, similar thermolysis (170 °C for 34 h) of (*E*,*Z*,*E*,*E*)-phenylnonatetraene **1c** gave somewhat different results (Table 2). In this case, GC analysis of the crude reaction products showed that all the starting material had reacted to form the now expected *exo*,*endo*-6-methyl-8-phenyltricyclo[3.2.1.$0^{2,7}$]oct-3-ene **3c** in 17% yield. Also obtained was a complex mixture of several as yet unidentified compounds, which by GC retention times appeared to be isomeric with product **3c**, together with polymerised material.

In conclusion, acyclic conjugated polyenes containing an (*E*,*Z*,*E*,*E*)-tetraene moiety predominantly undergo smooth thermal transformation to *endo*,*exo*-6,8-disubstituted tricyclo[3.2.1.$0^{2,7}$]oct-3-enes, via a domino process involving a disrotatory 6π electrocyclisation of the (*E*,*Z*,*E*)-triene moiety of the polyene to give *cis*-5,6-disubstituted 1,3-cyclohexadienes, followed by an IMDA reaction in which the (*E*)-prop-1-enyl substituent behaves as a dienophile. This work extends our knowledge of the occurrence of pericyclic processes in acyclic conjugated polyenes, and may provide an expedient entry into the tricyclic skeleton present in some complex natural products.[15]

Acknowledgements

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Supplementary data

Supplementary data (experimental procedures and selected data for compounds **1a**, **3a**, **3b** and **3c**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.03.011.

References and notes

1. (a) Woodward, R. B.; Hoffmann, R. *J. Am. Chem. Soc.* **1965**, *87*, 395; (b) Huisgen, R.; Dahmen, A.; Huber, H. *J. Am. Chem. Soc.* **1967**, *89*, 7130; (c) Marvell, E. N. *Thermal Electrocyclic Reactions*; Academic Press: New York, 1980; pp 376–401; (d) Okamura, W. H.; de Lera, A. R. 1,3-Cyclohexadiene Formation Reactions. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 743–745.
2. Morwick, T. M.; Paquette, L. A. *J. Org. Chem.* **1997**, *62*, 627.
3. (a) Marvel, E. N.; Seubert, J.; Vogt, G.; Zimmer, G.; Moy, G.; Siegmann, J. R. *Tetrahedron* **1978**, *34*, 1323; (b) Roth, W. R.; Peltzer, B. *Liebigs Ann.* **1965**, *685*, 56; (c) ten Have, R.; van Leusen, A. M. *Tetrahedron* **1998**, *54*, 1913; (d) Loeliger, P.; Mayer, H. *Helv. Chim. Acta* **1980**, *63*, 1604.
4. For examples of intramolecular Diels–Alder reactions of 5-vinyl-1,3-cyclohexadienes see: (a) Giomi, D.; Nesi, R.; Turchi, S.; Mura, E. *J. Org. Chem.* **2000**, *65*, 360; (b) Ng, S. M.; Beaudry, C. M.; Trauner, D. *Org. Lett.* **2003**, *5*, 1701; (c) Abad, A.; Agulló, C.; Cuñat, A. C.; de Alfonso, I.; Navarro, I.; Vera, N. *Molecules* **2004**, *9*, 287; (d) D'Souza, D. M.; Rominger, F.; Müller, T. J. J. *Chem. Commun.* **2006**, 4096.
5. Rickards, R. W.; Skropeta, D. *Tetrahedron* **2002**, *58*, 3793.
6. SPARTAN SG1, version 5.0.1, Open GL; Wavefunction Inc: California, 1991–1997.
7. Typical procedures for the synthesis of polyenes **1a**–**c** and their thermolysis to the corresponding tricyclo-[3.2.1.$0^{2,7}$]oct-3-enes **3a**–**c** are available as Supplementary data.
8. All new compounds gave satisfactory spectral and analytical data. Selected spectral data for compounds **1a**, **3a**, **3b** and **3c** are available as Supplementary data.
9. Ratio determined by analytical GC (BP1 column: $T_0 = 50$ °C, grad. = 10 °C/min, inj. temp. = 125 °C, $t_R =$ 11.89, 11.98 min).
10. One other product was detected by GC in ∼5% yield, however, its retention time differed to that of the tricylic product by only 0.1 min and the two products were inseparable; their close retention times suggest they are isomeric.
11. Zimmerman, H. E.; Grunewald, G. L.; Paufler, R. M.; Sherwin, M. A. *J. Am. Chem. Soc.* **1969**, *91*, 2330.

12. CS Chem-3D Pro., Version 3.1 for Apple Macintosh; CambridgeSoft Corporation: Cambridge, 1995.
13. Ratio determined by analytical GC (BP1 column: $T_0 = 50$ °C, grad. = 5 °C/min, inj. temp. = 150 °C, t_R = 11.69, 11.89 min).
14. Two minor products (<5% yield) were also detected by GC.
15. (a) Bohlmann, F.; Jakupovic, J.; Ahmed, M.; Grenz, M.; Suding, H.; Robinson, H.; King, R. M. *Phytochemistry* **1981**, *20*, 113; (b) Pelletier, S. W.; Djarmati, Z.; Mody, N. V. *Tetrahedron Lett.* **1976**, *21*, 1749.