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DIASTEREOSELECTIVITY IN THE INTRAMOLECULAR DIELS-ALDER REACTION OF DIENYLPROPYNOATES

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Summary The product ratio in Diels-Alder reactions of α-chiral dienes has been examined. Cycloaddition of E-3,5-hexadien-2-ol and methyl propynoate gives a mixture of all four diastereomers. Intramolecular condensation of the related ester (6) was completely regioselective however, and one stereoisomer predominated by 6.4:1. Similar results were obtained for the corresponding secondary amide, for propynoate esters of a homologous chiral dienol, and for a related 3-acetylpropenoate ester. These observations are related to a simple model in which stereoselectivity arises from minimisation of 1,3-alkyl-H interactions at the cycloaddition transition-state.

The stereochemical potential of intra- and intermolecular Diels-Alder reactions has been widely exploited[1]. This is particularly true for control of the substitution pattern around the cyclohexene ring generated in the cycloaddition step. The endo-relationship of dienophile substituents to the diene framework affords a powerful measure of stereoselectivity[2].

Effort has been expended on defining the relative configuration of exo and endo-cyclic sites in the cyclohexene ring. A majority of examples involve the intramolecular variant, and the stereochemical preference is less readily defined. Where the chain connecting the two reaction sites is short (i.e. 3-5 atoms) the ring-fused rather than the ring-bridged regioisomer is formed exclusively. The diene-dienophile reactivity can vary over a very wide range, and introduction of electron-withdrawing groups can reduce the temperature at which reaction is feasible by more than 100°C. Not surprisingly, high selectivity frequently correlates with higher reactivity.

DISCUSSION

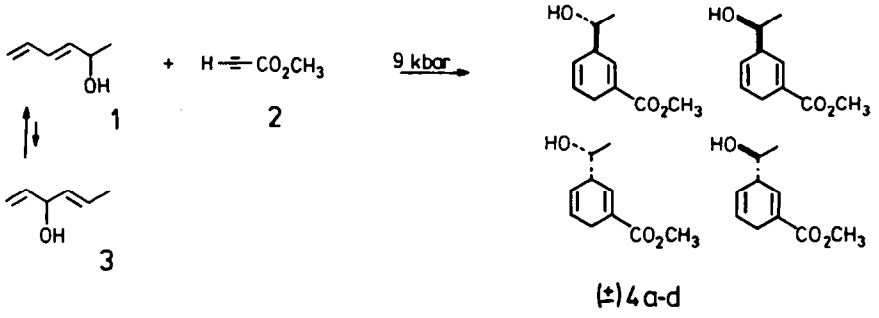
The object of the present work was to develop methods for stereoselective synthesis of exocyclic stereogenic centres in substituted cyclohexanes. Current approaches include aldol condensations, where stereocontrol is evident in special cases including molybdenum dienolates[3] and cyclohexanedione-derived nucleophiles[4]; the reaction of cyclohexenylboron compounds with aldehydes[5]; hydroboration of exocyclic allylic alcohols[6];and stereospecific cyclisation[7].

The intramolecular Diels-Alder reaction has been widely employed in natural product synthesis. To the extent that substituents may perturb the stereochemical course of reaction with complex reactants, simple ester-linked diene and dienophile fragments were selected.

a) Intermolecular reactivity : Intermolecular Diels-Alder reaction between E-3,5-hexadien-2-ol (1) and methyl propynoate (2) was first examined. The former compound was synthesised by acid-catalysed rearrangement of E-1,4-hexadien-3-ol[8].

Cycloaddition did not occur in $CDCl_3$ solution at 65°C over a protracted period. When the reaction was carried out in toluene at ambient temperature and 9 kbar pressure, the starting materials were consumed. Four peaks were then present in the analytical g.c. trace,

none to the extent of >40% of the total. The major fraction isolated by flash chromatography, m/z 183, was evidently still four components in comparable proportions, with an NMR spectrum consistent with cycloaddition to the diastereomeric cyclohexadienes (4a) - (4d). Regioselectivity is lacking, as it is in many cases provided in an extensive survey.[9]



b) Intramolecular reactivity : The first case to be examined was the acrylate ester of E-3,5-hexadien-2-ol (5). This was prepared from the alcohol employing a threefold excess of dicyclohexylcarbodiimide and acrylic acid with a catalytic quantity of 4-dimethylaminopyridine[10] in 51% yield. Attempts to carry out Diels-Alder reaction of (5) under moderately forcing conditions (refluxing xylene, 18 h) led to complete recovery of starting material.

This encouraged an effort to increase the reactivity of the dienophilic component by preparation of the corresponding propynoate (c.f. Figure 1). Initial attempts to prepare the ester (6) by the method described above led to its production in admixture with the allylic isomer (7) in comparable quantities. With a short reaction time and minimal excess of propynoic acid, the desired ester was formed to 91% of total product and further purified by preparative glc (5% SE30, 160°C). Ester (8) was formed in a similar manner, and purified by silica gel chromatography.

Cyclocondensation of the ester (6) was then investigated. Reaction was carried out in carefully degassed toluene (to avoid aromatisation of the product) and shown to be complete. after 15 h. The two products (9a) and (9b) were formed in a ratio of 6.4:1. They could be separated by preparative g.l.c. (15% OV225, 15, 210°C) giving the minor isomer (9b) pure, but the major isomer part-aromatised. In a further experiment, the mixture was hydrogenated with $ClRh(PPh_3)_3$ as catalyst, which proved selective for the disubstituted double bond. The major component (10a) (derived from (9a)) was isolated pure by preparative g.l.c., as above.

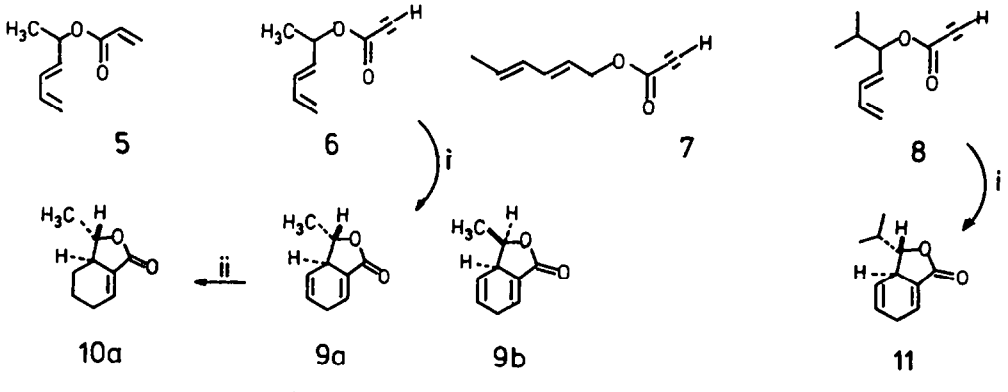


Figure 1. Synthesis and intramolecular Diels-Alder reaction of dienylpropynoates.

The relative stereochemistry of these lactones was assigned by N.m.r.. For compound (9a), the results of n.O.e. experiments were ambiguous, but analysis of the reduction product (10a) proved definitive. A full assignment of resonances was made through a 2D COSY experiment, and the configuration determined by n.O.e.. In particular irradiation of H9 enhances CH_3 (5%) and $H2_{ax}$ (3%) but not H1. Irradiation of CH_3 enhances H9, H1, $H2_{eq}$ (all 3.5%) and also H3 eq, permitting only the structure indicated (**Figure 1**). Compound (9b) was assigned directly by n.O.e.. Irradiation of H1 caused enhancement of H9 (6.8%) and H2 (5%); irradiation of H9 gave enhancement at H1 (7.2%) but irradiation of CH_3 did not. Hence H1 and CH_3 are trans-related, in the minor product as indicated (**Figure 2**).

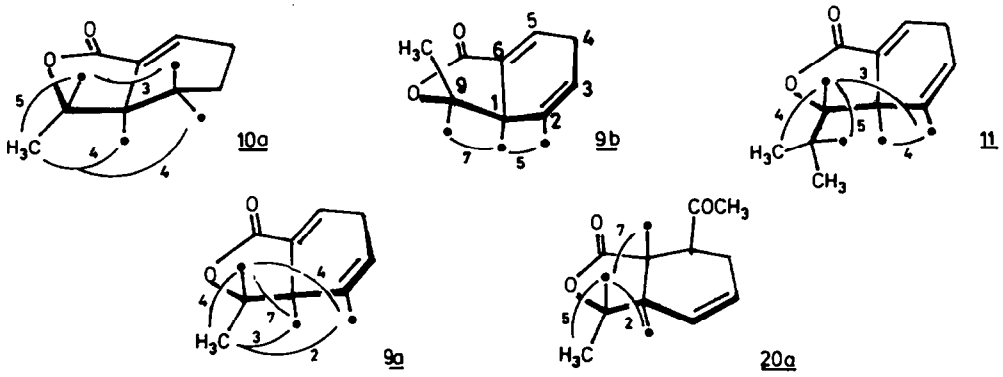
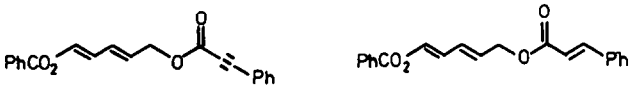


Figure 2. Stereochemical assignments on intramolecular Diels-Alder products through n.O.e. determinations.

The Diels-Alder reaction was now performed at ambient temperature and high pressure (19 kbr) for 18 h. The crude reaction product indicated quantitative conversion, but the ratio of (9a) to (9b) was reduced to 3:1. At increased pressure the selectivity is diminished rather than enhanced.

When reaction was carried out with the homologous ester (8), the product was found to aromatise rather readily. This was best averted by working under O_2 - free conditions in toluene at 80°C. G.l.c. analysis then indicated that the product was ≥ 96% of one component. This was assigned by n.O.e. in the manner previously described, demonstrating that the product was (11), in the same stereochemical series as (9a). As expected, the n.O.e. experiment demonstrates that H1 and H9 are remote from one another.

This sequence of intramolecular Diels-Alder reactions demonstrates firstly that acetylenic substrates are substantially more reactive than their ethylenic counterparts. This accords with observations made recently on the closely related achiral compounds (12) and (13). The former cyclises at 60°C whereas the latter is unreactive at 240°C.[11] Bicyclic lactone formation occurs readily, with no evident rate penalty arising from the enforced rotation of an ester away from its preferred Z-conformation[12]. Reactions proceed with substantial stereoselectivity and complete regioselectivity and increasing the steric bulk of the alkyl group adjacent to the ester enhances the degree of discrimination.



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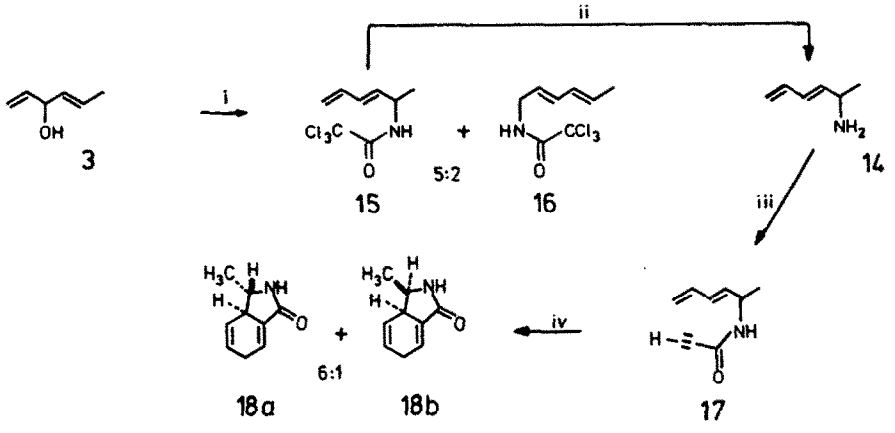
Other reactants: It was of interest to compose the cyclisation behaviour in the related amide series. E-2-Amino-3,5-hexadiene (14) was prepared via the trichloracetimidate route[13] starting from E-1,4-hexadien-3-ol (**Figure 3**). Rearrangement in refluxing toluene gave a mixture of trichloracetamides (15) and (16) in 5 : 2 ratio. These were hydrolysed together and the amine isolated by preparative g.l.c. (15% Carbowax 20M, 15', 120°C). Propynamide (17) was then prepared by the standard coupling route.

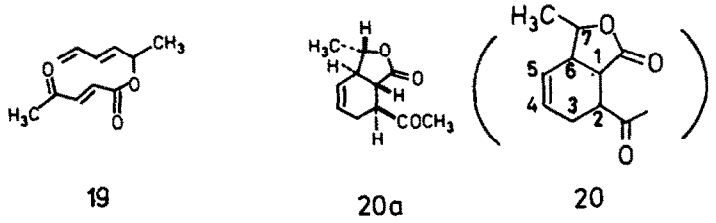
Cyclocondensation of amide (17) was carried out in toluene at 80°C for 2 days, when reaction appeared complete. Analysis of the product by ^{1}H N.m.r. indicated a 6:1 mixture of two bicyclic lactams (18a) and (18b). The key features of their spectra were very similar to those of the corresponding lactones (9a) and (9b), permitting stereochemical assignment by analogy. The reactivity and selectivity of Diels-Alder reaction are essentially unaffected by altering the bridging entity from ester to secondary amide.

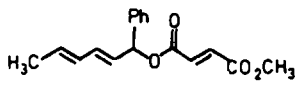
An earlier experiment involving an acrylate ester had failed to effect cyclisation under mild conditions. The analogue (19) possessing an activated dienophile was prepared from alcohol (1) and E-3-acetylpropenoic acid in the usual way. It polymerised slowly on standing and was therefore stored at -30°C. As expected, cyclocondensation occurred much more readily[14], and complete reaction was effected by refluxing in toluene for 18 h. Since the product contains two additional, but correlated, asymmetric centres, there are four possible diastereomeric products for a reaction which proceeds with complete regiochemical control. G.l.c. analysis (4% OV225. 8', 200°C) showed four components in the ratio 8:72:16:4. The major component (72%) was isolated from preparative g.l.c. and shown to be (20a). The ^{1}H N.m.r. spectrum was fully assigned by a 2D COSY analysis and further n.O.e. experiments. (Figure 2). Irradiation of H7 caused enhancement of CH_3 (5.3%) H1 (6.8%) and H6 (2.3%); irradiation of H1 likewise caused enhancement of H7 only (6.6%). Thus the main product is in the same stereochemical series as other alkyne cycloadducts discussed earlier. Recently the intramolecular Diels-Alder reaction of fumarate (21) was examined in Et_2O at ambient temperature[15]. Reaction proceeded through a double sigmatropic rearrangement to (22) and thence to the product (23). This was shown by X-ray crystallography to be a single diastereomer. Its configuration is identical to that of the preferred diastereomer (20a) in the acetylpropenoate series.



i. KH, CCl_3CN; C_7H_8, 110°C, 3h. ii. NaOH, H_2O; prep glc (CW 20M, 15%, 15', 120°C).
iii C_2HCOOH, DCC, DMAP iv C_7H_8, 80°C, 2d.

Figure 3 Synthesis and intramolecular Diels-Alder reaction of dienylpropynamides





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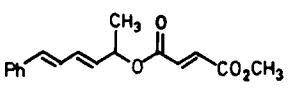

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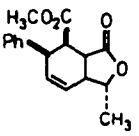

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Interpretation of results : In three different series, the intramolecular Diels-Alder reaction gives a single diastereomer predominantly or exclusively (Table 1). The relative configuration of exo- and endocyclic centres is identical, implying a common source of control.

Table 1. Stereochemistry of intramolecular Diels-Alder reactions.
*1S7R; 1S7S in this series

Reactant				Product		
	X	R	Method	(1S,9R) %	(1S,9S) %	d.e.
6	O	Me	Heat	87	13	74
6	O	Me	Pressure	75	25	50
8	O	i-Pr	Heat	96	4	92
17	NH	Me	Heat	86	14	72
19*	O	Me	Heat	>80	<20	>60

These observations may be compared first with intermolecular examples, where aspects of stereoselectivity have been subject to extensive recent discussion[9]. As reported herein, we observed that the Diels-Alder reaction between diene (1) and dienophile (2) lacked discrimination, since all four possible diastereomers were formed in comparable amounts. This compares with results for acetylenic dienophiles reported and discussed earlier[9,11]. At ambient pressure, the selectivity was never greater than 3:1 even when regiochemical control was achieved. The preferred course is indicated in Figure 4 . Interestingly, reaction of the same diene with maleic anhydride gives a major product with opposite relative configuration of the two stereocentres. Only those cases where the diene bears an oxygen substituent adjacent to the asymmetric centre give high selectivity, as shown[16]. Given the range of stereochemical outcomes, there is a lack of consensus about the correct stereochemical model for intermolecular reactions[1d,9].

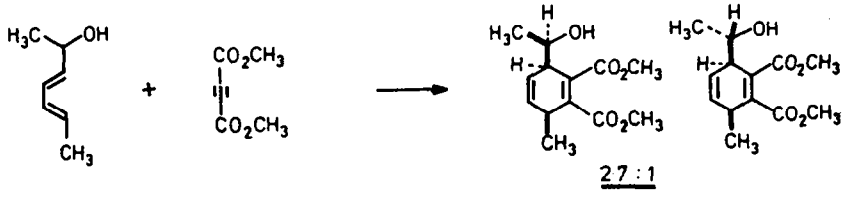

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Figure 4. Intermolecular dienol/propynoate Diels-Alder reaction.

The intramolecular variant provides a constraint which limits conformational freedom around the stereogenic centres at the transition-state. This simplifies the interpretation considerably. There are several literature precedents for stereoselectivity in related cycloadditions, where the existing centre is next to an acyclic diene, and part of the linking moiety. The most notable examples relate to intermediates in indanomycin synthesis,[17] and the relative configuration observed there is the same as is observed here. A similar rationalisation is appropriate. One group at the chiral centre (Figure 5) experiences a destablising 1,3 H-X contact with H_2 of the diene. For the disfavoured pathway, X is an alkyl group whilst for the favoured pathway it is H. This simple steric argument explains why selectivity is greater for $CH(CH_3)_2$ than CH_3.

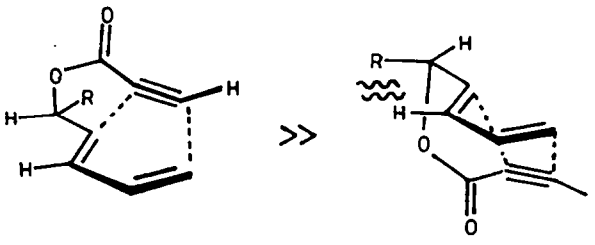

Figure 5. Steric effects at the transition-state for dienylpropynoate Diels-Alder reactions.

The model delineated by Figure 5 represents an intrinsic stereochemical preference, since the system is lightly substituted. It fits well for the indanomycin intermediates, and for several other examples in the literature[18]. The selectivity is generally modest and can be negated or overridden by other structural features in the reactant.[19].

Acknowledgements We thank SERC for a studentship (to DHB) under the CASE scheme, and Glaxo Group Research for support. A referee provided helpful comments and criticisms.

EXPERIMENTAL

Infra-red spectra were recorded on a Perkin-Elmer 297 instrument and were calibrated against polystyrene (1601 cm^{-1}). Absorption maxima are reported in wavenumbers (cm^{-1}) and are classified as strong (s), medium (m), weak (w) and broad (br).

Mass spectra were recorded by Dr.R.T. Aplin and his staff in the Dyson Perrins Laboratory on V.G. Micromass 16F or ZAB-1F/16F instruments.

^1H NMR spectra were recorded on Varian Gemini 200 (200 MHz), Bruker WH300 (300 MHz) or a Bruker AM500 (500 MHz) spectrometer.

Nuclear Overhauser enhancement (n.O.e) difference measurements and 2D-COSY experiments were performed either on the Bruker WH300 (300 MHz) or the Bruker AM500 (500 MHz) instrument using standard procedures.

Melting points were determined using a Reichert Kofler block and are uncorrected.

Elemental microanalyses were performed by Mrs. V. Lambourn of the Dyson Perrins Laboratory.

Preparative gas-liquid chromatography (g.l.c.) was carried out by Mr. P. Williams of the Dyson Perrins Laboratory using a Pye Series 105 Automatic Preparative Chromatograph with N_2 at 20 p.s.i. at the inlet and using columns of 7 mm internal diameter. Analytical g.l.c. was performed by the author on a Pye-Unicam Series 204 Chromatograph using 3 mm internal columns of the types specified in the text.

All solvents were purified before use according to standard procedures[20].

E-1,4-Hexadien-3-ol

To magnesium turnings (3.9 g, 0.16 mmoles) under argon in THF (80 ml) using initiation by iodine, vinyl bromide (16.05 g, 10.9 ml, 0.15 mole) was added at a rate which maintained gentle reflux. When the addition was complete (40 m) the brown soln. was cooled to 0°C and a solution of crotonaldehyde (8.5 g, 0.12 mole) in THF (10 ml) was added over 30 m. After complete addition the mixture was stirred a further 10 m then NH_4Cl (sat, 10 ml) was added slowly and with cooling. A green precipitate formed which was filtered off and washed well with Et_2O. The filtrate was dried ($MgSO_4$) and evaporated to give a yellow liquid which was distilled to give the required dienol (7.5 g, 66%) as a colourless liquid b.p. 51-52°C /14 mm (lit.[8] 86-87°C 100 mm). ν_{max} (Neat) 3340 (br, O-H); 990 (C=CH_2); 965 (CH=CH); 925 (C=CH_2). δ_H ($CDCl_3$) 300 MHz); 5.90 (1H, ddd, $J_{1a,2}$ = 17 , $J_{1b,2}$ = 10 , $J_{2,3}$ = 6 Hz,H_2); 5.74 (1H, ddq, $J_{4,5}$ = 16 , $J_{3,5}$ = 1 , $J_{5,6}$ = 4 Hz, H_5); 5.54 (1H, ddq, $J_{4,6}$ = 2 , $J_{3,4}$ = 7 Hz, H_4); 5.26 (1H, dt, $J_{1a,1b}$ = 1.5 Hz, H_{1a}); 5.12 (1H, dt, H_{1b}); 4.59 (1H, dd, H_3); 1.76 (3H, dd, Me_6) ppm.

E-3,5-Hexadien-2-ol

This material was prepared by the method of Heilbron, Jones et al.[8] from (E)-1,4-Hexadien -3-ol.

E-2-(3,5-Hexadienyl) propenoate

To a mixture of (E(-3,5-hexadien-2-ol (0.5 g, 5 mmoles), propenoic acid (1.08 g, 15 mmoles) and 4-dimethylaminopyridine (50 mg) in CH_2Cl_2 (50 ml) was added dicyclohexyl-carbodiimide (3.15 g, 30 mmoles) in CH_2Cl_2 (10 ml). After stirring the mixture under argon for 3 h the precipitate of dicyclohexylurea was removed by filtration, and the filtrate was evaporated to give a partially solid yellow residue. Et_2O (20 ml) was added which resulted in further solid being precipitated out, this again being removed by filtration. The filtrate was concentrated and distilled from trap to bucket (bath temp. 50°C/0.3 mm) to give colourless

E-2-(3,5-hexadienyl) propenoate (0.39 g, 51%). ν_{max} (Neat) 1720 (C=O); 993 ($C=CH_2$); 908 ($C=CH_2$). δ_H ($CDCl_3$, 300 MHz): 6.62-6.07 (4H, m, H_3, H_4,H_{3a} H_2'); 5.83 (1H, d, $J_{2,3b}$ = 10 Hz, H_{3b}); 5.72 (1H, dd, $J_{4,4}$ = 15, $J_{4,3}$ = 7 Hz, H_4). 5.48 (1H, dq, $J_{1,2}$ = $J_{2,3}$ = 6 Hz, H_2); 5.28-5.10 (2H, m, H_{5a} H_{5b}); 1.38 (3 H, d H_1) ppm. m/z (CI) 170 (100%, $[M+NH_4]^+$).

E-2-(3,5-Hexadienyl) propynoate

To a mixture of E-3,5-hexadien-2-ol (2 g, 20 mmoles), 4-dimethylaminopyridine (100 mg) and propynoic acid (1.86 ml, 30 mmoles) in CH_2Cl_2 (30 ml) at -78°C under argon, was added by syringe a solution of dicyclohexylcarbodiimide (5 g) in CH_2Cl_2 (15 ml). The solution was allowed to warm to room temp. over a period of 4 h during which time the mixture turned a dark brown and a precipitate formed. Filtration of this mixture using a cannula gave a brown solution. The solid residue of dicyclohexylurea from the filtration was washed well with Et_2O and filtered through a sinter. Combination of the filtrates and evaporation followed by dilution with more Et_2O caused the precipitation of more dicyclohexylurea which was removed by filtration through a bed of celite. Concentration of the Et_2O and distillation from trap to bucket (bath temp. 52°C/ 0.01 mm) gave the colourless E-2-(3,5-hexadienyl) propynoate (1.8 g, 50%) which by n.m.r. contained 9% of the isomeric E,E-1-(2,4-hexadienyl) propynate. The two materials were separated by glc (SE30, 5%, 8 ft, 60°C). (Found for E-2-(3,5-hexadienyl) propynoate, C, 71.6; H, 6.34; and for E,E-1-(2,4-hexadienyl) propynoate, C, 71.84; H, 6.86. $C_9H_{10}O_2$ requires: C, 71.98; H, 6.71%). Spectral data for E,E-2-(2,4-hexadienyl) propynoate: ν_{max} (Neat) 3260 (C≡CH); 2120 (C≡C); 1715 (C=O). δ_H ($CDCl_3$, 300 MHz): 6.38-6.02 (2H, m, H_3H_4);. 5.80 (1H, dq, $J_{5,6}$ = 6 , $J_{4,5}$ = 14 Hz, H_5); 5.63 (1H, dt, $J_{1,2}$ = 7 , $J_{2,3}$ = 15 Hz, H_2); 4.70 (2H, d, H_1); 2.90 (1H, s, C≡CH); 1.80 (3H, d, H_6) ppm m/z (CI) 151 (30%. $[M+1]^+$); 168 (100%, $[M+NH_4]^+$).
Spectral data for E-2-(3,5-hexadienyl) propynoate: ν_{max} (Neat) 3290 (C≡CH); 2111 (C≡C); 1708 (C=O); 1220 (C-O-C); 1000 ($C=CH_2$); 909 ($C=CH_2$). δ_H ($CDCl_3$, 300 MHz): 6.40-6.23 (2H, m, H_3,H_4); 5.77-5.63 (1H, m, H_5); 5.47 (1H, dq, $J_{1,2}$= $J_{2,3}$ = 7 Hz, H_2); 5.37-5.15 (2H, m, H_{5a},H_{5b}); 2.90 (1H, s, C≡CH); 1.43 (3H, d, H_1) ppm. δ_C ($CDCl_3$, 62.9 MHz); 152 (C_1'); 135; 133; 132 (C≡C); 118 (C_5'); 76 (C_2'); 75 (C_2); 73 (C_3') 20 (C_1) ppm. m/z (IBEI) 150 (2%, $[M]^+$); 105 (100%, $[PhCHCH_3]^+$).

Diels-Alder reaction between E-3,5-Hexadien-2-ol and methyl propynoate

A mixture of E-3,5-Hexadien-2-ol (211 mg) and methyl propynoate (181 mg) in chloroform (3 ml) was pressurised to 9 kbar pressure at 45°C for 18 h. The mixture was evaporated and chromatographed in 1:1 Et_2O: hexane to give one major product (160 mg) which by n.m.r. was shown to be a mixture of all four possible diastereomeric Diels-Alder products. Glc analysis (4% OV 225, 8 ft, 145°C) of the mixture provided confirmation with four main peaks being observed. ν_{max} (Neat) 3420 (br, O-H); 1700 (C=O); 1250 (C-O). δ_H ($CDCl_3$, 60 MHz): 7.3-6.9 (1H, m); 6.2-5.6 (2H, m); 3.80 (3H, s, O-Me); 3.7-3.4 (1H, m); 3.1-2.6 (3H, m); 1.4-1.2 (3H, m); ppm. m/z (CI) 183 (100%, $[M+1]^+$); 200 (10%, $[M+NH_4]^+$); 165 (80%, $[M-OH]^+$).

Attempted Diels-Alder reactions of E-2-(3,5-hexadienyl) propenoate

E-2-(3,5-Hexadienyl) propenoate (60 mg) was refluxed in xylene (5 ml) for 18 h. After this time analysis by t.l.c. (Et_2O or CH_2Cl_2) and NMR showed no evidence of product formation.
Attempts at Lewis acid catalysis using diethylaluminium chloride resulted only in decomposition of the substrate.

(1S,9R)- and (1S,9S)-9-Methyl-8-oxabicyclo[4.3.0]nona-2,5-dien-7-one

E-2-(3,5-Hexadienyl)-propynoate (38 mg) in toluene (2 ml) under argon was refluxed 18 h. Solvent was removed, with care being taken to keep the sample cold, to yield a brown oil which by glc analysis (4% OV225, 8 ft, 160°C) was shown to be a mixture of two isomers in ratio 6.4:1 (yield 97%). Separation of the two materials by glc (OV225, 15 ft, 210°C) gave the two isomers of 9-methyl-8-oxabicyclo[4.3.0]nona-2,5-dien-7-one. The major product, the (1S,9R)-isomer had m.p. 52-56°C (plates). (Found: C, 72.01; H, 6.75; $C_9H_{10}O_2$ requires: C, 71.98; H, 6.71). ν_{max} ($CHCl_3$) 1751 (C=O). δ_H ($CDCl_3$), 300 MHz): 6.85 (1H, m, H_3); 5.98-5.72 (2H, m, H_2H_3); 4.15 (1H, dq, $J_{1,9}$ = 9 , $J_{9,Me}$ = 6 Hz, H_9); 3.11-2.79 (3H, m, H_{5a} H_{5b} H_1); 1.57 (3H, d, 9-Me) ppm. n.O.e. (H_9*) - Me (4%), H_1 (7%), H_2 (4%). H_3 (2%); (Me)-H_1 (3%), H_2 (1.5%) H_9 (4%). δ_C ($CDCl_3$, 62.9 MHz): 185 (C_7); 132 (C_3); 126 (C_2); 122 (C_6); 80 (C_9); 45 (C_1); 28 (C_4); 19 (9-Me) ppm. m/z (CI) 151 (60%, $[M+1]^+$); 168 (100%, $[M+NH_4]^+$); 106 15%, $[M-CO_2]^+$).)
Spectral data for the minor product, the (1S,9S)-isomer: δ_H ($CDCl_3$, 300 MHz): 6.90 (1H, m, H_3); 5.98-5.72 (2H, m, H_2 H_3); 4.92 (1H, dq, $J_{1,9}$ = $J_{9,Me}$ = 7 Hz, H_9); 3.73-3.57 (1H, m, H_1); 3.11-2.79 (2H, m, H_{5a} H_{5b}); 1.16 (3H, d, 9-Me) ppm n.O.e. (H_1*)- H_2 (5%), H_9 (6.8%); (H_9*)-H_1 (7.2%), Me (2%); (Me*)- H_2 (10.2%), H_9 (13.6%).

(1S,9R)-9-Methyl-8-oxabicyclo[4.3.0]non-5-en-7-one

9-Methyl-8-oxabicyclo[4.3.0]nona-2,5-dien-7-one (130 mg) in THF (3 ml) was hydrogenated by the standard procedure using tris(triphenylphosphine) rhodium chloride (25 mg, 3 mol%) as the catalyst. After 3.5 h the reaction was worked up in the usual manner, chromatographed in 2:1 hexane: Et_2O and further purified by prep. glc (OV225, 15 ft, 200°C) to give (1S,9R)-9-methyl-8-oxabicyclo[4.3.0]non-5-en-7-one (plates m.p. 60-62°C) as a single isomer. (Found: C,70.93; H, 8.32; $C_9H_{12}O_2$ requires: C, 71.03; H, 7.95). ν_{max} (Nujol) 1750 (C=O). δ_H ($CDCl_3$, 300 MHz): 6.82-6.74 (1H, m, H_3);, 4.07 (1H, dq, $J_{1,9}$ = 9 Hz, $J_{9,Me}$ = 7 Hz, H_9);

2.54-2.36 (1H, m, H_1); 2.36-2.30 (1H, m, H_{4eq}); 2.26-2.13 (1H, m, H_{4ax}); 2.09-2.02 (1H, m, H_{2eq}); 2.00-1.88 (1H, m, H_{3eq}); 1.63-1.50 (1H, mm, H_{3ax}); 1.50 (3H, d, 9-Me); 1.16 (1H, dddd, $J_{1,2a}$ = $J_{2a,2e}$ = $J_{2a,3e}$ = 12 Hz, $J_{2a,3e}$ = 1 Hz, H_{2ax}) ppm. n.O.e. (H_3*)- H_{2ax} (3%), Me (5%); (Me*)- H_1 (3.5%); H_{2eq} (3.5%), H_3 (3.5%). m/z (IBEI) 152 (6%, $[M]^+$); 108 (100%, $[M-CO_2]^+$).

E-2-Methyl-hepta-4,6-dien-3-ol

To a solution of isopropylmagnesium bromide prepared in THF (25 ml) from magnesium (0.44 g) and 2-bromopropane (2.25 g) was added E-pentadienal (1.5 g) in THF (10 ml) prepared by the method of Woods *et al*[21]. After 2 h stirring at room temp., ater (3 ml) was added carefully, then Et_2O (50 ml). The mixture was filtered and the magnesium salts washed with with more Et_2O. The combined organics were washed with water (5 ml), dried ($MgSO_4$) and concentrated to give a crude material (1.5 g) which decomposed upon attempted chromatography to give only 0.3 g of the pure E-2-methyl-hepta-4,6-dien-3-ol as a slightly yellow liquid (b.p. 50°C/ 0.5 mm). The material was therefore used in its crude form in the ensuing reactions. ν_{max} (Neat) 3390 (br, O-H); 1362 (Me_2C); 1350 (Me_2C); 905 (C=CH_2). δ_H ($CDCl_3$, 60 MHz): 6.46-4.88 (5H, m, $H_4H_5H_6H_{7a}H_{7b}$); 3.88 (1H, dd, $J_{3,4}$ = $J_{2,3}$ = 5 Hz, H_3); 1.75 (1H, dqq, $J_{1,2}$ = $J_{2,}$Me = 7 Hz, H_2); 0.93 (3H, d, H_1); 0.87 (3H, d, 2-Me) ppm. m/z (CI) 144 (15%, $[M+NH_4]^+$); 126 (18%, $[M]^+$)109 (100%, $[M-OH]^+$).

E-3-(2-Methylhepta-4,6-dienyl) propynoate

A solution was prepared of E-2-methyl-hepta-4,6-dien-3-ol (0.75 g), propynoic acid (0.5 g, 430 µl) and 4-dimethylaminopyridine (50 mg) in CH_2Cl_2 (6 ml). This was cooled to -78°C and to it was added dropwise a solution of dicyclohexylcarbodiimide (1.5 g) in CH_2Cl_2 3 ml). The solution was warmed slowly over 4 h, going black and throwing down a precipitate upon approaching room temp. The mixture was diluted with 5 volumes of Et_2O, filtered, and the filtrates concentrated to give a dark red oil. Flash chromatography in 5:2 hexane : CH_2Cl_2 changing to neat CH_2Cl_2 gave a poor yield of E-3-(2-methylhepta-4,6-dienyl) propynoate (250 mg, 25%), (Found: C, 74.28; H, 8.26; $C_{11}H_{14}O_2$ requires C, 74.13; H, 7.92). ν_{max} (Neat) 3280 (CCH); 2116 (CC); 1708 (C=O); 1390 (Me_2C); 1370 (Me_2C). δ_H ($CDCl_3$), 300 MHz); 6.39-6.26 (2H, m, H_4 H_6); 5.62 (1H, dd, $J_{4,5}$ = 15 , $J_{5,6}$ = 7 Hz, H_5); 5.32-5.12 (2H, m, H_{7a} H7b); 2.87 (1H, s, CCH); 1.97 (1H, qq, $J_{1,2}$ = 6 Hz, H_2); 0.98 (3H, d, $J_{2,}$Me = 6 Hz, 2-Me); 0.95 (3H, d, H_1) ppm. m/z (CI) 196 (100%, $[M+NH_4]^+$); 179 (25%, $[M+1]^+$); 109 (15%, $[M-CH_2CO_2]^+$).

(1S,9R)-9-(1'-Methylethyl)-8-oxabicyclo[4,3,0]nona-2,5-dien-7-one

E-3-(2-Methylhepta-4,6-dienyl) propynoate (25 mg) in degassed toluene (1.5 ml) was heated under argon at 75°C for 18 h. Glc analysis (4% OV225, 8 ft, 170°C) at this stage showed the material to have been converted quantitatively into a 97:3 mixture of the two isomers of (1S,9R)-9-(1'-methylethyl)-8-oxabicyclo[4,3,0]nona-2,5-dien-7-one. ν_{max} (Nujol) 1745 (C=O). δ_H ($CDCl_3$, 300 MHz): 6.88-6.77 (1H, m, H_3); 5.97-5.77 (2H, m, H_2 H_5); 3.86 (1H, dd, $J_{9,2'}$ = 10 Hz, H_9); 3.25-2.76 (3H, m, H_1 H_{4a} H_{4b}); 2.02 (1H, dqq, $J_{1',2'}$ = $J_{2',3'}$ = 6 Hz, $H_{2'}$) 1.12 (3H, d, $H_{1'}$); 1.06 (3H, d, $H_{3'}$) ppm. n.O.e. (H1'*)- H_1 (5.3%), H_9 (4.1%), Me (8.8%); (H_6*) - H_4 (6%); (H_9*) - $H_{1'}$ (4%), H_2 (4%), Me (5.6%); (Me*) - H_1 (2.9%), $H_{1'}$ (5%), H_2 (2.4%), H_9 (2.9%), m/z (CI) 196 (100%, $[M+NH_4]^+$); 179 (60%, $[M+1]^+$); 106 (20%).

E-3-(1,4-Hexadienyl)-trichloroacetimidate

This material was prepared by a modification of the method of Overman.[13]

Potassium hydride (180 mg, 15 mol%) was washed with dry hexane, filtered by cannula filtration and dried on the vacuum line. This was added as a slurry in hexane (5 ml) to a solution of (E)-1,4-hexadien-3-ol (3.0 g) in THF (24 ml) under argon at -10°C. The solution quickly turned yellow and hydrogen was evolved. After all the base had dissolved, the alcohol/alcoholate mixture was transferred dropwise by cannula into a solution of trichloroacetonitrile (2.9 ml) in dry Et_2O at -10°C whereupon a dirty brown precipitate appeared. The solution was warmed over 30 m to room temp.

The material was concentrated to one quarter of its volume and hexane (120 ml) containing methanol (0.75 ml) was added. A dark precipitate settled out and the clear orange supernatant solution was collected by filtration and concentrated to give an orange/brown oil (6.25 g, 84%) which was stored at -30°C to suppress isomerisation. ν_{max} (Neat) 3340 (N-H); 1661 (C=O); 968 (CH=CH); 930 (C=CH_2). δ_H ($CDCl_3$, 60 MHz): 8.17 (1H, br s, N-H); 6.05-5.02 (5H, m, H_{1a} H_{1b} H_2 H_4H_5); 1.68 (3H, d, $J_{5,6}$ = 5.5 Hz, H_6).

E-2-(3,5-Hexadienyl)-trichloroacetamide

The crude trichloroacetimidate (117 mg) was refluxed in toluene (3 mg), the reaction being followed by t.l.c. (Et_2O). After 3 h the solvent was removed to give a mixture of E-2-(3,5-hexadienyl)-trichloroacetamide and E,E-1-(2,4-hexadienyl)-trichloroacetamide (quant.) in ratio of 5:2. ν_{max} (Neat) 3418 (N-H); 1698 (C=O); 1001 (CH=CH); 905 (C=CH_2). δ_H ($CDCl_3$, 300 MHz): 6.55 (1H, br s, N-H); 6.40-6.20 (2H, m, H_3 H_5); 5.68 (1H,dd, $J_{3,4}$ = 14 Hz, $J_{4,5}$ = 5 Hz, H_4); 5.32-5.12 (2 H, m, H_{6a} H_{6b}); 4.60 (1H, dq, $J_{1,2}$ = 6 Hz. $J_{2,3}$ = 12 Hz; H_2); 1.38 (3H, d, H_1) ppm.

E-2-Amino-3,5-hexadiene

The mixture of trichloroacetamides obtained from the Overman rearrangement (1.5 g, vide infra) was stirred with aqueous caustic soda (3M, 5 ml) for 18 h. The brown oil which formed on the surface of the aqueous phase was extracted into Et_2O (2 x 20 ml), dried ($MgSO_4$), and concentrated on an ice/water bath to give a brown crude sample of amines in the ratio 5:2 (0.6 g, quant). The material was separated by prep. g.l.c. (CW20M, 15 ft, 15%, 120°C) with poor efficiency to give **E-2-amino-3,5-hexadiene** (98 mg) and **E,E-1-amino-2,4-hexadiene.**
Spectral data for E-2-amino-3,5-hexadiene: ν_{max} ($CDCl_3$) 3375; 3305 ($-NH_2$). δ_H ($CDCl_3$), 300 MHz): 6.39-6.07 (2H, m, H_3 H_5); 5.71 (1H, dd, $J_{3,4}$ = 15 Hz, $J_{4,5}$ = 6 Hz, H_4); 5.16 (1H, dd, $J_{5,5a}$ = 17 Hz, $J_{5a,5b}$ = 1 Hz, H_{5a}); 5.04 (1H, dd, $J_{5,5b}$ = 10 Hz, H_{5b}); 3.54 (1H, dq, $J_{1,2}$ = 7 Hz, $J_{2,3}$ = 7 Hz, H_2); 1.46 (2H, br s, NH_2); 1.18 (3H, d, H_1) ppm. δ_C ($CDCl_3$, 62.9 MHz): 140; 137; 128 (C=C); 116 (C_5); 49 (C_2); 24 (C_1) ppm.

E-2-(3,5-Hexadienyl) propynamide

A solution of (E)-2-amino-3,5-hexadiene (130 mg), propynoic acid (117 mg), and 4-dimethylaminopyridine (20 mg) was cooled to -40°C. Dicyclohexylcarbodiimide (300 mg) in CH_2Cl_2 was added to this by syringe and the mixture was warmed to room temp. over 2.5 h. Et_2O (6 volumes) was added and the supernatant liquid was isolated by filtration and concentrated. Flash chromatography in Et_2O gave **E-2-(3,5-hexadienyl) propynamide** (168 mg, 84%) as a yellowish oil. ν_{max} (Neat) 3250 (CCH); 2120 (CC); 1635 (C=O). δ_H ($CDCl_3$, 300 MHz): 6.31-6.14 (2H, m, H_3 H_5); 6.10 (1H, br s, N-H); 5.68 (1H, dd, $J_{3,4}$ = 15 , $J_{4,5}$ = 4 Hz, H_4); 5.25 (1H, d, $J_{5,5a}$ = 16 Hz, H_{5a}); 5.08 (1H, d, $J_{5,5b}$ = 9 Hz, H_{5b}); 4.67 (1H, dq, $J_{1,2}$ = 7 Hz, $J_{2,3}$ = 14 Hz, H_2); 2.82 (1H, s, CCH); 1.31 (3H, d, H_1) ppm. δ_C ($CDCl_3$, 62.9 MHz): 153 (C_1); 136; 135; 132 (C=C); 120 (C_5); 81 (C_2'); 79 (C_3'); 75 (C_2); 22 (C_1) ppm. m/z (CI) 150 (100%, $[M+1]^+$).

(1S,9R)- and (1S,9S)-9-Methyl-8-azabicyclo[4,3,0]nona-2,5-dien-7-one

E-2-(3,5-Hexadienyl) propynamide (50 mg) in degassed toluene (2 ml) was heated at 80°C under argon for 2 days. G.l.c. analysis (4% OV225, 8 ft, 200°C) showed the reaction to give the desired **9-methyl-8-azabicyclo[4,3,0]nona-2,5-dien-7-one** in 85% yield as a 6:1 mixture of two diastereomers (plates m.p. 96-98°C). ν_{max} (Nujol) 3420 (N-H); 1682 (C=O). δ_H ($CDCl_3$, 300 MHz): 6.63-6.55 (1H, m, H_5); 5.94-5.87 (2H, m, H_2 H_3); 3.44 (1H, m, H_9); 2.96-2.77 (3H, m, H_{4a} H_{4b} H_1); 1.39 (3H, d, $J_{9,Me}$ = 7 Hz, 9-Me) ppm. m/z (DCI) 150 (100), $[M+1]^+$); 148 (40%, $[M-1]^+$).

E,E-2-(3,5-Hexadienyl)-3-acetylpropenoate

A mixture containing (E)-3,5-hexadien-2-ol (0.5 g), (E)-3-acetylpropenoic acid (0.67 g), and 4-dimethylaminopyridine (50 mg) was prepared in CH_2Cl_2 (10 ml). To this mixture was added dicyclohexylcarbodiimide (1.1 g) in CH_2Cl_2 (10 ml). The solution quickly turned orange then brown, and a precipitate appeared.

After stirring overnight under argon, a large quantity of Et_2O was added and precipitated dicyclohexylurea removed by filtration. Evaporation of the filtrate gave a reddish brown oil which was purified by flash chromatography in 3:1 hexane: Et_2O to give **E,E-2-(3,5-hexadienyl)-3-acetylpropenoate** as a yellow oil (785 mg, 79%). This material was found to polymerise slowly on standing at room temp. and consequently was stored at -30°C. ν_{max} (Neat) 1720 (C=O, ester); 1681 (C=O); 980 (CH=CH); 918 (C=CH_2). δ_H ($CDCl_3$, 300 MHz): 7.05 (1H, d, $J_{2',3'}$ = 16 Hz, $H_{2'}$); 6.65 (1H, d, $H_{3'}$); 6.40-6.23 (2H, m, H_3 H_4); 5.78-5.65 (1H, m, H_5); 5.52 (1H, dq, $J_{1,2}$ = $J_{2,3}$ = 7 Hz, H_2); 5.31-5.15 (2H, m, H_{5a} H_{5b}); 2.38 (3H, s, MeCO-); 1.43 (3H, d, H_1) ppm. m/z (CI) 195 (12%, $[M+1]^+$); 212 (8%, $[M+NH_4]^+$); 98 (90%, $[M-CH_2CHCHCHCH(OH)CH_3]^+$); 81 (100%, $[M-CH_2CHCHCHCH_3]^+$)

Diels-Alder reaction of E,E-2-(3,5-hexadienyl)-3-acetylpropenoate

(E,E)-2-(3,5-Hexadienyl) 3-acetylpropenoate (40 mg) in toluene (5 ml) was refluxed under argon for 18 h. Evaporation to dryness gave **(1R,2R,6R,7R)-2-acetyl-7-methyl-8-oxabicyclo [4.3.0]non-4-en-9-one** as a white solid product (38 mg, 95%).

G.l.c. analysis of this material (4% OV225, 8 ft, 200°C) showed it to be a mixture of four diastereomers A,B,C,D in the ratio 8:72:16.4. Preparative g.l.c. (Silicone oil, 15%, 15 ft, 220°C) gave a small amount of the major component B (microplates m.p. 85-89°C) which was assigned by n.O.e. and COSY experiments. ν_{max} ($CHCl_3$) 1765 (C=O, ester); 1710 (C=O, ketone). δ_H ($CDCl_3$, 300 MHz): 5.82 (2H, s, H_2 H_3); 4.23 (1H, dq, $J_{1,9}$ = 11 , $J_{9,Me}$ = 6 Hz, H_9); 2.71 (1H, dd, $J_{5,6}$ = $J_{1,6}$ = 12 Hz, H_6); 2.36 (3H s, 5-COMe); 1.48 (3H, d, 9-Me) ppm. n.O.e. (H_7*) - Me (5.3%), H_1 (6.8%), H_6 (2.3%); (H_1*) - H_7 (6.6%). m/z (IBEI) 194 (10%, $[M]^+$); 151 (25%, $[M-CH_3CO]^+$); 107 (30%, $[M-CH_3C=O-CO_2]^+$); 79 (100%); consistent with structure (20a).

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