PERKIN 1

Absence of the alleged retardation of the Diels–Alder reaction for dienes bearing a neighbouring hydroxy substituent

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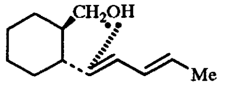
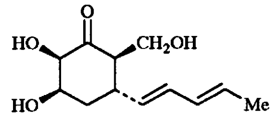
Contrary to earlier observations the diene 1 reacts readily in Diels–Alder additions. With *N*-methylmaleimide the stereoisomeric adducts 10a and 10b are formed in equal quantities. With maleic anhydride, ring-opening accompanies adduction to give 11 and two stereoisomers of gross structure 12. Dienes 1, 9 (X = OMe) and 9 (X = H) react at similar rates with *N*-methylmaleimide, discounting the alleged intramolecular retardation due to through space interaction between the hydroxy group and the diene system.

Our interest in the novel behaviour that could arise when a heteroatom is in close proximity to a diene system prompted us to re-examine the unusual properties reported for the diene **1**.[1] We had in mind comparing the properties of related dienes in which the OH group was replaced with other heteroatomic groups (SR, NR_2, *etc.*). Diene **1** had been synthesised as a model for the mould product palitantin **2**. Both **1**[1] and **2**[2] apparently failed to react with maleic anhydride and showed an absorption in the UV spectrum at λ_{max}(EtOH) 232 nm. In contrast the compound **3** lacking the hydroxymethyl group formed a maleic anhydride adduct and exhibited a normal UV absorption (λ_{max} 227 nm). In addition **1** and **2** reacted readily with aqueous alcoholic iodine to give iodo ethers *e.g.* **4** from **1**. Austin and Pearson[1] were interested in the role of chelation effects in determining reactivity and attributed the properties of **1** to "chelate interaction" of an oxygen lone pair with the proximate diene double bond *e.g.* as indicated by the dotted line in **1**. Conjugation of OH with the diene system was expected to shift λ_{max} to longer wavelength, and ground state stabilisation of the diene was supposed to retard its Diels–Alder addition. A neighbouring group participation enhanced by chelate interaction would explain the formation of iodo ethers. Later with the advent of correlation diagrams the failure of **1** to react with maleic anhydride was explained in a different way.[1b] Interaction of the oxygen lone pair with the double bond was thought to populate ψ_3 of the diene system mixing into the wave function a configuration for which the addition is forbidden, since ψ_3 correlates with the high energy $\sigma_1^* + \sigma_2^*$ orbital of the product. The addition is inhibited to the extent that such configuration interaction is required to describe the hydroxy-perturbed system. Although this explanation appeared speculative it received support from mapping analysis.[3] This showed that the "permissibility" of the Diels–Alder reaction was reduced from an unperturbed value of 0.3369 to 0.2555 for the hydroxy-perturbed system. These results contrast with what might have been expected on the basis of simple ideas of electron donation from the hydroxy group to the diene system. On that basis a hydroxy-perturbed diene might be expected to resemble to some extent a 1-alkoxydiene and react *more* not less readily than butadiene with electron-deficient dienophiles.



1



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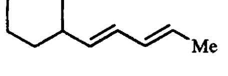

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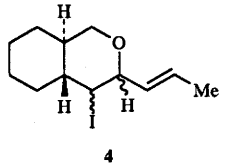

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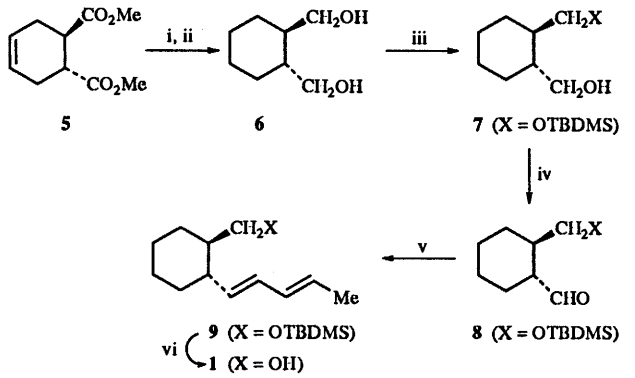
The diene **1** was synthesised from the Diels–Alder adduct **5** of butadiene with dimethyl fumarate as outlined in Scheme 1. The diol **6** was efficiently mono-protected as the *tert*-butyldimethylsilyl ether **7** (X = OTBDMS) which in turn was converted into **8** (X = OTBDMS) by Swern oxidation. The latter gave **9** (X = OTBDMS) upon reaction with the lithium salt of *E*-but-2-enyldiphenylphosphine oxide. This method, due to Lythgoe and his collaborators[4] is known to give as major product the new double bond in an *E*-configuration with strict retention of stereochemistry in the butenyl group derived from the phosphine oxide. The major product of step (v) was therefore expected to be **9** (X = OTBDMS). Indeed, the 400 MHz ^{1}H NMR spectrum of the diene **1** derived from **9** (X = OTBDMS) (HF–H_2O, MeCN, CH_2Cl_2) showed the resonances for the protons at the termini of the diene system as a dd (*J* 14.5 and 9.0 Hz) and a dq (*J* 14.0 and 7.0 Hz), clearly establishing the presence of the *E*,*E*-diene system. The same is true for the other dienes **9** (X = OTBDMS, X = OMe and X = H) prepared in our work (see Experimental section).



Scheme 1 *Reagents and conditions:* i, H_2/Pd–C; ii, $LiAlH_4$, Et_2O; iii, TBDMSCl, Et_3N, CH_2Cl_2, cat. DMAP; iv, Swern oxidation; v, *E*-$CH_3CH{=}CHCH_2POPh_2$, BuLi, THF, 1.5 h at 0 °C and 2 h at 20 °C; vi HF in H_2O, CH_3CN-CH_2Cl_2

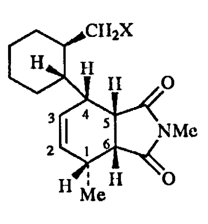
With *N*-methylmaleimide in boiling benzene, **1** gave two adducts (ratio 1 : 1). These are tentatively assigned as *endo*-adducts **10a** and **10b** (X = OH) derived by addition to the diastereotopic faces of diene **1**. In a similar way, the dienes **9** (X = OMe) and **9** (X = H) gave pairs of isomeric adducts. The 400 MHz ^{1}H NMR spectra of the adducts are very similar to one another; signals for the protons of the tetrahydrophthalimide ring are detailed in Table 1 and no decision has been

Table 1 400 MHz ^{1}H NMR data for tetrahydrophthalimide ring protons of adducts **10a** and **10b** [*J* values (Hz) given in parentheses]

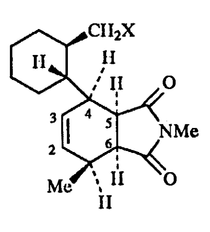
Ring proton[a]	**10** (X = OH)		**10** (X = OMe)		**10** (X = H)	
	Isomer 1	Isomer 2	Isomer 1	Isomer 2	Isomer 1	Isomer 2
1-H	2.44–2.53, m	2.43–2.51, m	2.43–2.50, m	2.43–2.50, m	2.43–2.48, m	2.40–2.58, m
2-H	5.71, dt, (9 + 3)	5.62, dt, (9 + 3)	5.67, dt, (9 + 3)	5.59, dt, (9 + 3)	5.56, dtd, (9 + 3 + 1)	5.67, dt, (9 + 3)
3-H	5.76, dt, (9 + 3)	5.83, dt, (9 + 3)	5.78, dt, (9 + 3)	5.79, dt, (9 + 3)	5.82, dt, (9 + 3)	5.81, dt, (9 + 3)
4-H	2.54–2.61, m	2.28–2.35, m	2.61–2.55, m	2.29–2.26, m	2.27–2.20, m	2.58–2.50, m
5-H	3.32, dd, (8 + 6)	3.32, dd, (8 + 5)	3.23, dd, (8 + 6)	3.32–3.29, obscured	3.33, dd, (9 + 5)	3.20, dd, (8 + 7)
6-H	3.05, dd, (8 + 7)	3.01, t, (8)	3.03, t, (8)	2.99, t, (7)	2.98, t, (8)	3.01, dd, (8 + 7)

[a] Numbering of ring protons given on structures of **10a** and **10b**.

made which isomer (1 or 2 in the Table) is **10a** or **10b**. These spectra and the further characterisation of the adducts in the Experimental section leave little doubt that diene **1** undergoes Diels–Alder addition to *N*-methylmaleimide. A rough comparison of the rates of addition of all three dienes to *N*-methylmaleimide at 120 °C in C_6D_6 was carried out using 300 MHz ^{1}H NMR spectroscopy to monitor reaction progress; all three dienes reacted at a similar rate (*k ca.* 1.4 $dm^3\ mol^{-1}\ h^{-1}$). Accordingly no deactivating effect is associated with either the hydroxy group in **1** or the methoxy group in **9** (X = OMe).

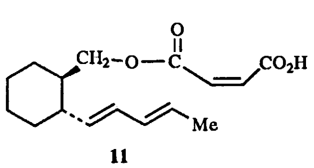


10a

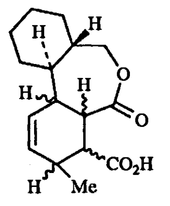


10b

With maleic anhydride in boiling benzene, **1** gave a mixture of **11**, formed by opening of the maleic anhydride ring, and two isomeric products of gross structure **12** whose formation involves both anhydride ring-opening and Diels–Alder addition, though not necessarily in that order. The IR spectra of the isomers **12** show the absence of the succinic anhydride ring and the presence of ester and carboxy groups. The NMR spectra are also consistent with the gross structure **12** for the isomers (see Experimental section). Related reactions with maleic anhydride have been described for the alcohols **13**,[5] **14**[6] and **15**,[6] but **16** was reported to give only polymeric material.[6]



11



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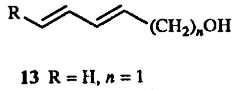
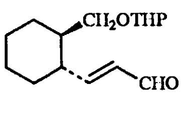


13 R = H, *n* = 1
14 R = Me, *n* = 1
15 R = Me, *n* = 2
16 R = Me, *n* = 3

It is likely that the previous synthetic approach to **1** involving Wittig reaction of ethylidenetriphenylphosphorane with the enal **17** and removal of the THP ether, actually gave the *Z,E*-diene **18**. Although the Wittig reaction involved a conjugated carbonyl group and proceeded in the presence of lithium bromide in THF as solvent, all factors known to increase formation of *trans*-alkene, the *cis*-isomer would probably still predominate.[7] For such dienes the population of the *cisoid* diene conformer is so small that Diels–Alder additions are strongly impeded[8] *e.g.* the reactivities of *cis* and *trans* piperylene towards tetracyanoethylene differ by a factor of 10^5. The model compound **3**, which underwent smooth Diels–Alder reactions and showed normal UV absorptions, was prepared by reaction of hexahydrobenzaldehyde with *trans*-but-2-en-1-ylidenetriphenylphosphorane, a semi-stabilised Wittig reagent expected to give more *trans*-alkene; **3** was obtained together with an equal quantity of its *cis*-isomer.[6] Firm identification of the product obtained earlier[1] would require repetition of that work. The earlier work did not have the benefit of high-field NMR spectra and rather less was known about the stereochemistry of the Wittig reaction. The apparent failure of palitantin **2** to undergo Diels–Alder addition to maleic anhydride is less easily understood as there is NMR and other evidence that the methyl substituted double bond is *trans* for palitantin.[9] The important conclusion reached at this stage is that hydroxy dienes of type **1** exhibit normal Diels–Alder reactivity in contradiction of the earlier claim.[1] These observations agree with semi-empirical molecular orbital calculations performed for the dienes **1**, **9** (X = OMe) and **9** (X = H), using MOPAC version 6.0 at the precise level, with the AM1 force field and fully optimised geometries. No variation in the electronic energy of the first singlet excited state over that of the ground state was found between the dienes, when either *cisoid* or *transoid* conformations were compared. Furthermore, no significant overlap between the orbitals of the oxygen atom of **1** or **9** (X = OMe), and the π-system of the diene was observed. It is likely that suitable substrates in our search for diene–heteroatom interactions will have the heteroatom held permanently in close proximity to the diene system.



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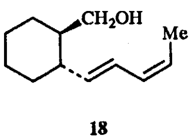

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Experimental

Mps were determined with a Kofler hot-stage apparatus and are uncorrected. Unless otherwise stated IR spectra were recorded as Nujol mulls on a Philips PU 8706 IR spectrophotometer and referenced to a peak at 1601 cm^{-1} of polystyrene. Unless otherwise stated ^{1}H NMR spectra were determined in $CDCl_3$, with tetramethylsilane as internal standard with a General Electric QE 300 instrument (300 MHz spectra); 400 MHz spectra were obtained on a Bruker AM 400 spectrometer. *J* Values are given in Hz. Mass spectra were recorded on an Autospec instrument. Short-column chromatography was performed using Kieselgel G60 (Merck).[10] Ether refers to diethyl ether.

***trans*-2-(*tert*-Butyldimethylsilyloxymethyl)cyclohexanemethanol 7 (X = OTBDMS)**

To a solution of *trans*-cyclohexane-1,2-dimethanol (2.18 g, 15.1 mmol), triethylamine (1.46 g, 15.1 mmol) and *N*,*N*-dimethylaminopyridine (DMAP; 3 mg) in dry dichloromethane (25 cm^3) stirred at 0 °C under argon, was added *tert*-butyldimethylsilyl chloride (2.30 g, 15.1 mmol). The mixture was stirred at room temp. for 17 h and then partitioned between water and ether. The aqueous layer was extracted with ether and the combined organic extracts were washed with aq. hydrochloric acid (5%) and brine, dried and concentrated under reduced pressure. Purification by flash chromatography, eluting with light petroleum (bp 60–80 °C)–ether (4:1) afforded the *alcohol* 7 (X = OTBDMS) as a colourless oil (2.22 g, 57%); R_f 0.20 [light petroleum (bp 60–80 °C)–ether (4:1)]; ν_{max}(thin film)/cm^{-1} 3390br, 1480 and 1265; δ_H(300 MHz) 3.78 (1 H, dd, *J* 5.5 and 8.0, CH_2OSi), 3.60–3.49 (2 H, m, CH_2OH), 3.54 (1 H, d, *J* 5, OH), 1.74–1.71 (2 H, m, cyclohexyl-CH), 1.64–1.54 (2 H, m, cyclohexyl-CH), 1.33–0.93 (6 H, m, cyclohexyl-CH), 0.90 [9 H, s, $C(CH_3)_3$] and 0.07 (6 H, s, $SiCH_3$); *m*/*z* (EI) 201 ($M^+ - C_4H_9$, 12%), 119 (14), 109 (76) and 75 (100).

***trans*-2-(*tert*-Butyldimethylsilyloxymethyl)cyclohexanecarbaldehyde 8 (X = OTBDMS)**

To a solution of oxalyl chloride (0.75 g, 5.9 mmol) in dry dichloromethane (25 cm^3) stirred at −60 °C under argon, was added dimethyl sulfoxide (0.93 g, 11.9 mmol) and the solution was stirred at −60 °C for 10 min. A solution of alcohol 7 (X = OTBDMS) (1.40 g, 5.4 mmol) in dry dichloromethane (2 cm^3) was added dropwise, the temperature being maintained between −60 and −55 °C, and the solution stirred for 15 min at −60 °C. Triethylamine (2.72 g, 27 mmol) was then added and the solution stirred for 10 min at −60 °C, after which it was allowed to warm to room temp. The mixture was diluted with water and extracted with dichloromethane. The combined organic extracts were washed with aq. hydrochloric acid (5%), water, aq. $NaHCO_3$ (5%) and brine, dried and concentrated under reduced pressure to afford the *aldehyde* 8 (X = OTBDMS) as a colourless oil (1.23 g, 87%); R_f 0.40 [light petroleum (bp 40–60 °C)–ether (1:1)]; (Found: M^+, 256.185. $C_{14}H_{28}O_2Si$ requires *M*, 256.186); ν_{max}(thin film)/cm^{-1} 1740, 1470, 1260 and 840; δ_H(300 MHz) 9.53 (1 H, d, *J* 4, CHO), 3.55 (1 H, dd, *J* 5 and 10, CH_2O), 3.40 (1 H, dd, *J* 7 and 10, CH_2O), 2.09–2.02 (1 H, m, *CH*CHO), 1.91–1.61 (5 H, m, cyclohexyl-CH), 1.35–1.18 (3 H, m, cyclohexyl-CH), 1.07–0.99 (1 H, m, cyclohexyl-CH), 0.87 [9 H, s, $C(CH_3)_3$] and 0.01 [6 H, s, $(CH_3)_2Si$]; *m*/*z* (EI) 255 ($M^+ - 1$, 0.1%), 199 (100), 169 (15), 107 (25), 89 (15) and 75 (90).

Preparation of dienes

***E*,*E*-1-[*trans*-2-(*tert*-Butyldimethylsilyloxymethyl)cyclohexyl]-penta-1,3-diene 9 (X = OTBDMS).** To a solution of *E*-but-2-enyldiphenylphosphine oxide[4] (920 mg, 3.60 mmol) in dry tetrahydrofuran (30 cm^3) stirred at 0 °C under argon was added a solution of butyllithium (1.56 mol dm^{-3} in hexanes, 2.19 cm^3, 3.42 mmol), and the solution was stirred at 0 °C for 15 min. A solution of aldehyde 8 (X = OTBDMS) (800 mg, 3.11 mmol) in dry tetrahydrofuran (2 cm^3) was added to the reaction mixture, which was then stirred for 1.5 h at 0 °C, allowed to warm to room temp. and stirred for a further 2 h. The mixture was diluted with ether and then washed with saturated aq. $NaHCO_3$ and brine and concentrated under reduced pressure. The residue was dissolved in light petroleum (bp 40–60 °C) and the solution was filtered through a plug of silica and evaporated to afford the *diene* 9 (X = OTBDMS) as a colourless oil (750 mg, 82%); R_f 0.30 [light petroleum (bp 40–60 °C)] (Found: M^+, 294.236. $C_{18}H_{34}OSi$ requires *M*, 294.238); ν_{max}(thin film)/cm^{-1} 1250, 1110 and 985; λ_{max}(EtOH)/nm 228; δ_H(400 MHz) 6.05–5.97 (2 H, m, CH=C*HCH*=CH), 5.56 (1 H, dq, *J* 14 and 7, *CH*CH$_3$), 5.37 (1 H, dd, *J* 14.5, 9.0, CHC*H*=CH), 3.56 (1 H, dd, *J* 9.5 and 3, CH_2O), 3.33 (1 H, dd, *J* 9.5 and 6.5, CH_2O), 1.90–1.60 (5 H, m, cyclohexyl-CH), 1.73 (3 H, d, *J* 7, CH_3CH), 1.26–1.02 (5 H, m, cyclohexyl-CH), 0.89 [9 H, s, $C(CH_3)_3$] and 0.01 [6 H, s, $Si(CH_3)_2$]; *m*/*z* (EI) 294 (M^+, 0.5%), 237 (80), 162 (80), 147 (40), 133 (30), 119 (30), 105 (30), 89 (40) and 75 (100).

***E*,*E*-1-(*trans*-2-Methylcyclohexyl)penta-1,3-diene 9 (X = H).** *trans*-2-Methylcyclohex-4-enecarbaldehyde[11] was hydrogenated over palladium on charcoal in tetrahydrofuran to give *trans*-2-methylcyclohexanecarbaldehyde, which was then treated by the above method to give diene 9 (X = H) (52%); R_f 0.60 [light petroleum (bp 40–60 °C)] (Found: M^+ 164.157. $C_{12}H_{20}$ requires *M*, 164.157); ν_{max}(thin film)/cm^{-1} 1445, 1375 and 985; λ_{max}(EtOH)/nm 227; δ_H(400 MHz) 6.06 (2 H, m, CH=C*HCH*=CH), 5.62–5.53 (1 H, m, *CH*CH$_3$), 5.37 (1 H, dd, *J* 9 and 14, CHC*H*=CHCH=CH), 1.86–1.40 (5 H, m, cyclohexyl-CH), 1.73 (3 H, d, *J* 6.5, CH=CHC*H*$_3$), 1.37–1.02 (4 H, m, cyclohexyl-CH), 1.01–0.87 (1 H, m, cyclohexyl-CH) and 0.82 (3 H, d, *J* 6, CH$_2$CHC*H*$_3$); *m*/*z* (EI) 164 (M^+, 12%), 105 (8), 96 (100) and 81 (55).

***E*,*E*-1-(*trans*-2-Hydroxymethylcyclohexyl)penta-1,3-diene 1.** To a stirred solution of diene 9 (X = OTBDMS) (710 mg, 2.41 mmol) in acetonitrile (30 cm^3) and dichloromethane (5 cm^3) was added aq. hydrofluoric acid (40%), and the solution stirred at room temp. for 45 min. The mixture was then partitioned between ether and aq. $NaHCO_3$ (5%) and extracted with ether. The combined organic extracts were washed with brine, dried and concentrated under reduced pressure. The residue was dissolved in ether, filtered through a plug of silica and concentrated under reduced pressure to afford the *alcohol* 1 as a colourless oil (400 mg, 92%); R_f 0.25 [light petroleum (bp 40–60 °C)–ether (2:1)] (Found: M^+, 180.152. $C_{12}H_{20}O$ requires *M*, 180.151); ν_{max}(thin film)/cm^{-1} 3350br, 1450 and 990; λ_{max}(EtOH)/nm 227; δ_H(400 MHz) 6.05–5.95 (2 H, m, CH=C*HCH*=CH), 5.59 (1 H, dq, *J* 7 and 13.5, *CH*CH$_3$), 5.43 (1 H, dd, *J* 8 and 13.5, CHC*H*=CHCH=CH), 3.59 (1 H, dd, *J* 4.5 and 11, CH_2O), 3.41 (1 H, dd, *J* 5.5 and 11, CH_2O), 1.89–1.62 (5 H, m, cyclohexyl-CH), 1.72 (3 H, d, *J* 6.5, CHC*H*$_3$), 1.46 (1 H, br, OH) and 1.33–1.03 (5 H, m, cyclohexyl-CH); *m*/*z* (EI) 180 (M^+, 45%), 149 (30), 133 (30), 119 (35), 105 (55), 91 (80) and 79 (100).

***E*,*E*-1-(*trans*-2-Methoxymethylcyclohexyl)penta-1,3-diene 9 (X = OMe).** To a mixture of alcohol 1 (90 mg, 0.50 mmol), powdered sodium hydroxide (50 mg, 1.20 mmol) and triethylamine (2 mg) in light petroleum (bp 60–80 °C) (0.5 cm^3) stirred at room temp. under argon, was added dimethyl sulfate (70 mg, 0.55 mmol) and the resulting suspension was stirred at room temp. for 17 h and then heated at reflux for 24 h. The mixture was allowed to cool, light petroleum (bp 60–80 °C) was added and the organic layer was washed with water, dried and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with light petroleum (bp 40–60 °C)–ether (99:1) to afford the *diene* 9 (X = OMe) as a colourless oil (47 mg, 48%); R_f 0.60 [light petroleum (bp 40–60 °C)–ether (1:1)]; ν_{max}(thin film)/cm^{-1} 1445, 1385, 1190, 1120 and 995; λ_{max}(EtOH)/nm 227; δ_H(400 MHz) 6.05–5.92 (2 H, m, CH=CHCH=CH), 5.57 (1 H, dq, *J* 6.5 and 13.5, *CH*CH$_3$), 5.37 (1 H, dd, *J* 9 and 14.5, CHC*H*=CHCH=CH), 3.35 (1 H, dd, *J* 3 and 9, CH_2O), 3.27 (3 H, s, OMe), 3.09 (1 H, dd, *J* 7.5 and 9, CH_2O), 1.93–1.62 (5 H, m, cyclohexyl-CH), 1.73 (3 H, d, *J* 6.5, CHC*H*$_3$) and 1.37–1.01 (5 H, m, cyclohexyl-CH); *m*/*z* (EI) 194 (M^+, 25%), 162 (57), 149 (23), 147 (66), 133 (59), 125 (70), 105 (81), 91 (94) and 79 (100).

Diels–Alder reactions of dienes 1,9 (X = OMe) and 9 (X = H) with *N*-methylmaleimide

A solution of the diene (0.2 mmol) and *N*-methylmaleimide (2 mmol) in dry, degassed benzene (2 cm^3) was heated at reflux under argon for 19 h. The reaction mixture was allowed to cool and concentrated under reduced pressure. The residue was purified by short column chromatography on Kieselgel G

(Merck), followed by recrystallisation of the adducts from light petroleum (bp 40–60 °C). The adducts were obtained in 70–90% yield. Each diene gave a 1 : 1 ratio of two adducts (NMR of the crude product).

Adducts of diene 1 {3-[2-(hydroxymethyl)cyclohexyl]-*N*,6-dimethylcyclohex-4-ene-1,2-dicarboximides 10a and 10b}. The *more polar adduct* had mp 95–99 °C; R_f 0.10 [light petroleum (bp 40–60 °C)–ether (1 : 4)] (Found: C, 70.05; H, 8.8; N, 4.8. $C_{17}H_{25}NO_3$ requires C, 70.10; H, 8.60; N, 4.80%); ν_{max}/cm^{-1} 3540, 1760, 1670 and 1285, δ_H(400 MHz) 5.76 (1 H, dt, *J* 9 and 3, 3-H), 5.71 (1 H, dt, *J* 9 and 3, 2-H), 3.90 (1 H, t, *J* 10, CH_2OH), 3.70 (1 H, dd, *J* 10 and 5, CH_2OH), 3.32 (1 H, dd, *J* 8 and 6, 5-H), 3.05 (1 H, dd, *J* 8 and 7, 6-H), 2.87 (3 H, s, NCH_3), 2.61–2.54 (1 H, m, 4-H), 2.53–2.44 (1 H, m, 1-H), 2.39–2.25 (2 H, m, 1′-H, 2′-H), 1.62–1.52 (5 H, m, cyclohexyl-CH_2, OH), 1.51–1.43 (2 H, m, cyclohexyl-CH_2), 1.47 (3 H, d, *J* 7, 1-CH_3) and 1.40–1.30 (2 H, m, cyclohexyl-CH_2); *m*/*z* (EI) 291 (M$^+$, 17%), 261 (21), 191 (21), 179 (100) and 162 (79).

The *less polar adduct* had mp 140–144 °C; R_f 0.20 [light petroleum (bp 40–60 °C)–ether (1 : 4)] (Found: C, 69.95; H, 8.8; N, 4.8. $C_{17}H_{25}NO_3$ requires C, 70.10; H, 8.60; N, 4.80%); ν_{max}/cm^{-1} 3400br, 3320br, 1765, 1690 and 1285; δ_H(400 MHz) 5.83 (1 H, dt, *J* 9 and 3, 3-H), 5.62 (1 H, dt, *J* 9 and 3, 2-H), 3.74 (1 H, dd, *J* 11 and 5, CH_2OH), 3.70 (1 H, dd, *J* 11 and 7, CH_2OH), 3.32 (1 H, dd, *J* 5 and 8, 5-H), 3.01 (1 H, t, *J* 8, 6-H), 2.86 (3 H, s, NCH_3), 2.51–2.43 (1 H, m, 1-H), 2.35–2.28 (1 H, m, 4-H), 2.19–2.12 (1 H, m, 1′-H), 2.00–1.93 (1 H, m, 2′-H), 1.65–1.43 (9 H, m, cyclohexyl-CH_2, OH) and 1.41 (3 H, d, *J* 7, 1-CH_3); *m*/*z* (EI) 291 (M$^+$, 9%), 273 (26), 192 (28), 179 (100) and 162 (87).

Adducts of diene 9 (X = OMe) {3-[2-(methoxymethyl)cyclohexyl]-*N*,6-dimethylcyclohex-4-ene-1,2-dicarboximides 10a and 10b}. *One diastereoisomer* had mp 99–100 °C (Found: C, 70.8; H, 8.8; N, 4.5. $C_{18}H_{27}NO_3$ requires C, 70.80; H, 8.90; N, 4.60%); ν_{max}(dichloromethane)/cm^{-1} 1775, 1700 and 1425; δ_H(400 MHz) 5.79 (1 H, dt, *J* 3 and 9, 3-H), 5.59 (1 H, dt, *J* 9 and 3, 2-H), 3.44 (1 H, dd, *J* 7 and 9, C$H_2$$OCH_3$), 3.38 (1 H, dd, *J* 5 and 9, CH_2OMe), 3.32–3.29 (1 H, m, 5-H), 3.31 (3 H, s, OCH_3), 2.99 (1 H, t, *J* 7, 6-H), 2.86 (3 H, s, NCH_3), 2.50–2.43 (1 H, m, 1-H), 2.29–2.26 (1 H, m, 4-H), 2.16–2.10 (1 H, m, 1′-H), 2.10–1.95 (1 H, m, 2′-H), 1.62–1.18 (8 H, m, cyclohexyl-CH_2) and 1.40 (3 H, d, *J* 7, 1-CH_3); *m*/*z* (EI) 305 (M$^+$, 17%), 290 (5), 258 (13), 179 (13), 162 (63) and 45 (100).

The *second diastereoisomer* had mp 88–90 °C (Found: C, 70.5; H, 8.85; N, 4.6. $C_{18}H_{27}NO_3$ requires C, 70.80; H, 8.90; N, 4.60%); ν_{max}/cm^{-1} 1765, 1685 and 1190; δ_H(400 MHz) 5.78 (1 H, dt, *J* 3 and 9, 3-H), 5.67 (1 H, dt, *J* 3 and 9, 2-H), 3.63 (1 H, t, *J* 9, C$H_2$$OCH_3$), 3.38 (3 H, s, NCH_3), 3.23 (1 H, dd, *J* 6 and 8, 5-H), 3.03 (1 H, t, *J* 8, 6-H), 2.61–2.55 (1 H, m, 4-H), 2.50–2.43 (1 H, m, 1-H), 2.26–2.16 (2 H, m, 1′-H, 2′-H), 1.68–1.37 (8 H, m, cyclohexyl-CH_2) and 1.44 (3 H, d, *J* 7, 1-CH_3); *m*/*z* (EI) 305 (M$^+$, 25%), 273 (54), 192 (28), 178 (67), 162 (76), 147 (19), 105 (57) and 95 (100).

Adducts of diene 9 (X = H) [*N*,6-dimethyl-3-(2-methylcyclohexyl)cyclohex-4-ene-1,2-dicarboximides 10a and 10b]. The *first diastereoisomer* had mp 114–116 °C; R_f 0.60 (ether) (Found: C, 73.95; H, 9.05; N, 5.05. $C_{17}H_{25}NO_2$ requires C, 74.15; H, 9.15; N, 5.10%); ν_{max}/cm^{-1} 1765, 1700 and 1185; δ_H(400 MHz) 5.82 (1 H, dt, *J* 9 and 3, 3-H), 5.56 (1 H, dtd, *J* 9, 3 and 1, 2-H), 3.33 (1 H, dd, *J* 5 and 9, 5-H), 2.98 (1 H, t, *J* 8, 6-H), 2.86 (3 H, s, NCH_3), 2.48–2.43 (1 H, m, 1 H), 2.27–2.20 (1 H, m, 4-H), 2.17–2.10 (1 H, m, 1′-H), 1.86–1.80 (1 H, m, 2′-H), 1.66–1.53 (2 H, m, cyclohexyl-CH_2), 1.52–1.15 (6 H, m, cyclohexyl-CH_2), 1.40 (3 H, d, *J* 7.5, 1-CH_3) and 1.03 (3 H, d, *J* 7, 2′-H); *m*/*z* (EI) 275 (M$^+$, 11%), 179 (100), 163 (93), 112 (44) and 91 (66).

A sample enriched in the *second diastereoisomer* from **9** (X = H) had mp 58–63 °C; R_f 0.60 (ether) (Found: C, 73.9; H, 9.35; N, 4.85. $C_{17}H_{25}NO_2$ requires C, 74.15; H, 9.15; N, 5.10%); ν_{max}/cm^{-1} 1765 and 1705; δ_H(400 MHz) 5.81 (1 H, dt, *J* 9 and 3, 3-H), 5.67 (1 H, dt, *J* 9 and 3, 2-H), 3.20 (1 H, dd, *J* 7 and 8, 5-H), 3.01 (1 H, dd, *J* 7 and 8, 6-H), 2.58–2.40 (2 H, m, 1-H, 4-H), 2.08–1.95 (1 H, m, 1′-H), 1.80–1.70 (1 H, m, 2′-H), 1.69–1.55 (2 H, m, cyclohexyl-CH_2), 1.45 (3 H, d, *J* 7, 1-CH_3), 1.44–1.20 (6 H, m, cyclohexyl-CH_2) and 1.10 (3 H, d, *J* 7, 2′-CH_3); *m*/*z* (EI) 275 (M$^+$, 11%), 179 (99), 163 (100), 13 (37) and 97 (48).

Diels–Alder reaction of 1 with maleic anhydride

A solution of diene **1** (130 mg, 0.72 mmol) and maleic anhydride (700 mg, 7.2 mmol) in dry, degassed benzene (5 cm^3) was heated at reflux for 19 h under argon. The reaction mixture was allowed to cool and concentrated under reduced pressure. The residue was purified by short column chromatography on Kieselgel G (Merck) eluting with ethyl acetate–acetic acid (50 : 1), to afford *trans*-[2-(*E*,*E*-penta-1,3-dienyl)cyclohexyl]methyl hydrogen maleate **11** as a colourless oil (20 mg, 10%); δ_H(300 MHz) 12.0–10.0 (1 H, br s, CO_2H), 6.40 (2 H, ABq, *J* 9 and 18, =$CHCO_2$), 6.30–6.18 (1 H, m, diene-CH), 6.01–5.90 (1 H, m, diene-CH), 5.74–5.30 (2 H, m, diene-CH), 4.33 (1 H, dd, *J* 9 and 3, CH_2O), 1.98–1.02 (10 H, cyclohexyl-CH) and 1.75 (3 H, d, *J* 7, CH_3). To aid characterisation, this material was treated with an ethereal solution of diazomethane, to give the *methyl ester* of **11** as a colourless oil; ν_{max}(thin film)/cm^{-1} 1735, 1640, 1440, 1400, 1210, 1160 and 990; δ_H(300 MHz) 6.34–6.19 (1 H, m, =C*H*-C*H*=), 6.23 (2 H, s, $O_2CCH{=}CHCO_2$), 6.02–5.90 (1 H, m, =CH-CH=), 5.70–5.35 (2 H, m, 1-H, 4-H), 4.24 (1 H, dd, *J* 3 and 11, CH_2O), 3.94–3.85 (1 H, m, CH_2O), 3.78 (3 H, s, CO_2CH_3), 1.88–1.40 (6 H, m, cyclohexyl-CH), 1.72 (3 H, d, *J* 7, 5-CH_3) and 1.39–1.00 (4 H, m, cyclohexyl-CH); *m*/*z* (EI) 292 (M$^+$, 1%), 233 (1), 179 (2), 162 (88), 147 (75), 133 (80), 119 (77) 113 (78), 105 (89) and 91 (100).

Further elution afforded a 1 : 1 mixture of two stereoisomers of 3-methyl-5-oxo-3,4,4a,5,7,7a,8,9,10,11,11a,11b-dodecahydrodibenzo[*c*,*e*]oxepine-4-carboxylic acid **12** (70 mg, 33%) which were partially separated by fractional recrystallisation from light petroleum (bp 40–60 °C) and ether to afford one *diastereoisomer* of **12** mp 162–163 °C (Found: C, 68.95; H, 8.15. $C_{16}H_{22}O_4$ requires C, 69.00; H, 8.00%); ν_{max}/cm^{-1} 3700–2240br, 1735 and 1705; δ_H(400 MHz) 5.71 (1 H, ddd, *J* 3, 4 and 10, CH=C), 5.64 (1 H, dt, *J* 10 and 2, CH=C), 4.67 (1 H, dd, *J* 13 and 5, CH_2OH), 3.88 (1 H, d, *J* 13, CH_2OH), 3.62 (1 H, dd, *J* 5 and 9, 5-H), 3.06 (1 H, dd, *J* 5 and 7, 6-H), 2.75–2.69 (1 H, m, 1-H), 2.35–2.30 (1 H, m, 4-H), 2.16–2.11 (1 H, m, cyclohexyl-CH), 1.80–1.01 (10 H, m, cyclohexyl-CH, OH) and 1.32 (3 H, d, *J* 7, CH_3); *m*/*z* (EI) 278 (M$^+$, 10%), 260 (22), 232 (14), 187 (13), 161 (15), 138 (27), 105 (54) and 95 (100). The *second diastereoisomer* of **12** mp 199–201 °C (Found C, 69.0; H, 8.2. $C_{16}H_{22}O_4$ requires C, 69.00; H, 8.00%); ν_{max}/cm^{-1} 3340–2240br, 1720 and 1695; δ_H(400 MHz) 5.71 (1 H, dt, *J* 10 and 2, CH=C), 5.67–5.63 (1 H, m, CH=C), 3.99–3.92 (2 H, m, CH_2OH), 3.54 (1 H, t, *J* 3, CHCO), 3.21 (1 H, dd, *J* 3 and 9, CHCO), 2.98–2.89 (1 H, m, 1-H), 2.50–2.49 (1 H, m, 4-H), 1.72–1.22 (11 H, m, cyclohexyl-CH, OH) and 1.38 (3 H, d, *J* 7, CH_3); *m*/*z* (EI) 278 (M$^+$, 15%), 260 (24), 232 (14), 187 (14), 161 (15), 138 (28), 119 (21), 105 (52) and 96 (100).

Kinetic studies of Diels–Alder reactions of dienes 1, 9 (X = OMe) and 9 (X = H) with *N*-methylmaleimide

In a typical experiment, a solution of the diene (0.03 mmol) and *N*-methylmaleimide (3.7 mg, 0.03 mmol) in C_6D_6 (*ca.* 0.5 cm^3) was degassed by repeated freeze thaw cycles under reduced pressure and sealed in an NMR tube. The reaction mixture was maintained at a temperature of 120 ± 1 °C. The mixture was periodically cooled rapidly to room temp., and the progress of the reaction monitored by ^1H NMR (300 MHz).

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