# Asymmetric Induction in the Electrocyclisations of 1,3 Dipolar Intermediates: the 1.7 Cyclisation of Diene-conjugated Diazo-compounds to give 1H-2,3-Benzodiazepines[1]

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In the cyclisation of the diene-conjugated diazo compounds 4 to give the diastereoisomeric pair of 1H-2,3-benzodiazepines 7 and 8, alkyl and silyl ethers when present as the 'medium' sized group R^3, showed the opposite effect in controlling face selectivity to that of alkyl groups and the alkoxide anion. Thus, for example, when R^3 = OMe the diastereoisomer ratio (7:8) was 8:92 while in contrast when R^3 = O⁻ Li⁺ the ratio was 85:15. The relative configurations of the chiral centres in the products 7 and 8 were determined by X-ray crystallography and their ratio in the cyclisations was measured by ¹H NMR spectroscopy and by HPLC. The results are rationalised in terms of a helical transition state for the cyclisation and the steric and polar effects of the substituents.

The electrocyclisation of diene-conjugated 1,3-dipolar intermediates provide a powerful general synthetic route to seven-membered heterocyclic ring systems.[2] We have been concerned for some years with synthetic and mechanistic aspects of these reactions, in particular with the cyclisations of diazo compounds[3] and nitrile ylides[4] to give diazepines and azepines, respectively, and with the measurement of relative reactivity.[5] This is the full report of the first study of asymmetric induction in reactions of this type.[1] The reaction chosen for this investigation was the cyclisation of the 2-alkenylaryl diazo compounds 1 to give 1H-2,3-benzodiazepines 3 (Scheme 1).
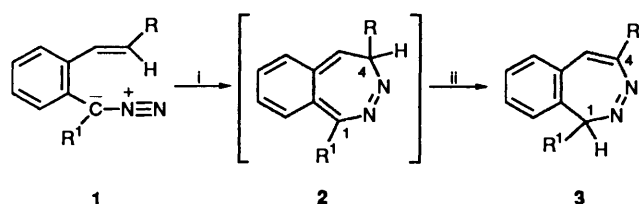
Scheme 1 i, 1.7 electrocyclisation; ii, [1,5]sigmatropic hydrogen shift

This is a high-yielding reaction which takes place in two-steps, firstly a 1.7 electrocyclisation to give the short-lived intermediate 2, and then a [1,5]sigmatropic hydrogen migration which converts 2 into the product 3. This paper is concerned with the effect on the course of this reaction of the presence of a chiral substituent at the cyclisation site, as shown in structure 4 in Scheme 2. Cyclisation of 4 can occur via the approach of the attacking nitrogen atom from either face of the terminal double bond so creating a new asymmetric centre at C-4 and leading to the formation of the diastereoisomeric intermediates 5 and 6. The suprafacial hydrogen migrations in the second step then transfer stereospecifically the chirality at C-4 to C-1 to give the product pair of diastereoisomers 7 and 8 which have the new chiral centre remote from the original stereogenic group. The objective was to vary the nature of the substituents R^2 and R^3 in 4 in order to determine the factors controlling diastereoselectivity in the cyclisation step. There is little previous work on asymmetric induction in electrocyclisations of any kind; however, much work has been done on the related cycloadditions of 1,3-dipolar intermediates, e.g. of nitrile oxides to alkenes 9,[6] (Scheme 3). Part of the objective therefore was to compare the effects of similar substituents on the two types of reaction.

Table 1 Substituents for compounds 4–8 and 10–15

| Comp.	R^2	R^3
a	Ph	Me
b	Bu^t	Me
c	Bu^t	Et
d	Ph	OMe
e	Bu^t	OMe
f	Bu^t	OSiBu^{t}Me$_2$
g	Bu^t	OCOPh
h	Bu^t	OH

Results and Discussion

The range of substituents studied is shown in Table 1. The smallest (S) substituent in the chiral group was always hydrogen; the largest (L) substituent R^2 was either phenyl or tert-butyl, and the medium-sized (M) substituent R^3 was varied over a range including alkyl, ether, ester and alcohol groups. In all cases the reactants were racemates, but for convenience and clarity their reactions will be discussed for the (R) enantiomer of the chiral substituent, which in all cases has its L, M and S groups disposed as shown in structure 4. The cyclisations of the racemate obviously produce the (R,R')-7 and (R,S')-8 diastereoisomers as shown in Scheme 2, and their enantiomers.

The diazo compounds 4 were generated by the Bamford–Stevens reaction from tosylhydrazones, as in the original synthetic work on these reactions.[7a,b]

*Synthesis of Diazo Compound Precursors.*—The tosylhydrazones 15 were prepared by the routes shown in Schemes 4 and 5. The 2-bromophenylethenes 11 were converted into the 2-acetylphenylethenes 14 by the three-step procedure shown (starting from aldehyde 10 and proceeding via compounds 12 and 13). Surprisingly, this proved to give higher yields and cleaner reactions than the more obvious alternative in which the Grignard reagent or lithium derivative of 11 was treated with acetaldehyde to give 13 directly. The low-temperature coupling reactions of the Grignard reagents of 11 with acetyl chloride were also unproductive. In cases a–c where R^3 was either methyl or ethyl, the bromo alkenes 11 were prepared by either Wittig or Wadsworth-Emmons reactions (Scheme 4) and in cases d–f, where R^3 is a methoxy or silyloxy group, they were prepared via Scheme 5. The more direct route to 14d–f illustrated in Scheme 6
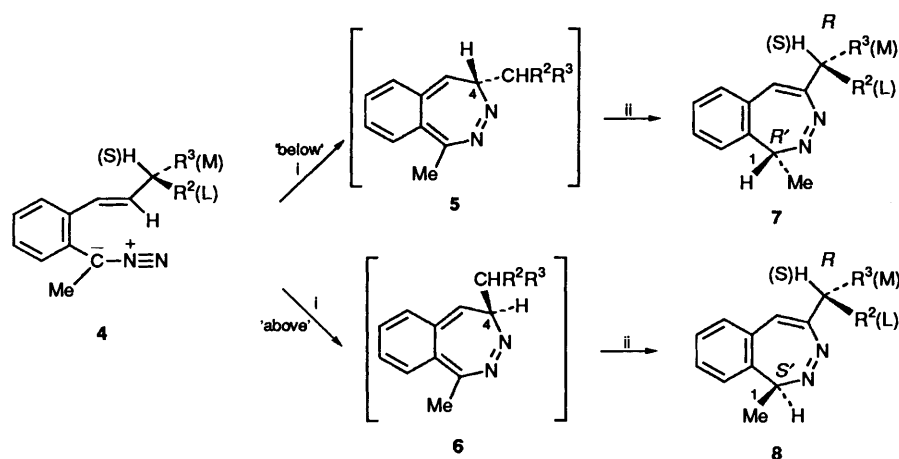
Scheme 2 i, 1.7 electrocyclisation; ii, [1,5]sigmatropic hydrogen shift
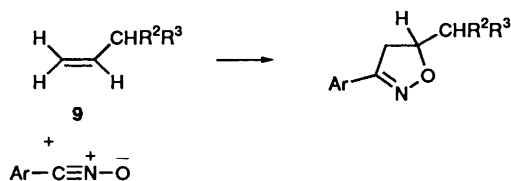
Scheme 3
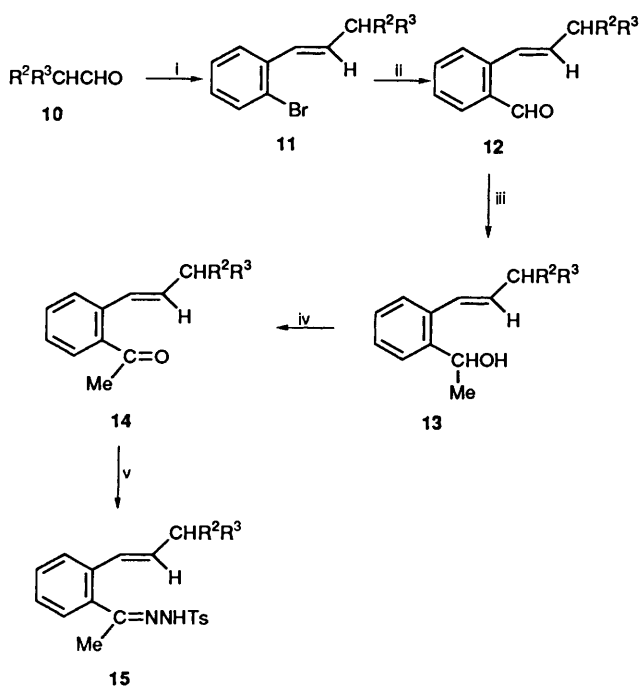
Scheme 4 i, Wittig reaction with 2-bromobenzyl bromide or Wadsworth–Emmons reaction with diethyl 2-bromobenzylphosphonate; ii, reaction of Grignard reagent or lithium derivative with DMF; iii, methyl magnesium iodide; iv, chromium trioxide–pyridine; v, 4-methylbenzenesulfonohydrazide

(from compound **19** via compound **20**) failed at the last step when it proved impossible to deprotect the acetyl group in **21** without effect on the allyl ether. Compound **14h**, where R³ is hydroxy, was prepared by the desilylation of **14f**; and benzoylated to give **14g**. The ketones **14a–g** were converted into their tosylhydrazone derivatives **15a–g** by the usual method of treating them with 4-methylbenzenesulfonohydrazide in the presence of a small amount of acid catalyst. In the case of the

allylic alcohol **14h** the use of acid was avoided in case of possible decomposition; the ketone was found to react slowly and cleanly under neutral conditions at room temperature. The tosylhydrazones were as usual formed as mixtures of *syn* and *anti* isomers. In some cases the mixed isomers crystallised without difficulty but in others the isomers had to be separated by chromatography before crystallisation could be induced. However in all cases the cyclisations were carried out with *syn/anti* mixtures as in the earlier synthetic work.[7a,b] The physical and spectroscopic properties of the synthetic intermediates and the tosylhydrazones are given in Tables 2 and 3, respectively.

Generation and Cyclisation of the Diazo Compounds **4**: *the Identification of the* 1H-2,3-*Benzodiazepines* **7** *and* **8**, *and the Determination of their Ratio.*—The diazo compounds **4a–g** were generated by the thermolysis of the sodium salts of the tosylhydrazones **15a–g** under aprotic conditions at *ca.* 80 °C. In the formation of the sodium salts a *ca.* 5% deficiency of sodium ethoxide was used in order to avoid the presence of excess of base which can cause isomerisation of the primary products, the 1*H*-2,3-benzodiazepines, into their 5*H* isomers.[7a] All the tosyl-hydrazones were decomposed in cyclohexane as solvent and in some cases the reactions were also carried out in 1,2-dimethoxyethane (DME) and *N,N*-dimethylformamide (DMF) in order to determine the effect of changing the solvent polarity. As usual for these reactions, the 1*H*-2,3-benzodiazepines (**7**/**8** Scheme 2) were formed in high yield in 2–6 h together with a white precipitate of sodium 4-methylbenzenesulfinate. The latter was removed either by filtration or by aqueous extraction and a sample of the crude reaction product mixture was retained for the determination of the product ratio (**7**:**8**) (see below). The diastereoisomeric benzodiazepines were then separated by chromatography and characterised by elemental analysis and/or accurate mass determination on the molecular ion (Table 4). Comparison of their ¹H NMR spectra, Table 5, with those obtained in earlier work[7a,b] confirmed their identity as the expected 1*H*-2,3-benzodiazepines. In cases **1a–e** and **g**, the relative configuration of the two chiral centres was determined by X-ray crystallography[8] for one of each pair of the diastereoisomers; these proved to be **7a**, **7b**, **7c**, **8d**, **8e** and **7g**. This method was not used in the case of the products **7f**/**8f** obtained from the cyclisation of the *tert*-butyldimethylsilyl ether **4f**; these were identified instead by comparison of the relative positions of the signals in their ¹H NMR spectra with those of the methoxy analogues **7e**/**8e** (see Table 5). The ratio of the products **7** and **8** was determined by ¹H NMR spectroscopy and confirmed in all cases except **7g**/**8g** by HPLC.
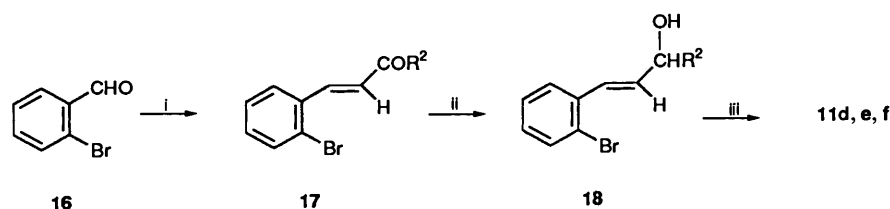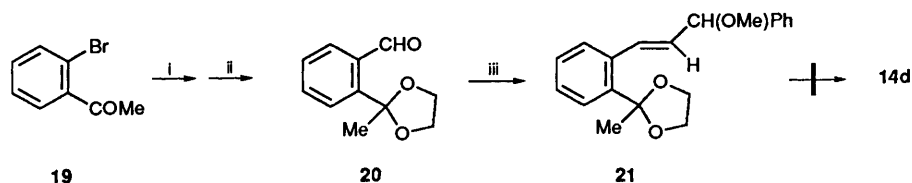
Scheme 5 i, Wadsworth–Emmons reaction with $R^2COCH_2P(O)(OEt)_2$; ii, sodium borohydride; iii, alkylation or silylation of OH

Scheme 6 i, $HOCH_2CH_2OH/H^+$; ii, reaction of Grignard reagent or lithium derivative with DMF; iii, steps i–iii of Scheme 5

Table 2 Yields and physical data on compounds 11a–f, 12a–f, 13a–f, 14a–h and 15a–h

Comp.	Yield (%)	Cryst. solv.[a]	M.p. or b.p./mmHg (°C)	Molecular formula	C(%) Found	C(%) Calc.	H(%) Found	H(%) Calc.	N(%) Found	N(%) Calc.	m/z (M⁺) Found	m/z (M⁺) Calc.
11a	44		140–142/0.5	$C_{16}H_{15}Br$	67.0	66.9	5.3	5.3			288.0334	288.0357
11b	88	b		$C_{14}H_{19}Br$							268.0655	268.0670
11c	65	b		$C_{15}H_{21}Br$							282.0816	282.0827
11d	95		147–150/0.1	$C_{16}H_{15}BrO$	63.6	63.6	5.1	5.0			304.0228	304.0287
11e	87		90–92/0.1	$C_{14}H_{19}BrO$							284.0608	284.0600
11f	100		110–113/0.01	$C_{19}H_{31}BrOSi$	59.2	59.7	8.2	8.2				
12a	86	b		$C_{17}H_{16}O$							236.1212	236.1201
DNP		E	168–169.5	$C_{23}H_{20}O_4N_4$	66.0	66.3	4.8	4.8	13.4	13.5		
12b	90		93–96/0.01	$C_{15}H_{20}O$	83.0	83.3	9.3	9.3			216.1512	216.1514
12c	94		104–106/0.01	$C_{16}H_{22}O$	83.4	83.4	9.6	9.6				
12d	76	b		$C_{17}H_{16}O_2$							252.1147	252.1150
12e	78		111–118/0.5	$C_{15}H_{20}O_2$							232.1470	232.1463
12f	90		146–148/0.05	$C_{20}H_{32}O_2Si$	72.6	72.2	10.0	9.7				
13a	96	b		$C_{18}H_{20}O$							252.1515	252.1514
13b	99	b		$C_{16}H_{24}O$							232.1826	232.1827
13c	96	b		$C_{17}H_{26}O$							246.1985	246.1984
13d	97	b		$C_{18}H_{20}O_2$							268.1461	268.1463
13e	98	b		$C_{16}H_{24}O_2$							248.1775	248.1776
13f	100	b		$C_{21}H_{36}O_2Si$							348.2484	348.2485[c]
14a	50	d										
DNP		E	103.5–105	$C_{24}H_{22}N_4O_4$	66.65	66.95	5.09	5.15	12.9	13.0		
14b	91		110–112/0.05	$C_{16}H_{22}O$	83.5	83.4	9.9	9.6			230.1674	230.1671
14c	86		108–111/0.01	$C_{17}H_{24}O$							244.1821	244.1827
DNP		E	180–181	$C_{23}H_{28}N_4O_4$	64.9	65.1	6.7	6.65	13.3	13.2		
14d	60	d		$C_{18}H_{18}O_2$							266.1300	266.1307
14e	77		102–104/0.05	$C_{16}H_{22}O_2$	78.2	78.0	9.1	9.0			246.1618	246.1620
14f	91		122–124/0.1	$C_{21}H_{34}O_2Si$							346.2328	346.2328[c]
14g	100		180–182/0.1	$C_{22}H_{24}O_3$	78.5	78.5	7.2	7.2			336.1724	336.1725
14h	80		119–121/0.1	$C_{15}H_{20}O_2$	77.8	77.5	8.7	8.7			232.1459	232.1463
15a[e]	44	B–P	94–95.5	$C_{25}H_{26}N_2O_2S$	71.6	71.7	6.2	6.3	6.7	6.7		
	23	B–P	104.5–105.5		71.6		6.2		6.7			
15b	94	E	121–122	$C_{23}H_{30}N_2O_2S$	69.6	69.3	7.8	7.6	7.05	7.0		
15c	81	E	131.5–132.5	$C_{24}H_{32}N_2O_2S$	69.6	69.9	7.75	7.8	6.8	6.8		
15d[e]	9	f	79.5–81									
	64	f	88–90	$C_{25}H_{26}N_2O_3S$	68.8	69.1	5.8	6.0	6.65	6.45		
15e[e]	20	f	78	$C_{23}H_{30}N_2O_3S$	66.7	66.6	7.6	7.3	6.4	6.8		
	60	f	48–49.5		66.4		7.3		7.0			
15f	70	E–P	128 (decomp.)	$C_{28}H_{42}N_2O_3SSi$	65.1	65.3	8.2	8.2	5.6	5.45		
15g[e]	9	f	62–63	$C_{29}H_{32}N_2O_4S$	68.5	69.0	6.4	6.4	5.5	5.55		
	84	f	79–80.5		68.5		6.3		5.5			
15h	83	f	62–63.5	$C_{22}H_{28}N_2O_3S$	66.0	66.0	7.35	7.05	6.5	7.0		

[a] B = Benzene, E = ethanol, P = light petroleum b.p. 60–80 °C. [b] Oil, not distilled. [c] FAB, thioglycerol. [d] Oil, purified by chromatography. [e] Syn and anti isomers. [f] Purified by chromatography but could not be crystallised.

In the NMR analyses, the peak area ratio of the 5-H signals of the two diastereoisomers, found in the δ 6–7 region, was normally used, together with the ratio of any other signals which were well enough resolved. The results are given in Table 6 and discussed in the next section. In order to be certain that the product ratios were determined by kinetic control and that compounds 7 and 8 did not interconvert under the reaction conditions, the product ratio was monitored by HPLC

Table 3 Spectroscopic data for compounds **11a–f, 12a–f, 13a–f, 14a–h** and **15a–h**

Comp.	Spectroscopic data[a]
11a	δ_H(200 MHz) 1.53 (d, J 7.0, Me), 3.72 (m, J 6.9, 1 H), 6.32 (dd, J 15.8 and 6.6, 2′-H), 6.85 (d, J 15.8, 1′-H), 7.0–7.6 (m, 9 H); m/z 288 (22%), 286 (27), 273 (16), 245 (14), 207 (12), 192 (31), 155 (14), 134 (16), 118 (100), 105 (70)
11b	δ_H(200 MHz) 0.93 (s, 9 H), 1.06 (d, J 6.9, 3′-Me), 2.15 (m, 3′-H), 6.09 (dd, J 15.6 and 9.0, 2′-H), 6.66 (d, J 15.6, 1′-H), 7.01–7.55 (m, 4-H); m/z 268 (9%), 266 (8), 211 (23), 130 (51), 128 (15), 57 (100)
11c	δ_H(200 MHz; C_6D_6) 0.86 (s, 9 H), 0.87–1.70 (m, Et and 1′-H), 5.75 (dd, J 15.6 and 9.9, 2′-H), 6.64–7.46 (m, 5 H); m/z 282 (16%), 280 (15), 223 (69), 145 (11), 144 (100), 129 (38), 115 (18)
11d	δ_H(80 MHz) 3.41 (s, OMe), 4.85 (d, J 6.9, 3′-H), 6.21 (dd, J 15.8 and 6.9, 2′-H), 6.93–7.60 (m, 10 H, ArH and 1′-H); $v_{max}{}^b$/cm^{-1} 1090 (C–O); m/z 304 (4%), 302 (4), 237 (4), 207 (19), 185 (20), 155 (11), 121 (54), 105 (100)
11e	δ_H(80 MHz) 0.98 (s, 9 H), 3.38 (s, OMe), 3.40 (d, J 6.7, 3′-H), 6.08 (dd, J 15.8 and 6.7, 2′-H), 6.87 (d, J 15.8, 1′-H), 6.90 (m, 4 H); $v_{max}{}^b$/cm^{-1} 1090 (C–O); m/z 284 (8%), 282 (6), 267 (13), 227 (64), 171 (13), 146 (46), 131 (100), 115 (89), 103 (83)
11f	δ_H(80 MHz) 0.04 (s, SiMe), 0.09 (s, SiMe), 0.94 (s, 18 H), 3.89 (d, J 7.2 and 1, 3′-H), 5.09 (dd, J 15.9 and 7.2, 1 H), 6.81 (d, J 15.9, 1 H), 7.04–7.60 (m, 4 H); m/z 327 (10%), 326 (15), 324 (15), 189 (7), 115 (15), 73 (26), 57 (100)
12a	δ_H(80 MHz) 1.50 (d, J 7.0, Me), 3.73 (m, 1 H), 6.32 (dd, J 15.7 and 6.8, 2′-H), 7.16–7.87 (m, 10 H, ArH and 1′-H), 10.28 (s, CHO); $v_{max}{}^b$/cm^{-1} 2720 (CHO), 1690 (C=O); m/z 236 (5%), 221 (7), 203 (18), 192 (39), 178 (28), 132 (73), 131 (100), 118 (80), 115 (35), 105 (70)
12b	δ_H(80 MHz) 0.95 (s, 9 H), 1.07 (d, J 7, 3′-Me), 2.16 (m, 3′-H), 6.07 (dd, J 15.7 and 8.9, 2′-H), 7.11 (d, J 15.7, 1′-H), 7.26–7.85 (m, 4 H), 10.03 (s, CHO); $v_{max}{}^b$/cm^{-1} 2740 (CHO), 1700 (C=O); m/z 216 (16%), 161 (9), 160 (68), 45 (100), 129 (15), 115 (28), 91 (30), 77 (15)
12c	δ_H(80 MHz) 0.92 (s, 9 H), 0.86–2.14 (m, Et and 3′-H), 5.88 (dd, J 15.6 and 9.6, 2′-H), 7.10 (d, J 15.6, 1 H), 7.24–7.87 (m, 4 H) 10.30 (s, CHO); $v_{max}{}^b$/cm^{-1} 2740 (CHO), 1695 (C=O); m/z 230 (16%), 174 (58), 146 (10), 145 (100), 131 (16), 119 (25), 100 (22), 77 (15)
12d	δ_H(80 MHz) 3.41 (s, OMe), 4.88 (d, J 6.7, 3′-H), 6.24 (dd, J 15.8 and 6.7, 2′-H), 7.16–7.85 (m, ArH and 1′-H, 10 H), 10.29 (s, CHO); $v_{max}{}^b$/cm^{-1} 2740 (CHO), 1695 (C=O), 1090 (C–O); m/z 252 (3%), 207 (44), 189 (60), 131 (42), 121 (27), 115 (100), 105 (15)
12e	δ_H(80 MHz) 0.94 (s, 9 H), 3.32 (s, OMe), 3.34 (d, J 7.9, 3′-H), 6.01 (dd, J 15.8 and 7.9, 2′-H), 7.23–7.85 (m, ArH and 1′-H, 5 H), 10.31 (s, CHO); $v_{max}{}^b$/cm^{-1} 2740 (CHO), 1695 (C=O), 1090 (C–O); m/z 232 (8%), 191 (26), 185 (8), 175 (100), 147 (50), 127 (51), 111 (98), 100 (28)
12f	δ_H(80 MHz) 0.03 (s, SiMe), 0.05 (s, SiMe), 0.92 (s, 18 H), 3.90 (d, J 7.3 and 1, 1 H), 6.10 (dd, J 15.8 and 7.3, 2′-H), 7.15–7.85 (m, 5 H), 10.31 (s, CHO); $v_{max}{}^b$/cm^{-1} 2740 (CHO), 1700 (C=O); m/z 274 (6%), 273 (23), 201 (23), 142 (11), 129 (9), 73 (100)
13a	δ_H(80 MHz) 1.33–1.68 (m, 2 × Me), 1.90 (br s, OH), 3.52–3.86 (m, 1 H), 5.19 (q, J 6.4, 1 H), 6.22 (dd, J 15.6 and 6.6, 2′-H), 6.75 (d, J 15.7, 1′-H), 7.09–7.57 (m, 9 H); $v_{max}{}^b$/cm^{-1} 3330 (OH); m/z 252 (12%), 234 (20), 219 (43), 208 (14), 193 (14), 178 (6), 147 (64), 134 (74), 105 (100)
13b	δ_H(80 MHz) 0.91 (s, 9 H), 1.04 (d, J 6.8, 3′-Me), 1.46 (d, J 6.4, Me), 2.33 (br s, OH), 2.11 (m, 1 H), 5.20 (q, J 6.4, 1 H), 5.98 (dd, J 15.6 and 8.8, 2′-H), 6.63 (d, J 15.6, 1′-H), 7.15–7.56 (m, 4 H); $v_{max}{}^b$/cm^{-1} 3340 (OH); m/z 232 (15%), 175 (12), 158 (84), 143 (100), 129 (50), 115 (45), 103 (12)
13c	δ_H(80 MHz) 0.93 (s, 9 H), 0.87–2.33 (m, 7 H), 1.49 (d, J 6.4, Me), 1.89 (br s, OH), 5.21 (q, J 6.4, 1 H), 5.80 (dd, J 15.5 and 9.5, 2′-H), 6.61 (d, J 15.5, 1′-H), 7.16–7.57 (m, 4 H); $v_{max}{}^b$/cm^{-1} 3340 (OH)
13d	δ_H(80 MHz) 1.45 (d, J 6.4 and 1, Me), 1.85 (br s, OH), 3.38 (s, OMe), 4.83 (d, J 6.7, 3′-H), 5.19 (q, J 6.4, 1 H), 6.14 (dd, J 15.8 and 6.7, 2′-H), 6.98 (d, J 15.8, 1′-H), 7.15–7.65 (m, 9 H); $v_{max}{}^b$/cm^{-1} 3420 (OH); m/z 286 (1%), 250 (9), 236 (10), 221 (46), 207 (60), 189 (77), 121 (58), 115 (100), 105 (64)
13e	δ_H(80 MHz) 0.94 (s, 9 H), 1.46 (d, J 6.5, Me), 2.09 (br s, OH), 3.30 (m, OMe and 3′-H), 5.19 (q, J 6.5, 1 H), 5.93 (dd, J 15.8 and 8, 2-H), 6.83 (d, J 15.8, 1′-H), 7.20–7.58 (m, 4 H); $v_{max}{}^b$/cm^{-1} 3380 (OH); m/z 248 (15%), 230 (10), 227 (19), 19 (57), 159 (64), 131 (100), 115 (27), 103 (7), 91 (10)
13f	δ_H(80 MHz) 0.03 (s, Me), 0.05 (s, Me), 0.91 (s, 18 H), 1.46 (d, J 6.4, Me), 1.69 (br s, OH), 3.85 (d, J 7.2 and 1, 3′-H), 5.19 (q, J 6.4, 1 H), 6.03 (dd, J 15.7 and 7.2, 2′-H), 6.76 (d, J 15.7, 1′-H), 7.18–7.49 (m, 4 H); $v_{max}{}^b$/cm^{-1} 3360 (OH); m/z 292 (19%), 291 (82), 161 (23), 131 (35), 115 (32), 75 (67)
14a	δ_H(80 MHz) 1.5 (d, J 7.0, Me), 2.54 (s, MeC=O), 3.69 (m, 3″-H), 6.24 (dd, J 15.8 and 6.8, 2″-H), 7.0 (d, J 15.8, 1″-H), 7.18–7.65 (m, 9 H); $v_{max}{}^b$/cm^{-1} 1685 (C=O); m/z 242 (17%), 216 (24), 201 (46), 164 (25), 144 (100), 130 (34), 114 (55), 105 (45)
14b	δ_H(80 MHz) 0.90 (s, 9 H), 1.04 (d, J 6.8, 3″-Me), 2.15 (m, 1 H), 2.53 (s, Me), 6.02 (dd, J 15.7 and 8.8, 2″-H), 6.97 (d, J 15.7, 1″-H), 7.12–7.61 (m, 4 H); $v_{max}{}^b$/cm^{-1} 1685 (C=O); m/z 230 (5%), 174 (8), 159 (43), 145 (100), 132 (19), 129 (26), 128 (30), 115 (43)
14c	δ_H(80 MHz) 0.86–1.86 (m, 6 H), 0.91 (s, 9 H), 2.54 (s, Me), 5.84 (dd, J 15.6 and 9.5, 2″-H), 6.75 (d, J 15.6, 1″-H), 7.20–7.62 (m, 4 H); $v_{max}{}^b$/cm^{-1} 1685 (C=O); m/z 244 (12%), 231 (80), 202 (8), 188 (26), 173 (33), 145 (100), 128 (18), 115 (20), 103 (12)
14d	δ_H(80 MHz) 2.53 (s, MeC=O), 3.40 (s, OMe), 4.82 (d, J 7.0, 3″-H), 6.10 (dd, J 15.8 and 7.0, 2″-H), 7.15 (d, J 15.8, 1″-H), 7.21–7.68 (m, 9 H); $v_{max}{}^b$/cm^{-1} 1685 (C=O), 1090 (C–O)
14e	δ_H(80 MHz) 0.93 (s, 9 H), 2.55 (s, MeC=O), 3.28 (d, J 8.1, 3″-H), 3.22 (s, OMe), 5.94 (dd, J 15.4 and 8.1, 2″-H), 7.03 (d, J 15.4, 1″-H), 7.30–7.59 (m, 4 H); $v_{max}{}^b$/cm^{-1} 1685 (C=O), 1090 (C–O); m/z 246 (5%), 231 (24), 227 (20), 215 (39), 199 (71), 189 (67), 145 (75), 131 (45), 115 (100), 103 (55)
14f	δ_H(80 MHz) 0.03 (s, SiMe), 0.05 (s, SiMe), 0.91 (s, 18 H), 2.55 (s, MeC=O), 3.84 (d, J 7.7, 3″-H), 6.02 (dd, J 15.8 and 7.7, 2″-H), 6.91 (d, J 15.8, 1″-H), 7.16–7.66 (m, 4 H); $v_{max}{}^b$/cm^{-1} 1690 (C=O); m/z 290 (26%), 289 (100), 221 (5), 203 (8), 145 (6), 129 (31), 115 (26), 75 (53)
14g	δ_H(80 MHz) 1.08 (s, 9 H), 2.50 (s, 3 H), 5.39 (d, J 7.2, 3-H), 6.08 (dd, J 15.8 and 7.2, 2-H), 7.12 (d, J 15.8, 1-H), 7.03–7.60 (m, 6 H), 8.06 (m, 2 H); $v_{max}{}^b$/cm^{-1} 1740 (ester C=O), 1685 (ketone C=O); m/z 336 (5%), 279 (18), 262 (15), 231 (17), 214 (40), 199 (25), 175 (38), 145 (60), 105 (100)
14h	δ_H(80 MHz) 0.95 (s, 9 H), 2.09 (s, OH), 2.53 (s, MeC=O), 3.92 (d, J 7.12 and 1,3″-H), 6.10 (dd, J 15.8 and 7.12, 2″-H), 7.00 (d, J 15.8 and 1,1″-H), 7.12–7.66 (m, 4 H); $v_{max}{}^b$/cm^{-1} 3540 (OH), 1680 (C=O); m/z 232 (1%), 19 (38), 175 (66), 145 (100), 131 (70), 115 (49), 103 (10)
15a	δ_H(80 MHz) 1.37 (d, J 7.0, Me), 2.00 (s, MeC=N), 2.40 (s, tosyl Me), 3.52 (m, J 7.0 and 6.3, 3″-H), 6.10 (dd, J 15.7 and 6.3, 2″-H), 6.44 (d, J 15.7, 1″-H), 7.04–7.95 (m, ArH and NH, 14 H); $v_{max}{}^c$/cm^{-1} 3205 (NH)
15b	δ_H(80 MHz) 0.85 (s, 9 H), (d, J 6.8, 3″-H), 1.93 (m, 3″-H), 2.09 (s, MeC=N), 2.41 (s, tosyl Me), 5.94 (dd, J 15.7 and 8.2, 2″-H), 6.30 (d, J 15.7, 1″-H), 7.01–7.98 (m, 8 H), 8.15 (br s, NH)
15c	δ_H(80 MHz) 0.76–1.67 (m, 6 H), 0.85 (s, 9 H), 2.08 (s, MeC=N), 2.41 (s, tosyl Me), 5.73 (dd, J 15.6 and 9.1, 2″-H), 6.25 (d, J 15.6), 7.00–7.97 (m, ArH and NH, 9 H); $v_{max}{}^c$/cm^{-1} 3210 (NH)
15d	δ_H(200 MHz) 2.05 (s, MeC=N), 2.39 (s, tosyl Me), 3.34 (s, OMe), 4.71 (d, J 7.3, 3″-H), 6.10 (dd, J 15.7 and 7.3, 2″-H), 6.73 (d, J 15.7, 1″-H), 7.07–7.45 (m, 11 H), 7.90 (d, J 8.3, ArH, 2 H), 8.28 (br s, NH); $v_{max}{}^c$/cm^{-1} 3220 (NH)
15e	δ_H(200 MHz) 0.87 (s, 9 H), 2.14 (s, 3 H), 2.44 (s, tosyl Me), 3.08 (m, 3″-H), 3.16 (s, OMe), 3.21 (s, OMe), 6.06 (m, 2″-H), 6.83 (m, 1″-H), 7.16–7.79 (m, ArH and NH, 9 H); δ_H(80 MHz) 0.88 (s, 9 H), 2.09 (s, MeC=N), 2.41 (s, tosyl Me), 3.13 (d, J 8.0, 3″-H), 3.21 (s, OMe), 5.93 (dd, J 15.9 and 8.0, 2″-H), 6.48 (d, J 15.9, 1″-H), 7.04–7.92 (m, ArH and NH, 9 H); $v_{max}{}^c$/cm^{-1} 3220 (NH)
15f	δ_H(80 MHz) 4.00 (s, SiMe), 4.04 (s, SiMe), 0.84 (s, 18 H), 2.06 (s, MeC=N), 2.41 (s, tosyl Me), 3.60 (d, J 7.2, 3″-H), 6.00 (q, J 15.9 and 7.2, 2″-H), 6.43 (d, J 15.9, 1″-H), 7.07–7.92, (m, ArH and NH, 9 H); $v_{max}{}^c$/cm^{-1} 3190, 3240 (NH, E and Z)
15g	δ_H(80 MHz) 1.01 (s, 9 H), 1.97 (s, MeC=N), 2.40 (s, tosyl Me), 5.22 (d, J 7.2, 3-H), 6.03 (dd, J 15.8 and 7.2, 2-H), 6.65 (d, J 15.8, 1-H), 7.10–8.10 (m, ArH and NH, 14 H); $v_{max}{}^c$/cm^{-1} 3320 (NH), 1740 (C=O)
15h	δ_H(200 MHz) 0.95 (s, 9 H), 1.84 (br s, OH), 2.12 (s, MeC=N), 2.40 (s, tosyl Me), 3.85 (d, J 6.5, 3″-H), 6.13 (dd, J 15.7 and 6.5, 2″-H), 6.73 (d, J 15.7, 1″-H), 7.13–7.47 (m, ArH, 6 H), 7.83 (m, ArH and NH, 3 H); v_{max}/cm^{-1} 3540 (OH), 3220 (NH)

[a] J Values given in Hz. [b] IR Spectra as thin films. [c] IR Spectra as Nujol mulls.

Table 4 Physical data for 1H-2,3-benzodiazepines 7a–h and 8a–h

Comp.	R^2	R^3	Cryst. solv.^{a}	M.P. (°C)	Molecular formula	C(%) Found	C(%) Calc.	H(%) Found	H(%) Calc.	N(%) Found	N(%) Calc.	m/z (M$^+$) Found	m/z (M$^+$) Calc.
7a	Ph	Me	H	63–64	C$_{18}$H$_{18}$N$_2$	82.6	82.4	7.0	6.9	10.8	10.7		
8a	Ph	Me	H	83–84		82.8		7.0		10.7			
7b	Bu^t	Me	H	102–103	C$_{16}$H$_{22}$N$_2$	79.0	79.3	9.0	9.2	11.5	11.6	242.1775	242.1783
8b	Bu^t	Me	H	90–90.5		79.3		9.1		11.5		242.2786	
7c	Bu^t	Et	H	113–114	C$_{17}$H$_{24}$N$_2$	79.8	79.6	9.75	9.4	10.9	10.9	256.1939	256.1939
8c	Bu^t	Et	H	110–110.5		79.6		9.6		10.9		256.1933	
7d	Ph	OMe	H	73.5–74.5	C$_{18}$H$_{18}$N$_2$O	77.8	77.7	6.5	6.5	10.1	10.1	278.1426	278.1419
8d	Ph	OMe	E	92.5–93.5		77.4		6.5		10.0		278.1429	
7e	Bu^t	OMe	H	88–89.5	C$_{16}$H$_{22}$N$_2$O	74.2	74.4	8.25	8.6	10.7	10.85	258.1730	258.1732
8e	Bu^t	OMe	H	107.5–108.5		74.6		8.7		10.8		258.1729	
7f	Bu^t	OSiBu^{t}Me$_2$	H	70.5–71.5	C$_{21}$H$_{34}$N$_2$OSi	70.0	70.3	9.7	9.6	7.2	7.8		
8f	Bu^t	OSiBu^{t}Me$_2$	M	98–99		70.5		9.65		7.7			
7g	Bu^t	OCOPh	E	165–166	C$_{22}$H$_{24}$N$_2$O$_2$	75.5	75.8	7.1	6.95	8.0	8.0		
8g	Bu^t	OCOPh	H	119–119.5		75.9		7.0		8.1			
7h	Bu^t	OH	H	105–106	C$_{15}$H$_{20}$N$_2$O	73.5	73.7	8.3	8.3	11.5	11.5		
8h	Bu^t	OH	H	110.5–111.5		73.5		8.2		11.5		244.1575	244.1576

^{a} B = benzene, E = ethanol, M = methanol

Table 5 ^{1}H NMR data for 1H-benzodiazepines 7a–h and 8a–h

Comp.	R^2	R^3	δ_H(J/Hz) 1-Me (d)	1-H (q)	5-H (s)	1′-H	R^2	R^3	ArH
7a	Ph	Me	2.26 (6.6)	2.69 (6.6)	6.32	4.40 (q, 7.2)	In ArH	1.73 (d, 7.2, 3 H)	7.23–7.57 (m, 9 H)
8a	Ph	Me	2.23 (6.6)	2.72 (6.6)	6.61	4.47 (q, 7.2)	In ArH	1.73 (d, 7.2, 3 H)	7.21–7.59 (m, 9 H)
7b	Bu^t	Me	2.12 (6.6)	2.70 (6.6)	6.18	2.34 (q, 7.2)	0.85 (s, 9 H)	1.71 (d, 7.2, 3 H)	7.08–7.30 (m, 4 H)
8b	Bu^t	Me	2.30 (6.6)	2.77 (6.6)	6.30	3.05 (q, 7.2)	0.97 (s, 9 H)	1.34 (d, 7.2, 3 H)	7.60–7.37 (m, 4 H)
7c	Bu^t	Et	2.30 (6.6)	2.83 (6.6)	6.41	2.57 (dd, 3, 12)	1.01 (s, 9 H)	1.59 (m, 1 H), 1.86 (m, 1 H), 0.95 (t, 7.3, 3 H)	7.32–7.64 (m, 4 H)
8c	Bu^t	Et	2.82 (6.6)	2.82 (6.6)	6.44	2.80 (m)	0.87 (s, 9 H)	1.90 (m, 1 H), 2.16 (m, 1 H), 1.11 (t, 7.0, 3 H)	7.34–7.60 (m, 4 H)
7d	Ph	OMe	2.31 (6.6)	2.86 (6.6)	6.37	5.61 (s)	In ArH	3.35 (s, 3 H)	7.31–7.60 (m, 9 H)
8d	Ph	OMe	2.18 (6.6)	2.58 (6.6)	6.70	5.70 (s)	In ArH	3.56 (s, 3 H)	7.22–7.65 (m, 9 H)
7e	Bu^t	OMe	2.33 (6.6)	2.78 (6.6)	6.64	3.73 (s)	1.00 (s, 9 H)	3.51 (s, 3 H)	7.25–7.64 (m, 4 H)
8e	Bu^t	OMe	2.31 (6.6)	2.73 (6.6)	6.75	4.41 (s)	0.85 (s, 9 H)	3.58 (s, 3 H)	7.36–7.70 (m, 4 H)
7f	Bu^t	OSiBu^t-Me$_2$	2.34 (6.6)	2.81 (6.6)	6.70	4.29 (s)	0.98 (s, 9 H)	1.09 (s, 9H), −0.08 (s, 3 H), 0.12 (s, 3 H)	7.37–7.62 (m, 4 H)
8f	Bu^t	OSiBu^t-Me$_2$	2.29 (6.6)	2.70 (6.6)	6.90	4.93 (s)	0.82 (s, 9 H)	1.04 (s, 9 H), 0.02 (s, 3 H), 0.09 (s, 3 H)	7.37–7.70 (m, 4 H)
7g	Bu^t	OCOPh	2.34 (6.6)	2.82 (6.6)	6.79	5.55 (s)	1.17 (s, 9 H)	In ArH	7.36–7.66 (m, 7 H), 8.14 (m, 2 H)
8g	Bu^t	OCOPh	2.31 (6.6)	2.80 (6.6)	6.75	6.26 (s)	1.08 (s, 9 H)	In ArH	7.33–7.67 (m, 7 H), 8.18 (m, 2 H)
7h	Bu^t	OH	2.34 (6.6)	2.72 (6.6)	6.65	4.31 (s)	0.88 (s, 9 H)	2.08 (br s, 1 H)	7.36–7.71 (m, 4 H)
8h	Bu^t	OH	2.31 (6.6)	2.73 (6.6)	6.94	4.97 (s)	0.92 (s, 9 H)	2.15 (br s, 1 H)	7.35–7.65 (m, 4 H)

throughout the reactions of 15a, 15b and 15d and found to be constant.

A slightly different method was used for the cyclisation of the tosylhydrazone 15h, which has R^3 = OH, so that the effect on face selectivity of the intact OH group and of the alkoxide ion O$^−$, could both be investigated. To determine the effect of the OH group, 1 mol equiv. of butyllithium was used in order to convert the tosylhydrazone into its lithium salt without deprotonating the hydroxy function. Cyclisation proceeded normally to give the diastereoisomers 7h and 8h in a 28 : 72 ratio which was shown by HPLC monitoring to be constant throughout the reaction. To determine the effect of the alkoxide ion, 1.95 equiv. of base was used, i.e. a 2.5% deficiency of the amount required for complete deprotonation of the tosylhydrazone NH and the OH group. This produced an inversion of the product ratio to 85:15; showing that the alkoxide ion O$^−$ has a strongly different effect to that of the intact OH group. Again the product ratio was constant throughout the reaction.

However, the use of a further small excess of base produced some unexpected effects. The use of 2.2 equiv., i.e. a 10% excess over the amount required to deprotonate both the tosylhydrazone and the OH groups, resulted in a remarkable enhancement of the products ratio 7h:8h to 97:3 and their isolation in a total yield of 71%, together with a low yield (7%) of the 5H-isomer 23. The formation of 5H isomers is a normal base-induced reaction of 1H-2,3-benzodiazepines,[7a] (Scheme 7) but its occurrence here raised the possibility that the increase in the proportion of compound 7h in the product might be due to the base-catalysed epimerisation of 8h at C-1. Monitoring a similar reaction by HPLC showed that the 7h:8h ratio did, in fact, change from 81:19 to 88:12 over 6 h. However, a control experiment in which compound 8h was treated with butyllithium under the same reaction conditions showed that, although it was converted steadily into the 5H isomer 23, it was not converted into its diastereoisomer 7h. It is concluded therefore that the enhancement of the proportion of 7h in the

Table 6 Yields and diastereoisomer ratios for the cyclisation of diazo compounds **4a–i** to give 1H-2,3-benzodiazepines **7a–h** and **8a–h**

Reactant 4[a]	R[2]	R[3]	Total yield (%)	7:8 Reaction solvent[b] C	DME	DMF	HPLC conditions[c] column; eluent
4a	Ph	Me	70	55:45	—	—	S; H–E, 95:5
4b	Bu^t	Me	85	58:42	55:45	57:43	S; H–E, 97.5:2.5
4c	Bu^t	Et	86	63:37	62 : 38	61:39	S; H–E, 97:3
4d	Ph	OMe	80	44:56	—	—	S; H–E, 92:8
4e	Bu^t	OMe	85	8 : 92	10:90	16:84	S; H–E, 95:5
4f	Bu^t	OSiBu^{t}Me$_2$	92	9 : 91	—	—	S; H–E, 96:4
4g	Bu^t	OCOPh	90	41:59	—	—	
4h	Bu^t	OH	80	—	28 : 72	—	G; A–T, 90:10
4i	Bu^t	O$^-$Li$^+$	70	—	85:15^d	—	

[a] Generated from tosylhydrazones **15**. [b] C = cyclohexane, DME = 1,2-dimethoxyethane, DMF = dimethylformamide. [c] S = 5 μm Hypersil (silica), G = porous graphitic carbon; H = hexane, E = diethyl ether, A = acetonitrile, T = tetrahydrofuran. [d] See text.
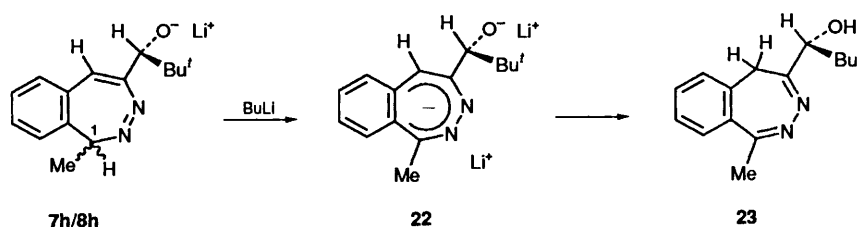

Scheme 7

product in the presence of excess of base is due, not to epimerisation, but to the preferential removal of the diastereoisomer **8h** via its isomerisation into the 5H isomer **23** (via intermediate **22**). The strong selectivity of this process in favour of **8h** may be due to assistance from the alkoxide in delivering the base to the 1-H site as illustrated in structure **24**. This can
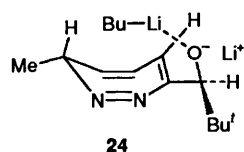

occur from a relatively unhindered conformation of **8h**, but for the diastereoisomer **7h** a similar conformation would be less accessible since it would bring the tert-butyl group into steric conflict with the adjacent hydrogen atom. The product **7h** was identified by converting it into its tert-butyldimethylsilyl ether which proved to be identical with the minor product **7f** from the cyclisation of the diazo compound **4f**. In confirmation it was found that **8f**, the major product from the cyclisation of **4f**, on fluorodesilylation gave a compound identical with **8h**.

Discussion of Selectivity.—It can be seen from the results shown in Table 6 that the nature of both the large group R[2] and of the medium-sized group R[3] have a strong influence both on the preferred face of attack on the double bond, and on the degree of selectivity obtained. In order to understand these effects it is necessary to know as much as possible about the transition state for the cyclisation step. We have suggested, on the basis of simple FMO theory and from observed substituent effects,[3,7b] that the transition state in electrocyclisations of this type is most likely helical in nature as depicted in structure **25**. This is supported by the results of ab initio (3-21G) calculations by Evanseck and Houk[9] on a simple unsubstituted

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$H_2C=CH-CH=CH-\overset{-}{C}H-N\overset{+}{\equiv}N$
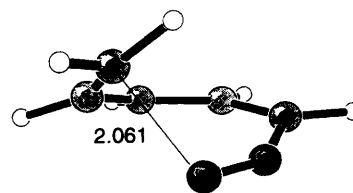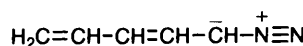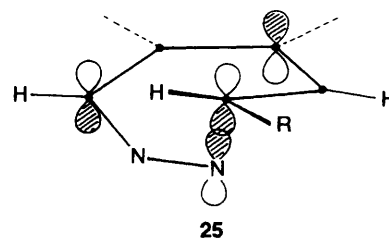
26

system which shows a transition state geometry as in structure **26**. In the following discussion we make the reasonable assumption that the more complicated system **4** will adopt a similar helical transition state as illustrated in **27**. In this representation, the terminal nitrogen of the diazo group is shown attacking the lower face of the alkene moiety. Partial views of this, and of the alternative diastereoisomeric transition state involving attack from the upper face of the alkene, are given in **28** and **29**. In both cases the chiral group is shown with the large (L) substituent in the position *anti* to the attacking N. It seems intuitively likely that this is the minimum energy conformation for this group; particularly so since Houk *et al.* have shown that this is true for the transition state for the nitrile

27

28   29
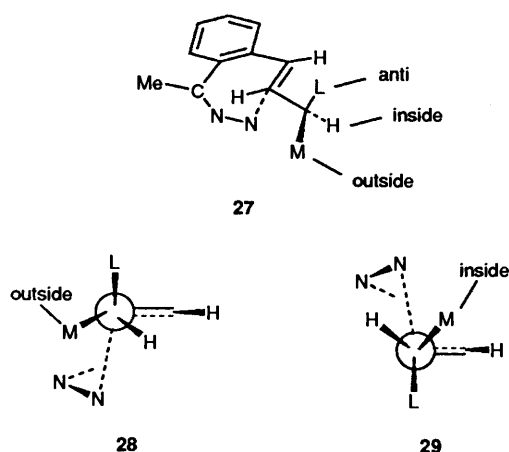
**Table 7** Favoured transition state **28** with M 'outside'

Entry	L(R²)	M(R³)	Ratio[a] 7:8
a	Ph	Me	55:45
b	Bu^f	Me	58:42
c	Bu^f	Et	63:37
d	Bu^f	O⁻Li⁺	85:15

[a] a, b, c in cyclohexane as solvent, d in DME.

Table 8 Favoured transition state **29** with M 'inside'

Entry	L(R²)	M(R³)	Ratio[a] 7:8
d	Ph	OMe	44:56
e	Bu^f	OMe	8:92
f	Bu^f	OSiMe₂Bu^f	9:91
g	Bu^f	OCOPh	41:59
h	Bu^f	OH	28:72

[a] d, e, f, g in cyclohexane as solvent, h in DME.

(a)

(b)

Fig. 1 Results of MM2 calculations on structure **30** for both enantiomers of the chiral substituent

30

oxide cycloaddition[6] shown in Scheme 3. However, in order to explore this more quantitatively, we have carried out molecular mechanics calculaions (MM2) on the simplified system shown in **30** using Houk's 'rigid' transition state method.[10] In these calculations all the atoms involved in bonding changes were fixed at the basic transition state geometry **26**, determined by Houk's *ab initio* calculations, and then the chiral group was rotated in 10° steps and its geometry fully optimised at each position (more detail is given in the Experimental section). The resulting steric energy plot is shown in Fig. 1(*a*) and that for the enantiomer of the chiral group (energetically identical to attack at the opposite face of the double bond) in Fig. 1(*b*). Since arbitrary values were used for the torsional constants involving the partly formed σ bond, these plots are valid only in a comparative sense and not for the absolute values of the steric energy. The results show that, as supposed above, the *tert*-butyl group is more or less *anti* to the partially formed C–N bond in the energy minima for both transition states. The *tert*-butyl group was used as the largest group in most of the cases studied and its bulk, and hence the strength of its preference for the *anti* position, is clearly important in achieving the high selectivity shown in some cases (Table 6, entry **e** *cf.* **d**). In describing and discussing the effects of the various substituents R² and R³ we adopt the 'inside'/ 'outside' designations for the small and medium sized groups, shown in structures **27–29**, as used by Houk *et al.* for cycloadditions.[6] The medium sized groups R³ thus fall experimentally into two groups, those shown in Table 7 in which the 'outside' position is favoured; and those in Table 8 which prefer to be 'inside'.
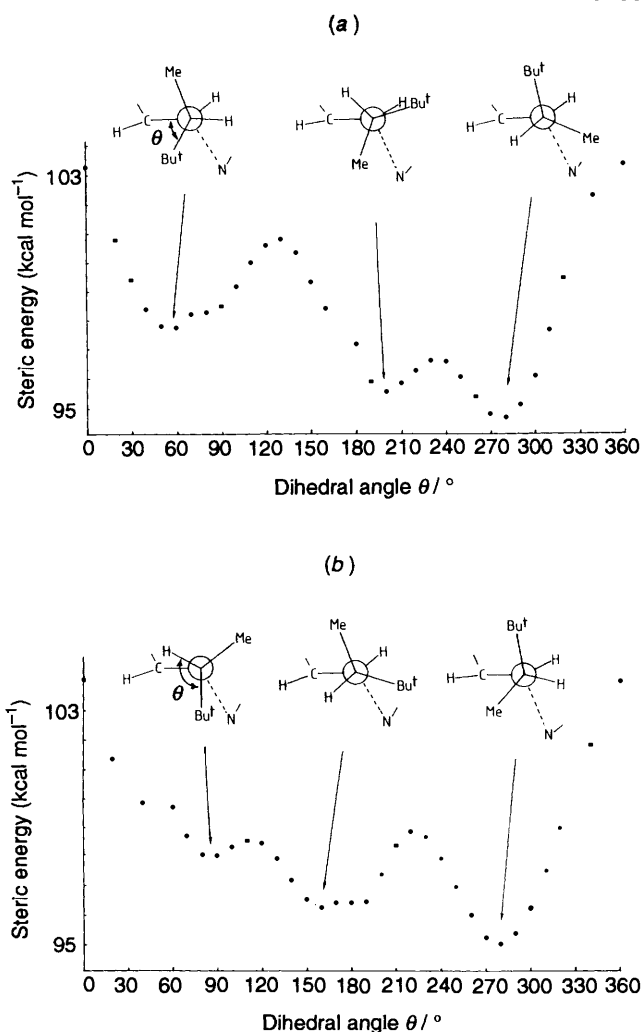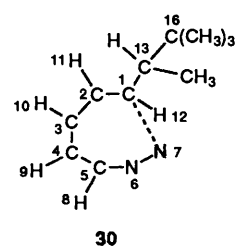
Cases where M(R³) = *alkyl*. The 'outside' preference of alkyl groups (entries **b**, **c**) is small for Me (58:42) but a little larger for Et (63:37) and thus seems most likely to result from a steric effect. That polar effects have minimal influence in this selectivity is supported by the observations that, in the cyclisations of **4b** and **4c**, the product ratio was unaffected by the nature of the solvent (Table 6). Remarkably, given the approximations involved, the MM2 calculation also shows [Fig. 1 (*a*) and (*b*)] that the best 'outside' transition state, **31**, for R³ = Me is *ca.* 0.2 kcal mol⁻¹ lower in energy than the alternative **32**[*]. These results therefore show that this electrocyclisation has an 'inside crowded' transition state, *i.e.* that on the basis of steric factors alone, the outside
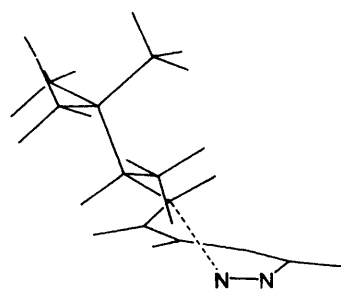
31
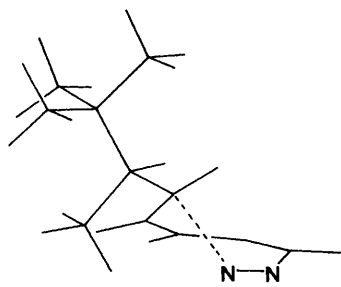
32

**Table 9** Fixed atom coordinates[a] (structure **30**) and atom types for MM2 calculations

| Atom	X	Y	Z	Type
C-1	−1.3999	−0.6661	0.5908	1
C-2	−1.4608	0.4745	−0.1675	2
C-3	−0.4534	1.4581	−0.2234	2
C-4	0.8634	1.2871	0.1115	2
C-5	1.5326	0.0609	0.2704	2
N-6	1.0186	−1.0502	−0.2188	37
N-7	0.0578	−1.6459	−0.4870	37
H-8	2.5445	0.0089	0.6020	5
H-9	1.4899	2.1586	0.1566	5
H-10	−0.7457	2.4268	−0.5850	5
H-11	−2.3381	0.6410	−0.7660	5
H-12	−0.7489	−0.7027	1.4438	5

[a] Coordinates in Å units.

position is favoured. It is interesting, but not unexpected, that this is different to the experimental and theoretical results[6] for the cycloaddition shown in Scheme 3. The electrocyclisations and cycloadditions are similar in that both are concerted reactions which involve bond formation between the terminal hetero-atom of the dipole and the trigonal carbon atom of a π-system; however the approach geometry is considerably different in the two cases. In the case of the cycloaddition, the inside position was thought to be 'less crowded' mainly because medium sized groups (M) there, as illustrated in **33**, have a lesser interaction with the incoming oxygen atom of the nitrile oxide than in the 'outside' position **34**.[6] In the helical transition state for electrocyclisation, the angle of approach of the diazo nitrogen atom is quite different and this apparently makes its steric interaction with the methyl group when 'outside', structure **31**, less important in a destabilising sense than the interaction of the methyl group, when in the 'inside' position as shown in structure **32**, with the hydrogen atom on the γ carbon.

Cases where M (R^3) = ether, ester or alcohol. In contrast, for all the cases where R^3 is an ether, ester or hydroxy group, these groups show a preference for the 'inside' position ranging from moderate to strong (Tables 6 and 8). The strongest 'inside' preference is that of the ethers, entry **e** where R^3 = OMe (8:92)
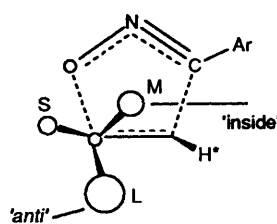

33
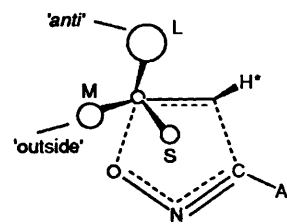
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and **f** where R^3 = OSiMe$_2$Bu^t (9:91). This parallels that observed[6] by Houk *et al.* for the methoxy group in the nitrile oxide cycloaddition (3:97). The explanations for the two different systems are closely related. In the electrocyclisation transition state **26**, there must be considerable p-orbital overlap throughout the π-system and hence the diene moiety must be electron deficient since it is subject to the electron withdrawing effect of the diazo group. The allylic oxygen in the ethers will tend to avoid the '*anti*' position in order to minimise electron withdrawal from the already electron deficient π-system and such groups will therefore prefer to be 'inside' or 'outside'. This electronic effect however does not appear to be very strong and, for good selectivity, *e.g.* entries **d/e**, requires to be reinforced by the presence of a bulky 'large' group with a strong 'steric' preference for the *anti* position. It has been suggested[6] that the strong 'inside' over 'outside' preference for the methoxy group in the cycloaddition transition states **33** and **34** occurs in order to minimise electrostatic repulsion between the allylic oxygen and the oxygen atom of the 1,3-dipole; this effect reinforces the natural steric preference for the 'inside' position in these reactions. Similarly, in the electrocyclistion transition states, the allylic oxygen is closer to the terminal nitrogen atom of the diazo group when it is 'outside' as in structure **28**, than when 'inside' as in structure **29**, and it seems likely that the relative destabilisation of the former also results from electrostatic repulsion between the two electronegative atoms. This effect must be considerable since, in this reaction, the 'electrostatic' preference for the 'inside' position is in opposition to, and clearly dominates over, the 'steric' preference of the medium sized groups for the 'outside' position.

The validity of this electrostatic repulsion argument has been tested in two ways; firstly by determining the effect on selectivity of changing the solvent polarity, and secondly by varying the substituents on the allylic oxygen in order to change its polar character. Increasing the solvent polarity in the cyclisation of **4e** (Table 6) resulted in a progressive decrease in selectivity; this is entirely consistent with the 'electrostatic' contribution, and hence the strength of the 'inside' preference is diminished due to the higher dielectric constant or by solvation in the more polar solvents. This effect may also be reinforced by an increase in the countervailing 'steric' contribution since any solvation would also increase the effective bulk of the methoxy group. Changing the nature of the allylic oxygen produced some interesting and in some cases unexpected effects, but none whose interpretation conflicts with the arguments above. The attachment of a benzoyl group, **4g** (Table 8), resulted in a marked decrease in the 'inside' preference (41:59) as expected since the negative character of the allylic oxygen is diminished by resonance in the ester group. The intact hydroxy group, **4h** (Table 8), showed an 'inside' preference (28:72) which is less than for the ethers **4e** and **4f**. This is at first sight rather surprising since the polar character of the oxygen should not be much different. The explanation probably lies in the intervention of another factor—hydrogen bonding between the hydroxy and diazo groups. This would selectively stabilise the 'outside' transition state **28** due to the closer proximity of the

groups and, acting in opposition to the N $\cdots$ O electrostatic repulsion, would therefore diminish the energy difference between the 'inside' and 'outside' transition states. The result from the cyclisation of **4i**, in which $R^3 = O^-$, was interesting and unexpected, Tables 6 and 7, entry i. It had been predicted from the model above that the presence of a full negative charge on the allylic oxygen would increase the N $\cdots$ O electrostatic repulsion and therefore make it show an even stronger 'inside' preference than the ethers **4e** and **4f**. In fact, the selectivity was strongly reversed and the alkoxide showed a ca. 85:15 preference for the 'outside' position. This result must be due to the participation of the alkoxide, not as a naked anion, but as an ion-pair with its lithium counterion. This close association with the lithium ion could favour the 'outside' preference in either or both of two ways. Firstly, by a steric effect: solvation of the lithium ion by 1,2-dimethoxyethane would effectively enlarge the size of the group and hence disfavour the more crowded 'inside' position. Secondly, by a polar effect in which the lithium ion acts as a Lewis acid and binds weakly to the diazo group in a bridging interaction as shown in structure **35**.
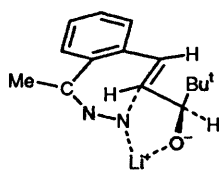
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As with the hydrogen bonding between the diazo and hydroxy groups discussed above, this would provide selective stabilisation of the 'outside' transition state **28** because of the closer proximity of the groups concerned. That diazo compounds can interact with lithium ions is already established as they are known to form carbenoid species.[11] It is hoped to carry out further study on the effects of other metal ions on the selectivity in this cyclisation.

The hydroxy group thus turns out to be a highly versatile 'medium' sized group in these reactions as can be used to promote strongly attack from either face of the double bond: its TBDMS ether **4f** gives a selectivity of 9:91 for one face and its lithium alkoxide **4h** gives 85:15 from the other. In the latter case, the kinetic selectivity can be enhanced, as discussed above, by the presence of a little extra base which selectively isomerises the minor product to the 5H-isomer **23**.

Experimental

NMR spectra were run as solutions in deuteriochloroform unless otherwise stated. Chemical shifts are recorded as δ values. J Values are given in Hz. In the ^{13}C spectra carbon multiplicity was established by single frequency off-resonance decoupling or by DEPT. Mass spectra were obtained using electron ionisation at 70 eV unless otherwise stated. Preparative chromatography was carried out either by the 'medium-pressure' technique[12] using Merck silica gel 60 (40–60 µm) in glass columns (1000 × 15 mm or 1000 × 25 mm), or by the 'dry-column flash' technique[12] using silica gel (15 µm, Fluka Kieselgel GF$_{254}$), and eluting solvents based on light petroleum b.p. 40–60 °C admixed with ether or ethyl acetate. Ether refers to diethyl ether. Evaporation of solvents indicates evaporation under reduced pressure using a rotary evaporator. All drying of solutions was done with anhydrous magnesium sulfate. The 'usual work-up' comprised the partitioning of the crude product between water and dichloromethane, separation, further extraction of the aqueous layer with dichloromethane, washing the combined organic solution with water, drying, filtration and removal of the solvent on a rotary evaporator.

Solvents, Reagents and Starting Materials.—Tetrahydrofuran (THF) was distilled under nitrogen from calcium hydride and lithium aluminium hydride immediately before use. Cyclohexane and 1,2-dimethoxyethane (DME) were distilled from calcium hydride as required. N,N-Dimethylformamide (DMF) was passed through an alumina column and distilled.

Diethyl 2-bromobenzylphosphonate. 2-Bromobenzyl bromide[13] (187.4 g, 0.75 mol) was added dropwise to triethyl phosphite (166.2 g, 1.0 mol) at 150 °C over 1 h. Ethyl bromide was collected by distillation during the addition and subsequent heating. The mixture was then heated to 160 °C for 4 h. After cooling, excess of triethyl phosphite was removed by evaporation under high vacuum to give a yellow oil (288 g). The crude reaction mixture was distilled to yield diethyl 2-bromobenzylphosphonate as a colourless oil (218 g, 94%), b.p. 130–134 °C/0.01 mmHg (Found: C, 42.7; H, 5.2%; m/z, 307.9976. $C_{11}H_{16}BrO_3P$ requires C, 43.0; H, 5.25%; M, 308.0001); δ_H(200 MHz) 1.18 (t, J 7, 2 × Me), 3.33 (d, J 22, PCH$_2$), 3.98 (q, J 7, 2 × CH$_2$) and 7.03–7.51 (m, ArH, 4-H); ν_{max}(film)/cm^{-1} 1255 (P=O).

The substituents R^2 and R^3 for compounds **7–8a–h** and **10–15a–h** are identified in Table 1.

Preparation of 1-(2-Alkenylphenyl)ethanones **14** and their Tosylhydrazones **15**.—The physical properties of compounds **11–13a–f** and **14–15a–h** are given in Table 2 and their spectroscopic properties in Table 3.

1-Bromo-2-alkenylbenzenes **11**.—(E)-1-Bromo-2-(3'-phenylbut-1'-enyl)benzene **11a**. A solution of sodium ethoxide [0.072 mol, from sodium (1.66 g)] in super dry ethanol (50 cm^3) was added over 0.5 h at room temperature to a stirred mixture of racemic 2-phenylpropionaldehyde (9.4 g, 0.07 mol) and 2-bromobenzyltriphenylphosphonium bromide[14] (35.8 g, 0.07 mol) in dry ethanol (50 cm^3). The mixture was stirred at room temperature for 1 h and then the solvent was evaporated. The usual work-up followed by chromatography (alumina, light petroleum) gave 1-bromo-2-(3'-phenylbut-1'-enyl)benzene (17.2 g, 86%) as a mixture of the (E) and (Z) isomers in the ratio 61:39 (GLC, 2.5% OV1, 200 °C) (Found: C, 66.6; H, 5.2%; m/z, 288.0338. $C_{16}H_{15}Br$ requires C, 66.9; H, 5.3%; M, 288.0338). This product in heptane (50 cm^3) containing iodine (100 mg) was heated under reflux for 24 h but GLC showed no change in the (E):(Z) isomer ratio. The isomers were inseparable by chromatography on silica. Crystallisation from light petroleum (b.p. 60–80 °C) at 0 °C gave the (Z)-isomer (27%), m.p. 65–67 °C (Found: C, 66.9; H, 5.3); δ_H(80 MHz) 1.36 (d, J 6.9, Me), 3.75 (m, J 6.9, 3'-H), 5.90 (dd, J 11.2 and 10.3, 2'-H), 6.47 (d, J 11.2, 1'H) and 7.04–7.64 (m, ArH, 9 H). The filtrate was shown by GLC (200 °C) to contain the isomers (E) and (Z) in the ratio 84:16. Evaporation of the solvent and distillation of the residue gave the pure (E)-isomer **11a** (44%).

(E)-1-Bromo-2-(3',4',4'-trimethylpent-1'-enyl)benzene **11b**. A solution of lithium diisopropylamide [prepared by the addition of butyllithium (1.35 mol dm^{-3} solution in hexane; 52 cm^3, 0.07 mol) to diisopropylamine (7.8 g, 0.077 mol) in THF (20 cm^3) at 0 °C] was added dropwise, with stirring, over 0.5 h to diethyl 2-bromobenzylphosphonate (21.5 g, 0.07 mol) in THF (70 cm^3) at −40 °C, under dry nitrogen. The reaction mixture was stirred at −40 °C for 0.75 h and then allowed to warm to 0 °C. 2,3,3-Trimethylbutanal[15] (7.3 g, 0.063 mol) in THF (50 cm^3) was then added with stirring and left for 1 h at 0 °C and then 2 h at 40 °C. After evaporation of the solvent the usual work-up using 10% w/v aqueous ammonium chloride (100 cm^3) gave an oil (18 g) which was purified by chromatography (alumina, light petroleum) to give the product **11b** (14.8 g, 88%).

(E)-1-Bromo-2-(3'-ethyl-4',4'-dimethylpent-1'-enyl)benzene **11c**. This was prepared as for **11b** using diethyl 2-bromobenzyl

phosphonate (19 g, 0.062 mol) and 2-ethyl-3,3-dimethyl-butanal[16,17] (7.2 g, 0.056 mol). After work-up, chromatography gave the product **11c** as a colourless oil (10.2 g, 65%).

(E)-1-*Bromo*-2-(3'-*methoxy*-3'-*phenylprop*-1'-*enyl*)*benzene* **11d**.—(a) (E)-1-*Bromo*-2-(3'-*phenyl*-3'-*oxoprop*-1'-*enyl*)*benzene* **17** (R² = Ph). A solution of diethyl phenacylphosphonate[18,19] (15.4 g, 0.06 mol) in THF (30 cm³) was added with stirring to sodium hydride (60% w/w dispersion in oil; 2.4 g, 0.06 mol) in THF (10 cm³) over 0.5 h under dry nitrogen. The mixture was stirred for 1 h at room temperature and then 2-bromo-benzaldehyde (10.6 g, 0.057 mol) in THF (30 cm³) was added to it over 0.1 h. The mixture was stirred for 1 h at room temperature, heated to reflux for 3 h and then stirred overnight at room temperature. After evaporation of the solvent the usual work-up gave a yellow oil (18 g). Crystallisation from hexane (−40 °C) gave (E)-1-bromo-2-(3'-phenyl-3'-oxoprop-1'-enyl)-benzene as a pale yellow solid (12.6 g, 77%), m.p. 46.5–47 °C (Found: C, 62.4; H, 3.7. C₁₅H₁₁BrO requires C, 62.7; H, 3.9%); δ_H(80 MHz) 7.12–8.21 (m, ArH and olefinic-H); ν_max(melt)/cm⁻¹ 1665 (C=O).

(b) (E)-1-*Bromo*-2-(3'-*hydroxy*-3'-*phenylprop*-1'-*enyl*)*benzene* **18** (R² = Ph). Sodium borohydride (2.26 g, 0.06 mol) was added in four portions over 1 h to (E)-1-bromo-2-(3'-phenyl-3'-oxoprop-1'-enyl)benzene (8.6 g, 0.03 mol) in THF (50 cm³) and methanol (25 cm³) at −30 °C. The mixture was stirred for 2 h at −30 °C, warmed to 0 °C and then water (5 cm³) was added to it. After evaporation of the solvent the usual work-up and crystallisation of the product from hexane gave (E)-1-bromo-2-(3'-hydroxy-3'-phenylprop-1'-enyl)benzene as a white solid (8.0 g, 92%), m.p. 72.0–73.0 °C (Found: C, 62.1; H, 4.5. C₁₅H₁₃BrO requires C, 62.3; H, 4.5%); δ_H(80 MHz) 2.22 (br s, OH), 5.41 (br d, J 6.3, 3'-H), 6.30 (dd, J 15.7 and 6.3, 2'-H) and 6.95–7.60 (m, ArH and 1'-H, 10 H); ν_max(melt)/cm⁻¹ 3360 (OH).

(c) (E)-1-*Bromo*-2-(3'-*methoxy*-3'-*phenylprop*-1'-*enyl*)*benzene* **11d**. (E)-1-Bromo-2-(3'-hydroxy-3'-phenylprop-1'-enyl)-benzene (7.2 g, 0.024 mol) in THF (70 cm³) was added dropwise over 0.25 h to a stirred suspension of sodium hydride (0.74 g, 0.03 mol) and methyl iodide (14.1 g, 0.1 mol) in THF (50 cm³) at 0–5 °C, under dry nitrogen. The mixture was stirred for 1.25 h at 5 °C and then allowed to warm to room temperature. Water (5 cm³) was added dropwise to the mixture and then the solvent was removed by evaporation. The usual work-up followed by distillation gave the product **11d** as a colourless oil (6.9 g, 95%).

(E)-1-*Bromo*-2-(3'-*methoxy*-4',4'-*dimethylpent*-1'-*enyl*)-*benzene* **11e**.—(a) (E)-1-*Bromo*-2-(4',4'-*dimethyl*-3'-*oxopent*-1'-*enyl*)*benzene* **17** (R² = Bu'). A solution of diethyl (3,3-dimethyl-3-oxobutyl)phosphonate[20,21] (9.0 g, 0.038 mol) in THF (30 cm³) was added with stirring to sodium hydride (0.96 g, 0.04 mol) in THF (20 cm³) over 1 h under dry nitrogen. The mixture was stirred for 1 h, then 2-bromobenzaldehyde (7.0 g, 0.038 mol) in THF (20 cm³) was added to it over 0.1 h and it was stirred at room temperature overnight. The mixture was heated to reflux for 2 h, cooled and then the solvent removed by evaporation. The usual work-up gave a yellow solid (10.3 g). Crystallisation from light petroleum (b.p. 60–80 °C) gave (E)-1-bromo-2-(4',4'-dimethyl-3'-oxopent-1'-enyl)benzene as a pale yellow solid (9.0 g, 89%), m.p. 65.0–66.5 °C (Found: C, 58.1; H, 5.65. C₁₃H₁₅BrO requires C, 58.4; H, 5.7%); δ_H(80 MHz) 1.22 (s, 9 H), 7.05 (d, J 15.5, 2'-H), 7.15–7.68 (m, ArH, 4 H) and 8.00 (d, J 15.5, 1'-H); ν_max(Nujol)/cm⁻¹ 1675 (C=O).

(b) (E)-1-*Bromo*-2-(3'-*hydroxy*-4',4'-*dimethylpent*-1'-*enyl*)-*benzene* **18** (R² = Bu'). Sodium borohydride (0.83 g, 0.022 mol) was added to a solution of (E)-1-bromo-2-(4',4'-dimethyl-3'-oxopent-1'-enyl)benzene (6.0 g, 0.022 mol) in THF (30 cm³) and methanol (15 cm³) at −25 °C. TLC (light petroleum-ether, 80:20) indicated that reduction was complete after 0.5 h. Water

(5 cm³) was added to it and the mixture was stirred at 0 °C for 0.5 h. After evaporation of the solvent the usual work-up and washing the combined organic layers with brine gave (E)-1-bromo-2-(3'-hydroxy-4',4'-dimethylpent-1'-enyl)benzene as a colourless oil (5.98 g, 99%) (Found: m/z, 270.0439. C₁₃H₁₇BrO requires M, 270.0443); δ_H(80 MHz) 0.97 (s, Bu'), 1.68 (d, J 3, OH), 3.94 (dd, J 7 and 3, 3'-H), 6.18 (dd, J 15.8 and 7, 1 H), 6.90 (d, J 15.8, 1'-H) and 6.91–7.54 (m, ArH, 4 H); ν_max(film)/cm⁻¹ 3360 (OH); m/z 270 (1%), 269 (2), 213 (13), 210 (100), 189 (41), 132 (78), 115 (9) and 103 (20). A 3,5-dinitrobenzoate derivative was prepared and recrystallised from isopropyl alcohol, m.p. 48.5–50 °C (Found: C, 51.9; H, 4.2; N, 6.05. C₂₀H₁₉BrN₂O₆ requires C, 51.85; H, 4.1; N, 6.1%).

(c) (E)-1-*Bromo*-2-(3'-*methoxy*-4',4'-*dimethylpent*-1'-*enyl*)-*benzene* **11e**. Sodium hydride (0.74 g, 0.031 mol) was added in three portions over 1.5 h, to a solution of (E)-1-bromo-2-(3'-hydroxy-4',4'-dimethylpent-1'-enyl)benzene (6.9 g, 0.026 mol) and methyl iodide (10.9 g, 0.077 mol) in THF (90 cm³) under dry nitrogen. The reaction mixture was stirred overnight in a water bath at room temperature. Water (2 cm³) was added carefully to hydrolyse excess of sodium hydride. After evaporation of the solvent the usual work-up gave a yellow oil (7.3 g) which was distilled to give the product **11e** as a colourless oil (6.3 g, 87%).

(E)-1-*Bromo*-2-[3'-(tert-*butyldimethylsilyloxy*)-4',4'-*dimethyl-pent*-1'-*enyl*]*benzene* **11f**.—*tert*-Butyldimethylsilyl chloride (15.4 g, 0.1 mol) was added to a solution of (E)-1-bromo-2-(3'-hydroxy-4',4'-dimethylpent-1'-enyl)benzene (23 g, 0.085 mol) and imidazole (14.45 g, 0.21 mol) in dry DMF (50 cm³) under dry nitrogen. The mixture was stirred for 18 h at room temperature. After evaporation of the solvent the usual work-up was followed by washing the combined organic solution with 1% v/v aqueous hydrochloric acid (100 cm³), saturated aqueous sodium hydrogen carbonate (100 cm³) and water (100 cm³). Drying, evaporation and distillation of the residue gave the product **11f** as a colourless oil (32.6 g, 100%).

(ii) 2-*Alkenylbenzaldehydes* **12**.—The preparation of compounds **12a** and **12b** are described in detail; compounds **12c, d, e, f** were prepared by the same general method as **12b**.

(E)-2-(3'-*Phenylbut*-1'-*enyl*)*benzaldehyde* **12a**. Butyllithium (1.50 mol dm⁻³ solution in hexane; 29 cm³, 0.044 mol) was added dropwise with stirring to (E)-1-bromo-2-(3'-phenylbut-1'-enyl)benzene **11a** (11.0 g, 0.038 mol) in THF (40 cm³) at −78 °C under dry nitrogen. The mixture was stirred for 0.5 h at −78 °C and then dry DMF (5.8 g, 0.08 mol) in THF (10 cm³) was added dropwise over 0.5 h. The mixture was stirred for 2 h at −78 °C and then overnight at room temperature. The mixture was poured into 25% w/v aqueous ammonium chloride (150 cm³), the organic phase was separated and the aqueous phase extracted with dichloromethane (3 × 50 cm³). The combined organic layers were washed with water (25 cm³), dried and then the solvent was evaporated to give a yellow oil (9.4 g). Flash chromatography, eluting with light petroleum–ether (99:1 to 98:2) gave the product **12a** as a colourless oil (7.9 g, 86%).

(E)-2-(3',4',4'-*Trimethylpent*-1'-*enyl*)*benzaldehyde* **12b**. A Grignard reagent was prepared by the addition of a solution of (E)-1-bromo-2-(3',4',4'-trimethylpent-1'-enyl)benzene **11b** (10.7 g, 0.04 mol) in THF (40 cm³) to magnesium (1.07 g, 0.044 mol) with stirring and under dry nitrogen. The temperature was maintained at 15–20 °C during the addition and then the mixture was stirred for 0.5 h at 15 °C and 1 h at room temperature. The mixture was cooled to 10 °C and dry DMF (6.6 g, 0.09 mol) in THF (40 cm³) was added dropwise over 0.25 h and then it was stirred overnight at room temperature. The reaction mixture was poured into 25% w/v aqueous ammonium chloride (100 cm³) and worked up as described for

compound 12a to give a yellow oil (9.0 g), which was distilled to give the product 12b (7.8 g, 90%).

1-(1'-Hydroxyethyl)-2-alkenylbenzenes 13.—Compounds 13a–f were prepared by the reaction of methylmagnesium iodide with the corresponding 2-alkenylbenzaldehyde 12 in ether. The reactions were quenched with aqueous ammonium chloride and worked up in the usual way to give the alcohols as oils which could not be distilled without decomposition. The crude products were characterised by accurate mass determination on their molecular ions (Table 2) and by their mass, IR and NMR spectra (Table 3).

(iv) *1-(2-Alkenylphenyl)ethanones* 14a–h *and their Tosylhydrazones* 15a–h.—Compounds 14a–f were prepared by the oxidation of the corresponding 1-(1'-hydroxyethyl)-2-alkenyl-benzene 13 with chromium trioxide in pyridine at 0 °C as described for the example 14b below. The tosylhydrazones were prepared by the admixture of warm (ca. 35 °C) ethanolic solutions of the ketone and 4-methylbenzenesulfonohydrazide, the latter acidified with hydrochloric acid [typically 4-methylbenzenesulfonohydrazide (2.5 g) in ethanol (20 cm^3) containing 5 drops of conc. hydrochloric acid], except in the case of 14h. The mixture was kept at room temperature and monitored by TLC until the ketone had been consumed, typically overnight. The products were purified by crystallisation where possible and by chromatography where suitable solvents could not be found. In some cases *syn* and *anti* forms of the tosylhydrazones were separated by 'dry-column flash' chromatography.

(E)-1-[2'-(3'',4'',4''-*Trimethylpent-1''-enyl)phenyl*]*ethanone* 14b. Chromium trioxide (7.8 g, 0.077 mol) was added during 0.25 h with stirring and ice cooling to pyridine (80 cm^3). (*E*)-1-Hydroxyethyl-2-(3',4',4'-trimethylpent-1'-enyl)benzene (6.21 g, 0.027 mol) was added, the mixture stirred at 0 °C for 0.5 h and then stirred at room temperature overnight. Ether (500 cm^3) was added and the brown precipitate filtered off and washed with ether (200 cm^3). The ethereal solution was washed with water (200 cm^3) and the solvent was removed by evaporation to give an orange oil (6.1 g). Distillation gave the product 14b as a pale yellow oil (5.6 g, 91%), b.p. 110–112 °C/0.05 mmHg.

(E)-1-[2'-(3''-*Hydroxy-4'',4''-dimethylpent-1''-enyl)phenyl*]-*ethanone* 14h. Tetrabutylammonium fluoride (1.0 mol dm^{-3} solution in THF; 53 cm^3, 0.053 mol) was added to a solution of (*E*)-1-[2'-(3''-*tert*-butyldimethylsilyloxy-4'',4''-dimethylpent-1''-enyl)phenyl]ethanone 14f (11.1 g, 0.032 mol) in THF (30 cm^3) with stirring at room temperature under dry nitrogen. The mixture was stirred for 40 h. After evaporation of the solvent the usual work-up, followed by washing the combined organic solutions with aqueous sodium hydrogen carbonate, gave a red oil (11.6 g). Dry-column flash chromatography, eluting with light petroleum (b.p. 40–60 °C)–ethyl acetate (88:12 to 80:20), gave a yellow oil (6.3 g). Distillation yielded the product 14h as a colourless oil (5.95 g, 80%).

(E)-1-(2'-*Acetylphenyl*)-4,4-*dimethylpent-1-en-3-yl benzoate* 14g. Benzoyl chloride (1.48 g, 0.01 mol) was added to a solution of (E)-1-[2'-(3''-hydroxy-4'',4''-dimethylpent-1''-enyl)phenyl]-ethanone 14h (1.63 g, 7 mmol) in dry pyridine (8 cm^3) with stirring at room temperature, under dry nitrogen. Water (8 cm^3) was added to it and the mixture was stirred for 1 h. Dichloromethane (40 cm^3) was added to the mixture and the aqueous layer separated and extracted with dichloromethane (2 × 20 cm^3). The combined organic solutions were washed with aqueous hydrochloric acid (1 mol dm^{-3}), saturated aqueous sodium hydrogen carbonate and water and dried and the solvent was evaporated to give an orange oil (2.3 g). Dry-column flash chromatography, eluting with light petroleum

(b.p. 40–60 °C)–ether (80:20), gave the product 14g (2.35 g, 100%).

Preparation and Thermal Decomposition of the Sodium Salts of the Tosylhydrazones 15 *to give the* 1H-2,3-*Benzodiazepines* 7 *and* 8.—The tosylhydrazones were dried overnight under high vacuum over phosphorus pentoxide. In the reactions of 15a–g, their sodium salts were prepared[7a,b] by the addition of a solution of the tosylhydrazone (in 5% mol excess) in dry DME or ethanol to an ethanolic solution of sodium ethoxide, freshly prepared by dissolving sodium in dry ethanol. The solution was then stirred in the dark for 0.5 h and the solvents were removed using a rotary evaporator under anhydrous conditions, with a water bath temperature below 40 °C. The solid sodium salt was then dried overnight in the reaction flask under high vacuum over phosphorus pentoxide. The reaction solvent was then added and the reaction mixture was heated in an oil bath, with magnetic stirring, under dry nitrogen, in the dark, until monitoring by TLC or HPLC showed that all the reactant had been consumed. In the reactions of 15a, 15b and 15d the ratio of the products 7 and 8 was monitored by HPLC throughout the reaction and found to be constant within experimental error. The reactions in DME and in cyclohexane were carried out at reflux temperature, and the reactions in DMF at an oil bath temperature of 80–85 °C. After cooling, the precipitated sodium 4-methylbenzenesulfinate was removed either by (a) filtration of the reaction mixture through Celite, followed by evaporation of the solvent to give the products, or (b) evaporation of the solvent on a rotary evaporator, addition of water, extraction of the organic product into dichloromethane, drying and evaporation. The ratio of the diastereoisomers 7 and 8 in the crude reaction mixture was determined by ^{1}H NMR spectroscopy and by HPLC, the results are given in Table 6. In the NMR method, the ratio was calculated using the integral signals of the C-5 hydrogen found in the δ 6-7 region. The conditions for the HPLC separations are given in Table 6. Small samples of the diastereoisomeric diazepines were then separated by medium-pressure chromatography; their physical properties are given in Table 4 and their spectra in Table 5.

Cyclisation of the Tosylhydrazone 15h.—This reaction was carried out using various amounts of butyllithium as base.

(i) *Using 2.2 equiv. of base.* (a) Butyllithium (1.45 mol dm^{-3} solution in hexane; 1.52 cm^3 2.2 mmol) was added dropwise over 10 min to the tosylhydrazone (0.40 g, 1 mmol) in dry DME (25 cm^3) at 0 °C under nitrogen. The reaction mixture was allowed to reach room temperature and then boiled under reflux for 4 h. Work-up as described above gave a brown oil (0.31 g). The diastereoisomer ratio 7h:8h was found to be 97:3 (by ^{1}H NMR spectroscopy). Dry-column flash chromatography, eluting with light petroleum–ether (80:20) gave a yellow solid (0.177 g, 72%). Recrystallisation from hexane gave 1-methyl-4-(1'-hydroxy-2',2'-dimethylpropyl)-1H-2,3-benzodizepine 7h as a yellow solid (0.13 g, 53%).

(b) A similar reaction using 15h (0.30 g, 0.75 mmol) and butyllithium (1.42 mol dm^{-3} in hexane; 1.14 cm^3, 1.65 mmol) in DME 20 cm^3, was carried out for 6 h during which the product ratio 7h:8h was monitored by HPLC. The usual work-up followed by dry-column flash chromatography, eluting with light petroleum–ether (80:20) gave a mixture of the diastereoisomeric 1-methyl-4-(1'-hydroxy-2',2'-dimethylpropyl)-1H-2,3-benzodiazepines 7h and 8h as a yellow oil (0.13 g, 71%) and 1-methyl-4-(1'-hydroxy-2',2'-dimethylpropyl)-5H-2,3-benzodiazepine 23 as white crystals (12 mg, 7%), m.p. 134.5 °C (from hexane) (Found: C, 73.9; H, 8.5; N, 11.5. C$_{15}$H$_{16}$N$_2$O requires C, 73.7; H, 8.3; N, 11.5%); δ$_H$(200 MHz) 1.02 (s, Bu^t), 1.06 (s, Bu^t) (ratio 1:2.6), 2.50 (s, 1-Me), 2.53 (s, 1-Me) (ratio 1:2.4), 2.84 (d, J_{AB} 12.3, 5-H$_B$), 3.04 (d, J_{AB} 12.7, 5-H$_B$) (ratio

Table 10

t/min	23:7h:8h
0	0:2:98
15	49:1:50
30	66:2:32
60	81:2:17
90	85:2:13
120	89:2:9
180	91:2:6
240	94:2:4

1:2.4), 3.35 (d, J_{AB} 12.7, 5-H_A), 3.74 (d, J_{AB} 12.3, 5-H_A) (ratio 2.4:1), 3.92 (s, 2'-H), 3.94 (s, 2'-H) (ratio 2.6:1) and 7.16–7.54 (m, 4 H, ArH); ν_{max}(Nujol)/cm^{-1} 3300 (OH); m/z 244 (4%), 229 (5), 188 (88), 172 (100), 159 (85), 144 (10), 130 (19), 116 (22) and 89 (14). The ratio of the products 23:7h:8h changed smoothly during the reaction from 1.5:80:18.5 after 15 min to 7:82:11 after 6 h.

(ii) *Using 1.95 equiv. of base.* A similar experiment using butyllithium (1.42 mol dm^{-3} in hexane; 1.37 cm^3, 1.95 mmol) and the tosylhydrazone **15h** (0.40 g, 1 mmol) in DME (25 cm^3) gave after work-up and chromatography a mixture of **7h** and **8h** as a yellow oil (0.17 g, 70%). HPLC monitoring showed the ratio of **7h:8h** to be 76:24 after 15 min but constant at 84:16 over the next 4 h.

(iii) *Using 1 equiv. of base.* A similar experiment using butyllithium 1.40 mol dm^{-3} in hexane, 0.72 cm^3, 1 mmol) and the tosylhydrazone **15h** (0.40 g, 1 mmol) in DME (20 cm^3) for 2.25 h gave, after work-up and chromatography a mixture of **7h** and **8h** as a yellow oil (0.196 g, 80%). HPLC monitoring showed that the ratio **7h:8h** was constant at 28:72 throughout.

(iv) *Using 2.8 equiv. of base in the presence of the benzodiazepine* **8h**. Butyllithium (1.45 mol dm^{-3} in hexane; 0.87 cm^3, 1.26 mmol) was added dropwise over 10 min to the tosylhydrazone **15h** (0.18 g, 0.45 mmol) in DME (11 cm^3) at 0 °C under nitrogen. The mixture was heated to 60 °C and then 1-methyl-4-(1'-hydroxy-2',2'-dimethylpropyl)-1H-2,3-benzo-diazepine **8h** (62 mg, 0.25 mmol) in DME (2 cm^3) was added in one portion. The mixture was then heated under reflux for 5 h. The usual work up gave the crude product as a brown oil (0.20 g), in which the benzodiazepine **8h** could not be detected by NMR. The usual work-up and chromatography gave 1-methyl-4-(1'-hydroxy-2',2'-dimethylpropyl)-1H-2,3-benzodiazepine **7h** (65 mg), m.p. 105–106 °C, recovered tosylhydrazone as a brown oil (35 mg) and 1-methyl-4-(1'-hydroxy-2',2'-dimethylpropyl)-5H-2,3-benzodiazepine **23** (36 mg), m.p. 134–135.5 °C.

Miscellaneous Reactions of the Benzodiazepines **7h**, **8h** *and* **8f**.—(i) *Base induced isomerisation of* 1-*methyl*-4-(1'-*hydroxy*-2',2'-*dimethylpropyl*)-1H-2,3-*benzodiazepine* **8h** *into the* 5H *isomer* **23**. Butyllithium 1.42 mol dm^{-3} in hexane; 0.26 cm^3, 0.37 mmol) was added dropwise to 1-methyl-4-(1'-hydroxy-2',2'-dimethylpropyl)-1H-2,3-benzodiazepine **8h** (90 mg, 0.37 mmol) (containing *ca.* 2% of the diastereoisomer **7h**) and diphenyl ether (225 mg) (as HPLC internal standard) in DME (10 cm^3) at 0 °C, under nitrogen. The mixture was then heated under reflux with HPLC monitoring for 4 h. The usual work up and chromatography, eluting with light petroleum–diethyl ether (80:20 to 50:50) gave recovered **7h/8h** as a yellow oil (5 mg, 6%) and 1-methyl-4-(1'-hydroxy-2',2'-dimethylpropyl)-5H-2,3-benzodiazepine **23** (60 mg, 66%), m.p. 134–136 °C. The ratios 23:7h:8h are given in Table 10. The total benzodiazepine peak area relative to the internal standard diminished to 64% of its initial value during the reaction.

(ii) *Conversion of* **7h** *into* **7f**. *tert*-Butyldimethylsilyl chloride (0.16 g, 1 mmol) was added to a solution of 1-methyl-4-

(1'-hydroxy-2',2'-dimethylpropyl)-1H-2,3-benzodiazepine **7h** (0.214 g, 0.88 mmol) and imidazole (60 mg, 0.88 mmol) in dry DMF (0.5 cm^3) under nitrogen. The mixture was then stirred for 48 h at room temperature and worked up in the usual way. The combined organic solutions were washed with aqueous hydrochloric acid (1 mol dm^{-3} 2 × 10 cm^3), saturated aqueous sodium hydrogen carbonate (10 cm^3) and water (10 cm^3), dried and the solvent was evaporated to give a yellow oil (0.24 g). Dry-column flash chromatography, eluting with light petroleum–ether (90:10) gave (i) 1-methyl-4-(1'-*tert*-butyldimethylsiloxy-2',2'-dimethylpropyl)-1H-2,3-benzodiazepine **7f** as a yellow solid (0.14 g, 45%), m.p. 70.5–71.5 °C (from methanol) and (ii) 1-methyl-4-(1'-hydroxy-2',2'-dimethylpropyl)-1H-2,3-benzodi-azepine **7h** (20 mg, 10%), m.p. 105–106 °C (from hexane).

(iii) *Conversion of* **8f** *into* **8h**. Tetrabutylammonium fluoride 1.0 mol dm^{-3} in THF; 1.75 cm^3 1.75 mmol) was added to a solution of 1-methyl-4-(1'-*tert*-butyldimethylsilyloxy-2',2'-di-methylpropyl)-1H-2,3-benzodiazepine **8f** (0.25 g, 0.7 mmol) in THF (0.75 cm^3) with stirring at 0 °C under nitrogen. The mixture was stirred at room temperature for 2 h. The usual work up and chromatography, eluting with light petroleum–ether (75:25) gave 1-methyl-4-(1'-hydroxy-2',2'-dimethylpropyl)-1H-2,3-benzodiazepine **8h** (0.12 g, 70%) (for properties see Tables 5 and 6).

Molecular Mechanics Calculations.—These were carried out using the MM2(87) version of the Allinger Molecular Mechanics II System[22] obtained from the Quantum Chemistry Program Exchange. The molecule studied is shown in structure **30**; the atoms undergoing bonding changes were fixed at the coordinates shown in Table 9, *i.e.* the transition state geometry determined by *ab initio* calculations.[9] All other natural bond lengths and angles are standard MM2 values. Atom C-1 shows considerable pyramidalisation in the transition state and was treated as product-like, *i.e.* MM2 type 1; atoms C-2–C-5 as type 2, and the nitrogen atoms as type 37. The torsional parameters for the interactions between the groups on C-13 and the partly formed bond C-1–N-7 were set at half the values for the full bond of the same type. A full steric energy minimis-ation was carried out for each rotational position of the 2–1–13–16 dihedral. The calculations were carried out for both enantiomers of the exocyclic chiral substituent with the results shown in Fig. 1.

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