Substituent Effects on the Reactivity of 2-Morpholinobutadienes in the Presence of Dienophiles

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2-Morpholinobutadienes (**1**) behave like typical enamines in their reactions with dimethyl acetylenedicarboxylate (**2**), β-nitrostyrene (**3**), diethyl 2-oxomalonate (**4**), and benzaldehyde (**5**). The nature of the resulting products is strongly dependent on the conformation which the 2-aminobutadienes (**1**) can adopt, as a function of the substituents. Only when the substituents can participate in the course of the reaction may the 2-morpholinobutadienes behave like a 4π-system in a concerted process.

The cross-conjugated enamines are a class of compounds scarcely described in the literature. Their chemical behaviour is not well known,[1] in spite of the fact that they are very highly functionalized compounds and can be expected to react in a variety of ways. For some years we have been interested in the catalytic amination of acetylenic triple bonds. This process yields different enamine derivatives under very mild conditions, and usually at room temperature.[2] When the reactions were carried out using conjugated enynes, 2-aminobutadienes (**1**) could be obtained exclusively under appropriate conditions.[3]

The easy preparation of 2-aminobutadienes (**1**) led us to study their chemical properties in order to test their ability to behave either as typical enamines or as 4π compounds in cycloaddition reactions. Recently, Koikov *et al.*[4] showed on the basis of model MINDO/3 calculations that the nucleophilicity of cross-conjugated enamines is greater than that of simple enamines. In addition, these calculations predicted that the conformational characteristics of the dienamines have a significant effect on their reactivity.

In the present work, the beaviour of five different 2-morpholinobutadienes (**1**) towards different dienophiles is described.

The substituents at positions 3 and 4 of the dienes were chosen so that they could play a role in determining the conformation of the system (*s-cis* or *s-trans*) and also participate directly in the course of the reaction (**1a** and **1c**).

Results and Discussion

Reaction of 2-Morpholinobutadiene Derivatives (**1a, b**) *with Dimethyl Acetylenedicarboxylate* (**2**), *β-Nitrostyrene* (**3**), *Diethyl 2-Oxomalonate* (**4**) *and Benzaldehyde* (**5**).—Treatment of 2-morpholinobutadienes (**1a, b**) with the dienophiles (**2**), (**3**), or (**4**) in a 1:1 molar ratio at room temperature afforded, after a few hours (*see* Experimental section), the open chain compounds (**6**), (**7**), and (**8**), respectively, as a *Z,E* mixture of diastereoisomeric enamines. The yield was almost quantitative and was independent of the solvent used (THF, $CHCl_3$, or CH_3OH) (see Scheme 1). It was found, however, that reaction of (**1a**) or (**1b**) with benzaldehyde must be carried out at 70 °C in THF and the presence of $ZnCl_2$ as a catalyst* to give, after hydrolysis with aqueous $NaHCO_3$, the divinyl ketone (**9a**) or (**9b**), respectively.

These results can be easily interpreted if it is assumed that the behaviour of these dienes is in every case similar to that of enamines with carbonyl compounds, electrophilic olefins, and activated acetylenes.[5] In the latter case, the formation of (**6**) can be easily understood through a cyclobutene intermediate, which might then undergo rearrangement reaction (Scheme 2). Because of the complexity of the ^1H and ^{13}C NMR of the product mixtures, the structures of (**6–8**) were determined from their hydrolysis products (see later).

The exclusive formation of the open chain compounds (the formation of six-membered rings were not observed in any case) is in agreement with a *s-trans* conformation of the 2-morpholinobutadienes (**1a, b**). This conformation could be the most favourable one due to a smaller steric effect.

Reaction of 2-Morpholinobutadienes (**1c–e**) *with Compounds* (**2–5**).—Treatment of 2-morpholinobutadienes (**1c–e**) with DMAD (**2**) under the same reaction conditions as above gives the same type of open chain compounds (**6**) (Scheme 3). However, the behaviour of these 2-aminobutadienes towards β-nitrostyrene[6] (**3**) and diethyl 2-oxomalonate (**4**) in THF at room temperature is different, leading to a mixture of cyclic and open chain compounds (Scheme 3). The stereochemistry of the products (**10**) and (**11**) was deduced by ^1H-NMR, and in every case the phenyl and nitro groups were found to be *trans*. Thus, (**10c**) shows a double doublet at 5.05 ppm for $CHNO_2$ ($J_{3\text{-H},4\text{-H}}$ 3.81 Hz and $J_{4\text{-H},5\text{-H}}$ 11.92 Hz), while isomer (**11c**) shows a double doublet at 4.9 ppm for $CHNO_2$ ($J_{3\text{-H},4\text{-H}}$ 9.45 Hz and $J_{4\text{-H},5\text{-H}}$ 12.30 Hz).

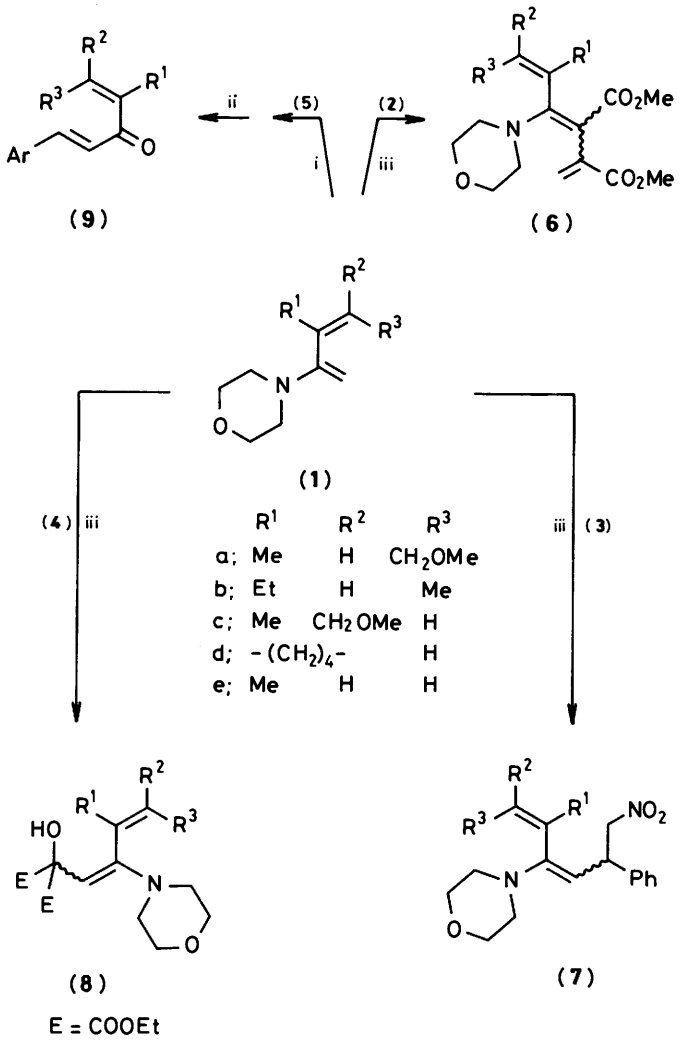
It is worth noting that in these reactions the polarity of the solvent plays a role not only in the ratio of the products formed, but also in the rate of the reactions.[6] For instance, the reaction of (**1c**) with (**3**) in THF at room temperature furnishes a mixture of (**10c**), (**11c**), and (**7c**) (molar ratio 49:13:38, respectively) after 10 hours, whereas in methanol, only the isomer (**10c**) is obtained after 45 min. Similar results were observed for (**1e**). In a similar way, (**12c–e**) and (**8c–e**) were formed (molar ratio 2:1) when the reactions of (**1c–e**) with (**4**) were carried out in THF (Scheme 3), while only the cyclic compounds (**12c–e**) were formed after a few minutes in good yields when methanol was the solvent.

On the other hand, the 2-morpholinobutadienes (**1c–d**) react with benzaldehyde in the presence of $ZnCl_2$ (molar ratio 1:2:2) in THF at 70 °C to afford, after hydrolysis, the compounds (**9c–d**) in moderate yields.†

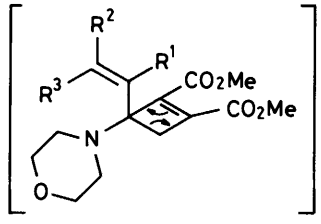
The results shown in Scheme 3 are also in agreement with the

* When the reaction is carried out without catalyst at room temperature, yields are very poor and the subsequent hydrolysis leads to a very complex mixture.

† The 2-morpholinobutadiene (**1e**) reacts with benzaldehyde to afford the aminal derivative from benzaldehyde and morpholine as main product.



Scheme 1. *Reagents:* i, $ZnCl_2$, THF, 70 °C, 12 h; ii, saturated aqueous $NaHCO_3$, room temp. 1 h; iii, THF, room temp.



Scheme 2.

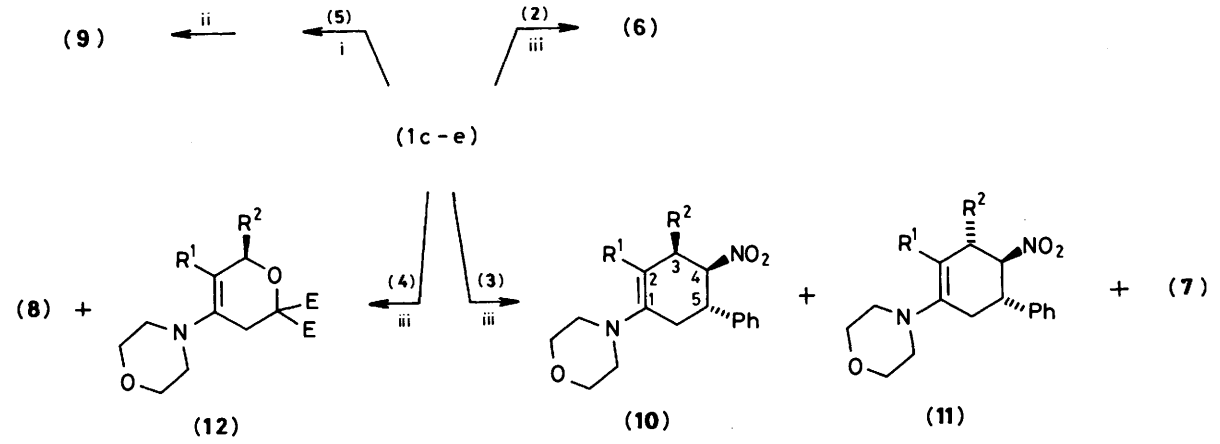
enamine behaviour of these 2-morpholinobutadienes. Effectively, the open chain compounds (**6**–**9**) could be justified in the same way as described in the previous section, in spite of the fact that the diene could now adopt the *s-cis* conformation. The formation of the cyclic compounds must be *via* a step-wise cyclization process of the *s-cis* diene, as shown by the dependence of the reaction rate on the solvent polarity. The exclusive formation of (**10**) in MeOH can be explained by a greater stabilization of the polar intermediate, which would provide high facial selectivity of carbanion attack during the cyclization (Scheme 4).

The β-attack of the carbanion on the electrophilic centre would lead to enamine (**10**). Similarly, α-attack would furnish enamine (**11**). The driving force for the equilibration seems to be the steric effect between the nitro group and the CH_2OCH_3 substituents. These impediments are greater for the α-attack, therefore favouring attack through the β-path.*

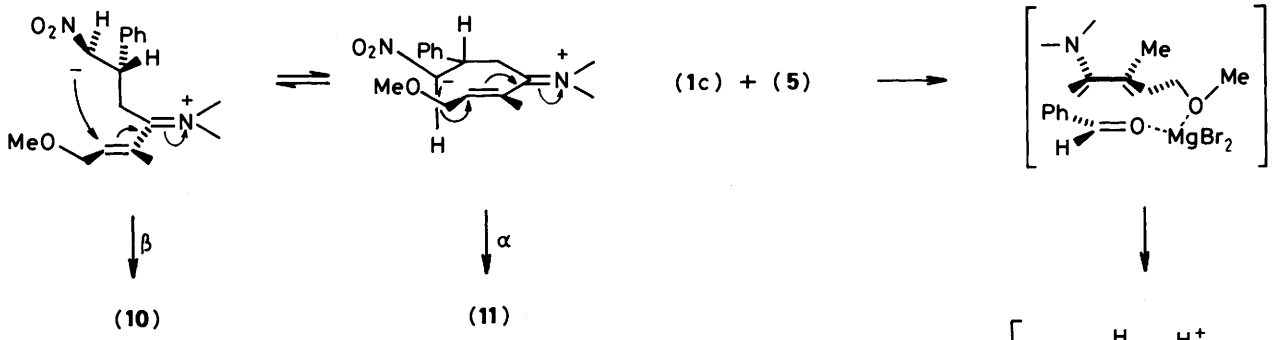
Reaction of 2-*Morpholinobutadiene* (**1c**) *with Aromatic Aldehydes in the Presence of* $MgBr_2$.[7]—In the reaction of (**1c**) with benzaldehyde in the presence of $ZnCl_2$ in THF, the open chain compound (**9**) was obtained as mentioned above. However, by changing the Lewis acid to $MgBr_2 \cdot OEt_2$ (molar ratio 1:2:2) at room temperature, a spectacular change in the resulting products is observed.† In this case, after hydrolysis of the reaction mixture with an HOAc–NaOAc buffer (pH = 4.6), the heterocyclic enamine (**13**) was obtained as only one diastereoisomer. Hydrolysis of the crude reaction mixture with aqueous acetic acid led to a single diastereoisomer of the tetrahydropyran-4-one (**14**). Treatment of (**14**) with 3M hydrochloric acid afforded the epimer (**15**) (Scheme 5). It is worth noting that hydrolysis of the enamine (**13**) with 50% aqueous acetic acid affords an epimeric mixture of the

* In this case the problem could be different to that described by Pitacco, G. *et al.*,[6] because a cyclic C–C double bond is involved in their proposed intermediate.

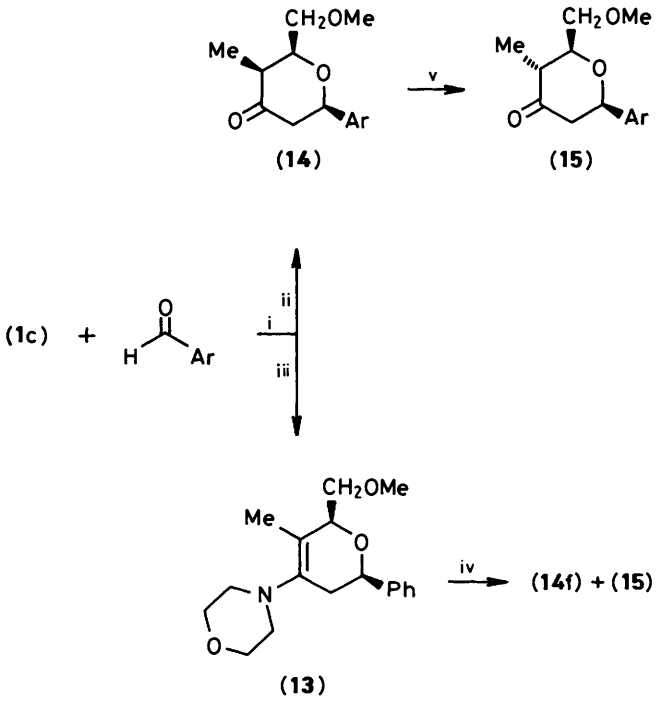
† The 2-morpholinobutadiene (**1d**) reacts with benzaldehyde to afford a mixture in which the divinylketone (**9d**) was detected by ^1H NMR, while under the same reaction conditions (**1e**) gave the aminal derived from benzaldehyde and morpholine as the main product.



Scheme 3. *Reagents:* i, $ZnCl_2$, THF, 70 °C, 12 h; ii, saturated aqueous $NaHCO_3$; iii, THF, room temp, 24 h.

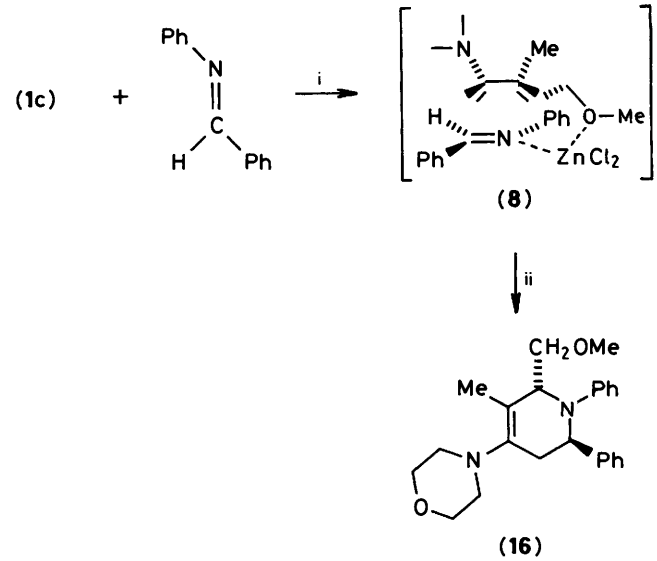


Scheme 4.

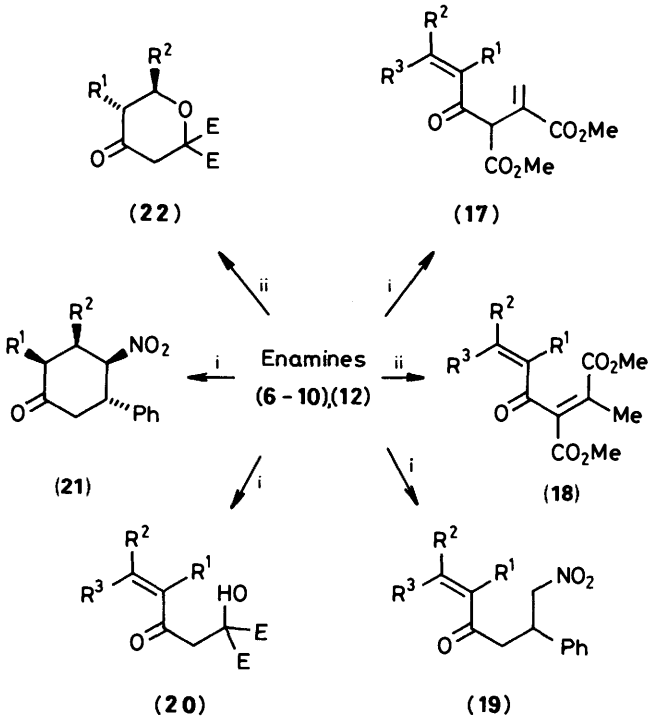


Scheme 5. Reagents: i, $MgBr_2$-Et_2O, THF, room temp, 12 h; ii, HOAc–H_2O (1:1), room temp., 1 h; iii, aqueous HOAc–NaOAc (pH 4.6), room temp, 1 h; iv, HOAc–H_2O (1:1), room temp., 1 h; v, THF, 3M HCl, room temp., 3 h.

Scheme 6.



Scheme 7. Reagents: i, $ZnCl_2$, THF, room temp., 12 h; ii, saturated aqueous $NaHCO_3$, room temp., 1 h.



Scheme 8. *Reagents:* i, Aqueous HOAc–NaOAc (pH 4.6), room temp., 3 h; ii, 3M HCl, room temp, 12 h. In the above scheme, **a**; R′ = Me, R^3 = CH_2OMe: **b**; R^1 = Et, R^3 = Me: **c**; R^1 = Me, R^2 = CH_2OMe: **d**; R^1, R^2 = $(CH_2)_4$: **e**; R^1 = Me, R^2 = H.

Table Tetrahydropyran-4-ones obtained by reaction of (**1c**) and aromatic aldehydes.

Compound[a]	Ar	Yield (%)[b]
(**14f**)	Phenyl	68
(**14g**)	4-Me-C_6H_4	67
(**14h**)	4-Cl-C_6H_4	58
(**14i**)	2-Furyl	42
(**14j**)	2-Thienyl	65

[a] Satisfactory elemental and spectral data for the proposed structure (see Experimental section). [b] Referred to 2-morpholinobutadiene (**1c**).

tetrahydropyran-4-one (**14**) and (**15**) in a molar ratio of *ca.* 1:1. The stereochemistry of (**14**) was deduced from ^1H NMR spectral data; the 2-H signal appears as a ddd at 3.9 ppm ($J_{2\text{-H},3\text{-H}}$ 3.3 Hz), and nuclear Overhauser enhancement experiments reveal a *cis* relationship between 2-H and 6-H. This reaction has been extended to other aromatic aldehydes with similar results (see Table).

The high *endo* selectivity of these cyclization processes could be explained by assuming that the reaction takes place in a concerted way, induced by the participation of the $MgBr_2$·OEt_2 which gives rise to a complex between the diene and the dienophile as indicated in Scheme 6.[8,9] In addition, the high degree of stereoselectivity in the hydrolysis process can be explained by assuming the presence of a complex between the cycloadduct and the Lewis acid, which would enable easier attack by the proton on the β-face as shown. On the other hand, the almost complete absence of diastereoselectivity in the hydrolysis of the enamine (**13**) (without catalyst) should be expected, because in this case both faces of the enamine can be attacked by the proton with a similar degree of probability.

The behaviour of (**1c**) towards benzylideneaniline is also interesting, and in the presence of $ZnCl_2$ as Lewis acid (reaction conditions as above) affords the tetrahydropyridine (**16**) as the only diastereoisomer (Scheme 7). The stereochemistry of this diastereoisomer was proven by NMR and X-ray diffraction data.[7]

It is worth noting that in this case the phenyl group attached to the imino carbon atom is now in an *exo*-orientation (the reaction of benzaldehyde affords the *endo* adduct). This result can be interpreted in a similar way as above (see Scheme 6) but now both phenyl groups have to be in a *trans* relationship, as shown in Scheme 7. It is possible that if the phenyl groups were in a *cis* relationship, steric interactions would prevent the cyclization process from taking place in a concerted way.

Hydrolysis of Enamines (**6**–**11**).—As shown in Scheme 8, the enaminic compounds (**6**–**12**) can be hydrolysed either to the corresponding open chain carbonyl compounds (**17**–**20**), or to the cyclic compounds (**21**) and (**22**) with a very high degree of stereoselectivity. Some of these products are interesting types of compounds; for instance, (**19**) and (**21**) are synthons of the important 1,4-aminocarbonyl and 1,4-dicarbonyl systems.

All these enamines are hydrolysed under very mild conditions, namely in HOAc–NaOAc buffer solution (pH = 4.6), except for (**6a**) and (**6b**), for which required treatment with aqueous hydrochloric acid for 24 h. Under the latter conditions, isomerization of the double bond takes place. Furthermore, for (**12**) use of 3M HCl gives only the epimer (**22**), but a mixture of (**22**) and its 2-epimer is obtained under milder conditions (HOAc–NaOAc buffer solution). The configurations of these compounds have been determined by their NMR data; for instance, (**21c**) shows a double doublet at 5.0 ppm corresponding to the $CHNO_2$ signal $J_{3\text{-H},4\text{-H}}$ 4.6 Hz and $J_{4\text{-H},5\text{-H}}$ 12.4 Hz) and also a positive NOE effect between 2-H and 4-H. Compound (**22d**) shows a double triplet at 3.47 ppm corresponding to 3-H ($J_{2\text{-H},3\text{-H}}$ 10.7 Hz).

In conclusion, the 2-morpholinobutadienes behave like typical enamines, as predicted by theoretical calculations, independently of their *s-cis* or *s-trans* conformation. Only when the aminodiene system has a substituent which can participate in the course of the reaction may its behaviour differ. This is the case in the reactions of (**1c**) with aromatic aldehydes and benzylideneaniline catalyzed by $MgBr_2$·OEt and $ZnCl_2$, respectively. The possibility of complex formation between the Lewis acid and the hetero substituent causes a decrease in the entropic factors, which makes the cycloaddition reaction more facile. Furthermore, the 2-morpholinobutadienes are interesting starting materials for the preparation of several important acyclic and cyclic systems with high regio-and stereo-selectivity.

Experimental *

General Methods.—Nuclear magnetic resonance (NMR) spectra were recorded either in solution in $CDCl_3$ or neat on a Varian FT-80 A or a Brücker AC-300 spectrometer with internal tetramethylsilane as the reference. GC-Mass spectra were taken on a Hewlett Packard 5930 A spectrometer. Microanalyses were performed on a Perkin Elmer Model 240 instrument.

Materials.—2-Morpholino-1,3-dienes were prepared according to the method described in previous papers.[3,7] All reactions were run under argon. All organic extracts were dried over anhydrous sodium sulphate. Tetrahydrofuran (THF) was distilled from sodium benzophenone prior to use, and methanol was distilled over magnesium turnings and aromatic aldehydes

* Spectral and analytical data for compounds (**9**–**12**), (**14**) and (**17**–**22**) are available as a supplementary publication (no. 56777) (see Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1990, issue 1).

were distilled under argon. All other reagents were of the best commercial grade available.

General Preparative Procedure for Butanedioates (**6**).—A solution of (**1**) (10 mmol) in dry THF (10 ml) was slowly added to a solution of dimethylacetylene dicarboxylate (**2**) (10 mmol, 1.21 ml) in dry THF (50 ml) at room temperature. The reaction mixture was stirred for 24 h. Removal of the solvents under reduced pressure (high vacuum) afforded an oily liquid. ^1H and ^{13}C NMR analysis show a mixture of *Z,E* isomeric enamines (**6**) which were not separated. Crude yields in the reaction for (**6a**), (**6b**), (**6c**), (**6d**), and (**6e**) were 81, 84, 91, 94, and 99%, respectively.

General Preparative Procedure for Nitroenamines (**7**).—A solution of (**1a**) or (**1b**) (10 mmol) in dry THF (10 ml) was added dropwise to a solution of β-nitrostyrene (**3**) (10 mmol, 1.17 g) in dry THF (40 ml) at room temperature. After 6 h, concentration under reduced pressure afforded an oily residue. ^1H and ^{13}C NMR analysis show a mixture of *Z,E* isomeric nitroenamines which were not separated. Crude yields in the reaction for (**7a**) and (**7b**) were 99 and 98%, respectively.

General Preparative Procedure for Hydroxyenamines (**8**).—The procedure is identical with that for enamines (**7**), but using diethyl 2-oxomalonate (**4**) (10 mmol, 1.6 ml). A mixture of *Z,E* isomeric enamines (**8**) was obtained in a ratio of *ca.* 1:1. Crude yields in the crude reaction for (**8a**) and (**8b**) were 99 and 96%, respectively.

General Preparative Procedure for Divinylketones (**9**).—$ZnCl_2$ (20 mmol, 2.72 g) was added to a solution of anhydrous benzaldehyde (20 mmol, 2 ml) in dry THF (80 ml). After 15 min, a solution of (**1**) (10 mmol) in dry THF (5 ml) was added dropwise. The mixture was stirred overnight at 70 °C, then the solution was allowed to cool to room temperature and saturated aqueous $NaHCO_3$ was added. The mixture was stirred for 1 h and then extracted with Et_2O and the organic extracts were evaporated under reduced pressure (high vacuum). The crude residue was distilled *in vacuo* (0.001 Torr) to give the divinylketone (**9**).

4-*Ethyl*-1-*phenylhexa*-1,4-*dien*-3-*one* (**9b**): $\delta_H(CDCl_3)$ 7.8–7.2 (m, 6 H), 6.9 (d, 1 H, *J* 16 Hz), 5.8 (m, 1 H), 2.3 (q, 2 H), 1.7 (d, 3 H), 1.0 (t, 3 H); δ_C (neat) 195.1 (s), 144.2 (d), 135.3 (d), 130.9 (s), 129.5 (s), 128.9 (d), 128.3 (d), 127.3 (d), 126.2 (d), 28.4 (t), 15.1 (q), 13.5 (q); *m/z* 200 (M^+) (Found: C, 83.75; H, 8.23. $C_{14}H_{16}O$ requires C, 83.96; H, 8.05%).

General Preparative Procedure for Cyclic Nitroenamines (**10**).—A solution of (**1c–e**) (10 mmol) in dry MeOH (10 ml) was added dropwise to a solution of β-nitrostyrene (**3**) (10 mmol, 1.17 g) in dry MeOH (50 ml) at room temperature. After 1 h, removal of the solvents afforded the corresponding cyclic enamine (**10**) as a pure product.

(4R*,5S*)-N-(2-*Methyl*-4-*nitro*-5-*phenyl*-*cyclohex*-1-*enyl*) *Morpholine* (**10e**): $\delta_H(CDCl_3)$ 7.3–7.1 (m, 5 H), 4.9 (td, 1 H), 3.7 (t, 4 H), 3.3 (td, 1 H), 2.8 (m, 2 H), 2.6 (t, 4 H), 2.4–2.1 (m, 2 H), 1.7 (s, 3 H); δ_C(neat) 139.6 (s), 139.1 (s), 128.7 (d), 127.5 (d), 127.1 (d), 119.6 (s), 86.8 (d), 67.1 (t), 50.0 (t), 44.8 (d), 35.9 (t), 30.0 (t), 17.1 (q); *m/z* 302 (M^+) (Found: C, 67.71; H, 7.46; N, 9.39. $C_{17}H_{22}N_2O_3$ requires C, 67.54; H, 7.28; N, 9.27%.)

General Preparative Procedure for Cyclic Enamines (**12**).—The procedure is identical with that for enamines (**10**), but employing diethyl 2-oxomalonate (10 mmol, 1.6 ml) as dienophile.

Diethyl 6-*Methoxymethyl*-5-*methyl*-4-*morpholino*-3,6-*dihydro*-2H-*pyran*-2,2-*dicarboxylate* (**12c**): $\delta_H(CDCl_3)$ 4.2–4.1 (m, 5 H), 3.8–3.5 (m, 6 H), 3.3 (s, 3 H), 2.9 (d, 1 H), 2.6 (t, 4 H), 2.4 (d, 1 H), 1.5 (s, 3 H), 1.2–1.0 (m, 6 H); δ_C (neat) 166.8 (s), 166.0 (t), 136.4 (s), 119.6 (s), 79.2 (s), 75.3 (d), 72.5 (t), 65.5 (t), 60.3 (t), 60.0 (t), 57.6 (q), 48.5 (t), 25.6 (t), 12.5 (q), 12.4 (q), 11.3 (q). (Found: C, 58.41; H, 8.02; N, 3.62. $C_{18}H_{29}NO_7$ requires C, 58.20; H, 7.87; N, 3.77%.)

Preparation of (2R*,6R*)-*2-Methoxymethyl*-3-*methyl*-4-*morpholino*-6-*phenyl*-5,6-*dihydro*-2H-*pyran* (**13**).—A solution of (**1c**) (10 mmol, 1.97 g) in dry THF (10 ml) was slowly added to an ice-cooled solution of benzaldehyde (20 mmol, 2.0 ml) and $MgBr_2$·OEt (20 mmol) in dry THF (80 ml). The mixture was allowed to warm to room temperature and stirred overnight. The resulting mixture was hydrolyzed with AcOH–AcONa aqueous buffer (15 ml) (pH 4.6) for 1 h, extracted with Et_2O and concentrated under reduced pressure (high vacuum) to give compound (**13**) as a single diastereoisomer (2.24 g, 74%), $\delta_H(CDCl_3)$ 7.4–7.1 (m, 5 H), 4.5 (ddd, 1 H), 4.3 (m, 1 H), 3.7 (m, 6 H), 3.4 (s, 3 H), 2.9–2.6 (m, 6 H), 1.7 (d, 3 H); δ_C (neat) 142.1 (s), 139.9 (s), 127.6 (d), 126.7 (d), 125.2 (d), 120.6 (s), 78.1 (d), 75.2 (d), 73.8 (t), 66.6 (t), 58.8 (q), 49.6 (t), 30.5 (t), 12.1 (q); *m/z* 303 (M^+).

General Preparative Procedure for the Tetrahydropyran-4-*ones* (**14**).—The procedure is identical with that for (**13**), but employing the appropriate aromatic aldehyde as dienophile. The resulting mixture was hydrolysed with 1:1 AcOH–H_2O (15 ml) for 1 h and was then extracted with Et_2O and concentrated under reduced pressure. The crude reaction product was distilled *in vacuo* (0.001 Torr; preheated oil bath temperature, 80–90 °C).

(2S*,3S*,6R*)-2-*Methoxymethyl*-3-*methyl*-6-*phenyltetrahydro*-4H-*pyran*-4-*one* (**14f**): $\delta_H(CDCl_3)$ 7.5 (s, 5 H), 4.8 (dd, 1 H), 3.9 (ddd, 1 H), 3.6 (dd, 1 H), 3.5 (dd, 1 H), 3.4 (s, 3 H), 2.8–2.5 (m, 3 H), 1.2 (d, 3 H); δ_C (neat) 208.0 (s), 139.8 (s), 128.0 (d), 127.4 (d), 125.2 (d), 78.3 (d), 77.1 (d), 71.7 (t), 58.6 (q), 46.3 (d), 45.6 (t), 10.3 (q); *m/z* 234 (M^+) (Found C, 71.85; H, 7.90. $C_{14}H_{18}O_3$, requires C, 71.77; H, 7.74%).

Epimerization of (**14f**); *Preparation of* (2S*,3R*,6R*)-2-*Methoxymethyl*-3-*methyl*-6-*phenyltetrahydro*-4H-*pyran*-4-*one* (**15**).—Compound (**14f**) (2.3 ml) was dissolved in THF (30 ml) and aqueous 3M HCl (15 ml) was added. The mixture was stirred for 3 h and extracted with Et_2O. Removal of the solvents under reduced pressure afforded the epimer (**15**) (2.21 g, yield 95%); $\delta_H(CDCl_3)$ 7.3 (m, 5 H), 4.7 (t, 1 H), 3.5 (s, 3 H), 3.7–3.2 (m, 3 H), 2.8–2.6 (m, 3 H), 1.1 (d, 3 H); δ_C (neat) 207.6 (s), 140.6 (s), 129.3 (d), 127.7 (d), 125.4 (d), 82.5 (d), 78.9 (d), 73.2 (t), 59.4 (q), 49.3 (d), 45.9 (t), 8.9 (q); *m/z* 234 (M^+).

Reaction of (**1c**) *with* N-*Benzylideneaniline; Preparation of* 6-*Methoxymethyl*-5-*methyl*-4-*morpholino*-1,2-*diphenyl*-1,2,3,6-*tetrahydropyridine* (**16**).—The procedure is identical with that described above for (**13**), employing $ZnCl_2$ (20 mmol, 3.62 g). After hydrolysis of the reaction mixture with saturated aqueous $NaHCO_3$, the excess of imine was removed by stirring with hexane, and (**16**) recrystallised from ethanol (1.81 g, yield 48%), m.p. 148–151 °C; $\delta_H(CDCl_3)$ 7.1 (m, 7 H), 6.6 (m, 3 H), 5.0 (dd, 1 H), 4.4 (dd, 1 H), 3.5 (m, 6 H), 3.4 (s, 3 H), 2.7 (m, 1 H), 2.6 (dd, 1 H), 2.1 (t, 4 H), 1.9 (d, 3 H); $\delta_C(CDCl_3)$ 144.8 (s), 142.3 (s), 136.9 (s), 127.3 (d), 126.4 (d), 125.1 (s), 125.0 (d), 124.9 (d), 114.7 (d), 111.7 (d), 73.7 (t), 69.6 (t), 57.8 (q), 57.6 (d), 56.6 (d), 47.7 (t), 29.0 (t), 15.4 (q); *m/z* 378 (M^+) (Found: C, 76.23; H, 8.15; N, 7.25. $C_{24}H_{30}N_2O_2$ requires C, 76.16; H, 7.99; N, 7.40%).

General Hydrolysis Procedure for Enamines (**6c–e**); *Preparation of Compounds* (**17c–e**).—The mixture of enamines (**6**) was dissolved in THF (20 ml) and HOAc–NaOAc buffer (20 ml, pH 4.6) was added. It was stirred for 30 min and then extracted with

Et_2O. The extracts were concentrated under reduced pressure and the residue was distilled under high vacuum (0.001 Torr; preheated oil bath temperature 100–110 °C).

Dimethyl [2-(4-*Methoxy*-2-*methylbut*-2-*enoyl*)-3-*methylene*]-*butanedioate* (**17c**): $\delta_H(CDCl_3)$ 6.3 (t, 1 H), 6.1 (s, 1 H), 5.5 (s, 1 H), 5.1 (s, 1 H), 3.8 (d, 2 H), 3.42 (s, 3 H), 3.40 (s, 3 H), 3.0 (s, 3 H), 1.4 (s, 3 H); $\delta_C(CDCl_3)$ 194.2 (s), 169.1 (s), 166.3 (s), 141.6 (d), 136.6 (s), 134.8 (s), 129.4 (t), 69.7 (t), 58.3 (q), 54.6 (d), 52.7 (q), 52.5 (q), 11.0 (q); *m/z* 270 (M^+) (Found: C, 57.78; H, 6.71. $C_{13}H_{18}O_6$ requires C, 57.90; H, 6.85%).

Hydrolysis of (**6a, b**); *Preparation of Compounds* (**18a, b**).—The mixture of enamines (**6**) was dissolved in THF (30 ml) and HCl 3M (20 ml) was added, stirred for 24 h and extracted with Et_2O. Removal of the solvents under reduced pressure afforded a yellow liquid. It was purified by flash chromatography on a SiO_2 column using Et_2O as the eluant.

Dimethyl 2-(4-*Methoxy*-2-*methyl*-1-*oxobut*-2-*enyl*)-3-*methyl-fumarate* (**18a**): $\delta_H(CDCl_3)$ 6.7 (t, 1 H), 4.25 (d, 2 H), 3.8 (s, 3 H), 3.6 (s, 3 H), 3.4 (s, 3 H), 1.9 (s, 3 H), 1.8 (d, 3 H); δ_C (neat) 192.0 (s), 167.1 (s), 162.7 (s), 144.0 (d), 140.4 (s), 136.1 (s), 132.6 (s), 68.3 (t), 57.2 (q), 51.4 (q), 51.3 (q), 16.0 (q), 14.3 (q) (Found C, 57.81; H, 6.75. $C_{13}H_{18}O_6$ requires C, 57.90; H, 6.85%).

Hydrolysis of Enamines (**7**); General Preparative Procedure for Nitrocompounds (**19a, b**).—The mixture of enamines (**7**) was dissolved in THF (20 ml) and HOAc–NaOAc buffer (20 ml; pH 4.6) was added. The mixture was stirred for 3 h and extracted with Et_2O. Removal of the solvents under reduced pressure afforded the ketone (**19**) which was distilled *in vacuo* (0.001 Torr; preheated oil bath temperature 100–110 °C).

(2Z)-1-*Methoxy*-3-*methyl*-7-*nitro*-6-*phenylhept*-2-*en*-4-*one* (**19a**): $\delta_H(CDCl_3)$ 7.1 (m, 5 H), 5.9 (t, 1 H), 4.9 (dd, 1 H), 4.8 (dd, 1 H), 4.0 (m, 3 H), 3.1 (s, 3 H), 2.9 (d, 2 H), 1.8 (s, 3 H); δ_C (neat) 200.4 (s), 139.8 (s), 135.1 (s), 134.3 (d), 128.8 (d), 127.6 (d), 127.5 (d), 79.3 (t), 70.8 (t), 58.0 (q), 43.7 (t), 38.8 (d), 19.7 (q) (Found: C, 65.03; H, 6.80; N, 5.12. $C_{15}H_{19}NO_4$ requires C, 64.97; H, 6.91; N, 5.05%).

Hydrolysis of Enamines (**8**); *General Preparative Procedure for Hydroxyketones* (**20**).—The procedure is identical with that for the ketones (**19**). The crude reaction product was an essentially pure, orange liquid.

Diethyl 2-*Hydroxy*-2-(5-*methoxy*-3-*methyl*-2-*oxo*-3-*pentenyl*)*propanedioate* (**20a**): $\delta_H(CDCl_3)$ 7.1 (s, 1 H), 6.0 (t, 1 H), 4.3–4.1 (m, 6 H), 3.4 (s, 2 H), 3.3 (s, 3 H), 2.0 (s, 3 H), 1.1 (t, 6 H); δ_C (neat) 198.5 (s), 168.8 (s), 139.5 (d), 133.1 (s), 75.9 (s), 70.3 (t), 61.5 (t), 57.1 (q), 45.1 (t), 18.9 (q), 13.0 (q); *m/z* 302 (M^+) (Found C, 55.70; H, 7.25. $C_{14}H_{22}O_7$ requires C, 55.62; H, 7.28%.)

Hydrolysis of Cyclic Enamines (**10**); *General Preparative Procedure for Nitroketones* (**21**).—Enamine (**10**) (10 mmol) was dissolved in THF (20 ml), then the solution was treated with HOAc–NaOAc buffer (pH 4.6) (15 ml) and stirred for 1 h. The mixture was extracted with Et_2O, washed with water, dried with Na_2SO_4 and concentrated under reduced pressure. The crude reaction product was an essentially pure, orange liquid which was purified by flash chromatography on a SiO_2 column using hexane–Et_2O (1:1) as eluant.

(2S*,3R*,4R*,5S*)-3-*Methoxymethyl*-2-*methyl*-4-*nitro*-5-*phenylcyclohexanone* (**21c**): $\delta_H(CDCl_3)$ 7.3–7.1 (m, 5 H), 5.3 (dd, 1 H, $J_{4\text{-H},5\text{-H}}$ 12.4 Hz, $J_{3\text{-H},4\text{-H}}$ 4.6 Hz), 4.2 (td, 1 H, $J_{5\text{-H},6\text{-H}_{ax}}$ 12.4, $J_{4\text{-H},5\text{-H}}$ 12.4, $J_{5\text{-H},6\text{-H}_{eq}}$ 6.0 Hz), 3.4 (t, 2 H), 3.1 (s, 3 H), 2.9–2.6 (m, 3 H), 2.3 (dd, 1 H), 1.1 (d, 3 H); δ_C (neat) 203.1 (s), 139.4 (s), 127.9 (d), 126.5 (d), 126.1 (d), 89.7 (d), 66.3 (t), 58.0 (q), 45.4 (t), 44.5 (d), 43.4 (d), 42.0 (d), 10.5 (q) (Found C, 64.91, H, 7.02; N, 5.02. $C_{15}H_{19}NO_4$ requires C, 64.97; H, 6.91; N, 5.05%.)

Hydrolysis of Cyclic Enamines (**12**); *General Preparative Procedure for Tetrahydropyran*-4-*ones* (**22**).—The enamine (**12**) (10 mmol) was dissolved in THF (20 ml). The solution was treated with 3M HCl (15 ml) and stirred at room temperature for 12 h. The organic layers were extracted with Et_2O, washed with water, dried with Na_2SO_4, and concentrated under reduced pressure. The crude reaction product was an essentially pure, orange liquid. ^1H and ^{13}C NMR analysis showed the presence of only one epimer. The crude produce was distilled *in vacuo* (0.001 Torr; preheated oilbath temperature, 100–110 °C).

Diethyl (5R*,6S*)-6-*Methoxymethyl*-5-*methyltetrahydro*-4H-*pyran*-4-*one*-2,2-*dicarboxylate* (**22c**): $\delta_H(CDCl_3)$ 4.4–4.2 (m, 5 H), 3.7 (d, 2 H), 3.4 (s, 3 H), 3.1 (d, 1 H), 2.8 (d, 1 H), 2.7 (dq, 1 H, $J_{5\text{-H},6\text{-H}}$ 10.6, $J_{3\text{-H},5\text{-H}}$ 6.6 Hz), 1.35 (t, 3 H), 1.34 (t, 3 H), 1.0 (d, 3 H); δ_C (neat) 203.1 (s), 166.7 (s), 166.0 (s), 81.5 (s), 78.6 (d), 71.7 (t), 61.5 (t), 58.6 (q), 44.0 (d), 43.2 (t), 13.0 (q), 8.3 (q) (Found C, 55.69; H, 7.19. $C_{14}H_{22}O_7$ requires C, 55.62; H, 7.28%.)

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