Cycloaddition *vs.* conjugative Michael-type addition of 2-ethoxy-3-morpholinobuta-1,3-diene with nitroolefins

Gašper Marc,† Patrizia Nitti, Giuliana Pitacco,* Alessandro Pizzioli and Ennio Valentin

Dipartimento di Scienze Chimiche, Università, Via L. Giorgieri 1, I-34127 Trieste, Italy

The reactivity of the title dienamine towards conjugated nitroolefins has been investigated. With 1-nitrocyclopentene carbocyclic products largely predominated, whereas with 1-nitrocyclohexene only Michael-type products were formed. The behaviour of β-nitrostyrene was found to be dependent on the reaction conditions used.

Introduction

2-Amino 1,3-dienes are interesting building blocks for cycloadditions.[1] However, their chemical behaviour has been little described in the literature because, in general, they are difficult to prepare. A few syntheses of chiral[1a–c] and achiral[1d–f] 2-aminobuta-1,3-dienes have recently been described. For instance, chiral systems were prepared by Wittig olefination of an α-oxo enamine derived from butane-2,3-dione and (*S*)-methoxymethylpyrrolidine.[1a] Of the achiral systems an interesting method makes use of catalytic aminomercuriation of terminal alkynes.[1a]

Their reactivity with electrophilic olefins is characterized by two different pathways. Either they behave as 4π electron donors upon cyclization or they undergo a Michael-type reaction with the formation of open-chain products. In particular, the dienamine **1** (R_2NH = morpholine) reacted with β-nitrostyrene in THF to give, after hydrolysis, the open-chain product **2** (Fig. 1), whereas in methanol the cyclic product **3** (Ar = Ph) was obtained as a single diastereoisomer, after hydrolysis of the enamine intermediate.[1e] The same ketone **3** was obtained by D. Enders[1a] with high diastereoselectivity and excellent enantiomeric excess, using the chiral dienamine **1** [R_2NH = (*S*)-(2-methoxymethyl)pyrrolidine] and a series of 2-aryl-1-nitroethenes. In contrast, because of its particular reactivity β-nitrostyrene reacted with 2,3-dimorpholinobuta-1,3-diene **4**[2] in a [3 + 2] carbocyclization, to yield the corresponding 2-aminocyclopentanone **5**, as a 3:1 mixture of two diastereoisomers, after hydrolysis of the diastereoisomeric morpholinocyclopentene intermediates.

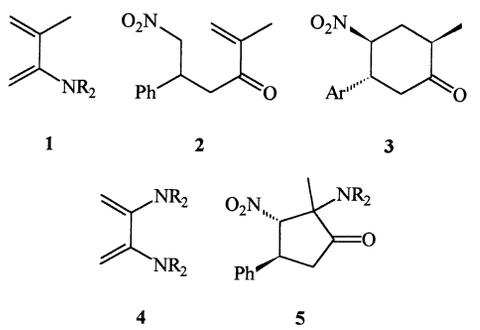
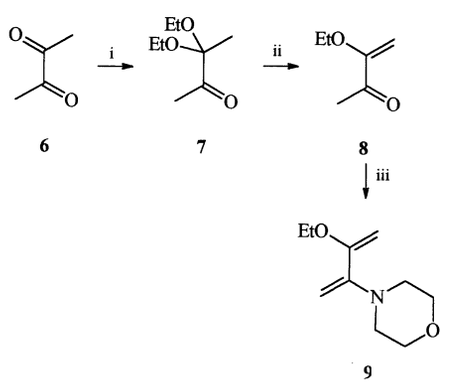


Fig. 1



Scheme 1 *Reagents and conditions*: i, $HC(OEt)_3$, conc. H_2SO_4, 5 °C; ii, H_2SO_4, 100 °C, 760 Torr, 4 h; 80–140 °C, 42 Torr, 1.5 h; iii, morpholine, $TiCl_4$, pentane, 6 h, 0 °C

Results

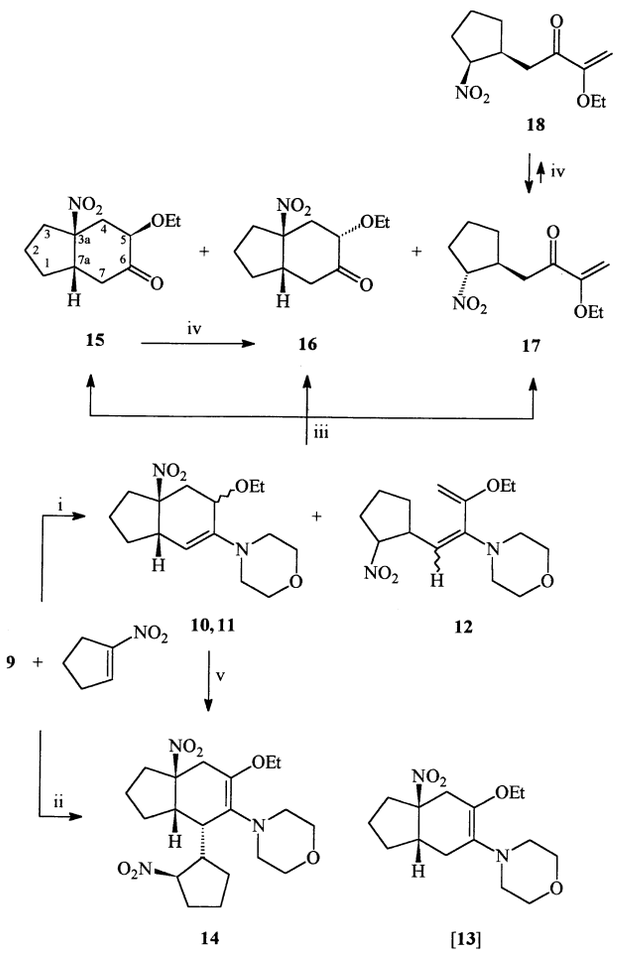
Owing to the continuing interest in nitroaliphatic compounds,[3] we now describe both the synthesis of a new 2-aminobuta-1,3-diene, which is simultaneously a dienol ether, and its application in the reactions with nitroolefins. Our investigations began with the synthesis of the αβ-unsaturated ketone **8**[4] from butane-2,3-dione **6** (Scheme 1). We found that when the diethyl ketal **7**[5] was heated at 80 °C, in the presence of a catalytic amount of toluene-*p*-sulfonic acid, partial deprotection of the protected carbonyl group occurred, to give the αβ-unsaturated ketone **8**. Although the ketone **8** was always contaminated by the monoacetalated butane-2,3-dione **7** (15–20%), condensation of the mixture with morpholine under White and Weingarten conditions[6] gave the desired 2-ethoxy-3-morpholinobuta-1,3-diene **9** as the only product, provided the temperature was maintained at 0 °C. Under these conditions the αβ-unsaturated ketone **8** reacts faster than the more hindered ketone **7** and the enamine **9** can be isolated in pure form. Although this compound is likely to exist in an s-*trans* conformation, an NOE experiment in which the CH_2N protons resonating at 2.86 ppm were irradiated showed a weak enhancement (3%) of the ethyl group's methylene resonance (3.86 ppm), thus indicating that there is some contribution of the s-*cis* form to the conformational equilibrium.

Reaction with 1-nitrocyclopentene (NCP)

Addition of 1-nitrocyclopentene to the dienamine **9** in chloroform, at room temperature, gave a mixture of cyclic and acyclic enamine intermediates, which could not be isolated by chromatography, owing to their instability towards hydrolysis. The ^1H

† On leave from the Faculty of Pharmacy of the University of Ljubljana, Slovenia.

NMR spectrum of the crude reaction mixture, however, clearly showed the presence of two trisubstituted enamines **10** and **11** (δ_H for their vinyl proton signal 4.59 ppm, d *J* 4.4 Hz and 4.66 ppm, d *J* 3.9 Hz) and only one dienamine derivative **12**, whose geometry was not determined (δ_H for its vinyl proton signal 4.30 ppm, d *J* 9.3 Hz) (Scheme 2). Since the reaction mixture



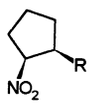
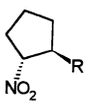
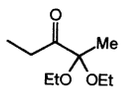
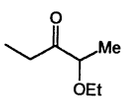
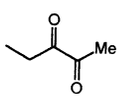
Scheme 2 *Reagents and conditions*: i, $CHCl_3$, RT, 72 h; ii, NCP, $CHCl_3$, RT, 72 h; iii, aq. HCl, RT, 2 h; iv, benzene, PTSA, 80 °C, 15 min; v, NCP, $CHCl_3$, RT, 72 h

had a very complicated NMR spectrum, nothing can be said about the presence in it of the tetrasubstituted enamine **13** which, however, is the product formed first from the reactants. On the other hand, equilibration of a tetrasubstituted enamine into the corresponding trisubstituted derivative is a well known process and might be due to the presence of traces of acid.[7]

Besides their identification in the reaction mixture, **10** and **11** in the equilibrium mixture were also trapped by the nitroolefin itself. In fact, by using 1-nitrocyclopentene in excess they underwent further reaction to yield the Michael-type adduct **14** (Scheme 2) as a single isomer. Its stereochemistry was assigned by means of NOE experiments (see Fig. 2). The *trans* configuration was attributed to the 2-nitrocyclopentyl residue on the basis of the pattern of the nitromethine proton (dt, *J* 7.8, 5.8, 5.8 Hz); this will be discussed below for other derivatives containing the same moiety.

In spite of its double nature as an enamine and an enol ether, compound **14** was very resistant to acidic hydrolysis, at room temperature. This is because conjugation of the nitrogen lone pair with the double bond, which is necessary for protonation of the enamine β carbon, cannot be achieved for steric reasons, owing to the presence of an $A^{1,2}$ strain.[8] This is also confirmed by the value of the C=C stretching band, 1660 cm^{-1}, characteristic of a non-conjugated tetrasubstituted enamine,[7,9] and also by the NOE effect (11%) found for the NCH_2 resonating at 3.17 ppm, when 7-H was irradiated.

Table 1 Chemical shift (ppm) and multiplicity (*J*/Hz) for the nitromethine proton

R	 *cis*	 *trans*
	δ_H 4.98 dt, *J* 6.2, 6.2, 1.7	δ_H 4.46 dt, *J* 8.3, 5.7, 5.7
	δ_H 5.09 dt, *J* 6.4, 6.4, 1.8	δ_H 4.60 dt, *J* 8.8, 6.0, 6.0
	δ_H 5.07 dt, *J* 6.6, 6.6, 2.0	δ_H 4.58 dt, *J* 7.8, 6.2, 6.2

Hydrolysis of the reaction mixture containing **10**, **11** and **12** with aqueous hydrochloric acid gave a mixture of 6-hydrindanone derivatives **15** and **16** along with the open-chain ketone **17** in a *trans* configuration.

Compounds **15** and **16** differed in the orientation of the ethoxy group, as indicated by a comparison of the ^{1}H NMR signal of their respective C*H*OEt resonances (3.58 ppm, ddd, *J* 0.9, 3.0, 5.0 Hz for **15** and 3.98 ppm, ddd, *J* 0.9, 6.1, 12.3 Hz for **16**) and by heating the mixture in the presence of an acid as a catalyst to equilibrate it. Conversion of **15** into **16** was complete, thus proving the axial orientation of the ethoxy group in the less thermodynamically stable compound. This stereochemical assignment was confirmed by NOE difference experiments carried out on **16** (Fig. 2), by which also the *cis* fusion between the rings was determined. It is interesting to note the presence in **16** of a large long-range coupling between 4_{eq}-H and 7a-H (^4J 2.4 Hz), which indicates a diequatorial relationship between the two protons, thus confirming the *cis* fusion between the rings.

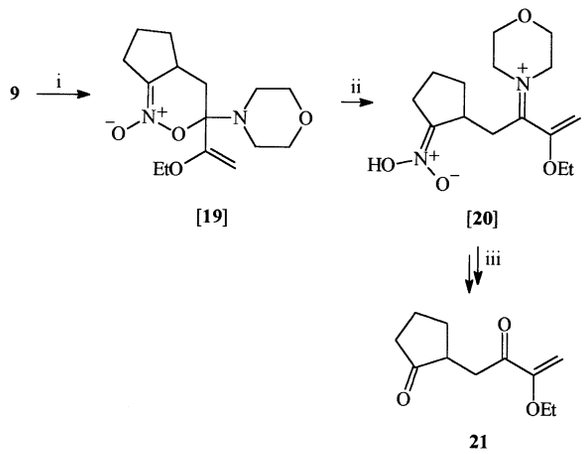
Equilibration of the ketone **17**, carried out in refluxing benzene with traces of toluene-*p*-sulfonic acid as a catalyst, afforded a 4:1 mixture of **17** and its *cis* isomer **18**. Since a differentiation between **16** and **17** by a comparison of their ^{13}C NMR spectra was not possible, their relative stereochemistry was determined by comparing the values of chemical shift and vicinal coupling constants of their nitromethine protons with those of similar compounds (Table 1).[10]

The ratio cyclic : acyclic products was 9 : 1, determined by ^{1}H NMR analysis of the spectrum of the hydrolysed crude reaction mixture. Approximately the same ratio was obtained after chromatographic separation of the products.

A repeat of the reaction between the dienamine **9** and 1-nitrocyclopentene in 1 : 1 molar ratio in ethanol at 80 °C for 1 h gave the same products in a similar relative ratio, no significant differences being observed.

In contrast, reaction of **9** and 1-nitrocyclopentene in diethyl ether at −20 °C gave the moisture-sensitive 1,2-oxazine *N*-oxide derivative **19** (Scheme 3) which could not be isolated as a pure compound. Its formation, however, was proved by the isolation of the diketone **21**, obtained by hydrolysis at pH 2 of the crude reaction mixture. This result is to be ascribed to a Nef-type reaction[11] occurring with compound **19** by protonation of the *N*-oxide oxygen, nucleophilic ring fission and attack of water onto the electrophilic carbon atom of the nitronic group of **20**

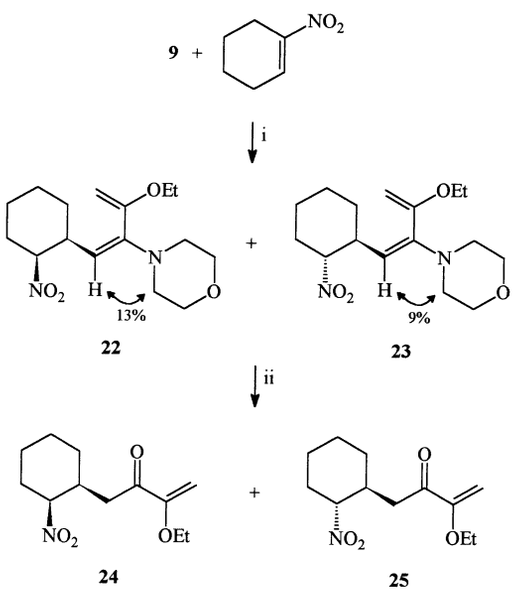
(see Scheme 3). Further, the iminium group was simultaneously hydrolysed, while the enol ether system remained unchanged.



Scheme 3 *Reagents and conditions*: i, NCP, diethyl ether, −20 °C, 24 h; ii, aq. HCl, RT, 1 h

Reaction with 1-nitrocyclohexene

The reaction of the dienamine **9** with 1-nitrocyclohexene, carried out in chloroform at room temperature was much simpler, leading to the exclusive formation of the Michael-type adducts as a mixture of *cis-trans* stereoisomers **22** and **23**, in the ratio of 15:85 (Scheme 4). Both isomers were assigned the *E*



Scheme 4 *Reagents and conditions*: i, $CHCl_3$, RT, 72 h; ii, aq. HCl, RT, 2 h

configuration, by means of NOE difference experiments. Irradiation of the enamine vinyl proton signals of **22** (4.53 ppm, d *J* 10.1 Hz) and **23** (4.15 ppm, d *J* 9.5 Hz) caused enhancement of their respective methylene protons adjacent to the amine nitrogen (η 13% and 9% for **22** and **23** respectively). As for the nitrocyclohexyl moiety, the *cis* configuration was assigned to **22** and the *trans* configuration to **23**, on the basis of the NMR values of their respective nitromethine proton signals (compound **22**: 4.32 ppm, q *J* 4.1 Hz; compound **23**: 4.00 ppm, dt *J* 14.9, 14.9, 3.9 Hz).

Hydrolysis of this mixture afforded the corresponding *cis* and *trans* ketones **24** and **25** in the ratio of 1:9, after acidic equilibration.

A repeat of the reaction at 80 °C in ethanol or benzene, followed by hydrolysis, allowed the isolation of the cyclization

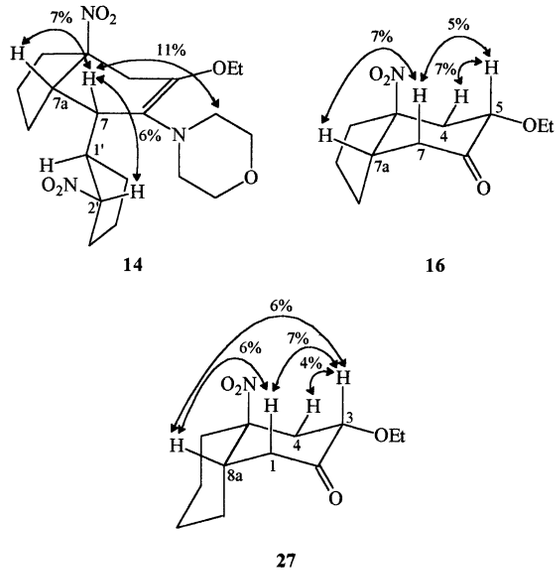


Fig. 2 The main data of DIFNOE measurements for compounds **14**, **16** and **27**

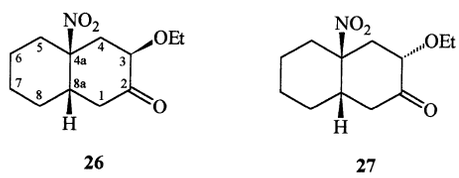
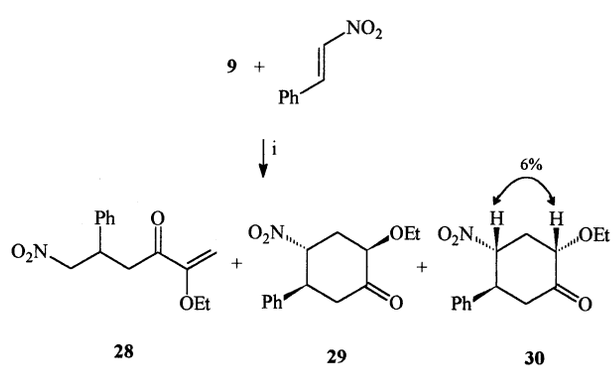


Fig. 3

products **26** and **27** (Fig. 3), albeit in low yield (18%), along with the already mentioned acyclic compounds **24** and **25**. Again these cyclization products differed in the configuration of the carbon atom bearing the ethoxy group, as shown by acidic equilibration which completely converted the 2-decalone **26** into **27**. The stereochemical assignment is based on NOE experiments carried out on **27** (Fig. 2).

Reaction with β-nitrostyrene

The reaction between the dienamine **9** and β-nitrostyrene, carried out in chloroform, furnished a mixture of acyclic and cyclic products, **28** and **29**/**30** respectively (Scheme 5), after



Scheme 5 *Reagents and conditions*: i, $CHCl_3$, RT, 24 h; ii, aq. HCl, RT, 2 h

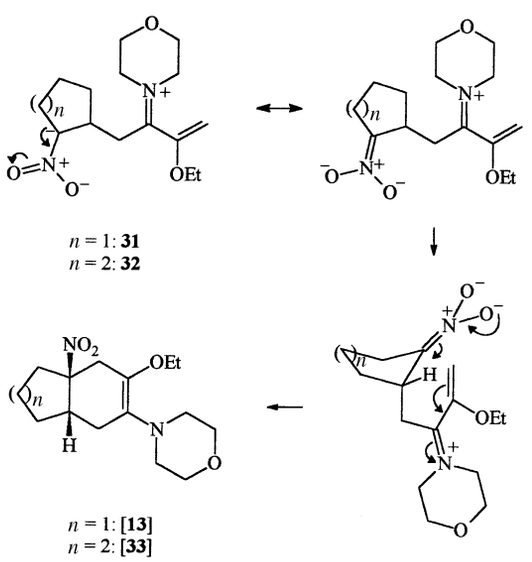
hydrolysis. The ratio acyclic:cyclic products was 3:1. The 2-ethoxycyclohexanone derivatives **29** and **30** were in the ratio of 4:1 in favour of the isomer with the ethoxy group in an axial orientation. The nitro group and the phenyl group are equatorial in both isomers as indicated by their respective nitromethine and benzylic proton signals, which showed the same multiplicities and very close values for the vicinal coupling constants. In contrast, the proton geminal to the ethoxy group was

a triplet (J 6.0 Hz) for compound **29** and a doublet of double doublets (^4J 0.1, ^3J 6.3 and 12.2 Hz) for compound **30**, thus suggesting the equatorial orientation of the former proton and the axial orientation of the latter. Also DIFNOE measurements carried out on **30** (Scheme 5) supported this assignment.

The same reaction performed in tetrahydrofuran at 5 °C led to the same products, although in a slightly different composition. The ratio between the acyclic product **28** and the cyclic products **29**/**30** was 1 : 1. In ethanol at room temperature only the linear product **28** was formed, whereas in refluxing ethanol the cyclic products were also formed, although in both cases a considerable amount of the adduct between morpholine and β-nitrostyrene was separated.

Mechanism

Although a Diels–Alder process cannot be excluded *a priori*, a stepwise mechanism could better explain the difference in reactivity observed. In particular, the different behaviour of the dienamine **9** towards 1-nitrocyclopentene and 1-nitrocyclohexene might be ascribed to the different lifetime of their respective dipolar intermediates **31** and **32** (Scheme 6). The zwitterion **31** is likely to be more stable than **32**, because of the existence of a resonance form with a double bond external to a five-membered ring.[12a] This would allow the formation of the suitable rotamer reactive for cyclization. The intermediacy of the nitronate form would also account for the exclusive occurrence of the *cis* fusion between the rings. The chain in fact would be forced into an axial conformation to avoid the $A^{1,3}$ strain with the nitronate group.[12b] It is worth noting that the initially formed enamine intermediate would be the tetrasubstituted systems **13** and **33**, from which the trisubstituted isomers would be generated by equilibration.



Scheme 6

It is interesting to note that the preferred orientation of the ethoxy group in our cyclohexanone derivative is axial and the preferred orientation of the same group in the bicyclic derivatives is equatorial. The former situation confirms what is already found for 2-ethoxycyclohexanone[13] while the latter is a consequence of the 1,3 diaxial interaction with the nitro group at the junction carbon atom.

A final observation regards the possibility of performing the hydrolyses of the Michael-type enamine intermediates (pH around 5, room temperature) leaving the vinyl ether group untouched. Deprotection leading to the corresponding 1,2-dicarbonyl compounds[10] in fact occurs in refluxing benzene in the presence of toluene-*p*-sulfonic acid as a catalyst and water in traces.

Experimental

IR spectra were determined with a Perkin-Elmer 1320 spectrometer. UV spectra were obtained on a Perkin-Elmer Lambda 5 spectrophotometer. ^{1}H and ^{13}C NMR spectra were scanned on a JEOL EX400 at 400 MHz and 100.4 MHz respectively, using deuteriochloroform as the solvent. All chemical shifts (δ) are reported in parts per million (ppm) and the coupling constants (J) are quoted in Hz. Mass spectra were determined with a VG 7070 spectrometer at 70 eV. Mps were determined on a Büchi apparatus and are uncorrected. Thin-layer chromatographic analyses (TLC) were performed on Merck 60F-254 glass-backed silica gel plates with visualisation by UV light (254 nm) or iodine. Flash chromatography was carried out using silica gel 60 H (Merck 7385). Gas chromatographic analyses were performed on a C. Erba GC 8000 instrument, the capillary column being OV 1701, size 25 m × 0.32 mm.

Synthesis of 3-ethoxybut-3-en-2-one 8

Triethyl orthoformate (29.7 g, 0.20 mol) was added to butane-2,3-dione **6** (17.2 g, 0.20 mol) at 5 °C followed by 5 drops of conc. H_2SO_4, added with vigorous stirring. The yellow solution turned brown and it was warmed to room temperature. The mixture was heated at 100 °C for 4 h in a distillation apparatus fitted with a Vigreux column. During this period approximately 10 g of light yellow product was collected, which consisted mainly of triethyl orthoformate. The mixture was cooled to room temperature and the pressure was reduced to 42 Torr, while the receiver was cooled at −40 °C. The temperature was increased to 80 °C in 20 min. After 1 h at 80 °C (distillation of yellow product slowly continued), the temperature was gradually increased to 140 °C. The distillate (18.2 g) was collected as a clear oil, bp 60 °C (42 Torr) and consisted of 80–85% of the desired 3-ethoxybut-3-en-2-one **8**,[4] the remaining being the compound **7**. Compound **8**: ν_{max}(neat)/cm^{-1} 1710 (C=O), 1610 (C=C) and 1155 (C–O–C); δ_H($CDCl_3$) 5.18 (1 H, d, J 2.4, vinyl-H *trans* to OEt), 4.46 (1 H, d, J 2.4, vinyl-H *cis* to OEt), 3.81 (2 H, q, CH_2CH_3), 2.31 (3 H, s, $COCH_3$) and 1.39 (3 H, t, CH_2CH_3); δ_C($CDCl_3$) 195.5 (s, C=O), 157.4 (s, EtO–*C*=C), 90.8 (t, $=CH_2$), 63.4 (t, OCH_2CH_3), 25.5 (q, CH_3CO) and 13.9 (q, OCH_2CH_3).

2-Ethoxy-3-morpholinobuta-1,3-diene 9

A solution of $TiCl_4$ (5.7 g, 0.030 mol) in pentane (10 cm^3) was added to a solution of morpholine (15.7 g, 0.15 mol) in pentane (200 cm^3) under an argon atmosphere. The mixture was stirred for 30 min at room temperature and then cooled to 0 °C. A solution of the ketone **8** (7.0 g, 0.05 mol) in pentane (50 cm^3) was added dropwise to the mixture which was then stirred for 6 h at 0 °C. The mixture was filtered through Celite and the filtrate evaporated under reduced pressure. The orange oily residue was distilled at 30 Torr to eliminate morpholine, then at 0.05 Torr. The first fraction contained the protected ketone **7** and the unchanged ketone **8**. The second fraction (51–52 °C) was the desired dienamine **9** (5.0 g, 55%) [Found ($M^{\cdot+}$ − 1), 182.11798. $C_{10}H_{16}NO_2$ ($C_{10}H_{17}NO_2$ − H) requires m/z, 182.11810]; ν_{max}(neat)/cm^{-1} 3045, 3020 (=CH_2), 1600, 1580 (C=C), 1260, 1200 (C–O–C=, asymm. stretch), 1110 (C–O–C), 1060 (C–O–C=, symm. stretch) and 860, 810 (=CH_2 wag); λ_{max}(EtOH)/nm 235 (ε_{max} 4438); δ_H($CDCl_3$) 4.55 (1 H, s, N–C=CH *trans* to morpholine), 4.45 (1 H, d, J 2.0, O–C=CH *trans* to OEt), 4.13 (1 H, d, J 2.0, O–C=CH *cis* to OEt), 4.11 (1 H, s, N–C=CH *cis* to morpholine), 3.80 (2 H, q, J 7.0, OCH_2CH_3), 3.75 (4 H, t, CH_2OCH_2), 2.86 (4 H, t, CH_2NCH_2) and 1.35 (3 H, t, J 7.0, OCH_2CH_3); δ_C($CDCl_3$) 158.4 (s, O–*C*=C), 153.1 (s, N–*C*=C), 91.3 (t, N–C=*C*H_2), 85.7 (t, O–C=*C*H_2), 66.7 (t, CH_2OCH_2), 63.2 (t, OCH_2CH_3), 49.6 (t, CH_2NCH_2) and 14.5 (q, OCH_2CH_3); m/z (EI) 182 ($M^{\cdot+}$ − 1,

40%), 153 ($M^{\bullet+}$ − H − Et, 94), 138 (18), 126 (36), 115 (16), 108 (24), 100 (60), 87 (30), 82 (16), 68 (24), 54 (36), 43 (100) and 41 (86).

Reaction with 1-nitrocyclopentene

To a solution of the enamine **9** (0.50 g, 2.75 mmol) in dry chloroform (10 cm^3) at 0 °C was added 1-nitrocyclopentene[14] (0.30 g, 2.75 mmol) in the same solvent (25 cm^3). The mixture was kept at room temperature for 3 days after which water (5 cm^3) and hydrochloric acid (2 mol dm^{-3}) were added. The mixture was stirred for 2 h, after which the two phases were separated and the oily residue was chromatographed with light petroleum–ethyl acetate (gradient from 100:0 to 80:20) as eluent to give a 1:1 mixture of compounds **15**/**16** (0.5 g, 80% yield) and the linear ketone **17** (0.06 g, 10% yield).

(3a*S,5*R**,7a*S**)-5-Ethoxy-3a-nitrooctahydro-6*H*-inden-6-one 15.** Oil; R_f 0.35 (eluent: light petroleum–EtOAc 4:1); $\delta_H(CDCl_3)$ 3.58 (1 H, ddd, $J_{5,7eq}$ 0.9, $J_{4ax,5}$ 3.0, $J_{4eq,5}$ 5.0, 5-H), 3.39, 3.40 (2 H, 2 q, *J* 7.1, CH_2CH$_3$), 3.42–3.35 (1 H, m hidden under CH_2CH$_3$, 7a-H), 3.15 (1 H, ddd, $J_{4eq,7a}$ 2.1, $J_{4eq,5}$ 5.0, $J_{4ax,4eq}$ 15.2, 4_{eq}-H), 3.10 (1 H, dd, $J_{7a,7ax}$ 6.6, $J_{7ax,7eq}$ 14.4, 7_{ax}-H), 2.40 (1 H, ddd, $J_{3\alpha,3\beta}$ 13.4, *J* 7.4, 10.7, 3β-H), 2.30–1.80 (2 H, m, 1α-H, 3α-H), 2.21 (1 H, dd, $J_{4ax,5}$ 3.0, $J_{4ax,4eq}$ 15.2, 4_{ax}-H), 2.11 (1 H, ddd, $J_{5,7eq}$ 0.9, $J_{7a,7eq}$ 3.6, $J_{7ax,7eq}$ 14.4, 7_{eq}-H), 1.75–1.60 (2 H, m, 2 2-H), 1.46–1.32 (1 H, m, 1β-H) and 1.11 (3 H, t, *J* 7.1, CH$_2$CH_3); $\delta_C(CDCl_3)$ 207.3 (C-6), 91.8 (C-3a), 78.8 (C-5), 65.4 (CH$_2$), 43.4 (C-7a), 38.09 (C-7), 38.06 (C-3), 37.6 (C-4), 29.5 (C-1), 20.6 (C-2) and 14.9 (CH$_3$).

(3a*S,5*S**,7a*S**)-5-Ethoxy-3a-nitrooctahydro-6*H*-inden-6-one 16.** Oil; R_f 0.40 (eluent: light petroleum–EtOAc 4:1); ν_{max}(neat)/cm^{-1} 1725 (C=O), 1530, 1360 (NO_2) and 1110 (C–O–C); $\delta_H(CDCl_3)$ 3.98 (1 H, ddd, $J_{5,7ax}$ 0.9, $J_{4eq,5}$ 6.1, $J_{4ax,5}$ 12.3, 5-H), 3.74 (1 H, dq, ^2J 9.0, ^3J 7.1, CHCH$_3$), 3.45 (1 H, dq, ^2J 9.0, ^3J 7.1, CHCH$_3$), 3.20 (1 H, m, 7a-H), 3.01 (1 H, ddd, $J_{4eq,7a}$ 2.4, $J_{4eq,5}$ 6.1, $J_{4ax,4eq}$ 14.9, 4_{eq}-H), 2.73 (1 H, ddd, $J_{5,7ax}$ 0.9, $J_{7a,7ax}$ 6.5, $J_{7ax,7eq}$ 14.9, 7_{ax}-H), 2.39 (1 H, dd, $J_{7a,7eq}$ 3.4, $J_{7ax,7eq}$ 14.9, 7_{eq}-H), 2.10–1.90 (3 H, m, 1α-H, 2 3-H), 2.07 (1 H, dd, $J_{4ax,4eq}$ 14.9, $J_{4ax,5}$ 12.2, 4_{ax}-H), 1.85, 1.65 (2 H, m, 2 2-H), 1.46–1.32 (1 H, m, 1β-H) and 1.22 (3 H, t, *J* 7.1, CH$_2$CH_3); $\delta_C(CDCl_3)$ 209.3 (C-6), 94.5 (C-3a), 77.4 (C-5), 66.3 (CH$_2$), 45.7 (C-7a), 39.7 (C-7), 38.4 (C-4), 38.1 (C-3), 29.2 (C-1), 20.4 (C-2) and 15.2 (CH$_3$).

The mixture **15**/**16**: *m*/*z* (EI) [Found: ($M^{\bullet+}$ − HNO_2), 180.11518. $C_{11}H_{16}O_2$ ($C_{11}H_{17}NO_2$ − HNO_2) requires *m*/*z*, 180.11503, 3%], 135 ($M^{\bullet+}$ − HNO_2 − OEt, 10), 134 (20), 123 (15), 109 (14), 106 (46), 94 (45), 80 (100), 77 (68) and 66 (32).

***trans*-3-Ethoxy-1-(2-nitrocyclopentyl)but-3-en-2-one 17.** Oil; R_f 0.55 (eluent: light petroleum–EtOAc 4:1) [Found: ($M^{\bullet+}$ + 1), 228.12324. $C_{11}H_{18}NO_4$ ($C_{11}H_{17}NO_4$ + H) requires *m*/*z*, 228.12358]; ν_{max}(neat)/cm^{-1} 1695 (C=O), 1610 (C=C), 1540, 1360 (NO_2) and 1125 (C–O–C); $\delta_H(CDCl_3)$ 5.18 (1 H, d, *J* 2.4, C=CH *trans* to OEt), 4.60 (1 H, dt, *J* 8.8, 6.0, 6.0, CHNO$_2$), 4.39 (1 H, d, *J* 2.4, C=CH *cis* to OEt), 3.80, 3.78 (2 H, 2q, OCH_2CH$_3$) 2.90 (3 H, m, CHCH_2CO), 2.28 (1 H, m, ring H), 2.14 (2 H, m, 2 ring H), 1.90 (1 H, m, ring H), 1.78 (1 H, m, ring H) and 1.38 and 1.36 (4 H, t and m, CH$_2$CH_3 and ring H); $\delta_C(CDCl_3)$ 195.9 (s), 157.3 (s), 90.8 (t), 90.7 (d), 63.8 (t), 41.6 (t), 41.4 (t), 32.0 (d), 31.5 (t), 23.8 (t) and 14.3 (q).

***cis*-3-Ethoxy-1-(2-nitrocyclopentyl)but-3-en-2-one 18.** In the ^{1}H NMR spectrum only a few signals of **18** were not superimposed with those of **17** in the 9:1 mixture **17**/**18**: $\delta_H(CDCl_3)$ 5.18 (1 H, d, *J* 2.4, C=CH), 5.09 (1 H, dt, *J* 1.8, 6.4, 6.4, CHNO$_2$) and 4.40 (1 H, d, *J* 2.4, C=CH); $\delta_C(CDCl_3)$ 196.5 (s), 157.3 (s), 91.0 (t), 90.9 (d), 63.8 (t), 41.5 (t), 41.3 (t), 31.9 (d), 31.4 (t), 23.9 (t) and 14.2 (q).

The mixture **17**/**18**: *m*/*z* (EI) 228 ($M^{\bullet+}$ + 1, 0.2%), 181 (M − 46, 8), 153 (11), 151 (8), 135 (9), 123 (14), 115 (10), 109 (28), 17 (13), 96 (11), 95 (12), 87 (12), 82 (14), 81 (52), 79 (22), 71 (25), 68 (14), 67 (100) and 43 (61).

(1′*R,2′*S**,3a*S**,7*S**,7a*S**)-5-Ethoxy-6-morpholino-3a-nitro-7-(2-nitrocyclopentyl)-2,3,3a,4,7,7a-hexahydro-1*H*-indene 14**

To a solution of the enamine **9** (0.25 g, 1.37 mmol) in dry chloroform (10 cm^3) at 0 °C was added 1-nitrocyclopentene (0.31 g, 2.75 mmol) in the same solvent (10 cm^3). The mixture was kept at room temperature for 3 days. Evaporation of the solvent left a solid which was crystallized from benzene–ligroin, mp 221 °C (85% yield, after crystallization) (Found: C, 58.70; H, 7.68; N, 10.51. $C_{20}H_{31}N_3O_6$ requires C, 58.66; H, 7.63; N, 10.26%); ν_{max}(Nujol)/cm^{-1} 1660 (C=C), 1540, 1360 (NO_2) and 1110 (C–O–C); $\delta_H(CDCl_3)$ 5.18 (1 H, dt, *J* 8.1, 8.1, 6.1, CHNO$_2$), 3.61 (1 H, dq, ^2J 9.0, ^3J 7.1, CHCH$_3$), 3.60 (4 H, t, *J* 4.5, CH$_2$OCH$_2$), 3.42 (1 H, dq, ^2J 9.0, ^3J 7.1, CHCH$_3$), 3.16 (2 H, dt, *J* 4.5, 4.5, 12.2, CH$_2$N), 3.06 (1 H, d *J* 14.9, 7β-H), 3.04 (1 H, m, 1′-H), 2.88 (1 H, m, 3a-H), 2.66 (2 H, dt, *J* 4.5, 4.5, 12.2, CH$_2$N), 2.62 (1 H, m, 5′-H *cis* with respect to the nitro group), 2.50 (1 H, d, 14.9, 7α-H), 2.23–2.10 (3 H, m, 3α-H, 2 3′-H), 2.00–1.93 (1 H, m, 2α-H), 1.83 (1 H, d, *J* 11.0, 4-H), 1.80–1.46 (5 H, m, 2 1-H, 2 4′-H, 5′-H *trans* with respect to the nitro group), 1.30–1.12 (2 H, m, 2β-H, 3β-H) and 1.17 (3 H, t, *J* 7.1, CH$_2$CH_3); $\delta_C(CDCl_3)$ 138.8 (s), 130.3 (s), 99.0 (s), 88.6 (d), 67.9 (2 t), 64.9 (t), 50.2 (2 t), 47.1 (d), 45.9 (d), 45.5 (d), 41.6 (t), 36.0 (t), 35.0 (t), 34.1 (t), 32.3 (t), 24.6 (t), 23.8 (t) and 15.4 (q); *m*/*z* (EI) 409 ($M^{\bullet+}$, 2%), 407 (22), 381 (13), 378 (61), 362 (42), 332 (100), 316 (32), 315 (26), 304 (22), 288 (19), 286 (29), 258 (19), 249 (26), 220 (35), 218 (29), 205 (22), 192 (19), 160 (16), 145 (13), 117 (19), 107 (19), 105 (22), 91 (35), 86 (29), 84 (22), 81 (22), 79 (35), 77 (26) and 67 (48).

3-Ethoxy-1-(2-oxocyclopentyl)but-3-en-2-one 21

The reaction between the dienamine **9** (0.25 g, 1.37 mmol) and 1-nitrocyclopentene (0.15 g, 1.37 mmol) was performed in anhydrous ether, at −20 °C. Hydrolysis of the crude mixture carried out after 2 h allowed the isolation of the diketone **21**, oil (0.1 g, 37%) (Found: $M^{\bullet+}$, 196.10970. $C_{11}H_{16}O_3$ requires *m*/*z*, 196.10994); ν_{max}(neat)/cm^{-1} 1730, 1700 (C=O), 1605 (C=C) and 1230 and 1105 (C–O–C); $\delta_H(CDCl_3)$ 5.18 (1 H, d, *J* 2.4, C=CH *trans* to OEt), 4.41 (1 H, d, *J* 2.4, C=CH *cis* to OEt), 3.79 (2 H, q, OCH_2CH$_3$), 3.19 (1 H, dd, *J* 3.4, 18.9, CHCO), 2.78 (1 H, dd, *J* 7.9, 18.9, CHCO), 2.50 (1 H, m, CHCH$_2$CO), 2.27 (3 H, m, ring H), 2.05 (1 H, m, ring H), 1.80 (1 H, m, ring H), 1.53 (1 H, dq, ring H), and 1.36 (3 H, t, OCH$_2$CH_3); $\delta_C(CDCl_3)$ 220.4 (s), 195.9 (s), 157.3 (s), 90.8 (t), 63.7 (t), 44.5 (d), 38.1 (t), 37.5 (t), 29.4 (t), 20.8 (t) and 14.3 (q); *m*/*z* (EI) 196 ($M^{\bullet+}$, 37%), 181 ($M^{\bullet+}$ − 15, 1), 168 ($M^{\bullet+}$ − CO, 10), 152 ($M^{\bullet+}$ − 44, 18), 139 (17), 125 (55), 113 (24), 97 (100), 83 (36) and 69 (67).

Reaction with 1-nitrocyclohexene

To a solution of the enamine **9** (0.5 g, 2.75 mmol), in dry chloroform (10 cm^3) at room temperature was added 1-nitrocyclohexene (0.35 g, 2.75 mmol) in the same solvent (25 cm^3). The mixture was kept at room temperature for 3 days after which water (5 cm^3) and hydrochloric acid (2 mol dm^{-3}) were added. After the mixture had been stirred for 2 h, the two phases were separated and the oily residue was chromatographed with light petroleum–ethyl acetate (gradient from 100:0 to 80:20) as eluent to give compounds **24** and **25** (0.45 g, 70%).

***cis*- and *trans*-3-Ethoxy-1-(2-nitrocyclohexyl)but-3-en-2-one 24 and 25.** Oil (Found: $M^{\bullet+}$, 241.13120. $C_{12}H_{19}NO_4$ requires *m*/*z*, 241.13141); ν_{max}/cm^{-1} 1700 (C=O), 1610 (C=C), 1540, 1360 (NO_2) and 1130 (C–O–C); $\delta_H(CDCl_3)$ 5.17 (0.1 H, d, *J* 2.4, C=CH), 5.16 (0.9 H, d, *J* 2.4, C=CH), 4.75 (0.1 H, q, *J* 4.9, CHNO$_2$), 4.40 (0.1 H, d, *J* 2.4, C=CH), 4.39 (0.9 H, d, *J* 2.4, C=CH), 4.37 (0.9 H, dt, *J* 4.2, 10.3, 10.3, CHNO$_2$), 3.52–3.35 (2 H, m, CH_2CH$_3$), 2.75–2.46 (3 H, m, CHCH$_2$CO), 1.92–1.70 (m, 8 H, ring H), and 1.38 (t, 3 H, CH$_2$CH_3); $\delta_C(CDCl_3)$ for the isomer **24** 195.5 (s), 149.9 (s), 90.9 (t), 85.3 (d), 63.7 (t), 40.5 (t), 34.1 (d), 28.3 (t), 27.3 (t), 23.0 (t), 21.3 (t) and 14.2 (q); $\delta_C(CDCl_3)$ for the isomer **25** 195.5 (s), 157.3 (s),

90.7 (t), 89.9 (d), 63.7 (t), 40.5 (t), 36.9 (d), 31.9 (t), 30.3 (t), 24.6 (t), 24.3 (t) and 14.2 (q); *m/z* (EI) 242 ($M^{\cdot+}$ + 1, 2), 241 ($M^{\cdot+}$, 2%), 240 (2), 196 (2), 195 (5), 193 (3), 116 (100), 106 (14), 96 (15), 95 (17), 89 (41), 81 (45), 80 (81), 78 (24), 69 (20), 66 (34) and 60 (78).

When the same reaction was carried out in refluxing ethanol for 2 h and hydrolysed, 2-decalone derivatives **26** and **27** were also formed. They were separated from the linear compounds **25**/**26** by chromatography in 7% yield.

(3*R,4a*S**,8a*S**)-3-Ethoxy-4a-nitrooctahydro-1*H*-naphthalen-2-one 26.** Only a few signals of the isomer **26** could be identified in the ^{1}H NMR spectrum of the 1:9 mixture with **27**: δ_H($CDCl_3$) 3.64 (0.1 H, dt, *J* 1.0, 4.8, 4.8, 3-H), 3.39 (0.2 H, q, CH_2CH_3), 3.18 (0.1 H, dd, *J* 5.8, 15.2), 3.1 (0.1 H, m), 2.81 (0.1 H, dd, *J* 3.6, 9.6), 2.43 (0.1 H, dd, *J* 4.0, 15.2), 1.98 (0.1 H, dd, *J* 4.0, 13.1) and 1.11 (0.3 H, t, CH_2CH_3).

(3*S,4a*S**,8a*S**)-3-Ethoxy-4a-nitrooctahydro-1*H*-naphthalen-2-one 27.** Oil (Found: $M^{\cdot+}$, 241.13128. $C_{12}H_{19}NO_4$ requires *m/z*, 241.13141); ν_{max}/cm^{-1} 1730 (C=O), 1540, 1380 (NO_2) and 1130 and 1100 (C–O–C); δ_H($CDCl_3$) 3.99 (1 H, ddd, $J_{1ax,3ax}$ 1.2, $J_{3ax,4ax}$ 11.9, $J_{3ax,4eq}$ 6.7, 3_{ax}-H), 3.79 (1 H, dq, ^2J 9.2, ^3J 7.0, $CHCH_3$), 3.48 (1 H, dq, ^2J 9.2, ^3J 7.0, $CHCH_3$), 3.01–2.94 (2 H, m, 4_{eq}-H, 8a-H), 2.61 (1 H, ddd, $J_{1ax,3ax}$ 1.2, $J_{1ax,8a}$ 5.5, $J_{1ax,1eq}$ 14.3, 1_{ax}-H), 2.37 (1 H, dd, $J_{3ax,4ax}$ 11.9, $J_{4ax,4eq}$ 15.0, 4_{ax}-H), 2.19 (1 H, dd, $J_{1eq,8a}$ 2.4, $J_{1ax,1eq}$ 14.3, 1_{eq}-H), 2.14–2.11 (1 H, m, 5_{eq}-H), 2.05-1.99 (1 H, m, 5_{ax}-H), 1.98–1.74 (3 H, m, 6_{eq}-H, 7_{ax}-H, 8_{ax}-H), 1.43–1.30 (2 H, m, 6_{ax}-H, 7_{eq}-H), 1.27–1.18 (1 H, m, 8_{eq}-H) and 1.25 (3 H, t, CH_2CH_3); δ_C($CDCl_3$) 206.4 (C-2), 93.1 (C-4a), 78.0 (C-3), 66.4 (CH_2CH_3), 42.6 (C-1), 40.9 (C-8a), 37.1 (C-5), 35.6 (C-4), 29.3 (C-8), 24.7 (C-7), 22.4 (C-6) and 15.2 (CH_2CH_3); *m/z* (EI) 241 ($M^{\cdot+}$, 1%), 193 (2), 149 (12), 148 (15), 138 (13), 120 (36), 106 (12), 94 (100), 92 (33), 90 (13), 80 (16), 78 (39) and 66 (46).

Reaction with β-nitrostyrene

To a solution of the enamine **9** (0.5 g, 2.75 mmol) in dry chloroform (10 cm^3) at room temperature was added β-nitrostyrene (0.4 g, 2.75 mmol) in the same solvent (15 cm^3). The mixture was kept at room temperature for 24 h after which water (5 cm^3) and hydrochloric acid (2 mol dm^{-3}) were added. After the mixture had been stirred for 2 h, separation of the two phases left an oil which was chromatographed with light petroleum–ethyl acetate (gradient from 100:0 up to 90:10) as eluent.

2-Ethoxy-6-nitro-5-phenylhex-1-en-3-one 28. Mp 64 °C (0.40 g, 55%), R_f 0.45 (eluent: light petroleum–EtOAc 4:1) [Found: ($M^{\cdot+}$ − HNO_2), 216.11523. $C_{14}H_{16}O_2$ ($C_{14}H_{17}NO_4$ − HNO_2) requires *m/z*, 216.11503]; ν_{max}(neat)/cm^{-1} 1710 (C=O), 1618 (C=C), 1600, 1485 (Ph) and 1540 (NO_2); δ_H($CDCl_3$) 7.30 (2 H, m, *o*-Ar-H), 7.25 (3 H, m, *m*- and *p*-Ar-H), 5.15 (1 H, d, *J* 1.4, C=CH), 4.71 (1 H, dd, ^2J 12.5, ^3J 6.7, $CHNO_2$), 4.60 (1 H, ^2J 12.5, ^3J 8.3, $CHNO_2$), 4.38 (1 H, d, *J* 1.4, C=CH), 4.06 (1 H, br quintet, C*H*Ph), 3.77 (2 H, q, OCH_2CH_3), 3.13 (2 H, 2 pseudo q, CH_2CO) and 1.36 (3 H, t, OCH_2CH_3); δ_C($CDCl_3$) 194.7 (s, C-3), 156.9 (s, C-2), 139.0 (s), 128.8 (2 d), 127.6 (d), 127.4 (2 d), 91.0 (t, C-1), 79.4 (t, C-6), 63.7 (t, OCH_2CH_3), 40.9 (t, C-4), 38.8 (d, C-5) and 14.1 (q, OCH_2CH_3); *m/z* (EI) 216 ($M^{\cdot+}$ − HNO_2, 24%), 188 ($M^{\cdot+}$ − HNO_2 − Et, 50), 187 (39), 173 (18), 159 (32), 145 (36), 143 (60), 131 (36), 117 (77), 104 (100), 91 (55), 78 (38) and 77 (33).

(2*R,4*R**,5*S**)-2-Ethoxy-4-nitro-5-phenylcyclohexanone 29.** Further elution gave compound **29** (0.11 g, 15%), oil; R_f (eluent: light petroleum–EtOAc 4:1); ν_{max}(neat)/cm^{-1} 1720 (C=O), 1540, 1380 (NO_2) and 1130 and 1100 (C–O–C); δ_H($CDCl_3$) 7.35–7.15 (5 H, m, Ph), 5.35 (1 H, dt, *J* 4.0, 11.9, 11.9, 4-H), 3.82 (1 H, t, *J* 6.0, 2-H), 3.58 (1 H, ddd, *J* 4.6, 11.0, 13.4, 5-H), 3.51 (2 H, q, *J* 6.7, OCH_2CH_3), 3.11 (1 H, t, *J* 13.7, 6_{ax}-H), 2.74 (1 H, dt, *J* 4.0, 4.0, 13.4, 3_{eq}-H), 2.52 (1 H, dd, *J* 4.6, 13.7, 6_{eq}-H), 2.40 (1 H, ddd, *J* 3.0, 11.9, 13.4, 3_{ax}-H) and 1.20 (3 H, t, *J* 6.7, OCH_2CH_3); δ_C($CDCl_3$) 206.6 (s, C-1), 137.9 (s), 129.0 (2 d), 128.2 (d), 126.9 (2 d), 85.1 (d, C-4), 79.3 (d, C-2), 65.6 (t, OCH_2), 47.8 (d, C-5), 42.0 (t, C-6), 36.5 (t, C-3) and 15.1 (q, CH_3).

(2*S,4*R**,5*S**)-2-Ethoxy-4-nitro-5-phenylcyclohexanone 30.** Further elution gave **30** (0.04 g, 5.5%), mp 127–129 °C; R_f 0.20 (eluent: light petroleum–EtOAc 4:1) (Found: C, 63.95; H, 6.36; N, 5.47. $C_{14}H_{17}NO_4$ requires C, 63.87; H, 6.51; N, 5.32); ν_{max}/cm^{-1} 1730 (C=O), 1540, 1380 (NO_2) and 1130 and 1100 (C–O–C); δ_H($CDCl_3$) 7.28–7.13 (5 H, m, Ph), 5.06 (1 H, dt, *J* 3.4, 12.0, 12.0, 4-H), 3.76 (1 H, dq, $OCHCH_3$), 3.55 (1 H, ddd, *J* 5.6, 11.5, 12.2, 5-H), 4.05 (1 H, ddd, *J* 0.1, 6.3, 12.2, 2-H), 3.46 (1 H, dq, $OCHCH_3$), 2.82 (1 H, ddd, *J* 3.9, 5.8, 12.2, 3_{eq}-H), 2.65 (2 H, m, 6-H), 2.38 (1 H, apparent q, *J* 12.2, 3_{ax}-H) and 1.21 (3 H, t, OCH_2CH_3); δ_C($CDCl_3$) 203.8 (s, C-1), 137.2 (s), 129.1 (2 d), 128.2 (d), 126.7 (2 d), 86.8 (d, C-4), 78.6 (d, C-2), 66.4 (t, OCH_2), 47.6 (d, C-5), 43.9 (t, C-6), 36.9 (t, C-3) and 15.1 (q, CH_3); *m/z* (EI): 191 (4%), 187 (7), 172 (55), 159 (17), 143 (43), 131 (31), 117 (100), 104 (57), 91 (59) and 77 (30).

The same reaction carried out in tetrahydrofuran gave the same products. The ratio acyclic:cyclic products was 1:1. In ethanol under reflux for 2 h, also the cyclic compounds **29** and **30** were recovered, after hydrolysis, in the ratio of 1:1. Acidic equilibration of the 1:1 mixture of **29** and **30**, performed in refluxing benzene, in the presence of toluene-*p*-sulfonic acid in traces, changed the ratio to 4:1 in favour of the isomer **29**, in which the ethoxy group is in the axial conformation.[13]

Acknowledgements

The authors thank the Ministero dell'Università e della Ricerca Scientifica (MURST) and the Consiglio Nazionale delle Richerche (CNR, Rome) for financial support. One of the authors (G. M.) thanks the Consorzio per lo Sviluppo Internazionale of the University of Trieste for a fellowship.

References

1 (*a*) D. Enders, O. Meyer and G. Raabe, *Synthesis*, 1992, 1242; (*b*) D. Enders, O. Meyer and G. Raabe, *Synthesis*, 1994, 66; (*c*) R. H. Schlessinger and T. R. R. Pettus, *J. Org. Chem.*, 1994, **59**, 3246; (*d*) J. Barluenga, F. Aznar, A. Martin and J. T. Vásquez, *J. Am. Chem. Soc.*, 1995, **117**, 9419; (*e*) J. Barluenga, F. Aznar, M. P. Cabal and C. Valdes, *J. Chem. Soc., Perkin Trans. 1*, 1990, 633; (*f*) J. Barluenga, F. Aznar, M. P. Cabal, F. H. Cano and M. C. Foces-Foces, *J. Chem. Soc., Chem. Commun.*, 1988, 1247.
2 D. Pocar, P. Trimarco, R. Destro, E. Ortoleva and M. Ballabio, *Tetrahedron*, 1984, **40**, 3579.
3 (*a*) *Nitroalkanes and Nitroalkenes in Synthesis*, A. G. M. Barrett ed., *Tetrahedron*, 1990, **46**, 7313; (*b*) G. Rosini and R. Ballini, *Synthesis*, 1988, 833; (*c*) A. G. M. Barrett and G. G. Graboski, *Chem. Rev.*, 1986, **86**, 751; (*d*) D. Seebach, E. V. Colvin, F. Lehr and T. Weller, *Chimia*, 1979, **33**, 1.
4 J. Quick and R. Jenkins, *J. Org. Chem.*, 1978, **43**, 2275.
5 D. A. Harris, *J. Chem. Soc.*, 1950, 2247.
6 W. A. White and H. Weingarten, *J. Org. Chem.*, 1967, **32**, 213.
7 F. Johnson, L. G. Duquette, A. Whitehead and L. C. Dorman, *Tetrahedron*, 1974, **30**, 3241.
8 F. Johnson, *Chem. Rev.*, 1968, **68**, 3759.
9 H. Mazarguil and A. Lattes, *Bull. Soc. Chim. France*, 1969, 319.
10 G. Pitacco, A. Pizzioli and E. Valentin, *Synthesis*, 1996, 242.
11 F. Felluga, P. Nitti, G. Pitacco and E. Valentin, *Tetrahedron*, 1989, **45**, 5667.
12 (*a*) E. L. Eliel, S. H. Wilen and L. N. Mandel, *Stereochemistry of Organic Compounds*, Wiley & Sons, New York, 1994, p. 769; (*b*) p. 738.
13 J. A. Kresge and Y. Yin, *Can. J. Chem.*, 1987, **65**, 1753.
14 E. J. Corey and H. Estreicher, *Tetrahedron Lett.*, 1981, **22**, 603.

Paper 6/05345I
Received 30*th July* 1996
Accepted 23*rd September* 1996