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HIGHLY DIASTEREOSELECTIVE SYNTHESIS OF CYCLIC NITRONIC ESTERS FROM 1-(4-MORPHOLINYL)-1-PHENYLPROPENE WITH NITROOLEFINS

F.Felluga, P.Nitti, G.Pitacco and E.Valentin*
Dipartimento di Scienze Chimiche, Università, 34127 Trieste, Italy

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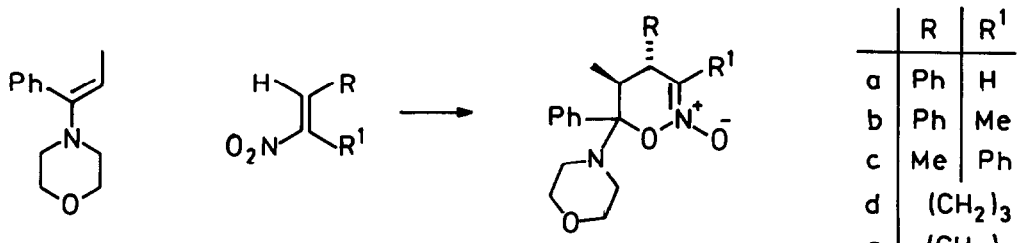
Abstract - 1,2-Oxazine N-oxide derivatives could be obtained as pure isomers from the title reagents. In methanol, they opened into the corresponding Michael-type adducts, as single double bond diastereoisomers. Hydrolyses of both the systems were also highly diastereoselective, leading to γ-diketones in the former case and to δ-nitroketones in the latter.

It is several years since we have been studying the reactivity of enamines with nitroolefins. So far however we have focused our attention essentially to the enamines derived from cyclic ketones,[1] with the exception of the enamines of methyl-cycloalkyl- and cycloalkenyl-ketones.[2,3] We wish to report here our first results of the reactions between some nitroolefins and the morpholino enamine of ethyl phenyl ketone **1** (Scheme 1),[4,5] which we have undertaken mainly with the purpose of identifying the amine intermediates, which might be either linear or cyclic.

The electrophiles used are listed in Scheme 1 and include ß-nitrostyrene (**2a**), 2-nitro-1-phenylpropene (**2b**), 1-nitro-1-phenylpropene (**2c**) and two alicyclic nitroolefins, namely 1-nitrocyclopentene (**2d**) and 1-nitrocyclohexene (**2e**) (Scheme 1).

Scheme 1



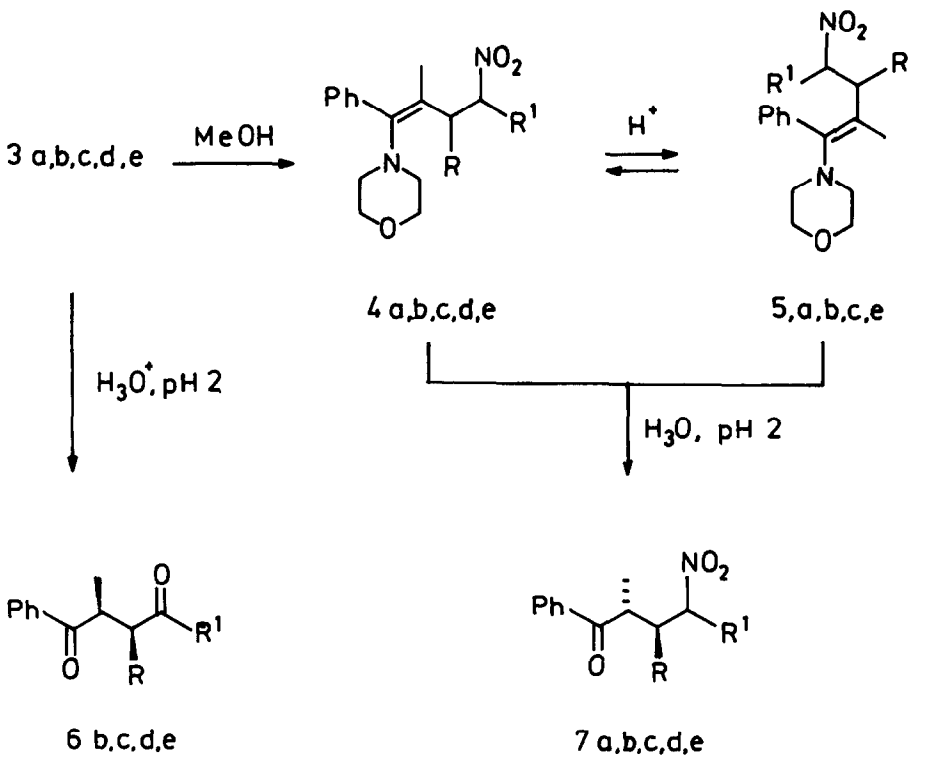
	R	R^1
a	Ph	H
b	Ph	Me
c	Me	Ph
d	$(CH_2)_3$	
e	$(CH_2)_4$	

1 **2a,b,c,d,e** **3a,b,c,d,e**

The reactions have been carried out in the absence of solvent, at 5-10 °C, conditions which improve the yields in the amine intermediates. In all the cases examined the product of kinetic formation was the 1,2-oxazine N-oxide derivative **3** as single diastereoisomer, in spite of the presence of three

chiral centres.[6] The reactions therefore are highly diastereoselective, firstly as far as the newly formed carbon-carbon bond is concerned. The relative configuration of these two chiral centres is a consequence of the Re*-Re* approach[4,5] of the two reactants. Unfortunately it was not possible to assign the stereochemistry of the remainder chiral centre formed by collapse of the oxygen negative charge onto the iminium carbon atom in the dipolar intermediate.[7] Also this reaction step in fact is highly diastereoselective and therefore a comparison with the other diastereoisomer, in which the configuration of the carbon atom bearing the amine is opposite, is not possible. This chirality however is lost in the subsequent tranformations of the heterocycles, namely the formation of the Michael-type adducts and the hydrolyses (Scheme 2). The former reaction can be carried out under kinetic control with the selective formation of either double bond isomer in all cases but one.

Scheme 2



Opening of the 1,2-oxazine N-oxides **3b,c,d,e** in fact, performed in methanol at room temperature, leads to the corresponding open-chain derivatives **4b,c,d,e**, whereas the heterocycle **3a** gives a 1:1 mixture of

compounds **4a** and **5a**. The system **3a** shows a further peculiar behaviour. In chloroform it reverts completely into the reagents, as it can be verified recording its ^1H NMR spectrum at fixed intervals. Once it is completely dissociated, the reagents react again to give the already mentioned mixture of **4a** and **5a**.

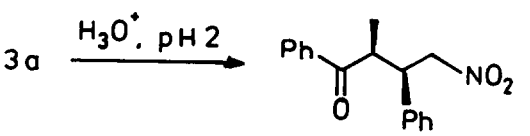
All the systems **4** have been attributed the **Z** configuration on the basis of the ^1H NMR chemical shift of the methyl group linked to the enamine ß carbon atom, which resonates at lower fields when it is cis to the base.[8] Consequently the systems **5** are attributed the **E** configuration.

Very mild acidic conditions ($CDCl_3$)[9] are sufficient to isomerize the nitroalkylated enamines **4** into a 1:1 mixture of **4** and **5**, with the exception of the derivative of 1-nitrocyclopentene **4d** which does not equilibrate even under more acidic conditions (TsOH in refluxing benzene).

Hydrolyses of both the 1,2-oxazine N-oxide derivatives **3** and the Michael-type adducts **4** have been performed subsequently (Schemes 2 and 3). The pH value of the solution is very important because at pH 5-6, which we have always considered the best for the hydrolysis of these systems,[1] the reaction rate is low and the competing equilibration reactions become important. On the contrary, at pH 2 the hydrolysis is fast enough to leave the original chiral centres unchanged. With the exception of **3a**, which gives the corresponding γ-nitroketone **7'a** (Scheme 3), the systems **3b,c,d,e** undergo the concomitant Nef reaction, allowing only the isolation of the corresponding δ-diketones **6**. They are single diastereoisomers, as expected, and they have been assigned the configuration shown in Scheme 2. The correctness of this attribution however has been demonstrated only for the ketone **6c**, which is a racemic form and not a meso form.[10,11,12]

The same hydrolysis conditions used for the adducts **4** lead to the corresponding δ-nitroketones **7** again as single diastereoisomers in all cases. It is evident therefore that also the protonation of the enamine ß-carbon atom is highly diastereoselective, which is unusual in the chemistry of enamines.[13] Interesting is also the fact that the same isomers **7** are obtained by hydrolysis of the mixtures **4** and **5** and this result can be explained only by admitting a stereoselective approach of the proton from the less hindered side of the prochiral centre.

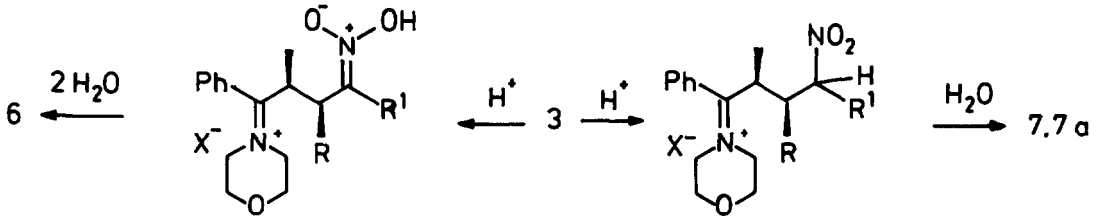
Scheme 3



7'a

This observation is supported by the fact that the γ-nitroketones 7a and 7'a, the former derived from the enamine 4a and the latter from the heterocycle 3a are diastereoisomers (Scheme 3).

It is evident that the formation of both the γ-nitroketone 7'a and the γ-diketones 6 from the heterocyclic systems 3 clearly occurs by attack of water on either the protonated dipolar intermediate 8 or 9 formed by nucleophilic ring fission of the 1,2-oxazine N-oxide ring.



8 9

In conclusion, these results on the linear enamine 1 show that it reacts with the nitroolefins in the same manner as the enamines from cyclic ketones. Under kinetic control, i.e. apolar solvents or absence of solvent, the amine intermediates are the 1,2-oxazine N-oxide systems, which however are more stable and tractable than those derived from cyclic ketones. Furthermore, important seems to be the possibility of getting to polysubstituted linear γ-nitroketones and γ-diketones with high diastereoselectivity, as already pointed out elsewhere.[4,5]

EXPERIMENTAL

Melting points were determined with a Büchi apparatus and are uncorrected. IR spectra were recorded in nujol mulls, unless otherwise indicated, on a Perkin Elmer 1320 spectrometer. UV spectra were determined on a Perkin-Elmer Lambda 5 spectrophotometer for ethanolic solutions. ^{1}H NMR spectra were measured on a Varian 360 A (60 MHz) spectrometer using deuterochloroform as solvent and tetramethylsilane as internal standard. ^{13}C NMR spectra were recorded on a Bruker WP-80 (20.1 MHz). MS spectra were obtained on a VG 7070 spectrometer at 70 eV. TLC were performed on Whatman K6F silica gel plates.

Synthesis of the reactants.

The enamine 1 [m.p. 56 °C (lit.[14] 59 °C] was prepared from ethyl-phenyl-ketone and morpholine by the method of W.White and T.A.Weingarten.[15] ß-Nitrostyrene (2a) was used as purchased (Aldrich), 2-nitro-1-phenyl-propene (2b) was prepared in accordance with ref. 16, 1-nitro-1-phenyl-propene (2c) in accordance with ref.1 and the cyclic nitroolefins 2d and 2e in accordance with E.Corey.[17]

Reaction of 1-(4-morpholinyl)-1-phenyl-propene (1) with ß-nitrostyrene (2a)

The nitroolefin 2a (0.73 g, 4.9 mmoles) was added to the enamine 1 (1.0 g, 4.9 mmoles) in an ice bath and the reactants mixed thoroughly with a rod. After 15 min the mass solidified and the solid was filtered with the aid of a small amount of ether. The product (1.6 g, 92 % yield) was identified as [4R*-(4α,5ß,6α or 6ß)]-5,6-dihydro-4,6-diphenyl-5-methyl-6-(4-morpholinyl)-4H-1,2-oxazine N-oxide (3a), m.p. 101-102 °C (Found: C, 71.41; H, 6.08; N, 7.80. $C_{21}H_{24}N_2O_3$ requires: C, 71.57; H, 6.86; N, 7.95%). IR, ν_{max}, cm^{-1} 1615 (C=N), 1580, 1495, 710 (Ph), 1115 (C-O-C); ^1H NMR, δ: 7.5 (m, 5 H, Ph), 6.3 (d, J 1.5 Hz, 1 H, HC=N), 4.1 (m, 1 H, CHPh), 3.7 (m, 4 H, CH_2OCH_2), 2.7 (m, 5 H, CH_2CH_2, CHMe), 1.0 ppm (d, J 6.0 Hz, 3 H, Me). MS: M^+ 352 (1), 306 (4), 292 (5), 203 (50), 202 (100), 176 (62), 117 (38), 105 (90), 91 (62), 77 (86).

When the heterocycle 3a was dissolved in chloroform, it reverted into the reactants within few hours. They reacted again to give a 55:45 mixture of the E and Z enamines 4a and 5a, from which the isomer 4a was isolated by flash chromatography (eluent: light petroleum-ethylacetate 1:9).

(Z)-1,3-diphenyl-2-methyl-1-(4-morpholinyl)-4-nitro-1-butene (4a)

Oil. IR, ν_{max}, cm^{-1}: 1640 (C=C), 1550 (NO_2), 1115 (C-O-C), 1600, 730, 700 (Ph). ^1H NMR, δ: 7.4 (m, 5 H, Ph), 5.8 (dd, 1 H, CHPh), 4.8 (d, 2 H, CH_2NO_2), 3.7 (m, 4 H, CH_2OCH_2), 2.5 (m, 4 H, CH_2NCH_2), 1.3 ppm (s, 3 H, Me).

When the heterocycle 3a (0.2 g) was dissolved in methanol (2 ml), it opened into an about 1:1 mixture of 4a and 5a, from which the enamine 5a precipitated as pure isomer. It was attributed the structure of (E)-1,3-diphenyl-2-methyl-1-(4-morpholinyl)-4-nitro-1-butene, m.p. 111-113 °C, from methanol (Found:C, 71.50; H, 6.73; N, 7.88. $C_{21}H_{24}N_2O_3$ requires: C, 71.57; H, 6.86; N, 7.95%). IR, ν_{max}, cm^{-1}: 1640 (C=C), 1600, 775, 700 (Ph), 1550, 1360 (NO_2), 1110 (C-O-C). ^1H NMR, δ: 7.3 (m, 5 H, Ph), 4.9 (m, 2 H, CH_2NO_2), 4.3 (dd, 1 H, CHPh), 3.7 (m, 4 H, CH_2OCH_2), 2.6 (m, 4 H, CH_2NCH_2), 1.9 ppm (s, 3 H, Me). ^{13}C NMR, δ: 148.7 (s), 138.3 (s), 135.8 (s), 129.2 (2 d), 128.4 (2 d), 128.0 (2 d), 127.5 (d), 126.9 (3 d), 122.5 (s), 76.9 (t), 66.9 (2 t), 50.8 (2 t), 45.3 (d), 11.7 ppm (q). MS: M^+ 352 (7), 306 (35), 292 (41), 276 (3), 260 (3), 246 (4), 232 (3), 218 (100), 202 (20), 129 (28), 105 (26).

(2S*,3R*)-1,3-diphenyl-2-methyl-4-nitro-1-butanone (7'a)[18]

The heterocycle 3a was hydrolysed in ethanol, water and HCl 10%, at pH 2, for 2 h, at r.t. Extraction with ether gave the ketone 7'a, oil. Its 2,4-dinitro-phenyl-hydrazone had m.p. 192-194 °C (Found: C, 59.83; H, 4.72; N, 15,03. $C_{23}H_{21}N_5O_6$ requires: C, 59.61; H, 4.57; N, 15.11%). IR, ν_{max}, cm^{-1}: 1670 (C=O), 1550, 1360 (NO_2), 800, 700 (Ph). ^1H NMR, δ: 8.0 (m, 2 H, o-ArH), 7.5 (m, 3 H, m- and p-ArH), 7.3 (m, 5 H, Ph); 4.7 (d, J 7.0 Hz, 2 H, CH_2NO_2), 3.9 (m, 2 H, CHPh, CHMe), 1.0 ppm (d, J 7.0 Hz, 3 H, Me). ^{13}C NMR, δ: 202.5 (s), 137.7 (s), 136.2 (s), 133.6 (d), 128.9 (d), 128.3 (d), 128.2 (d), 128.0 (d), 78.7 (t), 46.7 (d), 43.4 (d), 17.4 ppm (q). MS: 249 (1.5), 236.12045

($C_{17}H_{16}O$ = M - HNO_2: 236.12011) (0.7), 221 (1), 131 (2), 117 (5), 115 (5), 105 (100), 77 (39).

(2S*,3S*)-1,3-diphenyl-2-methyl-4-nitro-1-butanone (7a)[18]

When either the enamine **4a** or **5a** or a mixture of both is hydrolysed under the same conditions as above, the ketone **7'a** was obtained, m.p. 106 °C, from ethanol (Found: C, 71.82; H, 5.85; N, 4.87. $C_{17}H_{17}NO_3$ requires: C, 72.07; H, 6.05; N, 4.94%). IR, ν_{max}, cm^{-1}: 1670 (C=O), 1550, 1360 (NO_2), 790, 700 (Ph). ^1H NMR, δ: 7.8 (m, 2 H, o-ArH), 7.5 (m, 3 H, m- and p-ArH), 7.3 (m, 5 H, Ph), 4.8 (d, J 7.0 Hz, 2 H, CH_2NO_2), 4.0 (m, 2 H, CHPh, CHMe), 1.2 ppm (d, J 7.0 Hz, 3 H, Me). ^{13}C NMR, δ: 202.0 (s), 138.8 (s), 136.4 (s), 133.5 (d), 129.0 (d), 128.4 (d), 128.0 (d), 77.6 (t), 45.8 (d), 44.1 (d), 15.0 ppm (q). MS: 249 (4), 236.12045 ($C_{17}H_{16}O$ = M - HNO_2: 236.12011) (7), 221 (2), 144 (6), 117 (7), 105 (100), 77 (40).

The ketone **7a** was also obtained by equilibration of **7'a** in refluxing benzene, with traces of HPTS for 24 h, which furnished a 45:55 mixture of the isomers **7a** and **7'a**.

Reaction of 1-(4-morpholinyl)-1-phenyl-propene (1) with 2-nitro-1-phenyl-propene(2b)

[4R*-(4α,5ß,6α or 6ß)]-5,6-dihydro-3,5-dimethyl-6-(4-morpholinyl)-4H-1,2-oxazine N-oxide (3b)

The enamine **1** (1.0 g, 4.9 mmoles) and the nitrolefin **2b** were mixed intimately at 5 °C. After standing for 12 h, the mass was treated with dry ether and the solid filtered, **3b**, (1.4 g, 78% yield), m.p. 133-134 °C (Found:C, 72.00; H, 7.11; N, 7.56. $C_{22}H_{26}N_2O_3$ requires: C, 72.11; H, 7.15; N, 7.64%). IR, ν_{max}, cm^{-1}: 1620 (C=N), 1600, 1580, 780, 760, 710 (Ph), 1120 (C-O-C). UV: λ_{max} 231 nm (ε_{max} 15600). ^1H NMR, δ: 7.6 (m, 5 H, Ph), 7.4 (m, 3 H, m- and p-ArH), 7.2 (m, 2 H, o-ArH), 3.7 (m, 4 H, CH_2OCH_2), 2.8 (m, 6 H, CH_2NCH_2, CHMe, CHPh), 1.7 (d, J 2.0 Hz, 3 H, Me-C=N), 1.0 ppm (d, J 6.0 Hz, 3 H, Me). ^{13}C NMR, δ: 139.2 (s), 137.2 (s), 129.1 (2 d), 128.7 (4 d), 128.0 (d), 127.5 (2 d), 123.4 (s), 104.6 (s), 67.3 (2 t), 50.5 (d), 45.9 (2 t), 39.4 (d), 17.4 (q), 13.1 ppm (q). MS: M^+ 366 (1.6), 292 (33), 203 (52), 202 (100), 117 (60), 115 (90), 91 (90), 77 (39).

When the heterocycle **3b** was dissolved in methanol, the single diastereoisomer **4b** was isolated and identified as (Z)-1,3-diphenyl-2-methyl-1-(4-morpholinyl)-4-nitro-1-pentene, m.p. 111-113 °C, from methanol (Found: C, 72.25; H, 7.12; N, 7.84. $C_{22}H_{26}N_2O_3$ requires: C, 72.11; H, 7.15; N, 7.64%). IR, ν_{max}, cm^{-1}: 1630 (C=C), 1550 (NO_2), 1110 (C-O-C), 1600, 1500, 760, 700 (Ph). ^1H NMR, δ: 7.4 (m, 8 H, m- and p-ArH, Ph), 7.0 (m, 2 H, o-ArH), 5.4 (m, 2 H, $CHNO_2$, CHPh), 3.9 (m, 4 H, CH_2OCH_2), 2.5 (m, 4 H, CH_2NCH_2), 1.5 (s, 3 H, Me), 1.5 ppm (d, J 6.0 Hz, Me).

(2S*,3R*)-1,3-Diphenyl-2-methyl-1,4-pentandione (6b)

Hydrolysis of the heterocycle **3b**, carried out at pH 2 led to the corresponding diketone **6b**, m.p. 100-102 °C, from methanol (Found: C, 80.96; H, 6.90: $C_{18}H_{18}O_2$ requires: C, 81.17; H, 6.81%). IR, ν_{max}, cm^{-1}: 1700, 1675 (C=O), 1595, 760, 700 (Ph). ^1H NMR, δ: 8.0 (m, 2 H, o-ArH), 7.4 (m, 3 H, m- and p-ArH), 7.2 (s, 5 H, Ph), 4.1 (m, 2 H, CHPh, CHMe), 2.0 (s, 3 H, COMe), 0.85 ppm (d, J 7.0 Hz, Me). MS: M^+ 266.13217 ($C_{18}H_{18}O_2$: 266.13067) (3), 224 (36), 209 (7), 181 (5), 161 (4), 105 (100), 77 (33).

(2R*,3R*)-2,4-Dimethyl-1,3-diphenyl-4-nitro-1-pentanone (7b)

Hydrolysis of the enamine **4b**, carried out at pH 2, furnished the corresponding ketone **7b**, m.p. 111-112 °C, from methanol. IR, ν_{max}, cm^{-1}: 1670 (C=O), 1590, 1580, 1490, 720, 700 (Ph), 1535, 1350 (NO_2). ^1H NMR, δ: 7.8 (m, 2 H, o-ArH), 7.5 (m, 3 H, m-, p-ArH), 7.2 (s, 5 H, Ph), 5.2 (m, 1 H, $CHNO_2$), 4.1 (m, 2 H, CHPh, CHCO), 1.5 (d, J 7.0 Hz, 3 H, Me), 1.3 ppm (d, J 6.0 Hz, 3 H, Me). MS: M^+ 297.13694 ($C_{18}H_{19}NO_3$: 297.13648 (0.02), 263 (0.4), 251 (0.9), 247 (1), 235 (2), 117 (10), 115 (10), 105 (100).

Reaction of 1-(4-morpholinyl)-1-phenyl-propene (1) with 1-nitro-1-phenyl-propene (2c)

[4R*-(4α,5β,6α or 6β)]-5,6-dihydro-4,5-dimethyl-3,6-diphenyl-6-(4-morpholinyl)-4H-1,2-oxazine N-oxide (3c)

The nitroolefin 2c (1.2 g, 7.4 mmoles) was added to the enamine 1 (1.5 g, 7.4 mmoles) at 5 °C. After 8 h, the crude was treated with dry ether and the product 3c filtered (2.1 g, 77% yield), m.p. 126-128 °C (Found: C, 71.90; H, 7.16; N, 7.60. $C_{22}H_{26}N_2O_3$ requires: C, 72.11; H, 7.15; N, 7.54%). IR, ν_{max}, cm^{-1}: 1580 (C=N), 1600, 1570, 770, 750, 710 (Ph), 1120 (C-O-C). UV: λ_{max} 263.6 (ε_{max} 8100). ^1H NMR, δ: 7.4 (m, 10 H, Ph), 3.7 (m, 4 H, CH_2OCH_2), 2.8 (m, 6 H, CH_2NCH_2, 2 CHMe), 1.4 (d, J 6.0 Hz, 3 H, Me), 0.9 ppm (d, J 6.0 Hz, Me). ^{13}C NMR, δ: 132.3 (s), 129.1 (s), 128.7 (2 d), 128.5 (3 d), 128.4 (3 d), 127.3 (2 d), 105.7 (s), 67.2 (2 t), 45.8 (2 t), 38.2 (d), 36.6 (d), 16.7 (q), 13.3 ppm (q). MS: M^+ 366 (0.5), 230 (42), 203 (54), 202 (100), 163 (15), 117 (100), 115 (70), 91 (79), 77 (25).

Treatment of the heterocycle 3c with methanol allowed the isolation of (Z)- 1,4-diphenyl-2,3-dimethyl-1-(4-morpholinyl)-4-nitro-1-butene (4c), m.p. 149-150 °C (Found: C, 72.30; H, 7.10; N, 7.44. $C_{22}H_{26}N_2O_3$ requires: C, 72.11; H, 7.15; N, 7.54%). IR, ν_{max}, cm^{-1}: 1635 (C=C), 1540, 1350 (NO_2), 1600, 780, 760, 740, 700 (Ph), 1115 (C-O-C). ^1H NMR, δ: 7.5-6.4 (m, 10 H, Ph), 5.7, 5.4 (2 d, J 12.0 Hz, 1 H, $CHNO_2$), 4.8 (m, 1 H, CHMe), 3.8 (m, 4 H, CH_2OCH_2), 2.6, 2.4 (2 m, 4 H, CH_2NCH_2), 1.50, 1.25 (2 s, 3 H, C=C-Me), 1.3, 0.9 ppm (2 d, J 7.0 Hz, 3 H, Me).

In chloroform the enamine 4c isomerized into an about 1:1 mixture of 4c and 5c. ^1H NMR of the mixture, δ: 7.5-6.4 (m, 10 H, Ph), 5.7, 5.4 (2 d, J 12.0 Hz, 0.5 H, $CHNO_2$), 5.5, 5.4 (2 d, J 12.0 Hz, 0.5 H, $CHNO_2$), 4.8 (m,

1 H, CHMe), 3.8, 3.4 (m, 4 H, CH_2OCH_2), 2.6, 2.4 (2 m, 4 H, CH_2NCH_2), 2.0, 1.7 (2 s, 1.5 H, C=C-Me), 1.5, 1.25 (2 s, 1.5 H, C=C-Me), 1.3, 0.9 (2 d, J 7.0 Hz, 1.5 H, Me), 1.25, 0.80 ppm (2 d, J 7.0 Hz, 1.5 H, Me). (2S*,3S*)-2,3-Dimethyl- 1,4-diphenyl-1,4-butandione (6c)[10,11] The heterocycle 3c was hydrolysed at pH 2 and furnished the diketone 8c, m.p. 86 °C. IR, ν_{max}, cm^{-1}: 1670 (C=O), 1595, 780, 730, 700 (Ph). ^1H NMR, δ: 8.0 (m, 4 H, o-ArH), 7.4 (m, 6 H, m- and p-ArH), 3.9 (m, 2 H, CHMe), 1.2 ppm (m, 6 H, Me). MS: M^+ 266.13217 ($C_{18}H_{18}O_2$: 266.13067) (3), 161 (4), 147 (3), 134 (2), 105 (100), 77 (39).

(2R*,3S*)-2,3-dimethyl-1,4-diphenyl-4-nitro-1-butanone (7c)

Hydrolysis of the enamine mixture carried out at pH 2 furnished after the usual workup the ketone 7c, m.p. 98 °C. IR, ν_{max}, cm^{-1}: 1670 (C=O), 1595, 1585, 720, 640 (Ph), 1540, 1350 (NO_2). ^1H NMR, δ: 8.0 (m, 2 H, o-ArH), 7.5 (m, 8 H, m-, p-ArH, Ph), 5.6 (d, J 11.5 Hz, 1 H, $CHNO_2$), 3.7 (m, 1 H, COCHMe), 3.0 (m, 1 H, CHMe), 0.9 ppm (d, J 7.5 Hz, 3 H, Me). MS: 262.11759 ($C_{18}H_{16}NO$ = $C_{18}H_{19}NO_3$ - OH - H_2O: 262.12318) (0.6), 251.14068 (M - NO_2: 251.14358) (4), 230 (0.6), 145 (7), 131 (13), 105 (100), 77(5).

Reaction of 1-(4-morpholinyl)-1-phenyl-propene (1) with 1-nitro-cyclopentene (2d)

[4R*-(3α or 3ß,4α,4aα)]-4-methyl-3-(4-morpholinyl)-3-phenyl-4,4a,6,7-tetrahydro-cyclopenta-3H,5H-2,1-oxazine N-oxide (3d)[19]

The nitroolefin 2d (0.55 g, 4.9 mmoles) was added to a solution of the enamine 1 (1.0 g, 4.9 mmoles) in dry ether, at 0 °C. After 1 h a crystalline product, 3d, was separated (1.0 g, 65% yield), m.p. 113-115 °C (Found: C, 67.95; H, 7.49; N, 8.40. $C_{18}H_{24}N_2O_3$ requires: C, 68.33; H, 7.65; N, 8.55%). IR, ν_{max}, cm^{-1}: 1640 (C=N), 1600, 1580, 1495, 760, 710 (Ph), 1120 (C-O-C). ^1H NMR, δ: 7.3 (m, 5 H, Ph), 3.6 (m, 4 H, CH_2OCH_2), 2.7 (m, 6 H, CH_2NCH_2, CHMe, H-4a), 1.9 (m, 6 H, $(CH_2)_3$), 1.2 ppm (d, J 7.0 Hz, 3 H, Me). MS: M^+ 316 (5), 270 (6), 202 (4), 105 (100), 77 (44).

(Z)-1-(4-morpholinyl)-2-(2-nitrocyclopentyl)-1-phenyl-propene (4d)

The heterocycle 2d was dissolved in methanol and, after 4 h, the solvent was evaporated. The solid was crystallized from light petroleum, m.p. 62 °C (Found: C, 68.56; H, 7.62; N, 8.70. $C_{18}H_{24}N_2O_3$ requires: C, 68.33; H, 7.65; N, 8.55%). IR, ν_{max}, cm^{-1}: 1640 (C=C), 1600, 1500, 770, 700 (Ph), 1550, 1360 (NO_2), 1110 (C-O-C). ^1H NMR, δ: 7.4 (m, 3 H, m- and o-ArH), 7.1 (m, 2 H, o-ArH), 4.6 (m, 2 H, $CHNO_2$, H-1), 3.7 (m, 4 H, CH_2OCH_2), 2.4-1.9 (m, 10 H, CH_2NCH_2, $(CH_2)_3$), 1.4 ppm (s, 3 H, Me). ^{13}C NMR, δ: 166.7 (s), 148.3 (3), 136.3 (s), 129.5 (2 d), 128.1 (2 d), 127.1 (d), 89.5 (d), 67.0 (t), 52.0 (t), 47.5 (d), 31.7 (t), 29.6 (t), 24.0 (t), 13.5 ppm (q). MS: M^+ 316 (24), 286 (4), 270 (30), 242 (12), 231 (4), 226 (7), 218 (100), 202 (23), 157 (32), 129 (30), 117 (28), 115 (26), 105 (55).

(2S*,3S*)-2-(2-oxocyclopentyl)-1-phenyl-1-propanone (6d)

Hydrolysis of the heterocycle **3d** carried out under the usual conditions gave the γ-diketone **6d**, oil. IR, ν_{max}, cm^{-1}: 1735, 1680 (C=O), 1600, 1580, 1490, 710 (Ph). ^1H NMR, δ: 8.0 (m, 2 H, o-ArH), 7.6 (m, 3 H, m-, p-AeH), 3.9 (m, 1 H, CHCO), 3.3-1.6 (m, 7 H), 1.2 ppm (d, J 7.0 Hz, 3 H, Me). MS: M^+ 216.1114 ($C_{14}H_{16}O_2$: 216.11502) (8), 173 (2), 134 (7), 105 (100), 77 (24).

(2R*,3S*)-2-(2-nitrocyclopentyl)-1-phenyl-1-propanone (7d)

Hydrolysis of the enamine **4d** carried out in ethanol-10% HCl, at pH 2 led to the corresponding ketone **7d**, oil. IR, ν_{max}, cm^{-1}: 1665 (C=O), 1540, 1365 (NO_2), 1595, 1570, 700 (Ph). ^1H NMR, δ: 8.0 (m, 2 H, o-ArH), 7.5 (m, 3 H, m- and p-ArH), 4.7 (m, 1 H, $CHNO_2$), 3.6 (dq, J_1 7.0 Hz, J_2 8.5 Hz, 1 H, CHCO), 3.0 (m, 1 H, CHCHCO), 2.4-1.4 (m, 6 H, $(CH_2)_3$), 1.1 ppm (d, J 7.0 Hz, 3 H, Me). MS: M^+ 247.12126 ($C_{14}H_{17}NO_3$: 247.12083) (0.1), 134 (11), 105 (100), 95 (5), 77 (23).

Reaction of 1-(4-morpholinyl)-1-phenyl-propene (1) with 1-nitro-cyclohexene (2e)

[4R*-(3α or 3ß,4a,4aα)]-4,4a,5,6,7,8-hexahydro-4-methyl-3-(4-morpholinyl)-3-phenyl-3H-2,1-benzoxazine N-oxide (3e)

The nitroolefin (0.9 g, 7.3 mmoles) was added to the enamine **1** (1.5 g, 7.3 mmoles). After 12 h a solid was separated, **3e** (2.2 g, 92% yield), which was washed with ether, m.p. 124-125 °C (Found: C, 68.62; H, 7.82; N, 8.31. $C_{19}H_{26}N_2O_3$ requires: C, 69.06; H, 7.93, N, 8.48%). IR, ν_{max}, cm^{-1}: 1605 (C=N), 1600, 1500, 705 (Ph), 1120 (C-O-C). ^1H NMR, δ: 7.5 (s, 5 H, Ph), 3.7 (m, 4 H, CH_2OCH_2), 2.9-1.8 (m, 14 H, CH_2NCH_2, CHMe, $(CH_2)_4$, H-4a), 1.25 ppm (d, J 7.0 Hz, 3 H, Me). ^{13}C NMR, δ: 137.7 (s), 128.5 (2 d), 127.3 (3 d), 125.5 (s), 117.9 (s), 67.3 (2 t), 45.8 (2 t), 39.4 (2 d), 36.9 (t), 30.2 (t), 26.9 (t), 24.1 (t), 12.3 ppm (q). MS: M^+ 330 (10), 300 (2), 284 (6), 203 (50), 202 (100), 117 (44), 115 (34), 91 (55), 77 (42).

(Z)-1-(4-morpholinyl)-2-(2-nitrocyclohexyl)-1-phenyl-propene (4e)

The heterocycle **3e** was dissolved in methanol and after 24 h at room temp, the solvent was eliminated and the oily residue identified as **4e** (Found: C, 69.34; H, 7.86; N, 8.53:4. $C_{19}H_{26}N_2O_3$ requires: C, 69.06; H, 7.93; N, 8.48%). IR, ν_{max}, cm^{-1}: 1640 (C=C), 1600, 780, 700 (Ph), 1540, 1360 (NO_2), 1110 (C-O-C). ^1H NMR, δ: 7.4 (m, 3 H, m- and p- ArH), 7.0 (m, 2 H, o-ArH), 4.7 (m, 1 H, $CHNO_2$), 4.0 (m, 1 H, H-1), 3.7 (m, 4 h, CH_2OCH_2), 2.4 (m, 4 H, CH_2NCH_2), 1.6 (m, 8 H, $(CH_2)_4$), 1.4 ppm (s, 3 H, Me). When the enamine **4e** was left in $CDCl_3$ for 72 h, a 2:3 mixture of **4e** and **5e** was obtained. ^1H NMR, δ: 7.4 (m, 3 H, m- and p-ArH), 7.0 (m, 2 H, o-ArH), 4.7 (m, 0.6 H, $CHNO_2$), 4.4 (m, 0.4 H, $CHNO_2$), 3.7 (m, 4 H, CH_2OCH_2), 2.4 (m, 5 H, CH_2NCH_2, H-1), 1.8 (s, 1.8 H, Me), 1.7 (m, 8 H, $(CH_2)_4$), 1.4 ppm (s, 1.2 H, Me).

(2S*,3S*)-2-(2-Oxocyclohexyl)-1-phenyl-1-propanone (6e)

Hydrolysis of the heterocycle **3e**, carried out at pH 2 for 2 h led to the corresponding γ-diketone **6e**, oil. IR, ν_{max}, cm^{-1}: 1700, 1670 (C=O), 1600, 1500 (Ph). ^1H NMR, δ: 8.0 (m, 2 H, o-ArH), 7.5 (m, 3 H, m- and p-ArH), 3.7 (dq, J_1 7.0 Hz, J_2 9.0 Hz, 1 H, CHMe), 3.0 (m, 1 H, CHCO), 2.5-1.6 (m, 8 H, $(CH_2)_4$), 1.0 ppm (d, J 7.0 Hz, Me). MS: M^+ 230.13185 ($C_{15}H_{18}O_2$: 230.13067) (4), 147 (6), 134 (28), 105 (100), 77 (34).

(2R*,3S*)-2-(2-Nitrocyclohexyl)-1-phenyl-1-propanone (7e)

Hydrolysis of the enamine mixture **4e**, **5e** led to the corresponding ketone **7e**, oil (Found for its 2,4-dinitro-phenyl-hydrazone, m.p. 162-163 °C: C, 57.00; H, 5.32; N, 15.94. $C_{21}H_{23}N_5O_6$ requires: C, 57.14; H, 5.25; N, 15.86%). IR, ν_{max}, cm^{-1}: 1670 (C=O), 1595, 1500, 770, 700 (Ph), 1540, 1360 (NO_2). ^1H NMR, δ: 7.8 (m, 2 H, o-ArH), 7.5 (m, 3 H, m- and p-ArH), 4.4 (dt, 1 H, $CHNO_2$), 3.4 (dq, J_1 7.0 Hz, J_2 4.0 Hz, 1 H, CHMe), 2.7-1.7 (m, 9 H, $(CH_2)_4$-CH), 1.2 ppm (d, J 7.0 Hz, Me). MS: M^+ 261.13334 ($C_{15}H_{19}NO_3$: 261.13648) (0.5), 231 (0.3), 215 (1), 183 (0.7), 134 (23), 105 (100), 77 (37).

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REFERENCES AND FOOTNOTES

1. Asaro, F.; Pitacco, G; Valentin, E., Tetrahedron **1987**, 43, 3279-3287 and references therein cited.
2. Ferri, R.A.; Pitacco, G.; Valentin, E., Tetrahedron **1978**, 34, 2537-2543.
3. Benedetti, F.; Pitacco G.; Valentin, E., Tetrahedron **1979**, 35, 2293-2299.
4. Seebach, D.; Goliński, J., Helv. Chim. Acta **1981**, 64, 1413-1423.
5. Seebach, D.; Beck, K.; Goliński, J.; Hay, J.N.; Laube, J.T., Helv. Chim. Acta **1985**, 68, 162-162.
6. All compounds are racemic modifications.
7. Denmark, S.E.; Dappen, M.S.; Cramer, C.J., J. Am. Chem. Soc. **1986**, 108, 1306-1307.
8. Stradi, R.; Pocar, D.; Cassio, C., J. Chem. Soc. Perkin Trans. 1, **1974**, 2671-2672.
9. Truce, W.E.; Onken, D.W., J. Org. Chem. **1975**, 40, 3200-3208.
10. Perry, C.W.; Kalnins, M.V.; Deitcher, K.H., J. Org. Chem. **1972**, 37, 4371-4376.
11. Barba, F.; Velasco, M.D.; Guirado, A., Electrochim. Acta **1985**, 30, 1119-1120.
12. Russel, G.A.; Mudryk, B.; Jawdosiuk, M.; Wrobel, Z., J. Org. Chem. **1982**, 47, 1879-1884.
13. Johnson, F.; Duquette, L.G.; Whitehead, A.; Dorman, L.C., Tetrahedron **1974**, 30, 3241-3251.
14. Pocar, D., Bianchetti, G.; Dalla Croce, P., Gazz. Chim. Ital. **1965**, 95, 1220-1236.
15. White, W.; Weingarten, H., J. Org. Chem. **1967**, 32, 213-214.
16. Boberg, F.; Schultze, G.R., Chem. Ber. **1957**, 90, 1215-1225.
17. Corey, E ; Estreicher, H., J. Am. Chem. Soc **1978**, 100, 6294-6295.
18. Stevens, R.W.; Mukaiyama, T., Chem. Lett., **1985**, 855-858.
19. The reference centre is not the lowest-numbered chiral centre, as it should be, because its chirality is undetermined.