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INTRAMOLECULAR N-ALKENYLNITRONE-ADDITIONS

REGIO- AND STEREOCHEMISTRY

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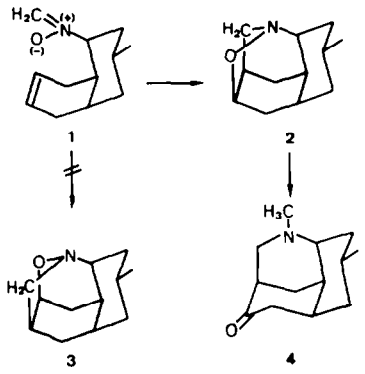
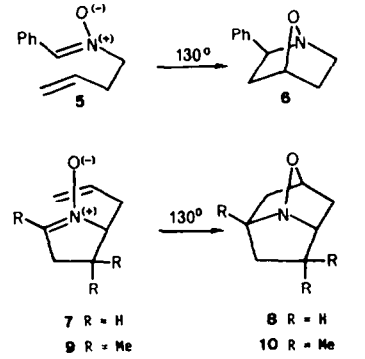
Abstract—Efficient intramolecular cycloadditions of N-3-alkenyl- and N-4-alkenylnitrones proceed with opposite regioselection which is modified by dipolarophile-substituent effects. Polycyclic isoxazolidines are obtained in a highly stereocontrolled fashion, consistent with an *endo*-addition of the *Z*-nitrones.

During an efficient synthesis of (+)-luciduline **4**[1] we have observed a strikingly uni-directional 1,3-dipolar addition[2] **1** → **2** with exclusive attack of the nitrone-carbon at the nearer centre of the non-polarized olefinic bond. Not even a trace of regioisomer **3** was formed (Scheme 1).



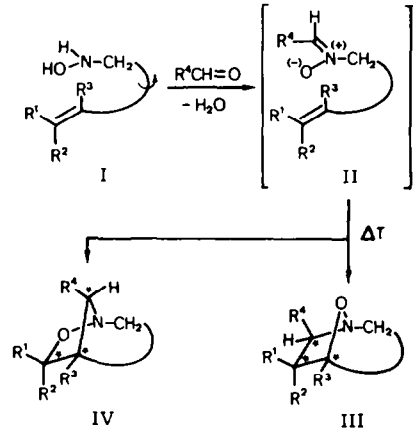
Scheme 1.

Prior to our work only three examples of intramolecular N-alkenylnitrone cycloadditions had been reported: **5** → **6**,[3] **7** → **8**[4] and **9** → **10**[5] (Scheme 2) showing a reversed regioselectivity, i.e. C—C bond formation with the more remote olefinic carbon.



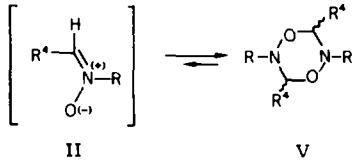
Scheme 2.

In extension of a preliminary communication[6] we now present a systematic study of intramolecular N-alkenylnitrone additions II → III and/or IV (Scheme 3) with the aim to understand and to predict their regio- and stereochemistry. Particular emphasis is given to the influence of bridge-length and substituent effects.



Scheme 3.

The required nitrones II were conveniently prepared *in situ* by condensation of the hydroxylamines I with aldehydes in toluene. [3+2]-Cycloadditions yielding the bridged isoxazolidines III and/or IV usually proceeded readily on heating the nitrone solutions at reflux for several hours. Nitrones derived from *p*-nitrobenzaldehyde occasionally dimerized rapidly to give V (Scheme 4); however, heating the isolated dimers V to 150–180° simply caused regeneration and olefin-trapping of nitrones II.

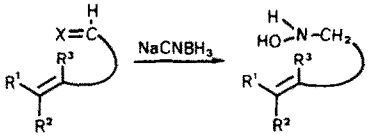


Scheme 4.

Preparation of N-*alkenylhydroxylamines* (Schemes 5–9)

The corresponding N-alkenylhydroxylamines I were smoothly obtained by reduction[7] of oximes VII with $NaBH_3CN$ (Scheme 5). Preparation of the starting aldehydes VI involved: (a) oxidations of primary alcohols[8] (**17**, **21**, Scheme 6); (b) cleavage of *trans,trans-*

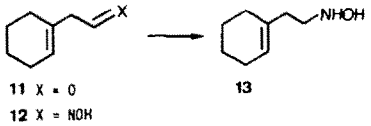
1,7-4,5-diols ($NaIO_4$), obtained from en-diynes[9] (**28**, **30**, Scheme 7); (c) Claisen rearrangements[10] (**40**, oximes: **37**, **39**) (Scheme 8); (d) 1-carbon chain-extension **44** → **47** (Scheme 8) or (e) 2-carbon chain-extension (Scheme 9) via alkylation of lithiated 2-methyl-2-thiazoline[11] and 5,6-dihydro-4,4,6-trimethyl-1,3-oxazine **55**[12] (oxime **56**). In several cases the unstable aldehydes were converted immediately into their stable oximes (**37**, **39**). Oxime **56** resulted from direct condensation of hydroxylamine with tetrahydro-oxazine **55**.



VI : X = O
VII : X = NOH

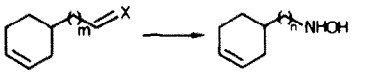
I

Scheme 5.



11 X = O
12 X = NOH

13



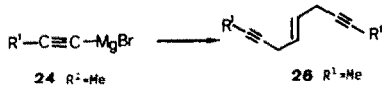
14 m=0 X=O
15 m=0 X=NOH
17 m=1 X=O
18 m=1 X=NOH

16 n = 1
19 n = 2

20 X = H, OH
21 X = O
22 X = NOH

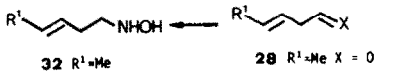
23

Scheme 6.



24 R¹=Me
25 R¹=Ph

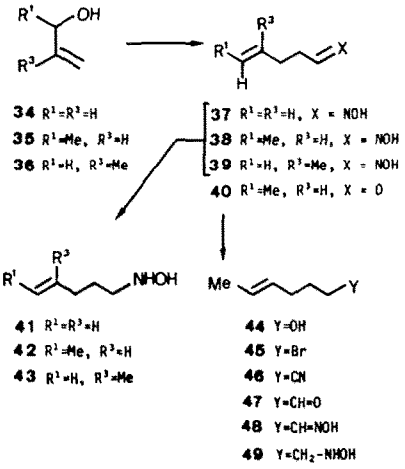
26 R¹=Me
27 R¹=Ph



32 R¹=Me
33 R¹=Ph

28 R¹=Me X = O
29 R¹=Me X = NOH
30 R¹=Ph X = O
31 R¹=Ph X = NOH

Scheme 7.



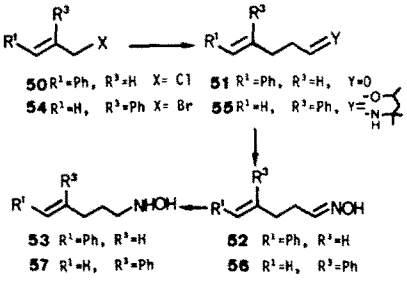
34 R¹=R³=H
35 R¹=Me, R³=H
36 R¹=H, R³=Me

37 R¹=R³=H, X = NOH
38 R¹=Me, R³=H, X = NOH
39 R¹=H, R³=Me, X = NOH
40 R¹=Me, R³=H, X = O

41 R¹=R³=H
42 R¹=Me, R³=H
43 R¹=H, R³=Me

44 Y=OH
45 Y=Br
46 Y=CN
47 Y=CH=O
48 Y=CH=NOH
49 Y=CH_2-NHOH

Scheme 8.



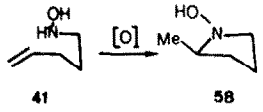
50 R¹=Ph, R³=H X= Cl
54 R¹=H, R³=Ph X= Br

51 R¹=Ph, R³=H, Y=O
55 R¹=H, R³=Ph, Y=

53 R¹=Ph, R³=H
57 R¹=H, R³=Ph

52 R¹=Ph, R³=H
56 R¹=H, R³=Ph

Scheme 9.



41

58

Scheme 10.

It is worth noting that the free olefinic hydroxylamines may cyclize readily, as illustrated by the extraordinarily smooth reaction **41** → **58**[6,13] (Scheme 10). In order to avoid this possible side reaction the hydroxylamines I were either used *in situ* (freshly prepared by reduction of oximes VII) or liberated from their stable hydrogenoxalates at 0° under argon immediately before condensation I → II.

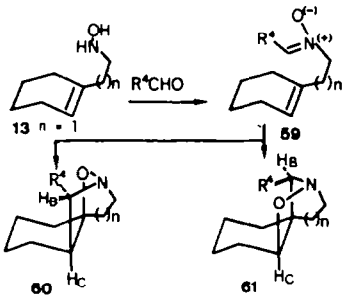
In situ *preparation and intramolecular cycloadditions of N-alkenylnitrones*

Technical. Methylene nitrones II (R^4 = H) were readily obtained by introducing a stream of gaseous formaldehyde at 0–5° into a solution of hydroxylamine I in toluene in the presence of anhydrous Na_2SO_4. Apart from **71b** (Table 3) the nitrones II, were not isolated but subjected to thermal cycloaddition *in situ* (toluene under reflux, Method A). Condensation of I with *p*-nitrobenzaldehyde, or n-hexanal in toluene in the presence of molecular sieves led to C-aryl (n-

pentyl)nitrones. These either cyclized on heating under reflux (Method A) or formed the corresponding dimers V which on heating either in *o*-dichlorobenzene under reflux (Method B), or in toluene at 150° using a sealed ampoule (Method C) furnished the required cycloadducts.

N-*Cycloalkenylnitrones*

Intrigued by the prospect of easily constructing structurally complex ring systems we studied first the intramolecular addition of N-cycloalkenylnitrones.



Scheme 11.

Table 1. Cycloadditions **59** → **60** + **61**

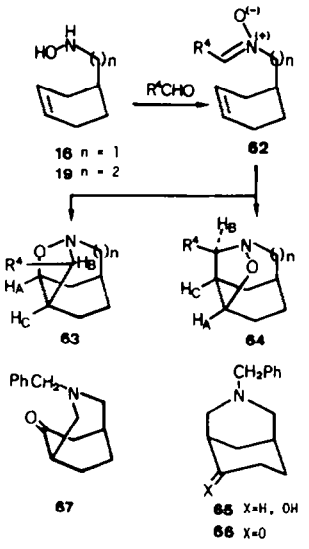
Entry	*n*	R^4	Method	Yields (%) **60**	**61**
a	1	H	A	74	0
b	1	*p*-NO_2Ph	B	97	0
c	2	H	A	20	50[14]

Thus heating nitrone **59a** (prepared *in situ* from **13**) in boiling toluene gave smoothly the tricyclic isoxazolidine **60a** as a single product (Scheme 11, Table 1, entry a, 74%). Similarly C-arylnitrone **59b** furnished exclusively adduct **60b** (entry b, 97%) with excellent stereochemical control. In both cases C—C bond formation occurred only at the remote olefinic centre. After publication of our preliminary communication, Snider reported the analogous addition of the homologous nitrone **59c** → **60c** + **61c** (2:5)[14] which served as a key step for the synthesis of (±)-nitramine. This example showed less distinct but reversed regioselectivity, apparently due to the longer chain.

The structures of **60** and **61** follow readily from their ^{1}H-NMR spectra. Compound **60a** shows no signal downfield from $\delta = 3.30$ thus ruling against structure **61a**. In the spectrum of **60b** H_B appears at $\delta = 4.24$ as a doublet $J_{BC} = 8$ Hz which indicates the *cis*-disposition of H_B and H_C (no other signal downfield from $\delta = 3.6$ is visible thus excluding structure **61b**). These assignments agree with those for the homologous adducts **60c** ($\delta R^4 = H$: 3.27, coupling with $H_C = 0$ Hz; δH_B: 2.94, $J_{BC} = 4$ Hz) and **61c** ($\delta H_C = 3.93$).[14]

In closer analogy to the conversion **1** → **2** the thermal cycloaddition of nitrones **62** were investigated (Scheme 12, Table 2).

In fact, condensation/addition **16** → **62a** → **64a** furnished only one product in 64% yield. The regiochemistry resulting from exclusive C—C bond formation with the nearer olefinic centre which parallels that of the reaction **1** → **2**, was unambiguously



Scheme 12.

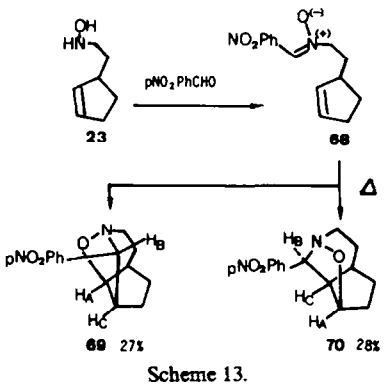
Table 2. Cycloadditions **62** → **63** + **64**

Entry	*n*	R^4	Method	Yields (%)[a] **63**	**64**
a	1	H	A	0	64
b	1	*p*-NO_2Ph	C	0	78
c	1	n-C_5H_{11}	B	8 (10)	67 (80)
d	2	*p*-NO_2Ph	B	32	48

[a] After isolation, GC in parentheses.

confirmed by N-benzylation ($PhCH_2Br$) of **64a** followed by N,O-hydrogenolysis ($LiAlH_4$), oxidation (PCC) of **65** and comparison of ketone **66** (m.p., IR, ^{1}H-NMR), with authentic samples of **66** and **67**.[15] Addition of the C-arylnitrone **62b** gave exclusively **64b** (78%), whereas the C-n-pentylnitrone **62c** reacted somewhat less regioselectively. Extension of the chain-length by one CH_2-group in the nitrone **62d** caused formation of **63d** and **64d**, with the latter isomer in slight excess.

The regiochemical assignments of **64b**, **63c**, **64c**, **63d** and **64d** are tentatively based on that of **64a**. The stereochemistry of **63d** and **64d** follows unambiguously from the ^{1}H-NMR data (**63d**: $\delta H_A = 4.39$ (m); $\delta H_B = 4.20$ (s), $J_{BC} = 0$ and **64d**: $\delta H_A = 4.61$ (d × t); $\delta H_B = 4.0$ (s), $J_{BC} = 0$). In both regioisomers $J_{BC} (= 0)$ indicates a dihedral angle of $H_B/H_C \cong 90°$ consistent only with a *trans*-disposition of H_B and H_C.



Scheme 13.

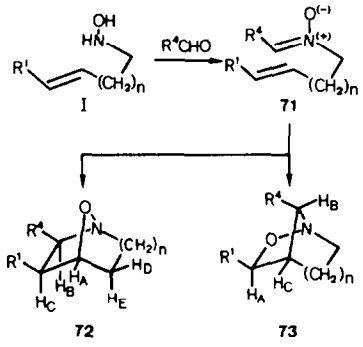
Complete loss of regioselectivity was observed in the thermal cycloaddition of nitrone **68** (Scheme 13, Method B) giving adducts **69** and **70**. In the ^{1}H-NMR spectra, **69** displays H_A as a triplet (J = 7 Hz) at $\delta = 4.7$ whereas **70** shows H_A as a triplet (J = 3 Hz) at $\delta = 4.0$ and H_B as a singlet at $\delta = 4.3$. Adduct **70** shows a coupling constant $J_{BC} = 0$, indicating the *trans*-relation of H_B and H_C.

Acyclic N-alkenylnitrones

In order to exclude secondary steric and electronic factors the thermal dipolar additions of straight chain N-3-butenyl-, N-4-pentenyl- and N-5-hexenylnitrones **71a**, **71b** and **71c**, containing a "symmetric" olefinic bond, were then studied (Scheme 14, Table 3).

Condensation of **32** with gaseous formaldehyde and heating the non-isolated nitrone **71a** in refluxing toluene furnished **72a** as the sole adduct (76%). On the other hand, the higher homologue **71b** gave exclusively **73b** (95%) with completely reversed regioselection. Increasing the distance between the dipole and the dipolarophile by yet another methylene group led via **71c** to a 1 : 3 mixture of **72c**/**73c**.

Complete and opposite regioselectivity was displayed by the intramolecular additions of the homologous C-*p*-nitrophenylnitrones **71d** → **72d** and **71e** → **73e**. A phenyl group on the terminal dipolarophilic centre slightly diminishes the regioselection of the N-3-alkenylnitrone addition **71f** → **72f** + **73f** (8 : 1).



Scheme 14.

In the higher homologues **71g** and **71h**, however, the intramolecularity and substituent effects[16] cooperate to ensure the exclusive formation of **73g** and **73h**, respectively.

Table 4. ^{1}H-NMR data of adducts **72**

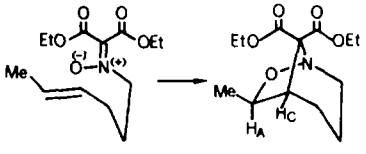
	δ Me	δH_A	J_{AC}	δ_{HB}	J_{BC}	J_{AD}	J_{AE}
72a	1.0	4.4	—	—	—	6	0
72c	1.1	4.1	—	—	—	8	~0
72d	[0.46]	4.50	0	4.04	[8]	5	0
72f	--	4.77	0	—	—	6	0

Table 5. ^{1}H-NMR data of adducts **73**

	δMe	δH_A	J_{AC}	δ_{HB}	J_{BC}	δPh
73b	1.2	4.35	0	—	—	—
73c	1.2	4.10	1.8	—	—	—
73e	[0.75]	4.35	0	4.20	[0]	—
73f	—	4.68	0	—	—	7.0–7.6
73g	—	5.30	0	—	—	7.3–7.5
73h	—	5.36	0	4.24	[0]	[6.9]

Structural assignments of the adducts **72** and **73** emerge readily from ^{1}H-NMR evidence (Tables 4 and 5). Regarding the stereochemistry the adducts derived from C-*p*-nitrophenylnitrones **71** exhibit clearly a *cis*-disposition of the R^1 and R^4 substituents. Thus, in **72d** the methyl is strongly shielded and $J_{BC} = 8$ Hz. Compounds **73e** and **73h** both show shielding of R^1 (Me or Ph) and a vicinal coupling constant $J_{BC} \cong 0$.

The completely selective transformation of the C,C-disubstituted nitrone **74** to give **75** (Scheme 15) is consistent with our previous regiochemical observations. (In the ^{1}H-NMR spectrum of **75** the Me-signal appears at $\delta = 1.08$ and the H_A-quadruplet (J = 7 Hz) at $\delta = 4.43$.)



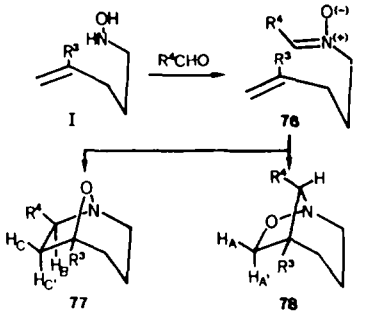
Scheme 15.

Table 3. Cycloadditions **71** → **72** + **73**.

Entry	*n*	I	R^1	R^4	Method	Yields (%)[a] 72	73
a	1	**32**	Me	H	A	76 (100)[b]	0
b	2	**42**	Me	H	A	0	95
c	3	**49**	Me	H	A	23 (25)[b]	68 (75)[b]
d	1	**32**	Me	*p*-NO_2Ph	B	85	0
e	2	**42**	Me	*p*-NO_2Ph	A	0	69
f	1	**33**	Ph	H	A	56 (88)[c]	9 (12)[c]
g	2	**53**	Ph	H	A	0	87
h	2	**53**	Ph	*p*-NO_2Ph	A	0	95

[a] Isolated product(s) after chromatography based on hydroxylamine I.
[b] GC of crude product(s) in parentheses.
[c] HPLC of crude product(s) in parentheses.

To test the relative directing power of intramolecularity vs substituent effects[16] on N-4-alkenylnitrone additions, substituents were attached to the nearer olefinic centre C(4) in **76** (Scheme 16). The regiochemical outcome is summarized in Table 6.



Scheme 16.

Table 6. Cycloadditions **76** → **77** + **78**

Entry	I	R^3	R^4	Method	Yields (%)[a] 77	78
a	**41**	H	H	A	23 (30)	48 (70)
b	**43**	Me	H	A	77 (80)	10 (10)
c	**43**	Me	*p*-NO_2Ph	D	93	0
d	**57**	Ph	H	A	82 (100)	0
e	**57**	Ph	*p*-NO_2Ph	B	68	0

[a]Isolated product(s) after chromatography, based on hydroxylamine I; GC of crude product(s) in parentheses.

With no terminal olefinic methyl group the regioselectivity is already reduced (**76a** → **77a** + **78a** (1 : 2)), while a methyl group at C(4) leads to a reversal of the directional control (**76b** → **77b** + **78b** (8 : 1) and **76c** → **77c**). The overwhelming effect of the C(4) phenyl substituent[16] over the intramolecular influence is illustrated by the additions **76d** → **77d** and **76e** → **77e**.

The structures of **77** and **78** were readily assigned based on ^{1}H-NMR data. Thus, **77a** (R^3 = H) exhibits only the R^3-multiplet (δ = 4.40, 1H, irradiation at δ = 2.3 → s) at low field, whereas both **77b** and **77d** show no signal downfield of δ = 3.5.

Stereochemical information on the *p*-nitrophenyl substituted adducts **77c** and **77e** is readily provided by the vicinal coupling constants J_{BC} and $J_{BC'}$ (Table 7) indicating clearly the *exo*-position of the *p*-nitrophenyl group. Both **78a** and **78b** show the signals of two protons H_A and $H_{A'}$ at low field (Table 8).

Table 7. ^{1}H-NMR data of **77c** and **77e**

	δH_B	J_{BC}	$J_{BC'}$
77c	4.43	4	10
77e	4.56	5	9

Table 8. ^{1}H-NMR data of **78a** ($R^4 = H_D$, $R^3 = H_C$) and **78b**

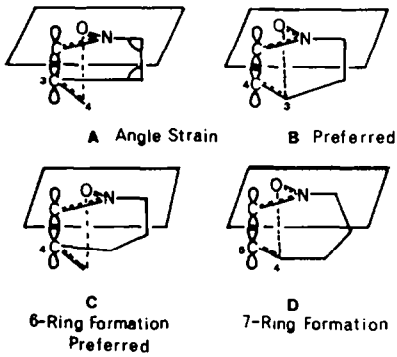
	δH_A	$\delta H_{A'}$	δH_D	$J_{AA'}$	J_{AC}	$J_{A'C}$	J_{CD}
78a	3.84	4.08	3.27	6	6	0	6
78b	~3.5	3.98	—	5	—	—	—

Rationalization

These orientational effects are apparently subject to kinetic control since the isomer pairs **72c**/**73c**, **77a**/**78a**, and **77b**/**78b** were not interconverted in boiling toluene (3 hr) and the isoxazolidines **73b** and **64** were thermally stable at 110 and 200°, respectively.

Regiochemistry

In order to understand this bridge-length dependent reversal of regioselectivity (Table 3),[17] transition state geometries were examined using Dreiding models. Considering coplanarity of the nitrone unit and the first bridge carbon atom,[18] the observed regiochemistry agrees with the assumption that in the corresponding transition state the new C—C bond is more developed than the C—O bond[19] (Scheme 17).



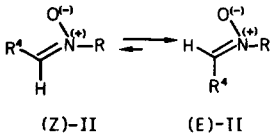
Scheme 17.

Thus, comparing the possible orientations for N-3-alkenylnitrone additions, C—C bond formation to the nearer olefinic centre C(3) invokes a strained transition state **A**, whereas the strongly predominating C—C(4) bond formation corresponds to the unstrained transition state **B**. With regard to N-4-alkenylnitrone additions, both orientations **C** and **D** do not exhibit strain. However, the observed preference of the transition state **C** over **D** may be ascribed to an entropically favoured 6-ring closure as compared with 7-ring formation. An analogous argument (preferred cyclization to a 7- rather than an 8-membered ring) applies to the less selective cyclization of N-5-alkenylnitrones.

The higher directing power of angle strain (**A** > **B**) vs entropy effects (**C** > **D**) is revealed by comparing their counterplay with dipolarophile-substituent effects.[16] For example, a phenyl group on C(4) lowers the regioselectivity of the N-3-alkenylnitrone addition **71f** → **72f** + **73f** (vs **71a** → **72a**, Table 3) but completely reverses that of the N-4-alkenylnitrone addition **76d** → **77d** (vs **76a** → **77a** + **78a**, Table 6). Substituents on the nitrone-carbon seem to play a less important role.

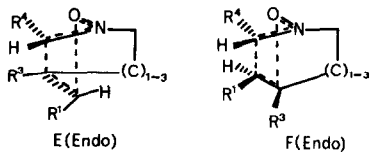
Stereochemistry

Bimolecular and intramolecular (C-alkenyl) nitrone additions to olefins suffer frequently from unpredictable *endo/exo*-product ratios. Another element of uncertainty is the possibility that the rate of *Z/E*-isomerization (Scheme 18) is comparable to that of the cycloaddition.[20] Accordingly, the formation of stereoisomer mixtures was difficult to rationalize and, even worse, undesirable in terms of synthetic applications. In contrast, the intramolecular N-alkenylnitrone cycloadditions described here display, without exception, virtually complete stereoselectivity. Up to four chiral centres were predictably controlled, which may be explained as follows. Examination of models (Scheme 19) reveals the incompatibility of a short bridge ($\leqslant 4$ atoms linking dipole and dipolarophile) with the *exo*-transition states **G** and **H** because of severe strain.[2c] Accordingly, the configurations of all C-*p*-nitrophenyl-N-alkenylnitrone adducts observed here are consistent with an exclusive reaction of the (*Z*)-*nitrones* II via the easily attainable *endo*-orientations **E** and/or **F**.

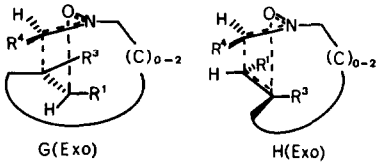


(Z)-II (E)-II

Scheme 18.



E(Endo) F(Endo)



G(Exo) H(Exo)

Scheme 19.

CONCLUSION

This work illustrates the feasibility of using the intramolecular version of a reaction to study the geometry of its transition state(s).[21] Above all, the high degree of structural complexity attained in one efficient synthetic operation I → III or IV with predictable regio- and stereochemical control should be of further value in organic synthesis.[1,22]

EXPERIMENTAL

General. All reactions were carried out under argon with magnetic stirring. Solvents were dried by distillation from drying agents as follows: diethylether (Et_2O, NaH), tetrahydrofuran (THF, K metal), toluene (Na metal), chloroform ($CHCl_3$, P_2O_5); pyridine was kept over molecular sieves (4 Å). The organolithium reagents were analyzed by Gilman's titration.[23] "Work-up" denotes extraction with an organic solvent, washing of the organic phase with sat NaCl aq, drying over $MgSO_4$ and removal of solvent by distillation *in vacuo* using a rotatory evaporator. Column chromatography was carried out on SiO_2 (Merck, Kieselgel 60). Gas chromatograms (GC): Carlo-Erba-Fractovap 2101, 1 atm N_2; steel columns (3 mm ID), stationary phases on chromosorb W (acid washed, 80–160 mesh): A: 1 m, 1 kg N_2/cm^2, 5% Carbowax; B: 2 m, 2.5 kg N_2/cm^2, 15% Carbowax, 3% KOH; retention time in min (area %). Melting points (m.p.) were determined on a Kofler hot stage and are uncorrected. Temperatures are expressed in degrees Celsius. IR spectra: CCl_4 or CH_2Cl_2 unless otherwise specified, $\tilde{\nu}_{max}$ in cm^{-1}. NMR spectra in $CDCl_3$, ^1H spectra at 100 MHz, unless otherwise specified, ^{13}C spectra at 25.2 MHz, standard tetramethylsilane δ (ppm) = 0; abbreviations: s singlet, d doublet, t triplet, q quartet, m multiplet, J spin–spin coupling constant (Hz). Mass spectra (MS): signals are given in *m/z* (rel. %).

Preparation of N-*alkenylhydroxylamines—general procedures*

Oximation of aldehydes. NaOAc (80 mmol) was added to a soln of the aldehyde (40 mmol) in MeOH (200 ml) at RT. Successive addition of $NH_2OH \cdot HCl$ (80 mmol) to the clear soln, stirring at RT for 1–6 hr (monitored by TLC) followed by evaporation, shaking with Et_2O–sat $NaHCO_3$ aq, drying ($MgSO_4$), evaporation of the organic phase and subsequent distillation (*in vacuo*) of the residue gave the corresponding oxime (*syn* and *anti*).

Reduction of aldoximes to N-*alkenylhydroxylamines*

A soln of $NaBH_3CN$ (139 mg, 2.2 mmol) in MeOH (2 ml) was added dropwise together with concurrent dropwise addition of aqueous 6 N HCl–MeOH (1 : 1) to a stirred soln of the oxime (2 mmol) in MeOH (10 ml) containing methylorange (3 mg) so as to keep the mixture at pH = 3 and at −40°. Then the mixture was allowed to attain −20° during 2 hr (maintaining the pH = 3). After evaporation the entire work-up was carried out at 0°; addition of sat NaCl aq, basification with 6 N KOH. Extraction with Et_2O, drying ($MgSO_4$) and evaporation of the organic phase gave the corresponding hydroxylamine which was used either without purification or crystallized preferably as its hydrogen oxalate salt.

Cyclohex-1-enyl-acetaldehyde oxime (**12**)

Diisobutylaluminium hydride (107 ml, ~150 mmol) was injected by means of a syringe into a soln of cyclohex-1-enyl-acetonitrile (12.1 g, 100 mmol) in toluene (500 ml) at −78°. Then the mixture was stirred at −78° (15 min), allowed to warm up to RT (over 1 hr) kept at RT for 1 hr and poured into sat sodium/potassium tartrate aq. Extraction with ether and work-up gave the crude **11** (12.2 g, 98%) of which 6.08 g (~49 mmol) gave **12** (5.31 g, 78%), b.p. 120°/0.1 Torr; IR: 3590, 3290 br, 2940, 2840, 1720, 1460, 1450, 1385, 1355, 1175, 1025, 995, 880. ^1H-NMR: 1.2–1.8 (4H); 1.8–2.5 (4H); 2.78 and 3.0 (two d, J = 6, 2H); 5.5 (s, br, 1H); 6.63 and 7.27 (two t, J = 6, 1H); 9.3 (br, 1H, disappears with D_2O). MS: 139 ($C_8H_{13}NO^+$, 19), 122 (14), 86 (58), 84 (100), 81 (68), 79 (46), 67 (31), 53 (24). The unstable oxime **12** was stored in soln (Et_2O) at −40°.

N-[2-(*Cyclohex-1-enyl*)*ethyl*]-*hydroxylamine* (**13**)

Reduction of **12** (0.86 g, 61 mmol) gave the crude unstable **13** (0.83 g, 97%) as a colourless solid, m.p. 49–51°, which was used directly without further purification. IR: 3590, 3270, 2930, 2857, 2835, 1480, 1135, 1048, 920. ^1H-NMR: 1.4–1.8 (4H); 1.8–2.4 (6H); 3.04 (t, J = 7, 2H); 4.99 (br, 2H, disappears with D_2O); 5.5 (m, 1H). MS: 141 ($C_8H_{15}NO^+$, 13), 96 (53), 81 (60), 46 (100), 67 (27).

Cyclohex-3-enyl-carbaldehyde oxime (**15**)

Aldehyde **14** (9.7 g, 88 mmol) gave crude **15** (10.08 g, 92%), colourless oil, IR (film): 3300, 3040, 1660. ^1H-NMR (CCl_4):

1.2–3.5 (7H), 5.60 (m, 2H), 6.55 (d, J = 7, 0.3 H); 7.30 (d, J = 7, 0.7 H); 9.2 (broad, 1H).

N-[*Cyclohex-3-enyl-methyl*]-*hydroxylamine* (**16**)

Reduction of **15** (513 mg, 4.11 mmol) gave crude **16** (503 mg, 96%), oil, IR (film): 3280, 3040, 1655. ^{1}H-NMR: 1.3–2.5 (7H); 2.80 (d, J = 5, 2H); 5.6 (m, 2H); 6.40 (broad s, 2H).

Cyclohex-3-enyl-acetaldehyde oxime (**18**)

A soln of cyclohex-3-enylethanol (5.05 g, 40 mmol) in CH_2Cl_2 (10 ml) was added, in one portion, to a mechanically stirred slurry of PCC (12 g, 60 mmol) in CH_2Cl_2 (300 ml) at 25°. After 1 hr at RT the mixture was diluted with Et_2O (1 l), filtered (Celite), and washed consecutively with 1 N NaOH, 1 N HCl, sat $NaHCO_3$ aq and sat NaCl aq. Removal of Et_2O by distillation at 760 Torr gave crude **17** which yielded **18** (4.3 g, 77% overall), b.p. 117–123°/14 Torr, IR: 3605, 3280 br, 3020, 1440, 942, 642. ^{1}H-NMR: 1.2–2.2 (7H); 2.2 and 2.4 (two t, J = 7, 2H); 5.67 (m, 2H); 6.82 and 7.48 (two t, J = 7, 1H); 9.81 (s, broad 1H, disappears with D_2O). MS: no $C_8H_{13}NO^{+\cdot}$, 121 (28), 120 (15), 81 (100), 80 (91), 79 (62), 54 (46).

N-[2-(*Cyclohex-3-enyl*)*ethyl*]-*hydroxylamine* (**19**)

Reduction of **18** (278 mg, 2 mmol) gave crude **19**, colourless solid (275 mg), IR: 3570, 3250 br, 2904, 1438, 911. ^{1}H-NMR: 1.1–2.4 (9H); 3.08 (broad t, J = 7, 2H); 5.67 (m, 2H); 7.88 (s, 2H, disappears with D_2O). MS: no $C_8H_{15}NO^{+\cdot}$, 125 (27), 121 (25), 93 (16), 81 (86), 80 (100), 79 (75). For purification and storage the hydrogen oxalate was prepared as follows: a soln of oxalic acid (180 mg, 2 mmol) in Et_2O (10 ml) was added dropwise to a stirred soln of crude **19** (255 mg) in Et_2O (15 ml) at RT. Filtration and recrystallization (EtOH–Et_2O) gave the hydrogen oxalate of **19** (282 mg, 61% from **18**), m.p. 153–158°.

2-(*Cyclopent-2-enyl*)-*ethanol* (**20**)

A soln of cyclopent-2-enylacetic acid (14.0 g, 111 mmol) in Et_2O (100 ml) was added to a suspension of $LiAlH_4$ (12.75 g, 236 mmol) in Et_2O (100 ml) over 1 hr. Stirring of the mixture at RT for 4 hr, consecutive addition of sat Na_2SO_4 aq, ice (200 g) and (slowly) 10% H_2SO_4 aq (350 ml), extraction with ether, work-up and distillation furnished **20** (11.9 g, 96%), oil, b.p. 110°/15 Torr. IR: 3630, 3580–3100, 3060, 2980–2840, 1620, 1070. ^{1}H-NMR: 1.2–3.0 (8H); 3.7 (t, J = 7, 2H); 5.7 (m, 2H). MS: 112 ($C_7H_{12}O^{+\cdot}$, 2), 94 (41), 79 (88), 67 (100), 53 (11), 41 (25), 31 (8).

Cyclopent-2-enyl-acetaldehyde oxime (**22**)

A soln of **20** (5.6 g, 50 mmol) in CH_2Cl_2 (50 ml) was added to a soln of PCC (33.8 g, 150 mmol) in CH_2Cl_2 (150 ml). After 2 hr at RT, work-up as described for the preparation of **18** furnished unstable **21** (3.4 g, 62%, oil) which gave pure **22** (2.4 g, 62% after distillation), b.p. 100°/0.1 Torr. IR: 3590, 3280, 3050, 2940, 2840, 1460, 1360, 1080, 905. ^{1}H-NMR: 1.2–2.6 (6H); 2.85 (m, 1H); 5.5–5.9 (2H); 6.74 and 7.39 (two t, J = 6, 1H); 10.0 (s, broad, 1H, disappears with D_2O). MS: 125 ($C_7H_{11}NO^{+\cdot}$, 1), 108 (9), 67 (100), 59 (12), 41 (21).

N-[2-(*Cyclopent-2-enyl*)-*ethyl*]-*hydroxylamine* (**23**)

Reduction of **22** (250 mg, 2 mmol) gave crude **23** (240 mg, 95%). IR: 3580, 3280, 2920, 1615, 1460, 1365, 1110, 1085, 1035, 915, 850. ^{1}H-NMR: 1.1–1.8 (3H); 1.8–2.46 (3H); 2.65 (m, 1H); 2.95 (t, J = 7, 2H); 5.46–5.82 (2H); 6.1 (br, 2H). MS: 127 ($C_7H_{13}NO^{+\cdot}$, 1), 94 (25), 82 (13), 79 (36), 67 (100), 41 (25), 30 (58).

trans-*Dec*-5-*en*-2,8-*diyne* (**26**)

1-Propyne (200 ml, 3.5 mmol) was condensed during 3.5 hr into a soln of EtMgBr (freshly prepared from Mg (67.2 g, 2.8 mol) and EtBr (270 g, 2.5 mol) in Et_2O (700 ml) at 5°. The mixture was kept at RT for 16 hr. Then $CuCl_2$ (anhyd 15 g) was added followed by the addition (over 4 hr) of a soln of 1,4-dibromo-2-butene (267.5 g, 1.25 mol) in Et_2O (400 ml) under reflux. The mixture was heated under reflux for 3 hr, kept at RT for 16 hr and then poured into ice–H_2O. Acidification (dilute aq HOAc), extraction with Et_2O, washing of the extracts successively with H_2O, sat $NaHCO_3$ aq, sat NaCl aq, drying, evaporation and distillation gave **26** as a colourless crystalline solid (47.6 g, 29%), b.p. 92–94°/12 Torr, m.p. 52–54°. IR: 3040, 2925, 1430, 1342, 970. ^{1}H-NMR: 1.82 (t, J = 2, 6H, irradiation at 2.91 → s); 2.91 (m, 4H); 5.70 (m, 2H, irradiation at 2.91 → s). MS: 132 ($C_{10}H_{12}^{+\cdot}$, 13), 117 (100), 115 (25), 91 (30), 79 (34), 77 (63).

trans-3-*Pentenal* (**28**)

A soln of **26** (30.4 g, 0.23 mol) in acetone (150 ml) was added dropwise during 40 min to a stirred mixture of N-methyl morpholine N-oxide monohydrate (34.3 g, 0.25 mol), OsO_4 (200 mg, 0.78 mmol), t-BuOH (20 ml), H_2O (120 ml) and acetone (50 ml) at 20°. During this addition a colourless ppt was formed and then re-dissolved as the addition progressed. After 16 hr at 20°, addition of $NaHSO_3$ (10 g), Celite (30 g) and H_2O (100 ml) followed by filtration (Celite), acidification (1 N HCl aq) to pH = 2, extraction (CH_2Cl_2), work-up and recrystallization gave deca-2,8-diyn-5,6-diol (28.2 g, 74%), m.p. 102–103°. This diol was added portionwise, during 15 min to a slurry of $LiAlH_4$ (33.8 g, 0.89 mol) in diglyme (270 ml) and THF (24 ml) at 10°. Heating of the mixture at 140–145° for 56 hr, cooling, pouring into ice–H_2O, acidification (1 N HCl) to pH = 2, extraction (Et_2O), work-up and distillation afforded pure *trans, trans*-deca-2,8-dien-5,6-diol (oil, 16.2 g, 75%), b.p. 96–98°/0.15 Torr. A soln of the dienyldiol (1.7 g, 10 mmol) in Et_2O (2 ml) was added in one portion to a rapidly stirred soln of $NaIO_4$ (2.14 g, 10 mmol) in H_2O (15 ml) at 10° which led to the immediate formation of a colourless ppt. After 30 min extraction (Et_2O), work-up (including removal of Et_2O by distillation at 760 Torr) and distillation gave **28** (oil, 1.2 g, 72%), b.p. 70–80°/760 Torr. IR: 2800, 2710, 1725, 1445, 1400, 1185, 970. ^{1}H-NMR: 1.64 (d, J = 5, 3H); 3.03 (m, 2H); 5.5 (m, 2H); 9.60 (t, J = 2, 1H). MS: 84 ($C_5H_8^{+\cdot}$, 39), 69 (9), 56 (22), 55 (100), 41 (43), 29 (78).

trans-3-*Pentenal oxime* (**29**)

Aldehyde **28** (1.2 g, 14.3 mmol) gave **29** (oil, after distillation 1.24 g, 88%), b.p. 90–100°/12 Torr. IR: 3590, 3240 br, 1450, 970, 910. ^{1}H-NMR: 1.69 (d, J = 5, 3H); 2.92 (m × t, J = 5.5, 1H); 3.12 (m × t, J = 5.5, 1H); 5.3–5.8 (2H); 6.76 (t, J = 5.5, 1H); 7.43 (t, J = 5.5, 1H); 9.66 (s, broad, 1H, disappears with D_2O). MS: 99 ($C_5H_9NO^{+\cdot}$, 22), 84 (30), 81 (39), 59 (35), 55 (57), 54 (100).

N-(trans-3-*Pentenyl*)-*hydroxylamine* (**32**)

Reduction of **29** (198 mg, 2 mmol) gave crude **32** as a colourless solid (184 mg, 91%). IR: 3620, 3590, 3240 br, 2930, 1510, 1462, 1460, 978. ^{1}H-NMR: 1.68 (d, J = 6, 3H); 2.29 (m × q, J = 6, 2H); 2.99 (t, J = 6, 2H); 5.2–5.8 (2H); 6.69 (s, 2H, disappears with D_2O). Conversion to the **29**-hydrogen oxalate gave, after crystallization, the pure salt m.p. 115–117° (85% from **29**).

trans-1,8-*Diphenyloct*-4-*en*-1,7-*diyne* (**27**)

A soln of phenylacetylene (50 g, 0.49 mol) in Et_2O (60 ml) was added during 1 hr to a soln of freshly prepared EtMgBr (0.49 mol) in Et_2O (250 ml) at 0–10°. The mixture was allowed to attain RT during 3 hr and left at RT for 2.5 hr. Cu^ICl (3 g) was then added, followed by the addition of a soln of 1,4-dichloro-2-butene (30.6 g, 0.245 mol) in Et_2O (20 ml) under reflux. The mixture was heated under reflux for 3.5 hr, then poured into ice–H_2O, filtered (Celite), acidified (AcOH aq), extracted (Et_2O) to give after work-up and distillation (until 125°/0.01 Torr) a brown residue which on recrystallization (hexane) afforded **27** as a pale-yellow solid (12.4 g, 9%), m.p. 109–110°. IR: 1600, 1492, 1445, 968, 690. ^{1}H-NMR: 3.22 (d, J = 3, 4H); 5.89 (t, J = 3, 2H); 7.24–7.54 (10H). MS: 256 ($C_{20}H_{16}^{+\cdot}$, 100), 241 (20), 239 (17), 215 (13), 178 (23), 141 (54).

trans-4-*Phenyl*-3-*butenal oxime* (**31**)

A soln of **27** (9.73 g, 38 mmol) in acetone (60 ml) was added dropwise, during 20 min, to a stirred mixture of N-methylmorpholine N-oxide monohydrate (5.4 g, 40 mmol),

OsO_4 (60 mg, 0.23 mmol), t-BuOH (5 ml), H_2O (60 ml) and acetone (30 ml). After 76 hr at RT $Na_2S_2O_5$ (3 g) was added followed by Celite (10 g) and the mixture was stirred for 10 min. Filtration (Celite), acidification (1 N HCl) to pH = 2, removal of acetone by distillation *in vacuo*, saturation with NaCl, extraction (CH_2Cl_2), work-up and recrystallization afforded 1,8-diphenylocta-1,7-diyn-4,5-diol (9.2 g, 84%) m.p. 125–126°. This diyn-diol (5.3 g, 18.2 mmol) was added portionwise during 10 min to a slurry of $LiAlH_4$ (3 g, 79 mmol) in THF (100 ml) at RT. The mixture was heated under reflux for 14 hr, then cooled and poured into ice–H_2O. Saturation with NaCl, extraction (EtOAc), work-up and recrystallization (CH_2Cl_2–hexane) gave *trans, trans*-1,8-diphenylocta-1,7-dien-4,5-diol (4.6 g, 86%) m.p. 112–116°. A soln of this dien-diol (4.41 g, 15 mmol) in MeOH–H_2O (5 : 1, 150 ml) was added dropwise to a stirred soln of $NaIO_4$ (3.21 g, 15 mmol) in MeOH–H_2O (5 : 1, 250 ml) at RT. After 2 hr at RT the mixture was poured into ice–H_2O. Extraction (Et_2O) and work-up gave the crude, unstable **30** (3.4 g, oil) which was immediately converted to its oxime **31** (3.2 g, 48% from **27**, after distillation) b.p. 80–90° (bath)/0.2 Torr. IR: 3590, 3270 br, 1498, 1450, 966, 690. ^{1}H-NMR: 3.07 (t, J = 6, 1H); 3.27 (t, J = 6, 1H); 5.9–6.3 (1H); 6.46 and 6.47 (two d, J = 16, 1H); 6.83 (t, J = 6, 0.5H); 6.9–7.5 (5H); 7.49 (t, J = 6, 0.5H); 9.66 (s broad, 1H, disappears with D_2O). MS: 161 ($C_{10}H_{11}NO^{+\cdot}$, 93), 144 (50), 143 (57), 132 (86), 117 (86), 115 (100).

N-(trans-4-*Phenyl*-3-*butenyl*)*hydroxylamine* (**33**)

Reduction of **31** (161 mg, 1 mmol) gave the crude hydroxylamine (155 mg), solid, IR: 3590, 3260 (br), 1604, 1500, 1454, 970. ^{1}H-NMR: 2.50 (q, J = 7, 2H); 3.10 (t, J = 7, 2H), 5.25 (s, broad, 2H, disappears with D_2O); 6.23 (t × t, J = 7 and 16, 1H); 6.52 (d, J = 16, 1H); 7.0–7.6 (5H). Crystallization of the **33**-hydrogen oxalate (EtOH) gave the pure salt (184 mg, 77% from **31**) m.p. 166–168°. ^{1}H-NMR (d-acetone): 3.04 (q, J = 7, 2H); 4.36 (t, J = 7, 2H); 6.6 (t × t, J = 7 and 16, 1H); 6.84 (d, J = 16, 1H); 7.4–7.9 (5H).

4-*Pentenal oxime* (**37**)

The mixture of 2-propenol (**34**) (14.5 g, 250 mmol), $Hg(OAc)_2$ (4.78 g, 15 mmol) and ethylvinyl ether (90 g, 1.25 mol) was heated in a sealed ampoule at 150° for 3 hr. Shaking of the mixture with 10% Na_2CO_3 aq (500 ml) for 1 hr, shaking of the organic phase with 10% Na_2CO_3 aq for 30 min, drying ($MgSO_4$), concentration to a third of its volume and conversion of the pentenal soln to **37** gave after distillation pure **37** (18.56 g, 75% from propenol), b.p. 70°/13 Torr. IR (film): 3250 br, 3070, 2970, 2900, 1645, 1450, 1300, 990, 910. ^{1}H-NMR: 2.0–2.6 (4H); 4.65–5.2 (2H); 5.6 (m, 1H); 6.74 (t, J = 6, 0.5H); 7.44 (t, J = 6, 0.5H); 9.2 (s, broad, 1H). MS: 99 ($C_5H_9NO^{+\cdot}$, 16), 82 (23), 67 (21), 55 (29), 54 (52), 41 (100).

N-(4-*Pentenyl*)*hydroxylamine* (**41**)

Reduction of **37** (6.0 g, 60.6 mmol) gave unstable **41** which was immediately transformed to its hydrogen oxalate (10.31 g, 89% from **37** after crystallization (EtOH)), m.p. 124–126°. (Found: C, 44.13; H, 6.96; N, 7.31. Calc for $C_7H_{13}NO_5$: C, 44.00; H, 6.80; N, 7.33%.) The free base shows the following spectra: IR: 3610, 3270 br, 3090, 2970, 1650, 1455, 1008, 930. ^{1}H-NMR: 1.05–2.3 (4H); 2.96 (t, J = 7, 2H); 4.8–5.3 (2H); 5.8 (m, 1H); 6.57 (s, br, 2H).

trans-4-*Hexenal* (**40**)

The mixture of **35** (36 g, 0.5 mol) ethylvinylether (180 g, 2.5 mol) and $Hg(OAc)_2$ (15.95 g, 50.8 mmol) was heated in a sealed ampoule at 120° for 14 hr. Work-up as described for the preparation of **37** and distillation/50 Torr gave **40** (oil, 28 g, 62%), b.p. 34°/50 Torr. IR: 3010, 2960, 2920, 2710, 1730, 1695, 1640, 1450, 1380, 1265, 965. ^{1}H-NMR: 1.5–1.65 (3H); 2.0–2.7 (4H); 5.2–5.6 (2H); 9.6 (s, 1H). MS: 98 ($C_6H_{10}O^{+\cdot}$, 30), 69 (40), 55 (87), 42 (44), 41 (100), 29 (35).

trans-4-*Hexenal oxime* (**38**)

Oximation of **40** (12.93 g, 132 mmol) gave after distillation the pure **38** (12.97 g, 87%), b.p. 80°/13 Torr. IR: 3590, 1440, 1280, 960. ^{1}H-NMR: 1.63 (d, J = 5, 3H); 1.9–2.6 (4H); 5.2–5.7 (2H); 6.65 and 7.34 (two t, J = 6, 1H); 9.65 (s, broad, 1H, disappears with D_2O). MS: 113 ($C_6H_{11}NO^{+\cdot}$, 2), 96 (7), 81 (17), 68 (28), 59 (18), 55 (100), 53 (13).

N-(trans-4-*Hexenyl*)*hydroxylamine* (**42**)

Reduction of **38** (2 g, 17.7 mmol) followed by addition of oxalic acid gave the **42**-hydrogen oxalate (3.07 g, 85%) recrystallized from isopropanol, m.p. 117–118°. The free **42** shows the following spectra: IR: 3590, 3010, 2930 br, 2850, 1500, 1450, 1440, 1380, 1260, 965. ^{1}H-NMR: 1.3–1.8 (5H); 1.8–2.2 (2H); 2.88 (t, J = 7, 2H); 5.25–5.5 (2H); 6.6 (s broad, 2H). MS: 115 ($C_6H_{13}NO^{+\cdot}$, 2), 98 (6), 67 (14), 55 (19), 46 (100).

4-*Methyl*-4-*pentenal oxime* (**39**)

The mixture of **36** (1.0 g, 13.9 mmol), $Hg(OAc)_2$ (250 mg, 0.8 mmol) and ethylvinyl ether (5.0 g, 69.5 mmol) was heated in a sealed ampoule at 150° for 6 hr. Work-up as described for the preparation of **37** and concentration of the organic phase to 25% of its original volume provided a soln of unstable 4-methyl-4-pentenal which was immediately converted to its oxime **39** (1.07, 68% after distillation), b.p. 83°/13 Torr. IR: 3630, 3330, 3110, 3000, 2960, 1675, 1570, 1460, 1280, 1030, 1000, 920. ^{1}H-NMR: 1.76 (s, broad, 3H); 2.1–2.7 (4H); 4.78 (d, broad, J = 4, 2H); 6.74 and 7.46 (two t, J = 5, 1H); 8.2 (s, 1H, broad, disappears with D_2O). MS: no $C_6H_{11}NO^{+\cdot}$, 95 (26), 81 (43), 68 (26), 55 (100), 41 (30), 39 (35).

N-(4-*Methyl*-4-*pentenyl*)*hydroxylamine* (**43**)

Reduction of **39** (2.0 g, 17.7 mmol) gave crude **43** (1.69 g, 83%). IR: 3600, 3270, 3070, 1650, 1460, 1378, 1120, 895. ^{1}H-NMR: 1.5–1.9 (2H); 1.72 (s, 3H); 1.9–2.2 (2H); 2.92 (t, J = 7, 2H); 4.7 (s, br, 2H); 6.7 (s, br, 2H). MS: 115 ($C_6H_{13}NO^{+\cdot}$, 42), 97 (27), 84 (100), 69 (39), 55 (58), 42 (79), 41 (79). After crystallization from isopropanol–ether the **43**-hydrogen oxalate (2.35 g, 78% from **39**) melted at 111–112°.

trans-4-*Hexen*-1-*ol* (**44**)

A soln of **40** (450 mg, 4.5 mmol) in Et_2O (20 ml) was added slowly to a stirred slurry of $LiAlH_4$ (130 mg, 3.4 mmol) in Et_2O (34 ml). The mixture was stirred at RT for 1.5 hr, then cooled to 0°. After slow addition of 10% H_2SO_4 aq, extraction of the aqueous phase (Et_2O), washing of the combined organic layers with sat $NaHCO_3$ aq, drying, evaporation and distillation gave **44** (oil, 410 mg, 91%), b.p. 62°/13 Torr. IR: 3650, 3500–3200, 3030, 2940, 1450, 1070, 950. ^{1}H-NMR: 0.7–2.0 (7H); 2.83 (s, broad, 1H, disappears with D_2O); 3.2 (t, J = 6, 2H); 4.7–5.5 (2H). MS: 100 ($C_6H_{12}O^{+\cdot}$, 7), 82 (45), 68 (100), 55 (45), 41 (66).

trans-1-*Bromo*-4-*hexene* (**45**)

A soln of PBr_3 (10.43 g, 38.5 mmol) in Et_2O (15 ml) was added to a mixture of **44** (10 g, 100 mmol) and pyridine (1 ml) in Et_2O (100 ml) at −30° over 2 hr. Stirring of the mixture at RT for 24 hr followed by slow addition of ice–H_2O (150 g), work-up and distillation furnished **45** (8.99 g, 55%), b.p. 80°/13 Torr. IR: 3040, 3000, 2980, 2840, 1960, 1450, 975. ^{1}H-NMR: 1.66 (d, J = 5, 3H); 1.8–2.3 (4H); 3.40 (t, J = 7, 2H); 4.9–5.8 (2H). MS: 164 ($C_6H_{11}{}^{81}Br^{+\cdot}$, 12), 162 ($C_6H_{11}{}^{79}Br^{+\cdot}$, 12), 83 (39), 69 (11), 67 (18), 55 (100), 41 (38).

trans-4-*Hexenylcarbonitrile* (**46**)

A soln of **45** (3.87 g, 23.7 mmol) in ethyleneglycol (13 ml) was added to a soln of KCN (3.19 g, 49.1 mmol) in ethyleneglycol (15 ml). Heating of the mixture at 100° for 4 hr followed by work-up and distillation gave **46** (2.23 g, 86%), b.p. 80°/13 Torr. IR: 3030, 2970, 2860, 2270, 1480, 1430, 980. ^{1}H-NMR: 1.5–1.95 (5H); 2.0–2.25 (2H); 2.35 (t, J = 7, 2H); 5.16–5.8 (2H). MS: 109 ($C_7H_{11}N^{+\cdot}$, 6), 81 (53), 69 (57), 55 (94), 41 (100).

trans-5-*Heptenal* (**47**)

1.4 N Diisobutylaluminiumhydride in toluene (21.4 ml, 30 mmol) was added at −78° to a soln of **46** (2.18 g, 20 mmol) in toluene (100 ml). The mixture was stirred at −70° for 2 hr, then poured into sat sodium/potassium tartrate aq, subjected to work-up and distilled to give **47** (2.1 g, 94%) b.p. 57°/18 Torr. IR: 3040, 2980, 2860, 2730, 1740, 1680, 1460, 980. ^{1}H-NMR: 1.4–2.2 (7H); 2.2–2.6 (2H); 5.2–5.7 (2H); 9.84 (t, J = 2, 1H). MS: 112 ($C_7H_{12}O^{+\cdot}$, 1), 92 (81), 91 (100), 69 (17), 39 (15).

trans-5-*Heptenal oxime* (**48**)

Oximation of **47** (2.83 g, 25.3 mmol) gave **48** (2.62 g, 82%), IR: 3590, 3540–3060, 3010, 2940, 2850, 1670, 1450, 970, 940. ^{1}H-NMR: 1.3–1.8 (5H); 1.8–2.6 (4H); 5.2–5.7 (2H); 6.6 (t, J = 6, 0.5H); 7.3 (t, J = 6, 0.5H); 9.0 (s broad, 1H, disappears with D_2O). MS: no $C_7H_{13}NO^{+\cdot}$, 87 (25), 73 (100), 58 (54), 41 (46).

N-(trans-5-*Heptenyl*)*hydroxylamine* (**49**)

Reduction of **48** (1.0 g, 7.9 mmol), followed by addition of oxalic acid (0.715 g, 7.9 mmol) to the crude hydroxylamine and crystallization (isopropanol) gave **49**-hydrogen oxalate (1.19 g, 69%) m.p. 121–123°. The free base shows the following spectra: IR: 3590, 2920, 2870, 1450, 1440, 965. ^{1}H-NMR: 1.2–1.8 (7H); 1.8–2.2 (m, 2H); 1.95 (t, J = 6, 2H); 5.2–5.6 (2H); 6.2 (s broad, 2H, disappears with D_2O). MS: 129 ($C_7H_{15}NO^{+\cdot}$, 4), 112 (6), 95 (10), 86 (8), 71 (19), 55 (31), 45 (100).

trans-5-*Phenyl*-4-*pentenal oxime* (**52**)

Oximation of *trans*-**51** (1.3 g, 8.3 mmol, prepared from **50**[11]) gave **52** (1.15 g, 80%), m.p. 104–106°, after crystallization (Et_2O–pentane, −40°). IR: 3580, 2850, 1650, 1600, 1490, 1450, 965. ^{1}H-NMR: 2.3–2.7 (4H); 6.2 (d × t, J = 16 and 6, 1H; irradiation at 2.5 → 1 d, J = 16); 6.5 (d, J = 16, 1H); 6.8 and 7.5 (two t, J = 5, 1H, irradiation at 2.5 → 2 s); 7.1–7.5 (5H); 9.5 (s, broad, 1H; disappears with D_2O). MS: 175 ($C_{11}H_{13}NO^{+\cdot}$, 10), 157 (4), 130 (16), 117 (100), 91 (24), 51 (9), 41 (4).

N-(trans-5-*Phenyl*-4-*pentenyl*)*hydroxylamine* (**53**)

Reduction of **52** (200 mg, 1.2 mmol) gave after crystallization (pentane, −40°) pure **53** (190 mg, 92%); m.p.: decomposition. IR: 3595, 3230 br, 3070, 3050, 3020, 2920, 2850, 1605, 1500, 1455, 1265, 1100, 965, 690. ^{1}H-NMR: 1.6–2 (2H); 2.1–2.5 (2H); 3.06 (t, J = 7, 2H); 3.5–4.5 (m, broad, 2H); 6.0–6.6 (2H); 7.1–7.5 (5H). MS: 177 ($C_{11}H_{15}NO^{+\cdot}$, 16), 160 (100), 144 (30), 129 (76), 117 (82), 113 (64), 91 (88), 86 (42).

4-*Phenyl*-4-*pentenaloxime* (**56**)

1 N n-BuLi (hexane, 50 ml, 50 mmol) was added during 30 min at −78° to a soln of 5,6-dihydro-2,4,4,6-tetramethyl-1,3-oxazine (7.0 g, 50 mmol) in dry THF (90 ml). After 1 hr at −78° a soln of 3-bromo-2-phenyl-1-propene (50 mmol) in THF (10 ml) was added during 10 min at −78°. The mixture was allowed to attain RT during 16 hr and then was poured into ice–H_2O. Acidification (1 N HCl), washing of the aq phase (Et_2O), rebasification (2 N NaOH), extraction (Et_2O) and work-up gave crude 5,6 - dihydro, 2 - [4 - (2 - phenyl - 1 - butenyl] - 4,4,6 - trimethyl - 1,3 - oxazine (10.9 g, 85%). A slurry of $NaBH_4$ (1.51 g, 41 mmol) in H_2O (3 ml) was added dropwise, together with concurrent addition of aq 9 N HCl, to a stirred solution of foregoing crude oxazine (10.3 g, 40 mmol) in THF–EtOH (1 : 1, 120 ml) at −40°, so as to keep the reaction mixture at pH = 7. Stirring of the mixture at pH = 7 at −30° for 1 hr, pouring into ice–H_2O, basification (2 N NaOH), extraction (Et_2O) and work-up gave crude **55** (oil, 8.6 g, 83%). NaOAc (4.18 g, 51 mmol) and $NH_2OH \cdot HCl$ (3.54 g, 51 mmol) were added to a soln of crude **55** (6.6 g, 25.5 mmol) at RT. After 1 hr, work-up and chromatography (SiO_2) gave **56** (2.76 g, 62%), solid m.p. 35–40°. IR: 3580, 3280 broad, 3080, 910, 710. ^{1}H-NMR: 2.25–2.9 (4H); 5.13 (m, 1H); 5.35 (m, 1H); 6.77 and 7.46 (two t, J = 7, 1H); 7.1–7.6 (5H); 8.14 and 8.52 (two s broad, 1H, disappear with D_2O). MS: no $C_{11}H_{13}NO^{+\cdot}$, 157 (34), 130 (12), 117 (37), 115 (22), 103 (13), 58 (100).

N-(4-*Phenyl*-4-*pentenyl*)*hydroxylamine* (**57**)

Reduction of **56** (350 mg, 2 mmol) gave crude **57** as a crystalline solid (379 mg). IR: 3570, 3240 broad, 2940, 1448, 910. ^{1}H-NMR: 1.5–2.4 (2H); 2.53 (t, J = 7, 2H); 2.89 (t, J = 7, 2H); 5.07 (m, 1H); 5.28 (m, 1H); 7.1–7.6 (7H). MS: no $C_{11}H_{15}NO^{+\cdot}$, 123 (32), 105 (36), 86 (64), 84 (100), 77 (36), 58 (48). The hydrogen oxalate of **57** (recrystallized from EtOH–ether) melts at 130–132°.

In situ *preparation and thermal cycloaddition of* N-*alkenylnitrones*

The corresponding N-alkenyl hydroxylamine I was either used as the crude product, freshly obtained by reduction of the oxime or liberated immediately before use at 0° from its hydrogen oxalate by shaking with 6 N KOH–Et_2O and evaporation of the dried (solid NaOH) organic phase.

General method for the preparation of methylene-nitrones

Gaseous CH_2O (prepared by heating paraformaldehyde (300 mg, 10 mmol) at 12 Torr) was introduced during 15 min into a partially evacuated (12 Torr) stirred soln of the free hydroxylamine I (4 mmol) in toluene (30 ml) containing anhyd Na_2SO_4 (2.84 g, 20 mmol) at −20°. The mixture was allowed to attain RT during 14 hr and subjected directly to the thermal cycloaddition (Method A).

General method for the preparation of C-*aryl- (or* C-*alkyl)*-N-*alkenylnitrones*

The aldehyde (*p*-$NO_2C_6H_4CHO$ or n-hexanal, 4 mmol) was added to a stirred mixture of hydroxylamine I (4 mmol) molecular sieves 4 Å (Merck, 2.0 g) in toluene (20 ml). The mixture was stirred at RT until complete disappearance of I (monitored by TLC, 0.5–2 hr). The resulting soln of the nitrone II was either subjected directly to thermal cycloaddition (Method A) or, in case of rapid dimerization II → V, the nitrone dimer V was isolated by chromatography and crystallization. The dimers V were fully characterized by IR, ^{1}H-NMR and MS. Regeneration of nitrone II → V coupled with the cycloaddition was carried out in *o*-dichlorobenzene at reflux (~160°, Method B) or in toluene using a sealed ampoule (~150°, Method C).

Analyses of crude cycloaddition products

The crude cycloaddition products were analyzed by ^{1}H-NMR, or TLC or GC or HPLC. In cases that only one product is described here, no other isomer was detected.

11-*Oxa*-4-*aza-tricyclo*[6.2.1.0^{1,6}]*undecane* (**60a**)

The toluene soln of **59a**, prepared from crude **13** (4 mmol) and CH_2O was heated under reflux for 3 hr. Chromatography (EtOAc) gave **61a** (453 mg, 74% from **12**), oil, GC (col. A, 160°): 12.15. IR: 2930, 1450, 1300, 1105, 925. ^{1}H-NMR: 1.18–2.28 (11H); 2.6–3.3 (4H). ^{13}C-NMR: 86.6, 65.2, 57.8, 44.2, 39.2, 31.7, 27.9, 24.7, 23.0. MS: 153 ($C_9H_{15}NO^{+\cdot}$, 100), 136 (63), 108 (97), 93 (74), 79 (69), 67 (40). **61a**-Hydrogen oxalate, m.p. 132–136° (EtOH–Et_2O).

(1*R**,5*S**,6*R**) - 5 - *p* - *Nitrophenyl* - 11 - *oxo* - 4 - *aza* - *tricyclo*[6.2.1.0^{1,6}]*undecane* (**60b**)

Condensation of crude **13** (0.83 g, 5.9 mmol) with *p*-nitrobenzaldehyde gave after heating at reflux (toluene) for 13 hr and subsequent crystallization (hexane–Et_2O 3 : 1) the dimer V (1.53 g, 94%) m.p. 167–169°. A soln of this dimer (20.4 mg, 0.074 mmol) in *o*-dichlorobenzene (2 ml) was heated at reflux for 1.5 hr. Evaporation (0.1 Torr) and chromatography (toluene–EtOAc 3 : 1 → 9 : 1) gave **60b** (19.6 mg, 97%), m.p. 172–173°. IR: 3000, 2930, 2850, 1605, 1520, 1375, 1200, 1115. ^{1}H-NMR: 1.0–2.5 (11H); 2.8–3.6 (2H); 4.24 (d, J = 8, 1H, irradiation at 2.2 → s); 7.4–8.4 (AA'BB', 4H). MS: 274 ($C_{15}H_{18}N_2O_3^{+\cdot}$, 32), 257 (100), 163 (24), 108 (69), 93 (21), 79 (29).

2-*Oxo*-1-*aza-tricyclo*[4.3.1.0^{3,8}]*decane* (**64a**)

Condensation of crude **16** (1.77 g, 14 mmol) with CH_2O in toluene and heating of the mixture under reflux for 9 hr,

filtration, addition of 2.5 N HCl in MeOH, evaporation and crystallization (isopropanol–ether 1 : 2) afforded the **64a** · HCl (1.57 g, 64%) decomp >220°. Shaking of the salt with 6 N aqueous KOH–ether, drying and evaporation of the ether layer gave free **64a**, m.p. 183–186° (sealed capillary), GC (col. B, 180°): 7.0. IR: 2950, 1460. ^{1}H-NMR: 1.5–2.4 (7H); 2.58 (m, 1H); 4.50 (m, 1H); 4.9–5.3 (4H). MS: 139 ($C_8H_{13}NO^{+\cdot}$, 61), 122 (23), 110 (17), 79 (64), 67 (23), 60 (100).

3-Benzyl-3-azabicyclo[3.3.1]*nonan-6-one* (**66**)

Benzylbromide (1.15 g, 6.7 mmol) was added to the ether soln of free isoxazolidine **64a** (70 ml, prepared from **64a** · HCl, 580 mg, 3.3 mmol). Heating the mixture under reflux for 18 hr, filtration of the insoluble salt gave the corresponding benzylammonium bromide (887 mg, 87%), m.p. 219–221° (dec). A slurry of this salt (425 mg, 1.37 mmol) and $LiAlH_4$ (332 mg, 8.7 mmol) in THF (40 ml) was stirred at RT for 16 hr. After addition of Et_2O (50 ml) and sat Na_2CO_3 aq (40 ml) the organic layer gave on drying and evaporation the amino alcohol **65**, oil (304 mg, 96%). IR (film): 3350, 1500, 720, 740. Following the established procedure[15] **65** (620 mg) was converted to **66** (583 mg, 93%), oil. IR (film): 3060, 1700, 1500, 740, 700. ^{1}H-NMR: 1.5–3.1 (12H); 3.35 (s, 2H); 7.15 (s, 5H). Ketone **66** was converted to its perchlorate, which was crystallized from EtOH–ether (1 : 4) m.p. 214–216° (sealed capillary), lit.:[15] m.p. 213–216°. IR (Nujol): 3060, 1700, 1500, 1450, 750, 700. ^{1}H-NMR (DMF d_7): 1.8–2.8 (6H); 3.52 (m, 4H); 4.55 (s, 2H); 7.55 (m, 5H). The IR and NMR spectra of free **66** and of **66** · $HClO_4$ are identical with the reference spectra provided by Johnson and distinctly different to those of **67** and **67** · $HClO_4$.

(3*R**,8*S**,9*S**) - 9 - *p* - *Nitrophenyl* - 2 - *oxo* - 1 - *aza* - *tricyclo*[4.3.1.0^{3,8}]*decane* **64b**

Condensation of crude **16** (340 mg, 2.7 mmol) with *p*-nitrobenzaldehyde gave after heating under reflux (toluene) and chromatography (toluene–EtOAc 3 : 1) the corresponding dimer, m.p. 98–100°, 50 mg (0.2 mmol) of which was heated in toluene using a sealed ampoule at 180° for 16 hr. Filtration through charcoal, evaporation and crystallization (CH_2Cl_2–Et_2O–hexane) gave **64b** (39 mg, 78% from **16**), m.p. 118–120°. IR: 3015, 2940, 2880, 1605, 1525, 1350, 1265, 1215, 1095. ^{1}H-NMR: 1.74–2.3 (7H); 2.91 (t broad, 1H; irradiation at 1.8 → d, J = 5); 3.24–3.56 (2H); 4.22 (t broad, 2H); 7.46–8.38 (AA'BB', 4H). MS: 260 ($C_{14}H_{16}N_2O_3^{+\cdot}$, 26), 243 (100), 181 (12), 165 (15), 163 (81), 136 (18), 117 (19), 94 (38), 79 (42).

(3*R**,8*S**,9*R**) - 9 - *n* - *Pentyl* - 2 - *oxo* - 1 - *aza* - *tricyclo*[4.3.1.0^{3,8}]*decane* (**64c**) *and* (2*R**,3*R**,8*R**) - 2 - *n* - *pentyl* - 9 - *oxo* - 1 - *aza-tricyclo*[4.3.1.0^{3,8}]*decane* (**63c**)

Condensation of crude **16** (260 mg, 2 mmol) with formaldehyde followed by heating under reflux (2 hr in toluene, then 1 hr in *o*-dichlorobenzene) and work-up yielded a crude product. GC (col. B, 160°) 8.69 (89), 11.55 (11). Chromatography (toluene–EtOAc 3 : 1) gave as the less polar, major product, **64c** (279 mg, 67%). IR: 3050, 2940, 2870, 1470, 1385, 1175, 1080, 955, 930, 865, 800. ^{1}H-NMR: 0.78 (t, broad, J = 6, 3H); 1.0–2.1 (15H); 2.27 (m, 1H); 2.77 (m, 1H); 2.94–3.12 (2H); 4.28 (d × d, J = 4 and 6, 1H). MS: 209 ($C_{13}H_{23}NO^{+\cdot}$, 8), 192 (8), 166 (3), 138 (100), 130 (15), 112 (10), 94 (15), 79 (25), 55 (15). Further elution furnished the more polar, minor product **63c** (35 mg, 8%). IR: 3060, 2940, 2860, 1470, 1090, 935, 815. ^{1}H-NMR: 0.87 (t, broad, J = 5, 3H); 1.08–2.16 (15H); 2.31 (m, 1H; irradiation at 4.44 → t broad, J = 5); 2.84 (m, 1H); 3.02–3.38 (2H); 4.44 (d × d, J = 4 and 6, 1H; irradiation at 2.31 → s broad). MS: 209 ($C_{13}H_{23}NO^{+\cdot}$, 6), 192 (7), 138 (100), 130 (12), 112 (15), 94 (18), 79 (32), 55 (24).

(3*R**,8*S**,9*S**) - 9 - *p* - *Nitrophenyl* - 2 - *oxo* - 1 - *aza* - *tricyclo*[4.3.2.0^{3,8}]*undecane* (**64d**) *and* (2*R**,3*S**,8*S**) - 2 - *p* - *nitrophenyl* - 9 - *oxo* - 1 - *aza* - *tricyclo*[4.3.2.0^{3,8}]*undecane* (**63d**)

Condensation of crude **19**, freshly prepared from **18** (350 mg, 2.8 mmol) with *p*-nitrobenzaldehyde at RT for 16 hr followed by chromatography (toluene–EtOAc 1 : 1) and crystallization (CH_2Cl_2–hexane) gave the corresponding dimer V (350 mg, 76%), m.p. 60–65°. Heating a soln of the foregoing dimer (50 mg, 0.18 mmol) in *o*-dichlorobenzene under reflux for 1.5 hr gave after chromatography (toluene–EtOAc 3 : 1 → 9 : 1) first the less polar **64d** (19.2 mg, 48%), IR: 2940, 2850, 1610, 1525, 1350, 1260, 1100, 1015. ^{1}H-NMR: 1.4–2.2 (9H); 2.85 (m, 1H, irradiation at 4.68 → s broad); 3.1 (m, 1H); 3.8 (m, 1H); 4.05 (s, broad, 1H); 4.68 (d, broad, J = 9, 1H, irradiation at 2.88 → s broad); 7.44–8.4 (AA'BB', 4H). MS: 274 ($C_{15}H_{18}N_2O_3^{+\cdot}$, 28), 257 (88), 151 (38), 137 (31), 125 (71), 11 (74), 97 (88), 83 (99), 69 (100). Further elution afforded the more polar adduct **63d** (12.8 mg, 32%), IR: 2970, 2850, 1610, 1525, 1350, 1260, 1100, 1015, 935, 905, 850. ^{1}H-NMR: 1.4–2.2 (9H); 2.84 (t broad, J = 7, 1H); 3.3–3.8 (2H); 4.28 (s, 1H); 4.39 (m, 1H); 7.5–8.4 (AA', BB', 4H). MS: 274 ($C_{15}H_{18}N_2O_3^{+\cdot}$, 39), 257 (100), 189 (14), 163 (17), 138 (13), 91 (6), 79 (16).

(2*R**,3*R**,7*S**) - 2 - *p* - *Nitrophenyl* - 8 - *oxo* - 1 - *aza* - *tricyclo*[4.2.2.0^{3,7}]*decane* (**69**) *and* (3*R**,7*R**,8*S**) - 8 - *p* - *nitrophenyl* - 2 - *oxo* - 1 - *aza* - *tricyclo*[4.2.2.0^{3,7}]*decane* (**70**)

Condensation of crude **23** (500 mg, 3 mmol) with *p*-nitrobenzaldehyde in toluene under reflux for 16 hr gave after crystallization (hexane–Et_2O 3 : 1) the corresponding dimer V (970 mg, ~100%), m.p. 83–85°. Heating a soln of the foregoing dimer (20 mg, 0.1 mmol) in *o*-dichlorobenzene (2 ml) under reflux for 3 hr gave after work-up and chromatography (toluene–EtOAc 3 : 1) the less polar **69** (5.3 mg, 27%), IR: 2860, 1525, 1385, 1350, 1260. ^{1}H-NMR: 1.3–1.9 (4H); 1.9–2.25 (2H); 2.4 (m, 1H); 2.85 (m, 1H); 3.07 (m, 1H); 3.6–4.0 (2H); 4.77 (t, broad, J = 7, 1H); 7.4–8.4 (AA'BB', 4H). MS: 260 ($C_{14}H_{16}N_2O_3^{+\cdot}$, 14), 243 (43), 163 (28), 69 (48), 67 (47), 59 (100), 55 (57). Further elution gave the more polar adduct **70** (5.6 mg, 28%), IR: 1610, 1600, 1520, 1350, 1260, 1015. ^{1}H-NMR: 1.5–2.4 (6H); 2.6–3.0 (2H); 3.3–3.8 (2H); 4.08 (t, broad, J = 3, 1H; irradiation at 2.8 → d broad, J = 2); 4.39 (s, 1H); 7.5–8.4 (4H). MS: 260 ($C_{14}H_{16}N_2O_3^{+\cdot}$, 9), 165 (35), 163 (22), 151 (35), 109 (67), 97 (83), 69 (100), 55 (87).

(3*R**,4*S**) - 3 - *Methyl* - 7 - *oxo* - 1 - *aza* - *bicyclo*[2.2.1]*heptane* (**72a**)

Liberation of the free **32** from its hydrogen oxalate (764 mg, 4 mmol) followed by immediate condensation with CH_2O in toluene (10°, 12 hr) furnished a soln of **71** which was heated under reflux for 6 hr. Filtration and evaporation gave crude **72a** (GC (col. A, 130°): 6.36, only peak), which after chromatography furnished pure **72a** (oil, 318 mg, 76%), GC (col. A, 130°): 6.36. IR: 2966, 1466, 1390, 975, 882. ^{1}H-NMR: 1.0 (d, J = 7, 3H, irradiation at 1.9 → s); 1.6 (m, 1H), 1.7–2.1 (2H, irradiation at 1.0 or at 4.44 → simplification of multiplicity); 2.4–3.2 (4H); 4.44 (d, J = 5, 1H, irradiation at 1.9 → s). ^{13}C-NMR: 83.4, 64.8, 55.5, 40.2, 32.2, 19.1. MS: 113 ($C_6H_{11}NO^{+\cdot}$, 63), 68 (81), 67 (41), 56 (52), 55 (71), 41 (100). The **72a**-hydrogen oxalate melts at 116–118°, ^{1}H-NMR (acetone-d_6): 0.98 (d, J = 7, 3H); 1.5–2.10 (3H); 2.4–3.1 (4H); 4.45 (d, J = 5, 1H).

N-(trans-4-*Hexenyl*)-*methylene nitrone* (**71b**)

Hydroxylamine **42**, liberated freshly from its hydrogen oxalate (56 mg, 0.4 mmol) was condensed with gaseous CH_2O in toluene (5 ml) at −20° for 15 min. Filtration, evaporation of the filtrate at 0° gave **71b** (56 mg, ~100%), oil. IR: 3010, 2950, 2850, 1600, 1445, 1405, 1165, 1120, 965. ^{1}H-NMR: 1.0–2.4 (7H); 3.7–4.2 (2H); 5.1–5.7 (2H); 6.33 (d, J = 8, 1H); 6.44 (d, J = 8, 1H).

(5*R**,6*R**) - 6 - *Methyl* - 7 - *oxo* - 1 - *aza* - *bicyclo*[3.2.1]*octane* (**73b**)

Condensation of **42** (230 mg, 2 mmol) with CH_2O in toluene and heating of the mixture under reflux for 3 hr gave crude **73b** (240 mg, 95%). GC (col. B, 130°): 9.03 only peak. IR: 1470, 1390, 1260, 1195, 1020, 1005. ^{1}H-NMR: 1.16 (d, J = 7, 3H); 1.4–2.2 (4H); 2.22 (m, 1H); 2.5–3.5 (4H); 4.35 (q, J = 7, 1H,

irradiation at 1.16 → s). MS: 127 ($C_7H_{13}NO^{+\cdot}$, 56), 99 (19), 81 (30), 67 (41), 55 (100), 42 (44). The **73b**-hydrogen oxalate (crystallized from isopropanol) melts at 158–160°.

(3R,4S*) - 3 - Methyl - 7 - oxo - 1 - aza - bicyclo[4.2.1]nonane* (**72c**) *and (6R*,7R*) - 7 - methyl - 8 - oxo - 1 - aza - bicyclo[4.2.1]nonane* (**73c**)

Condensation of freshly liberated (from its hydrogen oxalate) hydroxylamine **49** (1.4 g, 10.9 mmol) with CH_2O, followed by heating of the toluene solution under reflux for 3 hr, filtration, evaporation and chromatography (THF–EtOAc 1 : 1) furnished the less polar product **72c** (352 mg, 23%), oil, IR: 2940, 2870, 1460, 1385, 1050, 1025, 945, 922, 895, 870. ^{1}H-NMR: 1.18 (d, J = 7, 3H); 1.4–2.0 (6H); 2.42 (m, 1H); 2.6–3.6 (4H); 4.08 (d × q, J = 8 and 2, 1H; irradiation at 2.4 → q, J = 8 and irradiation at 1.18 → d broad, J = 2). MS: 141 ($C_8H_{15}NO^{+\cdot}$, 81), 124 (30), 98 (26), 68 (59), 60 (48), 55 (100), 41 (81). Further elution afforded the more polar adduct **73c** (1.041 g, 68%), oil, IR: 2970, 2930, 2860, 1470, 1358, 1375, 1180, 1075, 1035, 860. ^{1}H-NMR: 1.2 (d, J = 7, 3H); 1.4–2.0 (6H); 2.4 (m, 1H); 2.6–3.6 (4H; irradiation at 2.4 → simplification of multiplicity); 4.1 (d × q, J = 8 and 1.8, 1H, irradiation at δ = 1.2 → d, J = 1.8 and at δ = 2.4 → q, J = 8). MS: 141 ($C_8H_{15}NO^{+\cdot}$, 100), 124 (24), 82 (26), 68 (50), 55 (55), 44 (52).

(2R,3R*,4S*) - 2 - p - Nitrophenyl - 3 - methyl - 7 - oxo - 1 - aza - bicyclo[2.2.1]heptane* (**72d**)

Condensation of crude **32** (370 mg, 3.7 mmol) freshly prepared from **29** (4 mmol) with *p*-nitrobenzaldehyde in toluene at RT for 12 hr gave after chromatography (EtOAc) and crystallization ($CHCl_3$–hexane) the corresponding dimer V (539 mg, 63%), m.p. 62–64°. Heating a soln of this dimer (50 mg, 0.107 mmol) in *o*-dichlorobenzene under reflux for 1.5 hr, evaporation and crystallization (pentane–Et_2O) furnished **72d** (42.5 mg, 85%), m.p. 117–118°. IR: 2960, 2925, 2880, 1610, 1525, 1355, 1120, 890, 870, 855. ^{1}H-NMR: 0.46 (d, J = 7, 3H); 1.5–2.25 (m, 2H); 2.44 (d × q, J = 8 and 7, 1H); 2.7–3.4 (2H); 4.04 (d, J = 8, 1H; irradiation at 2.44 → s); 4.55 (d, J = 5, 1H); 7.4–8.4 (AA'BB', 4H). MS: 234 ($C_{12}H_{14}N_2O_3^{+\cdot}$, 44), 213 (40), 177 (12), 163 (41), 147 (10), 117 (18), 68 (100).

(6R,7R*,9S*) - 9 - p - Nitrophenyl - 7 - methyl - 8 - oxo - 1 - aza - bicyclo[3.2.1]octane* (**73e**)

Condensation of **42** (270 mg, 2.3 mmol) with *p*-nitrobenzaldehyde in toluene, followed by heating the mixture under reflux for 16 hr furnished, after work-up and crystallization (pentane–Et_2O 3 : 1) **73e** (400 mg, 69%), m.p. 110–112°, IR: 2950, 2870, 1605, 1528, 1355, 1110, 1055, 1030, 858, 840. ^{1}H-NMR: 0.75 (d, J = 7, 3H); 1.5–2.3 (4H); 2.7–3.2 (2H); 3.55 (m, 1H); 4.2 (s, 1H); 4.35 (q, J = 7, 1H, irradiation at 0.75 → s); 7.5–8.4 (AA'BB', 4H). MS: 248 ($C_{13}H_{16}N_2O_3^{+\cdot}$, 25), 231 (25), 204 (11), 180 (9), 163 (100), 107 (26), 82 (23).

(3R,4S*) - 3 - Phenyl - 7 - oxo - 1 - aza - bicyclo[2.2.1]heptane* (**72f**) *and (5R*,6R*) - 6 - phenyl - 7 - oxo - 1 - aza - bicyclo[2.2.1]heptane* (**73f**)

Condensation of crude **33** (freshly prepared from **31** (322 mg, 2 mmol)) with CH_2O at RT for 14 hr followed by heating of the mixture under reflux for 3 hr furnished after work-up crude adducts which on HPLC-analysis showed a ratio **72f**/**73f** = 88 : 12. Chromatography (toluene–EtOAc 3 : 1) furnished the less polar, major product **72f** (oil, 150 mg, 56%), GC (col. A, 200°): 7.80. IR: 1499, 1461, 1088, 875, 702. ^{1}H-NMR: 1.55–2.2 (2H); 2.65–3.45 (5H); 4.77 (d, J = 6, 1H); 7.0–7.6 (5H). ^{13}C-NMR: 143.8 (s), 128.4 (d), 127.1 (d), 126.4 (s), 84.6 (d), 67.0 (t), 55.8 (t), 52.0 (d), 33.1 (t). MS: 175 ($C_{11}H_{13}NO^{+\cdot}$, 20), 174 (27), 155 (27), 150 (16), 130 (100), 129 (34). Further elution gave the more polar, minor product **73f** (oil, 25 mg, 9%), GC (col. A, 200°): 10.41. IR: 1501, 1459, 989, 920, 702. ^{1}H-NMR: 1.5–2.05 (2H); 2.49 (d, broad, J = 9, 1H); 2.85–3.5 (4H); 4.68 (s, 1H); 7.0–7.6 (5H). ^{13}C-NMR: 141.6, 128.1, 127, 125.4, 84.3, 57.9, 57.4, 47.0, 28.7. MS: 175 ($C_{11}H_{13}NO^{+\cdot}$, 17), 174 (17), 155 (69), 130 (100), 129 (43), 105 (54).

(6R,7S*) - 7 - Phenyl - 8 - oxo - 1 - aza - bicyclo[3.2.1]octane* (**73g**)

Condensation of **53** (140 mg, 0.8 mmol) with CH_2O in toluene, subsequent heating of the mixture under reflux for 3 hr gave after filtration, evaporation and crystallization (hexane–Et_2O 3 : 1) **73g** (130 mg, 87%) m.p. 74–76°. IR: 1450, 1280, 1110, 975, 950, 910, 890, 700. ^{1}H-NMR: 1.4–2.4 (4H); 2.6 (m, 1H); 2.8–3.6 (4H); 5.3 (s, 1H); 7.2–7.5 (5H). MS: 189 ($C_{12}H_{15}NO^{+\cdot}$, 56), 172 (22), 143 (34), 129 (94), 105 (22), 91 (39), 83 (100), 77 (33), 59 (39).

(6R,7S*,9S*) - 9 - p - Nitrophenyl - 7 - phenyl - 8 - oxo - 1 - aza - bicyclo[3.2.1]octane* (**73h**)

Condensation of crude **53** (190 mg, 1.06 mmol) with *p*-nitrobenzaldehyde, in toluene, followed by heating the mixture under reflux for 11 hr gave after successive evaporation and chromatography (toluene–EtOAc 3 : 1) **73h** (312 mg, 95%) m.p. 144–146° (recrystallized from hexane–ether 1 : 1). IR: 3020, 1520, 1350, 1240. ^{1}H-NMR: 1.6–2.4 (4H); 2.9–3.9 (3H, irradiation at 2.15 → s); 4.24 (s, 1H); 5.36 (s, 1H); 6.9 (s, 5H); 7.4–8.1 (AA'BB', 4H). MS: 310 ($C_{18}H_{18}N_2O_3^{+\cdot}$, 17), 293 (19), 204 (100), 163 (75), 129 (25), 117 (17), 91 (11), 77 (10).

(6R,7R*) - 9,9 - Dicarboethoxy - 7 - methyl, 8 - oxo - 1 - aza - bicyclo[3.2.1]octane* (**75**)

To a soln of crude **42** (200 mg, 1.7 mmol) in toluene (10 ml) was added molecular sieves (4 Å, 500 mg) followed by diethyl mesoxalate (452 mg, 2.6 mmol). According to TLC evidence nitrone **74** was formed immediately. Heating the mixture at reflux for 16 hr, filtration (Celite, charcoal), evaporation and chromatography (toluene–EtOAc 1 : 1) afforded adduct **75**, oil (367 mg, 78%), IR: 2970, 2940, 2895, 2870, 1770, 1745, 1470, 1445, 1390, 1370, 1280, 1245, 1220, 1090, 1075, 1035. ^{1}H-NMR: 1.08 (d, J = 7, 3H); 1.22 (t, J = 7, 3H); 1.23 (t, J = 7, 3H); 1.48–2.22 (4H); 3.06 (d, broad, J = 3, 1H; irradiation at 1.9 → s); 3.16–3.46 (2H; irradiation at 1.9 → s broad); 4.23 (q, J = 7, 4H); 4.43 (q, J = 7, 1H; irradiation at 1.08 → s). MS: 271 ($C_{13}H_{21}NO_5^{+\cdot}$, 37), 198 (81), 182 (5), 170 (100), 152 (38), 126 (43).

8 - Oxo - 1 - aza - bicyclo[3.2.1]octane (**77a**) *and 7 - oxo - 1 - aza - bicyclo[3.2.1]octane* (**78a**)

Condensation of **41** (246 mg, 2.4 mmol, freshly liberated from its hydrogen oxalate) with CH_2O in toluene for 1 hr at 0° → RT, followed by heating of the mixture under reflux for 3 hr showed in the GC (col. B, 120°) two peaks 10.7 (29.7%) and 12.9 (70.3%). Chromatography of the evaporated mixture (Al_2O_3, activity II, THF–EtOAc 1 : 1) furnished the less polar, minor **77a**, oil (93 mg, 23%), **77a**-hydrogen oxalate (isopropanol), m.p. 148–151°, GC (col. B, 120°) 10.7. IR: 2980, 2870, 1450, 1390, 1360, 1260, 1130. ^{1}H-NMR: 1.2–2.5 (6H, irradiation at 4.4 → simplification of multiplicity 2.0–2.3); 2.8 (m × d, J = 14, 1H); 2.9–3.65 (3H); 4.40 (m, 1H, irradiation at 2.3 → s, $W_{1/2}$ = 5 Hz). MS: 113 ($C_6H_{11}NO^{+\cdot}$, 100), 86 (36), 84 (68), 68 (48), 55 (60), 42 (88). Further elution afforded the more polar major product **78a**, oil (129 mg, 48%). **78a**-hydrogen oxalate m.p. 127–129° (isopropanol). GC (col. B, 120°): 12.9. IR: 2950, 2870, 1465, 1115, 980, 900. ^{1}H-NMR: 1.3–2.4 (4H); 2.63 (m, 1H); 2.82 (m, 1H); 3.08 (s, 2H); 3.27 (d × d, J = 6 and 14, 1H; irradiation at 1.9 → d, J = 14); 3.84 (t, J = 6, 1H, irradiation at 2.63 → d, J = 6); 4.08 (d, J = 6, 1H). MS: 113 ($C_6H_{11}NO^{+\cdot}$, 61), 84 (23), 69 (33), 68 (46), 67 (66), 59 (44), 55 (61), 42 (70), 41 (100).

5 - Methyl - 8 - oxo - 1 - aza - bicyclo[3.2.1]octane (**77b**) *and 5 - methyl - 7 - oxo - 1 - aza - bicyclo[3.2.1]octane* (**78b**)

Condensation of **43** (475 mg, 4.1 mmol) with CH_2O in toluene followed by heating of the mixture under reflux for 4 hr gave a mixture of **77b** and **78b**, GC (col. B, 120°) 8.6 (80%), 11.4 (10%) which was separated by chromatography (THF–EtOAc 1 : 1) to give the less polar minor product **78b** (53 mg, 10%), oil GC (col. B, 120°) 11.4. IR: 2970, 1450, 1370, 1280, 1135, 1070, 915, 900. ^{1}H-NMR: 1.1 (s, 3H); 1.5–2.4 (4H); 2.5–3.1 (3H); 3.15–3.6 (2H); 3.98 (d, J = 5, 1H). MS: 127 ($C_7H_{13}NO^{+\cdot}$, 12), 122 (21), 82 (49), 68 (46), 55 (100), 45 (84), 42 (56). Further elution

furnished the more polar major product **77b** (400 mg, 77%, oil), GC (col. B, 120°): 8.6. IR: 1460, 1390, 1280, 1120, 1080, 920, 870. ^{1}H-NMR: 1.26 (s, 3H); 1.3–2.4 (6H); 2.5–3.5 (4H). MS: 127 ($C_7H_{13}NO^{+\cdot}$, 57), 116 (13), 100 (31), 82 (53), 66 (87), 55 (82), 43 (96), 42 (100).

(5R,7S*) - 5 - Methyl - 7 - p - nitrophenyl - 8 - oxo - 1 - aza - bicyclo[3.2.1]octane* (**77c**)

Condensation of **43** (1.032 g, 9.0 mmol, freshly liberated from its hydrogen oxalate) with *p*-nitrobenzaldehyde in toluene at RT for 14 hr gave after chromatography (toluene–EtOAc 3:1) and crystallization (hexane–ether) the corresponding dimer V (1.558 g, 70%). Heating of this dimer (248 mg, 0.1 mmol) in toluene (5 ml) in a sealed ampoule at 120° for 6 hr, filtration through charcoal and chromatography furnished **77c** (231 mg, 93%), crystallized from hexane–ether, m.p. 149–151°. IR: 2940, 2880, 1525, 1350, 1260, 1110, 1085, 1020, 970, 860. ^{1}H-NMR: 1.38 (s, 3H); 1.52–2.3 (5H); 2.7–3.2 (2H); 3.49 (m, 1H); 4.43 (d × d, J = 4 and 10, 1H, irradiation at 1.9 → d, J = 10, irradiation at 2.9 → d, broad, J = 4); 7.5–8.3 (AA'BB', 4H). MS: 248 ($C_{13}H_{16}N_2O_3^{+\cdot}$, 33), 218 (57), 163 (67), 99 (100).

5 - Phenyl - 8 - oxo - 1 - aza - bicyclo[3.2.1]octane (**77d**)

Condensation of crude **57** (freshly prepared from **56**, 700 mg, 4 mmol) with CH_2O in toluene followed by heating of the mixture under reflux for 6 hr, evaporation and chromatography (EtOAc → THF) gave **77d** (620 mg, 82% from **56**) m.p. 73–74° (after crystallization from CH_2Cl_2–pentane). GC (col. A, 200°): 15.0. IR: 1460, 1362, 1000, 951, 710. ^{1}H-NMR: 1.4–3.6 (8H); 7.0–7.6 (5H). ^{13}C-NMR: 128.0, 126.8, 124.8, 83.5, 54.9, 53.5, 40.4, 36.9, 17.6. MS: 189 ($C_{12}H_{15}NO^{+\cdot}$, 100), 161 (20), 144 (80), 129 (84), 105 (24), 77 (36).

(5R,7S*) - 7 - p - Nitrophenyl - 5 - phenyl - 8 - oxo - 1 - aza - bicyclo[3.2.1]octane* (**77e**)

Condensation of crude **57** (freshly prepared from **56**, 700 mg, 4 mmol) with *p*-nitrobenzaldehyde in toluene at RT during 12 hr, evaporation and chromatography, furnished the corresponding dimer V (893 mg, 72% from **56**), m.p. 108–110° (crystallized from $CHCl_3$–hexane). Heating a soln of the foregoing dimer (20 mg, 0.07 mmol) in *o*-dichlorobenzene (2 ml) under reflux for 11 hr, evaporation, chromatography and crystallization (CH_2Cl_2–hexane) furnished **77e** (15 mg, 68%), m.p. 117–119°. IR: 1598, 1525, 1342, 1160, 1110, 908, 860. ^{1}H-NMR: 1.2–2.14 (4H); 2.3 (d × d, J = 5 and 12, 1H, irradiation at 4.57 → d, J = 12); 3.11 (d × d, J = 5 and 14, 1H, irradiation at 2.0 → d, J = 14); 3.26 (d × d, J = 9 and 12, 1H, irradiation at 4.57 → d, J = 12); 3.6 (m, 1H, irradiation at 2.0 d, broad, J = 14); 4.55 (d × d, J = 5 and 9, 1H); 7.1–7.5 (5H); 7.6 (d, J = 9, 2H); 8.19 (d, J = 9, 2H). MS: 310 ($C_{18}H_{18}N_2O_3^{+\cdot}$, 25), 293 (10), 280 (100), 265 (20), 190 (40), 163 (65), 144 (75), 129 (80), 117 (40), 105 (50), 91 (40), 77 (75).

Thermal stability and attempted interconversion of cycloaddition products

General. The corresponding isoxazolidine was freshly liberated from its crystalline hydrogen oxalate and heated under argon in toluene at reflux for 3 hr. The mixture was analyzed by GC (col. B), showing no change, and reconverted to its hydrogen oxalate; the amount of recovery is based on recrystallized hydrogen oxalate possessing the same m.p. as before the experiment (Table 9). Isoxazolidine **64** was heated in toluene at 200° for 5 hr; GC analysis showed only unchanged **64**. A mixture **77b/78b** 64/36 (GC) gave after heating in toluene (3 hr reflux) a 60.2:39.8 mixture **77b/78b** with 92% recovery.

Table 9.

Isoxazolidine	m.p. of hydrogen oxalate (°)	Recovery (%)
73b	158–160	94
72c	109–111	93
73c	104–106	87
77a	148–151	87
78a	127–129	84
77b	127–130	87

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