Pergamon

Tetrahedron 57 (2001) 4237–4242

TETRAHEDRON

4-Nitroisoxazoles as nitroalkene heterodienes: diastereoselective synthesis of spiro tricyclic nitroso acetals by thermal reactions with ethyl vinyl ether

Donatella Giomi,* Stefania Turchi, Andrea Danesi and Cristina Faggi

Dipartimento di Chimica Organica 'Ugo Schiff'–Centro di Studio del CNR sulla chimica e la struttura dei composti eterociclici e loro applicazioni, Università di Firenze, Via Gino Capponi 9, I-50121 Firenze, Italy

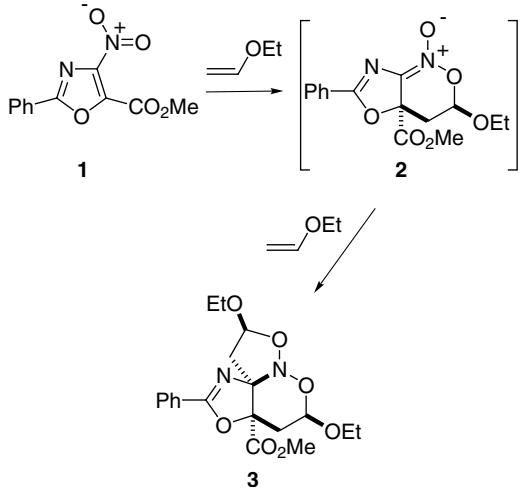
Received 21 December 2000; revised 19 February 2001; accepted 8 March 2001

Abstract—A few 4-nitroisoxazoles were found to undergo highly diastereoselective pericyclic homodomino processes with the title enol ether affording 1,6,9-trioxa-5,9a-diazacyclopenta[*d*]indenes through bicyclic nitronates as key intermediates. Formation of isoxazolo–oxepine systems is also reported together with a domino reaction with the above reagent and methyl acrylate. Two X-ray analyses of compounds **8** and **13** were carried out to firmly establish their stereochemistry.

1. Introduction

Nitroalkenes are well known as potent Michael acceptors and activated electrophilic carbodienophiles in conjugate addition reactions and normal-electron-demand [4+2] cycloadditions, respectively.[1] They have also been increasingly employed over the past two decades as excellent heterodienes in inverse-electron-demand hetero Diels–Alder (HDA) reactions.[2] Mainly due to the extensive studies of Denmark's group, they have proven extremely versatile for elegant, efficient, and highly stereocontrolled protocols leading to a great variety of polycyclic frameworks through diverse tandem [4+2]/[3+2] cycloaddition processes.[3] By contrast, the possibility of extending these attractive sequences to nitroheterocycles has scarcely been explored; only two examples have been reported, to our knowledge, for 3,5-dinitro-2-pyridones[4] and 3-nitro-2,5-dihydrofuran derivatives,[5] even if nitro group participation in HDA reactions was also evidenced for the 10π-electron heteroaromatic 4,6-dinitrobenzofuroxan.[6]

After the recent discovery that methyl 4-nitro-2-phenyloxazole-5-carboxylate (**1**) reacted very slowly with ethyl vinyl ether (EVE) to give the tricyclic compound **3** through the labile intermediate **2** (Scheme 1),[7] we decided to carry out a systematic investigation on the more easily available nitroisoxazoles **4**, **5**, and **12** as potential nitroalkene heterodienes.



Scheme 1.

2. Results and discussion

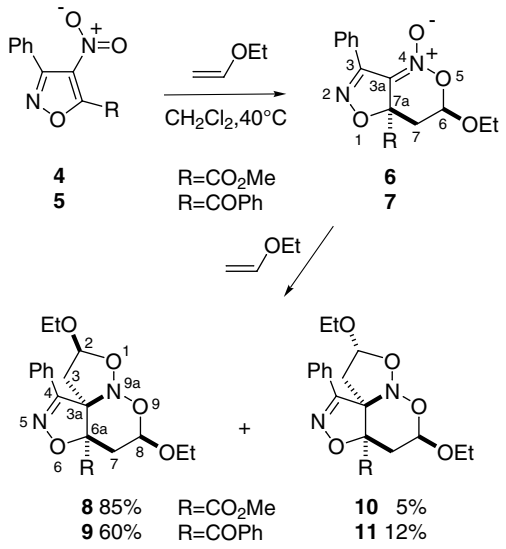
When the nitroester **4** was allowed to react with a large excess of EVE in anhydrous dichloromethane at 40°C for 4 days, a quantitative conversion into an 8:1 mixture of the diastereomeric spiro nitroso acetals **8** and **10** was observed (^{1}H NMR). This resulted from a two-step pericyclic homodomino process[8] involving an HDA reaction of the enol ether with the nitroalkene moiety of **4**, followed by 1,3-dipolar cycloadditions of the same species upon the first-formed bicyclic nitronate **6** (Scheme 2).

Although **6** escaped from isolation as a pure product, it was easily identified as the *only* intermediate (see below) by

Keywords: cycloadditions; 4-nitroisoxazoles; nitroalkene heterodienes; spiro nitroso acetals.

* Corresponding author. Fax: +39-055-2476964; e-mail: giomi@chimorg.unifi.it

0040–4020/01/$ - see front matter
PII: S0040-4020(01)00310-6



Scheme 2.

spectral monitoring of the reaction course at 8°C; its greater stability with respect to **2** probably arises both from a more effective conjugation between the nitronate and the C=N double bond of the isoxazoline ring and an increased encumbering of the phenyl group in the second cycloaddition ongoing from **2** to **6**.

Despite a nearly identical mobility for compounds **8** and **10**, careful chromatographic resolution of the original mixture afforded the former in 80% yield, together with a small fraction containing comparable amounts of the two isomers.

The full stereostructure of **8** was unambiguously determined by an X-ray analysis, which, in turn, confirmed the configuration of the direct precursor **6**. Whereas the substituents of the six-membered ring show a *trans* arrangement, the tricyclic skeleton is characterised by a *cis*-fused isoxazolo–oxazine system and a *cis* relationship for the ethoxy groups (Fig. 1).

This stereochemical outcome could be accounted for on the

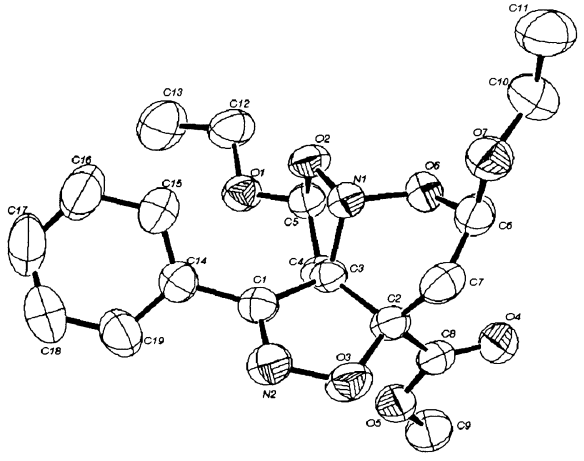


Figure 1. ORTEP drawing of the nitroso acetal **8** with hydrogens omitted for clarity.

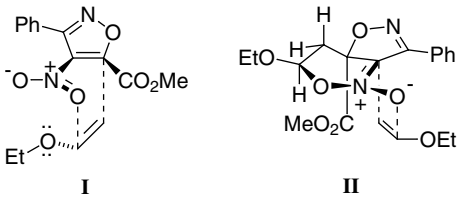


Figure 2.

basis of an exclusive *endo* addition of EVE upon **4**, followed by a highly diastereoselective *exo–syn* CO_2Me approach of the same reagent to **6**, leading to the transition structures I and II, respectively (Fig. 2). Whereas secondary orbital and coulombic interactions between the electron-rich oxygen of the vinyl ether and the positively charged nitrogen of the nitro group certainly favour I,[9] and the preferential orientation of EVE into II is simply dictated by steric factors, the alternative *anti* CO_2Me attack is probably rejected since it would afford more strained isomers containing a *trans*-fused [4.3.0] system.

The behaviour of the nitro ketone **5** closely paralleled that of **4**; indeed, treatment with EVE at 40°C afforded compounds **9** and **11** through the common intermediate **7**, which was again detected and characterised under milder conditions; both the tricyclic epimers were now isolated as pure products in 60% and 12% yields, respectively.

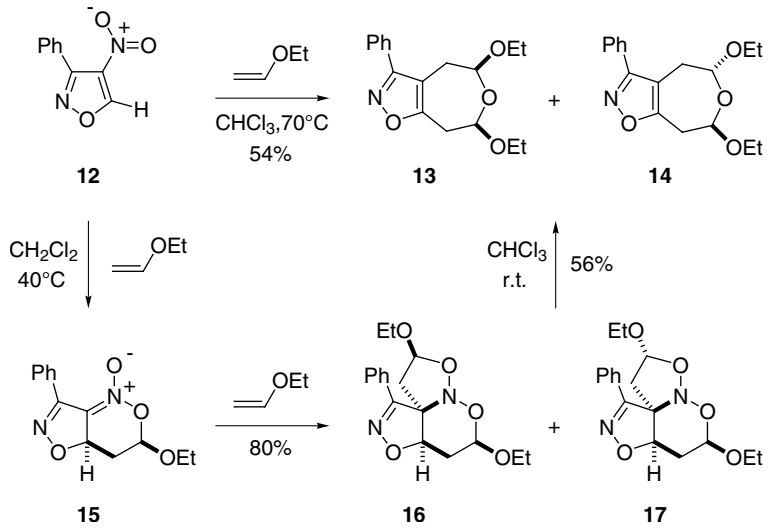
Conversely, a rather different pattern was observed by replacing the above difunctionalized derivatives with the nitroisoxazole **12**, which reacted with EVE in chloroform at 70°C to give a 3:2 mixture of the diastereomeric isoxazolo–oxepines **13** and **14** in 54% yield (Scheme 3). The formation of these compounds, whose relative stereochemistry was established by X-ray analysis of the predominant one (Fig. 3), could be explained by a more complex heterodomino process involving the nitroso acetals **16** and **17**.

A mixture of these products was indeed obtained, through the undetectable nitronate **15**, from **12** and EVE under standard conditions and easily converted into **13** and **14** by standing in chloroform at room temperature. Despite their remarkable instability both in the solid state and in solution, the inseparable epimers **16** and **17** were isolated in good yield by a very rapid chromatographic work-up.

The presence of a hydrogen atom at position 6a of **16** and **17** certainly plays a critical role for the final step, which likely occurs via an oxazine ring-opening followed by ring contraction of the resulting systems **18** and **19** with loss of the nitroxyl fragment (Scheme 4).

In order to test the possibility of synthesising the mixed compound **20** by a domino reaction, **4** was treated with an excess of EVE and methyl acrylate; the desired product was obtained in 52% yield together with **8** and **10** (35%) as a result of competitive cycloadditions of the two dipolarophiles upon the common intermediate **6** (Scheme 5).[10]

All the spectral data of the new compounds **6**–**11**, **13**, **14**, **16**, **17** and **20** (Experimental) are in agreement with the



Scheme 3.

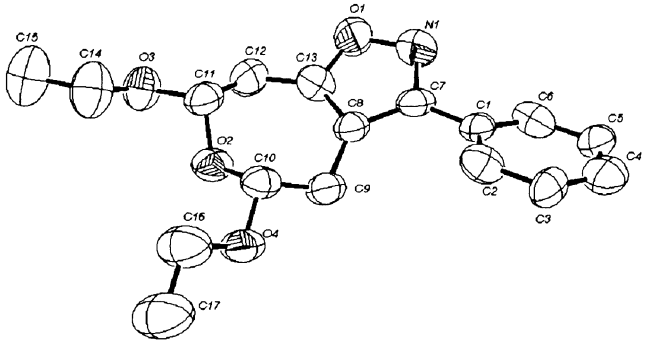
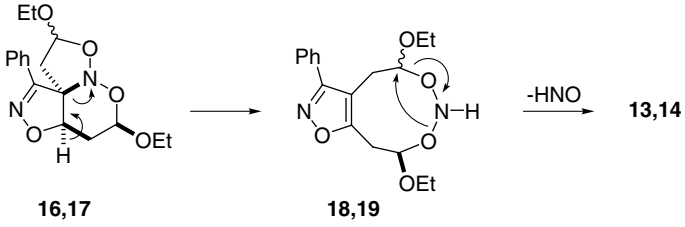
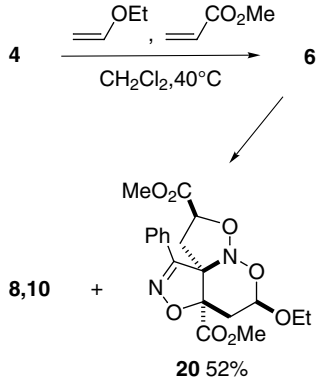


Figure 3. ORTEP drawing of **13** with hydrogens omitted for clarity.

assigned structures and the most diagnostic ones are discussed below. Whereas the ^{1}H NMR patterns of the primary cycloadducts **6** and **7** are characterised by three doublets of doublets (δ 2.23, 3.76, and 5.45 vs 2.34, 3.80, and 5.46) for the CH_2CH AMX system, the coupled ^{13}C NMR spectra show a triplet (δ 38.6 vs 40.0) and a doublet (δ 99.5 vs 99.6) for the same moiety, together with a singlet (δ 85.1 vs 89.4) assigned to the C-7a quaternary carbon.[11] With regard to the predominant nitroso acetals **8**, **9** and **16**, the resonances of the pseudoanomeric H-2 and H-8 protons are easily identified, according to the literature,[5,9] in well-separated ranges (δ 5.62–5.86 and 4.89–5.33, respectively); significantly, the inversion of configuration at C-2



Scheme 4.



Scheme 5.

for the corresponding epimers **10**, **11**, and **17** causes a remarkable upfield shift ($\Delta\delta$=0.6–0.79 ppm) for H-2, as a consequence of an increased shielding by the phenyl group at position 4. A minor complementary downfield shift ($\Delta\delta$=0.22–0.35 ppm) was also observed for the methyl protons of the ethoxy substituent.

In conclusion, this work shows a novel attractive feature of the cycloaddition chemistry of 4-nitroisoxazoles; previously used as versatile dienophiles,[12] dipolarophiles,[13] and 2-azadienes[14] for the synthesis of a variety of heterocyclic systems, they can be also exploited as activated nitroalkene heterodienes for a direct and highly diastereoselective approach to 1,6,9-trioxa-5,9a-diazacyclopenta[*d*]indenes through pericyclic homodomino reactions.

3. Experimental

3.1. General procedures

Melting points were taken on a Büchi 510 apparatus and are uncorrected. IR spectra of solid and oily products were measured as KBr pellets and liquid films, respectively, with a Perkin–Elmer 881 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions with a Varian Gemini instrument operating at 200 and 50 MHz, respectively. Chemical shifts are expressed in ppm (δ) and coupling constants in Hertz (Hz); the relative assignment of the ^{13}C NMR resonances was achieved by the use of coupled spectra and heteronuclear correlation experiments. Elemental analyses were obtained with a Perkin–Elmer 2400 Analyser. X-ray crystallographic analyses were carried out in a P4 diffractometer with Cu-K_α radiation. Silica gel plates (Merck F_{254}) and silica gel 60 (Merck, 230–400 mesh) were used for TLC and flash chromatographies, respectively; petroleum ether employed for chromatographic work-up refers to the fractions of bp 40–70°C. All the reactions were carried out in a screw-capped tube (Pyrex N. 18).

3.2. Thermal reactions of compounds 4, 5 and 12 with ethyl vinyl ether. General procedure

Unless otherwise stated, a solution of the nitroisoxazole (0.5 mmol) and EVE (0.754 g, 1.0 ml, 10.4 mmol) in anhydrous dichloromethane (2 ml) was stirred at 40°C until the starting material was completely consumed (TLC and ^{1}H NMR). The residue left by evaporation to dryness under reduced pressure was subjected to flash chromatography.

3.2.1. A. Chromatographic resolution [petroleum ether/ethyl acetate (6:1 v/v)] of the pale yellow residue coming from **4** (0.124 g) (4 days) afforded methyl (2*SR*, 3a*RS*, 6a*RS*, 8*RS*)-2,8-diethoxy-4-phenyl-2,3,7,8-tetrahydro-6a*H*-1,6,9-trioxa-5,9a-diazacyclopenta[*d*]indene-6a-carboxylate (**8**) (R_f=0.24, 0.157 g, 80%) as ivory-coloured crystals: mp 116–116.5°C (from *n*-pentane/ether); IR 1745, 1104 cm^{-1}; ^{1}H NMR δ 0.80 (t, J=7.0 Hz, 3H), 1.28 (t, J=7.0 Hz, 3H), 2.21 (dd, J=14.0 and 7.8 Hz, 1H), 2.26 (dd, J=14.0 and 3.0 Hz, 1H), 2.60 (dd, J=14.0 and 7.0 Hz, 1H), 2.69 (dd, J=14.0 and 6.6 Hz, 1H), 3.21–3.49 (m, 2H), 3.51–3.66 (m, 1H), 3.87 (s, 3H), 3.89–4.05 (m, 1H), 5.18 (dd, J=7.8 and 6.6 Hz, 1H), 5.68 (dd, J=7.0 and 3.0 Hz, 1H), 7.30–7.45 (m, 3H), 7.61–7.66 (m, 2H); ^{13}C NMR δ 14.5 (q), 15.0 (q), 32.7 (t), 38.5 (t), 53.0 (q), 63.9 (t), 65.0 (t), 89.3 (s), 92.6 (s), 97.3 (d), 109.5 (d), 127.0 (s), 127.7 (d), 129.7 (d), 129.8 (d), 157.0 (s), 169.7 (s). Anal. Calcd for $C_{19}H_{24}N_2O_7$: C, 58.16; H, 6.16; N, 7.14. Found: C, 58.34; H, 6.16; N, 6.98.

The following fractions gave a pale yellow solid (0.020 g) containing comparable amounts of **8** and (2*RS*, 3a*RS*, 6a*RS*, 8*RS*)-2,8-diethoxy-4-phenyl-2,3,7,8-tetrahydro-6a*H*-1,6,9-trioxa-5,9a-diazacyclopenta[*d*]indene-6a-carboxylate (**10**): ^{1}H NMR δ 1.15 (t, J=7.0 Hz, 3H), 1.29 (t, J=7.0 Hz, 3H), 2.24 (dd, J=13.9 and 8.1 Hz, 1H), 2.34–2.60 (m, 2H), 2.78 (dd, J=13.9 and 6.6 Hz, 1H), 3.24–3.80 (m, 3H), 3.86 (s, 3H), 3.90–4.08 (m, 1H), 4.91 (t, J=5.7 Hz, 1H), 5.22 (dd, J=8.1 and 6.6 Hz, 1H), 7.35–7.42 (m, 3H), 7.55–7.60 (m, 2H); ^{13}C NMR δ 15.1 (q), 15.2 (q), 33.3 (t), 39.1 (t), 53.2 (q), 63.8 (t), 65.8 (t), 89.1 (s), 93.9 (s), 97.5 (d), 110.5 (d), 126.55 (s), 128.3 (d), 129.5 (d), 132.3 (d), 156.4 (s), 169.3 (s).

3.2.2. B. When the above reaction was carried out at 8°C for the same time, the resulting mixture contained, together with the unreacted **4** as the predominant product and a small amount of **8**, (6*RS*, 7a*RS*)-6,7-dihydro-7a*H*-6-ethoxy-7a-methoxycarbonyl-3-phenylisoxazolo[4,5-*c*][1,2]-oxazine-4-oxide (**6**): ^{1}H NMR δ 1.19 (t, J=7.0 Hz, 3H), 2.23 (dd, J=13.6 and 3.5 Hz, 1H), 3.50–3.70 (m, 1H), 3.76 (dd, J=13.6 and 7.3 Hz, 1H), 3.79 (s, 3H), 3.85–4.15 (m, 1H), 5.45 (dd, J=7.3 and 3.5 Hz, 1H), 7.42–7.55 (m, 3H), 7.83–7.92 (m, 2H); ^{13}C NMR δ 14.4 (q), 38.6 (t), 53.8 (q), 65.6 (t), 85.1 (s), 99.5 (d), 124.9 (s), 128.4 (d), 128.8 (d), 131.0 (d), 151.0 (s), 166.0 (s).[11]

3.2.3. C. The solid residue obtained from **5** (0.147 g) (8 days) was resolved into two components with petroleum ether/ethyl acetate (10:1 v/v) as eluent. The first band yielded (2*SR*, 3a*RS*, 6a*RS*, 8*RS*)-6a-benzoyl-2,8-diethoxy-4-phenyl-2,3,7,8-tetrahydro-6a*H*-1,6,9-trioxa-5,9a-diazacyclopenta[*d*]indene (**9**) (R_f=0.29, 0.132 g, 60%) that was crystallised from *n*-hexane as colourless needles: mp 103–104°C; IR 1683, 1103 cm^{-1}; ^{1}H NMR δ 0.79 (t, J=7.0 Hz, 3H), 1.30 (t, J=7.0 Hz, 3H), 2.01 (dd, J=14.0 and 3.0 Hz, 1H), 2.21 (dd, J=13.8 and 8.0 Hz, 1H), 2.54 (dd, J=14.0 and 7.0 Hz, 1H), 2.78 (dd, J=13.8 and 6.5 Hz, 1H), 3.20–3.45 (m, 2H), 3.55–3.70 (m, 1H), 3.90–4.05 (m, 1H), 5.33 (dd, J=8.0 and 6.5 Hz, 1H), 5.62 (dd, J=7.0 and 3.0 Hz, 1H), 7.33–7.78 (m, 8H), 8.0–8.05 (m, 2H); ^{13}C NMR δ 14.55 (q), 15.1 (q), 34.2 (t), 39.1 (t), 63.9 (t), 65.2 (t), 92.9 (s), 93.0 (s), 98.0 (d), 110.1 (d), 127.1 (s), 127.8 (d), 128.8 (d), 129.8 (d), 130.0 (d), 130.1 (d), 134.0 (d), 134.9 (s), 158.9 (s), 195.8 (s). Anal. Calcd for $C_{24}H_{26}N_2O_6$: C, 65.74; H, 5.98; N, 6.39. Found: C, 66.03; H, 5.97; N, 6.52.

The second one afforded (2*RS*, 3a*RS*, 6a*RS*, 8*RS*)-6a-benzoyl-2,8-diethoxy-4-phenyl-2,3,7,8-tetrahydro-6a*H*-1,6,9-trioxa-5,9a-diazacyclopenta[*d*]indene (**11**) (R_f=0.18, 0.026 g, 12%) as a white solid: mp 137–138°C (from ether/30–50°C petroleum ether); IR 1673, 1106 cm^{-1}; ^{1}H NMR δ 1.09 (t, J=7.1 Hz, 3H), 1.32 (t, J=7.1 Hz, 3H), 2.14–2.34 (m, 3H), 2.88 (dd, J=13.6 and 6.7 Hz, 1H), 3.28–3.45 (m, 1H), 3.59–3.76 (m, 2H), 3.92–4.08 (m, 1H), 4.83 (t, J=5.8 Hz, 1H), 5.38 (dd, J=7.8 and 6.7 Hz, 1H), 7.37–7.64 (m, 8H), 8.01–8.06 (m, 2H); ^{13}C NMR δ 15.0 (q), 15.2 (q), 34.7 (t), 39.15 (t), 63.9 (t), 65.7 (t), 92.6 (s), 94.0 (s), 98.25 (d), 110.8 (d), 126.8 (s), 128.45 (d), 128.8 (d), 129.5 (d), 129.8 (d), 130.45 (d), 133.9 (d), 135.1 (s), 158.3 (s), 194.9 (s). Anal. Calcd for $C_{24}H_{26}N_2O_6$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.69; H, 5.89; N, 6.46.

3.2.4. D. Treatment of **5** with EVE at 8°C for 5 days afforded a crude product containing, in addition to a small amount of **11**, an 1:1 mixture of the starting material and (6*RS*, 7a*RS*)-7a-benzoyl-6,7-dihydro-7a*H*-6-ethoxy-3-phenylisoxazolo-[4,5-*c*][1,2]oxazine-4-oxide (**7**): ^{1}H NMR δ 1.20 (t, J=7.0 Hz, 3H), 2.34 (dd, J=13.5 and 3.6 Hz, 1H), 3.58–3.72 (m, 1H), 3.80 (dd, J=13.5 and 7.0 Hz, 1H), 3.90–4.05 (m, 1H), 5.46 (dd, J=7.0 and 3.6 Hz, 1H), 7.36–7.53 (m, 6H), 7.80–7.96 (m, 4H); ^{13}C NMR δ 14.4 (q), 40.0 (t), 65.7

(t), 89.4 (s), 99.65 (d), 125.0 (s), 128.4 (d), 128.75 (d), 128.8 (d), 129.9 (d), 131.3 (d), 133.7 (s), 133.8 (d), 152.2 (s), 190.3 (s).[11]

3.2.5. E. The yellow-brown residue coming from **12** (0.095 g) (6 days) was subjected as quickly as possible to flash chromatography [petroleum ether/ethyl acetate (5:1 v/v)]. After some faster fractions containing small amounts of **13** and **14** were discarded, the following ones afforded a 5:1 mixture of (2*SR*, 3a*RS*, 6a*RS*, 8*RS*)-2,8-diethoxy-4-phenyl-2,3,7,8-tetrahydro-6a*H*-1,6,9-trioxa-5,9a-diazacyclopenta-[*d*]indene (**16**) and (2*RS*, 3a*RS*, 6a*RS*, 8*RS*)-2,8-diethoxy-4-phenyl-2,3,7,8-tetrahydro-6a*H*-1,6,9-trioxa-5,9a-diazacyclopenta[*d*]indene (**17**) as a pale yellow oil (R_f=0.26, 0.134 g, 80%). An analytical sample was obtained by dissolution in anhydrous dichloromethane, filtration, evaporation to dryness, and rapid evacuation at room temperature (10^{-2} Torr): IR 1116 cm^{-1}; ^1H NMR δ 0.93 (t, J=7.0 Hz, 3H), [1.15 (t, J=7.0 Hz, 3H)], [1.20 (t, J=7.0 Hz, 3H)], 1.22 (t, J=7.0 Hz, 3H), 2.08 (ddd, J=13.5, 12.1 and 8.3 Hz, 1H), 2.36 (ddd, J=13.5, 6.7 and 5.5 Hz, 1H), 2.41 (dd, J=13.6 and 3.6 Hz, 1H), 2.83 (dd, J=13.6 and 6.8 Hz, 1H), 3.35–3.70 (m, 3H), 3.94–4.03 (m, 1H), 4.68 (dd, J=12.1 and 5.5 Hz, 1H), 4.89 (dd, J=8.3 and 6.7 Hz, 1H), [5.26 (dd, J=6.0 and 4.8 Hz, 1H)], 5.86 (dd, J=6.8 and 3.6 Hz, 1H), 7.15–7.45 (m, 3H), 7.75–7.85 (m, 2H); ^{13}C NMR δ 14.7 (q), 14.9 (q), [(15.0 (q)], [29.6 (t)], 29.9 (t), 41.7 (t), [42.3 (t)], 63.7 (t), [65.2 (t)], 65.3 (t), [83.1 (s)], 83.8 (s), 90.5 (s), [91.2 (s)], 96.8 (d), [97.2 (d)], 109.6 (d), [110.2 (d)], 127.4 (s), 127.9 (d), [128.5 (s)], [128.0 (d)], [128.6 (d)], 128.9 (d), 129.8 (d), [130.1 (d)], 158.0 (s), [158.8 (s)].[15] Anal. Calcd for $C_{17}H_{22}N_2O_5$: C, 61.07; H, 6.63; N, 8.38. Found: C, 61.27; H, 6.60; N, 8.12.

3.2.6. F. Chromatographic work-up [petroleum ether/ethyl acetate (10:1 v/v)], of the crude product obtained from **12** (0.095 g) and EVE (0.360 g, 0.48 ml, 5.0 mmol) in chloroform at 70°C for 48 h, gave a 3:2 mixture of (5*SR*, 7*RS*)-5,7-diethoxy-3-phenyl-4,5,7,8-tetrahydroisoxazolo[4,5-*d*]oxepine (**13**) and (5*RS*, 7*RS*)-5,7-diethoxy-3-phenyl-4,5,7,8-tetrahydroisoxazolo[4,5-*d*]oxepine (**14**) as a pale yellow solid (R_f=0.40, 0.082 g, 54%). An analytical sample of **13** was prepared by crystallisation from ethanol as colourless needles: mp 112–113°C; IR 1127 cm^{-1}; ^1H NMR δ 1.24 (t, J=7.0 Hz, 3H), 1.29 (t, J=7.0 Hz, 3H), 2.79–3.04 (m, 2H), 3.12–3.39 (m, 2H), 3.42–3.66 (m, 2H), 3.95–4.12 (m, 2H), 4.71 (dd, J=8.0 and 3.0 Hz, 1H), 4.87 (dd, J=8.7 and 2.6 Hz, 1H), 7.41–7.58 (m, 5H); ^{13}C NMR δ 15.0 (q), 30.9 (t), 35.6 (t), 64.0 (t), 64.2 (t), 99.65 (d), 101.6 (d), 108.8 (s), 128.2 (s), 128.5 (d), 128.8 (d), 129.6 (d), 163.0 (s), 164.7 (s). Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.41; H, 6.99; N, 4.48.

The minor diastereomer **14**, not available as a pure product, was characterised by spectral data: ^1H NMR δ 1.22 (t, J=7.2 Hz, 3H), 1.25 (t, J=7.2 Hz, 3H), 2.80–2.98 (m, 2H), 3.14–3.31 (m, 2H), 3.54–3.64 (m, 2H), 3.86–3.96 (m, 2H), 5.17 (dd, J=8.0 and 4.4 Hz, 1H), 5.28 (dd, J=8.2 and 4.2 Hz, 1H), 7.41–7.58 (m, 5H); ^{13}C NMR δ 14.95 (q), 29.6 (t), 34.1 (t), 63.8 (t), 63.9 (t), 95.5 (d), 97.0 (d), 108.8 (s), 128.2 (d), 128.7 (d), 128.9 (s), 129.5 (d), 162.3 (s), 165.3 (s).

When the original mixture of the nitroso acetals **16** and **17** (0.1 g, 0.3 mmol) was stirred in chloroform (0.75 ml) at room temperature for 15 h, the diastereomers **13** and **14** (ca. 3:2, 0.051 g, 56%) were obtained by flash chromatography of the resulting reaction product.

3.3. Methyl (2*SR*, 3a*RS*, 6a*RS*, 8*RS*)-8-ethoxy-4-phenyl-2,3,7,8-tetrahydro-6a*H*-1,6,9-trioxa-5,9a-diazacyclopenta[*d*]indene-2,6a-dicarboxylate (20)

A solution of **4** (0.124 g, 0.5 mmol), EVE (0.754 g, 1.0 ml, 10.4 mmol), and methyl acrylate (0.956 g, 1.0 ml, 11.2 mmol) in anhydrous dichloromethane (2 ml) was stirred at 40°C for 8 days; the residue left by evaporation to dryness was subjected to flash chromatography with petroleum ether/ethyl acetate 3:1 (v/v) as eluent. The faster moving band gave a 7:1 mixture of the epimers **8** and **10** (R_f=0.48, 0.069 g, 35%) whereas the slower one afforded compound **20** (R_f=0.23, 0.106 g, 52%) as an ivory-coloured waxy product. An analytical sample was prepared by dissolution in ether, filtration, evaporation to dryness and prolonged evacuation (10^{-2} Torr). IR 1739, 1106 cm^{-1}; ^1H NMR δ 1.28 (t, J=7.0 Hz, 3H), 2.22 (dd, J=14.0 and 7.7 Hz, 1H), 2.52 (dd, J=13.6 and 9.2 Hz, 1H), 2.69 (dd, J=14.0 and 6.6 Hz, 1H), 2.80 (dd, J=13.6 and 7.0 Hz, 1H), 3.58 (dq, J=9.6 and 7.0 Hz, 1H), 3.74 (s, 3H), 3.89 (s, 3H), 3.94 (dq, J=9.6 and 7.0 Hz, 1H), 4.29 (dd, J=9.2 and 7.0 Hz, 1H), 5.14 (dd, J=7.7 and 6.6 Hz, 1H), 7.33–7.45 (m, 3H), 7.55–7.62 (m, 2H); ^{13}C NMR δ 15.0 (q), 33.2 (t), 34.3 (t), 52.7 (q), 53.2 (q), 64.0 (t), 81.5 (d), 88.8 (s), 94.75 (s), 97.7 (d), 126.4 (s), 128.5 (d), 129.4 (d), 130.45 (d), 156.1 (s), 169.4 (s), 170.0 (s). Anal. Calcd for $C_{19}H_{22}N_2O_8$: C, 56.16; H, 5.46; N, 6.89. Found: C, 56.31; H, 5.57; N, 6.73.

3.4. X-Ray crystal structure determination for 8 and 13

Compound **8**: $C_{19}H_{24}N_2O_7$, M=392.40, monoclinic, space group $P2_1/c$, a=12.804(5) Å, b=11.590(5) Å, c=13.450(5) Å, β=98.500(5)°, V=1974.0(14) $Å^3$, Z=4, $F(000)$=832, μ=0.101 mm^{-1}, D_c=1.320 g cm^{-3}. Compound **13**: $C_{17}H_{21}NO_4$, M=303.35, monoclinic, space group $C2/c$, a=38.72(2) Å, b=4.853(1) Å, c=20.28(1) Å, β=120.83(3)°, V=32.73(2) $Å^3$, Z=8, $F(000)$=1296, μ=0.716 mm^{-1}, D_c=1.231 g cm^{-3}. Data sets, consisting of 3193 ($2\theta_{max}$=120°) and 2611 ($2\theta_{max}$=110°) reflections, respectively, were collected on a P4 diffractometer using the (Cu-K_α) radiation (λ=1.5418 Å) for the cell parameter determinations and data collections. The intensities of two standard reflections were monitored to check the stability of the crystals; no loss of intensity was observed. The integrated intensities, measured at room temperature (293 K) using the $\theta/2\theta$ scan mode, were corrected for Lorentz and polarisation effects.[16] The structures were solved by direct methods of SIR 92[17] and refined using the full-matrix least-squares on F^2 provided by SHELXL93.[18] Anisotropic thermal parameters were used for all the non-hydrogen atoms. The final R indexes were 0.049 and 0.130, respectively, for reflections having $I>2\sigma(I)$. Tables giving atomic coordinates, anisotropic displacement parameters, bond lengths and bond angles have been deposited at the Cambridge Crystallographic Data Centre.

Acknowledgements

We wish to thank Mrs Brunella Innocenti for the analytical data.

References

1. (a) Barrett, A. G. M.; Graboski, G. G. *Chem. Rev.* **1986**, *86*, 751. (b) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*, Pergamon Press: Oxford, 1992; Chapter 6. (c) Perekalin, V. V.; Lipina, E. S.; Berestovitskaya, V. M.; Efremov, D. A. *Nitroalkenes: Conjugated Nitro Compounds*, Wiley: New York, 1994; Chapter 2.
2. Tietze, L. F.; Kettschau, G. *Top. Curr. Chem.* **1997**, *189*, 70.
3. (a) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137. (b) Denmark, S. E.; Thorarensen, A.; Middleton, D. S. *J. Am. Chem. Soc.* **1996**, *118*, 8266. (c) Denmark, S. E.; Thorarensen, A. *J. Am. Chem. Soc.* **1997**, *119*, 127. (d) Denmark, S. E.; Hurd, A. R.; Sacha, H. *J. Org. Chem.* **1997**, *62*, 1668. (e) Denmark, S. E.; Marcin, L. R. *J. Org. Chem.* **1997**, *62*, 1675. (f) Denmark, S. E.; Guagnano, V.; Dixon, J. A.; Stolle, A. *J. Org. Chem.* **1997**, *62*, 4610. (g) Denmark, S. E.; Dixon, J. A. *J. Org. Chem.* **1997**, *62*, 7086. (h) Denmark, S. E.; Middleton, D. S. *J. Org. Chem.* **1998**, *63*, 1604. (i) Denmark, S. E.; Hurd, A. R. *J. Org. Chem.* **1998**, *63*, 3045. (j) Denmark, S. E.; Dixon, J. A. *J. Org. Chem.* **1998**, *63*, 6167. (k) Denmark, S. E.; Dixon, J. A. *J. Org. Chem.* **1998**, *63*, 6178. (l) Denmark, S. E.; Herbert, B. *J. Am. Chem. Soc.* **1998**, *120*, 7357. (m) Denmark, S. E.; Seierstad, M.; Herbert, B. *J. Org. Chem.* **1999**, *64*, 884. (n) Denmark, S. E.; Seierstad, M. *J. Org. Chem.* **1999**, *64*, 1610. (o) Denmark, S. E.; Martinborough, E. A. *J. Am. Chem. Soc.* **1999**, *121*, 3046.
4. Tohda, Y.; Tani, K.; Yamawaki, N.; Ariga, M.; Nishiwaki, N.; Kotani, K.; Matsumura, E. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1222.
5. Papchikhin, A.; Agback, P.; Plavec, J.; Chattopadhyaya, J. *J. Org. Chem.* **1993**, *58*, 2874.
6. (a) MacCormack, P.; Hallé, J.-C.; Pouet, M.-J.; Terrier, F. *J. Org. Chem.* **1988**, *53*, 4407. (b) Hallé, J.-C.; Vichard, D.; Pouet, M.-J.; Terrier, F. *J. Org. Chem.* **1997**, *62*, 7178. (c) Vichard, D.; Hallé, J.-C.; Huguet, B.; Pouet, M.-J.; Riou, D.; Terrier, F. *J. Chem. Soc., Chem. Commun.* **1998**, 791.
7. Nesi, R.; Turchi, S.; Giomi, D.; Danesi, A. *Tetrahedron* **1999**, *55*, 13809.
8. For a proper definition and classification of domino reactions, see: Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115.
9. The same interactions have been previously suggested for the totally diastereoselective reaction of EVE with a nitroalkenyl sugar: Avalos, M.; Babiano, R.; Cintas, P.; Higes, F. J.; Jiménez, J. L.; Palacios, J. C.; Silva, M. A. *J. Org. Chem.* **1996**, *61*, 1880.
10. The nitroisoxazole **4** was completely inert toward the α,β-unsaturated ester.
11. The C-3a resonance was not evidenced; a similar behaviour has been previously reported for other polycyclic nitronates: Denmark, S. E.; Cramer, C. J.; Starnberg, J. A. *Helv. Chim. Acta* **1986**, *69*, 1971.
12. (a) Nesi, R.; Giomi, D.; Papaleo, S.; Quartara, L. *J. Chem. Soc., Chem. Commun.* **1986**, 1536. (b) Nesi, R.; Giomi, D.; Papaleo, S.; Corti, M. *J. Org. Chem.* **1990**, *55*, 1227. (c) Giomi, D.; Nesi, R.; Turchi, S.; Fabriani, T. *J. Org. Chem.* **1994**, *59*, 6840. (d) Turchi, S.; Giomi, D.; Nesi, R.; Paoli, P. *Tetrahedron* **1995**, *51*, 7085.
13. (a) Nesi, R.; Giomi, D.; Quartara, L.; Bracci, S.; Papaleo, S. *J. Chem. Soc., Chem. Commun.* **1987**, 1077. (b) Nesi, R.; Giomi, D.; Papaleo, S.; Bracci, S.; Dapporto, P. *Synthesis* **1988**, 884. (c) Nesi, R.; Giomi, D.; Papaleo, S.; Bracci, S.; Dapporto, P. *J. Org. Chem.* **1989**, *54*, 706.
14. (a) Nesi, R.; Giomi, D.; Papaleo, S.; Corti, M. *Gazz. Chim. Ital.* **1989**, *119*, 363. (b) Nesi, R.; Giomi, D.; Papaleo, S.; Turchi, S. *J. Org. Chem.* **1992**, *57*, 3713.
15. The values in square brackets refer to the most evident resonances of the minor isomer.
16. Walker, N.; Stuart, D. D. *Acta Crystallogr. A* **1983**, *39*, 158.
17. Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Burla, M. C.; Polidori, G.; Camalli, M. *J. Appl. Crystallogr.* **1994**, *27*, 435.
18. Sheldrick, G.M. SHELXL93: Program for Crystal Structure Refinement. University of Göttingen, Germany.