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X = Y - ZH Systems as Potential 1,3-Dipoles. Part 37[1] Generation of Nitrones from Oximes. Tandem Intramolecular 1,3-Azaprotio Cyclotransfer - Intramolecular 1,3-Dipolar Cycloaddition Reactions. Class 4 Processes.

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Keywords: Nitrones, cycloaddition, intramolecular, oximes.

Abstract: Aldoximes and ketoximes containing two alkenyl moieties in different side chains undergo thermal conversion to 5 - and 6 - membered cyclic nitrones, via concerted 1,3 - azaprotio cyclotransfer, followed by stereospecific intramolecular cycloaddition to give tricyclic spiro- and fused- ring systems. An X-ray crystal structure of one such product is reported.

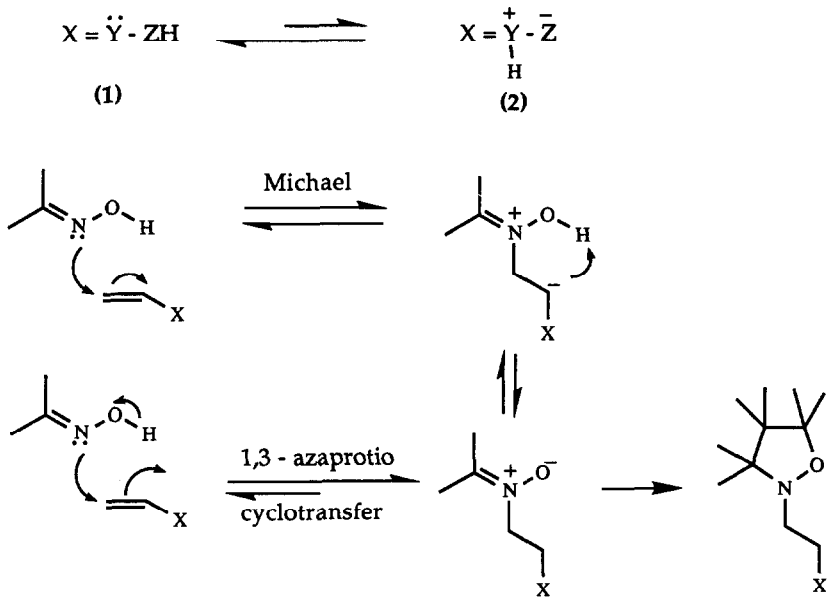
Over the past few years we have developed a range of oxime based tandem cycloaddition reactions of nitrones.[2] In all these processes the nucleophilicity of nitrogen was exploited to assemble a broad spectrum of fused-, bridged- and spirocyclic-isoxazolidines, by both inter- and intra-molecular processes. Further synthetic manipulation of these isoxazolidines affords a wide range of interesting natural and unnatural products.

The nucleophilic addition of oximes to an electronegative olefin which was previously considered to be a formal Michael addition reaction[3] has now been reinterpreted as a new concerted ene-like process that we have designated a 1,3-azaprotio cyclotransfer reaction (Scheme 1)[4]. This is based in part on the fact that addition of oximes to non-activated alkenes/alkynes has been observed. The main differences between the conventional ene reaction and the 1,3-azaprotio cyclotransfer reaction is that the former is a $2\pi + 2\sigma + 2\pi$ electron process proceeding via a 6-membered transition state whilst the latter is a $2\pi + 2\sigma + 2n$ electron process (n = lone pair electrons) and involves a 5-membered transition state.[4] Initially the involvement of radicals in the 1,3-azaprotio cyclotransfer reaction was considered because of a report by House *et al.*[5], of the involvement of radicals in related addition reactions of hydroxylamines to alkenes. However, we ruled this out due to the lack of any effect of peroxides and hydroquinones on our reactions.[6] Ciganek[7] and Holmes[8] have independently reported similar addition reactions, of hydroxylamines to alkenes and alkynes, to those of House and concluded they were concerted ene-like processes. The addition of oximes to non-activated alkenes has also been reported by Bishop and co-workers.[9] Further Pradhan *et al.*[10], have disclosed examples of reductive cyclisation of seco-steroidal oximes onto non-activated alkynes affording cyclic hydroxylamines. The initial step in this process is considered to be a further example of 1,3-azaprotio cyclotransfer.

Our systematic studies of the novel, general 1,2-prototropic processes in X = Y - ZH systems (1) ⇌ (2), demonstrated that in oximes,[4,6] the prototropic process is a higher energy process than the formal Michael addition (1,3-azaprotio cyclotransfer) when electronegative alkenes are involved.[3,11] However, suitable substrates which either incorporate the Thorpe-Ingold effect or which have a smaller HOMO-LUMO

dipole/dipolarophile energy gap favour the tandem 1,2-prototropy-cycloaddition reaction in oximes.[11] When the oxime α-carbon atom is disubstituted the novel 1,3-azaprotio cyclotransfer reaction competes with the 1,2-prototropy. In most cases, we observe stereospecific nitrone generation via the 1,3-azaprotio cyclotransfer reaction.[4,6,11,12]

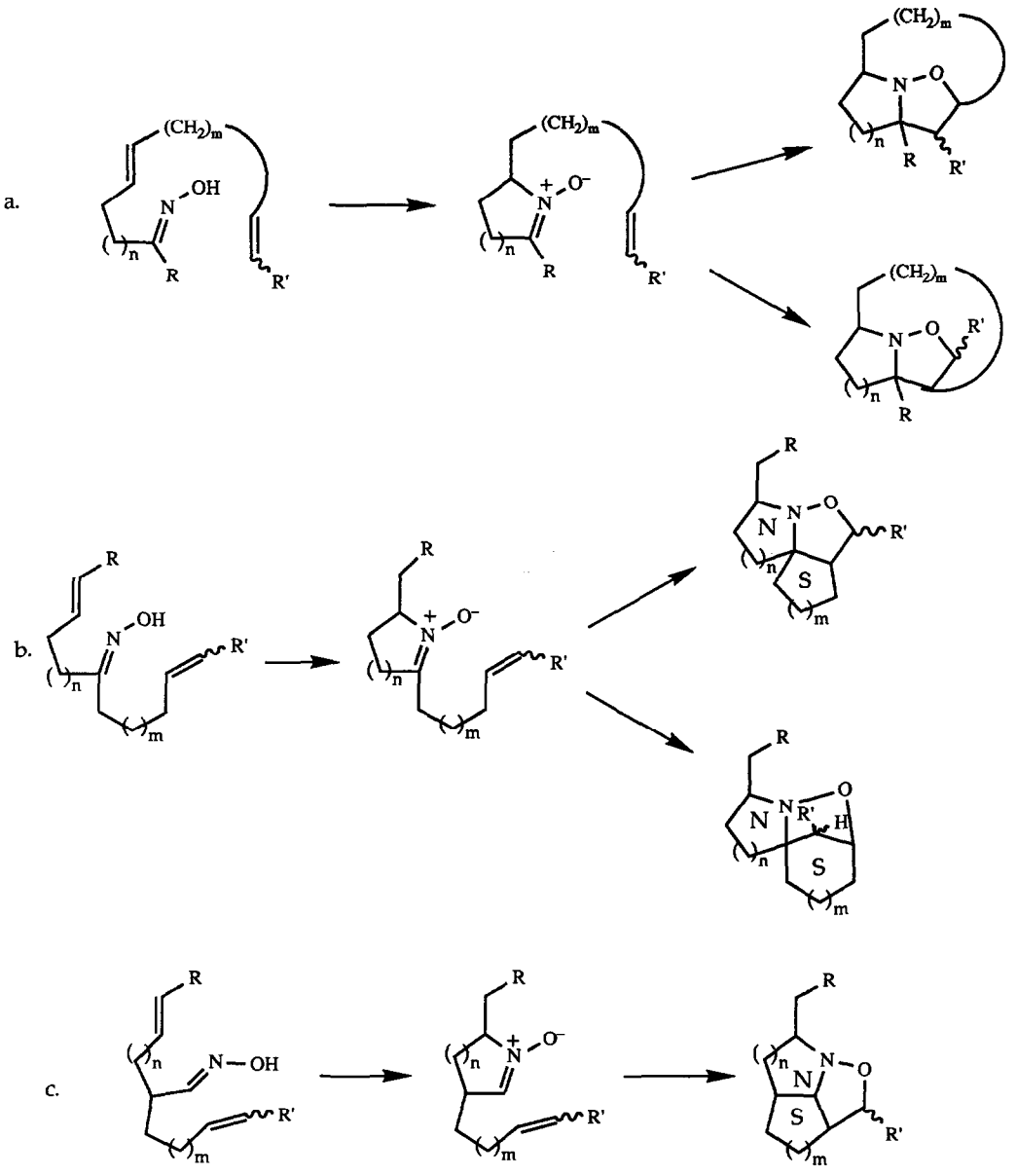
The tandem process, consisting of nitrone generation via 1,3-azaprotio cyclotransfer reaction and subsequent cycloaddition of the resulting nitrone to both activated and non-activated dipolarophiles, provides four broad synthetic variants. We have extensively discussed the first three classes in preceding papers in this series.[4,11,12] In this paper we describe the fourth class which comprises intramolecular 1,3-azaprotio cyclotransfer coupled with a subsequent intramolecular 1,3-dipolar cycloaddition reaction.



Scheme 1

The class 4 tandem processes can conceptually involve oximes possessing two alkenes or alkynes or an alkene/alkyne combination. To date we have only investigated substrates containing two alkene substituents. In each case the two unsaturated moieties can be positioned consecutively within one substituent of the oxime (Scheme 2a) or they can be positioned in each of the two substituents of a ketoxime (Scheme 2b) or of a branched aldoxime (Scheme 2c). In each case the nitrone, generated by the 1,3-azaprotio cyclotransfer, can conceptually undergo cycloaddition in two different ways (Scheme 2) [only one mode is shown for (2c) for brevity].

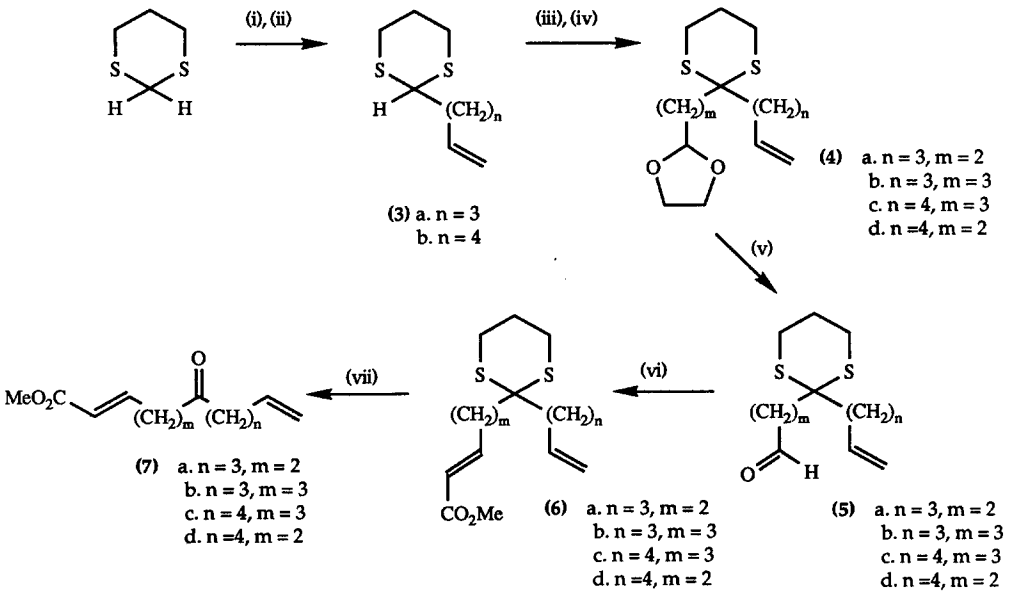
This paper is concerned only with substrates in which one alkene moiety is positioned in each of two chains (Scheme 2b and 2c). In each case tricyclic spiro- or fused ring- products are produced and these are classified in terms of the size of the two variable rings, the nitrone (N) ring, and the subsidiary (S) ring created in the cycloaddition step (Scheme 2b and 2c). The classification used in this paper gives the nitrone ring size first.



Scheme 2

1. Nitrone Generation Using an Electronegative Alkene

(i) 5/5-Spiro-ring.[13] Our first example of the intramolecular 1,3-azaprotio cyclotransfer - intramolecular 1,3-dipolar cycloaddition reaction involved a one-pot procedure from the ketone (7a, n=3 m=2).[14] The ω,ω′-dialkenyl ketones (7a-d) were prepared using standard dithiane methodology as outlined in Scheme 3. Thus, monoalkylation of 1,3-dithiane is effected in quantitative yield to give (3). Subsequent alkylation of (3) with the appropriate bromoacetal is achieved in 70-90% yield with n-butyllithium in the presence of HMPA to give (4). Selective hydrolysis of the acetal in (4) using 2N-HCl (aqueous THF, 65°C, 5h) gives the aldehydes (5) (65-80%). Wittig olefination of (5) affords (6) in excellent yields (90-96%). Finally, the hydrolysis of the dithiane is realised using N-chlorosuccinimide and silver nitrate in ca. 65-85% yield.[15]

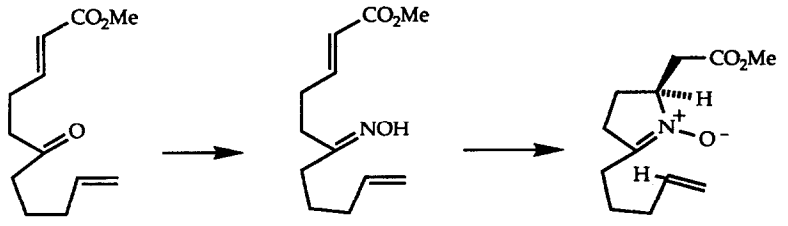


Reagents: (i) Bu^nLi / THF , -78 °C → -22 °C, 1.5h; (ii) $Br(CH_2)_nCH{=}CH_2$ at -78 °C; (iii) Bu^nLi / THF , -78 °C → -22 °C, 2.5h / HMPA at -78 °C, 0.5h; (iv) $Br(CH_2)_mCH$(O)(O) at -78 °C; (v) 2M HCl / aq.THF / 5h, reflux; (vi) $Ph_3P = CHCO_2Me$ / CH_2Cl_2, r.t, 16h; (vii) NCS / $AgNO_3$ / CH_3CN, r.t, 15 min.

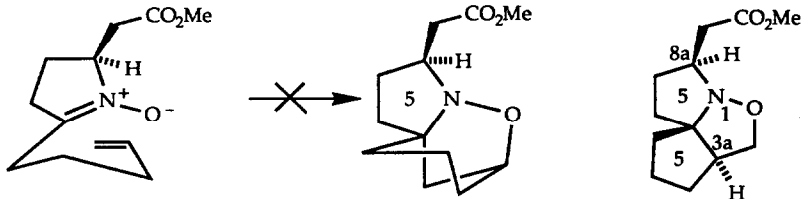
Scheme 3

When (7a) was heated with hydroxylamine in boiling xylene for 16h it afforded, stereo- and regio-specifically, the tricyclic product (8) in 82% yield. The intermediate oxime was not isolated. The stereochemistry was assigned by extensive 2D-COSY and n.O.e. experiments (See experimental). The cis - relationship of the two protons C_{3a}-H and C_{8a}-H in (8), indicates that the nitrone undergoes a facially specific exo-mode of cycloaddition on the face opposite to the methoxycarbonylmethyl group to afford the tricyclic

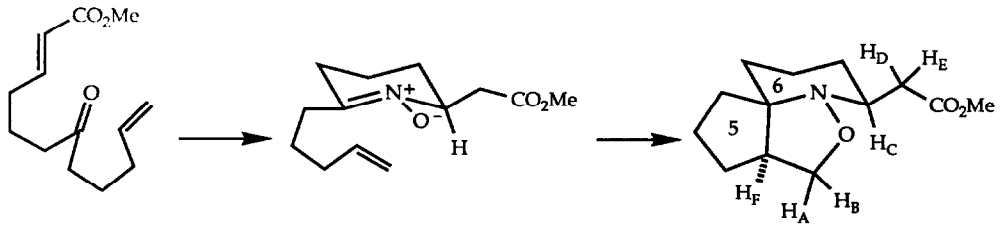
product (8). The alternative, 5/6 ring regioisomer (9) was not observed, presumably due to problems of obtaining adequate orbital overlap via a 2-plane approach. As the nitrone ring and subsidiary ring sizes increase this transition state becomes more easily accessible (See below).



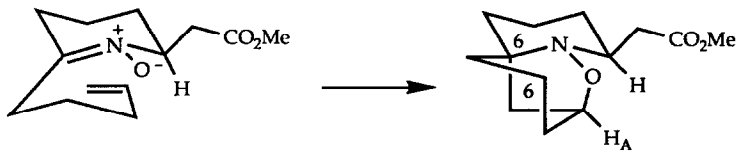
(7a)



(9) (8)



(7b) (10) (12)



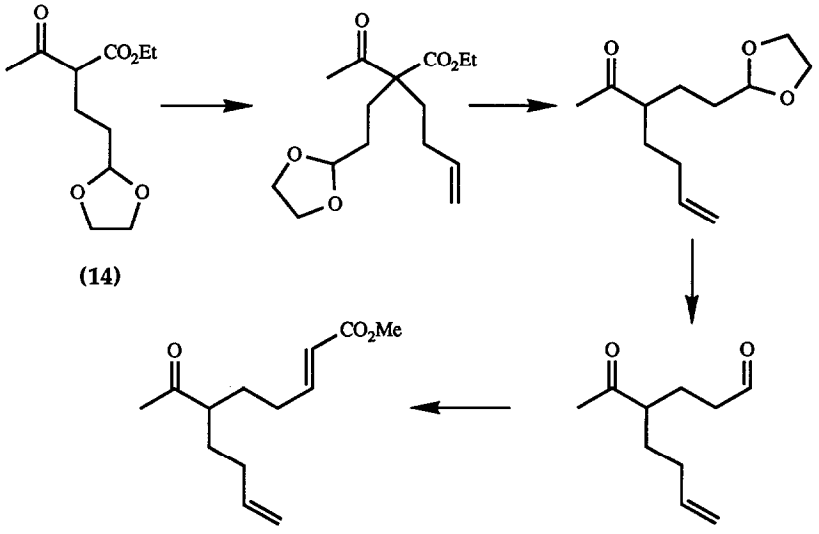
(11) (13)

(ii) 6/5-Spiro-ring. Ketone (7b) was reacted with hydroxylamine in water for 4.5h at room temperature. DMF was then added (DMF: H_2O ca.2:1) and the mixture heated at 100-105°C for 1h when the p.m.r. spectrum of an aliquot showed quantitative conversion to the 6/5-spiro product (12) (70% isolated yield).

The alternative cycloadduct structure (13) arising via the pre-transition state conformer (11) is ruled out by p.m.r. studies. Thus a low field (~δ 4-5) multiplet would be expected for H_A in (13) whilst the p.m.r. spectrum of the product (12) shows a triplet (δ 4.28) for H_A, a double doublet (δ 3.4) for H_B, a multiplet (δ 2.68) for H_F and two double doublets for H_D and H_E (δ 2.25 and 2.80) respectively.

The assignment of stereochemistry is based on n.O.e. experiments (See experimental). The cis-relationship between H_C and H_F in (12) arises from the diastereofacially specific exo-addition of the olefin to cyclic nitrone (10) from the side opposite to the methoxycarbonylmethyl group. There are reports in the literature[16] concerning approaches to the ring skeleton of histrionicotoxin and its perhydro derivative involving competition of transition states derived from analogous conformers to (10) and (11). In this case the 6/5-ring system is either formed exclusively or only trace amounts of the 6/6-ring system are observed. However, in one case it did prove possible to slowly thermally (125°C) rearrange the 6/5- to the 6/6-ring system.[16] In our case cycloadduct (12) remained unchanged (p.m.r. monitoring) when heated in xylene-d_{10} at 140°C for 24h.

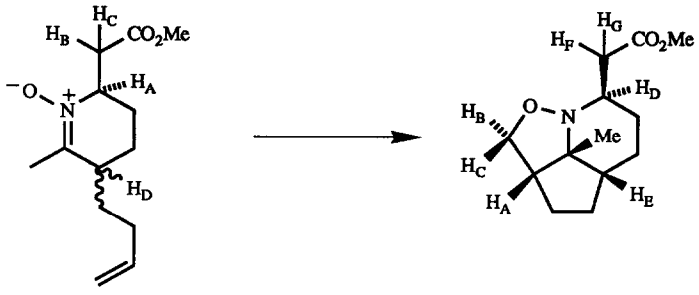
(iii) 6/5-Fused-ring. An example of the 6/5-fused-ring skeleton was achieved via the carbonyl derivative (15) which was prepared from the ketone (14) as shown in Scheme 4. Reaction of (15) with hydroxylamine in water at room temperature over 6h afforded a 4:1 mixture of isomeric nitrones (16) in 96% yield. Heating the nitrone mixture (16) in boiling toluene for 42h furnished a single cycloadduct (17) in ca. 70% yield (by p.m.r.) together with some unidentifiable products. The p.m.r. spectrum of (17) shows H_A as a multiplet at δ 2.58 whilst the signal due to H_D at δ 3.55 is partially obscured by the double doublet arising from H_C.



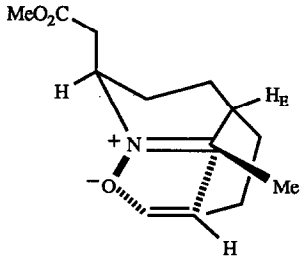
(14)

(15)

Scheme 4



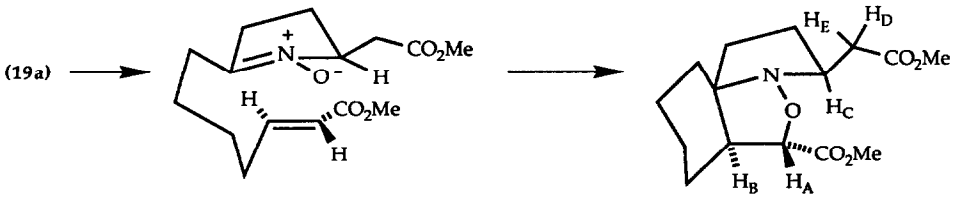
(16) (17)



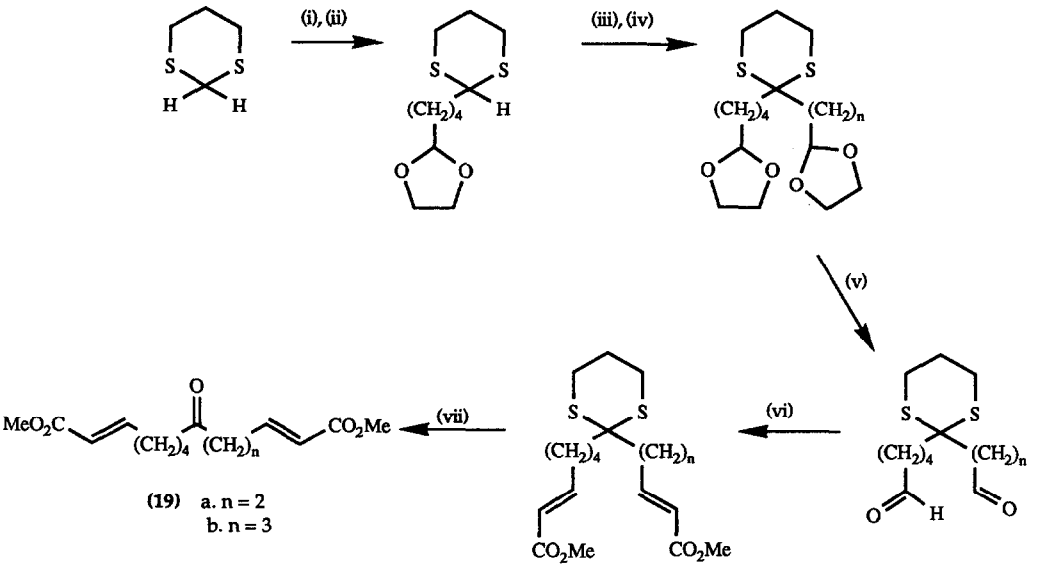
(18)

Examination of molecular models indicates that effective overlap between the nitrone and the dipolarophile can only be achieved when the alkenyl chain is pseudo-axial and addition occurs via an endo-orientation. If cycloaddition is to take place from the less hindered side of the nitrone, then the methoxycarbonylmethyl substituent must also be pseudo-axial (18). The slow cycloaddition reaction may reflect slow equilibration between the epimers of nitrone (16). Stereochemical assignment, based on n.O.e. studies, was hampered by overlapping signals although the available data were generally consistent with the structure (17). Thus, irradiation of the signal for C(Me) caused enhancements of H_A (2%), H_F (1%) and 3% on a multiplet at δ1.92 which was tentatively assigned as H_E. An enhancement of 2% of the signal at δ3.55 was attributed to the O-methylene proton H_C. Irradiation of the signal for H_B caused enhancements of H_C (9%) and H_A (3%) but had no effect on C(Me). A closely related 6/5-fused ring structure with analogous stereochemistry established by an X-ray crystal structure is reported later in this paper.

(iv) **5/6-Spiro-ring.** The ketone (19a) was prepared as outlined in Scheme 5. Reaction of (19a) with hydroxylamine gave the nitrone (20) which on heating in boiling acetonitrile under reflux for 16h afforded the cycloadduct (21) (75%) as a single stereoisomer together with trace amounts of a second isomer. This latter product may be the 5/7-spiro product analogous to (24) (below).



(20) (21)



(19) a. n = 2
b. n = 3

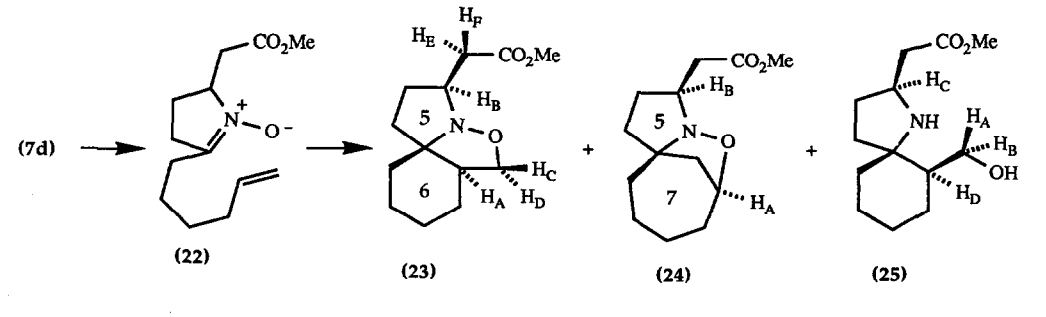
Reagents: (i) Bu^nLi / THF / –78 °C → -22 °C,1.5h; (ii) $Br(CH_2)_4CH$(O)(O) at –78 °C;

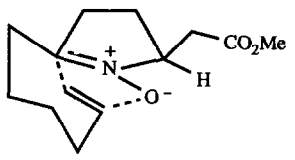
(iii) Bu^nLi / THF / -78 °C → -22 °C, 2.5h / HMPA at –78 °C, 0.5h; (iv) $Br(CH_2)_nCH$(O)(O) at -78 °C;

(v) 2M HCl / aq.THF / 5.5h, reflux; (vi) $Ph_3P = CHCO_2Me$ / CH_2Cl_2, r.t, 16h;

(vii) NCS / $AgNO_3$ / CH_3CN, r.t, 15 min.

Scheme 5

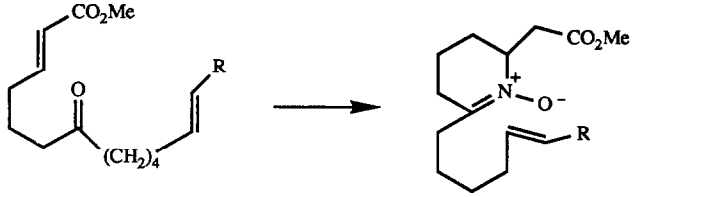




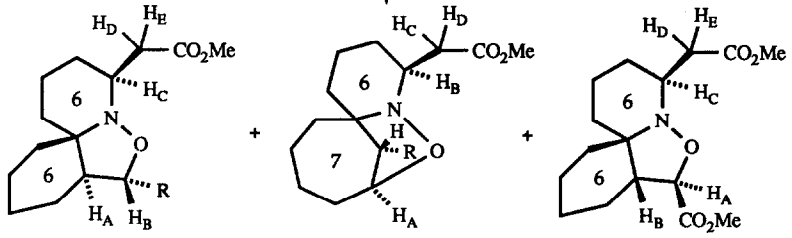
(26)

The effect of the electron withdrawing ester substituent in the dipolarophile in (20) on the regioselectivity of the cycloaddition step is illustrated by the intramolecular cycloaddition (DMF,110°C,30h) of (22). This reaction furnishes a 4:6:1 mixture of (23), (24) and (25). Thus the increased length of tether in (22) permits easier access to transition state (26) and in the absence of the electronic bias imparted by the alkene CO_2Me substituent in (20), the 5/7-spiro adduct is the major product.

(v) **6/6-Spiro-ring.** The ketone precursor (7c) was synthesised as outlined in Scheme 3. Reaction (MeCN,70°C,3h) of (7c) with hydroxylamine afforded the nitrone (27a) (83%). When (27a) was heated in DMF at 110°C it underwent a slow (2dy) intramolecular cycloaddition to give a 1:1 mixture (60%) of (28a) and (29a).



(27) a. R = H
b. R = CO_2Me



(28) a. R = H
b. R = CO_2Me

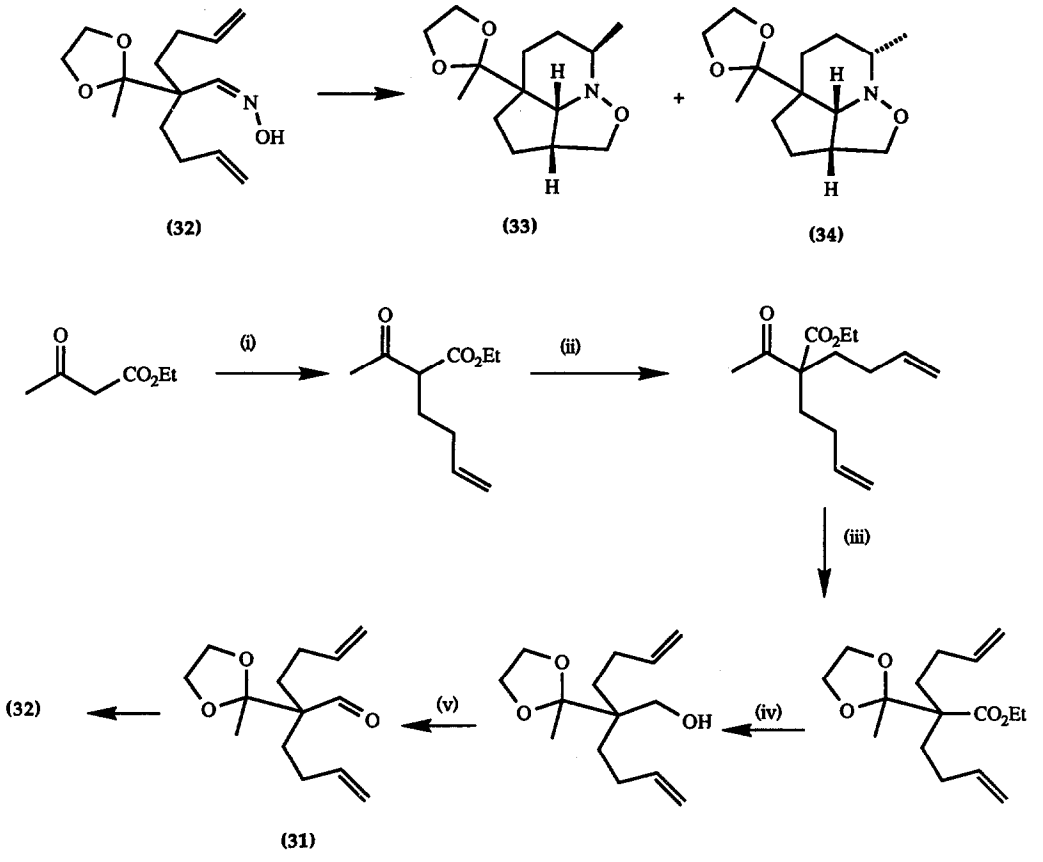
(29) a. R = H
b. R = CO_2Me

(30)

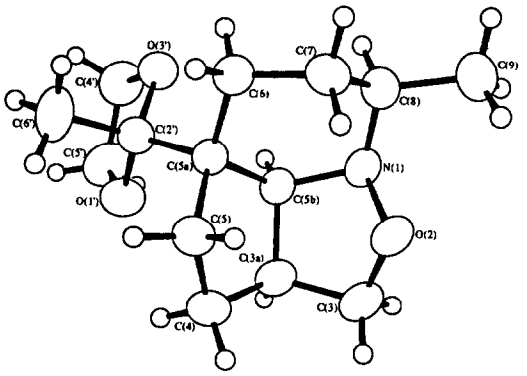
The effect of an electron withdrawing substituent on rate and regioselectivity is once again demonstrated by the results with (19b) (Scheme 5). Thus nitrone (27b) undergoes an intramolecular cycloaddition (MeCN, 80°C,16h) to give a 10:2:1 mixture (72%) of (28b), (30) and (29b). Thus selectivity for the 6/6-spiro system, via an endo-transition state, is substantially enhanced, as is the rate of reaction, by the terminal ester substituent on the dipolarophile moiety in (27b).

2. Nitrone Generation Using a Non-activated Alkene.

6/5-Fused-ring. Only one example of a tandem Class 4 process in which both olefinic moieties are unactivated has been explored using the oxime (32). The precursor (31) was synthesized from ethyl acetoacetate by standard methodology as shown in Scheme 6. Heating (32) in boiling xylene for 4h afforded a 1:1.2 epimeric mixture of (33) and (34) in essentially quantitative yield (p.m.r.). However, after separation by column chromatography on alumina the total isolated yield was only 58%. The stereochemistry of the minor isomer was assigned unambiguously as (33) on the basis of 2D-COSY and n.O.e. studies and the structure of the major epimer (34) was confirmed by X-ray crystallography (figure). Thus the intramolecular cycloaddition takes place on the opposite face to the bulky 1,3-dioxolanyl group in an endo-fashion in the epimeric nitrones formed by the 1,3-azaprotio cyclotransfer reaction.

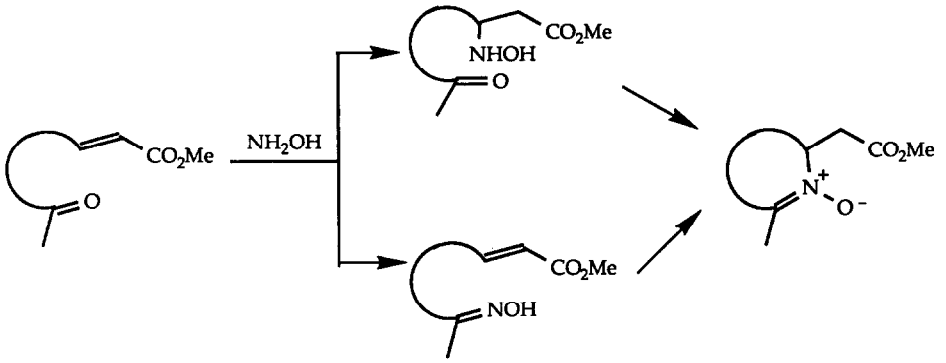


Scheme 6 Reagents: (i) NaOEt/EtOH/4-bromobutene; (ii) NaH/DMF/4-bromobutene/100-110°C; (iii) Ethyleneglycol/p-TsOH; (iv) $LiAlH_4$; (v) PCC, NaOAc; (vi) $NH_2OH.HCl/Na_2CO_3$.



FIGURE

The one-pot conversions of di(alkenyl) ketones to nitrone cycloadducts, where one alkenyl moiety has an ester substituent, could proceed via initial Michael addition, or 1,3-azaprotio cyclotransfer, of the hydroxylamine to the activated alkene rather than oxime formation (Scheme 7). Subsequent intramolecular condensation of the resulting hydroxylamine with the ketone would then furnish the nitrone (Scheme 7). Although we have no definitive evidence against this possibility we have previously prepared and isolated oximes of the type shown in Scheme 7.



Scheme 7

Experimental.

General experimental details were as previously described.[2] Ethyl 2-acetyl-5-hexenoate[18] was prepared according to the literature method. The following general procedures were employed for the reactions in Schemes 3 and 5.

Method A. Mono alkylation of 1,3-dithiane. A magnetically stirred nitrogen blanketed solution of 1,3-dithiane (10 g, 83 mmol) in dry THF (150 ml) at -78°C was treated with Bu^nLi(1.6M, 91.5 mmol, 57.2 ml). The mixture was kept at -22°C for 1.5 h before the alkyl bromide (83 mmol) was added dropwise with stirring over 10 min at -78°C. The mixture was allowed to slowly warm to room temperature overnight, quenched with water (75 ml), extracted with ether (2 x 100 ml), dried ($MgSO_4$), and the solvent removed under reduced pressure. The crude *product* was purified by chromatography (SiO_2) eluting with 4:1 v/v petroleum ether-ether.

Method B. Alkylation of 2-monosubstituted-1,3-dithiane. Bu^nLi (1.6M, 1.1 equiv.) was added to a nitrogen blanketed, magnetically stirred, solution of the 2-monosubstituted 1,3-dithiane (10 g) in dry THF (150 ml) at -78°C. The solution was kept at -22°C for 2.5 h before anhydrous HMPA (2 equiv.) was added at -78°C. After 15 min the appropriate alkyl bromide (1.1 equiv.) was added dropwise with stirring over 15 min. The reaction mixture was allowed to slowly warm to room temperature overnight, quenched with water (100 ml), extracted with ether (2 x 100 ml), dried ($MgSO_4$), and the solvent removed under reduced pressure. The crude *product* was purified by flash chromatography (SiO_2) eluting with 7:3 v/v petroleum ether-ether.

Method C. Hydrolysis of the acetal group. A solution of a 2-acetal functionalised 1,3-dithiane (7 g) in THF (100 ml) and HCl (2M, 75 ml) was boiled under reflux for 5 h. After cooling, the reaction mixture was neutralized with 5% $NaHCO_3$ (50 ml), extracted with ether (2 x 100 ml), dried ($MgSO_4$), and the solvent removed under reduced pressure. The residue was purified by flash chromatography (SiO_2) eluting with 7:3 v/v petroleum ether-ether.

Method D. Wittig olefination. A solution of a 2-substituted 1,3-dithiane (5 g), containing an aldehyde substituent, in dry methylene chloride (50 ml) was added dropwise with stirring over 0.5 h to a solution of methoxycarbonylmethylene triphenylphosphorane (1 equiv.) in dry methylene chloride (75-100 ml) under nitrogen. The reaction mixture was stirred at room temperature for 16 h and the solvent was removed under reduced pressure. Triphenylphosphine oxide was removed by repeated precipitation using ether-petroleum ether and the *product* was purified by flash chromatography (SiO_2) eluting with 1:1 v/v petroleum ether-ether.

Method E. Hydrolysis of a 2,2-disubstituted 1,3-dithiane to the ketone. A solution of 2,2-disubstituted 1,3-dithiane derivative (1 g) in acetonitrile (15 ml) was rapidly added to a well stirred solution of N-chlorosuccinimide (4 equiv.) and silver nitrate (4.5 equiv.) in 4:1 v/v CH_3CN-H_2O (80 ml). Silver chloride separated immediately as a voluminous white precipitate and the liquid phase became yellow. The reaction mixture was stirred for 15 min at room temperature and treated successively at 1 min intervals with saturated aqueous sodium sulphite (15 ml), saturated sodium carbonate (15 ml), and brine (15 ml). 1:1 v/v Hexane-methylene chloride (60 ml) was then added and the mixture was filtered through supercel. The filter cake was washed thoroughly with 1:1 v/v hexane-methylene chloride, the organic phases were combined, dried ($MgSO_4$), and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography (SiO_2) eluting with 1:1 v/v petroleum ether-ether.

2-(4′-Pentenyl)-1,3-dithiane(3a).[19] Obtained as colourless oil in quantitative yield, b.p 130-140°C (furnace temp.)/0.6 mmHg. (Found: C, 57.65; H, 8.55. $C_9H_{16}S_2$ requires C, 57.45; H, 8.50%); δ 5.73 (m, 1H, CH_2=C<u>H</u>CH_2), 5.00 (m, 2H, C<u>H</u>$_2$=CH), 4.05 (t, 1H, J 6.7Hz, SCHS), 2.84 (m, 4H), 2.08 (m, 2H), 1.58-1.92 (m, 6H); *m/z* (%) 188 (M^+, 100), 145 (28), 134 (28), 121 (10), 119 (97), 114 (23), 113 (15), 107 (23), 106 (61), 81 (55), 80 (61), 79 (19), 74 (36) and 73 (26).

2-(4′-Pentenyl)-2-[2"-(1,3-dioxolanyl) ethyl]-1,3-dithiane (4a). Prepared from 2-(4′-pentenyl)-1,3-dithiane and 2-(2′-bromoethyl)-1,3-dioxolane, according to general procedure B in 94% yield. The *product* was used directly in the next step without further purification. δ 5.80 (m, 1H, CH_2=C<u>H</u>), 4.95 (t, 1H, J 4.5Hz, CHO_2), 5.07 (m, 2H, CH_2), 3.94 (m, 4H, $(CH_2O)_2$), 2.82 (m, 4H), 2.05 (m, 4H), 1.93 (m, 1H), 1.82 (m, 5H) and 1.56 (m, 2H); ν_{max} 2915, 1630, 1420, 1275, 1135, 1030 and 910cm^{-1}

2-(4′-Pentenyl)-2-[3"-(1,3-dioxolanyl)propyl]-1,3-dithiane (4b). Prepared by procedure B from 2-(4′-pentenyl)-1,3-dithiane and 2-(3′-bromopropyl)-1,3-dioxolane in 75% yield as a colourless oil, b.p 136-140°C (mole still, furnace temp.)/0.1 mmHg. (Found: C, 59.75; H, 8.7; S, 21.05. $C_{15}H_{26}O_2S_2$ requires C, 59.55; H, 8.65; S, 21.2%); δ 5.8 (m, 1H, C<u>H</u>=CH$_2$), 4.9 (m, 2H, CH=C<u>H</u>$_2$), 4.87 (t, 1H, J 4.5Hz, OCHO), 3.92 (m, 4H, 2xCH_2O), 2.8 (m, 4H, 2xCH_2S), 2.08 (q, 2H, J 6.9Hz, CH_2CH_2), 1.92 (m, 6H) and 1.62 (m, 6H); ν_{max} 3080, 2950, 1640, 1430 and 1110 cm^{-1}; *m/z*(%) 302(M^+, 26), 119(76), 99(100), 87(31) and 73(96).

2-(5′-Hexenyl)-2-[3"-(1,3-dioxolanyl) propyl] -1,3-dithiane (4c) Prepared by method B from 2(5′-hexenyl)-1,3-dithiane and 2-(3′-bromopropyl)-1,3-dioxolane. The *product* (78%) was obtained as a colourless oil, b.p.(mole still, furnace temp.) 155-158°C/0.15 mmHg. (Found: C, 60.45; H, 9.05; S, 20.0. $C_{16}H_{28}O_2S_2$ requires C, 60.7; H, 8.9; S, 20.25%); δ 5.81 (m, 1H, CH_2=C<u>H</u>), 4.99 (m, 2H, C<u>H</u>$_2$=CH), 4.8 (t, 1H, J 4.6Hz, OCHO), 3.9 (m, 4H, 2xCH_2S), 2.1 (m, 2H, CH_2C<u>H</u>$_2CH_2$), 1.9 (m, 6H) and 1.4-1.7 (m, 8H); ν_{max} 3040, 2870, 2830, 1640 and 1070 cm^{-1}; *m/z*(%) 316(M^+, 23), 201(42), 99(100) and 73(47).

2-(5′-Hexenyl)-2-[2"-(1,3-dioxolanyl)ethyl]-1,3-dithiane(4d). Prepared by method B from 2-(5′-hexenyl)-1,3-dithiane and 2-(2′-bromoethyl)-1,3-dioxolane. The *product* (81%) was obtained as a colourless oil. (Found: C, 59.05; H, 8.35. $C_{15}H_{26}S_2O_2$ requires C, 59.5; H, 8.6%); δ 5.81 (m, 1H, CH_2=C<u>H</u>), 4.97 (m, 3H, C<u>H</u>$_2$=CH and OCHO), 3.92 (m, 4H, 2xCH_2O), 2.82 (m, 4H, 2xCH_2S), 2.01 (m, 6H), 1.81 (m, 4H) and 1.53 (m, 4H); ν_{max} 3072, 2933, 1683, 1452, 1363, 1273, and 1034 cm^{-1}; *m/z*(%) 302(M^+, 28), 86(100) and 73(75).

2-(4′-Pentenyl)-2-(3"-oxopropyl)-1,3-dithiane(5a). Obtained as a colourless oil (80%) using general method C. b.p. (mole still, furnace temp.) 130-135°/0. 5mmHg. (Found: C, 58.95; H, 8.35; S, 26.3. $C_{12}H_{20}S_2$ requires C, 59.05; H, 8.3; S, 26.3%); δ 9.85(t, 1H, CH=O), 5.79 (m, 1H, CH_2=C<u>H</u>), 5.02 (m, 2H, CH_2=), 2.79 (m, 4H), 2.64 (t, 2H, J 7.5Hz), 2.28 (dd, 2H, J 6.7 and 8.4Hz), 2.06 (m, 2H), 1.95 (m, 2H), 1.79 (m, 2H) and 1.55 (m, 2H); ν_{max} 2920, 2720, 1720, 1635, 1420, 1120, 910 and 620cm^{-1}; *m/z*(%) 244(M^+, 25), 188(20), 175(34), 169(29), 155(81), 143(100), 132(33), 106(48) and 85(80).

2-(4′-Pentenyl)-2-(4"-oxobutyl)-1,3-dithiane(5b). Prepared from acetal (4b) by method C. The *product* (70%) was a colourless oil b.p (mole still, furnace temp.) 103-105°C/0.1 mmHg. (Found: C, 60.7; H, 8.8; S, 24.5. $C_{13}H_{22}OS_2$ requires C, 60.4; H, 8.55 and S, 24.8%); δ 9.79 (t, 1H, J 1.5Hz, CHO), 5.81 (m, 1H, CH_2=C<u>H</u>), 5.02 (m, 2H, CH_2=C<u>H</u>), 2.81 (m, 4H, 2xCH_2S), 2.49 (dt, 2H, J 6.9 and 1.5Hz, C<u>H</u>$_2$CHO), 2.08 (q, 2H, J 6.9Hz, CH_2C<u>H</u>$_2$$CH_2$) 1.87 (m, 6H) and 1.58 (m, 4H).

2-(5′-Hexenyl)-2-(4"-oxobutyl)-1,3-dithiane(5c). Prepared by method C from acetal (4c). The *product* (74%) was obtained as a colourless oil, b.p.(mole still, furnace temp.) 115-119°C/0.3 mmHg. (Found: C, 61.25; H, 8.85. $C_{14}H_{24}S_2O$ requires C, 61.7; H, 8.85%); δ 9.8 (t, 1H, J 1.5Hz, CHO), 5.78 (m, 1H, CH_2=C<u>H</u>), 4.99 (m, 2H, C<u>H</u>$_2$=CH), 2.8 (m, 4H, 2xCH_2S), 2.5 (dt, 2H, J 6.9 and 1.5Hz, C<u>H</u>$_2$CH=CH_2), 2.06 (m, 2H, CH_2C<u>H</u>$_2$), 1.6-2.0 (m, 8H) and 1.38 (m, 4H); ν_{max} 3040, 2870, 2760, 1722 and 1640 cm^{-1}; *m/z*(%) 272 (M^+, 76), 201 (99), 189 (100),145 (53) and 106 (73).

2-(5′-Hexenyl)-2-(3"-oxopropyl)-1,3-dithiane(5d). Prepared by method C, from acetal (4d). The *product* (69%) was obtained as a colourless oil, b.p. (mole still, furnace temp.) 136-140°C/0.3 mmHg. (Found: C, 60.3; H, 8.6. $C_{13}H_{22}OS_2$ requires C, 60.4; H, 8.55%); δ 9.84 (t, 1H, J 1.1Hz, CHO), 5.8 (m, 1H, CH_2=C<u>H</u>), 4.99 (m, 2H, C<u>H</u>$_2$=CH), 2.79 (m, 4H, 2xCH_2O), 2.6 (dt, 2H, J 7.6 and 1.0Hz, C<u>H</u>$_2$CHO), 2.29 (t, 2H, J 7.0Hz, C<u>H</u>$_2$CH=CH_2), 1.76-2.17 (m, 6H) and 1.46 (m, 4H); *m/z*(%) 258(M^+, 69), 201(57) and 132(100)

2-(4′-Methoxycarbonyl-3′-butenyl)-2-(4"-pentenyl)-1,3-dithiane(6a). Prepared by method D from aldehyde(5a). The *product* was a colourless oil (95%) b.p. (mole still, furnace temp.) 170-180°C/0.5 mmHg. (Found: C, 60.3; H, 8.15; S, 21.05. $C_{15}H_{24}O_2S_2$ requires C, 60.05; H, 8.05; S, 21.35%); δ 6.99 (dt, 1H, J 6.8 and 15.7Hz, CH_2C<u>H</u>CHCO_2Me), 5.87 (d, 1H, J 15.7Hz, =C<u>H</u>C$O_2$$CH_3$), 5.79 (m, 1H, =C<u>H</u>CH_2), 5.02 (m, 2H, CH_2=), 3.73 (s, 3H, OMe), 2.80 (m, 4H, (CH_2S)$_2$), 2.36 (m, 2H, CH_2), 1.97 (m, 8H, 4xCH_2) and 1.56 (m, 2H, CH_2); ν_{max} 3060, 2930, 1715, 1650, 1635, 1430, 1320, 1270, 1210, 910 and 720 cm^{-1}; *m/z*(%) 300 (M^+, 42), 288(21), 269(11), 231(59), 225(61), 187(79), 175(29), 145(42), 132(31), 113(36) and 106(100).

2-(5′-Methoxycarbonyl-4′-pentenyl)-2-(4"-pentenyl)-1,3-dithiane(6b). Prepared by method D from aldehyde (5b). The *product* (87%) was obtained as a colourless oil, b.p.(mole still, furnace temp.) 110-114°C/0.1 mmHg. (Found: C, 61.0; H, 8.15. $C_{16}H_{26}S_2O_2$ requires C, 61.1; H, 8.35%); δ 6.97 (m, 1H, C<u>H</u>=CHCO_2Me), 5.82 (m, 2H, CH_2=C<u>H</u> and CH=C<u>H</u>CO_2Me), 5.02 (m, 2H, C<u>H</u>$_2$=CH), 3.73 (s, 3H, OMe), 2.8 (m, 4H, 2xCH_2S), 2.23 (dq, 2H, J 7.2 and 1.4Hz, C<u>H</u>$_2$CH=CHCO_2Me), 2.08 (q, 2H, J 6.9Hz, CH_2C<u>H</u>$_2$$CH_2$), 1.83-1.99 (m, 6H) and 1.48-1.67 (m, 4H); ν_{max} 3074, 2943, 1724, 1655, 1640, 1434, 1272 and 1200 cm^{-1}; *m/z*(%) 314(M^+, 20), 187(42), 145(40) and 106(100).

2-(5′-Methoxycarbonyl-4′-pentenyl)-2-(5"-hexenyl)-1,3-dithiane(6c). Prepared by method D from aldehyde derivative (5c). The *product* (90%) was colourless oil, b.p (mole still, furnace temp.) 147-150°C/0.1 mmHg. (Found: C, 62.0; H, 8.75; S, 20.05. $C_{17}H_{28}O_2S_2$ requires C, 62.15; H, 8.6; S, 19.5%); δ 6.97 (m, 1H, C<u>H</u>=CHCO_2Me), 5.82 (m, 2H, C<u>H</u>$_2$=CH and CH=C<u>H</u>CO_2Me), 5.02 (m, 2H, C<u>H</u>$_2$=CH), 3.73 (s, 3H, OMe), 2.81 (m, 4H, 2xCH_2S), 2.2 (dq, 2H, J 7.3 and 1.4Hz, C<u>H</u>$_2$CH=CHCO_2Me), 2.1 (m, 2H, CH_2C<u>H</u>$_2$$CH_2$), 1.9 (m, 4H), 1.6 (m, 4H) and 1.4 (m, 4H); ν_{max} 3074, 2940, 2863, 1725, 1657, 1641 and 1201 cm^{-1}; *m/z*(%) 328(M^+, 37),

253(57), 201(82), 106(100) and 99(82).

2-(4'-Methoxycarbonyl-3'-butenyl)-2-(5"-hexenyl)-1,3-dithiane(6d). Prepared by method D from aldehyde (5c). The *product* (90%) was a colourless oil. (Found: C, 61.3; H, 8.4; S, 20.2. $C_{16}H_{26}O_2S_2$ requires C, 61.1; H, 8.3; S, 20.35%); δ 6.91 (dt, 1H, J 15.3 and 6.8Hz, C<u>H</u>=CHCO$_2$Me), 5.83 (m, 2H, CH$_2$=C<u>H</u> and CH$_2$=C<u>H</u>CO$_2$Me), 4.99 (m, 2H, C<u>H$_2$</u>=CH), 3.73 (s, 3H, OMe), 2.81 (m, 4H, 2xCH$_2$S), 2.35 (m, 2H, C<u>H</u>CH$_2$=CHCO$_2$Me), 1.8-2.1 (m, 8H) and 1.45 (m, 4H); *m/z*(%) 314(M$^+$, 49), 231(95) and 201(100).

Methyl 6-oxoundeca-1,9-dienoate(7a). Prepared from (6a) by method E. The *product* (84%) was obtained as a colourless oil. b.p. (mole still, furnace temp.) 120-125°C/0.5 mmHg. (Found: C, 66.8; H, 8.6. $C_{12}H_{18}O_3$ requires C, 68.65; H, 8.65%); δ 6.94 (dt, 1H, J 6.5 and 15.7Hz, CH$_2$C<u>H</u>=CHCO$_2$Me), 5.83 (d, 1H, J 15.7Hz, CH=C<u>H</u>CH$_2$), 5.00 (m, 2H, CH$_2$=), 3.72 (s, 3H, OMe), 2.50 (m, 6H, 3xCH$_2$), 2.06 (m, 2H, CH$_2$), and 1.69 (q, 2H, J 7.2Hz, CH$_2$); ν_{max} 2920, 1710, 1650, 1430, 1270, 1170, 1120, 1020, 910, 720 and 700 cm^{-1}; *m/z*(%) 210(M$^+$, 3), 178(11), 156(26), 151(10), 141(16), 124(29), 113(79), 109(25) and 97(60).

Methyl 6-oxododeca-1,10-dienoate (7b). Prepared from (6b) by method E. The *product* (72%) was obtained as a colourless oil, b.p. (mole still, furnace temp.) 85-88°C/0.15 mmHg.(Found: C, 69.35: H, 8.95. $C_{13}H_{26}O_3$ requires, C, 69.6; H, 9.0%); δ 6.93 (m, 1H, C<u>H</u>=CHCO$_2$Me), 5.77 (m, 2H, CH$_2$=C<u>H</u> and CH=CO$_2$Me), 5.0 (m, 2H, CH$_2$=CH), 3.76 (s, 3H, OMe), 2.42 (q, 4H, J 7.1Hz, 2xCH$_2$O), 2.22 (dq, 2H, J 7.1 and 1.4Hz, C<u>H$_2$</u>CH=CHCO$_2$Me), 2.05 (q, 2H, J 7.0Hz, C<u>H$_2$</u>CH=CH$_2$) and 1.6-1.8 (m, 4H); ν_{max} 2949, 2319, 1723, 1657, 1436, 1270 and 1202 cm^{-1}; *m/z*(%) 224(M$^+$, 3), 192(37), 113(68), 73(94) and 41(100).

Methyl 7-oxotrideca-1,11-dienoate(7c). Prepared from (6c) by method E. The *product* (69%) was a colourless oil. b.p (mole still, furnace temp.) 100-104°C/0.15 mmHg.(Found: C, 70.55; H, 9.5. $C_{14}H_{22}O_3$ requires C, 70.55; H, 9.3%); δ 6.9 (dt, 1H, J 13.8 and 6.9Hz, C<u>H</u>=CHCO$_2$Me), 5.8 (m, 2H, CH$_2$=C<u>H</u> and CH=C<u>H</u>CO$_2$Me), 4.98 (m, 2H, C<u>H</u>=CH), 3.7 (s, 3H, OMe), 2.4 (q, 4H, J 7.2Hz, C<u>H$_2$</u>COC<u>H$_2$</u>), 2.2 (dq, 2H, J 7.2 and 1.3Hz, C<u>H$_2$</u>CH=CHCO$_2$Me), 2.0 (m, 2H, C<u>H$_2$</u>CH=CH$_2$), 1.74 (m, 2H), 1.58 (m, 2H) and 1.4 (m, 2H); ν_{max} 3076, 2973, 1718, 1688, 1641 and 1200 cm^{-1}; *m/z*(%) 238(M$^+$, 3), 206(22) and 73(100).

Methyl 7-oxododeca-1,10-dienoate(7d). Prepared from (6d) by method E. The *product* (70%) was a colourless oil. (Found: C, 69.4; H, 9.0. $C_{13}H_{20}O_3$ requires C, 69.6; H, 9.0%); δ 6.94 (dt, 1H, J 15.6 and 6.7Hz, C<u>H</u>=CHCO$_2$Me), 5.8 (m, 2H, CH$_2$=C<u>H</u> and CH=C<u>H</u>CO$_2$Me), 4.98 (m, 2H, C<u>H$_2$</u>=CH), 3.72 (s, 3H, OMe), 2.5 (m, 6H, 2xCH$_2$O and C<u>H</u>CH=CHCO$_2$Me), 2.05 (dq, 2H, J 8.3 and 1.2Hz, C<u>H$_2$</u>CH=CH$_2$), 1.59 (m, 2H) and 1.39 (m, 2H); *m/z*(%) 224(M$^+$,16), 156(69), 124(61) and 83(100).

1-Ethylenedioxy-4-methoxycarbonyl-5-one(14). 2-(2'-Bromoethyl)-1,3-dioxolane (36.2 g, 0.2 mol) was added with stirring over 1 h to a solution of the sodium enolate of ethyl acetoacetate [prepared from ethyl acetoacetate (26 g, 0.2 mol) and sodium (4.6 g, 0.2 mol)] in boiling ethanol (150 ml). The solution was boiled and stirred under reflux for a further 10 h when it was found to give a neutral litmus test. After decanting the solution the solvent was removed in *vacuo* and the residue partitioned between ether and water. The aqueous layer was further extracted with ether and the combined extracts washed with water. The organic phase was dried (Na_2SO_4) and evaporated. Distillation under reduced pressure (b.p 106-115°/0.05 mmHg) afforded the *product* as a colourless oil (23 g, 50%). (Found: C, 57.35; H, 7.7. $C_{11}H_{18}O_5$ requires C, 57.4; H, 7.9%); δ 4.75 (t, 1H, acetal CH, J 4.5 Hz), 4.09 (q, 2H, CO$_2$C<u>H$_2$</u>CH$_3$), 3.79 (m ,4H, acetal CH$_2$CH$_2$), 3.42 (t, 1H, J 7.4Hz, CH), 2.13 (s, 3H, Me), 1.86 (m, 2H, CH$_2$), 1.56 (m, 2H, CH$_2$), and 1.16 (t, 3H, CO$_2$CH$_2$C<u>H$_3$</u>); ν_{max} 2980, 2890, 1740, 1710 and 1145 cm^{-1}; *m/z*(%) 230 (M$^+$, 11), 110 (11), 99 (17) and 73 (100).

5-Ethoxycarbonyl-5-(3'-ethylenedioxypropyl)-6-oxo-1-heptene. Bute-4-enyl bromide (13.05 g, 0.1 mol) was added dropwise with stirring to a solution of the sodium enolate of the monoalkylated ketone (14) [prepared

from the mono-alkylated ketone (14) (23 g, 0.1 mol) and sodium hydride (0.11 mol, 4.4 g of 60% suspension in oil)] in DMF (40 ml). The reaction mixture was heated and stirred at 100°C for 4 h after which time the solution was neutral to litmus. The DMF was removed in *vacuo* and the residue partitioned between ether and water. The aqueous layer was further extracted with ether (2x15 ml). The combined extracts were dried (Na_2SO_4) and the solvent evaporated. Distillation of the residue, (b.p. 116-122°C/0.05 mmHg) afforded the dialkylated *product* (18.8 g, 66%) as a colourless liquid. (Found: C, 63.5; H, 8.7. $C_{15}H_{24}O_5$ requires C, 63.35; H, 8.5%); δ 5.68 (m, 1H, C<u>H</u>=CH_2), 4.88 (m, 2H, CH=C<u>H</u>$_2$), 4.75 (t, 1H, acetal CH), 4.09 (q, 2H, $CO_2C\underline{H}_2CH_3$), 3.80 (m, 4H, acetal CH_2CH_2), 2.04 (s, 3H, Me), 2.01-1,72 (m, 6H, 3xCH_2), 1.40 (m, 2H, CH_2) and 1.16 (t, 3H, $CO_2CH_2C\underline{H}_3$); ν_{max} 2900, 1735, 1710 and 1200 cm^{-1}; *m/z*(%) 284 (M^+,<1), 230 (10), 155 (13), 100 (20), 99 (44), 87 (31) and 73 (100).

5-(3′-Ethylenedioxypropyl)-6-oxo-1-heptene. A mixture of the dialkylated keto-ester (17 g, 0.06 mol)(above) and 5% aqueous sodium hydroxide (160 ml, 0.18 mol) was boiled and stirred under reflux for 16 h. The cooled solution was extracted with ether (4x200 ml). The combined extracts were dried (Na_2SO_4) and the solvent removed to afford the *product* as a pale yellow liquid (8.0 g, 63%) which was used without further purification. An analytical sample was obtained as a colourless liquid by distillation, b.p 92-96°C/0.4 mmHg. (Found: C, 68.0; H, 9.45. $C_{12}H_{20}O_3$ requires C, 67.9; H, 9.5%); δ 5.76 (m, 1H, C<u>H</u>=CH_2), 4.99 (m, 2H, CH=C<u>H</u>$_2$), 4.83 (t, 1H, acetal CH), 3.90 (m, 4H, acetal CH_2CH_2), 2.54 (m, 1H, methine CH), 2.14 (s, 3H, Me), 2.02 (m, 2H, CH_2) and 1.97-1.46 (m, 6H, 3xCH_2); ν_{max} 2930 and 1710 cm^{-1}; *m/z*(%) 212(M^+, <1), 158 (13), 99 (18) and 73 (100).

5-(2′-Formylethyl)-6-oxo-1-heptene. 1N Hydrochloric acid (111ml) was added dropwise with stirring to a cooled solution of the keto-acetal (7.82 g, 37 mmol) (above) in tetrahydrofuran (75 ml). The solution was allowed to warm to room temperature and then stirred for 22 h. After neutralization with sodium bicarbonate the product was extracted with methylene chloride (75 ml). The combined extracts were dried (Na_2SO_4) and evaporated. The residue was distilled, b.p. 62-66°C/0.1 mmHg to afford a slightly impure sample of the keto-aldehyde *product* (2.6 g, 42%). Despite repeated distillation an analytically pure sample could not be obtained. (Found: C, 70.15; H, 9.65. $C_{10}H_{16}O_2$ requires C, 71.4; H, 9.6%); δ 9.75 (s, 1H, CHO), 5.75 (m, 1H, C<u>H</u>=CH_2), 5.01 (m, 2H, CH=C<u>H</u>$_2$), 2.54 (m, 1H, methine CH), 2.42 (m, 2H, CH_2), 2.16 (s, 3H, Me), 2.04 (m, 2H, CH_2), 1.90, 1.74 and 1.51 (m, 4H, 2xCH_2); ν_{max} 3075, 2940, 2730, 1710, 1640, 1370, 1355 and 920 cm^{-1}; *m/z*(%) 169 (M+1, <1), 114 (31), 112 (15), 86 (33), 81 (12) and 43 (100).

Methyl trans-6-(3′-butenyl)-7-oxo-2-octenoate(15). A solution of methoxycarbonylmethylene triphenylphosphorane (5.01 g, 15 mmol) in methylene chloride (25 ml) was added dropwise with stirring to a solution of the keto-aldehyde (2.75 g, 15 mmol) (above) in methylene chloride (25 ml). The reaction mixture was then allowed to stir overnight at room temperature. After removal of the solvent the residue was repeatedly triturated with ether to remove the bulk of the triphenylphosphine oxide. Distillation of the residue afforded the *product*(2.2 g, 65%) b.p 104-106°C/0.2 mmHg as a colourless liquid. (Found: C, 69.9; H, 9.25. $C_{13}H_{20}O_3$ requires C, 69.9; H, 9.0%); δ 6.84 (d of t, 1H, J 6.9 and 15.7Hz, C<u>H</u>=CHCO_2Me), 5.75 (d, 1H, J 15.5Hz, C<u>H</u>CO_2Me), 5.69 (m, 1H, C<u>H</u>=CH_2), 4.92 (m, 2H, CH=C<u>H</u>$_2$), 3.65 (s, 3H, OMe), 2.45 (m, 1H, methine CH), 2.07 (m, 2H, CH_2), 2.07 (s, 3H, Me), 1.95 (m, 2H, CH_2), 1.66 (m, 2H, CH_2), and 1.46 (m, 2H, CH_2); ν_{max} 2940, 1720, 1655, 1640, 1440, 1355, 1275, 1200, 1050, 995 and 920 cm^{-1}; *m/z*(%) 225 (M+1, 20), 193(18), 125(23), 113(27), 100(80), 81(36) and 43(100).

Dimethyl 6-oxotrideca-2,11-dienedioate (19a).

a. 2-[4′-(1,3-Dioxolanyl)butyl]-1,3-dithiane. Prepared from 2-(4′-bromobutyl)-1,3-dioxolane by method A.

The *product* (81%) was a colourless oil, b.p. 133-134°C/0.15 mm Hg. (Found: C, 52.9; H, 8.35. $C_{11}H_{20}O_2S_2$ requires C, 53.2; H, 8.1%); δ 1.4-1.94 (m, 9H), 2.08 (m, 1H), 2.86 (m, 4H, 2x$CH_2\underline{CH_2}CH_2$), 3.9 (m, 4H, 2xCH_2O), 4.06 (t, 1H, J 6.7Hz, SCHS), and 4.85 (t, 1H, J 4.7Hz, OCHO); ν_{max} 2934, 2913, 1615, 1461 and 1275 cm^{-1}, *m/z*(%) 248 (M^+, 21), 119 (33) and 73 (100).

b. 2-[2′-(1,3-Dioxolanyl)ethyl]-2-[4"-(1,3-dioxolanyl)butyl]-1,3-dithiane. Prepared by method B via the monoalkylated 1,3-dithiane (above) and using 2- (2′-bromoethyl)-1,3-dioxolane as the alkylating agent. The *product* (75%) was obtained as a colourless oil. (Found: C, 55.0; H, 8.1; S, 18.15. $C_{16}H_{28}O_4S_2$ requires C, 55.15; H, 8.1; S, 18.4%); δ 1.47 (m, 4H), 1.70 (m, 2H), 1.81 (m, 4H), 2.0 (m, 4H), 2.81 (m, 4H, 2xCH_2S), 3.86 (m, 8H, 4xCH_2O), 4.85 (t, 1H, J 4.7Hz, OCHO), and 4.9 (t, 1H, J 4.4Hz, OCHO); *m/z*(%) 348 (M^+, 87), 219 (91), 247(38), 99(45) and 73(100).

c. 2-(3′-Oxopropyl)-2-(5"-oxopentyl)-1,3-dithiane. Prepared from the acetal (above) by method C. The product (68%) was a colourless oil. (Found: C, 55.45; H, 7.95. $C_{12}H_{20}O_2S_2$ requires C, 55.35, H, 7.75%); δ 1.4-2.0 (m, 8H), 2.27 (t, 2H, J 7.6Hz, $CH\underline{CH_2}CH_2$), 2.48 (dt, 2H, J 7.3 and 1.5Hz, CH_2CHO), 2.6 (dt, 2H, J 7.6 and 1.0Hz, $C\underline{H_2}CHO$), 2.8 (m, 4H, 2xCH_2S), 9.77 (t, 1H, J1.5Hz, CHO) and 9.8 (t, 1H, J 1.0Hz, CHO); ν_{max} 2939, 2861, 2722, 1721 and 1450 cm^{-1}; *m/z*(%) 260 (M^+,16), 175 (26) and 132 (100).

d. Dimethyl 6-(1′,3′-dithiopropyl)trideca-2,11-dienedioate. Prepared by method D from the aldehyde (above). The *product* (88%) was obtained as a colourless oil, b.p. (mole still, furnace temp.) 150-152°C/0.2 mmHg. (Found: C, 58.15; H, 7.65; S, 17.35. $C_{18}H_{28}O_4S_2$ requires C, 58.05, H, 7.55; S, 17.2%); δ 1.48 (m, 4H), 1.8 (m, 2H), 1.98 (m, 4H), 2.2 (m, 2H, $C\underline{H_2}CH{=}CHCO_2Me$), 2.3 (m, 2H, $C\underline{H_2}CH{=}CHCO_2Me$), 2.82 (m, 4H, 2x CH_2S), 3.73 (s, 6H, 2xOMe), 5.8 (m, 2H, 2xCH=C$\underline{H}$$CO_2Me$) and 6.97 (m, 2H, 2xCH=$CHCO_2Me$); *m/z*(%) 372($M^+$, 2), 259(6) and 132(100).

e. Dimethyl 6-oxotrideca-2,11-dienedioate (19a). Prepared from the 1,3-dithiane derivative (above) by method E. The *product* (68%) was obtained as a colourless oil, b.p. (mole still, furnace temp.) 160-165°C/0.2 mmHg. (Found: C, 63.8; H, 8.05. $C_{15}H_{22}O_5$ requires C, 63.8; H, 7.85%); δ 1.4 (m, 2H), 1.62 (m, 2H), 2.19 (dq, 2H, J 7.2 and 1.3Hz, $CH_2CH{=}CHCO_2Me$), 2.49 (m, 6H, CH_2COCH_2, and $C\underline{H_2}CH{=}CHCO_2Me$), 3.72 (s, 6H, 2xOMe), 5.82 (dd, 2H, J 14.5 and 1.5Hz, 2xCH=C$\underline{H}$$CO_2Me$), and 6.93 (m, 2H, 2xC$\underline{H}$=$CHCO_2Me$); ν_{max} 2948, 1717, 1656, 1435, 1313, 1274 and 1200 cm^{-1}; *m/z*(%) 282 (M^+, 10), 250 (47) and 73 (100).

Dimethyl 7-oxotetradeca-2,12-dienedioate.

a. 2-[3′-(1,3-Dioxolanyl)propyl]-2-[4"-(1,3-dioxolanyl)butyl]-1,3-dithiane. Prepared by method B via the monoalkylated 1,3-dithiane using 2-(3′-bromopropyl)-1,3-dioxolane as the alkylating agent. The product (73%) was a colourless oil, b.p. (mole still, furnace temp.) 200°C/0.05 mmHg. (Found: C, 56.5; H, 8.55. $C_{17}H_{30}S_2O_4$ requires C, 56.3; H, 8.35%); δ 1.4-1.7 (m, 10H), 1.9 (m, 6H), 2.8 (m, 4H, 2x$CH_2\underline{CH_2}CH_2$), 3.9 (m, 8H, 4xCH_2O), and 4.86 (m, 2H, 2xOCHO), ν_{max} 2944, 1456, 1141 and 1274 cm^{-1}; *m/z*(%) 362 (M^+, 10), 247 (90), 73 (100) and 99 (32).

b. 2-(4′-Oxobutyl)-2-(5"-oxopentyl)-1,3-dithiane. Prepared from the acetal (above) by method C. The *product* (74%) was a colourless oil, b.p. (mole still, furnace temp.) 155°C/0.07 mmHg. (Found: C, 56.8; H, 7.85.$C_{13}H_{22}O_2S_2$ requires C, 56.9; H, 8.05%); δ 1.45-2.0 (m, 12H), 2.5 (m, 4H, 2xCH_2CHO), 2.8 (m, 4H, 2xCH_2S), and 9.8 (m, 2H, 2xCHO); ν_{max} 2994, 2721, 1720, 1455 and 1389 cm^{-1}; *m/z*(%) 274 (M^+, 91), 203 (95), 189 (100) and 106 (33).

c. Dimethyl 7-(1′3′-dithiopropyl)tetradeca-2,12-dienedioate. Prepared by method D from the aldehyde (above). The *product* (85%) was a colourless oil, b.p. (mole still, furnace temp.) 178-180°C/0.3 mmHg. (Found: C, 59.2; H, 8.0. $C_{19}H_{30}O_4S_2$ requires C, 59.05; H, 7.8%); δ 1.2-1.7 (m, 6H), 1.9 (m, 6H), 2.2 (m, 4H,

2x$C\underline{H}_2CH{=}CHCO_2Me$), 2.8 (m, 4H, 2x$CH_2S$), 3.73 (s, 6H, 2xOMe), 5.8 (dq, 2H, J 15.6 and 1.4Hz, 2xCH=$C\underline{H}CO_2Me$), and 6.9 (dt, 2H, J 15.6 and 6.9Hz, 2x$C\underline{H}$=$CHCO_2Me$); *m/z*(%) 386 (M^+, 8), 245 (51), 259 (49), 145 (50) and 106 (100).

d. Dimethyl 7-oxotetradeca-2,12-dienedioate. Prepared from the 1,3-dithiane derivative (above) by method E. The *product* (81%) was obtained as a colourless oil. (Found: C, 64.3; H, 8.2. $C_{16}H_{24}O_5$ requires C, 64.8; H, 8.15%); δ 1.3-1.8 (m, 6H), 2.2 (dq, 4H, J 7.2 and 1.4Hz, 2x$C\underline{H}_2CH{=}CHCO_2Me$), 2.42 (m, 4H, 2x$CH_2CO$), 3.72 and 3.73 (2xs, 2x3H, 2xOMe), 5.8 (dq, 2H, J 15.6 and 1.2Hz, 2xCH=$C\underline{H}CO_2Me$), and 6.9 (m, 2H, 2x$C\underline{H}$=$CHCO_2Me$); *m/z*(%) 297 (M^+, 6) and 73 (100).

Ethyl 2-acetyl-2-(3′-butenyl)-5-hexenoate. Ethyl 2-acetyl-5-hexenoate(12.0 g)[18] was added dropwise to a stirred suspension of sodium hydride (3.8 g. 55% dispersion in oil) in DMF (70 ml). The reaction mixture was stirred and heated at 100°C for 20 min. and 4-bromobutene (10.5 g) was then added dropwise over 20 min followed by heating at 100-110°C for 5 h. The solvent was then removed in *vacuo* and the residue partitioned between ether and water. The organic phase was separated, washed with water and dried ($MgSO_4$). Evaporation of the solvent gave a brown liquid which was fractionally distilled to give the dialkylated *product* (6.8 g, 44%), b.p. 75-76°C/0.08 mmHg as a colourless liquid. (Found: C, 70.65; H, 9.45. $C_{14}H_{22}O_3$ requires C, 70.55; H, 9.3%); δ 5.80 (m, 2H, 2x$C\underline{H}$=CH_2), 5.00 (m, 4H, 2xCH=$C\underline{H}_2$, 4.21 (q, 2H, $CO_2C\underline{H}_2CH_3$), 2.15 (s, 3H, Me), 1.93 (m, 8H, 4xCH_2) and 1.30 (t, 3H, $CO_2CH_2C\underline{H}_3$); *m/z*(%) 238 (M^+, <1), 184 (10), 155 (39) and 143 (100).

Ketal of ethyl 2-acetyl-2-(3′-butenyl)-5-hexenoate. A solution of the dialkylated ketone (9.52 g, 0.04 mol), ethylene glycol (12.4 g, 0.2 mol) and þ-TsOH (0.1 g) in benzene (100 ml) was boiled and stirred under reflux using a Dean-Stark trap for 90 h. The solution was then washed with 10% aqueous sodium carbonate (2x100 ml) and then with water. The organic phase was separated, dried ($MgSO_4$) and evaporated. Fractional distillation of the residue gave the ketal-ester *product* (4.0 g, 35%) as a colourless liquid, b.p. 72-75°C/0.01 mmHg. (Found: C, 68.15; H, 9.1. $C_{16}H_{26}O_4$ requires C, 68.05; H, 9.3%); δ 5.83 (m, 2H, 2x$C\underline{H}$=CH_2), 5.00 (m, 4H, 2xCH=$C\underline{H}_2$), 4.18 (q, 2H, $CO_2C\underline{H}_2CH_3$), 3.95 (s, 4H, OCH_2CH_2O), 2.15 (m, 2H, CH_2), 2.00 (m, 2H, CH_2), 1.83 (dd, 4H, 2xCH_2) 1.38 (s, 3H, Me) and 1.28 (t, 3H, $CO_2CH_2C\underline{H}_3$); *m/z*(%) 282 (M^+, <1), 267(7), 187 (15), 143 (15), 97 (13), 88 (25) and 87 (100).

Ketal of 2-acetyl-2-(3′-butenyl)hex-5-ene-1-ol. A solution of the ketal-ester (3.85 g, 13.6 mmol) in dry ether (20 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (0.8 g, 21 mmol) in dry ether (75 ml). The reaction mixture was boiled gently for 5 h. The excess $LiAlH_4$ was then decomposed using water and aqueous caustic soda. The reaction mixture was filtered and the filter cake washed with ether. The combined ether solution was washed with brine, dried ($MgSO_4$), and evaporated. Distillation of the residue through a short Vigreux column gave the *product* (2.4 g, 73%) as a colourless liquid, b.p 110-112°C/0.1 mmHg. (Found: C, 70.25; H, 10.1. $C_{14}H_{24}O_3$ requires C, 69.95; H, 10.05%); δ 5.82 (m, 2H, 2x$C\underline{H}$=CH_2), 4.97 (m, 4H, 2xCH=CH_2), 3.95 (m, 4H, OCH_2CH_2O), 3.52 (d, 2H, $C\underline{H}_2OH$), 3.25 (t, 1H, $CH_2O\underline{H}$), 2.10 (m, 4H, 2xCH_2), 1.46 (m, 4H, 2xCH_2), 1.30 (s, 3H, Me); *m/z*(%) 241 (M+1, <1), 225 (1), 145 (4), 88 (11) and 87 (100).

Ketal of 2-acetyl-2-(3′-butenyl)hex-5-en-1-al(31). The alcohol (2.3 g, 9.6 mmol) (above) in methylene chloride (5 ml) was added in one portion to a stirred suspension of pyridinium chlorochromate (3.3 g, 15 mmol) and sodium acetate (0.25 g, 3 mmol) in methylene chloride (15 ml). The reaction mixture was stirred for 4.5 h and then diluted with ether (20 ml) and decanted. The remaining black gum was triturated with ether (3x20 ml) and the combined organic solutions filtered through a short florisil column. The solvent was evaporated and the residue distilled to give the *product* (1.6 g, 70%) as a colourless liquid, b.p 102-105°C/0.03

mmHg. (Found: C, 70.2; H, 9.4. $C_{14}H_{22}O_3$ requires C, 70.55; H, 9.3%); δ 9.66 (s, 1H, CHO), 5.80 (m, 2H, 2xC<u>H</u>=CH_2), 4.98 (m, 4H, 2xCH=C<u>H_2</u>), 3.99 (m, 4H, OCH_2CH_2O), 2.07 (m, 2H, CH_2), 1.90 (m, 2H, CH_2), 1.79 (m, 4H, 2xCH_2) and 1.25 (s, 3H, Me).

Oxime(32). To a stirred suspension of the aldehyde (0.53 g, 2.2 mmol) (above) and hydroxylamine hydrochloride (0.23 g, 3.3 mmol) in water (4 ml) was added a solution of sodium carbonate (0.17 g, 1.7 mmol) in water (3 ml). Ethanol (3 ml) was then added and the mixture heated at 70°C for 8 h. The ethanol was removed *in vacuo* and the product extracted with methylene chloride (3x15 ml). The combined extracts were dried ($MgSO_4$) and evaporated to give the oxime as a thick colourless oil (0.52 g, 93%). δ 8.8 (br s, 1H, OH), 7.42 (s, 1H, CH=N), 5.79 (m, 2H, 2xC<u>H</u>=CH_2), 4.95 (m, 4H, 2xCH=C<u>H_2</u>), 3.94 (m, 4H, OCH_2CH_2O), 2.1 (m, 4H, 2xCH_2), 1.70 (m, 4H, 2xCH_2) and 1.26 (s, 3H, Me); *m/z*(%) 253 (M^+,<1), 238 (3), 199 (3), 114 (4), 96 (6), 88 (21) and 87 (100).

NITRONES

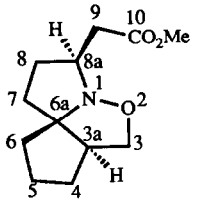
5-(3'-Butenyl)-2-methoxycarbonylmethyl-6-methyl-2,3,4,5-tetrahydropyridine 1-oxide(16). Prepared from keto-ester(15), using hydroxylamine hydrochloride and sodium acetate in water. The *product* (0.92 g, 96%) was obtained as a colourless oil whose p.m.r. spectrum showed it to comprise a 4:1 mixture of isomers. δ (major isomer) 5.78 (m, 1H, C<u>H</u>=CH_2), 5.05 (m, 2H, CH=CH_2), 4.25 (br m, 1H, H_A), 3.73 (s, 3H, OMe), 3.25 (dd, 1H, J 7 and 16.1Hz, H_B), 2.57 (dd, 1H, J 7.6 and 16.1Hz, H_C), 2.48 (m, 1H, H_D), 2.11 (d, 3H, J 1.3Hz, Me) and 2.23-1.38 (m, 8H, 4xCH_2). The presence of the minor isomer was inferred by the presence of double-doublets at δ 3.20 and 2.60; ν_{max} 2970, 1740, 1640, 1440, 1370, 1200, 1180, 1000 and 915 cm^{-1}; *m/z*(%) 239 (M^+, 6), 198 (31), 166 (31), 153 (21), 125 (21), 113 (24), 112 (24), 100 (80), 81 (33) and 73 (100).

Nitrone (22). A solution of ketone (7d) (0.3 g, 1.3 mmol), hydroxylamine hydrochloride (0.1 g, 1.4 mmol) and sodium acetate (0.13 g, 1.6 mmol) in acetonitrile (10 ml) and water (3 ml) was heated at 70°C for 3 h. After cooling, water (20 ml) was added and the mixture extracted with chloroform (2x25 ml). The combined organic layer was dried ($MgSO_4$), the solvent removed under reduced pressure and the residual oil distilled in a molecular still to afford the product (0.27 g, 91%) as a colourless oil, b.p (furnace temp.) 105-108°C/0.3 mmHg. (Found: C, 64.95; H, 9.05; N, 6.05. $C_{13}H_{21}O_3N$ requires C, 65.25; H, 8.85; N, 5.85%); δ 1.51 (m, 4H), 1.89 (m, 1H, H_D), 2.1 (q, 2H, J 6.9Hz, C<u>H_2</u>CH=CH_2), 2.4 (m, 1H, H_E), 2.5 (t, 2H, J 7.8Hz, C<u>H_2</u>C=N), 2.6 (m, 3H, H_C and C<u>H_2</u>C=N), 3.24 (dd, 1H, J 16.5 and 4.4Hz, H_B), 3.7 (s, 3H, CO_2Me), 4.4 (br s, 1H, H_A), 4.98 (m, 2H, C<u>H_2</u>=CH) and 5.78 (m, 1H, CH_2=CH); δ(^{13}C) 210 (ester C=O), 138 (<u>C</u>=N-O), 115 (<u>CH_2</u>=<u>C</u>H), 52.5 (OMe), 69(CHN=), 37, 34, 29, 28.5, 27, 24 and 23; ν_{max} 3075, 2940, 2850, 1735, 1635, 1600, 1440, 1275, 1200, 1005 and 900cm^{-1}; *m/z*(%) 239 (M^+, 30), 208 (31), 155 (64), 139 (100) and 171 (69).

3,4,5,6-Tetrahydro-6-methoxycarbonylmethyl-2-(5'-hexenyl)-pyridine N-oxide(27a). A solution of the ketone (7c) (0.3 g, 1.2 mmol), hydroxylamine hydrochloride (0.096 g, 1.3 mmol) and sodium acetate (0.124 g, 1.5 mmol) in acetonitrile (10 ml) and water (3 ml) was heated at 70°C for 3 h. After cooling, water (20 ml) was added and the mixture extracted with chloroform (2x25 ml). The combined organic layer was dried ($MgSO_4$), the solvent removed under reduced pressure and the residual oil distilled in a molecular still to afford the *product* (0.25 g, 83%) as a colourless oil, b.p (furnace temp.) 115-118°C/0.25 mmHg; (Found: C, 66.3; H, 9.2; N, 5.75. $C_{14}H_{23}NO_3$ requires C, 66.35; H, 9.15; N, 5.5%); δ 5.79 (m, 1H, CH_2=C<u>H</u>), 5.0 (m, 2H, C<u>H_2</u>=CH), 4.25 (m, 1H, H_a), 3.7 (s, 3H, CO_2Me), 3.24 (dd, 1H, J 5.4 and 16.1Hz, H_b), 2.64 (dd, 1H, J 8.6 and 16.1Hz, H_c), 2.53 (t, 2H, J 8.5Hz, C<u>H_2</u>C=N), 2.45 (t, 2H, J 6.1Hz, CH_2C=N), 2.08 (m, 4H), and 1.2-1.9 (m, 6H); δ (^{13}C) 210 (ester C=O), 137(C=N^+-O^-), 115(CH_2=CH), 52(C-N=), 64(OMe), 37, 34, 32, 29, 28, 26, 24 and 16; ν_{max} 3076, 2973, 1718, 1688, 1641 and 1200 cm^{-1}; *m/z*(%) 253 (M^+, 25), 222 (30) and 180 (94).

CYCLOADDUCTS

Cycloadduct(8). Methyl 6-oxoundeca-1,9-dienoate (7a) (1.11g, 5.29 mmol) was dissolved in xylene (10 ml) and a solution of hydroxylamine hydrochloride (0.38 g, 5.45 mmol) and sodium acetate (0.45 g, 5.45 mmol) in water (1.0 ml) was added. The resulting mixture was gently refluxed under nitrogen for 16 h, the solvent removed under reduced pressure, and the residue taken up in chloroform, washed with water, dried ($MgSO_4$) and the chloroform evaporated to give a pale yellow oil. Column chromatography (SiO_2), eluting with 1:1 v/v ether-petroleum ether gave the *product* (0.96 g, 82%) as a pale yellow oil. An analytically pure sample was obtained by molecular distillation. b.p 80-85°C (furnace temp.) /0.20 mmHg. (Found: C, 64.15; H, 8.55; N, 6.15. $C_{12}H_{19}NO_3$ requires C, 64.05; H, 8.5; N, 6.2%); δ 4.13 (dd, 1H, J 6.7 and 8.9Hz, 3H_α), 3.65 (s, 3H, OMe), 3.58 (dd, 1H, J 2.5 and 8.9Hz, 3-H_β), 3.40 (m, 1H, 8a-H_α), 2.74 (dd, 1H, J 5.2 and 15.4Hz, 9-H_β), 2.48 (m, 1H, 3a-H_α), 2.38 (dd, 1H, J 8.8 and 15.4Hz, 9-H_α), 2.03 (m, 2H, 7,8-H_α), 1.91 (m, 2H, 6,7-H_β), 1.80 (m, 1H, 4-H_α), 1.74 (m, 1H, 5-H_β), 1.70 (m, 1H, 5-H_α), 1.61 (m, 1H, 6-H_α), 1.54 (m, 1H, 4-H_β) and 1.52 (m, 1H, 8-H_β). ν_{max} 2940, 2860, 1735, 1440, 1370, 1335, 1200, 1170, 1000 and 930 cm^{-1}; *m/z*(%) 225 (M^+, 33) 196 (11), 194 (15), 171 (100), 166 (8), 153 (10), 152 (91), 139 (88), 134 (10), 122 (12), 98 (15) and 86 (17); ^1H NOEDSY(%): irradiation of the signal at δ 3.58 (3-H_β) showed an enhancement on the signal at δ 4.13(13%; 3-H_α). Irradiation of the signal at δ 4.13 effected enhancements of the signals at δ 3.58(3-H_β, 14.4%) and δ 2.48 (3a-H_α, 3.6%). Irradiation of the signal at δ 2.48 (3a-H_α) showed a small enhancement of the signal at δ 4.13 (3-H_α, 1.7%). Irradiation of the signal at δ 3.40 showed an enhancement on the signal at δ 4.13 (3-H_α).



Cycloadduct(12). Methyl 6-oxododeca-1,10-dienoate (7b) (0.5 g, 2.2 mmol), hydroxylamine hydrochloride (0.17 g, 2.46 mmol) and sodium acetate (0.22 g, 2.6 mmol) were stirred in water (3 ml) at room temperature for 4.5 h. DMF (7 ml) was then added and the mixture heated at 100-105°C for 1 h. After cooling, water (15 ml) was added, and the mixture extracted with chloroform (2x20 ml). The combined chloroform extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was purified by flash chromatography (SiO_2, ether) to afford the *product* (0.35 g, 70%) as colourless prisms from hexane, m.p 36-38°C. (Found: C, 65.4; H, 8.7; N, 5.55. $C_{13}H_{21}NO_3$ requires C, 65.25; H, 8.85 and N, 5.85%); δ 4.28 (t, 1H, J 8.6Hz, H_a), 3.66 (s, 3H, OMe), 3.4 (dd, 1H, J 8.6 and 4.2Hz, H_b), 2.99 (m, 1H, H_c), 2.8 (dd, 1H, J 15.2 and 5.7Hz, H_e), 2.68 (m, 1H, H_f), 2.25 (dd, 1H, J 15.2 and 6.5Hz, H_d), and 1.3-2.0 (m, 12H); ν_{max} 2932, 1735, 1596, 1435, 1296 and 1193 cm^{-1}; *m/z*(%) 239 (M^+, 76), and 166 (100). The assignment of stereochemistry is based on n.O.e. experiments (below).

Proton irradiated	Enhancements (%) H_a	H_b	H_c	H_d
H_a	-	25	8.4	6.1
H_b	6.7	-	-	3.5
H_c	-	-	4.2	-

Cycloadduct(17). A solution of the nitrone (16) (0.79 g, 3.3 mmol) in toluene (50 ml) was boiled under reflux for 42 h. Removal of the solvent afforded a dark brown oil (0.72 g) whose p.m.r. spectrum indicated that the desired cycloadduct (18) was present in ca. 70% yield. Flash chromatography (silica, 1:1 v/v ether-hexane) of the brown oil gave the *product* (43%) as a colourless oil. (Found: C, 65.15; H, 9.0; N, 5.75. $C_{13}H_{21}NO_3$ requires C, 65.25; H, 8.85; N, 5.85%); δ 3.94 (t, 1H, J 8.5Hz, H_B), 3.63 (s, 3H, OMe), 3.55 (dd, 1H, J 8.7 and 6.1Hz, H_C), 3.55 (m, 1H, H_D), 2.70 (dd, 1H, J 5.8 and 15.2Hz, H_F), 2.58 (m, 1H, H_A), 2.31 (dd, 1H, J 7.6 and 15.2Hz, H_G), 1.96-1.68 (m, 6H, H_E and 5-ring H's), 1.64 and 1.46 (m, 2H, CH_2), 1.30 (s, 3H, Me) and 1.26 (m, 1H, ring-H); m/z (%) 239 (M^+, 9), 224 (6), 182 (6), 167 (12) and 166 (100); ^{1}H NOEDSY (See discussion).

Cycloadduct(21). A solution of the nitrone (20) (0.3 g, 1.0 mmol) in acetonitrile (10 ml) was boiled under reflux for 16 h. Removal of the solvent afforded a dark brown oil. Flash chromatography (SiO_2, 4:1 v/v petroleum ether - ethyl acetate) of the brown oil gave the product (75%) as a colourless oil. (Found: C, 60.65; H, 8.0; N, 4.7; $C_{15}H_{23}NO_5$ requires C, 60.6; H, 7.8; N, 4.7%); δ 1.5-1.7 (m, 10H), 1.93 (m, 2H), 2.3 (m, 1H, H_B), 2.4 (dd, 1H, J 15.4 and 6.4Hz, H_E), 2.62 (m, 1H, H_C), 2.89 (dd, 1H, J 15.4 and 4.3 Hz, H_D), 3.67 and 3.68 (2xs, 2x3H, 2xOMe) and 4.48 (d, 1H, J 10.8 Hz.H_A); *m/z* (%) 297 (M^+, 47), 238(100) and 224(95).

Cycloadducts (23), (24) and (25). A solution of the nitrone (22) (0.3 g, 1.2 mmol) in DMF (10 ml) was heated at 110°C under a nitrogen atmosphere for 30 h. Removal of the solvent afforded a dark brown oil. Flash chromatography (SiO_2, 7:3 v/v petroleum ether - ethyl acetate) of the oil gave the products in 65% combined yield.

(23) Colourless oil. (Found: C, 65.2; H, 8.9; N, 5.75. $C_{13}H_{21}NO_3$ requires C, 65.25; H, 8.85; N, 5.85%); δ 1.3-1.9 (m, 11H), 2.06 (m, 1H), 2.3 (dd, 1H, J 15.4 and 9.1Hz, H_F), 2.4 (m, 1H, H_A), 2.7 (dd, 1H, J 15.4 and 4.7Hz, H_E), 3.4 (m, 1H, H_B), 3.6 (s, 3H, OMe), 3.7 (dd, 1H, J 9.3 and 7.9Hz, H_D), 4.1 (t, 1H, J 7.9Hz, H_C); *m/z*(%) 239 (M^+, 46). The stereochemistry of (23) is based on the n.O.e. data below.

Proton irradiated	Enhancements (%) H_A	H_B	H_C	H_D
H_A	-	7.8	-	-
H_B	7.2	-	2.7	3
H_C	3.4	-	-	21.7
H_D	5.1	-	21.6	-

(24) Colourless oil.(Found: C, 65.15; H, 8.6; N, 5.75. $C_{13}H_{21}NO_3$ requires C, 65.25; H, 8.85; N, 5.85%); δ

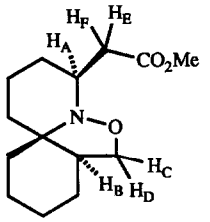
1.4-1.8 (m, 11H), 2.1 (m, 2H), 2.25 (m, 1H), 2.3(dd, 1H, J 15.4 and 9.5Hz, H_D), 2.8 (dd, 1H, J 15.4 and 4.3 Hz, H_C), 3.3 (m, 1H, H_B), 3.6 (s, 3H, OMe) and 4.6 (m, 1H, H_A); ^{1}H NOEDS(%): irradiation of H_A effects enhancement of H_B(2%) and irradiation of H_B effects enhancement of H_A(3.3%); *m/z*(%) 239(M^+, 37), 182(100) and 166(75).

(25) (Found: C, 65.05; H, 9.35; N, 5.75. $C_{12}H_{19}NO_2$ requires C, 64.7; H, 9.6; N, 5.8%); δ 1.3-1.8 (m, 13H), 2.2 (m, 1H, H_C), 2.6 (t, 2H, J 8.1Hz, $\underline{CH_2}CO_2Me$), 3.5 (dd, 1H, J 10.7 and 6.6Hz, H_B), 3.7 (dd, 1H, J 10.7 and 5.4Hz, H_A), 3.6 (s, 3H, CO_2Me), 4.5 (s, 1H, OH) and 8.4 (bs, 1H, NH).

Cycloadducts(28a) and (29a). A solution of the nitrone (27a) (0.3 g, 1.18 mmol) in DMF (10 ml) was heated at 110°C under a nitrogen atmosphere for 2 d. Removal of the solvent afforded a dark brown oil. Flash chromatography (SiO_2, 7:3 v/v petroleum ether-ethyl acetate) gave a 1:1 mixture (66%) of (28a) and (29a).

(28a) Colourless oil. (Found: C, 66.5; H, 9.30; N, 5.60. $C_{14}H_{23}NO_3$ requires C, 66.35; H, 9.15; N, 5.55%). δ 1.2-1.8 (m, 13H), 2.2 (m, 1H), 2.25 (dd, 1H, J 15.3 and 6.6Hz, H_F), 2.8 (m, 1H, H_B) 2.82 (dd, 1H, J 15.3 and 5.8Hz, H_E) 3.2 (m, 1H, H_A), 3.66 (s, 3H, OMe), 3.69 (dd, 1H, J 8.7 and 10.3Hz, H_C) and 4.2 (dd, 1H, J 10.3 and 7.4Hz, H_D).

Proton irradiated	Enhancements (%) H_A	H_B	H_C	H_D
H_A	-	-	-	2.7
H_B	-	-	-	25.6
H_C	3.0	4.8	23.7	-



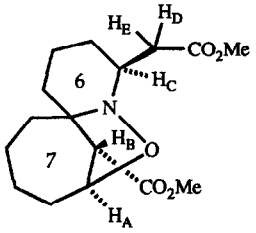
(29a) Colourless oil. (Found: C, 66.1; H, 9.4; N, 5.5%); δ 1.3-1.9 (m, 15H), 2.2 (dd, 1H, J 15.1 and 7.2Hz, H_C), 2.5 (m, 1H), 2.9 (dd, 1H, J 15.1 and 5.3Hz, H_D), 3.0 (m, 1H, H_B), 3.6 (s, 3H, OMe), and 4.6 (m, 1H, H_A); ^{1}H NOEDSY(%): irradiation of H_A effected enhancement of H_B(3.5) and irradiation of H_B effected enhancement of H_A (4.2).

Cycloadducts (28b), (29b) and (30). A solution of the nitrone (27b) (0.4 g, 1.28 mol) in CH_3CN(7 ml) was boiled under reflux for 16 h. Removal of the solvent afforded a brown oil. Flash chromatography (SiO_2, 4:1 v/v petroleum ether-ethyl acetate) of the oil gave a 10:1:2 mixture of (28b), (29b) and (30) in 72% combined yield.

(28b) Colourless prisms from ether-petroleum ether m.p. 66-67°C (Found: C, 61.5; H, 8.15; N, 4.45. $C_{16}H_{25}NO_5$ requires C, 61.7; H, 8.1; N, 4.5%); δ 1.2-1.99 (m, 13H), 2.22 (m, 1H), 2.29 (dd, 1H, J 15.3 and 9.3Hz, H_E), 2.89 (m, 1H, H_A), 3.16 (dd, 1H, J 15.3 and 3.3Hz, H_D), 3.27 (m, 1H, H_C), 3.67 and 3.77 (2xs, 2x3H, 2xCO_2Me) and 4.5 (d, 1H, J 9.5Hz, H_B); ^{1}H NOEDSY(%): irradiation of H_C effected enhancement of H_A(7), irradiation of H_A effected enhancement of H_C(11); ν_{max} 2939, 2861, 1734, 1653, 1434, 1358, 1283 and 1198 cm^{-1}; *m/z*(%) 311 (M^+, 15), 252 (87) and 238 (100).

(29b) Colourless prisms from petroleum ether, m.p. 92-94°C; (Found C, 61.55; H, 8.0; N, 4.75%); δ 1.0-1.8 (m, 2H), 2.0 (m, 1H), 2.2 (dd, 1H, J 15 and 7.2Hz, H_E), 2.3 (m, 1H), 2.85 (dd, 1H, J 15 and 5.1Hz, H_D), 3.0 (s, 1H, H_B), 3.5 (m, 1H, H_C), 3.6 (s, 3H, CO_2Me), 3.7 (s, 3H, CO_2Me), 5.07 (bs, 1H, H_A); the stereochemistry of (29b) is based on the n.O.e. data below.

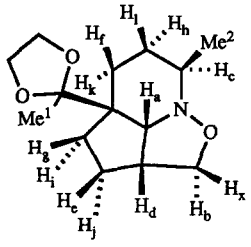
Proton irradiated	Enhancements (%) H_A	H_C	H_D	H_E
H_A	-	3.5	-	-
H_B	-	-	-	4.3
H_C	6.4	-	3.6	3.0



(30) Colourless rods from petroleum ether m.p.54-55°C (Found: C, 61.75; H, 7.9; N, 4.5%); δ 1.4-1.9 (m, 13H), 2.2 (t, 1H), 2.5 (m, 2H, H_E and H_B), 2.8 (dd, 1H, J 15.2 and 3.4Hz, H_D), 3.5 (m, 1H, H_C), 3.6 (s, 3H, CO_2Me), 3.7 (s, 3H, CO_2Me), and 3.9 (d, 1H, J 8.8Hz, H_A); ^1H NOEDSY (%): irradiation of H_C effects enhancement of only H_E (3.7) whilst irradiation of H_A does not cause any enhancements. Irradiation of H_B does not cause any enhancement of H_C.

Cycloadducts(33) and (34). A solution of the oxime (32) (0.43 g) in dry xylene (20 ml) was boiled and stirred under reflux for 4 h. The solvent was removed to give a pale brown oil (0.4 g) whose p.m.r. spectrum indicated the presence of two products (33) and (34) in the ratio 1:1.2. The products were separated by column chromatography (alumina; 3:2 v/v hexane-ether).

(33) Obtained as colourless gum (0.08 g, 20%) (Found: C, 66.45; H, 9.35; N, 5.65. $C_{14}H_{23}NO_3$ requires C, 66.4; H, 9.15; N, 5.55%), δ 3.95 (m, 4H, OCH_2CH_2O), 3.89 (t, 1H, J 8.2Hz, H_n), 3.81 (d, 1H, J 9.0Hz, H_a), 3.46 (dd, 1H, J 4.4 and 8.4Hz, H_b), 3.09 (m, 1H, H_c), 3.02 (m, 1H, H_d), 2.01 (m, 2H, H_e and H_f), 1.86 (m, 2H, H_g and H_h), 1.71 (d of t, 1H, H_i), 1.44 (m, 1H, H_j), 1.30 (m, 2H, H_k and H_l), 1.27 (s, 3H, Me^1) and 1.17 (d, 3H, Me^2); *m/z*(%) 253 (M^+, 27), 239 (13), 238 (100), 167 (17) and 87 (90); Assignments are based on 2D-cosy spectra and n.O.e. data (below).



Proton irradiated	Enhancements (%) a	b	c	d	e	f	h	j	x	Me^2
a	-	-	-	5	-	-	-	-	-	-
b	-	-	2	1	-	-	-	4	13	-
c	-	3	-	-	-	-	2	1	-	4.5
d	5	-	-	-	2	-	-	-	4.5	-
Me^1	1	-	-	-	4.5	4.5	-	-	1	-
Me^2	3	-	4.5	-	-	2	1.5	-	-	-
x	-	9	-	3.5	-	-	-	-	-	-

(34) Colourless prisms from ether, m.p 73-75°C. (Found: C, 66.4; H, 9.4; N, 5.45. $C_{14}H_{23}NO_3$ requires C, 66.35; H, 9.15; N, 5.55%); δ 3.90 (m, 4H, OCH_2CH_2O), 3.79 (t, 1H, J 7.3Hz, OCH), 3.68 (br m, 1H, NCH), 3.63 (d, 1H, J 8.3Hz, OCH), 2.99 (dd, 1H, J 7.8 and 15.6 Hz, $C\underline{H}CH_2O$), 2. 90 (br m, 1H, $NC\underline{H}CH_3$), 2.13 (m, 1H), 1.61-1.83 (m, 5H), 1.42 (m, 1H), 1.23 (m, 1H), 1.20 (d, 3H, J 6.8Hz, $CHC\underline{H}_3$) and 1.17 (s, 3H, Me).
The structure of (34) was unambiguously established by single crystal x-ray diffraction analysis - all crystallographic measurements were carried out at 290 K on a Nicolet P3/F diffractometer using graphite monochromated Molybdenum K_α-radiation (λ=71.069pm). Data were collected in the range of $4.0°<2\Theta<50.0°$ using ω-2Θ scans with no significant variation observed in the intensities of three standard reflections. Lorentz and polarisation corrections were applied to the data-set together with a post structure solution empirical absorption correction.[20]
The structure was solved by direct methods using SHELXS [21] and was refined by full-matrix least-squares using SHELXT 76. [22] All non-hydrogen atoms were refined with anisotropic thermal parameters. All hydrogen atoms were included in calculated positions (C-H=96pm) and were refined with an overall isotropic thermal parameter. The weighting scheme $w=[\sigma^2(F_o)\ 0.0002(F_o)^2]^{-1}$ was used.
Crystal data - $C_{14}H_{22}NO_3$, *M*=236.20, triclinic, space group *P*-1, a= 664.2(1),b=903.2(1),*4* = 1239.3(2) pm, α = 71.73(1), β=75.56(1), γ=69.59(1)°, U=0.6534(2) nm^3,*Z*=2, D_x=1.20 Mg m^{-3}, μ=0.52 cm^{-1}, *F*(000)=274. Data collection -scan speeds 2.0-29.3° min^{-1}, ω scan widths 2.0° + α-doublet splitting, $4.0<2\Theta<50.0°$, 2359 data collected, 1976 with $I>1.0\ \sigma(I)$ considered observed.
Structure refinement - Number of parameters = 170, R=0.0427, R_w=0.0494.

Table Non-hydrogen atom co-ordinates for (34) with estimated standard deviations (e.s.d.'s) in parentheses.

	x	y	z
N(1)	5315(2)	4951(2)	3157(1)
O(2)	6064(2)	4039(1)	2256(1)
C(3)	7291(3)	5009(2)	1422(2)
C(3a)	5849(3)	6763(2)	1326(2)
C(4)	4331(3)	7356(2)	430(1)
C(5)	2252(3)	6964(2)	1091(1)
C(5a)	1987(2)	7210(2)	2296(1)
C(5b)	4391(3)	6652(2)	2514(1)
C(6)	557(3)	6220(2)	3189(1)
C(7)	1751(3)	4426(2)	3559(2)
C(8)	3765(3)	4204(2)	4025(1)
C(9)	4903(4)	2443(2)	4574(2)
O(1′)	2355(2)	9952(2)	1627(1)
C(2′)	946(3)	9014(2)	2330(1)
O(3′)	830(2)	9130(1)	3466(1)
C(4′)	1103(4)	10662(2)	3368(2)
C(5′)	2302(4)	11102(3)	2187(2)
C(6′)	-1293(3)	9780(3)	1980(2)

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