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INTRAMOLECULAR NITRILE OXIDE CYCLOADDITION ON CHIRAL OLEFINS: A STEREOCONTROLLED APPROACH TO β-KETOL PRECURSORS.

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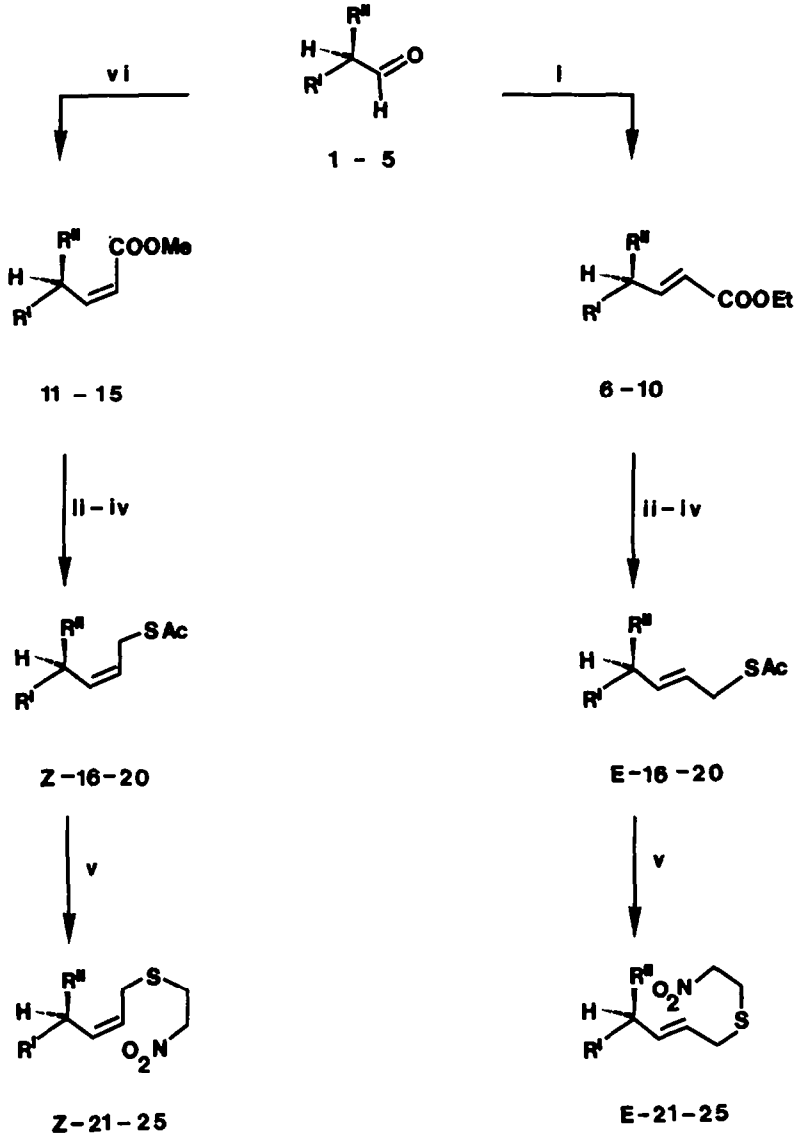
Abstract. The intramolecular nitrile oxide cycloaddition reaction on chiral (E) and (Z) olefins featuring a sulphur atom along the carbon chain connecting dipole and dipolarophile occurs with poor to excellent anti stereoselectivity, which is mainly affected by the substitutents at the allylic stereocenter. The possibility of converting the cycloadducts into stereoisomerically pure β-ketols has been established in one case.

The 4,5-dihydroisoxazoles (Δ^2-isoxazolines)[1-3] approach to β-hydroxy carbonyl compounds secures a successful solution to the problem of the control of "simple diastereoselection"[4] in aldol addition reaction. A limitation of the synthetic applicability of this route is the lack of regioselectivity observed in the synthesis of Δ^2-isoxazolines from nitrile oxides and unsymmetrical olefins.[5] Intramolecular nitrile oxide cyclo addition (INOC) reactions that are forced to occur in a regiochemically defined mode, should allow to overcome this problem. We recently reported[6] some INOC reactions on chiral allyl ethers, and found that these generally occur with stereoselectivities higher than those observed in analogous intermolecular cases.[7-9] As a part of our studies on the stereocontrolled synthesis of β-ketols *via* Δ^2-isoxazolines,[10] we here report an investigation on the stereoselection of INOC reactions that lead to isoxazolines that can be readily converted into acyclic aldol-type products.

As it is well known,[1-3] the un-masking of the β-hydroxy carbonyl moiety embedded in the isoxazoline heterocycle is best achieved by Raney-nickel catalyzed hydrogenolysis. Therefore, we thought that the insertion of an easily removable sulphur atom along the chain connecting dipole and dipolarophile should allow the synthesis of Δ^2-isoxazolines that can undergo simultaneous ring opening and desulphurization to deliver the desired acyclic β-ketols. The synthetic route to suitable substrates is reported in Scheme 1.

Ethyl esters (6)-(10) were prepared from (S)-O-benzyllactaldehyde (1), (S)-O-*t*-butyldimethylsilyllactaldehyde (2), (R)-2,3-O,O-dibenzylglyceraldehyde (3), (R)-2,3-O,O-cyclohexylideneglyceraldehyde (4), and (R,S)-2,3-dimethylbutanal

Scheme 1.



(1), (6), (11), (16), (21)	R' = OCH_2Ph R" = Me
(2), (7), (12), (17), (22)	R' = $OSiMe_2Bu$-t R" = Me
(3), (8), (13), (18), (23)	R" = OCH_2Ph R' = CH_2OCH_2Ph
(4), (9), (14), (19), (24)	R", R' = $O\text{-}C(CH_2)_5\text{-}OCH_2$
(5),(10), (15), (20), (25)≠	R' = Me. R"= Pr-i

Reagents: i, $(EtO)_2P(O)CH_2COOEt$, NaH, THF; ii, DIBAH, CH_2Cl_2; iii, $MeSO_2Cl$, Et_3N, CH_2Cl_2; iv, MeCOSH, Et_3N, MeCN; v, EtONa/EtOH, $AcOCH_2CH_2NO_2$; vi, $(CF_3CH_2O)_2P(O)CH_2COOMe$, KH, THF.

≠For compounds derived from (R,S)-2,3-dimethylbutanal only one enantiomer is shown for simplicity.

(5), respectively, by standard Horner-Emmons procedure. Conversion to the thiolacetates (E)-(16)-(20) was performed via DIBAH reduction, mesylation[11] of the resulting allylic alcohols, and reaction with thiolacetic acid. (E)-Nitrosulphides (21)-(25) were obtained by reaction of (E)-(16)-(20) with EtONa and 1-nitro-2-acetoxyethane in EtOH.[12] Accordingly (Z)-nitrosulphides (21)-(25) were synthesized from (Z)-esters (11)-(15), obtained from (1)-(5) by the Still-Gennari protocol.[13] Treatment of nitro derivatives (21)-(25) with 4-chlorophenylisocyanate and triethylamine in refluxing anhydrous benzene[14] gave (26)-(30) as reported in Scheme 2. Cycloaddition yields and diastereoisomeric ratios are collected in Table 1.

Table 1. Synthesis of 4,5-dihydroisoxazoles (26)-(30) from nitrosulphides (21)-(25).

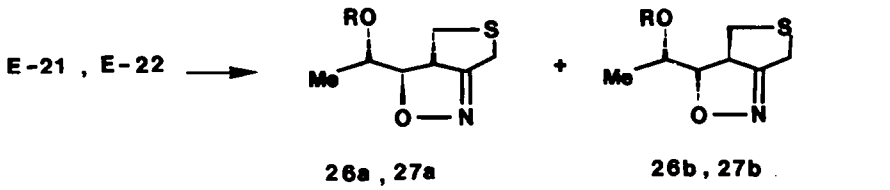
Nitrosulphide	Product	Yield %	Diastereoisomeric ratio[a]
(E)-(21)	(26a), (26b)	65	66:34[b]
(Z)-(21)	(26c), (26d)	91	66:34[b]
(E)-(22)	(27a), (27b)	70	64:36
(Z)-(22)	(27c), (27d)	80	67:33
(E)-(23)	(28a), (28b)	78	63:37
(Z)-(23)	(28c), (28d)	72	63:37
(E)-(24)	(29a), (29b)	71	83:17[b]
(Z)-(24)	(29c), (29d)	72	95: 5
(E)-(25)	(30a), (30b)	70	66:34
(Z)-(25)	(30c), (30d)	73	66:34

[a] As determined by ^{1}H and ^{13}C NMR spectroscopy.
[b] Isomeric product separated by flash chromatography.

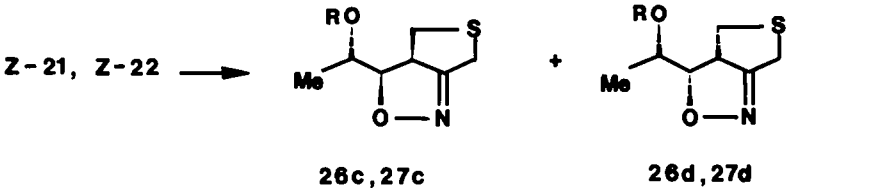
As can be seen from the reported data, chemical yields ranged from good to excellent. The products were generally obtained as mixtures of diastereoisomers. In some instances, however, diastereoisomerically pure compounds were obtained after flash chromatography. Diastereoisomeric ratios were evaluated by high field ^{13}C and ^{1}H NMR spectroscopy.

The assignment of the relative configuration of the stereocenters in the products resided on both chemical and spectroscopic evidences. As it is well demonstrated[5,15] for nitrile oxide cycloaddition to olefins the double bond geometry determines the relative configuration at C-4 and C-5 in the isoxazoline ring: thus, in our case from (E)-nitrosulphides C-4/C-5 anti[4] products, and from (Z)-nitrosulphides C-4/C-5 syn[4] products were obtained, respectively.

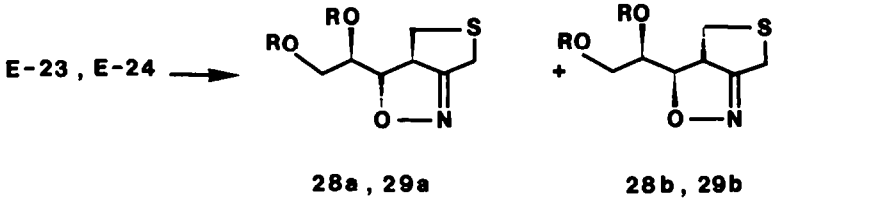
Scheme 2.



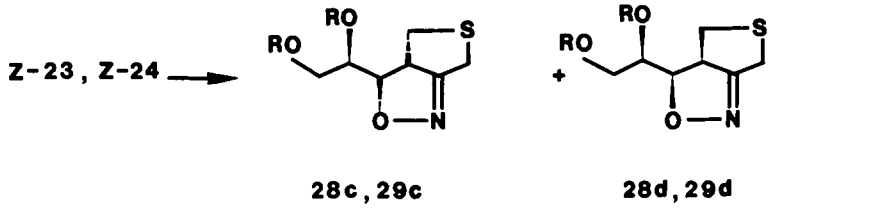
26a , 27a 26b , 27b



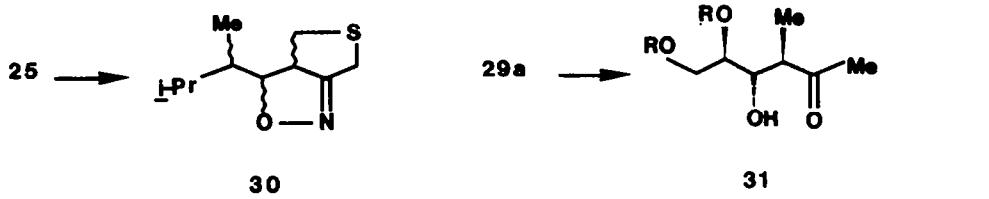
26c,27c 26d,27d



28a , 29a 28b , 29b



28c , 29c 28d , 29d



30 31

(26), (28) R=CH_2Ph (27) R=$SiMe_2Bu$-t (29),(31) R=-$C(CH_2)_5$-

The attribution of the relative stereochemistry at C-5/C-5' is less straightforward. Literature reports mainly rely on ^{1}H and ^{13}C NMR analysis, confirmed in some cases by chemical correlation with known products and/or by X-rays studies. Comparison of the NMR data obtained for our compounds (see Table 2) with those reported in the literature for related substates[1,8,16,17] led us to conclude that cycloadditions of both (E)- and (Z)- (21)-(24) are anti-selective giving (26a-29a) and (26c-29c) as predominant products over (26b-29b) and (26d-29d), respectively. Let us examine the various cases separately.

The attribution to the cyclohexylidene derivatives (29) is firmly based on ^{13}C and ^{1}H NMR. In the analogous examples reported[17] as well as in our compounds the ^{13}C chemical shift values of C-4, C-5, and CH_2-O always decrease and the ^{1}H chemical shift values[8,16,17] of HC-5 and HC-5' always increase on passing from anti to syn products. Furthermore anti isomers constantly[8,16,17] feature larger HC-5/HC-5' coupling constants with respect to their syn counterparts.

Only ^{1}H NMR data are available in the literature for cycloadducts structurally related to (26) and (27):[8] a definite trend has been observed in the HC-5 chemical shift values which increase on passing from anti to syn isomers. On this basis the anti relative configuration can be tentatively attributed to the predominant cycloadducts (26a), (27a) and (26c), (27c). In our case HC-5/HC-5' coupling constant values[8] were found not to be reliable: for instance the major product obtained from (Z)-(22) showed a coupling constant smaller than that of the minor one, while an opposite situation was found for the cycloadducts derived from (Z)-(21). However, (27c) was converted into (26c) by deprotection ($Bu_4N^+F^-$ in THF/H_2O) and benzylation ($PhCH_2Br$, NaH, cat. $Bu_4N^+J^-$, THF), thus showing that (Z)-(21) and (Z)-(22) give major products that belong to the same steric series.

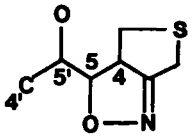
The configurational assignment to dibenzyloxy derivatives (28) was not possible via ^{1}H or ^{13}C NMR. However the C-5/C-5' anti stereochemistry was tentatively attributed to the predominant products (28a) and (28c) by analogy with the results of the above mentioned cycloadditions. Further evidence for the anti selectivity of these reactions, were obtained in a related study[18] on the INOC reactions of (E)- and (Z)- 5- and 6-alkenylnitrileoxides.

For sake of completeness we investigated also the behaviour of nitrosulphides (E)- and (Z)-(25), which display an allylic stereocenter substituted only by alkyl groups. The reactions occur with a degree of stereoselectivity very close to that observed in a related intermolecular case.[9] Although we do not have at present any evidence which allows the stereochemical assignment to the isomers of (30), the hypothesis[9] that also these reactions produce a predominance of C-5/C-5' anti derivatives seems quite reasonable.

As far as the stereoselectivity of these INOC reactions is concerned it must be noted that the cycloadditions of (E)- and (Z)- (21) and (22) occur with a diastereoselection that parallels that of similar intermolecular reactions,[7-9] no appreciable effect being exerted either by changing the double bond geometry or by increasing the bulkiness of the protecting group. The same level of

selectivity is obtained with glyceraldehyde derived nitrosulphides (E)- and (Z)-(23). On the other hand, cycloadditions of cyclohexylidene derivatives (E)- and (Z)-(24) proceed with a remarkable stereocontrol; in particular, the anti stereoselectivity of (Z)-(24) is superior to that of (E)-(24) and of other related intermolecular reactions.[7,8] Thus also in these intramolecular cycloadditions, as already observed in other inter-[7,8,19] and intramolecular[6,18] cases, the presence of two oxygens locked in a cycle by a ketal-type protection seems to secure top stereoselections. Whether the origin of this phenomenon is steric rather than stereoelectronic is still to be demonstrated.

Table 2. Relevant NMR data of isoxazolines (26)-(29).

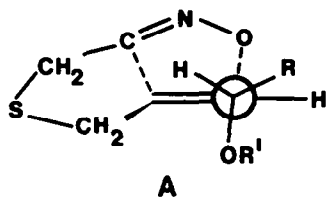


numbering scheme

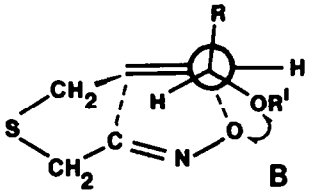
Compound	^{13}C[a] C-4	C-5	C-5'	C-4'	^{1}H[a] HC-5	HC-5'	$J_{HC-4/HC-5}$[b]	$J_{HC-5/HC-5'}$[b]
(26a)	57.4	90.9	74.0	17.3	4.29	3.82	9.7	5.0
(26b)	57.5	89.7	74.0	15.4	4.44	3.81	10.0	5.5
(26c)	57.9	84.8	73.0	16.7	4.43	3.68	11.2	8.5
(26d)	57.3	85.5	73.7	16.7	4.56	3.65	10.5	5.6
(27a)	56.7	91.6	67.7	20.8	4.20	4.06	9.3	4.2
(27b)	56.4	90.1	67.7	18.2	4.29	4.07	9.5	5.4
(27c)	57.1	85.9	68.2	20.6	4.33	4.04	11.0	5.3
(27d)	57.0	85.8	67.9	20.4	4.40	3.93	10.5	6.0
(28a)	57.0	87.9	76.6	69.8	4.55	3.92	9.6	4.4
(28b)	57.8	87.7	77.3	69.8	4.55	3.80	9.3	4.9
(28c)	58.0	80.5	76.3	69.1	4.76	4.18	11.0	8.2
(28d)	57.7	82.0	77.3	69.3	4.78	4.11	10.6	3.8
(29a)	59.6	87.3	75.7	66.9	4.28	4.20	9.0	7.5
(29b)	57.4	86.3	74.5	64.9	4.49	4.40	9.4	5.0
(29c)	58.7	83.1	71.9	67.5	4.45	4.11	10.0	10.0
(29d)	-[c]	82.6[d]	70.8[d]	-[c]	4.55[d]	-[c]	-[c]	7.5[d]

[a] In ppm. [b] In Hz. [c] Undetermined. [d] Tentative assignment.

As mentioned elsewhere[6,18] we propose for the INOC reaction of (Z)-(21)-(24) the transition states A and B for anti and syn products, respectively, where



A



B

the hydrogen atom of the allylic stereocenter occupies the "inside"[7] position to relieve steric interactions, and the repulsion between the oxygens of the alkoxy group and of the oncoming nitrile oxide disfavours B versus A.

As far as (E)-(21)-(24) cycloadditions are concerned, the results can be explained either by transition states similar to A and B or by models previously proposed for intermolecular reactions[7,9] featuring the alkoxy group in the inside position[19] (inside alkoxy effect).

Finally, in order to verify the possibility of converting isoxazolines (26)-(30) into the corresponding β-ketols, compound (29a) was subjected to Raney-nickel promoted hydrogenation[1] to give in quantitative yield (3R,4S,5R)-5,6-0,0-cyclohexylidendioxy-4-hydroxy-3-methyl-hexan-2-one (31).

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded on a Varian EM 390 or XL 300 instrument, using $CDCl_3$ as solvent. Optical rotations were measured on a Perkin-Elmer 241 spectrometer. Elemental analyses were performed with a Perkin Elmer 240 instrument. Silica gel was used for analytical and flash chromatography; organic extracts were dried over sodium sulphate and filtered before removal of the solvent under reduced pressure. THF was distilled from $LiAlH_4$, CH_2Cl_2 from CaH_2, CH_3CN from P_2O_5, and benzene from sodium. All reactions employing anhydrous solvents were run under Argon. Aldehydes were purified immediately before use. Aldehydes (S)-(1),[20] (S)-(2),[21] (R)-(3),[22] (R)-(4)[23] and (R,S)-(5)[24] were prepared as described.

General procedure for the synthesis of (E)-esters (6)-(10).
To a stirred suspension of oil free NaH (5.0 mmol) in THF (10 ml) cooled at -30°C, diethyl ethoxy-carbonylmethylposphonate (5.0 mmol, 1.25 g) in THF (10 ml) was added dropwise. After 30 min stirring at -30°C, a solution of the aldehyde (4.8 mmol) in THF (5 ml) was added over a period of 5 min, and the mixture stirred at -30°C for an additional 60 min. Usual work-up followed by flash chromatography (silica gel, diethyl-ether: hexanes mixtures as eluants) gave stereoisomerically pure products.

(S)-Ethyl-4-benzyloxy-2-(E)-pentenoate (6) was obtained in 83% yield with 1:9 diethylether: hexanes mixture as eluant. (E:Z ratio on the crude product 12:1). Found: C% 71.59; H% 7.83. $C_{14}H_{18}O_3$ requires: C% 71.77; H% 7.74. ^1H NMR: δ 7.25-7.35 (m, 5H, aromatic protons); 6.90 (dd, 1H, J 16.4, 6.3, CH-CH=); 5.95 (dd, 1H, J 16.4, 1.8, CO-CH=); 3.95-4.65 (m, 5H, CH_2-O, CH_2-Ar, CH-O); 1.10-1.50 (m, 6H, 2 CH_3). $[\alpha]_D^{22}$ - 32.2 (c 1 in $CHCl_3$).

(S)-Ethyl-4-t-butyldimethylsilyloxy-2-(E)-pentenoate (7) was obtained in 80% yield with 5:95 diethylether: hexanes mixture as eluant (E:Z ratio on the crude product 14:1). Found: C% 60.51; H% 10.29. $C_{13}H_{26}O_3Si$ requires: C% 60.42; H% 10.14. ^1H NMR: δ 6.85 (dd, 1H, J 15.3, 4.3, CH-CH=); 5.85 (dd, 1H, J 15.3, 1.8, CO-CH=); 3.90-4.45 (m, 3H, CH_2-O and CH-O); 1.10-1.35 (m, 6H, CH_2-CH_3 and CH-CH_3); 0.80 (s, 9H, $(CH_3)_3C$); 0.10 (s, 6H, $(CH_3)_2$-Si). $[\alpha]_{436}^{22}$ + 4.4 (c 1.2

in $CHCl_3$).

(R)-Ethyl-4,5-dibenzyloxy-2-(E)-pentenoate (8) was obtained in 88% yield with 1:3 diethylether: hexanes mixture as eluant (E:Z ratio on the crude product 16:1). Found: C% 73.90; H% 7.17. $C_{21}H_{24}O_4$ requires: C% 74.10; H% 7.11. ^{1}H NMR: δ 7.15-7.35 (m, 10H, aromatic protons); 6.85 (dd, 1H, J 16.0, 6.0, CH-CH=); 6.05 (dd, 1H, J 16.0, 1.8, CO-CH=); 4.40-4.60 (m, 4H, CH_2Ar); 4.05-4.30 (m, 3H, CH_2-CH_3 and CH-O); 3.55 (d, 2H, J 6.0, CH-CH_2); 1.25 (t, 3H, J 7.5, CH_3). $[\alpha]_D^{22}$ + 23.0 (c 0.5 in $CHCl_3$).

(R)-Ethyl-4,5-O,O-cyclohexylidendioxy-2-(E)-pentenoate (9) was obtained in 85% yield with a 1:3 diethylether: hexanes mixture as eluant (E:Z ratio on the crude product 26:1). Found: C% 65.08; H% 8.44. $C_{13}H_{20}O_4$ requires: C% 64.98; H% 8.39. ^{1}H NMR: δ 6.85 (dd, 1H, J 15.0, 6.0, CH-CH=); 6.05 (dd, 1H, J 15.0, 1.5, CO-CH=); 4.65-4.85 (m, 1H, CH-O); 4.05-4.30 (m, 3H, one H of CH-CH_2O and MeCH_2-O); 3.65 (t, 1H, J 7.5, one H of CH-CH_2O); 1.20-1.75 (m, 13H, C_6H_{10} and CH_3). $[\alpha]_D^{22}$ + 31.2 (c 1.2 in $CHCl_3$).

(R,S)-Ethyl-4,5-dimethyl-2-(E)-hexenoate (10)[25] was obtained in 73% yield with hexanes as eluant (only E isomer present in the crude product).

General procedure for the synthesis of (Z)-esters (11)-(15).
These products were prepared by a modification of the reported[13] procedure. To a stirred suspension of oil free KH (5.0 mmol) in THF (10 ml) cooled at -78°C, bis(2,2,2-trifluoroethyl)-(methoxycarbonylmethyl)-phosphonate (5.0 mmol, 1.59 g) in THF (10 ml) was added dropwise. After 45 min stirring at -78°C, a solution of the aldehyde (4.8 mmol) in THF (5 ml) was added over a period of 5 min, and the mixture stirred for an additional 60 min. The reaction was worked-up as described for the (E)-esters, and the products purified by flash chromatography with the above mentioned eluants.

(S)-Methyl-4-benzyloxy-2-(Z)-pentenoate (11) was obtained in 84% yield (Z:E ratio on the crude product 11:1). Found: C% 71.00; H% 7.20. $C_{13}H_{16}O_3$ requires: C% 70.89; H% 7.32. ^{1}H NMR: δ 7.15-7.30 (m, 5H, aromatic protons); 6.10 (dd, 1H, J 12.0, 8.0, CH-CH=); 5.70 (d, 1H, J 12.0, =CH-CO); 4.90-5.20 (m, 1H, CH-O); 4.40 (s, 2H, CH_2Ar); 3.65 (s, 3H, CH_3O); 1.25 (d, 3H, J 6.5, CH_3-CH). $[\alpha]_D^{22}$ + 25.5 (c 1 in $CHCl_3$).

(S)-Methyl-4-t-butyldimethylsilyloxy-2-(Z)-pentenoate (12) was obtained in 65% yield (Z:E ratio on the crude product 8:1). Found: C% 59.08; H% 9.81. $C_{12}H_{24}O_3Si$ requires: C% 58.97; H% 9.90. ^{1}H NMR: δ 6.05 (dd, 1H, J 12.0, 7.5, CH-CH=); 5.55 (d, 1H, J 12.0, =CH-CO); 5.30-5.55 (m, 1H, CH-O); 3.65 (s, 3H, CH_3-O); 1.20 (d, 3H, J 6.5, CH_3-CH); 0.85 (s, 9H, $(CH_3)_3C$); 0.10 (2s, 6H, 2 CH_3-Si). $[\alpha]_D^{22}$ + 49.0 (c 1.8 in $CHCl_3$).

(R)-Methyl-4,5-dibenzyloxy-2-(Z)-pentenoate (13) was obtained in 72% yield (Z:E ratio on the crude product 8:1). Found: C% 73.50; H% 6.87. $C_{20}H_{22}O_4$ requires: C% 73.60; H% 6.79. ^{1}H NMR: δ 7.15-7.30 (m, 10H, aromatic protons); 6.15 (dd, 1H, J 11.5, 7.5, CH-CH=); 5.80 (d, 1H, J 11.5, =CH-CO); 5.10-5.30 (m, 1H, CH-O); 4.55 (s, 4H, CH_2Ar); 3.65 (s, 3H, CH_3-O); 3.55 (d, 2H, J 5.0, CHCH_2). $[\alpha]_D^{22}$ + 18.3 (c 1 in $CHCl_3$).

(R)-Methyl-4,5-O,O-cyclohexylidendioxy-2-(Z)-pentenoate (14) was obtained in 80% yield (Z:E ratio on the crude product 10:1). Found: C% 63.85; H% 7.94. $C_{12}H_{18}O_4$ requires: C% 63.70; H% 8.02. ^{1}H NMR: δ 6.20 (dd, 1H, J 11.0, 6.5, CH-CH=); 5.70 (dd, 1H, J 11.0, 1.5, =CH-CO); 5.35 (dq, 1H, J 6.5, 1.5, CH-O); 4.20 (dq, 1H, J 7.5, 1.5, one H of CH_2-O); 3.65 (s, 3H, CH_3-O); 3.40-3.70 (m, 1H, one H of CH_2-O); 1.20-1.70 (m, 10H, C_6H_{10}). $[\alpha]_D^{22}$ + 85.1 (c 1 in $CHCl_3$).

(R,S)-Methyl-4,5-dimethyl-2-(Z)-hexenoate (15) was obtained in 83% yield as a 7:3 Z:E mixture which could not be separated. Found: C% 69.07; H% 10.21. $C_9H_{16}O_2$ requires: C% 69.19; H% 10.32.

General procedure for the synthesis of the thiolesters.
These products were prepared by a sequence of three reactions involving DIBAH reduction of the esters (6)-(15), mesylation of the allylic alcohols, and reaction with thiolacetic acid.

DIBAH reduction: To a stirred solution of ester (3 mmol) in CH_2Cl_2 (10 ml) cooled at -78°C, 3 ml of a 1N solution of DIBAH in CH_2Cl_2 were added dropwise. The reaction was stirred at -78°C for 30-60 min and monitored by TLC. If necessary additional reducing agent was added until complete desappearance of the starting material. Usual work-up with sat. NH_4Cl and diluted HCl gave the crude allylic alcohols which were used without further purification.

Reaction with mesyl chloride: To a stirred solution of allylic alcohol (3 mmol) and triethylamine (5 mmol, 0.7 ml) in CH_2Cl_2 (10 ml) cooled at -15°C, mesylchloride (3.3 mmol, 0.255 ml) was added dropwise. After 20 min stirring at -15° -10°C, ice cold water was added and the mixture rapidly extracted with CH_2Cl_2. The organic phase was dried and concentrated in vacuo at low temperature to give the crude product.

Reaction with thiolacetic acid: To a stirred solution of the crude mesylate in CH_3CN (10 ml) cooled at 0°C, triethylamine (3.3 mmol, 0.460 ml) and then thiolacetic acid (3.1 mmol, 0.240 ml) were added. The reaction was allowed to warm-up to room temperature and stirred for 2 hours. Work-up involved addition of water and extraction with CH_2Cl_2. The thiolesters were isolated by flash chromatography with diethyl ether: hexanes mixtures as eluants.

(S)-1-Acetylmercapto-4-benzyloxy-2-(E)-pentene (16), was obtained in 63% overall yield from (E)-(6) with a 4:6 diethylether:hexanes eluting mixture. Found: C% 66.84; H% 7.31. $C_{14}H_{18}O_2S$ requires: C% 67.16; H% 7.25. ^1H NMR: δ 7.25-7.40 (m, 5H, aromatic protons); 5.60-5.75 (m, 2H, HC=CH); 4.40-4.60 (m, 2H, CH_2Ar); 3.80-4.10 (m, 1H, CH-O); 3.55-3.65 (m, 2H, CH_2-S); 2.35 (s, 3H, CH_3-CO); 1.30 (d, 3H, J 7.0, CH_3-CH). The corresponding (Z) thiolester was obtained in 58% overall yield from (11). ^1H NMR: δ 7.25-7.40 (m, 5H, aromatic protons); 5.20-5.45 (m, 2H, HC=CH); 4.40-4.60 (m, 2H, CH_2Ar); 4.10-4.40 (m, 1H, CH-O); 3.25 (d, 2H, J 7.5, CH_2-S); 2.25 (s, 3H, CH_3CO); 1.25 (d, 3H, J 7.0, CH_3-CH).

(S)-1-Acetylmercapto-4-t-butyldimethylsilyloxy-2-(E)-pentene (17) was obtained in 50% overall yield from (E)-(7) with a 1:4 diethylether:hexanes eluting mixture. Found: C% 57.00; H% 9.50. $C_{13}H_{26}O_2SSi$ requires: C% 56.88; H% 9.55. ^1H NMR: δ 5.50-5.75 (m, 2H, HC=CH); 4.10-4.35 (m, 1H, CH-O); 3.40-3.50 (m, 2H, CH_2-S); 2.30 (s, 3H, CH_3-CO); 1.15 (d, 3H, J 5.8 Hz, CH_3-CH); 0.85 (s, 9H, $(CH_3)_3C$); 0.10 (s, 6H, $(CH_3)_2$-Si). The corresponding (Z) thiolester was obtained in 50% overall yield from (12). ^1H NMR: δ 5.00-5.45 (m, 2H, HC=CH); 4.45-4.60 (m, 1H, CH-O); 3.40 (d, 2H, J 7.5, CH_2S); 2.20 (s, 3H, CH_3-CO); 1.10 (d, 3H, J 6.5, CH_3-CH); 0.85 (s, 9H, $(CH_3)_3C$); 0.05 (s, 6H, $(CH_3)_2Si$).

(R)-1-Acetylmercapto-4,5-dibenzyloxy-2-(E)-pentene (18) was obtained in 60% overall yield from (E)-(8) with a 1:3 diethylether: hexanes eluting mixture. Found: C% 70.60; H% 6.89. $C_{21}H_{24}O_3S$ requires: C% 70.75; H% 6.79. ^1H NMR: δ 7.15-7.30 (m, 10H, aromatic protons); 5.55-5.70 (m, 2H, HC=CH); 4.30-4.60 (m, 4H, CH_2-Ar); 3.90-4.20 (m, 1H, CH-O); 2.85-3.15 (m, 4H, CH_2-S and CH_2-CH); 2.25 (s, 3H, CH_3-CO). The corresponding (Z) thiolester was obtained in 60% overall yield from (13). ^1H NMR: δ 7.15-7.30 (m, 10H, aromatic protons); 5.30-5.65 (m, 2H, HC=CH); 4.30-4.65 (m, 5H, CH_2Ar and CH-O); 3.40-3.60 (m, 2H, CH_2-S); 2.25 (s, 3H, CH_3-CO).

(R)-1-Acetylmercapto-4,5-O,O-cyclohexylidendioxy-2-(E)-pentene (19) was obtained in 71% yield from (E)-(9) with a 15:85 diethylether:hexanes eluting mixture. Found: C% 61.01; H% 7.77. $C_{13}H_{20}O_3S$ requires: C% 60.91; H% 7.86. ^1H NMR: δ 5.45-5.90 (m, 2H, HC=CH); 4.35-4.55 (m, 1H, CH-O); 4.00 (dd, 1H, J 7.5 and 6.7, one H of CH_2-O); 3.40-3.60 (m, 3H, CH_2-S and one H of CH_2-O); 2.30 (s; 3H, CH_3-CO); 1.30-1.70 (m, 10H, C_6H_{10}). The corresponding (Z) thiolester was obtained in 55% overall yield from (14). ^1H NMR: δ 5.35-5.75 (m, 2H, HC=CH); 4.75-5.00 (m, 1H, CH-O); 4.10 (dd, 1H, J 7.5, 6.0, one H of CH_2-O); 3.30-3.80 (m, 3H, CH_2-S and one H of CH_2-O); 2.35 (s, 3H, CH_3-CO) 1.30-1.70 (m, 10H, C_6H_{10}).

(R,S)-1-Acetylmercapto-4,5-dimethyl-2-(E)-hexene (20) was obtained in 58% yield from (E)-(10) with a 1:9 diethylether: hexanes eluting mixture. Found: C% 64.48. H% 9.66. $C_{10}H_{18}O_2S$ requires: C% 64.47; H% 9.74. ^1H NMR: δ 5.10-5.65 (m, 2H, HC=CH); 3.50 (d, 2H, J 6.5 Hz, CH_2-S); 2.30 (s, 3H, CH_3CO); 1.30-2.10 (2m, 2H, CH-Me and CH-Me_2); 0.75-1.00 (m, 9H, 3 CH_3). The corresponding (Z) thioleser was obtained in 58% overall yield from the mixture of (E) and (Z)-(15), as a 7:3 Z:E mixture.

General procedure for the synthesis of the nitrosulphides.
To a stirred solution of sodium ethoxide (1 mmol) in ethanol (5 ml) a solution of the thiolester (1 mmol) in ethanol (2 ml) was added and stirring continued for 1 h at room temperature. The reaction mixture is then cooled at 0°C and 1-nitro-2-acetoxyethane (1 mmol) in ethanol (2 ml) was added and stirring continued for 3h at 0°C. Sat. NH_4Cl was then added and ethanol evaporated *in vacuo*. The aqueous phase was extracted twice with dichloromethane, and the organic phase dried and concentrated *in vacuo*. The oily residue was purified by flash chromatography with diethylether:hexanes mixtures as eluants.

(S)-4-Benzyloxy-1-(2-nitroethylthio)-(E)-2-pentene (21) was obtained in 74% yield with a 3:7 diethylether:hexanes mixture as eluant. Found: C% 59.90; H% 6.71; N% 4.95. $C_{14}H_{19}NO_3S$ requires: C% 59.76; H% 6.81; N% 4.98. ^{1}H NMR: δ 7.10-7.30 (m, 5H, aromatic protons); 5.35-5.65 (m, 2H, HC=CH); 4.25-4.55 (m, 4H, CH_2Ar) and CH_2-NO_2); 3.80-4.10 (m, 1H, CH-O); 2.90-3.25 (m, 4H, CH_2-S-CH_2); 1.30 (d, 3H, J 6.5, CH_3). The corresponding (Z) isomer was obtained in 66% yield. ^{1}H NMR: δ 7.10-7.30 (m, 5H, aromatic protons); 5.30-5.60 (m, 2H, CH=CH); 4.10-4.55 (m, 5H, CH_2Ar, CH_2NO_2, and CH-O); 3.00-3.35 (m, 4H, CH_2-S-CH_2); 1.35 (d, 3H, J 7.0, CH_3)

(S)-4-t-Butyldimethylsilyloxy-1-(2-nitroethylthio)-(E)-2-pentene (22) was obtained in 71% yield with a 1:9 diethylether:hexanes mixture as eluant. Found: C% 50.99; H% 9.00, N% 4.49. $C_{13}H_{27}NO_3SSi$ requires: C% 51.11; H% 8.91; N% 4.58. ^{1}H NMR: δ 5.36-5.50 (m, 2H, HC=CH); 4.40 (t, 2H, J 7.5, CH_2-NO_2), 4.15-4.35 (m, 1H, CH-O); 2.85-3.10 (m, 4H, CH_2-S-CH_2); 1.05 (d, 3H, J 7.0, $\underline{CH}_3$-CH); 0.80 (s, 9H, $(CH_3)_3C$); 0.10 (s, 6H, $(CH_3)_2$-Si). The corresponding (Z) isomer was obtained in 74% yield. ^{1}H NMR: δ 5.30-5.45 (m, 2H, HC=CH); 4.10-4.35 (m, 3H, CH_2-NO_2 and CH-O); 2.80-3.05 (m, 4H, CH_2-S-CH_2); 1.00 (d, 3H, J 7.0, $\underline{CH}_3$-CH); 0.80 (s, 9H, $(CH_3)_3C$); 0.05 (s, 6H, $(CH_3)_2$-Si).

(R)-4,5-Dibenzyloxy-1-(2-nitroethylthio)-(E)-2-pentene (23) was obtained in 60% yield with a 35:65 diethylether:hexanes mixture as eluant. Found: C% 65.00; H% 6.60; N% 3.64. $C_{21}H_{25}NO_4S$ requires: C% 65.09; H% 6.50; N% 3.61. ^{1}H NMR: δ 7.15-7.30 (m, 10H, aromatic protons); 5.35-5.80 (m, 2H, HC=CH); 4.30-4.65 (m, 6H, CH_2Ar and CH_2-NO_2); 3.90-4.10 (m, 1H, CH-O); 3.35-3.65 (m, 2H, =C-CH_2-S); 3.15 (d, 2H, J 6.0, CH-$\underline{CH}_2$-O); 2.95 (t, 2H, J 7.5, S-$\underline{CH}_2$-CH_2). The corresponding (Z) isomer was obtained in 57% yield ^{1}H NMR: δ 7.15-7.30 (m, 10H, aromatic protons); 5.40-5.70 (m, 2H, HC=CH); 4.10-4.60 (m, 7H, CH_2Ar, CH_2-NO_2, CH-O); 3.35-3.70 (m, 2H, =C-CH_2-S); 3.10 (d, 2H, J 6.5, CH-$\underline{CH}_2$-O); 2.85 (t, 2H, J 7.0, S-$\underline{CH}_2$-CH_2).

(R)-4,5-O,O-Cyclohexylidendioxy-1-(2-nitroethylthio)-(E)-2-pentene (24) was obtained in 70% yield with a 1:1 diethylether:hexanes mixture as eluant. Found: C% 54.28; H% 7.44; N% 4.79. $C_{13}H_{21}NO_4S$ requires: C% 54.33; H% 7.36; N% 4.87. ^{1}H NMR: δ 5.40-5.85 (m, 2H, HC=CH); 4.35-4.60 (m, 3H, CH_2-NO_2 and CH-O); 4.05 (dd, 1H, J 7.0, 6.0, one H of CH_2-O); 3.55 (t, 1H, J 7.0, one H of CH_2-O); 3.15 (d, 2H, J 6.0, =C-CH_2-S); 2.95 (t, 2H, J 7.0, S-$\underline{CH}_2$-CH_2); 1.30-1.70 (m, 10H, C_6H_{10}). The corresponding (Z) isomer was obtained in 65% yield. ^{1}H NMR: δ 5.45-5.80 (m, 2H, HC=CH); 4.65-4.90 (m, 1H, CH-O); 4.55 (t, 2H, J 6.5, CH_2-NO_2); 4.10 (dd, 1H, J 7.0, 6.0, one H of CH_2-O); 3.55 (t, 1H, J 7.0, one H of CH_2-O); 3.00-3.40 (m, 4H, CH_2-S-CH_2); 1.40-1.70 (m, 10H, C_6H_{10}).

(R,S)-4,5-Dimethyl-1-(2-nitroethylthio)-(E)-2-hexene (25) was obtained in 77% yield with a 1:9 diethylether:hexanes mixture as eluant. Found: C% 55.12; H% 8.90; N% 6.39. $C_{10}H_{19}NO_2S$ requires: C% 55.27; H% 8.81; N% 6.44. ^{1}H NMR: δ 5.10-5.60 (m, 2H, HC=CH); 4.45 (t, 2H, J 7.5, CH_2-NO_2); 2.90-3.20 (m, 4H, CH_2-S-CH_2); 1.20-2.20 (2m, 2H, $\underline{CH}$-CH_3 e $\underline{CH}$-$(CH_3)_2$); 0.75-1.00 (m, 9H, 3 CH_3). The corresponding (Z) isomer was obtained in 57% yield as a 7:3 Z:E mixture; ^{1}H NMR: δ 5.10-5.50 (m, 2H, HC=CH); 4.40-4.60 (m, 2H, CH_2-NO_2); 2.90-3.30 (m, 4H, CH_2-S-CH_2); 1.10-2.20 (2m, 2H, $\underline{CH}$-CH_3 and $\underline{CH}$-$(CH_3)_2$); 0.75-1.00 (m, 9H, 3 CH_3).

Synthesis of 4,5-dihydroisoxazoles (26)-(30).
A stirred solution of nitrosulphide (1 mmol), *p*-Cl-phenylisocyanate (0.260 g, 2 mmol), and triethylamine (drops) in benzene (20 ml) was refluxed overnight. The mixture was then cooled, and pentane (40 ml) was added. The precipitate was filtered and the clear solution concentrated *in vacuo* and flash chromatographed with diethylether:hexanes mixtures as eluants. Yields and diastereoisomeric ratios are collected in Table 1. Relevant NMR data are collected in Table 2.

Isoxazoline (26a,b). Found: C% 63.73; H% 6.43; N% 5.37. $C_{14}H_{17}NO_2S$ requires: C% 63.85; H% 6.51; N% 5.32 Eluting mixture: 35:65 diethylether:hexanes.
(26a): $[\alpha]_D^{22}$ - 132.5 (c 2 in $CHCl_3$); (26b): $[\alpha]_D^{22}$ + 100.8 (c 1 in $CHCl_3$).

Isoxazoline (26c,d). Found: C% 63.88; H% 6.47; N% 5.26. $C_{14}H_{17}NO_2S$ requires: C% 63.85; H% 6.51; N% 5.32. Eluting mixture: 40:60 diethylether:hexanes.
(26c): $[\alpha]_D^{22}$ + 66.2 (c 0.5 in $CHCl_3$); (26d): $[\alpha]_D^{22}$ -17.3 (c 0.2 in $CHCl_3$).

Isoxazoline (27a,b). Found: C% 54.22; H% 8.85; N% 4.91. $C_{13}H_{25}NO_2SSi$ requires: C% 54.31; H% 8.76; N% 4.87. Eluting mixture: 15:85 diethylether:hexanes.

Isoxazoline (27c,d). Found: C% 54.27; H% 8.73; N% 4.90. $C_{13}H_{25}NO_2SSi$ requires: C% 54.31; H% 8.76; N% 4.87. Eluting mixture: 1:3 diethylether:hexanes.

Isoxazoline (28a,b). Found: C% 68.47; H% 6.17; N% 3.82. $C_{21}H_{23}NO_3S$ requires: C% 68.27; H% 6.27; N% 3.79. Eluting mixture: 45:55 diethylether:hexanes.

Isoxazoline (28c,d). Found: C% 68.32; H% 6.29; N% 3.73. $C_{21}H_{23}NO_3S$ requires: C% 68.27; H% 6.27; N% 3.79. Eluting mixture: 45:55 diethylether:hexanes.

Isoxazoline (29a,b). Found: C% 51.03; H% 7.16; N% 5.24. $C_{13}H_{19}NO_3S$ requires: C% 57.97; H% 7.11; N% 5.20. Eluting mixture: 1:1 diethylether:hexanes.
(29a): $[\alpha]_D^{22}$ + 211.6 (c 1 in $CHCl_3$). (29b): $[\alpha]_D^{22}$ - 190.3 (c 0.3 in $CHCl_3$).

Isoxazoline (29c,d). Found: C% 58.03; H% 7.09; N% 5.15. $C_{13}H_{19}NO_3S$ requires: C% 57.97; H% 7.11; N% 5.20. Eluting mixture: 1:1 diethylether:hexanes.
$[\alpha]_D^{22}$ - 65.7 (c 1.7 in $CHCl_3$).

Isoxazoline (30a,b). Found: C% 60.19; H% 8.64; N% 6.99. $C_{10}H_{17}NOS$ requires: C% 60.26; H% 8.60; N% 7.03. Eluting mixture 1:9 diethylether:hexanes. Relevant NMR data: (30a); ^{1}H: δ 4.25 (HC-5); J HC-4/HC-5 10.6; J HC-5/HC-5' 8.6; ^{13}C: δ 59.6 (C-4); 90.5 (C-5); 42.2 (C-5'). (30b); ^{1}H: δ 4.26 (HC-5); J HC-4/HC-5 10.0; J HC-5/HC-5' 7.0; ^{13}C: δ 60.0 (C-4); 91.3 (C-5); 42.6 (C-5').

Isoxazoline (30c,d). Found: C% 60.23; H% 8.55; N% 7.05. $C_{10}H_{17}NOS$ requires: C% 60.26; H% 8.60; N% 7.03. Eluting mixture: 1:9 diethylether:hexanes. Relevant NMR data: (30c); ^{1}H: δ 4.47 (HC-5); J HC-4/HC-5 10.8; J HC-5/HC-5' 8.4. ^{13}C: δ 56.7 (C-4); 85.7 (C-5); 39.4 (C-5'). (30d); ^{1}H: δ 4.39 (HC-5); J HC-4/HC-5' 10.8; J HC-5/HC-5' 10.8. ^{13}C: δ 56.5 (C-4); 85.0 (C-5); 38.5 (C-5').

Synthesis of β-ketol (31). In a hydrogenation vessel isoxazoline (29a) (0.37 mmol, 0.100 g); boric acid (0.74 mmol, 0.045 g), W-2 Ni-Ra (0.200 g), methanol (15 ml), and water (3 ml) were shaken under H_2 atmosphere for 2h at room temperature. Standard work-up gave, after flash chromatography (65:35 diethylether:hexanes mixture as eluant), β-ketol (31) (0.36 mmol, 0.087 g), diastereoisomerically pure within the limit of ^{1}H 300 MHz NMR spectroscopy. Found: C% 64.40; H% 9.08. $C_{13}H_{22}O_4$ requires: C% 64.44; H% 9.15. $[\alpha]_D^{22}$ + 5.8 (c 0.2 in $CHCl_3$). ^{1}H NMR: δ 4.08 (dd, 1H, J 7.6, 5.5, one H of CH_2O); 3.97 (ddd, 1H, J 7.6, 7.3, 6.0, CH-O); 3.93 (dd, 1H, J 7.3, 5.5, one H of CH_2O); 3.55 (dd, 1H, J 6.0, 5.0, CH-OH); 3.17 (bs, 1H, OH); 2.91 (dq, 1H, J 7.2, 5.0, CH-CH_3); 2.24 (s, 3H, CH_3-CO); 1.36-1.70 (m, 10H, C_6H_{10}); 1.24 (d, 3H, J 7.2, CH-CH_3).

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