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REGIO- AND STEREOCONTROL IN THE INTRAMOLECULAR NITRILE OXIDE CYCLOADDITION TO 2-FURYLTHIOL- AND 2-FURYLMETHANETHIOL DERIVATIVES.

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Abstract. A series of 2-furyl and 2-furylmethyl substituted nitrosulphides with a proper chain length were prepared and showed to undergo a totally regiocontrolled intramolecular furan-nitrile oxide cycloaddition to give cis-fused products in high yield. Insertion of a stereocenter on the cycloaddends did not allow satisfactory control of the absolute stereochemistry of the reaction. Enantiomerically enriched products (e.e.$\leqslant$95%) were obtained by a kinetic resolution process involving oxidation of the sulphide cycloadducts to the corresponding sulphoxides.

The proteiform variety of synthetic opportunities offered by furan makes its insertion into organic molecules an attractive goal.[1] One of the most popular approach to this result is to use furan as a reagent in cycloadditions, since this heterocycle can play the role of either 4π or 2π component. In this line intramolecular processes seem especially appealing, as they can help to overcome problems of poor reactivity and enhance regio- and stereochemical control.[2] However, only a very limited number of reports[3-6] deal with intramolecular 1,3 dipolar cycloadditions to furan, not withstanding its extremely scarce tendency to react intermolecularly as dipolarophile,[7-10] and the obvious synthetic bonus offered in particularly by the furan-nitrile oxide cycloaddition.[8] This reaction is indeed the most straightforward entry to C-4 oxygen substituted isoxazolines,[11] a very important building block for the stereoselective synthesis of various amino sugars.[8,11] In the course of our studies on stereoselective nitrone and nitrile oxide cycloadditions,[12] we became interested in

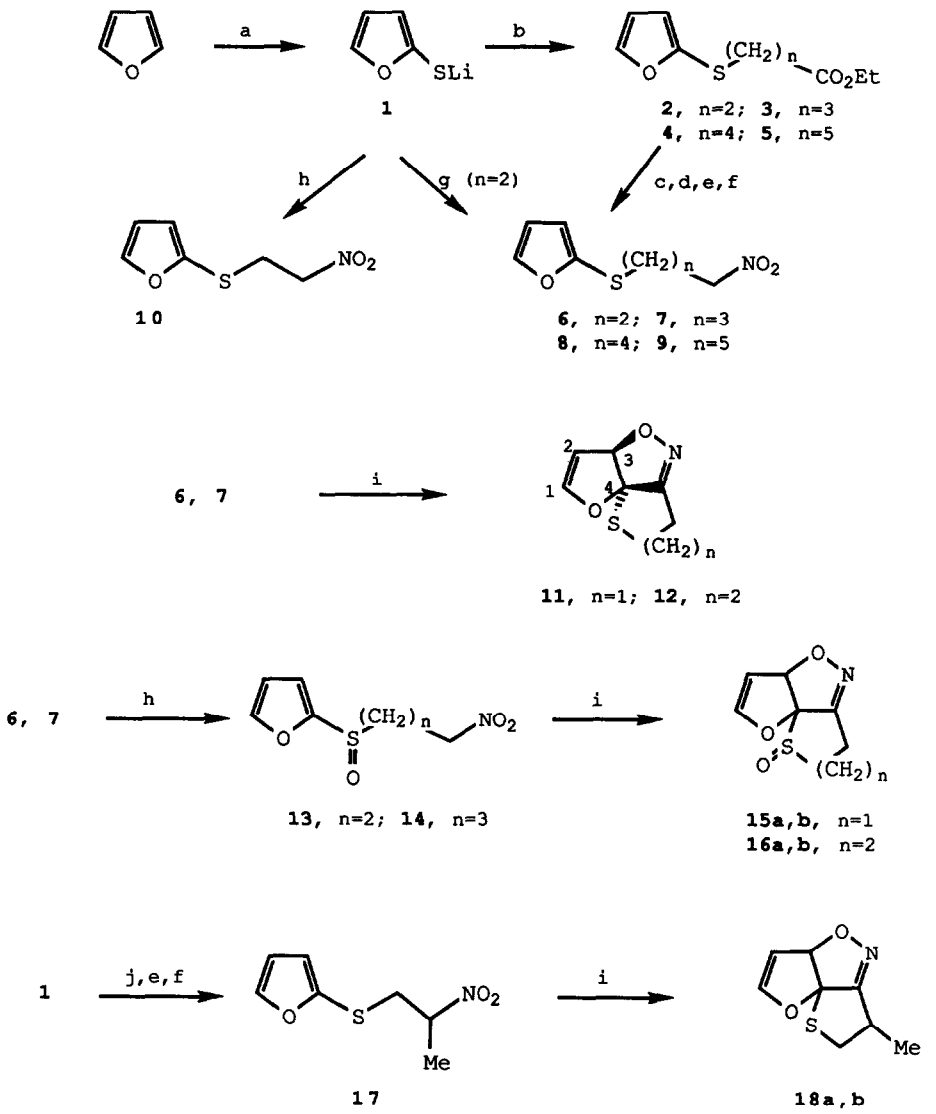
designing a furan-nitrile oxide intramolecular cycloaddition that could lead to precursors of acyclic products. On the basis of ours[13] and other's[14] previous experience in this field, we decided to insert a sulphur atom in the chain connecting dipole and dipolarophile, with the goal of simultaneously cleaving the tether and converting the isoxazolines into a functionalized β-ketol[15] or a γ-aminoalcohol.[11] This manuscript reports our results on the synthesis of two series of cycloaddends and on the regio- and stereochemical implications of their cycloaddition reaction.

2-Furylthiol series.[16]

The synthetic route to the cycloaddends of this series is reported in Scheme 1. Lithiation of furan[17] followed by reaction with sulphur[18] gave lithium 2-furyl thiolate **1**, that was treated in situ with ω-bromoesters to give compound **2-5**, in 68-77% overall yield from furan, in a convenient one pot procedure. Conversion to the nitro derivatives **6-9** was achieved in four steps involving reduction to the alcohols (94-100% yield), preparation of the tosylates (80-83% yield), synthesis of the iodides under PTC conditions (86-91% yield), and iodine-nitro exchange. This reaction could be carried out either in diethyl ether with silver nitrite (48-56% yield) or with sodium nitrite in DMF (58-62% yield); in both cases variable amounts of the nitrous esters and of the unreacted iodides were also obtained. The latter were recycled, while the former could afford the corresponding alcohols upon reduction. An alternative synthesis of compound **6** entailed alkylation of **1** with 1-iodo-3-nitropropane (40% yield). Compound **10** was also prepared in 57% yield by adding **1** to nitroethylene generated in situ from 2-acetoxynitroethane.[13]

With compounds **6-10** in hand we examined their intramolecular cycloaddition. Dilute (0.02M) benzene solutions[19] of the nitro compounds were refluxed for 24h in the presence of 3 mol equiv of p-chlorophenylisocyanate and catalytic triethylamine. Only compound **6** and **7** underwent intramolecular cycloaddition to give isoxazolines **11** and **12** in 79 and 75% yield, respectively, after purification by flash chromatography (that also allowed recovery of about 10% of the starting nitrosulphide). In the reaction of cycloaddends **8-10** only nitrile oxide self-addition products could be detected, while most of the reagent was recovered unchanged. Tricyclic derivatives **11** and **12** were single regioisomeric products to which the cis- fused[20] structure indicated in Scheme 1 was assigned on the basis of high field ^{1}H and ^{13}C NMR spectroscopic evidences, and comparison with the data reported for related systems.[3-6] The fact that nitrosulphide **10** did not afford any intramolecular cycloadduct lends additional support to the structural assignment. Two stereocenters of defined relative stereochemistry are formed in the syn-

Scheme 1



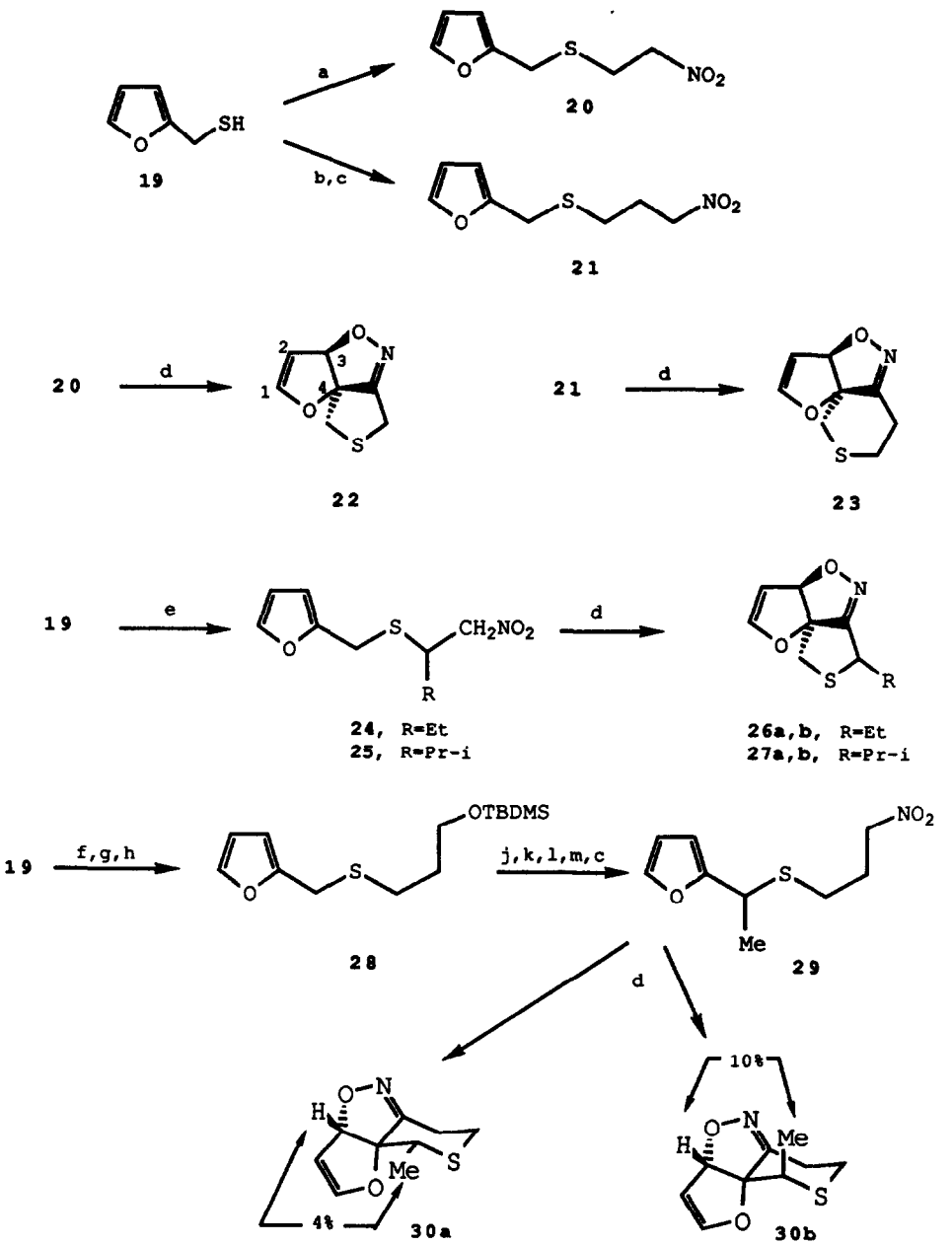
Reagents: a, n-BuLi; then S_8; b, $Br(CH_2)_nCOOEt$; c, $LiAlH_4$; d, TosCl, TEA; e, KI, $Bu_4N^+I^-$; f, $AgNO_2$ or $NaNO_2$; g, $I(CH_2)_3NO_2$; h, $AcOCH_2CH_2NO_2$; i, p-ClC_6H_4NCO, TEA; h, $NaIO_4$; j, $BrCH_2CH(Me)CH_2Cl$

thesis of **11** and **12** from **6** and **7**. The control of the absolute configuration requires the introduction of a stereocenter on the reagent.[12] To this end, the sulphur atom of **6** and **7** was oxidized with sodium metaperiodate to give the corresponding chiral, racemic sulphoxides **13** and **14** in 82 and 87% yield, respectively. Cycloaddition of these gave a mixture of diastereoisomeric cycloadducts **15a,b** and **16a,b**, in 63 and 60% yield. The diastereoisomeric ratio was evaluated by ^{1}H NMR spectroscopy and determined to be 75:25 for compound **15a,b** and 70:30 for compound **16a,b**. This low extent of stereocontrol was not unexpected: indeed, an allylic stereocenter located inside the chain connecting dipole and dipolarophile was reported[21] to promote practically identical extent of stereoselection in an intramolecular nitrile oxide cycloaddition on an E-configurated alkene. Similarly disappointing was the cycloaddition of nitrosulphide **17**, prepared in three steps from **1** as described in Scheme 1. In this case a stereocenter in position with respect to the nitrile oxide moiety can dictate to a very limited extent the stereochemical outcome of the cycloaddition, compound **18a,b** being obtained (73% yield) in a 66:34 diastereoisomeric ratio. Also this result has some precedents in the literature,[22] and the impossibility of controlling the stereochemical outcome of the cycloaddition prompted us to investigate new approaches to isoxazolines as **11** or **12** in enantiomerically enriched form (see below).

2-Furylmethanethiol series.[23]

The synthesis of the required products is described in Scheme 2. Addition of commercially available 2-furylmethanethiol **19** to 2-acetoxynitroethane in the presence of sodium ethoxide gave nitrosulphide **20** in 85% yield. Alkylation of the sodium salt of **19** with 1,3-dibromopropane followed by bromide-nitro exchange with sodium nitrite in DMF[24] gave compound **21** in 44% overall yield. These two cycloaddends underwent intramolecular cycloaddition, in the above described experimental conditions, to give tricyclic isoxazolines **22** and **23** in 77 and 76% yield, respectively, after purification by flash chromatography. Also in this case the cycloadducts were single regioisomers, to which the cis-fused structure was assigned on the basis of NMR evidences, analogy with the products of the 2-furylthiol series, and literature report[23] on a virtually identical system. Also in this case control of absolute stereochemistry was attempted. Oxidation of compound **20** to the corresponding sulphoxide was accomplished in fair yield by the usual metaperiodate oxidation: however, cycloaddition resulted only in extensive decomposition.[25] Next, two chiral racemic analogues of **20** were prepared in a very straightforward way by condensing **19** with nitromethane and propanal or 2-methylpropanal, in the presence of piperidine, to give nitrosulphides **24** and **25** in 78 and 80% yield,

Scheme 2



Reagents: a, $AcOCH_2CH_2NO_2$, EtONa; b, EtONa, $Br(CH_2)_3Br$; c, $NaNO_2$, DMF; d, p-ClC_6H_4NCO, TEA; e, CH_3NO_2, RCHO, Piperidine; f, $Br(CH_2)_2COOEt$, EtONa; g, $LiAlH_4$; h, t-$BuMe_2SiCl$, Imidazole; j, LDA, HMPA, MeI; k, $Bu_4N^+F^-$; l, MsCl, TEA; m, KI, $Bu_4N^+I^-$.

respectively.[26] However, their cycloaddition was totally non stereoselective, since compounds **26a,b** and **27a,b** were obtained in good yield (82 and 76%, respectively), both as 50:50 mixture of two diastereoisomers.[23] We then decided to investigate the reaction of a cycloaddend featuring an allylic stereocenter: starting from **19**, silyl derivatives **28** was prepared in three high yielding steps (71% overall yield). This compound was methylated (72% yield) and deprotected (91% yield), and the resulting alcohol converted into the nitrosulphide **29**, via the mesylate (76% yield) and the iodo derivative (87% yield), by the usual procedure (60% yield). Cycloaddition of **29** gave a 79% yield of a 66:34 mixture of two diastereoisomeric isoxazolines **30a** and **30b**, to which the indicated structures were assigned on the basis of NOE experiments.[27] The predominance of the isomer having the methyl group in an equatorial position can be rationalized on the basis of simple steric interaction considerations, and is in agreement with previous observations.[12]

The poor stereoselectivity observed for the reaction of **13, 14, 17, 24, 25,** and **29** clearly indicate that it would be very difficult to control the absolute stereochemistry of the cycloaddition by inserting a stereogenic center on the reagent. We therefore turned our attention to a different approach.

Diastereo- and enantioselective oxidation of cycloadducts 11, 12, 22, and 23.

We reasoned that the sulphur atom of our cycloadducts could represent a convenienc handle for obtaining these compounds in enantiomerically enriched form. Indeed, a number of enantioselective oxidations of sulphides has been reported,[28] and the rigid structure of our isoxazolines suggested the possibility of a highly stereodifferentiating process. This was confirmed by some preliminary experiments carried out on compound **11** and **12** (Table 1). The former, upon low temperature oxidation with m-chloroperbenzoic acid, gave sulphoxide **15a** as a single detectable isomer by ^{1}H NMR (70% yield), while from the latter sulphoxide **16a,b** was obtained in 85:15 diastereoisomeric ratio (76% yield). In both cases the predominant isomer obtained was the major products of the cycloaddition of **13** or **14**.[29] Oxidation of **22** and **23** proceeded in lower yield since the products (**31a,b** and **32a,b**, respectively) showed some tendency to decompose[23] (see below): this prevented a safe determination of the diastereoselectivity of the mCPBA oxidation.

Among the available reagents for enantioselective sulphide oxidation, we selected a modification of Sharpless's reagent,[30] that is known to secure good stereocontrol when the analogous mCPBA oxidation is also highly selective. The results are collected in Table 1. In kinetic resolution conditions (0.5 mol. equiv. of tBuOOH; 0.25 mol. equiv. of $Ti(OPr\text{-}i)_4$; 1.0 mol. equiv. of (+)-diethyl tartrate) sulphide **11** gave exclusively

Table 1. Stereoselective oxidation of **11**, **12**, **22**, and **23**.

Sulphide	Oxidant	Sulphoxide	Diastereoisomeric[a] **a:b** ratio	E.e.[b] %	$[\alpha]_D^{22}$ [c]
11	mCPBA	**15a,b**	⩾97: 3	-	-
12	mCPBA	**16a,b**	85:15	-	-
11	TBHP/Ti(OPr-i)$_4$/(+)DET	**15a,b**	⩾97: 3	85	-561.1
12	TBHP/Ti(OPr-i)$_4$/(+)DET	**16a,b**	⩾97: 3	95	-511.5
11[d]	TBHP/VO(acac)$_2$	**15a,b**	⩾97: 3	36	+233.1
12[d]	TBHP/VO(acac)$_2$	**16a,b**	⩾97: 3	43	+223.3
22	TBHP/Ti(OPr-i)$_4$/(+)DET	**31a,b**	80:20[e]	28	+185.3
23	TBHP/Ti(OPr-i)$_4$/(+)DET	**32a,b**	⩾97: 3	64	-151.6

[a]As determined by 300 MHz ^{1}H NMR spectroscopy. [b]As determined for **a** isomers by 300 MHz ^{1}H NMR spectroscopy in the presence of (-)-trifluoromethyl-9-anthrylcarbinol in conditions pre-established on racemic compound. [c]As determined for **a** isomers in $CHCl_3$ solution, c 0.5-1.0. [d]Sulphide recovered from the oxidation with TBHP/Ti(OPr-i)$_4$/(+)-DET. [e]**31b** had e.e. 35%.

sulphoxide (-)-**15a** in 60% yield based on the oxidant. The e.e. was determined as 85% by ^{1}H NMR spectroscopy in the presence of (-)-trifluoromethyl-9-anthrylcarbinol, in conditions pre-established on racemic **15a**. Oxidation of **12** afforded a single isomeric product (-)-**16a** (48% yield based on the oxidant), that was shown to be 95% enantiomerically pure by the above described technique. For sake of completeness, sulphides **11** and **12**, recovered from the kinetic resolution, were treated with tBuOOH/VO(acac)$_2$ to give sulphoxides (+)-**15a** (50% yield, 36% e.e.) and (+)-**16a** (36% yield, 43% e.e.), both as single diastereoisomers.[31] The oxidation of the cycloadducts of the 2-furylmethanethiol series was then examined. From compound **22** a 80:20 mixture[32] of **31a,b** was obtained in 48% yield (based on the oxidant) the major isomer, (+)-**31a**, being obtained 28% enantiomerically pure, as evaluated by the usual ^{1}H NMR technique. Compound **23** afforded a single isomeric sulphoxide (-)-**32a** (52% yield), the e.e. of which was determined as 64%.

The stereochemical outcome of the kinetic resolution experiments requires a few comments. The enantiomeric excesses observed with the 2-furylthiol derivatives were definitely higher than those obtained for the compounds of the 2-furylmethanethiol series: this is in line with a number of previous observations for similar reactions,[33] that always showed more stereoselective oxidations for sulphides with sterically well differentiated ligands. The greater difference in steric bulkiness of the substituent at sulphur in **11** and **12** than in **22** and **23** can account for this observation. Less evident are the reasons for the lower enantioselection of the oxidation of tetrahydrothiophene derivatives **11** and **22** with respect to that of thiopyran derivatives **12** and **23**. We do not have any reasonable explanation for that, and more experimental work is necessary to understand this result. A similar behaviour is not a common feature of literature reports.[30,33]

In conclusion we showed that intramolecular furan-nitrile oxide cycloadditions on 2-furylthiol- and 2-furylmethanethiol derivatives occur in a completely reigocontrolled fashion to give high yield of cis-fused products, that in principle are amenable to a number of synthetically useful transformations. Various attempts to control the absolute stereochemistry of the cycloaddition reaction by inserting a stereocenter in different locations on the chain connecting dipole and dipolarophile resulted in poor to fair stereocontrol. An alternative approach to enantiomerically enriched cycloadducts was established by a kinetic resolution process involving a diastereo- and enantioselective sulphide to sulphoxide oxidation.

Experimental.

^{1}H and ^{13}C NMR spectra were recorded with a Bruker WP 80 or a Varian XL 300 instrument on $CDCl_3$ solutions. Chemical shifts are in ppm downfield from TMS. 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 and Et_2O were distilled from $LiAlH_4$; HMPA, DMF and CH_2Cl_2 from CaH_2;benzene from sodium; Et_3N from KOH. All reactions employing anhydrous solvents were run under Argon.

General procedure for the synthesis of esters 2-5.

To a stirred solution of 2-furyllithium[17] (50 mmol) in THF (250 ml), sulphur (1.6 g, 50 mmol) was added portionwise at 0°C. The dark red solution was kept at 0°C for 1.5 h and then treated with ethyl ω-bromo alkanoate (45 mmol). The mixture was stirred at room

temperature overnight, and the reaction quenched by addition of water. Diethyl ether was then added; the organic phase washed twice with a 5% aqueous solution of sodium hydroxide, and then with brine. The products were isolated as pale yellow oils by flash chromatography with 90:10 hexanes:diethyl ether mixture as eluant.

Ethyl 3-(2-furylthio)propanoate 2 was obtained in 68% yield. Found: C, 54.06; H, 6.12. $C_9H_{12}O_3S$ requires: C, 53.98; H, 6.04. ^{1}H NMR: ∂ 6.31-7.46 (m, 3H); 4.09 (q, 2H); 2.93 (t, 2H); 2.56 (t, 2H); 1.21 (t, 3H).

Ethyl 4-(2-furylthio)butanoate 3 was obtained in 77% yield. Found: C, 55.93; H, 6.66. $C_{10}H_{14}O_3S$ requires: C, 56.05; H, 6.58. ^{1}H NMR: ∂ 6.22-7.40 (m, 3H); 4.04 (q, 2H); 2.73 (t, 2H); 2.35 (t, 2H); 1.80-2.05 (m, 2H); 1.15 (t, 3H).

Ethyl 5-(2-furylthio)pentanoate 4 was obtained in 75% yield. Found: C, 57.88; H, 7.00. $C_{11}H_{16}O_3S$ requires: C, 57.87; H, 7.06. ^{1}H NMR: ∂ 6.25-7.43 (m, 3H); 4.12 (q, 2H); 2.78 (t, 2H); 2.35 (t, 2H); 1.57-1.95 (m, 4H); 1.26 (t, 3H).

Ethyl 6-(2-furylthio)hexanoate 5 was obtained in 76% yield. Found: C, 59.18; H, 7.57. $C_{12}H_{18}O_3S$ requires: C, 59.48; H, 7.49. ^{1}H NMR: ∂ 6.30-7.46 (m, 3H); 4.10 (q, 2H); 2.73 (t, 2H); 2.27 (t, 2H); 1.37-1.71 (m, 6H); 1.21 (t, 3H).

General procedure for the synthesis of the tosylates.

To a suspension of $LiAlH_4$ (3 mol equiv) in diethyl ether (10 ml/mmol of ester) cooled at 0°C, a diethyl ether (5 ml/mmol of ester) solution of ester (20-30 mmol) was added dropwise. The reaction mixture was then warmed up to room temperature and refluxed for 15-30 min. After cooling at 0°C wet diethyl ether (ca. 100 ml), H_2O (1 ml/g of $LiAlH_4$), 15% aqueous NaOH (1 ml/g of $LiAlH_4$), H_2O (3 ml/g of $LiAlH_4$) were added in this order. The precipitate was filtered and the solvent was evaporated to give the crude alcohol in virtually quantitative yield and in very high purity (by ^{1}H NMR). To the alcohol, dissolved in dry CH_2Cl_2 (10 ml/mmol), Et_3N (1.2 mol equiv) and tosyl chloride (1.0 mol equiv) were added in this order. After overnight stirring at room temperature, the reaction mixture was washed with H_2O and the organic phase separated, dried, and concentrated to give the crude products that were isolated as oils by flash chromatography with a 70:30 hexanes:diethyl ether mixture as eluant.

4-Methylphenylsulphonic acid 3-(2-furylthio)propylester was obtained in 82% yield. Found: C, 54.01; H, 5.15. $C_{14}H_{16}O_4S_2$ requires: C, 53.83; H, 5.16. ^{1}H NMR: ∂ 6.29-7.81 (m, 7H); 4.13 (t, 2H); 2.71 (t, 2H); 2.43 (s, 3H); 1.87 (m, 2H).

4-Methylphenylsulphonic acid 4-(2-furylthio)butylester was obtained in 80% yield. Found: C, 55.11; H, 5.61. $C_{15}H_{18}O_4S_2$ requires: C, 55.19; H, 5.56. ^{1}H NMR: ∂ 6.29-7.82 (m, 7H); 4.05 (t, 2H); 2.74 (t, 2H); 2.47 (s, 3H); 1.55-1.92 (m, 4H).

4-Methylphenylsulphonic acid 5-(2-furylthio)pentylester was obtained in 82% yield. Found: C, 56.30; H, 5.87. $C_{16}H_{20}O_4S_2$ requires: C, 56.45; H, 5.92. ^{1}H NMR ∂ : 6.30-7.81 (m, 7H); 3.99 (t, 2H); 2.66 (t, 2H); 2.43 (s, 3H); 1.20-1.77 (m, 6H).

4-Methylphenylsulphonic acid 6-(2-furylthio)hexylester was obtained in 83% yield. Found: C, 57.70; H, 6.18. $C_{17}H_{22}O_4S_2$ requires: C, 57.60; H, 6.26. ^{1}H NMR: ∂ 6.25-7.78 (m, 7H); 3.98 (t, 2H); 2.68 (t, 2H); 2.41 (s, 3H); 1.20-1.65 (m, 8H).

General procedure for the synthesis of the nitrosulphides 6-9.

Synthesis of the iodides. To a solution of the tosylate (20 mmol), $Bu_4N^+I^-$ (1 mol equiv) and K_2CO_3 (1.2 mol equiv) in benzene (100 ml), a solution of KI (3 mol equiv) in water (50 ml) was added. The two-phase mixture was vigorously stirred at 60°C overnight. Diethyl ether was added, the phases were separated; the organic layer was washed with an aqueous solution of sodium thiosulphate, and then with water. Evaporation of the solvent gave the crude iodides that were purified by short path column chromatography with a 80:20 hexanes:diethyl ether mixture as eluant. The products were pale yellow mobile oils, that were used without further purification.

Synthesis of the nitrosulphides. Method A. To a solution of the iodide (1-3 mmol) in dry diethyl ether (5 ml/mmol), $AgNO_2$ (3 mol equiv) was added portionwise over a 2h period. The resulting suspension was stirred for 24-48 h at RT, then was filtered through celite and the filtrate concentrated and purified by flash chromatography with a 75:25 hexanes:diethyl ether mixture as eluant. Yields were 48-56% in yellow oily products. **Method B.** The iodide (1-3 mmol) was added to a solution of $NaNO_2$ (2 mol equiv) in DMF (2 ml/mmol), and the mixture stirred at RT for 24-48 h. Water was then added and the product was extracted several times with diethyl ether. The crude products were purified by flash chromatography as above. Yield were 58-62%.

3-(2-Furylthio)-1-nitropropane 6. Found: C, 44.99; H, 4.79; N, 7.53. $C_7H_9NO_3S$ requires:C, 44.91; H, 4.85; N, 7.48. ^{1}H NMR: ∂ 6.34-7.51 (m, 3H); 4.70 (t, 2H); 2.81 (t, 2H); 2.07-2.41 (m, 2H).

4-(2-Furylthio)-1-nitrobutane 7. Found: C, 47.85; H, 5.50; N, 7.00. $C_8H_{11}NO_3S$ requires: C, 47.75; H, 5.51; N, 6.96. ^{1}H NMR: ∂ 6.31-7.46 (m, 3H); 4.30 (t, 2H); 2.81 (t, 2H); 1.43-2.33 (m, 4H).

5-(2-Furylthio)-1-nitropentane 8. Found: C, 50.15; H, 6.01; N, 6.51. $C_9H_{13}NO_3S$ requires: C, 50.22; H, 6.09; N, 6.51. ^{1}H NMR: ∂ 6.31-7.48 (m, 3H); 4.36 (t, 2H); 2.73 (t, 2H); 1.17-2.07 (m, 6H).

6-(2-Furylthio)-1-nitrohexane 9. Found: C, 52.42; H, 6.61; N, 6.04. $C_{10}H_{15}NO_3S$ requires: C, 52.38; H, 6.59; N, 6.11. ^{1}H NMR: ∂ 6.31-7.47 (m, 3H); 4.34 (t, 2H); 2.71 (t, 2H);

1.18-2.14 (m, 8H).

2-(2-Furylthio)-1-nitroethane 10. To a solution of **1** (2 mmol) in THF (10 ml) cooled at 0°C, 2-acetoxy-1-nitroethane (0.266 g, 2 mmol) was added dropwise. The mixture was stirred at 0°C for 3h; the reaction was then quenched by addition of saturated NH_4Cl and the organic phase was separated. The products was purified by flash chromatography with a 70:30 hexanes:diethyl ether mixture as eluant, to give a yellow oil in 57% yield. Found: C, 41.51; H, 4.13; N, 8.02. $C_6H_7NO_3S$ requires: C, 41.61; H, 4.07; N, 8.09. ^1H NMR: ∂ 6.36-7.53 (m, 3H); 4.54 (t, 2H); 3.24 (t, 2H).

3-(2-Furylthio)-2-methyl-1-nitropropane 17 was prepared in three steps from **1** by alkylation with 1-bromo-3-chloro-2-methyl propane (70% yield, for experimental conditions see the synthesis of esters **2-5**), chlorine-iodine exchange (79% yield, for experimental conditions see the synthesis of the iodides), and iodine-nitro exchange (60% yield, method B). Found: C, 47.83; H, 5.57; N, 7.00. $C_8H_{11}NO_3S$ requires: C, 47.75; H, 5.51; N, 6.96. ^1H NMR: ∂ 6.25-7.41 (m, 3H); 4.15-4.67 (m, 2H); 2.68-2.78 (m, 2H); 2.32-2.52 (m, 1H); 1.12 (d, 3H).

Synthesis of nitrosulphoxides 13 and 14. To a stirred solution of sulphide (2 mmol) in MeOH (10 ml) cooled at 0°C, $NaIO_4$ (0.428 g, 2 mmol) in H_2O (3 ml) was added dropwise and the mixture stirred at RT overnight. Usual work-up gave the crude products that were purified by flash chromatography with a 98:2 diethyl ether:methanol mixture as eluant.

3-(2-Furylsulphinyl)-1-nitropropane 13 was obtained in 82% yield as an oil. Found: C, 41.44; H, 4.53; N, 6.96. $C_7H_9NO_4S$ requires: C, 41.37; H, 4.46; N, 6.89. ^1H NMR: ∂ 6.41-7.60 (m, 3H); 4.41-4.60 (m, 2H); 2.92-3.45 (m, 2H); 2.30-2.56 (m, 2H).

4-(2-Furylsulphinyl)-1-nitrobutane 14 was obtained in 87% yield as on oil. Found: C, 44.40; H, 5.12; N, 6.37. $C_8H_{11}NO_4S$ requires: C, 44.23; H, 5.10; N, 6.45. ^1H NMR: ∂ 6.55-7.69 (m, 3H); 4.43-4.63 (m, 2H); 3.06-3.34 (m, 2H); 1.80-2.25 (m, 4H).

2-[(Furylmethyl)thio]-1-nitroethane 20. To a solution of sodium etnoxide (2 mmol) in EtOH (10 ml), compound **19** (0.228 g, 2 mmol) was added dropwise at 0°C. After 10 min stirring at 0°C, 2-acetoxy-1-nitroethane (0.266 g, 2 mmol) was added dropwise. Work-up as described for compound **10** gave the only product in 85% yield. Found: C, 45.01; H, 4.76; N, 7.53. $C_7H_9NO_3S$ requires: C, 44.91; H, 4.85; N, 7.48. ^1H NMR: ∂ 6.25-7.37 (m, 3H); 4.45 (t, 2H); 3.83 (s, 2H); 3.15 (t, 2H).

3-[(2-Furylmethyl)thio]-1-nitropropane 21 was obtained , as an oil, in two steps from the sodium salt of **19** by alkylation with 1,3-dibromopropane (73% yield, see above for the experimental conditions) and bromine-nitro exchange (61%, method B). Found: C, 47.87; H, 5.57; N, 6.87. $C_8H_{11}NO_3S$ requires: C, 47.75; H, 5.51; N, 6.96. ^1H NMR: ∂ 6.15-

-7.39 (m, 3H); 4.48 (t, 2H); 3.83 (s, 2H); 2.05-2.80 (m, 4H).

2-[(2-Furylmethyl)thio]-1-nitrobutane 24 was prepared as described[23] for the synthesis of **25** in 78% yield. Found: C, 50.09; H, 6.01; N, 6.58. $C_9H_{13}NO_3S$ requires: C, 50.22; H, 6.09; N, 6.51. ^{1}H NMR: ∂ 6.15-7.32 (m, 3H); 4.37 (d, 2H); 3.71 (s, 2H); 3.05-3.38 (m, 1H); 1.40-1.82 (m, 2H), 0.95 (t, 3H).

3-[(2-Furylmethyl)thio]-1-[[(1,1-dimethylethyl)dimethylsilyl]oxy]propane 28 was prepared in three steps from the sodium salt of **19** *via* alkylation with ethyl 3-bromopropanoate (83%), reduction with $LiAlH_4$ (100%), and standard silylation with TBDMSCl and imidazole in DMF (85%). Found: C, 58.78; H, 9.23. $C_{14}H_{26}O_2SSi$ requires: C, 58.69; H, 9.15. ^{1}H NMR: ∂ 6.25-7.33 (m, 3H); 3.61-3.84 (m, 4H); 2.46-2.73 (m, 2H); 1.70-1.96 (m, 2H); 0.95 (s, 9H); 0.05 (s, 6H).

3-[[1-(2-Furyl)ethyl]-1-thio]-1-nitropropane 29 was prepared in five steps from **28**. To a solution of LDA (1.7 mmol) in THF (10 ml) cooled at -78°C, sulphide **28** (0.46 g, 1.61 mmol) was added dropwise. After 1h stirring at -78°C, HMPA (0.8 ml) was added, followed, after 10 min., by MeI (0.200 ml, 3.2 mmol). The reaction was allowed to warm-up to room temperature and stirred overnight. Usual work-up gave a mixture of product (72% by NMR) and unreacted starting material, that were not separable by flash chromatography. The mixture was deprotected by $Bu_4N^+F^-$ $3H_2O$ in THF in the standard conditions to give 91% yield of a mixture of the two alcohols. These were converted into the mesylates (CH_3SO_2Cl, Et_2O, Et_3N, 0°C, 30 min, 76%) that were stable enough to allow separation by flash chromatography (with a 50:50 hexanes: diethyl ether mixture as eluant). The methylated product was converted into the iodide (87%, see above), from which **29** was obtained in 60% yield as an oil in the usual conditions (method B). Found: C, 50.36; H, 6.03; N, 6.58. $C_9H_{13}NO_3S$ requires: C, 50.22; H, 6.09; N, 6.51. ^{1}H NMR: ∂ 6.15-7.32 (m, 3H); 4.41 (t, 2H); 4.00 (q, 1H); 2.45-2.67 (t, 2H); 1.90-2.30 (m, 2H); 1.60 (d, 3H).

General procedure for the intramolecular cycloaddition. A stirred solution of nitrosulphide (1-3 mmol), 4-chlorophenylisocyanate (3 mol equiv), and catalytic triethylamine in benzene (50 ml/mmol) was refluxed 24 h under nitrogen. The urea was filtered, benzene was evaporated and the residue purified by flash chromatography with the indicated mixtures as eluants to give the cycloadducts. Relevant NMR data are collected in Tables 2 and 3.

Compound 11, m.p. 76-77°C, was obtained in 79% yield with a 85:15 hexanes:diethyl ether mixture as eluant. Found: C, 49.77; H, 4.24; N, 8.31. $C_7H_7NO_2S$ requires: C, 49.69; H, 4.17; N, 8.28.

Compound 12, n_D^{25} 1.5578, was obtained in 75% yield with a 80:20 hexanes:diethyl ether

Table 2. Relevant ^{1}H NMR data of cycloadducts **11, 12, 15, 16, 18, 22, 23, 26, 30**[a] (see Schemes for numbering).

Compound	H-C_1	H-C_2	H-C_3
11	6.61	5.43	5.80
12	6.54	5.26	5.50
15a	6.63	5.67	6.00
15b	6.86	5.56	6.05
16a	6.51	5.56	5.96
16b	6.76	5.46	6.12
18a	6.58	5.36	5.76
18b	6.61	5.37	5.73
22	6.66	5.35	5.65
23	6.58	5.38	5.38
26a	6.63	5.30	5.60
26b	6.65	5.33	5.60
30a	6.63	5.28	5.43
30b	6.56	5.25	5.50
31a	6.59	5.44	5.84
31b	6.72	5.42	5.75
32a	6.61	5.38	5.68

[a] Typical $J_{1,2}$ and $J_{2,3}$ values were 2.5-3.0 Hz for all cycloadducts. $J_{1,3}$ was less than 1.0 Hz.

mixture as eluant. Found: C, 52.49; H, 5.00; N, 7.59. $C_8H_9NO_2S$ requires: C, 52.44; H, 4.95; N, 7.64.

Compounds 15a,b were obtained in a 75:25 ratio in 63% yield with a 97:3 dichloromethane:methanol mixture as eluant. **15a** had m.p. 150-151°C (dec). **15b** was obtained impure of **15a**. Found: C, 45.31; H, 3.86; N, 7.66. $C_7H_7NO_3S$ requires: C, 45.40; H, 3.81; N, 7.56.

Compounds 16a,b were obtained in a 70:30 ratio in 60% yield with a 94:6 diethyl ether:methanol mixture as eluant. **16a** had m.p. 128-129°C; **16b** had m.p. 120-121°C. Found: C, 48.11; H, 4.46; N, 7.11. $C_8H_9NO_3S$ requires: C, 48.23; H, 4.55; N, 7.03.

Compounds 18a,b, n_D^{25} 1.5561, were obtained in a 66:34 ratio in 73% yield with a 80:20 hexanes:diethyl ether mixture as eluant. Found: C, 52.47; H, 5.04; N, 7.58. $C_8H_9NO_2S$ requires: C, 52.44; H, 4.95, N, 7.64.

Compound 22, m.p. 76-77°C, was obtained in 77% yield with a 70:30 hexanes:diethyl ether mixture as eluant. Found: C, 49.78; H, 4.23; N, 8.36. $C_7H_7NO_2S$ requires: C, 49.69; H, 4.17; N, 8.28.

Compound 23, m.p. 102-103°C, was obtained in 76% yield with a 75:25 hexanes:diethyl ether mixture as eluant. Found: C, 52.31; H, 4.86; N, 7.69. $C_8H_9NO_2S$ requires: C, 52.44; H, 4.95; N, 7.64.

Compounds 26a,b were obtained in 78% yield as a 50:50 mixture of diastereoisomers with a 80:20 hexanes:diethyl ether mixture as eluant. The two products were not separated and appeared as a waxeous solid. Found: C, 54.69; H, 5.70; N, 7.17; $C_9H_{11}NO_2S$ requires: C, 54.80; H, 5.62; N, 7.10.

Compounds 27a,b were obtained as 50:50 mixture of diastereoisomers in 80% yield with a 70:30 hexanes:diethyl ether mixture as eluant. Spectral data were in agreement with those reported.[23]

Compounds 30a,b were obtained as a 66:34 mixture of diastereoisomers in 79% yield with a 70:30 hexanes:diethyl ether mixture as eluant. The two products were not separated and appeared as a thick oil that solidifies upon standing in the freezer. Found: C, 54.71; H, 5.68; N, 7.14. $C_9H_{11}NO_2S$ requires: C, 54.80; N, 5.62; N, 7.10.

General procedure for the mCPBA oxidation. A stirred solution of sulphide (0.05 mmol) in CH_2Cl_2 (5 ml) cooled at -78°C, 80% mCPBA (0.215 g, 0.5 mmol) was added in one portion. The reaction was warmed-up to 0°C and stirred at this temperature for 5h. A saturated aqueous solution of $NaHCO_3$ was then added, and the organic layer was separated, dried, and concentrated to give the crude product that was purified by flash chromatography. From compound **11**, sulphoxide **15a** was obtained as a single isomer in 70% yield. From compound **12**, a 85:15 mixture of **16a,b** was obtained in 76% yield. M.p.'s were in agreement with those reported above.

General procedure for the kinetic resolution of 11, 12, 22, 23 via oxidation. To a stirred solution of freshly distilled (+)-diethyl tartrate (0.260 ml, 1.5 mmol) in dry dichloroethane (2 ml), $Ti(OPri)_4$ (0.110 ml, 0.38 mmol) in dichloroethane (2 ml) was added at RT under vigorous stirring. The resulting yellow solution was stirred at RT for

Table 3. Relevant ^{13}C NMR data for cycloadducts **11, 12, 18, 22, 23, 26, 30** (see Schemes for numbering).

Compound	C-1	C-2	C-3	C-4	C-N
11	149.6	102.1	91.5	110.8	161.0
12	148.9	102.1	90.4	99.6	153.2
18a	149.6	102.1	92.5	110.7	163.9
18b	149.9	101.7	92.5	111.3	164.0
22	149.5	101.5	89.5	106.2	160.3
23	148.9	101.2	86.6	95.3	153.7
26a	149.4	101.2	89.6	106.7	162.4
26b	149.4	101.5	90.3	107.2	162.3
30a[a]	150.1	101.9	87.0	98.4	154.4
30b[a]	148.7	101.7	85.9	99.4	152.8

[a] In DMSO.

5 min. and then was cooled down at -20°C. After 5 min. at -20°C, TBHP (0.079 ml, 0.75 mmol) was added, followed after additional 5 min by a dichloroethane (3 ml) solution of sulphide (1.5 mmol). The yellow solution was stirred at -20°C for 17-20 h, quenched by addition of H_2O (5 ml), warmed-up to RT, and stirred for 1h. The resulting mixture was filtered through celite, and the filtrate extracted with $CHCl_3$. The organic layers were then washed with 10% aqueous sodium metabisulphite, 5% aqueous sodium hydroxide, and brine. Evaporation of the solvent gave a yellow oil that was purified by flash chromatography to give the unreacted sulphide and the sulphoxide. Yields, diastereoisomeric ratios, and enantiomeric excesses were mentioned in the text, optical rotations were reported in the Table 1.

Compound (+)-31a, e.e. 28%, had m.p. 122-124°C. Found: C, 45.48; H, 3.90; N, 7.55. $C_7H_7NO_3S$ requires: C, 45.40; H, 3.81; N, 7.56. **31b** was obtained impure of **31a**.

Compound (-)-32a, e.e. 64%, had m.p. 152-154°C. Found: C, 48.43; H, 4.63; N, 7.09. $C_8H_9NO_3S$ requires: C, 48.23; H, 4.55; N, 7.03.

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32. As mentioned in the text compound **31** and **32** showed some instability, especially in the presence of base. For instance basic (5% aqueous sodium hydroxide solution) work-up of the oxidation reaction of **22** improved the diastereoisomeric ratio of **31a,b** to 90:10, by preferentially decomposing the minor diastereoisomer **31b**.

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