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Stereocontrol in the Intramolecular Nitrone Cycloaddition to Vinyl Sulphur Derivatives.

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Abstract. The intramolecular cycloaddition to vinyl sulphur derivatives of a series of nitrones featuring an alkyl or alkoxy substituted α-stereocenter on the tether connecting dipole and dipolarophile occurs in a completely stereoselective fashion to give 3',3-anti configurated products. The synthetic potentialities of this reaction is illustrated by the synthesis of a precursor of (d)-biotin.

Nitrone cycloaddition to alkenes is a powerful and versatile method for the synthesis of a variety of cyclic and acyclic complex molecules.[1] Stereoselective versions of this process[2] provide valuable synthetic shortcuts en route to the stereocontrolled assembly of a series of contiguous stereocenters within a polyfunctional carbon framework.

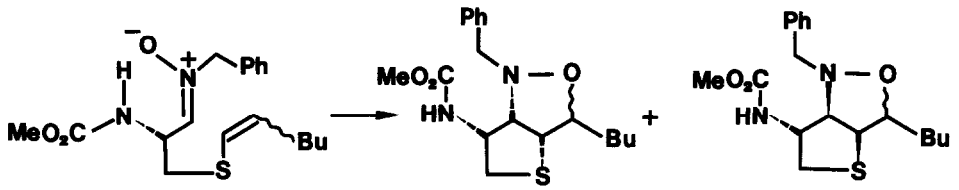
While intermolecular reactions often occur with unsatisfactory degrees of stereoselection,[2] intramolecular nitrone cycloaddition (INC) generally afford good results, since the formation of two fused[1,3] or bridged[1,3] cyclic systems acts as an additional element of stereocontrol.

In these INC reactions the position of the inducing stereocenter(s) is very important in determining the stereochemical outcome:[2] of the possible locations, i.e. inside the tether connecting dipole and dipolarophile, on the nitrone nitrogen substituent, and in the allylic position, the first choice secures best stereoselectivities. In particular a single stereocenter in the α-position to the nitrone moiety can completely control the formation of up to three new contiguous stereocenters in an INC reaction to both electron rich[2,4,5] and electron poor alkenes,[2,7] the 3',3-anti configurated isoxazolidines (see below for numbering) being the only product observed.

A remarkable exception to this trend is represented by the reaction reported in Eq. 1. In the total synthesis of (d)-biotin, Baggiolini and coworkers[8] observed that nitrone **1** undergoes a poorly stereoselective cycloaddition to give a mixture of **2** and **3**.

The preferential formation of the 3',3-syn product **2a** was rationalized by hydrogen bonding between the amide proton and the nitrone oxygen that inverts the usual sense of

Equation 1.



1 2 3

stereoselection.[4-7]

In the course of our studies on stereoselective intramolecular nitrone and nitrileoxide cycloadditions[2] we decided to investigate the stereocontrol of other INC to vinyl sulphur derivatives. This manuscript reports our results in this field.

A racemic α-alkyl substituted nitrone analogous to **1** was prepared according to Scheme 1.

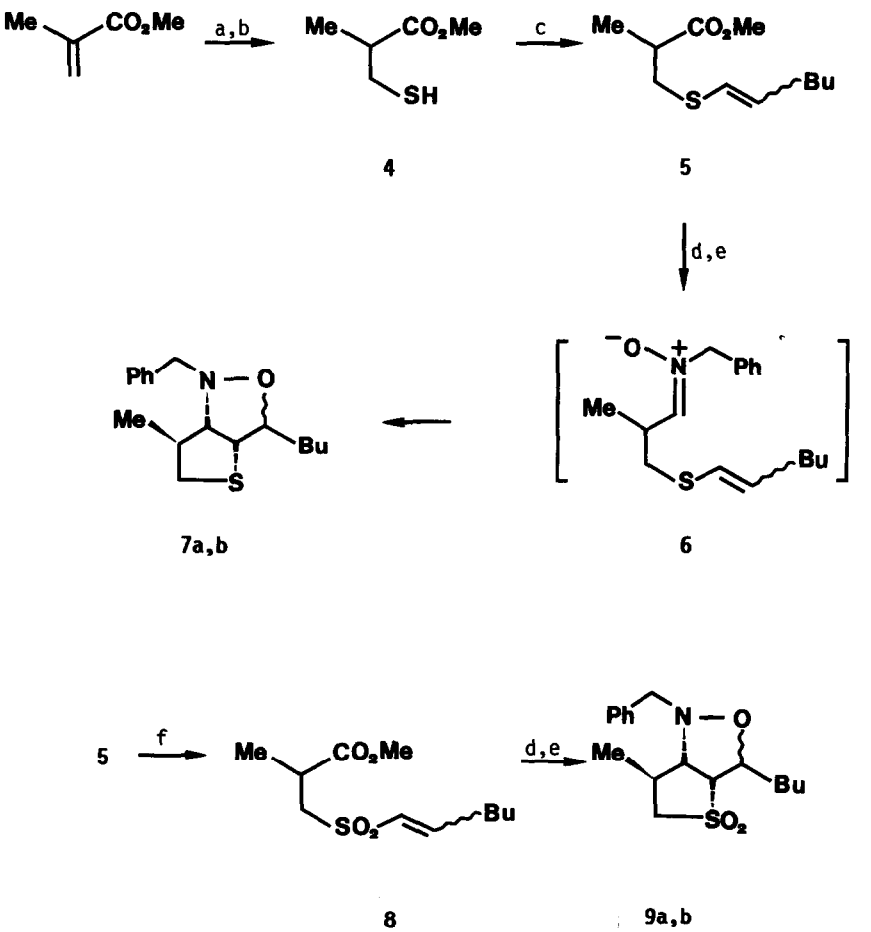
Addition of thiolacetic acid to methylmercaptacrylate and selective hydrolysis[9] gave ester **4**. AIBN promoted reaction of **4** with 1-hexyne[10] gave a roughly 1:1 (E)-(Z) mixture of sulphide **5**.

Reduction to the corresponding aldehyde and reaction with N-benzylhydroxylamine afforded via nitrone **6** (not isolated) isoxazolidines **7a,b**, that feature the same 3',3-anti-3,4-syn stereochemistry and are ca. 1:1 epimers at C-5, the configuration at this center depending on that of the alkene (see below for configurational assignment). When the reaction sequence was repeated on the corresponding sulphone **8**, obtained from **5**, the stereochemical result was the same, **9a,b** being obtained only in the 3',3-anti-3,4-syn configuration.

The synthetic route to an α-alkoxy substituted nitrone corresponding to **1** and **6** is outlined in Scheme 2. Starting from racemic thioglycerol, 1-hexyne addition to give **10** and standard functional group manipulation afforded alcohol **15**.[11]

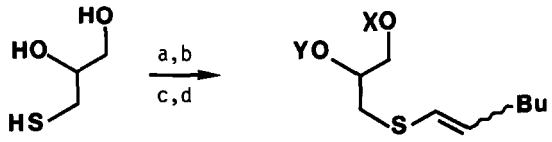
The roughly 1:1 mixture of (E) and (Z) sulphides was converted by a Moffatt oxidation to the aldehyde. Reaction with N-benzylhydroxylamine produced nitrone **17** that was not isolated but directly cyclized to 3',3-anti-3,4-syn isoxazolidines **18a,b**, epimers at C-5.[12]

Scheme 1.

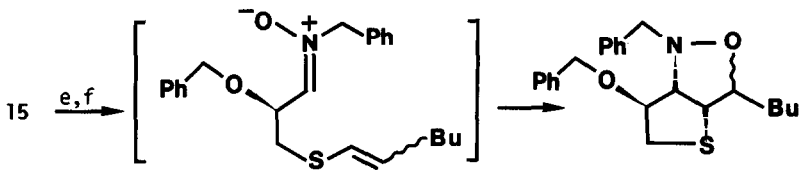


Reagents: a, AcSH, TEA; b, MeONa; c, 1-hexyne, AIBN; d, DIBAL-H; e, N-benzylhydroxylamine; f, MCPBA. For **7a,b** and **9a,b** only one configuration at C-3', C-3, and C-4 is indicated for simplicity.

Scheme 2.



10 X = Y = H
11 X = $SiMe_2Bu$-t; Y = H
12 X = H; Y = $SiMe_2Bu$-t
13 X = $SiMe_2Bu$-t; Y = $PhCH_2$
14 X = $PhCH_2$; Y = $SiMe_2Bu$-t
15 X = H; Y = $PhCH_2$
16 X = $PhCH_2$; Y = H

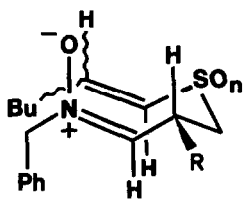


17 **18a,b**

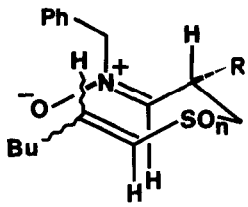
Reagents: a, 1-hexyne, AIBN; b, Bu-tMe_2SiCl, imidazole; c, benzylbromide, $Bu_4N^+I^-$, NaH; d, $Bu_4N^+F^-3H_2O$; e, DCC, DMSO, Py, TFA; f, N-benzylhydroxylamine. For compound **18a,b** only one configuration at C-3', C-3, and C-4 is indicated for simplicity.

The configurational assignment to **7a,b**, **9a,b**, and **18a,b** was based or ^1H and ^{13}C NMR spectroscopy (Table 1) and comparison with literature data for similar systems (see below).[2,6-8] The exclusive formation of 3',3-anti products in these INC reactions can be tentatively rationalized,[7] either by a transition structure such as **19** or **20**. In both the R group occupies a pseudoequatorial position in order to minimized 1,3-allyl-type interactions with the substituents of the nitrone nitrogen.[13,14]

Having in hand a totally stereoselective cycloaddition we turned our attention to a possible synthetic application. A synthesis of (d)-biotin appeared as a reasonable goal since this compound is still the target of considerable synthetic effort (Scheme 3).[15]



19



20

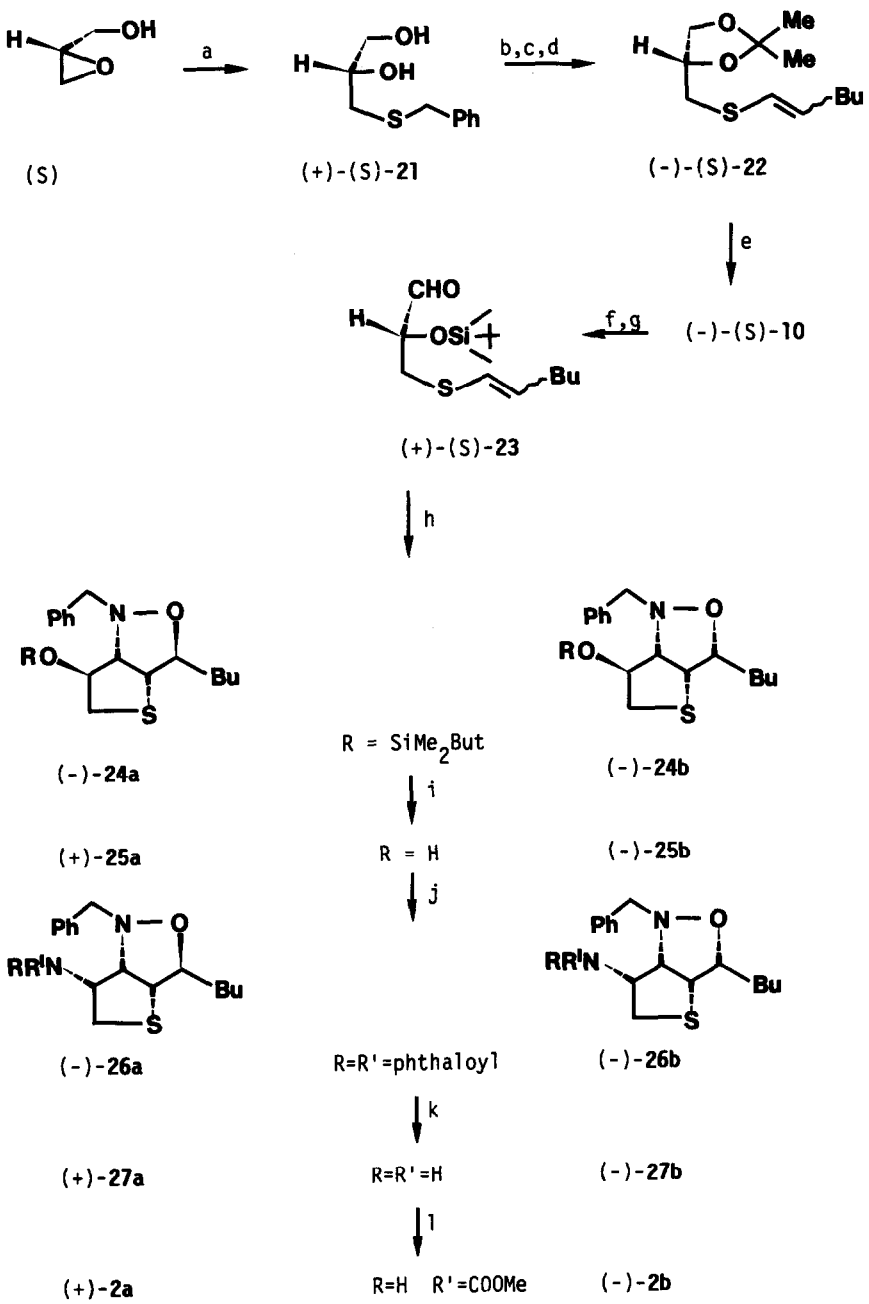
R = Me n = 0

R = Me n = 2

R = OCH_2Ph n = 0

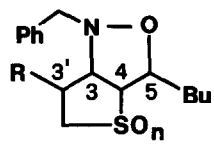
Titanium isopropoxide promoted[16] opening of commercially available (S)-glycidol gave compound (S)-**21** that was converted into (S)-**22** by the reaction sequence indicated in Scheme 4. Its enantiomeric purity was determined to be $\geqslant$95% by ^1H NMR spectroscopy in the presence of $Eu(hfc)_3$ in conditions pre-established on racemic **22** (prepared by ketalization of racemic **10**). Deprotonation of the diol function gave (S)-**10**, from which aldehyde (S)-**23** was obtained by silylation to (+)-(S)-**12** and Moffatt oxidation. Reaction with N-benzylhydroxylamine and cycloaddition afforded enantio- and diastereoisomerically pure **24a,b**. These two epimers at C-5 were separated by flash chromatography in order to better check the stereochemical consequences of the following synthetic steps. Thus, **24a** and **24b** were transformed into amines **27a** and **27b**, respectively, by a standard Mitsunobu protocol,[17] that occurred with complete inversion of configuration for isoxazolidine **27b**, and with 95% of inversion for isoxazolidine **27a**. Finally, reaction of **27a** and **27b** with methylchloroformate in acetone in the presence of potassium carbonate afforded the two epimers **2a** and **2b**,[18] advanced precursors of (d)-biotin.[8,10]

Scheme 3.



Reagents: a, $PhCH_2SH$, $Ti(OPri)_4$; b, DMP, PTS; c, Na, NH_3; d, 1-hexyne, AIBN; e, MeOH, PTS; f, TBDMSCl, imidazole; g, DCC, DMSO, Py, TFA; h, $PhCH_2NHOH$; i, $TBAF.3H_2O$; j, DEAD, phthalimide, Ph_3P; K, NH_2-NH_2; l, ClCOOMe, K_2CO_3.

Table 1. Relevant NMR data for isoxazolidines **7, 9, 18, 24, 25, 26, 27, 2.**



	C-3'	C-3	C-4	C-5	HC-3'	HC-3	HC-4	HC-5
7a	41.4	82.2	58.0	87.2	2.12	3.13	3.55	3.84
7b	43.8	79.5	56.2	80.8	2.24	3.38	4.21	4.32
9a	31.6	76.2	70.7	79.5	2.21	3.38	3.48	4.42
9b	35.5	74.9	67.9	80.5	2.46	3.51	3.97	4.58
18a	84.3	80.4	57.8	86.5	3.74	3.58	3.70	3.83
18b	85.9	77.7	56.7	79.5	3.94	3.80	4.28	4.33
24a	77.6	82.6	57.5	87.5	4.09	3.38	3.69	3.85
24b	79.2	79.5	56.7	80.4	4.11	3.57	4.24	4.31
25a	76.2	81.6	56.9	86.1	3.90	3.43	3.57	3.78
25b	79.1	78.3	56.1	79.4	4.20	3.71	4.17	4.31
26a	56.0	74.5	63.0	86.9	4.68	4.42	3.89	4.03
26b	58.6	71.6	53.1	80.2	4.76	4.44	4.34	4.44
27b	60.5	79.5	55.9	80.9	3.42	3.53	4.20	4.30
2a	58.2	80.6	57.0	86.0	4.23	3.45	3.51	3.78
2b	60.5	78.7	56.9	79.6	4.30	3.79	4.12	4.26

[a] Typical J values for **a** isomers: J_{4-5} = 6.5-7.6 Hz; J_{3-4} = 7.0-8.0 Hz; $J_{3-3'}$ = 1.0--2.3 Hz. For **b** isomers: J_{4-5} = 4.3-6.0 Hz; J_{3-4} = 6.0-7.0 Hz; $J_{3-3'}$ = 2.9-5.3 Hz.

Stereochemical assignments. A general trend in the chemical shift values of relevant signals (Table 1) for the cycloadducts **7, 9, 18, 24-27** allows to distinguish between **a**

and **b** isomers. In the **b** isomers the signals of HC-3', HC-3, HC-4, HC-5, and C-3' resonate at lower field and those of C-3, C-4, and C-5 at higher field with respect to those of the **a** isomers, with the only exception of C-5 in compound **9**. The C-4/C-5 anti configuration was assigned to **a** isomers (and hence the syn one to **b** isomers) by analogy with the attribution to similar system:[2,6,7] the lower chemical shift values of C-4 and C-5 observed for **b** isomers and n.O.e. data are in agreement with this assignment.

The relative configuration at C-3/C-4 can be assigned as syn in all the cycloadducts, in agreement with a number of previous observations for similar system.[1,3] N.O.e. experiments support this assignment: 7-10% enhancements have been observed for HC-4 upon irradiation of HC-3 in cycloadducts **7, 9, 24,** and **26.**

The determination of the relative stereochemistry at C-3'/C-3 resided on n.O.e. experiments, that were found to be more reliable than coupling constant values. In the case of compounds **7a** and **7b** a 6% enhancement of HC-3 was observed upon irradiation of the methyl group at C-3'. Irradiation of HC-3 gave a 5% enhancement of the C-3' methyl group in sulphones **9a** and **9b**; finally a 3% enhancement was observed for the signal of a methyl of the silyloxy group of **24b** upon irradiation of HC-4. Therefore on the basis of these data and in agreement with a variety of previous observations[2,6,7] the C-3'/C-3 anti configuration was assigned to cycloadducts **7, 9,** and **24,** and by analogy to **18** and **25.**

In the case of the phthalimide derivative **26a** it was possible to observe both enhancements of HC-3' upon irradiation of HC-3 (6%) and of HC-3 upon irradiation of HC-3' (7%), thus indicating that the Mitsunobu reaction occurred, indeed with inversion at C-3' to give C-3'/C-3 syn configurated products. NOESY experiments showed the same trend for **26b.**

Experimental.

^{1}H and ^{13}C NMR spectra were obtained on a Varian EM 390 and a Varian XL-300 spectrometer in $CDCl_3$ as solvent. Optical rotations were measured in $CHCl_3$ as solvent on a Perkin-Elmer 241 polarimeter. Elemental analyses were performed with a Perkin-Elmer 240 instrument. Silica gel was used for analytical and flash chromatography. Organic extracts were dried over Na_2SO_4 and filtered before removal of the solvent under vacuum . Reactions employing dry solvents were run under Argon. Relevant ^{1}H and ^{13}C NMR data for isoxazolidines are collected in Table 1.

Synthesis of ester **4**. A mixture of methylmethacrylate (1.0 mL, 9.4 mmol), thiolacetic acid (0.671 mL, 9.4 mmol), and triethylamine (1 drop) was stirred at 45°C for 24 h under Argon. Low boiling materials were evaporated under vacuum and the residue was filtered through a short pad of silica gel with a 9:1 hexanes:diethylether mixture as eluant. The crude product (5 mmol), satisfactorily pure by ^{1}H NMR, was treated with 1 mol equiv of sodium methoxide in methanol (5 mL) at room temperature for 15 min. Acetic acid was then added to reach pH 5 and the solvent was evaporated. The residue was taken up in water and extracted with diethylether. Evaporation of the solvent gave **4** in 52% yield, b.p.$_{14}$ 63-64°C (lit.[19] b.p.$_{14}$ 63.5-64°C).

Synthesis of sulphide **5**. A mixture of **4** (6.75 p., 50 mmol), 1-hexyne (3.96 mL, 34.5 mmol), and AIBN (0.05 g) in dry THF (50 mL) was refluxed for 48 h. Evaporation of the solvent and flash chromatography with a 95:5 hexanes:diethylether mixture as eluant gave **5** (4.48 g, 60% yield) as an oil. Found: C% 60.91; H% 9.29. $C_{11}H_{20}O_2S$ requires: C% 61.07; H% 9.32. ^{1}H NMR: δ 5.50-6.05 (m, 2H, CH=CH); 3.85 (s, 3H, OMe); 2.65-3.15 (m, 3H, CH and CH_2S); 2.10-2.40 (m, 2H, CH_2-C=); 1.30-1.70 (m, 7H, CH_2-CH_2 and Me-CH); 1.00 (bt, 3H, Me-CH_2).

Synthesis of isoxazolidines **7a,b**. Ester **5** (1.08 g, 5 mmol) was reduced to the corresponding aldehyde with diisobutyl aluminum hydride (1 M solution in hexane, 5 mL) in dry CH_2Cl_2 (15 mL) at -78°C for 30 min. The reaction was quenched by addition of a saturated solution of NH_4Cl. Usual work-up afforded the aldehyde (0.56 g, 60% yield) that was reacted with 1 mol equiv of N-benzylhydroxylamine (0.37 g, 3 mmol) in dry diethylether (10 mL) at room temperature for 24 h. Monitoring of the reaction by TLC and ^{1}H NMR showed that it proceeded directly to the cycloaddition products **7a,b**. These were obtained as low melting material by evaporation of the solvent and flash chromatography with a 9:1 hexanes:diethylether mixture as eluant in 82% yield (0.717 g) from the crude aldehyde. Found: C% 70.20; H% 8.59; N% 4.77.

$C_{17}H_{25}NOS$ requires: C% 70.06; H% 8.65; N% 4.81.

Synthesis of sulphone **8**. To a stirred solution of **4** (0.28 g, 1.29 mmol) in CH_2Cl_2 (10 mL), MCPBA (80%, 0.56 g, 2.6 mmol) was added at 0°C. The reaction was allowed to warm up to room temperature and stirred overnight. The mixture was filtered and the filtrate washed with a 5% aqueous solution of $NaHCO_3$. The organic phase was separated, dried and concentrated in vacuum. The crude residue was purified by flash chromatography with a 3:7 hexanes:diethyl- ether mixture as eluant to give **8** (0.24 g, 75% yield) as a thick oil. Found: C% 53.29; H% 8.18. $C_{11}H_{20}O_4S$ requires: C% 53.20; H% 8.12. ^{1}H NMR: δ 6.05-7.05 (m, 2H, CH=CH); 3.75 (s, 3H, OMe); 3.30-3.80 (m, 1H, CH); 2.00-3.10 (m, 4H,

CH_2-SO_2 and CH_2-C=); 1.10-1.80 (m, 7H, CH_2-CH_2 and Me-CH); 0.90 (bt, 3H, Me-CH_2).

Synthesis of isoxazolidines **9a,b**. Ester **8** (0.144 g, 0.58 mmol) was reduced to the corresponding aldehyde as described above. The crude product (0.072 g, 57% yield) was reacted with 1 mol equiv of N-benzylhydroxylamine in dry diethylether for 18h at room temperature to give directly the cycloaddition product. **9ab** were obtained in quantitative yield (0.106 g) by evaporation of the solvent and flash chromatography with a 1:1 hexanes:diethylether mixture as eluant. Found: C% 63.21; H% 7.83; N% 4.25. $C_{17}H_{25}NO_3S$ requires: C% 63.13; H% 7.79; N% 4.33.

Synthesis of diol **10**. A mixture of thioglycerol (3.86 mL, 46 mmol), 1-hexyne (7.7 mL, 67 mmol), and AIBN (0.05 g) in dry THF (50 mL) was refluxed for 48 h. Evaporation of the solvent and flash chromatography with diethylether as eluent gave **10** (6.2 g, 71% yield) as a thick oil that solidifies at ca. -20°C. Found: C% 56.69; H% 9.61. $C_9H_{18}O_2S$ requires: C% 56.80; H% 9.53. ^{1}H NMR δ 5.45-5.95 (m, 2H, CH=CH); 3.40-3.90 (m, 3H, CH_2-O and CH-O); 2.50-2.90 (m, 4H, CH_2-S and 2 OH); 1.95-2.25 (m, 2H, CH_2-C=); 1.30-1.55 (m, 4H, CH_2-CH_2); 0.90 (bt, 3H, Me).

Synthesis of silylethers **11** and **12**. A mixture of diol **10** (0.746 g, 4.95 mmol), t-butyldimethylsilylchloride (1.267 g, 6.7 mmol), and imidazole (0.750 g, 11 mmol) in DMF (1 mL) was stirred overnight at room tempetature. The reaction mixture was poured into water and extracted with diethylether. The organic phase was washed with water, dried and evaporated. The residue was chromatographed with a 9:1 hexanes:diethylether mixture as eluant to give ethers **11** (0.800 g) and **12** (0.400 g) as oils, in 80% overall yield. Found: C% 59.08; H% 10.48. $C_{15}H_{32}O_2SSi$ requires: C% 59.16; H% 10.59. ^{1}H NMR of **11**: δ 5.45-6.00 (m, 2H, CH=CH); 3.60-3.95 (m, 3H, CH_2-O and CH-O); 2.70-2.90 (m, 2H, CH_2-S); 2.60 (bd, 1H, OH); 2.00-2.30 (m, 2H, CH_2-C=); 1.15-1.60 (m, 4H, CH_2-CH_2); 0.95 (bt, 3H, Me-CH_2); 0.95 (s, 9H, CMe_3); 0.05 (s, 6H, Me_2Si). ^{1}H NMR of **12**: δ 5.40-5.95 (m, 2H, CH=CH); 3.35-4.00 (m, 3H, CH_2-O and CH-O); 2.70-2.90 (m, 2H, CH_2-S); 2.00-2.30 (m, 3H, CH_2-C= and OH); 1.20-1.60 (m, 4H, CH_2-CH_2); 0.95 (bt, 3H, Me-CH_2); 0.95 (s, 9H, Me_3C); 0.05 and 0.10 (2s, 6H, Me_2Si).

Synthesis of benzylethers **15** and **16**. Since benzylation of **11** gave both **13** and **14**, likely via equilibration of **11** and **12**, the mixture of **11** and **12** was employed. To an oil free suspension of NaH (0.117 g, 4.87 mmol) in dry THF (10 mL) cooled at 0°C a 2:1 mixture of **11** and **12** (1.48 g, 4.87 mmol) in THF (5 mL) was added. After 30 min stirring at room temperature, a THF (10 mL) solution of benzyl bromide (1.16 mL, 9.74 mmol) and tetrabutylammonium iodide (0.18 g, 0.5 mmol) was added and stirring continued for 1.5

h. A saturated aqueous solution of NH_4Cl was then added and the organic phase was separated, dried, and evaporated to give a mixture of **13** and **14**. These products were not purified but directly reacted with tetrabutylammonium fluoride trihydrate (4.7 g, 15 mmol) in THF (30 mL) to give after 3h stirring at room temperature, a 2:1 mixture of **15** and **16** in 55% overall yield from **11/12**. The primary alcohol **15** was obtained as an oil after flash chromatography with a 1:1 hexanes: diethylether mixture as eluant. Found: C% 68.46; H% 8.52. $C_{16}H_{24}O_2S$ requires: C% 68.53; H% 8.63. ^1H NMR of **15**: δ 7.20-7.40 (m, 5H, C_6H_5); 5.45-6.00 (m, 2H, CH=CH); 4.65 (AB system, 2H, $Ph\underline{CH_2}$); 3.50-3.85 (m, 3H, CH_2-O and CH-O), 2.75-2.90 (m, 2H, CH_2-S); 1.80-2.15 (m, 3H, CH_2-C= and OH); 1.20-1.50 (m, 4H, CH_2-CH_2); 0.90 (bt, 3H, Me).

Synthesis of isoxazolidines **18ab.** To a stirred solution of alcohol **15** (0.37 g, 1.32 mmol) in diethylether (10 mL) cooled at 0°C, DCC (0.517 g, 2.51 mmol), DMSO (0.112 mL, 1.58 mmol), pyridine (0.02 mL), and trifluoroacetic acid (0.02 mL) were added in this order. The reaction mixture was then allowed to warm up to room temperature and half of the amount of the reagents were then added for two times at 30 min intervals. After 30 min additional stirring, oxalic acid (0.79 g, 6.3 mmol) in methanol (5 mL) was then added and the mixture filtered through a celite cake. The crude aldehyde was purified by chromatography with a 6:4 hexanes:diethylether mixture as eluant, to give the product (0.191 g) in 52% yield. This compound was dissolved in dry diethylether (10 mL) and heated with N-benzylhydroxylamine (0.086 g, 0.7 mmol) at room temperature. After overnight stirring a certain amount of nitrone was still present by TLC analysis. The solvent was evaporated in vacuum and replaced by dry benzene and the mixture was refluxed for 2h. Evaporation of the solvent and flash chromatography with a 1:1 mixture of hexanes:diethylether as eluant gave the product as low melting material in 74% yield (0.194 g). Found: C% 71.87; H% 7.60; N% 3.59. $C_{23}H_{29}NO_2S$ requires: C% 72.02; H% 7.62; N% 3.65.

Synthesis of diol **21.**[16] To a stirred solution of (S)-glycidol (13.0 mL, 195 mmol), and benzylmercaptan (36.7 mL, 314 mmol) in dry benzene (100 mL) cooled at 0°C, titanium tetraisopropoxy (87.5 mL, 294 mmol) was added. After stirring 30 min at 0°C and 2h at room temperature 150 mL of a 10% solution of sulphuric acid in water were added and the mixture was extracted with diethylether. The organic phase was washed with a sodium hydroxide solution and then with water and the crude product was purified by flash chromatography with a 98:2 diethylether:methanol mixture as eluant to give **21** as a thick oil (23.3 g, 60% yield). Found: C% 60.66; H% 7.03. $C_{10}H_{14}O_2S$ requires: C% 60.59; H% 7.12. ^1H NMR: δ 7.30 (bs, 5H, C_6H_5); 3.80 (s, 2H, $\underline{CH_2}$-Ph); 3.35-3.70 (m, 3H, CH_2-O

and CH-O); 2.10-2.80 (m, 4H, CH_2-S and 2 OH). $[\alpha]_D^{22}$+39.2 (c 2).

Synthesis of sulphide **22.** Diol **21** was converted into the acetonide by reaction with 2,2-dimethoxypropane (solvent) in the presence of catalytic PTSA (overnight, room temperature, quantitative). A stirred solution of this product (8.8 g, 37 mmol) in liquid NH_3 (500 mL) was treated over 2 h with sodium metal (1.7 g, 74 mga) under an Argon atmosphere. After 15 min additional stirring NH_3 was evaporated, the residue taken up into water; the mixture was then acidified to pH 4 with a 3.7% aqueous solution of HCl and extracted with diethylether. Evaporation of the solvent gave the product that was reacted with 1-hexyne as described above without further purification. Compound **22** (4.6 g, 54% overall yield from **21**) was obtained as an oil by flash chromatography with a 95:5 haxanes: diethylether mixture as eluant. Found: C% 62.74; H% 9.56. $C_{12}H_{22}O_2S$ requires: C% 62.57; H% 9.63. ^{1}H NMR: δ 5.45-6.05 (m, 2H, CH=CH); 4.00-4.40 (m, 2H, CH_2-O); 3.60-3.85 (m, 1H, CH-O); 2.55-3.05 (m, 2H, CH_2-S); 1.95-2.25 (m, 2H, CH_2C=); 1.10-1.60 (m, 4H, CH_2CH_2); 1.30 and 1.35 (2s, 6H, Me_2C); 0.90 (bs, 3H, Me). $[\alpha]_D^{22}$-18.8 (c 1.5). This product was obtained in the racemic form from compound **10** by the described ketalization procedure.

Synthesis of (-)-**10.** A solution of **22** (1.3 g, 5.65 mmol) and catalytic PTSA in methanol (10 mL) was stirred at room temperatuire for 3h. Solid $NaHCO_3$ was then added and the mixture stirred for 15 min and filtered. Evaporation of the solvent gave the crude product that was purified by flash chromatography with diethyl ether as eluant. (-)-**10,** (0.86 g, 80% yield), had $[\alpha]_D^{22}$-2.4 (c 0.8) and was identical by ^{1}H NMR to rac-**10.** The starting acetonide could be recovered and recycled.

Synthesis of aldehyde (+)-**23.** Diol (-)-**10** was converted into (+)-**12,** $[\alpha]_D^{22}$-3.8 (c 1), as described above. Starting from (+)-**12** (0.242 g, 0.8 mmol), the reported Moffatt oxidation followed by flash chromatography with a 95:5 hexanes:diethylether mixture as eluant gave (+)-**23** (0.131 g, 54% yield) as an oil. It had $[\alpha]_D^{22}$+3.2 (c 0.6). Found: C% 58.99; H% 10.11. $C_{15}H_{30}O_2SSi$ requires: C% 59.55; H% 9.99.

Synthesis of isoxazolidines **24ab.** A solution of (+)-**23** (0.594 g, 1.97 mmol) and N-benzylhydroxylamine (0.246 g, 2 mmol) was refluxed in dry benzene (10 mL) overnight. The usual work-up followed by flash chromatography with a 95:5 hexanes:diethylether mixture as eluant, afforded compound **24a,** $[\alpha]_D^{22}$-11.4 (c 0.6), and **24b,** $[\alpha]_D^{22}$-22.9 (c 1.3), both as thick oils in 77% yield. Found: C% 64.75; H% 9.09; N% 3.39. $C_{22}H_{37}NO_2SSi$ requires: C% 64.81; H% 9.15; N% 3.44.

Synthesis of **25ab.** This reaction was performed on the pure isomers **24a** and **24b.** Following the procedure described above for the synthesis of **15,** alcohols **25a,** m.p.

70°C, $[\alpha]_D^{22}$+5.4 (c 14), and **25b**, thick oil, $[\alpha]_D^{22}$-24.0 (c 1.6), were obtained in 85% and 87% yield, respectively, after flash chromatography with a 4:6 hexanes:diethylether mixture as eluant. Found: C% 65.38; H% 7.81; N% 4.82. $C_{16}H_{23}NO_2S$ requires: C% 65.49; H% 7.90; N% 4.77.

Synthesis of **26ab.**[17] General procedure: to a stirred solution of alcohol **25** (0.129 g, 0.44 mmol), phthalimide (0.065 g, 0.44 mmol), and triphenylphosphine (0.115 g, 0.44 mmol) in THF (0.6 mL), DEAD (0.069 mL, 0.44 mmol) was added. After overnight stirring at room temperature, the mixture was filtered through a celite cake and the residue purified by flash chromatography with a 1:1 hexanes:diethylether mixture as eluant. Compound **26a**, a low melting material with $[\alpha]_D^{22}$-8.3 (c 1), was obtained in 35% yield, together with minor amounts of the C-3' epimer that was separated by chromatography. Compound **26b**, m.p. 101-103°C, $[\alpha]_D^{22}$-56.8 (c 1.8) was obtained in 66% yield. Found: C% 68.09; H% 6.11; N% 6.71. $C_{24}H_{26}N_2O_3S$ requires: C% 68.22; H% 6.20; N% 6.63.

Synthesis of **27ab**. General procedure: a stirred solution of phthalimide derivative **26** (0.174 g, 0.41 mmol) and hydrazine (0.1 mL) in absolute ethanol was refluxed for 3h. The solvent was evaporated and an aqueous solution of $NaHCO_3$ was added to the residue. The aqueous phase was extracted twice with dichloromethane and the organic phase was dried and evaporated to give the crude product that was purified by flash chromatography with a 88:7:5 diethylether:methanol:triethylamine mixture as eluant. Amine **27a**, a thick oil with $[\alpha]_D^{22}$+3.9 (c 0.5), was obtained in 77% yield. Amine **27b**, a waxeous solid with $[\alpha]_D^{22}$-49.0 (c 1.6), was obtained in 78% yield. Found: C% 65.70; N% 8.19; N% 9.69. $C_{16}H_{24}N_2OS$ requires: C% 65.71; H% 8.27; N% 9.58.

Synthesis of **2ab.** General procedure: a solution of amine **27** (0.042 g, 0.143 mmol), K_2CO_3 (0.06 g, 0.43 mmol) and methylchloroformate (0.022 mL, 0.286 mmol) in acetone (1 mL) was stirred overnight. The mixture was filtered and evaporated, and the residue purified by flash chromatography with a 45:55 hexanes:diethylether mixture as eluant. **2a**, a low melting material with $[\alpha]_D^{22}$+30.8 (c 0.4), was obtained in 86% yield. **2b**, m.p. 88-90°C, $[\alpha]_D^{22}$-4.2 (c 0.5), was obtained in 80% yield.

References and Notes.

1. Reviews: J.J. Tufariello in 1,3-Dipolar Cycloaddition Chemistry, A. Padwa Ed.; Wiley-Interscience, New York 1984, Vol. 2, p. 83; A. Padwa, ibid., p. 277. J.J. Tufariello, Acc. Chem. Res., **12**, 396, 1979; N. Balasubramanian, Org. Prep. Proced. Int., **17**, 23, 1985; P.N. Confalone, E.M. Huie, Org. React.,**36**, 1, 1988.

2. Review: R. Annunziata, M. Cinquini, F. Cozzi, L. Raimondi, Gazz. Chim. Ital., **119**, 253, 1989.
3. N.A. Le Bel, J.J. Whang, J. Am. Chem. Soc., **81**, 6334 1959.
4. N.A. Le Bel, M.E. Post, J.J. Whang, J. Am. Chem. Soc., **86**, 3759, 1964.
5. F.J. Vinick, I.E. Fengler, H.W. Gschwend, J. Org. Chem., **42**, 2936, 1977.
6. M. Ihara, M. Takahashi, K. Fukumoto, T. Kametani, J. Chem. Soc., Perkin Trans. 1, 2215, 1989.
7. R. Annunziata, M. Cinquini, F. Cozzi, L. Raimondi, Tetrahedron Lett., 2881, 1988.
8. E. Baggiolini, H.L. Lee, G. Pizzolato, M.R. Uskokovic, J. Am. Chem. Soc., **104**, 6460, 1982.
9. R.J. Parry, A.E. Mizusawa, I.C. Chiu, M.V. Naidu, M. Ricciardone, J. Am. Chem. Soc., **107**, 2519, 1985.
10. H.L. Lee, E.G. Baggiolini, M.R. Uskokovic, Tetrahedron, **43**, 4887, 1987.
11. The synthesis of **15** is best carried out by benzylation of the mixture of **11** and **12** to give **13** and **14**; reaction with $Bu_4N^+F^-.3H_2O$ gave **15** and **16** that were separated by chromatography (see Experimental).
12. While it was possible to oxidize **12** to the corresponding sulphone, conversion of the latter to the aldehyde, attempted with several methods, resulted in extensive product decomposition.
13. We could not establish the configuration at C=N of the nitrones here described. The (Z) configuration, commonly accepted for C-alkenyl nitrones can be assumed on the basis of previous observations for similar systems.[1,7,8,14] However, it must be remembered that (Z) ⟶ (E) isomerization can occur before cycloaddition.[1,14]
14. Y. Inouye, J. Hara, H. Kakisawa, Chem. Lett., 1407, 1980.
15. For recent syntheses of (d)-biotin see: ref. 7 and 11; E.J. Corey, M.M. Mehrotra, Tetrahedron Lett., 57, 1988; R.A. Volkmann, J.T. Davis, C.N. Meltz, J. Am. Chem. Soc., **105**, 5946, 1983.
16. M. Caron, K.B. Sharpless, J. Org. Chem., **50**, 1557, 1985.
17. O. Mitsunobu, Synthesis, 1, 1981.
18. We thank Professor E.G. Baggiolini for providing us with the ^1H NMR spectra of **2** and **3**.
19. I.L. Knunyants, M.G. Lin'kova, N.D. Kuleshova, Izv. Akad. Nauk SSSR, Ser. Khim., 644, 1964. C.A. **61**, 2966e, 1964.

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