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On the Absolute Stereochemistries of Homochiral Cycloadducts Derived from Oxygenated Aldoximes and Divinyl Sulphone *via* Azaprotio Cyclotransfer

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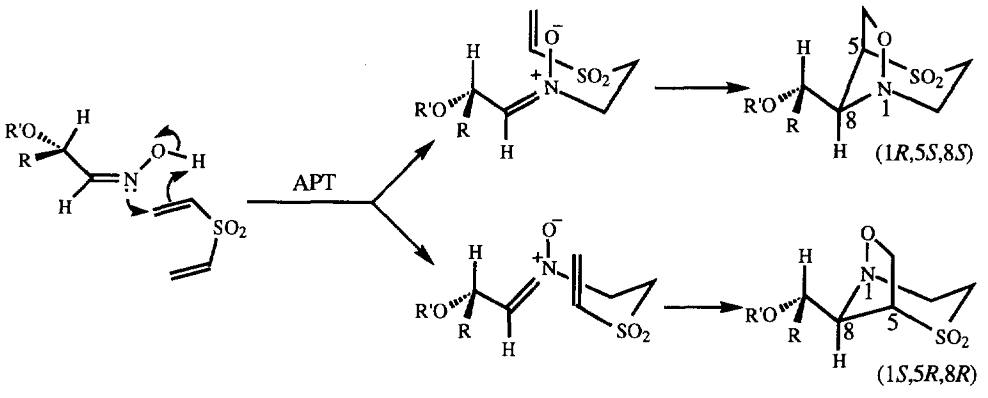
Abstract: Further studies into the regiospecific tandem nitrone generation/cycloaddition reaction between chiral oxygenated aldoximes and divinyl sulphone have shown that cycloaddition diastereoselectivity can be controlled by a single stereogenic centre located α- to the oxime moiety. Diastereoselectivity is greatly enhanced when the α-stereocentre constitutes part of a ring system and the absolute stereochemistry of the major cycloadduct can be accurately predicted based upon the absolute stereochemistry at the α-centre of the oxime.

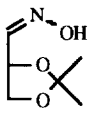
As part of our continuing research into the use of simple oximes as precursors to heterocyclic systems we have recently further developed our 1,3-azaprotio cyclotransfer (APT) cascade route for the synthesis of homochiral cycloadducts of pyranose and furanose oximes.[1] We have shown that bulky (*Z*)-aldoximes containing several contiguous stereogenic centres react regiospecifically and with high diastereoselectivity using divinyl sulphone as a bifunctional nitrone generation/dipolarophile co-reactant. In this paper we report the results of our studies concerning the use of chiral aldoximes derived from simpler oxygenated precursors in Class 2 APT cascades[2] with divinyl sulphone. These results indicate that cycloaddition diastereoselectivity can be effectively controlled by a single stereocentre located α- to the oxime moiety and that greatly enhanced selectivity results when the stereocentre constitutes part of a cyclic system. Additionally, in each case the absolute stereochemistry of the major diastereoisomeric cycloadduct can be accurately predicted based upon the absolute stereochemistry of the α-stereocentre.



Scheme

The regiospecific Class 2 APT nitrone generation/cycloaddition cascade reaction between divinyl sulphone and a chiral (*Z*)-aldoxime which bears hydrogen, carbon and oxygen functionality at a neighbouring stereocentre can occur *via* either of a pair of diastereomeric pre-transition state conformers (*Scheme*). The resulting cycloadduct species differ in their absolute stereochemistries at the three newly formed stereogenic centres (N-1, C-5 and C-8). We have previously observed[1] that conformationally restricted hemi-acetal derived cyclic sugar aldoximes containing four or five contiguous stereochemical centres show a marked tendency to undergo cycloaddition preferentially to one diastereotopic face of the chiral nitrone intermediate (d.e. >95%). We were similarly interested in the influence upon cycloaddition processes of more flexible chiral aldoximes derived from open chain sugars and α-hydroxy acids.

Oximes **1**-**7** were prepared from the corresponding aldehydes[3-9] as mixtures of geometric isomers, (*E/Z* ratios *ca.* 2:1, 3:2, 5:1, 3:1, 2:1 3:1 and 1:1 respectively), and were used as such without separation in subsequent experiments. Our previous studies have shown that APT processes involving aldoximes give rise to single nitrones arising from the (*Z*)-aldoxime and that (*Z*/*E*)-aldoxime isomerization is a facile process under the conditions of the APT reaction.[1,2]



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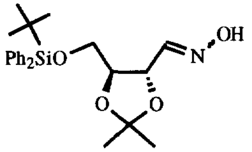

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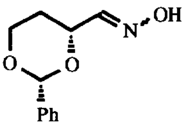

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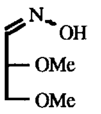

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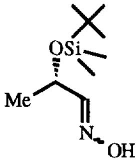

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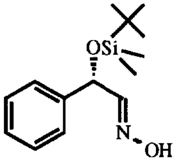

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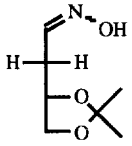

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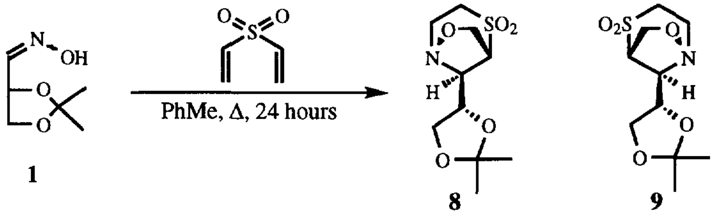
a) *Aldoximes containing an α-chiral centre that constitutes part of a ring system*

The D-glyceraldehyde derived aldoxime **1**[3] reacted smoothly with divinyl sulphone (1 equivalent) in toluene at 110°C. Monitoring the disappearance of aldoxime **1** by ^1H nmr showed that reaction occurred regiospecifically and substantially faster than with the more stereochemically complex pyranose and furanose oximes reported previously.[1] The reaction was found to be essentially complete within 24 hours and the ^1H nmr spectrum of the reaction mixture showed the presence of a *ca.* 19:1 mixture of isomeric cycloadducts **8** and **9**, (d.e. *ca.* 90%), that differed only in the absolute stereochemistry within the newly formed 1-aza-7-oxa-4-thiadioxybicyclo[3.2.1]octane ring system due to cycloaddition at opposite diastereotopic faces of the intermediate nitrone.



Column chromatography of the diastereomer mixture on silica afforded the major isomer **8** (48%). The markedly reduced yield of **8** when compared to cycloadducts derived from pyranose oximes[1] is believed to result from the comparative thermal instability of glyceraldehyde derivatives. The absolute stereochemistry of cycloadduct **8** was determined by single crystal X-ray analysis[10] (*Figure 1*). This showed that **8** has the (*S*)-configuration at the nitrogen atom; cycloadduct **9** therefore has (*R*)-stereochemistry at nitrogen. Notably, in this case the major cycloadduct **8** has the opposite stereochemistry at nitrogen to the major cycloadducts derived from either D-galactosyl or D-ribosyl aldoximes which have been shown previously to have (*R*)-stereochemistry at nitrogen.[1]

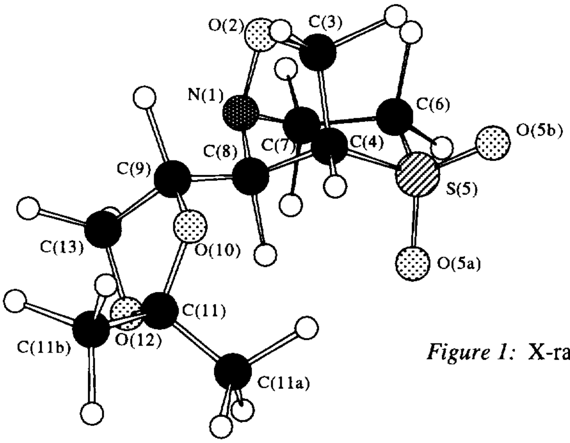
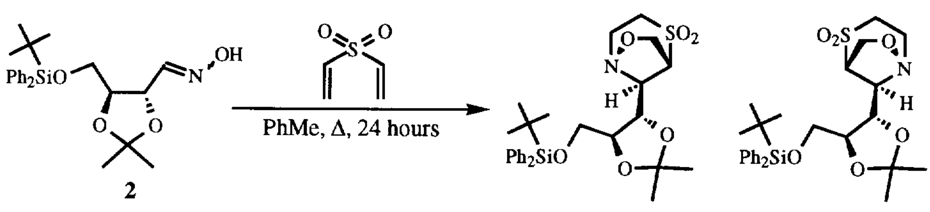
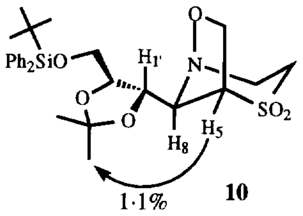


Figure 1: X-ray structure of **8**

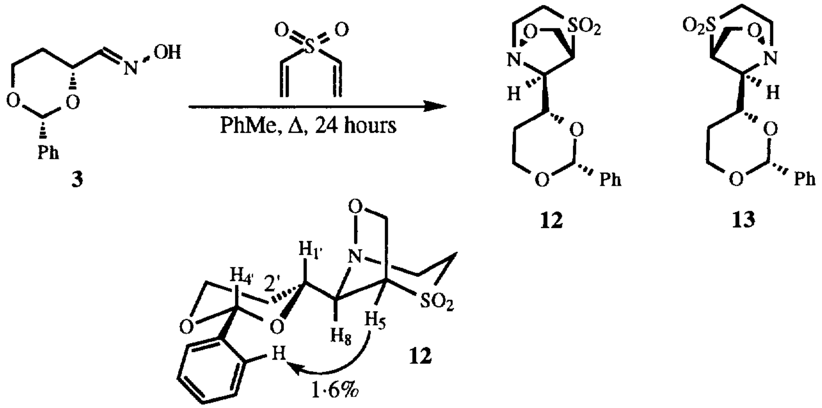
L-Threose derived aldoxime **2** reacted cleanly with divinyl sulphone over 24 hours at 110°C in toluene. ^{1}H Nmr monitoring of the reaction mixture showed the reaction to afford a single cycloadduct **10** (d.e. 100%) with none of the isomeric cycloadduct **11** being formed. Column chromatography on silica afforded the cycloadduct **10** (78%) in which absolute stereochemistry was determined on the basis of specific nOe enhancements in its nmr spectrum in $CDCl_3$. Irradiation of H-5 resulted in an enhancement in the signal for one of the isopropylidene methyl signals (1·1%) which when taken in conjunction with the antiperiplanar alignment of H-1' and H-8 (*J* 9 Hz) suggests that cycloadduct **10** has (*S*)-stereochemistry at nitrogen.



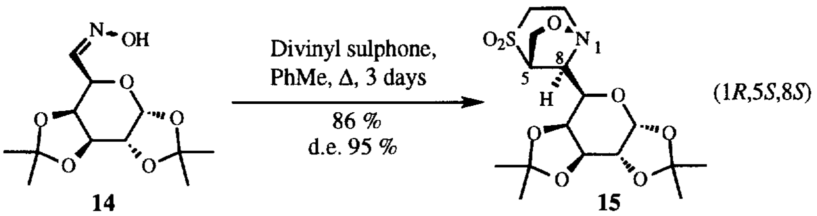
10 **11**

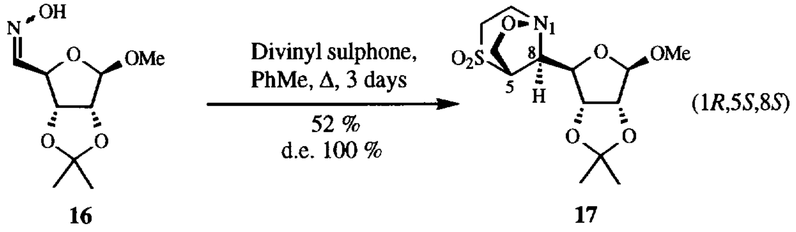


Aldoxime **3** similarly reacted cleanly with divinyl sulphone at 110°C over 24 hours to afford solely cycloadduct **12** (d.e. 100%). ^{1}H Nmr of the crude reaction mixture confirmed the absence of any isomeric cycloadduct **13**. Cycloadduct **12** was shown to possess (*S*)-stereochemistry at the bridgehead nitrogen atom on the basis of ^{1}H nmr nOe data. Upon irradiation of the signal corresponding to H-5 an enhancement was observed in the signal corresponding to the equatorially sited *ortho*-phenyl hydrogen resonances (1·6%) and not in the resonances corresponding to the hydrogens of the methylene unit at C-2'.



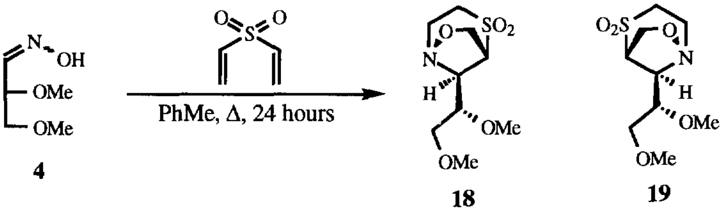
Similarly high diastereoselectivities have been reported by us previously for more complex aldoximes derived from both pyranose and furanose forms of sugars, (e.g. **14**→**15** and **16**→**17**).[1]

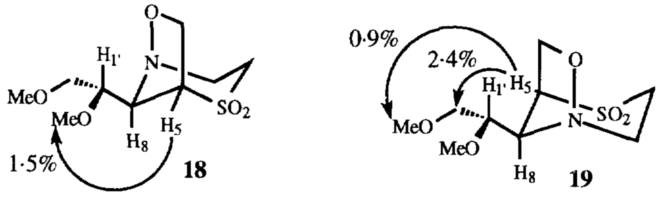




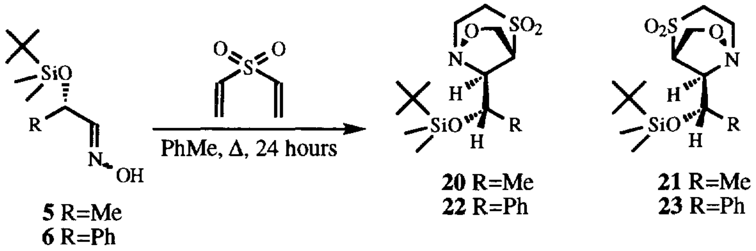
b) Aldoximes containing an α-chiral centre as part of an acyclic system

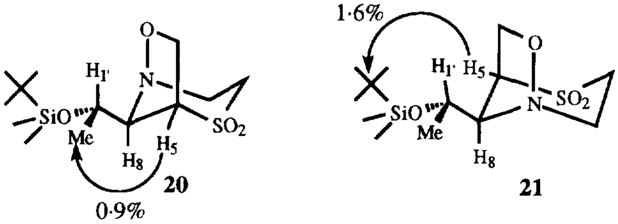
The acyclic D-glyceraldehyde derived aldoxime **4** reacted with divinyl sulphone (1 equivalent) under identical conditions over a similar time period to afford a mixture of cycloadducts **18** and **19**. ^{1}H Nmr analysis of the reaction mixture showed that the reaction was similarly regiospecific but was markedly less diastereoselective (isomeric ratio *ca.* 2:1, d.e. *ca.* 33%). Column chromatography on silica afforded **18** as a colourless solid (30%) and **19** as a colourless oil (15%). Absolute stereochemical assignments for cycloadducts **18** and **19** were made on the basis of the observation of specific nOe enhancements in the ^{1}H nmr spectra of **18** and **19** in d_8-toluene.





Irradiation of H-5 of **18** resulted in a positive enhancement of the α-methoxy signal (1·5%) which with the antiperiplanar alignment of H-1' and H-8 ($J_{1',8}$ 9 Hz) suggests that the major adduct **18** has (*S*)-stereochemistry at nitrogen; in contrast the minor isomer **19** [assigned as having (*R*)-stereochemistry at nitrogen] showed enhancements in both the methylene protons (2·4%) and the β-methoxy signal (0·9%) of the CH_2OMe moiety in similar experiments.





Similarly the α-hydroxy acid derived aldoximes **5** and **6** (from L-lactic acid and L-mandelic acid respectively) reacted smoothly with divinyl sulphone at 110°C over 24 hours. Aldoxime **5** was shown by ^{1}H nmr to afford a 1:2 mixture of adducts **20** and **21**, (d.e. 33%), which were separated on silica (**20**, colourless solid, 21%; **21**, colourless solid, 44%), stereochemical assignments of **20** and **21** again proved possible on the basis of nOe enhancements in the ^{1}H nmr spectra of **20** and **21** in d_8-toluene. Irradiation of H-5 of **21** resulted in a positive enhancement of the *tert*-butyldimethylsilyl resonances (1·6%)

which together with an antiperiplanar relationship between H-1' and H-8 ($J_{1',8}$ 9·5 Hz) allows the assignment at the nitrogen atom of **21** as (*R*); the minor isomer **20** exhibited enhancement in the α-methyl signal (0·9%) in similar irradiation experiments on H-5 and thus has (*S*)-stereochemistry at nitrogen.

Under similar conditions aldoxime **6** afforded a 1:3 mixture (54%) of adducts **22** and **23** (d.e. 50%) which could not be separated on silica. Fractional crystallization afforded a pure sample of the major cycloadduct **23** which was shown by single crystal X-ray crystallography[10] to have (*R*)-stereochemistry at nitrogen, (*Figure 2*).

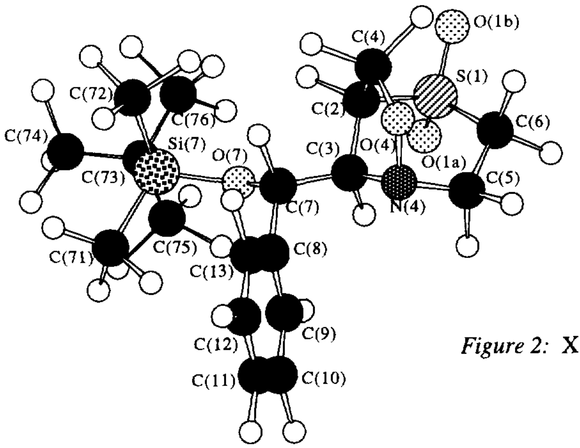
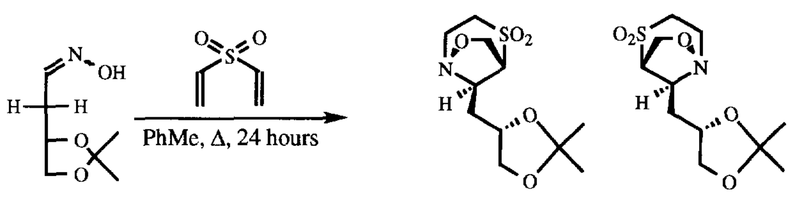


Figure 2: X-Ray structure of **23**

c) *Aldoximes containing a β-chiral centre*

Aldoxime **7** derived from L-malic acid also reacted regiospecifically with divinyl sulphone in toluene at reflux to afford a 4:5 mixture of stereoisomeric cycloadducts **24** and **25** (d.e. 11%). ^{1}H Nmr monitoring of the reaction mixture showed the reaction to be essentially complete within 24 hours. Column chromatography on silica allowed for the purification (but not the separation) of **24** and **25** (colourless solid, 4:5 ratio, 55%) which also proved to be inseparable by fractional crystallization. The major isomer in this case is tentatively assigned as **25** having the (*R*)-stereochemistry at nitrogen.[11]



7 24 25

d) *Mechanism of diastereoselection*

It is clear from these results that cycloaddition stereoselectivity in the reaction between a chiral aldoxime and divinyl sulphone can be effectively controlled with a neighbouring stereogenic centre bearing hydrogen, carbon and oxygen functionality if the stereocentre is located α- to the oxime moiety. In contrast, aldoximes in which the nearest stereocentres are located at the β-carbon or beyond (e.g. **7**) show little π-facial selectivity upon cycloaddition. Thus the factors controlling selectivity in these reactions operate only over relatively short distances. Cycloaddition stereoselectivity is greatly enhanced (d.e. >90%) when the α-stereocentre is conformationally restricted by incorporation into a ring system and neither further contiguous stereocentres nor further oxygen functionality located at more remote centres would appear to have much of a controlling effect in these cycloaddition processes.

L-Type D-Type

Figure 3

In order to explain the observed stereoselection in these reactions we have attempted to correlate the absolute stereochemistry of the α-stereocentre of the chiral α-aldoximes with the stereochemistry about the nitrogen atom in the major cycloadduct. We have classified aldoximes that contain an α-chiral centre bearing hydrogen, carbon and oxygen functionality into two distinct categories (L-Type and D-Type) depending on the absolute stereochemistry of the α-stereocentre.[12] This classification is analogous to that used to determine the L- or D- nature of sugars in that it results from the orientation of the oxygen functionality relative to the vertical carbon backbone of the aldoxime when portrayed as a Fischer projection, (*Figure 3*).

Using this classification system it is apparent that L-Type aldoximes (e.g. **5**,**6**,**14** and **16**) react with divinyl sulphone to afford mainly cycloadducts with (*R*)-stereochemistry at the nitrogen atom of the newly formed bicyclic system whereas D-Type aldoximes (e.g. **1**,**2**,**3**, and **4**) preferentially yield adducts with (*S*)-stereochemistry at nitrogen. Assuming that reaction occurs *via* a transition state in which the aldonitrone hydrogen and α-methine hydrogen atom adopt an antiperiplanar arrangement[13] in order to minimize steric compression between the (*Z*)-nitrone oxygen and the α-centre, (a Felkin like transition state),[14,15] then it is clear that in all cases cycloaddition occurs preferentially *syn* to the α-OR' functionality. Similar controlling effects have previously been observed in numerous Diels-Alder reactions of chiral 1,3-butadienes and cyclopentadienes[16] as well as in chiral nitrone cycloadditions;[17-19] but in the latter cases the authors have suggested the difference in the size of the carbon and oxygen substituents is the most important controlling factor.

We believe that our observations regarding diastereoselectivity in these cycloaddition processes are best rationalized on the basis of electronic effects similar to those suggested by Cieplak[20,21] with steric effects only being important in that they serve to effectively exclude reactions which would involve sterically less favourable rotamers of the intermediate nitrone. Conformationally constrained cyclic aldoximes would thus be expected to afford a much greater degree of diastereoselectivity upon cycloaddition due to a reduction in the number of easily accessible rotamers of the intermediate nitrone. In acyclic cases, averaging of molecular conformation should occur to a much greater extent because steric compression can be relieved and rotamer interconversion encouraged by angle deformation at the α-centre; cyclic cases restrict single bond rotation as a direct result of their reduced ability to relieve steric compression by angle deformation.

Thus reaction is believed to proceed *via* the least sterically hindered (*Z*)-oxime to afford a (*Z*)-nitrone intermediate[1] which undergoes reaction *via* a rotamer in which the α-methine hydrogen and (*Z*)-nitrone oxygen atom are essentially eclipsed (**A** or **B**; arrows indicate the subsequent preferred antiperiplanar approach of the internal dipolarophile).[22,23] In all cases (irrespective of the difference in bulk between the carbon and oxygen based substituents) cycloaddition should then occur preferentially *anti* to the most electron rich C-X sigma bond of the two larger substituents (X=R or OR'). This electronic control results from the enhanced stabilization of the cycloaddition transition state by hyperconjugative donation of electron density from the relatively high energy C-X σ-bond into the low lying σ* antibonding orbital of the developing C-C bond, (*Figure 4*).

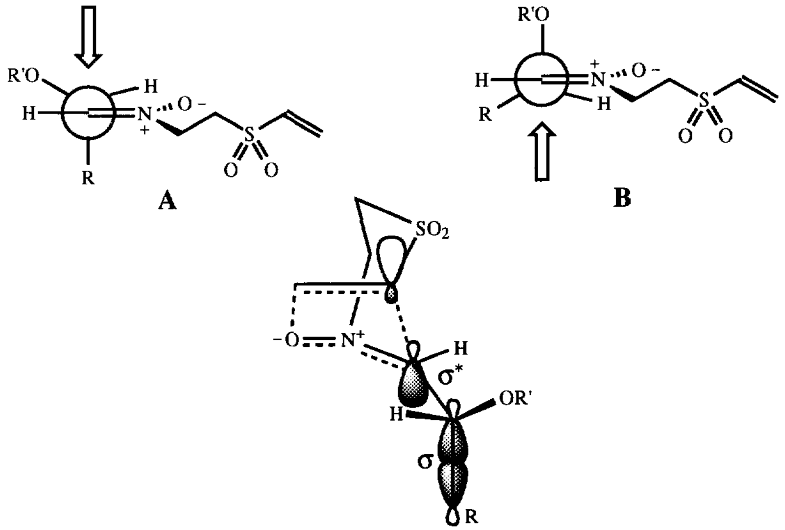
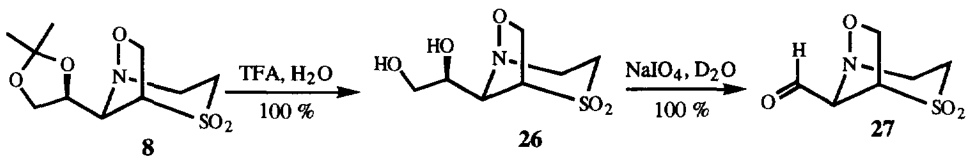
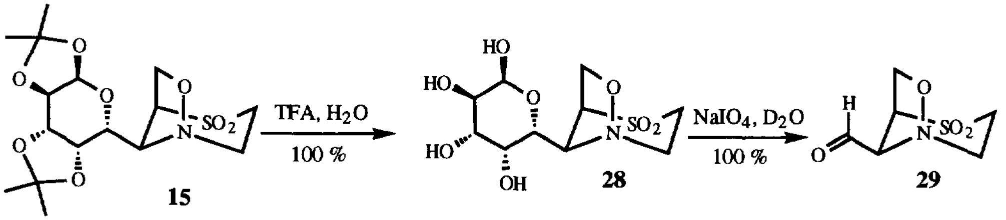


Figure 4: Stereoelectronic effects on π-facial selection in nitrone cycloaddition

Cieplak's theory[20,21] states that the more electron rich C-C bonds should have a greater controlling effect than C-O bonds with cycloaddition occurring preferentially *anti* to the C-C bond and hence *syn* to C-O; this would result in the dipolarophile preferentially approaching the nitrone as depicted in **A**. In this respect, L-Type and D-Type aldoximes would be expected to produce mainly adducts with (*R*)- and (*S*)-stereochemistries at nitrogen respectively, in accordance with our observations.

We have exploited the predictability of the π-facial selectivity in these cascade cycloaddition reactions to prepare the homochiral enantiomeric bicyclic aldehydes **27** and **29**. Cycloadducts **8** and **15** were deprotected in a rapid two stage procedure. Thus treatment of **8** and **15** with 50% aqueous trifluoroacetic acid at room temperature over 2 hours resulted in the quantitative removal of the isopropylidene protecting groups to afford **26** and **28** respectively. The resulting *vic*-diol functionalities of **26** and **28** were cleaved oxidatively with aqueous sodium periodate (room temperature, 2 hours) to afford the enantiomeric aldehydes **27** and **29**. Assessment of the reaction mixture by ^1H nmr suggested **27** and **29** were formed in quantitative yield but the aldehydes exist in aqueous solution exclusively as their hydrates which because of their high solubilities in water and high polarity could be neither readily extracted into common organic solvents nor purified by column chromatography on silica or alumina. Hence they could not be isolated free from byproducts and inorganic contaminants. Specific rotations were run on the crude materials at relatively low dilution (to avoid inaccuracies caused by salt induced aggregation phenomena) and are only indicative.





In summary, we have shown that aldoximes containing a neighbouring stereocentre bearing hydrogen, carbon and oxygen functionalities react regiospecifically with divinyl sulphone in tandem 1,3-APT/nitrone cycloaddition processes to afford chiral cycloadducts with varying degrees of diastereoselectivity. Diastereoselectivity is highest (d.e. >90%) for those aldoximes in which the stereocentre is both located α- to the oxime moiety and is constrained as part of a ring structure; those aldoximes with non-constrained α-stereocentres and those in which the chirality is at the β-carbon are less effective in controlling the cycloaddition step. In all cases that have an α-chiral centre, the absolute stereochemistry at the three contiguous stereocentres of the newly formed bicyclic system of the major cycloadduct can be accurately predicted based upon the absolute stereochemistry of the aldoxime α-centre. L-Type aldoximes preferentially afford bicyclic systems with (*R*)-stereochemistry at nitrogen whilst D-type aldoximes preferentially yield cycloadducts in which the nitrogen atom has (*S*)-stereochemistry. This predictability of π-facial selectivity has allowed for the preparation of a novel enantiomeric pair of heterocyclic bicyclic aldehydes containing nitrogen, oxygen and sulphur using a rapid and simple method for the removal of the chiral auxiliaries under mild conditions that do not effect cleavage of the N-O bond.

Further experiments are underway to extend the scope of these findings and to test their applicability to the control of stereochemistry in other related systems.

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EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Specific rotations were measured at ambient temperature with an Optical Activity Ltd., AA-1000 polarimeter. Microanalyses were obtained using a Carlo Erba MOD 1106 instrument. Fast atom bombardment mass spectra were recorded with a VG Autospec mass spectrometer using caesium as the ionizing agent. Infrared spectra were recorded on a Perkin Elmer 1310 spectrophotometer as thin films or as nujol mulls as indicated. Nuclear magnetic resonance spectra were recorded on a Bruker AM400 spectrometer operating at 400·1 MHz (^{1}H) and 100·6 MHz (^{13}C) or on a General Electrics QE300 spectrometer operating at 300·1 MHz (^{1}H) in the solvents specified. Flash column chromatography was performed using silica gel 60 (Merck 9385). Petroleum ethers (b.p. 40-60°C and b.p. 60-80°C) and water were distilled prior to use.

4-*O*-(*tert*-Butyldiphenylsilyl)-2,3-*O*-isopropylidene-L-threose oxime 2. A solution of 4-*O*-(*tert*-butyldiphenylsilyl)-2,3-*O*-isopropylidene-L-threose[4] (1·45 g, 3·62 mmol) in acetonitrile (15 ml) and water (15 ml) was treated with hydroxylamine hydrochloride (327 mg, 4·70 mmol) and sodium acetate (416 mg, 5·00 mmol) at room temperature overnight. The mixture was then extracted with diethyl ether (2 x 20 ml), the combined organic extracts dried over anhydrous magnesium sulphate, filtered and the solvent removed *in vacuo* to afford a pale yellow oil that was subjected to column chromatography. Elution with 4:1 v/v petroleum ether (b.p. 40-60°C)-diethyl ether afforded the *product* **2** (1·23 g, 83%) (*E*:*Z* 3:2), R_f 0·44 and 0·32, as a colourless oil. $[\alpha]_D$ +2·7° (*c* 0·2, CH_2Cl_2); (Found: C, 66·95; H, 7·75; N, 3·5. $C_{23}H_{31}NO_4Si$ requires C, 66·8; H, 7·5; N, 3·4%); *m/z* (%) 414 (MH^+, 60); δ_H ($CDCl_3$) 8·72 and 8·01 (2 x 1H, 2 x broad s, -OH), 7·71 and 7·68 (2 x 4H, 2 x t, *J* 7 Hz, *o*-ArH), 7·45-7·32 (2 x 6H, m, *m*-ArH and *p*-ArH), 7·38 and 6·89 (2 x 1H, 2 x d, *J* 8·5 Hz, H-1), 5·31 and 4·61 (2 x 1H, 2 x dd and t, *J* 8·5, 6 Hz, H-2), 4·08 and 4·04 (2 x 1H, 2 x dt, *J* 9, 6 Hz, H-3), 3·92 and 3·81 (2 x 2H, 2 x dd, *J* 9, 6 Hz, H-4α and H-4β), 1·52, 1·43, 1·43 and 1·42 (4 x 3H, 4 x s, CMe_2), 1·03 and 1·02 (2 x 9H, 2 x s, ^{t}Bu).

(2*R*,5*R*)-2,4-Benzylidenedioxybutanaldoxime 3. A solution of (2*R*,5*R*)-2,4-benzylidenedioxybutanal[5] (5·00 g, 26·04 mmol) in acetonitrile (25 ml) and water (25 ml) was treated with hydroxylamine hydrochloride (2·17 g, 31·25 mmol) and sodium acetate (2·77 g, 33·85 mmol) at room temperature overnight. The mixture was then extracted with diethyl ether (2 x 25 ml), the combined organic extracts dried over anhydrous magnesium sulphate, filtered and the solvent removed *in vacuo* to afford a pale yellow oil that was subjected to column chromatography. Elution with 7:3 v/v petroleum ether (b.p. 40-60°C)-diethyl ether afforded the *product* **3** (3·98 g, 74%) (*E*:*Z* 5:1), R_f 0·28, as colourless needles, m.p. 105-110°C; $[\alpha]_D$ +4·7° (*c* 0·86, CH_2Cl_2); (Found: C, 63·95; H, 6·1; N, 6·8. $C_{11}H_{13}NO_3$ requires C, 63·75; H, 6·3; N, 6·75%); *m/z* (%) 208 (MH^+, 100); δ_H ($CDCl_3$) 8·37 and 8·01 (2 x 1H, 2 x broad s, -OH), 7·52 (2 x 2H, d, *J* 7 Hz, *o*-ArH), 7·34 (2 x 3H, m, *m*-ArH and *p*-ArH), 7·34 and 6·92 (2 x 1H, d, *J* 7 Hz, H-1), 5·60 (2 x 1H, s, H-5), 5·19 and 4·61 (2 x 1H, ddd, *J* 9·5, 7, 2·5 Hz, H-2), 4·33 (2 x 1H, dd, *J* 11·5, 7 Hz, H-4α), 4·02 (2 x 1H, td, *J* 11·5 and 4 Hz, H-4β), 2·15 and 1·98 (2 x 1H, m, H-3β), 1·98 and 1·68 (2 x 1H, m, H-3α).

2,3-Di-*O*-methyl-D-glyceraldoxime 4. A stirred solution of hydroxylamine hydrochloride (1·31 g, 18·81 mmol) and 2,3-di-*O*-methyl-D-glyceraldehyde[6] (1·48 g, 12·54 mmol) in water (10 ml) was treated with anhydrous potassium carbonate (2·60 g, 18·81 mmol) and the resulting solution was stirred at room temperature overnight. After saturation of the solution with sodium chloride the mixture was extracted with diethyl ether (2 x 30 ml). The combined organic extracts were dried over anhydrous magnesium sulphate, filtered and the solvent removed *in vacuo* to afford a pale yellow oil that was subjected to column chromatography. Elution with 1:1 v/v petroleum ether (b.p. 40-60°C)-diethyl ether afforded the *product* **4** (1·42 g, 85%) (*E*:*Z* 3:1), R_f 0·28, as a colourless oil. $[\alpha]_D$ +85·7° (*c* 1·1, $CHCl_3$); (Found: C, 44·45; H, 8·3; N, 10·4. $C_5H_{11}NO_3$ requires C, 45·1; H, 8·3; N, 10·5%); *m/z* (%) 133 (M^+, 15); ν_{max} (film) 3340, 1630 cm^{-1}; δ_H ($CDCl_3$) 8·78 and 8·43 (2 x 1H, 2 x broad s, -OH), 7·36 and 6·78 (2 x 1H, 2 x d, *J* 7·5 Hz and *J* 6 Hz, H-1), 4·69 and 3·95 (2 x 1H, 2 x dt, *J* 6, 3 Hz and *J* 7·5, 5 Hz, H-2), 3·65-3·50 (2 x 2H, m, H-3α and H-3β), 3·41, 3·39, 3·39 and 3·37 (4 x 3H, 4 x s, 4 x OMe); δ_C ($CDCl_3$) 151·4 and 149·5 (C-1), 77·5 (C-2), 73·4 and 72·2 (C-3), 59·4 and 59·3 (OMe), 57·8 and 57·1 (OMe).

(*S*)-2-(*tert*-Butyldimethylsilyloxy)propanaldoxime 5. A solution of (*S*)-2-(*tert*-butyldimethylsilyloxy)propanal[7] (1·35 g, 7·18 mmol) in methanol (5 ml), water (1 ml) and pyridine (735 mg, 9·30 mmol) was treated with hydroxylamine hydrochloride (645 mg, 9·28 mmol) at room temperature overnight. Upon removal of the solvent *in vacuo* the residue was partitioned between dichloromethane (20 ml) and 2M sulphuric acid (20 ml). The aqueous layer was separated and extracted with a further portion of dichloromethane (20 ml). The organic extracts were combined, dried over anhydrous magnesium sulphate, filtered and the solvent removed *in vacuo* to afford a pale yellow oil that was subjected to column chromatography. Elution with 5:1 v/v petroleum ether (b.p. 40-60°C)-diethyl ether afforded the *product* **5** (1·10 g, 76%) (*E*:*Z* 2:1), R_f 0·46 and 0·37, as a colourless oil. $[\alpha]_D$ -10·6° (*c* 0·7, $CHCl_3$); (Found: C, 53·1; H, 10·35; N, 6·9. $C_9H_{21}NO_2Si$ requires C, 53·15; H, 10·4; N, 6·9%); *m/z* (%) 202 (M^+-H, 11), 159 (M^+-C_4H_8, 100); ν_{max} (film) 3300, 1650 cm^{-1}; δ_H ($CDCl_3$) 8·57 and 8·18 (2 x 1H, 2 x broad s, -OH), 7·32 and 6·73 (2 x 1H, 2 x d, *J* 6·5Hz and *J* 5·5 Hz, H-1), 5·02 and 4·39 (2 x 1H, 2 x quin, *J* 5·5 Hz and *J* 6·5 Hz, H-2), 1·30 and 1·29 (2 x 1H, 2 x d, *J* 6·5 Hz and *J* 5·5 Hz, H-3), 0·89 and 0·88 (2 x 9H, 2 x s, ^{t}Bu), 0·08, 0·08, 0·07 and 0·06 (4 x 3H, 4 x s, $SiMe_2$); δ_C ($CDCl_3$) 156·7 and 154·5 (C-1), 66·5 and 62·5 (C-2), 25·8 (C*Me*$_3$), 22·3 and 20·9 (C-3), 18·2 (*C*Me$_3$), -4·6, -4·8, -4·9 and -5·0 ($SiMe_2$).

(*S*)-2-(*tert*-Butyldimethylsilyloxy)-2-phenylacetaldoxime 6. A solution of (*S*)-2-(*tert*-butyldimethylsilyloxy)-2-phenylacetaldehyde[8] (1·00 g, 4·00 mmol) in methanol (8 ml), water (1 ml) and pyridine (475 mg, 6·00 mmol) was treated with hydroxylamine hydrochloride (420 mg, 6·00 mmol) at room temperature overnight. Upon removal of the solvent *in vacuo* the residue was partitioned between dichloromethane (30 ml) and 2M sulphuric acid (30 ml). The aqueous layer was separated and extracted with a further portion of dichloromethane (30 ml). The organic extracts were combined, dried over anhydrous magnesium sulphate, filtered and the solvent removed *in vacuo* to afford a pale yellow oil that was subjected to column chromatography. Elution with 5:2 v/v petroleum ether (b.p. 40-60°C)-diethyl ether afforded the *product* **6** (700 mg, 66%) (*E*:*Z* 3:1), R_f 0·60, as a colourless oil. $[\alpha]_D$ -38·8° (*c* 1·0, $CHCl_3$); (Found: C, 63·3; H, 8·9; N, 4·65. $C_{14}H_{23}NO_2Si$ requires C, 63·35; H, 8·75; N, 5·3%); *m/z* (%) 266 (MH^+, 25); ν_{max} (film) 3250, 1650, 1600 cm^{-1}; δ_H ($CDCl_3$) 8·40 and 7·98 (2 x 1H, 2 x broad s, -OH), 7·46 (1H, d, *J* 7 Hz, H-1), 7·40-7·26 (2 x 5H, m, ArH), 6·81 (1H, d, *J* 7 Hz, H-1), 6·10 and 5·32 (2 x 1H, 2 x d, *J* 7 Hz, H-2), 0·94 and 0·93 (2 x 9H, 2 x s, ^{t}Bu), 0·13, 0·11, 0·07 and 0·07 (4 x 3H, 4 x s, $SiMe_2$); δ_C ($CDCl_3$) 154·0 and 153·3 (C-1), 140·6 and 140·6 (ArC), 128·4 and 128·3 (*o*- or *m*-ArCH), 127·7 and 127·6 (*p*-ArCH), 126·2 and 125·8 (*m*- or *o*-ArCH), 72·3 and 75·9 (C-2), 25·9 and 25·8 (C*Me*$_3$), 18·3 (*C*Me$_3$), -4·6, -4·9 and -5·0 ($SiMe_2$).

(*S*)-3,4-Isopropylidenedioxybutanaldoxime 7. A stirred solution of hydroxylamine hydrochloride (1·16 g, 16·67 mmol) and (*S*)-3,4-isopropylidenedioxybutanal[9] (1·60 g, 11·11 mmol) in water (20 ml) was treated with anhydrous potassium carbonate (2·45 g, 17·78 mmol) and the resulting solution was stirred at room temperature overnight. After saturation of the solution with sodium chloride the mixture was extracted with diethyl ether (2 x 50 ml). The combined organic extracts were dried over anhydrous magnesium sulphate, filtered and the solvent removed *in vacuo* to afford a pale yellow oil that was subjected to column chromatography. Elution with 1:1 v/v petroleum ether (b.p. 40-60°C)-diethyl ether afforded the *product* **7** (1·31 g, 74%) (*E*:*Z* 1:1), R_f 0·26, as a colourless oil. $[\alpha]_D$ +15·2° (*c* 0·5, $CHCl_3$); (Found: C, 52·9; H, 8·45; N, 8·7. $C_7H_{13}NO_3$ requires C, 52·8; H, 8·2; N, 8·8%); *m/z* (%) 160 (MH^+, 24); ν_{max} (film)

3380, 1650 cm^{-1}; δ_H ($CDCl_3$) 8·95 and 8·42 (2 x 1H, 2 x broad s, -OH), 7·47 and 6·87 (2 x 1H, 2 x t, *J* 6 Hz and *J* 5·5 Hz, H-1), 4·35-4·27 (2 x 1H, m, H-3), 4·11-4·07 (2 x 1H, m, H-4α or H-4β), 3·64-3·59 (2 x 1H, m, H-4β or H-4α), 2·74-2·60 (2 x 1H, m, H-2α or H-2β), 2·55-2·17 (2 x 1H, m, H-2β or H-2α), 1·43, 1·42, 1·36 and 1·35 (4 x 3H, 4 x s, CMe$_2$); δ_C ($CDCl_3$) 148·3 and 148·1 (C-1), 109·4 and 109·3 (*C*Me$_2$), 73·2 and 72·8 (C-3), 68·9 and 68·8 (C-4), 33·8 and 29·0 (C-2), 26·8, 26·8, 25·5 and 25·5 (C*Me*$_2$).

(1*S*,4'*S*,5*R*,8*R*)-8-(2',2'-Dimethyl-1',3'-dioxolan-4'-yl)-1-aza-7-oxa-4-thiadioxybicyclo[3.2.1]octane 8. A solution of 2,3-*O*-isopropylidene-D-glyceraldoxime[3] **1** (580 mg, 4·00 mmol) and divinyl sulphone (472 mg, 4·00 mmol) in toluene (25 ml) was stirred and held at reflux for 24 hours. After cooling the solvent was removed *in vacuo* and the residue subjected to column chromatography. Elution with diethyl ether afforded the *product* **8** (504 mg, 48%), R_f 0·44, as a colourless solid that crystallized from petroleum ether (b.p. 60-80°C)-dichloromethane as colourless prisms, m.p. 114-115°C; [α]$_D$ +9·6° (*c* 0·5, CHCl$_3$); (Found: C, 45·5; H, 6·4; N, 5·3; S, 12·3. $C_{10}H_{17}NO_5S$ requires C, 45·6; H, 6·5; N, 5·3; S, 12·2%); *m/z* (%) 264 (MH$^+$, 100); ν_{max} (nujol) 1325, 1120 cm^{-1}; δ_H ($CDCl_3$) 4·51 (1H, d, *J* 10 Hz, H-6α), 4·17 (1H, dd, *J* 10, 6 Hz, H-6β), 4·09 (1H, dd, *J* 9, 5·5 Hz, H-5'β), 4·05 (1H, dd, *J* 6, 3 Hz, H-5), 4·00 (1H, dd, *J* 9, 3 Hz, H-5'α), 3·90 (1H, d, *J* 9·5 Hz, H-8), 3·81 (1H, ddd, *J* 9·5, 5·5, 3 Hz, H-4'), 3·59 (1H, dd, *J* 14, 5·5 Hz, H-2β), 3·34 (1H, ddd, *J* 14, 12, 5·5 Hz, H-3β), 3.23 (1H, ddd, *J* 14, 12, 4·5 Hz, H-2α), 3·00 (1H, ddd, *J* 14, 4·5, 3 Hz, H-3α), 1·46 (3H, s, Me), 1·31 (3H, s, Me); δ_C ($CDCl_3$) 110·5 (*C*Me$_2$), 72·8 (C-4' or C-8), 71·6 (C-8 or C-4'), 69·0 (C-5' or C-6), 67·8 (C-6 or C-5'), 64·5 (C-5), 53·6 (C-2), 46·3 (C-3), 27·3 and 25·2 (C*Me*$_2$).

(1*S*,2'*R*,3'*R*,5*R*,8*R*)-8-(3'-*tert*-Butyldimethylsilyloxy-1',2'-isopropylidenedioxypropyl)-1-aza-7-oxa-4-thiadioxybicyclo[3.2.1]octane 10. A solution of 4-*O*-(*tert*-butyldiphenylsilyl)-2,3-*O*-isopropylidene-L-threose oxime **2** (100 mg, 0·24 mmol) and divinyl sulphone (28 mg, 0·24 mmol) in toluene (10 ml) was stirred and held at reflux for 24 hours. After cooling the solvent was removed *in vacuo* and the residue subjected to column chromatography. Elution with 1:1 v/v petroleum ether (b.p. 40-60°C)-diethyl ether afforded the *product* **10** (98 mg, 78%), R_f 0·38, as a colourless solid that crystallized from petroleum ether (b.p. 60-80°C)-dichloromethane as colourless plates, m.p. 176-179°C; [α]$_D$ -19·0° (*c* 0·21, CH$_2$Cl$_2$); (Found: C, 61·1; H, 7·05; N, 2·4. $C_{27}H_{39}NO_6SiS$ requires C, 60·8; H, 7·3; N, 2·6%); *m/z* (%) 534 (MH$^+$, 100); δ_H ($CDCl_3$) 7·78 (4H, d, *J* 7 Hz, *o*-ArH), 7·41 (6H, m, *m*-ArH and *p*-ArH), 4·52 (1H, d, *J* 9·5 Hz, H-6α), 4·22 (1H, dd, *J* 9·5, 6 Hz, H-6β), 4·11 (1H, dd, *J* 8·5, 5 Hz, H-2'), 4·04 (1H, dd, *J* 6, 3 Hz, H-5), 3·88 (1H, d, *J* 9 Hz, H-8), 3·82 (2H, dd, *J* 9·5, 6·5 Hz, H-3'α and H-3'β), 3·68 (1H, dd, *J* 9, 5 Hz, H-1'), 3·59 (1H, dd, *J* 14·5, 6·5 Hz, H-2β), 3·38 (1H, ddd, *J* 14·5, 13, 6·5 Hz, H-3β), 3·18 (1H, ddd, *J* 14·5, 13, 5 Hz, H-2α), 3·02 (1H, ddd, *J* 14·5, 5, 3 Hz, H-3α), 1·44 (3H, s, Me), 1·41 (3H, s, Me), 1·04 (9H, s, ^{t}Bu); δ_C ($CDCl_3$) 136·1 (*o*-ArC), 129·6 (*p*-ArC), 127·8 (*m*-ArC), 110·4 (*C*Me$_2$), 81·7 (C-3'), 74·2 (C-1'), 72·1 (C-8), 69·4 (C-2' or C-6), 65·1 (C-6 or C-2'), 64·3 (C-5), 53·6 (C-2), 46·7 (C-3), 27·3 and 27·1 (C*Me*$_2$), 26·6 (C*Me*$_3$), 19·2 (*C*Me$_3$).

(1*R*,1'*R*,4'*R*,5*S*,8*S*)-8-(1',3'-Benzylidenedioxypropyl)-1-aza-7-oxa-4-thiadioxybicyclo[3.2.1]octane 12. A solution of (2*R*,5*R*)-2,4-benzylidenedioxybutanaldoxime **3** (309 mg, 1·49 mmol) and divinyl sulphone (176 mg, 1·49 mmol) in toluene (30 ml) was stirred and held at reflux for 24 hours. After cooling the solvent was removed *in vacuo* and the residue subjected to column chromatography. Elution with diethyl ether afforded the *product* **12** (395 mg, 81%), R_f 0·42, as a colourless solid that crystallized from petroleum ether (b.p. 60-80°C)-diethyl ether as colourless plates, m.p. 191-194°C; $[\alpha]_D$ +11·0° (*c* 0·23, $CHCl_3$); (Found: C, 55·55; H, 5·95; N, 4·45. $C_{15}H_{19}NO_5S$ requires C, 55·4; H, 5·85; N, 4·3%); *m/z* (%) 326 (MH^+, 100); δ_H ($CDCl_3$) 7·37 (5H, m, ArH), 5·42 (1H, s, H-4'), 4·48 (1H, d, *J* 10 Hz, H-6α), 4·30 (1H, dd, *J* 10, 6 Hz, H-6β), 4·12 (2H, m, H-3'α and H-3'β), 3·92 (1H, dd, *J* 6, 3 Hz, H-5), 3·76 (2H, H-1' and H-8), 3·61 (2H, m, H-2β and H-3β), 3·15 (2H, m, H-2α and H-3α), 1·81 (2H, m, H-2'α and H-2'β).

(1*S*,1'*S*,5*R*,8*R*)- and **(1*R*,1'*S*,5*S*,8*S*)-8-(1',2'-Dimethoxyethyl)-1-aza-7-oxa-4-thiadioxybicyclo[3.2.1]octane 18** and **19**. A solution of 2,3-di-*O*-methyl-D-glyceraldoxime **4** (798 mg, 6·00 mmol) and divinyl sulphone (708 mg, 6·00 mmol) in toluene (20 ml) was stirred and held at reflux for 24 hours. After cooling the solvent was removed *in vacuo* and the residue subjected to column chromatography. Elution with diethyl ether afforded the *product* **18** (452 mg, 30%), R_f 0·38, as a colourless solid that crystallized from petroleum ether (b.p. 60-80°C)-dichloromethane as colourless plates, m.p. 145-146°C; $[\alpha]_D$ +18·7° (*c* 0·6, $CHCl_3$); (Found: C, 43·05; H, 6·8; N, 5·55; S, 12·55. $C_9H_{17}NO_5S$ requires C, 43·0; H, 6·8; N, 5·55; S, 12.75%); *m/z* (%) 252 (MH^+, 100); ν_{max} (nujol) 1325, 1125 cm^{-1}; δ_H ($CDCl_3$) 4·53 (1H, d, *J* 8 Hz, H-6α), 4·19-4·10 (3H, m, H-2'β, H-5, and H-6β), 3·74-3·50 (3H, m, H-1', H-2'α and H-8), 3·43 (3H, s, OMe), 3·41 (3H, s, OMe), 3·36-3·25 (2H, m, H-2β and H-3β), 3·13 (1H, dm, *J* 12 Hz, H-2α), 3·01 (1H, dm, *J* 12 Hz, H-3α). Further elution with diethyl ether afforded the *product* **19** (226 mg, 15%), R_f 0·17, as a colourless oil. $[\alpha]_D$ -23·3° (*c* 1·0, $CHCl_3$); (Found: C, 42·95; H, 6·75; N, 5·5; S, 12·8. $C_9H_{17}NO_5S$ requires C, 43·0; H, 6·8; N, 5·55; S, 12.75%); *m/z* (%) 252 (MH^+, 100); ν_{max} (nujol) 1320, 1125 cm^{-1}; δ_H ($CDCl_3$) 4·49 (1H, d, *J* 10 Hz, H-6α), 4·18-4·12 (2H, m, H-2'β and H-6β), 4·07 (1H, d, *J* 10 Hz, H-8), 4·01 (1H, dd, *J* 6, 3 Hz, H-5), 3·71-3·53 (2H, m, H-1' and H-2'α), 3·51 (3H, s, OMe), 3·37 (3H, s, OMe), 3·35-3·19 (3H, m, H-2α, H-2β and H-3β), 3·03 (1H, dm, *J* 13 Hz, H-3α).

(1*S*,1'*S*,5*R*,8*R*) and **(1*R*,1'*S*,5*S*,8*S*)-8-[1'-(*tert*-Butyldimethylsilyloxy)ethyl]-1-aza-7-oxa-4-thiadioxybicyclo[3.2.1]octane 20** and **21**. A solution of (*S*)-2-(*tert*-butyldimethylsilyloxy)-propanaldoxime **5** (609 mg, 3·00 mmol) and divinyl sulphone (354 mg, 3·00 mmol) in toluene (8 ml) was stirred and held at reflux for 24 hours. After cooling the solvent was removed *in vacuo* and the residue was subjected to column chromatography. Elution with 1:1 v/v petroleum ether (b.p. 40-60°C)-diethyl ether afforded the *product* **20** (204 mg, 21%), R_f 0·30, as a colourless solid that crystallized from petroleum ether (b.p. 60-80°C)-dichloromethane as colourless plates, m.p. 158-159°C; $[\alpha]_D$ -5·0° (*c* 0·4, $CHCl_3$); (Found: C, 48·7; H, 8·7; N, 4·4; S, 9·85. $C_{13}H_{27}NO_4SiS$ requires C, 48·55; H, 8·45; N, 4·35; S, 9·95%); *m/z* (%) 322 (MH^+, 41), 264 (M^+-^tBu, 100); ν_{max} (nujol) 1320, 1110 cm^{-1}; δ_H ($CDCl_3$) 4·47 (1H, d, *J* 10 Hz, H-6α), 4·07 (1H, dd, *J* 10, 6 Hz, H-6β), 3·83-3·77 (2H, m, H-1' and H-8), 3·74 (1H, dd, *J* 6, 2·5 Hz, H-5), 3·62 (1H, dm, *J* 13·5 Hz, H-2β), 3·39-3·17 (2H, m, H-2α and H-3β), 3·00 (1H, dm, *J* 13·5 Hz, H-3α), 1·18 (3H, d, *J* 6 Hz, Me), 0·88 (9H, s, ^tBu), 0·09 (3H, s, SiMe), 0·08 (3H, s, SiMe). Further elution afforded the *product* **21** (426 mg, 44%), R_f 0·22, as a colourless solid that crystallized from petroleum ether (b.p. 60-80°C)-dichloromethane as fine colourless needles. m.p. 105-106°C; $[\alpha]_D$ +19·0° (*c* 0·4, $CHCl_3$); (Found: C, 48·6; H, 8·45; N, 4·5; S, 10·05. $C_{13}H_{27}NO_4SiS$ requires C, 48·55; H, 8·45; N, 4·35; S, 9·95%); *m/z* (%) 322 (MH^+, 76), 264 (M^+-^tBu, 100); ν_{max} (nujol) 1320, 1125 cm^{-1}; δ_H ($CDCl_3$) 4·49 (1H, dt, *J* 9, 4 Hz, H-6α), 4·08-4·02 (2H, m, H-1' and H-6β), 3·70 (1H, d, *J* 9 Hz, H-8), 3·66-3·52 (2H, m, H-2β and H-5), 3·38-3·18 (2H, m, H-2α and H-3β), 2·99 (1H, dm, *J* 13·5 Hz, H-3α), 1·31 (3H, d, *J* 6 Hz, Me), 0·88 (9H, s, ᵗBu), 0·08 (3H, s, SiMe), 0·04 (3H, s, SiMe).

(1*R*,1'*S*,5*S*,8*S*)-8-[1'-(*tert*-Butyldimethylsilyloxy)-1'-phenylmethyl]-1-aza-7-oxa-4-thiadioxybicyclo[3.2.1]octane 23. A solution of (*S*)-2-(*tert*-butyldimethylsilyloxy)-2-phenylacetaldoxime **6** (265 mg, 1·00 mmol) and divinyl sulphone (118 mg, 1·00 mmol) in toluene (8 ml) was stirred and held at reflux for 24 hours. After cooling the solvent was removed *in vacuo* and the residue subjected to column chromatography. Elution with 3:2 v/v petroleum ether (b.p. 40-60°C)-diethyl ether afforded cycloadducts **22** and **23** (206 mg, 54%, 1:3 mixture of diastereomers), R_f 0·19, as a colourless solid. Double crystallization from petroleum ether (b.p. 60-80°C)-dichloromethane afforded the *product* **23** as colourless needles, m.p. 167-168°C; $[\alpha]_D$ +49·6° (*c* 0·5, $CHCl_3$); (Found: C, 56·25; H, 7·85; N, 3·55; S, 8·3. $C_{18}H_{29}NO_4SiS$ requires C, 56·35; H, 7·6; N, 3·65; S, 8·35%); *m/z* (%) 384 (MH^+, 41); ν_{max} (nujol) 1320, 1120 cm^{-1}; δ_H ($CDCl_3$) 7·37-7·29 (5H, m, ArH), 4·56 (1H, d, *J* 9·5 Hz, H-6α), 4·35 (1H, d, *J* 9 Hz, H-1'), 4·22 (1H, dd, *J* 9·5, 6 Hz, H-6β), 4·18 (1H, dd, *J* 6, 2·5 Hz, H-5), 4·03 (1H, d, *J* 9 Hz, H-8), 3·50 (1H, dd, *J* 13, 5·5 Hz, H-2β), 3·33 (1H, ddd, *J* 13, 10·5, 5·5 Hz, H-3β), 3·01 (1H, ddd, *J* 13, 10·5, 4·5 Hz, H-2α), 2·94 (1H, ddd, *J* 13, 4·5, 3 Hz, H-3α), 0·87 (9H, s, ᵗBu), 0·06 (3H, s, SiMe), -0·28 (3H, s, SiMe); δ_C ($CDCl_3$) 141·5 (ArC), 128·3 (*o*- or *m*-ArCH), 128·2 (*p*-ArCH), 127·2 (*m*- or *o*-ArCH), 75·9 (C-1' or C-8), 73·1 (C-8 or C-1'), 68·9 (C-6), 64·7 (C-5), 53·6 (C-2), 46·1 (C-3), 25·7 (C*Me₃*), 18·1 (*C*Me₃), -4·5 and -5·2 ($SiMe_2$).

(1*S*,2'*S*,5*R*,8*R*)- and (1*R*,2'*S*,5*S*,8*S*)-8-(2',3'-Isopropylidenedioxypropyl)-1-aza-7-oxa-4-thiadioxybicyclo[3.2.1]octane 24 and 25. A solution of (*S*)-3,4-isopropylidenedioxybutanaldoxime **7** (318 mg, 2·00 mmol) and divinyl sulphone (236 mg, 2·00 mmol) in toluene (8 ml) was stirred and held at reflux for 24 hours. After cooling the solvent was removed *in vacuo* and the residue subjected to column chromatography. Elution with diethyl ether afforded cycloadducts **24 and 25** (306 mg, 55%, 4:5 mixture of diastereomers), R_f 0·30, as a colourless solid. Crystallization from petroleum ether (b.p. 60-80°C)-dichloromethane afforded the *products* **24 and 25** (4:5 mixture) as colourless plates. m.p. 158-60°C; $[\alpha]_D$ -9·6° (*c* 0·5, $CHCl_3$); (Found: C, 47·4; H, 6·75; N, 5·05; S 11·6. $C_{11}H_{19}NO_5S$ requires C, 47·6; H, 6·9; N, 5·05; S, 11·55%); *m/z* (%) 278 (MH^+, 65); ν_{max} (nujol) 1320, 1125 cm^{-1}; δ_H ($CDCl_3$) 4·51 (2 x 1H, d, *J* 10 Hz, H-6α), 4·29-4·22 (2 x 1H, m, H-2'), 4·20-4·11 (2 x 2H, m, H-3'α and H-3'β), 4·09 and 4·07 (2 x 1H, 2 x dd, *J* 10, 6 Hz, H-6β), 3·89 and 3·75 (2 x 1H, 2 x dd, *J* 6, 3 Hz, H-5), 3·73 (1H, dd, *J* 8, 7 Hz, H-8), 3·67-3·60 (2 x 1H, m, H-2β), 3·52 (1H, dd, *J* 8, 7 Hz, H-8), 3·40-3·20 (2 x 2H, m, H-2α and H-3β), 3·05-2·95 (2 x 1H, m, H-3α), 1·90 (1H, ddd, *J* 14, 8, 6 Hz, H-1'α or H-1'β), 1·73 (1H, ddd, *J* 14, 8, 3 Hz, H-1'α or H-1'β), 1·63 (1H, ddd, *J* 14, 7, 5·5 Hz, H-1'β or H-1'α), 1·55 (1H, ddd, *J* 14, 7, 6 Hz, H-1'β or H-1'α), 1·44, 1·39, 1·35 and 1·34 (4 x 3H, 4 x s, Me); δ_C ($CDCl_3$) 109·4 and 109·4 (*C*Me₂), 72·8 and 72·4 (C-2'), 69·4, 69·0, 68·9 and 68·3 (C-3' and C-6), 67·1, 67·0, 66·9 and 65·7 (C-5 and C-8), 53·4 and 53·4 (C-2), 45·9 and 45·9 (C-3), 36·1 and 35·1 (C-1'), 27·0, 26·8, 25·7 and 25·4 (C*Me₂*).

(1*S*,1'*S*,5*R*,8*R*)-8-(1',2'-Dihydroxyethyl)-1-aza-7-oxa-4-thiadioxybicyclo[3.2.1]octane 26. To a mixture of trifluoroacetic acid (5 ml) and water (5 ml) was added (1*S*,4'*S*,5*R*,8*R*)-8-(2',2'-dimethyl-1',3'-dioxolan-4'-yl)-1-aza-7-oxa-4-thiadioxybicyclo[3.2.1]octane **8** (526 mg, 2·00 mmol) and the resulting solution was stirred at room temperature for 1 hour after which time the solvent was removed *in vacuo*.

Residual traces of trifluoroacetic acid and water were removed from the crude product by the addition of toluene (3 x 20 ml) and evaporation to dryness *in vacuo* to afford the *product* **26** (446 mg, 100%) as a colourless solid that crystallized from petroleum ether (b.p. 60-80°C)-acetone as colourless prisms, m.p. 122-124°C (decomp.); $[\alpha]_D$ +77·7° (*c* 0·35, H_2O); (Found: C, 37·35; H, 5·65; N, 6·25; S, 14·4. $C_7H_{13}NO_5S$ requires C, 37·65; H, 5·85; N, 6·25; S, 14.35%); *m/z* (%) 224 (MH^+, 100); ν_{max} (nujol) 3500, 3360, 1325, 1120 cm^{-1}; δ_H (D_2O) 4·59 (1H, dd, *J* 10 Hz, H-6α), 4·37 (1H, dd, *J* 6, 2·5 Hz, H-5), 4·24 (1H, dd, *J* 10, 6 Hz, H-6β), 4·02 (1H, d, *J* 9·5 Hz, H-8), 3·77 (1H, dd, *J* 12, 3 Hz, H-2'α), 3·63 (1H, dd, *J* 12, 5·5 Hz, H-2'β), 3·59-3·25 (5H, m, H-1', H-2α, H-2β, H-3α and H-3β).

(1*S*,5*R*,8*R*)-1-Aza-7-oxa-4-thiadioxybicyclo[3.2.1]octane-8-carboxaldehyde 27. A stirred solution of (1*S*,1'*S*,5*R*,8*R*)-8-(1',2'-dihydroxyethyl)-1-aza-7-oxa-4-thiadioxybicyclo[3.2.1]octane **26** (26 mg, 0·10 mmol) in deuterium oxide (2 ml) was treated with sodium periodate (28 mg, 0·13 mmol) and the resulting solution was stirred at room temperature for 2 hours after which time ^1H nmr analysis showed the reaction to be complete. The solvent was removed *in vacuo* to afford the *product* **27** (19 mg, 100%) contaminated with formaldehyde and inorganic salts. $[\alpha]_D$ +10·7° (*c* 0·7, H_2O); *m/z* (%) 192 (MH^+, 9); δ_H (D_2O) 4·58 (1H, d, *J* 10 Hz, H-6α), 4·33 (1H, dd, *J* 6, 2·5 Hz, H-5), 4·21 (1H, dd, *J* 10, 6 Hz, H-6β), 3·90 (1H, d, *J* 7·5 Hz, H-8), 3·63 (1H, dm, *J* 14 Hz, H-2β), 3·52 (1H, dm, *J* 14 Hz, H-3β), 3·38-3·27 (2H, m, H-2α and H-3α).

(1*R*,5*S*,5'*R*,8*S*)-8-(α-L-*Arabino*-pyranosid-5'-yl)-1-aza-7-oxa-4-thiadioxybicyclo[3.2.1]-octane 28. (1*R*,5*S*,5'*R*,8*S*)-8-(1',2':3',4'-Di-*O*-isopropylidene-α-L-*arabino*-pyranosid-5'-yl)-1-aza-7-oxa-4-thiadioxybicyclo[3.2.1]octane **15**[1] (195 mg, 0·50 mmol) was added to a mixture of trifluoroacetic acid (2 ml) and water (2 ml) and the resulting solution was stirred at room temperature for 1 hour. Upon removal of the solvent *in vacuo* the residual traces of trifluoroacetic acid were removed by the addition of water (3 x 5 ml) and evaporation to dryness *in vacuo* to afford the *product* **28** (164 mg, 100%) as a colourless solid. m.p. 98-103°C (decomp.); $[\alpha]_D$ +26·0° (*c* 0·4, H_2O); (Found: C, 36·45; H, 5·6; N, 4·05; S, 9·9. $C_{10}H_{17}NO_8S{\cdot}H_2O$ requires C, 36·45; H, 5·8; N, 4·25; S, 9·75%); *m/z* (%) 312 (MH^+, 100); ν_{max} (nujol) 3400, 1320, 1120 cm^{-1}; δ_H (D_2O) 5·22 (1H, d, *J* 2·5 Hz, H-1'), 4·60 (1H, d, *J* 10 Hz, H-6α), 4·53 (1H, d, *J* 8 Hz, H-8), 4·39 (1H, dd, *J* 5·5, 3 Hz, H-5), 4·37-4·15 (2H, m, H-3' and H-6β), 4·05 (1H, dd, *J* 10, 3·5 Hz, H-2'), 3·78-3·25 (6H, m, H-2α, H-2β, H-3α, H-3β, H-4' and H-5').

(1*R*,5*S*,8*S*)-1-Aza-7-oxa-4-thiadioxybicyclo[3.2.1]octane-8-carboxaldehyde 29. A stirred solution of (1*R*,5*S*,5'*R*,8*S*)-8-(α-L-*arabino*-pyranosid-5'-yl)-1-aza-7-oxa-4-thiadioxybicyclo[3.2.1]octane **28** (31 mg, 0·10 mmol) in deuterium oxide (2 ml) was treated with sodium periodate (107 mg, 0·50 mmol) and the resulting solution was stirred at room temperature for 2 hours after which time ^1H nmr analysis showed the reaction to be complete. The solvent was removed *in vacuo* to afford the *product* **29** (19 mg, 100%) contaminated with formaldehyde, formic acid and inorganic salts. $[\alpha]_D$ -10·2° (*c* 0·7, H_2O); *m/z* (%) 192 (MH^+, 9); δ_H (D_2O) 4·58 (1H, d, *J* 10 Hz, H-6α), 4·33 (1H, dd, *J* 6, 2·5 Hz, H-5), 4·21 (1H, dd, *J* 10, 6 Hz, H-6β), 3·90 (1H, d, *J* 7·5 Hz, H-8), 3·63 (1H, dm, *J* 14 Hz, H-2β), 3·52 (1H, dm, *J* 14 Hz, H-3β), 3·38-3·27 (2H, m, H-2α and H-3α).

Single crystal X-ray diffraction analysis of 8 and 23.[10] All crystallographic measurements were carried out at ambient temperature on a Stoe STADI 4 diffractometer using graphite monochromated molybdenum K_α X-radiation (λ=0·71069 Å) (for **8**) and copper K_α X-radiation (λ=1·54184 Å) (for **23**). Two equivalent sets of data were collected in the range 4·0°<2θ<50° (for **8**) and 4·0°<2θ<130° (for **23**) using ω/θ scans. No significant variation was observed in the intensity of five standard reflections. Lorentz and polarisation corrections were applied to the data-sets together with a semi-empirical absorption correction based on azimuthal ψ-scans. The structures were solved by direct methods using SHELXS-86[24] and were refined by full-matrix least squares (based on F^2) using SHELXL-93[25] which uses all data for refinement. The weighting scheme was $\omega = [\sigma^2(F_0{}^2) + (0{\cdot}0354)^2 + 0{\cdot}2956P]^{-1}$ (for **8**) and $\omega = [\sigma^2(F_0{}^2) + (0{\cdot}0354)^2 + 0{\cdot}2956P]^{-1}$ (for **23**) where $P = (F_0{}^2+2F_c{}^2)/3$. All non-hydrogen atoms were refined with anisotropic thermal parameters. All hydrogen atoms were constrained to predicted positions (C-H = 0·96, 0·97, 0·98 and 0·93Å for primary, secondary, tertiary and aromatic hydrogens respectively).

Crystal data for **8**:[10] $C_{10}H_{17}NO_5S$, 0·76 x 0·45 x 0·40 mm, M = 263·31, orthorhombic, space group $P2_12_12_1$, a = 7·3186(8), b = 10·1626(13), c = 16·528(2) Å, U = 1229·3(3) Å^3, Z = 4, D_x = 1·423 gcm^{-3}, μ = 0·273 mm^{-1}, F(000) = 560.

Non-hydrogen atom co-ordinates (x 10^4) and equivalent isotropic thermal parameters (Å^2 x 10^3) for **8** with estimated standard deviations in parentheses. (U_{eq} = 1/3 x the trace of the orthoganalized U_{ij} matrix).

Atom	x	y	z	U_{eq}
N(1)	8253(2)	-1349·1(14)	8550·2(8)	28·7(3)
O(2)	7526(2)	-2076·9(11)	7858·5(7)	34·7(3)
C(3)	6207(2)	-1256(2)	7435·4(11)	33·3(4)
C(4)	6109(2)	11(2)	7917·0(9)	23·6(3)
S(5)	7723·1(5)	1176·0(4)	7538·5(2)	26·22(13)
O(5a)	7955(2)	2202·2(12)	8135·4(8)	37·8(3)
O(5b)	7194(2)	1566·6(13)	6735·8(7)	39·4(3)
C(6)	9714(2)	185(2)	7509·6(12)	29·2(3)
C(7)	9899(2)	-642(2)	8283·0(11)	31·7(4)
C(8)	6765(2)	-434(2)	8750·6(9)	23·0(3)
C(9)	5285(2)	-1129(2)	9252·6(10)	27·9(4)
O(10)	3685(2)	-325·5(14)	9286·7(7)	32·3(3)
C(11)	3713(3)	409(2)	10035·4(10)	31·0(4)
C11a)	3747(3)	1865(2)	9852·7(13)	42·4(5)
C(11b)	2090(3)	-7(2)	10548·8(11)	42·1(5)
C(12)	5385(2)	63·1(13)	10422·3(7)	33·1(3)
C(13)	5850(2)	-1224(2)	10131·7(10)	34·2(4)

Crystal data for **23**:[10] $C_{18}H_{29}NO_4SiS$, 0·57 x 0·19 x 0·19 mm, M = 383·57, monoclinic, space group $P2_12_12_1$, a = 6·9637(7), b = 28·570(3), c = 10·9036(11) Å, U = 2169·3(4) Å^3, Z = 4, D_x = 1·174 gcm^{-3}, μ = 0·224 mm^{-1}, F(000) = 824.

Non-hydrogen atom co-ordinates (x 10^4) and equivalent isotropic thermal parameters (Å^2 x 10^3) for **23** with estimated standard deviations in parentheses. (U_{eq} = 1/3 x the trace of the orthoganalized U_{ij} matrix).

Atom	x	y	z	U_{eq}
S(1)	802·8(12)	2542·9(3)	1849·6(7)	57·1(2)
O(1a)	-550(4)	2916·2(9)	1996(3)	82·2(8)
O(1b)	464(4)	2210·1(9)	886(2)	79·8(8)
C(2)	3143(5)	2791·8(11)	1706(3)	49·7(7)
C(3)	3512(5)	3097·0(10)	2837(2)	48·0(7)
N(4)	3933(4)	2751·3(9)	3786(2)	52·0(6)
O(4)	5089(3)	2398·9(8)	3149(2)	62·8(6)
C(4)	4687(5)	2421·9(12)	1849(3)	60·3(8)
C(5)	2168(5)	2520·4(13)	4217(3)	63·6(9)
C(6)	1044(6)	2238·7(13)	3256(3)	70·1(10)
O(7)	4367(4)	3789·5(7)	1826(2)	60·9(6)
Si(7)	5604(2)	4164·6(3)	983·1(9)	64·6(3)
C(71)	6703(10)	4626(2)	1960(5)	118(2)
C(72)	7464(7)	3851(2)	109(5)	95·8(15)
C(73)	3758(7)	4425·0(15)	-49(4)	83·0(13)
C(74)	4678(11)	4810(2)	-849(5)	130(2)
C(75)	2129(10)	4647(2)	703(6)	127(2)
C(76)	2894(9)	4036(2)	-880(5)	114(2)
C(7)	5144(5)	3448·3(11)	2650(3)	51·2(7)
C(8)	5791(6)	3666·7(10)	3838(3)	58·8(8)
C(9)	4563(8)	3926·3(14)	4556(4)	83·8(12)
C(10)	5197(11)	4120(2)	5669(4)	107(2)
C(11)	7075(11)	4061(2)	6026(5)	111(2)
C(12)	8298(9)	3811(2)	5318(5)	99(2)
C(13)	7675(6)	3616(14)	4222(4)	74·9(11)

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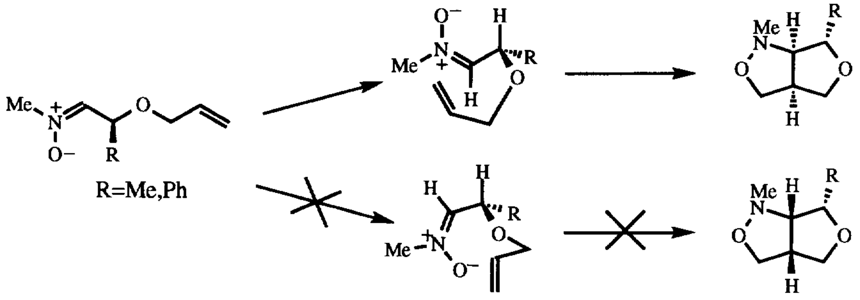
11. We assume that chiral nitrones derived from aldoximes in which the nearest stereogenic centre is located β- to the oxime moiety similarly undergo cycloaddition with the internal dipolarophile adding preferentially *syn* to the oxygenated functionality. We therefore tentatively assign the major isomer as **25** having (*R*)-stereochemistry at nitrogen.
12. We prefer not to use the Cahn-Ingold-Prelog system for describing the stereochemistry at the α-chiral centre in these aldoximes because of the confusion that can arise when compounds containing an identical stereogenic centre have different (*R*)- or (*S*)- descriptors as a result of a difference in remote substituents. This reversal is merely an artefact of the prioritization rules.
13. Stereochemistries of products reported in intramolecular cycloaddition reactions of nitrones containing internal dipolarophiles located at an α-stereocentre[26,27] indicate that reaction proceeds solely *via* transition states in which the α-methine hydrogen and nitrone hydrogen atom adopt an antiperiplanar alignment. e.g. The *O*-allyl substituents of the chiral aldonitrones shown below must undergo cycloaddition to either of the diastereotopic faces of the aldonitrone moiety from a fixed direction due to geometric constraints at the stereogenic centre. The observed ratio of the two possible cycloadducts thus effectively indicates the relative proportions of nitrone reacting *via* antiperiplanar and synperiplanar aligned transition states; compounds derived from an antiperiplanar aligned transition state are found to be the sole products.[27]



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23. The case illustrated is for a D-Type aldoxime which will react preferentially as shown in **A** to afford the isomer with (*S*) stereochemistry at nitrogen; L-Type aldoximes react similarly *via* the mirror image of **A**.
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