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Stereochemically Controlled Synthesis of Substituted 1,2–Oxathianes

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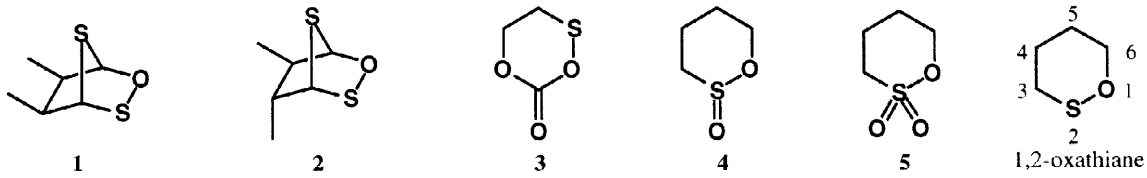
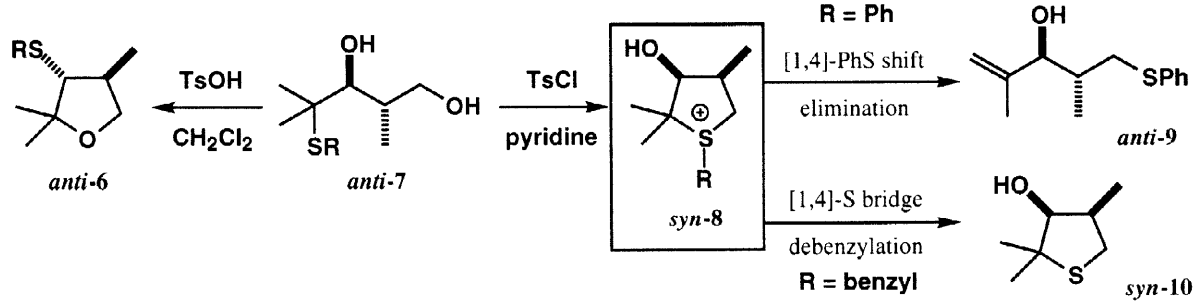
Abstract: Treatment of a series of 4-sulfanyl-1,3-diols with Et_3N/TsCl in CH_2Cl_2 gives substituted 1,2-oxathianes as single diastereoisomers in high yield by cyclisation with formation of the S–O bond. Stereochemistry can be controlled at each stereogenic centre (four in all) of the new oxathiane ring.

Acyclic sulfenic esters are much better known than the cyclic esters.[1] Among cyclic sulfenates, 1,2-oxathietanes are the least rare,[2] 1,2-oxathiolane itself is known,[3] but the 1,2-oxathiane system is rare. There are reports that sulfur bridged 1,2-oxathianes **1** and **2** are intermediates in the degradation of vinyl sulfides from the onion *Allium cepa*,[4] while oxidised versions, such as **3**, may be reactive species in the inactivation of the flavoenzyme cyclohexanone oxygenase by thiolactones.[5] The stable 1,2-oxathiane-2-oxides **4** and 2,2-dioxides **5** are well documented.[6] In this letter we report a general synthesis of substituted 4-hydroxy-1,2-oxathianes by a stereospecific cyclisation which forms the S–O bond by nucleophilic displacement at sulfur and which can control the stereochemistry at all the carbon atoms in the ring (C-3 to C-6).



We have previously reported numerous stereospecific [1,2]-RS migrations during acid-catalysed rearrangements of 4-RS-1,3-diols such as *anti*-**7** to give THFs *anti*-**6** in near quantitative yield and have shown that the rearrangement occurs irrespective of the nature of the migrating RS substituent (ArS, AlkS and HS).[7] By comparison, the nature of the R substituent *is* important in the [1,4]-RS migration which occurs when the same diols are rearranged with TsCl in pyridine. When R=Ph, the sulfonium ion intermediate **8** opens with elimination to give the allylic alcohols *anti*-**9** (85%) with an overall [1,4]-SPh shift, whereas, debenzylation of the sulfonium ion **8** is favoured when R=Bn to give the thiolane *syn*-**10** in near quantitative yield.[8]



In an attempt to synthesise the same thiolanes[8] (e.g. *syn*-**10**) by treatment of 4-HS-1,3-diols (e.g. *anti*-**11**) with TsCl in pyridine, we obtained not only the thiolane *syn*-**10** (52%), but to our surprise, the 1,2-oxathiane *syn*-**16** in 48% yield. This 1,2-oxathiane must have arisen from the competitive tosylation of the more nucleophilic tertiary SH group to give the S-tosyl derivative *anti*-**14**. Cyclisation by nucleophilic

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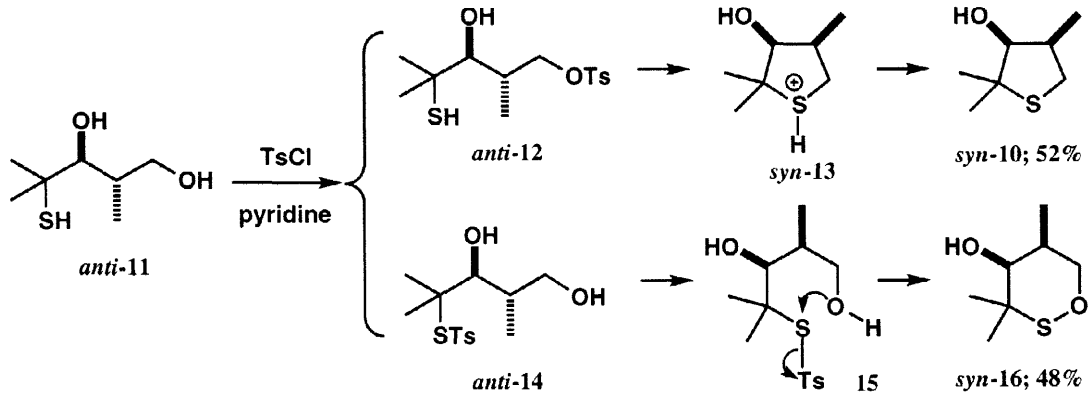
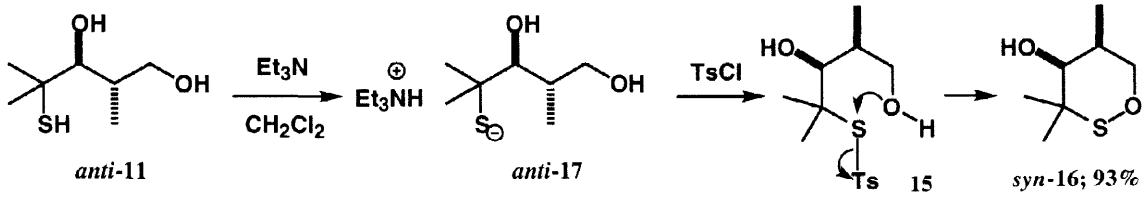
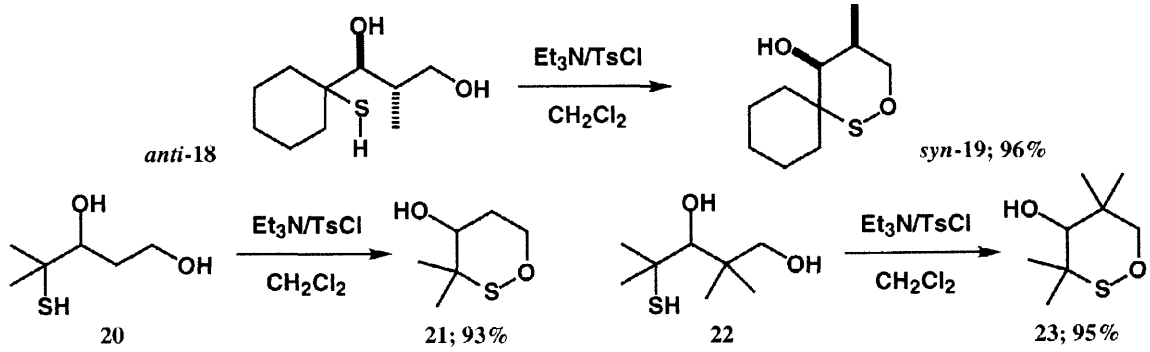
displacement[9] at sulfur with the primary OH group as nucleophile and the sulfinate, Ts^-, as leaving group (**15**) leads to the 1,2-oxathiane *syn*-**16**. Evidently, tosylation had occurred equally on the OH and SH groups when pyridine (pK_{aH} = 5.25) was used as the base catalyst.



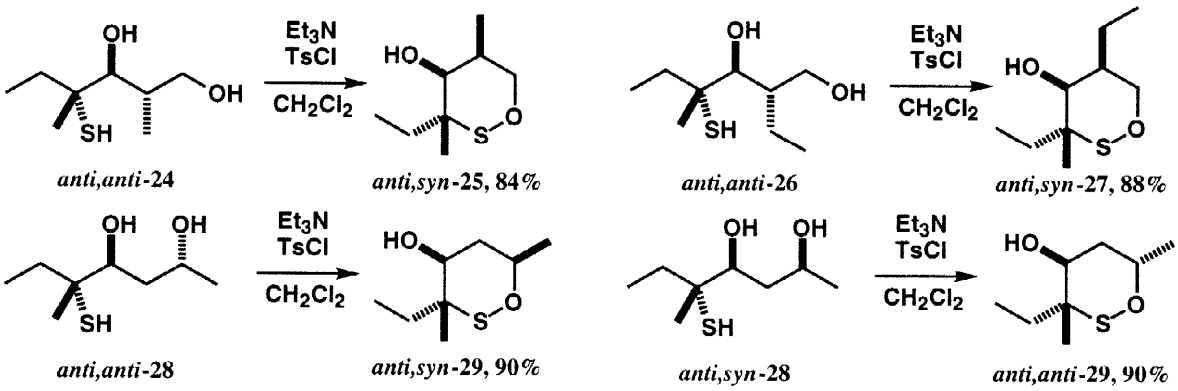
We were first interested in increasing chemoselective tosylation at the SH group to improve the yield of the 1,2-oxathianes. We argued that full deprotonation of the SH group (pK_a = 7) in *anti*-**11** (to form thiolate *anti*-**17**), would promote tosylation at sulfur since a thiolate is more nucleophilic than a thiol or an alcohol. Thus, initial treatment of the 4-HS-1,3-diol *anti*-**11** with the stronger base Et_3N (pK_{aH} = 9), followed by slow addition of TsCl gave solely the 1,2-oxathiane *syn*-**16** in an improved 93% yield.



We next investigated the scope and limitation of this cyclisation by changing the number and the stereochemistry of the substituents at each carbon atom in the oxathiane ring. The method of preparation of the 4-HS-1,3-diols starting materials has previously been reported.[7] The spirocyclic oxathiane *syn*-**19** has one substituent at C-5, as had *anti*-**11**. Diol **20** has no C-2 substituent and **22** has two. The corresponding oxathianes syn-**19**, **21**, and **23** were all formed in good yield.

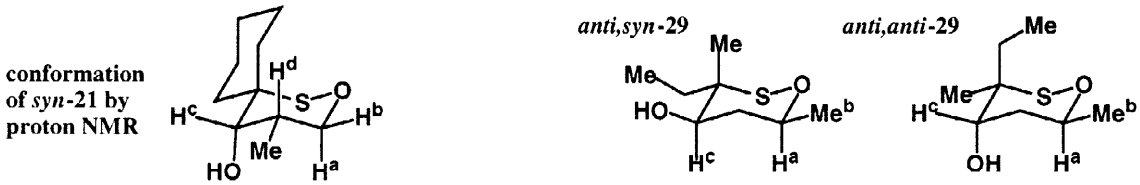


Structural variations at C-3, C-5 and C-6 were studied with a series of compounds (**24**, **26**, and **28**) with both methyl and ethyl substituents at C-3. Formation of oxathianes **25** and **27** show that cyclisation is efficient with an additional methyl or ethyl group at C-5. The diastereoisomers *anti,anti*-**28** and *anti,syn*-**28** with a methyl group at C-6 each cyclised stereospecifically to a different diastereoisomer of the oxathiane **29**.

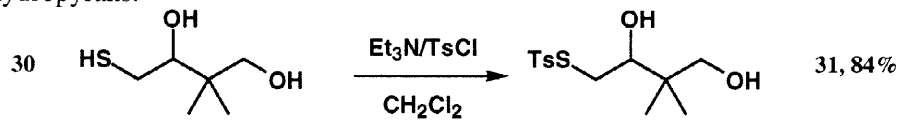


All the compounds we have described have a tertiary thiol group but this seems not to hinder the tosylation or the cyclisation. The diols **28** also have a secondary alcohol as nucleophile but again cyclisation is not sterically hindered. The stereochemical outcome of the reaction is retention at all carbon atoms - this was conformed by 500 MHz NOESY experiments on *syn*-**19** and *anti,syn*-**27**.

The 1,2-oxathianes were identified by NMR and MS (Table). Characteristically, *syn*-**21** has a triplet for H^a next to oxygen (δ 3.4) with large geminal (11.8 Hz) and axial/axial (11.8 Hz) coupling constants, typical for a six-membered ring. Harpp has observed similarly large geminal coupling in substituted 1,2-oxathiane-2-oxides.[6] The proton next to the secondary alcohol H^c is a double doublet with a small equatorial/equatorial (2.1 Hz) coupling and a large OH (11.2 Hz) coupling. This suggests that the 1,2-oxathiane *syn*-**21** has an axial OH and equatorial CH_3 group which correlates with A values[10] and is in agreement with the 500 MHz NOESY spectrum. The most noticeable features of the ^{13}C NMR spectrum of *syn*-**21** are a CH_2 group next to oxygen (δ 74.5), a CH group next to oxygen (δ 73.3) and a quaternary carbon next to sulfur (δ 51.7) — these peaks resemble those of the diol *anti*-**18** since there is no skeletal reorganisation in this formal oxidation. The molecular ion M^+ is observed in the MS at 100% intensity.



The ^1H NMR spectra of *anti, syn*-**29** and *anti, anti*-**29** are of more interest since the methyl group (Me^b) has a choice whether to be axial or equatorial. In fact (NOESY) it is equatorial in both diastereoisomers as shown above. This is not surprising for *anti, syn*-**29** since all the larger substitutents are equatorial as shown by the large vicinal axial-axial couplings for H^a and H^c (Table). However, for *anti, anti*-**29** the OH and ethyl groups are axial because OH has a smaller A value[10] (0.60) and Et a similar A value (1.79) to that of a methyl group (1.74). Additionally, the equatorial proton H^c in *anti-, anti*-**29** appears as a double doublet with small equatorial/equatorial (*J* 3.9 Hz) and equatorial/axial (*J* 2.7 Hz) couplings. We have found similar results with analogues tetrahydropyrans.[11]



Finally, investigating diol **30** was an attempt to probe the Thorpe-Ingold effect within the cyclisation.[12] Reaction of diol **30** with $TsCl/Et_3N$ in CH_2Cl_2 gave surprisingly the S-tosylate **31** in 84% yield. Cyclisation

does not occur even when the solution is refluxed, instead the tosylate **31** decomposes. It appears that it is actually *advantageous* to have a tertiary SH for ring closure to form the 1,2-oxathiane. Presumably cyclisation onto the tertiary S–Ts is more favoured due to a combination of both reduction of angle strain[12] and the S–Ts bond being in a more favoured conformation for cyclisation (rotamer effect).[13]

We have reported a general procedure for the synthesis of a series of 4-hydroxy-1,2-oxathianes. The cyclisation is stereospecific and occurs irrespective of the developing stereochemistry and structural nature of the cyclising chain. The reaction is sensitive to the *strength* of base used, full deprotonation of the SH group being required for high yields. Most importantly the cyclisation is dependent on the Thorpe-Ingold effect: cyclisation of the S–Ts intermediate occurs only with a tertiary sulfanyl group.

We have demonstrated that rearrangement of 4-RS-1,3-diols (like *anti*-**6**) with TsCl is dependent on the migrating substituent (R=Ph, Bn or SH) and can lead to three structurally diverse compounds; the allylic alcohol *anti*-**9** (when R=Ph), thiolanes *syn*-**10** (when R=Bn) and now 1,2-oxathianes *syn*-**16** (when R=SH); all of which are formed as single products in near quantitative yield.

Table : Identification of 1,2-Oxathianes, δ (ppm), *J* (Hz) or % abundance in MS

	syn-**16**	*syn*-**19**	**21**	**23**	*anti,syn*-**25**	*anti,syn*-**27**	*anti, syn*-**29**	*anti, anti*-**29**
δ H^a	3.4 (ddd)	3.4 (t)	4.2 (m)	3.6 (d)	3.9 (m)	3.9 (m)	4.2 (ddq)	4.2 (ddq)
J_{syn} H^a	0.0	0.0	a	—	a	a	6.3	6.2
J_{anti} H^a	11.8	11.8	a	—	a	a	11.5	11.7
J_{gem} H^a	11.8	11.8	a	11.2	11.6	11.5	—	—
δ H^b	3.9 (dd)	3.8 (dd)	3.8 (m)	3.9 (d)	3.5 (dd)	3.5 (dd)	—	—
J_{syn} H^b	4.8	4.8	a	—	4.8	4.8	—	—
δ H^c	3.4 (dd)	3.3 (dd)	3.9 (ddd)	3.5 (s)	3.9 (m)	3.9 (m)	3.9 (dd)	3.9 (dd)
J_{syn} H^c	2.0	2.1	3.5	—	a	a	2.6	2.7
J_{anti} H^c	—	—	8.6	—	—	—	7.9	3.9
M^+	100%	100%	100%	100%	55%	65%	20%	15%

[a] Coupling constants were not determined due to coalescence with other signals.

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