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PREPARATION OF THE LAEVOROTATORY *TRANS*-(4S,6S)-4,6-DIMETHYL-1,3-DITHIANE AND *TRANS*-(4S,6S)-4,6-DIMETHYL-1,3-OXATHIANE. AN INTERNAL DISPLACEMENT OF A SECONDARY SULPHONATE LEADING TO A CYCLIC THIOACETAL

D. DANNEELS, M. ANTEUNIS,* L. VAN ACKER and D. TAVERNIER

Department of Organic Chemistry, Laboratory for NMR Spectroscopy, State University at Ghent, Krijgslaan, 271, S.4bis, B-9000 GENT, Belgium

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Abstract—(−)(2R,4R)-2,4-dimesyloxypentane, treated with (i) potassium thiolacetate/DMF (ii) 12N hydrogen chloride/dimethoxymethane/methanol yields (−)(4S,6S)-4,6-dimethyl-1,3-oxathiane and (−)(4S,6S)-4,6-dimethyl-1,3-dithiane. The mechanism of the formation of the oxathiane is discussed.

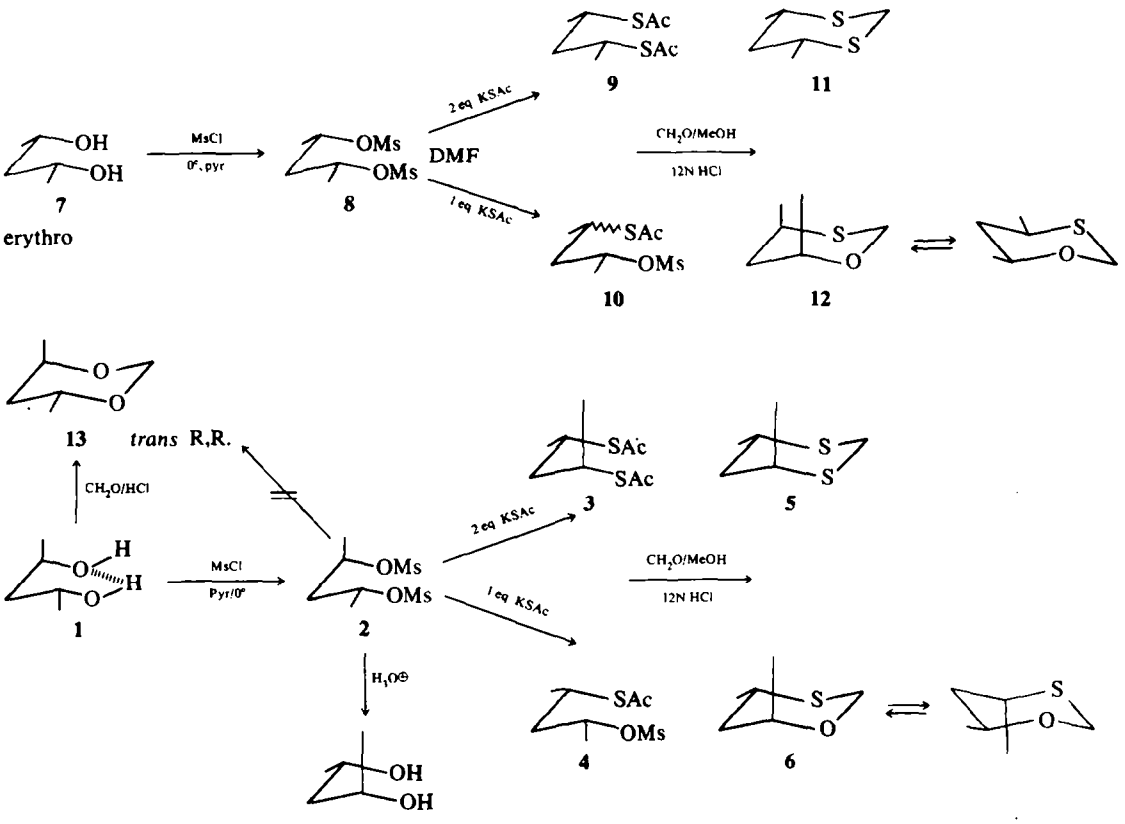
This work arises from our interest in the synthesis of optically active 1,3-oxathianes, 1,3-dithianes and their oxidation products, sulphoxides and sulphones, in order to obtain information on the chiroptical properties of these chromophores in the presence of chiral centres in the carbocyclic moiety of the ring. A synthesis of 1,3-oxathianes and 1,3-dithianes as described earlier,[1] which had been applied to a mixture of *threo*/*erythro* - 2,4 - dihydroxypentane, is outlined in Scheme 1. The reaction sequence involves (i) transformation of the diol into the dimesylate (ii) displacement of one or both the mesyloxy groups with potassium thiolacetate in dimethylformamide (iii) reaction with dimethoxymethane in 12N hydrogen chloride/methanol, yielding the oxathiane and/or the dithiane. Starting from optically-active *threo* - 2,4 - pentanediol, it should be possible to isolate optically-active oxathianes and dithianes in reasonable enantiomeric purity. However, we felt it necessary to test first the stereospecificity of these reactions by subjecting separately each diol stereoisomer to the reaction sequence.

Stereospecificity of the formation of oxathianes and dithianes

The reaction sequence proceeds stereospecifically, as shown in Scheme 1.† *Threo* - 2,4 - pentanediol **1** gave *threo* - 2,4 - dimesyloxypentane **2**, which after treatment with two equivalents of potassium thiolacetate yielded *threo* - 2,4 - dithiolacetoxypentane **3**. Ring closure (12N HCl, $CH_2(OCH_3)_2$) gave pure *trans* - 4,6 - dimethyl - 1,3 - dithiane **5**. Similarly, *erythro* - 2,4 - pentanediol **7** was transformed stereospecifically into *cis* - 4,6 - dimethyl - 1,3 - dithiane **11**. Reaction of *threo* - 2,4 - dimesyloxypentane with one equivalent of potassium thiolacetate gave a mixture of starting material, *threo* - 2,4 - dimesyloxypentane and a 2 - mesyloxy - 4 - thiolacetoxy - pentane **4**, the configuration of which could not be determined. Ring closure on that mixture afforded *trans* - 4,6 - dimethyl - 1,3 - oxathiane **6** and *trans* - 4,6 - dimethyl - 1,3 - dithiane. No 1,3 - dioxane was obtained. Also, *cis* - 4,6 - dimethyl - 1,3 - dithiane **12** and *cis* - 4,6 - dimethyl - 1,3 - oxathiane were obtained from *erythro* - 2,4 - dimesyloxypentane, which had been treated with one equivalent of potassium thiolacetate. The stereospecificity of the reaction is not quantitative, minor amounts of diastereomers are also formed. Their proportion varies somewhat from run to run. The stereospecificity was high enough to encourage us to repeat the reaction sequence with optically active *threo* - 2,4 - pentane diol.

Synthesis of optically active compounds. Izumi and coworkers have described[5-7] the enantioselective reduction of 2,4-pentanedione to (−) - 2,4 - pentanediol with the aid of Raney nickel, modified with (R,R) - (+) - tartaric acid. In a typical experiment, we found that the *threo* diol obtained from this reduction displays a specific rotation $[\alpha]_D^{25} = -13{\cdot}2°$ (10% solution in methanol). Although the enantiomeric purity was not known to Izumi, he considered that this large specific rotation pointed to a high optical purity. Izumi has proposed the existence of "special sites" in order to explain the enantioselectivity observed in the reduction. We have assessed the enantiomeric purity of the *threo* - 2,4 - dihydroxy - pentane $[\alpha]_D^{25} = -13{\cdot}2°$ at 27·6% (63·8% levorotatory and 36·2% dextrorotatory isomer). For this analysis we used the chiral lanthanide NMR shift reagent tris - 3(heptafluoro - n - propyl - hydroxymethylene) - D - camphorato-Eu III.[8] At 300 MHz, this reagent causes the lines of the H-3 protons of both enantiomers to be completely separated, allowing an easy integration. The

†NMR spectral parameters and the configurational assignment of the compounds presently reported on are well documented in the literature.[2-4]



SCHEME 1.

optical yield of 28% is very satisfactory. In a recent review[9] it has been noted that the vast majority of reported enantioselective syntheses is characterized by optical yields lower than 20%. The high optical purity of the *threo*-diol can however be rationalized by accepting that the reduction of the first and second carbonyl group proceeds almost independently and with the same, or nearly the same (enantio) selectivity.* Let us assume that this reduction proceeds each time with an enantioselectivity of 0·16† as was observed by Izumi[7] for the reduction of the structurally-related ethyl - 3 - keto - butyrate. Let R and S be the probabilities that each of the chiral centers is formed with the configuration R and S respectively. By definition the enantiomeric purity p after the reduction of only one keto function of the substrate 2,4-pentanedion is the excess of one enantiomer, say R,‡ over another:

$$p = \frac{[R]-[S]}{[R]+[S]} = \frac{R-S}{R+S}.$$

Similarly, the enantiomeric purity p′ of the *threo* isomer obtained after the reduction of both keto functions is given by:

$$p' = \frac{[RR]-[SS]}{[RR]+[SS]} = \frac{R^2-S^2}{R^2+S^2}.$$

The second relation arises because the probability of two independent events is given by the product of the probabilities of each of the events.

By expressing p′ in function of p one obtains $p' = 2p/(1+p^2)$. The ratio of *threo*/*erythro* concentration is easily shown to be equal to $(1+p^2)/(1-p^2)$. Substituting the presupposed enantioselectivity of 0·16 into these equations, we calculate (i) an enantiomeric purity for the *threo*-diol of 0·31 (experimentally this value is 0·28); (ii) a *threo*/*erythro* ratio of 1·05, again in agreement with the experimental value of about unity. Therefore the high optical purity of the *threo*-pentanediol has been paid for by the formation of an almost equal amount of inactive *meso* isomer. In fact, this outcome can be regarded as a

*Strictly speaking, only the reduction of the first carbonyl group can properly be named enantioselective, the reduction of the second carbonyl group, now contained in the chiral 4 - hydroxy - 2 - pentanone, is actually a diastereoselective one.

†This number expresses the excess, in mole fraction of the levoratory isomer.

‡This expression assumes the preponderent formation of an R centre over an S centre. It will be shown later in this paper that the use of a (+)-tartaric acid modified Raney Nickel indeed affords (R,R) - 2,4 - pentanediol in excess.

special application of Horeau's method[10] for the enrichment of an enantiomer, a method which is based on a statistical and temporary dimerization of the enantiomers to separable diastereomers.

The levorotatory *threo* - 2,4 - dihydroxypentane being secured, it was submitted to the reaction sequences depicted in Scheme 1 (1 equiv thiolacetate). The products (*trans* - 4,6 - dimethyl - 1,3 - oxathiane and *trans* - 4,6 - dimethyl - 1,3 - dithiane) were isolated by gas chromatography. These products are optically active, and laevorotatory. Specific rotations are displayed in Table 1.

Table 1. Specific rotation—of *threo* - 2,4 - pentanediol **1**, *threo* - 2,4 - dimesyloxypentane **2**, *trans* - 4,6 - dimethyl - 1,3 - oxathiane **6**, and *trans* - 4,6 - dimethyl - 1,3 - dithiane **5** from **2** and one equivalent of potassium thiolacetate

Run	$[\alpha]_D^{25}$			
	1[c]	**2**	**6**[ac]	**5**[b]
1	−6·8°	−6·4°	−13·4°	−15·9°
2	−12·8°	−12·5°	−20·9°	−22·0°
3	−13·2°	−12·7°	−26·5°	−28·4°

[a] The *cis*-isomer made up 10, 15 and 24% respectively of the total amount of the oxathianes.

[b] The *cis*-isomer made up 3, 13 and 10% respectively of the total amount of dithianes.

[c] Absolute rotations of **1** and **6** are calculated as being −47·7° and −121·6°.

The optical purity of the oxathiane could be assessed with the earlier mentioned chiral lanthanide shift reagent, the NMR signal of the H-2e ring hydrogen atom being used for integration. We found that a specific rotation $[\alpha]_D^{25}$ of −26·5° corresponds to an optical purity of 21·8%. Thus there occurs a slight loss of optical purity in the transformation of the diol to the 1,3-oxathiane.

The optical purity of the dithiane could not be determined by running the NMR spectra either in chiral solvents, or in the presence of the chiral lanthanide reagent. This came as no surprise, because it is known that lanthanide shift reagents do not complex with thioethers or dithianes.[11,12] We shall now turn to a discussion of the absolute configuration of the optically active compounds.

Determination of absolute configuration. (2*R*,4*R* - (−) - *Threo* - 2,4 - *pentanediol*

Threo - 2,4 - pentanediol prefers a conformation characterized by an intramolecular hydrogen bond (see **1**), as was found independently by French and Japanese authors.[13,14] Using Brewster's method,[15,16] we calculated for the (R,R) form a molecular rotation of −60°, the experimental value being −50°. Tocanne has studied[17] optically-active 1,3-dioxanes derived from natural β-diols of known absolute configuration. He has shown that dextrorotatory *trans* - 4,6 - dialkyl - 1,3 - dioxanes have the (4R,6R) configuration. After acetalization of our (−)-diol with formaldehyde we indeed obtained (+) - *trans* - 4,6 - dimethyl - 1,3 - dioxane. The acetalization itself is known to proceed with retention of configuration.[18]

Izumi[7] formulated as a rule that reduction of β-keto esters with the aid of Raney nickel modified with D - (+) - tartaric acid gives predominantly (R) - β - hydroxy esters. Our assignment of the (2R,4R) configuration to the levorotatory 2,4-pentanediol* extends the scope of this generalization to the reduction of β-diketones.

(4*S*,6*S*) - (−) - trans - 4,6 - *dimethyl* - 1,3 - *oxathiane*

The absolute configuration of the levorotatory *trans* - 4,6 - dimethyl - 1,3 - oxathiane is established by correlation with the known[19] configuration of dextrorotatory 2-methoxypentane. A sample of the oxathiane was boiled for 24 h with Raney Nickel W-7 catalyst. The sole reaction product was the dextrorotatory 2-methoxypentane, which has the (S)-configuration.[19] Djerassi[20] has shown that these desulphurization reactions proceed with retention of configuration at the oxygenated carbon atoms. He has reported[20] that in certain cases (e.g. benzhydryl substituted oxathiolanes) the alcohol is also produced. In the present case, however, no alcohol was formed. As *trans* - 4,6 - dimethyl - 1,3 - oxathiane has either the (R,R) or the (S,S) configuration (otherwise it would be a *cis* form), it follows that the levorotatory oxathiane has the (S,S) configuration, that is, opposite to the configuration of the starting pentanediol.

(4*S*,6*S*) - (−) - trans - 4,6 - *dimethyl* - 1,3 - *dithiane*

While we can offer at present no rigorous proof for the statement that the levorotatory 4,6 - dimethyl - 1,3 - dithiane has the (4S,6S) configuration, the following two arguments are compelling. On mechanistic grounds, one expects that the nucleophilic displacement of the mesyloxy groups in 2,4 - dimesyloxypentane by the thiolacetate anion in the polar solvent DMF will proceed with inversion.† As the starting diol has the (R,R) configuration, the dithiane should have the (S,S) configuration. Secondly, it is possible to correlate between configuration and rotation. It has been shown[16,17] that in these 1,3 - heterocyclic systems the rotatory power originates mainly from the conformational dissymmetry. Although 1,3-oxathianes have more deformed rings than 1,3-dithianes, their main forms are to be considered chair-like.[1,2,23] Therefore the levorotatory 1,3-dithiane has the same configuration as the levorotatory 1,3-oxathiane, that is the (4S,6S) configuration. It might be argued that the sign of the rotation due to conformational dissymmetry could be overwhelmed by a Cotton effect stemming from a chromophore β-interaction. Such interactions seem to be negligible,[24] even for 1,3-diaxially positioned

*After this work was completed, there appeared a paper[35] establishing the (R,R) configuration for (−) - 2,4 - pentanediol by correlation with R - (−) - 3 - hydroxybutyric acid.

†Using an alternative route for the synthesis of 1,3-dithianes (cf Ref 21) we obtained the same antimer of *trans* - 4,6 - dimethyl - 1,3 - dithiane. This method uses potassium rhodanide as incoming nucleophile in HMPT solvent. It is known[22] that such polar aprotic solvents promote S_N2 substitution, even of neopentyllike substrates.

sulphur atoms.[25] Moreover, we observed that the ORD curve (350–600 nm) of our 1,3-oxathiane and 1,3-dithiane are nearly identical, also refuting a possible S...S interaction.*

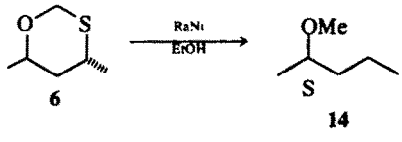
Reaction mechanism

We have shown above that the formation of both *trans* - 4,6 - dimethyl - 1,3 - oxathiane and *trans* - 4,6 - dimethyl - 1,3 - dithiane from *threo* - 2,4 - dihydroxypentane proceeds with inversion of the two chiral centres.

1,3-*dithianes. Threo* - 2,4 - dihydroxypentane is transformed into *threo* - 2,4 - dimesyloxypentane. The potassium thiolacetate nucleophilic displacement of the mesyloxy groups proceeds with inversion, by an S_N2-like† mechanism. Therefore the cyclization reaction on the 2,4 - dithiolacetoxypentane is most easily pictured as (i) hydrolysis of the thiolester‡ with retention of configuration and (ii) ring closure with retention of the dithiol with formaldehyde or some other reagent derived from dimethoxymethane.

1,3-*Oxathiane.* The formation of the *trans*-oxathiane from *threo*-pentanediol however must involve *inversion of configuration at the oxygenated chiral centre.* It seems unlikely that the formation of the oxathiane precursor itself, the 2 - mesyloxy - 4 - thiolacetoxypentane proceeds with inversion at the oxygen centre. For this would imply that the introduction of a second thiolacetoxy group (leading to the *trans*-dithiane) would occur with net retention.§ Therefore we have to accept that the inversion at this oxygen centre takes place during the cyclization reaction. The first possibility is a prior hydrolytic displacement of the mesyloxy group by a hydroxyl group. Weiner and Sneen[30] have indeed shown that the reaction of solvent water with secondary sulphonates to yield a secondary alcohol occurs with inversion of configuration. In fact, we observed that by boiling for 48 h an aqueous solution of the levorotatory 2,4-dimesyloxypentane a dextrorotatory 2,4 - dihydroxypentane solution is obtained.¶ However, this hydrolysis is slow, while the formation of the oxathiane is more rapid. Also, if hydrolysis of the mesyloxy groups were relatively easy and were to precede the ring closure, it should be possible to prepare 1,3-dioxanes by treating a 2,4 - dimesyloxypentane with dimethoxymethane–hydrogen chloride. Experimentally, it was *not* possible to prepare 4,6-dimethyl-1,3-dioxane in this way; we observed only a blackening of the reaction mixture resulting in a tarry residue. We concluded that solvolysis of the mesyloxy groups does not precede the formation of the oxathiane.

We rather propose the following course of events. From the 2 - mesyloxy - 4 - thiolacetoxy - pentane there is formed an intermediate mixed acetal, 2 - oxa - 4 - thia - 5 - methyl - 7 - mesyloxy - octane (Scheme 3) which then undergoes an intermolecular attack of a methoxy lone pair on the mesyloxy group to give an intermediate ion, from which the oxathiane with inverted configuration is formed by loss of methyl mesylate. It is known that methyl ethers are able to provide assistance to the solvolytic displacement of arylsulphonates,[31,32] with the concurrent formation of oxygen containing heterocycles. Neighbouring group participation by acetal groups has also been reported.[33] One may wonder why 3-participation involving the more nucleophilic sulphur atom, which seems equally possible with our proposed intermediate, 4 is not detected. This, however, would be a case of four-membered participation. Such participation is not very efficient and is usually not observed.[34] Various complicated schemes characterized by anchimeric participation could account for our observations. We have selected the most simple and straightforward way to rationalize the known facts.



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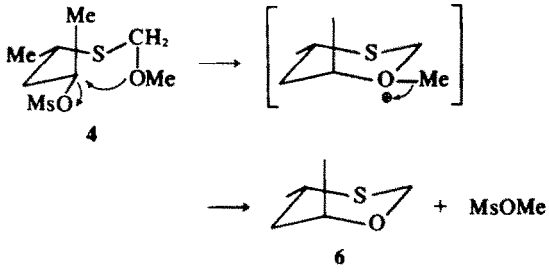
SCHEME 2



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SCHEME 3.

In conclusion, we may say that we have described a convenient synthetis of optically-active *trans* - 4,6 - dimethyl - 1,3 - oxathiane and *trans* - 4,6 - dimethyl - 1,3 - dithiane from *threo* - 2,4 - dihydroxy - pentane. It is noteworthy that, despite the rather drastic reaction conditions, the ring closure can also be effected† by simple aliphatic aldehydes such as ethanal, isobutanal, neopentanal, etc.

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*ORD and CD spectra are reported for substituted 1,3-oxathianes and 1,3-dithianes.[26,27]

†Our data do not distinguish between a classical S_N2 mechanism or an attack on an intermediate ion pair.[28] S_N2-like is here a shorthand expression to characterize a nucleophilic displacement featuring the classical S_N2 stereochemistry, i.e. inversion.

‡Thiolesters are hydrolyzed less easily than their oxygen analogues, hence the need for a highly acidic medium.[29]

§It is interesting to note that the mesyloxy group is necessary to obtain an oxathiane with inverted configuration at the oxygenated centre. We observed that a reaction sequence starting from *threo* - 2 - hydroxy - 4 - mesyloxy - pentane, produces the *cis* - 4,6 - dimethyl - oxathiane, whereas after mesylation of this starting material the *trans*-product is obtained.

¶This opens a simple route for the preparation of the enantiomers of the oxathiane and dithiane actually prepared, apart from the use of a (−)-tartrate-doped Raney Nickel catalyst.

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