The X-ray crystal structure, conformation and preparation of *anti*-3,3,6,6-tetramethylthiepane-4,5-diol: stereochemistry of reduction of a heterocyclic α-hydroxy ketone

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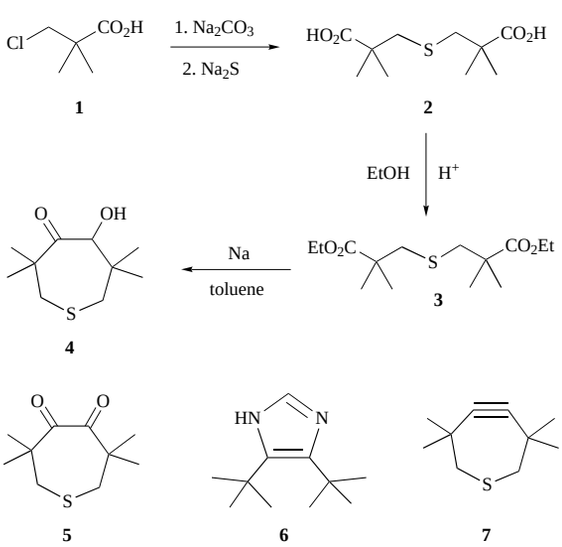
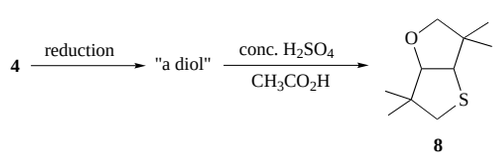
The X-ray crystal structure and conformation of the *anti* title diol is described together with stereoselective syntheses of *syn*- and *anti*-diols from a readily available acyloin. Some control of the stereoselective reduction of α-hydroxy ketones by chelating and non-chelating reducing agents is possible.

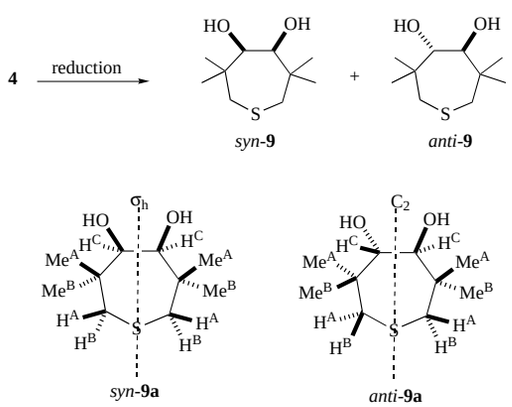
The hydroxythiepanone **4** can be prepared[1,2] from the chloro acid **1** in three steps, the key reaction being an efficient intramolecular acyloin condensation (enolisation is prevented by the tertiary alkyl groups) to give the seven-membered ring. The corresponding dione **5** has been used to prepare crowded molecules such as 4,5-di-*tert*-butylimidazole[1] **6** and the remarkable cycloheptyne[3] **7**.



de Groot and Wynberg also investigated the reduction[4] of the hydroxy ketone **4** to give a 'diol' and the rearrangements of this diol to give, for example, the bicyclic compound **8** in acid solution.[5] No mention was made in these papers of the stereochemistry of 'the diol' prepared in this way.



We now report the stereoselective preparation of both the *syn*- and the *anti*-diols **9** by the reduction of the hydroxy thiepanone **4**, and the assignment of their configurations by X-ray crystal structure determination of the *anti*-diol.[6] The stereochemistry of the two diols is interesting because each has a symmetry element: the *syn*-diol is a *meso* compound with a plane of symmetry while the *anti* compound is C_2 symmetric and, though chiral, can be expected to show the same number of signals in the NMR spectrum as the *syn* compound. The diagrams *syn*-**9a** and *anti*-**9a** show these features.



de Groot and Wynberg obtained[4,5] 'the diol, mp 179–180 °C' by reduction of **4** with $LiAlH_4$ without discussing stereochemistry but the characterisation suggests it was a single compound. They report 'four methylene protons' in the 60 MHz, NMR spectrum at δ_H 3.01, 2.78, 2.30 and 2.05. If these are, in fact, two AB systems, the separation of 0.24 ppm would be a coupling constant of 14 Hz. This is a geminal ($^2J_{HH}$) coupling and is neither diagnostic nor characteristic (see below).

Others have prepared one or both diols **9** without necessarily identifying the configuration. Johnson and co-workers[7] reduced the hydroxy ketone **4** with $LiAlH_4$ to give an 85:15 mixture of two diols and with $NaBH_4$ to get one diol in >90% yield. They identified the major diol as the *syn* isomer: 'The stereochemistry of this diol (a *meso* compound) was determined by using chiral shift reagents.[2c] A complete report of this approach to diol stereochemistry will be forthcoming.' Their reference 2*c* is 'P. Y. Johnson, I. Jacobs and D. J. Kerkman, *J. Org. Chem.*, in the press.' We do not believe that this paper appeared, though they did publish a paper[8] on the stereochemistry of the related azepinediols. Their method relied on the NMR spectrum of a prochiral CH_2 group in a substituent on the nitrogen atom in the azepines and would not apply to the thiepanes. It seems that they used Applequist's ingenious and reliable method[9] to assign the configuration of the thiepanediols **9** and we believe their assignments are correct.

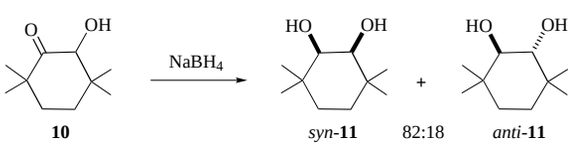
We reinvestigated this problem to clear up the assignment of stereochemistry and because we needed the *anti*-diol **9** for

Table 1 Diastereomeric ratios of diols *syn*- and *anti*-**9** from reduction of **4**

Reagent	Conditions	Ratio *syn*- : *anti*-**9**	Isolated Yield *syn* or *anti* (%)	Ref.
$NaBH_4$	EtOH 25 °C	>90% *syn*	*syn* 79	Johnson[7]
$NaBH_4$	EtOH room temp.	100 : 0	*syn* 92	This work
$NaBH_4/CeCl_3$	EtOH −78 °C	100 : 0	*syn* 74[a]	This work
$LiAlH_4$	THF reflux	85 : 15	Both isolated no yields given	Johnson[7]
$LiAlH_4$	Et_2O reflux	(100 : 0?)	64	de Groot[4]
$Zn(BH_4)_2$	Et_2O 0 °C	64 : 36	*syn* 61, *anti* 34	This work
DIBAL	CH_2Cl_2 −78 °C	95 : 5	—	This work
$DIBAL/ZnCl_2$	THF/Et_2O room temp.	39 : 61	*syn* 36, *anti* 56	This work

[a] After recrystallisation.

another project. It is also important to extend the well established control in the reduction of open-chain α-hydroxy ketones to their cyclic counterparts. The reduction of acyclic α-hydroxy ketones can usually be controlled to give either diol since the normal Felkin conformation with the CH–OH bond orthogonal to the plane of the C=O group can be changed by chelation into one in which the CH–OH bond is in the plane of the C=O group. The same freedom of rotation is not available to cyclic α-hydroxy ketones and 'the influence of polar groups on the stereoselectivity of reduction of cyclic ketones has not been widely studied'.[10] The only close analogy we can find is Applequist's six-membered ring example[9] **10** (which lacks only a sulfur atom in comparison with **4**!). Reduction with borohydride is also *syn*-selective here though not to such a pronounced degree. The assignment of structure, referred to above, depends on the NMR spectra of the cyclic sulfites derived from **11**. They did not attempt to make the *anti*-diol **11** in high yield.



10 *syn*-**11** 82:18 *anti*-**11**

Preparation and characterisation of the *syn* and *anti* diols 9

We first improved the preparation of the acyloin **4** by studying the only bad step, the formation of the symmetrical sulfide **2** from the hindered acid in alkaline soloution. de Groot and Wynberg reported[1] a 50% yield but we were able to get only 16% by their procedure. However, a simple adjustment of conditions, chiefly the proportions of the reagents, improved this to 89%. de Groot and Wynberg used 1 : 1 chloro acid **1** to Na_2S: we simply changed to the correct stoichiometric ratio of 2 : 1. Minor changes (see Experimental section) included recrystallisation of the $Na_2S{\cdot}9H_2O$ from water before use, dropwise addition of this reagent to the acid **1** rather than the reverse, and recrystallisation of the product **4** from water rather than acetic acid. The diester **3** can be made in 92% yield by continuous azeotropic distillation of water.

We then studied the reduction of **4** by various chelating and non-chelating reducing agents, measuring the diol ratio from the NMR spectrum of the reaction mixture and separating the diols (easily) by column chromatography. The results are given in Table 1 together with the previously published reductions. All non-chelating reducing agents gave a high proportion of one diol which we identified as the *syn* isomer (see below). Sodium borohydride in ethanol gave this isomer exclusively and it can be isolated in 92% yield by this method.

Reduction under Luche[11,12] conditions ($NaBH_4$–$CeCl_3$) gave surprisingly the same complete selectivity as $NaBH_4$. The cerium chloride evidently had very little effect in this case. Chelation with zinc proved to be the only way to get substantial amounts of the *anti*-diol **9**. Zinc borohydride gave some *anti*-**9** but with DIBAL–$ZnCl_2$ we at last got mostly the *anti* compound and could isolate it in 56% yield. The diols are easily separated by chromatography on silica, eluting with hexane–ethyl acetate (6 : 1). Both diols **9** are crystalline and the *syn*-diol crystallises particularly easily.

Table 2 Characteristic differences between the *syn*- and *anti*-diols **9**

Measurement	*syn*-**9**	*anti*-**9**	Lit.
Mp	180–182 °C	89–91 °C	*syn*-**9** 179–180 °C[4] *syn*-**9** 183–185 °C[7]
R_f (3 : 1, hexane–EtOAc)	0.17	0.33	
δ_C CHOH	82.9 ppm	73.6 ppm	

Table 3 Proton NMR spectra of *syn*- and *anti*-diols **9** (refer to diagrams **9a** – chemical shifts in ppm and coupling constant in Hz)

	CH^COH		CH^AH^B			CMe^AMe^B	
Diol	$\delta(H^C)$	δ(OH)	$\delta(H^A)$	$\delta(H^B)$	$^2J_{AB}$	$\delta(Me^A)$	$\delta(Me^B)$
syn-**9**	3.73	1.78	2.83	2.28	14.4	1.08	1.06
anti-**9**	3.56	2.76	2.52	2.27	14.7	1.09	0.95

The most obvious distinctions between the two diols are the melting points, the chromatographic behaviour and the chemical shift of the hydroxy-substituted carbon in the ^{13}C NMR spectrum. These are summarised in Table 2.

In the proton spectrum there are only small differences, chiefly the wider separation between the methyl signals in the *anti* isomer, the wider separation of the AB signal in the *syn* isomer (at 250 MHz, the *anti* isomer gives a sharper and more distorted AB system) and the large difference in chemical shift for the hydroxy proton. The ^1H NMR spectra are summarised in Table 3.

Determination of stereochemistry by X-ray crystal structure analysis

Determination of the crystal structures of *syn*- and *anti*-diols **9** was attempted by single-crystal X-ray diffraction. Data were collected using an Enraf-Nonius CAD4 four-circle diffractometer with graphite monochromated Mo-Kα radiation (sealed-tube source) and for the *syn*-diol also on a Rigaku AFC7R four-circle diffractometer. The structures were solved using SHELXS-86[13] and refined using SHELX-93.[14]

Crystals of both diols were grown by slow evaporation from ethanol solutions. Crystals of *anti*-**9** were colourless narrow needles (typical dimensions 0.40 × 0.10 × 0.10 mm) while crystals of *syn*-diol **9** were colourless plates (typical dimensions 0.30 × 0.20 × 0.10 mm). Since these structures are poorly refined we do not present the three dimensional co-ordinates here.

Both structures were refined to give high initial *R*-factors (*syn*-diol **9**, $R = 0.102$; *anti*-diol **9**, $R = 0.130$). In the case of *anti*-**9** this was a result of the weakly diffracting crystal giving a low reflection/parameter ratio ($F^2 > 3\sigma F^2 = 527$, number of parameters = 126). The structure of *syn*-**9** was found to exhibit severe disorder around the diol portion of the molecule. This disorder took the form of a number of slightly different ring conformations, although each had the same *syn*-diol stereo-

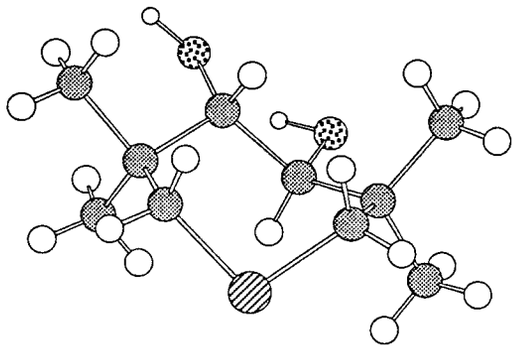


Fig. 1 X-Ray crystal structure of the *anti*-diol **9**

chemistry. This disorder was difficult to model and we do not present this structure. The geometry of the *anti*-diol obtained from this structure determination is of sufficient quality to distinguish the *syn* and *anti* stereochemistry of the two diols **9**.†

Stereoselectivity of reduction and conformation of the two diols

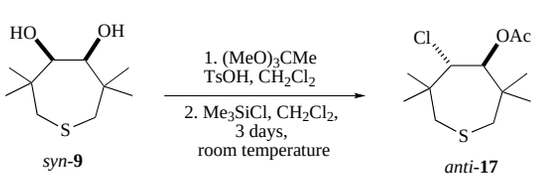
The *syn*-diol 9. The *syn*-diol is the one previously prepared. The stereoselectivity in favour of this diol with non-chelating reducing agents is most simply explained with a Felkin-like conformation **12** of the hydroxy ketone **4** with the OH group at right angles to the plane of the carbonyl group and attack occurring from the face opposite the OH group. This is a similar explanation to the high *syn*-selectivity in the attack of MeLi on 2-phenylsulfanylcycloheptanone **13** to give[15] *syn*-**14**.

The *anti*-diol 9. The *anti*-diol and the stereoselectivity of its formation are more interesting. The crystal structure shows a single conformation—a rather chair-like puckered ring with pseudo-equatorial hydroxy groups **16** (Fig. 1). Using this as a model for the transition state of the reduction, we suggest a zinc chelate **15** with pseudo-axial attack opposite the nearer pseudo-axial methyl group.

The closest analogy to our work with DIBAL and zinc salts is the work of Solladié and his group[16–18] who have used chelation by zinc to reverse the stereoselectivity of the reduction of cyclic β-keto sulfoxides by DIBAL. The analogy is not very close because, although the ketones are cyclic, the sulfoxide group is always outside the ring and therefore free to rotate.

Crossing from the *syn*- to the *anti*-series

We used the Sharpless[19] orthoester approach to convert the *syn*-diol **9** into the *trans*-acetoxy chloride **17** as a way of crossing from the *syn*- to the *anti*-series. The reaction was reasonably efficient (64% over two steps) and may provide an alternative source of thiepanes with *anti*-relationship between the substituents.



syn-**9** *anti*-**17**

Experimental

All solvents were distilled before use. Tetrahydrofuran (THF) and diethyl ether were dried by stirring over lithium aluminium hydride. Dichloromethane, hexane and toluene were dried by stirring over calcium hydride. Ether refers to diethyl ether. Thin layer chromatography was carried out on commercially available pre-coated plates (Merck silica Kieselgel $60F_{254}$). Flash column chromatography was carried out on Merck Kieselgel 60 (230–400 mesh). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker WM 200, Bruker WM 250 or a Bruker WM 400 Fourier transform spectrometer. The attached proton test (APT) for ^{13}C NMR spectra recorded on the 250 and 400 MHz machines is reported with (+) designating signals in the same direction as the solvent (quaternary carbon and CH_2) and (+) the opposite (*i.e.* CH and CH_3). For ^{13}C spectra recorded on the 200 MHz instrument, (−) and (+) have the same meaning as above with (q) representing quaternary carbons which do not show up by DEPT.

Melting points were recorded on a Reichart hot-stage microscope and are uncorrected. IR spectra were recorded on either a Perkin-Elmer 297 or a Perkin-Elmer 1600 FTIR spectrophotometer. Mass spectra (either electron impact or positive fast atom bombardment) were recorded on an AEI Kratos MS30 or MS890 machine using a DS503 data system for high-resolution analysis. Microanalyses were carried out using Carlo Erba 1106 or Perkin-Elmer 240 automatic analysers.

Improved preparation of 2,2,6,6-tetramethyl-4-thiaheptanedioic acid 2

Sodium carbonate (2.01 g, 19 mmol) was added to a stirred solution of 3-chloro-2,2-dimethylpropanoic acid **1** (5.27 g, 38.4 mmol) in water (3.5 cm^3). Sodium sulfide (4.6 g, 19 mmol, recrystallised from distilled water) in water (3.5 cm^3) was added dropwise to the reaction mixture which was then stirred overnight at 45 °C. The mixture was cooled and carefully acidified with 50% aq. H_2SO_4 and the precipitate collected. Extraction of the precipitate with ethanol and recrystallisation from distilled water gave the diacid **2** (4.49 g, 89%) (this acid has been prepared before[1] in low yield but not characterised spectroscopically); δ_H(200 MHz; CD_3OD) 2.80 (4 H, s, 2 × CH_2S) and 1.23 (12 H, s, 4 × Me); δ_C(63 MHz; CD_3OD) 180.4 (−), 45.9 (−), 45.0 (−) and 25.1 (+).

Improved preparation of diethyl 2,2,6,6-tetramethyl-4-thiaheptanedioate 3

The diacid **2** (800 mg, 3.4 mmol) was added to a stirred solution of dry ethanol (20 cm^3), dry benzene (20 cm^3) and a few drops of concentrated sulfuric acid. The reaction mixture was refluxed for 24 h, using a Dean–Stark apparatus to remove the azeotrope produced. After being cooled to room temperature, the reaction mixture was washed with water (40 cm^3) and dilute aqueous sodium hydrogen carbonate (40 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, hexane–ethyl acetate, 7:1) to give the diester **3** (910 mg, 92%) as a colourless oil (this diester has been prepared before[1] but not characterised spectroscopically) R_f [hexane–ethyl acetate (6:1)] 0.3; δ_H(200 MHz; $CDCl_3$) 4.10 (4 H, quartet, *J* 7.1, 2 × CO_2CH_2Me), 2.73 (4 H, s, 2 × SCH_2), 1.22 (6 H, t, *J* 7.1, 2 × CO_2CH_2*Me*) and 1.19 (12 H, s, 4 × Me); δ_C(100 MHz; $CDCl_3$) 176.5 (−), 60.6 (−), 45.1 (−), 44.2 (−), 24.6 (+) and 14.2 (+).

5-Hydroxy-3,3,6,6-tetramethylthiacycloheptan-4-one 4

The method of de Groot and Wynberg[1] gave the hydroxy ketone **4** as needles, mp 81–83 °C (from ethanol) (lit.,[1] 80–82 °C); R_f [hexane–ether (5:2)] 0.2; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3499 (OH) and 1697 (C=O); δ_H(250 MHz; $CDCl_3$) 4.17 [1 H, d, *J* 7.8, C*H*OH (collapses to a singlet upon D_2O shake)], 3.41 [1 H, d, *J* 7.8, CHO*H* (disappears upon D_2O shake)], 2.78 (1 H, d, *J* 14.7, SCH_AH_B), 2.69 (1 H, d, *J* 15.3, SCH_CH_D), 2.60 (1 H, d, *J* 15.7, SCH_CH_D), 2.46 (1 H, d, *J* 14.7, SCH_AH_B), 1.29 (3 H, s, Me_A), 1.15 (3 H, s, Me_B), 1.11 (3 H, s, Me_C) and 0.78 (3 H, s, Me_D); δ_C(100 MHz; $CDCl_3$) 216.6 (−), 78.8 (+), 50.3 (−), 47.4 (−), 42.6 (−), 42.2 (−), 27.6 (+), 27.3 (+), 23.5 (+) and 19.2

† Detailed crystallographic results for this work have been deposited with the Cambridge Crystallographic Data Centre and are available on request. Such a request should be accompanied by a full bibliographic reference for this work together with the reference number 207/147. Details of the deposition scheme are given in Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1997, Issue 1.

(+) (Found: M^+, 202.1033. $C_{10}H_{18}SO_2$ requires M^+, 202.1027); *m/z* 202 (M^+,13%), 147 (87), 118 [$M^+ - C(=O)C(Me)_2CH_2$, 30] and 56 [$C(Me)_2CH_2$, 100].

Stereoselective reductions of the α-hydroxy ketone 4: *syn*-3,3,6,6-tetramethylthiacycloheptane-4,5-diol, *syn*-9

Sodium borohydride (75 mg, 19.5 mmol) was added to a stirred solution of the hydroxy ketone **4** (80 mg, 3.9 mmol) in dry ethanol (1 cm^3). The reaction mixture was stirred at room temperature for 2 h, after which it was treated with dilute hydrochloric acid and concentrated by evaporation of most of the ethanol under reduced pressure. The residue was dissolved in dichloromethane (5 cm^3) and the solution was washed with water (5 cm^3), aqueous sodium hydrogen carbonate (5 cm^3) and water and then dried ($MgSO_4$) and evaporated under reduced pressure to give a colourless solid. This was purified by chromatography (SiO_2, hexane–ethyl acetate, 3:1), to remove any remaining starting material, to give the *syn*-diol **9** as prisms (75 mg, 92%), mp 180–182 °C (from hexane) (lit.,[4] 179–180 °C, lit.,[7] 183–185 °C); R_f [hexane–ethyl acetate (3:1)] 0.19; ν_{max}(Nujol)/cm^{-1} 3406 (OH) and 2922 (CH); δ_H(250 MHz; $CDCl_3$) 3.73 (2 H, d, *J* 6.2, 2 × C*H*OH), 2.83 (2 H, d, *J* 14.5, 2 × SCH_AH_B), 2.28 (2 H, d, *J* 14.5, 2 × SCH_AH_B), 1.78 (2 H, d, *J* 6.3, 2 × CHO*H*), 1.08 (6 H, s, 2 × C*Me*$_A$Me$_B$) and 1.07 (6 H, s, 2 × CMe$_A$*Me*$_B$); δ_C(100 MHz; CD_3COCD_3) 82.9 (+), 46.3 (−), 40.5 (−), 27.6 (+) and 19.6 (+) (Found: M^+, 204.1185. $C_{10}H_{20}O_2S$ requires M^+, 204.1184); *m/z* 204 (M^+, 48), 120 (78), 86 [$CH_2CMe_2C(OH)H$, 69] and 56 [CH_2CMe_2, 52].

Luche Reduction

Sodium borohydride (10 mg, 0.26 mmol), the hydroxy ketone **8** (16 mg, 0.08 mmol) and $CeCl_3 \cdot 7H_2O$ (33 mg, 0.09 mmol) in dry ethanol (0.5 cm^3) at −78 °C gave, after purification by washing through a plug of silica eluting with hexane–ethyl acetate (1:1) and recrystallisation, the *syn*-diol **9** (12 mg, 74%).

Preparation of $Zn(BH_4)_2$ solution[20]

Zinc chloride (1 mol dm^{-3} solution in diethyl ether; 27.5 cm^3) was added dropwise to a stirred solution of sodium borohydride (2 g, 52.8 mmol) in dry ether (150 cm^3). The reaction mixture was stirred at room temperature for 2 days. The solid material was then allowed to settle and the supernatant solution transferred by cannula to a bottle. The solution was stored at 5 °C under argon.

Reduction with $Zn(BH_4)_2$

Zinc borohydride solution in Et_2O (prepared as above) and the hydroxy ketone **4** (88 mg, 0.43 mmol) in dry ether (1.5 cm^3) at 0 °C for 6 h (with further reducing agent added until all the starting material was consumed) gave after acidification, extraction with ethyl acetate (3 × 5 cm^3), washing with saturated aqueous sodium hydrogen carbonate, drying ($MgSO_4$) and chromatography (SiO_2, hexane–ethyl acetate, 6:1) the *syn*-diol **9** (50 mg, 62%) and the *anti*-diol **9** (30 mg, 38%) (see below).

Reduction with $LiAlH_4$

The hydroxy ketone **4** (20 mg, 0.1 mmol) in dry ether (0.5 cm^3) and a solution of lithium aluminium hydride (5 mg, 0.13 mmol) in dry ether (1.5 cm^3) was refluxed for 4 h and quenched by the careful addition of water and then dilute aq. HCl. The organic layer was separated and the aqueous layer extracted with ether (3 × 5 cm^3) to give, after work-up, the *syn*- and *anti*-diols **9** in a 16:3 ratio (by NMR).

Reduction with DIBAL

A mixture of diisobutylaluminium hydride (1 mol dm^{-3} in CH_2Cl_2; 0.22 cm^3) and the hydroxy ketone **4** (9 mg, 0.044 mmol) in dry CH_2Cl_2 was stirred at −78 °C for 3 h, and then warmed to room temperature and treated with methanol. After the mixture had been stirred for a further 30 min the precipitate was filtered off and washed several times with dichloromethane. The filtrate and combined washings were evaporated under reduced pressure and the crude material was filtered through a plug of silica to give a 95:5 mixture (by NMR) of the *syn*- and *anti*-diols, **9**.

***anti*-3,3,6,6-Tetramethylthiacycloheptane-4,5-diol, *anti*-9**

Reduction with DIBAL and $ZnCl_2$. Zinc chloride (0.5 mol dm^{-3} solution in THF; 3 cm^3) was added to a stirred solution of the hydroxy ketone **4** (300 mg, 1.49 mmol) in dry THF. The solution was cooled to −78 °C and treated with a solution of DIBAL (1 mol dm^{-3} in THF; 1.5 cm^3, 1.5 mmol), added dropwise. The reaction mixture was allowed to warm to room temperature and then stirred overnight. After this, methanol was added to the mixture which was then stirred for a further 30 min. The resulting inorganic precipitate was filtered off and washed several times with dichloromethane. The filtrate and organic washings were combined and evaporated under reduced pressure. The crude material (a 39:61 ratio of *syn*- and *anti*-diols **9** by NMR) was chromatographed on silica eluting with hexane–ethyl acetate (5:2) to give the *syn*-diol (105 mg, 35%) and the *anti*-diol **9** (160 mg, 54%), R_f [hexane–ethyl acetate (3:1)] 0.33 (Found: C, 58.75; H, 9.89. $C_{10}H_{20}SO_2$ requires C, 58.78; H, 9.87%); ν_{max}(CH_2Cl_2)/cm^{-1} 3614–3495 (OH) and 2958–2871 (CH); δ_H(250 MHz; $CDCl_3$) 3.56 (2 H, br s, 2 × C*H*OH), 2.76 (2 H, br s, 2 × CHO*H*), 2.52 (2 H, d, *J* 14.7, 2 × SCH_AH_B), 2.27 (2 H, d, *J* 14.7, 2 × SCH_AH_B), 1.09 (6 H, s, 2 × C*Me*$_A$Me$_B$) and 0.95 (6 H, s, 2 × CMe$_A$*Me*$_B$); δ_C(63 MHz; $CDCl_3$) 73.6 (+), 47.1 (−), 38.8 (−), 28.3 (+) and 19.7 (+) (Found: M^+, 204.1181. $C_{10}H_{20}SO_2$ requires M^+, 204.1184); *m/z* 204 (M^+, 11%), 186 ($M^+ - H_2O$, 20), 139 (76) and 130 [$M^+ - H_2O - CH_2C(Me)_2$, 100], 86 [$CH_2C(Me)_2C(OH)H$, 40] and 56 [$CH_2C(Me)_2$, 52].

4-Acetoxy-5-chloro-3,3,6,6-tetramethylthiacycloheptane 17

Trimethyl orthoacetate (0.138 cm^3, 1.1 mmol) was added to a solution of the *syn*-diol **9** (170 mg, 0.83 mmol) and toluene-*p*-sulfonic acid (2 mg) in dry CH_2Cl_2 (2 cm^3). After the mixture had been stirred at room temperature for 1 h, volatile material was removed under reduced pressure and most of the residual methanol was removed by subjecting the sample to high vacuum for 1 min. The residue was then dissolved in dichloromethane and trimethylsilyl chloride (0.160 cm^3, 1.25 mmol) was added to the solution. The reaction mixture was stirred at room temperature for 4 days after which it was evaporated under reduced pressure. The residue was chromatographed (SiO_2, hexane–ether, 10:1) to give the α-*chloro acetate* **17** (141 mg, 64%) as a colourless oil; R_f [hexane–ethyl acetate (3:1)] 0.52; ν_{max}($CDCl_3$)/cm^{-1} 2962–2890 (CH) and 1732 (C=O); δ_H(250 MHz; $CDCl_3$) 5.18 (1 H, d, *J* 3.5, C*H*OAc), 3.78 (1 H, d, *J* 3.5, C*H*Cl), 3.40 (2 H, AB quartet, *J* 11.1, SCH_AH_B), 2.89 (1 H, d, *J* 10.1, SCH_CH_D), 2.52 (1 H, d, *J* 10.1, SCH_CH_D), 2.11 (3 H, s, CO_2Me), 1.12 (3 H, s, Me_C), 1.08 (6 H, s, *Me*$_A$*Me*$_B$) and 0.97 (3 H, s, Me_D); δ_C(100 MHz; $CDCl_3$) 170.2 (−), 82.6 (+), 56.7 (+), 55.4 (−), 47.7 (−), 41.2 (−), 38.1 (−), 25.4 (+), 24.4 (+), 24.2 (+), 22.8 (+) and 21.3 (+) (Found: M^+, 264.0954. $C_{12}H_{21}O_2SCl$ requires M^+, 264.0951); *m/z* 266 (M^+, 15%), 264 (M^+, 45), 221 [$M^+ - C(=O)Me$, 2], 204 ($M^+ - HCO_2Me$, 4) and 173 [$M^+ - Cl - C(Me)_2CH_2$, 100].

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References

1 A. de Groot and H. Wynberg, *J. Org. Chem.*, 1966, **31**, 3954.
2 H. Wynberg and A. de Groot, *J. Chem. Soc., Chem. Commun.*, 1965, 171.
3 A. Krebs and H. Kimling, *Tetrahedron Lett.*, 1970, 761.
4 A. de Groot, J. A. Boerma and H. Wynberg, *Rec. Trav. Chim. Pays-Bas.*, 1969, **88**, 994.

5 A. de Groot, J. A. Boerma and H. Wynberg, *Tetrahedron Lett.*, 1968, 2365.
6 N. Feeder, M. J. Ginnelly, R. V. H. Jones, S. O'Sullivan and S. Warren, *Tetrahedron Lett.*, 1994, **35**, 9095.
7 P. Y. Johnson and M. Berman, *J. Org. Chem.*, 1975, **40**, 3046.
8 P. Y. Johnson and D. J. Kirkman, *J. Org. Chem.*, 1976, **41**, 1768.
9 D. E. Applequist, P. A. Gebauer, D. E. Gwynn and L. H. O'Connor, *J. Am. Chem. Soc.*, 1972, **94**, 4272.
10 N. Greeves, in *Comprehensive Organic Syntheses*, ed. B. M. Trost and I. Fleming, Oxford, 1991, vol. 8, pp.1–24.
11 A. L. Gemal and J.-L. Luche, *J. Am. Chem. Soc.*, 1981, **103**, 5454.
12 J.-L. Luche, *J. Am. Chem. Soc.*, 1978, **100**, 2226.
13 G. M. Sheldrick, in 'SHELX86. Program for the Solution of Crystal Structures', University of Gottingen, Germany, 1990.
14 G. M. Sheldrick, in 'SHELXL93. Program for the Refinement of Crystal Structures', University of Gottingen, Germany, 1993.
15 M. Hannaby and S. Warren, *J. Chem. Soc.*, *Perkin Trans. 1*, 1989, 303.
16 M. C. Carreño, J. L. G. Ruano, A. M. Martín, C. Pedregal, J. H. Rodriguez, A. Rubio, J. Sanchez and G. Solladié, *J. Org. Chem.*, 1990, **55**, 2120.
17 M. C. Carreño, J. L. G. Ruano, M. Garrido, M. P. Ruiz and G. Solladié, *Tetrahedron Lett.*, 1990, **31**, 6653.
18 G. Solladié, C. Fréchou, G. Demailly and C. Greck, *J. Org. Chem.*, 1986, **51**, 1912.
19 H. C. Kolb and K. B. Sharpless, *Tetrahedron*, 1992, **48**, 10 515.
20 T. Nakata, Y. Tani, M. Hatozaki and T. Oishi, *Chem. Pharm. Bull.*, 1984, **32**, 1411.

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