Stereoselective Condensation of Bis-*p*-tolylthiomethane with Lactic Acid Derivatives through an Acylation–Reduction Strategy: Synthesis of Protected 4-Deoxy-L-threose and 4-Deoxy-L-erythrose

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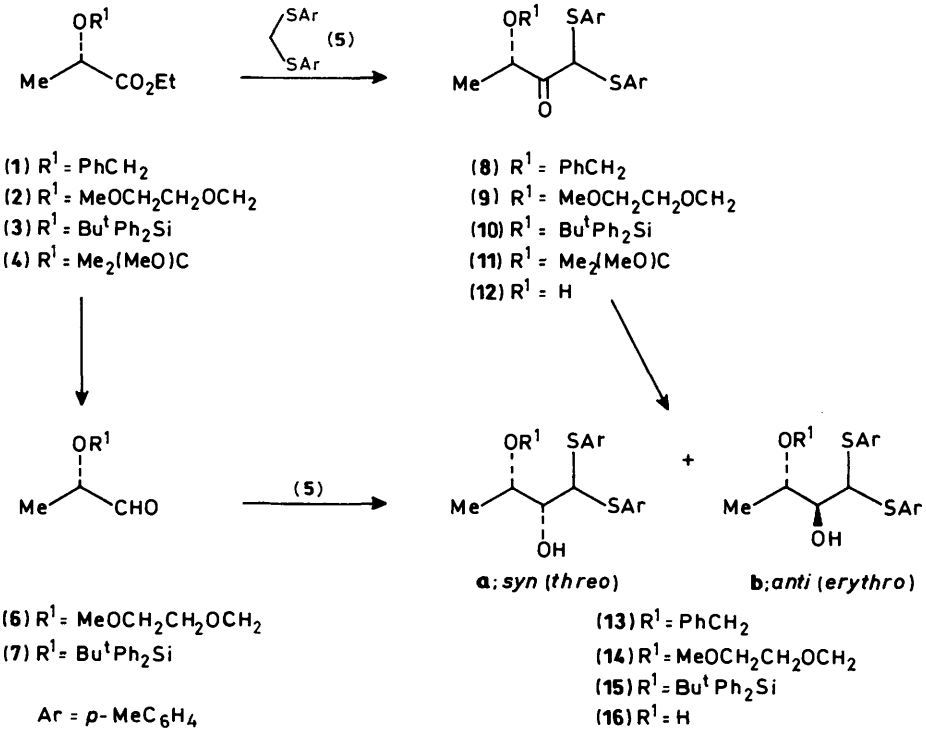
The condensation of lithium bis-*p*-tolylthiomethanide with protected ethyl-L-lactates gave a series of 3-alkoxy- (or 3-hydroxy-) 1,1-bis-*p*-tolylthiobutan-2-ones, which were stereoselectively reduced to the corresponding *syn*- or *anti*-alcohols with diastereoselectivities of up to 85:15 and 75:25, respectively. These alcohols were then converted into variously protected 4-deoxy-L-threose and 4-deoxy-L-erythrose derivatives.

In recent years, interest has grown in the synthesis of sugars from non-carbohydrate precursors. This goal has been accomplished *via* total asymmetric synthesis,[1–3] and through stereospecific elaboration of simple chiral building blocks derived from natural sources. As building blocks of this type, protected 4-deoxy-L-threose and -L-erythrose are particularly useful, and have given rise to numerous rare sugars.[4] However, their utility is not limited to the field of sugars: they have also been employed in the preparation of pheromones[5] and of the chemotactic factor LTB_4.[6]

Protected 4-deoxy-L-threose has been prepared from D-threonine[4c] and from L-tartaric acid,[4b,f,h] or through isomerization of the epimer;[4a] 4-deoxy-L-erythrose has been synthesized *via* ozonolysis of a diol prepared from cinnamaldehyde in fermenting baker's yeast.[4d,7]

Recently we reported some preliminary results on the synthesis of these important building blocks from ethyl L-lactate, a particularly cheap chiral precursor.[8] Now we present our results in full. Our strategy (Scheme 1) was based on the stereoselective homologation of a protected ethyl lactate with bis-*p*-tolylthiomethane (**5**), the lithium salt of which can be regarded as a formyl anion equivalent. This conversion can be accomplished in two ways: (*a*) reduction of the protected ethyl lactates to the corresponding α-alkoxy aldehydes followed by condensation with lithiated (**5**), and (*b*) direct coupling of the lactates (**1**)—(**4**) with (**5**) followed by the reduction of the resulting ketones. We have already shown[8,9] that the reaction of the lithium salt of (**5**) with esters, in contrast with the same reaction of lithium 1,3-dithianides,[10] gives ketones in excellent yields, without formation of undesired tertiary alcohols. These two approaches are equally straightforward and a choice between them must be made only on the basis of stereoselectivity.

Condensation of lithiated (**5**) with the protected lactaldehydes (**6**) and (**7**), prepared by known methods,[11–13] gave the adducts (**14a** and **b**) and (**15a** and **b**) in good yields, but with low stereoselectivity (*syn*:*anti*[14] 36:64 and 43:57, respectively). This result was not unexpected since condensation of organo-

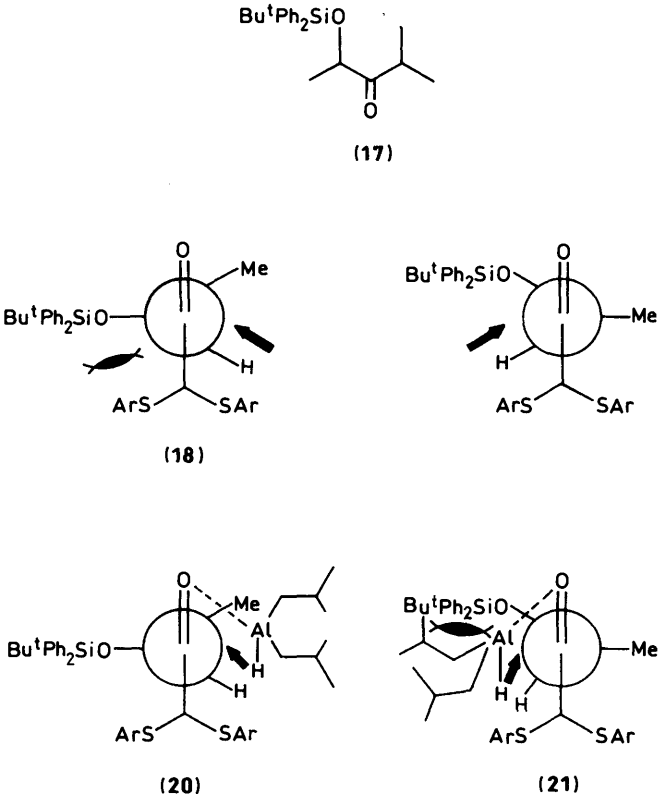


Scheme 1.

Table 1. Diastereoselectivity in the reduction of 3-alkoxy- (or 3-hydroxy) 1,1-bis-*p*-tolylthiobutan-2-ones

Entry	R^1	Reducing agent	Conditions	*syn*:*anti* ratio[a]	Yield (%)
1	$PhCH_2$	$NaBH_4$	−50 °C, MeOH	42:58	80
2	$PhCH_2$	$Zn(BH_4)_2$	−60 °C, Et_2O	65:35	75
3	$PhCH_2$	DIBAH[b]	−78 °C, CH_2Cl_2	77:23	80
4	$MeOCH_2CH_2OCH_2$	$NABH_4$	−50 °C, MeOH	42:58	80
5	$MeOCH_2CH_2OCH_2$	$LiAlH_4$	−78 °C, Et_2O	52:48	90
6	$MeOCH_2CH_2OCH_2$	DIBAH	−78 °C, CH_2Cl_2	78:22	80
7	$SiPh_2Bu^t$	$NaBH_4$	−78 °C, MeOH	34:66	83
8	$SiPh_2Bu^t$	MEAH[b]	−78 °C, toluene	40:60	90
9	$SiPh_2Bu^t$	DIBAH	−78 °C, toluene	85:15	75
10	$SiPh_2Bu^t$	BH_3·THF	Room temp., THF, 7 days	85:15	75
11	H	$NaBH_4$	−50 °C, MeOH	25:75	87
12	H	$Zn(BH_4)_2$	−78 °C, Et_2O	61:39	80
13	H	$NaBH_4/CeCl_3$	−78 °C, MeOH	60:40	75
14	H	$LiAlH_4$	−78 °C, Et_2O	50:50	65
15	H	MEAH	−78 °C, THF	46:54	80
16	$MeOCMe_2$	DIBAH	−78 °C, CH_2Cl_2	84:16[c]	70[d]

[a] Determined by standardized spectrodensitometry (254 nm) with diethyl ether–hexane as eluant except for R^1=$PhCH_2$ when CH_2Cl_2–hexane–diethyl ether was used; orders of elution (**13a**) > (**13b**); (**14b**) > (**14a**); (**15a**) > (**15b**); (**16b**) > (**16a**). [b] DIBAH = di-isobutyl aluminium hydride; MEAH = sodium bis-(2-methoxyethoxy)aluminium hydride. [c] Compounds (**16a** and **b**) were obtained directly. [d] Overall yield of (**16a** and **b**) from (**4**).

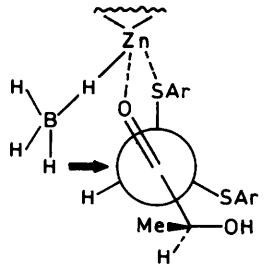


Scheme 2.

lithium derivatives with simple α-alkoxy aldehydes is known to afford *anti*-compounds with low diastereoselectivity.[15–17]

We therefore focussed our attention on the acylation–reduction approach. The 3-alkoxy-1,1-bis-*p*-tolythiobutan-2-ones (**8**)—(**11**) were obtained in high yield through condensation of (**5**) with the protected lactates (**1**)—(**4**); the α-hydroxy ketone (**12**) was synthesized by mild hydrolysis of the methoxy(methyl)ethoxy derivative (**11**). The stereoselectivity in the reduction of these α-alkoxy (or α-hydroxy) ketones with a series of reducing agents was then studied (Table 1).

The stereochemical course of reduction was in some cases unexpected, on the basis of previous literature reports. For example, although reduction of α-diphenyl(t-butyl)silyloxy ketones with sodium bis(methoxyethoxy)aluminium hydride (MEAH) is known usually to afford *syn*-alcohols, according to the Felkin model,[17] we found a reversed, albeit low, selectivity (entry 8). A similar deviation from the Felkin model had been reported by Oishi[17] for the reduction of the ketone (**17**) with the same hydride. In these two cases the bulk of the bis-*p*-tolythiomethyl (or isopropyl) group, coupled with the steric hindrance of the diphenyl(t-butyl)silyloxy moiety, is likely to cause a distortion of the reactive conformation from (**18**) to (**19**) (Scheme 2). This explanation can account also for the slight *anti* preference in the reduction of the silyloxy ketone (**10**) with



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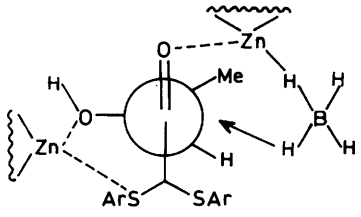


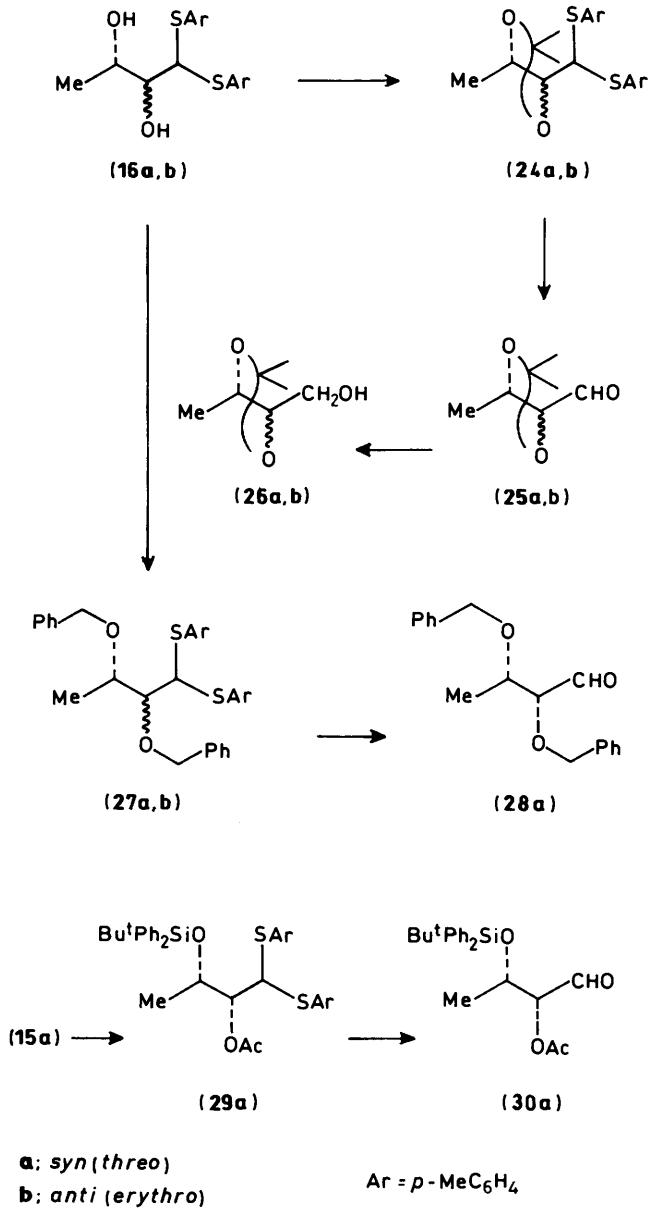
(23)

Scheme 3.

sodium borohydride (entry 7). In contrast, reduction with di-isobutylaluminium hydride (DIBAH) of the α-alkoxy ketones (**8**)—(**11**) led to the *syn* adducts with good diastereoselectivity, particularly in the case of bulky alkoxy groups (entries 3, 6, 9, and 16). It is likely that interaction with the two isobutyl groups disfavours the 'distorted' conformation (**21**) with respect to the 'normal' Felkin conformation (**20**) (Scheme 2).[18,19]

A similar result was obtained with another Lewis acid, diborane (entry 10). However in this case the reaction was sluggish. When the reaction was quenched with water after 2h, the isomeric alcohols (**15a** and **b**) were obtained in 40% yield in a reversed *syn*:*anti* ratio of 35:65, similar to that obtained with $NaBH_4$. When quenching was effected after 2 or 7 days, this ratio had increased to 68:32 or 85:15, respectively (and the yields to 65 or 75%). Since no equilibration of (**15b**) to (**15a**) was observed under the reaction conditions, this intriguing result is presumably due to reduction under quenching conditions.*

The course of reduction of the α-hydroxy ketone (**12**) was also somewhat surprising. While sodium borohydride furnished preferentially the expected *anti*-diol (**16b**), according to Cram's cyclic model (entry 11), zinc borohydride and *in situ*-generated cerium borohydride[20] gave opposite results (entries 12 and 13). The bulk of the *p*-tolylthiomethyl groups seems not to be responsible for this anomalous result, in the light of the high *anti*-selectivity obtained by Oishi[17] in the zinc borohydride reduction of α-hydroxy ketones regardless of the steric hindrance of the alkyl group attached to carbonyl. A possible interpretation is based on the capacity of sulphur to co-ordinate zinc in the transition state (**21**) leading to the alternative chelated conformations (**22**) and (**23**). Oishi and his co-workers[21] have recently demonstrated that in $Zn(BH_4)_2$ reduction of an α-alkylthio- β-hydroxy ketone the metal atom is chelated, in the preferred transition state, by the carbonyl oxygen and the hydroxy group (and not by the alkylthio group). In view of this finding, the transition state (**22**), in which, on the contrary, an alkylthio group rather than the hydroxy group contributes to the formation of a chelated transition state,



a; *syn* (*threo*)
b; *anti* (*erythro*)

Ar = *p*-MeC_6H_4

Scheme 4.

seems less likely. Nevertheless in that example the two types of co-ordination lead to differently sized rings (five-membered for sulphur and six-membered for oxygen), whereas in our case both kinds of co-ordination lead to five-membered rings. Thus we cannot definitely rule out the transition state (**22**).

Reduction with DIBAH of the methoxy(methyl)ethoxy ketone (**11**), followed by acidic work-up, led directly to the deprotected diols (**16**), and the silyloxy alcohols (**15**) were smoothly deprotected with Bu_4NF to (**16**). The *syn*- and *anti*-diols (**16a** and **b**) were easily separated by flash chromatography.[22] Thus we can conclude, from a synthetic point of view, that either (**16a**) or (**16b**) may be obtained in excellent yield and with good stereoselectivity by this acylation–reduction sequence, by employing the conditions of entry 9 (or 16) or 11, respectively.

We next examined the transformation of these compounds into the protected 4-deoxy-L-threoses and 4-deoxy-L-erythroses. Conversion of (**16a** and **b**) into the acetonides (**24a** and **b**) (2-methoxypropene and toluene-*p*-sulphonic acid, 98 and 97%

* The use of BH_3–Me_2S leads to identical results.

yield), followed by deblocking of the dithioacetal moiety (HgO and BF_3–Et_2O)[11] gave isopropylidene-4-deoxy-L-threose and -erythrose (**25a** and **b**), *in situ* reduction ($NaBH_4$) of which furnished the known[5a,23,24] isopropylidene-4-deoxy-L-threitol and -erythritol (**26a** and **b**) in, respectively, 40 and 60% overall yield from (**24**).*

This conversion allowed unequivocal establishment of the relative configuration of (**16a**) and (**16b**).†

Dibenzylation of (**16a**) [NaH, $PhCH_2Br$, and dimethylformamide (DMF); 65%] followed by hydrolysis of the dithioacetal (HgO and BF_3–Et_2O, 75%) gave the dibenzyl-4-deoxy-L-threose (**28a**). Finally a 4-deoxy-L-threose protected with two different groups was obtained in two steps [(1) Ac_2O, Et_3N, and dimethylaminopyridine, 80%; (2) HgO and BF_3–Et_2O, 70%] from (**15a**). Access to variously protected α,β-dialkoxy aldehydes may well allow the development of high stereoselectivities in their addition reactions.[25]

Finally, use of D-lactic acid, which will be soon easily available through a biotechnological method,[26] should allow us to obtain protected 4-deoxy-D-threose and 4-deoxy-D-erythrose; the latter is not available by previously known methods.

Experimental

N.m.r. spectra were recorded with a Varian FT 80 spectrometer (tetramethylsilane as internal standard). I.r. spectra were measured with a Perkin-Elmer 257 instrument for $CHCl_3$ solutions. Optical rotations were measured at 20 °C (1 dm cell) with a JASCO DIP-181 polarimeter. Elemental analyses were performed with a Perkin-Elmer 240 instrument. Spectrodensitometry analyses were performed with a CAMAG t.l.c. scanner, with Hewlett-Packard 3390 A integrator. Samples were deposited automatically on silica gel 60 F_{254} plates (Merck) (CAMAG Linomat III). Standardization was achieved by analyses of mixtures of known composition. Silica gel (Merck 270—400 mesh) was used for flash chromatography.[22] Organic extracts were dried over Na_2SO_4 and filtered before removal of the solvent under reduced pressure. All reactions in dry solvents were run under nitrogen. Protected ethyl lactates (**1**) and (**2**) were prepared by reported methods.[11,12,27,28]

(S)-(−)-*Ethyl* 2-[*Diphenyl*(*t-butyl*)*silyloxy*]*propanoate* (**3**).—Diphenyl(t-butyl)silyl chloride (4 ml, 15.3 mmol) was added to a solution of (*S*)-ethyl lactate (1.788 ml, 16.0 mmol) and imidazole (2 g, 30 mmol) in dry dimethylformamide (DMF) (5 ml). The solution was stirred at 25 °C for 18 h, then treated with H_2O and hexane; the phases were separated and the organic extracts evaporated to dryness. Flash chromatography (hexane–diethyl ether) gave pure (**3**) as a colourless *oil* (5.8 g, 96%) (Found: C, 71.05; H, 7.95. $C_{21}H_{28}O_3Si$ requires C, 70.7; H, 7.9%); $[\alpha]_D$ −41.1° (*c* 2 in $CHCl_3$); $\nu_{max.}$ 1 740, 1 590, 1 425, 1 140, 1 110, 1 020, and 820 cm^{-1}; $\delta_H(CDCl_3)$ 1.11 [9 H, s, $C(CH_3)_3$], 1.11 (3 H, t, *J* 7 Hz, CH_3CH_2), 1.40 (3 H, d, *J* 7 Hz, CH_3CH), 4.00 (2 H, q, *J* 7 Hz, CH_2CH_3), 4.29 (1 H, q, *J* 7 Hz, $CHCH_3$), and 6.95—7.80 (10 H, m, ArH).

(S)-(−)-*Ethyl* 2-(1-*Methoxy*-1-*methylethoxy*)*propanoate* (**4**).—2-Methoxypropene (32.4 ml, 339 mmol) was slowly added, at 0 °C, to (*S*)-ethyl lactate (19.2 ml, 169 mmol). A drop of $POCl_3$ was then added and the solution was stirred overnight at room temperature. After addition of few drops of triethylamine, the excess of 2-methoxypropene was evaporated off under reduced pressure to leave an *oil* which, after distillation, furnished pure (**4**) (27.5 g, 85%), b.p. 93 °C at 15 mmHg (Found: C, 56.7; H, 9.75. $C_9H_{18}O_4$ requires C, 56.8; H, 9.5%); $[\alpha]_D$ −75.9 (*c* in $CHCl_3$); $\nu_{max.}$ 2 830, 1 735, 1 445, 1 375, 1 180, 1 110, 1 095, 1 045, and 970 cm^{-1}; $\delta_H(CDCl_3)$ 1.27 (3 H, t, *J* 7.1 Hz, CH_3CH_2), 1.32 and 1.39 [2 × 3 H, 2 × s, $(CH_3)_2C$], 1.38 (3 H, d, *J* 6.9 Hz, CH_3CH), 3.21 (3 H, s, CH_3O), 4.18 (2 H, q, *J* 7.1 Hz, CH_3CH_2), and 4.33 (1 H, q, *J* 6.9 Hz, CH_3CH).

Bis-p-*tolylthiomethane* (**5**).—Sodium hydroxide (25.76 g, 644 mmol) was added to a cooled solution of *p*-thiocresol (80 g, 644 mmol) in absolute ethanol (300 ml). After 2 h, when nearly all the NaOH was dissolved, di-iodomethane (26.98 ml, 335 mmol) was slowly dropped in so that the temperature did not exceed 60 °C. The mixture was then heated at reflux for 2 h. Most of the ethanol was then evaporated off under reduced pressure; the residue was taken up with diethyl ether and water and the phases were separated. The organic extracts were washed with aqueous 5% KOH and brine, and evaporated to dryness to leave a yellowish oil which, after crystallization from hexane, afforded pure (**5**) as a white low-melting *solid* (70 g, 84%), m.p. <35 °C (Found: C, 69.1; H, 6.25. $C_{15}H_{16}S_2$ requires C, 69.2; H, 6.2%); $\delta_H(CDCl_3)$ 2.33 (6 H, s, CH_3), 4.27 (2 H, s, CH_2), and 7.15 and 7.36 (8 H, AB, *J* 8.5 Hz, ArH).

3-*Alkoxy*- (*or* 3-*Hydroxy*-) 1,1-*bis*-p-*tolylthiobutan*-2-*ones* (**8**)—(**10**) *and* (**12**): *General Procedure*.—A 1.6M solution of butyl-lithium in hexane (6.87 ml, 11 mmol) was added, at −65 °C, to a solution of (**5**) (2.60 g, 10 mmol) in dry tetrahydrofuran (THF) (20 ml). After 15 min a solution of the ester (**1**)—(**4**) (5 mmol) in THF (5 ml) was added at the same temperature. After 10 min the mixture was quenched with 3M acetic acid in THF (5 ml, 15 mmol), stirred for 10 min at −65 °C, warmed to room temperature, and diluted with water and diethyl ether. The organic phase was separated and evaporated to dryness to leave a crude oil, which was purified by flash chromatography (hexane–diethyl ether) to give pure product (**8**)—(**10**), and unchanged (**5**). The ketone (**11**) was quantitatively converted into (**12**) during silica gel chromatography. Yields [in parentheses that of unchanged (**5**)] were (**8**) 75% (40%) (Found: C, 70.8; H, 6.2. $C_{25}H_{26}O_2S_2$ requires C, 71.05; H, 6.2%); (**9**) 79% (41%) (Found: C, 62.9; H, 6.85. $C_{22}H_{28}O_4S_2$ requires C, 62.8; H, 6.7%); (**10**) 85% (36%) (Found: C, 71.45; H, 6.65. $C_{34}H_{38}O_2S_2Si$ requires C, 71.5; H, 6.7%); (**12**) 95% (32%) (Found: C, 64.9; H, 6.05. $C_{18}H_{20}O_2S_2$ requires C, 65.0; H, 6.1%). N.m.r. spectra showed $\delta_H(CDCl_3)$ (**8**) 1.33 (3 H, d, *J* 6.8 Hz, CH_3CH), 2.33 (6 H, s, CH_3Ar), 4.23 (1 H, q, *J* 6.8 Hz, $CHCH_3$), 4.51 (2 H, s, CH_2Ph), 5.33 (1 H, s, CHS), 7.29 (5 H, s, C_6H_5), and 7.00—7.50 (8 H, m, C_6H_4); (**9**) 1.35 (3 H, d, *J* 6.8 Hz, CH_3CH), 2.33 (6 H, s, CH_3Ar), 3.36 (3 H, s, CH_3O), 3.37—3.76 (4 H, m, OCH_2CH_2O), 4.47 (1 H, q, *J* 6.8 Hz, $CHCH_3$), 4.75 (2 H, s, OCH_2O), 5.30 (1 H, s, CHS), and 7.05—7.50 (8 H, m, ArH); (**10**) 1.04 [9 H, s, $C(CH_3)_3$], 1.22 (3 H, d, *J* 6.8 Hz, CH_3CH), 2.33 (6 H, s, CH_3Ar), 4.43 (1 H, q, *J* 6.8 Hz, $CHCH_3$), 5.65 (1 H, s, CHS), and 7.00—7.80 (18 H, m, ArH); (**12**) 1.30 (3 H, d, *J* 7.0 Hz, CH_3CH), 2.34 (6 H, s, CH_3), 3.04 (1 H, br s, OH), 4.56 (1 H, q, *J* 7.0 Hz, $CHCH_3$), 5.07 (1 H, s, CHS), and 7.00—7.50 (8 H, m, ArH).

General Procedure for Reduction with $NaBH_4$.—A solution of the ketone in absolute methanol was added to a suspension of $NaBH_4$ (5 equiv.) in MeOH. After completion the mixture was quenched with aqueous HCl and evaporated to dryness; the residue was taken up with diethyl ether and water and worked up as usual.

* The low yield in the hydrolysis of the dithioacetal moiety is due to partial hydrolysis of the acetonide under the reaction conditions. Better results could be probably obtained by the use of cyclohexylidene derivatives.

† The relative configuration of the benzyl ethers (**13a** and **b**) was determined through their conversion into the bisbenzyl ethers (**27a** and **b**); the methoxyethoxymethyl ethers (**14a** and **b**) were correlated with the analogues through clear ^1H n.m.r. analogies.

Table 2. Polarimetric and ^{1}H n.m.r.[a] data for compounds (**13a** and **b**)—(**16a** and **b**)

Compound	$[\alpha]_D$/° (C, in $CHCl_3$)	δ(CH_3Ar)	δ(1-H) ($J_{1,2}$)	δ(3-H)	δ(3-H) ($J_{2,3}$)	δ(CH_3CH) ($J_{3,4}$)	δ(aromatic)	δ(other)
(**13a**)		2.32	4.51 (10.9)	3.50—3.80 (m)	4.10 (4.2)	1.21 (6.2)	6.90—7.55 (m)	4.50 (2 H, s, CH_2Ph)
(**13b**)		2.31	4.82 (2.7)	3.50—3.78 (m)	3.91 (7.8)	1.29 (5.6)	6.90—7.55 (m)	4.54 and 4.30 (2 H, AB, J 11.2 Hz, CH_2Ph)
(**14a**)		2.32	4.41 (4.9)	3.50—3.80 (m)	4.23 (4.8)	1.19 (6.3)	6.90—7.55 (m)	3.40—3.80 (4 H, m, CH_2CH_2), 3.38 (3 H, s, OCH_3), 4.79 (2 H, s, OCH_2O)
(**14b**)		2.33	4.62 (3.9)	3.50—3.80 (m)	4.08 (6.4)	1.26 (6.1)	6.90—7.55 (m)	3.40—3.80 (4 H, m, CH_2CH_2), 3.35 (3 H, s, OCH_3), 4.69 (2 H, s, OCH_2O)
(**15a**)	−6.9	2.31	4.45 (6.0)	3.53	4.40 (4.3)	0.98 (6.0)	6.90—7.80 (m)	1.03 [9 H, s, $C(CH_3)_3$]
(**15b**)	−87.0	2.32	4.82 (3.7)	3.70	4.27 (6.9)	1.10 (7.5)	6.90—7.80 (m)	0.93 [9 H, s, $C(CH_3)_3$]
(**16a**)	+102.0	2.33	4.40 (5.5)	3.44	4.25 (4.4)	1.18 (6.3)	6.90—7.55 (m)	
(**16b**)	−79.3	2.32	4.61 (4.3)	3.57	4.12 (6.8)	1.25 (6.3)	6.90—7.55 (m)	

[a] Solutions in $CDCl_3$–D_2O; coupling constants in Hz.

General Procedure for Reduction with $NaBH_4$–$CeCl_3$.—The procedure of Gemal and Luche was followed.[20]

General Procedure for Reduction with $Zn(BH_4)_2$.—A solution of zinc borohydride (2.5 equiv.) in ether was added to a solution of the ketone in ether. The reaction was quenched with saturated aqueous NH_4Cl and worked up as usual.

General Procedure for Reduction with Di-isobutylaluminium Hydride (*DIBAH*).—A solution of DIBAH (1.2—1.3 equiv.) in the appropriate solvent was added to a solution of the ketone in the same solvent. After 3 h the reaction was quenched with 3M acetic acid in diethyl ether (1.1 equiv. with respect to DIBAH) and, after 15 min, with water (0.2 ml per mmol of DIBAH). The suspension was stirred for 2 h at room temperature and then filtered through Celite; the filter cake was washed with CH_2Cl_2. The filtrate was then washed with dilute aqueous $NaHCO_3$ and evaporated to dryness to give a crude product, purified by flash chromatography.

General Procedure for Reduction with Sodium Bis-(2-methoxyethoxy)aluminium Hydride (*MEAH*).—A 1M solution of the hydride in toluene (3 equiv.) was added to a solution of the ketone in THF [for (**12**)] or toluene [for (**10**)]. The mixture was quenched with saturated aqueous NH_4Cl, filtered through Celite, and worked up as for the DIBAH reduction.

General Procedure for Reduction with Diborane.—A solution of BH_3 in THF (5 equiv.) was added to a solution of the ketone at room temperature. After quenching with water, the reaction was worked up as usual.

All the reduction products were purified by flash chromatography [hexane–diethyl ether for (**14**)—(**16**) and CH_2Cl_2–hexane–diethyl ether for (**13**)] and gave correct elemental analyses. ^{1}H N.m.r. data and polarimetric powers (when determined) are reported in Table 2.

(2R,3S)-(+)-1,1-*Bis*-p-*tolylthiobutane*-2,3-*diol* (**16a**).—*From* (**4**). A solution of (**5**) (5 g, 19.2 mmol) in dry tetrahydrofuran (THF) (40 ml) was treated, at −78 °C, with a 1.6M solution of BuLi in hexane (13.2 ml, 21.1 mmol). After 10 min, neat (**4**) (1.826 g, 1.813 ml, 9.6 mmol) was added; the solution was stirred for 15 min, then quenched with aqueous 15% (2.8M) NH_4Cl (17.9 ml, 50 mmol). After warming to room temperature, extraction with diethyl ether and evaporation to dryness gave a crude oil (6.82 g) which was taken up with dry CH_2Cl_2 (30 ml); the solution was cooled to −80 °C, and treated with a 1.0M solution of DIBAH in CH_2Cl_2 (15.36 ml, 15.36 mmol). After 3.5 h, the solution was allowed to warm to room temperature and stirred overnight. The reaction was then quenched with 3M acetic acid in CH_2Cl_2 (7.5 ml) and, after 20 min, with water (4 ml). After being stirred for 2 h, the suspension was filtered through Celite, and the filtrate washed with 1M HCl, saturated aqueous $NaHCO_3$, and brine, and evaporated to dryness. The crude *product* was purified by flash chromatography (hexane–diethyl ether) to give pure (**16a**) (2.01 g, 63%) (Found: C, 64.55; H, 6.7. $C_{18}H_{22}O_2S_2$ requires C, 64.6; H, 6.6%) and (**16b**) (337 mg, 10.5%) (Found: C, 64.45; H, 6.75%) as oils, as well as unchanged (**5**) (1.83 g, 37%).

(*b*) *From* (**15a**). To a solution of (**15a**) (67 mg, 0.12 mmol) in dry THF (1 ml), a 1M solution of tetrabutylammonium fluoride trihydrate in THF (0.240 ml, 0.24 mmol) was added; the resulting solution was stirred for 2 h at room temperature. After quenching with water and dilution with diethyl ether, usual work-up gave, after flash chromatography (hexane–diethyl ether), pure (**16a**) (37 mg, 95%); (**16b**) was obtained similarly from (**15b**).

(4R,5S)-(−)-4-(*Bis*-p-*tolylthiomethyl*)-2,2,5-*trimethyl*-1,3-*dioxolane* (**24a**).—2-Methoxypropene (0.295 ml, 3.075 mmol) was added to a cooled (0 °C) solution of (**16a**) (412 mg, 1.23 mmol) in dry CH_2Cl_2 (6 ml), followed by a 0.01M solution of toluene-*p*-sulphonic acid in THF (0.2 ml, 0.002 mmol). The solution was stirred for 20 h, quenched with few drops of triethylamine, and evaporated to dryness. Flash chromatography (hexane–diethyl ether) gave pure (**24a**) as an *oil* (450 mg, 98%) (Found: C, 67.2; H, 7.1. $C_{21}H_{26}O_2S_2$ requires C, 67.3; H, 7.0%). $[\alpha]_D$ (*c* 1 in $CHCl_3$) −9.4°; $\delta_H(CDCl_3)$ 1.33 (3 H, d, J 6.0 Hz, CH_3CH), 1.41 and 1.46 (2 × 3 H, 2 × s, CH_3CCH_3), 2.32 (6 H, s, CH_3Ar), 3.88 (1 H, dd, CHCHS, J 4.0 and 7.6 Hz), 4.29 (1 H, dq, J 5.9 and 7.7 Hz, $CHCH_3$), 4.34 (1 H, d, J 4.0 Hz, CHS), 7.09 (4 H, d, J 8.1 Hz, CH *meta* to S), and 7.30 (4 H, d, J 8.1 Hz, CH *ortho* to S); $\delta_C(CDCl_3)$ 18.96 (CH_3CH), 21.18 (CH_3Ar), 26.94 and 27.62 (CH_3CCH_3), 61.68 (CHS), 74.84 and 83.57 (CHO), 109.06 (CH_3CCH_3), 130.73 and 130.66 (CCH_3), 129.77 and 133.29 (ArCH), and 138.04 and 138.10 (CS).

(4S,5S)-(−)-4-(*Bis*-p-*tolylthiomethyl*)-2,2,5-*trimethyl*-1,3-*dioxolane* (**24b**).—This *thioacetal* was prepared in 97% yield from (**16b**) as described for (**24a**) (Found: C, 67.15; H, 7.05.

$C_{21}H_{26}O_2S_2$ requires C, 67.3; H, 7.0%); $[\alpha]_D$ (*c* 1.2 in $CHCl_3$) −99.5°; $\delta_H(CDCl_3)$ 1.36 (3 H, d, *J* 5.7 Hz, CH_3CH), 1.33 and 1.54 (2 × 3 H, 2 × s, CH_3CCH_3), 2.34 (6 H, s, CH_3Ar), 4.10 (1 H, dd, CHCHS, *J* 5.3 and 7.6 Hz), 4.25 (1 H, d, *J* 7.6 Hz, CHS), 4.37 (1 H, quint, *J* 5.5 Hz, $CHCH_3$), and 6.90—7.55 (8 H, m, ArH); $\delta_C(CDCl_3)$ 15.78 (CH_3CH), 21.17 (CH_3Ar), 25.65 and 27.81 (CH_3CCH_3), 59.49 (CHS), 74.02 and 78.28 (CHO), 108.31 (CH_3CCH_3), 129.79 (CCH_3), 129.50, 129.79, 133.22, and 134.44 (ArCH), and 138.19 and 138.34 (CS).

(4R,5S)-(+)-4-*Hydroxymethyl*-2,2,5-*trimethyl*-1,3-*dioxolane* (**26b**).—To a suspension of red mercury(II) oxide (695 mg, 3.21 mmol) in THF–water (85:15; 9 ml), boron trifluoride–diethyl ether complex (0.395 ml, 3.21 mmol) was added. After 5 min, the suspension was cooled to 0 °C and a solution of (**24b**) (800 mg, 2.14 mmol) in THF–water (85:15; 3.5 ml) was added. The mixture was stirred for 40 min at room temperature, diluted with diethyl ether, filtered through Celite, washed with dilute aqueous $NaHCO_3$, and concentrated to a small volume. The white salts formed were filtered off and the filtrate was evaporated to dryness, without warming. The residue was taken up with absolute methanol (3 ml) and treated at 0 °C with sodium borohydride (405 mg, 10.7 mmol). After 30 min the reaction was quenched with saturated aqueous NH_4Cl, and most of the methanol was removed by careful evaporation under reduced pressure. The residue was taken up with diethyl ether and water; the phases were separated and the organic layer was evaporated to dryness to give a crude *oil*, which after flash chromatography (hexane–diethyl ether) furnished pure (**26b**) (178 mg, 57%) (Found: C, 57.8, H, 9.45. $C_7H_{14}O_3$ requires C, 57.5, H, 9.65%); $[\alpha]_D$ (*c* 1 in $CHCl_3$) +47.3° (lit.,[5a] +52°); $\delta_H(CDCl_3)$ 1.24 (3 H, d, *J* 6.2 Hz, CH_3CH), 1.36 and 1.47 (2 × 3 H, 2 s, CH_3CCH_3), 1.90 (1 H, br s, OH), 3.61 (2 H, br t, *J* 5.4 Hz, CH_2OH), 4.13 (1 H, q, *J* 5.8 Hz, $CHCH_2$), and 4.36 (1 H, quint, *J* 6.2 Hz, $CHCH_3$).

(4S,5S)-4-*Hydroxymethyl*-2,2,5-*trimethyl*-1,3-*dioxolane* (**26a**).—This *dioxolane* was prepared as described for (**26b**), in 37% yield from (**24a**) (Found: C, 57.9; H, 9.4. $C_7H_{14}O_3$ requires C, 57.5; H, 9.65%); $\delta_H(CDCl_3)$ 1.29 (3 H, d, *J* 5.9 Hz, CH_3CH), 1.41 and 1.42 (2 × 3 H, 2 × s, CH_3CCH_3), 2.30 (1 H, br s, OH), and 3.50—4.20 (4 H, m, CH and CH_2).

(2R,3S)-(+)-2,3-*Bis*(*phenylmethoxy*)-1,1-*bis*-p-*tolylthiobutane* (**27a**).—(a) *From* (**16a**). Benzyl bromide (0.755 ml, 6.355 mmol) and sodium hydride (50% suspension in mineral oil; 268 mg, 5.59 mmol) were added in succession to a cooled (0 °C) solution of (**16a**) (850 mg, 2.542 mmol) in dry dimethylformamide (DMF) (10 mol). After 1 h, the reaction was quenched with saturated aqueous NH_4Cl, diluted with hexane–diethyl ether (8:2; 150 ml) and water (70 ml), and the phases were separated. The organic extracts, evaporated to dryness, gave a yellow *oil* which was purified by flash chromatography (hexane–diethyl ether) to afford pure (**27a**) (908 mg, 69%) (Found: C, 74.65; H, 6.6. $C_{32}H_{34}O_2S_2$ requires C, 74.7; H, 6.7%); $[\alpha]_D$ (*c* 2.72 in $CHCl_3$) +9.6°; $[\alpha]_{365}$ (*c* 2.72 in $CHCl_3$) +76.7°; $[\alpha]_{435}$ (*c* 2.72 in $CHCl_3$) +31.7°; $\delta_H(CDCl_3)$ 1.18 (3 H, d, *J* 6.1 Hz, CH_3CH), 2.32 and 2.29 (2 × 3 H, 2 × s, CH_3Ar), 3.76 (1 H, dd, *J* 2.7 and 6.1 Hz, CHCHS), 3.99 (1 H, quint, *J* 6.2 Hz, $CHCH_3$), 4.47 (2 H, s, CH_2Ph), 4.55 (1 H, d, *J* 2.7 Hz, CHS), 4.78 and 4.91 (2 H, AB, *J* 11.5 Hz, CH_2Ph), and 6.95—7.50 (18 H, m, ArH),

(b) *From* (**13a**). Sodium hydride (50% suspension in mineral oil; 27 mg, 0.318 mmol) was added at room temperature to a solution of (**13a**) (90 mg, 0.212 mmol) in dry DMF (1 ml). After 5 min, benzyl bromide (0.030 ml, 0.254 mmol) was added to the stirred suspension. After 15 min the reaction was complete and was worked up as in (a) to give pure (**27a**) (89 mg, 82%).

(2S,3S)-(−)-2,3-*Bis*(*phenylmethoxy*)-1,1-*bis*-p-*tolylthiobutane* (**27b**).—This *thioacetal* prepared as described for (**27a**) either from (**16b**) (76% yield) or from (**13b**) (80% yield) (Found: C, 74.5; H, 6.8. $C_{32}H_{34}O_2S_2$ requires C, 74.7; H, 6.7%); $[\alpha]_D$ (*c* 1 in $CHCl_3$) −74.6°; $\delta_H(CDCl_3)$ 1.26 (3 H, d, *J* 5.7 Hz, CH_3CH), 2.29 (6 H, s, CH_3Ar), 3.79 (1 H, dd, *J* 1.8 and 7.8 Hz, CHCHS), 3.98 (1 H, dq, *J* 5.7 and 7.8 Hz, $CHCH_3$), 4.31 and 4.55 (2 H, AB, *J* 11.4 Hz, CH_2Ph), 4.94 (1 H, d, *J* 1.8 Hz, CHS), 4.70 and 5.04 (2 H, AB, *J* 11.5 Hz, CH_2Ph), and 6.95—7.50 (18 H, m, ArH).

(2R,3S)-(+)-2,3-*Bis*(*phenylmethoxy*)*butanal* (**28a**).—A suspension of red mercury(II) oxide (515 mg, 2.38 mmol) in THF–H_2O (85:15; 5 ml) was treated at room temperature with boron trifluoride–ether complex (0.293 ml, 2.38 mmol). After 5 min, a solution of (**27a**) (816 mg, 1.585 mmol) in THF–H_2O (85:15; 5 ml) was added. The suspension was stirred at room temperature for 50 min, diluted with hexane (15 ml), and filtered. The phases were separated and the organic phase was kept in a freezer for 30 min and filtered again. After washings with aqueous 3% $NaHCO_3$ and concentration (to 7 ml), the resulting white suspension was kept at 0 °C for 1 h and filtered. Evaporation to dryness left as a yellow *oil*, nearly pure (**28a**) (by n.m.r.), which upon flash chromatography (hexane–diethyl ether) furnished pure (**28a**) (340 mg, 75%) (Found: C, 75.75; H, 7.25. $C_{18}H_{20}O_3$ requires C, 76.0; H, 7.1%); $[\alpha]_D$ (*c* 1.93 in 95% EtOH) +17.6°; $\delta_H(CDCl_3)$ 1.25 (3 H, d, *J* 6.1 Hz, CH_3CH), 3.65—4.15 (2 H, m, CHO), 4.47 and 4.60 (2 H, AB, *J* 12 Hz, CH_2Ph), 4.55 and 4.79 (2 H, AB, *J* 12.2 Hz, CH_2Ph), 7.29 and 7.33 (2 × 5 H, 2 × s, ArH), and 9.74 (1 H, s, CH=O).

(2R,3S)-(+)-2-*Acetoxy*-1,1-*bis*-p-*tolylthiomethyl*-3-[*diphenyl*(*t-butyl*)*silyloxy*]*butane* (**29a**).—To an ice-cooled solution of (**15a**) (650 mg, 1.13 mmol) in dry CH_2Cl_2 (5 ml), triethylamine (0.261 ml, 1.87 mmol), acetic anhydride (0.161 ml, 1.70 mmol), and 4-dimethylaminopyridine (14 mg, 0.113 mmol) were added in this order. After 1 h, the reaction was quenched with saturated aqueous ammonium chloride; the phases were separated and the organic layer was evaporated to dryness leave a crude *oil*, which, upon flash chromatography (hexane–diethyl ether) gave pure (**29a**) (560 mg, 80%) (Found: C, 70.3; H, 6.9. $C_{36}H_{42}O_3S_2Si$ requires C, 70.3; H, 6.9%); $[\alpha]_D$ (*c* 1 in $CHCl_3$) +4.4°; δ_H 0.96 (3 H, d, CH_3CH), 1.02 [9 H, s, $(CH_3)_3C$], 1.98 (3 H, s, CH_3CO), 2.33 and 2.35 (2 × 3 H, 2 × s, CH_3Ar), 4.52 (1 H, quint, *J* 5 Hz, CHOSi), 4.59 (1 H, d, *J* 5.2 Hz, CHS), 5.19 (1 H, t, *J* 5 Hz, CHOAc), and 6.95—7.80 (18 H, m, ArH).

(2R,3S)-(−)-2-*Acetoxy*-3-[*diphenyl*(*t-butyl*)*silyloxy*]*butanal* (**30a**).—This *ester* was prepared from (**29a**) (500 mg, 0.813 mmol) by the same method as employed for (**28a**) (reaction time 2 h) to give pure (**30a**) (219 mg, 70%) (Found: C, 68.5; H, 7.5. $C_{22}H_{28}O_4Si$ requires C, 68.7; H, 7.3%); $[\alpha]_D$ (*c* 1.38 in 95% EtOH) −7.7°; $\delta_H(CDCl_3)$ 1.06 [9 H, s, $C(CH_3)_3$], 1.12 (3 H, d, *J* 6.4 Hz, CH_3CH), 2.13 (3 H, s, CH_3CO), 4.37 (1 H, dq, *J* 4.6 and 6.4 Hz, CHOSi), 5.07 (1 H, d, *J* 4.6 Hz, CHOAc), 7.25—8.00 (10 H, m, ArH), and 9.78 (1 H, s, CH=O).

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