Highly Diastereoselective Reduction of Chiral β-Ketosulphoxides under Chelation Control: Application to the Synthesis of (*R*)-(+)-n-Hexadecano-1,5-lactone

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The presence of zinc chloride in the reduction of chiral β-ketosulphoxides with di-isobutylaluminium hydride effects high 1,3-asymmetric induction to give β-hydroxysulphoxides; this method can be successfully applied to the synthesis of optically pure 1,4- or 1,5-lactones.

Chiral sulphoxides have recently gained considerable attention in terms of their usefulness as a chiral auxiliary for asymmetric synthesis.[1] In particular, the reduction of the carbonyl group in a chiral β-ketosulphoxide has been shown to be potentially useful for the preparation of optically active alcohols.[2] In conjunction with our studies on the synthesis of naturally occurring lactonic products, we chose a route to optically pure lactones (**4**) or their synthetic equivalents (**3**) *via* reduction of chiral ε- or δ-t-butoxycarbonyl-β-ketosulphoxides such as (**1a**) or (**1b**). We report herein the results that 1,3-asymmetric induction of chiral β-ketosulphoxides can be realized by the use of di-isobutylaluminium hydride (DIBAH) in the presence of zinc chloride, and the successful application of the present method to the synthesis of optically pure lactones.

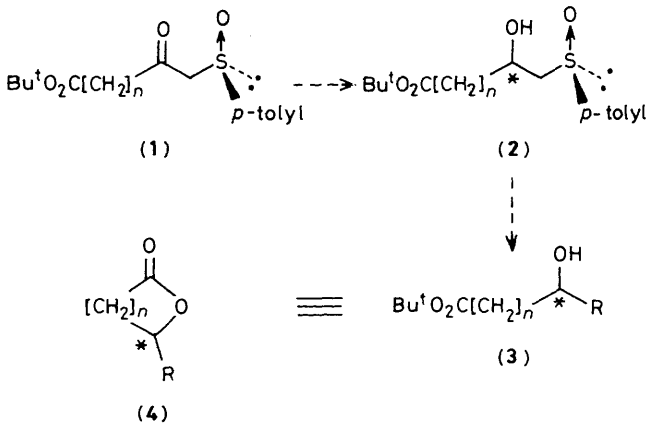
The enantiomerically pure (*R*)-β-ketosulphoxides (**1a**) and (**1b**)† were easily prepared in high yields from the reaction of the lithium carbanion of (*R*)-(+)-methyl *p*-tolyl sulphoxide, $[\alpha]_D$ +146° (*c* 1, acetone),[3] with t-butyl methyl glutarate or

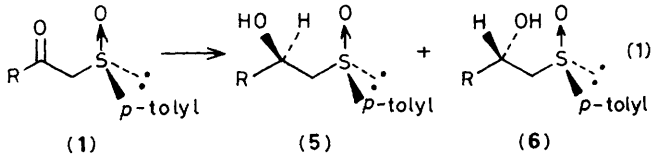
† Satisfactory analytical and spectral data were obtained for all new compounds. (**1a**): $[\alpha]_D$ +147.4° (*c* 0.39, $CHCl_3$), (**1b**): $[\alpha]_D$ +158.4° (*c* 0.36, $CHCl_3$).

Table 1. Reduction of β-ketosulphoxides (**1a—d**).

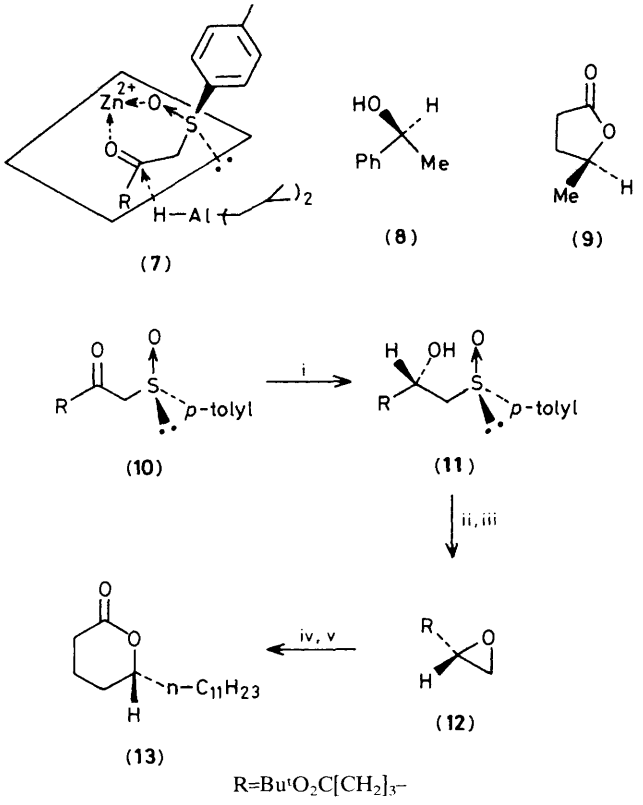
Entry no.	Substrate	Reducing agent (mol. equiv.) solvent[a]	Reaction time (h), temp. (°C)	Product ratio[b] (**5**):(**6**)	Yield[c] (%)
1	(**1a**)	Bu^i_2AlH(2)/THF	1.5, −100	12:88	78
2	(**1a**)	BH_3–THF (1)/toluene	0.7, −90	46:54	76
3	(**1a**)	$Zn(BH_4)_2$ (2)/Et_2O–THF	0.5, 0	58:42	76
4	(**1a**)	$LiAlH(OBu^t)_3$(1.2)/Et_2O	4, −100 to −40	71:29	68
5	(**1a**)	$NaBH_4$ (1)/EtOH	0.7, −100	79:21	72
6	(**1a**)	$ZnCl_2$ (1.2), Bu^i_2AlH (2) /THF	0.6, −100	99:1	78
7	(**1b**)		0.6, −100	97:3	93
8	(**1c**)		0.5, −78	>99:1	80
9	(**1d**)		0.6, −100	>99:1	80

[a] THF = Tetrahydrofuran. [b] Determined by h.p.l.c. on a Waters Assoc. μ-Bondapak C_{18} using 1:2—1:3 MeCN–H_2O. [c] Total isolated yields of (**5**) and (**6**) after silica-gel chromatography.





a; R = $Bu^tO_2C[CH_2]_3$–
b; R = $Bu^tO_2C[CH_2]_2$–
c; R = Et–
d; R = Ph–



Scheme 1. *Reagents:* i, $ZnCl_2$ (1.2 equiv.)–Bu^i_2AlH (2 equiv.)–THF; ii, Zn–Me_3SiCl–pyridine–THF (ref. 11); iii, $Me_3O^+BF_4^-$–CH_2Cl_2, 5% NaOH(aq.)–CH_2Cl_2 [60% yield from (**10**)]; iv, n-$C_{10}H_{21}MgBr$–CuI·Me_2S–THF; v, *p*-$MeC_6H_4SO_2OH$–benzene.

t-butyl methyl succinate, respectively.‡ The reduction of compound (**1a**) as a model substrate was examined by using a variety of reducing agents, as shown in equation (1) and Table 1. The best diastereofacial selectivity was achieved when (**1a**) was treated with $ZnCl_2$ (1.2 equiv.) in tetrahydrofuran (THF) at room temperature for 0.5 h, followed by addition of DIBAH (2 equiv.) in toluene at −100 °C (entry 6). The major diastereoisomer from the reaction was shown to be the (R_C,R_S)-hydroxysulphoxide (**5a**) as described later. In the same manner, (**1b**) as well as the known (*R*)-β-ketosulphoxides (**1c**) and (**1d**)[2a] were reduced with high diastereoselectivity to the corresponding (R_C,R_S)-hydroxysulphoxides, (**5b**), (**5c**), and (**5d**) (entries 7, 8, and 9), respectively. It should be noted that the presence of $ZnCl_2$ in the DIBAH reduction resulted in stereochemical reversal, compared to the reduction with DIBAH alone (entry 1). Therefore, it seems likely that the exclusive formation of the (R_C,R_S)-hydroxysulphoxides (**5**) from (*R*)-β-ketosulphoxides (**1**) is due to the initial complexation of the β-ketosulphoxide moiety with $ZnCl_2$[4] and the subsequent attack of a hydride from DIBAH on the less hindered site of the chelated species *i.e.* (**7**).

‡ Protection of one carboxylic group in the dicarboxylic acids as a t-butyl ester was essential for the preparation of (**1a**) and (**1b**) because the t-butyl ester did not react with the lithium carbanion of methyl *p*-tolyl sulphoxide. Furthermore, the t-butyl ester was found to be stable to the present reduction conditions.

The absolute configurations of the products and the utility of the present method are shown as follows. The hydroxysulphoxide (**5d**) was desulphurized with Raney-Ni to give optically pure (*S*)-(−)-1-phenylethanol (**8**) {$[\alpha]_D$ −43.8° (neat), lit.[5] $[\alpha]_D$ −43.5° (neat)}. The diastereoisomeric mixture (97 : 3) from (**1b**) was recrystallized once to afford the pure diastereoisomer (**5b**), which was desulphurized with Raney-Ni and then lactonised in refluxing benzene containing a catalytic amount of toluene-*p*-sulphonic acid to yield optically pure (*S*)-(−)-γ-valerolactone (**9**) {$[\alpha]_D$ −35.2° (*c* 1.02, CH_2Cl_2)}, {lit.[6] $[\alpha]_D$ +30.1° (*c* 0.85, CH_2Cl_2) for the (*R*)-(+)-enantiomer}.

Finally, we demonstrate the synthesis of (*R*)-(+)-n-hexadecano-1,5-lactone (**13**),[7] the pheromone responsible for some aspects of the social behaviour of the Oriental hornet, *Vespa orientalis*, as shown in Scheme 1. t-Butyl (*S*)-6-[(4-methylphenyl)sulphinyl]-5-oxohexanoate (**10**), the enantiomer of (**1a**),§ was reduced by the method described above ($ZnCl_2$–Bu^iAlH) to afford the (S_C,S_S)-hydroxysulphoxide (**11**) with 99 : 1 selectivity, which was converted into the (*S*)-epoxide (**12**) *via* the hydroxysulphide according to the known procedure.[8] Treatment of (**12**) with n-decylmagnesium bromide in the presence of $CuI \cdot Me_2S$ followed by lactonisation gave (*R*)-(+)-n-hexadecano-1,5-lactone (**13**) of 99% enantiomeric excess¶ in 64% yield, m.p. 40—41 °C, $[\alpha]_D$ +39.5° (*c* 0.85, THF), {lit.[10] m.p. 40—41 °C, $[\alpha]_D$ +39.97° (*c* 1, THF)}.

§ Compound (**10**) was obtained by the same procedure as for (**1a**) using (*S*)-(−)-methyl *p*-tolyl sulphoxide $[\alpha]_D$ −145° (*c* 0.49, acetone), prepared from the reaction of (+)-menthyl (+)-(*R*)-toluene-*p*-sulphinate, ref. 9, with methylmagnesium iodide.

¶ This is based on the reported value of the maximum specific rotation, ref. 10(d).

Thus, the present method offers a simple route to highly optically pure lactones.

Received, 18th October 1984; Com. 1472

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