Baker's Yeast-mediated Synthesis of Protected α-Hydroxy-aldehydes[1]

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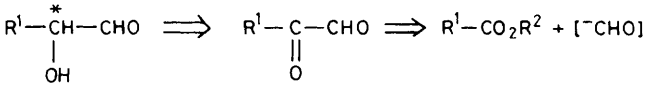
Several 3-substituted 2-hydroxy-1,1-bis-*p*-tolylthiopropanes, which are precursors of protected α-hydroxy-aldehydes, have been readily prepared in high optical purity *via* acylation of lithium bis-*p*-tolylthiomethanide and subsequent baker's yeast reduction of the resulting ketones.

Protected α-hydroxy-aldehydes are compounds of prime importance for the synthesis of many biologically active derivatives.[2] Unfortunately, although some, namely (*R*)-glyceraldehyde and (*S*)-lactaldehyde, are easily obtained from natural substances, the synthesis of other derivatives appears to be more troublesome.[3—5] As an extension of our previous work on the synthesis of homochiral α-hydroxyaldehydes[6—9] we now report a simple and straightforward approach to 3-hetero-substituted protected lactaldehydes.

The strategy is based on the disconnection showed in Scheme 1 involving the acylation of a formyl anion equivalent



Scheme 1

Table 1. Synthesis of 1,1-bis-*p*-tolylthioalkan-2-ones.

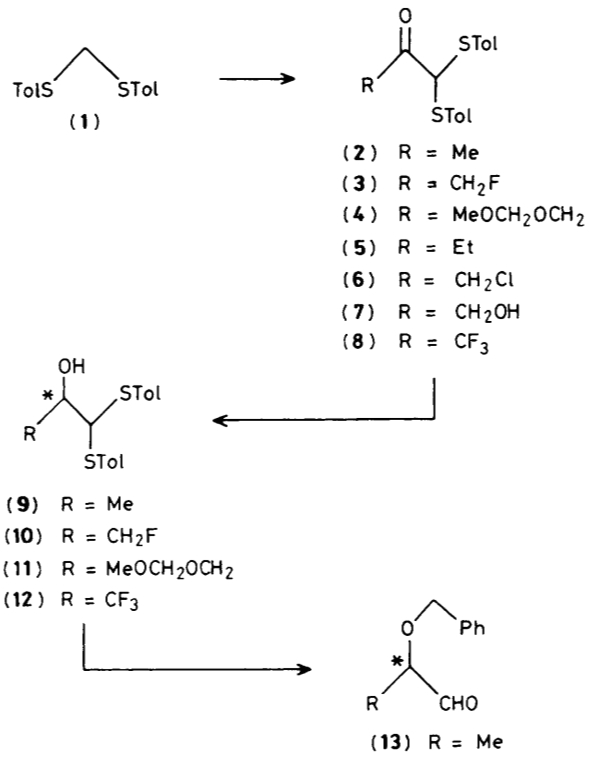
R	Me	Et	CF_3	$MeOCH_2OCH_2$	CH_2F	CH_2Cl	CH_2OH
% Yield[a]	75	68	60	85[b]	60	70	98[c]

[a] Isolated yields; ethyl esters were used unless otherwise noted. [b] Methoxymethyl ester was used. [c] Yields from ketone (**4**) *via* hydrolysis with 3 M HCl in tetrahydrofuran–water (3 : 1).

Table 2. Enantioselective reduction of 1,1-bis-*p*-tolylthioalkan-2-ones with baker's yeast.

R	Time/day	Temp./°C	% Yield[a]	% E.e.[d]
Me	3.5	27	50 (85)	95[b]
CH_2F	4	30	42 (63)	95[c]
$MeOCH_2OCH_2$	6	30	50 (85)	95[b]
Et	7	27	10	—
CH_2Cl	7	30	5	—
CH_2OH	7	30	5	—
CF_3	3	27	25	95[c]

[a] Not optimized. Yields from non-recovered starting material in parentheses. [b] Determined by ^1H n.m.r. spectroscopy in the presence of $Eu(hfc)_3$ [hfc = 3-(heptafluoropropylhydroxymethylene-(+)-camphorato]. [c] Determined by ^1H n.m.r. of Mosher's esters.[14] [d] Enantiomeric excess.



Scheme 2. Tol = *p*-MeC_6H_4.

with a carboxylic derivative followed by asymmetric reduction of the resulting ketone. Thus the lithium anion of bis-*p*-tolylthiomethane (**1**), which was found to be a particularly convenient reagent for the nucleophilic formylation of carboxylic esters,[9] was treated with a series of esters, giving the 1,1-bis-*p*-tolylthioalkan-2-ones (**2**)—(**8**) in good yields (Scheme 2 and Table 1). When these ketones were reduced with fermenting baker's yeast,[10,11] the rate of reduction seemed to be strongly dependent on the length of the carbon chain and on the type of hetero-substituent in position 3 (see Table 2).

Best results were obtained for R = Me, CH_2F, and $MeOCH_2OCH_2$. With R = CH_2OH, Et, or CH_2Cl the reduction was very sluggish and the extent of conversion was low even after one week. Finally, for R = CF_3 the reduction was relatively fast, but the yield was lowered by the low stability of the ketone (**8**).

However the most interesting result is the high enantiomeric excess observed in the cases when reaction occurred. In every case only one enantiomer was detected. The enantiomeric excesses were determined by ^1H n.m.r. comparison with the racemic alcohols (**9**)—(**12**), synthesized in high yield through $NaBH_4$ reduction of the ketones (**2**)—(**4**) and (**8**).

In a typical procedure baker's yeast (15 g; from Distillerie Italiane) was suspended in tap water (150 ml) and treated with glucose (16.5 g). After 40 min a solution of the ketone (1.5 mmol) in ethanol (3—4 ml) was added and the suspension stirred at the same temperature for the time indicated in Table 2. Celite (23 g) and ether (50 ml) were then added. Filtration, usual work-up, and silica gel chromatography gave the pure alcohols (**9**)—(**12**).

The alcohol (**9**) was shown to have the (*S*) configuration by its conversion [i, $PhCH_2Br$, NaH, dimethylformamide (DMF), 79%; ii, HgO, BF_3–Et_2O, 74%][12] into the known *O*-benzyl-(*S*)-lactaldehyde (**13**) {$[\alpha]_D^{20}$ −15.3° (*c* 1, 95% EtOH); lit.[13] −16.3°}. The stereochemical result is in accord with Prelog's rule which usually provides a good prediction of the stereoselectivity in yeast-mediated reduction of acyclic ketones.[10,11]

In summary the methodology reported here provides direct access to some 3-functionalised optically active α-alkoxyaldehydes. The use of different formyl anion equivalents, as well as the use of the compounds obtained here as building blocks in the enantiospecific synthesis of biologically active compounds is under study.

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