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MICROBIOLOGICAL SYNTHESIS OF VARIOUSLY PROTECTED L-GLYCERALDEHYDES IN HIGH OPTICAL PURITY

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Summary: Variously protected L-glyceraldehydes have been enantioselectively synthesized through a sequence involving acylation of formylanion equivalents with glycolic acid derivatives followed by baker's yeast mediated reduction of the resulting ketones.

Homochiral protected α-hydroxy-aldehydes are useful starting material for the synthesis of many biologically active derivatives. While some of them are easily achievable starting from natural low cost chiral precursors, the preparation of other derivatives appears more troublesome. Thus, protected D-glyceraldehydes are easily accessible starting from D-mannitol,[1] but, on the contrary, the corresponding L-enantiomers are more difficult to achieve, especially with the two OH groups differently protected. As anticipated by recent works by Reetz[2] and MacDonald,[3] the availability of a series of protected glyceraldehydes would be of great utility in natural products synthesis, not only in view of the possibility of chemoselective manipulations of the two hydroxyl groups, but also in order to better modulate the stereoselection in addition reaction to the carbonyl.

Here we report the synthesis of a series of protected L-glyceraldehydes based on the acylation of a formylanion equivalent followed by baker's yeast mediated enantioselective reduction of the resulting ketones.

Following this strategy, we recently prepared[4] glyceraldehyde equivalent 4 with good yield and excellent enantioselection, using bis-p-tolylthiomethane as formylanion equivalent. However, when we tried to utilize different protecting groups for the primary hydroxyl, yields dropped down, probably due to the severe steric requirements of the bis-p-tolylthio moiety in the biological reduction.

Thus, in order to extend the range of employable substrates, we examined two alternative formylanion equivalents: 1,3-dithiane[5] and 2-trimethylsilyl-thiazole.[6] The synthesis of 2-acyl-1,3-dithianes via the condensation of lithium 1,3-dithiane with esters furnished unsatisfactory yields (20-45%)[7a] due to the formation of considerable amount of tertiary alcohols derived by a second attack of the dithiane to the intermediate ketone. So, in order to optimise the yields of this conversion, we turned to the elegant method by Weinreb, which employes methyl N-methyl hydroxamates as acylating agents.[8] When the lithium anion of 1,3-dithiane was treated with the hydroxamates 1a-g[9], the corresponding 2-acyl-1,3-dithianes 2a-g were obtained in yields ranging from 80 to 95%[10] (No tertiary alcohol was detected in these reactions) (Scheme 1). 2-hydroxyacetyl-1,3-dithiane 2i was prepared from the tetrahydropyranyl derivative 2g by acidic hydrolysis (CF_3COOH/H_2O 3:1, R.T., 91%) and it was employed for the synthesis of 2j (Ac_2O, Et_3N, dimethylaminopyridine, CH_2Cl_2, R.T., 72%)[11,12] and 2k ($tBuMe_2SiCl$, imidazole, DMF, R.T., 59%). Finally, ketone 2h was prepared (45% yield) by reaction of lithium 1,3-dithiane with methoxymethyl methoxymethoxyacetate,[14] rather than through the hydroxamate method, since the preparation of 1h appeared to be troublesome.

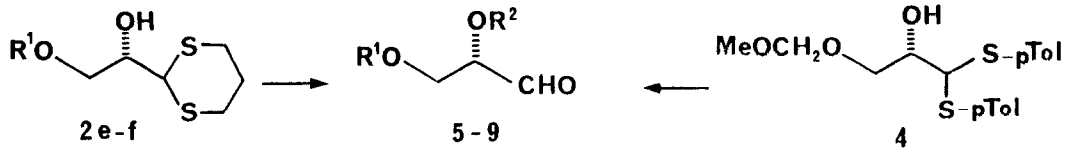
Table: Enantioselective Reduction of 2-Acyl-1,3-dithianes and 2-Acyl-thiazoles with Baker's Yeast.

Entry	Compound	R^1	Y	Time	Yield[a]	e.e.
1	2e	CH_2OBzl	dithianyl	5d	50% (67%)	≥95%[b]
2	2f	$CH_2O(4\text{-}MeO\text{-}C_6H_4)$	dithianyl	6d	27% (73%)	≥98%[b]
3	2g	CH_2OTHP[d]	dithianyl	3d	37%[d] (61%)[e]	≥95%[b]
4	2h	CH_2OCH_2OMe	dithianyl	1d	82% (91%)	≥95%[b]
5	2i	CH_2OH	dithianyl	5d	28% (55%)	≥95%[b]
6	2j	CH_2OAc	dithianyl	1d	58%[f] (71%)	87%[b]
7	2k	CH_2OSiMe_2tBu	dithianyl	7d	<10%	-
8	2l	CH_2OAc	thiazolyl	1d[g]	29%	88%[c]
9	2a	Me	dithianyl	4h	73%	≥95%[b]
10	2b	Et	dithianyl	3d	52% (71%)	≥95%[b]
11	2c	nHex	dithianyl	8d	38% (70%)	≥95%[b]
12	2d	CF_3	dithianyl	2h	96%	67%[b]
13	2m	Me	thiazolyl	2d	50%	≥95%[c]
14	2n	nHex	thiazolyl	3d	28%	28%[c]

a) Yields from non-recovered ketone in brackets. b) Determined by ^1H NMR in the presence of $Eu(hfc)_3$ and by comparison with the racemic compound. c) Determined through ^1H N.M.R. of Mosher's esters in presence of $Eu(FOD)_3$ and by comparison with a racemic sample; d) 3i was obtained. e) Yield from non recovered 2i; f) Partial hydrolysis to 3i had occurred; g) 20g of baker's yeast and 20 g of glucose for each mmol of substrate were used.

The (S) configuration (steric series L) was unambigously assigned to dibenzyl glyceraldehyde 5 by comparison of $[\alpha]_D$ of its semicarbazone (-40.2°) with literature polarimetric data for the (R) enantiomer (+ 41°)[20], thus proving the (S) configuration of 6 and 7 too. For the other products, configuration is most likely to be (S) as well in accordance with Prelog's rule, which is usually respected in this type of reduction.[21]

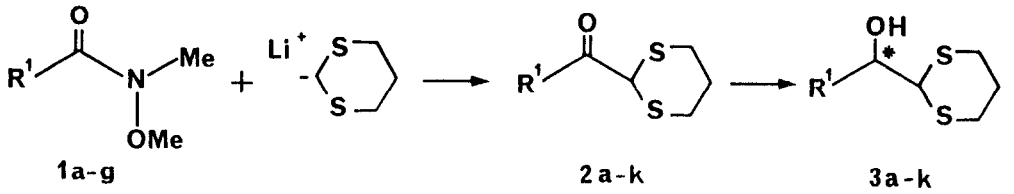
Scheme 2



5: R^1= R^2 = Bzl; 6: R^1=Bzl; R^2= Ac; 7: R^1= Bzl; R^2= $MeOCH_2$;
8:R^1= $pMeO\text{-}C_6H_4$; R^2= Bzl; 9: R^1= $MeOCH_2$; R^2= Bzl

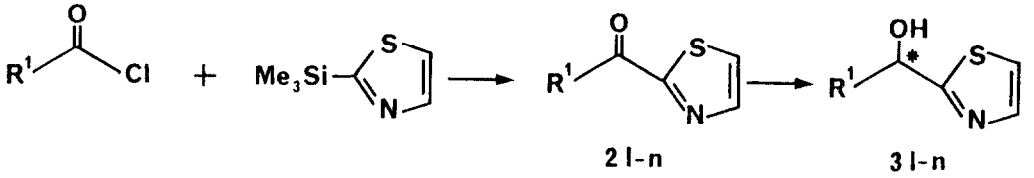
2-acyl-thiazoles were synthesized by reaction of 2-trimethylsilyl-thiazole with acyl chlorides[15] in 50-60% yield (Scheme 1).

Scheme 1



1a-g 2a-k 3a-k

a: R^1 = Me; b: R^1 = Et; c: R^1 = nHex; d: R^1 = CF_3; e: R^1 = CH_2OCH_2Ph; f: R^1 = CH_2O-(p-MeO-C_6H_4); g: R^1 = CH_2OTHP ; h: R^1 = CH_2OCH_2OMe; i: R^1 = CH_2OH; j: R^1 = CH_2OAc; k: R^1 = CH_2OSiMe_2tBu



2l-n 3l-n

l: R^1= CH_2OAc; m: R^1= Me; n: R^1= nHex

The course of baker's yeast mediated reduction of 3-hydroxy-2-oxo-propanal equivalents 2e-l was studied under the previously described conditions.[4] For comparison, we performed also the reduction of some 2-alkanoyl derivatives (see entries 9-14).[16,18] The results, showed in the table, indicate that the use of 1,3-dithiane instead of bis-p-tolylthiomethane permitted a broader range of α-alkoxy-aldehyde equivalents to be achieved. On the contrary, the reduction of 2-acyl-thiazoles gave poor results. Only in the case of R^1 = Me yields and enantioselectivities were satisfactory.

So, among the compounds studied, 1,3-dithiane seems the formylanion equivalent of choice for the synthesis of protected glyceraldehydes 3 as well as other α-alkoxy-aldehydes. However, in some particular cases, bis-p-tolylthiomethane is still to be preferred as in the case of trifluorolactaldehyde derivatives (in entry 12 the excellent yield is unfortunately accompanied by a not high e.e.) or when preparation of 2-acyl-1,3-dithianes is not straightforward (this is the case of methoxymethyl derivative 2h).

Finally it is interesting to note that the tetrahydropyranyl protecting group was completely cleaved under the reaction conditions (entry 3). Moreover even an acetyl group was partially hydrolysed (entry 8).

With a good method for the enantioselective synthesis of alcohols 3e-l in hand, we examined the conversion of some of them into a series of protected glyceraldehydes (Scheme 2). This was accomplished without difficulty by protection of the secondary alcohol[19] followed by cleavage of the dithioacetals with HgO, BF_3-Et_2O in THF/H_2O[4] or with MeI, $CaCO_3$ in aqueous acetone.[7a] The former method worked well in the case of bis-p-tolylthio derivatives (80-90% yields) while, in the case of 1,3-dithianes, longer reaction times and higher temperature were required with consequent lowering in yields (40-50%). Thus for this reaction the latter method was better suited (60-80% yields).

In conclusion, by the here presented procedure we were able to prepare a series of L-glyceraldehydes bearing protecting groups cleavable under acidic (methoxymethyl), basic (acetyl), reducing (benzyl) or oxidative (p-methoxyphenyl)[22] conditions. Studies directed to the applications of these synthons to the synthesis of biologically active compounds are in course.

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REFERENCES AND NOTES

1) J.Jurczak, S.Pikul, T.Bauer, Tetrahedron, 447 (1986).
2) M.T.Reetz, K.Kesseler, J.Org.Chem., 5434 (1985).
3) K.Mead, T.L.MacDonald, J.Org.Chem., 50, 422 (1985).
4) G.Guanti, L.Banfi, A.Guaragna, and E.Narisano, J.Chem.Soc., Chem.Commun., 138 (1986).
5) D.Seebach, and E.J.Corey, J.Org.Chem., 40, 231 (1975).
6) A.Dondoni, M.Fogagnolo, A.Medici, and P.Pedrini, Tetrahedron Lett., 5477 (1985).
7) a) T.Fujisawa, E.Kojima, T.Itoh, and T.Sato, Chem.Lett., 1751 (1985). b) T.Fujisawa, E.Kojima, T.Itoh, and T.Sato, Tetrahedron Lett., 6089 (1985).
8) S.Namm, and S.M.Weinreb, Tetrahedron Lett., 3815 (1981).
9) Preparation of hydroxamates 1a-g: 1a-c were prepared from the corresponding acyl chlorides according to ref. 6. 1d was prepared from trifluoroacetic anhydride and N,O-dimethylhydroxylamine;. Bromoacetic acid was employed as starting material for the synthesis of 1e (a: BzlONa, BzlOH; b: carbonyldiimidazole, MeO-N(Me)H·HCl, Et_3N, DMF, R.T., 71% overall yield) and 1f (a: p-methoxyphenol, NaH, DMF, R.T.; b: carbonyldiimidazole, MeO-N(Me)H·HCl, Et_3N, DMF, R.T., 69% overall yield). Finally 1g was prepared from glycolic acid in 60% overall yield (a: Dihydropyran, PTSA, R.T.; b: 0.5 N KOH in abs. MeOH; c: carbonyldiimidazole, MeO-N(Me)H·HCl, Et_3N, DMF, R.T.) (since O-tetrahydropyranyl-glycolic acid is unstable, on step b it is necessary to isolate it as the triethylammonium salt).
10) In a typical procedure to a solution of lithium 1,3-dithiane (ref. 5) in THF (1.1 eq.), cooled to -78°C, 1 eq. of methyl N-methyl hydroxamate 1 was added. The temperature was slowly raised to 0°C and then the reaction was quenched with saturated aqueous ammonium chloride and worked out as usual.
11) We noticed the formation, besides 2j, of another product, identified as 2-(1,2-diacetoxy-ethylidene)-1,3-dithiane. However this product can be utilized as well in the successive baker's yeast reduction, since it rapidly reverts, under reaction conditions, to 2j.
12) 2j was also synthesized in 25% yield by reaction of acetoxyacetyl chloride with 2-trimethylsilyl-1,3-dithiane (CH_3CN, reflux, 4d)(see ref. 13).
13) P.Jutzi, and O.Lorey, Phosphorus and Sulfur, 7, 203 (1979).
14) The tertiary alcohol was also isolated in 27% yield.
15) A.Medici, G.Fantin, M.Fogagnolo, and A.Dondoni, Tetrahedron Lett., 2901 (1983).
16) Baker's yeast mediated reductions of 2-hexanoyl-1,3-dithiane and 2-(8-oxo-ter-butyl-octanoate)-1,3-dithiane were already reported by C.J.Sih (Ref. 17).
17) Y.Takaishi, Y.L.Yang, D.DiTullio, and C.J.Sih, Tetrahedron Lett., 5489 (1982).
18) When this work was nearly completed, we took notice of a recent report by Fujisawa concerning the baker's yeast mediated reduction of several alkanoyl-1,3-dithianes (ref. 7).
19) 2e, 2f, and 4 were benzylated with BzlBr, NaH, DMF at room temp. in 80-90% yields; 2e was acetylated in quantitative yields with Ac_2O, dimethylaminopyridine, Et_3N, CH_2Cl_2, room temp.; finally 2e was protected as methoxymethyl ether with $MeOCH_2Cl$, NaI, $EtNiPr_2$, CH_2Cl_2, reflux, 24h, 60% yield.
20) H.F.G.Beving, H.B.Boren, P.J.Garegg, Acta Chem. Scandinavica, 21, 2083 (1967).
21) Absolute configuration of 3a was unambigously determined by Fujisawa (Ref. 7a). Moreover Sih reported that baker's yeast reduced ketone 2 (R^1= nC_5H_{11}) enantioselectively to the (S) alcohol (Ref. 17).
22) T.Fukuyama, A.A.Laird, L.M.Hotchkiss, Tetrahedron Lett., 6291 (1985).

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