Enantiospecific Synthesis of Protected 4-Deoxy-L-threose and 4-Deoxy-L-erythrose *via* Diastereoselective Reduction of L-Lactic Acid-derived Ketones

Giuseppe Guanti,* Luca Banfi, and Enrica Narisano

Istituto di Chimica Organica e C.N.R., Centro di studio sui diariloidi, Palazzo delle Scienze, corso Europa, 16132 Genova, Italy

The title compounds were synthesized from L-lactic acid *via* an acylation–reduction sequence employing lithium bis-*p*-tolylthiomethanide as a formyl anion equivalent.

Protected 4-deoxy-L-threose (**16a**) and 4-deoxy-L-erythrose (**16b**) are valuable intermediates for the synthesis of L-amino-sugars[1] as well as other naturally occurring substances.[2] In continuation of our work on the construction of sugars from non-carbohydrate precursors, we report here a synthesis of these derivatives starting from L-lactic acid and bis-*p*-tolylthiomethane (**1**),[3] using two different strategies. First we condensed the lithium anion from (**1**) with protected lactaldehydes (**2**) (R^1 = $CH_2OCH_2CH_2OMe$ or Ph_2Bu^tSi).[3] However, since this reaction proceeded in good yields but with low stereoselectivity (*syn* : *anti*[4] 36 : 64 and 43 : 57 respectively)† we focused our attention on another strategy which involved acylation of lithium bis-*p*-tolylthiomethanide with a suitably protected ethyl lactate followed by reduction of the resulting ketones. The required protected ethyl lactates (**7**) (R^1 = $PhCH_2$, $MeOCH_2CH_2OCH_2$, or Ph_2Bu^tSi) were prepared by literature methods[3,5,6] while the methoxyisopropyl derivative (**7**) (R^1 = $MeOCMe_2$) was obtained in 85%

† Further studies on this reaction with variation of the counter-ion or the formyl anion equivalent are in progress.

Table 1. Diastereoselectivity in the reduction of 3-alkoxy- (or 3-hydroxy-)1,1-bis-*p*-tolylthiobutan-2-ones (**8**)—(**12**).

Entry	R^1	Reducing agent	Conditions: *T*/°C, solvent	*syn* : *anti*[a]	% Yield
1	$PhCH_2$	$NaBH_4$	−50, MeOH	42 : 58	80
2	$PhCH_2$	$Zn(BH_4)_2$	−60, Et_2O	65 : 35	75
3	$PhCH_2$	Dibah	−78, CH_2Cl_2	77 : 23	80
4	$MeOCH_2CH_2OCH_2$	$NaBH_4$	−50, MeOH	42 : 58	80
5	$MeOCH_2CH_2OCH_2$	$LiAlH_4$	−78, Et_2O	52 : 48	90
6	$MeOCH_2CH_2OCH_2$	Dibah	−78, CH_2Cl_2	78 : 22	80
7	Ph_2Bu^tSi	$NaBH_4$	−78, MeOH	34 : 66	83
8	Ph_2Bu^tSi	Na(Vitride)	−78, toluene	40 : 60	90
9	Ph_2Bu^tSi	Dibah	−78, toluene	85 : 15	75
10	Ph_2Bu^tSi	BH_3·THF	Room temp., THF, 7 days	85 : 15	75
11	H	$NaBH_4$	−50, MeOH	25 : 75	87
12	H	$Zn(BH_4)_2$	−78, Et_2O	61 : 39	80
13	H	$NaBH_4/CeCl_3$	−78, MeOH	60 : 40	75
14	H	$LiAlH_4$	−78, Et_2O	50 : 50	65
15	H	Na(Vitride)	−78, THF	46 : 54	80
16	$MeOCMe_2$	Dibah	−78, CH_2Cl_2	84 : 16[b]	70[c]

[a] Determined by standardized spectrodensitometry (254 nm) with diethyl ether–n-hexane as eluant except for $R^1 = PhCH_2$ when CH_2Cl_2–n-hexane–diethyl ether was used; order of elution is (**3a**) > (**3b**); (**4b**) > (**4a**); (**5a**) > (**5b**); (**6b**) > (**6a**). [b] (**6a,b**) were obtained directly. [c] Overall yield of (**6a,b**) from (**7**, $R^1 = MeOCMe_2$).

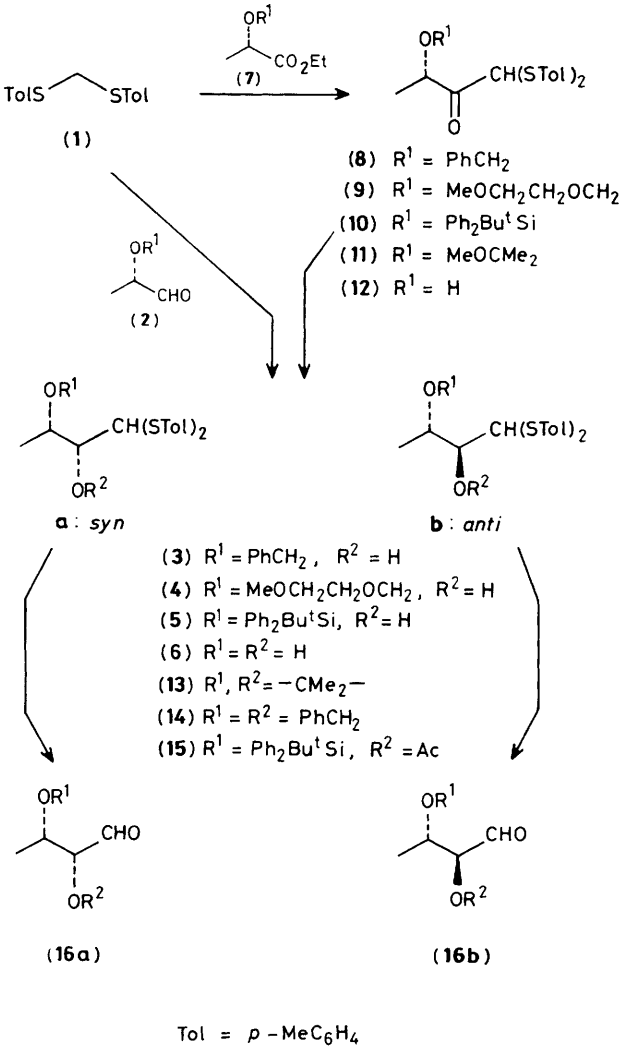
yield by reaction of ethyl lactate with 2-methoxypropene (0 °C, cat. $POCl_3$, 14 h).

When 2 equiv. of the lithium anion derived from (**1**)[3] were treated at −78 °C with 1 equiv. of the protected lactates, the α-alkoxyketones (**8**)—(**11**) were obtained in 80—90% yields. No tertiary alcohols were detected in this reaction. The clean and high-yield acylation of (**1**) with aliphatic esters seems to be of general application,[7] in contrast with the behaviour of the lithium derivative of 1,3-dithiane which usually affords mixtures of ketones and tertiary alcohols.[8] The methoxyisopropyl derivative (**11**) was quantitatively hydrolysed during silica gel chromatography, thus permitting easy access to the free hydroxy-ketone (**12**).

The reduction of the ketones (**8**)—(**12**) with a series of reducing agents gave in good yields mixtures of *syn*- and *anti*-alcohols (**3**)—(**6**) in a diastereoisomeric ratio varying from 85 : 15 to 25 : 75 (see Table 1). In each case the epimers could be readily obtained as pure products by silica gel chromatography.

The stereochemical course was in some cases unexpected. For example, although the reduction of α-diphenyl-t-butylsilyloxy ketones with sodium borohydride or sodium bis-(2-methoxyethoxy)aluminium hydride (Na-Vitride) is known to afford usually[9,10] *syn*-alcohols, according to the Felkin model, in our case we found a reversed, albeit low, selectivity (entries 7 and 8). In contrast 'Lewis acidic' reducing agents such as borane or di-isobutylaluminium hydride (Dibah), which were recently reported to furnish anti-Felkin adducts,[11,12] in the present work showed noticeable Felkin selectivity giving *syn*-alcohols with a diastereoisomeric ratio varying from 3.5 : 1 to 6 : 1 (entries 3, 6, 9, 10, and 16). This anomalous behaviour is probably due to the steric repulsion between the alkoxy and the bis-*p*-tolylthiomethyl groups, which leads to a distortion of the classical Felkin model.[9]‡

Another intriguing point was the reversal in the diastereoselectivity of the reduction of the α-hydroxy-ketone (**12**)



‡ A full discussion on the stereoselectivity of these reductions will be reported in a forthcoming full paper.

on passing from sodium borohydride to zinc borohydride. Indeed, although zinc borohydride is usually the reagent of choice for attaining high *anti*-selectivity in the reduction of α-hydroxy-ketones, according to Cram's cyclic model,[9] in the case of (**12**) the *syn*-diol was the major product (entry 12). The same result was obtained with *in situ*-generated cerium borohydride[13] (entry 13). Transition states involving co-ordination of the metal by the hydroxy group and one of the two sulphur atoms can be invoked in order to explain this behaviour.‡

From a synthetic point of view it is worth noting that both *syn*- and *anti*-diols (**6a**) and (**6b**) can be obtained as major products from the ketone (**11**) as a common intermediate, simply by deblocking the methoxyisopropoxy group after or before the reductive step and using di-isobutylaluminium hydride or sodium borohydride respectively (entries 16 and 11). The *syn*-diols (**6**) have also been synthesized in 95% yield from the silyloxy derivative (**5**) [Bu^n_4NF, tetrahydrofuran (THF)].

The relative configuration of the diols (**6a**) and (**6b**) was confirmed by their transformation, *via* the acetonides (**13a**) and (**13b**) (2-methoxypropene, cat. toluene-*p*-sulphonic acid, 98 and 97% yield), into isopropylidene-4-deoxy-L-threose and -erythrose (HgO, BF_3–Et_2O, THF, H_2O, room temp.)[3] *in situ* reduction ($NaBH_4$) of which furnished the known[14] isopropylidene-4-deoxy-L-threitol and -erythritol in, respectively, 40 and 60% overall yield from (**13a,b**).§ (**6a**) has also been converted into dibenzyl-4-deoxy-L-threose [i, NaH, $PhCH_2Br$, dimethylformamide (DMF), 65%; ii, HgO, BF_3–Et_2O, 75%], while (**5a**) was transformed into 2-*O*-acetyl-3-*O*-diphenyl-t-butyl-4-deoxy-L-threose (i, Ac_2O, Et_3N, 4-dimethylaminopyridine, CH_2Cl_2, 80%; ii, HgO, BF_3–Et_2O, 70%).

§ The relative configuration of the benzyl ethers (**3a,b**) was established *via* their conversion (NaH, $PhCH_2Br$, DMF, 80%) into the dibenzyl ethers which were also synthesized, by the same method, from the diols (**6a**) and (**6b**). Finally, the ethers (**4a,b**) were correlated through clear ^1H n.m.r. analogies with the differently protected analogues.

In conclusion the present new methodology for obtaining protected 4-deoxy-threose and 4-deoxy-erythrose derivatives appears particularly straightforward and versatile; the access to various protected α,β-dialkoxy aldehydes provides an opportunity to develop high stereoselectivities in addition reactions involving them.[15] This is being studied.

We thank Mr. Alberto Guaragna for assistance and the Progetto Finalizzato Chimica Fine e Secondaria for financial support.

Received, 2nd August 1985; Com. 1144

References

1 C. Fuganti, P. Grasselli, and G. Pedrocchi-Fantoni, *J. Org. Chem.*, 1983, **48**, 909, and references therein.
2 G. Fronza, C. Fuganti, P. Grasselli, G. Pedrocchi-Fantoni, and C. Zirotti, *Chem. Lett.*, 1984, 335, and references therein.
3 L. Banfi, A. Bernardi, L. Colombo, C. Gennari, and C. Scolastico, *J. Org. Chem.*, 1984, **49**, 3784.
4 S. Masamune, A.Sk. Ali, D. L. Snitman, and D. S. Garvey, *Angew. Chem., Int. Ed. Engl.*, 1980, **19**, 557.
5 S. J. Abbott, S. R. Jones, S. A. Weinman, F. M. Bockhoff, F. W. McLafferty, and J. R. Knowles, *J. Am. Chem. Soc.*, 1979, **101**, 4323.
6 S. K. Massad, L. D. Hawkins, and D. C. Baker, *J. Org. Chem.*, 1983, **48**, 5180.
7 G. Guanti, L. Banfi, A. Guaragna, and E. Narisano, *J. Chem. Soc., Chem. Commun.*, following communication.
8 D. Seebach and E. J. Corey, *J. Org. Chem.*, 1975, **40**, 231.
9 T. Nakata, T. Oishi, and T. Tanaka, *Tetrahedron Lett.*, 1983, 2653.
10 R. J. McCready and L. E. Overman, *Tetrahedron Lett.*, 1982, 2355.
11 T. Takahashi, A. Ootake, and J. Tsuji, *Tetrahedron Lett.*, 1985, 69.
12 M. M. Midland and Y. C. Kwon, *J. Am. Chem. Soc.*, 1983, **105**, 3725.
13 A. L. Gemal and J. L. Luche, *J. Am. Chem. Soc.*, 1981, **103**, 5454.
14 C. Fuganti, P. Grasselli, S. Servi, and C. Zirotti, *Tetrahedron Lett.*, 1982, 4269.
15 K. Mead and T. L. MacDonald, *J. Org. Chem.*, 1985, **50**, 422.