Pergamon

Tetrahedron Letters 40 (1999) 2863–2864

TETRAHEDRON LETTERS

Diastereoselective Reduction of (*S*)-1-Chloro-3-silyloxybutan-2-one. Synthesis of Enantiopure (2*S*,3*R*) and (2*S*,3*S*) *O*-*tert*-Butyldimethylsilyl-3,4-epoxybutan-2-ol.

José M. Concellón,* Pablo L. Bernad, R. Alvarez, A. Rodríguez and B. Baragaña.

Departamento de Química Orgánica e Inorgánica, Julián Clavería 8, Universidad de Oviedo, 33071 Oviedo, Spain

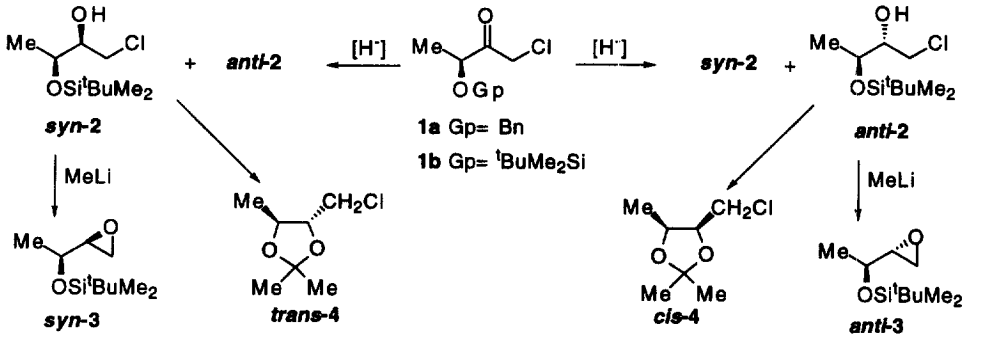
Received 22 December 1998; revised 1 February 1999; accepted 9 February 1999

Abstract: (2*S*,3*S*)- And (2*R*,3*S*)-3-[(*tert*-butyldimethyl)silyloxy]-1-chlorobutan-2-ol have been obtained with high diastereoselectivity by reduction of enantiopure (*S*)-3-[(*tert*-butyldimethyl)silyloxy]-1-chlorobutan-2-one using different reducing agents. The chiral alcohols were transformed into the corresponding (2*R*,3*S*)- and (2*S*,3*S*)-3-[(*tert*-butyldimethyl)silyloxy]-1,2-epoxybutane.

Keywords: chiral chloromethyl ketones; reduction; diastereoselection; β,γ-epoxy alcohols.

We have reported the direct preparation of chiral (*S*)-3-alkoxy-1-chlorobutan-2-one **1** by reaction of (chloromethyl)lithium generated *in situ* with *O*-protected ethyl lactate, [1].

In the present communication we report some synthetic applications of **1**. Thus, reduction of **1** with different reducing agents led to both diastereoisomeric β-alkoxy alcohols ***syn*-2** or ***anti*-2** [2] with high diastereoselectivity; epoxidation of these diols provided both diastereoisomers of the 3-alkoxy-1,2-epoxides ***syn*-3** and ***anti*-3**. The stereochemistry of the major diastereoisomers obtained in the reduction reactions was also established.



Scheme 1

Reduction using ketone **1a** and $NaBH_4$, gave the desired *O*-monoprotected diol **2** in high yield, but no diastereoselectivity was observed. By contrast, reduction of **1b** with $NaBH_4$ led to the ***anti*-2** β-silyloxy alcohol with high diastereoselectivity. Since *O*-*tert*-butyldimethylsilylated ketone **1b** shows enhanced diastereoselectivity relative to the corresponding *O*-benzylated

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00313-5

ketone **1a**, we investigated the reduction with other reducing agents using **1b.** Thus the reduction was also studied with $NaBH_3CN$, $LiBH_4$ and KBH_4 at -78 °C (Table 1). The major diastereoisomer obtained in these reductions was found to be ***anti*-2** in each case. In contrast, when $^iBu_2AlH$ or L-Selectride®in methanol were used, the ***syn*-2** product was synthesised as major diastereoisomer. (Table 1). The ratios of the diastereoisomers were obtained from the crude reaction mixtures using ^1H-NMR and/or GC-MS. The mixtures of diastereoisomers obtained using $NaBH_4$ or L-Selectride® were subjected to flash column chromatography over silica gel (hexane:ethyl acetate, 20/1) to provide the pure diastereoisomer of ***anti*-2** or ***syn*-2**, respectively.

The stereochemistry of the reduction was determined by deprotection of the major diastereoisomer ***anti*-2** or ***syn*-2** with tetrabutylammonium chloride [3] and acetonization using 2,2-dimethoxypropane [4]. The absolute configuration of the 1,3-dioxolane ***cis*-4** or ***trans*-4** was established by NOESY experiments.

Synthesis of ***anti*-2** (using $NaBH_4$) or ***syn*-2** (using L-Selectride®) took place with no detectable racemization. The enantiomeric purity of ***anti*-2** or ***syn*-2** was determined by chiral GC (HP Chiral 20 B) analysis, which showed an enantiomeric excess (ee) > 99%; racemic mixtures of ***anti*-2** or ***syn*-2** were prepared to exclude the possibility of comigration of both enantiomers in the GC analysis.

Treatment of ***anti*-2** or ***syn*-2** with methyllithium at -78°C gave the corresponding alcoholate. When the reaction mixture was allowed to warm to room temperature the enantiopure alkoxy epoxides ***anti*-3** or ***syn*-3** were obtained, respectively.

Table 1: Reduction of chiral ketone **1b** into ***anti*-2** and ***syn*-2**.

Entry	Reduction agent[a]	Yield (%)[b, c]	*anti*-2:*syn*-2
1	$NaBH_4$	86	84:16
2	$NaBH_3CN$	80	79:21
3	KBH_4	86	82:18
4	$LiBH_4$	73	66:34
5	L-Selectride®	75	5:95
6	$^iBu_2AlH$[d]	92	23:77

[a] All reactions were carried out at -78 °C. [b] All products were fully characterized by elemental analysis and spectroscopic methods (IR, ^1H- and ^{13}C-NMR, and HMRS). [c] Isolated yield based on the starting ketone **1b**. [d] The reaction was performed in hexane.

In conclusion, the results reported represent a direct method for the preparation of enantiopure *syn* and *anti* *O*-silylated β,γ-epoxy alcohols, which are useful chiral building blocks in organic synthesis, with high yield and diastereoselectivity.

Acknowledgments: We thank II Plan Regional de Investigación del Principado de Asturias (PBP-PGI97-01) for financial support.

References.

(1) Barluenga J, Baragaña B, Alonso A, Concellón JM. J. Chem. Soc., Chem. Commun. 1994:969-970.

[2] The stereoconfiguration was classified as *syn* or *anti* according to the definition given by Masamune S, Kaiho T, Garvey DS. J. Am. Chem. Soc. 1982;104: 5522-5523.

[3] Corey EJ, Venkateswarlu A. J. Am. Chem. Soc. 1972;94: 6190-6191.

[4] Rychnovsky SD, Richardson TL, Rogers BN. J. Org. Chem. 1997; 62:2925-2934.