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N-Hydroxymethyl group for configurationally stable *N*-alkoxycarbonyl α-amino aldehydes [1]

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Abstract

Attachment of an *N*-hydroxymethyl group to *N*-Boc-α-amino aldehyde enhanced greatly the configurational stability of the stereogenic carbon α to the aldehyde group by shifting the equilibrium from an open form of ω-hydroxyaldehyde to a closed form of hemiacetal. The *N*-hydroxymethyl group was introduced by treating *N*-Boc-α-amino acids with formaldehyde in the presence of an acid catalyst followed by reduction with DIBALH.

Key words: amino aldehydes; acetals; enantiomeric purity; amino acids.

α-Amino acids constitute one of the important classes of easily available chiral compounds [2]. They are rather cheap, mostly commercially available in both enantiomeric forms, and continued to be expanded in number beyond the naturally occurring members [3]. They are widely utilized in asymmetric syntheses of biologically active compounds as either chiral synthons or auxiliaries. *N*-Protected α-amino aldehydes among the derivatives of α-amino acids are of special interest for the former purpose owing to their pronounced versatility in organic synthesis [4]. In the course of our synthetic studies toward biologically active amino alcohols, we needed to prepare optically pure *N*-protected α-amino aldehydes. However, they have been well-known to be both chemically and configurationally labile due to the rather acidic α-proton to the carbonyl group [4-7]. The optical instability in particular made us utilize them without isolation or immediately after isolation in order to retain the required optical purity, which complicated the subsequent reactions and often gave poor results. Therefore, we wished to develop an efficient method for both chemically and configurationally stable *N*-protected α-amino aldehydes.

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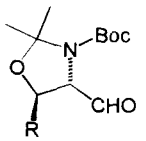
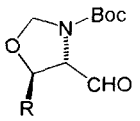
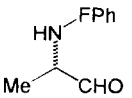
In the beginning of the present study, we were aware that there were a few reports on configurationally stable *N*-protected α-amino aldehydes as shown below [8-11]. Although **1** and **4** have been useful in the asymmetric syntheses of nitrogen-containing natural products, there are some limitations with compounds **1-4** as follows; (1) **1** and **2** are only applicable to a limited number of α-amino acids, (2) high cost of the protecting group, 9-phenylfluorenyl (PhF), for **3**, and (3) the basic amino group in **4** is often not desirable and sometimes interferes with electrophiles or oxidizing agents [12]. In addition, deprotection of the dibenzyl group by hydrogenolysis in the product derived from **4** is not compatible with double bonds or other benzylic groups present in an intermediate or target molecule [13]. Taken these into consideration, we have devised an efficient scheme of wide applicability for both chemically and configurationally stable α-amino aldehydes with *N*-alkoxycarbonyl protecting groups that are easily introduced and cleaved under various mild conditions [14].



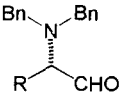
Garner aldehyde **1** [8]



2 [9]



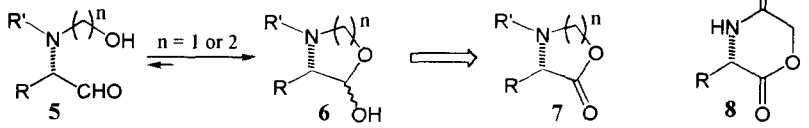
3 [10]



4 [11]

We envisioned that the goal would be achieved by temporarily changing the unsaturated carbonyl group of *N*-protected α-amino aldehydes into a saturated hemiacetal group as suggested by Ito et al. [5] for the limited racemization of *N*-Cbz-N^{G}-nitro-L-arginal, which in turn could be done by introducing an *N*-hydroxyalkyl group that would make the equilibrium shift from the open form of ω-hydroxyaldehyde **5** to the hemiacetal form **6** (Scheme 1). Length of the alkyl chain was kept to one or two carbons due to the favorable equilibrium toward 5- or 6-membered cyclic forms. Both the *N*-hydroxyalkyl group and the aldehyde group would be generated in one step by reducing **7** that could be readily derived from α-amino acids.

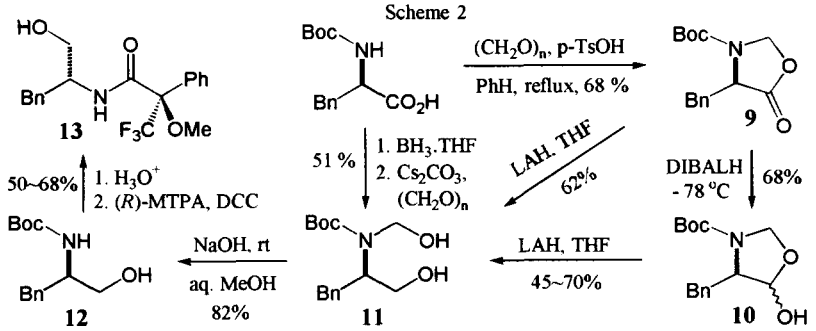
Scheme 1



Initially, an *N*-hydroxyacetyl group was chosen because it could serve two purposes; protection of the amino group and providing the ω-hydroxyl group. The *N*-hydroxyacetyl group was introduced into amino acids according to the literature procedure to give 3-alkylmorpholine-2,5-dione **8** [15]. However, reduction of **8** with DIBALH yielded complex results with not much desired product. The amide group in **8** seemed to interfere. The equilibrium for the 6-membered cyclic hemiacetal also did not look much favorable with the morpholinone structure because an aldehydic peak was observed on ^{1}H NMR spectra of the product. Thus, we turned our attention to a 5-membered analog, that is, an *N*-hydroxymethyl group (n=1). The hydroxymethyl group

attached to the acylamino groups was quite stable and successfully applied as intermediates by Hiemstra et al. [16]. Phenylalanine among α-amino acids was chosen for the present study since it was known to be rather configurationally unstable [6,7] and convenient to work with. A D form of Boc-protected phenylalanine was used as it was available in large quantity on the shelf.

Scheme 2



Heating *N*-Boc-D-phenylalanine with paraformaldehyde in the presence of p-TsOH introduced the *N*- hydroxymethyl group to give oxazolidinone **9** (Scheme 2) [17]. Reduction of **9** with DIBALH produced hemiacetal **10** along with overreduced diol **11**, which were separated by silica gel column chromatography in 68% and 17% yield, respectively. No decomposition of **10** was detected during the purification. Configurational stability of **10** was examined by conversion of purified **10** into diol **11** after storage for certain periods at different temperature, and then comparison of the optical rotation with that of diol **11** obtained directly from **9** (Table 1). Diol **11** was also derived from the starting amino acid to check the possibility of racemization during the cyclization to give **9**.

Although there was some fluctuation in measurements of the degree of optical rotation and

Table 1

Optical rotations of diols **11** and enantiomeric purities of **13**

No.	storage temp. (°C)	storage time (day)	$[\alpha]_D$ ($CHCl_3$)	yield (%) of **11**	dr[d] (*RR*:*SR*) of **13** (% ee)
1	-	0[a]	+28	51	> 200:1 (99)
2	-	0[b]	+27	62	> 200:1 (99)
3	-	0[c]	+26	70	59:1 (97)
4	-22	1	+27	64	-
5	-22	3	+27	61	-
6	-22	12	+27	69	-
7	-22	30	+28	50	60:1 (97)
8	2	1	+26	60	-
9	2	3	+27	66	-
10	2	12	+27	60	-
11	2	30	+26	45	58:1 (97)
12	rt	1	+27	56	48:1 (96)
13	rt	3	+27	65	51:1 (96)
14	rt	12	+28	51	58:1 (97)
15	rt	30	+25	59	31:1 (94)

[a] from reduction of *N*-Boc-D-phenylalanine followed by *N*-hydroxymethylation (Scheme 2).
[b] from reduction of oxazolidinone **9**. [c] from reduction of lactol **10**. [d] diastereomeric ratio.

the yield was not optimized, it was apparent that the hemiacetal form **10** as an isomer of an *N*-hydroxymethyl α-amino aldehyde was quite stable both chemically and configurationally. The enantiomeric purity judged by optical rotational measurement was confirmed by formation of Mosher amides **13** of several D-phenylalaninols (Scheme 2) [18] because the Mosher esters of **12** did not give a good separation on the NMR spectra (Table 1). Careful analysis of their ^{1}H NMR spectra indicated 1-1.5% racemization during the preparation of purified hemiacetal **10**. However, no racemization was observed during storage except the sample stored at room temperature for a month (entry 15) that showed additional 1-1.5% racemization. Therefore, the stabilizing effect by the *N*-hydroxymethyl group was quite evident, compared with 30% racemization of relatively stable *N*-Boc-leucinal during storage at room temperature for 9 days [6] and 3-5% racemization during the preparation of Garner aldehyde [8]. The stability of **10** was further supported by the successful Wittig reaction with $Ph_3P{=}CHCO_2Me$ in refluxing benzene without racemization.

The superfluous *N*-hydroxymethyl group was removed by simply stirring diol **11** in basic (NaOH) aqueous methanol to give **12** in a high yield. This method has been applied to L-serine successfully to produce the configurationally stable L-serinal derivative that did not show any decrease in optical rotation after being heated for 12 hr under refluxing THF [19].

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