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# A Novel Three-step Hydroxy-deamination Sequence: Conversion of Lysine to 6-Hydroxynorleucine Derivatives

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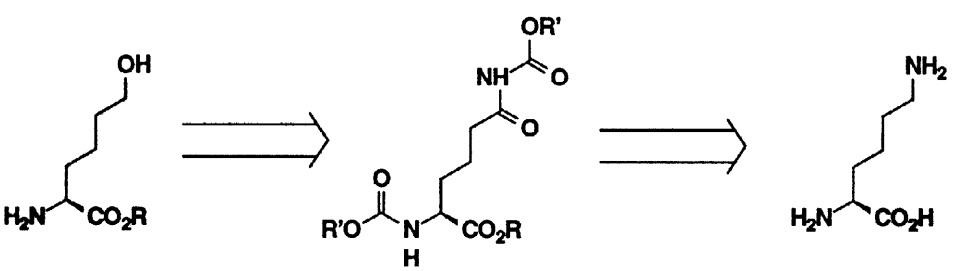
**Abstract:** Oxidation of carbamates with catalytic $RuO_4$, generated from $RuO_2$ and $NaBrO_3$, provides the corresponding acyl carbamates, which can be reduced with $NaBH_4$ to provide alcohols. Application of this methodology to L-lysine provides (*S*)-6-hydroxynorleucine derivatives.


The non-proteinogenic α-amino acid (*S*)-6-hydroxynorleucine (**1**) has been used recently for the synthesis of peptidomimetics[1] and L-α-aminoadipic acid derivatives.[2] Generally, **1** has been obtained by enzyme-catalyzed resolution of racemic *N*-acylated derivatives of **1**;[3] however, a recent report detailing a six-step route for preparation of **1** from lysine[4] prompted us to communicate our efforts in this area.

We required a process to prepare multi-gram quantities of (*S*)-6-hydroxynorleucine methyl ester (**2**) that used inexpensive starting materials and reagents. The naturally occurring amino acid L-lysine (**4**) was chosen as a starting material since it contained the requisite stereocenter and carbon skeleton found in (*S*)-6-hydroxynorleucine (**1**), is relatively inexpensive, and is readily available in kilogram quantities. It only remained to transform the ε-amine of lysine to an alcohol moiety. The classical method used for hydroxy-deamination is via formation of a diazonium intermediate followed by displacement with a nucleophile (i.e. $H_2O$); however, this method is not generally useful when applied to aliphatic primary amines since elimination and rearrangement products are formed competitively.[5] Application of this method to lysine is further complicated by the presence of two amine moieties which must be differentiated.[6]




1 R = H
2 R = OMe

3

4

The approach we sought to explore for the preparation of ester **2** from lysine was based upon the known ruthenium-catalyzed oxidation of carbamates to provide acyl carbamates such as **3**.[7] This method had been

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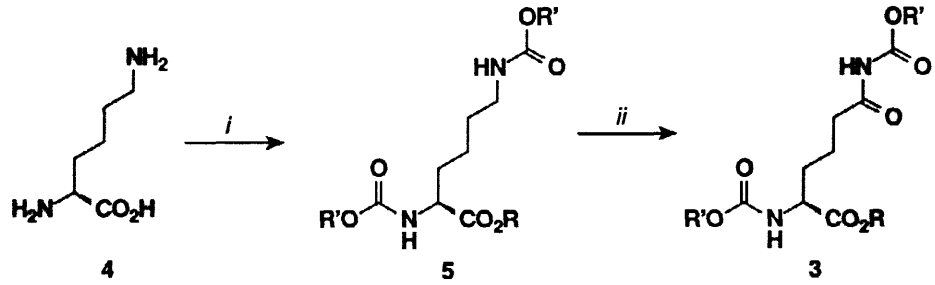
previously applied to derivatives of lysine to provide the corresponding homoglutamide derivatives.[8] Although this method does not directly provide the ε-carbon of lysine in the desired oxidation state, we thought with the appropriate reducing agent it would be possible to reduce selectively an intermediate like **3** to the oxidation state found in **1** or **2**. Thus, hydroxy-deamination of lysine would be accomplished in a three-step process of carbamate formation, oxidation to an acyl carbamate, and reduction of the acyl carbamate to an alcohol moiety.




**4** **5** **3**

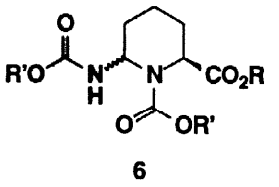
| | R | R' | | |
|---|---|---|---|---|
| **a** | Me | *t*-Bu | **5a** (100%) | **3a** (86%) |
| **b** | Et | *t*-Bu | **5b** (54%) | **3b** (64%) |
| **c** | *t*-Bu | *t*-Bu | **5c** (85%) | **3c** (86%) |
| **d** | *t*-Bu | Et | **5d** (60%) | **3d** (86%) |
| **e** | *t*-Bu | *i*-Bu | **5e** (70%) | **3e** (94%) |

*i*) **5a**: MeOH, $SOCl_2$ then *t*-$Boc_2O$, $Et_3N$, MeOH; **5b**: EtOH, $(EtO)_3CH$, HCl then *t*-$Boc_2O$; **5c**: *t*-$Boc_2O$, NaOH, dioxane/$H_2O$ then *t*-BuOC(NH)$CCl_3$, $BF_3OEt_2$, *c*-hexane/$CH_2Cl_2$; **5d**: $EtO_2CCl$, $NaHCO_3$, $H_2O$ then isobutylene, cat. $H_2SO_4$, $CH_2Cl_2$; **5e**: *i*-$BuO_2CCl$, NaOH, EtOH/$H_2O$ then isobutylene, cat. $H_2SO_4$, $CH_2Cl_2$; *ii*) cat. $RuO_2$, $NaBrO_3$, EtOAc/$H_2O$.

**Scheme 1**

In practice, lysine (**4**) was converted in two steps to a totally protected derivative **5** using standard conditions as outlined in Scheme 1. Oxidation of intermediates **5a-e** with catalytic amounts of $RuO_2$ using $NaBrO_3$ as the stoichiometric oxidant and a mixture of ethyl acetate and water as solvent provided acyl carbamates **3a-e** in 64-94% yield. Several aspects of the oxidation reaction are worthy of comment since there were modifications made to the reaction conditions originally described. Sakari and Yoshifuji used $NaIO_4$ as the stoichiometric oxidant in a mixture of ethyl acetate and water. Because of waste and safety concerns associated with the use and disposal on large scale of $NaIO_4$ and its corresponding reduced salts, an alternative stoichiometric oxidizing agent was sought. Giddings and Mills have described in a $CCl_4/H_2O$ solvent system that $NaBrO_3$ is a good stoichiometric oxidizing agent for the oxidation of alcohols catalyzed by $RuO_4$.[9] Building upon this observation led to a semi-optimized oxidation system which utilized $NaBrO_3$ (2.3-3.0 eq) and catalytic $RuO_2$ (0.05-0.1 eq) in an EtOAc/$H_2O$ (3/4 ratio by volume, *ca.* 0.3 M overall) solvent system at 40-45°C for 2-4 h. Normally, the hydrate of $RuO_2$ (Aldrich catalog number: 20,883-3) was used for oxidations. However, when non-hydrated $RuO_2$ was used, the reaction generally took longer to reach completion, and in one case did not go to completion even after stirring for 5.5 h at 45°C then 18 h at rt.[10] In general, the use of non-hydrated $RuO_2$ produced less $RuO_4$ as judged by the increased presence in the reaction mixture of unreacted $RuO_2$ as a black solid.

Except for the previously described piperidine **6** (<5%),[8] no significant by-products were observed from the oxidation of **5a-c**; however, oxidation of **5d** and **5e** afforded the corresponding α-keto esters **7d** and **7e** as minor by-products of the reaction. The **3d/7d** ratio was ca. 85/15 while the **3e/7e** ratio was >95/5. The amount of α-keto ester **7** formed seems to be dependent upon the steric bulk of the *N*-protecting group since **7** was not observed when R' = *t*-Bu.



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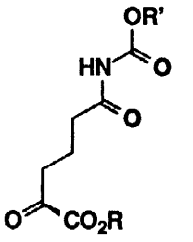

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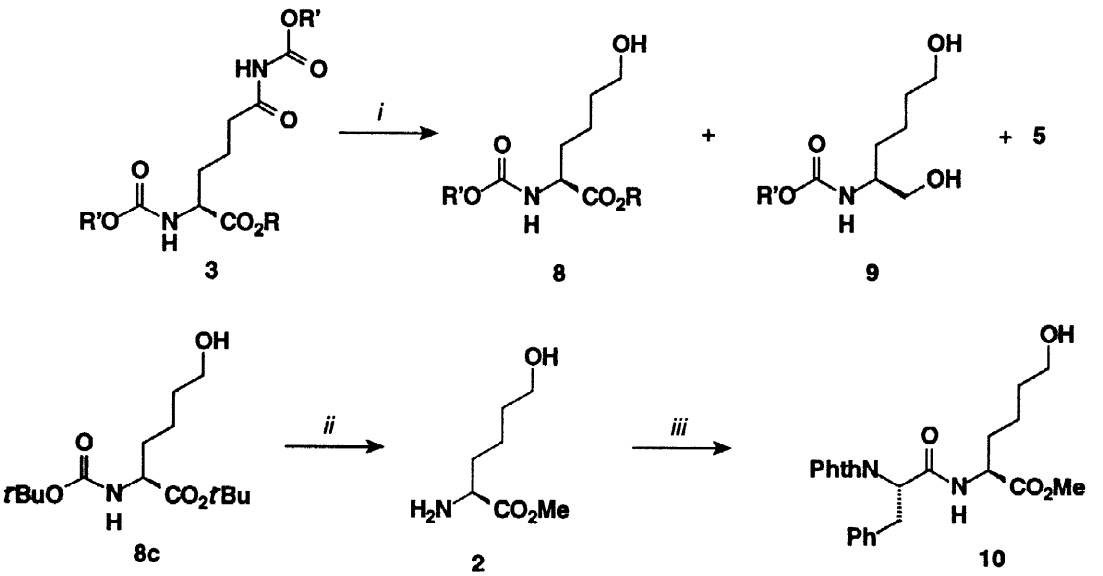
With **3** in hand, it now remained to find the appropriate reducing agent for conversion of the acyl carbamate moiety to the desired alcohol functionality while maintaining the ester functionality intact. Although the literature is replete with examples of the reduction of *N*-substituted acyl carbamates (i.e. *N*-acylated oxazolidinones), even some examples containing an unchanged ester moiety,[11] to the best of our knowledge there are no examples of *N*-unsubstituted acyl carbamates which have been reduced to their corresponding alcohols. A brief study was undertaken to find a suitable reducing agent for this transformation. Treatment of **3a** with $NaBH_4$ (1 eq) in a mixture of *i*-PrOH/$H_2O$ afforded a 90% yield of diol **9a** (Scheme 2); however, use of THF as the solvent under otherwise identical reaction conditions afforded a mixture of **8a** and **9a** in 45% and 23 % yield, respectively. Attempted reduction of methyl ester **3a** with $NaBH_3CN$ in *i*-PrOH/$H_2O$ afforded unchanged starting material. Reduction of ethyl ester **3b** with $NaBH_4$ gave similar results as those obtained with methyl ester **3a**. Treatment of ethyl ester **3b** with $BH_3$•THF afforded mainly unchanged starting material along with a trace amount (<5%) of reduced carbamate **5b**. Use of $Zn(BH_4)_2$ with **3b** afforded the reduced carbamate **5b** as the major product.



*i*) $NaBH_4$, *i*-PrOH/$H_2O$, rt, 16 h; *ii*) HCl, MeOH, reflux, 16 h then $Et_3N$, toluene; *iii*) PhthN-Phe-Cl, NMM, EtOAc/MeCN, -15 °C (58% from **3c**)

**Scheme 2**

Selective reduction of the acyl carbamate moiety in the presence of an ester was ultimately achieved when a bulkier *t*-butyl ester was present as in **3c-e**. Treatment of **3c** with $NaBH_4$ (1.5 eq) at rt in *i*-PrOH/$H_2O$ afforded an 80% yield of alcohol **8c** with no evidence for the formation of diol **9c** or carbamate **5c**. However, when THF was substituted for *i*-PrOH/$H_2O$, only a 55-60% yield of **8c** was obtained along with a 30% yield of carbamate **5c**. Interestingly, carbamate **5a** was not observed when methyl ester **3a** was reduced with $NaBH_4$ in

THF. It is not clear why changes at the relatively remote ester moiety would influence the distribution of reduced products the way it apparently does. Reduction of **3d** and **3e** using $NaBH_4$ in *i*-PrOH/$H_2O$ afforded **8d** and **8e** in 95% and 98% yield, respectively.[12]

Treatment of **8c** with HCl in MeOH afforded the methyl ester of 6-hydroxynorleucine (**2**) which was treated with phthaloylphenylalanine acid chloride[13] to provide crystalline dipeptide **10** in 58% yield from **3c**. Because **2** is not a solid and somewhat unstable in neat form, formation of **10** afforded a method for the evaluation of the purity and yield for the transformation of acyl carbmates **3** to **2**. Satisfactory conditions for the deprotection of **8d** and **8e** and subsequent conversion to desired methyl ester **2** were not elucidated.

In conclusion, a novel sequence has been developed to convert the ε-amine of lysine to an alcohol moiety by protecting the amine as a carbamate, oxidation of the carbamate to an acyl carbamate, and reduction of the acyl carbamate to an alcohol. It was found that $NaBrO_3$ was a suitable stoichiometric oxidant for the ruthenium-catalyzed oxidation of carbamates. The acyl carbamates formed from this oxidation can be selectively reduced to an alcohol in the presence of a *t*-butyl ester without reducing the ester moiety; however, methyl or ethyl esters are competitively reduced under the reaction conditions. This protocol was used to convert L-lysine (**4**) via *t*-butyl ester **8c** to dipeptide **10** in six steps in *ca.* 30% overall yield.

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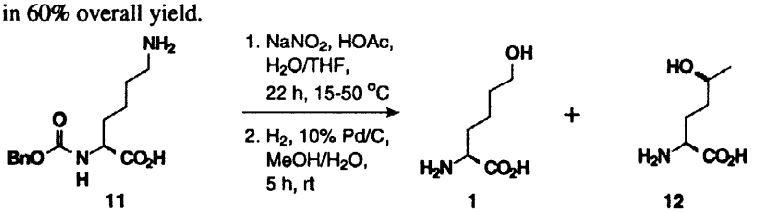
6. Despite these potential problems, a diazotization approach from mono-protected lysine derivative **11** was attempted providing a 95/5 ratio of **1** and **12** in 60% overall yield.




11 1 12

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10. This experiment utilized **5c** as a starting material.

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12. Compounds **8d** and **8e** contained an equivalent of corresponding carbamate (ethyl or *i*-butyl) which is a by-product of the reduction and was difficult to remove, unlike the *t*-butyl carbamate formed during reductions of **6a-c** which could be removed by sublimation.

13. This material was prepared from (*S*)-phenylalanine by treatment with phthalic anhydride (DMF, 110 °C, 1.5 h) followed by oxalyl chloride (cat. DMF, $CH_2Cl_2$, rt, 2 h).