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Asymmetric Synthesis of (+)-Hypusine

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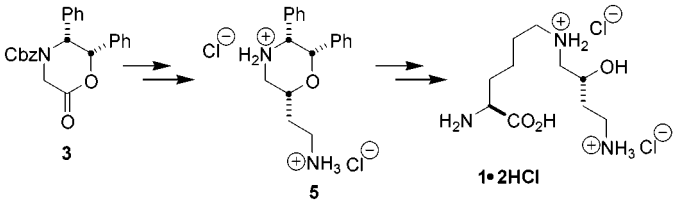
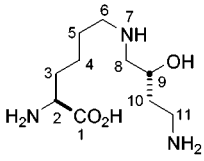
ABSTRACT

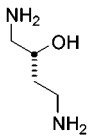


Wittig reaction of (triphenylphosphoranylidene)acetonitrile with the lactone carbonyl of (5*R*,6*S*)-4-(benzyloxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (3) and subsequent reduction generates morpholinylethylamine dihydrochloride (5) in quantitative yield and with excellent diastereoselectivity. Compound 5 was readily converted into hypusine dihydrochloride (1·2HCl) in overall 53% yield.

(+)-Hypusine (**1**) (Hpu, (2*S*,9*R*)-2,11-diamino-9-hydroxy-7-azaundecanoic acid) is an unusual naturally occurring amino acid that was first isolated from extracts of bovine brain in 1971 by Shiba et al.,[1] who also established its absolute configuration in 1982.[2] (+)-Hypusine (**1**) is formally a conjugate of hydroxyputrescine (**2**, Figure 1) and lysine.[1]



Hypusine (**1**)



Hydroxyputrescine (**2**)

Figure 1. Structures of hypusine (**1**) and hydroxyputrescine (**2**).

In 1983, Folk and co-workers[3] found that a precursor protein of eukaryotic initiation factor 5A (eIF-5A, formerly known as eIF-4D), found in all animal cells, undergoes posttranslational modification in growing cells to form hypusine. In 1986, Park et al.[4] isolated the eIF-5A protein from human red blood cells and determined the amino acid sequence around the single hypusine residue (Hpu) as Thr-Gly-Hpu-His-Gly-His-Ala-Lys. Recently, eIF-5A has been shown to play a key role in the replication of human immunodeficiency virus-1 (HIV-1).[5]

Synthesis of a reagent that enables the incorporation of hypusine into peptide sequences has also recently been reported.[6]

A number of approaches have been reported in the literature for the synthesis of hypusine, including (1) *N*-alkylation of a L-lysine fragment with a 4-amino-1-bromo-2-butanol derivative;[2] (2) reductive amination of a hydroxyputrescine fragment with a 2-amino-6-oxo-hexanoic acid derivative;[7] (3) reductive amination of a L-lysine fragment with a 4-amino-2-hydroxy-butyraldehyde derivative;[8] and (4) *N*-alkylation of a L-lysine fragment with epichlorohydrin, subsequent displacement of chloride with cyanide, and reduction.[9] In most of these approaches, L-lysine was utilized as a key substrate.

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(7) (a) Tice, C. M.; Ganem, B. *J. Org. Chem.* **1983**, *48*, 5043−5048. (b) Knapp, S.; Hale, J. J.; Bastos, M.; Molina, A.; Chen, K. Y. *J. Org. Chem.* **1992**, *57*, 6239−6256.
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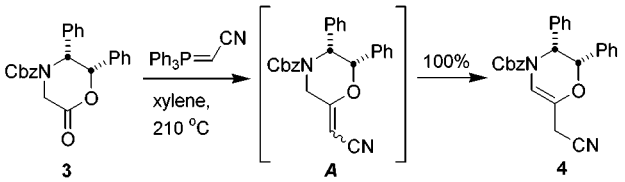
Scheme 1

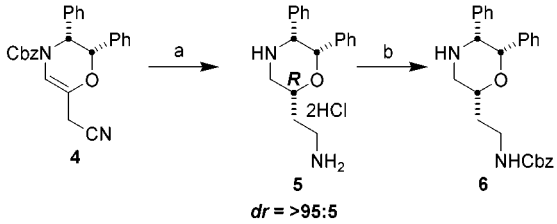


Herein, we report a concise method for the synthesis of (+)-hypusine by employing (5*R*,6*S*)-4-(benzyloxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (**3**)[10] as a starting material. This approach involves a de novo synthesis of both the L-lysine fragment and the hydroxyputrescine moiety and is amenable to the site-specific incorporation of stable and/or radioisotopes.

As shown in Scheme 1, Wittig reaction of (triphenylphosphoranylidene)acetonitrile[11] with the lactone carbonyl group of **3** (xylene, 210 °C, 2.5 h) generated the adduct **4** in quantitative yield. This species is reasonably presumed to arise via tautomerization of the initial olefination product ***A*** to the thermodynamically more stable trisubstituted olefin. Although a few isolated cases of stabilized Wittig olefinations of lactones and esters have appeared in the literature, this condensation is an underutilized reaction in synthetic organic chemistry.[12−18] Wittig reactions of stabilized ylides with the carbonyl groups of lactones,[12] esters,[13] thioesters,[14] anhydrides,[15] thioanhydrides,[16] amides[17] and imides[18] have been reported in the literature, but many of these systems were intramolecular ring-closure reactions. Attempts to conduct the reaction at lower temperatures (in toluene or xylene at reflux) required longer reaction times and incomplete transformations with poor yields of **4**.

Hydrogenation of **4** with $PdCl_2$ (30 mol %, 120 psi of H_2, MeOH, 4 equiv concentrated HCl, rt, 72 h) resulted in the formation of desired all *syn*-substituted oxazine **5** in essentially quantitative yield and with >95:5 diastereomeric ratio (by ^{1}H NMR, Scheme 2).

Scheme 2[a]



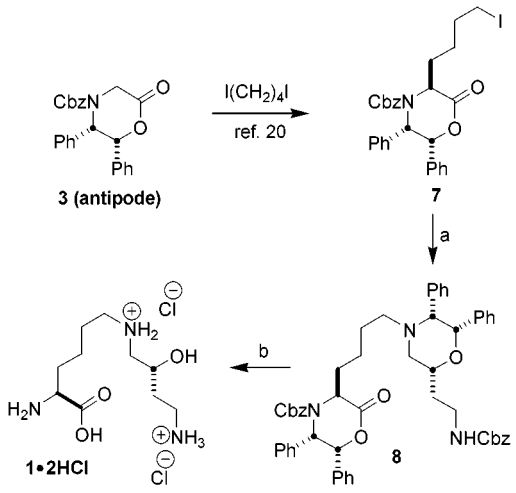
[a] Reagents and conditions: (a) 120 psi H_2, $PdCl_2$, MeOH, concentrated HCl, rt, 100%; (b) THF, 2 M NaOH, reflux; then Cbz_2O, rt, 70%.

The relative and absolute stereochemistry of the newly created stereogenic center in the major diastereomer of **5** was determined as *R* by ^{1}H NMR NOE measurements that revealed a *syn*-relationship of the protons at C2, C5, and C6 of the oxazine ring. The high degree of asymmetric induction in the reduction step can be explained by adsorption on the catalyst surface and subsequent hydrogenation of the double bond from the sterically less hindered face of the molecule.

Selective protection of primary amine in **5** was achieved by treatment of **5** with Cbz_2O (1 equiv, THF/2 M NaOH) yielding the desired monoprotected morpholine **6** in 70% yield (Scheme 2).

Compound **6** is a protected version of hydroxyputrescine **2** and may be suitable for related applications in the regioselective coupling of this fragment to other amino acids. The conversion of **6** into (+)-hypusine (**1**) required *N*-alkylation of the morpholine nitrogen in **6** with an electrophilic L-lysine fragment. The desired L-lysine fragment **7** required for this coupling reaction was easily synthesized by the glycine enolate alkylation method[19] by using the commercially available antipode of **3**[10] and 1,4-diiodobutane, as reported previously by our group[20] (Scheme 3).

Scheme 3[a]



[a] Reagents and conditions: (a) **6**, *N*,*N*-diisopropylethylamine, xylene, reflux, 78%; (b) 80 psi H_2, $PdCl_2$, THF/H_2O, 80−85 °C, 98%.

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(10) The requisite diphenyloxazinone and its antipode are commercially available from Aldrich Chemical Co.: catalog no. 33185-6 (CAS registry no. 105228-46-4). The antipode: catalog no. 33187-2 (CAS registry no. 100516-54-9).

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(17) See ref 12c.

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Treatment of **6** with **7** in the presence of *N*,*N*-diisopropylethylamine in xylene at reflux (2.5 h) generated the desired coupling product **8** in 78% yield. Complete hydrogenolysis of **8** with $PdCl_2$ (6 equiv, THF/H_2O, 80 psi of H_2, 80−85 °C, 6 h) resulted in the formation of (+)-hypusine (**1**) in essentially quantitative yield as its dihydrochloride salt ($[\alpha]^{25}_D = +7.3$ (*c* 0.52, 6M HCl); lit.[9] $[\alpha]^{23}_D = +7.6$ (*c* 0.5, 6 M HCl)). The spectral data for this substance matched that reported in the literature for hypusine.[2,7−9]

In summary, we have demonstrated a concise, asymmetric, and stereocontrolled method for the synthesis of (+)-hypusine. Since both antipodes of oxazinone **3** are commercially available,[10] the present method can provide access to all four stereoisomers of hypusine. Current efforts are focused on extending the stabilized Wittig homologation on the oxazinones to other amino acid-derived natural products and alkaloids.

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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