Tetrahedron Letters, Vol. 34, No. 28, pp. 4485-4488, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

N-(Boc)-L-(2-Bromoallyl)-Glycine: A Versatile Intermediate for the Synthesis of Optically Active Unnatural Amino Acids

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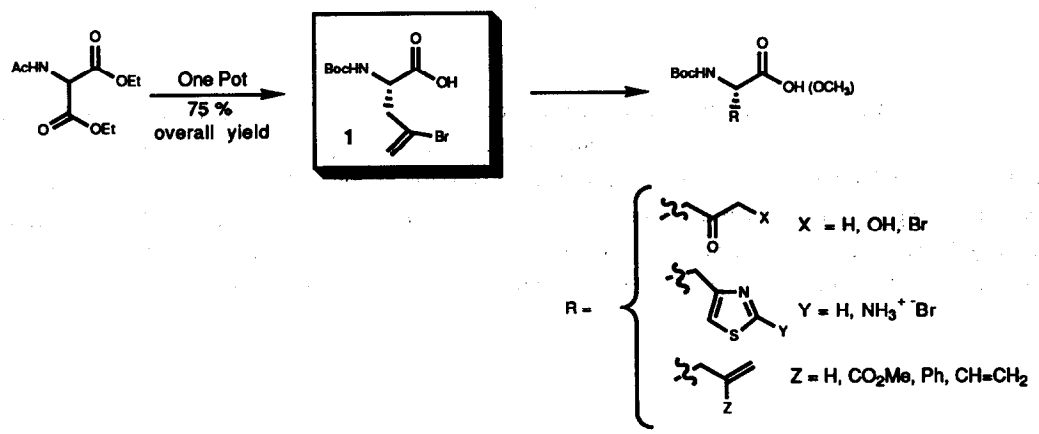
Summary: *N(Boc)-L-(2-Bromoallyl)-glycine (1) was synthesized from diethylacetamidomalonate and 2,3-dibromopropene in a one-pot procedure (75 % overall yield). The enantiomers were efficiently separated via a tandem biocatalytic kinetic hydrolytic resolution. 1 was elaborated to several other interesting unnatural amino acids.*

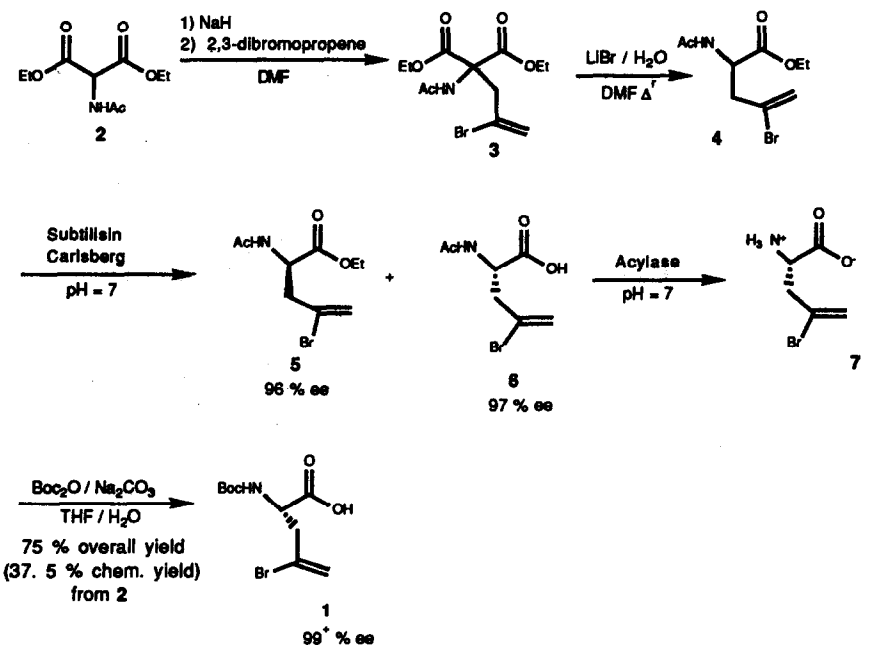
Substitution of unnatural amino acids into bioactive peptides commonly provides analogs with enhanced stability, improved pharmacokinetics, and receptor affinity. In general, the most frequently used methods for the synthesis of optically active amino acids have encompassed chiral glycine enolates, chiral phase transfer catalysis, manipulation of natural amino acids, and asymmetric hydrogenation of dehydro-amino acids.[1] Most recently, there have been several syntheses of optically active amino acids based on biocatalytic kinetic hydrolytic resolutions of racemic substrates.[2] These biocatalytic methods commonly utilize one enzyme and require several isolations. We wish to report herein the one-pot synthesis of N-(Boc)-L-(2-bromoallyl)-glycine **1**, which features a tandem biocatalytic kinetic resolution (esterase / acylase) serving a dual purpose of facile protecting group removal and nearly absolute enantioseparation. Furthermore, we wish to demonstrate the utility of **1** by its conversion (Scheme 1) to several biologically interesting amino acids.

Scheme 1



We felt it most convenient to start with diethylacetamidomalonate as our latent glycine fragment. Alkylation of the enolate of **2** (prepared by addition of 1.05 eq. NaH, 40 min.) with 2,3-dibromopropene[3] (1.10 eq.) in DMF (1 molar) afforded the alkylated diester cleanly. Addition of 1 eq. LiBr[4] and 2 eq. of H_2O to the reaction solution afforded pure monoester **4** after refluxing 6 hours. After removal of most of the DMF under high vacuum and dilution with pH 7.0 buffer (0.2 M phosphate) to give a 0.1 M solution of ester, the monoester was treated with Subtilisin Carlsberg,[5] affording a mixture of **5** and **6**. The D-ester **5**[6] was extracted (3x300 ml CH_2Cl_2) after the reaction had consumed 48.5 % of **4** as judged by C-18 HPLC. The aqueous solution containing N-acetyl-L-acid **6**[7] was then treated with Porcine Kidney Acylase I.[8] The reaction was adjusted to pH 9 by addition of solid Na_2CO_3, and 1.2 eq. Boc_2O in THF were added. After work-up,[9] pure acid **1**[10] was isolated by column purification (96/4/0.25 CH_2Cl_2-MeOH-AcOH; 10g SiO_2/ 1g substrate) in 75 % overall yield (37.5 chemical yield).

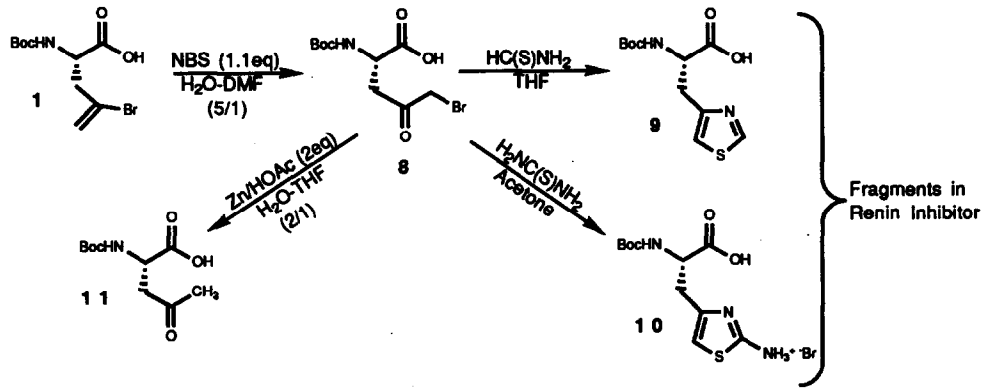
Scheme 2



With an efficient route to **1** in hand, we turned our attention to manipulation of the vinylbromide moiety. Recently we described the facile oxidative hydrolysis of a variety of vinylhalides to bromomethyl ketones.[11] Treatment of **1** with aqueous NBS (1.1eq) afforded the versatile bromomethyl ketone **8** in 60 % yield. The synthesis of fragments found in renin inhibitors was accomplished by condensation of **8** with thioformamide, affording the protected thiazoylalanine **9**,[12] a useful isosteric replacement of histidine, in 80 % yield. Likewise, condensation of **8** with thiourea afforded the 2-aminothiazoylalanine **10**[13] in 85 % yield. Reduction of **8** with

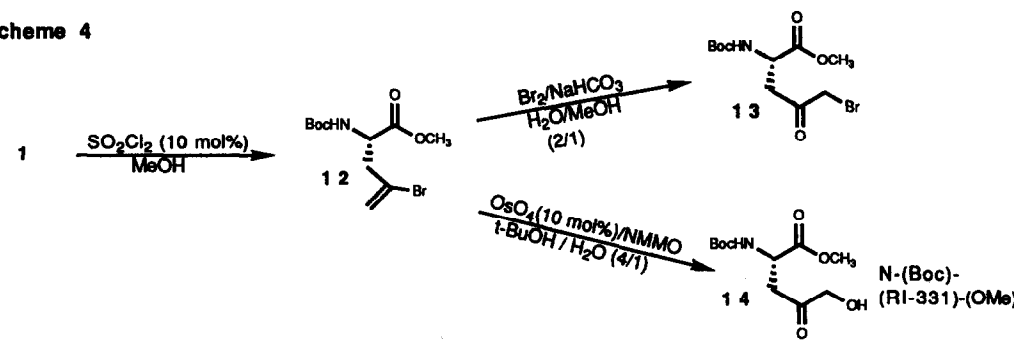
Zn/HOAc (2eq) gave the protected oxonorvaline **11**, a naturally occurring amino acid produced in bone marrow by α-aminolevulinic acid (ALA) synthetase,[14] in 92 %.

Scheme 3



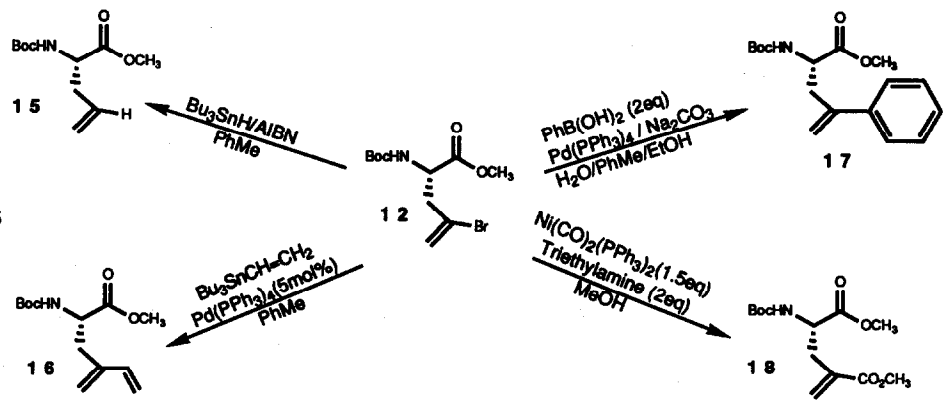
To minimize side reactions and loss of material due to water solubility, acid **1** was converted to methyl ester **12** in 78 % yield by treatment with a catalytic amount (10 mol %) of SO_2Cl_2 in methanol. The methyl ester underwent oxidative hydrolysis (Br_2 / $NaHCO_3$ / H_2O / MeOH), affording the halo ketone **13** in 58 % yield. Alternatively, oxidative hydrolysis with cat. OsO_4 / NMMO (t-BuOH/H_2O) afforded the protected potent antifungal agent **14**, isolated from a *Streptomyces* sp.,[15] in 86 % yield.

Scheme 4



The vinylbromide moiety can be elaborated into numerous unsaturated amino acids. For example, reaction of ester **12** (Scheme 5) under reductive conditions (Bu_3SnH/AIBN/PhMe) afforded the protected allyl glycine **15** in 92 % yield. The vinyl bromide also underwent vinylation with tributylvinyltin, affording the interesting diene **16** in 63 % yield. Elaboration of **12** to the versatile α-styrenyl intermediate **17** was accomplished in near quantitative yield (98 %) under standard Suzuki coupling conditions.[16] Finally, synthesis of the naturally occurring (2S)-γ-methylene glutamic acid methyl ester **18**[17] was achieved in 55 % yield by Ni(0)-promoted carbonylation in MeOH.

Scheme 5



In summary, this work demonstrates the ease of preparation of multigram quantities of **1** in a simple one-pot operation with high efficiency and optical purity. Furthermore, the versatility of the vinylbromide moiety is exploited by elaboration of **1** to several interesting unnatural amino acids.

Acknowledgment: We would like to thank Mr. Bruce Horrom for helpful discussions.

References and Notes:

1. Williams, R. M. *Synthesis of Optically Active α-Amino Acids*, Pergamon Press, New York, 1989.
2. See, for example: (a) Chenault, H. K.; Dahmer, J.; Whitesides, G. M. *J. Am. Chem. Soc.* **1989**, *111*, 6354. (b) Miyazawa, T.; Ueji, S.; Yamada, T.; Kuwata, S.*J. Chem Soc., Chem. Commun.* **1988**,1214.
3. 2,3-Dibromopropene was purchased from Aldrich Chemical Co., Ltd., and distilled prior to use.
4. For a review, see: Krapcho, A.P. *Synthesis* **1982**, 805 and 893. The use of LiBr led to dramatic increases in the rate of reaction compared to other salts.
5. The enzyme was purchased from Sigma Chemical Co.(catalog # P5380) 11 units / mg activity. For a 100 mmol run, 2 mg enzyme were used; the time to 48 % conversion was 1 hour.
6. The D-ester was recovered in 85 % of theory after washing CH_2Cl_2 extracts with 1X$NaHCO_3$(sat'd), drying over $MgSO_4$, filtration and treatment with Darco 60. The ee was 96 % (Chiracel OD [25cm x 4.6 mm]); 9/1 Hexanes - Isopropanol; 1.00 ml / min.; ret. times for D-ethyl ester 6.54 min, L-ethyl ester 10.44 min.
7. For analysis, the L-acid was acidified to pH 3, concentrated in vacuo at 70 °C, H_2O azeotroped off by addition of abs. EtOH. This afforded a 65 / 35 ratio of acid to ester. The ester was extracted and subjected to chiral assay;[6] 97 % ee.
8. The enzyme was purchased from Sigma Chemical Co.(catalog #A3010), 1900 units/mg; For a 100mmol run, 50 mg enzyme were used. The time for hydrolysis was ca. 20 hours. After the hydrolysis had stopped, there still remained ca. 1.5 % unreacted N-acetyl acid **ent-6**, presumably from nonselective D-ester hydrolysis in the previous reaction.
9. The mixture was washed 1x250 ml hexane (remove unreacted Boc_2O), acidified to pH 3 with solid $KHSO_4$, extracted (1x 300 ml ethyl acetate), dried ($MgSO_4$), filtered, and concentrated in vacuo.
10. Spectral data were consistent with the assigned structure, m.p. 96 °C (auto), $[\alpha]^D = +8.3°$ (C=1.00,$CHCl_3$). The ee was 99+% as judged by hplc: Chiracel OD [25cm x 4.6 mm]; 99/1 Hexanes - Isopropanol; 1.25 ml/min.; ret. times for D-methyl ester 7.8 minutes, L-methyl ester 9.2 minutes.
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(Received in USA 20 April 1993; accepted 19 May 1993)