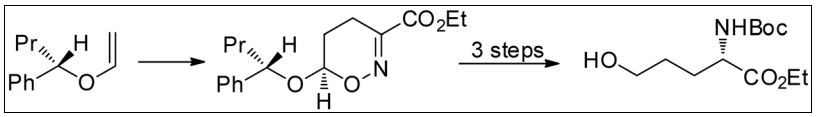
# Asymmetric Synthesis of Both Enantiomers of Protected 5-Hydroxynorvaline by Hetero-Diels-Alder Addition of ethyl 2-Nitrosoacrylate to (*R*)- and (*S*)-1-Phenylbutyl Vinyl Ether

Zoe S. Massen and John K. Gallos*

Department of Chemistry, Aristotle University of Thessaloniki, Thessaloniki 54124, Greece
*E-mail: igallos@chem.auth.gr

Received February 4, 2011
DOI 10.1002/jhet.907
Published online 29 October 2012 in Wiley Online Library (wileyonlinelibrary.com).




Both enantiomers of protected 5-hydroxynorvaline were prepared by hetero-Diels-Alder addition of ethyl 2-nitrosoacrylate to readily available (*R*)- and (*S*)-1-phenylbutyl vinyl ether and a further three-step manipulation. Attempted synthesis of (±)-vigabatrin from protected (±)-5-hydroxynorvaline was unsuccessful.

*J. Heterocyclic Chem.*, **49**, 1214 (2012).

## INTRODUCTION

The increasing interest in modified peptides in the chemical engineering of proteins has lately refreshed research towards the development of new methodologies for the stereoselective construction of α-amino acids [1]. The rational design of non-proteinogenic α-amino acids, in particular, is of exceptional importance, due to their implementation into nonscissile peptide mimics and peptide isosters.

Non-proteinogenic hydroxy-amino acids have been identified as biosynthetic precursors of natural products made by plants and microorganisms [2]. 5-Hydroxynorvaline **1** (Fig. 1) is a known constituent in the seeds of higher plants and in microorganisms and it has recently been described as a specific marker of oxidized proteins in the study of age-related diseases [3]. It was also recently found that drought stress increases the production of 5-hydroxynorvaline in two C4 grasses [4]. This unnatural amino acid has also been used to establish structure–activity relationships of bioactive molecules like cyclosporine, and of microbial enzymes [5]. In addition, 5-hydroxynorvaline has been used in the attachment of glycosyl derivatives in glycopeptide solid phase synthesis [6]. Finally, 5-hydroxynorvaline is essential as a starting material for the synthesis of conformationally restricted pseudopeptides presenting a 3-aminopiperidin-2-one backbone [7].

A number of synthetic methods toward 5-hydroxynorvaline have been reported in literature, starting from L-glutamic acid [8], D-glucosamine [9], L-methionine [10], and 2,3-dihydrofuran [11] leading either to (*S*)-1 or to racemate. We now report the asymmetric synthesis of both protected (*R*)- and (*S*)-5-hydroxynorvaline (2) by hetero-Diels-Alder addition of ethyl 2-nitrosoacrylate [12] to both enantiomers of a chiral vinyl ether and further reduction of the oxazine ring thus formed. Furthermore, we attempted the synthesis of (±)-vigabatrin (**3**) [13], a structurally related γ-amino acid, from (±)-2. (*S*)-Vigabatrin (**3**) is a GABA-analog which has been successfully introduced as a drug in the treatment of epilepsy, acting as a mechanism-based inactivator of the enzyme GABA aminotransferase [14].

## RESULTS AND DISCUSSION

Some years ago, we reported the synthesis of (±)-**2** by hetero-Diels-Alder addition of ethyl 2-nitrosoacrylate to ethyl vinyl ether as the key-step [15], but our attempts toward the asymmetric synthesis of (*R*)-**2** failed in the last step of oxazinane ring cleavage (Scheme 1). Our approach involved the addition of ethyl 2-nitrosoacrylate to (*R*)-1-phenylbutyl vinyl ether, known from the literature [16], and further conversion of the adduct to oxazinane **4.** The absolute configuration of C-3 and C-6 stereocenters in compound **4** was determined by conversion of **6** to the D-proline derivative (*R*)-**6** [15b].

To avoid pyrrolidine formation in the hydrogenation step, according to the established method, the Boc group was introduced in **4** by treatment with $Boc_2O$, $Et_3N$, and DMAP. In our initial publications [15a,b], we reported that we were unable to cleave the oxazinane ring in **5**, possibly due to the overcrowded environment of the N–O bond, which does not allow the approach of the catalyst. However, after several attempts, we found and report here that Raney Ni catalytic hydrogenation of **5** in refluxing MeOH in an autoclave for four days led to the formation of (*R*)-**2** in 78% yield.

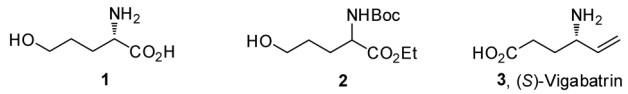
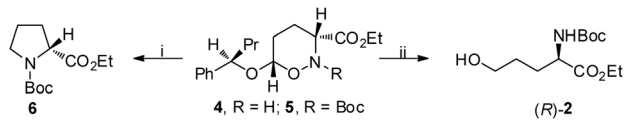



**Figure 1.** Target molecules.

**Scheme 1.** Reagents and conditions: i. Ref. [15b]; ii. Raney Ni, $H_2$, $H_3BO_3$ (20 equiv.), $MgSO_4$, MeOH, four days, autoclave, reflux, 78% from **5**.




Interestingly, both enantiomers of the starting enol ether are known and they can be readily prepared from the respective commercially available enantiomers of the parent (*R*)- and (*S*)-1-phenylbutanol. 5,6-Dihydro-4*H*-oxazine **8** (Scheme 2) was prepared according to the literature [16] from (*S*)-**7** and then converted to a mixture of oxazinane *ent*-**4** and its 3-epimer by $NaCNBH_3$ reduction [17], which was completely isomerized to *ent*-**4** by treatment with $Et_3N$ in refluxing chloroform. Apparently, the *cis*-isomer is the thermodynamically more stable product, since the oxazinane ring adopts a chair-like conformation with the $CO_2Et$ group equatorial and the R*O group axial, the last being favored by the anomeric effect [15,18]. After *N*-Boc protection, the N-O bond in *ent*-**5** was cleaved with Raney Ni catalytic hydrogenation with refluxing MeOH in an autoclave to afford (*S*)-**2** in 78% yield, as above.

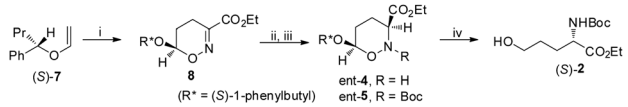
It is interesting to note that this reaction sequence is an example of remote asymmetry transfer in an organic molecule. The chiral enol ether generates temporarily a new chiral center in the C-6 carbon of the dihydro-4*H*-oxazine formed and then its asymmetry is transferred to the C-3 carbon by the C=N bond reduction and isomerization process, which is the C-2 chiral center of the final amino acid.

To achieve the synthesis of (*S*)-vigabatrin, we should convert the $CO_2Et$ of (*S*)-**2** to a vinyl group and then oxidize the primary hydroxyl group to carboxylate. We decided to work firstly with racemate **2** [15a,b], in order to optimise the method before switching to the chiral substrate. To this end, the hydroxyl group of (±)-**2** was protected as TBS ether in high yield. The conversion, however, of $CO_2Et$ to vinyl group was found to be quite tricky. After several attempts we were able to prepare vinyl derivative **10** in moderate yield (50%) by classical DIBAL-H reduction and Wittig olefination only in the scale of 50 mg. At higher scales the yield was dramatically reduced or no olefination product was obtained at all.

Despite this disadvantage, we proceeded in the next step and the TBS group was easily removed in quantitative yield by a standard method [19], but then, oxidation of the free hydroxyl group was unsuccessful. A wide range of oxidants were used, but we were not able to find protected vigabatrin among the products. In some cases, small amounts of the respective Boc- and unprotected lactams were isolated, evidently resulted from protected vigabatrin intermediately formed. Taking also into account the problems in the olefination step, our attempts toward vigabatrin in these lines were disconnected.

In conclusion, we have successfully applied the addition of ethyl 2-nitrosoacrylate to a chiral enol vinyl ether for the asymmetric synthesis of protected 5-hydroxynorvaline in five steps and 24% overall yield. Advantage of our method is the fact that it can be applied to the synthesis of both enantiomers of 5-hydroxynorvaline, simply by choosing the appropriate enantiomer of the starting enol ether.

**Scheme 2.** Reagents and conditions: i. $BrCH_2C(NOH)CO_2Et$, $Na_2CO_3$, 20 °C, overnight, 48% of **8** and 8% of 6-*epi*-**8**; ii. $NaCNBH_3$, AcOH, 0 °C → 20 °C, 24 h; then $Et_3N$, $CHCl_3$, reflux, 8 h, 63% from **8**; iii. $(Boc)_2O$, $Et_3N$, DMAP, $CH_2Cl_2$, 20 °C, overnight, 100%; iv. Raney Ni, $H_2$, $H_3BO_3$ (20 equiv.), $MgSO_4$, MeOH, 4 days, autoclave, reflux, 78%.



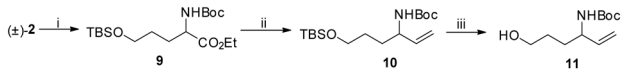

## EXPERIMENTAL

**Ethyl (3S,6R)-6-((S)-1-phenylbutyl)-1,2-oxazinane-3-carboxylate (*ent*-4).** This compound was prepared in 63% yield, according to the method of preparation of **4** as colorless oil with $^1H$ and $^{13}C$NMR data identical to those reported in the literature for **4**. $\alpha_D^{25}$ −143.6° (*c* 2.12, $CHCl_3$) [for **4** lit. [15] $[\alpha]_D$ +141.4 (*c* 0.3, $CHCl_3$)].

**2-tert-Butyl 3-ethyl (3S,6R)-6-((S)-1-phenylbutyl)-1,2-oxazinane-2,3-dicarboxylate (*ent*-5).** This compound was prepared in quantitative yield, according to the method of preparation of **5** as colorless oil with $^1H$ and $^{13}C$NMR data identical to those reported in the literature for **5**. $\alpha_D^{25}$ −124.9° (*c* 4.3, $CHCl_3$) [for **5** lit. [15] $[\alpha]_D$ +121.3 (*c* 0.3, $CHCl_3$)].

**Ethyl (*R*)-2-((tert-butoxycarbonyl)amino)-5-hydroxypentanoate [(*R*)-2] and Ethyl (*S*)-2-((tert-butoxycarbonyl)amino)-5-hydroxypentanoate [(*S*)-2].** To a solution of protected oxazinanes **5** or *ent*-**5** (407 mg; 1 mmol) in MeOH (30 mL) were added $H_3BO_3$ (1.23 g, 20 mmol), catalytic amount of Raney Ni and $MgSO_4$, and the mixture was refluxed with stirring under $H_2$ atmosphere for four days. $H_3BO_3$ was then neutralized by saturated aqueous $Na_2CO_3$, the mixture was

**Scheme 3.** Reagents and conditions: i. TBS-Cl, imidazole, DMF, 24 h, 90%; (ii) DIBAL-H, $CH_2Cl_2$ (dry), −78°C, 2 h then $Ph_3PCH_3Br$, n-BuLi, THF (dry), −50°C, 50%; (iii) oxone, MeOH/$H_2O$, 20°C, 2 h, 100%.



extracted with $CH_2Cl_2$ (3 × 50 mL) and the organic layer was dried over $Na_2SO_4$. The solvent was subsequently removed on a rotary evaporator and the residue was chromatographed on a column of silica gel with hexane/ethyl acetate as the eluent to give (*R*)-**2** or (*S*)-**2** as white crystals with $^1$H and $^{13}$CNMR data identical to those reported in the literature for (±)-**2** [15]. For (*R*)-**2**, m.p. 58–59°C (for racemate lit. [15b] 58–59°C); $\alpha_D^{25}$ +4.3° (*c* 4, $CHCl_3$). For (*S*)-**2**, m.p. 58–59°C (for racemate lit. [15b] 58–59°C); $\alpha_D^{25}$ −4.4° (*c* 3.4, $CHCl_3$).

**Ethyl 2-((tert-butoxycarbonyl)amino)-5-((tert-butyldimethylsilyl)oxy)pentanoate (9).** To a solution of (±)-**2** (518 mg; 2.0 mmol) in DMF (20 mL) was added imidazole (546 mg; 8 mmol) and TBS-Cl (606 mg; 4 mmol) and the mixture was stirred at room temperature for 24 h. Then, water (20 mL) was added and the resulting mixture was extracted with ethyl acetate (2 × 50 mL). The organic layer was dried over $MgSO_4$, the solvent was evaporated off and the residue was chromatographed an a silica gel column with hexane/ethyl acetate 5:1 as the eluent to give 678 mg of **9** as a colorless oil (90%). $^1$HNMR (300 MHz, deuteriochloroform) δ 5.20 (br d, *J* = 8.0 Hz, 1H, NH), 4.25 (m, 1H), 4.17 (q, *J* = 7.3 Hz, 2H), 3.62 (t, *J* = 6.1 Hz, 2H), 1.85 (m, 1H), 1.6 (m, 3H), 1.44 (s, 9H), 1.27 (t, *J* = 7.3 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H); $^{13}$CNMR (75 MHz, deuteriochloroform) δ 172.9, 155.4, 79.7, 62.3, 61.2, 53.3, 29.1, 28.3, 25.9, 25.6, 18.3, 14.1, −5.4. *Anal.* Calcd. for $C_{18}H_{37}NO_5Si$: C, 57.56; H, 9.93; N, 3.73. Found: C, 57.64; H, 10.02; N, 3.78.

**tert-Butyl (6-((tert-butyldimethylsilyl)oxy)hex-1-en-3-yl) carbamate (10).** 1st step Reduction of 9. To a solution of (50 mg; 0.13 mmol) in dry $CH_2Cl_2$ (1 mL) at −78°C was added DIBAL-H (0.13 mL, 1*M* solution in toluene, 1.1 equiv.) under argon atmosphere. The mixture was stirred at the same temperature for 2 h and then allowed to reach room temperature before quenched with saturated $NH_4Cl$. The resulting mixture was extracted with $CH_2Cl_2$ (10 mL) and the organic layer was dried over $Na_2SO_4$. The solvent was carefully evaporated off and the residue was used in step 2, without further purification.

***2nd step Wittig reaction.*** n-BuLi (0.77 mmol; 1.6*M* in hexane) was added dropwise to a stirring suspension of methyltriphenylphosphonium bromide (386 mg; 0.92 mmol) in dry THF at −50°C and 12-crown-4 (0.01 mL) and the mixture stirred for 1 h at the same temperature. It was then left to warm at 0°C to cool again at −40°C and the aldehyde prepared in 1st step dissolved in dry THF (1.5 mL) was added dropewise, while the temperature was kept below −20°C for 1 h. The mixture was then stirred at room temperature for an additional 4 h and after quenching with saturated $NH_4Cl$ (1 mL), it was disproportionated in water (10 mL) and $CH_2Cl_2$ (10 mL). The aqueous layer was extracted again with $CH_2Cl_2$ (10 mL), the combined organic layer was dried over $MgSO_4$, the solvent was then evaporated off and the residue was chromatographed an a silica gel column with hexane/ethyl acetate 10:1 as the eluent to give 30 mg of **10** as a colorless oil (50%). FTIR (film) 3351, 2955, 2930, 2858, 1705, 1505, 1366, 1253, 1173, 1100, 836, 776 $cm^{-1}$; $^1$HNMR (300 MHz, deuteriochloroform) δ 5.75 (ddd, *J* = 17.1, 10.4, 5.8 Hz, 1H), 5.15 (d, *J* = 17.1 Hz, 1H), 5.09 (d, *J* = 10.4 Hz, 1H), 4.64 (br s, 1H), 4.10 (m, 1H), 3.62 (t, *J* = 5.7 Hz, 2H), 1.55 (m, 4H), 1.44 (s, 9H), 0.89 (s, 9H), 0.05 (s, 6H). $^{13}$C NMR (75 MHz, deuteriochloroform) δ 155.5, 139.1, 114.4, 80.2, 62.8, 51.6, 31.5, 29.1, 28.9, 27.3, 18.4, −5.4. *Anal.* Calcd. for $C_{17}H_{35}NO_3Si$: C, 61.96; H, 10.70; N, 4.25. Found: C, 61.80; H, 10.18; N, 4.03.

***tert-Butyl (6-hydroxyhex-1-en-3-yl)carbamate (11).*** Oxone (51 mg; 0.08 mmol) was added to a solution of 10 (20 mg; 0.08 mmol) in aqueous MeOH (1 mL) [19] and the mixture was stirred at room temperature for 2 h. Then, the solids were removed by filtration through celite, MeOH was evaporated off and the aqueous layer was extracted with ethyl acetate (5 mL). The product was purified by column chromatography to give with hexane/ethyl acetate 3:1 as the eluent to give 18 mg of 11 as colorless oil, (100%). $^1$HNMR (300 MHz, deuteriochloroform) δ 5.74 (ddd, *J* = 17.1, 10.4, 5.5 Hz, 1H), 5.16 (d, *J* = 17.1 Hz, 1H), 5.11 (d, *J* = 10.4 Hz, 1H), 4.53 (br s, 1H), 4.14 (br s, 1H), 3.68 (t, *J* = 5.7 Hz, 2H), 1.56 (m, 4H), 1.45 (s, 9H); $^{13}$C NMR (75 MHz, deuteriochloroform) δ 155.5, 138.8, 114.7, 80.1, 62.6, 53.1, 31.6, 28.7, 28.4. *Anal.* Calcd. for $C_{11}H_{21}NO_3$: C, 61.37; H, 9.83; N, 6.51. Found: C, 61.65; H, 10.01; N, 6.44.

**Acknowledgments.** This work was co-funded by European Union and National fund PYTHAGORAS – EPEAEK II.

## REFERENCES AND NOTES

[1] Hughes, A. B. (Ed.) Amino Acids, Peptides and Proteins in Organic Chemistry, Vol. 1 and 2, Wiley-VCH: Weinheim; 2009.

[2] (a) Strack, D.; Schmitt, D.; Reznik, H.; Boland, W.; Grotjahn, L.; Wray, V. Phytochemistry 1987, 26, 2285; (b) Hill, R. E.; White, R. L.; Smith, K. C. J Nat Prod 1993, 56, 1246.

[3] Ayala, A.; Cutler, R. G. Free Radical Biol Med 1996, 21, 65.

[4] Carmo-Silva, A. E.; Keys, A. J.; Michael H. Beale, M. H.; Ward, J. L.; Baker, J. M.; Hawkins, N. D.; Arrabaça, M. C.; Parry, M. A. J. Phytochemistry 2009, 70, 664.

[5] (a) Judice, J. K.; Gamble, T. R.; Murphy, E. C.; de Vos, A. M.; Schultz, P. G. Science 1993, 261, 1578; (b) Mikol, V.; Papageorgiou, C.; Borer, X. J Med Chem 1995, 38, 3361.

[6] Broddefalk, J.; Bäcklund, J.; Almqvist, F.; Johansson, M.; Holmdahl, R.; Kihlberg, J. J. J Am Chem Soc 1998, 120, 7676.

[7] Estiarte, M. A.; de Souza, M. V. N.; del Río, X.; Dodd, R. H.; Rubiralta, M.; Diez, A. Tetrahedron 1999, 55, 10173.

[8] (a) Goodman, M.; Felix, A. M. Biochemistry 1964, 3, 1529; (b) Barlos, K.; Mamos, P.; Papaioannou, D; Patrianakou, E. J Chem Soc, Chem Commun 1987, 1583; (c) Luesch, H.; Hoffmann, D.; Hevel, J. M.; Becker, J. E.; Golakoti, T.; Moore, R. E. J Org Chem 2003, 68, 83; (d) Hannachi, J.-C.; Vidal, J.; Mulatier, J.-C.; Collet, A. J Org Chem 2004, 69, 2367; (e) García, M.; Serra, A.; Rubirata, M.; Diez, A.; Segarra, V.; Lozoya, E.; Ryder, H.; Palacios, J. M. Tetrahedron: Asymmetry 2000, 11, 991.

[9] Nin, A. P.; de Lederkremer, R. M.; Varela, O. Tetrahedron 1996, 52, 12911.

[10] Rosenthal, G. A.; Dahlman, D. L.; Crooks, P. A.; Phuket, S. N.; Trifonov, L. S. J Agric Food Chem 1995, 43, 2728.

[11] Gaudry, R. Can J Chem 1951, 29, 544.

[12] (a) Gilchrist, T. L. Chem Soc Rev 1983, 12, 53; (b) Gilchrist, T. L.; Wood, J. E. in Comprehensive Heterocyclic Chemistry II, Vol. 6, (Ed.: A. J. Boulton), Pergamon Press: Oxford, 1996; p 279; (c) Tietze, L. F.; Kettschau, G. Top Curr Chem 1997, 189, 1; (d) Tsoungas, P. G. Heterocycles 2002, 57, 1149; [e] Reissig, H.-U.; Zimmer, R. in Science of Synthesis, Houben-Weyl Methods of Molecular Transformations, Vol. 33, Molander, G. A., Ed., Georg Thieme Verlag: Stuttgart, 2007; p371; (f) Lemos, A. Molecules 2009, 14, 4098.

[13] Raj, V. P. I.; Sudalai, A. Tetrahedron Lett 2008, 49, 2646 and references therein.

[14] (a) Silverman, R. B.; Bichler, K. A.; Leon, A. J. J Am Chem Soc 1996, 118, 1241; (b) Welch, J. W. R.; Bhakoo, K.; Dixon, R. M.; Styles, P.; Sibson, N. R.; Blamire, A. M. NMR Biomed 2003, 16, 47.

[15] (a) Gallos, J. K.; Sarli, V. C.; Varvogli, A. C.; Papadoyanni, C. Z.; Papaspyrou, S. D.; Argyropoulos, N. G. Tetrahedron Lett 2003, 44, 3905; (b) Gallos, J. K.; Sarli, V. C.; Massen, Z. S.; Varvogli, A. C.; Papadoyanni, C. Z.; Papaspyrou, S. D.; Argyropoulos, N. G. Tetrahedron 2005, 61, 565; (c) Massen, Z. S.; Sarli, V. C.; Coutouli-Argyropoulou, E.;

Gallos, J. K. Carbohydr Res 2011, 346, 230; (d) Yioti, E. G.; Mati, I. K.; Arvanitidis, A. G.; Massen, S. S.; Elli, S.; Alexandraki, E. S.; Gallos, J. K. Synthesis 2011, 142.

[16] Boa, A. N.; Dawkins, D. A.; Hergueta, A. R.; Jenkins, P. R. J Chem Soc, Perkin Trans 1 1994, 953.

[17] Zimmer, R.; Arnold, T.; Homann, K.; Reissig, H.-U. Synthesis 1994, 1050.

[18] (a) Gallos, J. K.; Sarli, V. C.; Koftis, T. V.; Coutouli-Argyropoulou, E. Tetrahedron Lett 2000, 41, 4819; (b) Gallos, J. K.; Sarli, V. C.; Stathakis, C. I. Koftis, T. V.; Nachmia, V. R.; Coutouli-Argyropoulou, E. Tetrahedron 2002, 58, 9351 (c) Massen, Z. S.; Coutouli-Argyropoulou, E.; Sarli, V. C.; Gallos, J. K. Carbohydr Res 2011, 346, 508.

[19] Sabitha, G.; Syamala, M.; Yadav, J. S. Org Lett 1999, 1, 1701.