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A Convenient Synthesis of L- α -Vinylglycine from L-Homoserine Lactone

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Abstract

A procedure for the synthesis of L- α -vinylglycine from L-homoserine lactone is described. The route developed is convenient (only one chromatography step is required) and efficient (72% yield; 95% optical yield over 4 steps). Key features include the use of acid-labile protecting groups for the amino (Boc) and carboxyl (diphenylmethyl ester) groups, and the use of the phenylselenolate equivalent derived from sodium borohydride and diphenyl diselenide for L-homoserine lactone cleavage.

α -Vinylglycine, the simplest α -vinyl amino acid, occurs naturally in mushrooms.¹ This β , γ -unsaturated amino acid is an important mechanism-based inhibitor of a number of pyridoxal-linked enzymes. Five transaminases, including those for L-aspartate, L-alanine, L-serine and D-alanine^{2–6}, have been shown to be inactivated by racemic vinylglycine. In the case of the D-amino acid transaminases, Soper et al.⁴ noticed that only D-alanine, and not L-alanine, protected against inhibition and so presumed that D-vinylglycine was the actual suicide inhibitor. One decarboxylase, L-cysteine sulfinatase decarboxylase, is also known to be irreversibly inactivated by vinylglycine.⁷

Optically pure vinylglycine is also a versatile chiral building block, as evidenced by the range of synthetic applications for which it has been employed. Rapoport and coworkers used D-vinylglycine as an important building block in the construction of the mitomycin core.⁸ Crisp and Glink described the synthesis of a number of interesting chain-extended β , γ -unsaturated amino acids via Heck couplings of vinyl and aryl halides and triflates upon suitably protected L- α -vinylglycine derivatives.⁹ Most recently, Huwe and Blechert reported a clever route to hydroxypyrrolidines that employs a ring-closing olefin metathesis of an N-allyl-L- α -vinylglycinol as the key step.¹⁰

A number of syntheses of α -vinylglycine in both racemic¹¹ and enantiomerically enriched form¹² have been developed. As part of a program directed at the synthesis of unnatural, α -branched amino acids, we recently described a general procedure for the formal α -vinylation of protected amino acids to produce higher (i.e. bearing a second α -R group in addition to the α -vinyl group) α -vinyl amino acids in racemic form.¹³ The key steps in our formal vinylation procedure are: (1) alkylation of an amino acid-derived dianion with ethylene oxide as a vinyl cation equivalent to provide the corresponding α -substituted homoserine lactone;¹³ and (2) chemoselective alkyl cleavage of this γ -lactone through the agency of new non-reducing phenylselenolate equivalent developed in this work.^{14–16}

More recently, we have been investigating asymmetric versions of this methodology to access enantiomerically enriched α -vinyl amino acids.¹⁷ The approaches being taken include the use of chiral dianions for the initial alkylation step¹⁸ and enzymatic resolution.¹⁹ For vinylglycine, however, the simplest and only α -unbranched member of this class, it seemed reasonable that we might be able to intersect our vinylation procedure at step two. Namely, we envisioned phenylselenolate-mediated lactone cleavage as the key operation in the transformation of L-homoserine lactone into L- α -vinylglycine. Two important issues became apparent. (1) A suitable amino protecting group would need to be found that would withstand phenylselenolate anion at elevated temperatures, yet be removable under mild conditions, following unveiling of the β,γ -unsaturated ester functionality. (2) Racemization was seen as a potential problem, particularly in the first two steps from L-homoserine lactone: base-mediated amino group protection, and nucleophilic, phenylselenolate-mediated lactone cleavage. Optical purity would have to be assessed and, if necessary, conditions modified to minimize racemization.

We are pleased to report here that these issues have been addressed and that the general approach envisioned has now been reduced to practice. An important feature of the successful procedure includes the use of Boc protection for the α -amino group and diphenylmethyl ester protection for the α -carboxyl group, both of which may be removed quantitatively, under exceptionally mild conditions, in the final step. Another key element proved to be the choice of an appropriate phenylselenolate equivalent so as to prevent racemization in the lactone cleavage step.

Thus, Boc-protection of L-homoserine lactone proceeds smoothly to yield **1** in 97% yield (Scheme). Lactone **1** is then cleaved with the phenylselenolate equivalent generated from sodium borohydride and diphenyl diselenide.^{15a,15c,20} Gratifyingly, the Boc-amino protecting group survives these conditions quite well. This is significant as simple methyl carbamates are readily cleaved by sodium phenylselenolate anion.^{15d} The crude carboxylate salt is protonated and treated with diphenyldiazomethane in the workup to give phenylselenide **2** in 83% yield and in 96% ee.²¹

On the other hand, use of the phenylselenolate equivalent derived from the reduction of diphenyl diselenide with sodium trimethoxyborohydride here is efficient (72% yield after esterification with diphenyldiazomethane), but results in partial (8-13%) racemization.²¹ Consonant with previous findings, then, it appears that the NaBH₄-derived reagent is best for unhindered lactones,^{15a,15c,20} whereas the chemoselective (non-reducing) NaHB(OMe)₃-derived reagent is of advantage for sterically hindered α -branched lactones (for which racemization is also not an issue).^{13,14}

Ozone-mediated oxidation and pyrolysis of **2** under the previously reported conditions¹³ provides protected vinylglycine derivative **3**. Deprotection then ensues under very mild conditions. Specifically, treatment of **3** with trifluoroacetic acid, containing an equivalent of acetic acid as diphenylmethyl cation scavenger, at room temperature gives L- α -vinylglycine, as its trifluoroacetate salt **4** in 90% yield for the final two steps. The final product is judged to be 95% ee, based upon integration of a ¹H NMR spectrum of its Mosher amide, methyl ester.²³ This synthesis of L- α -vinylglycine from L-homoserine lactone is efficient (72% over

4 steps) and quite convenient (only one chromatography column is required). Since D-homoserine is also available commercially, the methodology described herein also constitutes a formal synthesis of D- α -vinylglycine.

Clear merits of this procedure for the synthesis of L-vinylglycine are its convenience, chemical efficiency and ready reproducibility. From an economic point of view, the procedure is quite acceptable for preparing several grams of vinylglycine [L-Homoserine currently sells for \$45/g (Aldrich) and is readily converted into the lactone,²⁴ whereas L-vinylglycine is priced at \$330/50 mg (Sigma)], but becomes expensive for large scale work. This is in contrast to the procedure of Afzali-Ardakani and Rapoport^{12e,f} which begins with L-methionine [\$27/100 g (Aldrich)], and to those of the Barton^{12b} and Hanessian^{12c} groups which emanate from L-glutamic acid [\$6/100 g]. To adapt the procedure described herein to large scale work, one could begin with L-methionine and convert it to L-homoserine, following Baldwin's "one-pot" procedure (90% yield).^{25a} Alternatively, it has been reported that L-asparagine [\$23/100 g (Aldrich)] can be electrochemically reduced to L-homoserine in 71% yield.^{25b}

All experimental procedures, analytical techniques and instruments employed were as previously described.¹³ For NMR spectra of the final product, sodium 3-(trimethylsilyl)propanesulfonate was employed as an internal capillary reference. Compounds **1-4** yielded satisfactory combustion analyses: C $\pm$ 0.25%; H $\pm$ 0.25%; N $\pm$ 0.15%.

N-(*tert*-Butoxycarbonyl)-homoserine lactone (**1**)

To a solution of homoserine lactone, trifluoroacetate salt (2.00 g, 9.29 mmol; readily obtained from L-homoserine)^{24,26} and NEt₃ (1.4 ml, 9.29 mmol) in CH₂Cl₂ (38 ml) at 0°C was added di-*tert*-butyl dicarbonate (2.03 g, 9.29 mmol). The reaction mixture was stirred for 12 h at rt and then washed with H₂O (1 $\times$ 25 ml) and 1N HCl (1 $\times$ 25 ml). The organic layer was dried (MgSO₄) and evaporated to give **1** (1.82 g, 97%) as a white solid, mp 111-113°C.

$[\alpha]_D^{24} = +8.16$ ($c = 2.5$, CHCl₃).

¹H NMR (300 MHz, CDCl₃): δ = 1.44 (s, 9 H), 2.16-2.25 (app quintet, $J = 12$ Hz, 1 H), 2.69-2.79 (m, 1 H), 4.18-4.28 (ddd, $J = 5, 9, 11$ Hz, 1 H), 4.29-4.38 (m, 1 H), 4.40-4.46 (app t, $J = 9$ Hz, 1 H), 5.03-5.10 (m, 1 H).

¹³C NMR (75 MHz, CDCl₃): δ = 28.1, 30.1, 50.0, 65.6, 80.3, 155.4, 175.4.

IR (ATR): ν = 3360 (br), 2981, 2931, 1776, 1684 cm⁻¹

Diphenylmethyl N-(*tert*-butoxycarbonyl)-2-[2'-(phenylseleno)ethyl]glycinate (**2**)

To an argon-purged flask containing sodium borohydride (310 mg, 8.19 mmol) was added a solution of diphenyl diselenide (1.58 g, 7.45 mmol) in DMF (60 ml), via cannula. To this solution was added, via cannula, a solution of lactone **1** (1.50 g, 7.45 mmol) in DMF (60

ml), and the reaction was heated at 100°C for 1 h. After cooling to 0°C, methanol (15 ml) was added and the crude mixture was stirred 5 h. The solvent was removed in vacuo, and the residue was partitioned between Et₂O (200 ml) and 100 mM NaOAc buffer (pH 5). The aqueous layer was extracted twice more with Et₂O (200 ml). The combined organics were dried (MgSO₄), filtered, and esterified with diphenyldiazomethane²⁷ (1.88 g, 9.69 mmol) in EtOAc. Evaporation of the solvent and chromatography (0-15% EtOAc/hexane) yielded **2** (3.24 g, 83%) as a white solid, mp 108-110°C.

$$[\alpha]_D^{24} = +12.28 \ (c=2.9, \text{CHCl}_3).$$

¹H NMR (300 MHz, CDCl₃): δ = 1.42 (s, 9 H), 1.96-2.06 (m, 1 H), 2.17-2.25 (m, 1 H), 2.76-2.85 (m, 2 H), 4.53-4.56 (app dd, J = 8, 12 Hz, 1 H), 5.05-5.08 (d, J = 8 Hz, 1 H), 6.86 (s, 1 H), 7.20-7.45 (m, 15 H).

¹³C NMR (75 MHz, CDCl₃): δ = 22.93, 28.24, 33.31, 53.61, 78.05, 80.01, 126.95, 127.07 (2C), 128.0, 128.1, 128.5, 128.6 (2C), 129.1, 133.0, 139.4, 139.5, 155.2, 171.2.

IR (ATR): ν = 3370 (br), 2981, 1743, 1712 cm⁻¹

Diphenylmethyl N-(*tert*-butoxycarbonyl)-2-vinylglycinate (**3**) and α -Vinylglycine, trifluoroacetate salt (**4**)

Ozone was bubbled into a solution of selenide **2** (474 mg, 0.913 mmol) in CH₂Cl₂ (10 ml) at -78°C until a light blue color persisted. After addition of 1-hexene (2 ml, 16 mmol), this cold solution was added dropwise to refluxing PhH (36 ml) and refluxing was continued for 1 h. Evaporation gave crude **3** as an oil. If desired, an analytical sample of **3** could be obtained by recrystallization (hexanes): mp 89-91°C.

$$[\alpha]_D^{24} = +10.11 \ (c=3.5, \text{CHCl}_3).$$

¹H NMR (300 MHz, CDCl₃): δ = 1.45 (s, 9 H), 4.97-5.04 (m, 1 H), 5.19-5.23 (d, J = 7 Hz, 1 H), 5.26-5.29 (d, J = 10 Hz, 1 H), 5.33-5.39 (d, J = 18 Hz, 1 H), 5.89-6.00 (m, 1 H), 6.90 (s, 1 H), 7.25-7.42 (m, 10 H).

¹³C NMR (75 MHz, CDCl₃): δ = 28.19, 55.88, 78.09, 79.98, 117.7, 126.9, 127.1, 127.97, 128.04, 128.2, 128.5, 132.4, 139.39, 139.45, 154.9, 169.71.

IR (ATR): ν = 3375 (br), 2977, 1743, 1711 cm⁻¹

It was found to be most convenient, however, to deprotect crude **3** without purification. To a solution of crude **3** in CH₂Cl₂ (18 ml) at 0°C were added CF₃COOH (10 ml) and AcOH (57 μ l, 1.01 mmol). The reaction mixture was allowed to warm to rt. After 8 h at rt, H₂O (30 ml) was added, followed by extraction with CH₂Cl₂ (3 $\times$ 20 ml) and Et₂O (3 $\times$ 20 ml). Evaporation of the aqueous layer, followed by thorough drying (50°C, 0.5 torr, P₂O₅ sidearm) yielded **4** (176 mg, 90% for two steps).

$$[\alpha]_D^{24} = +42.81 \ (c=1.1, \text{H}_2\text{O}).$$

¹H NMR (300 MHz, D₂O): δ = 4.52-5.55 (d, J = 7 Hz, 1 H), 5.48-5.50 (d, J = 5 Hz, 1 H), 5.53-5.54 (d, J = 2 Hz, 1 H), 5.87-6.00 (ddd, J = 7, 10, 17 Hz, 1 H).

^{13}C NMR (75 MHz, D_2O): δ = 57.69, 119.0 (q, J = 291 Hz), 125.7, 130.6, 165.5 (q, J = 35 Hz), 173.1.

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H₂CN₂ in step 2 and then treatment with: (a) TFA, CH₂Cl₂; (b) (S)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride, DMAP, NEt₃, CH₂Cl₂. In each case, the ¹H NMR spectrum thereby obtained was compared to that of the Mosher ester or amide derived from (±)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride.

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Scheme.