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Stereospecific Synthesis of the Amino Acid, (*S*)-2-Amino-(*Z*)-3,5-Hexadienoic Acid

Stuart Cameron and Bhupinder P.S. Khambay*

Department of Biological and Ecological Chemistry

IACR- Rothamsted, Harpenden

Herts. AL5 2JQ, U.K.

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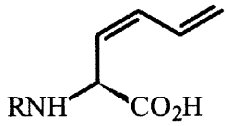
Abstract: The first synthesis of the amino acid, (*S*)-2-amino-(*Z*)-3,5-hexadienoic acid, a key component of the insecticidal dipeptide isolated from the Colorado Beetle, is reported. This was accomplished in 6 steps from Lajoie's protected serine aldehyde equivalent.

The dipeptide **1** was first isolated from the Colorado Beetle (*Leptinotarsa decemlineata*) by Pasteels[1] *et al* in 1986 and was reported to be toxic to the ant, *Myrmica rubra*.



1 R= γ-Glu

2 R=H

The authors were only able to isolate very small amounts of this compound, so only limited bioassays were possible. For a fuller evaluation of its biological activity, larger quantities are needed. This paper reports the first synthesis of the key and novel intermediate amino acid, (*S*)-2-amino-(*Z*)-3,5-hexadienoic acid **2**, necessary for the total synthesis of **1**. In addition **2**, in its racemic form, has recently been isolated from *Clavulinopsis helvola*.[2]

Initial attempts were based on previously reported syntheses[3] of amino acids containing simple unsaturated side chains (e.g. substituted olefins or acetylenes) from Garner's aldehyde.[4] In the first approach (Scheme 1) reaction of Garner's aldehyde with pinacol (*E*)-1-trimethylsilyl-1-propene-3-boronate (PTBP)[5] gave **4** as the sole addition product. Treatment of **4** with KH in THF gave the required *Z*-diene **5** in quantitative yield. The stereochemistry in the diene group was confirmed by the coupling constant observed for the 2,3 olefinic protons in **6** (10.6 Hz).[6]

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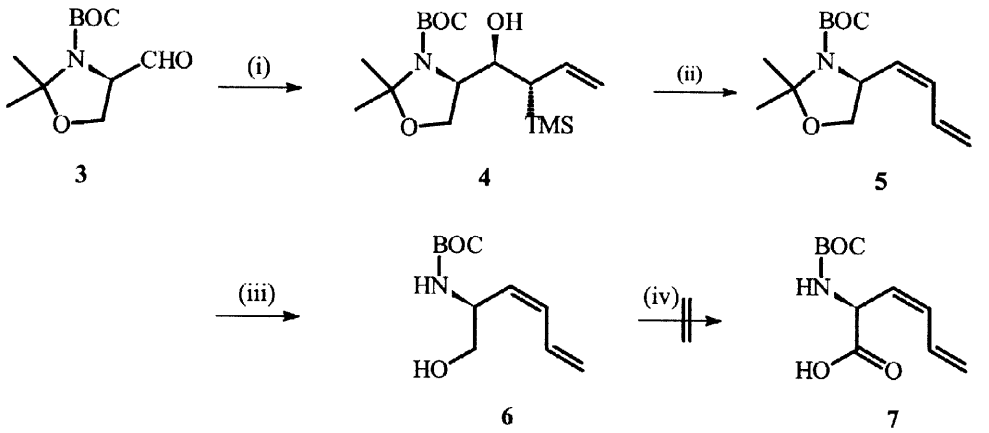
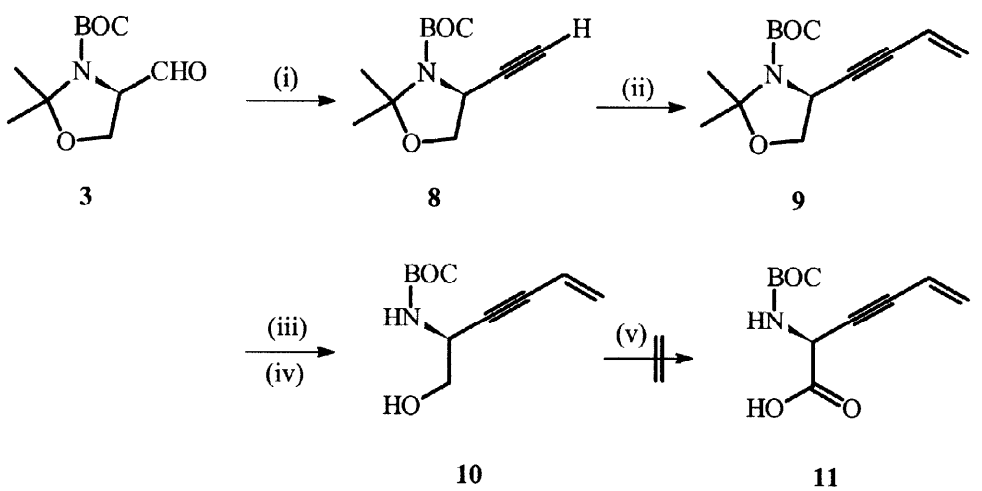


Reagents: (i) pinacol (*E*)-1-trimethylsilyl-1-propene-3-boronate, CH_2Cl_2, 4 days then triethanolamine; (ii) KH, THF, -10°C; (iii) pTSA, MeOH, 50°C; (iv) oxidation.

SCHEME 1

Mild acidic deprotection of the acetonide gave the BOC-protected amino alcohol **6**. However oxidation of **6** to the desired acid **7**, under a variety of conditions including PDC in DMF and Jones' oxidation (normal and inverse addition[3b]), gave a complex mixture of products.

In the second approach (Scheme 2) it was planned to generate the diene from the ene-yne amino acid **11**. So palladium coupling of vinyl iodide with the acetylene **8** derived from Garner's aldehyde **3**, gave the acetylenic olefin **9**, which was converted to the free alcohol **10**. As indicated in Scheme 1 oxidation of this compound also gave a complex mixture .

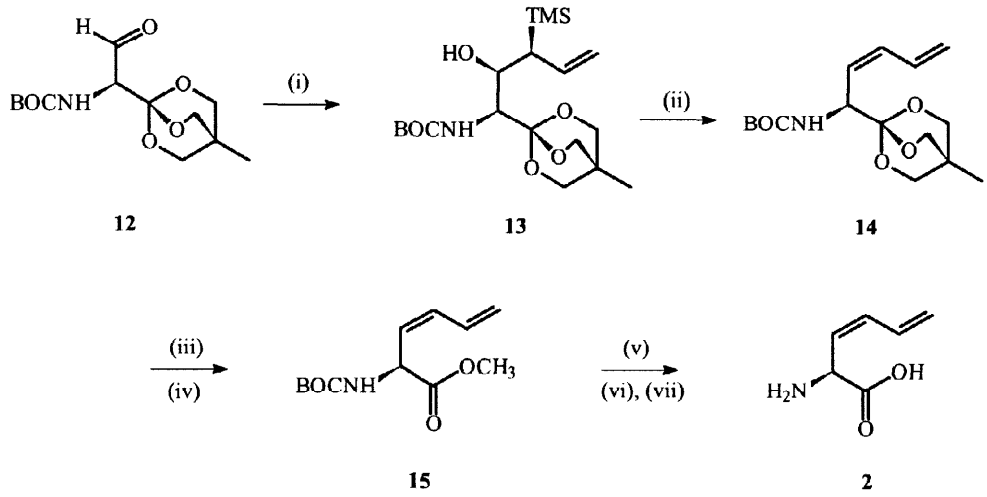


Reagents: (i) CBr_4, Ph_3P, THF; EtMgBr, THF; (ii) vinyl iodide, Et_2NH, $PdCl_2(PhCN)_2$, CuI; (iii) TFA, MeOH; (iv) $(BOC)_2O$, dioxane, $NaHCO_3$ soln.; (v) oxidation.

SCHEME 2

Success in the final oxidation step in approaches based on Garner's aldehyde are known to be sensitive to the nature of the functionality present.[3,8] Clearly the nature of the side-chains in **6** and **10** are also incompatible with this approach.

Finally, an approach avoiding oxidation but relying on hydrolysis of an ortho ester to generate the required acid was successful.



Reagents: (i) pinacol (*E*)-1-trimethylsilyl-1-propene-3-boronate, CH_2Cl_2, 4 days, then triethanolamine; (ii) KH, THF, -10°C; (iii) pTSA, MeOH; (iv) K_2CO_3, MeOH (aq.).; (v) 10% aq. $CsCO_3$, MeOH; (vi) HBr/AcOH; (vii) DOWEX® 50WX2-200 eluted with H_2O then 10% NH_4OH soln.

SCHEME 3

Thus, Lajoie's L-serine aldehyde equivalent[9] **12** was treated with PTBP (as in Scheme 1) to give the addition product **13**. Reaction with KH gave the stereochemically pure *Z*-diene **14**. Treatment with mild acid followed by transesterification with potassium carbonate in aqueous methanol[10] gave the fully protected amino dienoic acid **15** in 55% overall yield from the aldehyde. Deprotection of **15** was best accomplished with 10% aqueous caesium carbonate in methanol followed by acidolysis of the BOC group. The free amino acid **2**[11] was obtained by passing the resulting hydrobromide salt through an ion-exchange column eluting with water followed by 10% ammonium hydroxide solution.

Completion of the synthesis of the dipeptide **1** from **2** and biological evaluation of it and its analogues is under way and will be reported in due course.

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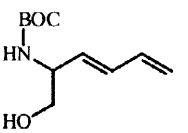
6. The *E*-diene could be generated by the treatment of **4** with a few drops of c H_2SO_4 in THF to give the ring opened product, $J_{3,4}$= 15.1 Hz.



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10. Care must be taken in this transformation to prevent formation of the protected amino-2,4-hexadienoic acid. Successful conditions involved reacting 1.5g of the acid treated product from **14** in 50ml 10% aqueous methanol containing 50 mg of K_2CO_3 for about 1 hour (monitored by TLC). The reaction was quenched by the addition of dilute ammonium chloride solution at 0^0C and extraction of the methyl ester **15** into ether.
11. Data for **2**: MS found 82.0657, [M^+-CO_2H], C_5H_8N requires 82.0657; NMR (D_2O) ^{1}H δ 4.73 ppm (1H, d, J=10.7 Hz, H-2), 5.41 (1H, d, J=10.7, H-6), 5.43 (1H, dd, J= 10.7, 10.7, H-3), 5.50 (1H, ddd, J=16.8, 0.8, 0.8, H-6), 6.45 (1H, dd, J=10.7, 10.7, H-4), 6.76 (1H, dddd, J=16.8, 10.7, 10.7, 1.1, H-5); ^{13}C 54.8 ppm (C-2), 124.4 (C-3), 125.2 (C-6), 133.3 (C-5), 139.2 (C-4), 175.9 (C-1)