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Stereoselective Synthesis of (2*S*,3*S*)-γ-Hydroxyvaline Utilising an Asymmetric Radical Hydrogen Bromide Addition

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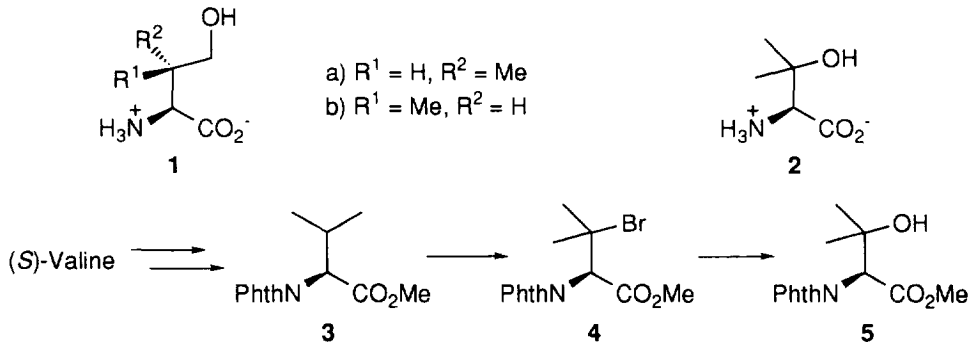
Abstract: *(S)*-Valine has been utilised in the stereocontrolled synthesis of (2*S*,3*S*)-γ-hydroxyvaline. The selectivity was achieved *via* 1,2-asymmetric induction in the *anti*-Markovnikov hydrobromination of a β,γ-dehydrovaline derivative. The relative and absolute stereochemistry of the γ-hydroxyvaline was determined using a variety of methods, including a nuclear Overhauser enhancement experiment with the diastereomeric lactones of γ-hydroxy-*N*-phthaloylvaline, and the synthetic material was shown to be identical to the natural product. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

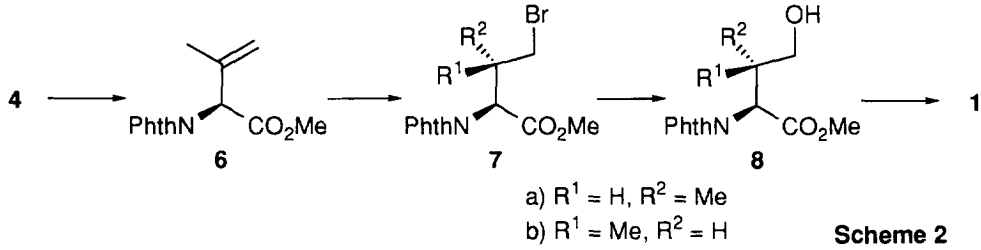
Hydroxy-substituted amino acids are an important class of natural products. They have been used in synthesis,[1] as enzyme inhibitors[2] and as probes in studies of biochemical pathways,[3] and many are constituents of biologically active peptides.[4] As a particular example, γ-hydroxyvaline has been isolated from the plant species *Kalanchoe daigremontiana*,[5] and it has since been used to determine the infidelity of the proof reading mechanism of the amino acylation of tRNA by valyl-tRNA synthetases, from *Saccharomyces cerevisiae* and *Escherichia coli*.[3] Given the importance of hydroxylated amino acids, there is much interest in routes for the stereocontrolled synthesis of these compounds. γ-Hydroxyvaline has been prepared previously.[6-9] One approach involved radical chlorination of (*S*)-valine, using either sulfuryl chloride[6] or chlorine,[9] followed by hydrolysis of the product chlorides to give a mixture of diastereomers of γ-hydroxyvaline.[6] The isomers were separated by crystallisation, affording the (2*S*,3*S*)-isomer **1a** in 6% yield, and the diastereomer **1b** in 0.2% yield.[6] Other syntheses afforded racemic mixtures.[7,8]

Recently it has been shown that treatment of *N*-phthaloyl-protected amino acid derivatives with *N*-bromosuccinimide results in side-chain bromination, and treatment of the product bromides with aqueous silver salts in acetone affords the corresponding hydroxy amino acid derivatives.[10-12] This procedure has been used in the stereocontrolled synthesis of hydroxy amino acid derivatives from readily available proteinogenic precursors, as illustrated by the synthesis of the β-hydroxyvaline derivative **5** from (*S*)-valine (Scheme 1).[12] The regioselectivity of the reaction is determined in the bromination, and is therefore limited to the site of the most stable side chain radical.[12-14] For example, while the derivative **5** of (*S*)-β-hydroxyvaline **2** can be obtained from the corresponding bromide **4**,[12] the derivatives **8a** and **8b** of γ-hydroxyvaline cannot be obtained directly using this approach. One aim of the work presented here was to manipulate the bromovaline derivative **4** for the stereocontrolled synthesis of isomers of γ-hydroxyvaline.



Scheme 1

It was envisaged that the (2*S*,3*S*)-isomer **1a** and the (2*S*,3*R*)-diastereomer **1b** of γ-hydroxyvaline could be obtained as shown in Scheme 2, *via* an elimination reaction of the bromide **4**, followed by an *anti*-Markovnikov hydrogen bromide addition. The latter reaction was also of interest due to the possibility of stereoselectivity. There have been many recent reports of 1,2-stereoinduction in radical reactions.[15,16] The stereochemical outcome of these processes has been attributed to a combination of minimised 1,3-allylic strain (A-strain), torsional strain, stereoelectronic effects and intramolecular hydrogen bonding.[15,16] A final goal of the present work was to determine the stereochemistry of γ-hydroxyvaline from *Kalanchoe daigremontiana*.[5]



Scheme 2

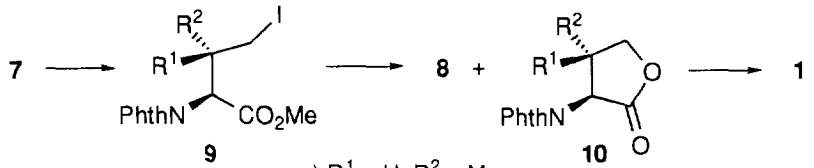
RESULTS AND DISCUSSION

The bromide **4** was prepared as reported previously.[12] A variety of methods were examined for the conversion of the bromide **4** into the alkene **6**. The reactions were complicated by competing formation of the corresponding α,β-dehydrovaline derivative and, in some cases, products of substitution of the bromine. The optimal conditions involved treatment of the bromide **4** with silver nitrate in anhydrous methanol, which gave the β,γ-dehydrovaline derivative **6** in 42% yield, after purification through repeated chromatography. This synthesis of the alkene **6** is complementary to that reported by Griesbeck *et al.*,[17] which involves photolysis of the valine derivative **3**, followed by oxidation. Hydrogen bromide was added to the alkene **6** by passing a dry stream of the gas through a solution of the alkene **6** in carbon tetrachloride at 0 °C, whilst irradiating the mixture with a 250 W mercury sunlamp. Analysis of the crude reaction mixture by ^{1}H NMR spectroscopy showed the presence of the diastereomeric γ-bromides **7a** and **7b**, in a 2.2:1 ratio. The diastereomers **7a** and **7b** were inseparable using chromatography on silica and the crude mixture was therefore used without purification.

Hydrolysis of the bromides **7a** and **7b** to the corresponding alcohols **8a** and **8b** was initially attempted by treatment with aqueous silver nitrate in acetone, first at room temperature, then at reflux, but no reaction occurred. Therefore, to facilitate the substitution reaction, the bromides **7a** and **7b** were converted

into the corresponding iodides **9a** and **9b** using sodium iodide in acetone. Treatment of the crude iodides **9a** and **9b** with aqueous silver nitrate in acetone at room temperature gave a mixture which contained the lactone **10a** and the alcohols **8a** and **8b**. Acidic hydrolysis of the mixture, followed by purification by ion exchange chromatography, gave a 3:1 mixture of the γ-hydroxyvaline diastereomers **1a** and **1b**, in 60% yield from the γ-bromides **7a** and **7b** (Scheme 3). The major isomer **1a** was separated from the mixture by fractional crystallisation, and isolated as a white crystalline solid.

The relative stereochemistry of the γ-hydroxyvaline diastereomers **1a** and **1b** is apparent from comparison of their ^{1}H NMR spectra with literature data.[6] Signals for the methyl group and the α-hydrogen occur as doublets at δ 0.94 and 3.85 for the isomer **1a**, indicating the (2*S*,3*S*)-stereochemistry, while the (2*S*,3*R*)-diastereomer **1b** shows the corresponding resonances at δ 1.02 and 3.74. The absolute stereochemistry of the alcohols **1a** and **1b** was confirmed by the optical rotation of the diastereomer **1a**.[6]



a) R^1 = H, R^2 = Me
b) R^1 = Me, R^2 = H

Scheme 3

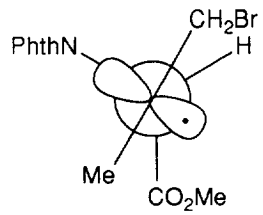
Repeated reactions of the iodides **9a** and **9b** with aqueous silver nitrate afforded various mixtures of the lactones **10a** and **10b** and the alcohols **8a** and **8b**, which were difficult to separate due to incomplete lactonisation of the alcohols **8a** and **8b**. For this reason, crude mixtures were used directly to synthesise the free amino acids **1a** and **1b**. On one occasion, a crude mixture from reaction of the iodides **9a** and **9b** was chromatographed on silica giving a *ca.* 6:1 mixture of the lactones **10a** and **10b**, in 67% yield.

The relative stereochemistry of the lactones **10a** and **10b** was determined using an NOE experiment. In the ^{1}H NMR spectrum, signals due to the H3, H4, H5 and H5' protons of the lactone **10b** occur at δ 5.01 (d, *J* 10.0 Hz), 3.06-2.90 (m), 4.66 (dd, *J* 8.4 and 8.7 Hz) and 4.26 (dd, *J* 8.0 and 8.7 Hz), respectively. Irradiation of the resonance centred at δ 2.98 affected the signals at δ 5.01 by +27%, at δ 4.66 by +0.2% and at δ 4.26 by -4.0%. The H3 and H5 protons of the lactone **10a** give rise to a multiplet at δ 4.66, while the H4 and H5' proton signals of that compound occur at δ 3.27-3.11 (m) and 3.98 (dd, *J* 9.2 and 10.3 Hz), respectively. Irradiation of the resonance at δ 3.20 affected the signals at δ 4.66 by +5.5% and at δ 3.98 by -1.7%. These values indicate a *syn*-relationship between the H3 and H4 protons of the isomer **10b**.

From the mass balance of the reactions, it is clear that the major iodide **9a** is derived from the predominant bromide **7a**, and it is the iodide **9a** which affords the lactone **10a** and the γ-hydroxyvaline **1a**. As expected, therefore, the stereochemistry of the lactone **10a** corresponds to that of the γ-hydroxyvaline **1a**. Using the same reasoning, the stereochemistry of the bromides **7a** and **7b** and the iodides **9a** and **9b** may be inferred from that of the alcohols **1a** and **1b**. The stereoselectivity which arises in hydrogen bromide addition to the alkene **6** can be attributed to delivery of hydrogen atom to the less hindered face of the intermediate radical **11**. The preferred conformation of the radical **11** results from minimising A-strain.[15]

Presumably the production of the 6:1 mixture of the lactones **10a** and **10b** from reaction of a 2.2:1 mixture of the iodides **9a** and **9b** is a consequence of selective lactonisation of the alcohol **8a**. This is in accord with the relative stereochemistry of the alcohols **8a** and **8b**. In the conformation required for lactonisation, unfavourable steric interactions exist between the phthalimido and methyl substituents of the (2*S*,3*S*)-isomer **8a**. In contrast, these unfavourable interactions are not present for the (2*S*,3*R*)-isomer **8b**.

In order to determine the absolute stereochemistry of the natural product, γ-hydroxyvaline was isolated from the plant species *Kalanchoe daigremontiana* using the procedure outlined by Pollard *et al.*[5] This material was determined to be the (2*S*,3*S*)-isomer **1a**, using the procedure outlined above to assign the stereochemistry of the synthetic material. Consequently the synthesis constitutes a stereoselective preparation of the natural isomer **1a**.



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EXPERIMENTAL

General. M.p.s were determined on a Reichert hot-stage apparatus and are uncorrected. IR spectra were recorded on a Hitachi 270-30 spectrophotometer. ^{1}H NMR (300 MHz) and ^{13}C NMR (75.5 MHz) spectra were recorded on a GEMINI 300 spectrophotometer, in $CDCl_3$ with Me_4Si as the internal standard, unless otherwise stated. Electron impact mass spectra were recorded on an AEI MS-30 spectrometer operating at 70 eV. Optical rotations were measured using a Perkin Elmer 241 polarimeter. Microanalyses were performed by Chemical and Microanalytical Services Pty. Ltd., Melbourne, Australia. Silica chromatography was performed on Merck-Keiselgel 60 (230-400 mesh ASTM), using ethyl acetate and light petroleum (b.p. 66-68 °C) as eluants. Organic solutions were dried over Na_2SO_4. All solvents were purified and dried using standard methods.

(S)-N-Phthaloyl-3,4-dehydrovaline Methyl Ester **6**. Silver nitrate (8.19 g, 48 mmol) was added to a solution of the bromovaline derivative **4**[12] (10.85 g, 32 mmol) in dry methanol (100 ml) over activated 4 Å sieves. The mixture was stirred at room temperature for 36 h in the dark, then saturated brine was added and the mixture was filtered. The filtrate was concentrated under reduced pressure, then the residue was partitioned between dichloromethane and water, and the organic layer was separated and concentrated. A ^{1}H NMR spectrum of the crude product showed that the β,γ-alkene **6** and the corresponding α,β-alkene were present in the ratio *ca.* 5:1. A portion of this material was chromatographed on silica to give the alkene **6** as a colourless oil (3.46 g, 42%). δ_H 7.75-7.92 (m, 4H), 5.38 (s, 1H), 5.14 (s, 1H), 5.11 (s, 1H), 3.79 (s, 3H), 1.92 (s, 3H). The ^{1}H NMR spectral data for this compound are consistent with those reported.[17]

(2S,3S)- and *(2S,3R)-4-Bromo-N-phthaloylvaline Methyl Ester* **7a** and **7b**. Through a solution of the β,γ-dehydrovaline derivative **6** (819 mg, 3.2 mmol) in carbon tetrachloride (50 ml), in an ice-water bath, was passed a dry stream of hydrogen bromide, for 5 mins. During this time, and for a further 40 mins, the solution was irradiated with a 250 W mercury sunlamp. The resultant solution was washed twice with water, then it was dried and concentrated under reduced pressure. The crude product was a colourless oil, which, when analysed using ^{1}H NMR spectrometry, showed a 2.2:1 mixture of the bromides **7a** and **7b** (944 mg, 88%). **7a** δ_H 7.78-7.94 (m, 4H, ArH), 5.02 (d, *J* 8.4 Hz, 1H, α-H), 3.90 (dd, *J* 5.1, 10.2 Hz, 1H, γ-H), 3.66 (dd, *J* 3.9, 10.2 Hz, 1H, γ'-H), 3.73 (s, 3H, OMe), 3.01 (m, 1H, β-H), 1.03 (d, *J* 6.9 Hz, 3H, β-Me); δ_C 168.2, 167.3, 134.2, 131.4, 123.5, 53.9, 52.5, 38.7, 34.8, 15.9; **7b** δ_H 7.78-7.94 (m, 4H, ArH), 4.91 (d, *J* 7.4 Hz, 1H, α-H), 3.74 (s, 3H, OMe), 3.65 (dd, *J* 3.7, 10.3 Hz, 1H, γ-H), 3.25 (dd, *J* 6.8, 10.3 Hz, 1H, γ'-H), 3.01 (m, 1H, β-H), 1.30 (d, *J* 6.6 Hz, 3H, β-Me); δ_C 168.5, 167.2, 134.0, 131.3, 123.7, 54.7, 52.3, 36.9, 35.3, 16.7; *m/z* (%) 341 ($M^{+\bullet}$, 1%), 339 ($M^{+\bullet}$, 1), 281 (20), 279 (20), 219 (50), 201 (100), 199 (100); *m/z* 339.009 ($M^{+\bullet}$) [Calc. for $C_{14}H_{14}{}^{79}BrNO_4$ ($M^{+\bullet}$) *m/z* 339.016].

(2S,3S)- and *(2S,3R)-4-Iodo-N-phthaloylvaline Methyl Ester* **9a** and **9b**. A solution of a 2.2:1 mixture of the bromides **7a** and **7b** (944 mg, 2.8 mmol) and sodium iodide (1.28 g, 8.5 mmol) in acetone (40 ml) was heated at reflux for 2 h. After cooling to room temperature, the mixture was filtered and the

filtrate was concentrated under reduced pressure. The residue was taken up in dichloromethane and the solution was washed with aqueous sodium metabisulfite solution and water, then it was dried and concentrated under reduced pressure, to give a 2.2:1 mixture of the iodides **9a** and **9b** as a yellow oil. **9a** δ_H 7.76-7.97 (m, 4H, ArH), 4.89 (d, *J* 8.3 Hz, 1H, α-H), 3.74 (s, 3H, OMe), 3.63 (dd, *J* 5.4, 10.2 Hz, 1H, γ-H), 3.50 (dd, *J* 3.9, 10.2 Hz, 1H, γ'-H), 2.59 (m, 1H, β-H), 0.99 (d, *J* 6.7 Hz, 1H, β-Me); **9b** δ_H 7.76-7.97 (m, 4H, ArH), 4.83 (d, *J* 7.3 Hz, 1H, α-H), 3.74 (s, 3H, OMe), 3.47 (dd, *J* 3.8, 10.2 Hz, 1H, γ-H), 3.01 (dd, *J* 7.8, 10.2 Hz, 1H, γ'-H), 2.79 (m, 1H, β-H), 1.25 (d, *J* 6.5 Hz, 3H, β-Me). The unstable iodides **9a** and **9b** were not purified and were used in the following reaction without characterisation.

(2S,3S)-4-Hydroxyvaline **1a**. To a stirred solution of the crude iodides **9a** and **9b** in aqueous acetone (30 ml) was added silver nitrate (711 mg, 4.2 mmol). The mixture was stirred at room temperature in darkness for 60 h, then brine was added. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was taken up in dichloromethane and the resultant solution was washed with brine, then dried and concentrated under reduced pressure. The crude product was analysed using ^{1}H NMR spectroscopy, which showed a mixture of the (3*S*,4*S*)-lactone **10a** and the alcohols **8a** and **8b**. **8a** δ_H 7.93-7.72 (m, 4H, ArH), 5.05 (d, *J* 5.4 Hz, 1H, α-H), 3.74 (s, 3H, OMe), 3.68 (dd, *J* 4.8, 11.8 Hz, 1H, γ-H), 3.39 (dd, *J* 8.3, 11.8 Hz, 1H, γ'-H), 2.82 (m, 1H, β-H), 0.93 (d, *J* 6.6 Hz, 3H, β-Me); **8b** δ_H 7.93-7.72 (m, 4H, ArH), 4.91 (d, *J* 6.3 Hz, 1H, α-H), 3.75 (s, 3H, OMe), 3.57 (dd, *J* 5.0, 12.0 Hz, 1H, γ-H), 3.51 (dd, *J* 6.6, 12.0 Hz, 1H, γ'-H), 2.79 (m, 1H, β-H), 1.10 (d, *J* 7.2 Hz, 3H, β-Me). The ^{1}H NMR spectral data for the lactone **10a** are given in the Results and Discussion.

The mixture containing the lactone **10a** and alcohols **8a** and **8b** was dissolved in a 2:1 mixture of 6 N hydrochloric and glacial acetic acid (25 ml), and the solution was heated at reflux for 4 h. After cooling to room temperature, the solution was concentrated under reduced pressure, then the residue was taken up in water and the mixture was filtered. The filtrate was concentrated under reduced pressure and the residue was dissolved in water, then the solution was applied to a column of Amberlite IR 120 cation exchange resin (NH_4^+ form). The column was washed with water (1 L), then eluted with aqueous ammonia solution (1 L). The eluate was boiled until no ammonia could be detected, then concentrated under reduced pressure affording a 3:1 mixture of the diastereomers **1a** and **1b** (223 mg, 60%). **1a** δ_H (D_2O) 3.85 (d, *J* 3.2 Hz, 1H, α-H), 3.69 (dd, *J* 5.2, 11.4 Hz, 1H, γ-H), 3.57 (dd, *J* 6.9, 11.4 Hz, 1H, γ'-H), 2.33 (m, 1H, β-H), 0.94 (d, *J* 7.2 Hz, 3H, Me); **1b** δ_H (D_2O) 3.74 (d, *J* 4.4 Hz, 1H, α-H), 3.64 (d, *J* 5.6 Hz, 2H, CH_2O), 2.17 (m, 1H, β-H), 1.02 (d, *J* 7.0 Hz, 3H, Me). Fractional crystallisation of this mixture from acetone and water afforded the (2*S*,3*S*)-isomer **1a** (94 mg, 25%), m.p. 219-221 °C (dec.) (Lit.[6] 212-214 °C (dec.)); δ_C (D_2O) 176.9, 67.0, 60.2, 38.4, 13.5; $[\alpha]_{365}^{24}$ +24.0° (c, 0.2 in H_2O) (Lit.[6] (2*S*,3*S*)-isomer **1a** +23.3°; (2*S*,3*R*)-isomer **1b** +26.4°); (Found: C, 45.0; H, 8.4; N, 10.5. Calc for $C_5H_{11}NO_3$: C, 45.1; H, 8.3; N, 10.5%).

(3S,4S)- and *(3S,4R)-4-Methyl-3-phthalimido-γ-butyrolactone* **10a** and **10b**. The title compounds were synthesised from a mixture of the iodides **9a** and **9b** by treatment with aqueous silver nitrate, using the procedure described above. In this case, however, the crude mixture was chromatographed on silica affording a *ca.* 6:1 mixture of the lactone diastereomers **10a** and **10b** as a colourless oil (607 mg, 67% from the bromides **7a** and **7b**). ν_{max}(neat)/cm^{-1} 3490, 2970, 1770, 1720, 1620, 1470, 1390, 1340, 1200, 1010. The ^{1}H NMR spectral data for the (3*S*,4*S*)-isomer **10a** and the (3*S*,4*R*)-diastereomer **10b** are given in the Results and Discussion. **10a+10b** *m/z* (%) 245 ($M^{+\bullet}$, 5%), 201 (25), 186 (100). *m/z* 245.070 ($M^{+\bullet}$) [Calc. for $C_{13}H_{11}NO_4$ ($M^{+\bullet}$) *m/z* 245.069]. (Found: C, 63.5; H, 5.0; N, 5.4. Calc. for $C_{13}H_{11}NO_4$: C, 63.7; H, 4.5; N 5.7%).

Extraction of γ-hydroxyvaline from Kalanchoe diagremontiana. γ-Hydroxyvaline was isolated from the lyophilised leaves and stems (20 g) of *Kalanchoe diagremontiana* using the procedure outlined by Pollard *et al.*,[5] then recrystallised from acetone and water (43 mg, 0.2%), m.p. 208-214 °C (Lit.[6] 212-214 °C). $[\alpha]_{365}^{20}$ +22.0° (c, 0.44 in H_2O) (Lit.[6] (2*S*,3*S*)-isomer **1a** +23.3°; (2*S*,3*R*)-isomer **1b** +26.4°) The ^1H NMR spectral data for this material are identical to those given above for the synthesised (2*S*,3*S*)-isomer **1a**.

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