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Towards a Total Synthesis of Ustiloxins A & B. Stereocontrolled Synthesis of *(2S,4S,6S)*-4-Hydroxy-5-phenylsulfinylnorvaline

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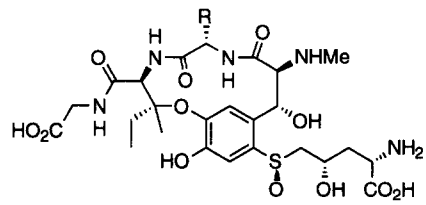
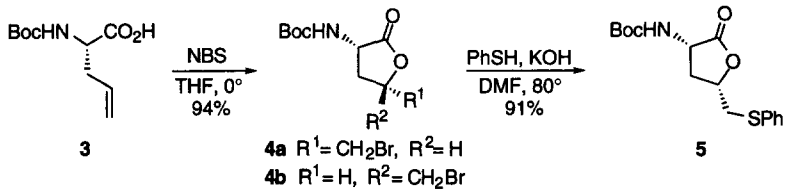
Abstract: A short, stereocontrolled synthesis of *(2S,4S,6S)*-4-hydroxy-5-phenylsulfinylnorvaline (**8**), an unusual amino acid component of ustiloxins A & B, has been achieved. Stereoselective bromolactonisation of N-Boc-*(S)*-allylglycine (**3**) is followed by substitution of the bromide **4a** with thiophenol to give the corresponding sulfide **5**. Highly stereoselective oxidation of the sulfide **5** gives the corresponding sulfoxide **6a**. Removal of the Boc group and lactone ring opening then complete the synthesis of the unusual amino acid.

The ustiloxins are a family of cyclic peptides recently isolated from the fungus *Ustilaginoidea virens*, which causes the growth of false smut balls on rice plants.[1] Ustiloxins A & B (**1** and **2**) are potent antimitotic agents and have been shown to inhibit the growth of several human cancer cell lines. Particular potency is exhibited against human breast and lung cancer lines, and consequently ustiloxins A & B are important anti-cancer drug leads. Ustiloxins A & B are highly functionalised cyclic peptides, containing three unusual amino acid components linked through a central aromatic core. A β-hydroxytyrosine residue provides the aromatic core, which is linked *via* an aryl-alkyl ether to a β-substituted isoleucine residue, and also constitutes part of the arylsulfinylnorvaline moiety. This paper describes the stereoselective synthesis of *(2S,4S,6S)*-4-hydroxy-5-phenylsulfinylnorvaline (**8**), one of the unusual amino acid components of ustiloxins A & B.



1 R = Me Ustiloxin A
2 R = iPr Ustiloxin B

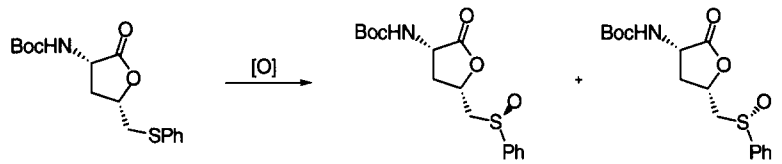
N-Boc-*(S)*-allylglycine[2] (**3**) underwent bromolactonisation according to the procedure of Ohfune *et al.*[3] to give the lactones **4a** and **4b** in a 4:1 ratio,[4] respectively. Subsequent treatment of the *cis*-lactone **4a** with thiophenol and potassium hydroxide in dimethylformamide at 80° for 16 hours gave the sulfide **5** in 91% yield (Scheme 1).[5]



3 **4a** $R^1 = CH_2Br$, $R^2 = H$ **4b** $R^1 = H$, $R^2 = CH_2Br$ **5**

Scheme 1

Many procedures for the asymmetric oxidation of sulfides to sulfoxides recently have been reported.[6-9] The most straightforward procedures involve the use of commercially available enantiopure reagents as chiral auxiliaries. Much work has been published on the use of modified Sharpless reagents in the asymmetric oxidation of sulfides,[6,7] particularly by Kagan *et al.*[6] Initial studies of the asymmetric oxidation of the sulfide **5** were performed following the procedures of Kagan *et al.*,[6] however little or no diastereoselectivity was observed (see Table 1). Efforts were then directed to the use of the similar system reported by Uemura *et al.*,[9] in which *(R)*- or *(S)*-1,1'-bi-2-naphthol (BINOL) is employed as the chiral auxiliary in place of *(R)*- or *(S)*-diethyltartrate (DET). Oxidation of the sulfide **5** under these conditions gave the corresponding sulfoxides **6a** and **6b**[10] in good yield and remarkably high stereoselectivity. Treatment of the sulfide **5** with *tert*-butylhydroperoxide in the presence of titanium(IV) isopropoxide and *(S)*-BINOL gave a 1:16 ratio of the sulfoxide isomers **6a** and **6b**, respectively. Treatment of the sulfide **5** under similar conditions but using *(R)*-BINOL as the chiral auxiliary gave the sulfoxide **6a** in 75% yield with the minor diastereomer not detectable in the crude ^1H NMR spectrum, indicating that asymmetric oxidation of **5** to **6a** occurs with greater than 50:1 diastereoselectivity. The difference in selectivity of the two reactions is indicative of a slight "matched pair *vs.* mismatched pair" effect due to the proximity of the asymmetric centres on the lactone ring. X-Ray crystallographic analysis of the sulfoxide isomer obtained from the reaction using *(R)*-BINOL as the chiral auxiliary showed this sulfoxide to be the desired *(6S)*-isomer (**6a**) (Figure 1).[11]



5 **6a** **6b**

Scheme 2

Table 1. Stereoselectivity of sulfide **5** oxidation to sulfoxides **6a** and **6b**.

oxidant	catalyst	chiral auxiliary	yield (%)	stereoselectivity
H_2O_2	-	-	78	1.1 : 1
t-BuOOH	Ti(O*i*-Pr)$_4$	*(S)*-DET	87	1.1 : 1
t-BuOOH	Ti(O*i*-Pr)$_4$	*(R)*-DET	93	1.2 : 1
t-BuOOH	Ti(O*i*-Pr)$_4$	*(S)*-BINOL	68	1 : 16
t-BuOOH	Ti(O*i*-Pr)$_4$	*(R)*-BINOL	75	> 50 : 1

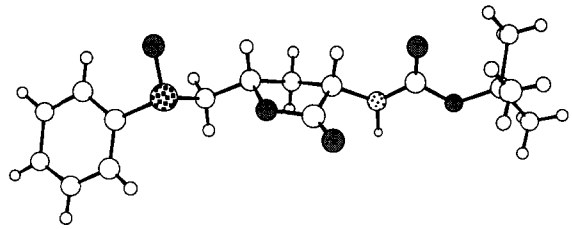
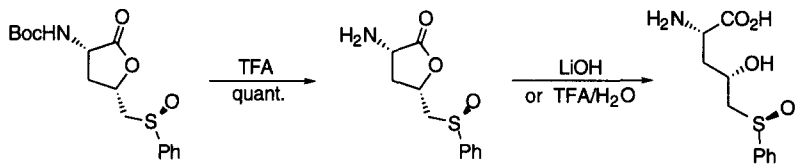


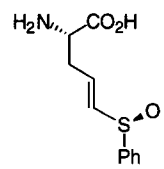
Figure 1. X-Ray crystal structure of sulfoxide **6a**.

Treatment of the sulfoxide **6a** with trifluoroacetic acid (TFA) in dichloroethane resulted in loss of the Boc protecting group to give the corresponding amine **7**[12] as its trifluoroacetate salt. Treatment of the amine **7** with lithium hydroxide resulted in opening of the lactone to give the amino acid **8**.[13] Alternatively, treatment of the sulfoxide **6a** with a catalytic amount of trifluoroacetic acid in acetone/water resulted in slow conversion to an equilibrium mixture of the lactone **6a** and the amino acid **8** (10:1 ratio of **8:7**) (Scheme 3). The acid catalysed ring opening procedure was the method of choice as it removed the possibility of formation of **9** through based catalysed elimination/ring opening.



6a **7** **8**

Scheme 3



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In summary, a straightforward and stereoselective synthesis of *(2S,4S,6S)*-4-hydroxy-5-phenylsulfinyl-norvaline (**8**), an unusual amino acid component of ustiloxins A & B, has been reported, including a highly stereoselective oxidation of sulfide **5** to sulfoxide **6a**. Incorporation of this procedure into a total synthesis of ustiloxins A & B is currently under investigation.

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References and notes

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2. N-Boc-*(S)*-allylglycine (**3**) was obtained by protection of *(S)*-2-amino-4-pentenoic acid (Aldrich) under standard conditions, or *via* the procedure of Williams *et al.*, see; Williams, R. M.; Sinclair, P. J.; Zhai, D.; Chen, D. *J. Am. Chem. Soc.* **1988**, *110*, 1547-1557.
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4. Ohfune *et al.* (ref. 3) report an 8:1 ratio of *cis*- and *trans*-lactones **4a** and **4b** is obtained. Fusetani *et al.* reported that a 4:1 ratio of isomers is obtained under these conditions, as our results confirm, see; Matsunaga, S.; Fusetani, N.; Hashimoto, K.; Wälchli, M. *J. Am. Chem. Soc.* **1989**, *111*, 2582-2588.
5. data for **5**: ^{1}H NMR ($CDCl_3$): δ 1.41 (s, 9H), 1.88 (m, 1H), 2.88 (m, 1H), 3.04 (dd, *J* = 7.6, 14.0 Hz, 1H), 3.36 (dd, *J* = 5.2, 14.0 Hz, 1H), 4.37 (m, 1H), 4.46 (m, 1H), 5.10 (br s, 1H), 7.39-7.20 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 28.1, 35.2, 38.1, 51.0, 75.7, 80.3, 126.9, 129.0, 130.2, 134.3, 155.2, 174.3.
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9. Komatsu, N.; Hashizume, M.; Sugita, T.; Uemura, S. *J. Org. Chem.* **1993**, *58*, 4529-4533.
10. data for **6a**: ^{1}H NMR ($CDCl_3$): δ 1.43 (s, 9H), 2.01 (m, 1H), 2.84 (m, 1H), 3.02 (dd, *J* = 3.6, 13.6 Hz, 1H), 3.08 (dd, *J* = 9.0, 13.6 Hz, 1H), 4.40 (m, 1H), 5.00 (dddd, *J* = 3.6, 5.6, 9.0, 10.7 Hz, 1H), 5.17 (br d, *J* = 5.4 Hz, 1H), 7.55 (m, 3H), 7.66 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 28.2, 35.6, 51.1, 63.1, 71.1, 80.8, 123.7, 129.6, 131.5, 143.4, 155.1, 173.6.
    data for **6b**: ^{1}H NMR ($CDCl_3$): δ 1.44 (s, 9H), 2.26 (m, 1H), 2.95 (m, 1H), 3.14 (dd, *J* = 6.2, 13.6 Hz, 1H), 3.32 (dd, *J* = 5.7, 13.6 Hz, 1H), 4.37 (m, 1H), 4.61 (m, 1H), 5.20 (br d, *J* = 5.3 Hz, 1H), 7.56 (m, 3H), 7.65 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 28.2, 35.7, 50.9, 60.2, 71.6, 80.7, 124.0, 129.6, 131.7, 142.3, 155.2, 173.7.
11. Crystal data: $C_{16}H_{21}NO_5S$, M 339.41, monoclinic, space group P 2_1, *a* 6.062(1), *b* = 8.007(1), *c* = 17.724(1) Å, β 92.52(1)°, V 859.5(2) A^3. Z 4, D_c 1.312 Mg/m^3, F(000) 360, μ_{Cu} = 1.888 mm^{-1}, specimen 0.25 x 0.05 x 0.01 mm. N 952, N_o 548 ; *R 1*0.0652, *wR2* = 0.1332.
12. data for **7**: ^{1}H NMR (d_6-acetone/D_2O): δ 2.22 (ddd, *J* = 10.5, 11.7, 12.7 Hz, 1H), 2.94 (ddd, *J* = 5.4, 8.8, 12.7 Hz, 1H), 3.32 (dd, *J* = 8.7, 14.0 Hz, 1H), 3.37 (dd, *J* = 4.0, 14.0 Hz, 1H), 4.55 (ddd, *J* = 8.8, 11.7, 12.7 Hz, 1H), 5.04 (dddd, *J* = 4.0, 5.4, 8.7, 10.5 Hz, 1H), 7.57 (m, 3H), 7.65 (m, 2H); ^{13}C NMR (d_6-acetone/D_2O): δ 32.4, 49.1, 60.5, 72.7, 124.2, 130.0, 132.3, 141.7, 171.9.
13. data for **8**: ^{1}H NMR (d_6-acetone/D_2O/TFA): δ 2.04 (m, 2H), 2.92 (dd, *J* = 9.1, 13.5 Hz, 1H), 2.98 (dd, *J* = 3.5, 13.5 Hz, 1H), 4.15 (dd, *J* = 4.2, 7.6 Hz, 1H), 4.19 (m, 1H), 7.44 (m, 3H), 7.57 (m, 2H); ^{13}C NMR (d_6-acetone/D_2O/TFA): δ 35.6, 50.4, 62.4, 63.4, 124.2, 129.8, 132.0, 141.1, 170.9.

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