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First Syntheses of (2*S*, 3*S*)- and (2*S*, 3*R*)- m-Prenyl-β-Hydroxytyrosine Derivatives : Bioactive Amino Acid Fragment of a Substance P Antagonist Novel Cyclic Heptapeptide[1]

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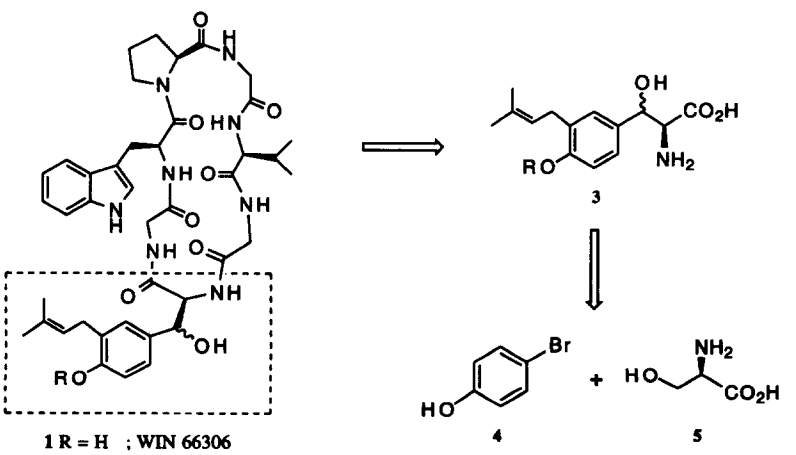
Dedicated to Professor H. Junjappa on the occasion of his 60th birthday

Abstract : A stereodefined synthesis of both the C-3 isomers of the title tyrosine related new amino acid **3** has been achieved starting from D-serine and 4-bromophenol.

Peptide **1**, a cyclic heptapeptide isolated from culture fermentation broths of *Aspergillus flavipes*[2], was found to be a competitive antagonist to substance P (SP) at the human NK1 receptor. The structure of **1** was determined by spectroscopic and chemical means and was shown to contain a tyrosine related novel amino acid, m-prenyl-β-hydroxytyrosine (**3**). The semi-synthetic monomethyl derivative **2** was 60 times more potent than the parent peptide **1**. Structure-activity relationship studies revealed the amino acid unit **3** to be an essential component for bioactivity, where both the prenyl and the β-hydroxy group contribute significantly towards its

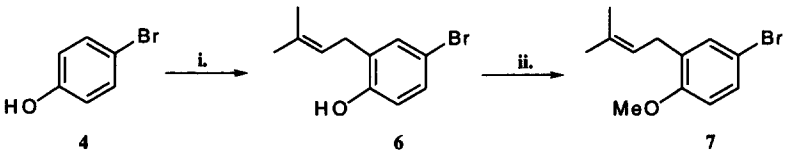


Scheme 1

activity. The configuration at the α-carbon of this new amino acid was determined to be *S*, but the chirality at the β-carbon has not yet been defined.[2] The above observations prompted us to undertake a stereodefined synthesis

of both the C-3 isomers of this novel amino acid, which can help determine the configuration at the β-carbon of this unit present in peptide **1** and also provide a route for the synthesis of new analogs of **1** *via* structural modification of **3**. Results of the synthesis thus undertaken are reported herein.

As per the retrosynthetic strategy shown in Scheme 1, a convergent approach was planned for assembling the amino acid skeleton, starting from commercially available 4-bromophenol (**4**) and D-serine (**5**). Accordingly,

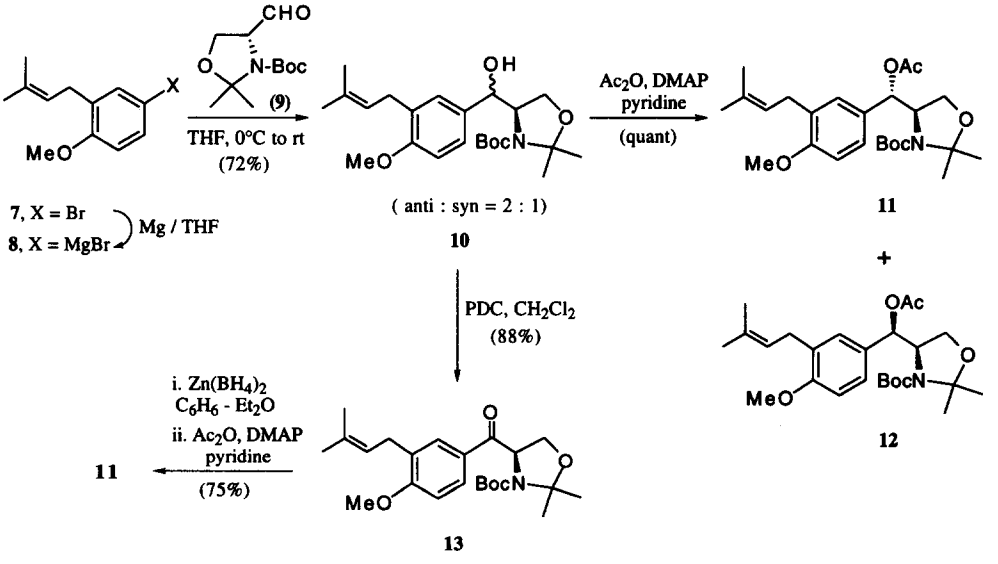


4 **6** **7**

i. a) Na / C_6H_6, Δ, 8h. b) $BrCH_2CH{:}C(CH_3)_2$, C_6H_6 , rt, 24h, 56%. **ii.** Me_2SO_4 , K_2CO_3 , acetone, Δ, 2h, 95%.

Scheme 2

4-bromophenol was converted to the 2-prenyl derivative **6** by modification of a known procedure.[3] Subsequent O-methylation afforded **7** (Scheme 2), the left half fragment of the desired amino acid. Reaction of the corresponding Grignard reagent **8** with Garner aldehyde **9** (derived from D-serine, **5**)[4] yielded the carbinol **10** (Scheme 3) as a diastereomeric mixture (2:1), in favour of the *anti*- diastereomer as per literature precedence.[5] Acetylation of this mixture and separation of the components by preparative HPLC afforded the pure diastereo -



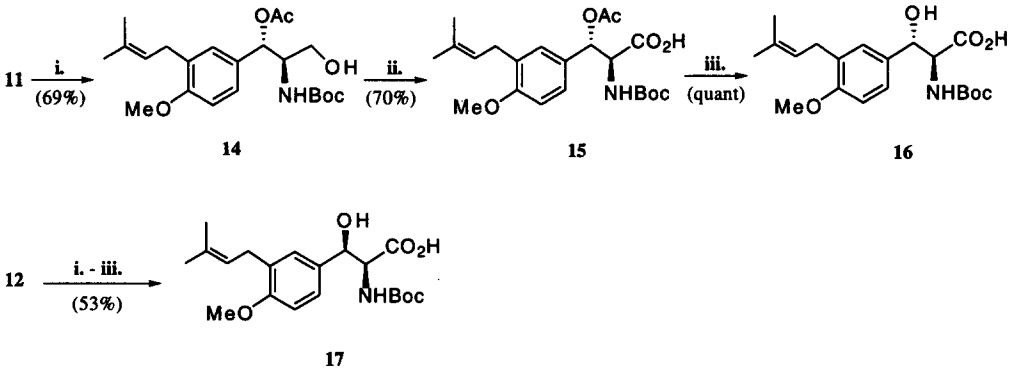
Scheme 3

isomers **11** and **12** respectively.

In a separate experiment, oxidation of the diastereomeric mixture of carbinol **10** to the corresponding ketone **13** followed by stereoselective reduction of the keto carbonyl with $Zn(BH_4)_2$ (formation of *erythro*

product)[6] and subsequent O-acetylation (Scheme 3) resulted in the formation of the *anti*- isomer **11** (>95% de), similar in all respect to the compound **11**, as obtained previously *via* direct acetylation of **10**.

Deketalisation of **11** afforded the hydroxy derivative **14** (Scheme 4), oxidation of which yielded the corresponding acid **15** in good yield. Finally, removal of the acetyl group completed the desired synthesis of the amino acid derivative **16**. Following the same sequence of reactions, compound **12** was similarly converted to the corresponding *syn*-β-hydroxy amino acid derivative **17** in good overall yield.[7]



i. 80% aq. AcOH, rt, 12h. ii. PDC, DMF, rt, 8-10h. iii. NaOMe, MeOH, rt, 3h.

Scheme 4

In conclusion, the described syntheses of both the C-3 isomers of the above amino acid provides a pathway towards determining the stereochemistry of this moiety present in the peptide **1** and also opens up the possibility of further structural modifications in search of more potent analogs. Further work is in progress.

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References and Notes

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7. All new compounds were characterized by ^{1}H NMR, ^{13}C NMR and FAB/HRMS. Some characteristic data are given below :

11 : m.p. 73 -75°C; $[\alpha]_D$ +0.6 (c = 1.07, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 1.46, 1.50 and 1.59 (3s, 15H), 1.69 and 1.74 (2s, 6H), 2.16 (s, 3H), 3.26 (d, J = 6.7 Hz, 2H), 3.76 (m, 1H), 3.81 (s, 3H), 4.04 (m, 2H), 5.25 (br m, 1H), 6.24 (d, J = 2.6 Hz, 1H), 6.76 (br d, J = 8.4 Hz, 1H), 7.04 (m, 2H) : ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.7, 156.5, 130.2, 129.5, 127.1, 126.6, 124.4, 123.7, 121.8, 110.0, 94.6, 80.2, 73.4, 73.1, 62.9, 61.5, 55.3, 28.3, 26.8, 26.2, 25.7, 24.5, 23.1, 21.1, 17.6 : MS (FAB+) 447 (M+).

12 : $[\alpha]_D$ +1.6 (c = 0.98, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 1.41 and 1.45 (2s, 6H), 1.57 and 1.59 (2s, 9H), 1.72 and 1.74 (2s, 6H), 2.07 (br s, 3H), 3.30 (d, J = 7.2 Hz, 2H), 3.73 (m, 2H), 3.84 (s, 3H), 4.29 (m, 1H), 5.27 (m, 1H), 5.95 (br d, 1H), 6.80 (d, J = 8.4 Hz, 1H), 7.11 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.8, 157.4, 129.1, 128.8, 126.4, 125.8, 122.2, 121.9, 109.9, 109.8, 94.4, 80.2, 75.1, 74.1, 64.0, 60.1, 55.3, 29.6, 28.3, 26.8, 25.6, 24.5, 23.0, 21.2, 17.7: MS (FAB+) 446 (M^+ -1).

16 : $[\alpha]_D$ +37.5 (c = 1.4, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 1.41 (br s, 9H), 1.68 and 1.71 (2s, 6H), 3.25 (d, J = 7.3 Hz, 2H), 3.53 (br s, 2H), 3.80 (s, 3H), 4.62 (br s, 1H), 5.19 (br s, 1H), 5.22 (br t, J = 7 Hz, 1H), 6.75 (d, J = 7.0 Hz, 1H), 7.10 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.3, 157.2, 132.4, 130.5, 130.0, 127.7, 127.5, 124.9, 122.3, 110.0, 80.7, 74.5, 59.5, 55.4, 29.6, 28.6, 28.2, 25.8, 17.7; HRMS calcd. for $C_{20}H_{30}NO_6$ (MH^+) : 380.2073, found : 380.2065.

17 : $[\alpha]_D$ +3.6 (c = 1.4, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 1.14 and 1.26 (2s, 9H), 1.65 and 1.67 (2s, 6H), 3.22 (d, J = 6.9 Hz, 2H), 3.71 (s, 3H), 4.65 (br s, 2H), 5.12 - 5.42 (m, 2H), 6.71 (d, J = 7.5 Hz, 1H), 7.21 (m, 2H) ; ^{13}C NMR (50 MHz, $CDCl_3$) δ 157.1, 130.0, 127.2, 124.5, 122.3, 110.1, 77.2, 77.2, 62.2, 55.4, 31.9, 30.0, 29.7, 29.3, 28.6, 28.2, 25.8, 17.8 ; MS (FAB+) 380 (MH^+).

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