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Stereoselective Synthesis of (+)-CP-99,994: A Substance P Non-peptide Antagonist.

S.Chandrasekhar* and Pradyumna K. Mohanty

Indian Institute of Chemical Technology, Hyderabad, India, 500007.

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Abstract: A highly stereoflexible total synthesis of (+)-CP-99,994 is achieved starting, from (*S*)-serine, key steps being a diastereoselective Grignard addition, a one-pot reductive protection of an azide, and one-pot oxidative Wittig olefination.

Key words: Stereoselective; Nonchelation control; One-pot reactions. Piperidine; (+)-CP-99,994.

Substance P[1] (SP)an undecapeptide belonging to the tachykinin class has been implicated in the pathogenesis of diverse diseases such as arthritis, asthma, inflammatory bowel disease besides others.[2] Almost all the SP receptor antagonists discovered until recently have been made by modification of SP itself.

Our interest in the development of new synthetic protocols for clinically useful chemical entities in general[3] and enantiopure compounds in particular has prompted us to develop a stereoflexible total synthesis of the highly potent non-peptide SP antagonist (+)(2*S*,3*S*)-3-(2-methoxylbenzylamino)-2-phenylpiperidine[4](+)-CP-99,994 (1) as its HCl salt. This substance has been shown to bind with high affinity to the human NK_1 receptor.

Retrosynthetic analysis of **1** revealed that fully protected (*S*)-serine could be a useful chiral starting material which should furnish the target CP-99,994 in highly optically pure form.

The readily accessible *N,N*-dibenzyl-O-*tert*-butyldimethylsilyl serinol **3** was subjected to one-pot Swern oxidation and phenylmagnesium bromide addition to generate the phenyl carbinol **4** in 86% yield (*anti:syn*, 97: 3). The stereoselective formation of the major *anti* product may be attributed to non-chelation control.[5] The minor isomer was easily removed by column chromatography (eluent:hexane/ethyl acetate 15/1 then 10/1). Displacement of the –OH group with $-N_3$ at C-3 was achieved efficiently in one step using a Mitsunobu protocol[6] (80% yield). A one-pot reduction-deprotection of the azido group and simultaneous deprotection of the *O*-silyl ether using $LiAlH_4$[7] and *in situ* addition of $(BOC)_2O$ gave a 76% yield of the primary alcohol **6.** The alcohol **6** was subjected to another one-pot reaction, this time Swern oxidation-Wittig olefination[8] to realize the α,β-unsaturated ester 7 in 95% yield. Olefin reduction[9] followed by ester reduction[10] furnished

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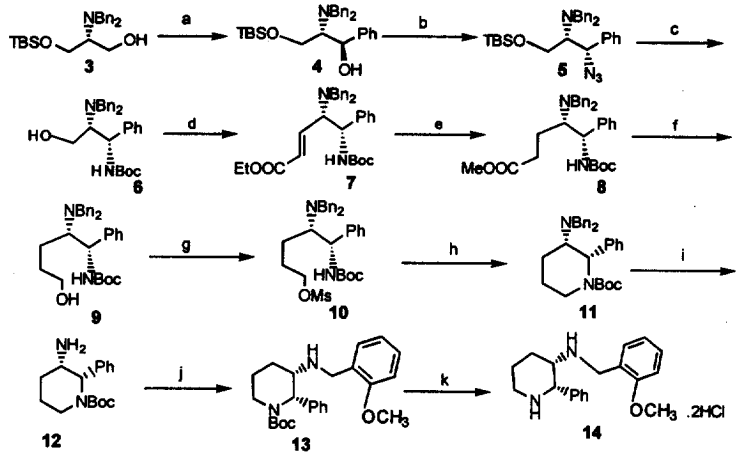
the homologated carbinol **9** in 74% yield. This upon mesylation and treatment with NaH provided the piperidine skeleton in 70% yield. (Scheme).



Scheme: **a)** (i) $(COCl)_2$, DMSO, TEA,DCM, (ii) PhMgBr, THF. **(b)** TPP, DEAD, DPPA, THF.**(c)**LAH, $(BOC)_2O$, THF. **(d)** (i) $(COCl)_2$, DMSO, TEA,DCM,. (ii) Ph_3P=CH-COOEt. **(e)** Mg, MeOH.**(f)** LiCl, $NaBH_4$,EtOH,THF, **(g)** MsCl, TEA, DCM, **(h)** NaH, THF **(i)** $Pd(OH)_2$/C, MeOH. **(j)** 2-Methoxybenzaldehyde, $NaCNBH_3$.MeOH, **(k)**Dry HCl, EtOAc.

Debenzylation and one-pot reductive amination and removal of the –BOC protective group resulted in the targeted CP-99,994 as its HCl salt (14.5% overall yield) whose spectroscopic data were consistent with literature data.[4a]

In summary, a highly stereoselective total synthesis of CP-99,994 has been achieved involving very high yielding one-pot reactions. The flexibility in the approach allows the synthesis of analogs of this class of compound.[11]

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