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SYNTHESIS OF RPR 100893, PROTOTYPE OF A NEW SERIES OF POTENT AND SELECTIVE NON PEPTIDE NK1 ANTAGONISTS : THE TRIARYLPERHYDROISOINDOLOLS.

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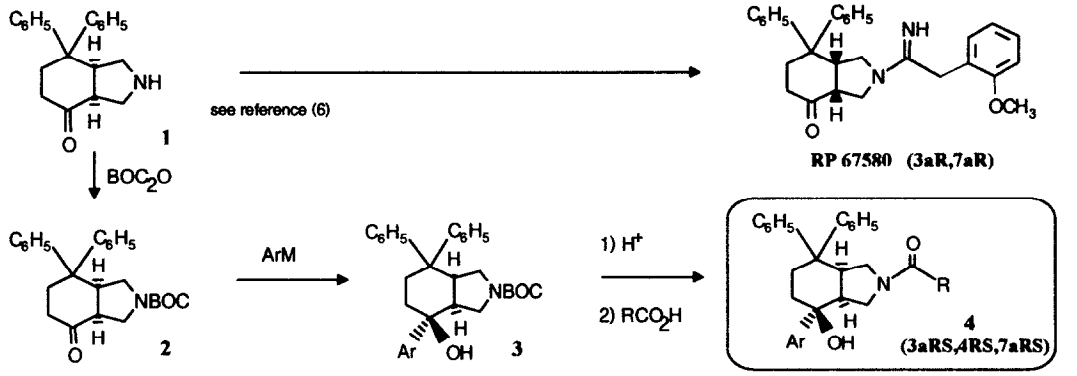
Abstract : The synthesis of enantiomerically pure RPR 100893, a novel non peptide NK1 Substance P antagonist, is described. This compound is a representative of 7,7,4-triaryl perhydroisoindol-4-ols, a new series of perhydroisoindole Substance P antagonists with high affinity for human NK_1 receptor.

Substance P, the first isolated and characterised member of the tachykinin family of peptides which share the same C-terminal sequence Phe-X-Gly-Leu-Met, acts preferentially through NK_1 receptor[1]. It is widely distributed in both central and peripheral nervous systems and was early recognized as a neurotransmitter or neuromodulator[2]. There is now much evidence that it plays a role in pain transmission and associated responses[3] besides a wide variety of other biological effects including smooth muscle contraction, secretion of endocrine and exocrine glands, vasodilation, neurogenic inflammation, and regulation of immune responses[4]. The discovery of the first potent nonpeptide substance P (SP) antagonists[5,6] helped to enlighten the physiological, and pharmacological role of this peptide and provided a confirmed rationale of the therapeutic potential of substance P antagonists in the treatment of important diseases where SP is involved, like pain[7], migraine[8], asthma[9] or inflammation[10].

Following our discovery of 2-arylacetyl 7,7-diphenyl perhydroisoindolones NK_1 antagonists (RP 67580 series)[6], the study of structure-activity relationships in this family led us to replace the carbonyl function by various surrogates, such as fluorine atom[11], alcohol[11], or sulfoxide[12]. The success in this approach prompted us to further investigate the chemistry of this carbonyle function, and especially to study its attack by various organometallics, according to Scheme **1**.

(3aRS,7aRS)-7,7-Diphenyl perhydroisoindol-4-one **1**[6], protected as its BOC derivative **2**, was reacted with various organometallics like Grignard reagents in the presence of cerium chloride, to give alcohols **3** as single isomers resulting from exclusive equatorial attack of the carbonyle, i.e. from the less hindered side of the heterobicycle. The BOC protecting group was removed under acidic conditions (usually dry HCl in dioxan) and the resulting amines were acylated with various carboxylic acids to give (3aRS,4RS,7aRS)-7,7,4-triarylperhydroisoindol-4-ols **4.**

SCHEME 1 : General synthesis of 7,7 diarylperhydroisoindol-4-ones and 7,7,4 triarylperhydroisoindol-4-ols



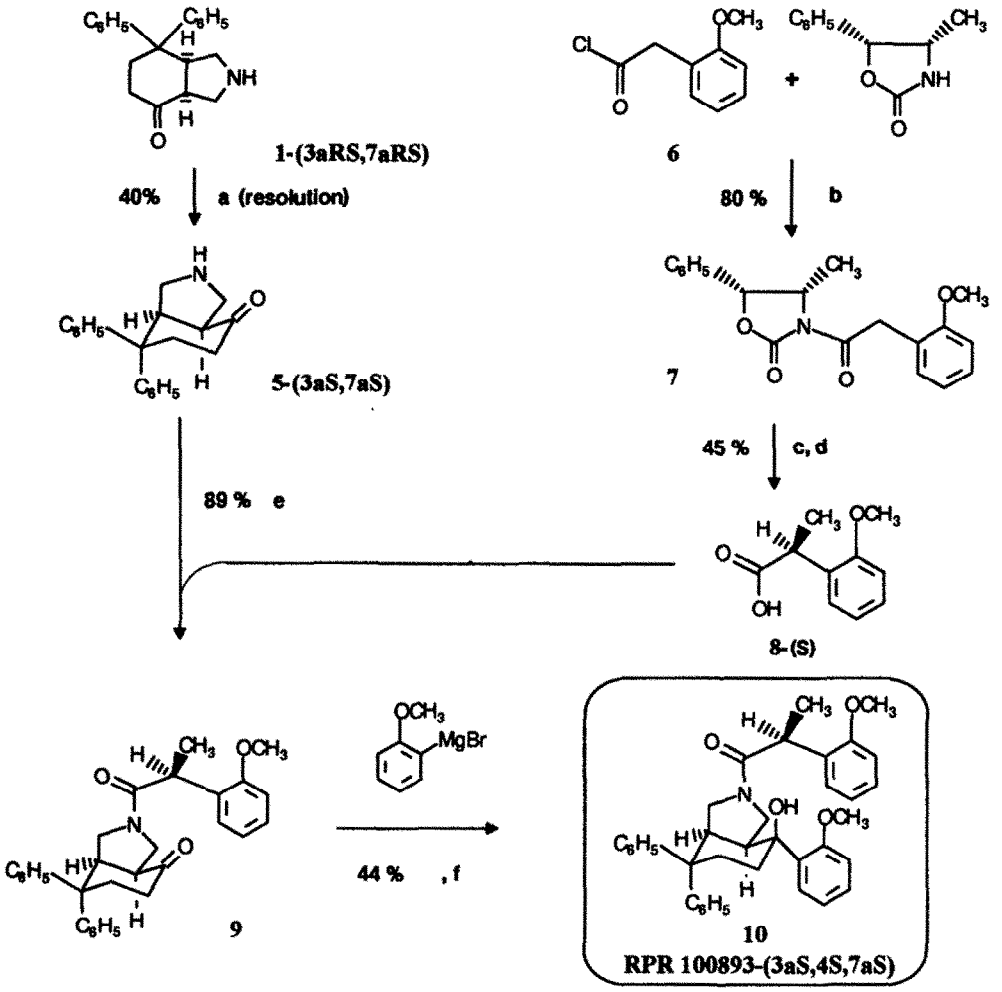
Surprisingly, the absolute configuration of the active isomers in this new series proved to be S at the two ring-junction carbons (i.e. 3aS,7aS), contrary to the previous perhydroisoisolones series where the active enantiomer was shown to possess 3aR,7aR absolute configuration at the heterobicycle ring junction, as in the case of RP 67580[6b]. Molecular modeling studies are in progress in order to understand and rationalize this observation and will be reported in due course.

One of the most interesting combinations (leading to RPR 100893) for Ar and R was when the aromatic group was orthoanisyl and the carboxylic acid was (S)-2-(2-methoxyphenyl)-propionic acid[11]. Interestingly, the Grignard reaction could be performed on the keto-amide **9** without epimerization of the chiral side chain center, yielding an alternative, convergent and efficient synthesis of RPR 100893 (scheme **2**). The racemic amino-ketone **1** was resolved in its (3aS,7aS) enantiomer **5** in 40% yield by crystallisation of its salt with (R) mandelic acid in acetonitrile/water followed by treatment with NaOH. Synthesis of the second chiral precursor (acid **8**) was performed using Evans methodology[14] : the anion of (4S,5R)-4-methyl-5-phenyl-oxazolidine-2-one was condensed on 2-methoxyphenylacetyl chloride **6** to give (4S,5R)-2-(2-methoxyphenyl-acetyl)-4-methyl-5-phenyl-oxazolidine-2-one **7** (80% yield), which was stereospecifically alkylated with methyl iodide in THF using NaHMDS as base. The chiral auxiliary was removed by treatment with LiOH in THF/water followed by acidification to give (S)-2-(2-methoxy-phenyl)-acetic acid **8** in 45% yield. Coupling of the two chiral moieties was performed by acylation of amine **5** with acid **8** in the presence of 3-ethyl-1-(3-dimethyl-aminopropyl)-carbodiimide (EDCI), diisopropylethylamine and catalytic 1-hydroxybenzotriazole (HOBT) in dry dichloromethane to give (3aS,7aS)-7,7-diphenyl-2-[(S)-2-(2-methoxy-phenyl)-propionyl]-perhydro-isoindol-4-one **9**[15] (89% yield), which was reacted with orthoanisylmagnesium bromide, in the presence of cerium chloride, in THF, to give (3aS,4S,7aS)-4-(2-methoxy-phenyl)-2-[(S)-2-(2-methoxy-phenyl)propionyl]-7,7-diphenylperhydroisoindol-4-ol **10**[16] **(RPR 100893)** in 44 % yield.

The absolute configuration of the ring system was confirmed to be (3aS,4S,7aS) by X rays analysis on RPR 100893 single crystal, considering the known (S) configuration of the amide chain[13]

Triarylperhydroisoindolols, like RPR 100893, appear as new potent, NK_1 selective non peptide SP antagonists, both in vitro and in vivo They exhibit high affinity for human NK_1 receptor with an IC_{50} value

SCHEME 2 : Synthesis of RPR 100893



Reagents (all the yields are unoptimized) : a) (R)-mandelic acid, acetonitrile/water, then NaOH 1N. b) BuLi, THF, -78°C 1h, then 25°C 1h. c) NaHMDS, THF, MeI, - 78°C 1h. d) LiOH, THF/H_2O, -5°C 3h, then HCl 1N. e) HOBT/EDCI, CH_2Cl_2, 5°C 1.5h then 25°C 24h. f) $CeCl_3$, THF, reflux 8h.

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of 13 nM for RPR 100893 in [^{3}H]-SP binding assay on human IM_9 lymphoblast cultured cell line[17]. In contrast with the results obtained with RP 67580[18] and perhydroisoindolones series, the affinity of RPR 100893 is about 100-fold weaker for the rat or mouse brain NK_1 receptors than for human NK_1 receptor. In guinea pig ileum preparation, RPR 100893 inhibits (pA_2 = 8.05) the contractile effects of septide, a SP agonist[19]. In future publications, we will report on biochemical and pharmacological studies on RPR 100893 as well as detailed biological activities and structure-activity relationships investigations in this new family.

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(15) White solid; ^{1}H-NMR (DMSO d_6, 250 MHz, mixture of the two rotamers at room temperature): 1.13 and 1.23 (2d, J=7.5, 3H, -CH_3), 1.9 to 2.3 (mt, 2H, -CH_2- in 5), 2.6 to 4.2 (mt, -CH_2- and -CH-), 3.36 and 3 86 (2s, 3H, -OCH_3), 6.7 to 7.7 (mt, 14H, aromatics).

(16) White solid, m.p. 244°C; ^{1}H-NMR (DMSO d_6, 250 MHz, mixture of the two rotamers at room temperature with partial coalescence at 423°K) : 1.2 (d, 3H, -CH_3), 1.48 to 2.35 (mt, 3H, -CH_2), 2.8 to 3.45 (mt, -CH_2- and -CH-), 3.45 (s, 3H, -OCH_3), 3.6 (vbs, 3H, -OCH_3), 6.8 to7.5 (mt, 18H, aromatics); MS/DCI: M/z=562 (MH^+)

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