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PERHYDROTHIOPYRANOPYRROLES DERIVATIVES : A NOVEL SERIES OF POTENT AND SELECTIVE NONPEPTIDE NK1 ANTAGONISTS.

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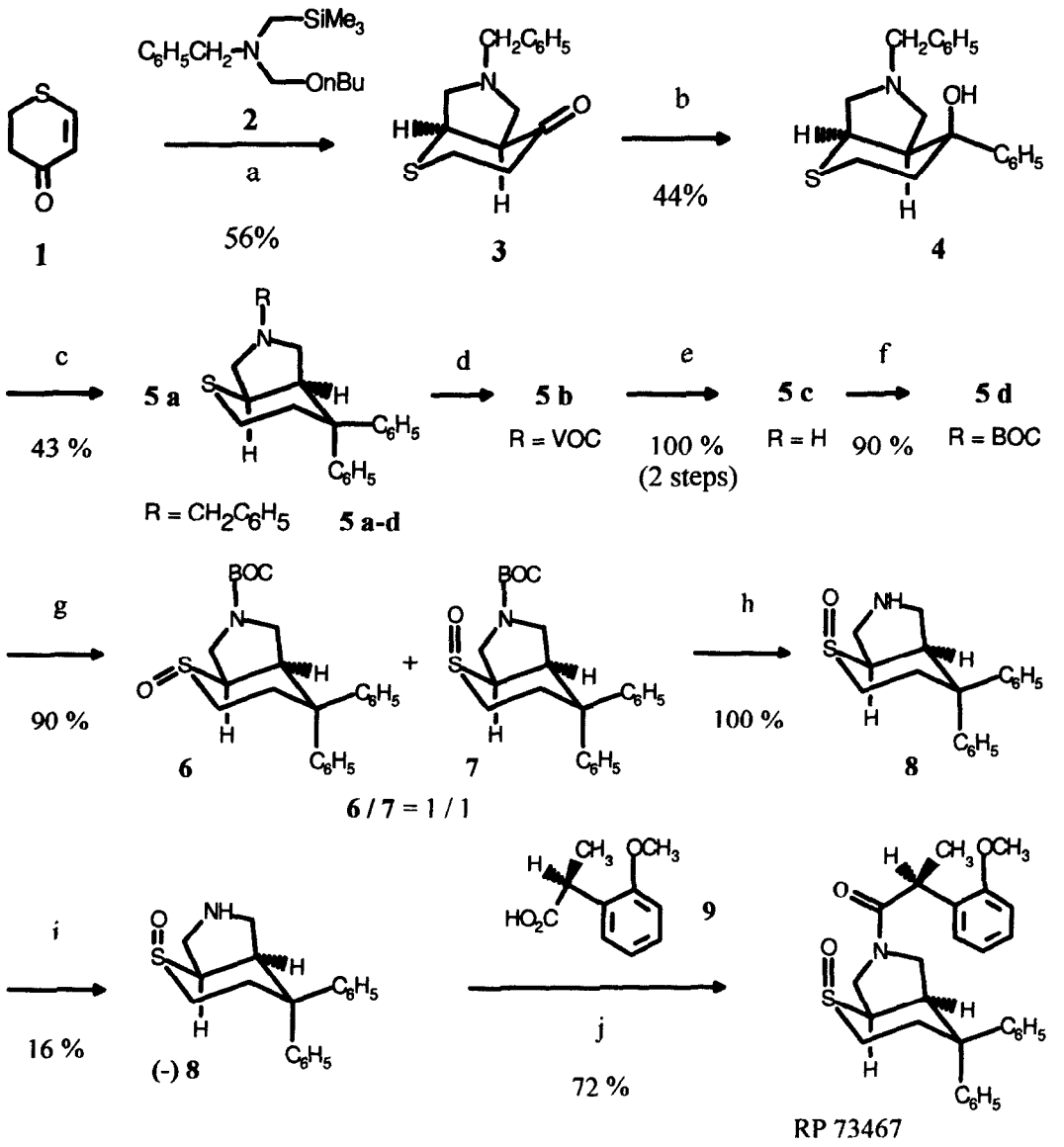
Abstract · The synthesis of RP 73467, a representative of 4,4-diphenyl perhydrothiopyrano[2,3-c]-pyrroles 1-oxides, a new series of potent and selective nonpeptide NK1 Substance P antagonists, is described.

Neuropeptide Substance P (SP) belongs to the tachykinins group, a family of related peptides sharing the common carboxy terminus Phe-X-Gly-Leu-Met-NH_2. It is widely distributed in the central and peripheral nervous system, and its role as a neurotransmitter or neuromodulator is now clearly established especially in pain transmission and associated responses [1], through its preferential interaction with the NK_1 receptor [2]. SP antagonists are expected to provide novel therapies for important diseases where SP is involved, such as pain [3], migraine [4] or asthma [5]. However, only the use of potent, selective and bioavailable antagonists can help to define the exact physiological, pharmacological and pathological role of SP. Thus, intensive research has been carried out during the last decade to discover SP antagonists. The screening strategy of non-peptide compounds using [H^3]-SP binding tests, led independently, to the discovery of CP-96,345 [6] and RP-67580 [7], the two first non-peptide antagonists of the tachykinin NK_1 receptor, which helped to enlighten the biological role of Substance P and provided a confirmed rationale of the therapeutic potential of its antagonists [8].

After our discovery of the 2-arylacetyl 7,7-diphenyl perhydroisoindolones NK_1 antagonists, and the study of main structure activity relationships, concerning amide chain and stereochemistry [9], we sought to inspect more precisely the structural requirements of this series. We recognized the importance of the carbonyl function and considered its replacement by various surrogates. This paper intends to give a first account of this research which led to the development of a novel series of nonpeptide Substance P antagonists, the 4,4-diphenyl perhydrothiopyrano[2,3-c]pyrroles 1-oxides[10].

The sulfoxide functional group being known as a bioisoster of a ketonic carbonyl [11], we decided to synthesize the sulfoxide analogues of perhydroisoindol-4-ones. This was achieved (scheme 1) by adaptation of the [3+2] azomethine ylid dipolar cycloaddition methodology[12], the essential gemdiphenyl moiety being introduced subsequently by an original geminal arylation method.

Scheme 1 : Synthesis of 4,4-diphenyl perhydrothiopyrano[2,3-c]pyrroles and 1-oxides.



Reagents and conditions : a) CH_2Cl_2, CF_3CO_2H (cat.), 20°C, 4h; b) C_6H_4MgBr, Et_2O, reflux, 3h then 25°C, 24 h; c) $ZrCl_4$ (excess), C_6H_6 reflux, 1 h; d) Vinyl chloroformate (VOC-Cl), $(CH_2Cl)_2$, reflux, 2h; e) Dry HCl, Dioxan, 25°C, 1 h then EtOH reflux and NaOH. f) BOC_2O, NEt_3, DMAP, CH_2Cl_2, 25°C, 24 h; g) mCPBA, CH_2Cl_2, 0°C, 2 h; h) Conc. HCl, Dioxan, 25°C, 1h; i) (S)-mandelic acid resolution j) Acid (S)-**9** , EDCI, HOBT, $EtN(i\text{-}Pr)_2$, CH_2Cl_2, 5°C, 2 h then 25°C, 2 h. (Unoptimized yields)

Reaction of 4-dehydrothiapyranone **1** [13], with N-methoxymethyl-N-trimethylsilylbenzylamine **2** and catalytic trifluoroacetic acid [14], gave perhydrothiopyrano[2,3-c]pyrrol-4-one **3** which was converted to the alcohol **4**[15] by treatment with phenylmagnesium bromide. The second phenyl group of the quaternary center was introduced by arylation of the benzylic carbocation derived from tertiary alcohol **4**. This Friedel-Crafts type reaction is catalyzed by zirconium tetrachloride in good yield while other Lewis acids ($AlCl_3$,$TiCl_4$) or protic acids (H_2SO_4, CF_3SO_3H) failed to give acceptable yields of the desired 6-benzyl-4,4-diphenyl perhydrothiopyrano[2,3–c]pyrrole **5a** [16]. Removal of benzyl group was effected in two steps by action of vinyl chloroformate [17] and acid alcoholysis of the intermediate vinyl carbamate. Amine **5c** was reprotected as its BOC derivative **5d** [18] then oxidized by 3-chloroperoxybenzoic acid to give a mixture of two sulfoxides **6** (equatorial) and **7** (axial) which can be chromatographically separated. However, amine deprotection of this epimeric mixture under acidic conditions led to pure axial amino-sulfoxide (±) **8** as the result of an acid catalyzed isomerisation at sulfur atom [19]. This compound could be resolved by crystallization of its salt with (S)-mandelic acid in acetonitrile/water mixtures. The levorotatory (S)-mandelate was converted to enantiomerically pure (-)-**8** [20]. Coupling (EDCI, HOBT in dichloromethane) with (S)-2-(2-methoxy-phenyl)-propionic acid **9** [10] gave (1R,4aR,7aR)-6-[2-(2-methoxy)-phenyl)propionyl-(S)] 1-oxide 4,4-diphenyl perhydrothiopyrano[2,3-c]pyrrole, RP73467 [21]. Stereochemistry at the sulfur atom and absolute configurations of the ring system were ascertained by X-ray analysis considering the known (S) configuration of the amide chain [22].

4,4-diphenyl perhydrothiopyrano[2,3-c]pyrrole 1-oxides appear as new potent, NK_1 selective, nonpeptide SP antagonists. For instance, affinity of RP73467 for rat and guinea-pig NK_1 receptors is similar to that of RP 67580 with IC_{50} values of 10 and 70 nM respectively (compared to 7 and 84 nM for RP 67580) and somewhat higher for human NK_1 receptor (IC_{50} = 23 nM vs 49 nM measured in [^{3}H]SP binding assay on human IM_9 lymphoblast cultured cell line). In guinea pig ileum preparation, RP73467 antagonizes the contractile effects of septide (SP agonist) (IC_{50} = 20 nM). In vivo, by the oral route, it inhibits PBQ induced writhing in mice (ED_{50} = 5 mg/kg/po) [23]. Activities of other members of this new promising family, together with detailed structure-activity relationship study will be reported in due course.

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(15) m.p. = 137°C; ^{1}H NMR (DMSO d_6) 1.83 (ddd, J=14, 5 and 4 Hz, 1H), 2.05 (ddd, J=14, 11.5 and 3 Hz, 1H), 2.63 (ddd, J=14, 5 and 4 Hz, 1H), 2.45 - 2 65 (m, 3H), 2.93 (ab, 2H), 3.13 (ddd, J=14, 11 5 and 3 Hz, 1H), 3.51 (m, 1H), 3.68 (s, 2H), 6.68 (bb, 1H), 7 15 - 7.55 (m, 10H).

(16) m.p. 130°C; ^{1}H NMR ($CDCl_3$) 2.20 and 3.15 (2dd, J=9.5 and 7 Hz and J=11 5 and 9 5 Hz, 2H), 2 37 (ddd, J=13, 3.5 and 3 Hz, 1H), 2 46 (td, J=13 and 2.5 Hz, 1H), 2.57 and 3.36 (bd and dd, J=12 and 6 Hz, 2H), 2.63 (bdd, J=13 and 3.5 Hz, 1H), 2.87 (dt, J=13 and 3 Hz, 1H), 3.46 (m, 1H), 3.70 and 3.80 (2d, J=12.5 Hz, 2H), 4.09 (m, 1H), 7.10 - 7.40 (m, 15H).

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(18) m.p. 162°C; ^{1}H NMR (DMSO d6, at 403°K) 1.39 (s, 9H), 2.25 - 2.85 (m, 4H), 2.61 and 3.39 (dd and t, J=11 and 8 Hz and J=11 Hz, 2H), 3.20 and 3.75 (d, and dd, J=11.5 Hz and J=11.5 and 4.5 Hz, 2H), 3.63 (m, 1H), 4.05 (t, J=4.5 Hz, 1H), 7.10 - 7.50 (mt, 10H).

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(20) m.p. 192°C; $[\alpha]_D^{20}$ = - 413° (c = 0 45, AcOH); ^{1}H NMR (DMSO d_6), δ (ppm) , J (Hz) : 2 01 and 2.66 (dd , J=10 and 9 and t, J=10, 2H), 2.12 and 2.96 (bt, J=14 and bdd, J= 14 and 4.5, 2H), 2.39 and 3.19 (bdd J=14 and bt, J=5 and J=14, 2H), 3 28 (bt, J=6 5, 1H), 3.37 and 3.45 (dd J=12 and 6.5 and bd, J=12, 2H), 3.50 (m, 1H), 7.10 - 7 45 (m, 10H).

(21) m.p. 170°C, $[\alpha]^{20}_D$ = - 316° (c = 0.50; AcOH); ^{1}H NMR (DMSO d_6, at ambient temperature, we observe a mixture of rotamers), δ (ppm) , J (Hz) 1 10 and 1.22 (2d, J=7, 3H), 2.05 - 2.25 (m, 1H), 2.30 - 2.55 (m, 1H), 2 55 - 2.75 (m, 1H), 2.85 - 4.10 (m, 7H), 3.53 and 3.87 (2s, 3H), ca 3.80 and 4 18 (m and q, J=7, 1H), 6.75 - 7.45 (m, 14H).

(22) X-ray crystallographic analysis was actually performed on the 1S,4aS,7aS isomer of RPR 73467, obtained by acylation of (+) **8** with acid (S)-**9**

(23) Biological test methods have been described in reference (7).

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