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SYNTHESIS of RP-67,580, a NEW POTENT NONPEPTIDE SUBSTANCE P ANTAGONIST

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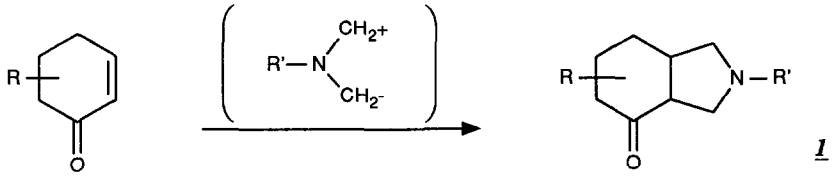
Abstract: The synthesis of enantiomerically pure RP-67,580, a novel nonpeptide Substance P receptor antagonist, is described as well as the resolution of intermediate perhydroisoindolone.

The undecapeptide Substance P (SP), belongs to a family of chemically related peptides the neurokinines (NK), sharing a common C-terminal aminoacid sequence. Widely distributed in the central and peripheral nervous system, SP is considered to function as a neurotransmitter or neuromodulator. It is involved in numerous physiological activities such as pain transmission, vasodilatation, plasmatic extravasation, smooth muscle contraction [1]. Thus, SP antagonists are highly desirable for the elucidation of its physiological and pathological functions. When we initiated a binding screen for potential NK antagonists, only peptidic antagonists of low activity and specificity were known [2]. The recent disclosure by Pfizer investigators of the aminoquinuclidine CP-96,345 [3] prompts us to present our results with another class of potent nonpeptide SP antagonists.

As part of a prospective chemistry research programme, we synthesized series of substituted or fused pyrrolidines, using azomethine ylids 1,3-dipolar cycloaddition methodology. One of the series, perhydroisoindolones **1**, was obtained by cycloaddition to cyclohexenones (scheme 1). When properly substituted,



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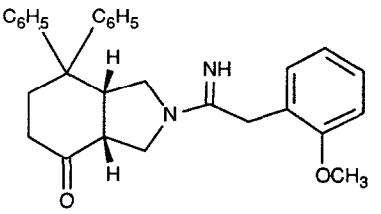
Scheme 1. : Perhydroisoindolone synthesis by 1,3-dipolar cycloaddition of azomethine ylids on cyclohexenones

these structures revealed interesting activity in [^{3}H]SP binding assays, with EC_{50} in the micromolar range. Optimization of this activity led to a new family of potent, nonpeptidic SP antagonists. RP-67,580, (-)-7,7-diphenyl-2-[1-imino-2-(2-methoxy-phenyl)-ethyl]-perhydroisoindol-4-one **2**, was selected for extensive studies in order to establish the biological properties of these compounds. It is a potent SP



(-)-2

RP-67,580

antagonist, both in vitro and in vivo and acts specifically and competitively on NK_1 receptors. In [^{3}H]SP binding assay in rat brain membranes its K_i is 4.16 nM and in guinea pig ileum preparation, RP 67,580 inhibits the contractile effects of SP ($pA_2 = 7.2$) [4].

In this paper we describe the synthesis and resolution of RP-67,580. X-ray crystallographic data relative to absolute configuration determination are reported separately [5], as well as biological and pharmacological studies [4].

RP-67,580 and its analogues were prepared according to the route shown in scheme 2 [6]. Reaction of 4,4-diphenylcyclohex-2-enone **3** [7], with N-methoxymethyl-N-trimethylsilylbenzylamine **4** [8], under the conditions reported by Achiwa (1 % CF_3CO_2H in CH_2Cl_2, 1h / 25°C) [9], gave 2-benzyl-7,7-diphenyl-2-perhydroisoindol-4-one **5** in 80 % yield [10]. Removal of benzyl group was effected by palladium catalysed hydrogenolysis (1 atm., 10 % Pd/C, in ethanol in the presence of hydrochloric acid) yielding 7,7-diphenyl-2-perhydroisoindol-4-one as its hydrochloride (±)-**6** [11]. The aminoketone could be resolved by crystallization of its salt with (S)-mandelic acid. Crude mixture of diastereoisomeric salts (obtained from equimolar amounts of components in EtOAc) was boiled in water and the insoluble salt filtered and recrystallized from acetonitrile/water mixture (2/1) to give levorotatory (S)-mandelate (-)-**7** ($[\alpha]_D^{20}$ = - 164°, c = 1, MeOH). This salt was converted to enantiomerically pure (-)-**6**, which was shown to possess 3aR,7aR absolute configuration [12].

Amine (-)-**6** was acylated with (2-methoxy-phenyl)acetic acid in the presence of N,N-carbonyl-diimidazole and triethylamine to give amide **9** in 66 % yield [13]. Treatment of **9** with triethyloxonium tetrafluoroborate in dichloromethane led to crude alkoxyimmonium **10** which was converted to amidine RP 67,580 by action of ammonia in ethanol (20.7 % yield from **9**) [14]. Alternatively, when reacted with ethyl (2-methoxy-phenyl)acetimidate tetrafluoroborate (obtained from (2-methoxy-phenyl)acetamide by treatment with triethyloxonium tetrafluoroborate in dichloromethane), (-)-**6** gave RP-67,580 in one step and with improved yield (53 %).

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Reference and notes:

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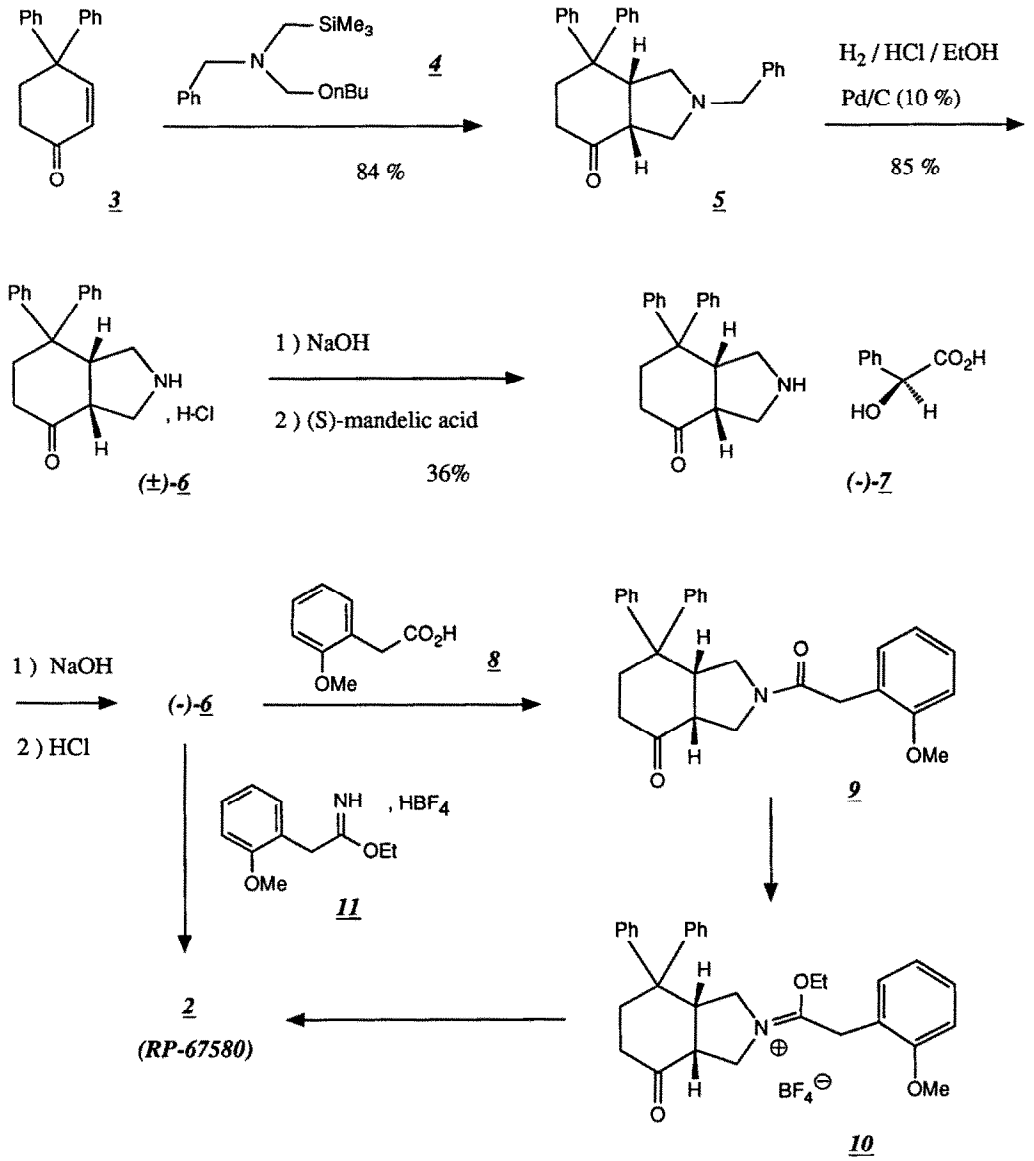
Scheme 2 : Synthesis of RP-67,580



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10. m.p. 132°C; ^{1}H-NMR ($CDCl_3$, 250 MHz): 1.95 (ddd, J=18, 13 and 6, 1H, H-5$_{ax}$), 2.30 (m, 2H, CH_2-3), 2.45 (ddd, J=18, 6 and 2.5, 1H, H-5$_{eq}$), 2,55 (dddd, J=13, 6, 2.5 and 2.5, 1H, H-6$_{eq}$), 2.75 (dd, J=9 and 6, 1H, H-1), 2.90 (ddd, J=13, 13 and 6, 1H, H-6$_{ax}$), 3.0 (dd, J=9 and 7, 1H, H-1), 3.20 (bddd, J=9, 9 and 9, 1H, H-7a), 3.45 and 3.65 (2d, J=13, 2x1H, CH_2Ph), 3.7 (bddd, J=9, 9 and 9, 1H, H-3a), 7.2-7.45 (m, 15H, 3 Ph).

11. m.p.= 270°C with decomposition; ^{1}H-NMR (DMSO-d_6, 250 MHz): 2.05 (bddd, J=15, 13 and 5, 1H, H-5$_{ax}$), 2.30 (bddd, J=15, 2.5 and 2.5, 1H, H-5$_{eq}$), 2.45 (dd, J=12 and 7, 1H, H-1), 2,7 (dd, J=12 and 12, 1H, H-1), 2.8 (bm, 2H, CH_2-6), 3.5 (bdd, J=7 and 7, 1H, H-3a), 3.35 (bdd, J=11 and 7, 1H, H-3), 3.8 (bd, J=11, 1H, H-3), 3.95 (bm, 1H, H-7a), 7.10-7.60 (m, 10H, 2 Ph), 9.45 (bs, 2H, $NH_2^{+)}$.

12. X-Ray analysis was performed on a single crystal of dextrorotatory (R)-mandelate (enantiomer of (-)-**7**). Considering the configuration of the chiral acid, 3aS,7aS absolute configuration was established. (see ref. (5)). This salt was converted to (+)-**6**, then to the inactive 3aS,7aS enantiomer of RP-67,580.

13. m.p. = 200°C; $[\alpha]_D^{20}$ = - 274° (c=0,49 , AcOH); ^{1}H-NMR (DMSO-d_6, 250 MHz, 423°K): 2.14 (td, J=14 and 5, 1H, H-5$_{ax}$), 2.30 (dt, J=14 and 3, 1H, H-5$_{eq}$), 2.65-3.1 (m, 4H, CH_2-1 and CH_2-6), 3.3 (m, 1H, H-3a), 3.45 (m, 3H, H-3 and >NCOCH_2Ar), 3.74 (s, 3H, OCH_3), 3.98 (mt, 1H, H-7a), 4.27 (d, J=10, 1H, H-3), 6.8-7.7 (m, 14H, 2 Ph + Ar).

14. m.p. = 191°C; $[\alpha]_D^{20}$ = - 255° (c=1 , MeOH); ^{1}H-NMR (DMSO-d_6, 250 MHz, 383°K): 2.10 (ddd, J=15, 13 and 5, 1H, H-5$_{ax}$), 2.30 (ddd, J=15 2.5 and 2.5, 1H, H-5$_{eq}$), 2.6-3.1 (m, 4H, CH_2-1 and CH_2-6), 3.3 (bdd, J=6.5 and 6, 1H, H-3a), 3.40 (dd, J=10 and 6.5, 1H, H-3), 3.45 (s, 2H, >NCOCH_2Ar), 3.75 (s, 3H, OCH_3), 4.0 (mt, 1H, H-7a), 4.15 (d, J=10, 1H, H-3), 6.9-7.6 (m, 14H, 2 Ph + Ar), 13 (vbs, 1H, NH). IR (KBr): 3320, 3080, 3040, 3020, 2960, 2920, 2835, 1725, 1590, 1490, 1250, 1030, 755, 705.