Pergamon

*Tetrahedron Letters*, Vol. 37, No. 18, pp. 3125-3128, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00519-9

# Enantiospecific Synthesis of RPR 107880 : A New Non Peptide Substance P Antagonist

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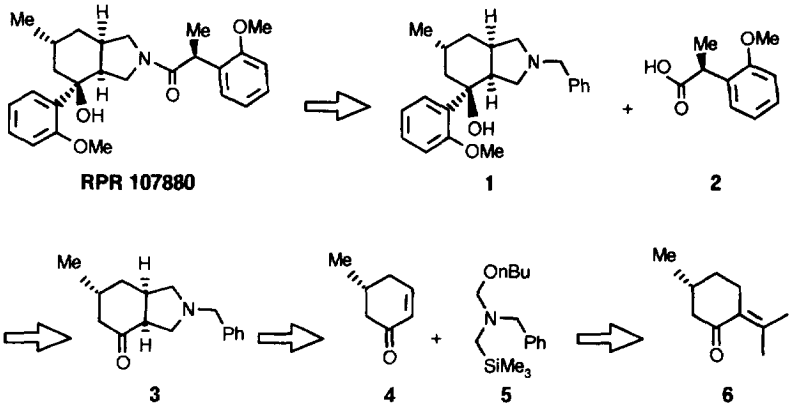
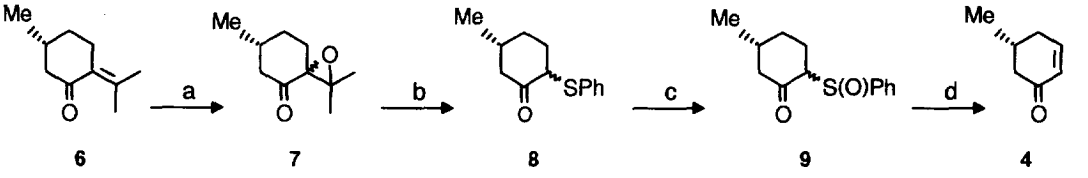
**Abstract** : The synthesis of enantiomerically pure RPR 107880 is described. The synthetic strategy is based on the use of the readily available and inexpensive (R)-(+)-pulegone. Copyright © 1996 Elsevier Science Ltd

As part of an on-going program aimed at the development of a novel non peptide NK1 Substance P antagonist[1], we have devised an efficient large scale synthesis of (3aS,4S,6R,7aR)-4-(2-methoxy-phenyl)-2-[(2)-2-(2-methoxy-phenyl)propionyl]-6-methyl perhydroisoindol-4-ol (**RPR 107880**)[2] according to retrosynthetic plan illustrated in scheme I. Optically pure (R)-5-methylcyclohex-2-en-1-one **4**, the key intermediate in our approach, was prepared from (R)-Pulegone **6**[3] (scheme II) by slight modification of the procedure reported by Caine et al.[3b] in order to meet with safety and process standards. Thus commercially available (R)-pulegone was converted to a diastereomeric mixture[4] (trans/cis = 66/34) of ketoepoxides **7**[5], in 94%[4] yield by reaction with 30 % hydrogen peroxide in aqueous lithium hydroxide. In order to avoid degradation of pulegone under basic conditions, lithium hydroxide was used instead of sodium hydroxide and added as an aqueous solution to the mixture of **6** and hydrogen peroxide in methanol. The use of different oxidizing agents, such as $ZnEt_2$-$O_2$[6] or m-CPBA did not improve the diastereoselectivity of this reaction. Preparation of ketoepoxides **7** from **6** via the corresponding bromohydrins, using NBS, gave the reverse diastereoselectivity (trans/cis = 20/80). The crude ketoepoxides **7** were then converted to a diatereoisomeric mixture[8] (trans/cis = 40/60) of ketosulfides **8**, by reaction with sodium thiophenoxide in MTBE at reflux for 5 h (73% yield)[8]. It is noteworthy that complete reaction was not achieved. This is due to the fact that cis-ketoepoxide **7** was less reactive than its trans-isomer when treated with sodium thiophenoxide. The crude ketosulfides **8** were converted quantitatively to the sulfoxides **9** by oxidation with sodium perborate[9] in acetic acid at 40°C (instead of m-CPBA[3a]). Under these conditions, competing sulfone formation was not observed. Thermal elimination of phenylsulfinic acid[10] from the crude sulfoxides **9** was accomplished in absence of solvent ($CCl_4$[3] was removed for industrial hygiene) and provided isomerically and optically pure (R)-5-methylcyclohex-2-en-1-one **4** in 52% yield from **8**. Enone **4** was trapped by contineous distillation during the reaction. RPR 107880 was then prepared according to the route shown in scheme III. The [3+2] azomethine ylid dipolar cycloaddition with N-(butoxymethyl)-N-(trimethylsilylmethyl)benzylamine **5**[12] and cyclohexenone **4**, under conditions reported by Achiwa et al. [13] afforded perhydroisoindolone **3** as a diastereomeric mixture[8]

**Scheme I** : Retrosynthetic analysis of RPR 107880




**Scheme II** : Synthesis of (R)-5-methylcyclohex-2-en-1-one 4



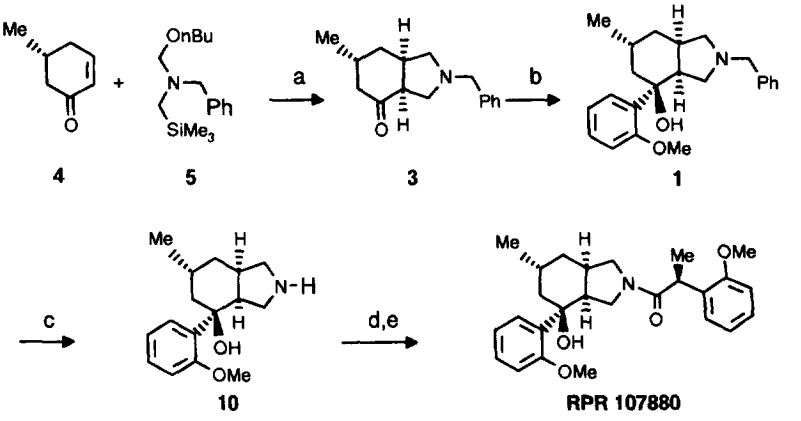

**Reagents** : (a) 30% aq. $H_2O_2$ ; aq. LiOH ; MeOH ; 30°C (b) PhSH, tAmONa, MTBE ; reflux
(c) $NaBO_3$, AcOH, 40°C (d) $CaCO_3$ cat., 80°C.

(trans/cis = 90/10) in 70% overall yield. Attempts to improve the diastereoselectivity of this reaction, using chiral azomethine ylids derived from(α)-methylbenzylamine[14]failed. Since the trans-isomer **3** could only be purified by silica gel chromatography, the decision was taken to react the crude product with o-anisyllithium[15], in presence of LiBr[16] in THF at -78°C. The reaction was completely diastereoselective producing the alcohol **1** from exclusive equatorial attack of the carbonyl, i.e; from the less hindered side of the heterobicycle. After crystallization, perhydroisoindolol **1**[17] was isolated diastereoisomerically and enantiomerically pure in 68% yield. Removal of the benzyl group was accomplished by palladium catalysed hydrogenolysis, yielding amine **10** quantitatively. Coupling of the two chiral moieties was achieved by reaction of **10** with the acylchloride derived from (S)-2-(2-methoxyphenyl) propanoic acid[18], in presence of sodium carbonate and catalytic Aliquat 336®, in a mixture of toluene and water. This gave RPR 107880 in 93% yield. It is noteworthy that no epimerization at the chiral side chain center was observed during this coupling. RPR 107880[19] was finally recrystallized from ethanol-$H_2O$, in 96% yield.

In conclusion, a very efficient enantioselective synthesis of RPR 107880 (13,6% overall yield, 8 steps) has been developed. This route was conveniently amenable to a pilot scale synthesis.

**Acknowledgements** : We thank M. Vuilhorgne and his collaborators for spectroscopic analysis, M. Descarpentry for HPLC and GC analysis and S. Grisoni for fruitfull discussions.

**Scheme III** : RPR 107880 synthesis by 1,3-dipolar cycloaddition




**Reagents** : a/ Cat. $CF_3CO_2H$, toluene, 35°C b/ o-Anisyllithium, LiBr, THF, - 78°C c/ Ammonium formate, Pd.C (10%), EtOH, 40°C. d/ (S)-2-(2-methoxy-phenyl) propanoic acid, $SOCl_2$, Toluene, cat. DMF, e/ $Na_2CO_3$, cat. Aliquat 336®, Toluene-$H_2O$.

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(15) o-Anisyllithium was prepared by orthometallation of anisole by nBuli in THF at O°C.

(16) LiBr salts were added to reduce enolization and to improve chemical yield.

(17) White solid, m.p. 102-104°C; $[\alpha]_D$ = -51.7 (c = 0.5, EtOH); $^1$H-NMR (300 MHz, DMSO $d_6$ with a few drops of $CD_3CO_2D$, at a temperature of 300 K, $\delta_H$ in ppm): 0.88 (3H, d, J=6Hz, $CH_3$), 1.30 and 1.75 (1H each, respectively m and d, J=16Hz, $CH_2$), 1.58 and 2.17 (each 1H, respectively d and t, J=12Hz, $CH_2$), 2.65 (1H, m, CH), 2.82 and 3.08 (each 1H, respectively d and dd, J=8 and 5Hz, $CH_2CN$), 2.93 (1H, t, J=5Hz, CH), 3.17 and 3.45 (each 1H , respectively d and t, J=8 and 5Hz, $NCH_2$), 3.80 (3H, s, $OCH_3$), 4.30 (2H, m, $NCH_2Ph$), 6.95 (2H, m, aromatic H), 7.23 (1H, t, J=7Hz, aromatic H), 7.35 to 7.55 (5H, m, aromatic H), 7.62 (1H, d, J=7Hz, aromatic H); calculated for $C_{23}H_{29}NO_2$ : C78.6, H8.32, N3.98, O9.1, found : C78.3, H8.7, N4.1, O8.9.

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(19) White solid, m.p. 178-180°C; $[\alpha]_D$ = +89.5 (c = 0.5, $CHCl_3$); $^1$H-NMR (250 MHz, DMSO $d_6$ with a few drops of $CD_3CO_2D$, at a temperature of 383 K, $\delta_H$ in ppm): 0.9 (3H, d, J=6.5Hz, $CH_3$), 1.25 (3H, d, J=7Hz, $CH_3$),1.25 to 2.25 (5H, m, CH and 2 $CH_2$), 2.45 (1H, m, CH), 2.77 (1H, t, J=6Hz, CH), 3,00 to 3,75 (4H, m, 2 $CH_2CN$ ), 3.80 (6H, s, $OCH_3$), 4.10 (1H, m, COCH), 6,80 to 7,70 (8H, m, aromatic H); calculated for $C_{26}H_{33}NO_4$ : C73.73, H7.85, N3.31, O15.11, found : 73.66, H8.11, N3.45, O14.71.

(*Received in France* 16 *January* 1996; *accepted* 14 *March* 1996)