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Expedient Enantiospecific Synthesis of RP 73613 : A New Selective Non-Peptide NK1 Antagonist

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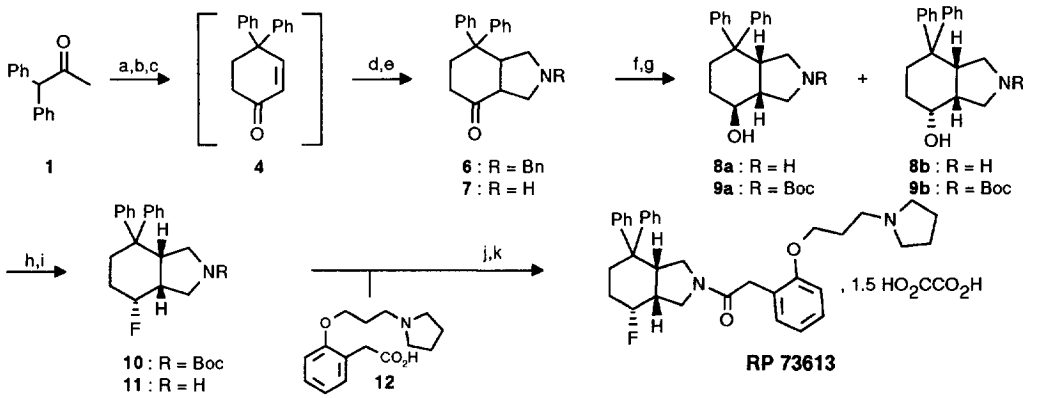
Abstract : The synthesis of RP 73613 was achieved in 13 steps with an overall yield of 12%. The strategy was based on a [3+2] azomethine ylid dipolar cycloaddition to generate the bicyclic framework and the asymmetry was introduced by resolution. Copyright © 1996 Elsevier Science Ltd

During the course of process research aimed at the development of novel non-peptide substance P antagonists[1], an efficient large scale synthesis of **RP 73613**[2] has been devised, according to synthetic plan depicted in scheme I. Optically pure amino-alcohol **8a**, the key intermediate in our approach, was prepared from 1,1-diphenylacetone **1**. 6,6-Diphenyl-1,3-cyclohexanedione **2**[3] was readily prepared as a single enolic form, through a tandem Michael-Claisen reaction of ethyl acrylate and **1**. Diketone **2** was easily purified by a simple extraction in water, as its potassium salt, then isolated in 98% yield after precipitation by addition of concentrated HCl. Enone **4** was obtained by treatment of the enol-ether **3** (non isolated intermediate) with Red-Al® followed by acidic work-up. So, **4** was obtained as a toluene solution in a very good chemical purity and yield[4] (80% from **2**).The [3+2] azomethine ylid dipolar cycloaddition with N-(butoxymethyl)-N-(trimethylsilyl methyl)benzyl amine **5** and **4**, under conditions reported by Achiwa et al.[5] afforded perhydroisoindolone **6**[6], which crystallized in the reaction mixture, in 70% yield. Removal of the benzyl group was accomplished by palladium catalyzed hydrogenolysis. Then resolution[6] of the racemic amine was readily performed using (S)-mandelic acid in n-butanol. Amino-ketone **7** was obtained with a very good chemical yield (37% from **6**) and enantiomeric purity[7] (> 99%). **7** was quantitatively converted to a diastereoisomeric mixture of alcohols **8** (**8a/8b**:85/15)[4], by reaction with $NaBH_4$. Then N-BOC-protection reaction was concatenated to afford alcohols **9**, as a mixture of two diastereoisomers (**9a/9b**:85/15)[4], in 98% yield after precipitation (2 steps). All our attempts to improve the diastereoselectivity of this reduction were not avail. Initial conversion of alcohol **9a** was achieved by a two-step procedure via its O-triflate on reaction with Bu_4NF in acetone into its corresponding fluoride **10**. Due to the difficulty in handling triflic anhydride on large scale and to the relative instability of O-triflate derivative, new conditions to perform this transformation by a one pot procedure have been devised[8]. Thus, **10** was readily prepared by reaction of alcohol **9a** with n-perfluorobutanesulfonyl fluoride in presence of diethylamine in THF, via its O-nonaflate. It is noteworthy that under these conditions, alcohol **9b** did not react. So a mixture of fluoride **10** and **9b** was obtained, **10** was easily purified by a simple crystallization and isolated in a very good purity and in 90% yield (from **9b**). This reaction can also be performed efficiently using n-perfluorooctanesulfonyl fluoride (70% yield) or trifluoromethanesulfonyl fluoride (90% yield). The N-BOC- deprotection of **10**, in a mixture iso-propanol and concentrated HCl, afforded

Scheme I : Synthesis of RP73613



Reagents : *(a) 1/ Ethyl acrylate, MTBE, tBuOK, 20°C 2/ H_2O 3/ conc. HCl (b) s-BuOH,cat.PTSA, toluene, Dean-Stark (c) 1/ Red-Al, toluene, 0 to 20°C 2/ aq. HCl (d) N-(butoxymethyl)-N-(trimethylsilylmethyl)benzylamine 5, cat. CF_3CO_2H, toluene, 35°C (e) 1/ H_2, Pd.C (5%), n-BuOH-AcOH, 20°C 2/ aq. NaOH 3/ (S)-mandelic acid (f) $NaBH_4$, MeOH, cat. aq. NaOH, -20°C (g) 1/ BOC_2O, MeOH 2/ H_2O. (h) 1/ n-$C_4F_9SO_2F$, diethylamine, THF, 20°C 2/ iPrOH-H_2O (crystallization).(i) iPrOH, conc. HCl, 60°C (j) 1/ Acid* **2**, *$SOCl_2$, CH_2Cl_2 2/ CH_2Cl_2-H_2O, KOH, cat. Aliquat 336 (k) oxalic acid, DME-THF*

amine **11** which crystallized in the reaction mixture, in 90% yield. Acid **12** was readily prepared in 55% yield (3 steps) from (2-hydroxyphenyl) acetic acid. Final coupling was achieved by reaction of **11** with the acylchloride derived from **12**. RP 73613[9] was then purified and isolated by salification with oxalic acid, in 90% yield.

In conclusion, a process has been developed and successfully implemented to prepare multi-kilogram quantities of RP 73613. The overall yield from 1,1-diphenyl acetone is 12% (13 steps).

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(7) The enantiomeric purity was determined by HPLC using a chiral phase. This work has been performed by G. Ducrotoy.
(8) Concurrently, combination of n-perfluorobutanesulfonyl fluoride and DBU has been shown to be efficient to convert alcohols into their corresponding fluorides : Bennua-Skalmowski, B.; Vorbrüggen, H. *Tetrahedron Lett.* **1995**, *36*, 2611-2614.
(9) White solid; ^{1}H-NMR (300 MHz, DMSO d_6 with a few drops of CD_3CO_2D, at a temperature of 383 K, δ_H in ppm): 1.3 (1H, dt, J=45 and 12Hz, CFCH), 1.9 to 2.25 (7H, m, 3 CH_2 and CFCH),2.3 (1H, d, J=14Hz, HCH), 2.5 to 4.2 (17H, m), 4.82 (1H, dd, J=51 and 9Hz, FCH), 6.8 to 7.4 (14H, m, aromatic H); calc. for $C_{35}H_{41}FN_2O_4$, 1.5 $C_2H_2O_4$: C67.47, H6.51, N4.14, F2.81 found : C67.11, H6.67, N4.17, F2.78.

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