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Practical Enantiospecific Synthesis of RPR 111905 : A Novel Non-Peptide Substance P Antagonist

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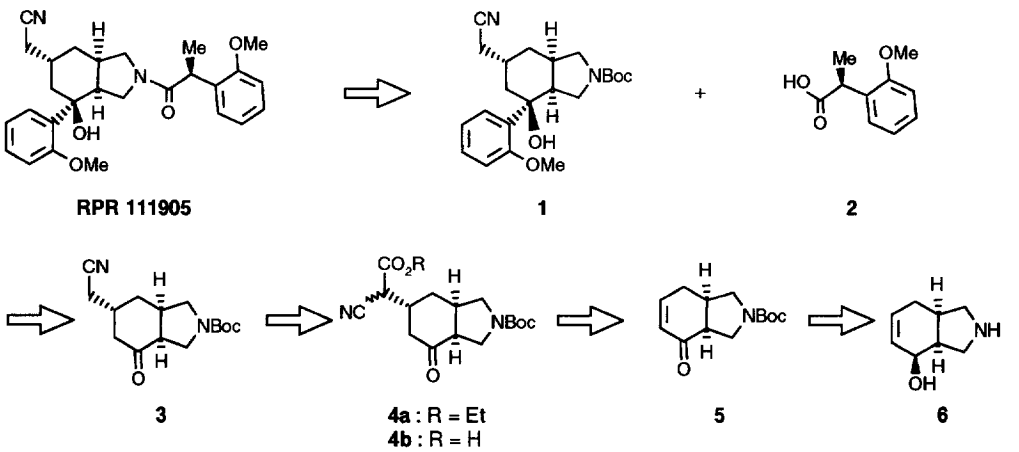
Abstract : The synthesis of enantiomerically pure RPR 111905 was achieved in twelve steps with an overall yield of 6.9%. The synthetic strategy was based on a Diels-Alder reaction to generate the bicyclic framework and the asymmetry was introduced by resolution.

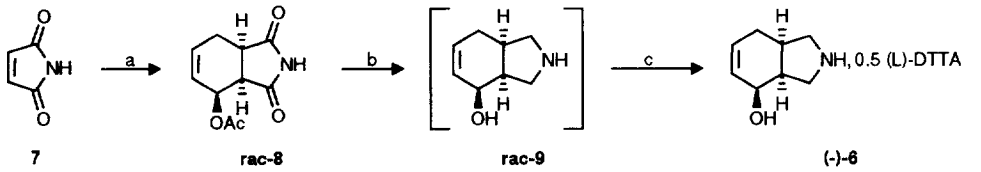
During the course of process research on the synthesis of a new non-peptide NK1 Substance P antagonist[1], an efficient route for production of kilogram quantities of (3aS,4S,6R,7aR)-6-cyanomethyl-4-(2-methoxyphenyl)-2-[2-(2-methoxyphenyl)-(S)-propionyl]-perhydroisoindol-4-ol (**RPR 111905**)[2] had to be implemented. The retrosynthetic analysis of RPR 111905, based on amino-alcohol **6** (or a suitable protected equivalent) as the key intermediate is outlined in scheme I.

Scheme I : Retrosynthetic analysis of RPR 111905



The optically pure amino-alcohol **6**, the key intermediate in our approach, was prepared from maleimide **7** (scheme II). Since 1-acetoxy-1,3-butadiene **10** is not commercially available in bulk quantity and as it is well known that only the E isomer[3] reacts in the Diels-Alder reaction, we have investigated its synthesis. The diene **10** was prepared by slight modification of procedure reported by Mc Donald et al.[4] This way, diene **10** was obtained in 58% yield[5] from crotonaldehyde in isopropenylacetate at 80°C (96:4 E:Z ratio)[5], without

Scheme II : Synthesis of enantiomerically pure amino-alcohol **(-)-6**

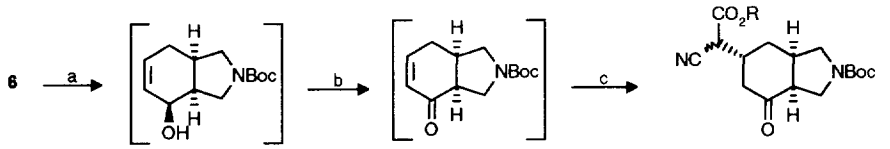


7 rac-8 rac-9 (-)-6

Reagents : (a) 1-Acetoxy-1,3-butadiene **10**, toluene, 80°C (b) $LiAlH_4$, THF, 40°C (c) 1/ Di-p-toluyl-L-tartaric acid ((L)-DTTA), THF 2/ EtOH-H_2O, recristallization.

copper acetate catalysis.Since distillation of **10** was risky and hazardous (exothermic degradations of reaction mixtures have been observed), the decision was taken to bring the crude product to react with maleimide **7**, in toluene at 80°C. The reaction was completely diastereoselective producing exclusively the racemic endo-cycloadduct **rac-8**, which crystallized in the reaction mixture in 84% yield. It is noteworthy that this reaction can be successfully achieved in water (instead of toluene) using a purified diene **10** (85% yield). The amino-alcohol **rac-9** was prepared by reduction of **rac-8** with $LiAlH_4$ in THF at 40°C. **rac-9** was purified and isolated by salification with di-p-toluyl-L-tartaric acid in THF, in 61% yield. A simple recrystallization of the previous salt[6] in a mixture of ethanol and water afforded product **(-)-6** in high yield[6] (45.5%) and in good enantiomeric purity[7] (94%). The N-Boc-protection was achieved in a mixture of toluene and aqueous NaOH at 40°C (scheme III).

Scheme III : Synthesis of acid **4b**



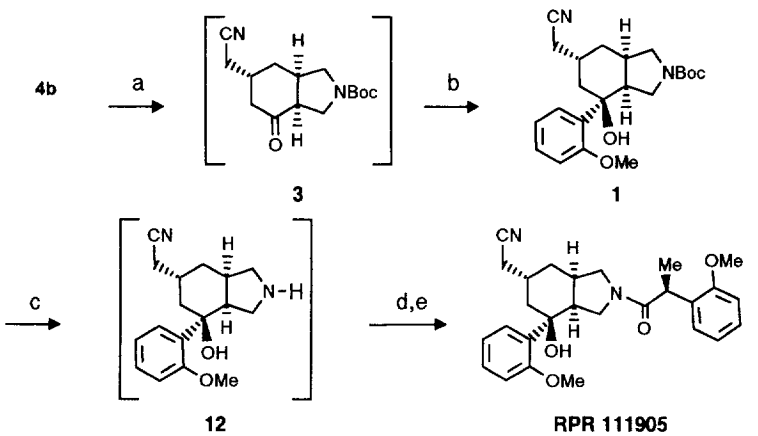
11 5 **4a** : R = Et **4b** : R = H

Reagents : (a) 1/ EtOAc, aq. NaOH 2/ $(Boc)_2O$, toluene, aq. NaOH, 40°C (b) 1/ MiBK, cat. $Al(OiPr)_3$, toluene, 55°C 2/ Aq. Seignette salt (c) Ethyl cyanoacetate **or** cyanoacetic acid , toluene, aq. NaOH, cat. Aliquat 336.

The N-Boc-protected amino-alcohol **11** was obtained in toluene, in 96% yield. This solution was dried by azeotropic distillation, then enone **5** was prepared via an Oppenauer oxidation[8], with methylisobutylketone and a catalytic amount of aluminium isopropoxide in toluene at 55°C. Treatment of the resulting solution with aqueous Seignette salt[8a] was very efficient to keep the aluminium ions in solution. Enone **5** was isolated as a toluene solution in a very good chemical purity and yield[9] (89%). In a first step, **5** was brought to react with ethyl cyanoacetate under phase transfer catalysis (PTC) conditions. The Michael addition was shown to be completely diastereoselective, producing the adduct **4a** from exclusive conjugate addition by the less hindered side of the heterobicycle. After crystallization in *tert*-butyl methyl ether (TBME), compound **4a** was isolated diastereomerically and enantiomerically pure in 60% yield. All our attempts to accomplish direct decarboxylation of **4a** to generate ketone **3** were unsuccessful : degradation and retro-Michael addition

were essentially observed. These problems were overcome using acid **4b**, prepared by mild saponification of ester **4a**. We then decided to focus our efforts to prepare directly **4b** from ketone **5**. Therefore, preparation of acid **4b** was performed by diastereospecific conjugate addition of cyanoacetic acid to enone **5**, under PTC conditions. After crystallization in TBME, adduct **4b** was isolated diastereomerically and enantiomerically pure in 71% yield. Efficient decarboxylation of **4b** (scheme IV) was cleanly performed in acetonitrile at reflux, in presence of a catalytic amount of copper oxide.[10]

Scheme IV : Synthesis of RPR 111905



Reagents : (a) Cat. Cu_2O, acetonitrile, reflux (b) o-Anisylmagnesium bromide, toluene, 0°C (c) HCl-THF 4.4N, 20°C. (d)(S)-2-(2-methoxy-phenyl) propanoic acid **2**, $SOCl_2$, toluene, cat. DMF, (e) EtOAc, toluene-H_2O, K_2CO_3, cat. Aliquat 336.

Intermediate **3** was isolated as a toluene solution in 96% yield.[9] Ketone **3** was reacted with o-anisylmagnesium bromide[11] in toluene at 0°C. The reaction was completely diastereoselective producing alcohol **1** from exclusive attack of the carbonyl, i.e; from the less hindered side of the heterobicycle. After crystallization, perhydroisoindolol **1** was isolated in 68% yield. Removal of the Boc-protecting group was accomplished using a 4.4 M solution of HCl in THF, without jeopardizing the sensitive tertiary alcohol, yielding amino-alcohol **12** quantitatively. Coupling of the two chiral moieties was achieved by reaction of **2** with the acylchloride derived from (S)-2-(2-methoxyphenyl) propanoic acid[12], in presence of potassium carbonate and catalytic Aliquat 336®, in a mixture of toluene, EtOAc and water. This gave RPR 111905 as its EtOAc solvate in 85% yield. It is noteworthy that no epimerization at the chiral side chain center was observed during this coupling. RPR 111905[13] was finally recrystallized from acetone, in 89% yield.

In conclusion, a process has been developed and demonstrated to be suitable for multi-kilogram quantities of RPR 111905. The overall yield from maleimide is 6.9% (12 steps).

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References and notes :

(1) a/ Mutti, S.; Daubié, C.; Decalogne, F.; Fournier, R.; Rossi, P. *Tetrahedron Lett.* **1996**, *37*, 3125-3128.
b/ Daubié, C.; Mutti, S. *Tetrahedron Lett.* Submitted for publication.
c/ Tabart, M.; Peyronel, J.F. *Bioorga. Med. Chem. Lett.* **1994**, *4*, 673-676.
(2) Achard, D.; Peyronel, J.F.; Tabart, M. Rhône-Poulenc Rorer Patent FR 94 14345.
(3) Mayer, S.C.; Pfizenmayer, A.J.; Cordova, R.; Li, W.R.; Joullié, M.M. *Tetrahedron : Asymmetry* **1994**, *5*, 519-522.
(4) McDonald, E. ; Suksamrarn, A.; Wilye, R.M. *J. Chem. Soc.Perkin Trans I* **1979**, 1893-1900.
(5) The chemical yield and E : Z ratio were determined by GC analysis using an external standard.
(6) This salt exists as a monohydrate and is a hemi-salt.
(7) The enantiomeric purity was determined by HPLC using a chiral phase, after N-Boc-derivatisation. This work has been performed by M. Descarpentry (Rhône-Poulenc Rorer).
(8) a/ *Org. Syntheses Coll. Vol 4*, **1956**, 192-195. b/ *Org. Syntheses Coll. Vol 3*, **1955**, 207-209.
(9) The chemical yield was determined by HPLC analysis using an external standard.
(10) Toussaint, O. *Thèse de l'Université Paris VI*, 26 Juin 1986.
(11) o-Anisylmagnesium bromide was purchased from Chemetall GMBH as a 20% w/w solution in THF.
(12) Mutti, S.; Daubié, C.; Decalogne, F.; Fournier, R.; Montuori, O.; Rossi, P. *Synth. Comm.***1996**, *26*, 2349-2354.
(13) White solid, melting range 85-131°C; $[\alpha]_D$ = +77.6 (c = 5, CH_2Cl_2); ^{1}H-NMR (400 MHz, DMSO d_6, at a temperature of 423 K, δ_H in ppm): 1.25 (3H, d, J=6Hz, CH_3), 1.50 and 1.90 (1H each, respectively m and d, J=16Hz, CH_2), 1.70 and 2.25 (1H each, respectively m and t, J=12Hz, and dd, J=4 and 16Hz, CH_2), 2.40 (2H, s, CH_2CN), 2.50 (1H, m, CH), 3,00 to 3,75 (7H, m broad, 2 NCH_2 and 3 CH), 3.80 (6H, s, OCH_3), 4.3 (1H, m, CH), 6.95 and 7,25 (8H, m, 8 aromatic H); calc. for $C_{27}H_{32}N_2O_4$: C72.30, H7.19, N6.25, found : 71.98, H7.21, N6.19.

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