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A RELIABLE AND EFFICIENT SYNTHESIS OF SR 142801

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Abstract: A convenient synthesis of the potent human NK-3 receptor antagonist SR 142801, (S)-(+)-N-{{3-[1-benzoyl-3-(3,4-dichlorophenyl)piperidin-3-yl]prop-1-yl}-4-phenylpiperidin-4-yl}-N-methylacetamide [(S)-(+)-(**15**)], is described. Improvements over the previously reported procedure are the preparation of the intermediate **5** *via* the novel imide **3** and subsequent reaction with the nucleophile **14**, which reacts, regioselectively, at the endocyclic nitrogen.

The tachykinins are a family of small peptides, released from sensory nerves, sharing the common carboxy-terminal region Phe-X-Gly-Leu-MetNH_2 and supposed to be implicated in a wide range of pathophysiological conditions.[1] Tachykinin actions are mediated by, at least, three distinct G-protein coupled receptors,[2] named neurokinin-1 (NK-1), neurokinin-2 (NK-2) and neurokinin-3 (NK-3), preferentially bound by the endogenous mammalian tachykinins substance P (SP), neurokinin A (NKA) and neurokinin B (NKB), respectively.[2,3]

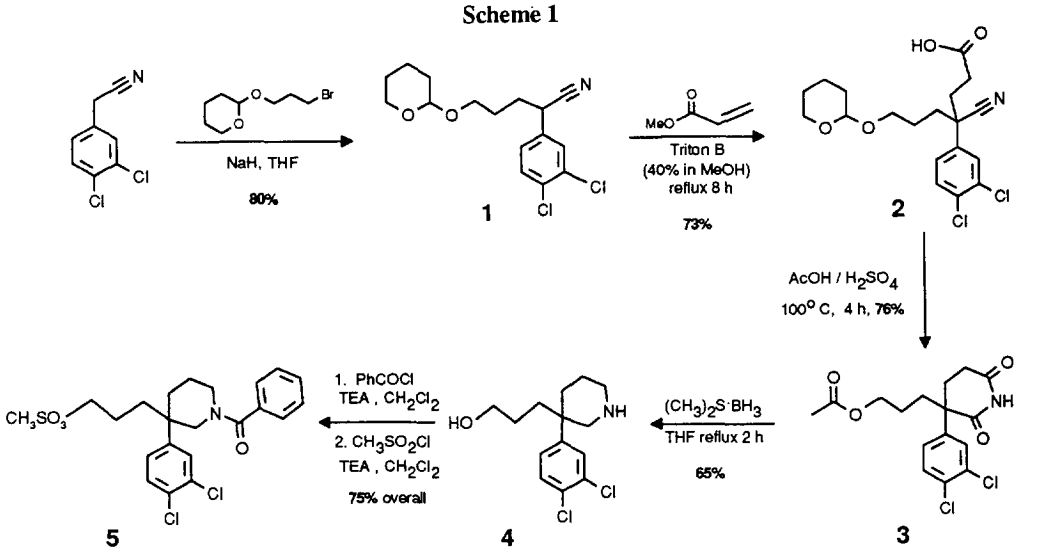
Despite the disclosure in the last years of several examples of specific non-peptide antagonists of the tachykinin NK-1 and NK-2 receptors,[4,5] only recently potent and selective non-peptide NK-3 receptor antagonists from diverse chemical classes, appeared in the literature.[6-9] Among them, SR 142801,[7] (S)-(+)-N-{{3-[1-benzoyl-3-(3,4-dichlorophenyl)piperidin-3-yl]prop-1-yl}-4-phenylpiperidin-4-yl}-N-methylacetamide [(S)-(+)-(**15**)], was the first to be disclosed and used by many research groups for comparative purposes in pharmacological studies. We wish to decribe here a new, convenient, reliable and efficient synthesis of SR 142801 which showed improvements over the published patent procedure.[10]

Results and discussion

Intermediate **2** was prepared according to a procedure reported for analogues[11] of SR 142801 and slightly modified. Thus, (3,4-dichlorophenyl)acetonitrile (Scheme 1) was alkylated with 3-bromopropanol protected as tetrahydropyranyl (THP) derivative. A subsequent alkylation of **1** with methyl acrylate (1.5 equiv) and benzyltrimethylammonium hydroxide (triton B® 1.5 equiv) gave the γ-cyanoacid **2** in 73% yields. Unfortunately, in our hands, the one step/one pot reduction of the corresponding γ–cyanoacid methyl ester to γ–aminoacid methyl ester and consequent intramolecular cyclization were unsuccessful, using either H_2-Ni Raney as described in both the patents,[10,11] or other reagents, such as H_2-Pd/C, H_2-Rh/alumina or $LiAlH_4$.

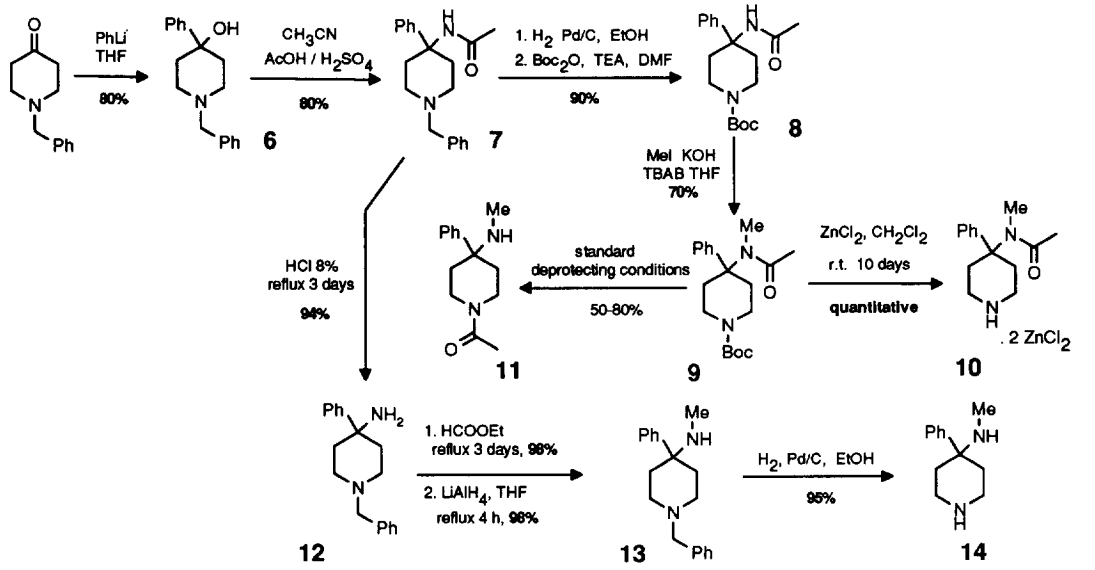
Analogously, the alternative two-steps route *via* selective hydrolysis of the γ–cyanoacid methyl ester with KOH/H_2O_2 and cyclization of the resulting amide to the corresponding imide[12] with NaOEt/THF was ineffective. Thus, the γ-cyanoacid **2** was converted into imide **3**, by refluxing in glacial AcOH[13] in the presence of a catalytic amount of H_2SO_4; in this reaction the THP protective group was spontaneously replaced *in situ* by the acetate. Reduction of the imide functionality, using borane dimethylsulfide complex (10 equiv) in refluxing THF, afforded the piperidine derivative **4** with the free hydroxylic function. After acylation of the amine with benzoyl chloride, the hydroxy group was converted into the mesylate (MsCl 1.3 equiv, TEA 1.3 equiv, from 0°C to r.t.) to allow the subsequent reaction with the nucleophiles **10** or **14**.

Scheme 1



To prepare fragment **10** (Scheme 2), we followed the synthesis described in the patent[11] for the analogue lacking the methyl group on the amidic nitrogen. However, methylation of **7** was difficult due to the easy quaternarisation of the piperidine nitrogen in different alkylating conditions (NaH/MeI, BuLi/MeI, KOH/ tetrabutylammonium bromide (TBAB)/MeI). Attempts to prepare the methylol derivative to be afterwise reduced, a classical route to N-methylamides,[14] were also unsuccesful. Also failed the Ritter reaction of the tertiary alcohol **6** with KCN in $AcOH/H_2SO_4$ in order to obtain the N-formyl derivative[15] to be reduced in turn to methylamine and then acylated. Therefore, to avoid quaternarisation of the piperidine nitrogen, the benzyl protecting group was replaced by the *t*-butoxycarbonyl (Boc), affording **8** which was easily alkylated using phase-transfer conditions (MeI 3 equiv, KOH 3 equiv, TBAB 0.1 equiv, in THF at 40°C, 24 h) to compound **9**. Very surprisingly, deprotection of the N-methylacetamide **9**, with classical Boc-cleaving reagents (10-50% TFA/ CH_2Cl_2, 95% TFA/H_2O, $HCl\text{-}Et_2O/MeOH$, BBr_3/CH_2Cl_2), afforded the undesired amide **11** (50-80%) in which the acetyl group of the methylamide has migrated onto the piperidine nitrogen. The desired compound was obtained only by using zinc chloride (2.0 equiv) as a deprotecting agent,[16] which gave rise to the stable complex **10**, thus inhibiting the possibly thermodynamically favoured transamidation to **11**.

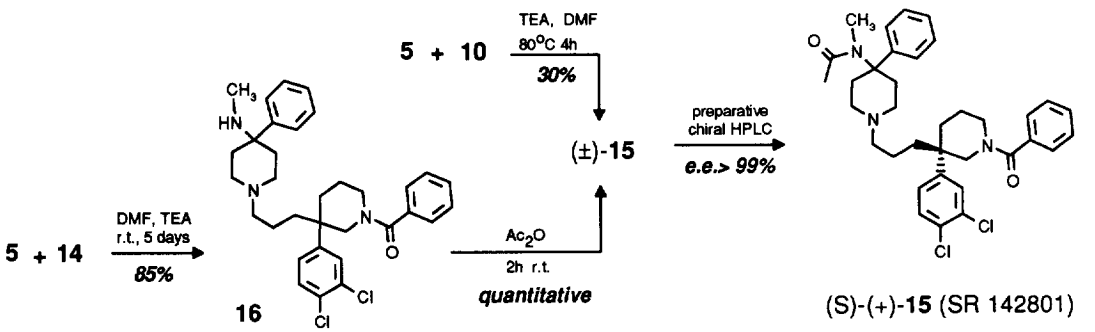
Scheme 2



The nucleophilic displacement of the mesylate **5** by the amine **10** (Scheme 3), using 4 equivalents of triethylamine in refluxing dimethylformamide, afforded (±)-**15** (racemate of SR 142801) in 30% yield.

However, the potentially stronger nucleophilic nature of the piperidine - in respect to the exocyclic - nitrogen suggested the use of the intermediate **14** (Scheme 2) as the nucleophile.

Scheme 3



Compound **14** was obtained from **7** by hydrolysis, formylation and subsequent $LiAlH_4$ reduction of the amine **12** and final hydrogenolytic debenzylation of **13**. Reaction of the mesylate **5** (1.0 equiv) with diamine **14** (2.0 equiv) in the presence of TEA (1.0 equiv) afforded **16** in much higher yields (85%) than the previous pathway. By dissolving **16** in acetic anhydride (10 equiv), the desired racemic N-methylacetamide (±)-**15** (Scheme 3) was obtained in quantitative yield.

Finally, the pure (S)-(+) enantiomer (**15**), SR 142801, was obtained by preparative chiral HPLC, eluting (±)-**15** on Daicel Chiralcel OD column (10 μ, 21.2 x 250 mm, 10 ml/min, UV 280 nm) with a unique mobile phase, consisting of 25% EtOH, 75% hexane, 0.5% TFA and 0.1% TEA. This system has not been previously reported in the literature for the chromatographic separation of amines and afforded pure enantiomers in quantitative yields on gram scale. As an example, automated preparative separation of 2.50 g of (±)-**15** (injection of 200 mg in 4 ml of mobile phase) gave 1.15 g of (S)-(+) stereoisomer ($[a]_D^{25}$ = + 20.0; c=0.3, EtOH) and 1.05 g of (R)-(-) stereoisomer ($[a]_D^{25}$ = - 19.9; c=0.3, EtOH), both with an enantiomeric excess greater than 99%.

In conclusion, by taking advantage of the unexpected reactivity of the nucleophile **14**, we set up a novel synthetic route to SR 142801; although the number of steps (*i.e.*, 9) is the same as the previously disclosed patent procedure,[10] the overall yield of our process (18% from 3,4-dichlorophenylacetonitrile) is, at least, twice as much as that reported in the patent.[17]

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17. We had difficulties in establishing the overall yield for SR 142801 from the patent description;[10] three steps appear to exceed 100% yield.

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