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A PRACTICAL AND SCALABLE SYNTHESIS OF SR 142801, A TACHYKININ NK3 ANTAGONIST

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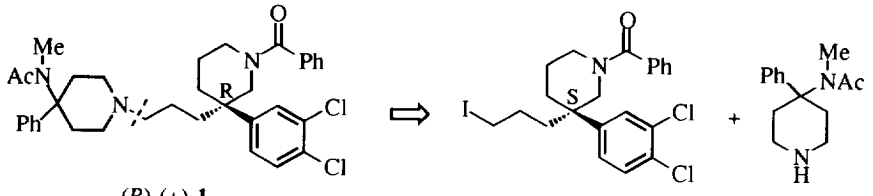
Abstract: A practical and scalable total synthesis of tachykinin NK3 receptor antagonist SR 142801, *(R)*-N-[1-[3-[1-benzoyl-3-(3,4-dichlorophenyl)-3-piperidinyl]propyl]-4-phenyl-4-piperidinyl]-N-methyl acetamide **1** is described. The absolute configuration of the key intermediate **7** was determined by single crystal X-ray crystallography, on the basis of which, the absolute configuration of SR 142801 should be *(R)*-(+), instead of the recently reported *(S)*-(+).[1] © 1997 Elsevier Science Ltd. All rights reserved.

The tachykinin peptides, which include substance P, NKA, and NKB, are widely distributed in the peripheral and central nervous systems and are known to be involved in many important biological functions, including pain transmission, bronchoconstriction, intestinal motility, saliva secretion, and neurogenic inflammation.[2] The biological effects of substance P, NKA, and NKB are mediated preferentially through the activation of three distinctive G protein-coupled receptors, NK1, NK2, and NK3, respectively.[3,4] The pharmacological results of the first potent and selective nonpeptide NK3 receptor antagonist *(R)*-N-[1-[3-[1-benzoyl-3-(3,4-dichlorophenyl)-3-piperidinyl]propyl]-4-phenyl-4-piperidinyl]-N-methyl acetamide (SR 142801) were disclosed by X. Emonds-Alt and coworkers,[5] and recently a synthesis was published by Giardina and coworkers,[1] which used chiral HPLC to separate the two enantiomeric isomers. However, the stereochemistry of the active isomer SR 142801 was incorrectly assigned as *(S)*-(+). We found, during our multigram scale synthesis of the same compound and other analogs, that the absolute configuration of SR 142801 should be *(R)*-(+) as determined by single crystal X-ray crystallography of a key intermediate. This result prompted us to report our practical, facile on large scale, synthesis of this chiral compound **1**. The penultimate compounds **A** and **B** can be conveniently synthesized on hundred-gram scale. The advantages of the present process are better overall yield (8.5% vs 5.6%[1]), fewer steps, application of routine resolution technique in place of chiral HPLC, and generally applicable novel Ritter reaction conditions. Using iodide **A** instead of the mesylate **10** in the final coupling step, the reaction ran much faster (18 h compared to 5 days[1]) and gave better yield.

The retro-synthesis of *(R)*-(+)-**1** is described in Scheme 1. The disconnection of the C-N bond of the side chain gives iodide **A** and the substituted piperidine **B** as two precursors.

Scheme 1

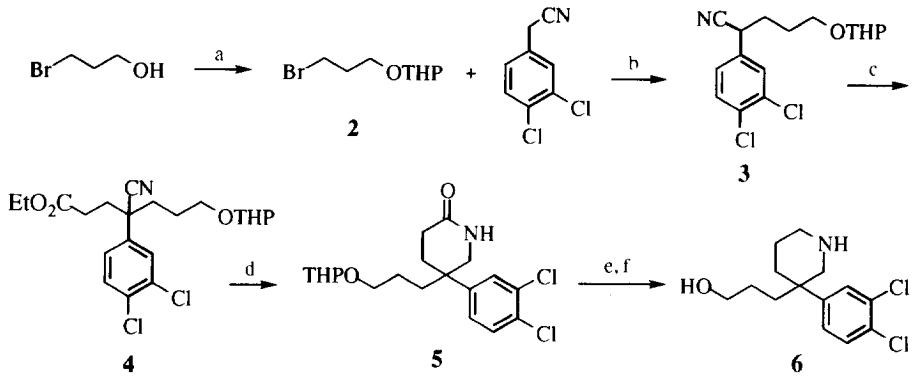


(*R*)-(+)-**1**
(SR 142801)

A **B**

Important improvements in the synthesis of intermediate **A** were made compared to the published synthesis of SR 142801[1] and analogs[6] (Scheme 2). Protection of 3-bromopropanol with dihydropyran (1.1 equiv) and a catalytic amount of *p*-TsOH in THF gave quantitative yield of THP protected bromopropanol **2**, which was then reacted with 3,4-dichlorophenylacetonitrile (1.0 equiv), deprotonated by NaH (1.1 equiv) in dry THF, at rt, for 20 h to yield compound **3** (82%). Compound **3** was further deprotonated with KHMDS (1.2 equiv), followed by addition of ethyl 3-bromopropionate (1.5 equiv) in THF at -78 °C to yield the ester **4** in 94% yield. Lower yield (35%) was obtained with LDA as base. Reduction of the cyano

Scheme 2

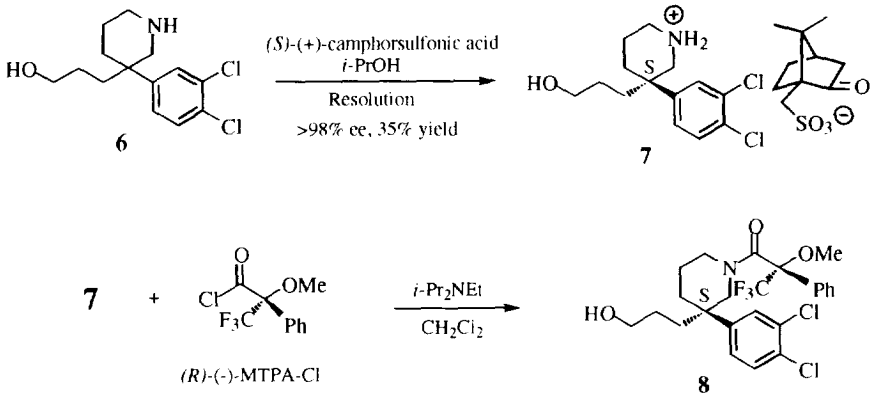


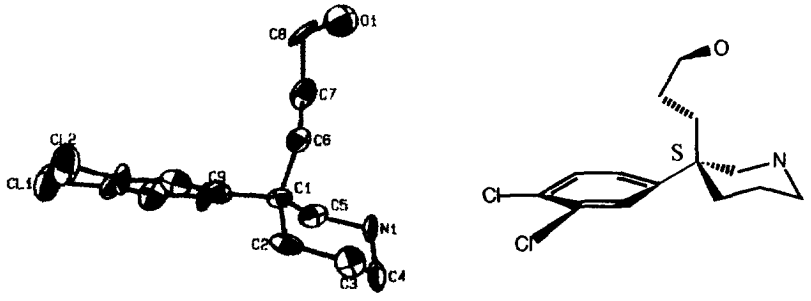
(a) DHP, p-TsOH, THF, (quantitative); (b) NaH, THF, rt, 82%; (c) KHMDS, $BrCH_2CH_2CO_2Et$ THF, -78 °C, 94%; (d) H_2, Ra Ni, EtOH, NH_4OH, 60 °C, 85%; (e) LAH, THF, 60 °C, 92%; (f) HCl•Et_2O, MeOH, 30 min, 85%.

group in **4** by hydrogenation with Raney Ni at 60 °C in EtOH and NH_4OH for 65 h produced the substituted piperidone **5** in 85% yield. The reduction of the amide group in **5** with LAH (2 equiv) in refluxing THF for 5 h gave the corresponding piperidine. Deprotection of the THP group by treatment with HCl gas-ether solution in methanol yielded the free alcohol **6** (85% from **5**).

The resolution of the enantiomeric mixture of the hydroxypiperidine **6** was accomplished using *(S)*-(+)-camphorsulfonic acid (1.0 equiv) in *i*-PrOH (Scheme 3). After three careful crystallizations from *i*-PrOH, the (*S*)-(+)-piperidine *(S)*-(+)-camphorsulfonic acid salt **7** was obtained in 35% yield (from racemic **6**, mp 186 - 187°C, $[\alpha]_D^{24}$ = +24.1; c 1.03, MeOH) in greater than 98% ee. The enantiomeric excess was determined by making the diastereomer **8** from the reaction of *(R)*-(-)-MTPA acid chloride and the salt **7**.[7] The diastereomers of *(R)*-**6**-*(R)*-MTPA and *(S)*-**6**-*(R)*-MTPA are separable by GLC.[8] The absolute configuration of the chiral salt **7** was determined by single crystal X-ray crystallography (Figure 1), which showed an *(S)* configuration at the chiral center of the piperidine ring in **7**.

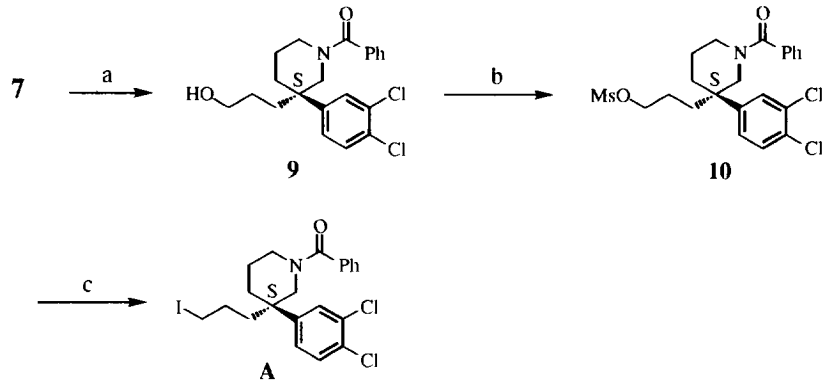
Scheme 3





The salt *(S)*-(+)-**7** was treated with benzoyl chloride (1.1 equiv) and *i*-Pr_2NEt (5.0 equiv) in CH_2Cl_2 at ambient temperature for 1 h to give the amide **9** (90% yield) (Scheme 4). The hydroxy group of **9** was then mesylated with methanesulfonyl chloride (1.2 equiv), DIPEA (3.0 equiv) in dry CH_2Cl_2 as solvent at ambient temperature for 2 h to yield mesylate **10** (99%). The conversion of mesylate **10** to the corresponding iodide **A** was accomplished by treatment with KI (1.1 equiv) in refluxing acetone for 18 h in 98% yield.

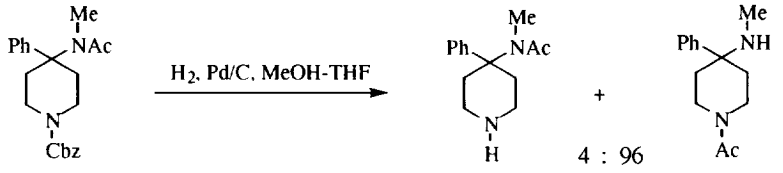
Scheme 4



(a) PhCOCl, *i*-Pr_2NEt, CH_2Cl_2, rt, 90%; (b) CH_3SO_2Cl, *i*-Pr_2NEt, CH_2Cl_2, rt, 99%; (c) KI, acetone, reflux, 98%.

In the synthesis of intermediate **(B)**, the same acetyl group migration problem was encountered as described by Giardina and coworkers[1] (Scheme 5). The removal of the Cbz group of piperidine **12** by catalytic hydrogenation gave mainly the *N*-acetyl piperidine **13** instead of the expected product **B**. An

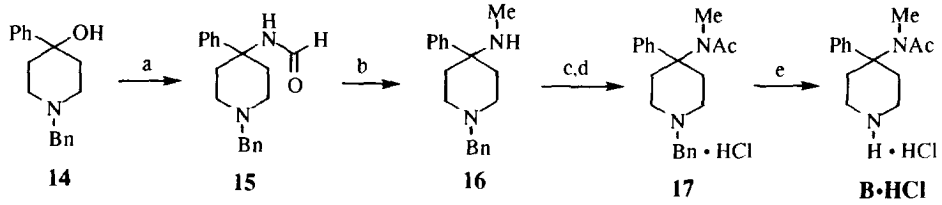
Scheme 5



alternative synthetic route was designed (Scheme 6), which started with a new modified Ritter reaction.[9] The hydroxy piperidine **14** was treated with TMSCN (2.0 equiv) and H_2SO_4 (3.0 equiv) at -20 °C and warmed to ambient temperature for 18 h to give 70% of the formamide **15**. This was then reduced to the corresponding methyl amine **16** by LAH (8.0 equiv) in THF at 60 °C for 7 h, in quantitative yield.

Standard acetylation of **16** with AcCl (1.1 equiv) and Et_3N (2.5 equiv) in CH_2Cl_2 at rt, followed by conversion of the resulting acetamide to the corresponding HCl salt with $HCl•Et_2O$ gave **17** (89%, two steps). This was then subjected to catalytic hydrogenation (H_2, 50 psi, 20% Pd-C) in MeOH-THF (5 : 1), 40 h, to yield the expected **B** as hydrochloride salt in quantitative yield.

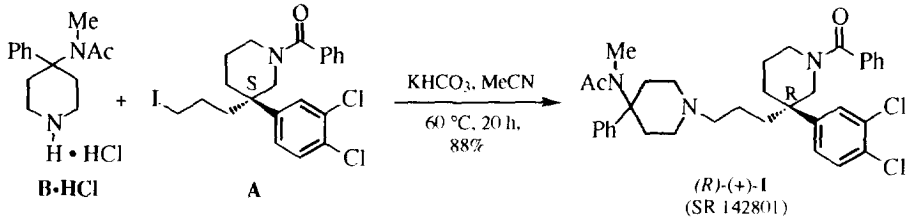
Scheme 6



(a) TMSCN, H_2SO_4, -20 °C to rt, 70%; (b) LAH, THF, 60 °C, quantitative; (c) AcCl, Et_3N, CH_2Cl_2, rt; (d) $HCl•Et_2O$, 89% (two steps); (e) H_2, Pd/C, MeOH-THF, rt, quantitative.

The coupling of intermediate **B•HCl** and mesylate **10** in DMF with TEA at 60 °C gave low yield (25%) of compound **1**. However, the reaction of iodide **A** with **B•HCl** (1.5 equiv) using $KHCO_3$ as base in MeCN, at 60 - 65 °C for 18 h gave 88% yield of *(R)*-(+)-**1**, SR 142801, $[\alpha]_D^{24}$ = +24.3 (c 1.02, MeOH)[10] (Scheme 7).

Scheme 7



In conclusion, we have developed a practical and scalable synthesis of SR 142801. The absolute configuration of SR 142801 was determined as *(R)*-(+) by single crystal X-ray crystallography of the key intermediate **7**. The tachykinin NK3 inhibitory activity (IC_{50})[11] of the compound was determined to be 0.8 nM in our laboratories.

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8. Analytical GLC was performed with Hewlett Packard Model 5890 Series II Plus Gas Chromatograph instrument; Alltech capillary column, phase: EC-1 (SE-30), length: 10 m, ID: 0.53 mm, film thickness: 1.2 μ; mobil phase: helium gas, flow rate: 2.0 mL/min; to give *(S)*-**6**-*(R)*- MTPA peak at t_R = 13.57 min, and *(R)*-**6**-*(R)*-MTPA peak ar t_R = 14.58 min.
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10. $[\alpha]_D^{24}$ = +24.5 (c 1.0, MeOH) was reported by Emonds-Alt, X. of Sanofi Co.
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