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A Facile Synthesis of the Novel Neurokinin A Antagonist SR 48968

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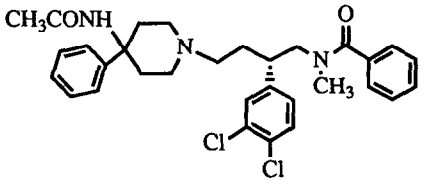
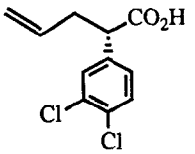
Abstract: *A convenient synthesis of the potent Neurokinin A antagonist SR 48968 (N-methyl-N-(4-(4-acetamido-4-phenylpiperidinyl)-(2S)-(3,4-dichlorophenyl)butyl)benzamide) is described.*

The mammalian tachykinins, Substance P (SP), Neurokinin A (NKA), and Neurokinin B (NKB), are neuropeptides that are widely distributed in the central and peripheral nervous systems and intestinal tract of many species[1,2]. They have been implicated as mediators of a variety of human inflammatory diseases[3] and the search for non-peptide based antagonists of SP and NKA is currently a subject of great interest[4,5].

SR 48968, N-Methyl-N-(4-(4-acetamido-4-phenylpiperidinyl)-(2S)-(3,4-dichlorophenyl)butyl)benzamide (**1**), was recently reported to be a potent, competitive antagonist of NKA[4e,5a]. *In vitro* , SR 48968 was reported to inhibit the binding of [^{125}I]-NKA to its receptor in rat duodenum membranes with an inhibition constant (K_i) of 0.51 ± 0.09 nM. *In vivo*, SR 48968 produced a dose-dependent inhibition of the [Nle^{10}]-NKA_{4-10} induced bronchoconstriction with an ED_{50} = 37 μg/kg (i.v.) and 350 μg/kg (i.p.).[5a] We sought a sample of SR 48968, but found the published patent procedure[6] for the synthesis of this compound to be less than optimal due to the number of steps involved (9) and the need to resolve an advanced intermediate in order to obtain the S stereochemistry of the active enantiomer. We wish to report herein an improved synthesis of SR 48968 using the key intermediate **2**.

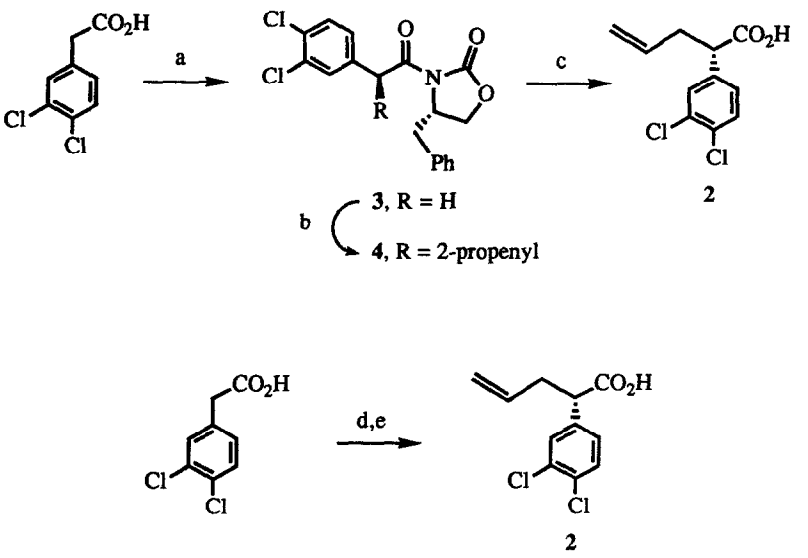


1



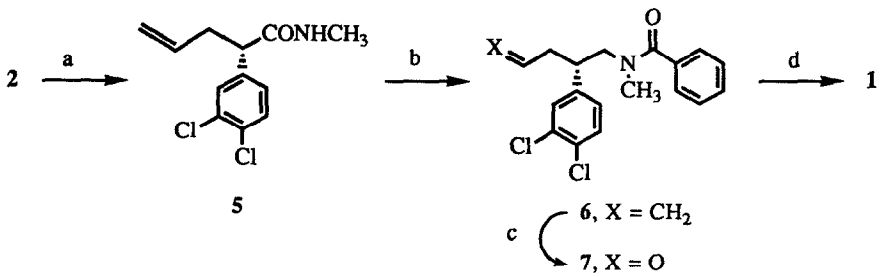
2

Scheme 1



Reagents: (a) trimethylacetyl chloride, triethylamine, THF, -10 °C, then 3-lithio-(4S)-benzyl-2-oxazolidinone, -78 °C (83%); (b) sodium bis(trimethylsilyl)amide, THF, -78 °C, then allyl iodide, -20 °C (80%); (c) lithium hydroperoxide, 4:1 v/v THF/H_2O, 0 °C (86%); (d) 2.2 equiv lithium bis(trimethylsilyl)amide, -10 °C, then 2.5 equiv allyl bromide (95%); (e) (1S)-phenylethylamine, ethyl acetate, recrystallize, then ether/1.0 N HCl (18%).

Scheme 2



Reagents: (a) $(COCl)_2$, cat. DMF, CH_2Cl_2, then 40% aqueous methylamine solution, toluene, 0 °C (97%); (b) DIBALH, CH_2Cl_2/toluene, rt, then benzoyl chloride, toluene/sat'd $NaHCO_3$ solution (83%); (c) cat. OsO_4, N-methylmorpholine N-oxide 2:1:1 v/v/v acetone/t-butanol/water, then $NaIO_4$, 4:1 v/v THF/water (72%); (d) 1.5 equiv 4-acetamido-4-phenylpiperidine • HCl, $Na(CN)BH_3$, 1:1 v/v THF/methanol (93%).

(2S)-(3,4-Dichlorophenyl)-4-pentenoic acid (**2**)[7] was first prepared using the Evans chiral oxazolidinone methodology[8] (**Scheme 1**). Thus, 3,4-dichlorophenylacetic acid was converted to the pivalic acid mixed anhydride[9] and reacted with lithiated (4S)-benzyl-2-oxazolidinone to afford acyl oxazolidinone **3**. Alkylation of the sodium enolate of **3** (generated by treating **3** with sodium bis(trimethylsilyl)amide) with allyl iodide afforded the (S)-alkylated oxazolidinone **4**[10]. Treatment of **4** with lithium hydroperoxide gave enantiomerically pure **2**[11]. Alternatively, **2** was obtained by resolving[12] the diastereomeric (1S)-phenylethylamine salts of (±)-2-(3,4-dichlorophenyl)-4-pentenoic acid (prepared by alkylating the lithium dianion of 3,4-dichlorophenylacetic acid with allyl bromide, **Scheme 1**). The routes to **2** offer the advantage of generality for analog preparation while the latter can be employed on a larger scale.

Elaboration of acid **2** into **1** was accomplished using straightforward functional group transformations (**Scheme 2**). Acid **2** was converted to amide **5** via the acid chloride. Amide **5** was reduced to the secondary amine using diisobutylaluminum hydride (DIBALH) and isolated, after acylation with benzoyl chloride, as the benzamide **6**. Cleavage of the double bond of **6** was most efficiently accomplished via the diol[13] to afford the aldehyde **7**. Reductive amination of **7** with 4-acetamido-4-phenylpiperidine • HCl[6] using sodium cyanoborohydride afforded SR 48968 (**1**) in 54% yield from **2**.

Our route offers several advantages over the published synthesis of SR 48968 and compounds of its general structure. The chiral oxazolidinone methodology affords an enantiomerically pure starting material in a highly predictable manner and eliminates the often tedious trial and error work involved with chromatographic or crystallization resolutions. The brevity and convergence of the route allows great freedom in analog preparation as complex or expensive variations in the structural features are carried through relatively few steps. The synthesis can afford both enantiomers and be performed on a multigram scale without difficulty.

In conclusion, this convenient synthesis of SR 48968 should be quite useful to those interested in extended evaluations of this highly promising pharmacologic and potential therapeutic agent.

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7. All new compounds had satisfactory spectral (^{1}H NMR, IR and MS) and C, H, N analytical data.

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10. The 400 MHz ^{1}H NMR of the crude product revealed that the alkylation resulted in a 92:8 mixture of diastereomers. The diastereomers were readily separated using silica gel chromatography.

11. Reduction of **2** (DIBALH, CH_2Cl_2/toluene) afforded the corresponding benzyl alcohol which was converted to the (R)-α-methoxy-α-trifluoromethylphenylacetate ((R)-MTPA) ester (Dale, J.A.; Dull, D.L.; Mosher, H.S. *Journal of Organic Chemistry*, **1969**, *34*, 2543). **2** had > 99.5% e.e. as determined by measurement of the integrals of the diastereomeric resonances in the 400 MHz ^{1}H NMR of the (R)-MTPA ester.

12. **2** obtained from the resolution had 98% e.e.

13. Direct cleavage of the double bond to the aldehyde using catalytic OsO_4 and $NaIO_4$ or via ozonolysis afforded **7** in 20-30% yield. For the use of 4-methylmorpholine N-oxide as the secondary oxidant in the *cis*-glycolization of olefins, see Van Rheenen, V.; Kelly, R.C.; Cha, D.Y. *Tetrahedron Letters*, **1976**, *23*, 1973.