Synthesis of a Chiral Key Intermediate of Neurokinin Antagonist SSR 240600 by Asymmetric Allylic Alkylation

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Abstract: The preparation of optically active morpholine-2-aryl-2-acetaldehyde from morpholine-2-aryl-3-one is reported. The quaternary carbon is introduced during a palladium-promoted asymmetric allylic alkylation. This is a useful intermediate in the synthesis and development of potent NK antagonist.

Key words: alkylation, palladium, asymmetric catalysis, heterocycle

The neurokinins (also known as tachykinins) are a peptide family of neurotransmitters comprising substance P (SP), neurokinin A (NKA), and neurokinin B (NKB) that share the common carboxy-terminal sequence Phe-X-Gly-Leu-Met-NH_2. They are widely distributed in the central and peripheral nervous systems.[1] Based on the affinity of natural neurokinins, three distinct 7-transmembrane G protein-coupled receptor types have been identified: NK1 (SP-preferring), NK2 (NKA-preferring), NK3 (NKB-preferring).[2] The various forms of neurokinin in the mammalian body affect a large number of biological activities, including muscle contraction and relaxation, vasodilatation, secretion, activation of the immune system, pain transmission, and neurogenic inflammation. Thus, antagonists of these NK receptors have attracted a great deal of interest as potent therapeutic agents.[3]

Amongst optically active morpholines, SSR 240600 and SSR 241586 have been described to be active against depression, emesis, irritable bowel syndrome, schizophrenia, and urinary trouble (Figure 1).[4]

To implement the stereogenic center of optically active 2,2-disubstituted morpholines,[5] several methodologies have been applied. The first reported methodology relies on a Sharpless dihydroxylation providing intermediate **A**.[6] A crystallization of an arylmorpholine carried out in the presence of D-(–)-tartaric acid furnished the building block **B**.[7] Then, an asymmetric cyanosilylation allowing an access to compound **C**,[8] an enantioselective epoxydation of a homoallylic alcohol providing synthon **D**,[9] and, very recently, an organocatalyzed Henri reaction delivering **E**[10] have been reported successively (Scheme 1).

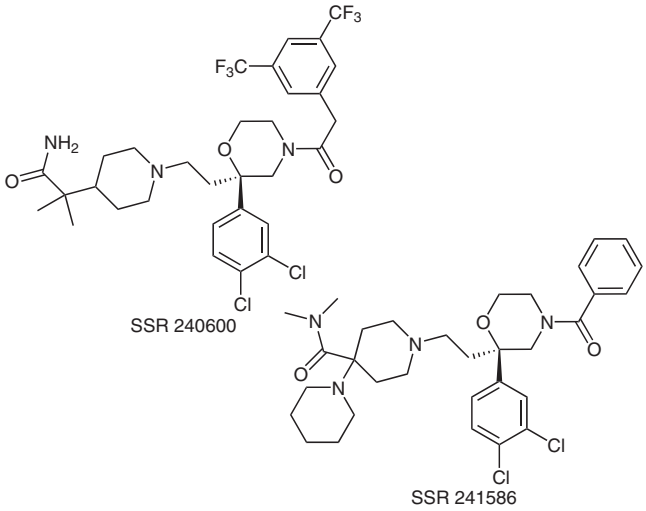
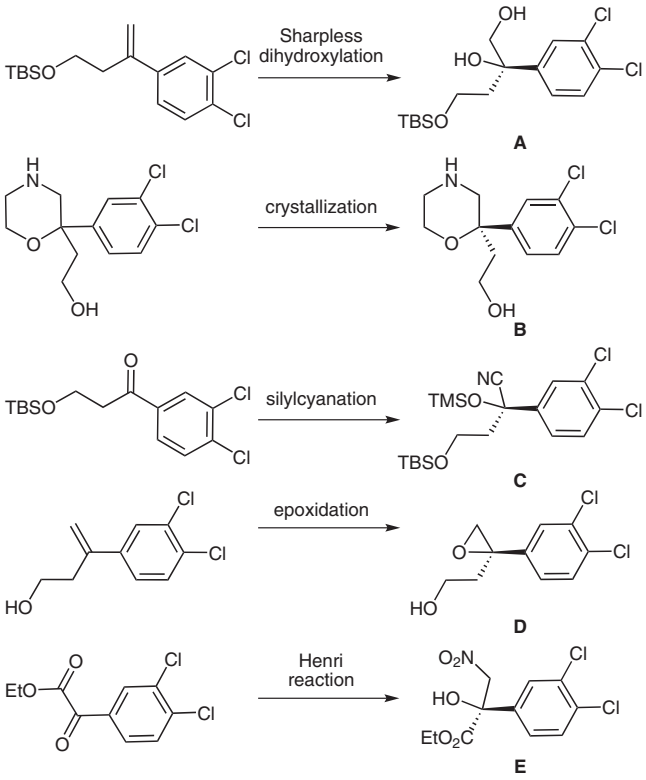


Figure 1 Two examples of morpholine-based NK antagonists



Scheme 1 Different routes to access the benzylic sterocenter of arylmorpholine precursors

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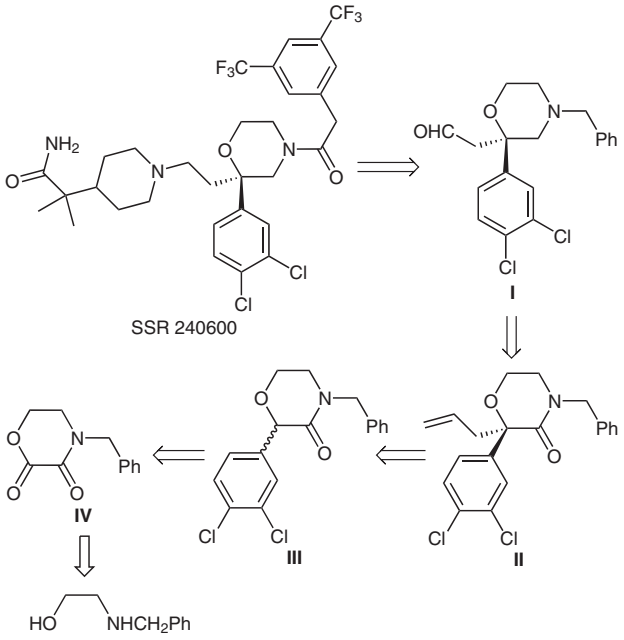
Following our interest in the use of asymmetric allylic alkylation in order to prepare quaternary stereocenters,[11] and our interest in the preparation of intermediates for the synthesis of potent NK antagonist,[12,13] we considered the preparation of a key intermediate of SSR 240600 based on such a methodology.

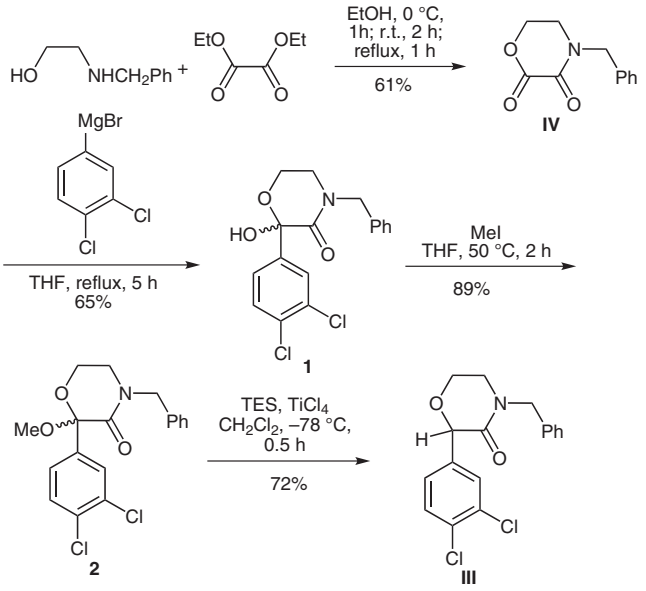
The synthesis of SSR 240600 was meant from the optically active aldehyde **I** which would be the result of an oxidative cleavage of the olefin and a reduction of chiral morpholinone **II**. The latter would result from an asymmetric allylation of **III**. This morpholinone could be obtained easily from morpholinedione **IV** prepared from 2-(benzylamino)ethanol (Scheme 2). We focused thus on the preparation of optically active **I**.



Scheme 2 Retrosynthetic analysis of SSR 240600

Morpholinedione **IV** was easily prepared from 2-(benzylamino)ethanol.[14] Thus, the reaction of commercially available 2-(benzylamino)ethanol (1 equiv) and diethyloxalate (1 equiv) led to **IV** in 61% yield after purification. The reaction of **IV** with freshly prepared (3,4-dichlorophenyl)magnesium bromide (1.1 equiv) afforded the cyclic hemiketal **1** in 65% yield. Then, **1** was reacted with methyliodide (1.5 equiv) in the presence of NaH (1.5 equiv).[15] After workup, the cyclic ketal **2** was isolated in 89% yield. Then, a Lewis acid promoted silane reduction of ketal **2** furnished morpholinone **III**. Thus, ketal **2** was reacted with TES (3 equiv) in the presence of $TiCl_4$ (6 equiv) in dichloromethane providing morpholinone **III** in 72% yield (Scheme 3).[15] The preparation of **III** could also be achieved in one step from **1** under similar conditions (3 h, –78 °C, 73%).

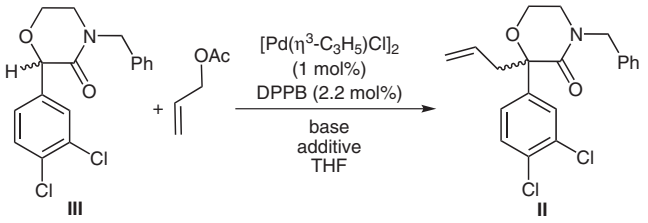
In order to find the most appropriate conditions for the palladium-catalyzed allylic alkylation of **III**, we first carried out experiments to screen different bases with the use of the diphosphine DPPB [1,4-bis(diphenylphosphino-



Scheme 3 Synthesis of the alkylation substrate **III**

butane] ligand and allylpalladium chloride dimer (Scheme 4). Results are reported Table 1.

Among the various bases tried, the best catalytic conditions were found by using a combination of *n*-BuLi and TMEDA (Table 1, entry 7) in conjunction with the palladium complex. Hence, the combined use of THF and a bidentate ligand like TMEDA proved to be crucial breaking down *n*-BuLi aggregates to form monomers and dimers and thereby increasing significantly their basicity.[16] Asymmetric allylic alkylation of **III** was then studied in the presence of a chiral Trost ligand (Figure 2) and allylpalladium chloride dimer (Table 2). The highest optical purity was obtained with DACH-naphthyl Trost ligand (Table 2, entry 3, 83% ee).



Scheme 4 Alkylation of the prochiral morpholinone by palladium-promoted reaction

The absolute configuration of **II** could be determined by X-ray structure determination (Figure 3).[17] The allyl derivative **II** obtained from the (*R*,*R*)-DACH-naphthyl ligand has an *R*-configuration similar to the C2 quaternary carbon center of the morpholine heterocycle in SSR 240600.

We next reduced compound **II** with lithium aluminium hydride. The morpholine **4** was isolated in 70% yield. The allyl moiety was next oxidized in a two-step procedure using first *N*-methylmorpholine-*N*-oxide along with a catalytic amount of osmium tetroxide, second using sodium

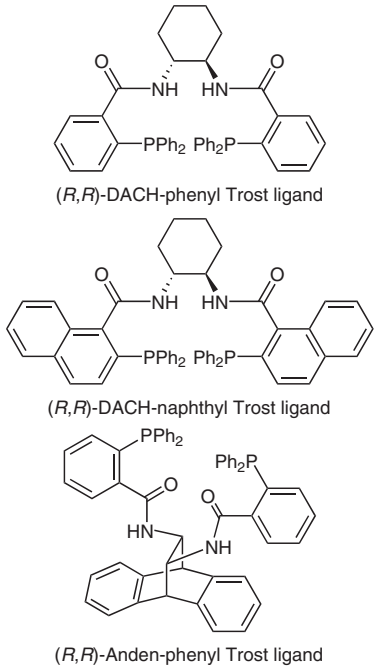


Figure 2 Chiral Trost ligands

Table 1 Variation of the Base and Additives in the Alkylation of **III**[a]

Entry	Base (equiv)	Additive (equiv)	Yield (%)
1	LDA (1.5)	–	68
2	LiHMDS (1.5)	–	49
3	(–)-sparteine	–	0
4	NaH	–	6
5	*s*-BuLi (2)	–	0
6	*s*-BuLi (2)	$ZnCl_2$ (1.3)	27
7[b]	*n*-BuLi (1.5)	TMEDA (1)	95

[a] Reactions were carried out in the presence of $[Pd(h^3\text{-}C_3H_5)Cl]_2$ (1 mol%), DPPB (2.2 mol%) in THF at r.t. for 4 h.
[b] Addition of the base at –78 °C; the reaction was carried out at r.t. for 12 h.

Table 2 Asymmetric Allylation of **III**[a]

Entry	Ligand	Yield (%)	ee (%)
1	(*R*,*R*)-BINAP	95	46
2	(*R*,*R*)-DACH-phenyl Trost ligand	93	64
3	(*R*,*R*)-DACH-naphthyl Trost ligand	90	83
4	(*R*,*R*)-Anden-phenyl Trost ligand	83	16

[a] Reactions were carried out in the presence of $[Pd(h^3\text{-}C_3H_5)Cl]_2$ (1 mol%), chiral ligand (2.2 mol%) in THF (0.15 M). The addition of the base and TMEDA was done at –78 °C, and reaction was carried out at r.t. for 12 h.

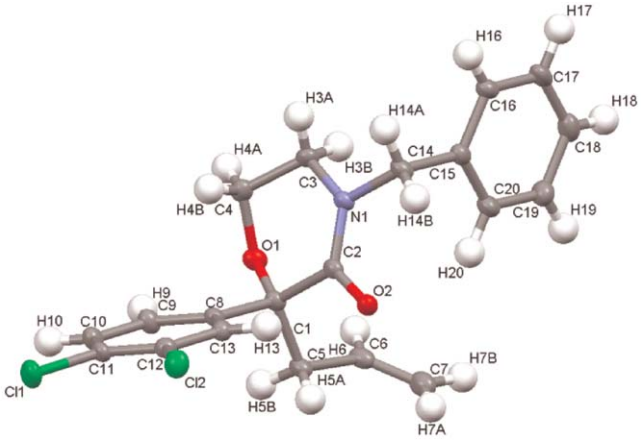
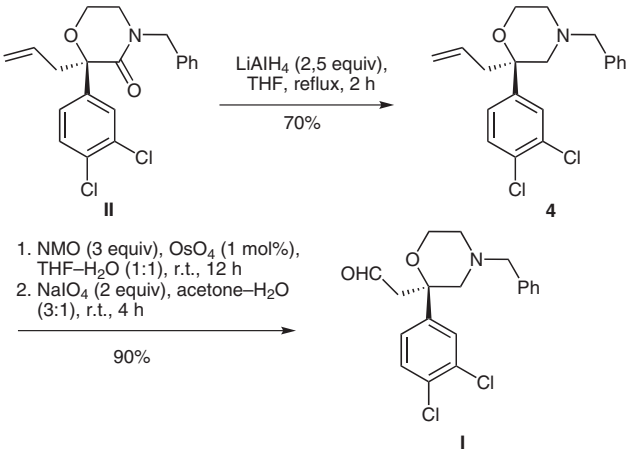


Figure 3 ORTEP view of compound **II** with ellipsoids drawn at 50% probability level[16]



Scheme 5 Synthesis of chiral aldehyde **I**

periodate. After workup, the aldehyde **I** was isolated in 90% yield (Scheme 5).

In summary, we have developed an efficient route to optically enriched morpholine-2-aryl-acetaldehyde, a key intermediate of potent neurokinin antagonists, exhibiting a quaternary carbon center. To access the desired *R* configuration of such a quaternary carbon center, the palladium-catalyzed asymmetric allylic alkylation proved to be a powerful methodology. Further investigations are under way to apply this methodology to the preparation of piperidines bearing also a quaternary carbon center.[13]

In a first Schlenk tube under nitrogen, the substrate (1 equiv) was dissolved in dry THF and cooled to –78 °C. After addition of TMEDA (1 equiv) and *n*-BuLi (1.5 equiv), the resulting mixture was stirred for 30 min at –78 °C. In a second Schlenk tube, $[Pd(allyl)Cl]_2$ (0.01 equiv) and the desired ligand (0.021 equiv) were dissolved in dry THF (2 mL). After addition of allyl acetate (1.5 equiv), the mixture was stirred 30 min at r.t. and then cooled to –78 °C. The solution containing the catalyst was slowly added by cannula to the substrate solution. The resulting mixture was then allowed to warm up to r.t. overnight (12 h). The reaction was quenched by the addition of a sat. aq NH_4Cl solution (5 mL) and of H_2O (5 mL). The allyl product was extracted with Et_2O, and the organic phases were washed with a sat. $NaHCO_3$ solution. After dry-

ing over $MgSO_4$ and filtration on silica wool, the solvents were evaporated under vacuum. The resulting product was further purified by flash chromatography on silica gel using a solvent mixture of PE–EtOAc–Et_3N (90:5:5). Evaporation of solvents afforded a colorless oil.

Compound II

$[\alpha]_D^{20}$ –32 (CH_2Cl_2, *c* 2.8 mM, for 83% ee). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.81 (d, 1 H, *J* = 2.0 Hz), 7.58 (dd, 1 H, *J* = 8.5, 2.3 Hz), 7.43 (d, 1 H, *J* = 8.1 Hz), 7.29 (m, 5 H), 5.78 (m, 1 H), 5.10 (m, 2 H), 4.68 (d, 1 H, *J* = 14.6 Hz), 4.62 (d, 1 H, *J* = 14.3 Hz), 3.85 (m, 1 H), 3.70 (dt, *J* = 11.1, 3.3 Hz), 3.54 (dt, *J* = 11.7, 4.6 Hz), 3.03 (m, 1 H), 2.94 (dd, 1 H, *J* = 7.2 Hz), 2.59 (dd, 1 H, *J* = 6.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.1 (CO), 141.3 ($C_{Ar}C$, C_{IV}), 136.3 ($C_{Ar}C$, C_{IV}), 132.7 ($C_{Ar}Cl$, C_{IV}), 132.6 (C_{All}, C_{III}), 132.0 ($C_{Ar}Cl$, C_{IV}), 130.4 (C_{Ar}, C_{III}), 128.9 (C_{Ar}, C_{III}), 128.5 (C_{Ar}, C_{III}), 128.3 (C_{Ar}, C_{III}), 127.9 (C_{Ar}, C_{III}), 126.0 (C_{Ar}, C_{III}), 119.3 (C_{All}, C_{II}), 83.1 (C_{All}, C_{IV}), 59.7 (C_{Bn}, C_{II}), 50.4 (CH_2, C_{II}), 46.6 (C_{All}, C_{II}), 46.4 (CH_2, C_{II}). IR (KBr): 3075, 3029, 2924, 1653, 1484, 1465, 1190, 1030, 995, 920, 825, 786, 727 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{20}H_{20}O_2NCl_2$ [MH$^+$]: 376.0870; found: 376.0870. HPLC [DAICEL CHIRALPAK OJ-H, hexane–*i*-PrOH (9:1), 0.3 mL/min, 200 nm]: t_R (major, *R* enantiomer) = 41.4 min; t_R (minor, *S* enantiomer) = 49.4 min.

Compound III

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.57 (d, 1 H, *J* = 2.2 Hz), 7.40 (d, 1 H, *J* = 8.4 Hz), 7.31 (m, 4 H), 7.23 (m, 2 H), 5.15 (s, 1 H), 4.65 (d, 1 H, *J* = 14.5 Hz), 4.53 (d, 1 H, *J* = 14.5 Hz), 3.95 (dt, 1 H, *J* = 4.4 Hz), 3.82 (m, 1 H), 3.45 (m, 1 H), 3.24 (dt, 1 H, *J* = 3.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.8 (CO), 137.6 ($C_{Ar}C$, C_{IV}), 136.1 ($C_{Ar}C$, C_{IV}), 132.6 ($C_{Ar}Cl$, C_{IV}), 132.5 ($C_{Ar}Cl$, C_{IV}), 130.4 (C_{Ar}, C_{III}), 129.7 (C_{Ar}, C_{III}), 129.0 (C_{Ar}, C_{III}), 128.4 (C_{Ar}, C_{III}), 128.0 (C_{Ar}, C_{III}), 127.3 (C_{Ar}, C_{III}), 78.3 (CH, C_{III}), 62.3 (C_{Bn}, C_{II}), 50.2 (CH_2, C_{II}), 46.0 (CH_2, C_{II}). IR (KBr): 3094, 3025, 2988, 2960, 2921, 1684, 1653, 1484, 1472, 1448, 1199, 1030, 802, 749, 728 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{17}H_{16}O_2NCl_2$ [MH$^+$]: 336.05526; found: 336.05510.

Compound I

$[\alpha]_D^{20}$ +102 (CH_2Cl_2, *c* 11.0 mM, for 83% ee). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.62 (t, 1 H, *J* = 3.0 Hz), 7.43 (dd, 2 H, *J* = 5.7, 5.3 Hz), 7.33 (m, 5 H), 7.17 (dd, 1 H, *J* = 8.4, 2.4 Hz), 3.85 (m, 1 H), 3.75 (m, 1 H), 3.59 (d, 1 H, *J* = 13.1 Hz), 3.42 (d, 1 H, *J* = 13.1 Hz), 3.04 (dd, 1 H, *J* = 15.7, 3.1 Hz), 2.83 (d, 1 H, *J* = 12.6 Hz), 2.63 (dd, 1 H, *J* = 15.5, 2.3 Hz), 2.54 (t, 1 H, *J* = 4.9 Hz), 2.48 (d, 1 H, *J* = 11.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.7 (CO), 142.8 ($C_{Ar}C$, C_{IV}), 137.4 ($C_{Ar}C$, C_{IV}), 132.9 ($C_{Ar}Cl$, C_{IV}), 131.7 ($C_{Ar}Cl$, C_{IV}), 130.6 (C_{Ar}, C_{III}), 129.2 (2 C_{Ar}, C_{III}), 128.7 (C_{Ar}, C_{III}), 128.6 (2 C_{Ar}, C_{III}), 127.7 (C_{Ar}, C_{III}), 125.7 (C_{Ar}, C_{III}), 75.9 (C, C_{IV}), 63.1 (CH_2, C_{II}), 62.2 (CH_2, C_{II}), 59.8 (CH_2, C_{II}), 53.5 (CH_2, C_{II}), 52.2 (CH_2, C_{II}). IR (KBr): 3028, 2965, 2873, 2766, 1722, 1469, 1461, 1138, 818, 791, 747 cm^{-1}. ESI-MS: *m/z* 320.0597 [MH$^+$ – CH_2CHO], 364.0859 [MH$^+$], 396.1117 [MH$^+$ + CH_3OH]. ESI-HRMS: *m/z* calcd for $C_{19}H_{20}O_2NCl_2$ [MH$^+$]: 364.08656; found: 364.08585.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(17) X-ray crystal data of compound **II** were deposited under reference CCDC 836129. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre: www.ccdc.cam.ac.uk/data_request/cif.