Efficient Synthesis of a Key Intermediate of Neurokinin Receptor Antagonists Using a Bifunctional Asymmetric Catalyst

Makoto Takamura,*[a] Kazuo Yabu,[a] Takahide Nishi,[a] Hiroaki Yanagisawa,[a] Motomu Kanai,[b] Masakatsu Shibasaki[b]

[a] Medicinal Chemistry Research Laboratories, Sankyo Co., Ltd., Hiromachi, Shinagawa-ku, Tokyo 140-8710, Japan
Fax +81(3)54368563; E-mail: takamu@shina.sankyo.co.jp

[b] Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

Received 18 November 2002

Abstract: We report herein an efficient synthetic method for the preparation of 2-[(2*R*)-arylmorpholin-2-yl]ethanol, a key intermediate of neurokinin receptor antagonists. Catalytic asymmetric cyanosilylation of ketone **3** using titanium complex **4** was employed to introduce the required stereochemistry.

Key words: asymmetric, catalysis, ketones, ligands, titanium

Introduction

The neurokinins are a family of neuropeptides comprising substance P (SP), neurokinin A (NKA) and neurokinin B (NKB), that share the common C-terminal sequence Phe-X-Gly-Leu-Met-NH_2 in 10- or 11-amino acid residue. Based on the different orders of potency of natural neurokinins, three distinct receptor subtypes, which belong to the G-protein-coupled 7-transmembrane superfamily, have been identified: NK_1 (SP-preferring), NK_2 (NKA-preferring) and NK_3 (NKB-preferring).[1] The presence of the various forms of neurokinin in the mammalian body is associated with a variety of biological actions such as pain transmission, vasodilation, smooth muscle contraction, and neurogenic inflammation. Airway inflammation and bronchoconstriction in asthma and chronic airway obstructive disease continue to be the major foci of clinical interest in neurokinin research. Based on the speculation that combined (NK_1/NK_2/NK_3) neurokinine receptor antagonist would be of greater benefit in the treatment of pulmonary diseases than selective antagonist, a series of novel morpholine analogues **1** exhibited high binding affinities for NK_1, NK_2 and NK_3 receptors were already reported.[2] Preliminary studies indicated that the stereochemistry of the 2-substituents of the morpholine ring has great impact on the binding activity to neurokinin receptor, and the (*R*)-configuration has been shown to be an essential requirement for more potent binding affinity. An asymmetric synthetic method using Sharpless asymmetric dihydroxylation and the Mitsunobu reaction was also developed for preparation of 2-[(2*R*)-arylmorpholin-2-yl]ethanol **2**, the key intermediate of **1**.[3] Although this method is useful for the preparation of an optically active form, it is not preferable for practical synthesis because of the toxic osmium used in the asymmetric dihydroxylation.[4] Meanwhile, some of the authors have developed a highly enantioselective catalytic cyanosilylation of ketones with broad substrate generality, using a Lewis acid Lewis base bifunctional catalyst **4** (Figure 1).[5] We now describe a new efficient route to **2** (Scheme 1) using this catalytic asymmetric cyanosilylation as a key step.

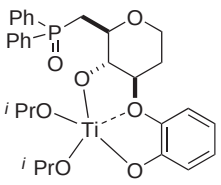

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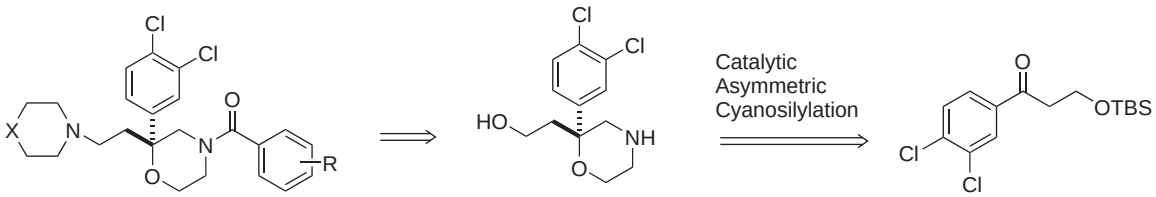
Figure 1 Catalyst **4**

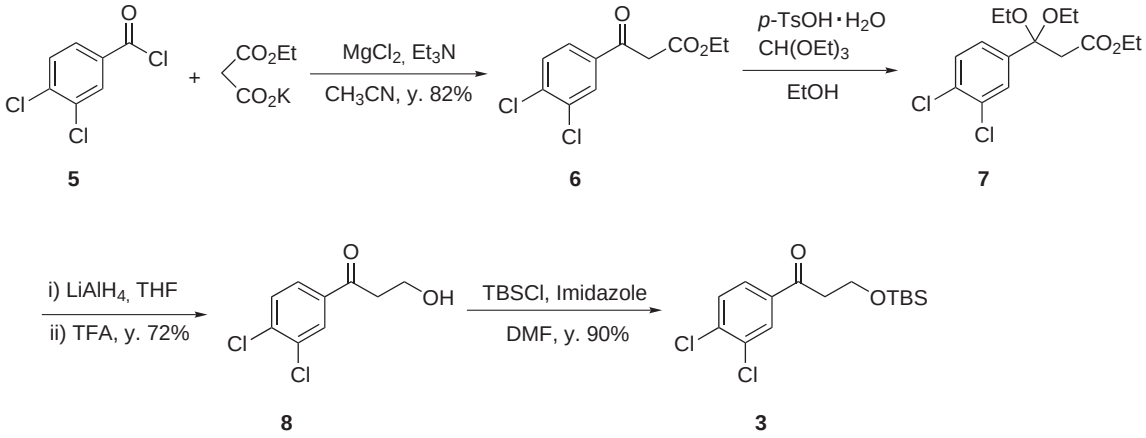


1 **2** **3**

Scheme 1 Retrosynthesis

Synlett 2003, No. 3, Print: 19 02 2003.
Art Id.1437-2096,E;2002,0,02,0353,0356,ftx,en;U11502ST.pdf.

ISSN 0936-5214



5 **6** **7** **8** **3**

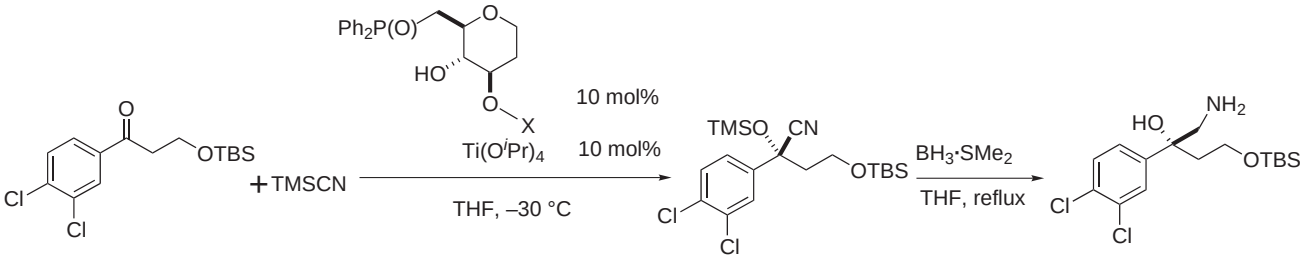
Scheme 2 Synthesis of **3**

Results and Discussion

The synthetic procedure to the starting material of the catalytic asymmetric cyanosilylation is shown in Scheme 2. At first we synthesized ethyl 3-(3,4-dichlorophenyl)-3-oxo propionate **6** from acid chloride **5** and potassium ethyl malonate in 82% yield.[6] The 3-oxo group of **6** was then protected with diethylacetal and the obtained ester **7** was reduced with $LiAlH_4$ followed by deprotection of the acetal group to obtain alcohol **8** in 72% yield (3 steps). Protection of alcohol **8** with a *t*-butyldimethylsilyl (TBS) group provided a desired ketone **3** in 90% yield.

Although excellent results were obtained from a wide range of ketones by catalytic enantioselective cyanosilylation using **4**, there have been no precedents of using an aryl alkyl ketone having a bulky *t*-butyldimethylsiloxy group at the end of the alkyl chain. Therefore, we were pleased when we found that application of a representative procedure[7] (10 mol% of catalyst **4**, THF, 30 °C for 92 h) gave the product cyanohydrin trimethylsilylether **9** in 91% yield with 79% ee (Table 1, entry 1). The chemical yield was determined after reduction to aminoalcohol **10**[8] because of decomposition of **9** to the starting ketone in silica gel chromatography. Enantiomeric excess was determined by chiral HPLC analysis after conversion to **10**

Table 1 Catalytic Asymmetric Cyanosilylation of **3** Using Ti Complex



3 (*R*) - **9** (*R*) - **10**

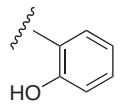
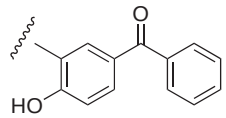
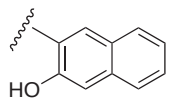
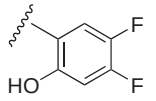
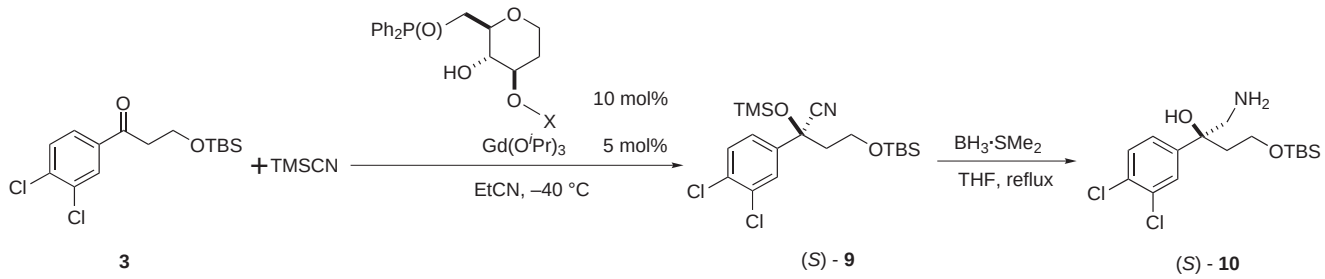
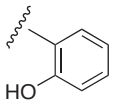
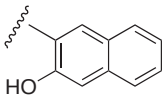
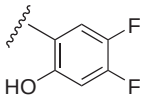
Entry	X	Time (h)	Yield	ee (%)
1		92	91%	79
2		92	67%	75
3		113	quant.	86
4		111	quant.	89

Table 2 Catalytic Asymmetric Cyanosilylation of **3** Using Gd Complex

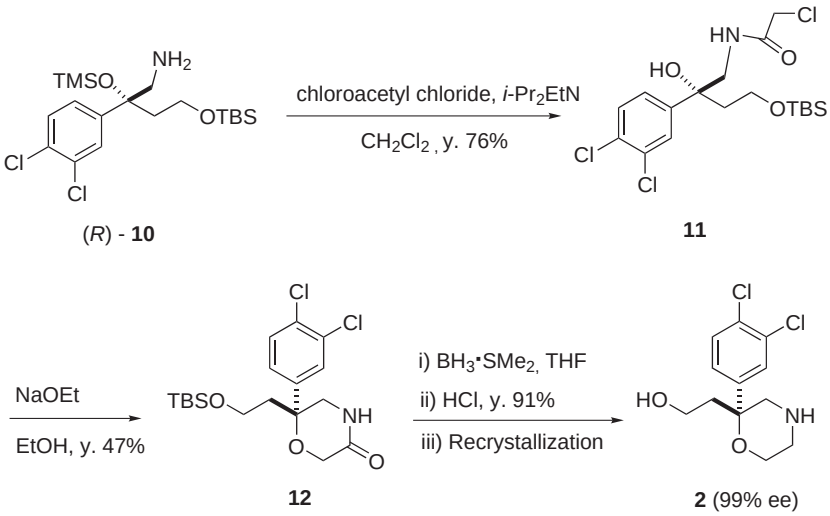


3 (*S*) - **9** (*S*) - **10**

Entry	X	Time (h)	Yield	ee (%)
1		4	quant.	81
2		3	quant.	75
3		3	quant.	86

and its benzamide form. Next, we tried to tune up the ligand in this asymmetric reaction. We selected ligands, which have an electron deficient and bulky cathecol unit in place of the cathecol unit of **4** according to previous reports.[9,10] Surprisingly, the 4-benzoyl cathecol ligand, which is the current best ligand on the Ti-system, gave **9** only in 67% yield with 75% ee (Table 1, entry 2). Then the ligand having a naphthalene-2,3-ol unit (Table 1, entry 3) or difluoro cathecol unit (Table 1, entry 4) was used, and chemical yields were gratifyingly improved to quantitative yield in both cases. Enantiomeric excesses were also improved to 86% ee and 89% ee, respectively. Absolute configuration of the product was determined to be *R* after converting to the key intermediate **2**. Next, to obtain the catalyst structure-activity relationship, we changed the Lewis acid metal of this catalyst to Gd (Table 2).[11,12] In this case the absolute configuration of the obtained **10** was switched to an (*S*)-configuration as reported[11] and using a difluoro cathecol ligand, comparable enantioselectivity was obtained to the Ti-difluoro cathecol ligand system.

Synthetic procedure from (*R*)-**10** to the key intermediate **2** is shown in Scheme 3. Amino alcohol (*R*)-**10** was then condensed with chloroacetyl chloride to amide **11**. Obtained **11** was converted to desired key intermediate **2** after ring construction using NaOEt, reduction with borane dimethylsulfide complex and following deprotection of



(*R*) - **10** **11** **12** **2** (99% ee)

Scheme 3 Synthesis of **2**

the TBS group with 1 N HCl. The key intermediate **2** was obtained without any loss of enantiomeric purity from **10** and recrystallization of **2** of 89% ee from a mixture of *n*-hexane and ethyl acetate yielded **2** of >99% ee in the form of white crystals.

In summary, an efficient synthesis of the key intermediate **2** of neurokinin receptor antagonist has been achieved by the use of a bifunctional asymmetric catalyst. Further work in this area is now in progress.

Acknowledgment

Financial support was provided by JSPS's Research for the Future Program.

References

(1) Regoli, D.; Boudon, A.; Fauchere, J.-L. *Pharmacol. Rev.* **1994**, *46*, 551; and references cited therein.
(2) Nishi, T.; Fukazawa, T.; Kurata, H.; Ishibashi, K.; Nakajima, K.; Yamaguchi, T.; Itoh, K. Sankyo Co. Ltd, Japan, EP-776893-A1, **1996**.
(3) Nishi, T.; Ishibashi, K.; Nakajima, K.; Iio, Y.; Fukazawa, T. *Tetrahedron: Asymmetry* **1998**, *9*, 3251.
(4) A synthetic method using iodoetherification and optical resolution was already reported: Takemoto, T.; Yukiko lio, Y.; Nishi, T. *Tetrahedron Lett.* **2000**, *41*, 1785.
(5) Hamashima, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 7412.
(6) Clay, R. J.; Collom, T. A.; Karrick, G. L.; Wemple, J. *Synthesis* **1993**, 290.
(7) A representative procedure: To a suspension of the chiral ligand (0.0565 mmol) in toluene (1 mL) was added Ti(*i*-Pr)$_4$ (16 μL, 0.054 mmol) at ambient temperature, and the whole mixture was stirred at 75 °C for 1 h. After the yellow solution was cooled to room temperature, toluene was evaporated under reduced pressure. The resulting pale yellow residue was further dried in vacuo for 1 h. The residue was dissolved in THF (0.9 mL), then $(CH_3)_3SiCN$ (14 μL, 0.108 mmol) was added using an ice bath, and the whole was stirred at room temperature for 30 min. To this catalyst solution, ketone **3** (180 mg, 0.54 mmol) in THF (0.9 mL) was added, followed by the addition of $(CH_3)_3SiCN$ (144 μL, 1.08 mmol) at 30 °C. The reaction was monitored by TLC, and after the reaction period described in Table 2, pyridine (0.1 mL) and H_2O (1 mL) were added. Usual workup gave the crude cyanohydrintrimethylsilylether **9**. ^{1}H NMR ($CDCl_3$, δ in ppm): 0.02 (6 H, s), 0.16 (9 H, s), 0.84 (9 H, s), 2.08–2.15 (1 H, m), 2.20–2.28 (1 H, m), 3.60–3.66 (1 H, m), 3.73–3.79 (1 H, m), 7.35 (1 H, dd, *J* = 2.0 Hz, 8.5 Hz), 7.46 (1 H, d, *J* = 8.5 Hz), 7.60 (1 H, d, *J* = 2.0 Hz).
(8) ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.04 (3 H, s), 0.01 (3 H, s), 0.87 (9 H, s), 1.44 (2 H, br. s), 1.88 (1 H, ddd, *J* = 14.6 Hz, 3.7 Hz, 3.7Hz), 2.16 (1 H, ddd, *J* = 14.6 Hz, 10.2 Hz, 4.6 Hz), 2.86 (1 H, d, *J* = 13.1 Hz), 2.91 (1 H, d, *J* = 13.1 Hz), 3.53 (1 H, ddd, *J* = 10.3 Hz, 10.2 Hz, 3.7 Hz), 3.73 (1 H, ddd, *J* = 10.3 Hz, 4.6 Hz, 3.7 Hz), 4.91 (1 H, br. s), 7.22 (1 H, dd, *J* = 8.6 Hz, 2.2 Hz), 7.42 (1 H, d, *J* = 8.6 Hz), 7.56 (1 H, d, *J* = 2.2 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 5.82, 5.77, 17.94, 25.70, 39.61, 53.27, 60.40, 77.21, 125.21, 128.28, 130.10, 130.59, 132.44, 145.46. IR (liquid film) cm^1: 3454, 2954, 2930, 1092, 837. HRMS: 364.1275 (calcd for $C_{16}H_{28}NO_2Cl_2Si$ 364.1266).
(9) Hamashima, Y.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2001**, *42*, 691.
(10) Masumoto, S.; Yabu, K.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 2919.
(11) Yabu, K.; Masumoto, S.; Yamasaki, S.; Hamashima, Y.; Kanai, M.; Du, W.; Curran, D. P.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 9908.
(12) A representative procedure: To a suspension of the chiral ligand (0.030 mmol) in THF (0.3 mL), Gd(*i*-PrO)$_3$ (0.2 M solution in THF, 75 μL, 0.015 mmol) was added at 0 °C, and the mixture was stirred at 45 °C for 30 min. The solvent was evaporated at ambient temperature, the resulting white powder was dissolved in EtCN (0.1 mL), and $(CH_3)_3SiCN$ (60 μL, 1.5 equiv) was added at –40 °C. After stirring for 15 min, the reaction was started by adding a solution of ketone **3** (0.30 mmol) in EtCN (0.1 mL).