



**HAL**  
open science

## Asymmetric Synthesis of an Antagonist of Neurokinin Receptors: SSR 241586

Thomas-Xavier Métro, Anne Cochi, Domingo Gomez Pardo, Janine Cossy

► **To cite this version:**

Thomas-Xavier Métro, Anne Cochi, Domingo Gomez Pardo, Janine Cossy. Asymmetric Synthesis of an Antagonist of Neurokinin Receptors: SSR 241586. *Journal of Organic Chemistry*, 2011, 76 (8), pp.2594 - 2602. 10.1021/jo102471r . hal-03228837

**HAL Id: hal-03228837**

**<https://hal.science/hal-03228837v1>**

Submitted on 18 May 2021

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

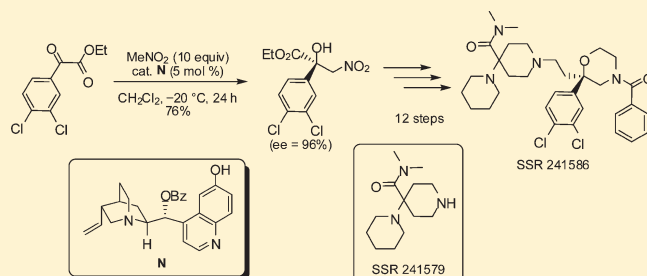
# Asymmetric Synthesis of an Antagonist of Neurokinin Receptors: SSR 241586<sup>†</sup>

Thomas-Xavier Métro, Anne Cochi, Domingo Gomez Pardo,\* and Janine Cossy\*

Laboratoire de Chimie Organique, ESPCI ParisTech, CNRS, 10 rue Vauquelin, 75231 Paris Cedex 05, France

Supporting Information

**ABSTRACT:** SSR 241586 is a 2,2-disubstituted morpholine, developed by Sanofi-Aventis, which is active in the treatment of schizophrenia and irritable bowel syndrome (IBS). Different strategies have been studied to synthesize this molecule and among the strategies an organo-catalyzed Henry reaction, applied to an  $\alpha$ -keto ester, has produced SSR 241586 in excellent enantiomeric excess.



## INTRODUCTION

The tachykinins, a family of neuropeptides including substance P (SP), neurokinin A (NKA), and neurokinin B (NKB) possess a number of biological properties such as pain transmission, gastrointestinal and urogenital tracts, vasodilatation, neurogenic inflammation, airway inflammation, bronchoconstriction in asthma, and chronic airway-obstructive disease. Three distinct types of receptors have been identified, NK1 (SP-preferring), NK2 (NKA preferring), and NK3 (NKB preferring),<sup>1</sup> and antagonists of these NK receptors have attracted considerable attention as powerful therapeutic agents.<sup>2</sup>

Among them, optically active morpholines SSR 241586 and SSR 240600 have been reported to be active in the treatment of depression, schizophrenia, urinary trouble, emesis, and irritable bowel syndrome (IBS) (Figure 1).<sup>3</sup>

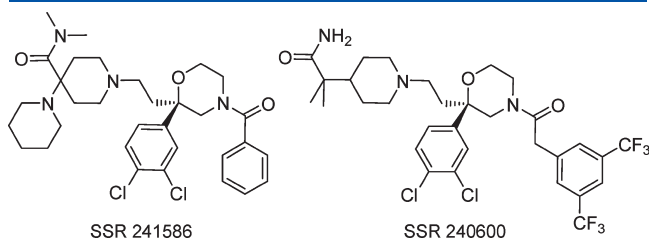


Figure 1. Structure of SSR 241586 and SSR 240600.

Different methods have been reported to synthesize optically active 2,2-disubstituted morpholines<sup>4</sup> such as crystallization of A with D-tartaric acid to produce E (Scheme 1, pathway 1),<sup>5</sup> Sharpless dihydroxylation (AD-mix  $\beta$ ) leading to F, which was then transformed to E (Scheme 1, pathway 2),<sup>6</sup> enantioselective epoxydation of homoallylic alcohol C, using cumene hydroperoxide in the presence of catalytic diisopropyl D-tartrate and Zr(O*t*-Bu)<sub>4</sub>, to produce epoxide G, which, after a few steps,

was also transformed to morpholine ring E (Scheme 1, pathway 3).<sup>7</sup> Synthesis of E was also achieved by using an asymmetric cyanosilylation of ketone D, using TMSCN in the presence of an optically active Lewis acid/base bifunctional catalyst J (Scheme 1, pathway 4).<sup>8</sup>

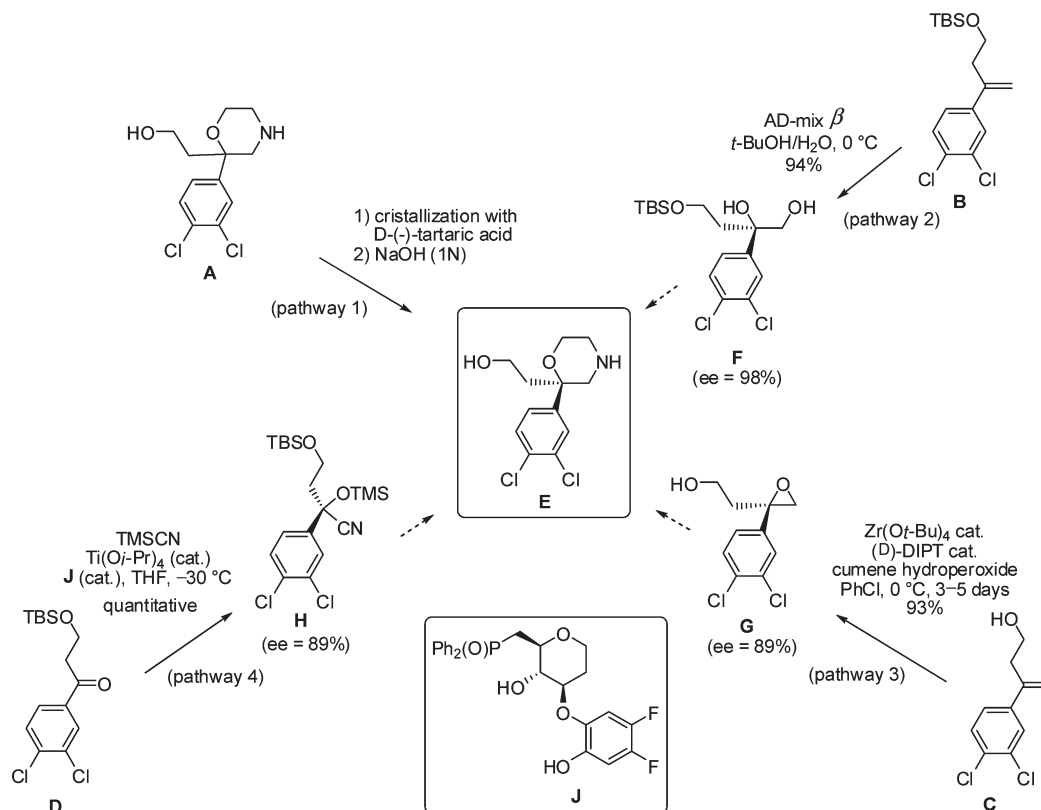
## RESULTS AND DISCUSSION

**First Strategy.** Recently, we have reported that  $\beta$ -amino alcohols of type K can be rearranged enantioselectively<sup>9–11</sup> to produce rearranged amino alcohols of type L that can be useful to synthesize biologically active products (Scheme 2).<sup>12</sup>

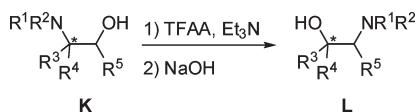
The use of this rearrangement to synthesize SSR 241586 was considered. Thus, the synthesis of this latter was planned from compound I, which would be transformed to a morpholine ring by *N,O*-alkylation, and amino alcohol I would be the result of the rearrangement of amino alcohol II by treatment with TFAA followed by the addition of Et<sub>3</sub>N and NaOH.<sup>10a,b</sup> This latter amino alcohol would be obtained from imino ester III possessing a quaternary center that would be controlled with use of the enantioselective alkylation of the Schiff base IV derived from V, using chiral phase transfer catalysis under the conditions developed by Maruoka et al. (Scheme 3).<sup>13</sup>

The synthesis of SSR 241586 started with the preparation of dichloro imino ester 5, which was realized in three steps from the commercially available 3,4-dichlorophenylacetonitrile 1. Treatment of 1 with isoamyl nitrite (1.25 equiv) in the presence of KOH (4 equiv) in a mixture of CH<sub>3</sub>CN/MeOH (1/1) (90 °C, 10 h) led to 2 in 89% yield.<sup>14</sup> The latter was treated with zinc (8.3 equiv) in the presence of formic acid (26.8 equiv) (MeOH/H<sub>2</sub>O 2/1; 5 °C for 1.5 h, then 0 °C for 15 h),<sup>15</sup> followed by

Scheme 1. Different Pathways To Access E



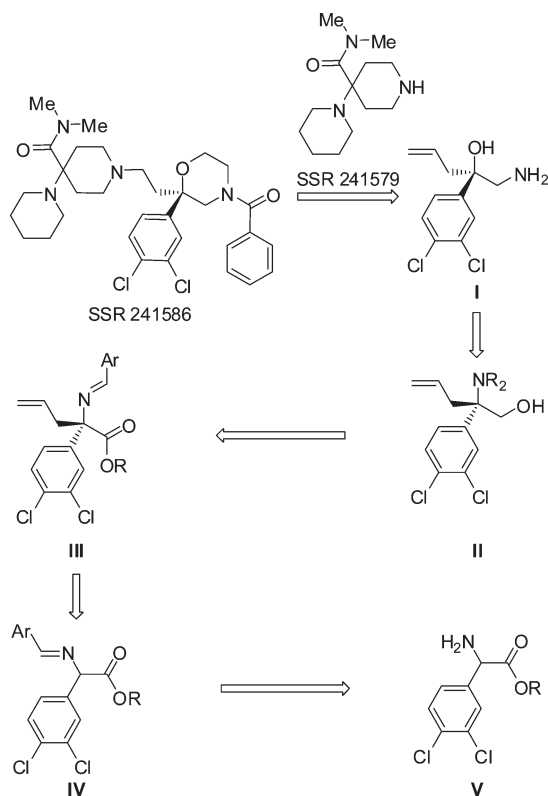
Scheme 2. Rearrangement of Amino Alcohols of Type K to L



esterification of the amino acid intermediate **3** (isobutylene,  $\text{H}_2\text{SO}_4$ , dioxane, rt, 24 h),<sup>16</sup> which produced the desired amino ester **4** with an overall yield of 27% (from **2**). The obtained amino ester **4** was then transformed to the Schiff base **5** (99% yield) by using *p*-chlorobenzaldehyde (1 equiv) in the presence of trimethylorthoformate (rt, 66 h) in order to trap the water formed during the process (Scheme 4).<sup>17</sup>

The alkylation of **5**, according to the phase transfer catalyst (PTC) conditions,<sup>13</sup> was achieved by using allyl bromide as the electrophile. Thus, compound **5** was treated with allyl bromide in the presence of catalyst **M** [(*S,S*)-3,4,5-trifluorophenyl-Nas],  $\text{CsOH} \cdot \text{H}_2\text{O}$  (5.0 equiv) as the base in toluene at  $-40^\circ\text{C}$ . After 24 h, acidic treatment ( $\text{HCl}$ , 1 N) afforded amino ester **6** in 42% yield with an enantiomeric excess of 45% (Table 1, entry 1). To improve the enantiomeric excess of **6**, the temperature was decreased to  $-80^\circ\text{C}$ . Under these conditions, the enantiomeric excess was increased to 52% but, unfortunately, the yield in **6** was low (16%) (Table 1, entry 2). When  $\text{CsOH} \cdot \text{H}_2\text{O}$  was replaced by  $\text{KOH}$ ,  $\text{NaOH}$ , or  $\text{LiOH} \cdot \text{H}_2\text{O}$ , the yield in **6** was not satisfactory (7% to 35%) and the enantiomeric excesses were similar to the one obtained previously with  $\text{CsOH} \cdot \text{H}_2\text{O}$  (40%–45%) (Table 1, entries 3–5). Compared to the results obtained by Maruoka et al. with other Schiff bases, it seems

Scheme 3



Scheme 4

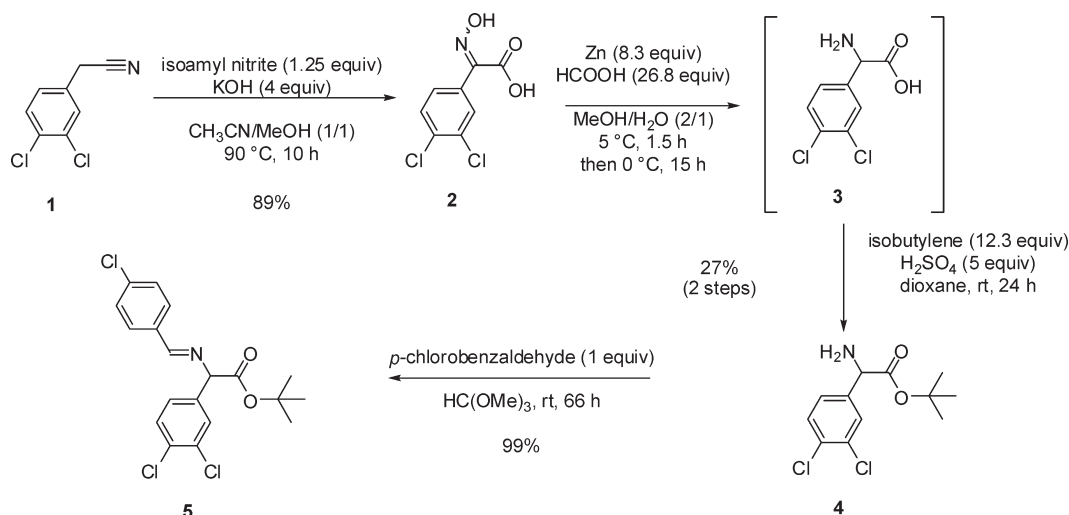
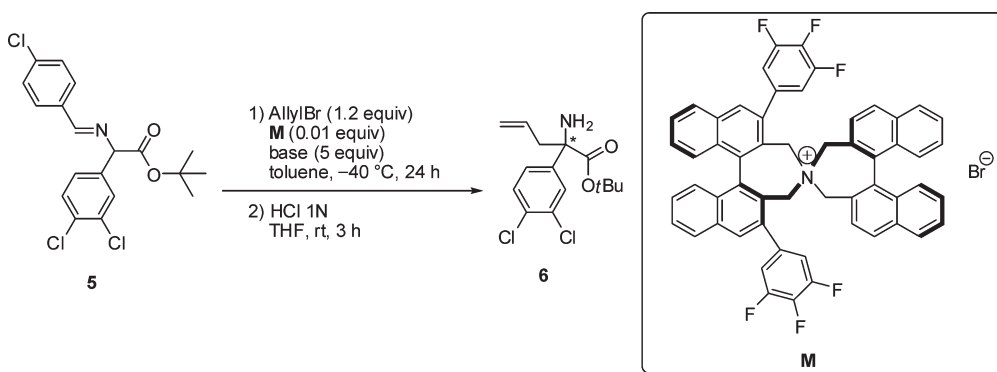


Table 1. Optimization of the Alkylation of 5 under PTC



entry	base	yield in 6, %	ee <sup>a</sup> of 6, %
1	CsOH·H <sub>2</sub> O	42	45
2	CsOH·H <sub>2</sub> O (−80 °C, 88 h)	16	52
3	KOH	13	41
4	NaOH	35	45
5	LiOH·H <sub>2</sub> O	7	40

<sup>a</sup> Enantiomeric excess determined by supercritical fluid chromatography (SFC) on Daicel chiralcel AD-H column.

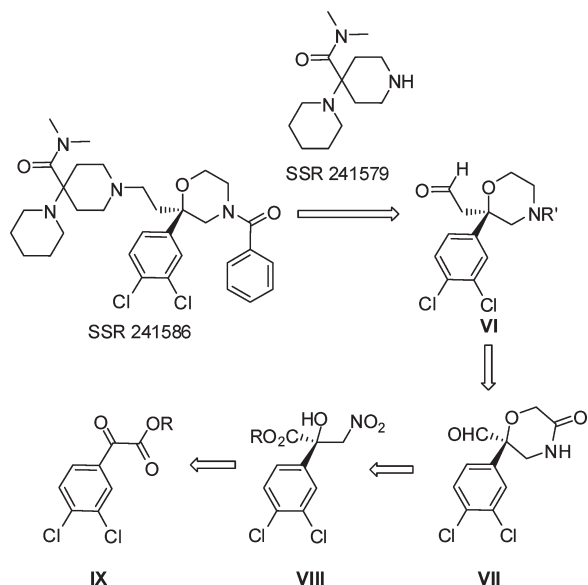
that the presence of the two chlorine atoms on the aromatic ring is troublesome in achieving the alkylation of 5 under phase transfer catalyst conditions. Due to this failure, a second strategy to synthesize SSR 241586 was envisaged.

**Second Strategy.** The synthesis of SSR 241586 using an enantioselective organo-catalyzed Henry reaction to control the (*R*)-configuration of the stereogenic center was then envisaged. The Henry reaction allows the synthesis of  $\beta$ -nitro alcohols which can be transformed easily to  $\beta$ -amino alcohols and  $\alpha$ -hydroxy carboxylic acids.<sup>18</sup> Since the work of Shibasaki et al.,<sup>19</sup> the catalytic asymmetric Henry reaction<sup>20</sup> by metal catalysis,<sup>21</sup> organocatalysis,<sup>22</sup> as well as biocatalysis<sup>23</sup> has been developed. Many successful examples involving enantioselective nitro-aldol reaction with aldehydes have been reported.<sup>24</sup> On the contrary, limited success was obtained with ketones.<sup>25</sup> Among the successful ones, the Henry reaction conditions tuned up by Deng et al.<sup>25f</sup> have inspired us

for approaching the synthesis of SSR 241586. The synthesis of SSR 241586 was planned from a reductive amination of aldehyde VI using the appropriate piperidine SSR 241579. Aldehyde VI would be the result of a one carbon homologation of aldehyde VII, which would be issued from  $\beta$ -nitro-alcohol VIII. The latter would be the result of an enantioselective addition of nitromethane to  $\alpha$ -keto ester IX according to an enantioselective Henry reaction (Scheme 5).

The synthesis of SSR 241586 started with the transformation of the commercially available ethyl oxalyl chloride 7, which was transformed to 9 in two steps. After the transformation of compound 7 to ethyl  $\alpha$ -oxo-1*H*-imidazole-1-acetate 8<sup>26</sup> (imidazole, THF, 0 °C, 3 h, 95%), the latter was treated with 3,4-dichlorophenylmagnesium bromide to produce the desired  $\alpha$ -ketoester 9 in 74% yield (THF, −78 °C to rt, 2 h). An organo-catalyzed Henry reaction was then applied to 9, utilizing nitromethane (10 equiv) and catalyst N (5 mol %, CH<sub>2</sub>Cl<sub>2</sub> at −20 °C).<sup>25f</sup>  $\beta$ -Nitro

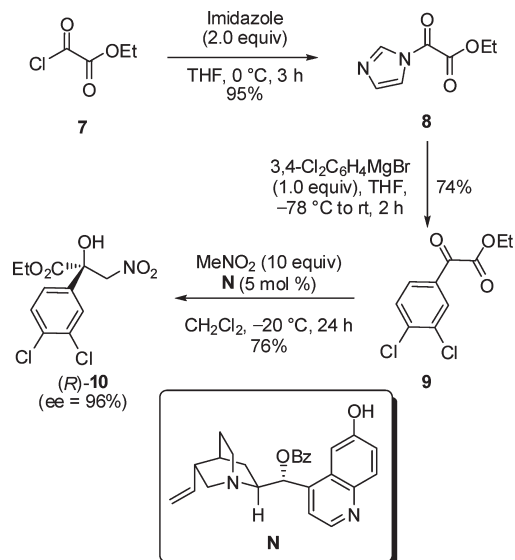
## Scheme 5



alcohol (*R*)-**10**<sup>27</sup> was isolated in 76% yield with an enantiomeric excess of 96% (Scheme 6).<sup>28</sup>

To construct the morpholine ring present in SSR 241586, the nitro group present in **10** has to be reduced. At first, different conditions were tested on the racemic compound **10**. Treatment of compound **10** with Pd/C in the presence of ammonium formate in MeOH did not allow us to isolate compound **11** (Table 2, entry 1). On the other hand, in the presence of an excess of Raney nickel in EtOH under H<sub>2</sub> (1 atm), amino alcohol **11** was isolated in 20% yield as well as the hydroxy ester **12** in 35% yield (Table 2, entry 2). After a retro-Henry reaction that takes place in compound **10**, the reduction of **9** led to hydroxyl ester **12**. The strong basicity of the aqueous phase in which the Raney nickel is stored could explain this side reaction. However, washing the Raney nickel with water several times did not allow the isolation of the amino alcohol **11** with a better yield (Table 2, entry 3). Due to this result, a reduction in acidic conditions was envisaged. Thus, treatment of  $\beta$ -nitro alcohol **10** with zinc dust in acetic acid provided the desired amino alcohol **11** in 88% yield without any traces of hydroxy ester **12** (Table 2, entry 4). When these conditions were applied to the enantiomeric compound (*R*)-**10**, the amino alcohol (*R*)-**11** was obtained without any racemization (cf. vide infra).

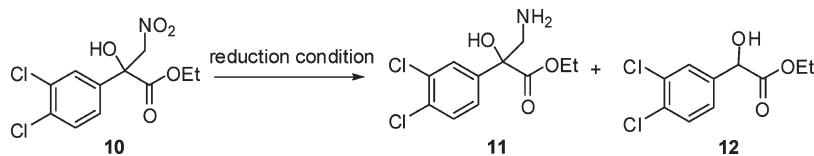
## Scheme 6



After *N*-chloroacetylation of the resulting amine (*R*)-**11** (ClCH<sub>2</sub>COCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, rt, 4 h), the transformation of the obtained compound **13** to morpholinone **14** was realized by treatment with NaH (2 equiv, THF, 0 °C, 1 h, 75%) leading to 2,2-disubstituted morpholine derivative **15** after reduction of both the amide and ester groups present in **14** by using BH<sub>3</sub>·THF (6 equiv, refluxing THF, 3 h, 88%). To access SSR 241586, morpholine **15** was benzoylated to furnish **16** (BzCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, rt, 1 h, 99%). We have to point out that all these steps were achieved without any racemization (Scheme 7).<sup>29</sup>

The transformation of alcohol **16**, via enol ether **17**, to aldehyde **18** has to be performed to achieve a reductive amination, involving amine SSR 241579, which will produce the desired SSR 241586. Thus, alcohol **16** was oxidized by Dess–Martin periodinane (CH<sub>2</sub>Cl<sub>2</sub>, rt, 1 h) and the crude aldehyde was treated with methoxymethylene-triphenylphosphonium chloride in the presence of *n*-BuLi in THF, and different conditions were tested. The first assay was realized in the presence of methoxymethylene-triphenylphosphonium chloride (5 equiv) and *n*-BuLi (4.5 equiv), unfortunately compound **17** was not isolated (Table 3, entry 1). In the presence of 7.0 equiv of methoxymethylene-triphenylphosphonium chloride and 6.0 equiv of *n*-BuLi, compound **17** was isolated in a poor yield of 31% (Table 3, entry 2). It is worth noting that the yield was increased

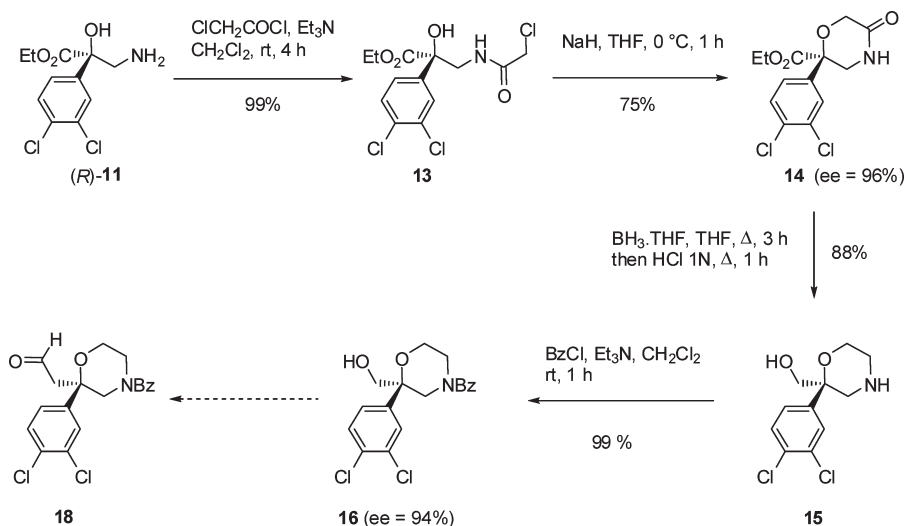
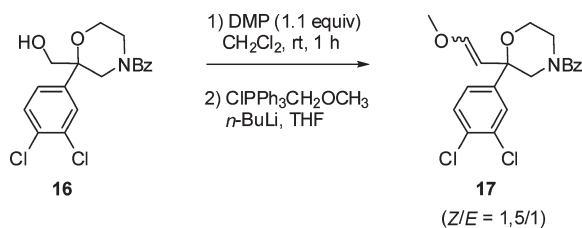
Table 2. Reaction Conditions To Reduce  $\beta$ -Nitro Alcohol **10**<sup>a</sup>



entry	conditions	yield in <b>11</b> , %	yield in <b>12</b> , %
1	Pd/C, NH <sub>4</sub> HCO <sub>2</sub> , MeOH	0	0
2	H <sub>2</sub> , Raney Ni, EtOH	20	35
3	H <sub>2</sub> , Raney Ni, EtOH Raney Ni first washed with water	25	12
4	Zn (40 equiv), AcOH <sup>b</sup>	88	0

<sup>a</sup> Reaction conditions tested on ( $\pm$ )-**10**. <sup>b</sup> Conditions applied to (*R*)-**10**.

Scheme 7

Table 3. Oxidation/Wittig Conditions<sup>a</sup>

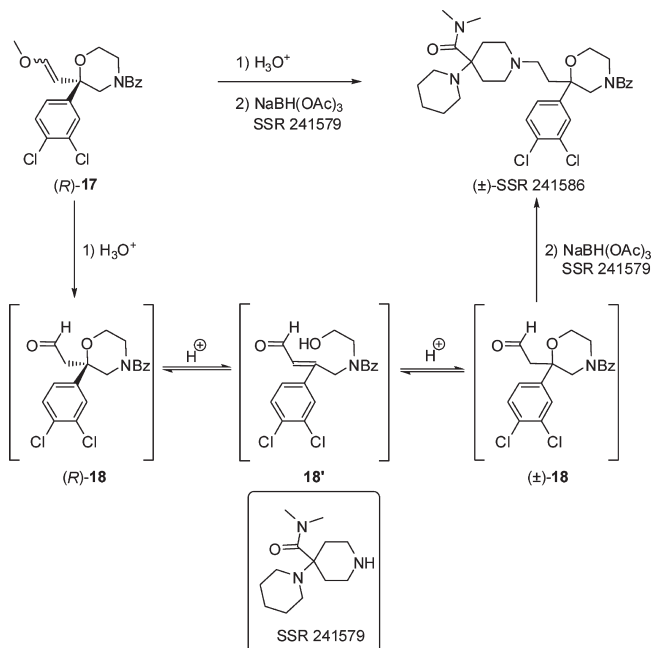
entry	conditions	yield in 17, %
1	$\text{Cl}^- \text{PPh}_3\text{CH}_2\text{OCH}_3$ (5 equiv), <i>n</i> -BuLi (4.5 equiv), $-45^\circ\text{C}$ to rt	0
2	$\text{Cl}^- \text{PPh}_3\text{CH}_2\text{OCH}_3$ (7 equiv), <i>n</i> -BuLi (6 equiv), $-78^\circ\text{C}$ to rt	31
3	$\text{Cl}^- \text{PPh}_3\text{CH}_2\text{OCH}_3$ (7 equiv), <i>n</i> -BuLi (6 equiv), <sup>b</sup> $0^\circ\text{C}$ then rt	59

<sup>a</sup> Reaction conditions tested on ( $\pm$ )-17. <sup>b</sup> Reaction conditions applied to (*R*)-17.

when the reaction was achieved on a larger scale (0.22 mmol versus 0.04 mmol) at  $0^\circ\text{C}$  as enol ether 17 was isolated with a yield of 59% as a mixture (*Z*)-17 and (*E*)-17 isomers in a ratio of 1.5 to 1 (Table 3, entry 3).

When methylenol ether (*R*)-17 was hydrolyzed with 5 N HCl in THF for 2 h at rt, the crude aldehyde 18 was formed and directly condensed with piperidine SSR 241579 [*N,N*-dimethyl-4-(piperidin-1-yl)piperidin-4-carboxamide].<sup>30</sup> The addition of  $\text{NaBH}(\text{OAc})_3$  ( $\text{CH}_2\text{Cl}_2$ , rt, 1 h) allowed the isolation of the desired SSR 241586 in 90% yield; however, a racemization was observed (ee = 54%) (Table 4, entry 1). Other conditions for the hydrolysis of 17 were tried by using 1 N HCl (Table 4, entry 2), 12 N HCl (Table 4, entry 3), and oxalic acid dihydrate (Table 4, entry 4) but, unfortunately, in each case a racemization was observed (ee was respectively 24%, 50%, and 14%). This racemization is probably the result of a retro-oxa-Michael/oxa-Michael sequence that takes place under acidic conditions producing ( $\pm$ )-18 via 18'.

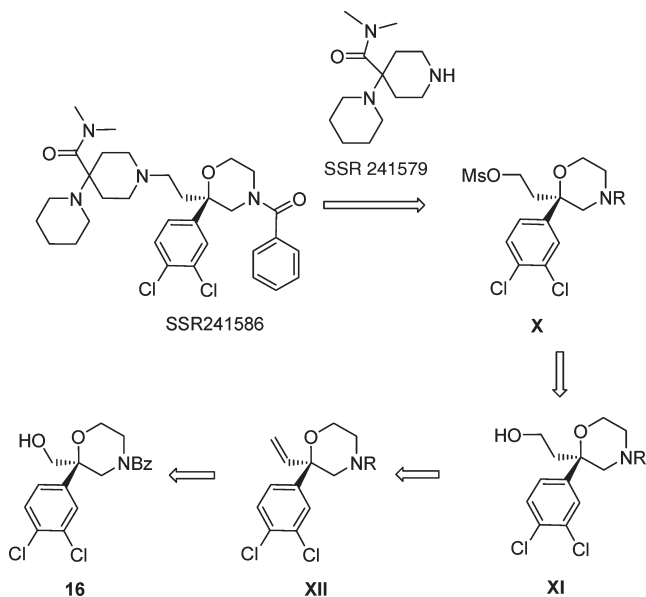
**Third Strategy.** Due to this racemization, our retrosynthetic analysis was revised. Instead of synthesizing SSR 241586 by a reductive amination of an aldehyde using SSR 241579, a

Table 4. Hydrolysis of Enol Ether (*R*)-17 Followed by Reductive Amination

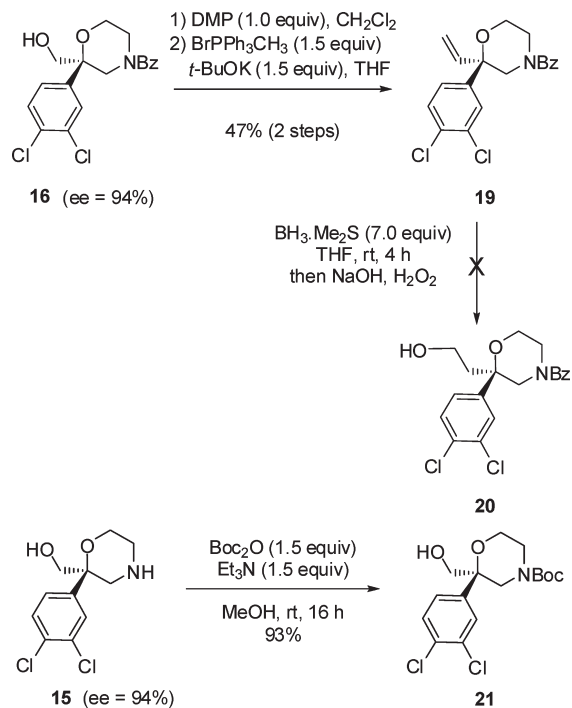
entry	acidic conditions	yield in SSR 241586, %	ee of SSR 241586, %
1	HCl 5 N, THF 1 h, rt	90	54
2	HCl 1 N, THF, 26 h, rt	39	24
3	HCl 12 N, THF, 0.75 h, rt	43	50
4	$(\text{CO}_2\text{H})_2 \cdot 2\text{H}_2\text{O}$ , MeOH/ $\text{H}_2\text{O}$ 10/2, 28 h, rt	12	14

nucleophilic substitution of mesylate X by SSR 241579, which would lead to SSR 241586, was considered. This strategy implies

Scheme 8



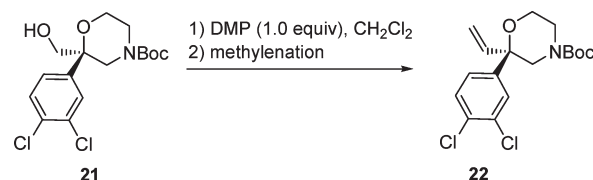
Scheme 9



the synthesis of alcohol XI, which would be the result of a hydroboration of olefin XII issued from alcohol 16 (Scheme 8).

Alcohol 16 was transformed to olefin 19 after oxidation (DMP,  $\text{CH}_2\text{Cl}_2$ ) and an olefination of the resulting aldehyde was performed ( $\text{BrPPh}_3\text{CH}_3$ ,  $t\text{-BuOK}$ , THF). Attempts to achieve a hydroboration/oxidation sequence on 19 ( $\text{BH}_3 \cdot \text{Me}_2\text{S}$ , THF,  $\Delta$  then  $\text{H}_2\text{O}_2$ , NaOH) were unsatisfactory as the desired alcohol 20 was not isolated. Among the side products, one product was the result of the reduction of the *N*-benzoyl group. Thus, the protection of the hydroxymethylmorpholine 15 before the

Table 5. Conditions of Methylenation



entry	conditions	yield in 22, %
1	$\text{Br}^+\text{PPh}_3\text{CH}_3$ (7 equiv), <i>n</i> -BuLi (6 equiv), 0 °C then rt	21
2	$\text{Br}^+\text{PPh}_3\text{CH}_3$ (15 equiv), <i>n</i> -BuLi (14 equiv), 0 °C then rt	21
3	$\text{Br}^+\text{PPh}_3\text{CH}_3$ (1.5 equiv), KHMDS (1.5 equiv), 0 °C then rt	53
4	$\text{Br}^+\text{PPh}_3\text{CH}_3$ (3 equiv), KHMDS (3 equiv), 0 °C then rt	82
5	$\text{Cp}_2\text{TiMe}_2$ (6 equiv), 60 °C	0
6	(i) $\text{RhCl(PPh}_3)_3$ (2.5 mol %), <i>i</i> PrOH, PPh <sub>3</sub> ; (ii) TMSCHN <sub>2</sub>	10

hydroboration/oxidation was planned ( $\text{Boc}_2\text{O}$ ,  $\text{Et}_3\text{N}$ , MeOH, rt, 16 h, 93%) (Scheme 9).<sup>28</sup>

The resulting compound 21 was oxidized (DMP,  $\text{CH}_2\text{Cl}_2$ , rt, 1 h) to produce the corresponding aldehyde, which was transformed to olefin 22. Different conditions of methylenation were tested, as in the previous strategy, the Wittig reaction was performed with methyltriphenylphosphonium bromide ( $\text{BrPPh}_3\text{CH}_3$ ) and *n*-BuLi (6–14 equiv) and the desired olefin was isolated in 21% yield (Table 5, entries 1–2). By using 1.5 equiv of  $\text{BrPPh}_3\text{CH}_3$  and KHMDS the yield in 22 was significantly improved to 53% and increased to 82% by utilizing 3 equiv of  $\text{BrPPh}_3\text{CH}_3$  and KHMDS (Table 5, entries 3–4). We have to point out that the Petasis reagent<sup>31</sup> applied to the aldehyde coming from the oxidation of 21 did not produce olefin 22 (Table 5, entry 5), and by using rhodium-catalyzed methylenation,<sup>32</sup> compound 22 was isolated with a poor yield of 10% (Table 5, entry 6).

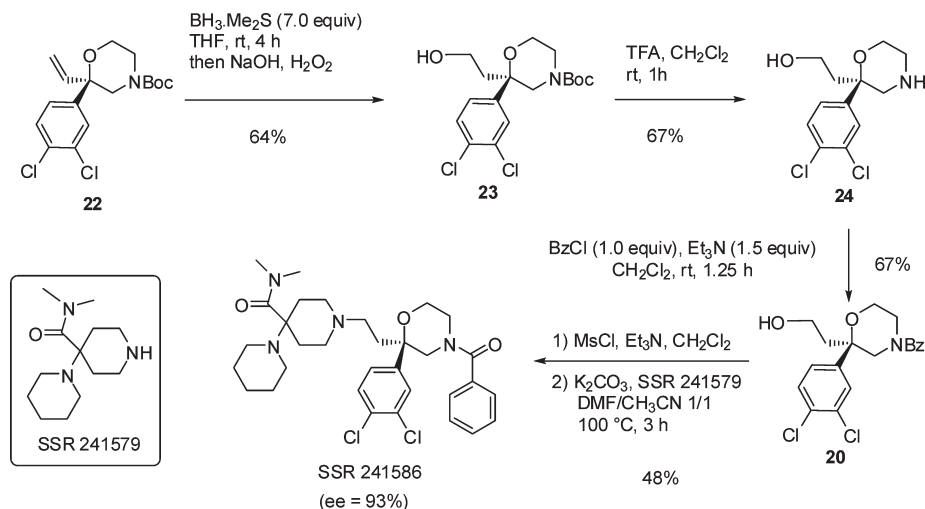
The hydroboration/oxidation sequence of olefin 22 was successfully achieved and the desired alcohol was isolated in 64% yield ( $\text{BH}_3 \cdot \text{Me}_2\text{S}$  then  $\text{H}_2\text{O}_2$ , NaOH). After a deprotection/protection sequence (TFA, then  $\text{BzCl}$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ ) the desired *N*-benzoylmorpholine 20 was produced in 45% yield (for the two steps) and its transformation to SSR 241586 was achieved in two steps. After mesylation and addition of SSR 241579 in the presence of  $\text{K}_2\text{CO}_3$  (DMF/ $\text{CH}_3\text{CN}$ : 1/1, 100 °C, 3 h), SSR 241586<sup>33</sup> was isolated in 48% yield with an enantiomeric excess of 93% (Scheme 10).<sup>28</sup>

Among the three examined strategies, one of them was successful and SSR 241586 was synthesized without racemization in 15 steps with an overall yield of 3% by using an enantioselective organo-catalyzed Henry reaction, an oxidation/methylenation/hydroboration sequence.<sup>28</sup> Due to the versatility of the utilized reactions, a library of SRR 241586 analogues should be easily synthesized for SAR studies.

## EXPERIMENTAL SECTION

(3,4-Dichlorophenyl)hydroxyiminoacetic acid (2):<sup>14</sup> To a suspension of 3,4-dichlorophenylacetonitrile (1) (10.0 g 53.8 mmol, 1.0 equiv) and KOH (12.1 g 216.0 mmol, 4.0 equiv) in MeCN/MeOH (1/1; 70 mL) was added dropwise isoamyl nitrite (9.0 mL, 67.2 mmol, 1.25 equiv). After 1.5 h at 50 °C then 10 h at 90 °C, water (25 mL) and  $\text{CHCl}_3$  (50 mL) were added to the reaction mixture. The aqueous phase is extracted with  $\text{CHCl}_3$  (2  $\times$  50 mL), acidified with an addition of an aqueous solution of HCl (2.4 M) until pH <2, then extracted with AcOEt (3  $\times$  50 mL). The organic layer was dried over  $\text{MgSO}_4$ , filtered, and then evaporated under reduced pressure. (3,4-Dichlorophenyl)hydroxyiminoacetic acid (2) (11.2 g, 48.0 mmol, 89%) was isolated as a white solid. Mp 210–211 °C; IR

Scheme 10



(neat) 3500–2100, 1879, 1718, 1593, 1462, 1373, 1284, 1260, 1237, 1059, 1029, 847, 746, 725, 653  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz, acetone- $d_6$ )  $\delta$  7.74 (d,  $J = 1.7$  Hz, 1H), 7.65 (d,  $J = 8.4$  Hz, 1H), 7.50 (dd,  $J = 8.3$  and 1.7 Hz, 1H);  $^{13}\text{C}$  NMR (100 MHz, acetone- $d_6$ )  $\delta$  164.4 (s), 147.9 (s), 133.4 (s), 132.4 (d), 132.1 (s), 131.1 (s), 130.8 (d), 130.5 (d); MS  $m/z$  (%) 175 ( $\text{M}^+ - \text{CO}_2 - \text{H}_2\text{O}$ , 10), 173 ( $\text{M}^+ - \text{CO}_2 - \text{H}_2\text{O}$ , 65), 171 ( $\text{M}^+ - \text{CO}_2 - \text{H}_2\text{O}$ , 100), 136 (18), 100 (16), 75 (7).

**tert-Butyl (3,4-dichlorophenyl)glycinate (4):** To a solution of compound 2 (5.0 g, 21.4 mmol, 1.0 equiv) and zinc dust (washed with a solution of 1 N HCl; 11.6 g, 177 mmol, 8.3 equiv) in MeOH/ $\text{H}_2\text{O}$  (2/1; 60 mL) was added dropwise formic acid 90% (24.0 mL, 573 mmol, 26.8 equiv). After 1.5 h at 5 °C then 15 h at 0 °C, the reaction mixture was concentrated under reduced pressure. To a suspension of the pale gray solid obtained (5.0 g from the 16.7 g obtained; 6.4 mmol, 1.0 equiv) and concentrated  $\text{H}_2\text{SO}_4$  (98%) (1.7 mL, 31.9 mmol, 5.0 equiv) in distilled dioxane (7.5 mL) was added very slowly isobutylene (6.8 mL, 78.8 mmol, 12.3 equiv) previously condensed in a bath at  $-78$  °C. The reaction mixture was placed in a sealed bottle. After 24 h at rt, the reaction mixture was cautiously degassed then poured on an aqueous solution of 2 N NaOH (50 mL). The aqueous phase was extracted with  $\text{Et}_2\text{O}$  (2  $\times$  50 mL), and the organic phase was dried over  $\text{Na}_2\text{SO}_4$ , filtered, and then evaporated under reduced pressure. After purification by flash chromatography on silica gel ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ : 99/1), 4 (475 mg, 1.7 mmol, 27% over 2 steps) was isolated as a yellow oil. IR (neat) 3384, 2978, 1729, 1469, 1368, 1251, 1148, 1030, 843, 789  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.51 (d,  $J = 2.1$  Hz, 1H), 7.41 (d,  $J = 8.3$  Hz, 1H), 7.24 (dd,  $J = 8.4$  and 2.1 Hz, 1H), 4.46 (s, 1H), 1.84 (br s, 2H), 1.41 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  172.2 (s), 141.0 (s), 132.6 (s), 131.7 (s), 130.5 (d), 128.9 (d), 126.1 (d), 82.2 (s), 58.2 (d), 27.9 (q); MS  $m/z$  (%) 178 ( $\text{M}^+ - \text{CO}_2\text{tBu}^+$ , 8), 176 ( $\text{M}^+ - \text{CO}_2\text{tBu}^+$ , 62), 174 ( $\text{M}^+ - \text{CO}_2\text{tBu}^+$ , 100), 147 (2), 139 (2), 111 (6), 104 (5), 75 (3), 57 (16). Anal. Calcd for  $\text{C}_{12}\text{H}_{15}\text{Cl}_2\text{NO}_2$ : C, 52.19; H, 5.47; N, 5.07. Found: C, 52.06; H, 5.25; N, 4.83.

**tert-Butyl N-(4-chlorobenzylidene)(3,4-dichlorophenyl)glycinate (5):** To a solution of 4 (437 mg, 1.58 mmol, 1.0 equiv) in trimethylorthoformate (9 mL) was added *p*-chlorobenzaldehyde (222 mg, 1.58 mmol, 1.0 equiv). After 66 h at rt, the reaction mixture was concentrated under reduced pressure and compound 5 (640 mg, 1.58 mmol, 99%) was isolated as a yellow oil. IR (neat) 2978, 1733, 1642, 1469, 1369, 1249, 1146, 1089, 1032, 825  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.29 (s, 1H), 7.77 (d,  $J = 8.5$  Hz, 2H), 7.63 (d,  $J = 1.9$  Hz, 1H), 7.46–7.34 (m, 4H), 4.99 (s, 1H), 1.42 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  169.0 (s), 162.7 (d), 138.7 (s), 137.5 (s), 134.0 (s), 132.6 (s), 132.0 (s), 130.9 (d), 130.4 (d), 129.9 (d), 129.8 (d), 129.5 (d), 128.9

(d), 127.2 (d), 82.5 (s), 75.8 (d), 27.9 (q); MS  $m/z$  (%) 300 ( $\text{M}^+ - \text{CO}_2\text{tBu}^+$ , 33), 298 ( $\text{M}^+ - \text{CO}_2\text{tBu}^+$ , 100), 296 ( $\text{M}^+ - \text{CO}_2\text{tBu}^+$ , 98), 282 (3), 261 (8), 233 (5), 199 (16), 159 (43), 125 (49), 89 (26), 57 (63). Anal. Calcd for  $\text{C}_{19}\text{H}_{18}\text{Cl}_3\text{NO}_2$ : C, 57.24; H, 4.55; N, 3.51. Found: C, 56.85; H, 4.44; N, 3.38.

**tert-Butyl allyl(3,4-dichlorophenyl)glycinate (6):** To a solution of 5 (100 mg, 0.25 mmol, 1.0 equiv), allyl bromide (26  $\mu\text{L}$ , 0.30 mmol, 1.2 equiv), and optically active catalyst **M** (2 mg, 2  $\mu\text{mol}$ , 0.01 equiv) in dry toluene (2 mL, degassed by Argon bubble) was added at  $-40$  °C  $\text{CsOH}\cdot\text{H}_2\text{O}$  (211 mg, 1.25 mmol, 5.0 equiv). After 24 h at  $-40$  °C, water was added to the reaction mixture. The aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (2  $\times$  10 mL). The organic phase was dried over  $\text{Na}_2\text{SO}_4$ , filtered, and then evaporated under reduced pressure. To a solution in THF (2 mL) of the yellow oil obtained was added an aqueous solution of 1 N HCl (1 mL). After 3 h at rt, the reaction mixture is neutralized with addition of an aqueous solution of 2.5 M NaOH (10 mL). The aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (2  $\times$  10 mL). The organic phase was dried over  $\text{Na}_2\text{SO}_4$ , filtered, and then evaporated under reduced pressure. After purification by flash chromatography on silica gel ( $\text{CH}_2\text{Cl}_2$  then  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  99/1), 6 (33 mg, 0.10 mmol, 42% over 2 steps) was isolated as a yellow oil. ee = 45% determined by supercritical fluid chromatography on Daicel chiralcel AD-H column (MeOH 10%, flow rate 5 mL/min,  $t_{\text{major}} = 1.17$  min,  $t_{\text{minor}} = 1.40$ ); IR (neat) 3387, 3078, 2978, 2927, 2855, 1726, 1467, 1369, 1248, 1150, 1030, 924, 844, 678  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.73 (d,  $J = 1.2$  Hz, 1H), 7.41–7.40 (m, 2H), 5.68 (m, 1H), 5.22–5.17 (m, 2H), 2.90 (dd,  $J = 13.7$  and 6.4 Hz, 1H), 2.53 (dd,  $J = 13.7$  and 8.0 Hz, 1H), 1.80 (br s, 2H), 1.44 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  173.4 (s), 143.7 (s), 132.5 (d), 132.4 (s), 131.4 (s), 130.1 (d), 128.0 (d), 125.2 (d), 120.4 (t), 82.4 (s), 62.7 (s), 44.8 (t), 27.9 (q); MS  $m/z$  (%) 218 ( $\text{M}^+ - \text{CO}_2\text{tBu}^+$ , 28), 216 ( $\text{M}^+ - \text{CO}_2\text{tBu}^+$ , 65), 214 ( $\text{M}^+ - \text{CO}_2\text{tBu}^+$ , 100), 174 (18), 172 (25), 162 (5), 145 (4), 136 (3), 109 (2), 57 (9); HRMS (ESI) calcd for  $\text{C}_{15}\text{H}_{20}\text{Cl}_2\text{NO}_2$  ( $\text{M} + \text{H}^+$ ) 316.0866, found 316.0868.

**[2-(3,4-Dichlorophenyl)-2-(*Z*)-2-methoxyvinyl]morpholin-4-yl]phenylmethanone (Z-17):** To a solution of 16 (82 mg, 0.22 mmol, 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (10 mL) was added Dess–Martin periodinane (105 mg, 0.25 mmol, 1.1 equiv). After 1 h at rt, the reaction mixture was quenched by addition of a saturated aqueous solution of  $\text{Na}_2\text{S}_2\text{O}_3$  followed by the addition of an aqueous saturated solution of  $\text{NaHCO}_3$  and then extracted with AcOEt (10 mL). The organic layer was dried over  $\text{MgSO}_4$ , filtered, and then evaporated under reduced pressure. The crude aldehyde was used without further purification. To a solution of methoxymethyltriphenylphosphonium



chloride (537 mg, 1.57 mmol, 7.0 equiv) in THF (15 mL) was added *n*-BuLi (2.5 M in hexane, 540  $\mu$ L, 1.35 mmol, 6.0 equiv) at 0 °C. After being stirred for 30 min at 0 °C, a solution of the crude aldehyde in THF (10 mL) was added at 0 °C. After 1 h at rt, the reaction mixture was neutralized by addition of a saturated aqueous solution of NaHCO<sub>3</sub> and then extracted with AcOEt (80 mL). The organic layer was dried over MgSO<sub>4</sub>, filtered, and then evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/AcOEt 90/10 to 50/50) to give the products as yellow oils *Z*-17 (31 mg, 79  $\mu$ mol, 35%) and *E*-17 (21 mg, 54  $\mu$ mol, 24%). *R*<sub>f</sub> 0.3 (PE/AcOEt 50/50); IR (neat) 2924, 2855, 1631, 1427, 1271, 1078, 1027 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub> at 120 °C)  $\delta$  7.60 (d, *J* = 1.4 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.47–7.43 (m, 3H), 7.39–7.34 (m, 3H), 6.09 (d, *J* = 6.9 Hz, 1H), 4.51 (d, *J* = 6.9 Hz, 1H), 4.09 (d, *J* = 13.4 Hz, 1H), 3.85–3.79 (m, 2H), 3.70–3.60 (m, 2H), 3.39 (s, 3H), 3.33 (m, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  170.4 (s), 148.9 (d), 143.6 (s), 135.4 (s), 132.2 (s), 131.1 (s), 130.0 (d), 129.9 (d), 128.5 (d), 128.2 (d), 127.0 (d, 2C), 125.5 (d, 2C), 106.7 (d), 77.26 (s), 61.2 (t), 60.5 (q), 49.9 (t), 47.5 (t); HRMS (ESI) calcd for C<sub>20</sub>H<sub>20</sub>NO<sub>3</sub>Cl<sub>2</sub> (M + H<sup>+</sup>) 392.0815, found 392.0816.

[2-(3,4-Dichlorophenyl)-2-((*E*)-2-methoxyvinyl)morpholin-4-yl]phenylmethanone (*E*-17): *R*<sub>f</sub> 0.5 (PE/AcOEt 50/50); IR (neat) 2924, 2860, 1629, 1430, 1221, 1076, 1027 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub> at 100 °C)  $\delta$  7.60–7.58 (m, 2H), 7.47–7.45 (m, 3H), 7.37 (dd, *J* = 8.5 and 1.8 Hz, 1H), 7.34–7.31 (m, 2H), 6.47 (d, *J* = 12.9 Hz, 1H), 4.89 (d, *J* = 12.9 Hz, 1H), 3.98 (d, *J* = 13.7 Hz, 1H), 3.85 (m, 1H), 3.81 (d, *J* = 13.7 Hz, 1H), 3.62 (m, 1H), 3.54 (m, 1H), 3.52 (s, 3H), 3.42 (m, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  170.0 (s), 151.5 (d), 143.1 (s), 135.1 (s), 132.6 (s), 131.6 (s), 130.5 (d), 130.0 (d), 128.7 (d), 128.6 (d), 127.1 (d), 126.9 (d), 125.9 (d), 125.3 (d), 105.1 (d), 77.24 (s), 61.0 (t), 56.4 (q), 48.9 (t), 47.5 (t); HRMS (ESI) calcd for C<sub>20</sub>H<sub>20</sub>NO<sub>3</sub>Cl<sub>2</sub> (M + H<sup>+</sup>) 392.0815, found 392.0816.

## ASSOCIATED CONTENT

**S** Supporting Information. NMR spectra of compounds 2, 4–6, and 17 and SFC spectra of compound 6. This material is available free of charge via the Internet at <http://pubs.acs.org>.

## AUTHOR INFORMATION

### Corresponding Author

\*E-mail: [domingo.gomez-pardo@espci.fr](mailto:domingo.gomez-pardo@espci.fr); [janine.cossy@espci.fr](mailto:janine.cossy@espci.fr).

## ACKNOWLEDGMENT

Sanofi-Aventis is greatly acknowledged for financial support (T.-X.M.). The authors also wish to thank Dr. Vincent Ferey and Sylvie Vigne (Sanofi-Aventis) for furnishing a sample of SSR 241579.

## DEDICATION

<sup>†</sup>Dedicated to Professor Carmen Najerá on the occasion of her 60th birthday.

## REFERENCES

- (1) Pennefather, J. N.; Lecci, A.; Candenias, M. L.; Patak, E.; Pinto, F. M.; Maggi, C. A. *Life Sci.* **2004**, *74*, 1445–1463.
- (2) (a) Rupniak, N. M. J.; Kramer, M. S. *Trends Pharmacol. Sci.* **1999**, *20*, 485–490. (b) Severini, C.; Improta, G.; Falconieri-Erspamer, G.; Salvadori, S.; Erspamer, V. *Pharmacol. Rev.* **2002**, *54*, 285–322. (c) Lecci, A.; Capriati, A.; Maggi, C. A. *Br. J. Pharmacol.* **2004**, *141*, 1249–1263.
- (3) (a) Emonds-Alt, X.; Proietto, V.; Steinberg, R.; Oury-Donzot, F.; Vigé, X.; Vilain, P.; Naline, E.; Daoui, S.; Advenier, C.; Le Fur, G.;

Maffrand, J.-P.; Soubrié, P.; Pascal, M. *J. Pharmacol. Exp. Ther.* **2002**, *303*, 1171–1179. (b) Steinberg, R.; Alonso, R.; Rouquier, L.; Desvignes, C.; Michaud, J.-C.; Cudenneq, A.; Jung, M.; Simiand, J.; Griebel, G.; Emonds-Alt, X.; Le Fur, G.; Soubrié, P. *J. Pharmacol. Exp. Ther.* **2002**, *303*, 1180–1188.

(4) For a review on C-substituted morpholine, see: Wijtmans, R.; Vink, M. K. S.; Schoemaker, H. E.; van Delft, F. L.; Blaauw, R. H.; Rutjes, F. P. J. T. *Synthesis* **2004**, 641–662.

(5) Takemoto, T.; Iio, Y.; Nishi, T. *Tetrahedron Lett.* **2002**, *41*, 1785–1788 and references cited therein.

(6) Nishi, T.; Ishibashi, K.; Nakajima, K.; Iio, Y.; Fukazawa, T. *Tetrahedron: Asymmetry* **1998**, *9*, 3251–3262.

(7) Okachi, T.; Murai, N.; Onaka, M. *Org. Lett.* **2003**, *5*, 85–87.

(8) Takamura, M.; Yabu, K.; Nishi, T.; Yanagisawa, H.; Kanai, M.; Shibasaki, M. *Synlett* **2003**, 353–356.

(9) For reviews, see: (a) Cossy, J.; Gomez Pardo, D. *Chemtracts* **2002**, *15*, 579–605. (b) Métro, T.-X.; Gomez Pardo, D.; Cossy, J. *Chem.—Eur. J.* **2009**, *15*, 1064–1070. (c) Cossy, J.; Gomez Pardo, D.; Dumas, C.; Mirguet, O.; Dechamps, I.; Métro, T.-X.; Burger, B.; Roudeau, R.; Appenzeller, J.; Cochi, A. *Chirality* **2009**, *21*, 850–856. (d) Métro, T.-X.; Duthion, B.; Gomez Pardo, D.; Cossy, J. *Chem. Soc. Rev.* **2010**, *39*, 89–102.

(10) For rearrangement of linear  $\beta$ -amino alcohols see: (a) Métro, T.-X.; Appenzeller, J.; Gomez Pardo, D.; Cossy, J. *Org. Lett.* **2006**, *8*, 3509–3512. (b) Métro, T.-X.; Gomez Pardo, D.; Cossy, J. *J. Org. Chem.* **2007**, *72*, 6556–6561. (c) Métro, T.-X.; Gomez Pardo, D.; Cossy, J. *Synlett* **2007**, 2888–2890. (d) Duthion, B.; Métro, T.-X.; Gomez Pardo, D.; Cossy, J. *Tetrahedron* **2009**, *65*, 6696–6706.

(11) For rearrangement of cyclic  $\beta$ -amino alcohols see: (a) Cossy, J.; Dumas, C.; Michel, P.; Gomez Pardo, D. *Tetrahedron Lett.* **1995**, *36*, 549–552. (b) Cossy, J.; Dumas, C.; Gomez Pardo, D. *Eur. J. Org. Chem.* **1999**, 1693–1699.

(12) (a) Cossy, J.; Dumas, C.; Gomez Pardo, D. *Bioorg. Med. Chem.* **1997**, *7*, 1343–1344. (b) Dechamps, I.; Gomez Pardo, D.; Karoyan, P.; Cossy, J. *Synlett* **2005**, 1170–1172. (c) Dechamps, I.; Gomez Pardo, D.; Cossy, J. *Arkivoc* **2007**, *v*, 38–45. (d) Dechamps, I.; Gomez Pardo, D.; Cossy, J. *Tetrahedron* **2007**, *63*, 9082–9091. (e) Métro, T.-X.; Gomez Pardo, D.; Cossy, J. *J. Org. Chem.* **2008**, *73*, 707–710. (f) Cochi, A.; Burger, B.; Navarro, C.; Gomez Pardo, D.; Cossy, J.; Zhao, Y.; Cohen, T. *Synlett* **2009**, 2157–2161.

(13) Ooi, T.; Takeuchi, M.; Ohara, D.; Maruoka, K. *Synlett* **2001**, 1185–1187.

(14) Shuman, R. T.; Rothenberger, R. B.; Campbell, C. S.; Smith, G. F.; Gifford-Moore, D. S.; Gesellchen, P. D. *J. Med. Chem.* **1993**, *36*, 314–319.

(15) Kukolja, S.; Draheim, S. E.; Pfeil, J. L.; Cooper, R. D. G.; Graves, B. J.; Holmes, R. E.; Neel, D. A.; Huffman, G. W.; Webber, J. A.; Kinnick, M. D.; Vasileff, R. T.; Foster, B. J. *J. Med. Chem.* **1985**, *28*, 1886–1896.

(16) Kyba, E. P.; Timko, J. M.; Kplan, L. J.; De Jong, F.; Gokel, G. W.; Cram, D. J. *J. Am. Chem. Soc.* **1978**, *100*, 4555–4568.

(17) Look, G. C.; Murphy, M. M.; Campbell, D. A.; Gallop, M. A. *Tetrahedron Lett.* **1995**, *36*, 2937–2940.

(18) (a) Henry, L. C. R. *Hebd. Seances Acad. Sci.* **1895**, *120*, 1265–1267. (b) Rosini, G. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 2, pp 321–340. (c) Shibasaki, M.; Gröer, H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. III, pp 1075–1090. (d) Luzzio, F. A. *Tetrahedron* **2001**, *57*, 915–945. (e) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001.

(19) Sasai, H.; Suzuki, T.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1992**, *114*, 4418–4420.

(20) For reviews on the asymmetric Henry reaction, see: (a) Luzzio, F. A. *Tetrahedron* **2001**, *57*, 915–945. (b) Palomo, C.; Oiarbide, M.; Mielgo, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5442–5444. (c) Boruwa, J.; Gogoi, N.; Saikia, P. P.; Barua, N. C. *Tetrahedron: Asymmetry* **2006**, *17*, 3315–3326. (d) Palomo, C.; Oiarbide, M.; Laso, A. *Eur. J. Org. Chem.* **2007**, 2561–2574.

- (21) (a) Sasai, H.; Suzuki, T.; Arai, S.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1992**, *114*, 4418–4420. (b) Arai, T.; Yamada, Y. M. A.; Yamamoto, N.; Sasai, H.; Shibasaki, M. *Chem.—Eur. J.* **1996**, *2*, 1368–1372. (c) Trost, B. M.; Yeh, V. S. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 861–863. (d) Evans, D. A.; Seidel, D.; Rueping, M.; Lam, H. W.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2003**, *125*, 12692–12693. (e) Kogami, Y.; Nakajima, T.; Ashizawa, T.; Kezuka, S.; Ikeno, T.; Yamada, T. *Chem. Lett.* **2004**, *33*, 614–615. (f) Kogami, Y.; Nakajima, T.; Ikeno, T.; Yamada, T. *Synthesis* **2004**, 1947–1950. (g) Palomo, C.; Oiarbide, M.; Laso, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3881–3884. (h) Choudary, B. M.; Ranganath, K. V. S.; Pal, U.; Kantam, M. L.; Sreedhar, B. *J. Am. Chem. Soc.* **2005**, *127*, 13167–13171. (i) Maheswaran, H.; Prasanth, K. L.; Krishna, G. G.; Ravikumar, K.; Sridhar, B.; Kantam, M. L. *Chem. Commun.* **2006**, 4066–4068. (j) Blay, G.; Climent, E.; Fernández, I.; Hernández, V.; Pedro, J. R. *Tetrahedron: Asymmetry* **2006**, *17*, 2046–2049. (k) Tur, F.; Saá, J. M. *Org. Lett.* **2007**, *9*, 5079–5082. (l) Ma, K. Y.; You, J. S. *Chem.—Eur. J.* **2007**, *13*, 1863–1871. (m) Qin, B.; Xiao, X.; Liu, X. H.; Huang, J. L.; Wen, Y. H.; Feng, X. M. *J. Org. Chem.* **2007**, *72*, 9323–9328. (n) Bandini, M.; Benaglia, M.; Sinisi, R.; Tommasi, S.; Umani-Ronchi, A. *Org. Lett.* **2007**, *9*, 2151–2153. (o) Xiong, Y.; Wang, F.; Huang, X.; Wen, Y. H.; Feng, X. M. *Chem.—Eur. J.* **2007**, *13*, 829–833. (p) Arai, T.; Watanabe, M.; Yanagisaka, A. *Org. Lett.* **2007**, *9*, 3595–3597. (q) Blay, G.; Climent, E.; Fernández, I.; Hernández, V.; Pedro, J. R. *Tetrahedron: Asymmetry* **2007**, *18*, 1603–1612. (r) Bandini, M.; Picinelli, F.; Tommasi, S.; Umani-Ronchi, A.; Ventrici, C. *Chem. Commun.* **2007**, 616–618. (s) Lai, G. Y.; Wang, S. J.; Wang, Z. Y. *Tetrahedron: Asymmetry* **2008**, *19*, 1813–1819. (t) Liu, S. L.; Wolf, C. *Org. Lett.* **2008**, *10*, 1831–1834. (u) Bulut, A.; Aslan, A.; Dogan, Ö. *J. Org. Chem.* **2008**, *73*, 7373–7375. (v) Zhang, G. Q.; Yashima, E.; Woggon, W. D. *Adv. Synth. Catal.* **2009**, *351*, 1255–1262. (w) Kowalczyk, R.; Kwiatkowski, P.; Skarzewski, J.; Jurczak, J. *J. Org. Chem.* **2009**, *74*, 753–756. (x) Zulauf, A.; Mellah, M.; Schulz, E. *J. Org. Chem.* **2009**, *74*, 2242–2245. (y) Steurer, M.; Bolm, C. *J. Org. Chem.* **2010**, *75*, 3301–3310.
- (22) (a) Corey, E. J.; Zhang, F. Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 1931–1934. (b) Ooi, T.; Doda, K.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 2054–2055. (c) Sohtome, Y.; Hashimoto, Y.; Nagasawa, K. *Adv. Synth. Catal.* **2005**, *347*, 1643–1648. (d) Marcelli, T.; van der Haas, R. N. S.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 929–931. (e) Sohtome, Y.; Hashimoto, Y.; Nagasawa, K. *Eur. J. Org. Chem.* **2006**, 2894–2897. (f) Mandal, T.; Samanta, S.; Zhao, C. G. *Org. Lett.* **2007**, *9*, 943–945. (g) Bandini, M.; Sinisi, R.; Umani-Ronchi, A. *Chem. Commun.* **2008**, 4360–4362.
- (23) For the first biocatalytic asymmetric nitroaldol reaction, see: (a) Purkarthofer, T.; Gruber, K.; Gruber-Khadjawi, M.; Waich, K.; Skrane, W.; Mink, D.; Griengl, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 3454–3456. (b) Gruber-Khadjawi, M.; Purkarthofer, T.; Skrane, W.; Griengl, H. *Adv. Synth. Catal.* **2007**, *349*, 1445–1450.
- (24) Selected examples for both aromatic and aliphatic aldehydes: (a) Tanaka, K.; Hachiken, S. *Tetrahedron Lett.* **2008**, *49*, 2533–2536. (b) Spangler, K. Y.; Wolf, C. *Org. Lett.* **2009**, *11*, 4724–4727. (c) Chen, L.; Dong, J.; You, J.; Gao, G.; Lan, J. *Chem.—Eur. J.* **2010**, *16*, 6761–6765. (d) Jin, W.; Li, X.; Wan, B. *J. Org. Chem.* **2011**, *76*, 484–491.
- (25) (a) Christensen, C.; Juhl, K.; Jørgensen, K. A. *Chem. Commun.* **2001**, 2222–2223. (b) Christensen, C.; Juhl, K.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2002**, *67*, 4875–4881. (c) Misumi, Y.; Bulman, R. A.; Matsumoto, K. *Heterocycles* **2002**, *56*, 599–606. (d) Lu, S. F.; Du, D. M.; Zhang, S. W.; Xu, J. X. *Tetrahedron: Asymmetry* **2004**, *15*, 119–126. (e) Du, D. M.; Lu, S. F.; Fang, T.; Xu, J. X. *J. Org. Chem.* **2005**, *70*, 3712–3715. (f) Li, H.; Wang, B.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 732–733. (g) Xu, H.; Wolf, C. *Chem. Commun.* **2010**, 8026–8028. (h) Xu, H.; Wolf, C. *Synlett* **2010**, 2765–2770.
- (26) Nimitz, J. S.; Mosher, H. S. *J. Org. Chem.* **1981**, *46*, 211–213.
- (27) The (R) absolute configuration of the stereogenic center was determined by comparison of the  $[\alpha]_D$  to a precedently described compound. See ref 28.
- (28) Cochi, A.; Métro, T.-X.; Gomez Pardo, D.; Cossy, J. *Org. Lett.* **2010**, *12*, 3693–3695.
- (29) Enantiomeric excess were measured via SFC. See the Supporting Information of ref 28 for details.
- (30) (a) Edmonds-Alt, X.; Proietto, V. F. R. Patent 2824828 *Chem. Abstr.* **2002**, *137*, 384848. (b) SSR 241579 was provided by Sanofi-Aventis.
- (31) Payack, J. F.; Hughes, D. L.; Cai, D.; Cottrell, I. F.; Verhoeven, T. R. *Org. Synth.* **2002**, 19.
- (32) Label, H.; Paquet, V. *J. Am. Chem. Soc.* **2004**, *126*, 320–328.
- (33) Edmonds-Alt, X.; Grossriether, I.; Gueule, P.; Proietto, V.; Van Broeck, D. W.O. Patent 9623787 *Chem. Abstr.* **1996**, *125*, 247839.