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

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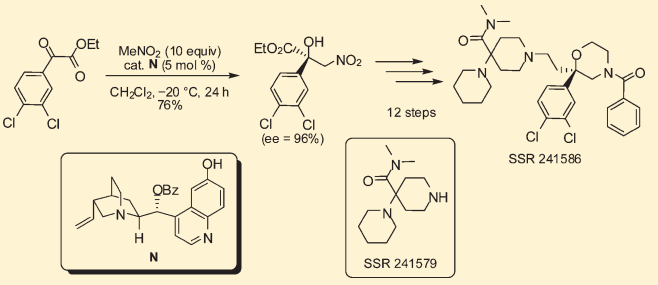
Supporting Information

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 α-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),[1] and antagonists of these NK receptors have attracted considerable attention as powerful therapeutic agents.[2]

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).[3]

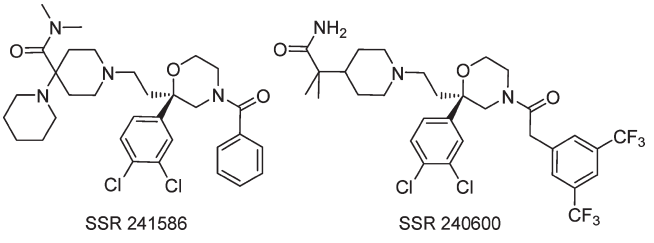


Figure 1. Structure of SSR 241586 and SSR 240600.

Different methods have been reported to synthesize optically active 2,2-disubstituted morpholines[4] such as crystallization of **A** with D-tartaric acid to produce **E** (Scheme 1, pathway 1),[5] Sharpless dihydroxylation (AD-mix β) leading to **F**, which was then transformed to **E** (Scheme 1, pathway 2),[6] enantioselective epoxydation of homoallylic alcohol **C**, using cumene hydroperoxide in the presence of catalytic diisopropyl D-tartrate and $Zr(Ot\text{-}Bu)_4$, to produce epoxide **G**, which, after a few steps, was also transformed to morpholine ring **E** (Scheme 1, pathway 3).[7] 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).[8]

RESULTS AND DISCUSSION

First Strategy. Recently, we have reported that β-amino alcohols of type **K** can be rearranged enantioselectively[9−11] to produce rearranged amino alcohols of type **L** that can be useful to synthesize biologically active products (Scheme 2).[12]

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_3N and NaOH.[10a,b] 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).[13]

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_3CN/MeOH (1/1) (90 °C, 10 h) led to **2** in 89% yield.[14] The latter was treated with zinc (8.3 equiv) in the presence of formic acid (26.8 equiv) ($MeOH/H_2O$ 2/1; 5 °C for 1.5 h, then 0 °C for 15 h),[15] followed by

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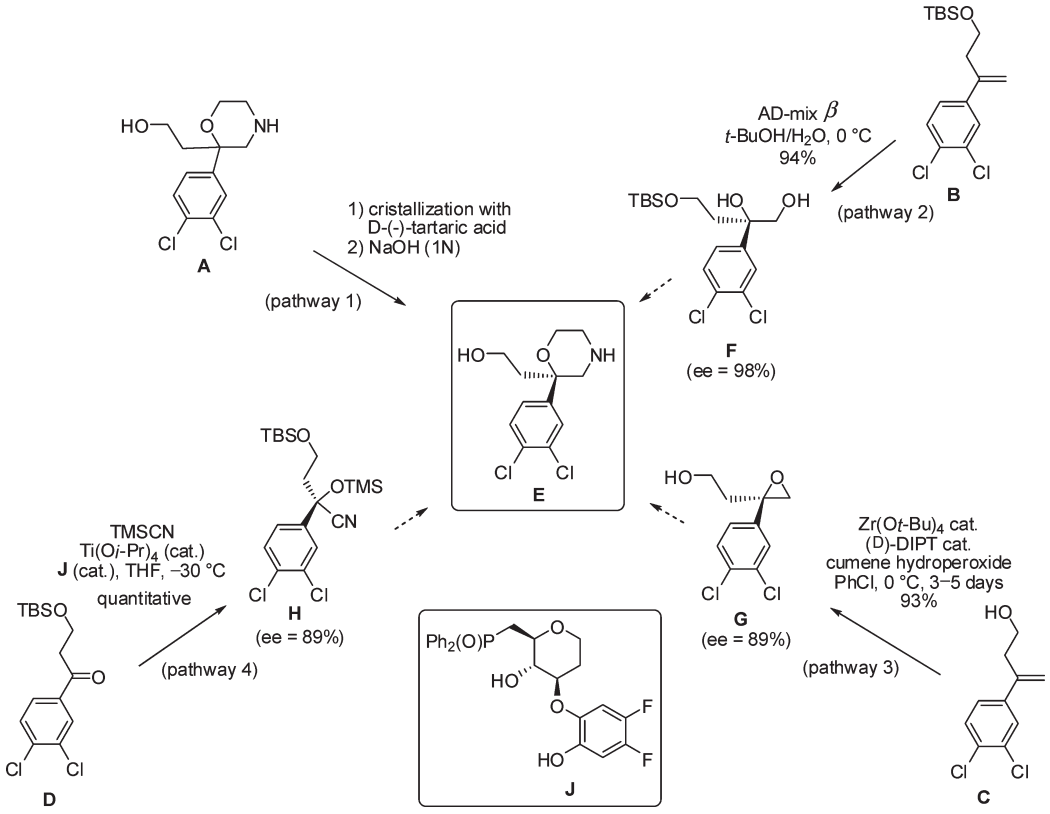
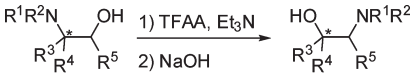
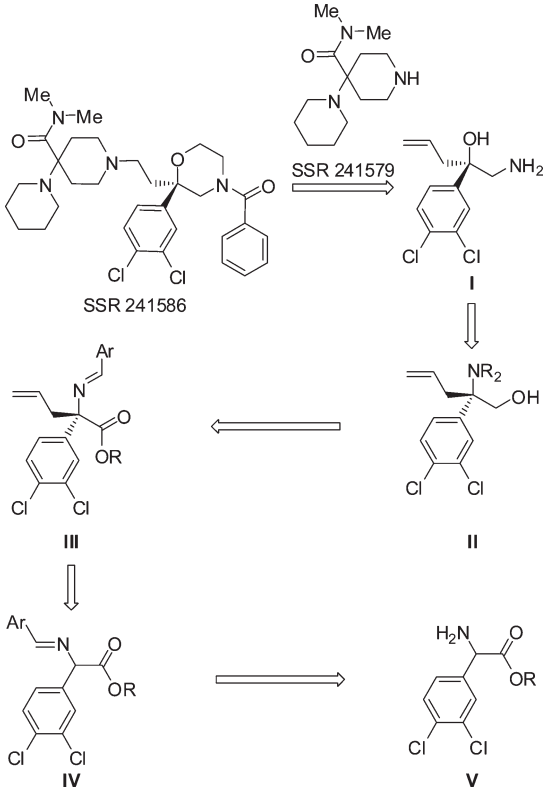
Scheme 1. Different Pathways To Access E



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



Scheme 3



esterification of the amino acid intermediate **3** (isobutylene, H_2SO_4, dioxane, rt, 24 h),[16] 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).[17]

The alkylation of **5**, according to the phase transfer catalyst (PTC) conditions,[13] 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], CsOH·H_2O (5.0 equiv) as the base in toluene at −40 °C. After 24 h, acidic treatment (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 °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 CsOH·H_2O was replaced by KOH, NaOH, or LiOH.H_2O, the yield in **6** was not satisfactory (7% to 35%) and the enantiomeric excesses were similar to the one obtained previously with CsOH·H_2O (40%−45%) (Table 1, entries 3−5). Compared to the results obtained by Maruoka et al. with other Schiff bases, it seems

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Scheme 4

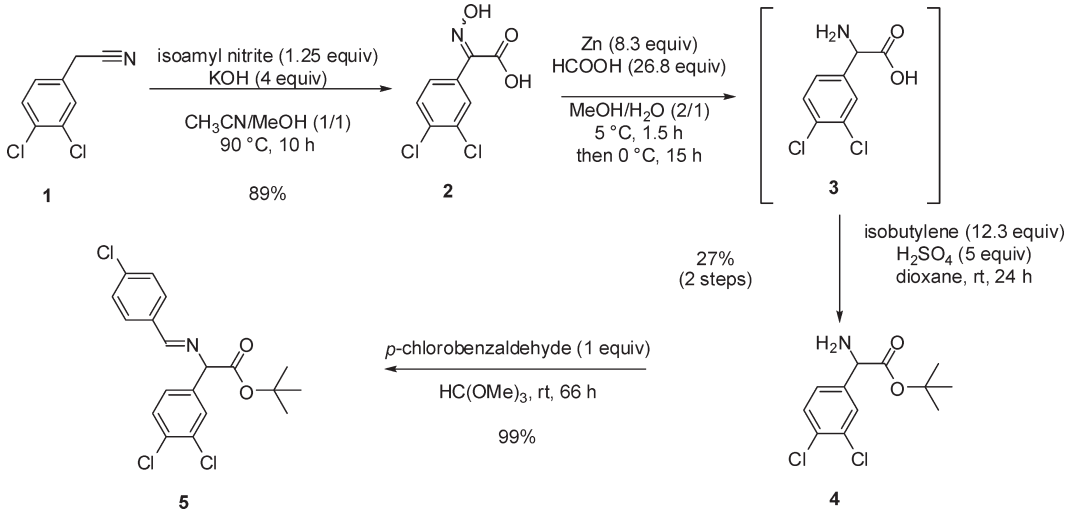
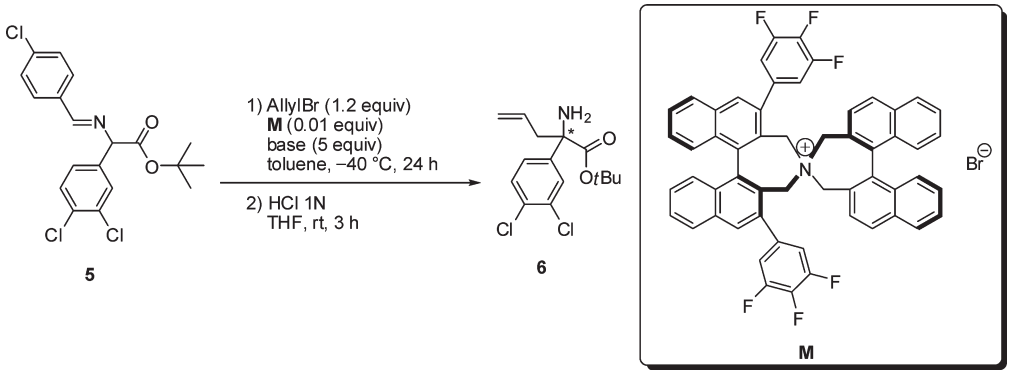


Table 1. Optimization of the Alkylation of 5 under PTC



entry	base	yield in **6**, %	ee[a] of **6**, %
1	$CsOH·H_2O$	42	45
2	$CsOH·H_2O$ (−80 °C, 88 h)	16	52
3	KOH	13	41
4	NaOH	35	45
5	$LiOH·H_2O$	7	40

[a] 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 β-nitro alcohols which can be transformed easily to β-amino alcohols and α-hydroxy carboxylic acids.[18] Since the work of Shibasaki et al.,[19] the catalytic asymmetric Henry reaction[20] by metal catalysis,[21] organocatalysis,[22] as well as biocatalysis[23] has been developed. Many successful examples involving enantioselective nitro-aldol reaction with aldehydes have been reported.[24] On the contrary, limited success was obtained with ketones.[25] Among the successful ones, the Henry reaction conditions tuned up by Deng et al.[25f] 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 β-nitro-alcohol **VIII**. The latter would be the result of an enantioselective addition of nitromethane to α-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 α-oxo-1*H*-imidazole-1-acetate **8**[26] (imidazole, THF, 0 °C, 3 h, 95%), the latter was treated with 3,4-dichlorophenylmagnesium bromide to produce the desired α-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_2Cl_2 at −20 °C).[25f] β-Nitro

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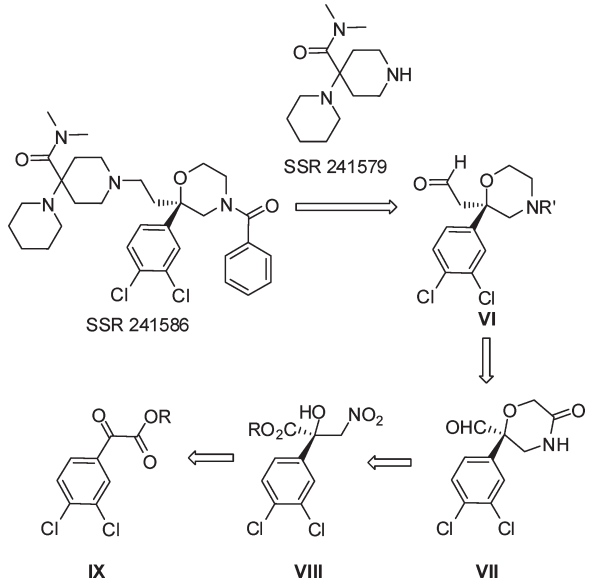
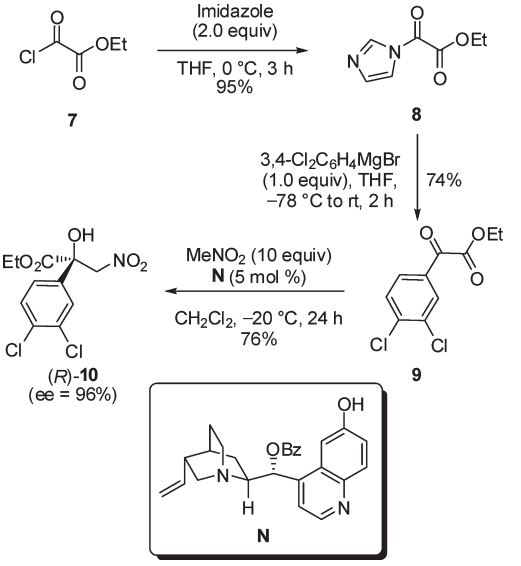
Scheme 5



Scheme 6



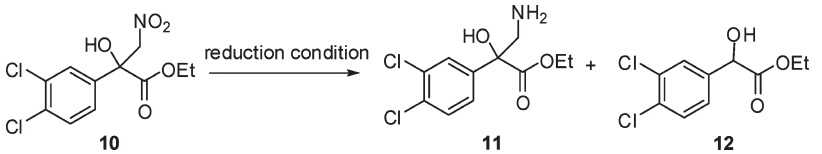
alcohol (*R*)-**10**[27] was isolated in 76% yield with an enantiomeric excess of 96% (Scheme 6).[28]

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_2 (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 β-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).

After *N*-chloroacetylation of the resulting amine (*R*)-**11** ($ClCH_2COCl$, Et_3N, CH_2Cl_2, 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 $BH_3 \cdot$THF (6 equiv, refluxing THF, 3 h, 88%). To access SSR 241586, morpholine **15** was benzoylated to furnish **16** (BzCl, Et_3N, CH_2Cl_2, rt, 1 h, 99%). We have to point out that all these steps were achieved without any racemization (Scheme 7).[29]

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_2Cl_2, 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 β-Nitro Alcohol 10[a]



entry	conditions	yield in **11**, %	yield in **12**, %
1	Pd/C, NH_4HCO_2, MeOH	0	0
2	H_2, Raney Ni, EtOH	20	35
3	H_2, Raney Ni, EtOH Raney Ni first washed with water	25	12
4	Zn (40 equiv), AcOH[b]	88	0

[a] Reaction conditions tested on (±)-**10**. [b] Conditions applied to (*R*)-**10**.

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Scheme 7

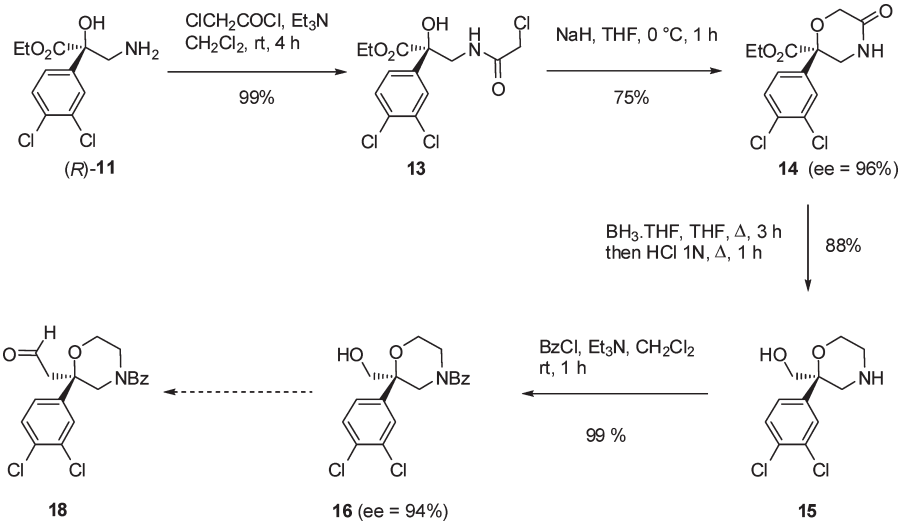
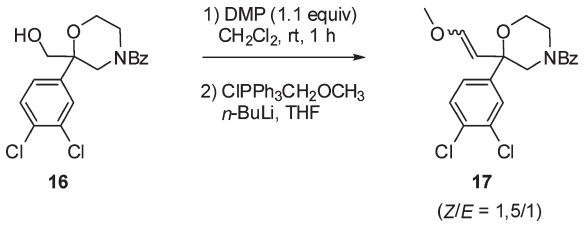


Table 3. Oxydation/Wittig Conditions[a]



entry	conditions	yield in **17**, %
1	$Cl^{-+}PPh_3CH_2OCH_3$ (5 equiv), *n*-BuLi (4.5 equiv), −45 °C to rt	0
2	$Cl^{-+}PPh_3CH_2OCH_3$ (7 equiv), *n*-BuLi (6 equiv), −78 °C to rt	31
3	$Cl^{-+}PPh_3CH_2OCH_3$ (7 equiv), *n*-BuLi (6 equiv),[b] 0 °C then rt	59

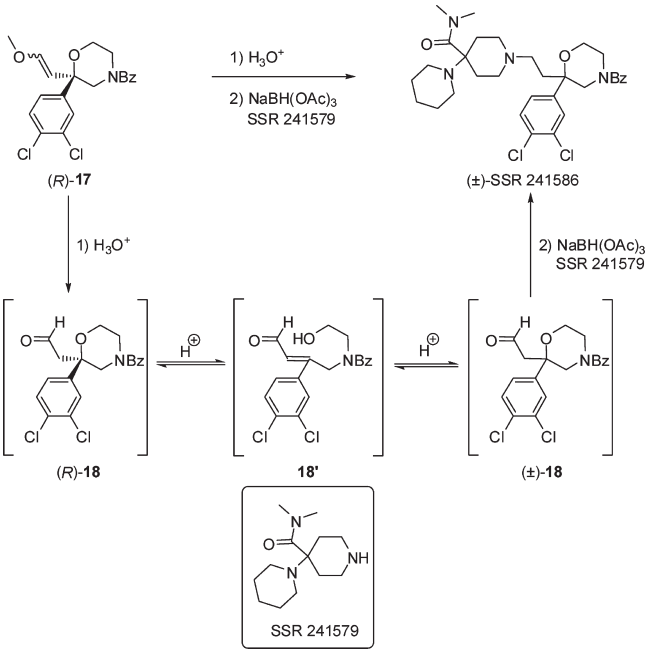
[a] Reaction conditions tested on (±)-**17**. [b] Reaction conditions applied to (*R*)-**17**.

when the reaction was achieved on a larger scale (0.22 mmol versus 0.04 mmol) at 0 °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-caboxamide].[30] The addition of $NaBH(OAc)_3$ (CH_2Cl_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 (±)-**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 nucleophilic substitution of mesylate **X** by SSR 241579, which would lead to SSR 241586, was considered. This strategy implies

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	$(CO_2H)_2 \cdot 2H_2O$, $MeOH/H_2O$ 10/2, 28 h, rt	12	14

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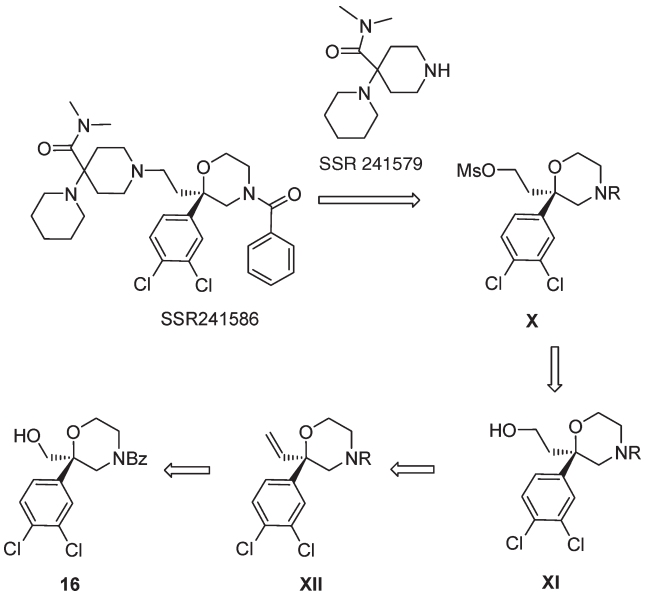
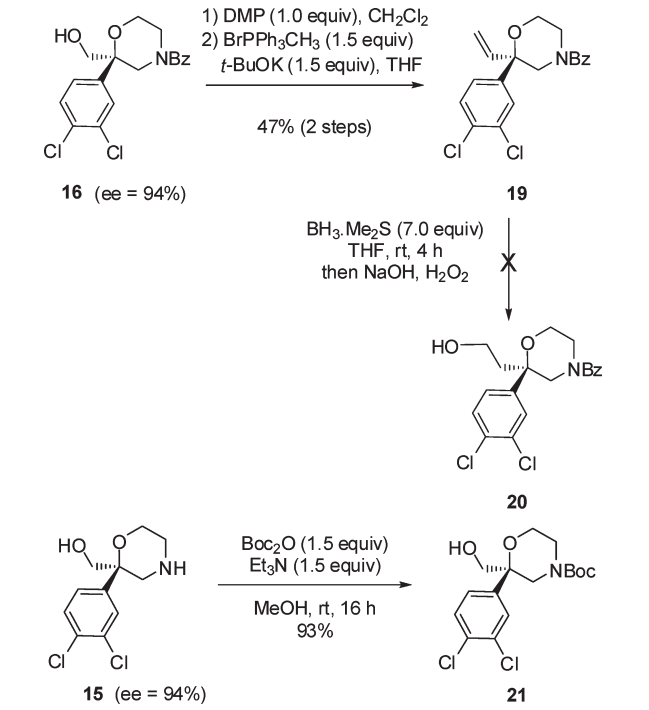
Scheme 8



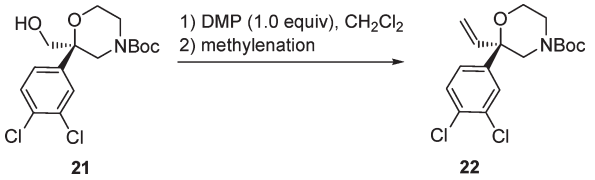
Scheme 9



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, CH_2Cl_2) and an olefination of the resulting aldehyde was performed ($BrPPh_3CH_3$, *t*-BuOK, THF). Attempts to achieve a hydroboration/oxidation sequence on **19** ($BH_3 \cdot Me_2S$, THF, Δ then H_2O_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 hydroboration/oxidation was planned (Boc_2O, Et_3N, MeOH, rt, 16 h, 93%) (Scheme 9).[28]

Table 5. Conditions of Methylenation



entry	conditions	yield in **22**, %
1	$Br^{-+}PPh_3CH_3$ (7 equiv), *n*-BuLi (6 equiv), 0 °C then rt	21
2	$Br^{-+}PPh_3CH_3$ (15 equiv), *n*-BuLi (14 equiv), 0 °C then rt	21
3	$Br^{-+}PPh_3CH_3$ (1.5 equiv), KHMDS (1.5 equiv), 0 °C then rt	53
4	$Br^{-+}PPh_3CH_3$ (3 equiv), KHMDS (3 equiv), 0 °C then rt	82
5	Cp_2TiMe_2 (6 equiv), 60 °C	0
6	(i) $RhCl(PPh_3)_3$ (2.5 mol %), *i*PrOH, PPh_3; (ii) $TMSCHN_2$	10

The resulting compound **21** was oxidized (DMP, CH_2Cl_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 ($BrPPh_3CH_3$) 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 $BrPPh_3CH_3$ and KHMDS the yield in **22** was significantly improved to 53% and increased to 82% by utilizing 3 equiv of $BrPPh_3CH_3$ and KHMDS (Table 5, entries 3−4). We have to point out that the Petasis reagent[31] 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,[32] 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 ($BH_3 \cdot Me_2S$ then H_2O_2, NaOH). After a deprotection/protection sequence (TFA, then BzCl, Et_3N, CH_2Cl_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 K_2CO_3 (DMF/CH_3CN: 1/1, 100 °C, 3 h), SSR 241586[33] was isolated in 48% yield with an enantiomeric excess of 93% (Scheme 10).[28]

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.[28] 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):[14] 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 droppwise 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 $CHCl_3$ (50 mL) were added to the reaction mixture. The aqueous phase is extracted with $CHCl_3$ (2 × 50 mL), acidified with an addition of an aqueous solution of HCl (2,4 M) until pH <2, then extracted with AcOEt (3 × 50 mL). The organic layer was dried over $MgSO_4$, 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

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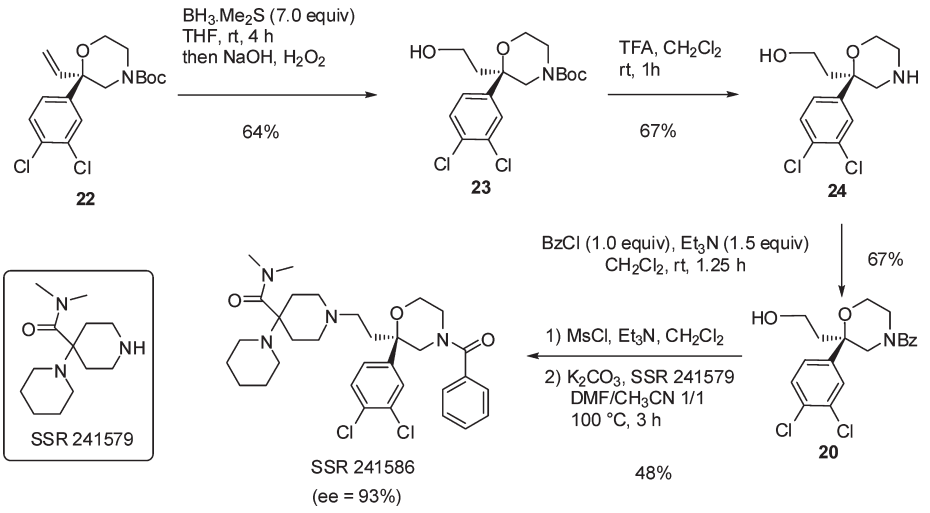
Scheme 10



(neat) 3500−2100, 1879, 1718, 1593, 1462, 1373, 1284, 1260, 1237, 1059, 1029, 847, 746, 725, 653 cm^{-1}; H^1 NMR (400 MHz, acetone-d_6) δ 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}C NMR (100 MHz, acetone-d_6) δ 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 ($M^{+\bullet}$ − CO_2 − H_2O, 10), 173 ($M^{+\bullet}$ − CO_2 − H_2O, 65), 171 ($M^{+\bullet}$ − CO_2 − H_2O, 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/H_2O (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 H_2SO_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 Et_2O (2 × 50 mL), and the organic phase was dried over Na_2SO_4, filtered, and then evaporated under reduced pressure. After purification by flash chromatography on silica gel (CH_2Cl_2/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 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 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}C NMR (100 MHz, $CDCl_3$) δ 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 ($M^{+\bullet}$ − CO_2tBu$^\bullet$, 8), 176 ($M^{+\bullet}$ − CO_2tBu$^\bullet$, 62), 174 ($M^{+\bullet}$ − CO_2tBu$^\bullet$, 100), 147 (2), 139 (2), 111 (6), 104 (5), 75 (3), 57 (16). Anal. Calcd for $C_{12}H_{15}Cl_2NO_2$: 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 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 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}C NMR (100 MHz, $CDCl_3$) δ 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 ($M^{+\bullet}$ − CO_2tBu$^\bullet$, 33), 298 ($M^{+\bullet}$ − CO_2tBu$^\bullet$, 100), 296 ($M^{+\bullet}$ − CO_2tBu$^\bullet$, 98), 282 (3), 261 (8), 233 (5), 199 (16), 159 (43), 125 (49), 89 (26), 57 (63). Anal. Calcd for $C_{19}H_{18}Cl_3NO_2$: 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 μL, 0.30 mmol, 1.2 equiv), and optically acive catalyst **M** (2 mg, 2 μmol, 0.01 equiv) in dry toluene (2 mL, degazed by Argon bubble) was added at −40 °C CsOH·H_2O (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 CH_2Cl_2 (2 × 10 mL). The organic phase was dried over Na_2SO_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 CH_2Cl_2 (2 × 10 mL). The organic phase was dried over Na_2SO_4, filtered, and then evaporated under reduced pressure. After purification by flash chromatography on silica gel (CH_2Cl_2 then CH_2Cl_2/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_{majo} = 1.17 min, t_{mino} = 1.40); IR (neat) 3387, 3078, 2978, 2927, 2855, 1726, 1467, 1369, 1248, 1150, 1030, 924, 844, 678 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 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}C NMR (100 MHz, $CDCl_3$) δ 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 ($M^{+\bullet}$ − CO_2tBu$^\bullet$, 28), 216 ($M^{+\bullet}$ − CO_2tBu$^\bullet$, 65), 214 ($M^{+\bullet}$ − CO_2tBu$^\bullet$, 100), 174 (18), 172 (25), 162 (5), 145 (4), 136 (3), 109 (2), 57 (9); HRMS (ESI) calcd for $C_{15}H_{20}Cl_2NO_2$ ($M + H^+$) 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 CH_2Cl_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 $Na_2S_2O_3$ followed by the addition of an aqueous saturated solution of $NaHCO_3$ and then extracted with AcOEt (10 mL). The organic layer was dried over $MgSO_4$, 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 μL, 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 $NaHCO_3$ and then extracted with AcOEt (80 mL). The organic layer was dried over $MgSO_4$, 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 μmol, 35%) and *E*-**17** (21 mg, 54 μmol, 24%). R_f 0.3 (PE/AcOEt 50/50); IR (neat) 2924, 2855, 1631, 1427, 1271, 1078, 1027 cm^{-1}; ^1H NMR (DMSO-d_6 at 120 °C) δ 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); ^{13}C NMR ($CDCl_3$) δ 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 $C_{20}H_{20}NO_3Cl_2$ ($M + H^+$) 392.0815, found 392.0816.

[2-(3,4-Dichlorophenyl)-2-((*E*)-2-methoxyvinyl)morpholin-4-yl]phenylmethanone (*E*-17): R_f 0.5 (PE/AcOEt 50/50); IR (neat) 2924, 2860, 1629, 1430, 1221, 1076, 1027 cm^{-1}; ^1H NMR (DMSO-d_6 at 100 °C) δ 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); ^{13}C NMR ($CDCl_3$) δ 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 $C_{20}H_{20}NO_3Cl_2$ ($M + H^+$) 392.0815, found 392.0816.

■ ASSOCIATED CONTENT

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.

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DEDICATION

†Dedicated to Professor Carmen Najerá on the occasion of her 60th birthday.

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