

# Enantioselective Synthesis of SSR 241586 by Using an Organo-Catalyzed Henry Reaction

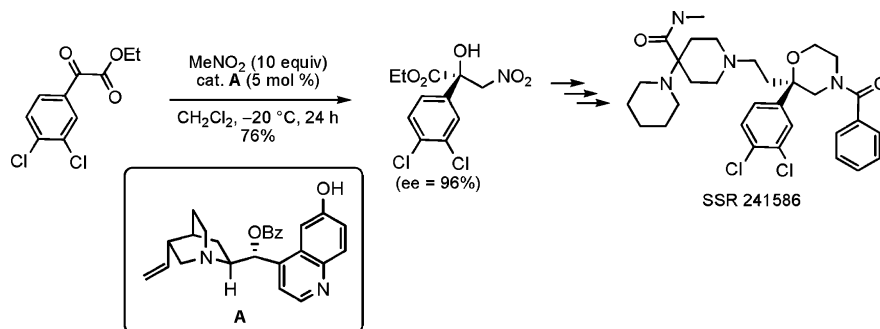
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## ABSTRACT



An organo-catalyzed Henry reaction, applied to an  $\alpha$ -keto ester, has allowed the enantioselective synthesis of SSR 241586, a 2,2-disubstituted morpholine active in the treatment of schizophrenia and irritable bowel syndrome (IBS).

Substance P (SP), neurokinin A (NKA), and neurokinin B (NKB) are the best known members of the tachykinin neuropeptide family which activity is mediated by at least three distinct receptors: NK1 (SP-preferring), NK2 (NKA-preferring), and NK3 (NKB-preferring).<sup>1</sup> Due to their pharmacological effects on pain, on the central and peripheral system, as well as on the gastrointestinal and urogenital tracts, antagonists of NK receptors have attracted considerable attention as potentially powerful therapeutic agents.<sup>2</sup> Among them, the optically active 2,2-disubstituted morpholines SSR 241586 and SSR 240600, developed by Sanofi-Aventis, were shown to be active in the treatment of depression, schizophrenia, urinary trouble, emesis, and irritable bowel syndrome (IBS) (Figure 1).<sup>3</sup>

So far, the methods reported to isolate the appropriate isomer of the 2,2-disubstituted morpholine include crystal-

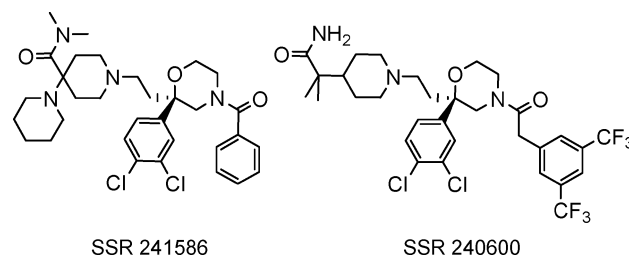


Figure 1. SSR 241586 and SSR 240600.

lization with D-tartaric acid,<sup>4</sup> Sharpless dihydroxylation (AD-mix  $\beta$ ),<sup>5</sup> asymmetric epoxidation of a homoallylic alcohol catalyzed by  $Zr(O-t-Bu)_4$  and diisopropyl D-tartrate,<sup>6</sup> as well as asymmetric cyanosilylation of a ketone using a Lewis acid/Lewis base bifunctional catalyst.<sup>7</sup>

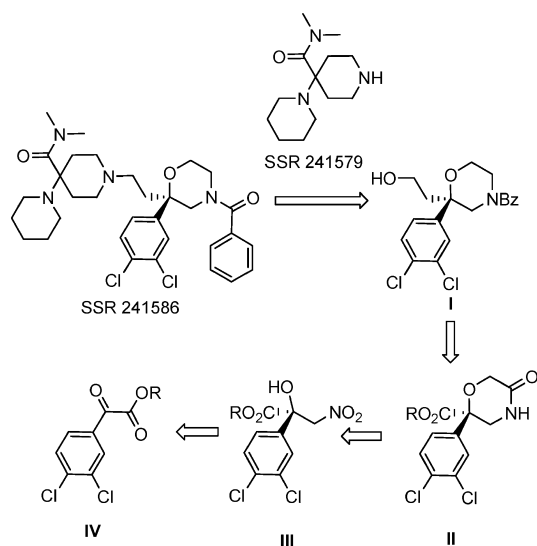
Here, we disclose an enantioselective synthesis of SSR 241586 using an organo-catalyzed Henry reaction to control the quaternary stereogenic center of (*R*)-configuration present at C2 in the

(1) Pennefather, J. N.; Lecci, A.; Candenat, M. L.; Patak, E.; Pinto, F. M.; Maggi, C. A. *Life Sci.* **2004**, *74*, 1445–1463.

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morpholine ring. The synthesis of SSR 241586 was planned from the nucleophilic substitution of alcohol **1** with the appropriately substituted piperidine SSR 241579. Alcohol **1** would be obtained by homologation of ester **II**, and the construction of the morpholine ring would be achieved from the  $\beta$ -nitro alcohol **III**, which would be the result of an enantioselective Henry reaction applied to  $\alpha$ -keto ester **IV** (Scheme 1).

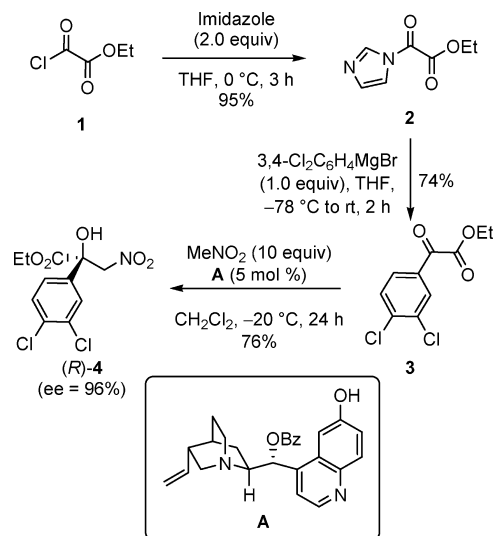
**Scheme 1.** Retrosynthesis of SSR 241586



The synthesis of SSR 241586 started with the transformation of commercially available ethyl chlorooxacetate (**1**) to ethyl  $\alpha$ -oxo-1*H*-imidazole-1-acetate (**2**).<sup>8</sup> When **2** was treated with 3,4-dichlorophenylmagnesium bromide, the desired  $\alpha$ -keto ester **3** was isolated in 74% yield. An organo-catalyzed Henry reaction was subsequently applied to  $\alpha$ -keto ester **3**. Quinine-derived compound **A** was chosen as the appropriate catalyst due to its ability to furnish Henry adducts with high enantiomeric excess on a broad range of substrates.<sup>9</sup> Thus, treatment of **3** with nitromethane (10 equiv) in the presence of catalyst **A** (5 mol %) in  $\text{CH}_2\text{Cl}_2$  at  $-20^\circ\text{C}$  produced  $\beta$ -nitro alcohol **4**<sup>10</sup> in 76% yield and with an enantiomeric excess of 96% (Scheme 2).

The synthesis of the morpholine ring was achieved in four steps from nitro alcohol **4**. At first, this latter was selectively reduced to

**Scheme 2.** Synthesis of the Optically Active Intermediate (*R*)-**4**



the corresponding amino alcohol **5**. Under hydrogenation conditions, using Raney nickel ( $\text{H}_2$ , Raney Ni/EtOH), a retro-Henry reaction was observed. On the contrary, when the reduction of the nitro group was performed using zinc dust in acetic acid, the amino alcohol **5** was isolated without any racemization. *N*-Acetylation of the resulting primary amine ( $\text{ClCH}_2\text{COCl}$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ , rt, 4 h) produced amide **6** (99%) which, after treatment with NaH, afforded the cyclic amide **7** in 75% yield and with an enantiomeric excess of 96%. The amide and ester groups were reduced by  $\text{BH}_3\cdot\text{THF}$  (6 equiv, THF, reflux, 3 h) to produce the 2,2-disubstituted morpholine **8** in 88% yield (Scheme 3).

In order to synthesize SSR 241586, compound **8** has to be transformed to its homologue **11**. Thus, **8** was treated with di-*tert*-butyl dicarbonate ( $\text{Boc}_2\text{O}$ ,  $\text{Et}_3\text{N}$ , MeOH, rt, 16 h) to produce the *N*-protected morpholine **9** (93% yield). An oxidation step [Dess–Martin periodinane (DMP),  $\text{CH}_2\text{Cl}_2$ , rt, 1 h] followed by a Wittig reaction ( $\text{KHMDs}$ ,  $\text{BrPPh}_3\text{CH}_3$ , THF) provided olefin **10** (82% for the two steps), and after an oxidative hydroboration ( $\text{BH}_3\cdot\text{Me}_2\text{S}$ , then  $\text{H}_2\text{O}_2$ , NaOH), alcohol **11** was isolated in 64% yield. In order to introduce the *N*-benzoyl group present in the final product, a deprotection/protection step was achieved.

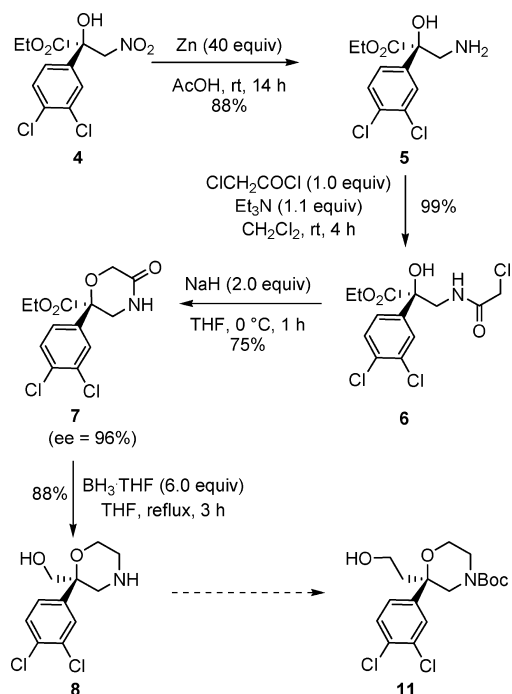
Thus, *N*-*tert*-butyl carbamate **11** was treated with TFA ( $\text{CH}_2\text{Cl}_2$ , rt, 1 h), and the resulting morpholine was then transformed into the *N*-benzoylmorpholine **13** ( $\text{PhCOCl}$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ , rt, 1.25 h) in 45% yield (for the two steps) (Scheme 4).

We have to point out that the straightforward access to SSR 241586 from **8**, by transforming the latter in *N*-benzoylmorpholine, was not possible. Indeed, after transformation of **8** to *N*-benzoylmorpholine **9'**, this compound was converted to olefin **10'** in two steps (DMP,  $\text{CH}_2\text{Cl}_2$ ;  $\text{BrPPh}_3\text{CH}_3$ , *t*-BuOK, THF), but unfortunately, the oxidative hydroboration of **10'** was not successful as **13** was not formed (Scheme 5).

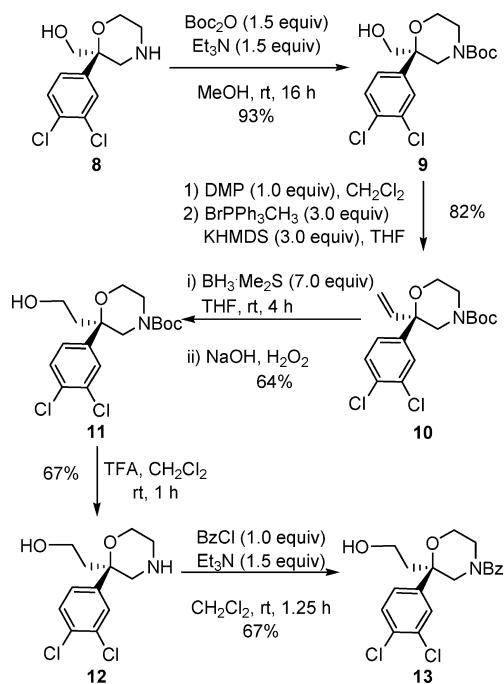
The formation of SSR 241586 was completed from **13** in two steps. After mesylation ( $\text{MsCl}$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ , rt, 1 h) and treatment of the resulting mesylate with piperidine SSR

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### Scheme 3. Synthesis of the 2,2-Disubstituted Morpholine 8

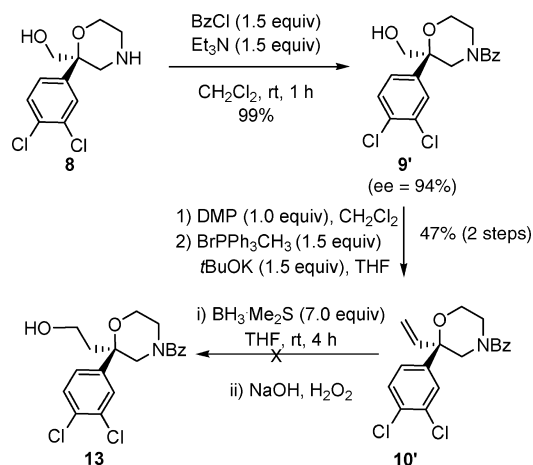


### Scheme 4. Homologation of the Side Chain

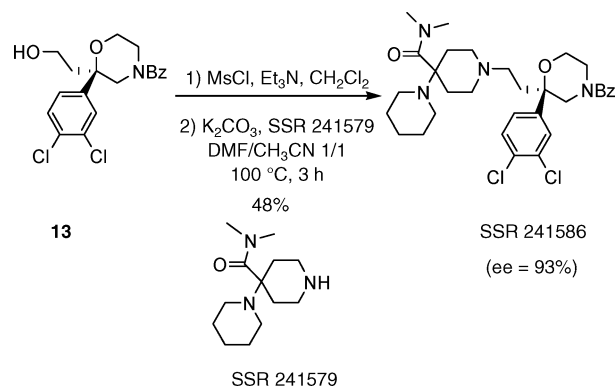


241579 [N,N-dimethyl-4-(piperidin-1-yl)piperidine-4-carboxamide]<sup>11</sup> under basic conditions ( $\text{K}_2\text{CO}_3$ , DMF/ $\text{CH}_3\text{CN}$  1:1, 100  $^\circ\text{C}$ , 3 h), the desired SSR 241586 was isolated in 48% yield (two steps) with an enantiomeric excess of 93% (Scheme 6).<sup>12</sup>

### Scheme 5. Homologation of the Side Chain with N-Benzoylmorpholine 9'



### Scheme 6. Synthesis of SSR 241586



By using an organo-catalyzed Henry reaction, SSR 241586 was synthesized in 15 steps with an excellent enantiomeric excess. As this method is versatile, a number of optically active 2,2-disubstituted morpholine analogues of SSR 241586 could be obtained.

**Acknowledgment.** Sanofi-Aventis is greatly acknowledged for financial support (T.-X.M.). We also thank Dr. Vincent Ferrey and Sylvie Vigne (Sanofi-Aventis) for furnishing a sample of SSR 241579.

**Supporting Information Available:** Experimental procedure and characterization data of compounds 2–13 and SSR 241586. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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