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Process Development of the Synthetic Route to R116301

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Abstract:

We describe in this paper the synthesis of compound 1 (R116301), which was developed to prepare pilot scale quantities (20–50 kg) of drug substance. The synthesis involves the ^{s}BuLi deprotonation of Boc-protected piperidone acetal 2, followed by benzaldehyde addition and ring closure to cyclic carbamate 4. Piperidine acetal 5 is resolved with Brown's acid and acylated. The ketone obtained after piperidine acetal deprotection undergoes reductive amination with *N*-benzyl piperazine, the most critical step in the synthesis. After debenzylation, final coupling and salt formation, compound 1 is obtained over 10 steps with 4% overall yield.

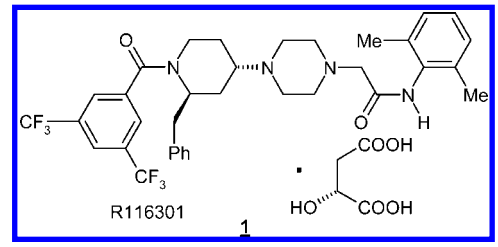
Introduction

Tachykinin peptides are central and peripheral neurotransmitters and neuromodulators. Substance P (SP), neurokinin A (NKA) and neurokinin B (NKB) interact with, respectively, the NK_1, NK_2 and NK_3 receptors.[1] The interaction of SP with the NK_1 receptor activates neuronal pathways regulating mood, anxiety, emesis and pain.

Several NK_1 antagonists have been reported to show good activity in preclinical assays relevant to pathological conditions.[2] This was recently supported by clinical findings demonstrating that Aprepitant, a CNS penetrating NK_1 antagonist, has efficacy as antidepressant[3] and antiemetic.[4]

The aim of this discovery project was to identify nonpeptidic, orally active, centrally penetrating and selective NK_1 small molecule receptor antagonists.[5]

The production of kilogram batches of compound **1** was required to carry out several toxicological, formulation and clinical studies.



The original synthetic route to **1** is depicted in Scheme 1.

As evident from its inefficiency (<1% overall yield), this synthesis was not suitable for pilot scale.

The most efficient way to supply **1** in sufficient quantity (up to 20 kg) and within the required time scale was to adapt the current synthesis procedures. We discuss our improvements in the next section.

Results and Discussion

The reaction of the anion derived from compound **2** (1.3 equiv of ^{s}BuLi in diethyl ether (Et_2O)[6] in the presence of 1 equiv of TMEDA at −70 °C) with benzaldehyde (1.1 equiv),[7] followed by quenching at −50 °C with NH_4Cl and evaporating the solvent, led to residue **3**.

Originally, **3** was cyclized to **4** (45% yield from **2**) by adding toluene and NaOMe/MeOH (1 equiv), evaporating MeOH/toluene and adding di-isopropyl ether (DIPE) to the oily residue in order to precipitate the product. This laborious procedure was circumvented by replacing toluene by ^{i}PrOH (1 L/mol) and using catalytic quantities of ^{t}BuOK (0.05 equiv): compound **4** precipitated as pure crystalline product in 55% overall yield from **2**. We also tried the more straightforward carbanion attack on benzyl bromide. In this case, however, exchange reactions together with Wurtz coupling prevented us from obtaining pure material and acceptable yields.

In the next step, the benzylic C-O hydrogenolysis was followed by carbamate fragmentation to amine **5** in almost quantitative yield.[8] At this stage, we had to solve the following problem: build-up of CO_2 within the vessel induced progressive

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

(2) (a) Rupniak, N. M. J.; Kramer, M. S. *Trends Pharmacol. Sci.* **1999**, *20*, 485. (b) Seward, E. M.; Swain, C. J. *Expert Opin. Ther. Pat.* **1999**, *9*, 571. (c) Diemunsch, P.; Grélot, L. *Drugs* **2000**, *60*, 533. (d) Rupniak, N. M. *J. Curr. Opin. Invest. Drugs* **2002**, *3*, 257. (e) Humphrey, J. M. *Curr. Top. Med. Chem.* **2003**, *3*, 1423.

(3) Kramer, M. S.; Rupniak, N. M. J. *Science* **1998**, *281*, 1640. (b) Argyropoulos, S. V.; Nutt, D. J *Expert Opin. Invest. Drugs* **2000**, *9*, 1871. (c) Sorbera, L. A.; Castaner, J.; Bayés, M.; Silvestre, J. *Drugs Future* **2002**, *27*, 211.

(4) (a) Patel, L.; Lindley, C. *Expert Opin. Pharmacother.* **2003**, *4*, 2279. (b) Hesketh, P. J.; Grunberg, S. M.; Gralla, R. J.; Warr, D. G.; Roila, F.; de Wit, R.; Chawla, S. P.; Carides, A. D.; Ianus, J.; Elmer, M. E.; Evans, J. K.; Beck, K.; Reines, S.; Horgan, K. J. *J. Clin. Oncol.* **2003**, *21*, 4112.

(5) Megens, A. A. H. P.; Ashton, D.; Vermeire, J. C. A.; Vermote, P. C. M.; Hens, K. A.; Hillen, L. C.; Fransen, J. F.; Mahieu, M.; Heylen, L.; Leysen, J. E.; Jurzak, M. R.; Janssens, F. J. *Parmacol. Exp. Ther.* **2002**, *302*, 696.

(6) The use of this highly flammable solvent, associated with the low temperature of the reaction, led us to out-source the reaction in an ad hoc facility, where special care was taken for prior peroxide testing, reactor inertization, and connection to earth. Interestingly, we performed more recently at lab scale a couple of experiments using 2-Me-THF as solvent and successfully obtained comparable results as with Et_2O. Aycock, D. F. *Org. Process Res. Dev.* **2007**, *11*, 156.

(7) (a) For reviews on this topic, see: Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2282. (b) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552.

(8) Effenberger, F.; Jäger, J. *Chem. Eur. J.* **1997**, *3*, 1370.

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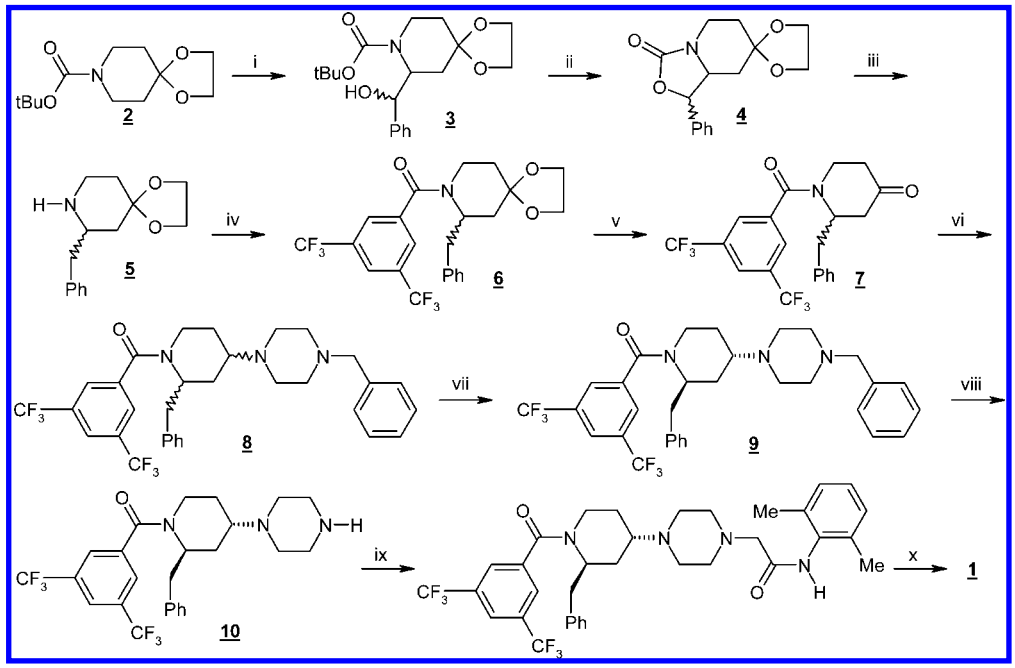
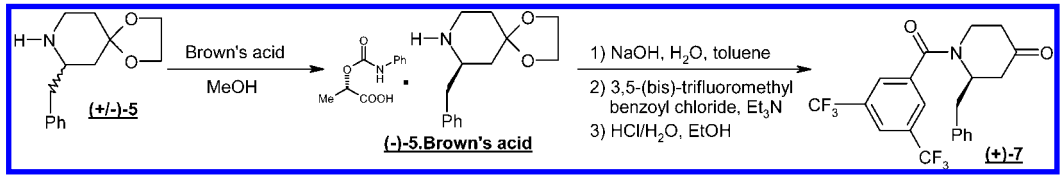
Scheme 1. **Synthesis of compound 1**[a]



[a] (i) Et_2O, TMEDA, ^{s}BuLi, PhCHO; (ii) NaOMe (1 equiv), toluene, rfx (45% over 2 steps); (iii) H_2, Pd/C, MeOH, 50 °C (85%); (iv) 3,5-bis-trifluoromethyl benzoyl chloride, Et_3N, toluene; (v) HCl, THF/H_2O (38% over 2 steps); (vi) *N*-benzyl-piperazine, Ti(O^iPr)$_4$, $NaBH_3CN$, CH_2Cl_2 (10%); (vii) chromatography (quant); (viii) H_2, Pd/C, MeOH, 50 °C (quant); (ix) *N*-(α-chloroacetyl)-2,6-dimethylanilide **11**, K_2CO_3, MIK, 100°C (82%); (x) L-malic acid (1.1 equiv), EtOH (80%).

Scheme 2



slowing of the rate of hydrogenation and several reflushing cycles with H_2 were necessary in order to bring the reaction to completion. Therefore, we added 1.05 equiv of NaOMe to take up the CO_2. That resulted in a much faster reaction (100% conversion after 2 h, 91% yield) and led to protected piperidone (±)-**5** as an oily residue after work-up.

Originally, enantiomers were separated later in the synthesis by means of preparative chiral chromatography. However, we decided to perform the resolution at this stage: the use of Brown's acid[9] led to (*R*)-(–)-**5** in 30% yield (max 50%!) and 90% ee after the release of the base. This ee, albeit modest, was sufficient to obtain eventually final compound **1** with 98% ee.

After amine release, residue (*R*)-(–)-**5** was reacted with 3,5-bis(trifluoromethyl)-benzoyl chloride in toluene.

In the original synthesis, the ketone underwent deprotection in THF/H_2O. We performed this step with aqueous 5 N HCl (5 equiv) in EtOH at 50 °C. Compound (+)-**7** was obtained in 85% yield (Scheme 2).

The reductive amination step to **8** proved to be by far the most difficult in the synthesis (Scheme 3).

Originally, the ketone **7** was reacted with *N*-benzylpiperazine in the presence of Ti(O^iPr)$_4$ (1 equiv) and then reduced with $NaBH_3CN$ according to a classical procedure;[10] the desired *trans* diastereomer was obtained with only 25:75 *trans/cis*-selectivity.

We improved this step by performing a catalytic hydrogenation instead of the borohydride reduction.[11] Through Pt-catalyzed hydrogenation, we obtained a 70:30 *trans/cis*-selectivity.

We performed more than 150 experiments to further improve the *trans*-selectivity but did not obtain better results despite the many variations we tried (Table 1).

The experiments shown below are representative of the parameters we varied in order to improve selectivity:

(i) metal catalysts: **Pt**, Ni, Pd, Rh and Ir

(ii) alkaloid-modified Pt/C catalyst[12]

(iii) catalyst support: **C**, Al_2O_3, acid-treated C, sulfur-treated C, $CaCO_3$

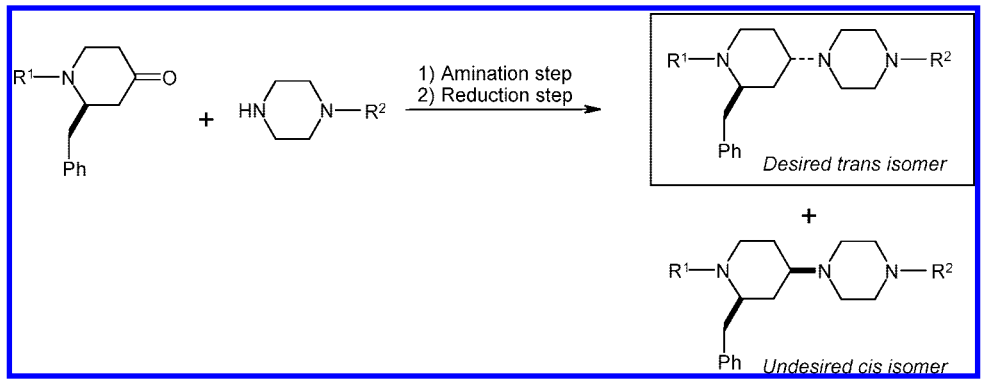
(9) (a) Brown, E.; Viot, F.; Le Floc'h, Y. *Tetrahedron Lett.* **1985**, *26*, 4451. (b) Brown, E.; Chevalier, C.; Huet, F.; Le Grumelec, C.; Lézé, A.; Touet, J. *Tetrahedron: Asymmetry* **1994**, *5*, 1191. For lab scale purposes, Brown's acid was purchased at Acros Organics. Large scale quantities of this reagent were made according to an internal, unpublished experimental procedure. Other chiral acids were screened as well but proved unsuccessful for this resolution: L-(+)-tartaric acid, L-(–)-dibenzoyl-tartaric acid monohydrate, (–)-di-*p*-toluil-L-tartaric acid, *S*-(+)-mandelic acid, L-(–)-malic acid, L-(+)-lactic acid, L-pyroglutamic acid, and D-(+)-10-camphorsulfonic acid.

(10) (a) Mattson, R. J.; Pham, K. M.; Leuck, D. J.; Cowen, K. A. *J. Org. Chem.* **1990**, *55*, 2552. (b) Kumpaty, H. J.; Bhattacharyya, S.; Rehr, E. W.; Gonzalez, A. M. *Synthesis* **2003**, 2206 and references therein.

(11) Previous trials with $NaBH_4$, $NaBH_4/ZnCl_2$, and $NaBH_4/CaCl_2$ always showed limited selectivity for the undesired *cis*-isomer.

(12) For a review on this topic, see: Kacprzac, K.; Gawroński, J. *Synthesis* **2001**, 961.

Scheme 3



(iv) solvent: EtOH, MeOH, THF, toluene and EtOAc

(v) amination conditions: **Ti(O^{i}Pr)$_4$**, **Al(O^{i}Pr)$_3$**, Ti(O^{n}Bu)$_4$, Ti(OEt)$_4$, $MgSO_4$, Mg(OEt)$_2$

(vi) ketone substrate: ***N*-bis(3,5-trifluoromethyl benzoyl)-** (compound **7**), *N*-carbethoxy-, *N*-benzyloxycarbonyl-, *N*-BOC-, *N*-acetyl-, *N*-benzoyl-, *N*-trifluoroacetyl-, *N*-benzyl-, *N*-1-naphtoyl-, *N*-2-naphtoyl- and *N*-tosyl piperidones

(vii) amine substrates: ***N*-benzyl-**, *N*-Boc- and *N*-carbethoxy piperazine

The results clearly indicate a strong influence of the piperidone substitution and of the reducing system (Pt > Pd ≈ $NaBH_3CN$) on the *trans*-selectivity.

A practical problem arose at this stage when Ti alkoxide were used for the amination step: after the hydrogenation, work-up with water and toluene generated a milky precipitate that was almost impossible to filter. Use of acid to dissolve the precipitate was incompatible with the amine, which would also transfer into the aqueous phase. While magnesium sulfate and magnesium ethoxide did not lead to completion of the reaction, aluminum isopropoxide (Al(O^{i}Pr)$_3$) gave similar conversion and similar *trans*-selectivity as Ti(O^{i}Pr)$_4$. A simple alkaline work-up, followed by extraction with toluene, afforded the 70:30 *trans/cis* mixture, which after chromatography gave compound *trans*-**9**.

For the separation of the *cis*- and *trans*-isomers, a standard analytical screen on normal silica gel, polar modified silica gel (diol-, aminopropyl-, cyanopropyl-) and some reversed phase materials was performed. However, these experiments did not result in an acceptable separation for large-scale preparative chromatography. Therefore, some experimental work was done on a number of chiral stationary phases. On Chiralcel OD [Daicel (3,5-dimethyl phenyl carbamate of cellulose)], the isomers were nicely separated using EtOH denatured with 2% of MeOH as the mobile phase.

Compound **9** was debenzylated to **10** (Pd/C, 50 °C, MeOH); once the reaction was complete, the catalyst was filtered off, the solvent was evaporated, and methyl isopropyl ketone (MIK) was added for the next step. To this solution were added compound **11** (1 equiv) and Na_2CO_3 (1.2 equiv). After reaction (2 h at 100 °C) and work-up (water and toluene), the organic phase was evaporated and ^{i}PrOH added for the following step. This solution was filtered through Dicalite (in order to avoid insoluble particles in the end product). (*S*)-Malic acid was added, and the reaction mixture was heated to reflux and then cooled. The precipitate, obtained in 80% yield, was in turn recrystallized from EtOH, leading to pure compound **1** as white crystals (80% yield).

Using the experimental procedure described here, we were able to produce about 20–50 kg of drug substance.

In order to have a more efficient synthesis, the more convergent reductive amination depicted in Scheme 4 was tried.

Despite its apparent simplicity, a convenient process to manufacture piperazine **12** was demanding to develop. We described this topic in a preceding paper.[13]

Ketone **7** underwent reductive amination with secondary amine **12** under the same conditions as described above [Al(O^{i}Pr)$_3$, neat, then ^{i}PrOH, H_2, Pt/C]. However, a 50:50 *cis/trans* mixture was obtained. Further optimization would be necessary to improve selectivity if this convergent approach were to be pursued further.

In conclusion, process development on R116301 resulted in the manufacture of multikilogram quantities of drug substance. The overall yield of about 4% represents a 5- to 10-fold increase compared with the former synthesis.

The most difficult step was the reductive amination, to which we brought two modifications: the catalytic hydrogenation conditions (Pt/C) for the reduction, which led to an inversion of the stereochemical selectivity (from *trans/cis* 25:75 to 70:30), and the use of Al(O^{i}Pr)$_3$ instead of Ti(O^{i}Pr)$_4$ to avoid the formation of insoluble material.

Experimental Section

General Procedures. All materials were purchased from commercial suppliers and used without further purification. All reactions were conducted under an atmosphere of nitrogen unless noted otherwise. In the laboratory, only glass vessels were used; in the pilot plant, either steel or glass-lined vessels were used. For each reaction, a sample of the reaction mixture was collected and analyzed by means of GC or HPLC.

(±)-Tetrahydro-1′-phenylspiro(1,3-dioxolan-2,7′(8′*H*)-3*H*-oxazolo[3,4-*a*]pyridin)-3′-one 4. A mixture of **2** (24.3 g, 0.1 mol) and TMEDA (15.1 mL, 1 equiv) in diethyl ether (150 mL, 1.5 L/mol) was cooled down to −70 °C with acetone/dry ice. ^{s}BuLi 1.3 M (100 mL, 1.3 equiv) was added dropwise so

(13) Guillaume, M.; Cuypers, J.; Vervest, I.; De Smaele, D.; Leurs, S. *Org. Process Res. Dev.* **2003**, *7*, 939.

Table 1. **Representative experiments for the reductive amination step[a]**

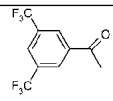
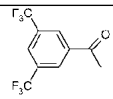
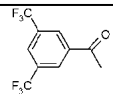
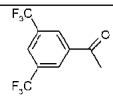
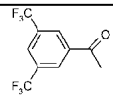
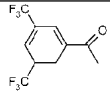
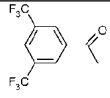
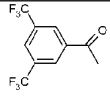
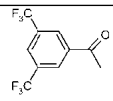
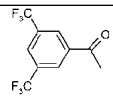
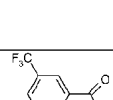
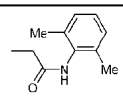
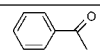
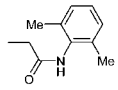
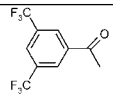
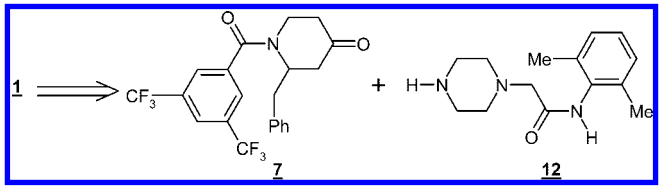
Entry	R^1	R^2	Amination		Reduction			% trans/cis	% yield*
			Water Scavenger	Conditions	Reducing agent	Solvent	Conditions		
1		-Bn	$Ti(O^iPr)_4$ (1.1 eq.)	neat, 40°C, 2h	Pt/C, H_2	^{i}PrOH	1 bar, 50°C, 16h	65:35	53%
2		-Bn	$Ti(O^iPr)_4$ (1.1 eq.)	neat, 40°C, 2h	Pt/C, H_2	^{i}PrOH	10 bar, 40°C, 18h	69:31	51%
3		-Bn	$Ti(OEt)_4$ (1 eq.)	neat;, 50°C, 3h	Pt/C, H_2	EtOH	1 bar, 40°C, 3h	68:32	46%
4		-Bn	$Ti(O^nBu)_4$ (1 eq.)	neat, 50°C, 3h	Pt/C, H_2	^{s}BuOH	1 bar, 40°C, 3h	64:36	43%
5		-Bn	$Ti(O^iPr)_4$ (1 eq.)	ncat, 40°C, 4h	Pt/C-cinchonine [6:1], H_2	^{i}PrOH	1 bar, 40°C, 20h	69:31	37%
6		-Bn	$Ti(O^iPr)_4$ (1 eq.)	neat, 40°C, 4h	Rh/C, H_2	^{i}PrOH	1 bar, 40°C, 18h	no reaction	
7		-Bn	$Ti(O^iPr)_4$ (1 eq.)	neat, 40°C, 3h	Ir/C, H_2	iPrOH	1 bar, 40°C, 18h	no reaction	
8		-Bn	$Ti(O^iPr)_4$ (1 eq.)	neat, 40°C, 4h	Pd/C, H_2	^{i}PrOH	1 bar, 40°C, 18h		
9		-Bn	$Al(O^iPr)_3$ (1 eq.)	^{i}PrOH, 40°C, 4h	Pt/C, H_2	^{i}PrOH	1 bar, 40°C, 1h30	65:35	51%
10		-Bn	$Al(O^iPr)_3$ (1 eq.)	^{i}PrOH, 40°C, 4h	Pt/C-nicotine [16:1], H_2	^{i}PrOH	1 bar, 40°C, 19h	64:36	48%
11		-Bn	$Al(O^iPr)_3$ (1 eq.)	^{i}PrOH, 60°C, 4h	Pt/C, H_2	^{i}PrOH	1 bar, 60°C, 22h	60:40	46%
12	Bn-		$Ti(O^iPr)_4$ (1.1 eq.)	^{i}PrOH, 50°C, 2h	Pt/C, H_2	^{i}PrOH	1 bar, 50°C	38:62	20%

Table 1. **Continued**

Entry	R^1	R^2	Amination		Reduction			%	%
			Water Scavenger	Conditions	Reducing agent	Solvent	Conditions	trans/cis	yield*
13		-Bn	$Ti(O^iPr)_4$ (1.1 eq.)	EtOH, 40°C, 3h	Pt/C, H_2	EtOH	1 bar, 50°C, 23h	34:66	28%
14			$Ti(O^iPr)_4$ (1.1 eq.)	^{i}PrOH, 40°C, 2h	Pt/C, H_2	^{i}PrOH	1 bar, 50°C	29:71	15%
15			$Ti(O^iPr)_4$ (1 eq.)	^{i}PrOH, 40°C, 3h	Pt/C, H_2	^{i}PrOH	1 bar, 40°C, 1h	60:40	87%

[a] The yield (*) refers to the desired *trans*-isomer. In most cases, limited amounts (0–3%) of reduced ketone and starting material are found in the reaction mixture as well.

Scheme 4



that the temperature remained under −60 °C. After the addition, the mixture was stirred at −70 °C. Benzaldehyde (11.7 mL, 1.1 equiv) was added at such a rate that the temperature remained under −60 °C. After stirring 2 h at −70 °C, NH_4Cl 1 N (100 mL) was added and the temperature was allowed to rise to room temperature. The organic layer was evaporated to afford **3** as a yellow oil. Intermediate analysis (GC area %) indicated 92% conversion.

^{i}PrOH (100 mL, 1 L/mol) and ^{t}BuOK (600 mg, 5 mol%) were added, and the reaction mixture was heated to reflux, stirred at that temperature for 4 h, and then cooled down to room temperature. After 1 h, a precipitate appeared (seeding is sometimes necessary), and the mixture was further cooled down to 0 °C. After stirring 30 min at that temperature, the precipitate was filtered off, washed with ^{i}PrOH (20 mL, 0.02 L/mol), and dried over 16 h at 40 °C under vacuum. Yield: 15.2 g (55%). Mp: 129 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, major diastereomer): δ 1.59–1.82 (m, 3H), 1.98 (m, 1H), 3.10 (m, 1H), 3.76 (ddd, J = 11.9, 6.6, 4.0 Hz, 1H), 3.80–4.04 (m, 5H), 5.03 (d, J = 6.6 Hz, 1H), 7.25–7.44 (m, 5H). Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.56; H, 6.30; N, 4.89.

(±)-7-(Phenylmethyl)-1,4-dioxa-8-azaspiro[4.5]decane (±)-5. *1. Laboratory Procedure.* A mixture of **4** (27.5 g, 0.1 mol) was dissolved in MeOH (100 mL, 1 L/mol). A 30% NaOMe solution in MeOH (20 mL, 1.05 equiv) was added, followed by Pd/C (5% wet, 2.5 g, 25 g/mol). The reaction mixture was heated up to 50 °C and hydrogenated over 2 h. After it was cooled down, HCl 5 N (40 mL, 2 equiv) was added (CO_2 evolution!), the catalyst was filtered off, and the product was extracted with toluene (100 mL, 1 L/mol). After drying the organic layer over Na_2SO_4, the solvent was distilled off. **(±)-5** was obtained as yellow oil. It was used directly in the next step. Yield: 21.1 g (91%).

2. Pilot Plant Procedure. Note: The above-described laboratory procedure had not been yet implemented in the pilot plant when the project was discontinued. We describe therefore the process performed without NaOMe.

To an inertized 2000 L hydrogenation reactor was added **4** (200 kg, 726.5 mol), followed by MeOH (1300 L, 1.8 L/mol) and Pd/C 5% wet (15.40 kg, 21.2 g/mol). After starting the stirrer, the reaction mixture was heated up to 50 °C and hydrogenated at that temperature. When an uptake drop was observed, the vessel was degassed (CO_2 was removed) and reflushed with H_2. After a couple of degas/reflush operations, a process control (GC analysis) indicated that the SM had completely disappeared. The reaction mixture was flushed with nitrogen, and then thiophene (73 g, ca. 1 g/200 g catalyst) was added. The catalyst was filtered over Dicalite, rinsed with MeOH (145 L, 0.2 L/mol) and water (145 L, 0.2 L/mol); 1100 L solvent was evaporated and the remaining solution was collected and weighed. Yield: 493.2 kg solution. Base titration: 36.6% w/w ⇒ 174 kg **4** (quantitative yield).

7-(Phenylmethyl)-1,4-dioxa-8-azaspiro [4.5] decane (–)-5·Brown's Acid. *1. Laboratory Procedure.* Compound **4** (233 g, 1 mol) was dissolved in MeOH (1900 mL, 1.8 L/mol). Brown's acid (209.0 g, 1 equiv) was added, and the mixture was heated to reflux. After 15 min at reflux, the reaction mixture was cooled down to 55 °C, seeded and stirred at that temperature for 1 h, and then further cooled down to 20 °C over 4 h; the precipitate was filtered off, washed with MeOH (120 mL, 0.12 L/mol), and dried at 40 °C for 4 h under vacuum. Yield: 133 g (30%). Mp: 174 °C. HPLC: 100.6% (% w/w abs). ee = 90% (HPLC).

As mentioned above, the enantiomeric purity is sufficient to eventually obtain **1** of sufficient enantiomeric purity. However, for analytical purposes, we recrystallized 5 g of **5** from MeOH (10 mL/g). Yield: 3 g (60% from raw **5**). Mp: 181 °C. HPLC: 100.5% (% w/w abs). ee >99% (chiral HPLC). Anal. Calcd for $C_{24}H_{30}N_2O_6$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.08; H, 6.75; N, 6.26.

A sample of this salt (2.3 g) was in turn neutralized with NaOH 1 N and extracted twice with toluene. After drying the extract and evaporating the solvent, (–)-**5** was obtained as a transparent oil (1.1g, 92%) with the following characteristics: HPLC:[14] 99.3% w/w abs. ee >99% (derivatization + HPLC[15]). $[\alpha]^D_{20} = -16.6°$. ^{1}H NMR ($CDCl_3$, 360 MHz): δ 1.45 (dd, J = 11.4, 12.9 Hz, 1H), 1.57–1.71 (m, 3H), 1.77 (bdt, J = 12.9 Hz, 1H), 2.59 (dd, J = 13.3, 8.5 Hz, 1H), 2.66–2.79 (m, 2H), 2.92–3.03 (m, 2H), 3.89–3.98 (m,4H), 7.17–7.25 (m, 3H), 7.26–7.33 (m, 2H). Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 73.33; H, 8.91; N, 6.01.

2. Pilot Plant Procedure. In a 1000 L reactor, **4** (24.2 kg, 104 mol), MeOH (187 L, 1.8 L/mol) and Brown's acid (21.8 kg, 1 equiv) were mixed together. After refluxing the mixture for 20 min, cooling down to 55 °C, seeding at that temperature, cooling down further to 20 °C over 3 h, and stirring at that temperature for 1 h, the white precipitate was centrifuged, washed with MeOH (12.5 L, 0.12L/mol) and dried at 40 °C under vacuum for 18 h to afford 15.9 kg of (–)-**5**·Brown's acid (35% yield), which was pure enough to use further in the next step. ee = 86.2%.

(+)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-piperidinone (+)-7. *1. Laboratory Procedure.* (–)-**5**·Brown's acid (140.0 g, 0.32 mol) was suspended in water (640 mL, 2 L/mol). NaOH 50% (18.0 mL, 1.1 equiv) and toluene (640 mL, 2 L/mol) were added, and the mixture was stirred vigorously at room temperature. The water layer was extracted again with toluene (64 mL, 0.2 L/mol). The combined organic fractions were dried over Na_2SO_4 and put in a 3-necked flask, which was cooled to 15 °C with water. The addition of triethylamine (44.8 mL, 1.5 equiv) was followed by the dropwise addition of 3,5-bis(trifluoromethyl)benzoyl chloride (88.3 g, 1 equiv) so that the temperature remained under 30 °C. After stirring 30 min at 25 °C, water (320 mL, 1 L/mol) was added, and the toluene extract was evaporated at 50 °C under vacuum. EtOH (160 mL, 0.5 L/mol) was added, followed by water (160 mL, 0.5 L/mol) and HCl 5 N (160 mL, 2.5 equiv). The reaction mixture was heated to 60 °C for 16 h and then cooled to 25 °C. Toluene (320 mL, 1 L/mol) was added, the water layer was discarded, the organic extract was dried over Na_2SO_4, and the solvent was distilled off at 50 °C under vacuum. Yield: 130.0 g (85% yield). An analytical sample of (–)-**5** (1 g, see above) was reacted as described above to afford after flash chromatography 1 g (+)-**7** (54%). HPLC:[16] 98.5%. $[\alpha]^D_{20}$ = +7.3° (0.01% in MeOH). Anal. Calcd for $C_{21}H_{17}F_6NO_2$: C, 58.75; H, 3.99; N, 3.26. Found: C, 56.43; H, 4.02; N, 3.25.. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 2.24 (bd, J = 13.7 Hz, 1H), 2.40 (bd, J = 13.3 Hz, 1H), 2.67 (m, 1H), 2.82 (m, 1H), 2.96 (m, 1H), 3.11 (bdd, J = 14.2, 6.2 Hz, 1H), 3.57 (m, 1H), 4.10 (m, 1H), 4.75 (m, 1H), 6.99 (bd, J = 6.2 Hz, 2H), 7.16–7.39 (m, 3H), 7.48 (bs, 2H), 8.13 (bs, 1H).

2. Pilot Plant Procedure. The following procedure describes the process starting from racemic **5** (not as a salt). Compound (±)-**5** (50.7 kg) was brought in the reactor together with toluene (434 L) and triethylamine (22.2 kg), which formed a clear solution. The acid chloride (63.4 kg) was added dropwise at a temperature <50 °C. The reaction mixture was cooled to 25 °C and stirred at that temperature over 2 h. Water (87 L) was added, and the mixture was stirred for 30 min. The water layer was discarded, and the organic layer was evaporated at 80 °C under vacuum. Water (107 L), EtOH (107 L), and HCl (12 N, 107 L) were added to the residue. The mixture was heated to 60 °C, stirred for 8 h at that temperature, and then cooled to 15–20 °C. The precipitate (±)-**7** was centrifuged, washed with water, and dried (35 °C, vac, 52 h). Yield: 87%.

(+)-(2*R-trans*)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-[4-(phenylmethyl)-1-piperazinyl]piperidine 9. *1. Laboratory Procedure. Method A (with Ti(O^iPr)$_4$).* Compound (+)-**7** (171.7 g, 0.4 mol) was stirred at room temperature with *N*-benzyl piperazine (206.1 g, 0.48 mol, 1.2 equiv) and Ti(O^iPr)$_4$ (125.1 g, 0.44 mol, 1.1 equiv) at 40 °C for 3 h. ^{i}PrOH (1.2 L, 3 L/mol) and Pt/C (5% dry, 16 g, 40 g/mol) was added, and the reaction mixture was heated to 50 °C and hydrogenated over 16 h at that temperature. After purging the vessel with N_2, the mixture was cooled to 20–25 °C, and the catalyst was filtered off and washed with toluene (2 × 320 mL, 2 × 0.8L/mol). Toluene (800 mL, 2 L/mol) was added to the filtrate, followed by Dicalite (40 g, 100 g/mol) and NaOH (800 mL, 2 equiv). After stirring 30 min at room temperature, the milky precipitate was filtered over Dicalite (difficult filtration!). The layers of the filtrate were separated, and the organic one was filtered over Na_2SO_4 and evaporated. The oily residue (*cis/trans* mixture) was chromatographed to afford pure *trans*-isomer as a pale yellow oil, which was used further in the next step.*Method B (with Al(O^iPr)$_3$).* *N*-Benzyl piperazine (17.6 g, 0.1 mol), Al(O^iPr)$_3$ (20.4 g, 0.1 mol), Pt/C 5% dry (2 g, 20 g/mol), and ^{i}PrOH (200 mL, 2 L/mol) were added to (+)-**6** (42.9 g, 0.1 mol) in toluene (200 mL, 2 L/mol). The mixture was heated to 60 °C, stirred at that temperature for 3 h, and then hydrogenated over 16 h. After the reaction mixture was cooled to room

(14) **HPLC Method.** Hypersil BDS 100 × 4.0 mm i.d., 3 μm spherical material; eluent A 0.2% $(NH_4)_2CO_3$; eluent B CH_3CN; temp 30 °C; injection volume 6 mL; flow 1 mL/min. Gradient: 0 min 95% A, 5% B; 7 min 75% A, 25% B; 14 min 25% A, 75% B; 16 min 5% A, 95% B; 19 min 5% A, 95% B; 19.5 min 95% A, 5% B; 25 min 95% A; 5% B. UV detection at 210 nm. Retention time: 9.5 min.

(15) **HPLC Method.** the compound is derivatized with GITC (excess) in DMF, followed by achiral HPLC. Hypersil BDS 100 × 4.0 mm i.d., 3 μm spherical material; eluent A 0.5% $(NH_4)OAc$; eluent B MeOH; temp 25 °C; injection volume 6 mL; flow 1 mL/min. Gradient: 0 min 45% A, 55% B; 25 min 45% A, 55% B. UV detection at 225 nm. Retention time: 20.4 min.

(16) **HPLC Method.** Hypersil BDS 100 × 4.0 mm i.d., 3 μm spherical material; eluent A 1% H_3PO_4; eluent B CH_3CN; temp 25 °C; injection volume 6 mL; flow 1.2 mL/min. Gradient: 0 min 95% A, 5% B; 15 min 0% A, 100% B; 18 min 0% A, 100% B; 19 min 95% A, 5% B; 19 min 5% A, 95% B; 25 min 95% A; 5% B. UV detection at 210 nm. Retention time: 10.9 min.

temperature and flushed with N_2, NaOH 5 N (100 mL, 5 equiv) was added, and the catalyst was filtered off over Dicalite and rinsed with toluene (20 mL, 0.2 L/mol). The layers were separated, the organic layer waswas dried over Na_2SO_4, and the solvent was distilled off at 50 °C under vacuum. Yield: 70.4g (corresponds to 46% active yield of *trans*-isomer). The mixture was chromatographed to afford (+)-**9** as a pale yellow oil that was directly dissolved in MeOH, titrated, and used further in the next step. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.49–1.70 (m, 2H), 1.97 (m, 1H), 2.14 (m, 1H), 2.38–2.72 (m, 8H), 2.75–2.90 (m, 2H), 3.09–3.21 (m, 2H), 3.46–3.58 (m, 2H), 3.91 (m, 1H), 4.76 (m, 1H), 6.87 (d, J = 6.2 Hz, 2H), 7.11 (s, 2H), 7.18–7.37 (m, 8H), 7.78 (s, 1H).

2. Pilot Plant Procedure (with Al(O^iPr)$_3$). To a 300 L glass-lined inertized vessel were added (+)-**6** (55 kg, 128 mol) in ^{i}PrOH (128 L, 1 L/mol), *N*-benzyl piperazine (22.5 kg, 1 equiv), Al(O^iPr)$_3$ (26.1 kg, 1 equiv), and Pt/C 5% dry (2.56 kg, 20 g/mol). The mixture was heated to 60 °C, stirred at that temperature for 3 h, and then hydrogenated over 16 h. The reaction mixture was cooled to room temperature, flushed with N_2, and then transferred to another vessel. Toluene (512 L, 4 L/mol) and NaOH 5 N (256 L, 10 equiv) were added over 15 min, followed by Dicalite (3.8 kg, 30 g/mol). After filtration, the layers were separated, and the organic layer was evaporated under vacuum. EtOH denatured with 2% MeOH (141 L, 1.1 L/mol) was added, and the mixture was further chromatographed as such. Yield: 43 kg (corresponds to 57% active yield of *trans*-isomer).

Chromatographic Separation at Large Scale. (Not the same batch as the one described in the preceding paragraph!) Stationary phase: Chiralcel OD [Daicel (3,5-dimethyl phenyl carbamate of cellulose)]. Mobile phase: EtOH denatured with 2% of MeOH. A solution of 100 g of product/L eluent was prepared. A 20 cm i.d. dynamic axial compression column was filled with 6 kg of the stationary phase and the total amount of product (148 kg) was chromatographed by means of repetitive injections of 1 L of sample solutions corresponding to an injection amount of 100 g (a loading capacity of 16.7 mg/g of packing material). After evaporation of the solvent, 86.6 kg of the desired isomer was obtained, which corresponds to 59% active yield (based on (+)-**9**.

(+)-(2*R*-*trans*)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-(1-piperazinyl)piperidine 10. *1. Laboratory Procedure.* Compound (+)-**9** (137.5 g, 0.23 mol) was dissolved in MeOH (700 mL, 3 L/mol) and Pd/C 5% wet (7.0 g, 30 g/mol) was added. The reaction mixture was heated to 50 °C and hydrogenated at that temperature for 5 h. The catalyst was filtered off over Dicalite, rinsed with MeOH (35 mL, 0.15 L/mol). The solvent was distilled off at 50 °C under vacuum to afford (+)-**10** as a pale yellow oil. Yield: 114.5 g (95% yield). ^{1}H NMR ($CDCl_3$, 360 MHz) δ: 1.49–1.75 (m, 2H), 1.90 (bs, 1H, NH), 1.98 (m, 1H), 2.16 (m, 1H), 2.49–2.68 (m, 4H), 2.77–2.97 (m, 6H), 3.18 (m, 2H), 3.93 (m, 1H), 4.77 (m, 1H), 6.88 (d, J = 6.3 Hz, 2H), 7.08 (bs, 2H), 7.20–7.37 (m, 3H), 7.78 (bs, 1H).

2. Pilot Plant Procedure. The hydrogenation vessel was inerted with nitrogen, and then (+)-**9** (40.2 kg in MeOH), MeOH (28 L) and Pd/C 5% wet (580 g) were introduced. Stirring was started, and the mixture was heated to 50 °C. The debenzylation through hydrogenolysis was performed at that temperature. After 16 h, a process control indicated complete conversion. The reaction mixture was cooled to 25 °C, thiophene (3 g) was added, and the filtration was performed. The cake was washed with MeOH (12.5 L), and the solution was evaporated to dryness. For the next step, 4-methyl-2-pentanone (38.8 L) was added and stirring was continued for 30 min The solution of (+)-**10** so obtained was used further after quantitative HPLC analysis. Yield: 92%.

(+)-(B-*trans*)-4-[1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-piperidinyl]-*N*-(2,6-dimethylphenyl)-1-piperazineacetamide·(L)-Malic Acid 1. *1. Laboratory Procedure.* Compound (+)-**10** (0.22 mol) was dissolved in MIK (440 mL, 2 L/mol). *N*-(α-Chloroacetyl)-2,6-dimethylanilide **11** (54.4 g, 0.22 mol) and Na_2CO_3 (26.5 g, 1.2 equiv) were added, and the reaction mixture was heated to 100 °C. After stirring 2 h at that temperature, the mixture was cooled to room temperature, water (880 mL, 4 L/mol) was added, and the organic layer was evaporated at 50 °C under vacuum. ^{i}PrOH (440 mL, 2 L/mol) was added, and the solution was filtered over Dicalite in order to remove the insoluble materials. Malic acid (29.5 g, 1 equiv) was added, and the mixture was heated to reflux, while a precipitate formed. After 30 min reflux, the mixture was cooled to 20 °C and stirred at that temperature for 3 h. The precipitate was filtered off, washed with 44 mL (0.2 L/mol) ^{i}PrOH, and dried for 16 h at 50 °C under vacuum. Yield: 122.2 g (70% over 2 steps), off-white precipitate. The salt was recrystallized from EtOH (8 mL solvent/g salt, 80% yield) to obtain a purity which was always consistent with quality requirements. HPLC:[17] 99.6% w/w. ee: 98% (CE[18]). Anal. Calcd for $C_{35}H_{38}F_6N_4O_2.C_4H_6O_5$: C, 58.94; H, 5.58; N, 7.05. Found: C, 58.76; H, 5.44; N, 7.01. ^{1}H NMR ($CDCl_3$, 400 MHz, free base): δ 1.58 (m, 1H), 1.68 (m, 1H), 1.97 (m, 1H), 2.14 (m, 1H), 2.23 (s, 6H), 2.55–2.80 (m, 9H), 2.82–2.94 (m, 1H), 3.10–3.22 (m, 4H), 3.94 (m, 1H), 4.77 (m, 1H), 6.87 (d, J = 6.6 Hz, 2H), 7.03–7.10 (m, 3H), 7.12 (s, 2H), 7.20–7.36 (m, 3H), 7.79 (s, 1H), 8.62 (s, 1H, CONH).

2. Pilot Plant Procedure. In an inerted reactor, (+)-**10** (146 kg solution in MIK) was introduced together with *N*-(α-chloroacetyl)-2,6-dimethylanilide **11** (8.6 kg) and Na_2CO_3 (5.37 kg). The reaction mixture was heated to 100 °C and stirred at that temperature for 2 h. Process control (HPLC) indicated a complete conversion, the reaction mixture was then cooled to 25 °C and water (174 L) was added. After stirring for 30 min the water layer was discarded. The organic layer was evaporated at 70 °C under vacuum to dryness. ^{i}PrOH (84 L) and Dicalite

(17) **HPLC Method.** Hypersil BDS 100 × 4.0 mm i.d., 3 μm spherical material; eluent A 10mM TBAHS; eluent B CH_3CN; eluent C MeOH; temp 25 °C; injection volume 6 mL; flow 1 mL/min. Gradient: 0 min 90% A, 5% B, 5% C; 15 min 0% A, 50% B, 50% C; 18 min 0% A, 50% B, 50% C; 19 min 90% A, 5% B, 5% C; 25 min 90% A, 5% B, 5% C. UV detection at 215 nm. Retention time: 10.1 min.

(18) **CE Method.** TSP capillary electrophoresis system; capillary uncoated fused silica i.d. 75 μm, 25 cm total length, temp 20 °C. Background electrolyte: 25 mM hydroxypropyl-γ-CD in 100 mM H_3PO_4/triethanolamine, buffer pH = 2.5; separate +100 mA; UV detection at 200 nm. Retention time: 15.8 min.

(435 g) were added. The mixture was filtered and transferred into another reactor. A solution of L-malic acid (6.52 kg) in ^{i}PrOH (78 L) was added to the solution of the free amine. The mixture was heated to reflux (ca. 80 °C). During this process, crystallization occurred. The solution was refluxed for 30 min The reaction mixture was cooled to 25 °C over 3 h and stirred overnight at 22 °C. The precipitate was centrifuged, washed with 10 L ^{i}PrOH and dried (50 °C, vac, 16 h). Yield: 86%.

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