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Communication

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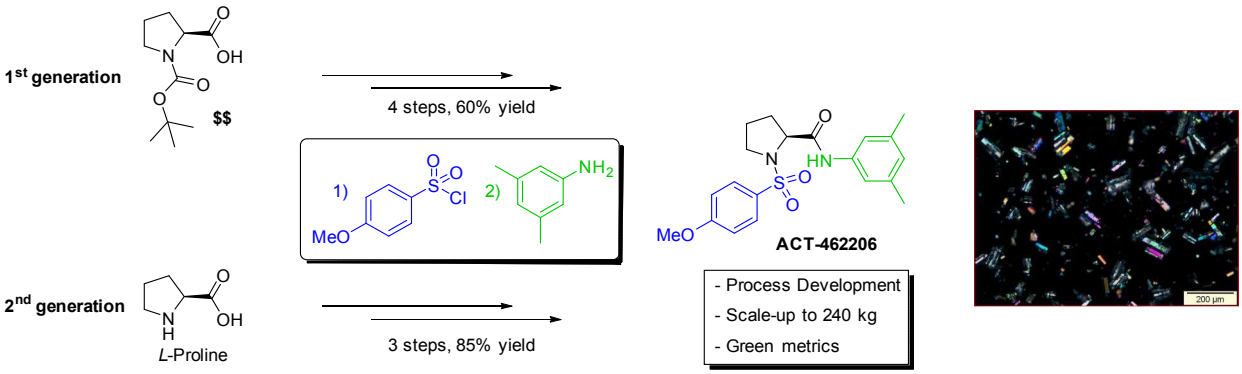
TOC


1st generation
$$
4 steps, 60% yield
1)
2)
MeO
NH2
ACT-462206
- Process Development
- Scale-up to 240 kg
- Green metrics
2nd generation
L-Proline
3 steps, 85% yield

Short Synthesis of a Proline Amide Orexin Receptor Antagonist on Pilot Plant Scale

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KEYWORDS *L*-proline, amide coupling, scale-up, process mass intensity.

ABSTRACT

A three step fully telescoped synthesis of an N-sulfonyl proline amide, a non peptide antagonist of human orexin receptors is described. The process development from the Medicinal Chemistry route up to the 240-kg production of **1** is discussed with a focus on an economical and efficient amide bond formation and identification of a new polymorph. The routes are compared using green metrics.

Introduction

(S)-1-(4-Methoxybenzenesulfonyl)-pyrrolidine-2-carboxylic acid (3,5-dimethylphenyl)-amide (**1**) (ACT-462206) is a non-peptide antagonist of human orexin receptors for potential use in the treatment of sleep disorders, stress-related syndromes, addictions, cognitive dysfunctions as well

as eating or drinking disorders. This Active Pharmaceutical Ingredient (API) is currently being studied for clinical use by Actelion.[1]

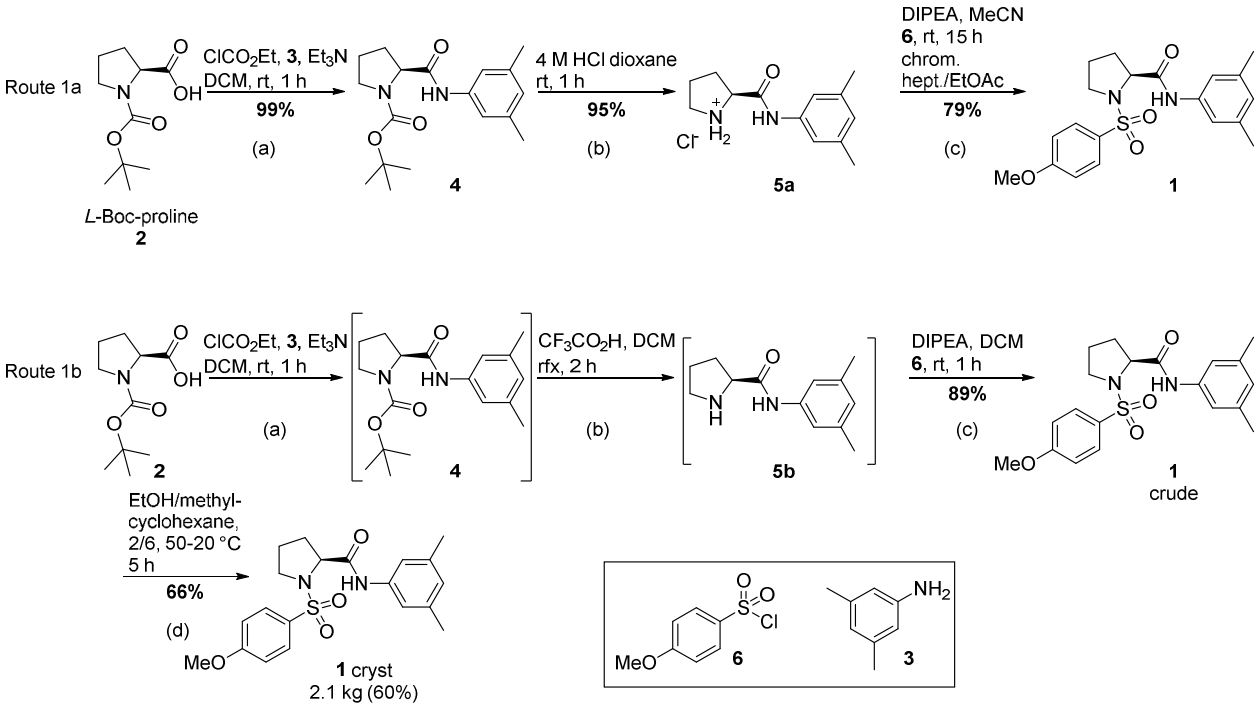
Compound **1** is a derivative of *L*-proline by 'simple' functionalization of both secondary amine and carboxylic acid functions. From discovery to scale-up to the latest 240-kg production,[2] different routes have been evaluated resulting in significant improvements of the overall synthetic process. In this communication we wish to describe the three main processes studied and to compare them in terms of green metrics.[3]

Results and discussion

N-Boc-*L*-proline **2** was the starting material employed in the medicinal chemistry route. A sequence of coupling with 3,5-dimethylaniline (**3**), Boc-removal to afford HCl salt **5a** and sulfonamide formation with 4-methoxybenzenesulfonyl chloride (**6**) afforded pure API **1** after chromatography in 74% yield (Route A, Scheme 1).

The same route was initially used by process chemistry to deliver the first 2 kg of API enabling early pilot toxicity studies. As improvements to this route, intermediates **4** and **5b** were kept in DCM solution and Boc removal was carried out with TFA while product **1** was purified by crystallization providing 2.1 kg of enantiopure (100% *ee*) API with a telescoped process in 60% yield with one isolated intermediate (Route A', Scheme 1).

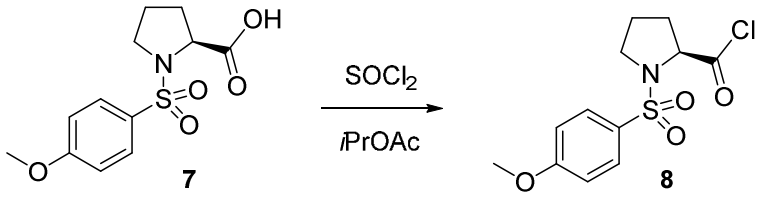
Scheme 1. Medicinal chemistry (Route 1a) and 2-kg syntheses (Route 1b).



For larger supply of this API it was decided to further simplify the synthesis meeting the requirements of atom-economy and environmental friendliness. For this reason, N-Boc-*L*-proline was replaced by *L*-proline[4] and an alternative solvent for the undesirable chlorinated solvent DCM was investigated.

Sulfamidation of *L*-proline in aqueous base provided intermediate **7** (Scheme 2). For the amide coupling, $SOCl_2$ was used since it is one of the cheapest coupling reagents also on a molar basis. Being one step shorter, this new process (Route 2a/2b) represents a significant improvement over Route 1a/1b. Table 1 reports the study of the key amide coupling step with a focus on the acid chloride formation.[5] As soon as the acid chloride **8** was formed in high purity, the amide coupling with amine **3** proceeded smoothly to give the API **1** which, after work-up, was crystallized from *i*PrOAc/methyl-cyclohexane in high yields.

Table 1. Acid chloride **8** formation with $SOCl_2$.



entry	conditions	$SOCl_2$ (equiv)	conv. (%)[a]	time (h)
1	NMM (1.5 equiv), 0 °C to 20 °C	1.5	80[b]	5
2	0 °C to 40 °C	1.3	90	3
3	DMF (0.1 equiv), rt to 45 °C	1.2	99	2
4	DEF (0.1 equiv), rt to 45 °C	1.2	99	3
5	DABCO (0.1 equiv), rt to 45 °C	1.2	92	3
6	DMAc (0.1 equiv), rt to 45 °C	1.2	96	4
7	rt to 45 °C, water wash	1.5	97[c]	3
8	DMF (0.05 equiv), 45 °C	1.05	97[d]	2

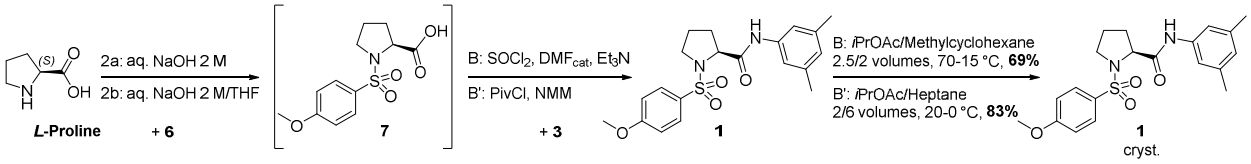
[a] Conversion (% a/a) as calculated by LC/MS analysis (sample quenched with MeOH): [area methyl ester / (area acid + area Me-ester)] x 100. [b] 11% a/a of anhydride observed. [c] 37% a/a of acid **7** formed. [d] **1** was obtained as off white solid after crystallization.

By employing N-methyl-morpholine (NMM) as base, (entry 1) a slow conversion of the acid to the chloride was observed along with the symmetrical anhydride (up to 11% a/a). Without the base and at 40 °C the acid chloride formation was clean and fast (entry 2, 90%, 3 h), but a higher loading of $SOCl_2$ was required. To lower the amount of $SOCl_2$, different catalysts were tested, most of them forming a Vilsmeier-type intermediate (entries 3-6).[6] With 10 mol% of DMF or diethylformamide (DEF) full conversion into the chloride was achieved in 2-3 h at 45 °C respectively (entry 3 and 4) while 1,4-diazabicyclo[2.2.2]octane (DABCO) and dimethyl

acetamide (DMAc) were less efficient (entries 5 and 6). Gratifyingly, racemization of API **1** was never observed.[7]

Having opted for DMF as catalyst, the removal of excess of $SOCl_2$ (responsible for grey colour in the final API) was examined. An aqueous wash of the acid chloride solution could not be used since rapid hydrolysis to the acid was observed (entry 7, 37% of **7** formed). $SOCl_2$ could instead be removed by distillation, as reported on plant scale.[8] In a test experiment, full conversion into the acid chloride was obtained with 0.05 equivalents of DMF and 1.05 equivalents of $SOCl_2$ (entry 8). Excess of thionyl chloride was removed by two distillation cycles with *i*PrOAc and the acid chloride was converted in 1 h into **1** upon addition of aniline **3** in the presence of triethylamine. The full telescoped process gave 980 g of API **1** as a pale yellow/off white solid with 69% yield and high purity (99.6% a/a and 99.7% w/w, >99% *er*).

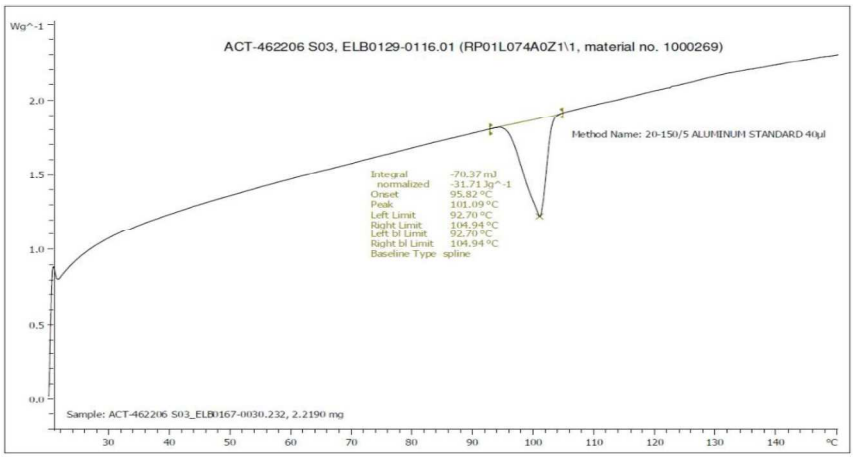
Scheme 2. Routes 2a and 2b.

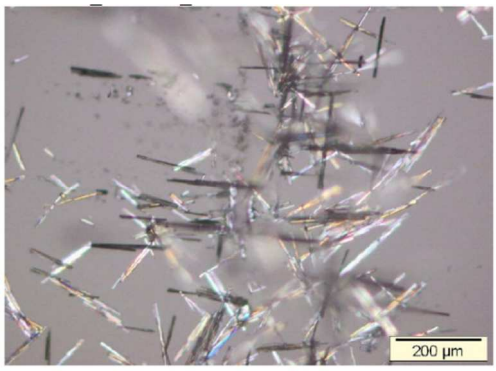


During the process development work, a new and more stable polymorphic form of **1** was identified. The new polymorph displayed a higher melting point (103 °C vs 96 °C, Figure 1a vs 1b), different solubility and different crystal shape (bigger crystals instead of needles, microscope pictures, Figure 1a vs Figure 1b). API for clinical development needed to be supplied in the correct solid state, so additional development on the synthesis was done focusing on the preparation of the new polymorph of the API.

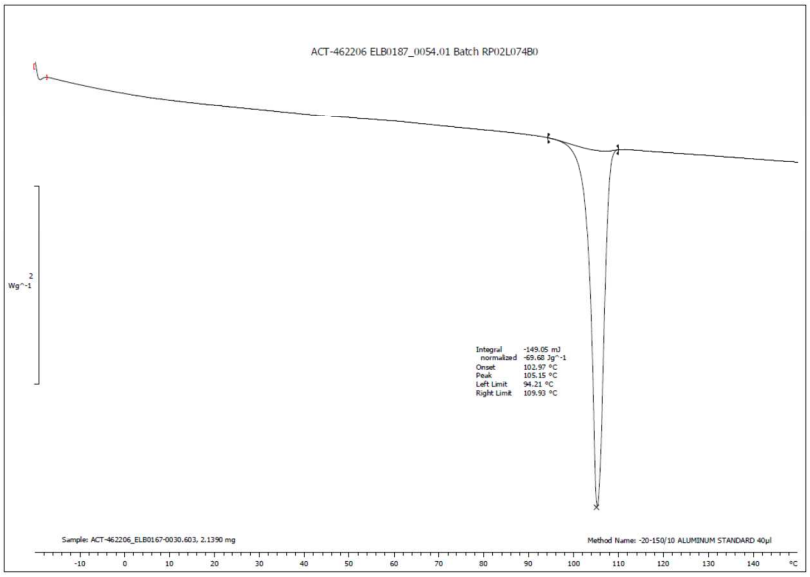
Figure 1.

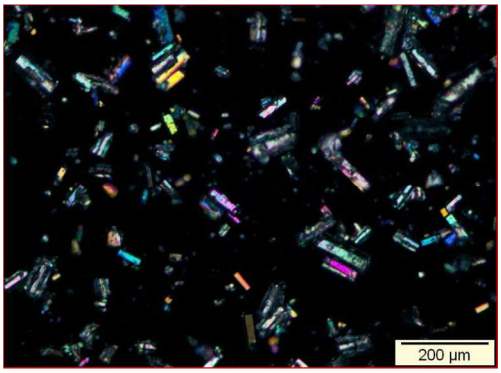
1a)





1b)





Fortunately, the more stable polymorph could be easily obtained by the use of seed crystals obtained by crystallization from solutions of *i*PrOAc/methyl cyclohexane or heptane, resulting in 79% yield.[9]

For the amide coupling, the use of pivaloyl chloride (PivCl) and N-methyl morpholine (NMM) as coupling reagents followed by the addition of the aniline **3** resulted in clean and efficient conversion into **1,** and it was preferred over the use of $SOCl_2$ since the distillation to remove excess of coupling reagent was no longer necessary. This improved process resulted into Route 2b (conditions 2b, Scheme 2) and it was used by DSM to produce 240 kg (4 batches, 85% average yield) of GMP material to supply Phase I and Phase II studies.

Finally, the three routes were compared considering the number of steps, yields, the use of class-2 solvents,[10] protecting groups (PG), Process Mass Intensity (PMI),[3c,d] Reaction Mass Efficiency (RME)[3f], and Costs (Costs of Goods normalized (%) to the most expensive route) as parameters. Results are summarized in Table 2.

Table 2. Routes comparison.

	no. steps	yield (%)	PG	class 2 solvents	PMI[a]	RME (%)[b]	Costs[c] (%)
route 1b	4	60	1	1	45	20.1	100
route 2a	3	69	0	1	51	47.5	4.5
route 2b	3	85	0	0	40	55.3	5.2

[a] PMI = Process Mass Intensity, defined as: (sum of all reagents, solvents and aqueous solutions (kg))/API produced (kg) (ref. 3c,d). [b] RME = Reaction Mass Efficiency, defined as the mass of the reactants that remain in the product: [mass of product (kg)/sum of mass of the reactants]x100 (ref. 3f). [c] Costs = relative costs of raw materials/kg of API (normalized to the most expensive route at 100%).

Second generation routes 2a and 2b are superior to the Discovery Route 1b since they are shorter with higher yields as no protecting group is employed. This is well reflected in the value of 20.1% of Reaction Mass Efficiency (RME) for route 1b which means that 80% of the mass of the reactants is wasted during the process and only 20% incorporated in the final product. The value is increased to ca. 50% for second generation routes and the average of 70-74% for each of

the two chemical steps is a good score for amide and sulfamide formation reactions.[3f] Routes 2a and 2b achieve also a significant cost reduction. In addition, the use of dichloromethane (chlorinated, class 2 solvent) makes route 1b less attractive.

Route 2b has the highest yield, is not using any class 2 solvents (heptane instead of methyl cyclohexane employed in the API crystallization of route 2a) and is generating the lower amount of waste as evidenced by its low PMI (40). However, PMI also in the other two routes are quite low compared to the average value of 100-120 for the pharmaceutical industry[3c,d] and this reflects the low molecular complexity and the short synthetic sequence of this API.[11] The difference between route 2a and 2b (51 *vs.* 40) is due to the use of higher amounts of *i*PrOAc for the removal of $SOCl_2$ by distillation (2 cycles with 5 volumes) in route 2a.

Regarding costs, route 2a is significantly cheaper than 2b (> 10%) thanks to the use of $SOCl_2$ instead of the more costly pivaloyl chloride. Despite route 2b scores better in all the other parameters considered, the cost factor would play an important role at the ton-scale level for the selection of the process to be used.

In conclusion, three different processes for the preparation of a novel dual orexin receptor antagonist have been described. The racemization-free amide coupling was efficiently performed with two very cheap coupling reagents. During the course of these optimization studies, two polymorphic forms were also identified and characterized. Higher yield, cost reduction, lower amount of waste produced, and greener conditions were developed for the 2nd generation process. Route 2b was also used to produce a total of 240 kg of API for clinical supply.

Experimental Section

General

Compounds are characterized by ^{1}H NMR (400 MHz, Bruker) or ^{13}C NMR (100 MHz, Bruker); internal standard for quantitative NMR was 1,4-dimethoxybenzene. Details for the HPLC and LC−MS methods are listed in the Supporting Information. Unless stated otherwise, yields are given as is.

(S)-1-(4-Methoxybenzenesulfonyl)-pyrrolidine-2-carboxylic acid (3,5-dimethylphenyl)-amide (1).

A reactor was charged with L-proline (21.25 kg, 185 mol), water (195.5 kg), NaOH 50% (34.0 kg, 425 mol) at 22 °C. In a second reactor a solution of 4-methoxybenzenesulfonyl chloride (41.96 kg, 203 mol) in THF (75.4 kg) was prepared. The latter solution of 4-methoxybenzenesulfonyl chloride was dosed to the first reactor at 22-23 °C in 55 min and the line rinsed with THF (7.6 kg). After ca. 1.5 h, the pH was adjusted from 12.1 to 7.7 by the addition of 3 M HCl (9.2 kg, 26.3 mol). The solution was concentrated by distillation under reduced pressure at 24-50 °C to ca. 250 L. *i*PrOAc (274.0 kg) was added and the pH was adjusted from 7.5 to 2.1 by the addition of 3 M HCl (66.8 kg, 191 mol) and stirred for 30 min. The organic phase was washed with water (166.5 kg) and concentrated by distillation under reduced pressure at 20-29 °C to ca. 100 L. *i*PrOAc (195.5 kg) was added and the mixture was again concentrated by distillation at 29-30 °C under reduced pressure to ca. 106 L. *i*PrOAc (195.5 kg) was added (water content was 0.07% w/w by Karl-Fisher titration). N-methylmorpholine (19.60 kg, 194 mol) was added at 24 °C in 20 min washing the line with of *i*PrOAc (8.90 kg). Pivaloyl chloride (22.30 kg, 185 mol) was added at 23-24 °C in 40 min rinsing with *i*PrOAc (3.9 kg). A second reactor was charged with 3,5-dimethylaniline (22.40 kg, 185 mol) and *i*PrOAc (164.2 kg). After ca. 2 h at 22-24 °C this solution was added to the reaction mixture at 5 °C in 1 h and the line rinsed with *i*PrOAc (25.4 kg). After 2.5 h at 3-4 °C, water

(85.0 kg) was added at 3-4 °C in 10 min followed by 3 M HCl (48.0 kg) in 30 min. The mixture was stirred at 3 °C for 15 min and then stirred at 18 °C for 30 min. The organic phase was washed with water (64.0 kg), aqueous saturated sodium bicarbonate (139.5 kg) and finally water (64.0 kg). The organic phase was concentrated by distillation under reduced pressure to about 475 L at 21-34 °C, then transferred to a second reactor via polish filtration and the line rinsed with *i*PrOAc (58.7 kg). The solution was further concentrated by distillation in vacuo to about 210 L at 26-40 °C (water content by Karl-Fisher titration: 0.05% w/w). Heptane (43.5 kg) were added at 22 °C. 64 g of seeds suspended in heptane (ca. 1.1 L) were added. After 2 h at 22-24 °C, heptane (246.0 kg) were added and stirred for 30 min. The mixture was cooled to 5 °C and kept 1 h. The suspension was split on two filters for filtration. Heptane (38.0 + 38.0 kg) were charged into the reactor followed by *i*PrOAc (17.0 +17.0 kg) at 2 °C. The washing solution was split into two equal portions for washing the two filters. The products were dried under reduced pressure under a stream of nitrogen at 30-52 °C on the two filters for approximately 15 h. A total of 59.72 kg (83%) of a white crystalline solid corresponding to proline amide **1**[1] (ACT-460206) was obtained. Purity (HPLC): 99.3% a/ a; MS $[M + 1]^+ = 389.09$; ^{1}H NMR ($CDCl_3$): δ 8.70 (br s, 1 H), 7.84 (m, 2 H), 7.25 (m, 2 H), 7.06 (m, 2 H), 6.80 (s, 1 H), 4.17 (dd, J = 2.5, 8.8 Hz, 1 H), 3.91 (m, 3 H), 3.63 (m, 1 H), 3.26 (td, J = 6.6, 9.6 Hz, 1 H), 2.30-2.38 (m, 7 H), 1.76-1.87 (m, 1 H), 1.66-1.73 (m, 1 H), 1.56-1.63 (m, 1 H).

ASSOCIATED CONTENT

Supporting Information. NMR spectra, HPLC analysis, MS and UV spectra for compound **1**. This information is available free of charge via the Internet at http://pubs.acs.org/.

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(2) Batch size was approximately 60 kg.

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(7) Chiral HPLC analyses of crude **1** (before crystallization) in all cases showed er of 99-100%. Chiral purity of commercially available *L*-proline is >98% er.

(8) Fiore P. J.; Puls, T. P.; Walker, J. C. *Org. Process Res. Dev.* **1998**, *2*, 151-156. See also ref. 6b and 6c.

(9) The crystallization process resulted from a screening of solvents and temperatures which is not described here. Critical was seeding with the desired polymorph.

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