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Stereoselective Synthesis of Monoamine Reuptake Inhibitor NS9544 Acetate

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ABSTRACT: (−)-3-(2-Benzothienyl)-8-*H*-8-azabicyclo[3,2,1]oct-2-ene acetate, NS9544 acetate, is a candidate drug intended to treat pain and other CNS disorders. In the synthetic route tropinone was enantioselective deprotonated with a chiral lithium amide derived from [*R*-(*R**,*R**)]-bis(α-methylbenzyl)amine hydrochloride. The formed enolate was trapped as triflate and coupled with benzo[*b*]thiophene-2-boronic acid under Suzuki conditions. To further enhance the enantiomeric purity crystallisation with L-(+)-tartaric acid was performed. Finally *N*-demethylation with trichloroethylchloroformate followed by treatment with acetic acid afforded NS9544 as the acetate salt with high enantiomeric purity.

INTRODUCTION

Tropane alkaloids consists of around 200 natural products, mostly occurring in plants of *Solanaceae* family.[1] They all have tropinone as the core structure, and many of them have interesting pharmacological properties;[1] some members are shown in Figure 1.

We were interested to use tropinone as a starting material for synthesis of a candidate drug for treatment of neuropathic pain. NS9544 acetate (**1**) (Figure 2) shows an interesting pharmacological profile as a triple monoamine reuptake inhibitor, altering the level of activity of the monoamine neurotransmitters by the ratio of the serotonin (5-HT), noradrenaline (NA), and dopamine (DA) reuptake inhibition[2] for the treatment of neuropathic pain.

Neuropathic pain conditions involve a heterogeneous patient population in which the underlying disease process may result in damage to nerve transmission processes. The underlying mechanisms are numerous and complex, and contribute to a poor diagnosis and treatment outcome for neuropathic pain patients. Antidepressant drugs typically increase extracellular levels of the catecholamine neurotransmitters serotonin, noradrenaline and/or dopamine via inhibition of transporter function and subsequent block of presynaptic transmitter uptake. In this regard, tricyclic antidepressants that act to nonselectively block the reuptake of 5-HT and/or NA have been widely used in the clinical treatment of neuropathic pain, albeit that they possess a poor side-effect profile. However, selective 5-HT and NA reuptake inhibitors such as duloxetine are devoid of many of these side effects and can still robustly attenuate preclinical and clinical signs and symptoms of persistent and especially neuropathic pain. Compounds that can selectively modulate pain transmission within 5-HT, NA, and DA pathways are likely to possess a superior analgesic profile to dual mechanism of action compounds and offer a realistic alternative to currently approved compounds for the clinical treatment of chronic pain.[3]

Many asymmetric methods that appear in literature give ee values that are not accepted in drug candidates aimed for clinical trials. Additional methods, e.g. crystallisation, are required for enhancing the enantiomeric excess. Despite this, asymmetric methods are preferred over resolutions where 50% of the material is useless without further operations. In order to perform phase I studies, access to **1** with more than 98% ee was required. We now report a versatile protocol for the stereoselective synthesis of (−)-3-(2-benzothienyl)-8-*H*-8-azabicyclo[3,2,1]oct-2-ene acetate, NS9544 acetate (**1**) at multikilogram scale.

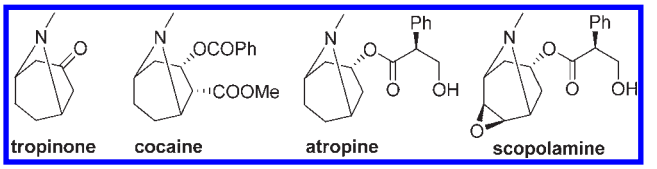

Figure 1. Tropinone and members of the tropinone family.

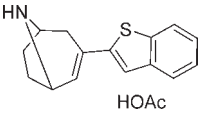

Figure 2. NS9544 acetate, 1.

RESULTS AND DISCUSSION

Initially optically pure **1** was obtained from the corresponding racemate via chiral preparative HPLC. This methodology is advantageous in early development since it will give access to both enantiomers for evaluation of the pharmacological properties. However, after choosing the desired enantiomer, other methods will be more expedient. Tropinone is a conformationally restricted prochiral cyclic ketone suitable for enantioselective deprotonation. A number of chiral lithium amide bases have been reported to be able to discriminate between enantiotopic hydrogens

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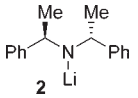

Figure 3. Chiral lithium amide base derived from [*R*-(*R**,*R**)]-bis(α-methylbenzyl)amine hydrochloride.

in such structures.[4] The C_2 symmetrical lithium amide **2** (Figure 3) based on [*R*-(*R**,*R**)]-bis(α-methylbenzyl)amine was reported to work well with tropinone.[5,6] This base is commercially available for a reasonable price and can be recycled. It is also possible to abstract different protons with different bases.[7] Majewski et al. reported that addition of one equivalent of lithium chloride was crucial for high enantioselectivity; addition of one equivalent of lithium chloride increased the ee from 36 to 90% in their application.[6,7] The method has mainly been used for α-functionalisation of tropinone, but in the present case we wanted to create a carbon−carbon bond at the carbonyl carbon. The chiral base **2** was formed by mixing one equivalent of [*R*-(*R**, *R**)]-bis(α-methylbenzyl)amine hydrochloride with two equivalents of *n*-butyllithium. By using the corresponding hydrochloride of the chiral amine and two equivalents of *n*-buthyllhium, the chiral base and one equivalent of lithium chloride were formed in situ. From a scale-up perspective this solution is advantageous because the solid hydrochloride is easier to handle compared to the free base. Free amines readily absorb carbon dioxide and moisture from air; furthermore, they are difficult to purify. The hydrochloride, on the other hand, is a crystalline solid which is easy to recycle via crystallisation, and it is stable over time. In addition the procedure ensures that dry lithium chloride is present in the reaction.

Dry tropinone in tetrahydrofuran was added to the chiral base in tetrahydrofuran/*n*-hexane at −70 °C under which the enolate was formed. The enolate was then trapped as the triflate by adding *N*-phenyl-bis-(trifluoromethanesulfonimide). The use of dry tropinone was important; low enantioselectivity was achieved when using less anhydrous tropinone. Still, without isolation a Suzuki coupling was performed. The formed enol triflate was reacted with benzo[*b*]thiophene-2-boronic acid catalysed by tetrakis-(triphenylphosphine)palladium in the presence of tripotassium phosphate and lithium chloride in water/tetrahydrofuran. After 2−2.5 h full conversion was verified with HPLC. Extractive workup and treatment with *n*-heptane gave **3** as white crystals. In accordance with the results from Simpkins and Majewski[5−7] the enantiomeric excess was 90%. For clinical trials such optical purity is not sufficient and a method for enhancing the optical purity must be developed. Conversion to a suitable salt of an optically active acid, followed by crystallisation may be an option to enhance the optical purity. When **3** was converted to the corresponding tartrate salt, enantiomeric excess was raised to 98.3%. A recrystallisation from ethanol raised the optical purity even further, and 99.2% enantiomeric excess was achieved. In addition, byproduct **5**, which was a result from homocoupling in the Suzuki reaction, was removed in the recrystallisation. The overall yield from tropinone to tartrate salt **4** was 63%.

Initially the intention was to isolate **3** as hydrochloride and perform the enhancement of the optical purity at a later stage. This was, however unsuccessful; when the free base of **1** was converted to tartaric acid salt or salts of other acids, sufficient increase of ee was not obtained. In laboratory-scale development it was found that the Suzuki coupling suffered from low yield due to a tedious workup. It was important to control the pH and keep

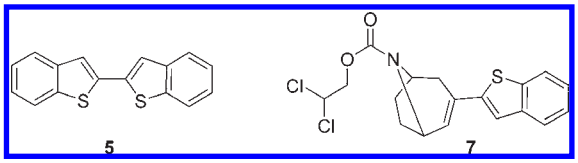

Figure 4. Impurities formed during the reactions.

it basic during the extractions. Also, the use of nonpolar solvent *n*-heptane for precipitation was found important. To avoid gas evolution, potassium carbonate, initially used in laboratory scale, was replaced by tripotassium phosphate. During the Suzuki coupling, byproduct **5** was formed as a result of homocoupling of benzo[*b*]thiophene-2-boronic acid (Figure 4). By performing a treatment with activated charcoal followed by hot filtration in the recrystallisation of tartrate **4** this impurity was almost completely removed. At this stage the assay was 97%. The recrystallisation also had a positive effect on the palladium level which went down from 155−215 ppm to 70 ppm.

N-Demethylation of alkaloids can be performed via a plethora of methods.[8] The first method was developed by von Braun in the in the early 1900s.[9] In the von Braun reaction the *N*-methylamine is reacted with cyanogen bromide prior to cleavage of the resulting cyanamide. The yields are low in the von Braun reaction, and recently more efficient protocols including chloroformates have been developed.[10]

To demethylate **4**, it was converted to the free base with sodium hydroxide. After solvent change from dichloromethane to toluene and addition of 2,2,2-trichloroethylchloroformate, carbamate **6** was formed. After another solvent change (at this point to tetrahydrofuran), zinc dust and acetic acid were added. After extractive workup and treatment with acetic acid, **1** was obtained as the acetate. To our dismay we found that **1** was contaminated with an impurity. The impurity was found to be **7** (Figure 4) evidenced by MS and UV spectroscopy. It was formed because of abstraction of a chlorine atom under the reductive reaction conditions. Impurity **7** was formed in various degrees in the produced batches, and typically levels were 8−15%. In order to obtain pure material, a method for purification was developed. **1** was converted to free base in toluene. This toluene solution was dried with azeotropic distillation followed by cooling and precipitation with acetic acid. This gave a very pure material, free from **7**. However, new challenges appeared since it was not possible to remove toluene residues to the required level. Crystallisation from ethanol afforded **1** as acetate with high purity in all aspects and in good yield. The assay was 100% with only one reported impurity in 0.04%. Palladium was found to be less than 2 ppm; lithium, less than 0.1 ppm, and zinc, about 40 ppm. During development it was noticed that ee dropped considerably during acetate formation, and in addition yield was low. By optimizing the concentration it was possible to raise the yield and to minimise the loss of optical purity; ee went down from 99.3% to 98.9% during the transformation.

■ CONCLUSION

The current approach was one out of ten evaluated. The most obvious route would be to resolve the free base of racemic **1** with a chiral acid, since racemic **1** is synthesised very easily. However all attempts to resolve racemic **1** were unsuccessful. On the other hand, it was possible to raise the enantiomeric excess in a nonracemic mixture with classical resolution agents as described in the presented method.

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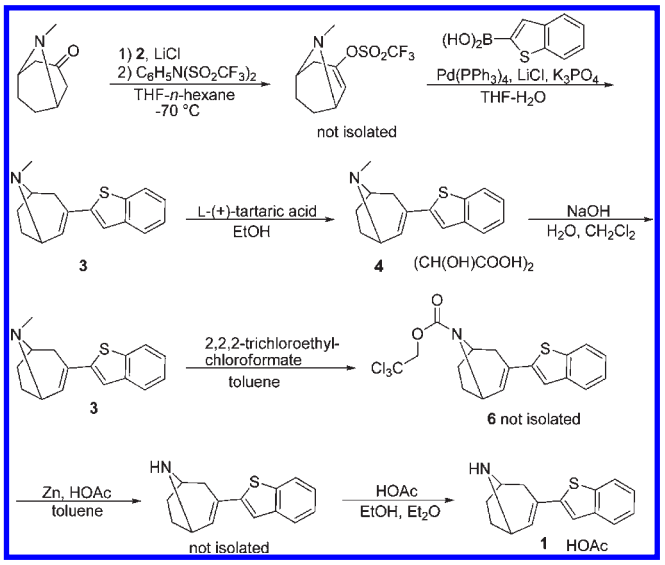
Scheme 1. Large-scale route to NS9544 acetate, 1



In summary the monoamine reuptake inhibitor, NS9544 acetate (**1**), was prepared in essentially four steps in 22% yield from tropinone (see Scheme 1). Chirality was introduced through an asymmetric deprotonation of tropinone using a chiral lithium base derived from [*R*-(*R**,*R**)]-bis(α-methylbenzyl)amine hydrochloride. Recrystallisation of the corresponding tartrate salt was used to enhance the enantiomeric purity from 92% ee to 99% ee. Two impurities were effectively removed during the sequence, and several steps were telescoped in order to increase efficiency. The synthesis was performed at multikilogram scale and gave a product of very high quality.

EXPERIMENTAL SECTION

General. Chiral HPLC analyses were performed using a Chiracel OD-H, 4.6 mm ×250 mm. Eluation conditions were employed with ethanol/*n*-hexane (10:90). The flow rate was 0.5 mL/min and UV-detection at 290 nm. HPLC analyses were performed using a YMC ODS-A, 5 μ, 250 × 4.6 mm, 120 Å equipped with an SB-C18 guard PAK. Elution conditions were employed with 20% acetonitrile in aqueous ammonium acetate (3 mM). The flow rate was 1.0 mL/min and UV detection at 220 nm. GC analyses were performed using a J&W DB WAX, Bodman part # 123-7033, 0.5 μm film thickness, 0.32 mm i.d., and 30 m length. Inlet temperature/detector temperature was 200−250 °C. Temperature gradient was 40 °C isothermal for 5 min then ramped to 200 °C at profile 50 °C/min and held at 200 °C for 10 min. Optical rotations were measured with a Perkin-Elmer 241. NMR spectra were recorded at 300.14 MHz (proton) and 75.47 MHz (carbon). Thin layer chromatography was performed on Merck precoated TLC plates, and were visualised with UV light or sprayed with a solution of *p*-methoxybenzaldehyde (26 mL), glacial acetic acid (11 mL), concentrated sulphuric acid (35 mL), and 95% ethanol (960 mL). Solvents and reagents were obtained from commercial sources and were used as such without any further purification. All reactors used are standard multipurpose equipment, either glass-lined or stainless steel. All reactions in pilot-plant scale are, for safety reasons, routinely carried out under an atmosphere of nitrogen.

NS9542 Tartrate (4). In a Hastelloy reactor charged with [*R*-(*R**,*R**)]-bis(α-methylbenzyl)amine hydrochloride (13.6 kg, 52.9 mol) and tetrahydrofuran (98 kg) was added *n*-butyllithium (41.6 L, 104 mol, 2.5 M in *n*-hexane) under stirring at 0−10 °C during 1 h. After stirring for an additional hour the mixture was cooled to −80 °C, and dry tropinone[11] (6.3 kg, 45.3 mol) in tetrahydrofuran (23 L) was added during 45 min. After stirring for 3 h, *N*-phenyl-bis-(trifluoromethanesulfonimide) (17.4 kg, 48.7 mol) was added during 30 min at −70 °C. After stirring for 2 h at −70 °C the mixture was allowed to warm to room temperature overnight. The mixture was transferred to a glass-lined reactor followed by addition of water (74 L). Benzo-[*b*]thiophene-2-boronic acid (9.7 kg, 54.5 mol), tripotassium phosphate (31.2 kg, 147 mol), and lithium chloride (2.3 kg, 54.2 mol) were added to the mixture under stirring at room temperature. The mixture was degassed by bubbling argon through the liquid, followed by addition of tetrakis(triphenylphosphine) palladium(0) (0.175 kg, 0.15 mol). The mixture was heated to reflux and kept at this temperature for 2 h. The mixture was cooled to below 30 °C, and then water (77 L), diethyl ether (106 L), and aqueous sodium hydroxide (34 L, 2 M) were added, followed by stirring for 10 min. After phase separation the organic phase was transferred to another vessel. To the remaining aqueous phase were added diethyl ether (34 L) and aqueous sodium hydroxide (11 L, 2 M). After stirring for 10 min followed by phase separation the organic phases were combined and washed two times with aqueous sodium hydroxide (2 × 120 L, 0.4 M). Dry magnesium sulfate was added to the organic phase followed by stirring for 2 h. The mixture was filtered and then transferred to a stainless steel reactor. The solvent was distilled off under reduced pressure (30→50 °C, 20 mbar) after which the residue was cooled to −20 °C. The solidified residue was kept at −20 °C for 1 h, then *n*-heptane (57 L) was added slowly. The stirring was continued so that a suspension was formed, and after 8 h the crystals were filtered off. The crystals were washed with *n*-heptane (7 L) and then charged in a glass-lined reactor. Ethanol (139 L) was added, and the mixture was stirred for 30 min. L-(+)-Tartaric acid (6.8 kg, 45.3 mol) in water (13.8 L) was added under stirring. After the crystallisation started, the mixture was cooled to 0−5 °C and stirred at this temperature during 2 h. The crystals were isolated via centrifugation then dried at 50 °C under reduced pressure (20 mbar) to give **4** as white crystals. Yield 12.75 kg, 70%.

Recrystallisation of NS9542 Tartrate (4). In a stainless steel reactor charged with **4** (34,4 kg, 85.5 mol) and ethanol (618 L) was added a suspension of activated charcoal (Carboraffin P, 1.9 kg) in water (69 L) under stirring. After 15 min of stirring the mixture was heated to reflux and kept at reflux for 15 min. The hot mixture was filtered, and the filter was rinsed with hot ethanol (17 L). The solution was cooled to 0−5 °C and was kept at this temperature for at least 2 h. The crystals were isolated via centrifugation, then dried at 50 °C under reduced pressure (20 mbar). The yield of the title compound was 31.1 kg (90%) with an ee of 99.3%. $[\alpha]^{23}_D = +24.5$ (*c* = 1.6, EtOH.); IR 3052 broad, 1717, 1591, 1125, 1069 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.79−7.71 (m, 2H), 7.37−7.33 (m, 2H), 7.22 (s, 1H), 6.29 (d, *J* = 5.4 Hz, 1 H), 4.22 (s, 2H), 4.19−4.08 (m, 2 H), 3.29−3.10 (m, 1 H), 2.87 (s, 3 H), 2.64 (d, *J* = 19.0 Hz, 1 H), 2.63−2.46 (m, 2 H), 2.32−2.23 (m, 1 H), 2.02−1.89 (m, 1 H); HRMS calcd for $C_{20}H_{19}NO_6S$ (M + H) 242.1003, found 242.1002.

NS9544 Acetate or (−)-3-(2-Benzothienyl)-8-*H*-8-azabicyclo[3,2,1]oct-2-ene Acetate (1). In a stainless steel reactor

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charged with **4** (31.0 kg, 77.1 mol) dissolved in water (310 L) were added dichloromethane (310 L) and aqueous sodium hydroxide (81 L, 2 M, 162 mol) under stirring. The mixture was stirred for 10 min after which the phases were allowed to separate. The organic phase was transferred to another vessel and the remaining aqueous phase was extracted with dichloromethane (86 L) followed by a combination of the organic phases. The combined organic phases were then washed with water (258 L) and dried over magnesium sulfate (13 kg). After filtration the solvent was distilled off under reduced pressure (20 mbar) at 45 °C. Toluene (256 L) was added under stirring. To dry the solution and eliminate residues of dichloromethane 35 L of toluene was distilled off under atmospheric pressure. The mixture was cooled to 20−25 °C after which 2,2,2-trichloroethyl chloroformate (21.3 kg, 100.5 mol) was added under stirring. After at least 10 h with stirring at room temperature, water (172 L) was added, and stirring was continued for 1 h. Diethyl ether (327 L) was added followed by stirring for 15 min. The organic phase was separated and washed with water (2 × 86 L). Five hundred and fifty liters of solvent were distilled off under reduced pressure (20 mbar) with the jacket temperature set to 60 °C. To the residue was added tetrahydrofuran (172 L), and the mixture was stirred for 15 min. Under stirring was added acetic acid (37 L) and water (65 L) followed by addition of zinc dust (8.7 kg, 133 mol) in 10 portions during 1 h (*CAUTION! Exothermic, evolution of carbon dioxide; risk for foaming!*). The temperature of the reactor was kept below 50 °C during the addition. After cooling to 20 °C the mixture was stirred for 10 h. To eliminate residues of zinc, the mixture was transferred to another reactor via a cartridge filter. Aqueous hydrochloric acid (28 L, 4 M) was added to the reaction mixture under stirring. Then 200 L of tetrahydrofuran was distilled off under reduced pressure (20 mbar); meanwhile, the precipitation started. The mixture was cooled to 0−5 °C and stirred at this temperature for at least 90 min. The precipitate was isolated on a filter and washed with water (2 × 45 L) and diethyl ether (2 × 45 L). The wet filter cake was charged to a glass-lined reactor after which water (172 L), dichloromethane (172 L), and aqueous sodium hydroxide (100 L, 2 M) were added. The mixture was heated to reflux and kept at reflux for 10 min; after cooling to 20 °C the phases were allowed to separate. The organic phase was transferred to another reactor, and the aqueous phase was extracted with dichloromethane (86 L). After separation, the organic phases were combined and dried over magnesium sulfate (13 kg). After filtration the mixture was concentrated to approximately 20 L under reduced pressure (20 mbar) at 45 °C in a reactor. The final concentration was performed in a 50-L evaporator under the same conditions. Rapidly, before solidification started, the warm oil was transferred to a reactor. To the oil was added ethanol (63 L), and the mixture was heated to reflux. After 30 min at reflux, acetic acid (3.63 L, 75.6 mol) was added, and the mixture was cooled to 20−25 °C during 30 min. Diethyl ether (56 L) was added and the mixture was cooled to 0−5 °C, then left for at least 3 h. The precipitated product was collected on a filter and washed with cold ethanol (8.2 L) and diethyl ether (10.8 L). Drying of the product at reduced pressure (20 mbar) at 60 °C for 10 h gave 10.9 kg (47%) of the title compound as white crystals.

Purification of NS9544 Acetate (1). In a reactor charged with toluene (66 kg) was added **1** (10.88 kg, 36.12 mol) under stirring. To the resulting solution were added water (77 kg) and aqueous sodium hydroxide (22 kg, 2 M). The mixture was heated to reflux and kept at reflux for 30 min. After cooling to 20−25 °C the phases were separated, and the organic phase was washed with water (77 kg). The solution was filtered trough a 0.5 μm polish filter to another reactor. The mixture was dried by azeotropic distillation until no more water was separated. A solution of acetic acid (2.4 kg, 40 mol) in toluene (10 kg) was added at 100 °C. The mixture was cooled to 20−25 °C which initiated crystallisation; stirring was continued overnight. Isolation was performed with centrifugation; the filter cake was washed with ether (7 kg), followed by drying at reduced pressure at 40 °C and 20 mbar. The dry material was charged in a reactor together with ethanol (36 kg) and heated to reflux. Acetic acid (0.18 kg, 3 mol) was added, after which crystallisation was induced by cooling. At room temperature, diethylether (32 kg) was added, and the mixture was kept at 0−5 °C overnight. The product was isolated via filtration and dried at 50 °C and 20 mbar to give the title compound as white crystals in 9.0 kg (83%) yield, ee 98.9%, mp 182−183 °C (lit.177 °C);[2] $[\alpha]^{23}_{D}$ = −15.1 (*c* = 2.2, EtOH.); IR 2937 (broad), 1719, 1552, 1393 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.76−7.64 (m, 2H), 7.32−7.26 (m, 2H), 7.12 (s, 1H), 6.42 (d, J = 5.7 Hz, 1 H), 4.18−4.08 (m, 2H), 3.21 (dd, J_1 = 17.2 Hz, J_2 = 4.9 Hz, 1H), 2.43 (d, J = 17.2 Hz, 1H), 2.34−2.19 (m, 1H), 2.11 (dd, J_1 = 8.1 Hz, J_2 = 3.6 Hz, 1H), 1.86 (s, 3H), 1.82−1.71 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 177.3, 143.2, 139.7, 138.2, 128.3, 127.2, 124.5, 124.1, 123.2, 121.8, 119.4, 52.7, 51.8, 35.9, 33.4, 28.5, 22.7; Anal. Calcd for $C_{17}H_{19}NO_2S$: C, 67.7, H, 6.3, N, 4.6; Found C, 67.5, H, 6.4, N, 4.6.

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(11) In a glass-lined reactor tropinone (19.3 kg) was dissolved in diethyl ether (43 kg). Magnesium sulfate (1.2 kg) was added, and the mixture was stirred for 3 h. The mixture was filtered through a bag filter followed by filtering through a cartridge filter. The reactor and filter were washed with diethyl ether (11 kg). The combined organic solutions were evaporated to dryness in a Buchi Rotavapor R-250. Yield 18.4 kg (95.3%).

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