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ORIGINAL PAPER

Efficient and single pot process for the preparation of enantiomerically pure solifenacin succinate, an antimuscarinic agent

Navnath C. Niphade · Kunal M. Jagtap · Anil C. Mali · Pavankumar V. Solanki · Madhukar N. Jachak · Vijayavitthal T. Mathad

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Abstract The development of an efficient and economic one-pot process, in which the configuration of the chiral centers of the starting materials is retained, for the preparation of highly pure solifenacin succinate, an antimuscarinic agent, is presented in this communication. The earlier reported processes suffer from the drawbacks of racemization and low yields due to the use of strong base, higher temperatures, and longer reaction times. The present work circumvents these issues by activating (3*R*)-quinuclidin-3-ol into a mixed active carbonate derivative by treating it with bis(4-nitrophenyl)carbonate. The subsequent reaction of the active carbonate with an enantiomerically pure amine without using any base at ambient temperature provided enantiomerically pure solifenacin with an overall yield of 90%.

Keywords Solifenacin · Antimuscarinic agent · Bis(4-nitrophenyl)carbonate · One-pot synthesis

Introduction

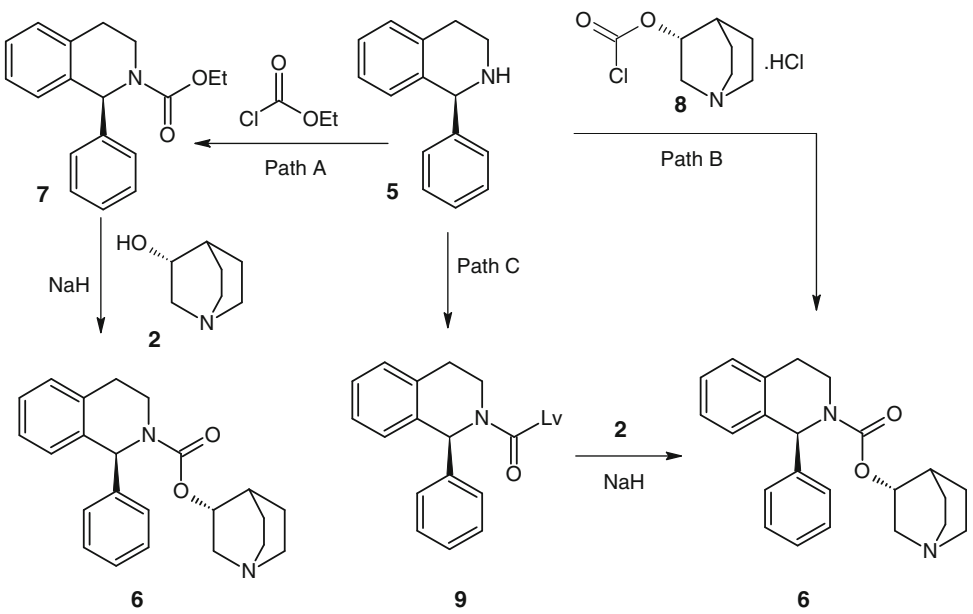
(3*R*)-1-Azabicyclo[2.2.2]oct-3-yl (1*S*)-3,4-dihydro-1-phenyl-2(1*H*)-isoquinolinecarboxylate as its succinate salt (solifenacin succinate, **1**) is a well-known urinary antispasmodic drug, acting as a selective antagonist to the M(3) receptor. This drug is used for the treatment of patients with overactive bladder, such as urinary urgency, urinary incontinence, and high urinary frequency, and marketed under the brand name of Vesicare™ with a dose of 5–10 mg once daily [1–5]. The first reported synthesis for the preparation of solifenacin (**6**) by Makoto and co-workers [6, 7] used a convergent approach (Scheme 1, path A) that involved the reaction of (1*S*)-1-phenyl-1,2,3,4-tetrahydroisoquinoline (**5**) with ethyl chloroformate in dichloromethane to give ethyl (1*S*)-1-phenyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (**7**). Transesterification of **7** with **2** in the presence of sodium hydride in toluene at 140 °C for 48 h with continuous removal of ethanol formed during the reaction, followed by usual work-up and column chromatography purification provided solifenacin **6** in 12.3% yield. The second approach reported by the same authors [7] involved conversion of **2** to its quinuclidinyl chloroformate monohydrochloride derivative **8**, followed by portionwise addition of the chloroformate **8** to a solution of **5** in pyridine at 80 °C (Scheme 1, path B). Improved processes reported by others [8, 9] follow the same approach (Scheme 1, path A) but do not overcome the problems associated with this approach. One more process reported (Scheme 1, path C) for **6** is similar to path A but using different leaving groups such as 1*H*-imidazol-1-yl, 2,5-dioxopyrrolidine-1-yloxy, 3-methyl-1*H*-imidazol-3-ium-1-yl, chloro, trichloromethyl, and haloalkyl [10–12].

Recently, Jordi et al. [13] have reported the synthesis of a carbamate intermediate by reacting 1,1′-carbonyl-bis(1,2,4-triazole) and (3*R*)-quinuclidin-3-ol (**2**) in isopropyl acetate in the presence of triethylamine at reflux temperature for 4–5 h, which was subsequently converted

N. C. Niphade · K. M. Jagtap · A. C. Mali · P. V. Solanki · V. T. Mathad (✉)
Department of Process Research and Development, Megafine Pharma (P) Ltd, 201 Lakhmapur, Dindori, Nashik 422 202, Maharashtra, India
e-mail: drvtmathad@yahoo.co.in; vt.mathad@megafine.in

M. N. Jachak
Department of Chemistry, Organic Chemistry Research Center, KRT Arts, B.H. Commerce and A.M. Science College, Gangapur Road, Nashik 422 002, India

Scheme 1



into solifenacin by reacting with amine **5** with an overall yield of 63%.

Reported routes have several drawbacks such as (1) use of hazardous, lachrymatory, and pyrophoric reagents like NaH (path A), metal alkoxides, ethyl chloroformate, and Lewis acids (path C), (2) use of strong bases at higher temperatures for transesterification leads to racemization and thus fails to provide enantiomerically pure solifenacin, (3) ethylcarboxylate derivative **7** produces ethanol as a by-product (path A) that hinders the nucleophilic attack of **2** in the presence of a base, (4) use of column chromatography for the purification of **6**, which is expensive and industrially not feasible, (5) the reaction requires longer time for the completion and hence turnaround time of batch in production makes it less attractive, (6) use of moisture sensitive and expensive leaving groups (Lv) in path C along with the use of sodium hydride is industrially not feasible, (7) use of carcinogenic pyridine as a reaction medium (path C) is not safe, and (8) the additional step of converting **2** to its chloroformate derivative **8** makes the process (path C) lengthy and uneconomical.

Here, we report an efficient and economic one-pot process, which retains the configuration of the chiral centers of the starting materials, for the large-scale preparation of compound **1** (Scheme 2, path A) by surmounting the aforementioned challenges. The process involves the activation of alcohol **2** by treating with **3** in DMF at ambient temperature to form the mixed active carbonate (3*R*)-1-azabicyclo[2.2.2]oct-3-yl 4-nitrophenyl carbonate (**4**), which is then treated in situ with **5** to give solifenacin (**6**) with 90% yield and 98% purity by HPLC. Solifenacin is further treated with succinic acid in acetone to obtain solifenacin succinate (**1**) with 72% yield, 99.94% chemical purity, and 99.9% enantiomeric purity by HPLC.

Results and discussion

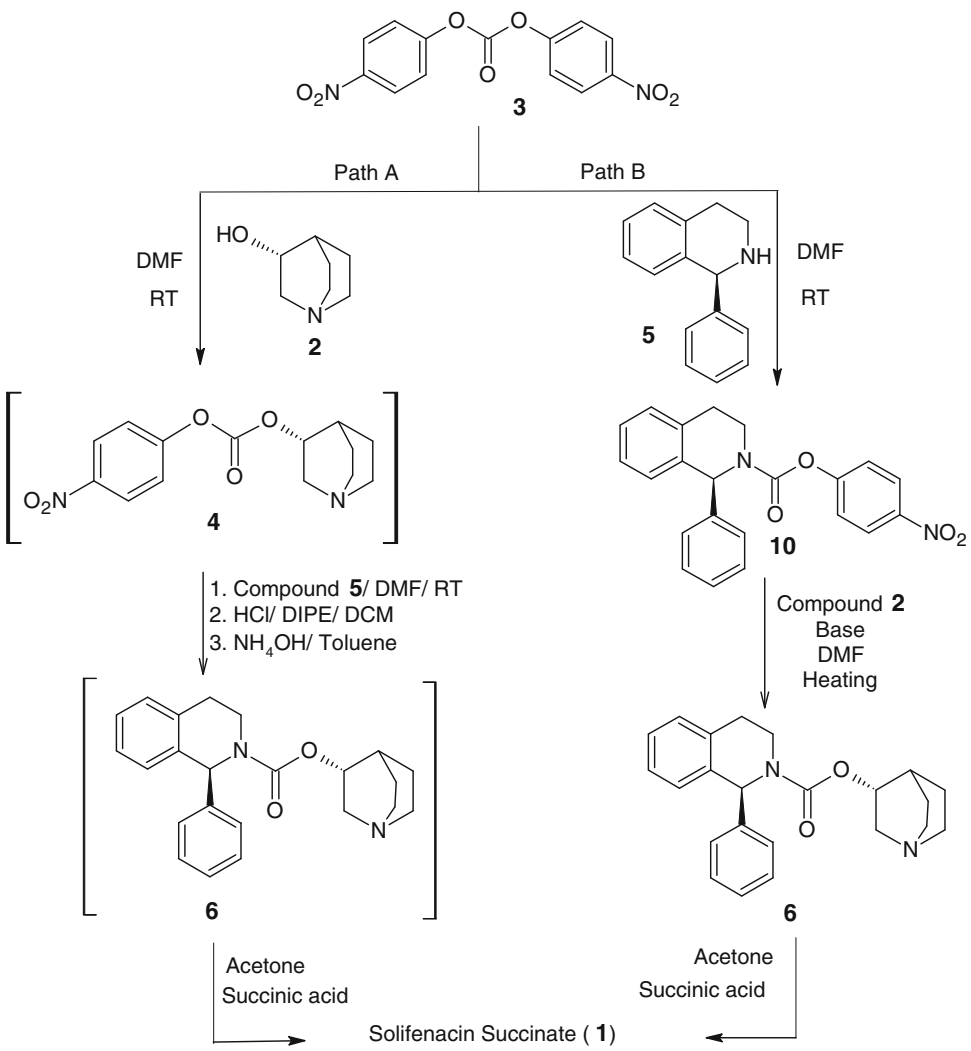
*Synthesis of solifenacin succinate (**1**) as per Scheme 2, path A*

Synthesis of solifenacin (**6**) via formation of active carbonate **4**

In our approach, we identified bis(4-nitrophenyl)carbonate (**3**) as a suitable reagent to prepare the mixed active carbonate **4** as designed in Scheme 2, path A. Synthesis of **4** was explored by reacting **2** with **3** in various solvents (toluene, tetrahydrofuran, dimethylformamide, pyridine, dichloromethane, and acetonitrile) at different temperatures with and without the use of bases.

During feasibility studies, dimethylformamide was found to be a highly suitable solvent for this reaction without base, but the removal of DMF was an issue for isolation of **4** as it has to be distilled at higher temperature. However, we have isolated **4** as oil by conducting the reaction in tetrahydrofuran in the presence of pyridine or triethylamine as a base to explore further. With isolated **4** in hand, we have explored the synthesis of solifenacin by treating **4** with isoquinoline **5** in various solvents at different temperatures. Fortunately, the reaction of **4** with **5** went for completion in DMF in the absence of base at 25–30 °C. Meanwhile, we have also noticed that the isolated **4** is unstable, moisture sensitive, and converted back to compound **2** if exposed to air. Contrarily, it was found

Scheme 2



stable as a solution in DMF at ambient temperature. Thus, we have telescoped both the reactions in a single pot using DMF as a solvent.

The optimized process involves stirring **2** and **3** in DMF at 25–30 °C for 2–3 h followed by adding compound **5** to the reaction mixture and stirring the contents for 3 h at 25–30 °C. After completion of the reaction (detected by HPLC), the mass is diluted with water, adjusted to pH 1–2 using conc. hydrochloric acid, and extracted with diisopropylether (DIPE) to remove the by-product *p*-nitrophenol exclusively into the organic layer. The solifenacin hydrochloride present in the acidic aqueous layer was extracted into dichloromethane leaving behind the un-reacted compounds and by-products **2**, **5**, and **10** in the aqueous layer. The dichloromethane layer was then concentrated to yield a thick syrup containing solifenacin hydrochloride (SOL-HCl) with 98.0% purity by HPLC. The obtained residue was dissolved in water, adjusted pH to 9–10 with ammonium hydroxide solution, and extracted with toluene. The toluene layer was washed with 5% sodium hydroxide solution to remove the traces of *p*-nitrophenol followed by water, and concentrated to yield solifenacin as syrup with 90% yield and 99.8% chemical purity by HPLC.

Preparation of solifenacin succinate (**1**)

Solifenacin (**6**) obtained was dissolved in acetone, treated with succinic acid, and the mass was heated to 50–55 °C for 30 min. The suspension was cooled to 5–10 °C, solid crystals obtained were filtered and dried under vacuum to yield solifenacin succinate (**1**) with 99.94% chemical purity by HPLC and 99.9% enantiomeric purity by chiral HPLC. Analytical results of the samples at various stations of work-up during the process development to monitor the elimination of impurities in few laboratory batches (entries 1–3) and a scale-up batch at 5.0 kg level (entry 4) are given in Table 1.

The chiral purity of the obtained product **1** is measured by chiral HPLC and the results are shown in Table 2 (entries 1–3: laboratory batches; and entry 4: scale-up batch) indicating retaining the chiral centers during the

Table 1 Monitoring of impurities by HPLC in downstream process

Sample. no.	Sample station (for HPLC analysis)	Impurities and their content by HPLC/%				
		Comp. **5** (RRT 0.42)	*p*-Nitrophenol (RRT 0.54)	Comp. **10** (RRT 1.95)	Unknown imp (RRT 1.14)	Comp. **1** (RRT 1.0)
1	MDC layer (SOL-HCl)	3.15	0.5	0.02	0.09	96.26
	Solifenacin base	0.03	ND	0.01	0.10	99.76
	Solifenacin succinate	ND	ND	ND	0.04	99.94
2	MDC layer (SOL-HCl)	3.47	1.02	0.08	0.05	95.68
	Solifenacin base	0.01	ND	ND	0.04	99.86
	Solifenacin succinate	ND	ND	ND	0.04	99.94
3	MDC layer (SOL-HCl)	3.30	0.85	0.09	0.09	96.0
	Solifenacin base	0.01	ND	ND	0.05	99.85
	Solifenacin succinate	ND	ND	ND	0.05	99.93
4	MDC layer (SOL-HCl)	0.81	2.2	0.08	0.03	96.65
	Solifenacin base	0.04	ND	ND	0.03	99.85
	Solifenacin succinate	ND	ND	ND	0.03	99.95

Table 2 Chiral purity of **1** for laboratory and scale-up batches

Batch no.	(*RR*)-isomer	(*RS*)-isomer	(*SS*)-isomer
1	<0.03	<0.03	<0.03
2	<0.03	<0.03	<0.03
3	<0.03	<0.03	<0.03
4	<0.03	<0.03	<0.03

0.03% is the LOQ value for all the diastereomers of solifenacin succinate

developed process due to prevention of the use of any bases at higher reaction temperature and longer reaction time.

All stereoisomers of solifenacin (**6**) were synthesized and provided for the method development to the Analytical Research and Development Department. The (*RR*) isomer was synthesized by treating **4** with (1*R*)-1-phenyl-1,2,3,4-tetrahydroisoquinoline [(*R*)-**5**, synthesized by resolving (*RS*)-1-phenyl-1,2,3,4-tetrahydroisoquinoline using D-(+)-tartaric acid in methanol) following the procedure described in the "Experimental" section for **6** as a brown oil, whereas (*SS*) and (*RS*) isomers were provided as (*SR*)–(*SS*) and (*RR*)–(*RS*) mixtures, respectively. The (*SR*)–(*SS*) and (*RR*)–(*RS*) pairs were synthesized by treating racemic quinuclidin-3-ol [(*RS*)-**2**] with bis(4-nitrophenyl)carbonate to obtain the corresponding carbonate derivative, which was subsequently reacted with (1*R*)-1-phenyl-1,2,3,4-tetrahydroisoquinoline [(*R*)-**5**] and (1*S*)-1-phenyl-1,2,3,4-tetrahydroisoquinoline (**5**), respectively (Fig. 1). We adopted this strategy as (3*S*)-quinuclidin-3-ol was not available. The resolution experiments to obtain (3*S*)-quinuclidin-3-ol are under progress.

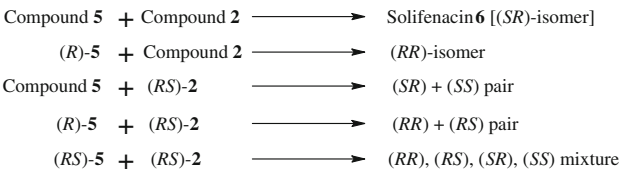


Fig. 1 Strategy to prepare different isomers for analytical method development

Recovery of *p*-nitrophenol

During the optimization, we have explored different solvents such as methyl *t*-butyl ether (MTBE), *n*-heptane, hexane, and cyclohexane to extract the impurities, specifically *p*-nitrophenol to avoid the use of diisopropylether (DIPE). Unfortunately, DIPE was found to be highly specific and efficient in extracting these impurities from the reaction mixture. The huge quantity requirement of other solvents (almost 70–80 parts per part of **2**) discouraged us to select them as large amount of effluent in the mind. In contrast, 20–30 volumes of DIPE were sufficient to extract these impurities specifically without any trace of impurities left in the reaction mixture and hence was opted. The careful concentration of the extracted DIPE layer under nitrogen atmosphere provided *p*-nitrophenol quantitatively, which can be recycled further for preparing compound **3**.

*Synthesis of solifenacin succinate (**1**) as per Scheme 2, path B*

Alternatively, by changing the reaction sequence amine **5** was reacted with **3** in toluene at 25–30 °C to obtain the carbamate derivative **10** with 83.6% yield after usual

work-up as a crystalline solid. The *trans* esterification reaction of **10** with **2** conducted without a base was found to be unsuccessful, but the reaction was progressed when a strong base like NaH was used with toluene as a reaction medium at 110 °C with a yield of 40% with few potential impurities. Although the process (Scheme 2, path B) is successful in preparing solifenacin succinate, it was found to be inferior over path A in the following aspects: (1) the overall yield of the process is 40%, (2) a strong base like NaH at higher temperature was essential to carry out the *trans* esterification, (3) it produces several process-related impurities, and (4) the enantiomeric purity of the product was much lower and it requires multiple purifications to achieve the desired quality.

Conclusions

An efficient and single-pot process for the preparation of enantiomerically pure solifenacin succinate (**1**) via the formation of active carbonate derivative **4** is reported. The established process does not require any base and higher temperatures either for the formation of active carbonate **4** or solifenacin (**6**). The total time cycle to finish a batch is around 45–50 h, thus making the process suitable for commercial production with efficient turn-around time. The developed process was successfully implemented in the plant level with high production throughput.

Experimental

The ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Varian Gemini 400 MHz FT NMR spectrometer. Chemical shifts are reported in δ units in ppm from the internal standard tetramethylsilane (TMS). The solvent for NMR spectra was DMSO-d_6 unless otherwise stated. Infrared spectra were taken on a Perkin Elmer Spectrum 100 in potassium bromide pellets unless otherwise stated. High-resolution mass spectra were obtained with a Mat 112 Varian Mat Bremen (70 eV) mass spectrometer. All reactions were monitored by thin layer chromatography (TLC) carried out on 0.2-mm silica gel 60F254 (Merck) plates using UV light (254 and 366 nm) or high performance liquid chromatography (HPLC) on Agilent Technologies 1200 series for detection. Common reagent-grade chemicals are either commercially available and were used without further purification or were prepared by standard literature procedures.

Related substances of solifenacin succinate (**1**) were estimated by gradient HPLC analysis developed at Megafine using an Inertsil ODS 3 V, 250 × 4.6 mm ID column; mobile phase A comprising 0.025 M K_2HPO_4 in water (pH adjusted to 4.5 with orthophosphoric acid); mobile phase B comprising acetonitrile/methanol/water in the ratio 40:40:20 v/v/v; gradient elution: *t*/%B: 0/45, 30/85, 50/85, 53/45, 60/45; flow rate 1.0 cm^3/min; column temperature 40 °C; wavelength 220 nm. Isomeric impurities of solifenacin succinate (**1**) were estimated by NP-HPLC analysis developed at Megafine using Chiralpak-IC, 250 mm × 4.6 mm ID column; mobile phase comprising *n*-hexane/ethanol/isopropyl alcohol/diethylamine (60:15:25:0.1, v/v/v/v); flow rate 1.0 cm^3/min; column temperature 30 °C; wavelength 220 nm.

Solifenacin succinate (**1**)

To a stirred solution of 100 g (3*R*)-quinuclidin-3-ol (**2**, 0.78 mol) in 400 cm^3 dimethylformamide was added 285.04 g bis-(4-nitrophenyl)carbonate (**3**, 0.93 mol) with stirring at 25–30 °C under nitrogen atmosphere. The stirring was maintained at 25–30 °C for 2–3 h. After reaction completion (by TLC, mobile phase: dichloromethane/methanol/ammonia = 8.0:2.0:0.5 cm^3) 171.44 g (1*S*)-1-phenyl-1,2,3,4-tetrahydroisoquinoline (**5**, 0.82 mol) was added to the resultant brown-colored reaction solution and further stirred at 25–30 °C for 3–4 h. After completion of the reaction (by HPLC), the reaction mixture was diluted with 1,000 cm^3 water and the pH of the solution was adjusted to 1–2 using concentrated hydrochloric acid. The resulting reaction mass was extracted with diisopropylether (1,000 cm^3 × 2) to separate the *p*-nitrophenol. The aqueous layer was then mixed with 1,000 cm^3 dichloromethane, the contents were stirred, and the dichloromethane layer was separated. The aqueous layer was re-extracted with 1,000 cm^3 dichloromethane and combined with the main layer. The combined dichloromethane layer was distilled off completely to obtain the residue. The residue was dissolved in 1,000 cm^3 water and 1,000 cm^3 toluene and the pH of the biphasic mixture was adjusted to 9–10 using ammonium hydroxide. The toluene layer was separated and the aqueous layer was re-extracted with 1,000 cm^3 toluene. The combined toluene layer was washed with 1,000 cm^3 water, treated with 0.5% sodium hydroxide solution (1000 cm^3 × 2) and further washed with 1,000 cm^3 water and 1,000 cm^3 brine solution. The toluene layer was distilled off completely to obtain the residue, which was dissolved in 1,600 cm^3 acetone, decolorized with activated charcoal, and treated with 88.0 g succinic acid (0.74 mol). The contents were heated at 50–55 °C for 30 min, cooled to 5–10 °C, and maintained for 60 min. The crystalline solid obtained was filtered and dried under vacuum (870–930 mbar) to afford pure solifenacin succinate as white crystalline solid. Yield: 272 g (72%, calculated starting from (3*R*)-quinuclidin-3-ol); chemical purity by HPLC: 99.94%; enantiomeric purity by HPLC: 99.99%.

The spectral data of compound **1** prepared by our process were found to agree with the reported data [6].

4-Nitrophenyl (1S)-1-phenyl-3,4-dihydroisoquinoline-2(1H)-carboxylate (**10**)

To a stirred solution of 20.0 g (1*S*)-1-phenyl-1,2,3,4-tetrahydroisoquinoline (**5**, 0.095 mol) in 50 cm^3 dimethylformamide was added 30.55 g bis(4-nitrophenyl)carbonate (**3**, 0.1 mol) with stirring at 25–30 °C under nitrogen atmosphere. The stirring was maintained at 25–30 °C for 2–3 h. After reaction completion (by TLC, mobile phase: dichloromethane/methanol/ammonia = 8.0:2.0:0.5 cm^3), the reaction mixture was diluted with 100 cm^3 water and the pH of the solution was adjusted to 9–10 using ammonium hydroxide. The resulting reaction mass was extracted with toluene (100 cm^3 × 2), the combined toluene layer was washed with water (50 cm^3 × 2), treated with 0.5% sodium hydroxide solution (50 cm^3 × 2), and further washed with 50 cm^3 water. The toluene layer was distilled off completely to obtain the residue, which was stirred in 100 cm^3 *n*-heptane for 25–30 min at 5–10 °C. The crystalline solid obtained was filtered and dried under vacuum (870–930 mbar) to afford pure compound **10**. Yield: 30.0 g (83.6%); chemical purity by HPLC: 99.00%. The spectral data of compound **10** were found to agree with the reported data [14].

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