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Some Reaction Safety Aspects of Ruthenium-Catalyzed Allylic Oxidations of Δ-5-Steroids in the Pilot Plant

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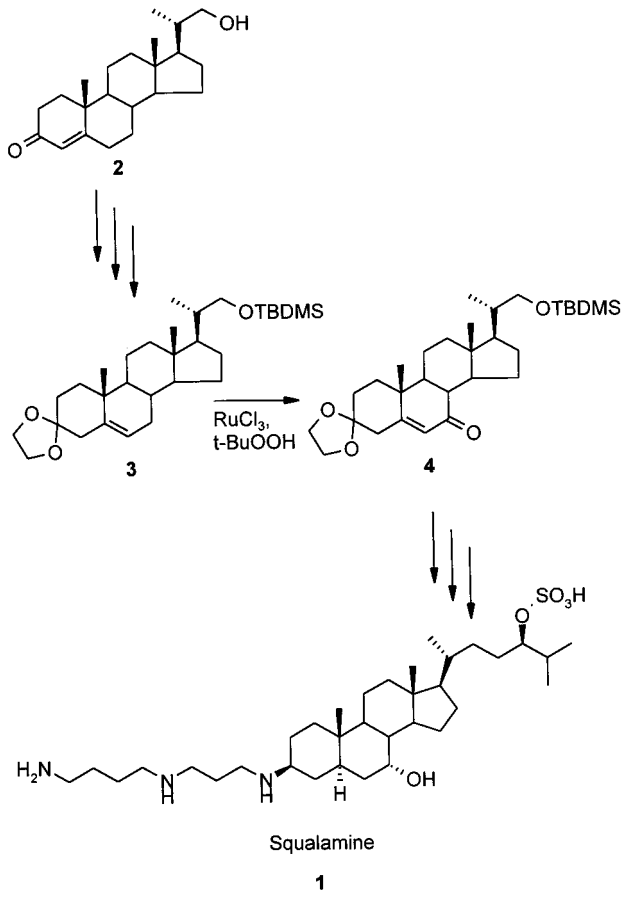
Abstract:
The ruthenium-catalyzed allylic oxidation of Δ-5-steroids with *tert*-butyl hydroperoxide to the corresponding unsaturated ketones was studied. During the scale-up to the pilot plant level, serious safety problems were detected, and the identified runaway potential of this reaction was studied. By modifying the original oxidation procedure, it was possible to establish this reaction safely in the pilot plant at 17-kg scale. Furthermore, the procedure was applied successfully to several other steroids on the laboratory scale.

Introduction

Squalamine (**1**) is a novel polyaminosteroidal sulfate which was isolated recently from tissues of the dogfish shark, *Squalus acanthias*.[1] The interesting biological activity of squalamine against Gram-negative and Gram-positive bacteria and, especially, its potent tumor-inhibiting properties triggered some synthetic efforts in this class of compounds.[2]

During studies concerning the scale-up of the intermediate **4** (Scheme 1) for the preparation of squalamine, we faced the problem of an allylic C−H oxidation at C-7 of a Δ-5-steroid to the corresponding unsaturated 7-ketone. This transformation is an old problem in steroidal chemistry[3] for which there were no really satisfying solutions until recently. Several methods for such an allylic oxidation are described in the literature. The classic and probably best-known variation of this theme is the chromium(VI) oxide-mediated oxidation, which can also be accomplished with the more modern reagents pyridinium chlorochromate (PCC) and pyridinium dichromate (PDC).[4] Although the yields are moderate to good, this method suffers from the high excesses of the chromium reagents, which sometimes make the isolation of the products difficult and environmental problems arise. Catalytic variations of the chromium oxidation with chromium hexacarbonyl and *tert*-butyl hydroperoxide in acetonitrile or benzene[5] seemed also not so attractive to us from an environmental and process point of view. The more environmental friendly oxidation by molecular oxygen and *N*-hydroxyphthalimide as the catalyst[6] seems to be restricted, more or less, to the laboratory scale until now. Besides the technical and safety problems connected with a reaction under an oxygen atmosphere in the pilot plant, we found the scale-up difficult. In our case, experiments in the range of 500 g and above did not proceed satisfactorily.

Scheme 1



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For these reasons, we found the recently published protocol by Miller et al. for a ruthenium-catalyzed allylic oxidation with *tert*-butyl hydroperoxide the most attractive alternative.[7]

Results and Discussion

The Δ-5-ketal **3**, which was the starting material for our oxidation studies, can be easily prepared from the commercially available 20-hydroxy-4-pregnen-3-one (**2**) in a few steps. With this material in our hands, we first checked the original oxidation method described by Miller et al. and were glad to find the reaction working very smoothly in the 5-g scale. With cyclohexane as solvent, using 10 molar equiv of *tert*-butyl hydroperoxide and 0.62 mol % $RuCl_3 \cdot H_2O$ at 20 °C, **3** was transferred to the unsaturated ketone **4** and isolated in 85% yield as a white solid. This result is especially remarkable since the structure of the Δ-5-steroid **3** contains a fragile ketal and *tert*-butyldimethylsilyl ether moiety. We found no significant difference in yield and reaction time when we changed from *tert*-butyl hydroperoxide in isooctane to *tert*-butyl hydroperoxide in water (70%). Cyclohexane and MTBE were the solvents of choice. Acetone, ethyl acetate, dichloromethane, and toluene gave lower yields or no reaction at all. Because of electrostatic problems connected with reactions in pure cyclohexane, we decided to use the aqueous *tert*-butyl hydroperoxide solution for the scale-up experiments and the reactions in the pilot plant. For the same reason, we used MTBE in the first experiments on the laboratory scale. On a 50-g scale, we were able to run the reaction successfully in MTBE, although the yield was slightly decreased to 76% of **4**.

During our initial studies, the addition time of the peroxide to the reaction mixture was found not to be a critical parameter and had been, more or less, neglected. Although it is common knowledge that peroxides are catalytically destroyed by heavy metals, we had not detected any exothermic reaction in the laboratory scale. The routine safety assessment of our laboratory procedure showed a safety hazard risk because of accumulation of the *tert*-butyl hydroperoxide, which gives rise to a dangerous runaway potential. A calorimetric study of the originally desired process on an 80-g scale, using MTBE as solvent at 20 °C, was carried out to determine the overall heat of reaction (ΔH_r), the rate of heat production, and the thermal accumulation potential in the reactor due to unreacted material, using isothermal reaction calorimetry (Mettler's RC-1). The heat of reaction measured is strongly exothermic, $\Delta H_r = -582$ kJ/$kg_{reaction\ mass}$ or −2257 kJ/mol of **3** due to the high excess of peroxide which is decomposed in the course of the reaction by the catalyst. The exothermic reaction was finished after ca. 6 h. The reaction energy implies a direct measure of the potential for a severe runaway, i.e., the destructive potential.[8] Usually, an indicator for this is the adiabatic temperature increase, ΔT_{ad}. From

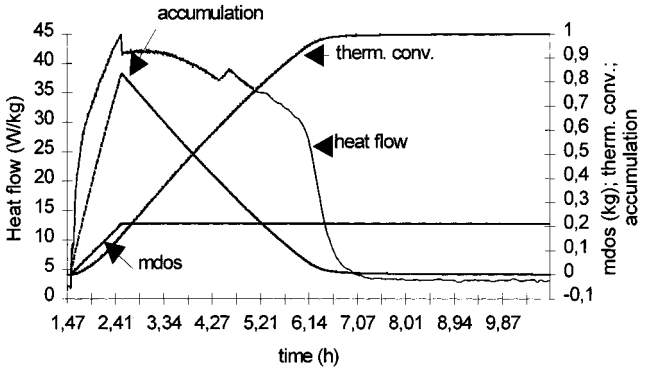

Figure 1. **RC1: synthesis of 4, TBHP dosage 1 h (mdos = balance, therm. conv. = thermal conversion).**

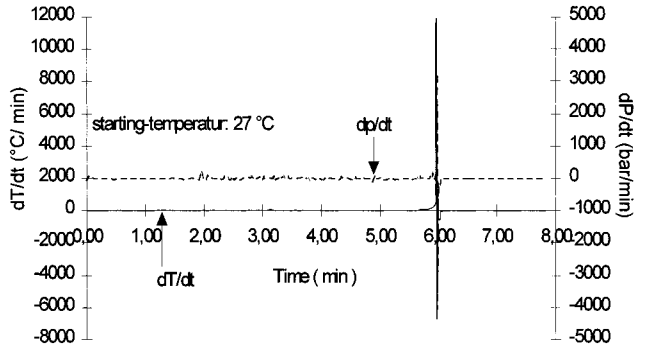

Figure 2. **Phe-Tec II: runaway scenario, original laboratory procedure.**

the measured heat of reaction, an adiabatic temperature increase of $\Delta T_{ad} = 263$ K was estimated, indicating a high potential for a severe runaway. A maximum thermal accumulation of up to 84% of the total heat output was determined at the end of the peroxide addition, indicating a heat output not proportional to the addition rate of the peroxide (Figure 1). To improve the evaluated results of the runaway scenario, a batch addition of peroxide was considered as a worst-case scenario. Thus, a further study using adiabatic reaction calorimetry (HEL's Phi-Tec II) on an 8-g scale was conducted (40 mL of MTBE, 0.025 g of $RuCl_3$ in 4.8 mL of H_2O, addition of 22.5 mL of *tert*-butyl hydroperoxide solution). The peroxide was added in one portion, and the reaction under adiabatic conditions was monitored. Within less than 10 min, the runaway up into a heat explosion occurred, with a maximum rate of temperature rise, d*T*/d*t*, up to 11 000 °C/min and a maximum rate of pressure rise, d*P*/d*t*, up to 5000 bar/min (Figure 2). Hereby, a maximum pressure of $p = 55$ bar was measured, and $\Delta T_{ad} = 236$ K was determined (Figure 3). In a blank experiment, the stability of *tert*-butyl hydroperoxide in the reaction mixture without the steroidal alkene **3** was investigated using adiabatic reaction calorimetry, following the same protocol as described above (40 mL of MTBE, 0.025 g of $RuCl_3$ in 4.8 mL of H_2O, addition of 22.5 mL of *tert*-butyl hydroperoxide solution). In this case, a runaway occurred also within less than 10 min, with a maximum rate of temperature rise, d*T*/d*t*, up to 1500 °C/min and a maximum rate of pressure rise, d*P*/d*t*, up to 1200 bar/min. A maximum pressure of $p = 45$ bar and $\Delta T_{ad} = 220$ K were determined. After these studies revealed major safety concerns for running

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(8) Steinbach, J.; Ebertz, A.; Stoessel, F. In *Ullmann's Encyclopedia of Industrial Chemistry*; VCH: Weinheim, 1995; Vol. B8, p 343.

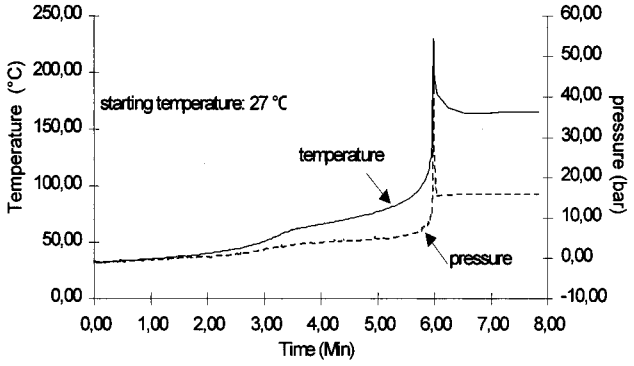


Figure 3. **Phi-Tec II: runaway scenario, original laboratory procedure.**

the pilot plant batches with the procedure we followed successfully at the laboratory scale, a new experimental program was started in process research to find a method to control the evolving reaction heat.

As we had found a slight increase of impurities with MTBE as solvent when we oxidized larger amounts of the steroid, we switched back to cyclohexane. In our first attempts, we tried to avoid the accumulation of peroxide by performing the oxidation at higher temperatures (60 or 80 °C) and adding the *tert*-butyl hydroperoxide (10 molar equiv) over longer intervals (2−6 h). Although these methods worked and gave an improvement concerning the accumulation, all of these reaction mixtures contained more impurities and unreacted starting material than the original room-temperature variation. For these reasons, we returned to the original protocol and tried to minimize the large excess of aqueous *tert*-butyl hydroperoxide (10 molar equiv). With only 2.5 molar equiv of the peroxide and an addition time of 6 h, the conversion was incomplete and 50% of the starting material was left unreacted after a 24-h reaction time. Under the same conditions using 5 molar equiv, 20% of the starting material was left. With longer reaction times, the number and amount of impurities increased. The optimum conditions which we found finally were to add 7 molar equiv of the aqueous *tert*-butyl hydroperoxide during 7 h at 20 °C under vigorous stirring to the Δ-5-steroid **3** in cyclohexane and to quench the reaction after an additional hour at this temperature. Lower amounts of peroxide gave only incomplete conversion, whereas higher amounts are connected with a severe safety hazard risk because of potential accumulation. This new protocol led to a maximum thermal accumulation of approximately 20% of the *tert*-butyl hydroperoxide. In a control experiment (8 g of steroidal alkene **3**, 40 mL of cyclohexane, 0.025 g of $RuCl_3$ in 4.8 mL of water, 4.5 mL (=2 molar equiv of *tert*-butyl hydroperoxide) using adiabatic reaction calorimetry, the exotherm reaction occurred within 20 min, reaching a maximum rate of temperature rise, dT/dt, of 65 °C/min and a maximum rate of pressure rise, dP/dt, of 70 bar/min. A maximum pressure of $p = 1$ bar and $\Delta T_{ad} = 67$ K were determined, indicating only a moderate runaway potential, which is in the range of common organic reactions. During the course of this run, no further exothermic reaction was detected (even after heating to 90 °C in the adiabatic reaction calorimeter).

After this catalytic oxidation method had been adjusted to the safety issues in the manner described above, we transferred the procedure to the pilot plant. Two batches with 17 and 15.72 kg of the ketal **3** were run in a 250-L enamelled reaction vessel. To ensure a fast and safe reaction, the reaction mixture was stirred vigorously while nitrogen was bubbled through the solution. Seven molar equivalents of the *tert*-butyl hydroperoxide were added during 7 h, and the mixture was stirred for another 10 h. After this time, no peroxides could be detected any longer. After the usual aqueous workup, the cyclohexane phase was concentrated and cooled to 5 °C to induce crystalization. Concentration of the mother liquor and purification by chromatography yielded a second crop. The total yield of the two batches was 17.46 kg (52%) of **4** as a white solid. Although the yield was decreased compared to the good results in the laboratory scale (85%), it was shown that it is possible to perform this oxidation successfully in a safe way in the multikilogram scale. The moderate yield is probably connected with the inefficient mixing of the heterogeneous reaction mixture in the pilot plant reaction vessel compared to that in the laboratory.

As described above, we were interested not only in an oxidation procedure for the preparation of the intermediate **4** but also in a general application of this allylic oxidation for the preparation of Δ-5,7-ketosteroids. For this reason, we applied the developed oxidation procedure to several other steroids and received moderate to good isolated yields of the reaction products. These results are summarized in Table 1.

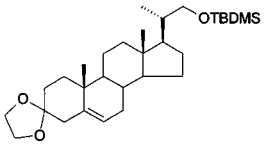
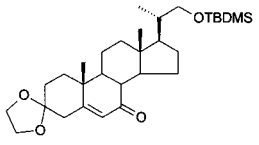
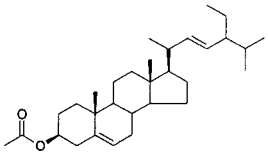
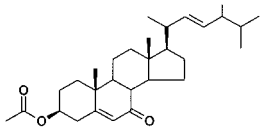
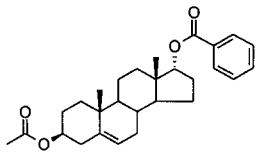
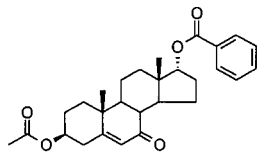
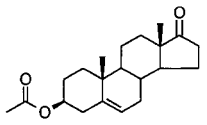
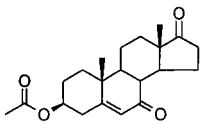
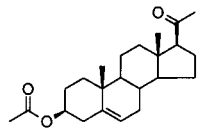
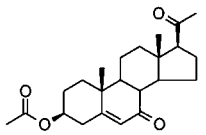
Conclusions

The ruthenium-catalyzed allylic oxidation method[7] recently described by Miller et al. was successfully adjusted to our transformation problem, considering the described safety study data. The oxidation of **3** to **4** was accomplished in a safe way in the multikilogramm scale in the pilot plant. Due to scale-up problems, the yield was reduced compared to that at the laboratory scale. Although we got a smaller amount of the product than we had expected, we had sufficient material for the performance of the next steps. The generality of the adjusted oxidation method was shown with several other steroidal compounds. In our opinion, this transformation is a typical example of the general difficulties one encounters on the safe scaling-up of catalytic heterogeneous reactions with reagents of high energy content. A combined effort of chemical and technical solutions is needed to overcome such problems.

Experimental Section

Commercial reagent grade solvents were used as obtained. Melting points were measured with a Büchi 510 melting point apparatus and are uncorrected. IR spectra were measured on a Bruker FT-IFS 25 spectrometer. ^{1}H NMR spectra were recorded on a Bruker AC 300 (300 MHz), and δ values are given in ppm relative to tetramethylsilane as internal standard. Mass spectra were determined with a Fisons Instruments VG 70-70 E spectrometer at 70-eV

Table 1. **Ruthenium-catalyzed allylic oxidations of Δ-5-steroids**

Starting Material	Product	Yield (scale)
 **3**	 **4**	85 % (5 g)
 **5**	 **6**	42 % (1 g)
 **7**	 **8**	71 % (1 g)
 **9**	 **10**	69 % (1 g)
 **11**	 **12**	51 % (1 g)

ionizing voltage, using NH_3 in case of chemical ionization (CI). Microanalytical data were provided by Schering analytical department. TLC analyses were performed on Merck F_{254} silica gel plates. The peroxide test was performed with the Merckoquant peroxide test kit.

General Procedure for the Ruthenium-Catalyzed Allylic Oxidation of Δ-5-Steroids. Δ-*5,7-Ketosteroid* ***4***. To 5 g (10.2 mmol) of Δ-5-steroid **3** (M = 488.8 g/mol) and 14.3 mg (0.063 mmol, 0.62 mol %) of ruthenium trichloride monohydrate (M = 225.4 g/mol) was added under nitrogen 25 mL of cyclohexane. To the vigorously stirred suspension was added at room temperature over 7 h 9.8 mL of an aqueous 70% *tert*-butyl hydroperoxide solution (71.6 mmol, 7 molar equiv). After an additional hour of stirring, the peroxide test was negative, and the reaction mixture was quenched with water (30 mL). Extraction of the aqueous phase with cyclohexane (40 mL) and concentration of the combined organic phases yielded a yellow oil, which was further purified by silica gel chromatography with ethyl acetate/hexane. Yield: 4.36 g (8.67 mmol, 85%) of a white solid; mp 129 °C; $[\alpha]^{25}_D$ −43.0° (c = 1, $CHCl_3$). IR (KBr): 2950, 1660, 1100 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.0 (s, 6 H), 0.68 (s, 3 H), 0.86 (s, 9 H), 0.98 (d, 3 H, J = 7 Hz), 1.18 (s, 3 H), 1.0−2.5 (m, 18 H), 2.65 (dd, 1 H, J = 2, 15 Hz), 3.16−3.28 (m, 1 H), 3.5−3.6 (m, 1 H), 3.8−4.0 (m, 4 H), 5.64 (d, 1 H, J = 2 Hz). MS (*m*/*z*) (relative intensity): 504 (47, $M^+ + 1$), 503 (100, M^+), 99 (7), 52 (13). Anal. Calcd for $C_{30}H_{50}O_4Si$: C, 71.66; H, 10.02; Si, 5.59. Found: C, 71.24; H, 9.91; Si, 5.25.

Δ-*5,7-Ketosteroid* ***6***. Yield: 0.433 g (42%) of a white solid; mp 182 °C; $[\alpha]^{25}_D$ −106.0° (c = 1, $CHCl_3$). IR (KBr): 2950, 1730, 1670, 1250 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.7 (s, 3 H), 0.75−0.9 (m, 9 H), 1.02 (d, 3 H, J = 7 Hz), 1.2 (s, 3 H), 1.05−2.6 (m, 23 H), 2.07 (s, 3 H), 4.65−4.8 (m, 1 H), 5.03 (dd, 1 H, J = 10, 15 Hz), 5.18 (dd, 1 H, J = 10, 15 Hz), 5.7 (d, 1 H, J = 1 Hz). MS (*m*/*z*) (relative intensity): 469 (32, M^+), 410 (39), 409 (100). Anal. Calcd for $C_{31}H_{48}O_3$: C, 79.44; H, 10.32. Found: C, 79.42; H, 10.02.

Δ-*5,7-Ketosteroid* ***8***. Yield: 0.730 g (71%) of a colorless oil. IR: 2950, 1730, 1710, 1670, 1280, 1240 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.82 (s, 3 H), 1.24 (s, 3 H), 1.4−2.0 (m, 12 H), 2.07 (s, 3 H), 2.25−2.75 (m, 6 H), 4.65−4.8 (m, 1 H), 5.09 (d, 1 H, J = 5 Hz), 5.78 (d, 1 H, J = 2 Hz), 7.4−7.49 (m, 2 H), 7.5−7.6 (m, 1 H), 8.03 (d, 1 H, J = 7 Hz). MS (*m*/*z*) (relative intensity): 468 (46, $M^+ + NH_3$), 451 (19, M^+), 392 (41), 391 (100). Anal. Calcd for $C_{28}H_{34}O_5$: C, 74.64; H, 7.61. Found: C, 74.29; H, 7.61.

Δ-*5,7-Ketosteroid* ***10***. Yield: 0.716 g (69%) of a white solid; mp 184 °C; $[\alpha]^{25}_D$ −86.6° (c = 1, $CHCl_3$). IR (KBr): 2950, 1740, 1670, 1240 cm^{-1}. ^1H NMR: δ 0.9 (s, 3 H), 1.25 (s, 3 H), 1.3−2.0 (m, 10 H), 2.07 (s, 3 H), 2.1−2.2 (m, 1 H), 2.35−2.68 (m, 5 H), 2.75−2.9 (m, 1 H), 4.55−4.7 (m, 1 H), 5.78 (d, 1 H, J = 2 Hz). MS (*m*/*z*) (relative intensity): 362 (12, $M^+ + NH_3$), 345 (10, M^+), 286 (35), 285 (100). Anal. Calcd for $C_{21}H_{28}O_4$: C, 73.23; H, 8.19. Found: C, 72.96; H, 8.18.

Δ-*5,7-Ketosteroid* ***12***. Yield: 0.528 g (51%) of a white solid; mp 147 °C; $[\alpha]^{25}_D$ −72.9° (c = 1, $CHCl_3$). IR (KBr): 2950, 1730, 1705, 1670, 1240 cm^{-1}. ^1H NMR: δ 0.68 (s, 3 H), 1.24 (s, 3 H), 1.28−2.0 (m, 12 H), 2.07 (s, 3 H), 2.14 (s, 3 H), 2.2−2.3 (m, 1 H), 2.4−2.6 (m, 5 H), 4.65−4.8 (m, 1 H), 5.74 (d, 1 H, J = 2 Hz). MS (*m*/*z*) (relative intensity): 373 (36, M^+), 314 (37), 313 (100). Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 73.88; H, 8.46.

Procedure for the Preparation of Δ-5,7-Ketosteroid 4 in the Pilot Plant. In a 250-L enamelled reaction vessel, to 17 kg (34.77 mol) of Δ-5-steroid **3** was added 49 g (0.22 mol, 0.62 mol %) of ruthenium trichloride monohydrate dissolved in 5 L of deionized water. After addition of 85 L of cyclohexane, the reaction mixture was stirred vigorously, and nitrogen was bubbled through the solution. Next, 33.3 L of a 70% aqueous *tert*-butyl hydroperoxide solution (243.0 mol, 7 equiv) was added slowly over 7 h, during which time the internal temperature was controlled between 20 and 25 °C. The reaction mixture was stirred for another 10 h. At that time, the peroxide test was negative. Next, 30 L deionized water was added, and the mixture was stirred for

30 min. After separation of the phases, the organic phase was filtered over a pad of 25 kg of silica gel, and the filter was washed with 100 L of cyclohexane. The solution was concentrated to 90 L, cooled to 5 °C, and stirred for 1 h. The product crystals were filtered off, and the mother liquor was concentrated to 35 L. Purification by silica gel chromatography (450 kg of silica gel) with 95:5 hexane/ethyl acetate yielded a second crop. The combined yields of this batch and a second batch with 15.72 kg of starting material gave 17.46 kg (34.72 mol, 52%) of **4** as a white solid, which was fully identical with the material prepared in the laboratory.

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