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Ceftibuten:† Development of a Commercial Process Based on Cephalosporin C. Part III. Process for the Conversion of 3-Exomethylene-7(*R*)-glutaroylaminocepham-4-carboxylic Acid 1(*S*)-Oxide to Ceftibuten

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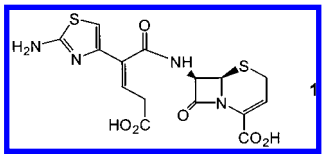
Abstract:

The foregoing papers (Bernasconi, E.; Lee, J.; Roletto, J.; Sogli, L.; Walker, D. *Org. Process Res. Dev.* 2002, *6*, 152 and Bernasconi, E.; Genders, D.; Lee, J.; Longoni, D.; Martin, C. R.; Menon, V.; Roletto, J.; Sogli, L.; Walker, D.; Zappi, G.; Zelenay, P.; Zhang, H. *Org. Process Res. Dev.* 2002, *6*, 158) describe a high-yielding, all-aqueous process for the preparation of 3-exomethylene-7(*R*)-glutaroylaminocepham-4-carboxylic acid 1(*S*)-oxide (3) from fermented cephalosporin C broth via enzyme transformations and electrochemical reduction without isolation of any precursors. In this paper we describe the efficient recovery of 3 from aqueous solution, by extractive esterification employing diphenyldiazomethane, and the conversion of the obtained bis(diphenylmethyl) ester (4) into intermediates both for Ceftibuten (1) and cefaclor (8). Several routes to the key Ceftibuten building block, diphenylmethyl 7(*R*)-aminoceph-3-em-4-carboxylate (6) are described. This key building block is acylated, deblocked, and purified using chemistry described by Shionogi workers to give Ceftibuten.

Introduction

In Parts I and II of this series of papers[1] we outlined a new strategy for the preparation of Ceftibuten (**1**) from fermented cephalosporin C broths. As a byproduct of this work we also created a new opportunity for the realization of a safer and environmentally more friendly process for the manufacture of cefaclor (**8**).



The new strategy is summarized in Scheme 1.

The foundation of Scheme 1 is based on our discovery[1b] that 3-acetoxymethyl-7(*R*)-glutaroylaminoceph-3-em-4-carboxylic acid (**2**), already commercially produced by Antibioticos S.p.A. for the manufacture of 7(*R*)-aminocephalosporanic acid (7-ACA), can be sulfoxidized and electrochemically reduced in almost quantitative yield to give the new low-cost intermediate, 3-exomethylene-7(*R*)-glutaroylaminocepham-4-carboxylic acid 1(*S*)-oxide (**3**). This process is economically and environmentally advantageous in that all process operations to produce **3** are carried out in water without isolation of any intermediates. We anticipated that **3** would be recoverable from aqueous solution using previously described extractive esterification techniques, specifically the system using diphenyldiazomethane (DDM)[2] reported by Glaxo workers.[3] Our objective was to make bis(diphenylmethyl) 7(*R*)-glutaroylamino-3-hydroxyceph-3-em-4-carboxylate 1(*S*)-oxide (**5**), the first product isolated from the fermenter!

Results and Discussion

Extractive Esterification. Extractive esterification using DDM originates from Glaxo's commercialization of diphenylmethyl as a carboxyl-protecting group in the manufacture of cephalexin.[2d,3] The commercial availability of benzophenone hydrazone and the relatively innocuous nature of the readily recycled benzhydrol waste add to the attractiveness of using the highly reactive DDM. Although in our work we prepare and use solutions of DDM in methylene chloride

† Ceftibuten was discovered by Shionogi and Co. Ltd., Osaka, Japan, and licensed to Schering-Plough Corporation, Kenilworth, New Jersey. The drug is manufactured by Shionogi.

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(1) (a) Part I: Bernasconi, E.; Lee, J.; Roletto, J.; Sogli, L.; Walker, D. *J. Org. Process Res. Dev.* **2002**, *6*, 152. (b) Part II: Bernasconi, E.; Genders, D.; Lee, J.; Longoni, D.; Martin, C. R.; Menon, V.; Roletto, J.; Sogli, L.; Walker, D.; Zappi, G.; Zelenay, P.; Zhang, H. *Org. Process Res. Dev.* **2002**, *6*, 158.

(2) (a) For the preparation of diphenyldiazomethane see Adamson, J. R.; Bywood, R.; Eastlick, D. T.; Gallagher, G.; Walker, D.; Wilson, E. M. *J. Chem. Soc., Perkin Trans. I* **1975**, 2030 and Gallagher, G.; Walker, D. (Glaxo). U.S. Patent 4,083,837, 1978. (b) Safety considerations drove the commercialization of the in situ preparation of diphenyldiazomethane and its instant scavenging by penicillin G 1(*S*)-oxide: Bywood, R.; Gallagher, G.; Sharma, G. K.; Walker, D. *J. Chem. Soc., Perkin Trans. I* **1975**, 2019. (c) The stability of DDM has been reported by Sakamoto, D.; Hirayama, Y.; Kohno, Y.; Sakai, T.; Shiraishi, Y.; Saijo, S. (Taoka Chemical Ltd.). European Patent 177,248, 1987. These workers report that crystalline DDM undergoes no decomposition when held at 5° for 100 hours, but that solutions in CH_2Cl_2 deteriorate faster—a 50% solution decomposes 4.9% in 20 days and 30.5% in 40 days at 0 °C. The polymer version of DDM, sold commercially by Bachem, Switzerland, is said to deteriorate at a rate of ca. 4%/month at 4 °C: Dr. J. Gosteli, private communication. DDM is described as emitting toxic vapors of NO_x when heated to decomposition—Lewis, R. J. *Sax's Dangerous Properties of Industrial Materials*, 9th ed.; Van Norstrand Reinhold: New York, 1996; p 1404. (d) For preparation of cephalexin from Penicillin G 1(*S*)-oxide via diphenylmethyl protection see Bywood, R. Gallagher, G.; Walker, D. (Glaxo). German Patent 2,311,597, 1973.

(3) (a) Bywood, R.; Robinson, C.; Stables, H. C.; Walker, D.; Wilson, E. M. In *Recent Advances in the Chemistry of β-Lactam Antibiotics*; Elks, J. Ed.; Special Publication No. 28; The Royal Society of Chemistry: London, 1977; p 139. (b) Robinson, C.; Walker, D. (Glaxo). U.S. Patent 4,059,573, 1977.

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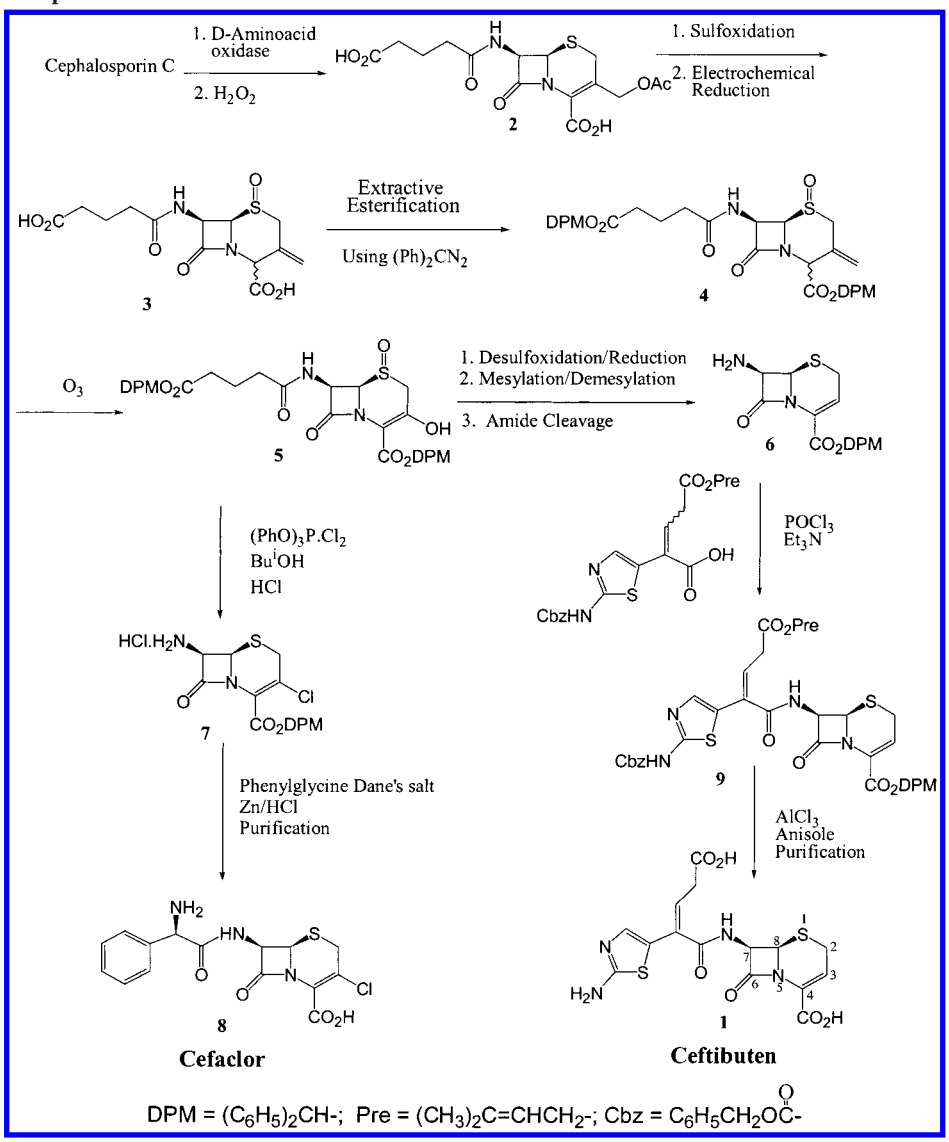
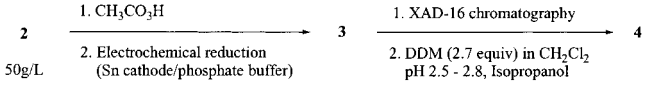
Scheme 1. **Outline of processes for the manufacture of Ceftibuten and cefaclor**



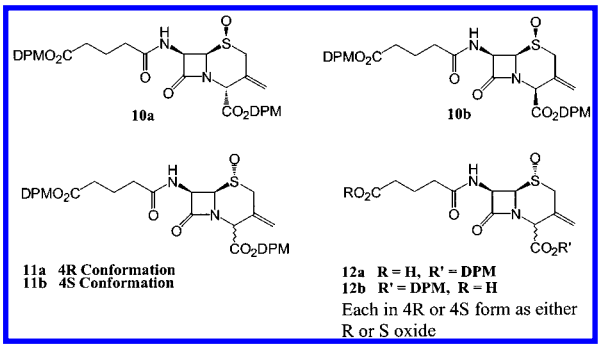
it is probable, based on the earlier publications,[2,3] that, in a fully developed process, DDM would be prepared and used in situ.

Although the extractive esterification of **3** required more than 2 mol of DDM, adding to costs, we were able to minimize the usage of DDM by first purifying aqueous solutions of **3** using column chromatography on a Rohm and Haas XAD-16 resin. This purification (see Table 13 in Part II[1b]) efficiently removed most of the phosphate buffer, thereby reducing DDM usage. Scheme 2 illustrates the process for converting an Antibioticos solution of **2** to a solution of bis(diphenylmethyl) 3-exomethylene-7(*R*)-glutaroylaminocepham-4-carboxylate 1(*S*)-oxide (**4**).

Scheme 2. **Antibioticos solution of 2 to a solution of 4**



Using a freshly prepared solution of **2** (98% purity by HPLC) the overall solution yield (**2** to **4**) was 88%. The isolation of **4** in a pure crystalline form as the predominant single enantiomer (**10a**) reduced the overall yield to 70% (no optimization carried out). In large part crystallization losses are due to the presence of small amounts of several useable byproducts (**10b, 11**, and **12**). As expected, the



extractive esterification step virtually eliminated tin contamination (the **4** produced contained <20 ppm of tin).

To avoid product and economic losses by isolating a pure crystalline enantiomer (**10a**), it is clear that it would be most desirable to capture all the 3-exo-methylenecepham products

produced. This has been achieved by direct ozonolysis of the methylene chloride solution of **4** obtained via Scheme 2.

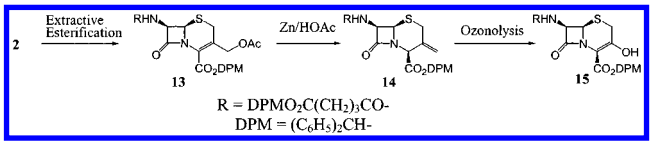
Ozonolysis. The efficient ozonolysis of 3-exomethylenecephams in either sulfide or sulfoxide form, has been described by several workers.[4,5] In the case of our compound **4**, obtained as in Scheme 2, the solution in methylene chloride was first washed with aqueous base to remove very small amounts of monoacids (**12**); these extracts were recycled to the next extractive esterification run. The resulting methylene chloride solution of **4** was partially stripped, made up with methanol (17−20% CH_3OH), and ozonolyzed at ca. −55 °C over 4−6 h to give **5** in almost quantitative yield.

Our work showed that ozonolysis of the sulfoxide **4** was advantageous over ozonolysis of the sulfide form of **4** in that the sulfoxide proved more stable, giving ∼95% yield of **5** at −15 °C in methylene chloride containing some acetic acid. In contrast ozonolysis of the sulfide form of **4**, even at −55 °C, led to the formation of small amounts of sulfoxide **5** as a byproduct. Although there is a possibility that aqueous solutions of **3** might be ozonolyzed, further extending the principle of carrying out as many reactions as possible in water, we did not test this.

The isolation of **5** was achieved by replacing the methylene chloride−methanol solvent with 2-propanol. The isolated yield of **5** based on the content of **2** in the starting aqueous solution was ca. 76%. Typically the purity of **5** was ca. 97%. The 1(*R*)-oxide content of **5** was generally ca. 1%. The mother liquor from the crystallization of **5** contained additional **5**, usually ca. 5%. Recovery of further **5** was not undertaken.

In addition to defining and developing the electrochemically based route to **5** we also undertook an evaluation of a chemically based route for the conversion of 3-acetoxymethyl-7(*R*)-glutaroylaminoceph-3-em-4-carboxylic acid (**2**) to sulfide **15** for cost comparison purposes. The chemical route is outlined in Scheme 3.

Scheme 3. **Alternative chemically based route for the manufacture of 15**



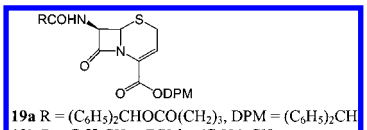
Although the chemical route worked well to give high-quality **15**, it is environmentally less satisfactory in that organic solvents and reagents are introduced at an earlier point than is the case in the electrochemical route. Furthermore, the use of metallic zinc for the reduction step introduces hazardous waste handling and disposal problems. Greater volumes of solvent and reagents such as DDM are needed in abrogating the advantage of working in water for the electrochemical reduction. In contrast the step of reducing the sulfoxide (**5**), produced via the electrochemical route, to the corresponding sulfide seemed likely, from the literature,[6] to be quite simple. Although our work on the desulfoxidation step was not optimized, we showed that the desulfoxidation step could be achieved, often in high yield, with acetyl chloride/iodide and Lawesson's reagent. Our work also showed that the desulfoxidation step could be carried out in situ.

Conversion of 5 to Diphenylmethyl 7(*R*)-Aminoceph-3-em-4-carboxylate (6). Several routes were investigated in an effort to determine which approach would be the most efficient and practical for the conversion of **5** to **6**. These routes are outlined in Scheme 4.

The desulfoxidation step to initiate Route A results in immediate access to an analogous compound (**15**) to Shionogi's diphenylmethyl 3-hydroxy-7(*R*)-phenylacetamidoceph-3-em-4-carboxylate (This compound is an intermediate in Shionogi's manufacturing process[7] for Ceftibuten; see Scheme 1 in Part II of this series of papers).[1b] Route B describes a different order of the reactions to that used in Route A. Route C involves chlorination of the 3-hydroxyl group of **5** to give **16** followed by zinc/acetic acid reduction of 3-Cl to 3-H using procedures described by earlier workers.[8]

Route A was selected because of the harmonization with Shionogi's Ceftibuten manufacturing process, and the likely minimum capital requirements for adopting this route. The alternative Route B was not pursued because the reduction step to cepham sulfoxide (**17**) was much less efficient than the reduction of **15** to **18**. Although laboratory work indicated that route C would provide a shorter higher-yielding route from **5** to **6**, this route was not pursued for time and cost considerations. New capital equipment would be required to operate the route C process, particularly for the zinc/acetic acid reduction step, including disposal of the zinc waste. Potentially even more time-consuming, new process steps would have to be proven, validated, and registered with regulatory authorities.

Operation of the Route A process (**5** → **15** → **18** → → → **6**) proved to be similar, in both handling and performance, to the Shionogi process (see Scheme 1 in Part II of this series[1b] and Yoshioka[7]). As expected the only difference in quality is the structure of the trace impurity in **6**. The trace impurities are **19a** (this work) and **19b** (Shionogi).

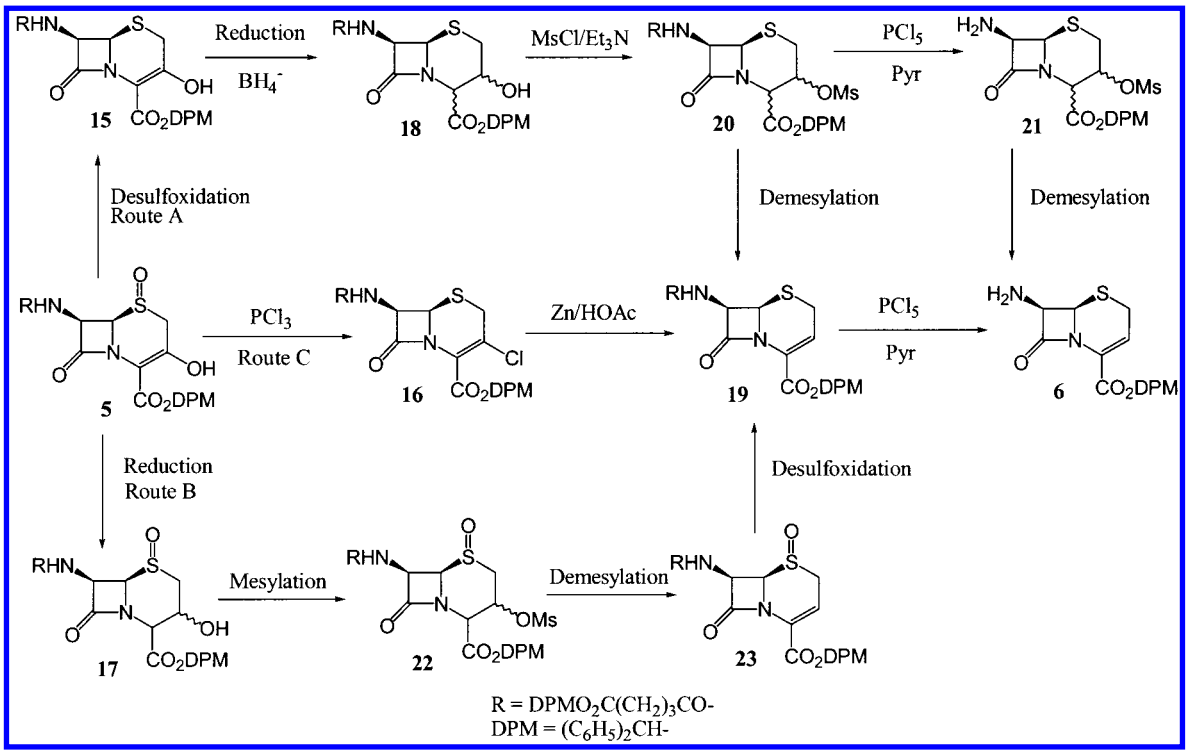


Impurity **19a** is generally present in an amount of <0.5% and is routinely purged in subsequent processing to Ceftibuten, in an analogous manner to **19b** in the Shionogi process.

Conversion of 6 to Ceftibuten. The procedures we followed were those described by Shionogi for the conversion of **6** derived from penicillin G 1(*S*)-oxide. Results and

(4) Scartazzini, R.; Bickel, H. *Helv. Chim. Acta* **1974**, *57*, 1919.
(5) (a) Chauvette, R. R.; Pennington, P. A. *J. Am. Chem. Soc.* **1974**, *96*, 4986. (b) Chauvette, R. R. (Eli Lilly). U.S. Patent 3,917,587, 1975. (c) Chauvette, R. R. (Eli Lilly). U.S. Patent 4,060, 688, 1977.
(6) Kaiser, G. V.; Cooper, R. D. G.; Koehler, R. E.; Murphy, C. F.; Webber, J. A.; Wright, I. G.; Van Heyningen, E. M. *J. Org. Chem.* **1970**, *35*, 2430.
(7) Yoshioka, M. *Pure Appl. Chem.* **1987**, *59*, 1041.
(8) (a) Nagata, W.; Narisada, M.; Hamashima, Y.; Okada, K. (Shionogi). U.S. Patent 4,081,595, 1978. (b) See also Takaya, T.; Kochi, H.; Masugi, T. (Fujisawa). U.S. Patent 4,246,405, 1981.

Scheme 4. **Outline of routes for conversion of 5 to 6**



product quality were identical, irrespective of the source of **6**.

Preparation of the Key Cefaclor Intermediate (7). We were encouraged to determine whether the new electrochemically based route to Ceftibuten intermediate could be beneficially applied to the manufacture of other cephalosporin antibiotics now accessed from penicillin intermediates. The two obvious candidates are cefaclor[9] and ceftizoxime.[10] We briefly evaluated the cefaclor opportunity simply because it appeared us that the use of diphenylmethyl (DPM) as a readily removable protecting group for carboxyl should be superior to use of the *p*-nitrobenzyl (PNB) group now employed in cefaclor manufacture. There are several safety and industrial hygiene issues associated with the reagents used for introducing PNB protection, with the reductive removal of this group and with the disposal of process wastes. Although our use of the highly reactive diphenyldiazomethane (DDM) is potentially hazardous, if its in situ preparation and use can be realized as in the case of cephalexin,[2d] it provides a safer and more environmentally friendly alternative to PNB. In addition, the benzhydryl waste from the removal of DPM protection can be readily recycled.[11]

In regard to harnessing the 3-hydroxycephem intermediate **5** for cefaclor manufacture we found that the key intermediate **7** can be readily produced in an essentially one-pot process, in high yield and high quality. It appears probable, although we did not test this, that the DPM ester group of **7** might be removed in situ such that the first isolated product from **5** could be 7(*R*)-amino-3-chloroceph-3-em-4-carboxylic acid.

Conclusions

The efficient conversion of 3-exomethylene-7(*R*)-glutaroylaminocepham-4-carboxylic acid 1(*S*)-oxide (**3**) to diphenylmethyl 7(*R*)-glutaroylamino-3-hydroxyceph-3-em-4-carboxylate 1(*S*)-oxide (**5**) and thence diphenylmethyl 7(*R*)-aminoceph-3-em-4-carboxylate (**6**) and Ceftibuten (**1**) completes the synthesis sequence to establish a practical and economically attractive new strategy for the manufacture of Ceftibuten from fermented cephalosporin C. The new strategy also introduces new opportunities for producing other cephalosporin antibiotics, particularly cefaclor, from fermented cephalosporin C.

Experimental Section

Materials and General Methods. UV spectra were measured with a Hitachi U-3501 spectrophotometer. The HPLC analysis was carried out on a Brownlee HPLC analytical column (RP 18 SPHER I-1. 250 × 4.6 mm) maintained at a temperature of 35 °C. The mobile phase was typically 6:94, CH_3CN/0.025 M K_2HPO_4 (aqueous) at a flow rate of 1 mL/min. An UV detector (225 nm) was used.

Electrospray MS was performed in a VG Quattro SQ Mass Spectrometer (Fison Instruments). NMR experiments were conducted using WP-300 NMR (Bruker) and AM-400 NMR (Bruker) spectrometers.

Ozonolysis experiments were carried out using a Polyozone (formerly Welsbach) generator, model T-816 L.[12]

(9) (a) Chauvette, R. R.; Pennington, P. A. *J. Med. Chem.* **1975**, *18*, 403. (b) Kukolja, S. (Eli Lilly). U.S. Patent 4,052,387, 1977.

(10) Yamanaka, H.; Chiba, T.; Kawabata, K. Takasugi, H. Masugi, T.; Takaya, T. *J. Antibiot.* **1985**, *38*, 1738.

(11) (a) Benzhydryl wastes are readily converted to benzophenone by refluxing in aqueous 30% nitric acid—see ref 2d, Example 37. The benzophenone produced is easily converted to benzophenone hydrazone for recycle to the DDM process. (b) See also Rivkin, S. M. *J. Appl. Chem (USSR)*, **1938**, 11, 83 *(Chem Abstr*. **1938**, *32*, 4566).

(12) This unit generates 8 g O_3/h (air input) or 16 g O_3/h (oxygen input) operating at 115 V, 60 Hz, and 8 psig pressure.

Preparation of Bis(diphenylmethyl) 3-Exomethylene-7(*R*)-glutaroylaminocepham-4-carboxylate 1(*S*)-oxide (4). To an aqueous solution of 3-exomethylene product **3** (2 L, 70 g, 0.202 mol) obtained from the XAD-1600 resin purification (See Part II)[1b] was added a solution of diphenyldiazomethane[2a] (93.47 g, 0.508 mol) in 1.5 L of methylene chloride. The biphasic mixture was agitated at 5 to 10 °C. The pH was then adjusted to 3.5 with a solution of 5 N hydrochloric acid and was maintained for 2 h. Additional hydrochloric acid solution was added, and the reaction mixture was stirred overnight until the extractive esterification was complete. The phases were separated, and the aqueous phase was extracted with 0.5 L of methylene chloride. The organic phases were combined and washed with water (500 mL) and a solution of sodium bicarbonate to a pH of 7.5. The organic phase was then washed with saturated sodium chloride solution (300 mL). The product was isolated after replacement of methylene chloride with isopropyl alcohol (500 mL) via distillation. After cooling, the product was stirred for 2 h, filtered, and dried to give 120.21 g (88%) of desired product (**4**), having >98% purity. Alternatively, the methylene chloride solution after work up can be used directly for the next step without isolation. The tin content of **4** was <20 ppm.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.92−2.04 (m, 2H), 2.25 (t, 2H, J = 7.5 Hz), 2.48 (t, 2H, J = 7.5 Hz), 3.36−3.62 (ABq, 2H), 4.80 (d, 1H, J = 4.8 Hz), 5.32 (s, 1H), 5.42 (s, 1H), 5.77 (s, 1H), 5.92 (dd, 1H, J = 10, 1 Hz), 6.83 (s, 1H), 6.87 (s, 1H), 7.22−7.39 (m, 20H). ES-MS M^+ 676.2. HRMS calcd for $C_{39}H_{37}N_2O_7S$ (MH^+) m/z, 677.22, found 677.2307. Elemental analysis: found C, 69.21; H, 5.36; N, 4.14; O, 16.55; S, 4.74; calcd C, 69.23; H, 5.33; N, 4.14; O, 16.57; S, 4.74.

Preparation of Bis(diphenylmethyl) 7(*R*)-Glutaroyl-amino-3-hydroxyceph-3-em-4-carboxylate 1(*S*)-oxide (5). To a 2-L three-necked round-bottom flask connected to an ozonizer, a scrubber, and nitrogen purge was added 135 g of the product **4** (0.2 mol) and 900 mL of methylene chloride followed by 150 mL of methanol. The mixture was cooled to −65 °C. Ozone was bubbled in at a flow rate of ca. 1 L/min (at an air pressure of 8 psi) over a period of 4−6 h at −65 to − 55 °C. The reaction was monitored every hour by TLC. The typical ozonolysis takes ca. 3.5−4 h to complete. After completion, the excess of ozone was removed by insufflating oxygen for 30 min and then nitrogen for 30 min. Trimethyl phosphite (75 mL, 0.04 mol) was then added slowly over 40 min while maintaining the temperature between −10 to 0 °C. At the end of the addition, the solution gave a negative response to the peroxide test (KI-soluble starch). The resulting solution was stirred for 30 min before warming to room temperature.

The reaction mixture was poured into 1.5 L of aqueous solution containing *p*-toluenesulfonic acid monohydrate (24 g) and *tert*-*n*-butylammonium bromide (4 g). The resulting mixture was then agitated at 15−20 °C for 1.5 h. The organic phase was separated and washed with 5% aqueous sodium chloride (2 × 1 L). The water used for the above workup contained about 0.08% *tert*-*n*-butylammonium bromide. After concentration to remove most of the methylene chloride, 2-propanol (1.3 L) was added. The trace amount of methylene chloride was removed via continuous distillation to a volume of 800 mL. The mixture was then slowly cooled to 0 °C over 30 min and then agitated for 2 h. The product was filtered and dried under vacuum at 45−50 °C. The yield of product **5** (129 g) was ∼95%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.02 (m, 2H), 2.32 (t, 2H), 3.41−3.72 (ABq, 2H, J = 19.0, 1.0), 4.52 (dd, 1H, J = 4.0, 1.0 Hz), 6.03 (dd, 1H, J = 4.0, 1.0 Hz), 6.66 (d, 1H, J = 10.0 Hz), 6.89 (s, 1H), 6.92 (s, 1H), 7.20−7.40 (m, 20H), 11.70 (s, 1H). ES-MS M^+ 678.20. HRMS calcd for $C_{38}H_{35}N_2O_8S$ (MH^+) 679.20; m/z; 679.2137. Found C, 67.24; H, 5.05; N, 4.13; O, 18.86; S, 4.72. Calculated C, 67.26; H, 5.01; N, 4.13; O, 18.88; S 4.72.

Alternative Preparation of Bis(diphenylmethyl) 7(*R*)-Glutaroylamino-3-hydroxyceph-3-em-4-carboxylate 1(*S*)-oxide (5). The methylene chloride solution of **4** (101.25 g, 0.15 mol) obtained from the extractive esterification step, was concentrated via distillation to approximately 350 mL to remove water. An additional 250 mL of methylene chloride and 100 mL of methanol was added. The solution was cooled to −65 °C. Ozone was bubbled in at a flow rate of ca. 1 L/min (at an air pressure of 8 psi) over a period of 4−6 h at −65 to − 55 °C. The reaction was monitored every hour by TLC. The typical ozonolysis takes ca. 3.5−4 h to complete. After completion, the excess of ozone was removed by insufflating oxygen for 30 min and then nitrogen for 30 min. Trimethyl phosphite (56 mL, 0.03 mol) was then added slowly over 40 min while maintaining the temperature between −10 to 0 °C. At the end of the addition, the solution gave a negative response to the peroxide test (KI-soluble starch). The resulting solution was stirred for 30 min before warming to room temperature.

The reaction mixture was poured into 1.1 L of aqueous solution containing *p*-toluenesulfonic acid monohydrate (20 g) and *tert*-*n*-butylammonium bromide (3 g). The resulting mixture was then agitated at 15−20 °C for 1.5 h. The organic phase was separated and washed with 5% aqueous sodium chloride (2 × 500 mL). The water used for the above workup contained about 0.08% *tert*-*n*-butylammonium bromide. After concentration to remove most of the methylene chloride, 2-propanol (1 L) was added. The trace amount of methylene chloride was removed via continuous distillation to a volume of 650 mL. The mixture was then slowly cooled to 0 °C over 30 min and then agitated for 2 h. The product was filtered and dried under vacuum at 45−50 °C. The yield of product **5** (115 g) was ∼85%.

Preparation of Bis(diphenylmethyl) 7(*R*)-Glutaroyl-amino-3-hydroxyceph-3-em-4-carboxylate (15). To an ozonized solution of **5** (15 g, 0.022 mol) in methylene chloride (135 mL) was added Lawesson's reagent (2,4-bis-(4-methoxyphenyl)-1,3, 2, 4-dithiaphosphetane 2,4-disulfide, 10.5 g, 0.026 mol) at 20−25 °C. The mixture was stirred at 35 °C for 30 min. After reduction was complete (monitored by TLC) the reaction mixture was filtered[13] and methylene

chloride was removed via vacuum distillation. The residue was triturated with *n*-pentane (100 mL) to give 12 g (82%) of product **15** starting from **4**.

^{1}H NMR ($CDCl_3$, 400 MHz): 2.01 (m, 2H); 2.30 (t, 2H); 2.53 (t, 2H); 3.27−3.45 (AB quartet, 2H, J = 17 Hz); 5.01 (d, 1H, J = 4.5 Hz); 5.71 (d of d, 1H, J = 4.5 Hz, J = 8.5 Hz); 6.37 (d, 1H, J = 8.5 Hz); 6.89−6.91 (s, 2H); 7.23−7.45 (br s, 20H); 11.68 (s, 1H).

Preparation of Bis(diphenylmethyl) 7(*R*)-aminoceph-3-em-4-carboxylate (6). *Step A. Extractive Esterification.* To a 1-L solution of 21.0 g (0.064 mol) of 3-exomethylene-7(*R*)-glutaroylaminocepham-4-carboxylic acid prepared as in Part II (tin cathode)[1b] was added a solution of 34.2 g (0.17 mol) of diphenyldiazomethane in methylene chloride. The mixture was cooled to 0−5 °C. Aqueous hydrochloric acid (18%) was slowly added to adjust to pH = 3. The reaction mixture was warmed to room temperature and stirred for 6 h. The pH of the reaction was again adjusted to 2−2.5. After overnight agitation, the organic phase was separated, and the aqueous phase was extracted with methylene chloride (2 × 50 mL). The combined organic phases were washed with 500 mL of water and then concentrated in vacuo to a volume of about 70 mL. 2-Propanol (300 mL) was then added, and the remaining methylene chloride was distilled off at 45 °C. The resulting solution was cooled to 25 °C and seeded. The slurry was stirred at 25 °C for 4 h and at 0−5 °C for 0.5 h. The product, bis(diphenylmethyl) 3-exomethylene-7(*R*)-glutaroylaminocepham-4-carboxylate was filtered and dried in a vacuum oven at 35 °C to give 34 g (80.5%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.98 (m, 2H); 2.23 (t, 2H); 2.5 (t, 2H); 3.09−3.50 (AB quartet, 2H, J = 13 Hz, J = 9 Hz); 5.21−5.24 (s, 2H); 5.32 (s, 1H); 5.35 (d, 1H, J = 4.3 Hz); 5.64 (d of d, 1H, J = 4.3 Hz, J = 9.2 Hz); 6.10 (d, 1H, J = 9.2 Hz); 6.86−6.88 (s, 2H); 7.23−7.37 (br s, 20H).

Step B. Ozonolysis. A solution of 46.26 g (0.070 mol) of the bis-DPM ester product **14** from Step A in 500 mL of EtOAc was cooled to −75 °C. A stream of ozone (about 2.7 mmol/min) was bubbled through the stirred solution at −75 °C for 35 min. After the reaction was complete, the excess ozone was removed by bubbling oxygen through the mixture for 5 min, followed by nitrogen for 15 min. Approximately 25 mL (0.143 mol) of $P(OEt)_3$ was slowly added to the reaction mixture over 20 min while maintaining the temperature at <−65 °C. The resulting mixture was stirred for 1 h and poured into 105 mL of 5% aqueous hydrochloric acid. After 1 h agitation at 15−20 °C, the organic phase was separated and washed with 5% aqueous NaCl solution (2 × 250 mL). After removal of solvent, the residue was triturated with *n*-pentane to give a 90% yield of the 3-hydroxycephem product (**15**).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.01 (m, 2H); 2.30 (t, 2H); 2.53 (t, 2H); 3.27−3.45 (AB quartet, 2H, J = 17 Hz); 5.01 (d, 1H, J = 4.5 Hz); 5.71 (d of d, 1H, J = 4.5 Hz, J = 8.5 Hz); 6.37 (d, 1H, J = 8.5 Hz); 6.89−6.91 (s, 2H); 7.23−7.45 (br s, 20H); 11.68 (s, 1H).

Step C. Reduction to 3-Hydroxycepham. 3-Hydroxycephem product (**15**) (10.6 g, 0.016 mol) from Step B was dissolved in a mixture of 8.2 mL of glacial acetic acid, 90 mL of methanol, and 180 mL of methylene chloride. The resulting mixture was cooled to −55 °C. Sodium borohydride (1.84 g, 0.049 mol) was added, and reaction mixture was stirred at −50 °C for 20 min. After the reaction was complete, the reaction mixture was poured into a mixture of 300 mL of methylene chloride and 105 mL of 7% aqueous $NaHCO_3$ solution at room temperature and stirred for 15 min. The organic phase was washed with aqueous 5% NaCl solution (2 × 200 mL) and then concentrated in vacuo. Toluene (100 mL) was added, and the crystalline product was stirred at 5 °C for 12 h to give 7.4 g (70%) of the product (**18**).

^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.96 (m, 2H); 2.23 (t, 2H); 2.48 (t, 2H); 2.61−2.98 (AB of ABX, 2H, J_{AB} = 13.8 Hz, J_{AX} = 10.0 Hz, J_{BX} = 3.5 Hz); 3.32 (d, 1H, J = 7.8 Hz); 4.08 (m, 1H); 4.84 (d, 1H, J = 6.0 Hz); 5.07 (d, 1H, J = 4.0 Hz); 5.53 (dd, 1H, J = 9.0, 4.0 Hz); 6.51 (d, 1H, J = 9.0 Hz); 6.87−6.92 (s, 2H); 7.2−7.4 (br s, 20 H).

Step D. Mesylate Preparation. Product **18** (45.1 g, 0.068 mol) from Step C was suspended in methylene chloride (330 mL) at −20 °C under nitrogen. Methanesulfonyl chloride (9.3 g, 0.081 mol) was added slowly at −20 °C. A 1.2% solution of Et_3N (8.9 g, 0.088 mol) in CH_2Cl_2 was added over a period of 20 min with the temperature at <−20 °C and then warmed to −10 °C for 1 h. The resulting mixture containing the mesylate **19** was used for the next step as is. A small portion of reaction mixture was poured into a chilled aqueous NaCl solution. The organic phase was separated, washed with 5% aqueous NaCl, and then concentrated in vacuo. Methanol was added to crystallize the product **20**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.00 (m, 2H); 2.27 (t, 2H); 2.49 (t, 2H); 2.68 (s, 3H); 2.83−3.51 (AB or ABX, 2H, J_{AB} = 13.5 Hz, J_{AX} = 10.5 Hz, J_{BX} = 3.3 Hz); 5.04 (m, 2H); 5.25 (d, 1H, J = 4.4 Hz); 5.50 (dd, 1H, J = 4.4, 9.0 Hz); 6.55 (d, 1H, J = 9.0 Hz); 6.89−6.95 (s, 2H); 7.2−7.4 (br s, 20H).

Step E. Side-Chain Cleavage. The mesylate **20** from Step D (50.5 g, 0.068 mol based on **18**) in methylene chloride was cooled to −50 °C. Pyridine (10.7 g, 0.135 mol) and phosphorus pentachloride (24.0 g, 0.115 mol)) were gradually added followed by 1,5-cyclooctadiene (21.6 g, 0.20 mol). The reaction temperature was raised to −10 °C, and the stirring was continued for 2−3 h. Methanol (440 mL) was added very slowly while the temperature was maintained at <0 °C. The reaction mixture was stirred for 2 h at 0−5 °C. The slurry containing diphenylmethyl 7(*R*)-amino-3-methanesulfonyloxycepham-4-carboxylate (**21**) was used for the next step as is. A small portion of sample was treated with water and saturated aqueous Na_2CO_3 to adjust the pH to 7. The organic phase was separated and washed twice with aqueous 5% NaCl, then concentrated in vacuo. 2-Propanol was added, and the crystalline product was filtered and dried at 45 °C to give diphenylmethyl 7(*R*)-amino-3-methanesulfonyloxycepham-4-carboxylate **21**.

(13) Lawesson's reagent is made and used commercially in the manufacture of Quazepam. After completion of the thionation step the primary waste product, believed to be $[CH_3OC_6H_4P\bullet(S)O\bullet]_3$, is filtered and disposed of by incineration. When ammonia is used to quench the reaction, the primary waste is the diamide, $CH_3OC_6H_4P(S)(NH_2)_2$. This information kindly provided by Dr. B. Brady, Schering−Plough, (Avondale), Ireland.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.05 (s, 3H); 3.16−3.23 (AB of ABX, 2H, J_{AB} = 13.8 Hz, J_{AX} = 7.2 Hz, J_{BX} = 2.7 Hz); 4.93 (d, 1H, J = 4.3 Hz); 5.15 (d, 1H, J = 4.3 Hz); 5.20 (d, 1H, J = 5.7 Hz); 5.37 (m, 1H); 6.92 (s, 1H); 7.3−7.6 (br s, 10 H); 9.34 (br s, 2H).

Step F. Elimination. The slurry product **21** of Step E (0.068 mol based on **18**) was cooled to −10 °C. Diethylamine (47.0 g, 0.643 mol) was slowly added while keeping the temperature below −10 °C. The mixture was warmed to 10 °C and stirred for 3−4 h. After the reaction was complete, the resulting mixture was poured into 10% aqueous H_3PO_4 solution (200 mL). The organic phase was separated and washed sequentially with 5% aqueous NaCl, 10% aqueous $NaHCO_3$, and aqueous 5% NaCl. The methylene chloride was replaced by isopropyl acetate (200 mL) via distillation. The product crystals were filtered and washed with cold isopropyl acetate (50 mL) and dried at 50 °C to give 21 g (85% overall from **18**) of diphenylmethyl 7(*R*)-aminoceph-3-em 4-carboxylate (**6**). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.78 (br s, 2H); 3.41−3.59 (AB of ABX, 2H, J_{AB} = 19.3 Hz, J_{AX} = 6.4 Hz, J_{BX} = 2.7 Hz); 4.80−4.91 (d, 2H, J = 5.3 Hz); 6.63 (dd, 1H, J = 6.4, 2.7 Hz); 6.95 (s, 1H); 7.2−7.4 (br s, 10 H).

Step G. Alternative Elimination. Product **20** from Step D (12.4 g, 0.017 mol) in methylene chloride without isolation was cooled to −50 °C, and diethylamine (17.2 mL) was added. The mixture was warmed to −10 °C and stirred for 1 h. The cold reaction mixture was poured into 5% aqueous HCl solution (1.0 L), while the temperature was kept at <10 °C. The organic phase was washed with 5% aqueous NaCl, then combined with 500 mL of water and adjust to pH = 6.5 with 7% aqueous $NaHCO_3$. The aqueous phase was back extracted with methylene chloride. The organic phases were combined, washed with 5% aqueous NaCl, then concentrated in vacuo to give 8.6 g (78.9%) of bis(diphenylmethyl) 7(*R*)-glutaroylaminoceph-3-em-4-carboxylate **19** as a crystalline compound. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.03 (m, 2H); 2.27 (t, 2H); 2.53 (t, 2H): 3.38−3.59 (AB of ABX, 2H); 4.94 (d, 1H); 5.90 (dd, 1H); 6.14 (d, 1H); 6.66 (dd, 1H); 6.89−6.96 (s, 2H); 7.2−7.5 (br s, 20H).

Step H. Alternative Side Chain cleavage. Product **19** from Step G (13.2 g, 0.02 mol) was dissolved in 150 mL of methylene chloride and cooled to −50 °C. Pyridine (6.6 mL) and PCl_5 (8.5 g) were added. Methanol (150 mL) was then slowly added while maintaining the temperature at <0 °C. The resulting mixture was stirred for 2 h at −10 °C. Water (300 mL) was added and agitation continued at 0 °C for 2 h. Aqueous $NaHCO_3$ (7%) was added to adjust the pH to 6.5. The organic phase was separated and washed with 5% aqueous NaCl. The solvent was replaced with 2-propanol via vacuum distillation. After cooling the product was filtered and dried under vacuum at 45 °C to give 6.6 g (92.6%) of the title compound (**6**).

Preparation of Diphenylmethyl (*6R,7R*)-7-[(*E,Z*)-2-(2-Benzyloxycarbonylamino-4-thiazolyl)-4-(3-methyl-2-butenyloxycarbonyl)-2-butenoylamino]-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylate (9). To a 1-L three-neck round-bottom flask was added **6** (24.8 g, 67.7 mmol) in methylene chloride (400 mL), and side chain (*E,Z*)-2-(2-benzyloxycarbonylamino-4-thiazolyl)-4-(3-methyl-2-butenyloxycarbonyl)-2-butenoic acid (36.4 g, 84.6 mmol). The resulting solution was cooled to about −30 °C with stirring under nitrogen and thereto were added triethylamine (33.8 mL, 243 mmol) and then rapidly phosphoryl chloride (12.5 g, 81.5 mmol). The reaction temperature was allowed to warm to 10 °C. Stirring was continued for about 30 min, and the reaction mixture was poured into an aqueous (∼7%) sulfuric acid solution (120 mL). The organic layer was separated and washed with water (120 mL), an aqueous 2% sodium hydrogen carbonate solution (70 mL) containing about 7% sodium chloride and 1% tetra-*n*-butylammonium bromide, and water (100 mL) containing 15% 2-propanol. The aqueous layers were back-extracted with methylene chloride (120 mL). The combined organic layers were treated with activated carbon (10 g) and then filtered. The filtrate and washings were combined and concentrated to 100 mL. The slurry of product crystals was prepared by addition of isopropyl acetate (200 mL), by concentration to 180 mL to remove residual methylene chloride and, finally, by addition of 15 mL of isopropyl acetate and 250 mL of isopropyl alcohol. The resulting slurry was stirred at −5 to 0 °C for 12 h, filtered, and washed with a cold mixture of isopropyl acetate and 2-propanol (1:1, 200 mL). After drying, 48.5 g (92%) of product **9** was obtained.

Preparation of Crude Ceftibuten. A solution of anhydrous aluminum chloride (25.4 g, 190.6 mmol) in anisole (320 mL) was stirred in a 1-L three-neck round-bottom flask under nitrogen and treated with a solution of compound **9** (33 g, 42.2 mmol) in anisole (350 mL) at 10−30 °C over a period of 30 min. After stirring at 25 °C for 1 h, the reaction mixture was cooled to about −10 °C and poured into 2% aqueous hydrochloric acid solution (250 mL) while the temperature was kept below 15 °C. After stirring for 20 min the slurry was filtered, and the aqueous layer was separated and washed with 100 mL of isopropyl acetate. The organic layers were back-extracted with 2% hydrochloric acid (100 mL). The acid layers were combined and mixed with 25 mL of acetonitrile. The resulting solution was cooled to −5 °C and treated with malic acid (77 g) and acetic acid (35 g). The pH of the stirred mixture was adjusted to about 2.9−3.3 by addition of an aqueous (28%) sodium hydroxide solution (∼140 mL) maintaining the temperature below 35 °C. After stirring at 20−30 °C, the pH of the mixture was adjusted to about 2.9 by addition of 35% hydrochloric acid. The resulting slurry of crude Ceftibuten was stirred at 20 °C for 10 h to complete crystallization and then filtered. The product crystals were washed with water (50 mL) and acetonitrile (76 mL) to give crude Ceftibuten as wet crystals, which was subjected to further purification as described below.

Preparation of Ceftibuten Sulfate. A stirred mixture of the wet crystals of crude Ceftibuten, deionized water (15 mL), and acetonitrile (250 mL) in a 1-L three-neck round-bottom flask was treated with 75% sulfuric acid (7 mL) below 30 °C. After stirring below 20 °C for about 1 h, the resulting slurry was filtered, and the product crystals were washed with a cold (below 20 °C) solution of sulfuric acid (about 1%) in acetonitrile (50 mL). The wet crystals of

Ceftibuten sulfate thus obtained were used as-is in the final purification.

Preparation of Purified Ceftibuten 1. In a 1-L three-neck round-bottom flask the wet Ceftibuten sulfate was dissolved in a mixture of water (130 mL), sodium hydrogen carbonate (15 g), and acetonitrile (30 mL) below 30 °C. Thereto were added activated alumina (8 g) and activated carbon (1 g). After stirring for 60 min, the resulting mixture was pressure-filtered, and the filter cake washed with water. The combined filtrate and washings were poured into a mixture of aqueous sulfuric acid (9%, 100 mL) and acetonitrile (120 mL) at 20 °C. The resulting mixture was adjusted to about pH 3 by the addition of aqueous potassium carbonate (30%, 150 mL) over 15 min. After stirring at 20 °C for about 30 min, the slurry was filtered and the product crystals were washed with water (150 mL). The wet crystals were dried at 45 °C in a vacuum-dryer to give 15 g of desired product **1**. The overall yield from **6** to **1** was about 76%. Purity (HPLC, anhydrous basis), 99.6%. The total heavy metals content was <10 ppm.

Preparation of Diphenylmethyl 7(*R*)-Amino-3-chloroceph-3-em-4-carboxylate HCl Salt (7). *Step I. Generation of the Dichlorotriphenyl Phosphite Amylene-Stabilized Reagent.* To a 5-L four-neck flask equipped with a thermometer, nitrogen purge, agitator, addition funnel, and dry ice−acetone bath, was added 1.4 L of methylene chloride and 12.9 mL of pyridine (0.16 M, 15% of total). The solution was cooled to −35 to −25 °C. Chlorine gas (95 g, 1.33 mol) was bubbled into the solution slowly at a rate of 3 g/min while maintaining the temperature at −20 °C. Triphenyl phosphite (320 mL, 1.22 mol) was added as quickly as possible, maintaining the temperature of the solution between −10 to −15 °C. A final light green to yellow solution was obtained. The mixture was then cooled to −25 to −30 °C. Amylene (59 mL, 0.55 mol) was added slowly, maintaining the temperature below −20 °C. The resulting dichlorotriphenyl phosphite amylene stabilized reagent (1.86 L) was stored at −20 to −25 °C.

*Step II: Conversion of **5** to Diphenylmethyl 7(R)-Amino-3-chloroceph-3-em-4-carboxylate Hydrochloride (7).* To a 2-L four-neck flask equipped with a thermometer, nitrogen purge, agitator, addition funnel, and dry ice−acetone bath, was added two-seventh the volume of the reagent generated in Step I (0.377 mol) with constant stirring while maintaining the batch temperature below −30 °C. Compound **5** (61 g, 0.09 mol) was added to the solution and the batch temperature was allowed to rise to −10 °C with the exothermic reaction. The reaction mixture was then stirred at −10 to −15 °C for 20 min. A solution of pyridine (21 mL, 0.26 mol) in methylene chloride (60 mL) was added over a 60 min period at −10 to −15 °C. The resulting mixture was stirred at −10 to −15 °C for 15 min, and isobutyl alcohol (75 mL, 0.4 mol) was added, while maintaining the batch temperature below −3 °C. After 1 h stirring at −15 °C, dry hydrochloric acid gas was the bubbled into the reaction mixture. The resulting slurry was stirred at 20−30 °C for 1 h. The crystalline product was filtered, washed with 100 mL of methylene chloride and dried at 40 °C in a vacuum oven to give 33.4 g (85%) of the cefaclor nucleus HCl salt (**7**).

Preparation of Bis(diphenylmethyl) 3-Chloro-7(*R*)-glutaroylaminoceph-3-em-4-carboxylate (16). To a solution of 135.4 g of the compound **5** (0.2 mol) in 1.1 L of *N*,*N*-dimethylformamide at −50 to −55 °C was added slowly 98.1 g of phosphorus trichloride (0.7 mol). The reaction mixture was left under stirring at −55 °C for 1 h and at room temperature for 4 h. After the reaction was complete, the mixture was poured into a solution of 0.75 L of 5% hydrochloric acid while maintaining the temperature below 10 °C. The suspension was extracted with methylene chloride (2 × 1 L), and the combined organic extracts were washed with 5% hydrochloric acid solution (0.5 L) followed by a sodium carbonate buffer (1 L) at pH 6.5. The organic phase was treated with Darco and Celite and then filtered. The resulting solution was concentrated to remove water which was replaced with 1.3 L of methanol. After stirring at 0−5 °C for 1 h, the light yellow crystalline product was isolated via filtration and dried under vacuum at 45−50 °C. Product **16** (92.4 g, 68%) was obtained. The product purity (HPLC) was >95%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.97 (m, 2H), 2.24 (t, 2H), 2.48 (t, H), 3.41−3.71 (ABq, 2H, J = 19.0, 1.0), 4.98 (d, 1H, J = 5.0 Hz), 5.81 (dd, 1H, J = 9.0, 3.0 Hz), 6.45 (d, 1H, J = 9.0 Hz), 6.89 (s,), 6.99 (s, 1H), 7.23−7.45 (m, 20H).

Alternative Preparation of Bis(diphenylmethyl) 3-Chloro-7(*R*)-glutaroylaminoceph-3-em-4-carboxylate (16). To a solution of compound **5** (135.4 g, 0.2 mol) was added two-seventh the volume of the reagent generated in Step I (0.377 mol) with constant stirring while maintaining the batch temperature below −30 °C. Compound **5** (61 g, 0.09 mol) was added to the solution, and the batch temperature was allowed to rise to −10 °C with the exothermic reaction. The reaction mixture was then stirred at −10 to −15 °C for 20 min. A solution of pyridine (21 mL, 0.26 mol) in methylene chloride (100 mL) was added over a 60 min period at −10 to −15 °C. The resulting mixture was stirred at −10 to −15 °C for 15 min, and water (75 mL) was added, while maintaining the batch temperature below −3 °C. After 1 h stirring at 5 to 10 °C, the organic layer was separated. The aqueous layer was extracted with methylene chloride (2 × 500 mL). The organic phase was treated with Darco and Celite and then filtered. The resulting solution was concentrated to remove water which was replaced with 1.1 L of methanol. After stirring at 0 to 5 °C for 1 h, the light yellow crystalline product was isolated via filtration and dried under vacuum at 45 to 50 °C. The yield of the product was 92%. The product purity (HPLC) was >97%.

Preparation of Bis(diphenylmethyl) 7(*R*)-Glutaroylaminoceph-3-em-4-carboxylate (19a). Compound **16** (32.2 g, 0.047 mol) was dissolved in methylene chloride (300 mL). Acetic acid (600 mL) was added followed by freshly activated zinc powder (80.5 g, 1.23 mol). The mixture was stirred at room temperature for 3 h until the reduction was complete. The mixture was then filtered, and water (400 mL) was added. The organic layer was separated. The aqueous layer was extracted with methylene chloride (2 × 200 mL). The combined organic layers were washed with water (2 × 250 mL) and brine (250 mL). The solvent was replaced with

2-propanol (210 mL) via distillation. The resulting crystals were stirred at 5 °C for 2 h, then filtered, and dried at 50 °C under vacuum to give the desired product **19a** (26 g, 85%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.84 (m, 2H), 2.29 (m, 2H), 2.51 (m, 2H), 3.67 (ABq, 2H), 5.10 (d, 1H, J = 4.96 Hz), 5.81 (dd, 1H, J = 8.25, 4.96 Hz), 6.79 (m, 1H), 6.82 (s, 1H), 6.94 (s, 1H), 7.36 (m, 16H), 7.50 (d, 2H, J = 8.0 Hz), 7.59 (d, 2H, J = 8.0 Hz), 8.96 (d, J = 8.24 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.4, 173.4, 166.6, 162.1, 142.3, 142.2, 121.7, 130.5, 129.7, 129.6, 128.5, 128.3, 127.8, 124.2, 79.4, 77.6, 60.5, 58.4, 34.8, 34.0, 24.7, 21.5.

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