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An alternative procedure for preparation of cefdinir

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Abstract

Cefdinir, a broad spectrum third-generation cephalosporin for oral administration, was prepared by the following synthetic pathway: synthesis of diphenylmethyl 7β-amino-3-vinyl-3-cephem-4-carboxylate hydrochloride from 7-aminocephalosporanic acid (7-ACA), preparation of sodium 2-(2-tritylaminothiazol-4-yl)-(*Z*)-2-(tritylhydroxyimino) acetate from ethyl acetoacetate, coupling of both intermediaries to obtain diphenylmethyl 7β-[2-(2-tritylaminothiazol-4-yl)-(*Z*)-2-tritylhydroxyimino-3-vinyl-3-cephem-4-carboxylate and final cleavage of trityl and diphenylmethyl protective groups. This procedure allows to obtain better yields of cefdinir and to avoid the use of diketene during the synthesis of this antibiotic by the previously reported method.

Keywords: Cephalosporins; 7-Aminocephalosporanic acid; Cefdinir; Synthesis

1. Introduction

Cefdinir (Fig. 1) is a new orally effective semisynthetic cephalosporin with an extended antibacterial spectrum, which was found to be active against Gram-positive and Gram-negative bacteria, and demonstrated advantages in the antimicrobial activity over the currently available oral cephalosporins cefixime, cefpodoxime proxetil, cefaclor and cephalexin [1–4]. Cefdinir is different to other oral cephalosporins by virtue of its high activity against oxacillin-susceptible staphylococci while maintaining potency against streptococci and Gram-negative bacterial agents of community-acquired infection [2]. This antibiotic has been used in the treatment of respiratory and urinary tract infections and also in the treatment of skin structure infections [5–12].

Structurally, cefdinir is characterized by a vinyl group at C-3 position and a (*Z*)-2-(2-aminothiazol-4-yl)-2-(hydroxyimino)acetyl moiety at C-7 position which result in a marked increase in its antimicrobial activity against Gram-positive and Gram-negative bacteria and also enhance its pharmacokinetic properties [13].

The best current synthetic method to prepare cefdinir is outlined in Scheme 1. This method is characterized by the fact that (*Z*)-2-(2-aminothiazol-4-yl)-2-(hydroxyimino)acetyl moiety is constructed directly over the cephalosporanic nucleus [14,15]. This synthetic pathway has few reaction steps and allows to obtain relatively good overall yields (ca. 11.3% from 7-ACA). However, it has a relevant drawback: the necessity to prepare the 4-bromoacetoacetyl bromide by reaction of bromine with diketene, a highly toxic and difficult to handle reagent.

Although not used before to obtain cefdinir, there is another general synthetic route to prepare (*Z*)-2-(2-aminothiazol-4-yl)-2-(hydroxyimino)acetamido 3-acetoxymethyl or 3-propenyl cephalosporins, which consists in synthesizing an intermediary carrier of the (*Z*)-2-(2-aminothiazol-4-yl)-2-(hydroxyimino)acetyl moiety, which is further coupled to the 3-acetoxymethyl or 3-propenyl cephem nucleus [16,17]. The objective of the present paper is to show the results obtained during the synthesis of cefdinir trough this method. This procedure allows to overcome the drawback of the use of diketene during the synthesis of cefdinir by to the first method described (Scheme 1).

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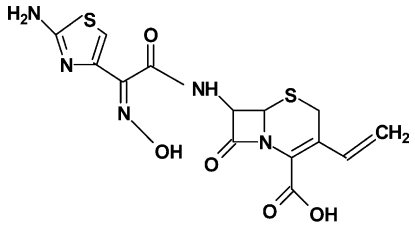


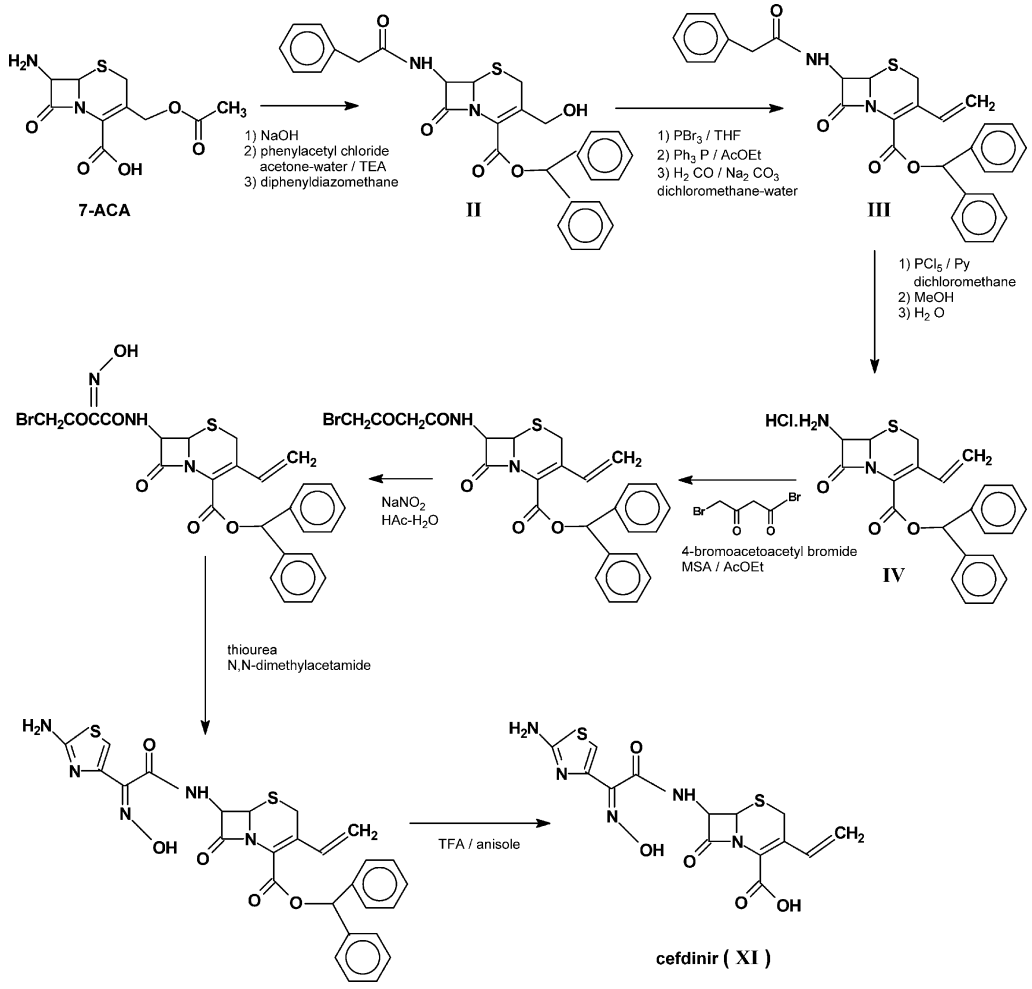
Fig. 1. Chemical structure of cefdinir.

2. Results and discussion

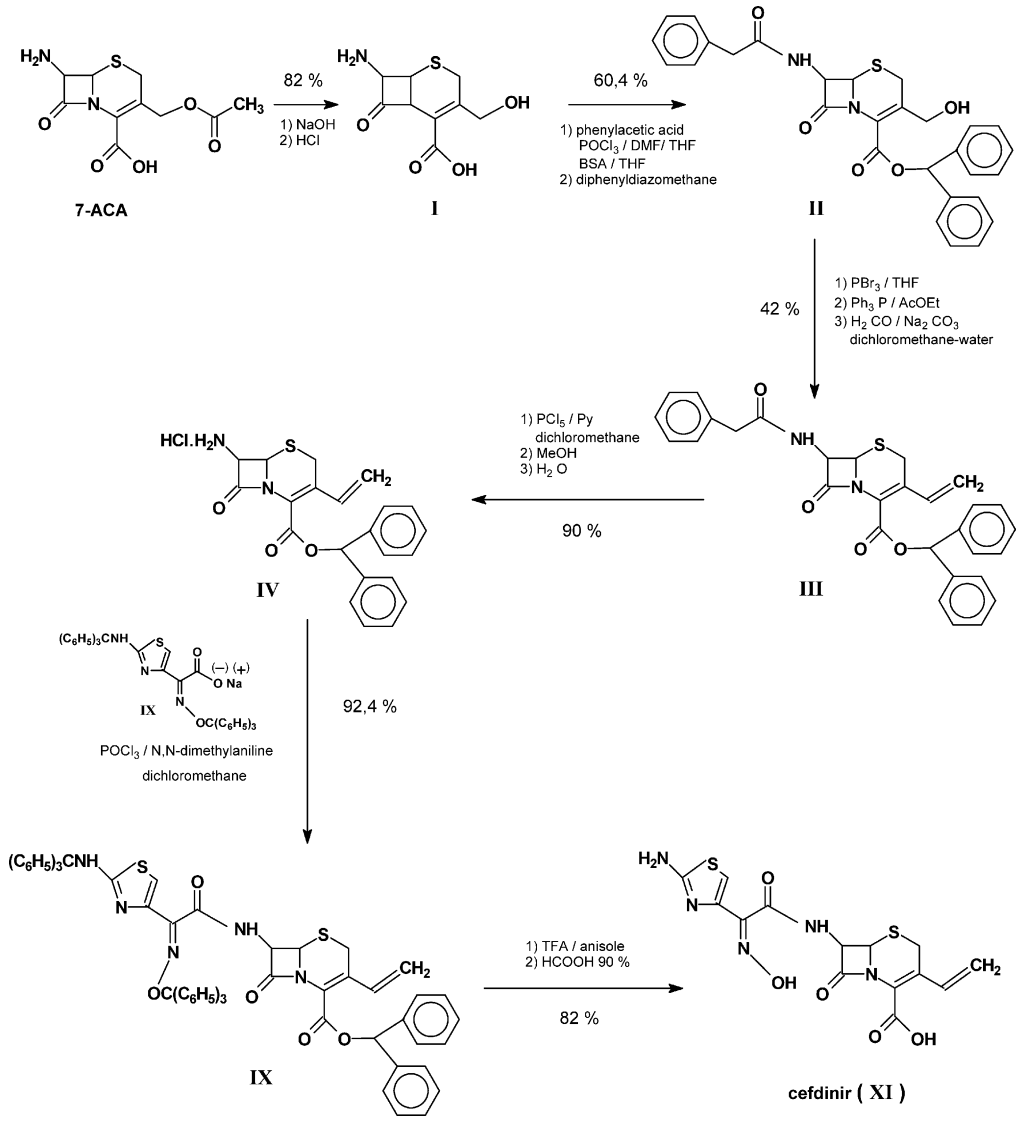
2.1. The proposed synthetic route is as follows (Scheme 2)

The compound carrier of the 3-vinyl modified cephem nucleus (**IV**) was synthesized in three steps from 7-ACA. The most critical step is the one corresponding to the synthesis of derivative II. According to the method reported in the literature consulted [18], basic hydrolysis of 7-ACA is effected with sodium hydroxide in aqueous media and the 3-hydroxymethyl derivative (**I**) formed is not isolated from the reaction mixture. The 7β-amino group is then protected by acylation with phenylacetyl chloride in aqueous acetone according to Schotten-Baumann's procedure and by keeping an almost neutral pH with triethylamine (TEA). Finally, the acid function of cephem nucleus is blocked by treating it with diphenyldiazomethane to afford **II**. When this process was repeated in our laboratory, we found that only 32% yield of **II** could be obtained. Thin layer chromatography (TLC) analysis at the end of the phenylacetylation reaction revealed the presence of three spots, one of them corresponding to the desired phenylacetamido derivative and the others probably owing to the phenylacetyl ester and diphenylacetyl derivative of **I**. This fact, together with the partial decomposition of phenylacetyl chloride in aqueous media, may be the causes of the low yields obtained.

To overcome the problems cited above, two methods were developed for preparing **II** characterized by the



Scheme 1. Synthesis of cefdinir according to the method reported in the literature.



Scheme 2. Synthetic pathway used to prepare cefdinir.

fact that the protection of 7β-amino group was achieved in totally organic media and the 3-hydroxymethyl group was blocked in order to avoid the formation of the phenylacetylated by-products.

In consequence, it was necessary to isolate the 3-hydroxymethyl derivative (**I**) after basic hydrolysis of the acetoxy group of 7-ACA. This process was performed by treating 7-ACA with sodium hydroxide in a mixture of methanol–water at temperatures between −10 and −20 °C, followed by adjusting the reaction mixture to pH 3 in order to precipitate **I** which was obtained in good yields (82%).

In the first method developed, **I** was dissolved in *N*,*N*-dimethylacetamide by treatment with *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and the phenylacetylation of the 7β-amino group was achieved by reaction with phenylacetyl chloride. In the second procedure, **I** was dissolved in tetrahydrofuran (THF) by reaction with BSA and phenylacetylation was performed with the phenylacetic acid activated by the Vilsmeier reagent. In both cases, TLC analysis of the reaction mixture revealed the presence of only one spot corresponding to the desired phenylacetamido derivative. It was evident that the protection of 3-hydroxymethyl group as the corresponding trimethylsilyl ether with BSA avoided the formation of the phenylacetyl ester. On the other hand, the absence of water in the reaction media reduced the decomposition of the acylating agents and allowed to obtain better yields, as can be observed in Table 1.

The best results were obtained when phenylacetylation was effected by activating phenylacetic acid with Vilsmeier reagent and in consequence this procedure was selected for the preparation of **II**.

Compound **III** was synthesized by means of the Wittig reaction according to the method reported in the literature consulted [19]. **II** was reacted with phosphorous tribromide in THF to obtain the 3-bromomethyl derivative, followed by treatment with triphenylphosphine in ethyl acetate to afford the corresponding phosphonium salt. Further reaction of this salt with aqueous formaldehyde in the presence of sodium carbonate as a base allowed to obtain **III** with 42% yield.

The phenylacetamido protective group of **III** was cleaved by the known iminochloride method [19–21]. Treatment of **III** with a phosphorous pentachloride-pyridine mixture in dichloromethane, followed by a reaction with methanol and a final hydrolysis of the imino ether, afforded **IV** in very good yields (90%).

Although it was necessary to introduce an additional step during the synthesis of **IV**, the overall yield obtained from 7-ACA was 18.9%, that is to say a yield ca. 9% higher than the reported in the literature consulted (11.8%) when the preparation of **II** was performed without isolating the 3-hydroxymethyl derivative (**I**).

The second part of the proposed synthetic pathway to prepare cefdinir, was the synthesis of the protected intermediary **IX** which carries the (*Z*)-2-(2-aminothiazol-4-yl)-2-(hydroxyimino)acetyl moiety that characterizes this antibiotic.

The method for preparing **IX** has been previously described [16,22,23] while obtaining other cephalosporins and is outlined in Scheme 3.

The oxime **V** is obtained from ethyl acetoacetate by treatment with sodium nitrite in acetic acid. The methyl group of **V** is then halogenated with sulfuryl chloride to prepare **VI**. Reaction of the derivative **VI** with thiourea afforded the 2-aminothiazol ring according to the conditions of Hantzch's method. In the next step the amino and the hydroximino groups of **VII** are simultaneously protected by treatment with trityl chloride to give compound **VIII**. Finally, the basic hydrolysis of the ester group of **VIII** occurs in the presence of sodium hydroxide to obtain **IX**.

The most critical step in the sequence of reactions is the formation of the 2-aminothiazol ring during the preparation of compound **VII**. In the analyzed literature two methods are reported to prepare **VII** from **VI**. In the first one, **VI** is treated with thiourea in ethanol and in the presence of *N*,*N*-dimethylaniline as a base [23]. In the second one, no base is used and the solvent employed is a mixture of ethanol–water [22]. Although the formation of oxime **V** and synthesis of the halogenated derivative **VI** occur in almost quantitative yields when both procedures were used, poorly overall yields of **VII** were obtained.

To overcome the drawback cited above, two methods were developed in the present work in order to synthesize **VII** from **VI** by reaction with thiourea. In the first procedure developed, **VI** was treated with thiourea by using a mixture of THF–water as solvent and sodium acetate as basic catalyst, while in the second one, *N*,*N*-dimethylacetamide was used as a solvent without addition of any basic catalyst. Both synthetic variants allowed to obtain better yields than the previously reported as can be observed from Table 2.

The best results were obtained when the reaction was effected in *N*,*N*-dimethylacetamide as a solvent without using any catalyst. In consequence, this procedure was selected for the preparation of **VII**.

In the following step amino function and hydroxyimino group of **VII** were simultaneously blocked by treatment with trityl chloride in chloroform and in the presence of TEA as an acceptor of the hydrogen chloride formed. The protection of both functional groups are necessary in order to avoid side reactions during the further acylation of cephalosporanic nucleus. The protected intermediary **VIII** was obtained in 52.2% yield as reported in the literature consulted.

Finally, the ester group of **VIII** was hydrolyzed by treatment with sodium hydroxide in a mixture of dioxane–water as a solvent affording the corresponding sodium salt **IX** in 97.6% yield.

In the last part of the synthesic pathway used, the compound carrier of the (*Z*)-2-(2-aminothiazol-4-yl)-2-(hydroxyimino)acetyl moiety (**IX**) was coupled to the modified cephem nucleus (**IV**) to obtain the protected derivative **X**, and in the next step all the protective groups were removed to prepare cefdinir (**XI**).

Usually (during the synthesis of other cephalosporins) the acylation of the cephem nucleus is performed with the compound **IX** in its free acid form, and by formation of a reactive derivative such as an acid chloride, an active ester, a mixed anhydride, etc. It means that sodium salt **IX** has to be transformed into the corresponding free acid by treatment with dilute hydrochloric acid in the presence of an organic solvent such as ethyl

Table 1
Yields of II obtained through the developed procedures in comparison with the reported method.

Acylating agent	Catalyst	Reaction solvent	From **I** (%)	From 7-ACA (%)
Phenylacetyl chloride	TEA	acetone–water		32
Phenylacetyl chloride	BSA	*N*,*N*-dimethylacetamide	51.9	42.6
Phenylacetic acid	BSA	THF	60.4	49.6

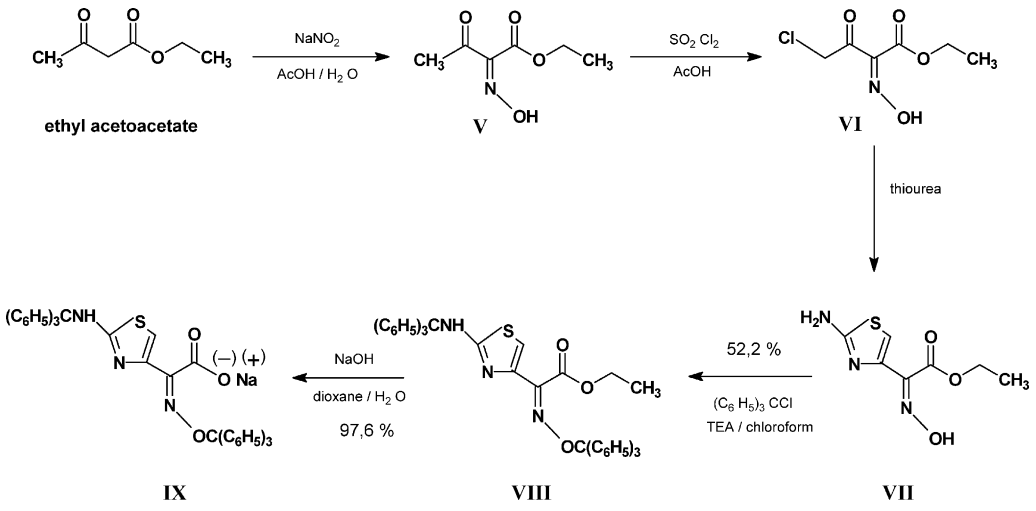


Table 2
Results obtained during the synthesis of **VII**

Solvent	Catalyst	Yield of **VII** (%) (from ethyl acetoacetate)
ethanol	*N*,*N*-dimethylaniline	15.1
ethanol–water	none	17.2
THF–water	sodium acetate	26.1
N,*N*-dimethylacetamide	none	36.9

acetate [24] or dichloromethane [16,22]. We found that this apparently simple step causes a lot of trouble because partial desprotection of the amino function of **IX** occurs. In consequence difficult to break emulsions are formed and reduced yields of the free acid are obtained.

In order to overcome the problems cited above, in the present work a method was developed which allowed to perform the acylation reaction directly with the sodium salt **IX**. It is known that a reaction of carboxylic acid salts with phosphorous oxychloride produces the corresponding acid chloride. In this case a mixture of the cephem nucleus (**IV**) and compound **IX** in the presence of *N*,*N*-dimethylaniline was treated with phosphorous oxychloride to generate in situ the acid chloride of **IX** as acylating agent. The acylation of **IV** occurred in a short time and the protected derivative **X** was obtained in very good yields (92.4%).

The final step to prepare cefdinir was the cleavage of protective groups of **X**. The trityl protective group of amino function and the diphenylmetyl group were removed by treating **X** with trifluoroacetic acid (TFA) in the presence of anisol as cation scavenger. The trityl protective group of oxyimino moiety was further cleaved with 90% formic acid to afford cefdinir (**XI**) in 82% yield (calculated from **X**).

Although the procedure used in the present work has more synthetic steps, the overall yield of cefdinir (calculated from 7-ACA) was 14.3%, that is to say, higher than the reported when the best current procedure is employed (11.3%) to prepare this antibiotic.

3. Experimental

Melting points (m.p.) were determined using the Gallenkamp capillary apparatus with a system of measurement and temperature control. ^{1}H NMR and ^{13}C NMR spectra were recorded at 250 and 62.5 MHz, respectively, on a Bruker AC 250F spectrometer, using deuterated dimethylsulfoxide (DMSO-d_6) as solvent and tetramethylsilanne (TMS) as an internal standard.

TLC was performed on pre-coated plates of silica gel GF-254 (Merck). In the development of chromatograms four mobile phases were used; (FM A) ethyl acetate–*n*-hexane (4:1); (FM B) ethyl acetate–ethanol–water–formic acid (60:25:15:1); (FM C) ethyl acetate–methanol (8:1) and (FM D) *n*-hexane–ethyl acetate (3:1). The chromatograms were visualized in a Camag UV–Vis lamp with a wavelength of 254 nm.

The synthesis of each compound was confirmed by comparison of registered ^{1}H NMR spectra with the ^{1}H NMR data reported in the literature consulted.

The base structures of the synthesized compounds are shown in Fig. 2, with an arbitrary numeration of carbon atoms, in order to support the assignment of ^{13}C NMR chemical shifts given below for each compound. Chemical shifts of aromatic carbon atoms corresponding to diphenylmethyl and trityl protective groups are not reported.

3.1. Diphenyldiazomethane

Benzophenone hydrazone (10.78 g, 55 mmol) and iodine (2.2 ml, 1% W/V) were dissolved in *N*,*N*-dimethylacetamide (55 ml) and water (5 ml). A solution of chloramine T (15.5 g, 55 mmol) in *N*,*N*-dimethylacetamide (55 ml) and water (5 ml) was then added slowly over 30 min at 20 °C. The mixture was stirred for 15 min before partition between dichloromethane (110 ml) and 5% sodium hydroxide aqueous solution (275 ml). The organic layer was washed with water (1 × 100 ml and 3 × 50 ml), dried over anhydrous sodium sulfate and made up to 200 ml in a volumetric flask with dichloromethane.

3.2. Quantitative determination of diphenyldiazomethane

Diphenyldiazomethane solution (10 ml) was exactly measured and the solvent was evaporated until dryness at reduced pressure. The obtained residue was dissolved with 10 ml of 1,2-dichloroethane, cooled down to 0–5 °C and glacial acetic acid was added until the total fading of the breakup. The content of diphenyldiazomethane was determined by measurement of the nitrogen volume that came off during the reaction to afford 8.70 g (81.53%) of diphenyldiazomethane.

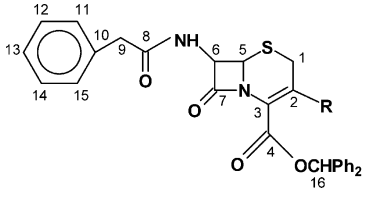
3.3. β-Amino-3-hydroxymethyl-3-cefem-4-carboxylic acid (*I*)

7-ACA (9.0 g, 33 mmol) was suspended in methanol (60 ml), water (60 ml) was added and the mixture was cooled to −20 °C. A 10 M sodium hydroxide aqueous solution (7 ml) was then added slowly and the resulting solution was stirred for 25 min between −10 and −20 °C. The solution was adjusted to pH 3 by addition of concentrated hydrochloric acid at 0–5 °C. The precipitated solid was separated by vacuum filtration, washed successively with methanol (30 ml), acetone (30 ml) and diethyl ether (2 × 30 ml), and dried to obtain **I** (6.24 g, 82%).

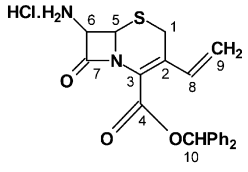
3.4. Diphenylmethyl 7β-phenylacetamido-3-hydroxymethyl-3-cephem-4-carboxylate (*II*)

3.4.1. Acylation with phenylacetyl chloride in aqueous-organic media (method reported in the literature)

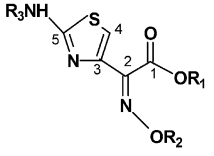
A solution of sodium hydroxide (5.2 g, 130 mmol) in water (26 ml) was added to a stirred suspension of 7-ACA (16.0 g, 59 mmol) in water (64 ml) during 5 min to keep the reaction temperature between 2 and 5 °C under cooling in an ice bath. After stirring for 5 min at this temperature, the reaction solution was adjusted to pH 8.5 with glacial acetic acid and diluted with acetone (48 ml). A solution of phenylacetyl chloride (11.0 g, 71 mmol) in acetone (11 ml) at 0–5 °C was dropwise added to the solution, keeping the pH between 7.5 and 8.5 with triethylamine (TEA) (~ 13 ml). The reaction mixture was stirred for 1 h at the same temperature and then concentrated in vacuo to remove the organic solvent. Ethyl acetate (220 ml) was added to the resulting solution and the stirred mixture was acidified to pH 3.5 with 6 M hydrochloric acid (~ 10 ml). The aqueous layer was further extracted with ethyl acetate (100 ml). The combined organic layers were washed with brine (80 ml), dried over anhydrous sodium sulfate and filtered. A solution of diphenyldiazomethane (13.77 g, 71 mmol) in ethyl acetate (50 ml) was added to the filtrate and the mixture was stirred for 1 h at room temperature (r.t.). The reaction solution was concentrated to a volume of



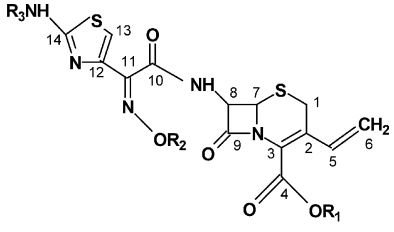
Base structure for compounds II and III



Compound IV



Base structure for compounds VII, VIII and IX



Base structure for compounds X and XI

Fig. 2. Base structures for compounds **II**, **III**, **IV**, **VII**, **VIII**, **IX**, **X** and **XI**.

ca. 50 ml and then cooled to 0–5 °C during 12 h. The resulting white precipitate was collected by vacuum filtration, washed successively with ethyl acetate (3 × 25 ml), *n*-hexane (3 × 25 ml) and dried to give **II** (9.7 g, 32%). TLC (FM A) 0.26 and 0.60; m.p. 178–180 °C; ^{1}H and NMR (DMSO-d_6) δ (ppm): 3.52 and 3.57 (2H, ABq, CH_2CO); 3.63 (2H, s, H-2); 4.23 (2H, d, CH_2OH); 5.12 (1H, d, H-6); 5.18 (1H, t, OH); 5.73 (1H, dd, H-7); 6.91 (1H, s, $CHPh_2$); 7.20-7.55 (15H, m, aromatics); 9.14 (1H, d, NH); ^{13}C NMR (DMSO-d_6) δ (ppm): C-1 25.51; C-2 134.40; C-3 121.95; C-4 160.83; C-5 57.66; C-6 58.86; C-7 165.17; C-8 170.92; C-9 41.54; C-10 135.75; C-11 128.95; C-12 126.71; C-13 128.16; C-14 126.71; C-15 128.95; C-16 78.29; C-17 59.72.

3.4.2. Acylation with phenylacetyl chloride in organic media

N,*O*-bis(Trimethylsilyl)acetamide (BSA) (16 ml, 57.8 mmol) was added to a suspension of **I** (5.0 g, 21.7 mmol) in *N*,*N*-dimethylacetamide (50 ml) and the mixture was stirred for 30 min at r.t. The resulting solution was cooled to −30 °C, phenylacetyl chloride (3.5 ml, 26.4 mmol) was added over 10 min and the mixture was stirred for 90 min between −10 and −20 °C. The reaction mixture was poured into ice-water (200 ml) and extracted with ethyl acetate (100 ml). The aqueous layer was further extracted with ethyl acetate (45 ml). The combined organic layers were washed with brine (35 ml), dried over anhydrous sodium sulfate and filtered. A solution of diphenyldiazomethane (5.12 g, 26.4 mmol) in ethyl acetate (25 ml) was added to the filtrate and the mixture was stirred for 1 h at r.t. The reaction solution was concentrated to a volume of ca. 25 ml and then cooled to 0–5 °C during 12 h. The resulting white precipitate was collected by vacuum filtration, washed successively with ethyl acetate (3 × 15 ml), *n*-hexane (3 × 15 ml) and dried to give **II** (5.81 g, 42.6% from 7-ACA).

3.4.3. Acylation with phenylacetic acid activated by Vilsmeier reagent

Phosphorous oxychloride (3.3 ml, 36 mmol) at 0–5 °C was dropwise added to a mixture of *N*,*N*-dimethylformamide (DMF) (2.7 ml, 35 mmol) and tetrahydrofuran (THF) (30 ml) under stirring, and the mixture was stirred at this temperature for 30 min to prepare the Vilsmeier reagent. phenylacetic acid (4.33 g, 31.8 mmol) was added to the above solution under ice-cooling, and the reaction mixture was stirred at the same temperature for 1 h to prepare an activated solution of phenylacetic acid.

BSA (24 ml, 98.16 mmol) was added to a suspension of **I** (7.33 g, 31.87 mmol) in THF (70 ml) and the mixture was stirred for 15 min at 40 °C. The above activated phenylacetic acid solution was added to the obtained solution (cooled to −30 °C) and the mixture was stirred at −20 °C for 1 h. The reaction mixture was poured into ice-water (200 ml) and extracted with ethyl acetate (145 ml). The aqueous layer was further extracted with ethyl acetate (65 ml). The combined organic layers were washed with brine (50 ml), dried over anhydrous sodium sulfate and filtered. A solution of diphenyldiazomethane (7.42 g, 26.4 mmol) in ethyl acetate (35 ml) was added to the filtrate and the mixture was stirred for 1 h at r.t. The reaction solution was concentrated to a volume of ca. 35 ml and then cooled to 0–5 °C during 12 h. The resulting white precipitate was collected by vacuum filtration, washed successively with ethyl acetate (3 × 25 ml), *n*-hexane (3 × 25 ml) and dried to give **II** (6.76 g, 49.6% from 7-ACA).

3.5. Diphenylmethyl 7β-phenylacetamido-3-vinyl-3-cephem-4-carboxylate (*III*)

Phosphorous tribromide (1.88 g, 6.98 mmol) was dropwise added to a suspension of **II** (9.7 g, 18.9 mmol) in THF (38 ml) at −5 °C with stirring. After being stirred at this temperature for 20 min, the reaction mixture was poured into ice-water (56 ml), and extracted with ethyl acetate (38 ml). The separated organic layer was washed with brine (10 ml), dried over anhydrous sodium sulfate, filtered and evaporated in vacuo. The residue was dissolved in ethyl acetate (38 ml) and triphenylphosphine (5.94 g, 22.56 mmol) was added. After stirring at r.t. for 5 h, the precipitated phosphonium salt was collected by filtration, washed with ethyl acetate (3 × 15 ml) and dried. Thirty-seven percent aqueous formaldehyde (62.7 ml, 752 mmol) and a solution of sodium carbonate (7.97 g, 75.2 mmol) in water (30 ml) were added to a solution of the phosphonium salt in dichloromethane (90 ml) at r.t. After being stirred at this temperature for 90 min, the reaction mixture was neutralized with 20% sulfuric acid (∼32 ml). The separated organic layer was washed with brine (25 ml), dried over anhydrous sodium sulfate, filtered and evaporated in vacuo until dryness. The residue was stirred with methanol (30 ml) for 1 h and the obtained solid was separated by filtration, washed with methanol (3 × 10ml) and dried to afford **III** (4.04 g, 42%). TLC (FM B) 0.89; m.p. 188–189 °C; ^{1}H NMR (DMSO-d_6) δ (ppm): 3.52 and 3.58 (2H, ABq, $PhCH_2CO$); 3.61 and 3.94 (2H, ABq, H-2); 5.20 (1H, d, H-6); 5.30 (1H, d, $=CH_2$ (*cis*)); 5.66 (1H, d, $=CH_2$ (*trans*)); 5.77 (1H, dd, H-7); 6.72 (1H, dd, CH=); 6.96 (1H, s, $CHPh_2$); 7.20–7.50 (15H, m, aromatics); 9.21 (1H, d, NHCO); ^{13}C NMR (DMSO-d_6) δ (ppm): C-1 23.24; C-2 127.84; C-3 123.77; C-4 160.89; C-5 57.86; C-6 59.13; C-7 165.09; C-8 170.90; C-9 41.52; C-10 135.75; C-11 128.94; C-12 126.75; C-13 128.49; C-14 126.75; C-15 128.94; C-16 78.46; C-17 131.24; C-18 118.61.

3.6. Diphenylmethyl 7β-amino-3-vinyl-3-cephem-4-carboxylate hydrochloride (**IV**)

Pyridine (1.9 g, 24 mmol) was added to a suspension of phosphorous pentachloride (4.95 g, 23.8 mmol) in dichloromethane (48 ml) under ice-cooling, and the suspension was stirred at this temperature for 1 h. Then, **III** (4.04 g, 7.9 mmol) was added and the reaction mixture was stirred for 90 min keeping the temperature between 8 and 10 °C. The mixture was cooled to −35 °C, methanol (31.7 ml, 782 mmol) was added and the resulting solution was stirred between −10 and −20 °C for 75 min. The temperature was raised to −5 °C and water (6.3 ml) was added. After removing the solvent in vacuo, the residue was stirred with a mixture of water (1.6 ml) and diethyl ether (16 ml). The resulting precipitate was collected by vacuum filtration, washed successively with water (10 ml) and diethyl ether (10 ml), and dried to give **IV** (3.05 g, 90%) TLC (FM A) 0.47; m.p. 170–171 °C; ^{1}H NMR (DMSO-d_6) δ (ppm): 3.75 and 4.00 (2H, ABq, H-2); 5.24 (1H, d, H-6); 5.33 (1H, d, H-7); 5.44 (1H, d, =CH_2 (*cis*)); 5.81 (1H, d, =CH_2 (*trans*)); 6.93 (1H, dd, CH=); 6.95 (1H, s, $CHPh_2$); 7.25–7.52 (10H, m, aromatics); ^{13}C NMR (DMSO-d_6) δ (ppm): C-1 23.71; C-2 132.67; C-3 123.77; C-4 160.37; C-5 54.80; C-6 57.94; C-7 160.58; C-8 130.68; C-9 120.74; C-10 78.41.

3.7. Ethyl 2-(2-aminothiazol-4-yl)-(Z)-2-hydroxyiminoacetate (**VII**)

3.7.1. Oxime preparation. Ethyl 2-hydroxyimino-3-oxobutyrate(**V**)

A solution of sodium nitrite (18 g, 308 mmol) in water (40 ml) was added to an ice-cooled solution of ethyl acetoacetate (29.2 g, 225 mmol) in glacial acetic acid (29.6 ml) keeping the temperature below 10 °C. The obtained solution was stirred for 30 min at 10 °C and the solvents were evaporated under reduced pressure until dryness. The residue was dissolved in ethyl acetate (50 ml) and the solution was washed with a 5% sodium hydrogen carbonate aqueous solution (2 × 50 ml). The separated organic layer was dried over anhydrous sodium sulfate, filtered and evaporated until dryness to give **V** as an oil.

3.7.2. Oxime halogenation. Ethyl 4-chloro-2-hydroxyimino-3-oxobutyrate (**VI**)

Compound **V** was dissolved in glacial acetic acid (23 ml), the solution was heated to 58–60 °C and sulfuryl chloride (23.12 g, 171 mmol) were added slowly over 3.5 h. The mixture was heated for an additional hour at the same temperature and then it was evaporated under reduced pressure until dryness. The residue was dissolved in ethyl acetate (90 ml) and was washed with brine (3 × 30 ml). The separated organic layer was dried over anhydrous sodium sulfate, filtered and evaporated in vacuo until dryness to give **VI** as an oil.

3.7.3. Formation of 2-aminothiazol ring. Ethyl 2-(2-aminothiazol-4-yl)-(Z)-2-hydroxyiminoacetate (**VII**)

3.7.3.1. Using ethanol as the reaction solvent and N,N-dimethylaniline as base. *N*,*N*-Dimethylaniline (7.7 ml, 59.3 mmol) and thiourea (4.2 g, 55.2 mmol) were added successively to a solution of **VI** (36 g, 186 mmol) in ethanol (50 ml) and the mixture was stirred for 2 h at r.t. The precipitated solid was collected by filtration, washed with ethanol (20 ml), acetone (20 ml) and diethyl ether (20 ml) and dried to give **VII** (7.3 g, 15.1% from ethyl acetoacetate). TLC (FM C) 0.73; m.p. 191–193 °C; ^{1}H NMR (DMSO-d_6) δ (ppm): 1.25 (3H, t, CH_3); 4.24 (2H, q, OCH_2); 6.83 (1H, s, thiazol); 7.20 (2H, s, NH_2); 11.65 (1H, s, NOH); ^{13}C NMR (DMSO-d_6) δ (ppm): C-1 163.35; C-2 146.74; C-3 142.09; C-4 106.14; C-5 168.57; C-6 60.96; C-7 13.96.

3.7.3.2. Using an ethanol–water mixture as the reaction solvent without any base. A solution of **VI** (36 g, 186 mmol) in water (42 ml) was added to a solution of 14.0 g (184 mmol) of thiourea in a mixture of ethanol (42 ml) and water (84 ml). The mixture was stirred for 1 h at r.t., the resulting solution was concentrated to about 1/2 of the initial volume and it was adjusted to pH 6 with a 5% sodium hydrogen carbonate aqueous solution. The precipitated solid was collected by filtration, was washed successively with diethyl ether (50 ml) and acetone (50 ml), and dried to afford **VII** (8.3 g, 17.2% from ethyl acetoacetate).

3.7.3.3. Using a mixture of THF–water as a reaction solvent and sodium acetate as a base. Water (48 ml), thiourea (8.5 g, 111.6 mmol) and anhydrous sodium acetate (15.0 g, 182.8 mmol) were added successively to a solution of **VI** (18 g, 93 mmol) in THF (48 ml). The mixture was stirred for 4 h at r.t., adjusted to pH 6.7–6.8 with sodium hydrogen carbonate (5.2 g, 61.8 mmol) and extracted with ethyl acetate (2 × 100 ml). The organic layer was discarded and the precipitated formed in the aqueous phase was collected by filtration, washed with a mixture of ethyl acetate–water (1:1) (2 × 20 ml) and vacuum dried to afford **VII** (6.3 g, 26.1% from ethyl acetoacetate).

3.7.3.4. Using N,N-dimethylacetamide as reaction solvent without any base. Thiourea (4.3 g, 56.5 mmol) was added to a solution of **VI** (18 g, 93 mmol) in *N*,*N*-dimethylacetamide (40 ml) and the mixture was stirred for 3 h at r.t. The reaction solution was poured into ice-water (200 ml), ethyl acetate (200 ml) was added and the resulting mixture was adjusted to pH 6.1–6.2 with sodium hydrogen carbonate (4.3 g, 51.1 mmol). The

organic layer was discarded and the precipitated formed in the aqueous phase was collected by vacuum filtration, washed with a mixture of ethyl acetate–water (1:1) (2 × 20 ml) and vacuum dried to afford **VII** (8.9 g, 36.9% from ethyl acetoacetate).

3.8. Ethyl 2-(2-tritylaminothiazol-4-yl)-(Z)-2-(tritylhydroxyimino) acetate (*VIII*)

A suspension of **VII** (8.3 g, 38.6 mmol) in chloroform (60 ml) was cooled to 0–5 °C and then TEA (11.5 ml, 82.7 mmol) was added. A solution of trityl chloride (23.2 g, 83 mmol) in chloroform (46 ml) was added to the resulting mixture over 40 min keeping the temperature between 0–5 °C. The reaction mixture was stirred for 90 min at r.t. and the obtained solution was washed successively with water (140 ml), diluted hydrochloric acid (60 ml) and water (3 × 150 ml). The separated organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure until dryness. The residue was stirred with isopropyl alcohol (60 ml) and the white solid formed was collected by filtration, washed with cold isopropyl alcohol (3 × 10 ml) and dried to give **VIII** (14.1g, 52.2%). TLC (FM D) 0.60; m.p. 126–127 °C; ^{1}H NMR (DMSO-d_6) δ (ppm): 1.18 (3H, t, CH_3); 4.13 (2H, q, OCH_2); 6.74 (1H, s, thiazol); 7.10–7.40 (15H, m, aromatics); 8.80 (1H, s, $HNCPh_3$); ^{13}C NMR (DMSO-d_6) δ (ppm): C-1 162.54; C-2 147.49; C-3 140.31; C-4 109.66; C-5 166.42; C-6 61.26; C-7 13.90; C-8 90.81; C-9 71.72.

3.9. Sodium 2-(2-tritylaminothiazol-4-yl)-(Z)-2-(tritylhydroxyimino) acetate (*IX*)

A 2 M sodium hydroxide aqueous solution (17 ml) was added to a suspension of **VIII** (12.2 g, 17.4 mmol) in dioxane (62 ml) over 5–10 min and the mixture was stirred for 2 h at 100–110 °C. The reaction mixture was cooled to 0–5 °C and the precipitated solid was collected by filtration, washed successively with a mixture of dioxane–water (3:1) (3 × 20 ml), diethyl ether (2 × 20 ml) and dried to afford **IX** (11.8 g, 97.6%). TLC (FM C) 0.61; m.p. 248–249 °C; ^{1}H NMR (DMSO-d_6) δ (ppm): 6.47 (1H, s, thiazol); 7.10–7.40 (15H, m, aromatics); 8.50 (1H, s, $HNCPh_3$); ^{13}C NMR (DMSO-d_6) δ (ppm): C-1 165.95; C-2 155.33; C-3 144.28; C-4 109.67; C-5 166.38; C-8 88.56; C-9 71.17.

3.10. Diphenylmethyl 7β-[2-(2-tritylaminothiazol-4-yl)-(Z)-2-tritylhydroxyimino-3-vinyl-3-cephem-4-carboxylate (*X*)

A solution of **IV** (3.05 g, 4.67 mmol) in dichloromethane (40 ml) was cooled to −20 °C and then *N*,*N*-dimethylaniline (2 ml, 15.65 mmol) followed by **IX** (5.19 g, 7.49 mmol) were added. Phosphorous oxychloride (0.69 ml, 7.5 mmol) was added to the resulting suspension and the formed solution was stirred for 90 min at temperatures between −15 and −10 °C. The temperature was raised to 25–30 °C and the solvent was evaporated under reduced pressure. Ethyl acetate (75 ml) and diluted hydrochloric acid (30 ml) were added to the residue and the mixture was stirred for 10 min at r.t. The separated organic layer was washed successively with water (30 ml), 5% sodium hydrogen carbonate aqueous solution (30 ml) and brine (30 ml), dried over anhydrous sodium sulfate, filtered and evaporated in vacuo until dryness. The residue was stirred with methanol (30 ml), the formed precipitate was collected by filtration, washed with methanol (3 × 15 ml) and dried to give **X** (6.71 g, 92.4%). TLC (FM D) 0.30; m.p. 124–129 °C; ^{1}H NMR (DMSO-d_6) δ (ppm): 3.62 and 3.88 (2H, ABq, H-2); 5.30 (1H, d, H-6); 5.32 (1H, d, =CH_2 (*cis*)); 5.66 (1H, d, =CH_2 (*trans*)); 5.94 (1H, dd, H-7); 6.63 (1H, s, thiazol); 6.82 (1H, dd, CH=); 6.95 (1H, s, $CHPh_2$); 7.10–7.55 (40H, m, aromatics); 8.80 (1H, s, $HNCPh_3$); 9.95 (1H, s, HNCO); ^{13}C NMR (DMSO-d_6) δ (ppm): C-1 23.52; C-2 127.86; C-3 123.75; C-4 160.86; C-5 131.20; C-6 119.07; C-7 57.95; C-8 58.90; C-9 164.31; C-10 163.75; C-11 149.29; C-12 142.07; C-13 111.70; C-14 166.64; C-15 78.47; C-16 90.43; C-17 71.45.

3.11. β-[2-(2-Aminothiazol-4-yl)-(Z)-2-(hydroxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid (*XI*) (cefdinir)

Anisole (10 ml) and trifluoroacetic acid (TFA) (22 ml, 288 mmol) were added successively to an ice-cooled solution of **X** (6.72 g, 6.43 mmol) in dichloromethane (9 ml). The resulting solution was stirred for 1 h at 0–5 °C and the solvent was evaporated under reduced pressure. The residue was stirred with isopropyl ether (iPE) (130 ml), the precipitate formed was separated by filtration, washed with iPE (3 × 20 ml) and dried. Ninety percent formic acid (34 ml) was added to the obtained solid and the mixture was stirred for 3 h at r.t. The reaction mixture was concentrated in vacuo and the residue was stirred with iPE (100 ml) for 10 min at r.t. The resulting solid was collected by filtration, washed with iPE (3 × 10 ml) and dried to afford **XI** (2.54 g, 82%). TLC (FM B) 0.37; m.p.; ^{1}H NMR (DMSO-d_6) δ (ppm): 3.60 and 3.83 (2H, ABq, H-2); 5.20 (1H, d, H-6); 5.34 (1H, d, =CH_2 (*cis*)); 5.60 (1H, d, =CH_2 (*trans*)); 5.80 (1H, dd, H-7); 6.69 (1H, s, thiazol); 6.92 (1H, dd, CH=); 7.21 (2H, s, NH_2); 9.50 (1H, d, NHCO); 11.37 (1H, s, NOH); ^{13}C NMR (DMSO-d_6) δ (ppm): C-1 23.18; C-2 124.28; C-3 125.45; C-4 163.18; C-5 131.95; C-6 117.21; C-7 57.83; C-8 58.73; C-9 163.80; C-10 163.76; C-11 148.30; C-12 143.16; C-13 106.80; C-14 168.23.

4. Conclusions

Cefdinir was prepared by an alternative synthetic route which allowed to avoid the use of diketene and to obtain better yields than in the previously reported method.

In the course of the present research, two procedures were developed to protect the cephem amino function by phenylacetylation during the synthesis of compound **II**. In both cases, yields were higher than those described in the previously reported method. It was demonstrated that the use (as acylating agent) of phenylacetic acid activated by Vilsmeier reagent allowed to obtain the best yields of **II**.

On the other hand, two methods were developed in order to form the 2-aminothiazol ring during the synthesis of compound **VII**. It was demonstrated that the use of *N*,*N*-dimethylacetamide as a solvent was the best choice and allowed to obtain better yields of **VII** than those described in the previously reported methods. Finally, it was developed a method to acylate compound **IV** directly with the sodium salt **IX**. This procedure allowed to overcome the drawback corresponding to the conversion of **IX** into its free acid form.

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