

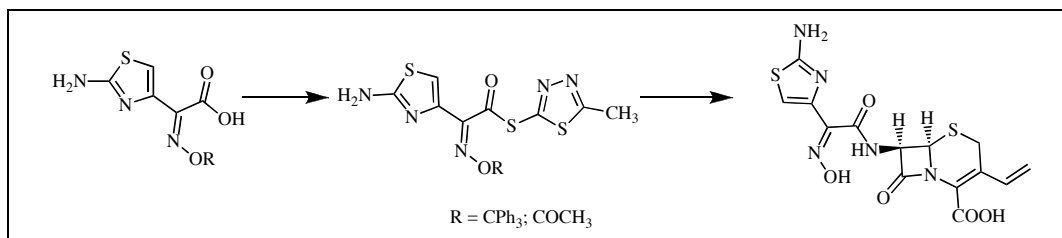
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Received April 12, 2006



Preparation of two new compounds 2-mercapto-5-methyl-1,3,4-thiadiazolyl-(Z)-2-(2-amino-4-thiazolyl)-2-trityloxyiminoacetate (**14**) and 2-mercapto-5-methyl-1,3,4-thiadiazolyl- (Z)-2-(2-amino-4-thiazolyl)-2-acetyloxyiminoacetate (**12**) and their use in the preparation of 7β-[(Z)-2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetamido]-3-vinylcephem-4-carboxylic acid, also known by the generic name Cefdinir (**1**) has been accomplished in a single step by coupling with 7-amino-3-vinylcephem-4-carboxylic acid (**7**) with purity of greater than 99% by HPLC.

J. Heterocyclic Chem., **44**, 309 (2007).

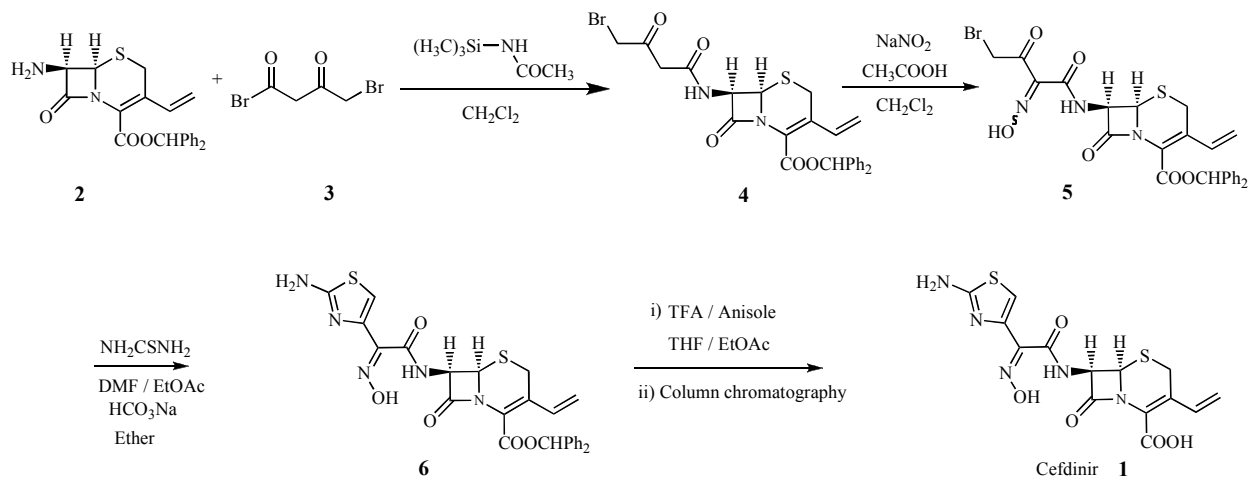
INTRODUCTION

Cefdinir is a third generation Cephalosporin antibiotic for oral administration and has a broad antibacterial spectrum over the gram positive and gram negative bacteria [1]. Many synthetic approaches have been reported for this preparation [2-7]. It was first discovered in the New Drug Research Laboratories of Fujisawa Pharmaceutical Company Ltd, in 1985 [2]. In this process, 7-amino-3-vinylcephem-4-carboxylic acid diphenylmethyl ester (**2**) was acylated with the 4-bromoacetoacetyl bromide (**3**) to afford amide (**4**). Compound **4** was converted to Cefdinir in the sequence of reactions

described in Scheme 1. This route was suitable for the preparation of small quantities of compound; the chemistry was prohibitively responsive due to its length and high cost of raw materials and low yields. Therefore, this route was not utilized for commercial scales.

In reported methods [3,4], trityl protected cefdinir was prepared and isolated as a mixed PTSA and DMAc solvate (**11**). The deprotection of **11** either with trifluoroacetic acid or with formic acid affords Cefdinir (Scheme II). This is the unique method for the isolation of trityl protected Cefdinir (**11**) in crystalline form. But the major problems in this process are use of N,O-

Scheme I

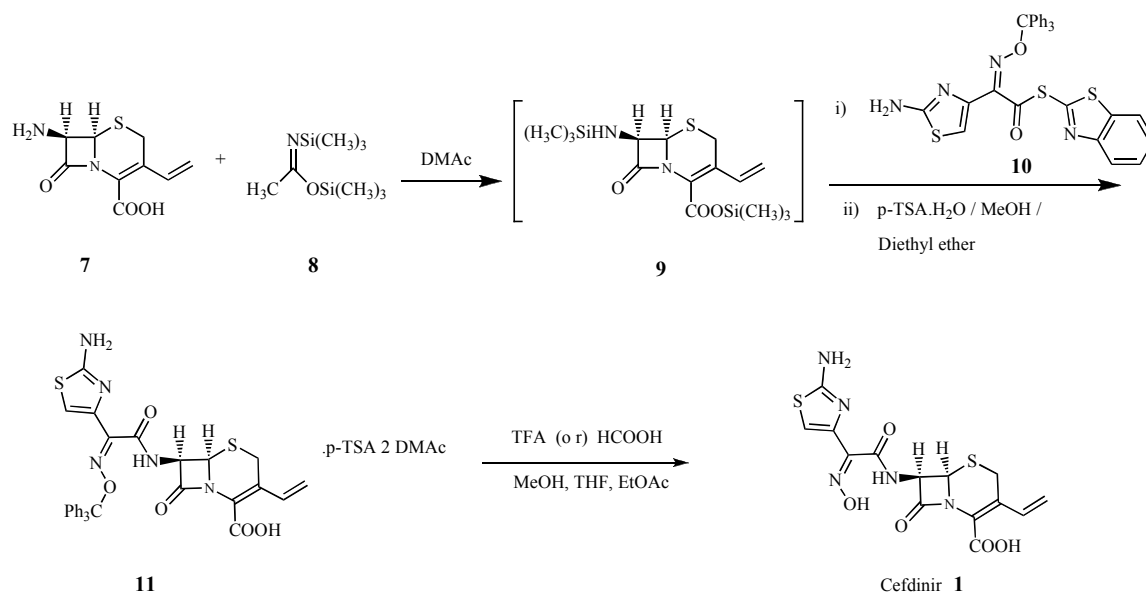


bis(trimethylsilyl)acetamide, which is an expensive silylating agent and use of huge quantity of ether to isolate solvate (**11**) which greatly enhances danger of fire hazard on commercial scale, quantity of output is very low due to high molecular weight of compound (**11**) and poor solvent recovery. Therefore this procedure is not suitable for commercialization.

RESULTS AND DISCUSSION

The present paper describes two novel compounds (**12** and **14**) for preparing Cefdinir with excellent yield and high purity. In the first method, a novel compound, trityl ether (**14**) was prepared from anhydrous (Z)-2-(2-amino-4-thiazolyl)-2-trityloxyimino acetic acid (**18**) [7]. In this method, compound (**18**) was dehydrated by azeotropic

Scheme II



It was also reported in literature [5,6] that the acetyl cefdinir (**12**) was hydrolyzed with potassium carbonate [5] to afford Cefdinir in a low purity of 95%. Similarly the hydrolysis was also carried out with sodium carbonate [6] to obtain Cefdinir in 80% yield. In both these methods the hydrolysis of **12** was carried out in the absence of ammonium chloride (see later). The low yield was believed to be a result of incomplete hydrolysis of compound **12** and decomposition of Cefdinir.

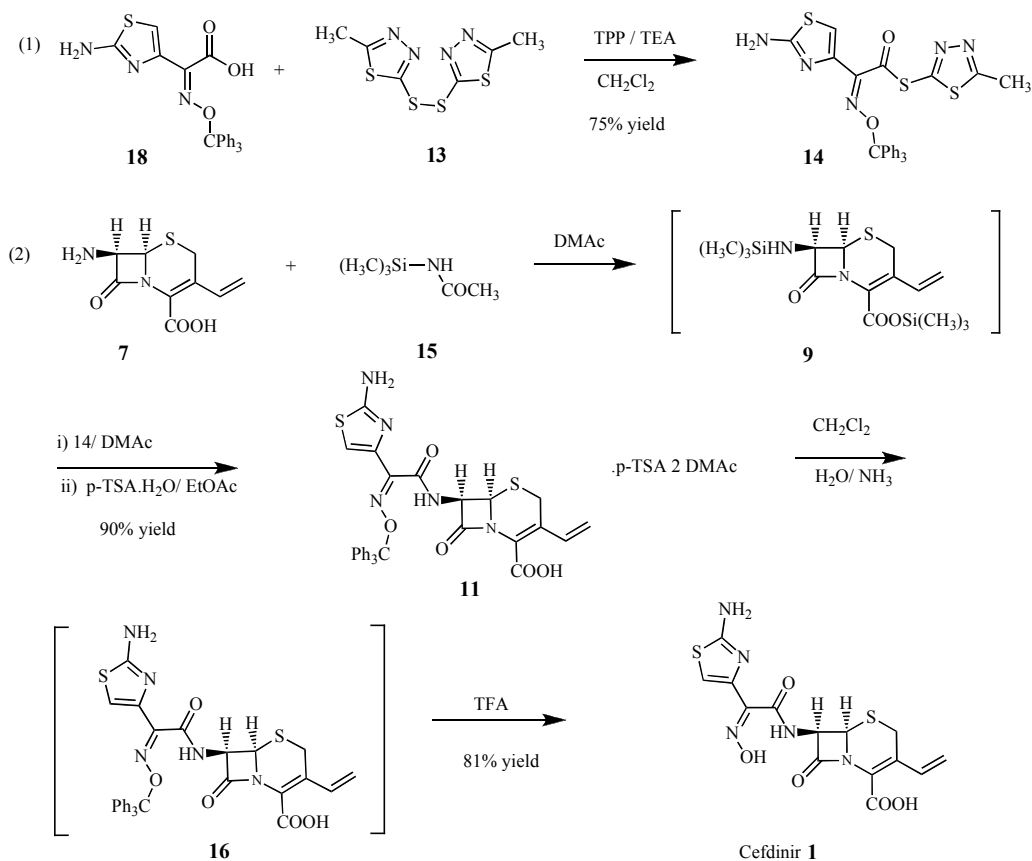
Ascher developed a new method for the preparation of thioesters by using triphenylphosphine and 2,2-dithio-bis-benzothiazole [9]. These esters were used for the acylation of 7-aminocephalosporin derivatives. Hebeisen and Reinach developed a process for the preparation of 2,2-dithio-bis-benzothiazole [8]. The important point is that the Hebeisen's thiazole ester cannot be filtered and is not stable even at low temperatures. Furthermore, process related impurities were not discussed in the literature. Considering foregoing limitations in the reported methods, we undertook an investigation in our laboratory to develop a process, which is cost effective and plant friendly for the preparation of Cefdinir, from novel compounds trityl ether (**14**) and acetyl ester (**12**) which offers an attractive alternative to currently available methods.

removal of methylene chloride till water content comes down to <0.05% w/w. Thereafter, treated with disulphide (**13**) in presence of triphenylphosphine in small aliquots to obtain compound (**14**), which was converted to Cefdinir (**1**) (Scheme III) by acylating with silylated amino acid (**9**) in a manner similar to that described in Scheme 1.

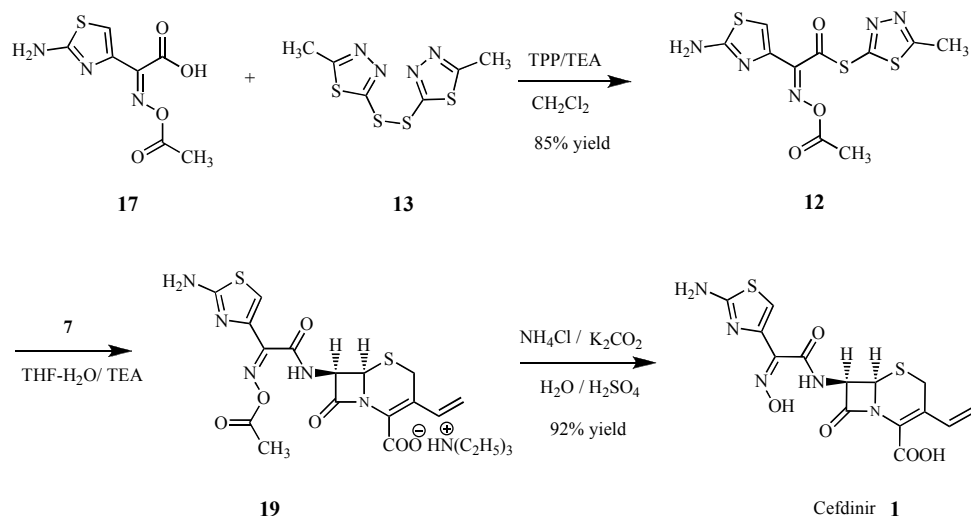
The direct deprotection of Solvate (**11**) with trifluoroacetic acid or with formic acid leads to very poor yields and requires excess trifluoroacetic acid or formic acid for deprotection and difficulty in the precipitation of Cefdinir due to presence of *p*-toluenesulfonic acid. Therefore it required further purification, which lowers the yield another 15-20%. Therefore, it is necessary to neutralize compound (**11**) with ammonia to get 81 % yield of Cefdinir with purity greater than 99 %.

In the second method, protection of the oxime group was realized by acetylation, and the new compound acetyl ester (**12**) was prepared in high yield from (Z)-2-(2-amino-4-thiazolyl)-2-acetoxyiminoacetic acid (**17**) [7], which was converted to Cefdinir in single step by coupling with compound (**7**) (Scheme IV). It is necessary to maintain the water content of < 0.5% w/w in compound (**17**) for the preparation of (**12**). Higher amount of water leads to incomplete reaction and required excess amount of reagents.

Scheme III



Scheme IV



Hydrolysis of the acetyl group of oxime **19** proved to be a crucial step. It was observed that the best yields and purities were obtained by using K_2CO_3 and NH_4Cl in carefully controlled protocol, as described in Experimental. Cefdinir obtained from both these methods,

contains 0.22% of Methyl Cefdinir (**20**), 0.11% of Cefdinir delactam isomers (**21**), 0.14% of Anticefdinir (**22**), 0.06% of Cefdinir sulfoxide (**23**) and Cefdinir Δ^2 -isomer (**24**). The structures of these process related impurities are described below (Figure 1). The analytical

data of Cefdinir and impurities were given in Table 1. Hydrolysis in an aqueous methanol and potassium carbonate in the absence of ammonium chloride results in poor yields and low quality of Cefdinir. Similarly the hydrolysis with sodium carbonate in the absence of ammonium chloride leads incomplete conversion, low yield, 80% of Cefdinir and the purity was low.

In the present procedure NH_4Cl was used as buffering agent to maintain the pH 8-8.2 during the addition of K_2CO_3 . In the absence of NH_4Cl the pH goes to more than

10 with specified quantity of K_2CO_3 . A higher pH value degrades Cefdinir in no time. Therefore it is necessary to maintain the pH 8-8.2 by buffering with NH_4Cl .

CONCLUSION

In conclusion, we reported how with only small changes to intermediates, a strong improvement in yields and purity of antibacterial drug Cefdinir synthesis were obtained. Especially intermediate **12** which was highly stable and gives very high yield of Cefdinir with excellent

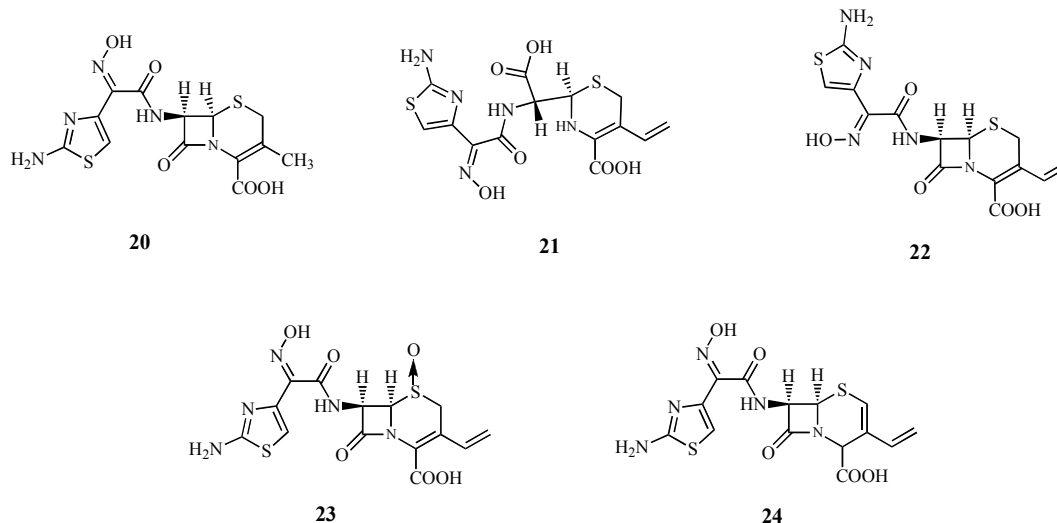


Figure 1. Chemical structures of impurities of Cefdinir

Table 1.

Physical and Analytical Data of Cefdinir (**1**) and its Impurities (**20**), (**21**), (**22**), (**23**) and (**24**)

Compound	Mp (°C)	Molecular Formula / MW	IR (KBr)	Analysis ¹ H nmr (dimethyl sulfoxide- <i>d</i> ₆)
1	180-187 (decomp)	C ₁₄ H ₁₃ N ₃ O ₅ S ₂ (395.42)	NH 3302, 3176, Aliphatic CH 2980, β-lactam C=O 1784, CONH 1668, NH 1520, C=O in COOH 1611, 1429, NH ₂ 1350, 1334, NO 1010 cm ⁻¹	δ 3.53-3.80 (ABq, 2H), 5.19 (d, 1H), 5.30 (d, 1H), 5.60 (d, 1H), 5.80 (m, 1H), 6.67(s, 1H), 6.80-6.90 (m, 1H), 7.10 (bs, 2H), 9.50(d, 1H), 11.33 (s, 1H)
20	177-182 (decomp)	C ₁₃ H ₁₃ N ₃ O ₅ S ₂ (383)	NH 3297, 3200, Aliphatic CH 2980, β-lactam C=O 1760, CONH 1658, C=O in COOH 1622, 1400, NH 1534, NH ₂ 1380, 1365, NO 1015 cm ⁻¹	δ 2.02 (s, 3H), 3.35 & 3.55 (ABq, 2H), 5.10 (d, 1H), 5.71 (dd, 1H), 6.69 (s, 1H), 7.40 (brs, 2H), 9.49 (d, 1H), 11.46 (brs, 1H)
21	165-170 (decomp)	C ₁₃ H ₁₃ N ₃ O ₅ S ₂ (413)	OH and NH 3200, β-lactam C=O 1743, CONH 1599, NH 1537, NH ₂ 1397, 1332, NO 1047, NOH 988 cm ⁻¹	δ 1.78 (d, 3H), 3.55 (ABq, 2H), 4.66 (s, 1H), 5.29 (s, 1H), 6.30 (q, 1H), 7.18 (s, 1H)
22	165-172 (decomp)	C ₁₄ H ₁₃ N ₃ O ₅ S ₂ (395.42)	OH and NH 3188, β-lactam C=O 1760, CONH 1671, NH 1525, NH ₂ 1395, 1350, NO 1029, NOH 997 cm ⁻¹	δ 3.50-3.64 (ABq, 2H), 5.01 & 5.03 (ABq, 2H), 5.06 (d, 1H), 5.68 (dd, 1H), 7.00 (dd, 1H), 7.21 (s, 2H), 7.58 (s, 1H), 9.30 (d, 1H), 12.61 (brs, 1H);
23	220-225 (decomp)	C ₁₄ H ₁₃ N ₃ O ₆ S ₂ (411)	NH 3320, 3150 (NH), Aliphatic CH 2900, β-lactam C=O 1777, CONH 1666, C=O in COOH 1633, 1425, NH ₂ 1303, NO1023 cm ⁻¹	δ 3.55 & 4.29 (2d, 1H), 5.04 (d, 1H), 5.34 & 5.60 (2d, 2H), 5.98 (dd, 1H), 6.81 (s, 1H), 7.08 (dd, 1H), 7.30 (brs, 2H), 8.59 (d, 1H), 11.67 (brs, 1H)
24	257-265 (decomp)	C ₁₄ H ₁₃ N ₃ O ₅ S ₂ (395.42)	NH 3300, 3196, Aliphatic CH 3000, β-lactam C=O 1760, CONH 1674, C=O in COOH 1614, 1401, NH 1533, NH ₂ 1370, 1310, NO 1046 cm ⁻¹	δ 4.73 (s, 1H), 4.89 & 5.34 (2d, 1H each), 5.36 (d, 1H), 5.45 (dd, 1H), 6.27 (dd, 1H), 6.44 (s, 1H), 6.70 (s, 1H), 7.38 (brs, 2H), 9.42 (d, 1H), 11.61 (brs, 1H)

purity. These methods were very simple, non-hazardous and suitable for manufacture of Cefdinir in bulk scales.

EXPERIMENTAL

Solvents and reagents were obtained from commercial sources and used without purification. Melting points were determined on a Polmon melting point apparatus. ^1H NMR spectra were obtained on a Bruker 300 MHz spectrometer with TMS as internal standard. IR spectra were recorded on a Perkin Elmer Spectrum of FTIR spectrometer and Mass spectra obtained on API 2000 Perkin Elmer (PE-SCIEX) mass spectrometer.

2-Mercapt-5-methyl-1,3,4-thiadiazolyl-(Z)-2-(2-amino-4-thiazolyl)-2-trityloxyiminoacetate (14) 100 g (0.232 moles) of (Z)-2-(2-amino-4-thiazolyl)-2-trityloxyiminoacetic acid (**18**) was suspended in 1500 mL of methylene chloride and distilled 500 mL of methylene chloride at atmospheric pressure to remove the traces of water. Thereafter cooled the Suspension to 15°C . 28 g (0.277 moles) of triethylamine was added in 15 min and stirred for 1 h at $15\text{--}20^\circ\text{C}$. 73.2 g (0.273 moles) of bis (5-methyl-1, 3,4-thiadiazol-2-yl) disulfide (**13**) was added followed by 73.2g (0.273 moles) of triphenylphosphine at $15\text{--}20^\circ\text{C}$ in small lots in 10 min. The precipitated solid was cooled to $0\text{--}5^\circ\text{C}$ and stirred for 30 min. The solid was filtered, washed with 100 mL of chilled methylene chloride and dried at $35\text{--}40^\circ\text{C}$ under reduced pressure to obtain title compound (**14**), 124g (75%); mp $140\text{--}141^\circ\text{C}$; ^1H nmr (dimethyl sulfoxide- d_6); δ 2.85 (s, 3H, methyl), 6.86 (s, 1H, thiazolyl), 7.16-7.42 (m, 17H, triphenyl & NH_2); ^{13}C nmr (dimethyl sulfoxide- d_6); 16.4, 55.8, 111.1, 128.1, 128.3, 128.5, 128.7, 128.8, 129.2, 129.4, 129.5, 140.4, 143.9, 150.4, 154.2, 170.2, 171.5, 186.7; ir: 3429, 3242, 1708, 1609, 1537, 1491, 1447 cm^{-1} ; ms: m/z 566.2 $[(\text{M}+\text{Na})]^+$; Anal. Calcd. For $\text{C}_{27}\text{H}_{21}\text{N}_5\text{O}_3\text{S}_3$ (534.1): C, 60.66; H, 3.93; N, 13.10; S, 17.96. Found: C, 60.70; H, 3.94; N, 13.05; S, 18.00.

7 β -(Z)-2-(2-Amino-4-thiazolyl)-2-(trityloxyimino)acetamido]-3-vinylcephem-4-carboxylic acid. p-toluenesulphonic acid 2 N,N-dimethylacetamide solvate (11). To a suspension of 100 g (0.442 moles) of compound (**7**) [12] in 1000 mL of N,N-dimethylacetamide was added 180 g (1.27 moles) of N-trimethylsilylacetamide (**15**) and stirred for 30 min at $25\text{--}30^\circ\text{C}$. To the resulting clear solution, 260 g (0.50 moles) of 2-mercapto-5-methyl-1,3,4-thiadiazolyl-(Z)-2-(2-amino-4-thiazolyl)-2-trityloxyiminoacetate (**14**) was added and stirred for 5 h at $28\text{--}32^\circ\text{C}$. Thereafter, the reaction mixture was cooled to $0\text{--}5^\circ\text{C}$. A solution of 101 g (0.531 moles) of p-toluenesulphonic acid monohydrate in 100 mL of methanol was added in 30 min at $0\text{--}5^\circ\text{C}$ and stirred for 30 min at below 5°C . The resulting solution was cooled to -10°C . 1500 ml of ethyl acetate was added. Thereafter, the slurry obtained was stirred for 15 h at $0\text{--}5^\circ\text{C}$. The solid was filtered, washed with 500 mL of chilled ethyl acetate and dried to obtain title compound (**11**) as a white crystalline powder, 254 g (90%). mp $165\text{--}166^\circ\text{C}$ [4]; ^1H nmr (dimethyl sulfoxide- d_6); δ 2.03 (s, 6H), 2.31 (s, 3H), 2.96 (s, 6H), 2.08 (s, 6H), 3.70 (s, 2H), 5.00-6.01 (m, 4H), 6.99-7.54 (m, 17H), 7.78 (d, 2H); ir: 3061, 1782, 1621, 1194 cm^{-1} ; ms: m/z 639.5 (M^+).

7 β -(Z)-2-(2-Amino-4-thiazolyl)-2-hydroxyiminoacetamido]-3-vinylcephem-4-carboxylic acid (1) 100 g (0.0998 moles) of solvate (**11**) was dissolved in a mixture of 1000 mL of methylene chloride and 200 ml of water at $25\text{--}30^\circ\text{C}$. Thereafter, pH was adjusted to 4.0-4.5 with ammonium hydroxide at $25\text{--}30^\circ\text{C}$. Methylene chloride layer was separated, washed with 100

mL of water, dried over sodium sulphate and cooled to $10\text{--}15^\circ\text{C}$. 162 mL of trifluoroacetic acid was added at $10\text{--}15^\circ\text{C}$ in 30 min. Thereafter, the reaction mass was stirred for 4 h at $10\text{--}15^\circ\text{C}$. 800 mL of cold water was added in 15 min and stirred for 10 min. The aqueous layer was separated and washed with 200 mL of methylene chloride at $15\text{--}20^\circ\text{C}$. The aqueous layer was degassed under reduced pressure at $25\text{--}30^\circ\text{C}$ to remove traces of methylene chloride and cooled to $5\text{--}10^\circ\text{C}$. pH was adjusted to 3.0-3.2 with ammonium hydroxide at below 15°C and stirred for 1 h. The precipitated solid was filtered, washed with 500 mL of precooled water to obtain title compound (**1**) as an off white powder, 39.5g (81%) %; mp $180\text{--}187^\circ\text{C}$ (decompose) [13]; ^1H nmr (dimethyl sulfoxide- d_6); δ 3.53-3.80 (ABq, 2H), 5.19 (d, 1H), 5.30 (d, 1H), 5.60 (d, 1H), 5.80 (m, 1H), 6.67 (s, 1H), 6.80-6.90 (m, 1H), 7.10(bs, 2H), 9.50(d, 1H), 11.33 (s, 1H); ^{13}C nmr (dimethyl sulfoxide- d_6); 24.1, 58.6, 59.5, 108.4, 118.6, 125.7, 126.0, 132.6, 143.9, 149.0, 164.0, 164.6, 164.8, 169.2; ir: NH 3302, 3176, aliphatic CH 2980, beta lactam C=O 1784, amide C=O 1668, C=O of acid 1611 & 1429, NH_2 1350 & 1334, NO 1010 cm^{-1} ; ms: m/z 396 (M^+). Anal. Calcd. For $\text{C}_{14}\text{H}_{13}\text{N}_5\text{O}_3\text{S}_2$ (395.42): C, 42.49; H, 3.29; N, 17.70; S, 16.19. Found: C, 42.33; H, 3.28; N, 17.63; S, 16.17.

2-Mercapto-5-methyl-1, 3,4-thiadiazolyl- (Z)-2-(2-amino-4-thiazolyl)-2-acetyloxyiminoacetate (12) 100 g of (0.436 moles) of (Z)-2-(2-amino-4-thiazolyl)-2-acetyloxyiminoacetic acid (**17**) [14] was suspended in 1000 mL of methylene chloride and distilled 400 mL of CH_2Cl_2 at atmospheric pressure to remove traces of water present in compound 17. Thereafter cooled the suspension to 25°C . 48 g of (0.475 moles) of triethylamine was added at $25\text{--}35^\circ\text{C}$. The reaction mixture was stirred for 2 h at $25\text{--}30^\circ\text{C}$. 125.8 g (0.480 moles) disulfide (**13**) was added and cooled to $10\text{--}15^\circ\text{C}$. 125.8 g (0.480 moles) of triphenylphosphine was added in small lots in 10 min and the reaction mass was stirred for 2 h at $10\text{--}15^\circ\text{C}$. Thereafter the slurry was cooled to $0\text{--}5^\circ\text{C}$ and filtered, the solid washed with chilled methylene chloride. The wet material was dried at $35\text{--}40^\circ\text{C}$ under vacuum to obtain title compound (**12**), 127.4g (85%); mp $120\text{--}123^\circ\text{C}$; ^1H nmr (dimethyl sulfoxide- d_6); δ 2.07 (s, 3H, methyl), 2.39 (s, 3H, methyl), 7.42 (s, 3H, thiazolyl & amine); ^{13}C nmr (dimethyl sulfoxide- d_6); 17.0, 20.0, 112.9, 122.0, 140.0, 153.3, 159.8, 168.0, 170.0, 189.2; ir: 3429, 3261, 1776, 1741, 1618, 1542, 1375, 1286, 1236, 1196, 1179, 1011, 1000, 918, 834, 721 cm^{-1} . Anal. Calcd. For $\text{C}_{10}\text{H}_9\text{N}_5\text{O}_3\text{S}_3$ (343.41): C, 34.95; H, 2.65; N, 20.50; S, 27.99. Found: C, 34.81; H, 2.66; N, 20.59; S, 28.02.

7 β -(O)-2-(2-Amino-4-thiazolyl)-2-hydroxyiminoacetamido]-3-vinylcephem-4-carboxylic acid (1). To a stirred suspension of 100 g (0.442 moles) of compound (**7**) in 1000 mL of tetrahydrofuran was added 176 g (0.671 moles) of 2-mercapto-5-methyl-1,3,4-thiadiazolyl-(Z)-2-(2-amino-4-thiazolyl)-2-acetyloxyiminoacetate (**12**) at $25\text{--}30^\circ\text{C}$. Thereafter the reaction mass was cooled to 15°C and 1000 mL water was added followed by 52 g (0.515 moles) of triethylamine in 30 min. The reaction mass was stirred for 5 h at $18\text{--}20^\circ\text{C}$ and 1000 mL of methylene chloride was added. After 10 min stirring the aqueous layer was separated and washed with 500 mL of methylene chloride. The aqueous extract contains compound (**19**), which was degassed with reduced pressure at $25\text{--}30^\circ\text{C}$ to remove traces of methylene chloride. 66 g (1.21 moles) of ammonium chloride was added followed by 350 ml of 20% w/v potassium carbonate solution in 30 min at $20\text{--}25^\circ\text{C}$ to the aqueous extract. The solution obtained was stirred for 10 min and the pH adjust to 5 by the addition of

10% v/v sulfuric acid at 20-25°C. Thereafter, the reaction mixture was warmed to 35°C and pH adjusted to 2.5-2.6 by the addition of 10% v/v sulfuric acid. The precipitated solid was stirred for 1 h at 35-40°C and filtered, washed with 1000 mL of water and dried to obtain title compound (**1**), 160 g (92%); ¹H nmr (dimethyl sulfoxide-d₆): δ 3.53-3.80 (ABq, 2H), 5.19 (d, 1H), 5.30 (d, 1H), 5.60 (d, 1H), 5.80 (m, 1H), 6.67(s, 1H), 6.80-6.90 (m, 1H), 7.10 (bs, 2H), 9.50(d, 1H), 11.33 (s, 1H); ¹³C nmr (dimethyl sulfoxide-d₆): 24.1, 58.6, 9.5, 108.4, 118.6, 125.7, 126.0, 132.6, 143.9, 149.0, 164.0, 164.6, 164.8, 169.2; ir: NH 3302, 3176, aliphatic CH 2980, beta lactam C=O 1784, amide C=O 1668, C=O of acid 1611 & 1429, NH₂ 1350 & 1334, NO 1010 cm⁻¹; ms: m/z 396 (M⁺). *Anal.* Calcd. For C₁₄H₁₃N₅O₅S₂ (395.42): C, 42.49; H, 3.29; N, 17.70; S, 16.19. Found: C, 42.33; H, 3.28; N, 17.63; S, 16.17.

Acknowledgements. Authors thank the management of Aurobindo Pharma Limited for allowing us to carry out the present work. The authors are also thankful to the colleagues of Analytical Research Department and Chemical Research Department for their cooperation.

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