ANIONIC 4+2 CYCLIZATION ROUTE TO 3-SULFUR SUBSTITUTED ISOCEPHEM ANALOGS

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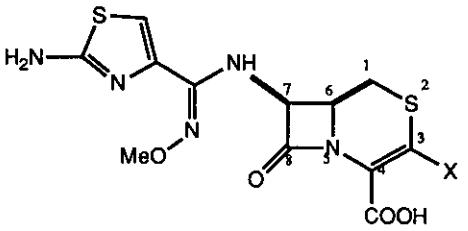
Abstract-Four different isocephem analogs have been synthesized. The key step in the construction of the bicyclic ring involves an anionic 4+2 cyclization. The lithio derivative obtained from a suitably protected *N*-carboxymethyl-2-azetidinone was condensed with carbon disulfide. Subsequent intramolecular alkylation of the 4-tosyloxymethyl substituent by the resultant sulfur nucleophile completed the cyclization sequence.

INTRODUCTION

Isocephems[1] (1-dethia-2-thiacephems) have received relatively little attention despite the fact that the preparation of the nuclear analogs of penicillins and cephalosporins continues as an active area of the β-lactam synthesis. Increased anti-staphylococcus activity has been reported in isocephems having a sulfur substituent at the 3-position[2] (*e. g.* **2**) when compared to its parent isocephem (**1**).

A major problem in the clinical use of β-lactam antibiotics is the development of resistance by bacteria towards these antibiotics *via* the production of β-lactamases. Modification of both the bicyclic ring and the various substituents has helped partly to overcome this problem. One important structural variation, especially among the cephems such as **3**, is the introduction of a methoxy group α to the β-lactam carbonyl function. This substituent results in a better compromise between antibacterial activity and β-lactamase stability when compared to other groups such as CH_2OH, OH and CHO in penicillin analogs (**4**).[3] The addition of a methoxy group α to the lactam

carbonyl group has been reported to enhance the renal dehydropeptidase stability of PS-5 (**5**) analogs such as 6-methoxy-epi-PS-5.[4]



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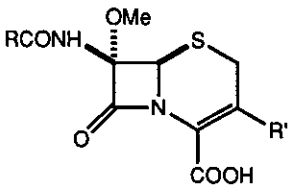
2. X = SR



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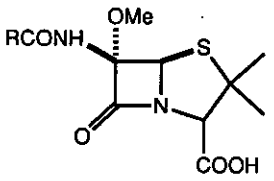

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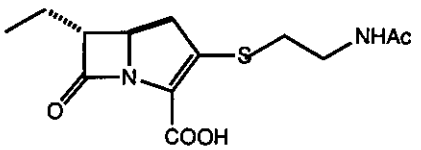

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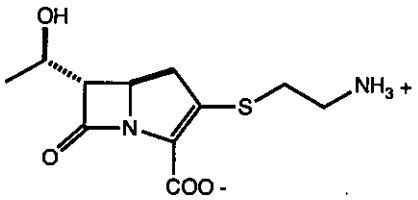

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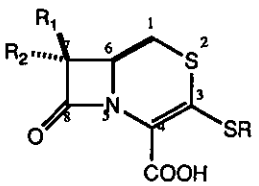

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a: R_1 = OMe, R_2 = Et, R = Bn
b: R_1 = OMe, R_2 = (S)-hydroxyethyl, R = Bn
c: R_1 = H, R_2 = (R)-hydroxyethyl, R = Bn
d: R_1 = OMe, R_2 = H, R = Et

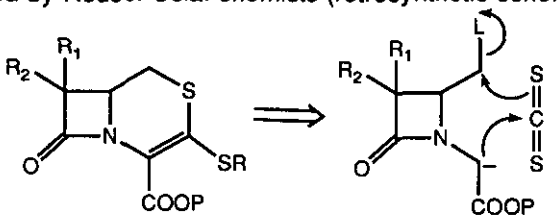
Scheme 1

We therefore decided to investigate the biological activities of 3-sulfur substituted isocephems having substituents other than nitrogen at position 7. Although homothienamycin was found to be inactive,[5] oxacephems having thienamycin type substituent at the 7-position were found to have modest activity.[6] At this stage we wished to incorporate either thienamycin (**6**) or PS-5 type

substituents at C-7 in addition to the methoxy group. We now report the successful completion of total syntheses of 3-sulfur substituted isocephems (**7a-d**).

RESULTS AND DISCUSSION

The overall strategy was to assemble the β-lactam ring via a ketene-imine 2+2 addition and complete the isocephem nucleus using an anionic 4+2 cyclization methodology an example of which was recently reported by Rousel-Uclaf chemists (retrosynthetic scheme).[7]

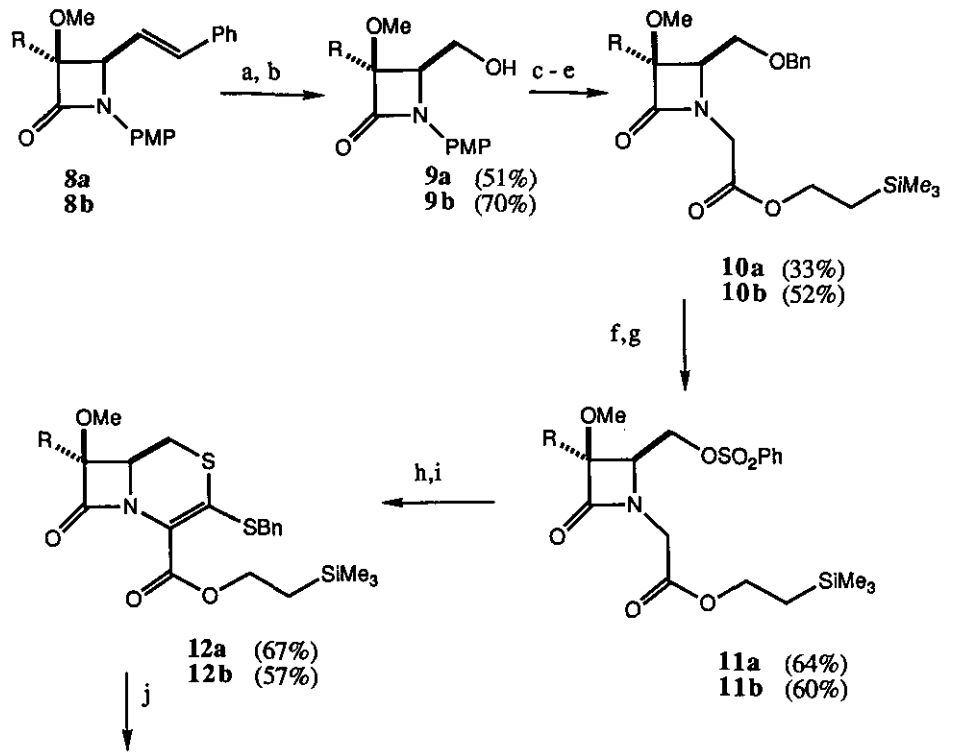


Retrosynthetic Scheme

The compounds (**8a**) and (**8b**) were chosen as starting materials for the synthesis of the target bicyclic compounds (**7a**) and (**7b**), respectively (Scheme 2). These compounds were prepared on a 30-40 mmol scale,[8] then ozonolyzed and the resultant reasonably stable aldehydes were reduced with sodium borohydride to afford the alcohols (**9a**) and (**9b**) in 51% and 70% overall yield.

The hydroxyl group in each of these compounds was protected as its benzyl ether (NaH/benzyl bromide) prior to the oxidative removal of the *p*-methoxyphenyl (PMP) group using ceric ammonium nitrate (CAN).[9] The byproduct, benzoquinone, and residual starting material were removed by passing the mixture through a silica gel column and the crude product was then reacted with β-trimethylsilylethyl bromoacetate to introduce the required acetic acid side chain at nitrogen. The ^{1}H nmr of **10a** verified the introduction of the β-trimethylsilylethyl acetate unit (δ 0.00, s, 9H; 0.88-1.00, CH_2TMS; 4.12-4.47, OCH_2), and the ir showed that the β-lactam ring had been retained (1754 cm^{-1}). The benzyl protective group was subsequently removed in near quantitative yield from the *N*-alkylated compound (**10a**) with hydrogen and 10% palladium on carbon and the resultant free hydroxyl function was activated as its benzenesulfonate by adding a mixture of alcohol and benzenesulfonylimidazole[10] in dry DMF to the suspension of sodium hydride in DMF. The yield of **11a** from the alcohol (**9a**) was 21%. Treatment of **11a** with freshly prepared LDA solution in THF generated the ester enolate which was quenched with carbon disulfide. Purification of the product

enethiol via silica gel chromatography was difficult due to streaking. Therefore the crude reaction product was placed on a column, washed with 1:5 ethyl acetate: hexanes to remove the faster



8a
8b

9a (51%)
9b (70%)

10a (33%)
10b (52%)

11a (64%)
11b (60%)

12a (67%)
12b (57%)

7a (74%) R=Et
7b (75%) R=(S)-hydroxyethyl

8a-12a R=Et
8b-12b R=(S)-hydroxyethyl protected as TBDMS derivative

a) O_3, CH_2Cl_2, DMS, - 78 °C to 25 °C, 18 h; b) $NaBH_4$, EtOH, 25 °C, 30 min; c) NaH, BnBr, DMF, 0 °C to 25 °C, 18 h; d) CAN, MeCN, -10 to -5 °C; e) $BrCH_2COOCH_2CH_2TMS$, NaH, DMF, 0 °C to 25 °C, 18 h; f) H_2, Pd-C (10%), EtOH, 25 °C, 18 h.; g) NaH, $PhSO_2Imd$, DMF, 0 °C to 25 °C, 18 h; h) LDA, THF, CS_2, -78 °C to 25 °C, 18 h; i) NaH, THF, BnBr, 0 °C to 25 °C , 1 h; j) TBAF, THF, 25 °C, 18 h.

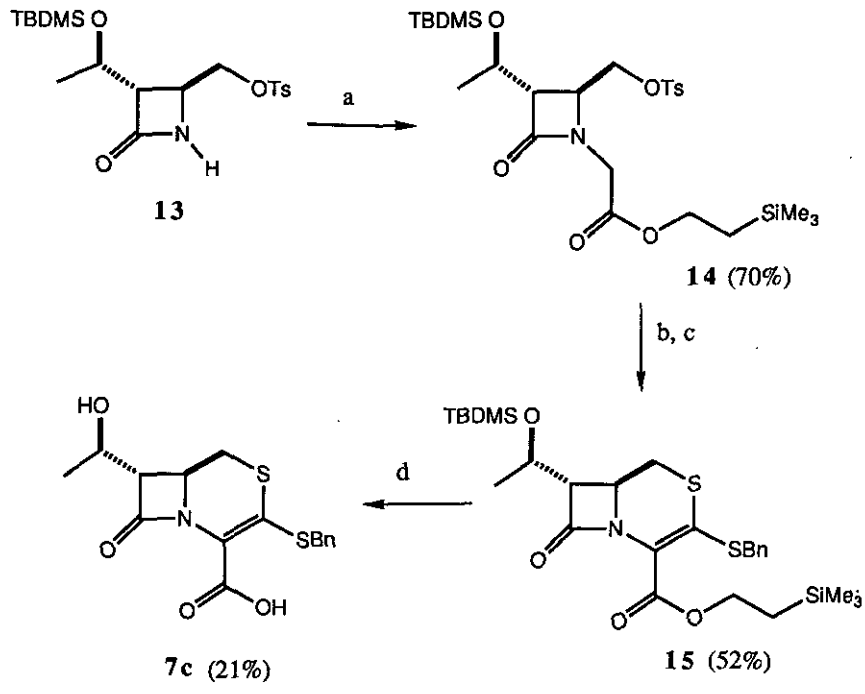
Scheme 2

moving impurities; the desired compound was then desorbed by an ethyl acetate wash. *S*-Benzylation was accomplished in 95% yield by treatment with sodium hydride and benzyl bromide. The product (**12a**), a yellowish solid, mp 80-82 °C, showed carbonyl peaks at 1760 and 1710 cm^{-1} attributed to the β-lactam and the unsaturated ester moieties respectively. The key features in the

^{1}H nmr spectrum of **12a** were the ABX pattern due to the $NCHCH_2S$ grouping at δ 2.88, 3.27 and 3.58 (J_{AB} = 12.4 Hz, J_{AX}= 9.8 Hz and J_{BX}=3.2 Hz), a singlet at δ 4.09 for SCH_2Ph group and the 9H singlet at 0.01 due to the β-TMS group. Finally, the free acid (**7a**), mp 189-191 ^{0}C, was obtained in 74% yield by deprotection with 1.5 equivalent of tetrabutylammonium fluoride (TBAF)[11] in THF at room temperature for 17 h. This compound was characterised by ^{1}H nmr, ms, including HRms of the molecular ion peak and ir (3437, 1763 and 1654 cm^{-1}).

The sequence leading from **8b** to **7b** was completed by a similar manner with sequences shown in Scheme 2; details concerning yields and spectroscopic properties are given in the experimental section. Interestingly, amongst the four bicyclic acids (**7a-d**) , the isocephem carboxylic acid (**7b**), bearing both the methoxy and hydroxyethyl groups at C-7 , has a surprisingly low β-lactam carbonyl streching frequency, 1736 cm^{-1}, compared to 1752-1763 cm^{-1} for other derivatives (**7a**), (**7c**) and (**7d**). This unusually low carbonyl frequency brings into the question whether the structural assignment for **7b** is correct. Careful comparison of other spectroscopic properties of **7b** and the remaining members of this group, *e. g.* the vicinal coupling constants between the methylene group at C-1 and the C-6 hydrogen (J_{AB}=12.5, J_{AX}=4.8, J_{BX}=8.3 vs. J_{AB}=12.0-12.5, J_{AX}=3.3-4.6, J_{BX}= 8.6-10.1 Hz for the analogs), the chemical shifts of the remaining hydrogen on C-6 (3.88 ppm vs. 3.60-4.05 ppm) revealed no anomalies. The mass spectrum of **7b** excluded the possibility of a simple β-lactam ring opening by an external nucleophile. Finally, the internal esterification of the side chain hydroxy group with concominant β-lactam ring opening to form a 4.3.1 bicyclic system having amino, carboxylic acid and a 7-membered lactone functionalities, would account for the 1736 cm^{-1} carbonyl band. This is excluded by the observation that the chemical shift of the secondary hydrogen on the hydroxyethyl group does not undergo the expected 0.5 ppm deshielding upon esterification. We therefore conclude that the structure assignment of **7b** is correct.

The optically active isocephem (**7c**) was prepared as shown in Scheme 3. The monocyclic 4-tosyloxymethyl-β-lactam (**13**), available from L-threonine[12] was *N*-alkylated with β-trimethylsilylethyl bromoacetate to afford **14** (oil, ir 1760 cm^{-1}) in 70% yield. Cyclisation as above with LDA and CS_2



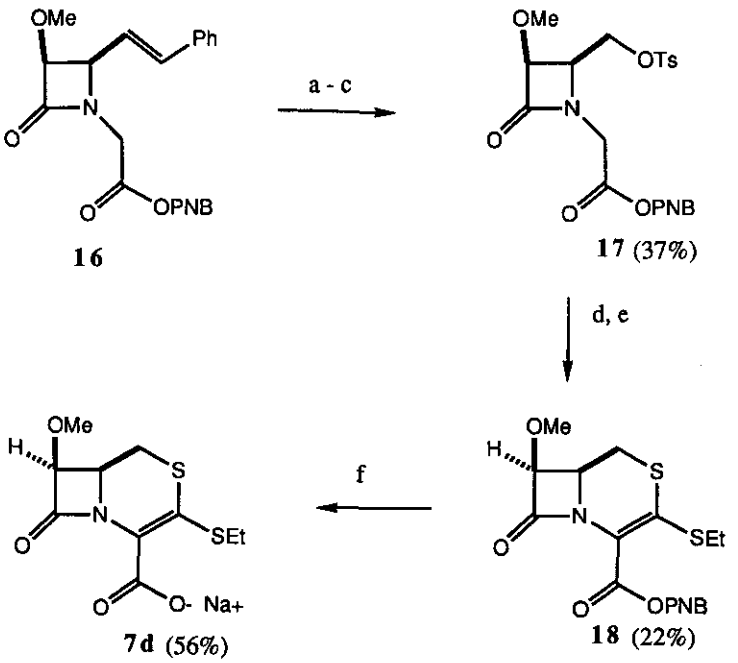
a) $BrCH_2COOCH_2CH_2TMS$, NaH, DMF, 0 °C to 25 °C, 18 h; b) LDA, THF, CS_2, -78 °C to 25 °C, 18 h; c) NaH, THF, BnBr, 0 °C to 25 °C , 1 h; d) TBAF, THF, 25 °C, 18 h.

Scheme 3

afforded a 3-mercaptoisocephem intermediate which was immediately *S*-benzylated to give **15**, mp 99-101 °C, in 52% yield. The deprotection of both the 6-hydroxyethyl and the acid function occurred on overnight treatment with TBAF in THF to afford (+)-**7c**.

Finally, the synthesis of 3-*S*-ethyl-7-methoxyisocephem (**7d**) followed a similar cyclization strategy with reactions shown in Scheme 4. However in this case the monocyclic precursor (**16**) was prepared by a much shorter route. 2+2 Cycloaddition of the imine derived from the *p*-nitrobenzyl ester of glycine and *trans*-cinnamaldehyde with *in situ* generated methoxyketene afforded **16**, albeit in only 18% yield. Ozonolysis of the compound (**16**) followed by sodium cyanoborohydride reduction[13] and tosylation afforded **17** which was suitable for a 4+2 cyclization. Reaction of **17** with freshly prepared LHMDS solution followed by carbon disulfide addition gave the desired bicyclic intermediate which was alkylated with iodoethane. The overall yield of **18** (oil, ir 1767, 1699, 1517, 1342 cm^{-1}) from **16** via this five step sequence was 8%. The other spectroscopic properties

were also in agreement with the structure assignment. The sodium salt (**7d**) was obtained in 56% yield as a white powder, mp 190-191 °C, ir 1752 and 1610 cm^{-1} after hydrogenolysis of **18** with 10% palladium on carbon and purification *via* reverse phase flash column chromatography.



a) O_3, CH_2Cl_2, DMS, -78 °C to 25 °C, 6 h; b) $NaCNBH_3$, EtOH, pH = 3-4, 25 °C, 3.5 h; c) TsCl, Py, 0 °C to -5 °C, 18 h; d) LHMDS, THF, CS_2, -78 °C to 25 °C, 18 h; e) NaH, EtI, THF, 0 °C to 25 °C, 18 h; f) H_2, Pd-C (10%), EtOH-THF, 18 h.

Scheme 4

CONCLUSION

The synthesis of these new isocephems further illustrates the applicability of the anionic 4+2 cyclization method for the preparation of bicyclic β-lactams. Biological screening studies of these compounds showed no useful antibiotic activity.

EXPERIMENTAL

The general protocol concerning the obtaining of spectroscopic properties, solvent purification, chromatographic separation and workup procedures have previously been described.[8] Unless specifically mentioned, the chromatographic purification is carried out using 230-400 mesh silica gel by means of the flash column technique.

3-Ethyl-4-hydroxymethyl-3-methoxy-1-*p*-methoxyphenyl-2-azetidinone(9a). Azetidinone (**8a**)[8] (8.0 g, 24 mmol) was dissolved in 300 ml of dry CH_2Cl_2 and 3 ml of MeOH containing about 1 g of crushed 4Å mol. sieves. The reaction mixture was cooled to -78 °C under N_2 and ozone was passed through the solution until the bluish color of excess ozone appeared. Dimethyl sulfide (5-10 ml, excess) was added after the removal of excess ozone and the resulting mixture was warmed to 25 °C over a period of 18 h. The reaction mixture was filtered and the filtrate was concentrated in vacuum. Flash column chromatography of the crude product (1:10 EtOAc: hexanes) gave 4.0 g (64%) of a yellowish oil; ^{1}H nmr (200 MHz) 1.05 (3H, t, J=7.4 Hz, CH_3), 1.77-1.95 (1H, m, CH_2CH_3), 2.05-2.23 (1H, m, CH_2CH_3), 3.48 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 4.22 (1H, d, J=3.3 Hz, CHN), 6. 84 (2H, dd, J=2.3 and 6.9 Hz , PMP), 7.23 (2H, dd, J=2.3 and 6.9 Hz, PMP), 9.70 (1H, J=3.3 Hz, CHO); ir 1744 cm^{-1} (C=O); ms 263 (M^+, 38), 235 (M^+-28, 5), 206 (M^+-28-29, 46), 204 (M^+-28-31, 12); HRms for $C_{14}H_{17}NO_4$ calcd 263.1156, found 263.1139.

The above aldehyde (4.0 g, 15.2 mmol) was dissolved in 50 ml of EtOH at 25 °C. $NaBH_4$ (0.164 g, 4.56 mmol) was added in one portion and the mixture was stirred for 30 min. The excess $NaBH_4$ was destroyed by stirring with Amberlite (1-2 g) for 10 min and was filtered. Purification of the crude product by column chromatography (1:3 EtOAc : hexanes) afforded 3.2 g (80%) of **9a** as a colorless oil; ^{1}H nmr (200 MHz) 0.99 (3H, t, J=7.4 Hz, CH_3), 1.62-1.82 (m, 1H, CH_2CH_3), 2.06-2.24 (1H, m, CH_2CH_3), 2.55 (1H, broad, OH), 3.60 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.94-3.96 (3H, broad m, CHN, CH_2O), 6.83 (2H, dd, J=2.4 and 6.8 Hz, PMP), 7.32 (2H, dd, J=2.4 and 6.8 Hz, PMP); ir (film) 3300 (OH), 1735 cm^{-1} (C=O); ms 265 (M^+, 26), 206 (M^+-59, 39), 192 (M^+-73, 8), 164 (imine-1$^+$, 4), 149 (M^+-116, 80), 116 (M^+-149, 19); HRms for $C_{14}H_{19}NO_4$ calcd 265.1311, found 265.1321.

3-t-Butylsilyloxyethyl-4-hydroxymethyl-3-methoxy-1-*p*-methoxyphenyl-2-azetidinone (9b). Colorless oil (88% from aldehyde), chromatography solvent (1:4 EtOAc: hexanes); ^{1}H nmr (300 MHz) 0.07 (6H, s, $(CH_3)_2Si$), 0.84 (9H, s, t-BuSi), 1.23 (3H, d, J=6.5 Hz, CH_3), 3.72 (3H, s,

OCH_3), 3.77 (3H, s, OCH_3), 3.78-4.00 (2H, m, H_2CO), 4.13 (1H, dd, J=3.6 and 6.3 Hz, HCN), 4.28 (1H, q, J=6.5 Hz, CH_3CHO), 6.85 (2H, dd, J=2.3 and 6.9 Hz, PMP), 7.36 (2H, dd, J=2.2 and 6.9 Hz, PMP); ir (film) 1740 cm^{-1}(C=O); ms 395 (M^+, 9), 380 (M^+-15, 1), 338 (M^+-57, 76), 246 (M^+-149, 1), 215 (230-15$^+$, 0.3).

β-Trimethylsilylethyl 4-benzyloxymethyl-3-ethyl-3-methoxy-2-azetidinon-1-ylacetate (10a). NaH (0.64 g, 0.013 mol) was added to 3.2 g (0.012 mol) of alcohol (**9a**) dissolved in 50 ml of dry DMF and cooled to 0 °C under N_2. This suspension was stirred for 10 min. Benzyl bromide (1.43 ml, 0.012 mol) was added and stirring was continued without further cooling for 18 h. Usual workup gave a brownish oil which was purified by column chromatography (1:8 EtOAc: hexanes). The yield of benzyl ether (oil) was 3.4 g (80%); ^{1}H nmr (200 MHz) 0.96 (3H, t, J=7.4 Hz, CH_3), 1.62-1.82, (1H, m, CH_2CH_3), 2.06-2.24, (1H, m, CH_2CH_3), 3.53 (3H, s, OCH_3), 3.76 (4H, s with overlapping dd, OCH_3, CH_2O), 3.87 (1H, dd, J=3.7 and 10.8 Hz, CH_2O) 4.06 (1H, dd, J=3.7 and 6.5 Hz, CHN), 4.52-4.53 (2H, broad, CH_2Ph), 6.83 (2H, dd, J=2.2 and 6.8 Hz, PMP), 7.23-7.37 (5H, m, Ph), 7.55 (2H, dd, J=2.2 and 6.8 Hz, PMP); ir 1744 cm^{-1} (C=O); ms 355 (M^+, 16), 327 (M^+-28, 6), 297 (M^+-28-30, 2), 206 (M^+-149, 54), 149 (M^+-206, 38).

The benzylated compound (3.2 g, 9.01 mmol) was dissolved in 50 ml of MeCN and cooled in ice salt bath (-10 to -5 °C). CAN (14.82 g, 27.03 mmol) in 25 ml of ice cold water was added dropwise over 15 min. Brown color appeared and disappeared during early stages. No noticeable color change was observed at the end of addition. The solution was stirred 10 min more. [The progress of reaction must be followed carefully by tlc.] Typical workup and chromatography (1:2 EtOAc: hexanes) gave 1.32 g (59%) of a brownish oil which was not characterised and taken to the next step without further purification.

NaH (0.26 g, 5.47 mmol) was suspended in 25 ml of dry DMF and cooled to 0 °C under N_2. A mixture of the free NH compound (1.24 g, 4.97 mmol) and β-trimethylsilylethylbromoacetate (1.3 g, 5.47 mmol) in 10 ml of dry DMF was added by cannula and stirred overnight at 25 °C. The reaction mixture was diluted with 35 ml of ether and subjected to the usual workup procedure and purification by column chromatography (1:8 EtOAc: hexanes) to yield 1.4 g (70%) of **10a** as a yellow oil; ^{1}H nmr (200 MHz) 0.00 (9H, s, TMS), 0.88-1.00 (5H, overlapping t, CH_3, CH_2TMS), 1.69-2.11 (2H, m, J=7.4 Hz, CH_2CH_3), 3.45 (3H, s, OCH_3), 3.68 (1H, dd, J=7.3 and 3.7 Hz, CHN), 3.75-

3.91 (3H, m, CH_2OBn, NC*H*HCOOR), 4.12-4.47 (3H, m, OC*H*$_2$$CH_2TMS$, NCH*H*COOR), 7.23-7.33 (5H, m, Ph); ir 1754 cm^{-1} (C=O, broad, 2 overlapping peaks); ms (CI) 408 (M^++1, 4), 380 (M^++1-28, 100), 352 (M^++1-56, 71), 244 (M^++1-164, 15), 149 (M^++1-269, O=CNCH$_2$COOCH$_2$CH$_2$TMS$^+$, 76).

β-Trimethylsilylethyl 4-benzyloxymethyl-3-ethyl-3-methoxy-2-azetidinon-1-ylacetate (10b). Yellow oil (68% from corresponding NH compound), chromatography solvent (1:8 EtOAc: hexanes); ^1H nmr (200 MHz) 0.01 (9H, s, TMS), 0.013 (3H, s, CH_3Si), 0.03 (3H, s, CH_3Si), 0.83 (9 H, s, t-BuSi), 0.84-0.96 (2H, m, CH_2Si), 1.25 (3H, d, J=6.4 Hz, CH_3), 3.56 (3 H, s, OCH_3), 3.65-3.76 (2H, m, CH_2O), 3.92-4.20 (6H, m, CHN, CHO, NCH_2COO, CH_2O), 4.46 (2H, s, CH_2Ph), 7.23-7.30 (5H, m, Ph); ir (film) 1756 cm^{-1} (broad, C=O); ms (CI) 538 (M^++1, 6), 523 (M^++1-15, 0.3), 510 (M^++ 1-28, 71), 495 (510-15$^+$, 3), 482 (M^++1-56, 17).

β-Trimethylsilylethyl 4-benzenesulfonyloxymethyl-3-ethyl-3-methoxy-2-azetidinon-1-ylacetate (11a). Benzyl ether (**10a**) (1.32 g, 3.23 mmol) was dissolved in 20 ml of EtOH and 200 mg of Pd-C (10%) was added and hydrogenated at 40 psi and 25 °C for 18 h. After removal of the catalyst the solution was concentrated in vacuum. The crude product was purified by passing through a small silica gel plug (EtOAc) to yield 0.82 g (80%) of a colorless oil; ^1H nmr (200 MHz) 0.00 (9H, s, TMS), 0.93-1.00 (5H, m, CH_3, CH_2TMS), 1.60-1.82 (1H, m, C*H*$_2$$CH_3$), 2.01-2.20 (1H, m, C*H*$_2$$CH_3$), 2.59 (1H, dd, J=5.6 and 5.9 Hz, OH), 3.51 (3H, s, OCH_3), 3.53-3.72 (1H, m) , 3.83 (2H, m), 4.20 (4H, m) these multiplets could not be assigned completely (HCN, CH_2O, NCH_2COOR); ir (film) 3441 (broad, OH), 1746 cm^{-1} (C=O) ; ms 274 (M^+-43, 3), 246 (M^+-43-28, 1), 216 (imine-1$^+$, 0.7), 173 (M^+-116-28, 1), 116 (M^+-201, 36).

To a solution of the above alcohol (0.8 g, 2.52 mmol) in 20 ml of THF was added 1.03 g (5.1 mmol) of benzenesulfonyl imidazole in 20 ml of dry DMF (**sol A**). NaH (0.11 g, 2.77 mmol) was suspended in 20 ml of THF and DMF (1:1) mixture and cooled to 0 °C under N_2 and all **sol A** obtained as mentioned above was added slowly by cannula and the mixture was stirred without further cooling for 18 h. The reaction mixture was diluted with 40 ml of ether washed with 10% HCl, 5% $NaHCO_3$ and brine (30 ml each) respectively. Column chromatography (1: 9 EtOAc: hexanes) gave 0.92 g (80%) of **11a** as a colorless oil; ^1H nmr (200 MHz) 0.00 (9H, s, TMS), 0.87-1.02 (5H, m, CH_3, CH_2TMS), 1.73-1.81 (1H, m, C*H*$_2$CH3), 1.96-2.01 (1H, m, C*H*$_2$$CH_3$), 3.37 (3H, s, OCH_3), 3.72 (1H, d, J=18.1 Hz, NC*H*HCOOR), 3.87 (1H, dd, J=5.5 and 6.6 Hz, CHN), 4.15 (5H, m, 2 x

OCH_2, NCH*H*COOR), 7.51-7.66 (3H, m, Ph), 7.85-7.90 (2H, m, Ph); ir (film) 1770 and 1740 cm^{-1} (C=O), 1370, 1190 (SO_2); ms 414 (M^+-43, 2), 386 (M^+-71, 2), 256 (M^+-201, 12), 242 (256-14^+, 2).

β-Trimethylsilylethyl 4-benzenesulfonyloxymethyl-3-t-butyldimethylsilyloxyethyl-3-methoxy-2-azetidinon-1-ylacetate (11b). Colorless oil (63% from corresponding 4-hydroxymethyl azetidinone), chromatography solvent (1:7 EtOAc: hexanes); ^1H nmr (200 MHz) 0.01 (15H, s, TMS, $(CH_3)_2Si$), 0.77 (9H, s, t-BuSi), 0.93-0.99 (2H, m, CH_2Si), 1.20 (3H, d, J=6.7 Hz, CH_3), 3.48 (3H, s, OCH_3), 3.85 (1H, d, J=17.9 Hz, NC*H*HCOOR), 4.00-4.31 (7H, m, HCO, H_2CO, HCN, NCH*H*COOR), 7.49-7.89 (5H, m, Ph); ir (film) 1757 cm^{-1} (C=O); ms (CI) 588 (M^++1, 2), 573 (M^++1-15, 0.4), 560 (M^++1-28, 98), 530 (M^++1-57, 12), 502 (530-28^+, 6).

β-Trimethylsilylethyl 4-tosyloxymethyl-3-(R)-t-butyldimethylsilyloxyethyl-2-azetidinon-1-ylcarboxylate (14). NaH (0.052 g, 1.176 mmol) was suspended in 5 ml of DMF and cooled to 0 °C under N_2. Tosylate (**13**) (0.364 g, 0.98 mmol) and β-trimethylsilylethyl bromoacetate (0.28 g, 1.17 mmol) were dissolved in 10 ml of dry DMF . It was then added to the NaH suspension by cannula (color becomes reddish) and stirred overnight at 25 °C. The crude product obtained upon usual workup was purified by column chromatography (1:5 EtOAc: hexanes) to give 0.391g (70%) of **14** as a yellow oil: $[\alpha]_D^{22}$ -9.2° (*c*1.0, $CHCl_3$); ^1H nmr (200 MHz) 0.02 (15H, s, $(CH_3)_2Si$), 0.78 (9H, s, t-BuSi), 0.92-1.01 (2H, m, CH_2Si), 1.16 (3H, d, J=5.2 Hz, CH_3), 2.43 (3H, s, CH_3Ph), 2.80 (1H, dd, J=2.2 and 6.0 Hz, HC-C=O), 3.80 (1H, d, J=17.9 Hz, NC*H*HCOOR), 3.95 (1H, d, H=17.9 Hz, NCH*H*COOR), 3.94-4.27 (6H, m, HCO, H_2CO), 7.32 (2H, d, J=8.1Hz, Tol), 7.75 (2H, d, J=8.5 Hz, Tol); ir (film) 1760 (broad, C=O) , 1367, 1182 cm^{-1} (SO_2); ms (CI) 572 (M^++1, 5), 557 (M^++1-15, 0.6), 544 (M^++1-28, 100), 515 (M^++1-57, 7), 272 (M^++1-200, 2).

***p*-Nitrobenzyl 3-methoxy-4-tosyloxymethyl-2-azetidinon-1-ylacetate (17).** The ozonolysis of **16** (2.5 g, 6.31 mmol) was done as in case of compound (**9a**). The corresponding aldehyde (2.0 g, 98%) was purified by column chromatography (2:1 EtOAc: hexanes) and reduced directly as described.

The aldehyde was dissolved in 20 ml of THF and 20 ml of EtOH. Two drops of bromocresol green and 2 drops of 10% HCl were added followed by sodium cyanoborohydride (0.78 g, 12.41 mmol). The reaction mixture turned blue. The yellowish color was maintained by adding 10% HCl. After 3.5 h the reaction mixture was diluted with 40 ml of water and extracted with 3 x 30 ml of CH_2Cl_2.

The crude product was purified by column chromatography (1.5:1 EtOAc: hexanes) to give 1.2 g (60%) of oil; ^{1}H nmr (200 MHz) 3.53 (3H, s, OCH_3), 3.84 (2H, d, J=4.2 Hz, C*H*$_2$OH), 3.98 (1H, d, J=18.1 Hz, NC*H*HCOOR), 3.98 (1H, m overlaps with other peak at 3.98, HCN), 4.26 (1H, d, J=18.1 Hz, NCH*H*COOR), 4.58 (1H, d, J=4.9 Hz, HCC=O), 5.21 (2H, s, OCH_2PNB), 7.46 (2H, d, J=8.8 Hz, PNB), 8.16 (2H, d, J=8.8 Hz, PNB); ir (film) 3442 (broad, OH), 1750 (C=O), 1522 and 1348 cm^{-1} (NO_2); ms (CI) 325 (M^++1, 2), 297 (M^++1-28, 1), 279 (M^+-46, 3), 247 (279-32$^+$, 12), 228 (M^++1-97, 93).

Tosyl chloride (0.49 g, 2.57 mmol) was dissolved in 4 ml of pyridine and added to the alcohol (0.564 g, 1.7 mmol) at room temperature under N_2. It was stored at -5 to 0 °C for 18 h. Purification of the crude product by column chromatography (1:3 EtOAc: hexanes) yielded 0.579 g (69%) of **17** as a colorless oil. ^{1}H Nmr (200 MHz) 2.43 (3H, s, CH_3Ph), 3.45 (3H, s, OCH_3), 3.97 (1H, d, J=18.1 Hz, NC*H*HCOOR), 4.20-4.21 (4H, m, H_2CO, HCN, NCH*H*COOR), 4.59 (1H, d, J=5.6 Hz, HCC=O), 5.24 (2H, s, CH_2PNB), 7.33 (2H, d, J=8.3 Hz, Tol), 7.50 (2H, d, J=8.9 Hz, PNB), 7.72 (2H, d, J=8.2 Hz, Tol), 8.21 (2H, d, J=8.9 Hz, PNB); ir (film) 1762 (C=O), 1522 and 1353 cm^{-1} (NO_2); ms (CI) 479 (M^++1, 0.6), 451 (M^++1-28, 0.6), 371 (M^++1-108, 14), 343 (M^++1-143, 0.6).

β-Trimethylsilylethyl 3-benzylthio-7-methoxy-7-ethyl-1-dethia-2-thia-3-cephemcarboxylate (12a). A solution of compound (**11a**) (0.389 g, 0.851 mmol) in 10 ml of dry THF was cooled to -78 °C under N_2 and added to a LDA solution (1.1 eq.) in 5 ml of THF at -78 °C *via* cannula. The yellow solution was stirred for 15 min and excess CS_2[14] was added by cannula (pinkish tinge appeared). The reaction mixture was allowed to warm slowly to room temperature over a period of 18 h. The solvent was removed. The faster moving impurities in the crude product were removed by eluting with 1:4 EtOAc: hexanes and the desired compound was obtained by an EtOAc flush. The yellowish oil (0.22 g, 71%), reasonably pure by nmr, was carried to next step without further purification; ^{1}H nmr (200 MHz) 0.00 (9H, s, TMS), 1.00 (3H, t, J=7.4 Hz, CH_3), 1.07-1.10 (2H, m, CH_2TMS overrlapping with CH_3), 1.85-2.14 (2H, m, C*H*$_2$CH$_3$), 2.85 (1H, dd, J=3.0 and 12.2 Hz, CH_2S), 3.46 (4H, s overlapping with dd, J=9.7 and 12.2 Hz, OCH_3, CH_2S), 3.61 (1H, dd, J=3.0 and 9.7 Hz, HCN), 4.02 (1H, broad, SH), 4.23-4.36 (2H, m, OCH_2); ir (film) 1770 and 1690 cm^{-1} (C=O); ms (CI) 376 (M^++1, 6), 361 (M^++1-15, 2), 348 (M^++1-28, 28), 320 (M^++1-56, 100), 332 (M^++1-44, 22).

NaH dispersion (0.025 g, 0.63 mmol) was added to the solution of the above enethiol (0.215 g, 0.573 mmol) in 5 ml of dry THF at 0 °C. When the effervescence subsided, benzyl bromide (0.7 ml, 0.573 mmol) was added by syringe (white ppt. appeared). The cooling bath was removed and the reaction mixture was stirred for 30 min, diluted with 5 ml of EtOAc and washed with brine. Further workup and purification by column chromatography (1:8 EtOAc: hexanes) yielded 0.254 g (95%) of a yellowish solid (**12a**): mp 80-82 °C; ^{1}H nmr (200 MHz) 0.01 (9H, s, TMS), 0.96-1.08 (5H, m, CH_3, CH_2TMS), 1.87-2.12 (2H, m, CH_2CH_3), 2.88 (1H, dd, J=3.2 and 12.4 Hz, CH_2S), 3.27 (1H, dd, J=9.8 and 12.3 Hz, CH_2S), 3.45 (3H, s, OCH_3), 3.58 (1H, dd, J=3.2 and 9.8 Hz, HCN), 4.09 (2H, s, SCH_2Ph), 4.23-4.32 (2H, m, OCH_2), 7.22-7.32 (5H, m, Ph); ir 1760 and 1710 (C=O); ms 465 (M^+, 8), 437 (M^+-28, 7), 422 (M^+-28-15, 7), 378 (M^+-56-31, 6), 346 (M^+-91-28, 0.5), HRms for $C_{22}H_{31}NO_4S_2Si$ calcd 465.1461, found 465.1448.

β-Trimethylsilylethyl 3-benzylthio-7-methoxy-7-t-butyldimethylsilyloxyethyl-1-dethia - 2-thia-3-cephemcarboxylate (12b). Yellowish solid (65% from enethiol), mp 111-112 °C, chromatography solvent (1:15 EtOAc: hexanes); ^{1}H nmr (200 MHz) 0.00 (9H, s, TMS), 0.05 (3H, s, CH_3Si), 0.06 (3H, s, CH_3Si), 0.85 (9H, s, t-BuSi), 0.99-1.07 (2H, m, CH_2TMS), 1.26 (3H, d, J=6.4 Hz, CH_3), 2.85 (1H, dd, J=3.3 and 12.6 Hz, CH_2S), 3.25 (1H, dd, J=9.8 and 12.6 Hz, CH_2S), 3.56 (3H, s, OCH_3), 3.71 (1H, dd, J=3.3 and 9.7 Hz, HCN), 4.10 (2H, s, SCH_2Ph), 4.19-4.30 (3H, m, HCO, H_2CO), 7.24-7.30 (5H, m, Ph); ir 1748 (C=O), 1692 cm^{-1} (COOR); ms 595 (M^+, 31), 580 (M^+-15, 0.7), 567 (M^+-28, 14), 552 (M^+-43, 26), 538 (M^+-57, 11).

β-Trimethylsilylethyl 3-benzylthio-7-(R)-t-butyldimethylsiloxyethyl-1-dethia-2-thia-3-cephemcarboxylate (15). Yellow solid (63% from enethiol), mp 99-101 °C, $[\alpha]_D^{22}$ -4.7° (*c* 0.7, $CHCl_3$), chromatography solvent (1:5 EtOAc: hexanes); ^{1}H nmr (200 MHz) 0.02 (9H, s, TMS), 0.06 (6H, s, $(CH_3)_2Si$), 0.86 (9H, s, t-BuSi), 1.03-1.20 (2H, m, H_2CSi), 1.22 (3H, d, J=6.2 Hz, CH_3), 2.86 (1H, dd, J=3.6 and 5.1 Hz, HCC=O), 2.88 (1H, d, J=10.1 Hz, H_2CS), 3.81 (1H, dd, J=3.4 and 12.4 Hz, H_2CS), 3.68-3.74 (1H, m, HCN), 4.04 (2H, s, SCH_2Ph), 4.22-4.34 (3H, m, HCO, H_2CO), 7.22-7.40 (5H, m, Ph); ir 1766 (C=O), 1719 cm^{-1} (C=O); ms 565 (M^+, 3), 537 (M^+-28, 2), 522 (M^+-43, 2), 508 (M^+-57, 0.8), 480 (508-28$^+$, 4).

***p*-Nitrobenzyl 3-ethylthio-7-methoxy-1-dethia-2-thia-3-cephemcarboxylate (18).** Yellow solid (39% from enethiol), mp 149-150 °C; ^{1}H nmr (300 MHz) 1.29 (3H, t, J=7.4 Hz, CH_3),

2.89-2.98 (2H, overlapping q, H_2CCH_3), 3.03 (1H, dd, J=12.6 and 3.4 Hz, CH_2S), 3.32 (1H, dd, J=9.9 and 12.7 Hz, CH_2S), 3.54 (3H, s, OCH_3), 3.91-3.97 (1H, m, HCN), 4.82 (1H, d, J=4.6 Hz, HCC=O), 5.27 (1H, d, J=13.4 Hz, CH_2PNB), 5.37 (1H, d, J=13.4 Hz, CH_2PNB), 7.61 (2H, d, J=8.9 Hz, PNB), 8.20 (2H, d, J=8.7 Hz, PNB); ^{13}C nmr (200 MHz) 14.2 (CH_3), 27.6 (CH_2S), 28.6 (CH_2S), 50.3 (OCH_3), 59.2 (CHN), 65.8 (CH_2PNB), 85.3 (H*C*C=O), 104.7 (C=C), 123.6 and 128.7 (CH of PNB), 142.8 and 147.6 (C of PNB), 160.6 (C=O), 164.1 (C=O); ir 1767 (C=O), 1699 (COOR), 1517 and 1342 cm^{-1} (NO_2); ms 411 (M^++1, 1), 410 (M^++, 7), 382 (M^+-28, 12), 351 (382-31$^+$, 14), 337 (M^+-84, 1); HRms for $C_{17}H_{18}N_2O_6S_2$ calcd 410.0623, found 410.0621.

3-Benzylthio-7-ethyl-7-methoxy-1-dethia-2-thia-3-cephemcarboxylic acid (7a). TBAF (0.28 ml, 0.27 mmol, 1M solution in THF) was added to the solution of the compound (**12a**) (86 mg, 0.185 mmol) in 1 ml of THF at 25 °C. It was then stirred overnight (17 h) under N_2. EtOAc (5 ml) and 0.3 N HCl (1 ml) were added to the reaction mixture (pH=1). The aqueous layer was separated and extracted with EtOAc twice (5 ml each). The combined organic layer containing some white crystalline particles was concentrated without drying and the crude product was recrystallised from ether-acetone (1:1) mixture containing traces of water (1-2 drops) to give 50 mg (74%) of **7a** as a white solid: mp 189-191 °C (decomp.); ^{1}H nmr (300 MHz, acetone-d_6) 0.92 (3H, t, J=7.4 Hz, CH_3), 1.73-2.26 (2H, m, CH_2CH_3) acetone peak overlaps, 3.10-3.14 (2H, ovrlapping 2 sets of dd, J=12.0, 4.6 and 8.6 Hz, CH_2S), 3.34 (3H, s, OCH_3), 3.60-3.65 (1H, m, HCN), 4.04 (2H, d, J=3.4 Hz, SCH_2Ph), 7.17-7.30 (5H, m, Ph); ^{13}C nmr (300 MHz) 7.8 (CH_3), 23.5 (CH_2), 28.8 (CH_2), 39.9 (CH_2), 55.2 (CH), 55.9 (CH_3O), 128.2 (CH), 129.3 (CH), 130.1 (CH), 137.6 (C); ir 3437 (broad, OH), 1763 and 1654 cm^{-1} (C=O); ms 365 (M^+, 20), 337 (M^+-28, 38), 321 (M^+-44, 22), 293 (M^+-44-28, 47), 262 (M^+-100, 4); HRms for $C_{17}H_{19}NO_4S_2$ calcd 365.0745, found 365.0750.

3-Benzylthio-7-hydroxyethyl-7-methoxy-1-dethia-2-thia-3-cephemcarboxylic acid (7b). White solid (75% from **12b**), mp 209-211 °C, crystallization in aq. MeOH; ^{1}H nmr (300 MHz, acetone-d_6 + 1 drop D_2O with HOD irradiation) 1.24 (3H, d, J=6.5 Hz, CH_3), 3.17-3.21 (2H, overlapping 2 sets of dd, J=12.5, 4.8 and 8.3 Hz, H_2CS), 3.48 (3H, s, OCH_3), 3.88 (1H, dd, J=4.8 and 8.3 Hz, HCN), 4.10 (2H, d, J=1.7 Hz, H_2CPh), 4.30 (1H, q, J=6.6 Hz, HCO), 7.21-7.33 (5H, m, Ph); ^{13}C nmr (THF-d_8) (300 MHz) 18.0 (CH_3), 29.9 (CH_2), 40.6 (CH_2), 52.7 (CH), 54.6 (CH_3), 64.9 (HC), 96.1 (C), 124.5 (C=C), 125.2 (C=C), 128.0 (CH), 129.1 (CH), 130.1 (CH), 137 8 (C, Ph

carbons), 162.4 (C=O), 163.9 (C=O); ir 3549 (broad, OH), 1736 (C=O), 1655 cm^{-1} (COOH); ms 381 (M^+, 2), 353 (M^+-28, 3), 337 (M^+-44, 5), 309 (M^+-72, 8), 293 (M^+-88, 1); HRms for $C_{16}H_{19}NO_3S_2$ (M^+-44) calcd 337.0805, found 337.0784.

(+)-3-Benzylthio-7-(R)-hydroxyethyl-1-dethia-2-thia-3-cephemcarboxylic acid (7c). Yellowish white solid (21 % from **15**), mp 155-156 °C (decomp.), $[\alpha]_D^{22}$ +21.2° (*c*1.9, MeOH), recrystallization from aq. MeOH (2-3 drops of water per ml); ^1H nmr (300 MHz, acetone-d_6) 1.27 (3H, d, J=6.3 Hz, CH_3), 3.06 (1H, dd, J=2.4 and 6.4 Hz, CHCO), 3.15 (1H, dd, J=12.4 and 10.1 Hz, CH_2S), 3.41 (1H, dd, J=3.3 and 12.4 Hz, CH_2S), 3.79-3.84 (1H, m, HCN), 4.12 (2H, s, CH_2Ph), 4.16 (1H, q, J=6.5 Hz, CH_3CHO), 7.24-7.38 (5H, m, Ph); ^{13}C nmr (300 MHz) 22.3 (CH_3), 32.7 (CH_2), 40.3 (CH_2), 49.5 (CH), 65.3 (CH), 65.9 (CH), 128.2 (CH), 129.3 (CH), 130.1 (CH) and 137.8 (C) (Ph carbons), 162.5 (C=O), 165.4 (C=O); ir 3371 (OH, broad), 1758 cm^{-1} (C=O); ms (CI) 352 (M^++1, 25), 337 (M^++1-15, 0.5), 324 (M^++1-28, 0.6), 308 (M^++1-44, 89), 293 (308-15$^+$, 1).

Sodium 3-ethylthio-7-methoxy-1-dethia-2-thia-3-cephemcarboxylate (7d). The compound (**18**) (0.12 g, 0.292 mmol) was dissolved in 30 ml of THF and 30 ml of EtOH and hydrogenated in presence of 50 mg of Pd-C (10%) at 14 psi. Tlc after 10 h showed presence of starting material. An additional 20 ml of EtOH and 150 mg of catalyst were added and hydrogenation was continued at 30 psi for 3 h. The mixture was filtered through a celite pad and concentrated in vacuum. The yellowish foam was treated with 1 eq. of $NaHCO_3$ (based on starting material) in 10 ml of water. The aq. layer was washed twice with EtOAc (10 ml each) and lyophilised to give crude sodium salt. Purification by reverse phase flash column chromatography (10% MeCN in H_2O) gave 45 mg (56%) of **7d** as white powder: mp 190-191 °C (decomp.); ^1H nmr (300 MHz, D_2O) 1.26 (3H, t, J=7.4 Hz, CH_3), 2.86-2.94 (2H, overlapping q, J=7.3 Hz, SCH_2CH_3), 3.20 (1H, dd, J=12.5 and 9.6 Hz, CH_2S), 3.29 (1H, dd, J=12.5 and 3.7 Hz, CH_2S), 3.50 (3H, s, OCH_3), 4.05 (1H, ddd, J=3.6, 4.5 and 9.6 Hz, HCN), 4.98 (1H, d, J=4.5 Hz, HCC=O); ^{13}C nmr (300 MHz, D_2O) 13.6 (CH_3), 27.5 (CH_2S), 28.3 (CH_2S), 51.8 (CH_3O), 58.8 (HCN), 85.0 (*H*C*C*=O), 115.8 (C=C), 165.0 (C=O), 167.9 (C=O); ir 1752 (C=O), 1610 cm^{-1} (COO^-); ms (for free acid) 275 (M^+, 1), 247 (M^+-28, 4), 231 (M^+-44,16), 203 (M^+-72, 22); HRms for $C_{10}H_{13}NO_4S_2$ calcd 275.0305, found 275.0296.

p-Nitrobenzyl 3-methoxy-4-cinnamyl-2-azetidinon-1-ylacetate (16). *p*-Nitrobenzyl glycine (7.5 g, 0.036 mol) and *trans*-cinnamaldehyde (5.1 g, 0.039 mol) in 200 ml of CH_2Cl_2 was stirred with excess of anhyd $MgSO_4$ for 1 h. [Longer reaction period yields poor quality imine.] The imine[15] solution was quickly filtered into a dry flask containing 1.5 g of 4Å mol. sieves and cooled to -78 °C under N_2. Et_3N (6.5 ml, 0.047 mol) was added by syringe and an additional 50 ml of CH_2Cl_2 was introduced to dissolve imine. Methoxyacetyl chloride (3.5 ml, 0.037 mol) in 20 ml of CH_2Cl_2 was added dropwise over 15 min and the solution was allowed to slowly warm to 25 °C. After 5 h, 100 ml of 10% HCl was added and resulting layers were separated. The crude product, obtained *via* standard workup procedure, was purified by repeated column chromatography (1:2 EtOAc: hexanes) to give 3.0 g (18%) of **16** as a yellow oil which solidified after a week: mp 102-103 °C; ^{1}H nmr (200 MHz) 3.44 (3H, s, OCH_3), 3.79 (1H, d, J=18.2 Hz, NC*H*HCOOR), 4.25 (1H, d, J=18.4 Hz, NCH*H*COOR), 4.49 (1H, dd, J=9.2 and 4.4 Hz, HCN), 4.70 (1H, d, J=4.4 Hz, HCC=O), 5.20 (2H, s, CH_2PNB), 6.20 (1H, dd, J=15.9 and 9.2 Hz, HC=C), 6.66 (1H, d, J=15.9 Hz, C=CHPh), 7.24-7.46 (7H, m, Ph and PNB), 8.13 (2H, d, J=18.32 Hz, PNB); ir (film) 1750-1770 (broad, C=O), 1520 and 1350 cm^{-1} (NO_2); ms 396 (M^+, 3), 366 (M^+-30, 5), 325 (imine+1$^+$, 26), 235 (M^+-161, 1), 160 (M^+-236, 89); HRms for $C_{21}H_{20}N_2O_6$ calcd 396.1318, found 396.1320.

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