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Studies on the Reactivity of Cephalosporins. 6.[1] Ozonolysis of Δ^2-Cephem Derivatives as a New Entry to Highly Functionalized 2-Oxoazetidine and 2-Oxoazetidine-4-sulfenic Acid Derivatives.

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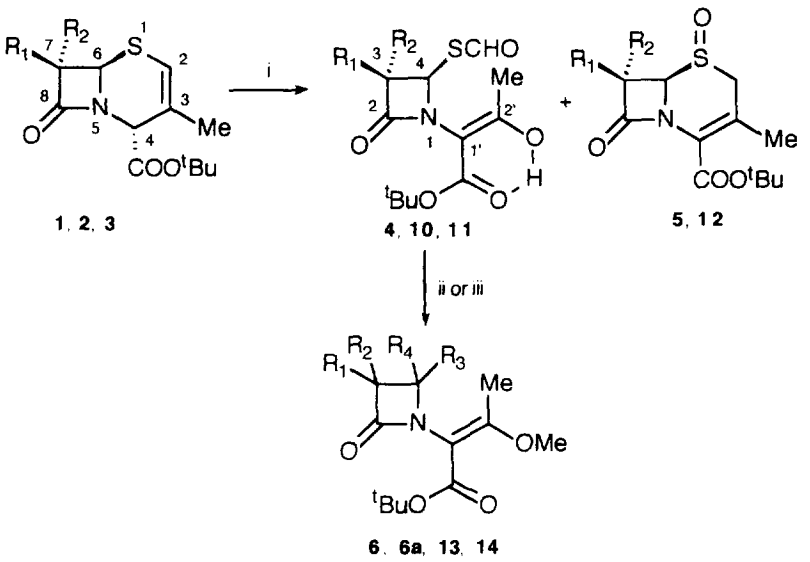
Abstract: The ozonolysis of Δ^2-cephem derivatives **1**, **2**, and **3**, to obtain highly functionalized 2-oxoazetidine and 2-oxoazetidine-4-sulfenic acid derivatives is described. An efficient and selective synthesis of the oxapenem derivative **16** is also reported.

Ozonation is generally recognized as a clean, mild, and selective method of oxidation and therefore its use would be attractive for several synthetic transformations.[2] Ozonation of penicillin and dihydroacetoxycephalosporin derivatives in aqueous media has been reported to give high yields (usually greater than 95%) of diastereomeric sulfoxide mixtures.[3,4] Sulfoxides did not react further with ozone, and in the case of penicillin derivatives the S/R ratio varied with the size of the N(7)- and C(2)-substituents present on the heterocyclic ring. Nevertheless, up today, no general informations about the ozonation of easily available Δ^2-cephem derivatives have been described, probably because of their low reactivity[5] and biological inactivity.[6] The carbon-carbon double bond present in Δ^2-cephems is sterically less hindered than that present in Δ^3-cephem isomers,[7] and it should be reactive enough toward ozone to compete with the sulfur atom in the oxidative trasformation. In this paper we describe selective ozonolyses of t-butyl 3-methyl-7-substituted-2-cephem-4-carboxylate derivatives **1**, **2**, and **3** to give highly functionalized 2-oxoazetidine and 2-oxoazetidine-4-sulfenic acid derivatives.

The reaction of t-butyl 3-methyl-7-phenoxyacetamido-2-cephem-4-carboxylate **1**, prepared as reported from 7-aminodeacetoxycephalosporanic acid (7-ADCA),[8] with ozone in CH_2Cl_2 at -20°C for 20 minutes, followed by quenching with dimethyl sulfide, afforded 4-(formyl)thio-3-phenoxyacetamido-N(1)-(1'-t-butyl

carboxylate-propan-2'-one-1'-yl)azetidin-2-one **4** (85%) as the main product,[9] and t-butyl 3-methyl-7-phenoxyacetamido-3-cephem-4-carboxylate-1-oxide **5** (9%) as by product (Scheme 1). Compound **5** was found stable when subjected to further ozonation and was identical to an authentic sample prepared by oxidation of **1** with m-chloroperbenzoic acid (m-CPBA) followed by double bond isomerization.[10]

Scheme 1



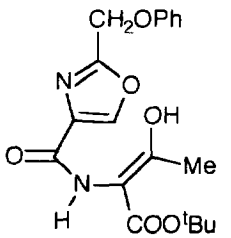
1, **4**, **5**: R_1= NHCOCH$_2$OPh, R_2=H
6: R_1= NHCOCH$_2$OPh, R_2=H, R_3= H, R_4= SCHO
6a: R_1= NHCOCH$_2$OPh, R_2=H, R_3= SCHO, R_4= H
2, **10**, **12**: R_1= Phthalimido, R_2=H
3, **11**: R_1= H, R_2= Br
13: R_1= Phthalimido, R_2=H, R_3= H, R_4= SCHO
14: R_1= H, R_2= Br, R_3= SCHO, R_4= H

i: Ozone, CH_2Cl_2, -20°C, 20 minutes (procedure A). ii: CH_2N_2, ether, 25°C. iii: Distilled CH_2N_2, ether, 25°C.

It is interesting to note that the reported ozonolysis was very selective. In fact, only a little amount of the sulfoxide **5** was isolated, showing that the possible sulfur atom oxidation[11] and double bond isomerization were uncompetitive reactions under these experimental conditions. The ^{1}H-NMR spectrum of compound **4** revealed the presence of the enol form (broad singlet at 12.61 δ readily disappearing by addition of D_2O) probably because of the presence of intramolecular hydrogen bond. Selective alkylation of the enol moiety was obtained by treatment of compound **4** with an excess of undistilled diazomethane (prepared from nitrosomethylurea in the presence of ether and 30% KOH aqueous solution and stored over KOH) in ether at 25°C to give the methyl enol ether derivative **6** in good (72%) yield. The *trans* relationship between H-3 and H-4 protons was determined by ^{1}H-NMR coupling-constant value ($J_{H(3),H(4)}$= 2.2 Hz) [Scheme 1]. The use of an alkaline ethereal solution of diazomethane is an essential requirement in the formation of **6**. In fact, only the

cis-isomer **6a** ($J_{H(3),H(4)}$= 4.7 Hz) was obtained in acceptable (53%) yield when a distilled diazomethane ethereal solution was used (Scheme 1). The mechanism of the epimerisation has not been studied in detail. It is possible to suggest that the epimerisation may occur through simple deprotonation-protonation at the 3-position in accordance with the results previously described by Stoodley[12] and coworkers in the investigation on epimerisation of penicillin derivatives.

Compound **4** was stable only few days when stored at 5°C under nitrogen atmosphere, and the oxazole derivative **7** was the only detectable degradation product.[13] Compound **7** was charactherized as mixture of enol and keto (not shown) tautomers in a 10:1 ratio as determined by ^{1}H-NMR analysis. An unusual nucleophilic ring opening of the 2-oxoazetidine nucleus and the displacement of the whole (formyl)thio moiety may be important steps in the formation of **7**. Precedent for the formation of oxazoles from 4-thioazetidinones can be found in the work of Stoodley.[14] The presence of a compound similar to **4** has been proposed by Woodward[15] as intermediate in the synthesis of penems, but never spectroscopic data were described probably because of its instability.



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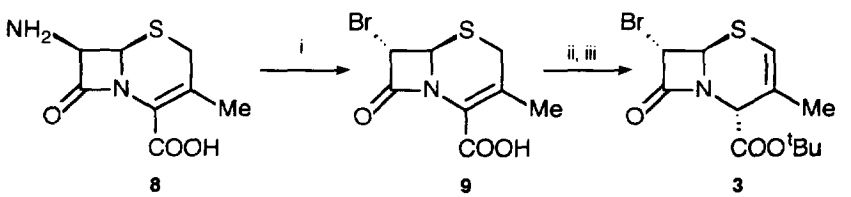
The versatility of the ozonolysis of Δ^2-cephem derivatives is further illustrated by the oxidation of t-butyl 3-methyl-7-phthalimido-2-cephem-4-carboxylate **2** and t-butyl 3-methyl-7-α-bromo-2-cephem-4-carboxylate **3**. Compound **2** was prepared from 7-ADCA using N-carboethoxyphthalimide as protective group.[16] Compound **3**, never described in the literature, was prepared using a modified procedure previously reported for penicillin derivatives (Scheme 2).[17]

Scheme 2



8 **9** **3**

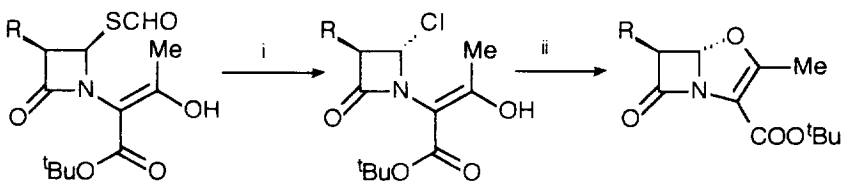
i: NaBr, $NaNO_2$, H_2SO_4, 2°C. ii: Oxalyl chloride, CH_2Cl_2, 25°C. iii: t-Butyl alcohol, NEt_3, 25°C.

In this case, the reaction of 7-ADCA **8** with sodium bromide and sodium nitrite in the presence of sulfuric acid at 2°C afforded 3-methyl-7-α-bromo-3-cephem-4-carboxylic acid **9** in acceptable yield (62%). Treatment with oxalyl chloride followed by reaction with t-butyl alcohol in the presence of catalytic amount of triethylamine afforded **3** in an overall 61% yield for the two steps.

The ozonolysis of compounds **2** and **3** in CH_2Cl_2 at -20°C for 20 minutes, followed by quenching with dimethyl sulfide, afforded 4-(formyl)thio-3-phthalimido-N(1)-(1'-t-butylcarboxylate-propan-2'-one-1'-yl) azetidin-2-one **10** and 4-(formyl)thio-3-α-bromo-N(1)-(1'-t-butylcarboxylate-propan-2'-one-1'-yl) azetidin-2-one **11** in good (72% and 78%, respectively) yields. In the ozonolysis of compound **2** less amount of t-butyl 3-methyl-7-phthalimido-3-cephem-4-carboxylate-1-oxide **12** was isolated (5%), showing a high chemoselectivity for the reaction (Scheme 1). Compounds **10** and **11** were found more stable than **4** when stored at 5°C under nitrogen atmosphere. As expected, treatment of 2-oxoazetidine derivatives **10** and **11** with alkaline diazomethane in ether at 25°C afforded the methyl enol ether derivatives **13** and **14** in good (69% and 78%, respectively) yields (Scheme 1). Compounds **13** and **14** were characterized by a *trans* relationship between H-3 and H-4 protons as determined by ^{1}H-NMR coupling-constant values (see experimental).

To evaluate the synthetic usefulness of 2-oxoazetidine derivatives, compound **10** was used as substrate for the synthesis of the oxapenem **16** (Scheme 3).

Scheme 3



10 **15** **16**

R= Phthalimido

i: N-chlorosuccinimide, CH_2Cl_2, 25°C. ii: Triethylamine, CH_2Cl_2, 25°C.

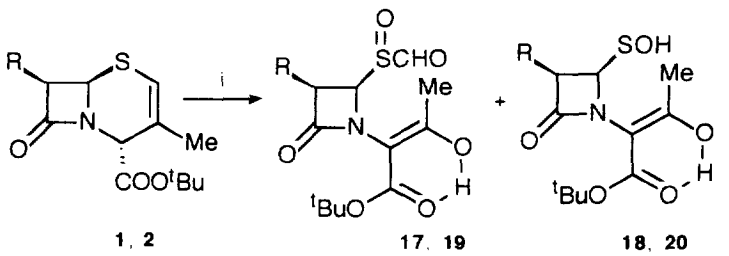
The reaction of **10** with N-chlorosuccinimide (3 equiv/mol) in CH_2Cl_2 at 25°C afforded *trans*-3-phthalimido-4-α-chloro-N(1)-(1'-t-butylcarboxylate-propan-2'-one-1'-yl)azetidin-2-one **15** in acceptable (35%) yield, along with decomposition products that were not further characterized. The *trans* relationship between protons H-3 and H-4 was determined by ^{1}H-NMR coupling-constant value ($J_{H(3),H(4)}$= 2.0 Hz). Subsequent treatment of **15** with an excess of triethylamine[18] in CH_2Cl_2 at 25°C afforded the oxapenem **16** ($J_{H(3)/H(4)}$= 1.8 Hz) in 36% yield, giving a new entry to this family of compounds.[19]

Finally, it is noteworthy that the reaction of compound **1** with a large excess of ozone for longer reaction time (2-4 hrs) afforded 3-phenoxyacetamido-N(1)-(1'-t-butylcarboxylate-propan-2'-one-1'-yl)azetidin-2-one-4-sulfenic acid **18** as the main product (52%), and compound **17** as by product [Scheme 4]. In a similar way, the

ozonolysis of **2** with a large excess of ozone afforded 3-phthalimido-N(1)-(1'-t-butylcarboxylate-propan-2'-one-1'-yl)azetidin-2-one-4-sulfenic acid **20** as the main product (45%), and compound **19** as by product. Compounds **17** and **19** showed low stability even if stored at low temperature and gave **18** and **20** as main degradation products. Analytical samples of **17** and **19** were obtained by thin layer chromatography purification and quickly characterized by usual spectroscopic procedures. Compounds **17** and **19** were tentatively considered as formylsulfoxide derivatives on the basis of the presence of the chemical shift of the aldehydic protons (δ 9.40-10.0 and δ 10.05-10.11 [$CDCl_3$], respectively) in the ^{1}H-NMR spectra, and of the absorption of the aldehydic and sulfoxide groups (1800-1785 cm^{-1} and 1110-1100 cm^{-1}[$CHCl_3$]) in the IR spectra, even if, those compounds, which to the best of our knownledge have never been described, might be expected to be rather labile species. Moreover, it is reasonable to suggest that compounds **17** and **19** might undergo decarbonylation to yield sulfenic acids **18** and **20**.

Although sulfenic acids are usually "transient species",[20] the synthesis of stable azetidinone sulfenic acids by thermolysis of penicillin sulfoxide esters has been reported by Chou.[21] More recently, the synthesis of 3-phthalimido-N(1)-(dimethyl-t-butylsilyl)azetidin-2-one-4-sulfenic acid (not shown) exhibiting an unusually high thermal stability has been described by Bachi and Gross.[22]

Scheme 4



1, **17**, **18**: R= $PhOCH_2CONH$
2, **19**, **20**: R= Phthalimido

i: Ozone (large excess), CH_2Cl_2, -20°C, 2-4 hrs (procedure B).

In conclusion, the ozonolysis of Δ^2-cephem derivatives is a mild and efficient method for the synthesis of highly functionalized 2-oxoazetidine and 2-oxoazetidine-4-sulfenic acid derivatives.

Experimental

NMR spectra were recorded on a Bruker (200 MHz) and are reported in δ values. Chemical shifts are in ppm downfield from tetramethylsilane as internal standard (δ_H=0.0) Infrared spectra were recorded on a Perkin Elmer 298 spectrophotometer using NaCl plates. Microanalyses were performed by C. Erba 1106 analyzer. Mass spectra were recorded on a VG 70/250S spectrometer with an electron beam of 70 eV. Melting points were obtained on a Reichert Kofler apparatus and are uncorrected. All solvents were ACS reagent grade and were redistilled and dried according to standard procedures. Chromatographic purifications were performed on

columns packed with Merck silica gel 60, 230-400 mesh for flash technique. Thin-layer chromatography was carried out using Merck plates Kieselgel 60 F_{254}.

Starting Compounds

Tert-butyl-3-methyl-7-phenoxyacetamido-2-cephem-4-carboxylate **1** was prepared using the procedure described by Murphy.[8] Tert-butyl 3-methyl-7-phthalimido-2-cephem-4-carboxylate **2** was prepared using the procedure described by Botta.[16]

Synthesis of t-butyl-3-methyl-7-α-bromo-2-cephem-4-carboxylate **3**: 7-ADCA (5g., 23 mmol) and NaBr (12g, 116.5 mmol) were dissolved in H_2SO_4 (57 ml, 2.5N) in a becker equipped with mechanical stirrer and cooled at 0°C. To this mixture a solution of $NaNO_2$ (2.5 g in 12 ml of H_2O) was added slowly to prevent temperature raised over 2°C. The reaction, kept at 0°C for 1h and than warmed until room temperature, gave a gummy solid which was extracted with ethyl acetate (2x100 ml). The organic layer was washed with brine and dried. After evaporation of the solvent under reduced pressure, the crude was purified by flash-chromatography ($CHCl_3$/AcOH= 93/7) to give 3-methyl-7-α-bromo-3-cephem-4-carboxylic acid **9** (62%). Compound **9** (4g, 14.4 mmol) was dissolved in dry benzene (400 ml) and DMF (0.1 ml) and cooled at 0°C. Oxalyl chloride (2.8 ml, 32.6 mmol) was added slowly and the reaction was kept at 60°C for 1h and concentrated under anhydrous conditions. Acid chloride so obtained was slowly added to a cooled (0°C) solution of t-butanol (12.5g) in dry benzene (100 ml) in the presence of dry NEt_3 (3.7 ml). The reaction was washed with H_2O, HCl 2N, still H_2O and dried. After evaporation of the solvent, the crude was purified by flash-chromatography (n-hexane/ethyl acetate= 4/1) to give t-butyl 3-methyl-7-α-bromo-2-cephem-4-carboxylate **3** (4.76g, 61%).

Tert-butyl-3-methyl-7-α-bromo-2-cephem-4-carboxylate **3**: oil; I.R. ($CHCl_3$) ν_{max} 1785, 1740, 1155 cm^{-1}; δ_H [$CDCl_3$, 200 MHz] 1.50 (9H, s, CH_3), 1.81 (3H, s, CH_3), 4.50 (1H, b.s., H-4), 4.60 (1H, b.s., H-6), 5.01 (1H, s, H-7), 5.92 (1H, b.s., H-2); m/z 334 (M^+, 21%). Anal. Calcd. for $C_{12}H_{16}NBrO_3S$: C, 43.12%; H, 4.82%; N, 4.19%. Found. C, 43.19%, H, 4.87%; N, 4.25%.

3-Methyl-7-α-bromo-3-cephem-4-carboxylic acid **9:** oil; I.R. ($CHCl_3$) ν_{max} 3480, 1780, 1740; δ_H [$CDCl_3$, 200 MHz] 1.77 (3H, s, CH_3), 3.39 (1H, d, J 18 Hz, H-2), 3.58 (1H, d, J 18 Hz, H-2), 4.73 (1H, b.s., H-6), 5.07 (1H, s, H-7); m/z 278 (M^+, 18%). Anal. Calcd. for $C_8H_8NBrO_3S$: C, 34.54%; H, 2.90%; N, 5.04%. Found. C, 34.61%, H, 2.95%; N, 5.0%.

Ozonation of Δ^2-cephem derivatives 1, 2, and 3. General procedures.

Procedure A

1 mmol of substrate was dissolved in 5 ml of CH_2Cl_2 and placed in a 100 ml, three-necked flask equipped with a magnetic stirrer, a gas inlet tube, and a bubble flow meter. The substrate was allowed to react with an ozone-oxygen stream introduced at a flow of 660 ml/min (27 mg of O_3/min) for 20 minutes (TLC, $CHCl_3$/AcOEt=4.0:1.0 as eluent). The resulting mixture was quenched with dimethyl sulfide (0.1 ml) and purged with nitrogen for 30 min, transferred to a round bottomed flask and concentrated in vacuo. When necessary, the residue was purified by flash-chromatography using chloroform/ethyl acetate as eluent.

Procedure B

1 mmol of substrate was dissolved in 5 ml of CH_2Cl_2 and placed in a 100 ml, three-necked flask equipped with a magnetic stirrer, a gas inlet tube, and a bubble flow meter. The substrate was allowed to react with an ozone-oxygen stream introduced at a flow of 660 ml/min (27 mg of O_3/min) for 2-4 hrs (TLC, $CHCl_3$/AcOEt=4.0:1.0 as eluent). The resulting mixture was purged with nitrogen for 30 min, transferred to a round bottomed flask and concentrated in vacuo.

4-(Formyl)thio-3-phenoxyacetamido-N(1)-(1'-t-butylcarboxylate-propan-2'-one-1'-yl)azetidin-2-one **4**: (370mg, 85%); oil; I.R. ($CHCl_3$) ν_{max} 3420, 1785, 1720, 1690, 1660 cm^{-1}; δ_H [$CDCl_3$, 200 MHz] 1.55 (9H, s, CH_3), 2.20 (3H, s, CH_3), 4.50 (2H, s, CH_2), 5.35 (1H, m, H-3), 6.10 (1H, d, J 4.5 Hz, H-4), 6.90-7.30 (6H, m, Ph-H and NH), 10.0 (1H, s, CHO), 12.61 (1H, b.s., OH); m/z 436 (M^+, 35%). Anal. Calcd. for $C_{20}H_{24}N_2O_7S$: C, 55.03%; H, 5.54%; N, 6.42%. Found. C, 54.99%, H, 5.61%; N, 6.48%.

Tert-butyl-3-methyl-7-phenoxyacetamido-3-cephem-4-carboxylate-1-oxide **5**: (38mg, 9%) oil; I.R. ($CHCl_3$) ν_{max} 3420, 1820, 1730, 1705 cm^{-1}; δ_H [$CDCl_3$, 200 MHz] 1.50 (9H, s, CH_3), 2.15 (3H, s, CH_3), 3.50 (2H, m, CH_2), 4.45 (1H, m, H-6), 4.60 (2H, s, CH_2), 6.31 (1H, m, H-7), 6.90-7.55 (6H, m, Ph and NH); m/z 420 (M^+, 35%). Anal. Calcd. for $C_{20}H_{24}N_2O_6S$: C, 57.13%; H, 5.75%; N, 6.64%. Found. C, 57.21%, H, 5.76%; N, 6.69%.

Oxazole derivative **7**: compound **7** was charactherized as an unseparable mixture of enol and keto tautomers in a 10:1 ratio (determined by ^{1}H-NMR): oil; I.R. ($CHCl_3$) ν_{max} 3420, 1730, 1705 cm^{-1}; δ_H [$CDCl_3$, 200 MHz] of the main isomer, 1.53 (9H, s, CH_3), 2.09 (3H, s, CH_3), 4.50 (2H , s, CH_2), 6.82-7.34 (5H, m, Ph-H), 7.15 (1H, bs, NH), 8.0 (1H, s, CH); δ_H [$CDCl_3$, 200 MHz] main signals of the keto isomer, 5.60 (1H, d, J 7.5 Hz, CH), 7.09 (1H, d, J 7.5 Hz, NH); m/z 374 (M^+, 53%). Anal. Calcd. for $C_{19}H_{22}N_2O_6$: C, 60.95%; H, 5.92%; N, 7.48%. Found. C, 60.87%, H, 5.94%; N, 7.51%.

4-(Formyl)thio-3-phthalimido-N(1)-(1'-t-butylcarboxylate-propan-2'-one-1'-yl)azetidin-2-one **10**: (311mg, 72%); oil; I.R. ($CHCl_3$) ν_{max} 1785, 1730, 1690 cm^{-1}; δ_H [$CDCl_3$, 200 MHz] 1.61 (9H, s, CH_3), 2.32 (3H, s, CH_3), 5.91 (1H, d, J 4.0 Hz, H-3), 6.43 (1H, d, J 4.0 Hz, H-4), 7.81 (4H, m, C_6H_4), 10.11 (1H, s, CHO), 12.66 (1H, b.s., OH); m/z 432 (M^+, 47%). Anal. Calcd. for $C_{20}H_{20}N_2O_7S$: C, 55.55%; H, 4.66%; N, 6.48%. Found. C, 55.67%, H, 4.73%; N, 6.60%.

4-(Formyl)thio-3-α-bromo-N(1)-(1'-t-butylcarboxylate-propan-2'-one-1'-yl)azetidin-2-one **11**: (286mg, 78%); oil; I.R. ($CHCl_3$) ν_{max} 1790, 1698, 1651 cm^{-1}; δ_H [$CDCl_3$, 200 MHz] 1.54 (9H, s, CH_3), 2.71 (3H, s, CH_3), 4.82 (1H, d, J 1.8 Hz, H-3), 5.85 (1H, d, J 1.8 Hz, H-4), 10.22 (1H, s, CHO), 12.63 (1H, b.s., OH); m/z 366 (M^+, 31%). Anal. Calcd. for $C_{12}H_{16}NBrO_5S$: C, 39.35%; H, 4.40%; N, 3.82%. Found. C, 39.29%, H, 4.42%; N, 3.95%.

Tert-butyl-3-methyl-7-phthalimido-3-cephem-4-carboxylate-1-oxide **12**: (21mg, 5%) oil; I.R. ($CHCl_3$) ν_{max} 1800, 1750, 1720 cm^{-1}; δ_H [$CDCl_3$, 200 MHz] 1.50 (9H, s, CH_3), 2.34 (3H, s, CH_3), 3.30-4.20 (2H, m, CH_2), 4.70 (1H, d, J 4.8 Hz, H-6), 6.01 (1H, d, J 4.8 Hz, H-7), 7.60-7.93 (4H, m, C_6H_4); m/z 416 (M^+,

67%). Anal. Calcd. for $C_{20}H_{20}N_2O_6S$: C, 57.68%; H, 4.84%; N, 6.73%. Found. C, 57.77%, H, 4.91%; N, 6.70%.

Formylsulfoxide derivative **17**: (59mg, 13%) ; I.R. ($CHCl_3$) ν_{max} 3450, 3150, 1800, 1750, 1720, 1110 cm^{-1}; δ_H [$CDCl_3$, 200 MHz] as mixture of R/S (1:1) sulfoxide isomers: 1.35 (9H, s, CH_3), 2.25-2.50 (3H, s, CH_3), 4.45 (2H, s, CH_2), 5.25-5.45 (2H, m, H-6), 6.10 (1H, m, H-7), 6.80-7.25 (5H, m, Ph), 7.75 (1H, b.s., NH), 9.40-10.0 (1H, s, CHO), 12.0 (1H, b.s., OH); m/z 452 (M^+, 43%). Anal. Calcd. for $C_{20}H_{24}N_2O_8S$: C, 53.09%; H, 5.35%; N, 6.19%. Found. C, 53.11%, H, 5.40%; N, 6.22%.

3-Phenoxyacetamido-N(1)-(1'-t-butylcarboxylate-propan-2'-one-1'-yl)azetidin-2-one-4-sulfenic acid **18**: (220 mg, 52%) oil; I.R. ($CHCl_3$) ν_{max} 3455, 3200 1780, 1750, 1720 cm^{-1}; δ_H [$CDCl_3$, 200 MHz] 1.53 (9H, s, CH_3), 2.38 (3H, s, CH_3), 3.30-4.20 (2H, m, CH_2), 5.20 (1H, m, H-3) [becomes a doublet, J 5.10 Hz, after addition of D_2O], 5.30 (1H, m, H-4) [becomes a doublet, J 5.10 Hz, after addition of D_2O], 6.85-7.40 (5H, m, Ph), 7.60 (1H, m, NH), 12.51 (1H, b.s., OH); m/z 424 (M^+, 29%). Anal. Calcd. for $C_{19}H_{24}N_2O_7S$: C, 53.76%; H, 5.70%; N, 6.60%. Found. C, 53.81%, H, 5.70%; N, 6.68%.

Formylsulfoxide derivative **19**: (112mg, 25%) ; I.R. ($CHCl_3$) ν_{max} 3200, 1785, 1750, 1720, 1100 cm^{-1}; δ_H [$CDCl_3$, 200 MHz] as mixture of R/S (1:1) sulfoxide isomers: 1.54 (9H, s, CH_3), 2.25-2.33 (3H, s, CH_3), 5.80-5.92 (2H, m, H-6), 6.38-6.44 (1H, m, H-7), 7.70-7.95 (4H, m, C_6H_4), 10.05-10.11 (1H, s, CHO), 12.60 (1H, b.s., OH); m/z 448 (M^+, 23%). Anal. Calcd. for $C_{20}H_{20}N_2O_8S$: C, 53.57%; H, 4.49%; N, 6.25%. Found. C, 53.60%, H, 4.46%; N, 6.20%.

3-Phthalimido-N(1)-(1'-t-butylcarboxylate-propan-2'-one-1'-yl)azetidin-2-one-4-sulfenic acid **20**: (189mg, 45%) oil; I.R. ($CHCl_3$) ν_{max} 3450, 3100, 1790, 1750, 1720 cm^{-1}; δ_H [$CDCl_3$, 200 MHz] 1.21 (9H, s, CH_3), 2.30 (3H, s, CH_3), 5.61 (1H, d, J 5.0 Hz, H-3), 5.71 (1H, d, J 5.0 Hz, H-4), 7.77-7.98 (4H, m, C_6H_4), 12.50 (1H, b.s., OH); m/z 420 (M^+, 54%). Anal. Calcd. for $C_{19}H_{20}N_2O_7S$: C, 54.28%; H, 4.79%; N, 6.66%. Found. C, 54.31%, H, 4.82%; N, 6.68%.

Alkylation of compounds ***4***, ***10***, ***11****-General procedure.*

To a stirred solution of the substrate (1 mmol) in CH_2Cl_2 (5 ml) was added CH_2N_2 (wet ethereal solution alkaline for KOH) at 0°C until the substrate disappeared ($CHCl_3$/EtOAc= 40/10). The excess of CH_2N_2 was distilled under a flow stream of nitrogen at room temperature. The solvent was evaporated under reduced pressure and the crude purified by preparative thin layer chromatography ($CHCl_3$/EtOAc= 40/10) to give compounds **6**, **13**, and **14** . In the case of compond **4** the reaction was also performed, in similar experimental conditions, using careful distilled CH_2N_2 to obtain compound **6a**.

Methyl enol ether derivative **6**: (324mg, 72%); oil; I.R. ($CHCl_3$) ν_{max} 3435, 1780, 1755, 1690 cm^{-1}; δ_H [$CDCl_3$, 200 MHz] 1.53 (9H, s, CH_3), 2.48 (3H, s, CH_3), 3.81 (3H, s, OCH_3), 4.57 (2H, s, CH_2), 5.65 (1H, m, H-3), 6.04 (1H, d, J 2.2 Hz, H-4), 6.81-7.43 (6H, m, Ph-H and NH), 10.05 (1H, s, CHO); m/z 450 (M^+, 75%). Anal. Calcd. for $C_{21}H_{26}N_2O_7S$: C, 55.99%; H, 5.82%; N, 6.22%. Found. C, 56.08%, H, 5.80%; N, 6.25%.

Methyl enol ether derivative **6a**: (239mg, 53%); oil; I.R. ($CHCl_3$) ν_{max} 3433, 1781, 1755, 1695 cm^{-1}; δ_H [$CDCl_3$, 200 MHz] 1.56 (9H, s, CH_3), 2.52 (3H, s, CH_3), 3.80 (3H, s, OCH_3), 4.59 (2H, s, CH_2), 5.76 (1H, m, H-3), 6.12 (1H, d, J 4.7 Hz, H-4), 6.78-7.43 (6H, m, Ph-H and NH), 10.05 (1H, s, CHO); m/z 450 (M^+, 63%). Anal. Calcd. for $C_{21}H_{26}N_2O_7S$: C, 55.99%; H, 5.82%; N, 6.22%. Found. C, 56.09%, H, 5.83%; N, 6.29%.

Methyl enol ether derivative **13**: (308mg, 69%); oil; I.R. ($CHCl_3$) ν_{max} 1785, 1730, 1690 cm^{-1}; δ_H [$CDCl_3$, 200 MHz] 1.58 (9H, s, CH_3), 2.43 (3H, s, CH_3), 3.92 (3H, s, OCH_3), 5.91 (1H, d, J 2.2 Hz, H-3), 6.49 (1H, d, J 2.2 Hz, H-4), 7.70-7.98 (4H, m, C_6H_4), 10.15 (1H, s, CHO); m/z 446 (M^+, 18%). Anal. Calcd. for $C_{21}H_{22}N_2O_7S$: C, 56.49%; H, 4.97%; N, 6.27%. Found. C, 56.53%, H, 4.89%; N, 6.28%.

Methyl enol ether derivative **14**: (296mg, 78%); oil; I.R. ($CHCl_3$) ν_{max} 1790, 1750, 1690 cm^{-1}; δ_H [$CDCl_3$, 200 MHz] 1.50 (9H, s, CH_3), 2.61 (3H, s, CH_3), 3.84 (3H, s, OCH_3), 4.80 (1H, d, J 1.9 Hz, H-3), 5.83 (1H, d, J 1.9 Hz, H-4), 10.15 (1H, s, CHO); m/z 380 (M^+, 39%). Anal. Calcd. for $C_{13}H_{18}NBrO_5S$: C, 41.06%; H, 4.77%; N, 3.68%. Found. C, 41.09%, H, 4.83%; N, 3.70%.

Synthesis of the oxapenem derivative **16**: 4-(Formyl)thio-3-phthalimido-N(1)-(1'-t-butylcarboxylate-propan-2'-one-1'-yl)azetidin-2-one **10** (432mg, 1 mmol) and N-chlorosuccinimmide (399 mg, 3 mmol) were dissolved in CH_2Cl_2 (5 ml) and the solution was stirred at 25°C for 6h. The solvent was evaporated under reduced pressure and the crude purified by flash-chromatography ($CHCl_3/CH_3OH$= 9.5:0.5) to give 4-α-chloro-3-phthalimido-N(1)-(1'-t-butylcarboxylate-propan-2'-one-1'-yl)azetidin-2-one **15** (142 mg, 35%) as the only recovered product. Treatment of compound **15** (406 mg, 1 mmol) with triethylamine (5 mmol) in dry THF (5 ml) under nitrogen atmosphere at 25°C afforded, after usual purification procedure, the oxapenem derivative **16** (133 mg, 36%).

4-α-Chloro-3-phthalimido-N(1)-(1'-t-butylcarboxylate-propan-2'-one-1'-yl)azetidin-2-one **15**: oil, δ_H [$CDCl_3$, 200 MHz] 1.51 (9H, s, CH_3), 1.90 (3H, s, CH_3), 5.10 (1H, d, J 2.0 Hz, H-3), 5.62 (1H, d, J 2.0 Hz, H-4), 7.85-7.92 (4H, m, C_6H_4), 12.50 (1H, b.s., OH); m/z 406 (M^+, 39%). Anal. Calcd. for $C_{19}H_{19}N_2ClO_6$: C, 56.10%; H, 4.71%; N, 6.89%. Found. C, 56.12%, H, 4.77%; N, 6.91%.

Oxapenem derivative **16**: oil, δ_H [$CDCl_3$, 200 MHz] 1.51 (9H, s, CH_3), 2.36 (3H, s, CH_3), 5.65 (1H, d, J 1.8 Hz, H-5), 6.20 (1H, d, J 1.8 Hz, H-6), 7.84 (4H, m, C_6H_4); m/z 370 (M^+, 45%). Anal. Calcd. for $C_{19}H_{18}N_2O_6$: C, 61.62%; H, 4.90%; N, 7.56%. Found. C, 61.64%, H, 4.93%; N, 7.58%.

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