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Synthesis Of 6α-Methoxy-6β-Hydroxymethylpenems

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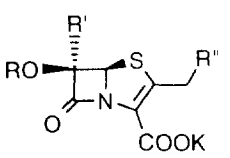
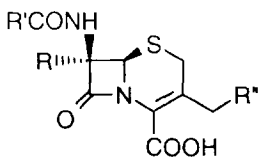
Abstract: The synthesis of 6α-methoxy-6β-hydroxymethyl-2-phenoxy-methylpenem and of 6α-methoxy-6β-hydroxymethyl-2-(1-methyltetrazol-5-yl)thiomethylpenem was accomplished *via* reaction of pivaloyl 6-diazopenicillanate with methyl orthoformate in the presence of boron trifluoride as a catalyst. The resulting pivaloyl 6α-methoxy-6β-trimethoxymethyl penicillanate was processed to the final penems *via* the corresponding secopenicillanate by well established procedures.

We described previously[1] the synthesis of a number of 6,6-disubstituted penems (**1**, Figure 1) designed to obtain novel compounds with high potency and stability towards hydrolytic enzymes. It is well documented that 7,7-disubstituted cephalosporins (**2**, Figure 1) retain their activity against β-lactamase producing strains[2,3] and that, in the case of PS-5 (**3a**, Figure1), the 6-epi-methoxy- and the 6-epi-hydroxy-PS 5[4,5] (**3b,c** Figure 1) are more stable than the parent compound towards human renal dehydropeptidase (DHP-I).



1



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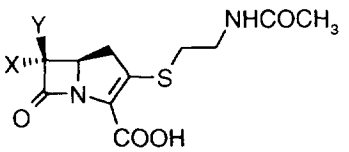
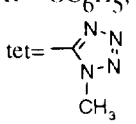


3

R= CH_3, $COCH_3$
R'= C_2H_5
R"= OC_6H_5, S-tet



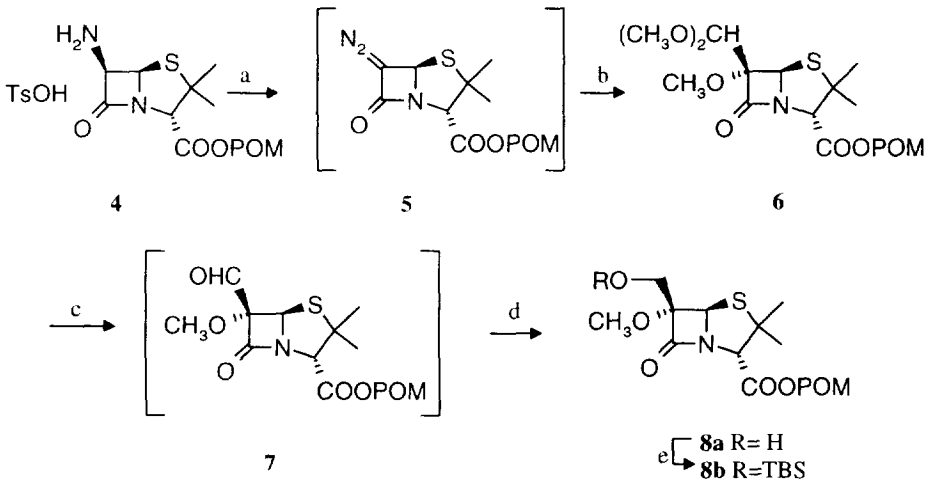
3a Y= H, X= C_2H_5
3b Y= C_2H_5, X= OCH_3
3c Y= C_2H_5, X= OH

Figure 1

We decided therefore to synthesize a number of 6α-methoxy-6β-hydroxymethyl- and of 6β-methoxy-6α-hydroxymethylpenems to study their antibacterial activity and stability to DHP-I and we wish to report here the synthesis of the potassium 6α-methoxy-6β-hydroxymethylpenems (**13a,b**) (Scheme **2**).

The synthesis of some representatives of the epimeric 6β-methoxy-6α-hydroxymethyl- series is reported in the following paper.

A number of potentially useful reactions between 6-diazopenicillanates and carbonyl compounds,[6-10] alcohols and thiols,[11-15] acyl chlorides,[16] *N*-halosuccinimides,[17-19] alkenes[20,21] are reported in the literature and the field has been reviewed.[22] It is also known that diazocarbonyl compounds undergo Lewis acid catalyzed carbon-oxygen insertion reaction with orthoesters to give α-alkoxy-β-dialkoxymethyl acetates.[23]



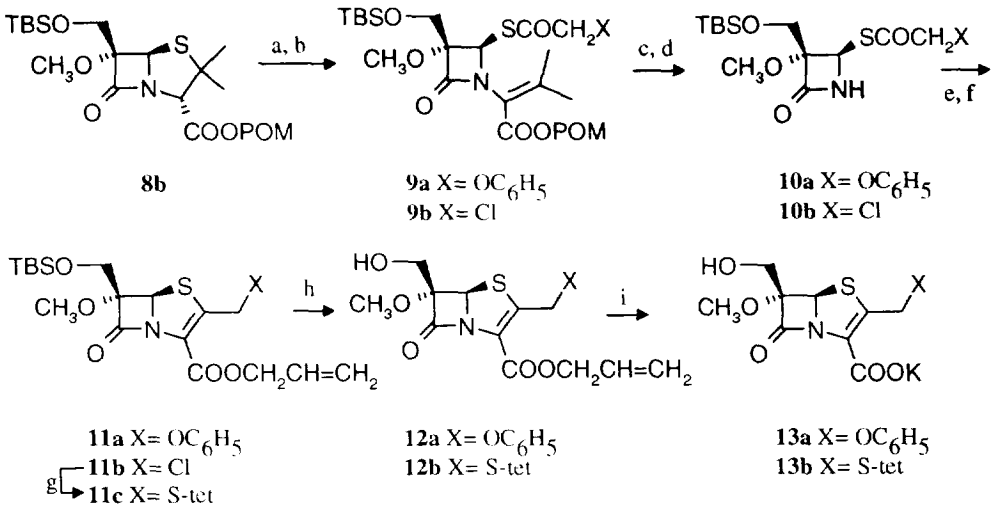
TBS= t-$C_4H_9(CH_3)_2Si$, POM= -$CH_2OOC(CH_3)_3$;
a= $NaNO_2$, TsOH, H_2O/CH_2Cl_2; b = $CH(OCH_3)_3$, $BF_3.(C_2H_5)O$, CH_2Cl_2; c= TMSI, $CHCl_3$;
d= $NaBH_4$, dioxane/ H_2O, e= TBSCl, imidazole, DMF

Scheme 1

This reaction seems to be unprecedented for 6-diazopenicillanates and, upon reaction with methyl orthoformate, we expected the formation of 6α-methoxy-6β-dimethoxymethyl- penicillanates from which the desired 6α-methoxy-6β-hydroxymethylpenems could be obtained. Our expectations were verified when pivaloyloxymethyl 6-diazopenicillanate (**5**) was reacted with methyl orthoformate in anhydrous dichloromethane with boron trifluoride etherate as a catalyst to yield exclusively pivaloyloxymethyl 6α-methoxy-6β-dimethoxymethyl penicillanate (**6**) (Scheme 1).

The 6β-acetalic function of **6** was stable under various mild hydrolytic conditions such as aqueous mineral acids at room temperature, silica gel and oxalic acid[24], silica gel and sulfuric acid[25] whereas the penicillanic ring system decomposed under stronger hydrolytic conditions. The use of trimethylsilyl iodide in chloroform[26] eventually allowed the isolation of the somewhat unstable aldehyde (**7**) which at room temperature undergoes rearrangement to give **14** (Figure 2) and therefore **7** was immediately reduced with sodium borohydride in aqueous dioxane to give **8a** in 35% yield. The formation of the thiazolooxazinone (**14**) was not unexpected because structurally related compounds have already been described by Jephcote.[6,7]

Protection of the hydroxyl group with *t*-butyldimethylsilyl chloride under standard conditions[27] gave the key intermediate penicillanate (**8b**) (Scheme 1) in 70% yield.



8b

9a X= OC_6H_5
9b X= Cl

10a X= OC_6H_5
10b X= Cl

11a X= OC_6H_5
11b X= Cl
g → **11c** X= S-tet

12a X= OC_6H_5
12b X= S-tet

13a X= OC_6H_5
13b X= S-tet

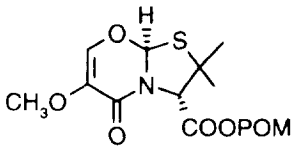
tet= 1-methyltetrazole;
a= PhHgCl, DBU, CH_3CN; b= $ClCOCH_2X$; c= O3, CH_2Cl_2, -70°C; d= SiO_2, CH_3OH;
e= $ClCOCOOCH_2CH=CH_2$, TEA, CH_2Cl_2; f= $P(OC_2H_5)_3$, xylene; ref.; g= sodium 5-mercapto-1-methyl tetrazole, $(n\text{-}C_4H_9)_4NBr$, CH_2Cl_2/H_2O; h= TBAF, CH_3COOH, THF;
i = $Pd(PPh_3)$, potassium 2-ethylhexanoate, $CH_3COOC_2H_5/CH_2Cl_2$.

Scheme 2

Fission of the S-C_2 bond of the thiazolidine ring with phenylmercuric chloride and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[28] in acetonitrile, followed by acylation with phenoxyacetyl chloride gave the secopenicillanate (**9a**) (Scheme 2) in 84% yield, which upon treatment with ozone in dichloromethane at -78 °C followed by treatment with silica in a 1/1 mixture of methanol/ethyl acetate gave the azetidinone (**10a**) in 45% overall yield. Acylation of **10a** with allyl oxalyl chloride followed by heating of the resulting oxalimido derivative in toluene in the presence of triethyl phosphite, gave penem (**11a**) in 40% yield after chromatography. Deprotection of the hydroxyl group with tetrabutylammonium fluoride and acetic acid in THF,[28,29] followed by palladium catalyzed deallylation in the presence of potassium 2-ethylhexanoate gave the final compound (**13a**) as the potassium salt.

The same procedure was used for the preparation of **13b** : chloroacetyl chloride was used instead of phenoxy acetyl chloride to give secopenicillanate (**9b**); penem (**11b**) was not isolated and the crude material was treated with the sodium salt of 5-mercapto-1-methyltetrazole under phase transfer conditions (water/dichloromethane, tetrabutylammonium bromide) and **11c** was isolated and processed as described before to **13b**.

The reaction between 6-diazopenicillanate and methyl orthoformate proceeds with high predicted stereoselectivity to 6α-methoxy-6β-dimethoxymethyl penicillanate which is then transformed into 6α-methoxy-6β-hydroxymethylpenems. This reaction is new for 6-diazopenicillanate; we did not study it with orthoesters other than methyl orthoformate.The data reported here together with those of the following paper provide a versatile entry to 6α-methoxy-6β-hydroxymethylpenems and to their epimers 6β-methoxy-6α-hydroxymethylpenems. Compounds (**13a,b**) showed a good chemical stability (t½ = 600 min for **13a** and >1000 min for **13b** in phosphate buffer at pH 7.4) and , as predicted, were more stable towards DHP-I than the corresponding 6β-hydroxymethylpenems.



14

Figure 2

EXPERIMENTAL SECTION

Ir spectra were recorded on a FT Bruker IFS48. ^{1}H-Nmr were recorded at 80 MHz on a Bruker WP80SY or at 300 MHz on a VXR5000-300S Varian according to the case, using deuterated chloroform or D_2O as solvent. Chemical shifts are stated in ppm (δ scale) using tetramethylsilane as an internal standard. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Analytical thin layer chromatography (tlc) were carried out with E.Merck F-254 silica gel plates. Column chromatography was performed as described by Still[30] et al with silica gel 60 (particle size 0.040-0.063 mm E.Merck). Solvents and reagents were used without any further purification and all reactions were carried out with stirring and under a nitrogen atmosphere unless otherwise stated. "The usual work up" means that: the organic layer was washed with brine, dried over sodium sulphate and evaporated to dryness under vacuum or according to the cases washed with 5% aqueous solution of sodium hydrogencarbonate and then with brine as before. The following abbreviations were used throughout: CyH: cyclohexane, DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene, DMF: dimethylformamide, Et_2O: ether, EA: ethyl acetate, MeOH: methanol, NBS : *N*-bromosuccinimide, Hex: n-hexane, TBAF: tetrabutylammonium fluoride trihydrate, TBSCl: *tert*-butyldimethylsilyl chloride, THF: tetrahydrofuran.

(2S,5R)-3,3-Dimethyl-2-[(2,2-dimethyl-1-oxo)propoxy]methoxycarbonyl-6-diazo-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane (5): The compound was prepared following the published procedure.[31] ^{1}H-Nmr ($CDCl_3$), (δ, ppm): 1.21 (s, 9H, $C(CH_3)_3$); 1.45 (s, 3H, 2α-Me); 1.63 (s, 3H, 2β-Me); 4.38 (s, 1H, H3); 5.81 (m, 2H, O-C<u>H</u>$_2$-O); 6.16 (s, 1H, H5). Ir($CDCl_3$), υ_{max}: 2080 (N=N), 1760 (broad, β-lactam and esters) cm^{-1}.

(2S,5R,6S)-3,3-Dimethyl-2-[(2,2-dimethyl-1-oxo)propoxy]methoxycarbonyl-6-6-dimethoxymethyl-6-methoxy-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane (6): A solution of freshly prepared **5** (5.8 g, 15 mmol) and trimethyl orthoformate (5 ml, 49 mmol) in anhydrous dichloromethane (30 ml) was added over 10 min, under vigorous stirring, to a solution of $BF_3{\cdot}(C_2H_5)_2O$ (2.1g, 15 mmol) in anhydrous dichloromethane (100 ml), precooled at -10°C. The reaction was let proceed for 3 h at -10°C, then concentrated under reduced pressure, diluted with EA (200 ml) and washed with a 5% aqueous solution of sodium hydrogencarbonate (200 ml). The usual work up produced an oily residue which was purified by flash chromatography (CyH/EA gradient from 9/1 to 7/3) to yield **6** (2.2 g, 34%) as a colourlesss oil. ^{1}H-Nmr ($CDCl_3$), (δ, ppm): 1.21 (s, 9H, $C(CH_3)_3$); 1.50 (s, 3H, 2α-Me); 1.63 (s, 3H, 2β-Me); 3.49 (s, 3H, OMe); 3.54 (s, 3H, CH-$(OMe)_2$); 3.61 (s, 3H, CH-$(OMe)_2$); 4.46 (s, 1H, H3); 4.70(s, 1H, -C<u>H</u>-$(OCH_3)_2$); 5.37 (s, 1H, H5); 5.82 (ABm, J= 12.5 Hz, 2H, -O-C<u>H</u>$_2$-O). Ir($CDCl_3$), υ_{max}: 1770 cm^{-1} (broad, β-lactam and esters). *Anal.* Calcd for $C_{18}H_{29}NO_8S$: C, 51.54; H, 6.97; N, 3.34; S, 7.64. Found: C, 51.42; H, 6.90; N, 3.38; S, 7.67.

(2S,5R,6S)-3,3-Dimethyl-2-[(2,2-dimethyl-1-oxo)propoxy]methoxycarbonyl-6-oxomethyl-6-methoxy-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane(7): Penicillanate (**6**) (1.7g, 4 mmol) was dissolved in anhydrous chloroform (30 ml). Trimethylsilyl iodide (1.1 ml, 8 mmol) was added over 10 min under stirring and the stirring was maintained untill disappearance of the starting material (tlc). The reaction mixture was then poured onto a 10% aqueous solution of sodium thiosulphate (30 ml). The usual work up yielded an oily residue which

was purified by short path flash chromatography (pentane/EA gradient 9/1 to 6/4). The product is rather unstable and was immediately used in the following reaction.

(2S,5R,6S)-3,3-Dimethyl-2-[(2,2-dimethyl-1-oxo)propoxy]methoxycarbonyl-6-hydroxymethyl-6-methoxy-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane (8a):Intermediate (**7**), obtained after evaporation of the solvent, was redissolved in dioxane (30 ml) and sodium borohydride (0.7 g, 20 mmol) was added portionwise with stirring. The reaction was allowed to proceed for 30 min, then water was added and the resulting mixture extracted with methylene chloride. The usual work up produced an oily residue which was purified by flash chromatography (pentane/EA, gradient from 9/1 to 6/4) to give the title compound (350 mg, 23%) as an oil. ^{1}H-Nmr ($CDCl_3$), (δ, ppm): 1.22 (s, 9H, $C(CH_3)_3$); 1.52 (s, 3H, 2α-Me); 1.60 (s, 3H, 2β-Me); 2.10 (m, 1H, -OH); 3.60 (s, 3H, -OMe); 4.00 (m, 2H, $HOC\underline{H}_2$); 4.46 (s, 1H, H3); 5.42 (s, 1H, H5); 5.83 (ABm, J= 11.2 Hz, 2H, -O-$C\underline{H}_2$-O). Ir ($CDCl_3$), υ_{max}: 3510 (OH), 1767 (β-lactam) cm^{-1}. *Anal.* Calcd for $C_{16}H_{25}NO_7S$: C, 51.19; H, 6.71; N, 3.73; S, 8.54. Found: C, 51.39; H, 6.81; N, 3.76; S, 8.53.

(2S,5R,6S)-3,3-Dimethyl-2-[(2,2-dimethyl-1-oxo)propoxy]methoxycarbonyl-6-(*tert*-butyldimethylsilyloxy)methyl-6-methoxy-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane (8b): Compound (**8a**) (1.25 g, 3.32 mmol) was dissolved in anhydrous DMF (7 ml), *tert*-butyldimethylsilyl chloride (1 g, 6.64 mmol) was added followed by imidazole (2.26 g, 33.2 mmol). The resulting solution was stirred for 6 h then diluted with water (50 ml) and extracted with ether. The usual work up gave an oily residue which was purified by flash chromatography to yield **8b** as a colourless oil (0.75 g, 46%). ^{1}H-Nmr ($CDCl_3$), (δ, ppm): 0.08 (s, 6H, $Si(CH_3)_2$); 0.90 (s, 9H, -$C(CH_3)_3$); 1.22 (s, 9H, $C(CH_3)_3$); 1.50 (s, 3H, 2α-Me); 1.60 (s, 3H, 2β-Me); 3.56 (s, 3H, -OMe); 4.02 (m, 2H, $SiOC\underline{H}_2$); 4.38 (s, 1H, H3); 5.30 (s, 1H, H5); 5.82 (ABm, J= 11.8 Hz, 2H, -O-$C\underline{H}_2$-O). Ir ($CDCl_3$), υ_{max}: 1763 cm^{-1} (β-lactam). *Anal.* Calcd for $C_{22}H_{39}NO_7SSi$: C, 53.96; H, 8.03; N, 2.86; S, 6.55. Found : C, 54.04; H, 7.90; N, 2.71; S, 6.67.

(3R,4S)-1-[1-(2,2-Dimethyl-1-oxo)propoxymethoxycarbonyl]-2-methyl-1-propenyl]-3-(*tert*-butyldimethylsilyloxy)methyl-3-methoxy-4-(2-chloro-1-oxoethyl)thio-2-azetidinone (9b): DBU (0.35 ml, 2.25 mmol) was added over 15 min to a stirred suspension of phenylmercuric chloride (0.72 g, 2.25 mmol) in dry acetonitrile (30 ml). The reaction was allowed to proceed for 15 min at room temperature and then cooled to 10°C. A solution of **8b** (0.75 g, 1.53 mmol) in dry acetonitrile (5 ml) was added and the mixture was stirred for 1 h at room temperature. Chloroacetyl chloride (0.23 ml, 2.3 mmol) dissolved in anhydrous acetonitrile (2 ml) was added and the resulting mixture was stirred for 2 h at room temperature. The reaction mixture was filtered, concentrated to small volume and diluted with ether (50 ml). The oily residue resulting from the usual work up was purified by flash chromatography. The title compound (0.6 g, 75%) was obtained as a light yellow oil. ^{1}H-Nmr ($CDCl_3$), (δ, ppm): 0.07, 0.09 (s,s, 3H, 3H, $Si(CH_3)_2$); 0.89 (s, 9H, -$C(CH_3)_3$); 1.18 (s, 9H, $C(CH_3)_3$); 1.94 (s, 3H, =$(C\underline{H}_3)_2$); 2.21 (s, 3H,=$(C\underline{H}_3)_2$); 3.56 (s, 3H, OMe); 3.93, 3.78 (ABm, J= 10.9 Hz, 2H, -$SiOC\underline{H}_2$); 4.12 (s, 2H, $COC\underline{H}_2Cl$); 5.85 (ABm, J= 12.0 Hz, 2H, O-$C\underline{H}_2$-O); 6.02 (s, 1H, H4). Ir ($CDCl_3$), υ_{max}: 1765 (β-lactam),1711 (C=O), 1603 (C=C) cm^{-1}. *Anal.* Calcd for $C_{24}H_{40}NO_8ClSSi$: C, 50.91; H, 7.12; N, 2.47; S, 5.66; Si, 4.96. Found: C, 51.26; H, 7.34; N, 2.49; S, 5.85.

(3R,4S)-1-[1-(2,2-Dimethyl-1-oxo)propoxymethoxycarbonyl]-2-methyl-1-propenyl]-3-(*tert*-butyldimethylsilyloxy)methyl-3-methoxy-4-(2-phenoxy-1-oxoethyl)thio-2-azetidinone (9a): The title compound was prepared essentially by the same procedure described for **9b** (63%) as a colourless oil. **^{1}H-Nmr** ($CDCl_3$), (δ, ppm): 0.08 (s, 6H, $Si(CH_3)_2$); 0.80 (s, 9H, -$C(CH_3)_3$); 1.23 (s, 9H, $C(CH_3)_3$); 3.54 (s, 3H, OMe); 3.86 (ABm, J= 12.3 Hz, 2H, -$SiOC\underline{H}_2$); 4.78 (s, 2H, $COC\underline{H}_2O$); 5.90 (ABm, J= 12.1 Hz, 2H, O-$C\underline{H}_2$-O); 6.29 (s, 1H, H4); 7.4-6.8 (m, 5H, Ph). Ir ($CDCl_3$), υ_{max}: 1817(C=O), 1757(β-lactam), 1723(C=O), 1599 (C=C)cm^{-1}. *Anal.* Calcd for $C_{30}H_{45}NO_9SSi$: C, 57.76; H, 7.27; N, 2.25; S, 5.14. Found :C, 57.49; H, 6.98; N, 2.38; S, 4.61.

(3R,4S)-3-(*tert*-Butyldimethylsilyloxy)methyl-3-methoxy-4-(2-phenoxy-1-oxoethyl)thio-2-azetidinone (10a) : The same procedure as described for **10b** gave, starting from **9a** (1.850 g, 2.96 mmol), 0.530 g of the title compound as a white foam (44%). ^{1}H-Nmr ($CDCl_3$), (δ, ppm): 0.07 (s, 6H, $Si(CH_3)_2$); 0.88 (s,9H,-$C(CH_3)_3$); 3.53 (s, 3H, -OMe); 3.82 (ABm, J= 11.0 Hz, 2H, -$C\underline{H}_2$OSi-); 4.72 (s, 2H, R-$C\underline{H}_2$OPh); 5.64 (s, 1H, H4); 6.16 (br s, 1H, NH); 7.45-6.90 (m, 5H, Ph). Ir ($CDCl_3$), υ_{max}: 3414 (=NH),1780 (β-lactam),1684 (C=O), 1600 (C=C)cm^{-1}. *Anal.* Calcd for $C_{19}H_{29}NO_5SSi$: C, 55.45; H, 7.10; N, 3.40; S,. 7.79. Found: C, 55.39%; H, 6.98; N, 3.38; S, 7.77.

(3R,4S)-3-(*tert*-Butyldimethylsilyloxy)methyl-3-methoxy-4-(2-chloro-1-oxoethyl)thio-2-azetidinone (10b): Ozone was bubbled through a solution of **9b** (1.3 g, 2.3 mmol) in anhydrous methylene chloride (90 ml) at -60°C until the solution turned to a stable (10 min) light blue colour. The reaction mixture was then warmed to room temperature transferred into a separatory funnel and washed with 10% aqueous solution of sodium thiosulphate (30 ml). The usual work up of the organic layer gave a residue which was redissolved in methanol and silica gel (3 g) was added and the resulting slurry was stirred for 16 h. Filtration and evaporation of the solvent gave an oil which upon purification by flash chromatography yielded **10b** (0.6 g, 67%) as a white wax. ^{1}H-Nmr ($CDCl_3$), (δ, ppm): 0.10 (s, 6H, $Si(CH_3)_2$); 0.90 (s, 9H, -$C(CH_3)_3$); 3.52 (s, 3H, -OMe); 3.89, 3.76 (ABm, J= 11.0 Hz, 2H, -$C\underline{H}_2$OSi-); 4.21 (s, 2H, R-$C\underline{H}_2$Cl); 5.60 (s, 1H, H4); 6.20 (br s, 1H, NH). Ir ($CDCl_3$), υ_{max}: 3412 (=NH),1782 (β-lactam),1700(C=O), 1601(C=C) cm^{-1}. *Anal.* Calcd for $C_{13}H_{24}NO_4ClSSi$: C, 44.12; H, 6.83; N, 3.96. Found: C, 44.12; H, 7.04; N, 3.75.

(5R,6S)-3-Allyloxycarbonyl-6-(*tert*-butyldimethylsilyloxy)methyl-6-methoxy-2-phenoxymethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene (11a): **10a** (0.530 g, 1.29 mmol) gave the title compound upon treatment with allyloxalyl chloride (0.290g, 2.19 mmol) and trimethyl phosphite (0.645 g, 5.20 mmol) following the procedure described for **11c** (colourless oil, 0.250 g, 39%). ^{1}H-Nmr ($CDCl_3$), (δ, ppm): 0.06 (s, 6H, $Si(CH_3)_2$); 0.88 (s, 9H,-$C(CH_3)_3$); 3.56 (s, 3H, OMe); 4.09 (s,2H,-SiOC$\underline{H}_2$); 4.75 (m, 2H, -$C\underline{H}_2$CH=CH_2); 5.30 (m, 2H, -CH_2CH=C$\underline{H}_2$); 5.32 (m, 2H, -$C\underline{H}_2$-OPh); 5.64(s, 1H, H5); 6.00 (m, 1H, -$CH_2C\underline{H}$=CH_2); 7.25-6.90 (m, 5H, Ph). Ir ($CDCl_3$), υ_{max}: 1788 (β-lactam),1701 (C=O), 1599,1580 (C=C) cm^{-1}. *Anal.* Calcd for $C_{24}H_{33}NO_6SSi$: C, 58.63; H, 6.77; N, 2.85. Found: C, 58.42; H, 6.90; N, 3.02.

(5R,6S)-3-Allyloxycarbonyl-6-(*tert*-butyldimethylsilyloxy)methyl-6-methoxy-2-(1-methyltetrazol-5-yl)thiomethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene (11c): Anhydrous potassium carbonate (0.5 g) was added to a solution of **10b** (0.58 g, 1.5 mmol) in anhydrous methylene chloride (30 ml) and after stirring of the mixture for 5 min allyloxalyl chloride (0.505 g, 3,4 mmol) was added dropwise *via* a syringe. Triethylamine (0.473 ml, 3.4 mmol) was then added dropwise and the mixture was stirred untill **10b** disappeared (nmr). The reaction mixture was filtered, water (20 ml) was added and the separated organic layer worked up in the usual manner. Anhydrous toluene (30 ml) was added and the resulting solution was heated at 50°C under nitrogen; anhydrous trimethyl phosphite (1 g, 8.06 mmol) was added dropwise and the mixture was maintained at 50°C for 1 h and then refluxed for two additional h. The solvent was removed under reduced pressure and the oily residue was treated with methylene chloride (10 ml) and water (10 ml), followed by sodium 1-methyl-5-thiotetrazole (1 g, 6.1 mmol) and tetrabutylammonium bromide (100 mg, 0.3 mmol). The heterogeneous mixture was stirred for 1 h and then the organic layer separated and worked up in the usual manner. The resulting residue was purified by flash chromatography to give **11c** (0.290 g, 30%) as a colourless oil. ^{1}H-Nmr ($CDCl_3$), (δ, ppm): 0.04 (s, 6H, $Si(CH_3)_2$); 0.86 (s, 9H, -$C(CH_3)_3$); 3.54 (s, 3H, OMe); 3.95 (s, 1H, -NMe); 4.12 (s, 2H,-SiOC$\underline{H}_2$); 4.77 (m, 2H, -$C\underline{H}_2$CH=CH_2); 4.89, 4.54 (ABm, J= 12.3 Hz, 2H, -$C\underline{H}_2$S); 5.36 (m, 2H,-CH_2CH=C$\underline{H}_2$); 5.64 (s, 1H, H5); 5.94 (m, 1H, -$CH_2C\underline{H}$=CH_2). Ir ($CDCl_3$), υ_{max}: 1782 (β-lactam),1744,1709 (C=O),1580 (C=C) cm^{-1}. *Anal.* Calcd for $C_{20}H_{31}N_5O_5S_2Si$: C, 46.76; H, 6.08; N, 13.63; S,12.48. Found: C, 46.57; H, 6.09; N, 13.73; S, 12.57.

(5R,6S)-3-Allyloxycarbonyl-6-hydroxymethyl-6-methoxy-2-phenoxymethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene (12a): 11a (0.1 g, 0.2 mmol) gave the title compound (white wax, 0.030 g, 39%) following the procedure described for **12b**. ^{1}H-Nmr ($CDCl_3$), (δ, ppm): 3.60 (s, 3H, OMe); 4.10 (s, 2H, -HOC$\underline{H}_2$); 4.75 (m, 2H, -C$\underline{H}_2$CH=CH$_2$); 5.29 (ABm, J= 12.5 Hz, -C$\underline{H}_2$OPh); 5.60 (m, 2H, -CH$_2$CH=C$\underline{H}_2$); 5.74 (s, 1H, H5); 6.00 (m, 1H, -CH$_2$C$\underline{H}$=CH$_2$); 7.05 (m, 5H, Ph). Ir ($CDCl_3$), υ_{max}: 3610 (OH), 1790 (β-lactam), 1720 (C=O), 1602, 1599, 1578 (-C=C-) cm^{-1}. *Anal.* Calcd for $C_{18}H_{19}NO_6S$: C, 57.28: H, 5.07; N, 3.71. Found: C, 57.42; H, 5.29; N, 3.44.

(5R,6S)-3-Allyloxycarbonyl-6-hydroxymethyl-6-methoxy-2-(1-methyltetrazol-5-yl)thiomethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene (12b): 11c (0.250 g, 0.5 mmol) was dissolved in distilled THF (10 ml); glacial acetic acid (0.445 ml, 7.5 mmol) was added under vigorous stirring followed by a 1M solution of tetrabutylammonium fluoride in THF (2.6 ml). The stirring was maintained for 20 h, the solution was poured in a 5% aqueous solution of sodium hydrogencarbonate (50 ml) and then extracted with EA. The residue resulting from the usual work up was purified by flash chromatography to give the title compound (0.090 g, 44%) as a colourless oil. ^{1}H-Nmr ($CDCl_3$), (δ, ppm): 2.18 (br s, 1H, OH); 3.60 (s, 3H, OMe); 3.95 (s, 3H, N-Me); 4.10 (s, 2H, -HOC$\underline{H}_2$); 4.65 (ABm, J= 12.3 Hz, -C$\underline{H}_2$S); 4.74 (m, 2H, -C$\underline{H}_2$CH=CH$_2$); 5.35 (m, 2H, -CH$_2$CH=C$\underline{H}_2$); 5.73 (s, 1H, H5); 5.98 (m, 1H, -CH$_2$C$\underline{H}$=CH$_2$). Ir ($CDCl_3$), υ_{max}: 3603 (OH), 1792 (β-lactam), 1702 (C=O), 1582 (C=C) cm^{-1}. *Anal.* Calcd for $C_{14}H_{17}N_5O_5S$: C, 42.10; H, 4.29; N, 17.53. Found: C,42.42; H, 4.17; N, 17.38.

(5R,6S)-Potassium 3-oxycarbonyl-6-hydroxymethyl-6-methoxy-2-phenoxymethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene (13a): Triphenylphosphine (6.3 mg, 0.025 mmol), tetrakis(triphenylphosphine) palladium(0) (8.3 mg, 0.008 mmol) in THF (3 ml) and potassium 2-ethylhexanoate (0.5 ml of 0.5 sol. in AcOEt) were added in the order to a solution of compound (**12a**) (85 mg, 0.23 mmol) in EA (5 ml) and THF (2 ml) and the reaction was allowed to proceed for 1 h at room temperature after which time it was then diluted with ether (7 ml). The precipitated material was separated from the mother liquors by centrifugation, washed twice with ether (10 ml) and dried under vacuum to afford the title compound as a white solid (53 mg, 63%) (mp 122°C, decomp.). ^{1}H-Nmr (D_2O), (δ, ppm): 3.5 (m, 2H,-C$\underline{H}_2$-OH); 3.67 (s, 3H, -OMe); 5.33 (ABm, J= 12.7 Hz, 2H,-C$\underline{H}_2$-Ph); 5.68 (s, 1H, H5); 7.5-6.7 (m, 5H, Ph). Ir (nujol mull), υ_{max}: 1761 (β-lactam), 1599,1580 (C=C) cm^{-1}. *Anal.* Calcd for $C_{15}H_{14}NO_8NaS$: C, 50.28; H, 3.93; N, 3.91. Found: C, 49.82; H, 4.16; N, 3.78.

(5R,6S)-Potassium 3-oxycarbonyl-6-hydroxymethyl-6-methoxy-2-(1-methyltetrazol-5-yl)-thiomethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene (13b): The title compound was prepared from **12b** (90 mg, 0.2323 mmol) similarly to what described for **13a** (white solid, 47 mg, 50%) (mp 97-99°C, decomp.). ^{1}H-Nmr (D_2O), (δ, ppm): 3.45 (s, 3H, OMe); 3.52 (br s, 2H,-C$\underline{H}_2$-OH); 3.97 (s, 3H, N-C$\underline{H}_3$); 4.45 (ABm, J= 12.3 Hz, 2H, -C$\underline{H}_2$-S); 5.72 (s, 1H, H5). Ir(nujol mull), υ_{max}: 1761 (β-lactam),1616,1576 (C=C) cm^{-1}. *Anal.* Calcd for $C_{11}H_{12}N_5O_5NaS$: C, 37.90; H, 3.47; N, 20.10. Found: C, 37.42; H, 3.61; N, 19.87.

(2S)-3,3-Dimethyl-2-[(2,2-dimethyl-1-oxo)propoxy]methoxycarbonyl-8-methoxy-9-oxo-4-thia-6-oxa-1-azabicyclo[3,4,0]non-7-ene (14)

7 undergoes spontaneous rearrangement to **14** when left at room temperature for at least 3 h both in solution and as an oil. ^{1}H-Nmr ($CDCl_3$), (δ, ppm): 1.22 (s, 9H, C(CH$_3$)$_3$); 1.46 (s, 3H, 2α-Me); 1.75 (s, 3H, 2β-Me); 3.66 (s, 3H, OMe); 4.79 (s, 1H, N-C$\underline{H}$COO); 5.82 (m, 2H, -OC$\underline{H}_2$O-); 6.62 (s, 1H, O-C$\underline{H}$-S); 6.86 (s, 1H, C=C$\underline{H}$O). The compound was not further characterized.

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