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Synthesis of 6β-Methoxy-6α-Hydroxymethylpenems

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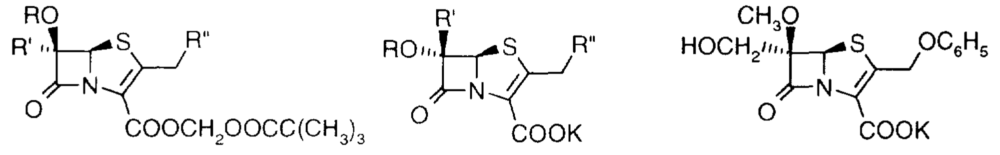
Abstract: 6α-Hydroxymethyl-6β-methoxy-2-phenoxymethylpenem was synthesized from benzyl 6β-bromo-6α-methoxypenicillanate *via* radical addition at 6α-position of methyl tributyltinacrylate and tributyltinstyrene *inter alia*. The reaction sequence to penem proceeds *via* secopenicillanates according to established procedures. The good yield of the radical reaction and its stereoselectivity provide a useful entry to the 6α-substituted 6β-methoxypenems and in particular to the 6α-hydroxymethyl-6β-methoxypenems.

We reported previously[1,2] some 6,6-disubstituted penems (**1** and **2**, Figure 1) obtained by synthetic procedures whose key steps are the reaction of cadmium alkyls on 6-oxo-penicillanate, the copper mediated Grignard type addition of alkylcuprates to 6β-bromo-6α-methoxypenicillanates[1] or the reaction of methyl orthoformate with diazopenicillanates.[2] These compounds had been designed with the aim to obtain novel penems stable towards human renal dehydropeptidases (DHP-I).



1 **2** **3**

R= CH_3, $COCH_3$
R'= CH_2CH_3
R"= OC_6H_5, S-tet

R= CH_3
R'= CH_2OH
R"= OC_6H_5, S-tet

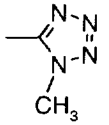
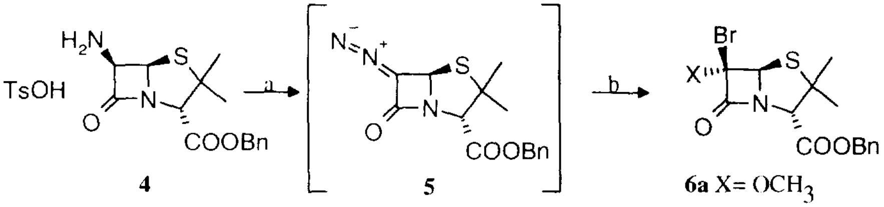
tet=


Figure 1

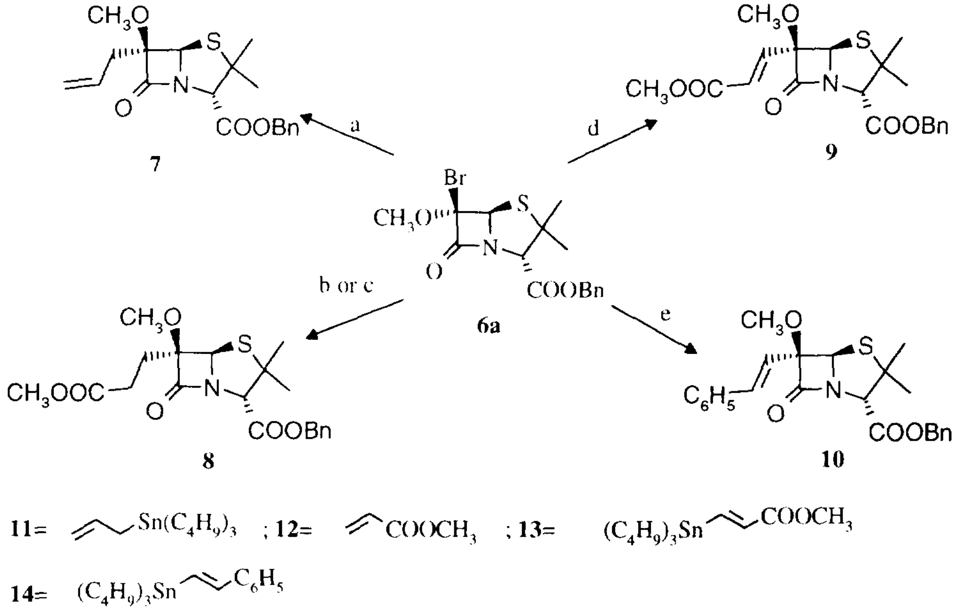
The 6β-hydroxymethyl-6α-methoxypenems[2] (**2**) showed a promising stability to DHP-I and this result encouraged us to investigate the epimeric 6α-hydroxymethyl-6β-methoxypenem (**3**). We wish to report here our results on the synthesis of this compound.



Bn= $CH_2C_6H_5$;
a= $NaNO_2$, TsOH; b= NBS, CH_3OH, CH_2Cl_2

Scheme 1

Hanessian reported[3] that 6-bromo- and 6,6'-dibromopenicillanates undergo radical reaction with tributylallyltin to give mono- and gem-6-allylpenicillanates thus demonstrating the possibility to generate a stable radical at C-6.



a= **11**, AIBN, C_6H_6, 80°C; b= **12**, $(C_4H_9)_3SnH$, AIBN, C_6H_6, 80°C; c= **12**, $(C_4H_9)_3SnH$, hv, $(C_2H_5)_2O$; d= **13**, AIBN, C_6H_6, 80°C; e= **14**, AIBN, C_6H_6, 80°C.

Scheme 2

This finding and the good stereocontrol in the addition of an allyl at the 6α position prompted us to examine this reaction on 6β-bromo-6α-methoxypenicillanate[1,4] (Scheme 1) as in this case the carbon centered radical arising from C-Br homolytic cleavage would benefit from captodative stabilisation by geminal donor and acceptor groups.[5,6] Our results are outlined in Scheme 1.

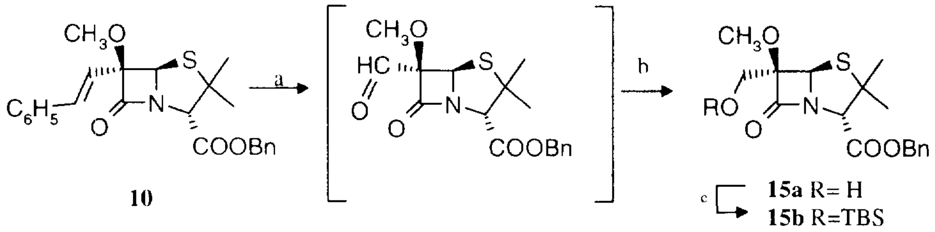
Reaction of **5** with *N*-bromoacetamide in methanol gave modest yield of **6a** (15%) together with 6,6-dibromopenicillanate (**6b**) (10%), whereas the use of *N*-bromosuccinimide significantly increased the yield (64% from **4**) and suppressed the formation of the dibromopenicillanate. Benzyl 6α-methoxy-6β-bromopenicillanate (**6a**) (Scheme 2) was successfully reacted with tri-*n*-butylallyltin under radical conditions (AIBN, benzene, 80°C) and penicillanate (**7**) was isolated after flash chromatography (Scheme 2) in 22% yield. Compound (**6a**) underwent radical reaction with a variety of substrates to yield compounds (**7-10**).

Table 1

No	reactant (eq.)	$(C_4H_9)_3Sn$ H (eq.)	AIBN (eq.)	solvent	temp.	time	yield(%)
1	**11** (2)	-	0.4	C_6H_6	80°C	29 h	22
2	**12** (10)	1.1	0.5	C_6H_6	65°C	24 h	25
3	**12** (10)	1.1	*	$(C_2H_5)_2O$	23°C	24 h	27
4	**13**[7] (2)	-	1	C_6H_6	80°C	52 h	31
5	**14**[7] (3)	-	1	C_6H_6	80°C	72 h	51

*= hv

Table 1 summarizes the results of these reactions. Penicillanate (**15a**) was successfully obtained when **10** was treated with ozone in a 1/1 methylene chloride/methanol mixture followed by reduction with tributyltin hydride and silica[8] (Scheme 3).



TBS= t-$(C_4H_9)(CH_3)_2Si$;
a= O_3, dimethyl sulfide, CH_2Cl_2, CH_3OH, -78°C; b= $(C_4H_9)_3SnH$, SiO_2, CH_2Cl_2;
c= TBSCl, imidazole, DMF.

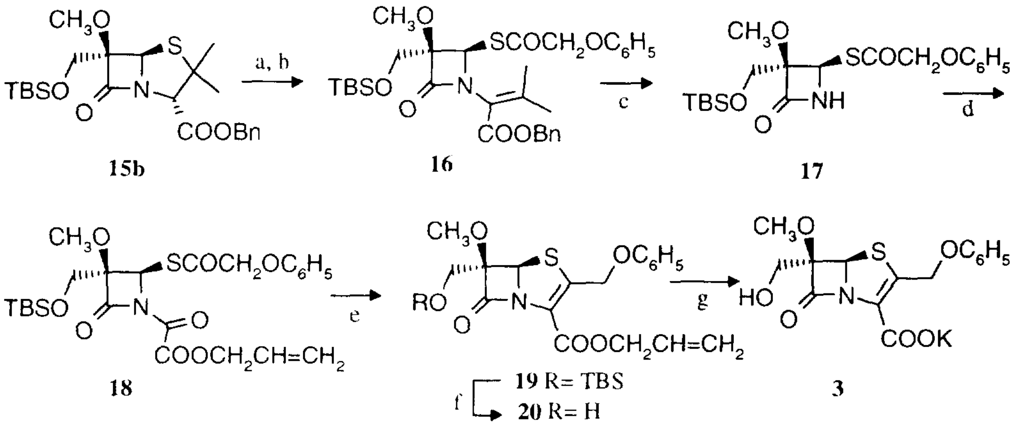
Scheme 3

The C2-S bond of the thiazolidine ring system of penicillanate (**15b**) (from **15a** upon treatment with *tert*-butyldimethylsilyl chloride and imidazole in anhydrous DMF) was cleaved (PhHgCl, DBU) in acetonitrile followed by acylation with phenoxyacetyl chloride to give secopenicillanate (**16**) (Scheme 4) (64% yield) which was treated with ozone in dichlorometane at -78°C and the oxalimido intermediate hydrolyzed with silica in a 1/1 methanol/ethyl acetate mixture to isolate azetidinone (**17**) in 45% overall yield.

Acylation of **17** with allyloxalyl chloride followed by heating of the resulting oxalimido derivative in toluene in the presence of triethylphosphite gave penem (**18**) in 40% yield after flash chromatography. The silyl protecting group was then removed (tetrabutylammonium fluoride, acetic acid in THF) followed by palladium catalysed deallylation to give the final compound (**3a**) as the potassium salt (Scheme 4).

Our results indicate that radical substitution of 6β-bromo in benzyl 6β-bromo-6α-methoxypenicillanate proceeds in useful yield to give exclusively the 6β-methoxy-6α-substituted penicillanate. This reaction is formally a radical insertion with inversion of configuration.

The results described in this paper are an extension of the original report by Hanessian[3] and they provide an entry to the 6β-methoxy-6α-alkenyl-, 6β–methoxy-6α-alkyl- and 6β-methoxy-6α-hydroxymethylpenems due to the ease of synthesis of the 6β-bromo-6α–methoxypenicillanate from benzyl 6-diazopenicillanate.



a= PhHgCl, DBU, CH_3CN; b= $C_6H_5OCH_2COCl$; c= O_3, CH_2Cl_2, -78°C then SiO_2, CH_3OH; d= $ClCOCOOCH_2CH{=}CH_2$, TEA, CH_2Cl_2; e= $P(OC_2H_5)_3$, xylene, ref.; f= TBAF, CH_3COOH, THF; g= Potassium 2-ethylhexanoate, $Pd(PPh_3)_4$, THF.

Scheme 4

The radical nature of the reaction allows the synthesis of 6,6'-disubstituted penems that could not be obtained or that could be obtained with difficulty by the methods reported previously.[1] With reference to the stability of the compound of this study, **3** showed a good both DHP-I and chemical stability in *in vitro* tests similarly to what observed for the epimeric 6α-methoxy-6β-hydroxymethylpenems.[2]

The class needs further exploration to be judged for its potential.

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[9] 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 sulfate 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:

cy-Hex: cyclohexane, DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene, DMF: dimethylformamide, Et_2O: ether, EtOAc: ethyl acetate, MeOH: methanol, NBS: *N*-bromosuccinimide, Hex: n-hexane, TBAF: tetrabutylammonium fluoride trihydrate, TBSCl: *tert*-butyldimethylsilyl chloride, THF: tetrahydrofuran.

(2S,5R,6S)-Benzyloxycarbonyl-6-bromo-6-methoxy-7-oxo-1-thia-4-azabicyclo[3.2.0]heptane (6a): Solid NBS (0.14 g; 0.79 mmol) was added portionwise to a cooled (-10°C) solution of benzyl 6-diazopenicillanate (0.25 g; 0.79 mmol) in a 1/1 mixture of dichloromethane/MeOH (30 ml) and the reaction mixture was maintained under stirring and under a nitrogen atmosphere for 1 h. Water was added after this time, the organic layer was separated and extracted with dichloromethane (3x10 ml). The usual work up of the organic layer gave a residue (230 mg) which was flash-chromatographed (SiO_2 ; column 1 cm width, 15 cm height; cy-Hex/ EtOAc=9/1) to yield **6a** as a white wax (200 mg; 64%). ^{1}H-Nmr ($CDCl_3$): (δ, ppm): 1.38 (s, 3H, 2α-Me); 1.60 (s, 3H, 2β-Me); 3.66 (s, 3H, -O$\underline{Me}$); 4.70 (s, 1H, H3); 5.25-5.14 (ABm, J=11.9 Hz , 2H, -C$\underline{H}_2$-Ph); 5.44 (s, 1H, H5); 7.37 (m, 5H, Ph). Ir ($CDCl_3$): υ_{max}: 1786 (β-lactam), 1745 (C=O ester) cm^{-1}. *Anal.* Calcd for $C_{16}H_{18}NO_4BrS$: C, 48.01; H, 4.53; N, 3.50; Br, 19.96; S, 8.01. Found C, 47.89; H, 4.88; N, 3.31; Br, 20.01; S, 8.10.

(2S,5R,6R)-Benzyloxycarbonyl-6-allyl-6-methoxy-7-oxo-4-thia–1-azabicyclo[3.2.0]heptane (7): Allyl tri-*n*-butyltin (0.29 ml, 1.25 mmol) was added to a solution of **6a** (0.25 g, 0.625 mmol) and then AIBN (20.5 mg, 0.125 mmol) in benzene (2 ml) was added during 6 h. The reaction was allowed to proceed for 12 h and then additional AIBN (20.5 mg, 0.125 mmol) in benzene (2 ml) was added during 6 h and the reaction allowed to proceed for 5 additional hours. The reaction mixture was concentrated under vacuum and the residue was treated with acetonitrile, filtered and the solid material washed with n-Hex (4x10 ml). The organic solutions were mixed and evaporated under vacuum to yield a crude material (230 mg) which was submitted to chromatography eluting with cy-Hex/EtOAc=95/5 to obtain starting material (**6a**) (70 mg, 28%) and **7** (40 mg, 24.6%). ^{1}H-Nmr ($CDCl_3$), (δ, ppm): 1.45 (s, 3H, 2α-Me); 1.60 (s, 3H, 2β-Me); 2.70 (m, 2H, CH_2=CHC$\underline{H}_2$); 3.50 (s, 3H, OMe); 4.50 (s, 1H, H3); 5.10-5.30 (m, 4H, C$\underline{H}_2$-Ph; C$\underline{H}_2$=CHCH_2); 5.50-5.40 (m, 2H, CH_2=C$\underline{H}$CH_2; $\underline{H}$5); 7.36 (m, 5H, Ph). Ir ($CDCl_3$), υ_{max}: 1770 (β-lactam), 1745 (C=O ester) cm^{-1}. *Anal.* Calcd for $C_{19}H_{23}NO_4S$: C. 63.14; H; 6.41; N 3.88; S, 8.87. Found C, 63.34; H, 6.38; N, 3.74; S, 8.98.

(2S,5R,6R)-Benzyloxycarbonyl-6-(2-methoxycarbonylethyl)-6-methoxy-7-oxo-4-thia-1-azabicyclo [3.2.0]heptane (8): A solution of tri-n-butyltin hydride (0.248 ml, 0.938 mmol) and AIBN (0.11 g, 0.68 mmol) in benzene (3 ml) was added, during 15 h, to a refluxing solution of **6a** (0.25 g, 0.625 mmol) and of methyl acrylate (0.56 ml, 6.25 mmol) in refluxing benzene (5 ml), at the end of the addition the reaction was stirred at reflux for further 14 h. The reaction mixture was concentrated under vacuum and the residue (0.505 g) was flash chromatographed (SiO_2, diameter 2.5 cm, height 11 cm, Et_2O/petroleum ether 43-62 °C=1/9) to obtain **8** (64 mg, 25%) as a colourless oil. ^{1}H-Nmr ($CDCl_3$), (δ, ppm): 1.40 (s, 3H, 2α-Me); 1.60 (s, 3H, 2β-Me); 2.30-2.60 (m, 4H, MeOCOC$\underline{H}_2$C$\underline{H}_2$-R); 3.50 (s, 3H, OMe); 3.70 (s, 3H, COOMe); 4.50 (s, 1H, H3); 5.20 (m, 2H, C$\underline{H}_2$-Ph); 5.20 (s, 1H, H5); 7.40 (m, 5H, Ph). Ir ($CDCl_3$), υ_{max}: 1770 (β-lactam), 1735 (C=O ester) cm^{-1}. *Anal.* Calcd. for $C_{20}H_{25}NO_6S$: C, 58.95; H, 6.19; N, 3.44; S, 7.85. Found C, 58.82; H, 5.98; N, 3.54; S, 7.98.

(2S,5R,6R)-Benzyloxycarbonyl-6-(2-methoxycarbonylvinyl)--6-methoxy-7-oxo-4-thia-1-azabicyclo [3.2.0]heptane (9): Stannyl acrylate (**13**) (8.44 g, 15 mmol) and AIBN (1.232 g, 7.5 mmol) were added to a stirred solution of benzyl 6β-bromo-6α-methoxypenicillanate (**6a**) (3.0 g, 7.5 mmol) in benzene (80 ml). The reaction mixture was maintained at the reflux temperature under a nitrogen atmosphere for 52 h. The solvent was then evaporated under vacuum and the residue was treated with acetonitrile (50 ml) and washed with Hex (5x10 ml). The acetonitrile solution was evaporated under vacuum and the residue (4.7 g) submitted to flash-chromatography on SiO_2 in a column of 3 cm of diameter and 15 cm height eluting with cy-Hex/Et_2O = 9/1 to yield 0.950g (31%) of the title compound (**9**) as a colourless oil. ^{1}H-Nmr ($CDCl_3$), (δ, ppm): 1.40 (s, 3H, 2α-Me); 1.60 (s, 3H, 2β-Me); 3.50 (s, 3H, OMe); 3.80 (s, 3H, COOMe); 4.55 (s, 1H, H3); 5.20 (m, 2H, -C$\underline{H}_2$-

Ph); 5.30 (s, 1H, H5); 6.30 (d, J=15.5 Hz, 1H, OCOCH=C$\underline{H}$R); 7.05 (d, J=15.5 Hz, 1H, OCOC$\underline{H}$=CHR); 7.33 (m, 5H, Ph). Ir ($CDCl_3$), υ_{max}: 1770 (β-lactam), 1735 (C=O ester) cm^{-1}. *Anal.* Calcd for $C_{20}H_{23}NO_6S$: C, 59.24; H, 5.72; N, 3.46; S, 7.89. Found C, 59.36; H, 5.78; N, 3.34; S, 8.01.

(2S,5R,6R)-Benzyloxycarbonyl-6-(2-phenylvinyl)-6-methoxy-7-oxo-4-thia-1-azabicyclo[3.2.0]-heptane (10): Phenylvinyl-tri-*n*-butyl tin (11.15 g, 43 mmol) and AIBN (0.75 g, 4.5 mmol) were added to a solution of **6a** (5.7 g, 14.23 mmol) in benzene (7.5 ml). The resulting mixture was maintained at the reflux temperature for 72 h adding additional AIBN (0.75 g, 4.5 mmol) every 12 h. The reaction mixture was concentrated under vacuum diluted with acetonitrile (50 ml) and washed with n-hex (5x10 ml). The acetonitrile layer was evaporated under vacuum and the residue (6.5 g) was flash-chromatographed (SiO_2, width 3.5 cm, height 15 cm, Et_2O/petroleum ether = 1/9) to yield **10** (3.25 g, 54%) as a pale yellow oil. ^{1}H-Nmr ($CDCl_3$), (δ, ppm): 1.45 (s, 3H, 2α-Me); 1.65 (s, 3H, 2β-Me); 3.50 (s, 3H, -OMe); 4.57 (s, 1H, H3); 5.19 (m, 2H,-C$\underline{H}_2$-Ph); 5.38 (s, 1H, H5); 6.86 (d, d, J=15.8 Hz, 2H, -C$\underline{H}$=C$\underline{H}$-Ph); 7.33 (m, 5H, Ph). Ir ($CDCl_3$), υ_{max}: 1770 (β-lactam), 1745 (C=O ester)0, 1640 cm^{-1}. *Anal.* Calcd for $C_{24}H_{25}NO_4S$: C, 68.06; H, 5.95; N, 3.31; S, 7.56. Found C, 68.32; H, 5.78; N, 3.14; S, 7.78.

(2S,5R,6R)-Benzyloxycarbonyl-6-hydroxymethyl-6-methoxy-7-oxo-4-thia–1-azabicyclo[3.2.0]-heptane (15a): Ozone was bubbled through a cooled (-40 °C) stirred solution of **10** (500 mg) in methanol (2 ml) for 1.5 h, after which time the solution was warmed to 0°C, added of dimethyl sulfide (0.1 ml, 1.6 mmol) and maintained at 0°C overnight. The solvent was evaporated under vacuum and the residue (400 mg) redissolved in dichloromethane (1.3 ml) and cy-Hex (38.5 ml). Tributyltin hydride (Aldrich 97%) (0.4 ml, 1.5 mmol), SiO_2 (6.4 g) and the resulting mixture were allowed to react for 3 h at room temperature under a nitrogen atmosphere. The reaction mixture was then filtered, the SiO_2 was washed several times with cy-Hex to eliminate the excess tributyltin hydride and subsequently it was washed with dichloromethane to obtain an oily residue which was purified by column chromatography eluting with a 98/2 chloroform/MeOH mixture to yield **15a** (white wax, 100 mg, 25%). ^{1}H-Nmr ($CDCl_3$), δ (ppm): 1.40 (s, 3H, 2α-Me); 1.60 (s, 3H, 2β-Me); 3.60 (s, 3H, -OMe); 4.10 (m, 2H, -C$\underline{H}_2$OH); 4.50 (s, 1H, H3); 5.20 (m, 2H, -C$\underline{H}_2$-Ph); 5.35 (s, 1H, H5); 7.40 (m, 5H, Ph). Ir ($CDCl_3$), υ_{max}: 1780 (β-lactam), 1745 (C=O ester) cm^{-1}. *Anal.* Calcd for $C_{17}H_{21}NO_5S$: C, 58.10; H, 6.03; N, 3.99; S, 9.11. Found C, 58.06; H, 6.18; N, 3.84; S, 9.01.

(2S,5R,6R)-Benzyloxycarbonyl-6-(*tert*-butyldimethylsilyloxy)methyl-6-methoxy-7-oxo-4-thia–1-azabicyclo[3.2.0]heptane (15b): *tert*-Butyldimethylsilyl chloride (2.14 g, 14.2 mmol) and imidazole (4.0 g, 60 mmol) were added to a solution of **15a** (2.0 g 5.7 mmol) in DMF (20 ml), the mixture was stirred overnight at room temperature, diluted with water (100 ml) and extracted with EtOAc (4x50 ml). The usual work up of the organic layers and flash chromatography of the residue (SiO_2, diameter 3 cm, height 15 cm, cy-Hex/EtOAc=1/1) gave **15b** (pale yellow oil, 1.86 g, 70%). ^{1}H-Nmr ($CDCl_3$), (δ, ppm): 0.07 (s, 6H, $Si(CH_3)_2$); 0.87 (s, 9H, $C(CH_3)_3$); 1.40 (s, 3H, 2α-Me); 1.60 (s, 3H, 2β-Me); 3.56 (s, 3H, OMe); 4.01 (ABm, J= 10.9 Hz, 2H, SiOC$\underline{H}_2$R); 4.48 (s, 1H, H3); 5.17 (ABm, J= 12.0 Hz, 2H, C$\underline{H}_2$-Ph); 5.37 (s, 1H, H5); 7.37 (m, 5H, Ph). Ir ($CDCl_3$), υ_{max}: 1776 (β-lactam), 1750 (C=O ester) cm^{-1}. *Anal.* Calcd for $C_{23}H_{35}NO_5SSi$: C, 59.32; H, 7.58; N, 3.01; S, 6.88. Found C, 59.54; H, 7.65; N, 3.04; S, 6.79.

(3R,4R)-1-[1-Benzyloxycarbonyl-2-methyl-1-propenyl]-3-(*tert*-butyldimethylsilyloxy)methyl-3-methoxy-4-(2-phenoxy-1-oxoethyl)thio-2-azetidinone (16): DBU (0.37 ml, 2.38 mmol) in acetonitrile (6 ml) was added over 5 min to a solution of phenylmercuic chloride (0.76 g, 2.4 mmol) in acetonitrile (45 ml) and, after 10 min, **15b** (750 mg, 1.6 mmol) in acetonitrile (10 ml) was added during 15 min and the reaction was let proceed for 1 h at room temperature. Phenoxyacetyl chloride (0.33 ml, 2 mmol) in acetonitrile (4 ml) was added over 5 min and the mixture was stirred for 20 min at room temperature. The reaction mixture was concentrated under vacuum and the residue extracted with ether (2x50 ml) and water (50 ml). The organic layers were worked up in the usual manner and the crude residue was purified by flash chromatography (SiO_2, diameter 2 cm, height 15cm, Cy-H/ EtOAc=95/5) to yield **16** (white foam, 520 mg, 57 %). ^{1}H-Nmr ($CDCl_3$), (δ, ppm): 0.07 (s, 6H, $Si(CH_3)_2$); 0.86 (s, 9H, $C(CH_3)_3$); 1.95 (s, 3H, $=C(Me)_2$); 2.19 (s, 3H, $=C(Me)_2$); 3.43 (s, 3H, OMe); 3.86(s, 2H, $-C\underline{H}_2O-$); 4.62 (s, 2H, $C\underline{H}_2OPh$); 5.14 (ABm, J= 12.5 Hz, 2H, $C\underline{H}_2Ph$); 5.90 (s, 1H, H4); 7.30-6.80 (m, 10H, Ph). Ir ($CDCl_3$), υ_{max}: 1750 (β-lactam), 1705 (C=O ester), 1585 (-C=C) cm^{-1}. *Anal.* Calcd for $C_{31}H_{41}NO_7SSi$: C, 62.08; H, 6.89; N, 2.34; S, 5.34. Found C, 61.99; H, 6.84; N, 2.44; S, 5.22.

(3R,4R)-3-(*tert*-Butyldimethylsilyloxy)methyl-3-methoxy-4-(2-phenoxy-1-oxoethyl)thio-2-azetidinone (17): Ozone was bubbled through a solution of **16** (2.0 g, 3.34 mmol) in dichloromethane (200 ml) cooled at -70°C until the solution turned light blue for 10 min. The reaction mixture was allowed to warm to room temperature and the solvent evaporated under vacuum. The residue was dissolved in EtOAc (100 ml) and the organic phase washed with a 2% aqueous solution (100 ml) of sodium dithionite and worked up in the usual manner. The crude residue was dissolved in MeOH/EtOAc=1/1 (80 ml) and SiO_2 (1.3 g) was added to the solution and the mixture stirred overnight at room temperature. The solvent was evaporated under vacuum and the residue absorbed on SiO_2 was purified by flash chromatography (SiO_2, diameter 2 cm, height 15 cm, EtOA/cy-Hex = 1:9) to yield **17** (white wax, 550 mg, 40%). ^{1}H-Nmr ($CDCl_3$), (δ, ppm): 0.09, 0.08(s, s, 3H, 3H, $Si(CH_3)_2$); 0.89 (s, 9H, $C(CH_3)_3$); 3.59 (s, 3H, OMe); 3.97-3.74 (d, J= 10.7 Hz, d, J= 10.7 Hz, 2H, $C\underline{H}_2OSi$); 4.70 (s, 2H, $CO-C\underline{H}_2-OPh$); 5.56 (s, 1H, H4); 6.30 (br s, 1H, NH); 7.32-6.94 (m, 5H, Ph). Ir ($CDCl_3$), υ_{max}: 3410 (NH), 1792 (β-lactam), 1686 (C=O), 1599 (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, 55.43; H, 6.94; N,3.44; S, 7.82.

(3R,4R)-1-[1-Allyloxy-1,2-dioxoethyl]-3-(*tert*-butyldimethylsilyloxy)methyl-3-methoxy-4-(2-chloro-1-oxoethyl)-thio-2-azetidinone (18): K_2CO_3 (714 mg, 5.1 mmol) was added to a cooled (0°C) solution of **17** (790 mg, 1.92 mmol) in dichloromethane (25 ml) and after 5 min allyloxalyl chloride (300 mg, 3 mmol) and triethylamine (0.600 ml, 4.2 mmol) were added, the mixture allowed to react for 4 h and then filtered to eliminate K_2CO_3. The organic layer was washed with a saturated solution of sodium hydrogen carbonate (70 ml) and water (40 ml) and processed in the usual manner to yield the oxalimido intermediate (**18**) (1.10 g) which was used in the following reaction without any further purification.

(5R,6R)-3-Allyloxycarbonyl-6-(*tert*-butyldimethylsilyloxy)methyl-6-methoxy-2-phenoxymethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene (19): Triethyl phosphite (1.34 ml, 9 mmol) and hydroquinone (5 mg) were added to a solution of oxalimide (**18**) (1.10 g, 1.92 mmol) in dry xylene (80 ml) and the mixture was allowed to react at 50°C for 1 h and then at 110 °C for 9 h. The solvent was evaporated under vacuum and the residue purified by flash chromatography (SiO_2, diameter 30 mm height 18 cm, petroleum ether 40-60/EtOAc =95/5) to yield **19** (colourless oil, 340 mg, 36%). ^{1}H-Nmr ($CDCl_3$), (δ, ppm): 0.12, 0.08 (s, s, 3H, 3H, $Si(CH_3)_2$); 0.86 (s, 9H, $C(CH_3)_3$); 3.63 (s, 3H, OMe); 4.01 (ABm, J= 10.9 Hz, 2H, $C\underline{H}_2OSi$); 4.80-4.60 (m, 2H, $CH_2=CHC\underline{H}_2$); 5.13, 5.45 (ABm, J= 12.3 Hz, 2H, $R-C\underline{H}_2OPh$); 5.50-5.13 (m, 2H, $C\underline{H}_2=CHCH_2$); 5.62 (s, 1H, H5); 5.85-6.02 (m, 1H, $CH_2=C\underline{H}CH_2$); 7.40-6.90 (m, 5H, Ph). Ir ($CDCl_3$), υ_{max}: 1780 (β-lactam), 1740, 1701 (C=O ester), 1601 (C=C) cm^{-1}. *Anal.* Calcd for $C_{24}H_{33}NO_6SSi$: C, 58.63; H 6.77; N, 2.85; S, 6.52. Found C, 58.47; H, 6.84; N, 2.78; S, 6.52.

(5R,6R)-3-Allyloxycarbonyl-6-hydroxymethyl-6-methoxy-2-phenoxymethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene (20): Acetic acid (0.59 ml, 10 mmol) and subsequently TBAF (2.07 ml ,1M solution in THF) were added to a solution of **19** (340 mg, 0.69 mmol) in THF (12 ml). The reaction was allowed to proceed at room temperature for 4 h, diluted with EtOAc (50 ml) and washed with 2% aqueous sodium hydrogen carbonate (3x30 ml) and then submitted to the usual work up to yield a crude residue (270mg) which upon flash-chromatography (SiO_2, diameter 2.2 cm height 21.5 cm, EtOAc/petroleum ether 40-6=4/6) yielded **20** (40 mg, 15.3%) as a pale yellow oil. ^{1}H-Nmr ($CDCl_3$), (δ, ppm): 3.69 (s, 3H, OMe); 4.01-4.16 (ABm, J= 10.6 Hz, 2H, $C\underline{H}_2OSi$); 4.90-4.60 (m, 2H, $CH_2=CHC\underline{H}_2$); 5.18-5.42 (ABm, J= 12.5 Hz, 2H, $R-C\underline{H}_2OPh$); 5.46-5.25 (m, 2H, $C\underline{H}_2=CHCH_2$); 5.61 (s, 1H, H5); 5.96 (m, 1H, $CH_2=C\underline{H}CH_2$); 7.40-6.90

(m, 5H, Ph). Ir ($CDCl_3$), υ_{max}: 3.609 (OH),1786 (β-lactam), 1707 (C=O ester), 1598 (-C=C-) cm^{-1}. *Anal.* Calcd for $C_{18}H_{19}NO_6S$: C, 53.32; H, 4.72; N, 3.45; S, 7.91. Found C, 53.27; H, 4.67; N, 3.58; S, 7.92.

(5R,6R)-Potassium 6-hydroxymethyl-6-methoxy-2-phenoxymethyl-7-oxo-4-thia-1-azabicyclo[3.2.0] hept-2-ene-2-carboxylate(3): Potassium 2-ethylhexanoate (0.2 ml of a 0.5M AcOEt solution), triphenylphosphine (3 mg) and tetrakis(triphenylphosphine)palladium(0) (3 mg) were added to a solution of **19** (37 mg 0.1 mmol) in THF (1.5 ml) and the reaction was allowed to proceed at room temperature for 15 min. Ether and petroleum ether 40-6 (1/1 mixture) were added to precipitate crude **3**. The solid was collected by centrifugation repeating the washing with the ether/petroleum ether and centrifrugation step three times to obtain **3** (20 mg, 50%) as a white powder (mp 90°C, decomp.). ^1H-Nmr (D_2O), δ (ppm): 3.34 (s, 3H, OMe); 3.94 (s, 2H, $C\underline{H}_2OH$); 5.08-5.39 (ABm, J= 12.4 Hz, 2H, R-$C\underline{H}_2OPh$); 5.42 (s, 1H, H5); 7.40-6.80 (m, 5H, Ph).

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