Synthesis of 6,6-Disubstituted Penems

Tino Rossi*, Daniele Andreotti, Bruno Tamburini and Carla Marchioro

Glaxo Research Laboratories,
Via Fleming 4, 37100 Verona, Italy

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The synthesis of a series of 6,6-disubstituted penems starting from penicillanate **5a** is described. These penems were isolated and characterized as their pivaloyloxy methyl ester.

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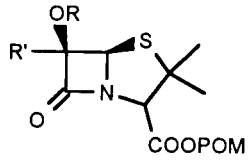
Since Woodward's [1] first descriptions of the penem nucleus, the efforts of a great number of chemists and biologists have been directed towards overcoming both synthetic and biological problems associated with this class of β-lactams. Although these compounds have a very broad spectrum of antimicrobial activity and high resistance to β-lactamase, they are generally sensitive to mammalian renal dehydropeptidase I (DHP-I) resulting in poor therapeutic effect *in vivo*.

In our search for novel penems bearing a substituent at C-6 differing from groups already described in the literature we envisaged 6,6-disubstituted penems **1** (Figure 1) as compounds of potential biological interest. It is well documented that 7,7-disubstituted cephalosporins **2** retain their satisfactory antibacterial potency against β-lactamase producing strains [2,3]. In two papers from Sanraku [4,5], describing the synthesis of 6-*epi*-methoxy- and 6-*epi*-hydroxy-PS-5 **3b**, **3c**, it was shown that the introduction of a second substituent at C-6 position effectively increases the stability to DHP-I when compared to PS-5 **3a**. However a dramatic loss of potency was observed.

As the ethyl group in 6-*epi*-methoxy- and 6-*epi*-hydroxy-PS-5 is attached at the C-6 position with a different configuration compared to PS-5 it is a reasonable hypothesis that the inverted configuration at C-6 could be responsible for the low potencies observed.

We decided to concentrate our attention on the 6α-alkyl-6β-hetero-substituted penems **1** (Figure 1) where OR could be a hydroxy, alkoxy or an acyloxy group and R' a well-known substituent and this paper describes our results in this field.

Figure 2



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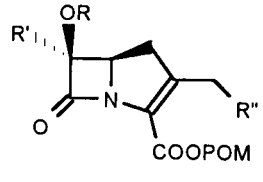
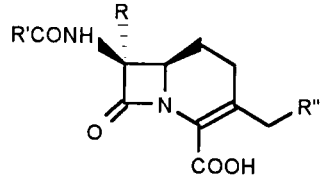
As the final compounds were synthesized as pivaloyloxymethyl (POM) esters and both the antibacterial activity and DHP-I stability were measured after enzymatic hydrolysis of these labile esters.

As the conversion of starting penicillanates to final penems is a well established route [6] (Scheme 1), the crucial step was shown to be the synthesis of penicillanates **4** (Figure 2) and in particular **4a**. Compound **4a** was synthesized as a single isomer by reacting diethyl cadmium with freshly prepared 6-oxopenicillanate **6a** [7] (Scheme 1). Organocadmium reagents were chosen [8] for their low basicity, their poor reactivity toward inactivated carbonyl compounds and the ease of synthesis. The formation of a single 6α-ethyl-6β-hydroxypenicillanate was presumed to take place by attack of the anion upon the less hindered α-face (*e.g.*, the *si*-face) of the ketone, as un-

Figure 1



1



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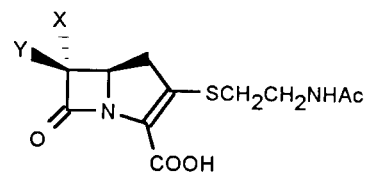


3a Y=H, X=C2H5

3b Y=C2H5, X=OCH3

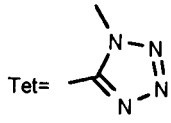
3c Y=C2H5, X=OH

R=H, CH3, C(O)CH3

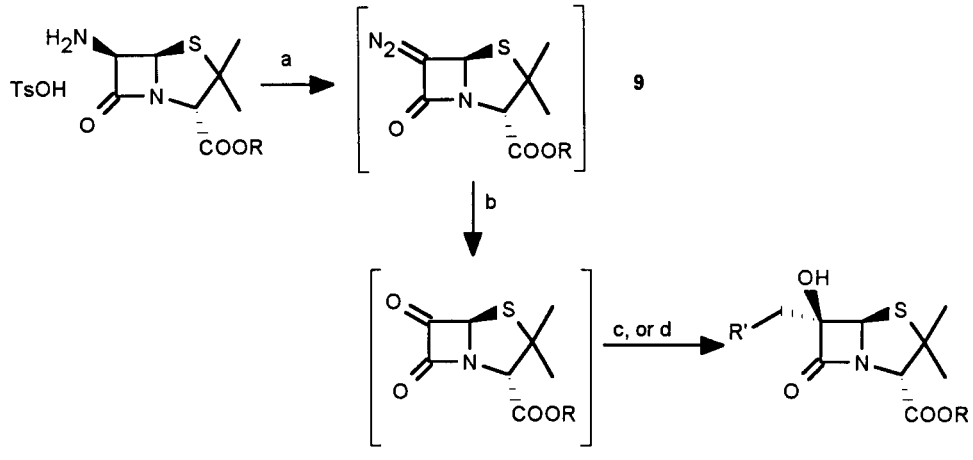
R'=C2H5, OCH3

R"=OOCCH3, S-Tet

POM=CH2OOCC(CH3)3



Scheme 1



5a R = POM **6a** R = POM **4a** R = POM, R' = CH_3

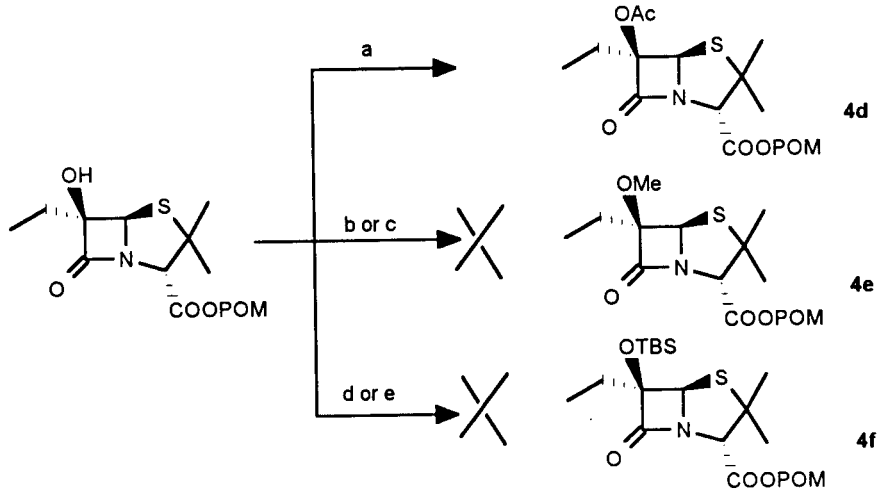
5b R = CH_2CCl_3 **6b** R = CH_2CCl_3 **4b** R = POM, R' = Ph

4c R = CH_2CCl_3, R' = Ph

a = $NaNO_2$, TsOH, CH_2Cl_2, H_2O; b = O_3, CH_2Cl_2, -30°C; c = C_2H_5MgBr, $CdCl_2$, THF,

d = $PhCH_2MgBr$, $CdCl_2$, THF.

Scheme 2

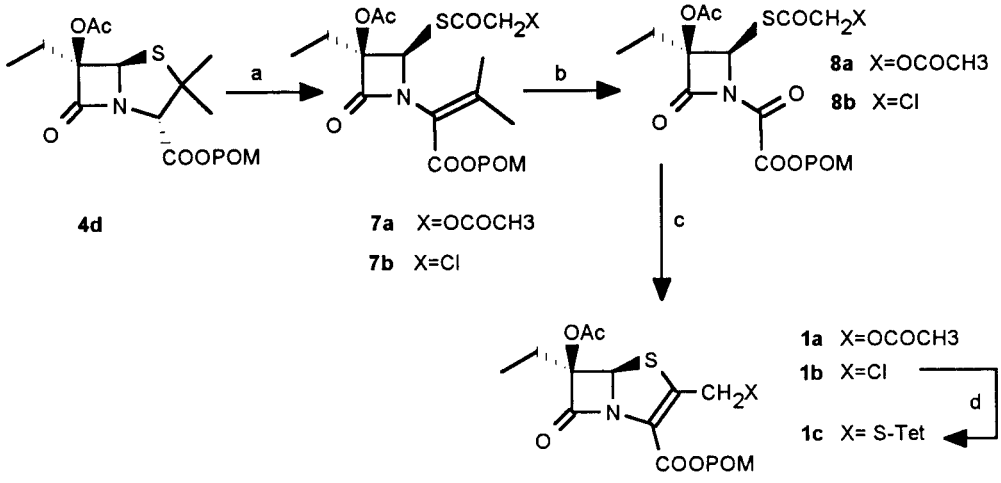


a = AcCl, TEA, Et_2O; b = NaH, MeI, DMF; c = Ag_2O, MeI, DMF; d = TBSCl, TEA, DMF;

e = TBSOTf, lutidine, CH_2Cl_2. TBS = t-Butyldimethylsilyl.

ambiguously proven by Brenner [9]. Unfortunately no nuclear Overhouser effect (nOe) was observed between the proton at C-5 and the CH_2 of the ethyl side chain and the same result was observed when the trichloroethyl ester of penicillanate **6b** was employed. When dibenzylcadmium was reacted with trichloroethyl 6-oxopenicillanate **6b** a single isomer **4c** was isolated in 18% yield. The absolute configuration at C-6 was confirmed by ^{1}H-nmr with the

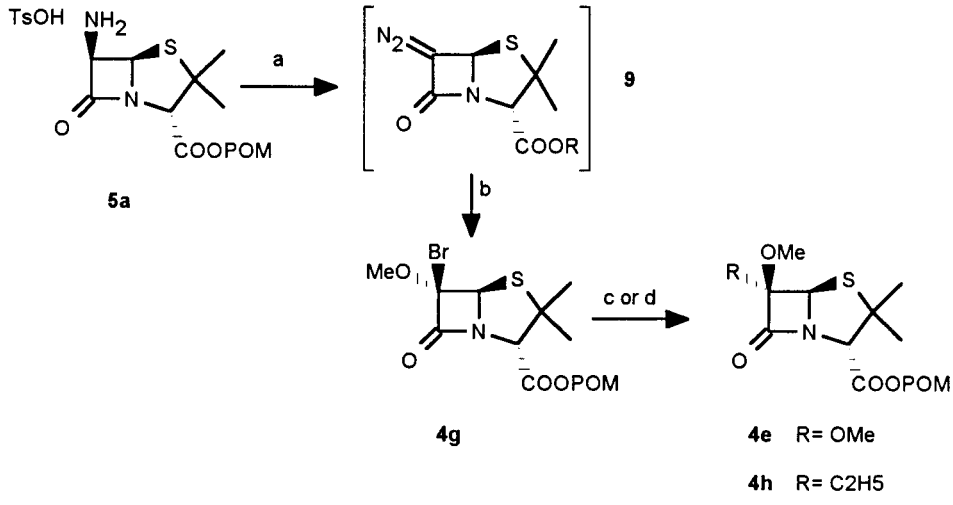
Scheme 3



a= $AgNO_3$, DBN, CH_3CN, then XCH_2COCl; b= O_3, CH_2Cl_2, -78°C; c= $(EtO)_3P$, toluene, ref.;

d= 5-mercapto-1-methyltetrazole sodium salt, Bu_4NBr, CH_2Cl_2/H_2O

Scheme 4



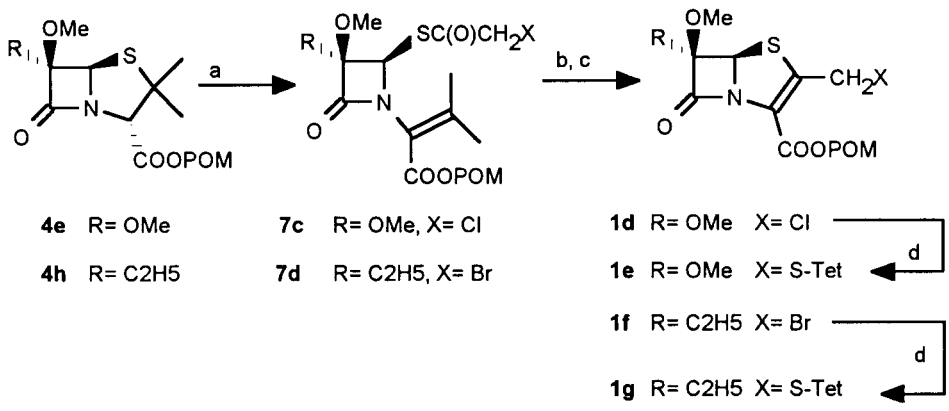
a= Na NO_2, TsOH, CH_2Cl_2/H_2O; b= $CH_3CONHBr$, MeOH; c= EtMgBr, CuI, Et_2O; d= $AgBF_4$,

MeOH.

proton at C-5 and the benzylic CH_2 showing a nOe of about 36%. The absolute configuration *R* at C-6 of compound **4a** was thus indirectly confirmed.

Further evidence supporting the proposed stereochemistry at C-6 of **4a** was obtained when all the attempts to derivatize the highly sterically hindered hydroxyl function were unsuccessful, except the formation of the acetoxy derivative **4d** with acetyl chloride and triethylamine in boiling ether (Scheme 2). The resulting penicillanate was converted to secopenicillanate **7a** in 40% yield by treatment with silver nitrate and 1,5-diazabicyclo[4.3.0]non-5-ene in acetonitrile followed by acylation with acetoxyacetyl chloride, then converted, after ozonolysis (dichloromethane, −78°), into intermediate **8a** which was immediately cyclized by heating the compound with an excess of triethyl phosphite in toluene. Penem **1a** was obtained in only 2% yield due to extensive decomposition observed during the cyclization reaction. The same intermediate **4d**, treated with silver nitrate and 1,5-diazabicyclo[4.3.0]non-5-ene in acetonitrile followed by acylation with chloroacetyl chloride gave secopenicillanate **7b** in 33% yield which, after ozonolysis and ring closure as described above gave the

Scheme 5



a= PhHgCl, DBU, CH_3CN then XCH_2COX; b= O_3, CH_2Cl_2, -78°C; c= $P(OEt)_3$, xylene, ref.; d= 5-mercapto-1-methyltetrazole sodium salt, Bu_4NBr, CH_2Cl_2/H_2O.

relatively unstable penem **1b**. This compound was immediately converted into **1c** by treatment with the sodium salt of 5-mercapto-1-methyltetrazole under phase transfer conditions [10] in reasonable yields (30% from **7b**).

As it was impossible to protect the hydroxyl group of penicillanate **4a** (Scheme 2) under a range of reaction conditions and by using different protecting groups we turned our attention to penem **1g** which could have been obtained from **4h**. We were unable to convert **4a** to the desired penicillanate **4h**, and therefore decided to use penicillanate **4g** [11] (Scheme 4). This compound, after treatment with silver tetrafluoroborate in anhydrous methanol, gave 6,6-dimethoxypenicillanate **4e** in 37% yield from **5a** which was converted to secopenicillanate **7c** (phenylmercuric chloride, 1,8-diazabicyclo[5.4.0]undec-7-ene in acetonitrile then chloroacetyl chloride, 82%) and transformed by standard procedures into penem **1e** in 33% yield. Compound **4g** successfully reacted with the organocopper reagent formed from ethylmagnesiumbromide and copper(I) iodide to give penicillanate **4h** in 23% yield.

The absolute configuration at C-6 was assigned by mechanistic considerations: it is well known that cuprates undergo nucleophilic substitution *via* an SN2 mechanism with inversion of configuration at the carbon atom bearing the leaving group, moreover in the case of **4g** the face of the nucleophilic attack is more sterically favored α-face. Compound **4h** was first converted to secopenicillanate **7d** (phenylmercuric chloride, 1,8-diazabicyclo[5.4.0]undec-7-ene in acetonitrile ten bromoacetyl bromide, 55%) and then to penem **1g** (18% yield from **4h**).

Despite the fact we were able to obtain a good stability to human renal DHP-I for our compounds their low potency and poor spectrum of activity discouraged any further work in this class of compounds.

EXPERIMENTAL

The ir spectra were recorded on a FT Bruker IFS 48. The ^{1}H-nmr spectra were recorded at 80 MHz on a Bruker WP 80SY using deuterated chloroform and chemical shifts were given in ppm using tetramethylsilane as an internal standard. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Analytical thin layer chromatography (tlc) was carried out with E. Merck F-254 silica gel plates. Column chromatography was performed as described by Still [12] with silica gel 60 (particle size (0.040-0.063 mm. E. Merck). Solvents and reagents were used without any further purification unless stated otherwise.

(2*S*,5*R*,6*R*)-3,3-Dimethyl-2-[(2,2-dimethyl-1-oxo)propoxy]methoxycarbonyl-6-ethyl-6-hydroxy-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane **4a**.

A 1.6 *M* solution of ethylmagnesium bromide (60 ml, 96 mmoles) in anhydrous tetrahydrofurane was added to a suspension of cadmium chloride (9 g, 50 mmoles) in anhydrous tetrahydrofuran (40 ml) at 0° and the resulting mixture was transferred (*via* cannula) into a cooled (−10°) solution of **6a** (9 g, 24 mmoles) (prepared in accord with Ursini [7]) in anhydrous tetrahydrofuran (100 ml), during the addition the temperature was maintained below 0°. At the end of the addition the mixture was stirred for 1 hour at 0°, then quenched with a saturated solution of ammonium chloride (100 ml) and extracted with ether (100 ml) to give after evaporation, of the dried organic phase over sodium sulfate, an oil which was purified by flash chromatography to obtain the title compound (3.5 g, 38% yield) as a pale yellow oil; ir (deuteriochloroform): ν 3500 (OH), 1770 (β-lactam); ^{1}H-nmr: δ 5.81 (2H, dd, -OCH_2O-), 5.32 (1H, s, H5), 4.49 (1H, s, H3), 3.25 (1H, bs, OH), 2.1-1.8 (2H, m, -CH_2CH$_3$), 1.61 (3H, s, 2β-CH$_3$), 1.52 (3H, s, 2α-CH$_3$), 1.21 (9H, s, C(CH$_3$)$_3$), 1.07 (3H, t, CH$_2$CH_3).

Anal. Calcd. for $C_{16}H_{25}NO_6S$: C, 53.47; H, 7.01; N, 3.90; S, 8.92. Found: C, 53.62; H, 6.88; N, 3.91; S, 8.80.

(2*S*,5*R*,6*R*)-3,3-Dimethyl-2-[(2,2-dimethyl-1-oxo)propoxy]methoxycarbonyl-6-benzyl-6-hydroxy-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane **4b**.

Reacting dibenzylcadmium with **6a**, using the same procedure applied for compound **4a** the title compound was obtained in 56% yield as a white solid, (mp 40-43°, hexane); ir (nujol): ν 3484

(OH), 1776 (β-lactam), 1705 (C=O, ester); ^{1}H-nmr δ 7.3 (5H, m, Ph), 5.81 (2H, dd, -OCH_2O-), 5.45 (1H, s, H5), 4.53 (1H, s, H3), 3.25 (2H, m, CH_2Ph); 1.58 (3H, s, 2β-CH_3), 1.48 (3H, s, 2α-CH_3); 1.20 (9H, s, C(CH_3)$_3$).

Anal. Calcd. for $C_{21}H_{27}NO_6S$: C, 59.84; H, 6.46; N, 3.32; S, 7.61. Found: C, 59.60; H, 6.51; N, 3.27; S, 7.54.

(2*S*,5*R*,6*R*)-3,3-Dimethyl-2-(2,2,2-trichloroethoxy)carbonyl-6-benzyl-6-hydroxy-7-oxo[4-thia-1-azabicyclo[3.2.0]heptane] **4c**.

Reacting diethyl cadmium and **6b** using the same procedure applied for compound **4a** the title compound was obtained in 18% yield as a colourless gum; ir (deuteriochloroform): ν 3488 (-OH), 1774 (β-lactam), 1730 (C=O, ester); ^{1}H-nmr: δ 7.28 (5H, m, Ph), 5.45 (1H, s, H5), 4.72 (2H, s, CH_2CCl$_3$), 4.59 (1H, s, H3), 3.25 (3H, bs, CH_2Ph), 1.64 (3H, s, 2β-CH_3), 1.56 (3H, s, 2α-CH_3).

Anal. Calcd. for $C_{17}H_{18}Cl_3NO_4S$: C, 46.54; H, 4.14; Cl, 24.24; N, 3.19; S, 7.31. Found: C, 46.80; H, 4.28; Cl, 24.12; N, 3.09; S, 7.2.

(2*S*,5*R*,6*R*)-3,3-Dimethyl-2-[(2,2-dimethyl-1-oxo)propoxy]methoxycarbonyl-6-ethyl-6-acetoxy-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane **4d**.

To a solution of compound **4a** (6.5 g, 18.1 mmoles) in anhydrous ether (100 ml), under vigorous stirring, was added triethylamine (3.25 ml, 21.2 mmoles) followed by acetyl chloride (1.7 g, 21.2 mmoles). The resulting mixture was refluxed for 1 hour, then cooled to room temperature. The solid was filtered off, water was added and the organic layers were extracted and separated. The organic layer was washed twice with water then with a cold 2% solution of hydrochloric acid followed by a saturated solution of sodium hydrogen carbonate, dried over sodium sulfate and evaporated under reduced pressure. The oil obtained was purified by filtration on a silica pad (ether as eluant) to give the title compound as a light yellow oil (6.1 g, 84%); ir (deuteriochloroform): ν 1790 (β-lactam), 1750 (C=O, ester); ^{1}H-nmr: δ 5.81 (2H, dd, O-CH_2O), 5.49 (1H, s, H5), 4.51 (1H, s, H3), 2.3-2.0 (5H, m, CH_2CH$_3$), 2.13 (3H, s, OOCCH_3), 1.58 (3H, s, 2β-CH_3), 1.43 (3H, s, 2α-CH_3), 1.21 (9H, s, OOC(CH_3)$_3$), 1.09 (3H, t, -CH$_2$CH_3).

Anal. Calcd. for $C_{18}H_{27}NO_7S$: C, 53.85; H, 6.78; N, 3.49; S, 7.99. Found: C, 53.98; H, 6.78; N, 3.60; S, 7.78.

(2*S*,5*R*,6*S*)-3,3-Dimethyl-2-[(2,2-dimethyl-1-oxo)propoxy]methoxycarbonyl-6-bromo-6-methoxy-7-oxo-1-thia-4-azabicyclo[3.2.0]heptane **4g**.

To a stirred solution of intermediate **9** (12.00 g, 34.5 mmoles) (prepared in accord with Ursini [7]) in anhydrous methanol (100 ml) and anhydrous methylene chloride, *N*-bromoacetamide (4.72 g, 34.5 mmoles) was added portionwise within 20 minutes. At the end of the addition, the solvent was removed under reduced pressure and the residue extracted with ethyl acetate (200 ml) and water (200 ml). The organic layer was dried over sodium sulfate and evaporated under reduced pressure to give an oily residue, which was purified by flash chromatography (cyclohexane-ethyl acetate gradient 95/5 to 7/3) to yield 6,6-dibromopenicillanate (1.8 g) eluted first and the title compound (5.5 g, 37%) as a white solid (mp 83-85°); ir (deuteriochloroform): ν 1790 (β-lactam), 1760 (esters); ^{1}H-nmr: δ 5.82 (2H, m, OCH_2O), 5.41 (1H, s, H5), 4.51 (1H, s, H3), 3.67 (3H, s, OCH_3), 1.59 (3H, 2β-CH_3), 1.48 (3H, s, 2α-CH_3), 1.22 (9H, s, OOC(CH_3)$_3$).

Anal. Calcd. for $C_{15}H_{22}BrNO_6S$: C, 42.46; H, 5.23; Br, 18.83; N, 3.30; S, 7.56. Found: C, 42.38; H, 5.23; Br, 18.80; N, 3.27; S, 7.50.

(2*S*,5*R*)-3,3-Dimethyl-2-[(2,2-dimethyl-1-oxo)propoxy]methoxycarbonyl-6,6-dimethoxy-7-oxo-[4-thia-1-azabicyclo[3.2.0]heptane **4e**.

To a stirred solution of intermediate **5a** (15 g, 44 mmoles) in anhydrous methanol (150 ml) and anhydrous methylene chloride (300 ml), *N*-bromoacetamide (5.4 g, 40 mmoles) was added portionwise within 20 minutes. At the end of the addition the solvent was removed under reduced pressure and the residue dissolved in dry methanol (100 ml). Silver tetrafluoborate (7.7 g, 40 mmoles) was added portionwise over 30 minutes. At the end of the addition the mixture was stirred for further 30 minutes, then filtered and the filtrate concentrated to a small volume. Ethyl acetate (200 ml) was added and the resulting mixture was extracted 3 times with water (200 ml) before drying over sodium sulfate and concentrate under reduced pressure to give an oily residue, which was purified by flash chromatography (cyclohexane-ethyl acetate gradient 95/5 to 7/3) obtaining the title compound (5.5 g, 37%) as a white solid (mp 83-84°); ir (deuteriochloroform): ν 1790 (β-lactam), 1760 (C=O, esters); ^{1}H-nmr: δ 5.82 (2H, m, OCH_2O), 5.27 (1H, s, H5), 4.47 (1H, s, H3), 3.51 (3H, s, β-OCH_3), 3.45 (3H, s, α-OCH_3), 1.57 (3H, s, 2β-CH_3), 1.49 (3H, s, 2α-CH_3), 1.22 (9H, s, OOC(CH_3)$_3$).

Anal. Calcd. for $C_{16}H_{25}NO_7S$: C, 51.19; H, 6.71; N, 3.73; S, 8.54. Found: C, 50.98; H, 6.84; N, 3.65; S, 8.32.

(2*S*,5*R*,6*R*)-3,3-Dimethyl-2-[(2,2-dimethyl-1-oxo)propoxy]methoxycarbonyl-6-ethyl-6-methoxy-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane **4h**.

To a suspension of copper(I) iodide (11 g, 57.76 mmoles) in dry ethyl ether (50 ml) stirred under nitrogen and cooled at −30°, was added 100 ml of a precooled to −20°, 5 molar solution of ethylmagnesium bromide in dry ether (20 ml) dropwise. The resulting mixture was stirred for 1.5 hours at 0° then cooled again to −30° and a solution of intermediate **4g** (3.1 g, 7.3 mmoles) in dry ether (20 ml) was added. The reaction was warmed to room temperature stirred for 1.5 hours then cooled again to −50° and quenched with a saturated solution of ammonium chloride (100 ml), the organic layer was separated and washed twice with brine (50 ml), dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by flash chromatography (cyclohexane-ethyl acetate gradient from 95/5 to 7/3) to afford the title compound (640 mg, 23%) as a colourless oil; ir (deuteriochloroform): ν 1770 (β-lactam); ^{1}H-nmr: δ 5.76 (2H, m, OCH_2O), 5.26 (1H, s, H5), 4.36 (1H, s, H3), 3.44 (3H, s, OCH_3), 1.8 (2H, m, CH_2CH$_3$), 1.50 (3H, s, 2β-CH_3), 1.43 (3H, s, 2α-CH_3), 1.15 (9H, s, OOC(CH_3)$_3$), 0.89 (3H, t, CH$_2$CH_3).

Anal. Calcd. for $C_{17}H_{27}NO_6S$: C, 54.67; H, 7.29; N, 3.75; S, 8.58. Found: C, 54.38; H, 7.49; N, 3.66; S, 8.35.

(3*R*,4*R*)-1-[1-((2,2-dimethyl-1-oxo)propoxy)methoxycarbonyl-2-methyl-1-propenyl]-3-ethyl-3-acetoxy-4-(2-acetoxy-1-oxoethyl)thioazetidinone **7a**.

Intermediate **4d** (2.3 g, 5.72 mmoles), dissolved in anhydrous acetonitrile (35 ml), was added dropwise to a mixture formed by silver nitrate (1.87 g, 11.4 mmoles) and 1,5-diazabicyclo[4.3.0]-non-5-ene (1.37 g, 11.4 mmoles) in dry acetonitrile (35 ml). The mixture was stirred at room temperature in the dark for 64 hours then silver nitrate (0.94 g, 5.7 mmoles) and 1,5-diazabicyclo-[4.3.0]non-5-ene (0.69 g, 5.7 mmoles) were added and the mixture stirred for 24 hours. Acetoxyacetyl chloride (1.5 g, 11.4 mmoles) in dry acetonitrile (15 ml) was added at room temperature and the reaction stirred for 1 hour, filtered and the filtrate was diluted with ethyl acetate (100 ml) and extracted three times with

water and the organic layer was dried over sodium sulfate. The oily residue obtained after evaporation of the solvent was purified by flash chromatography (cyclohexane-ethyl acetate 8/2) to afford the starting material (0.9 g) and the title compound as an oil (0.7 g, 40%); ir (deuteriochloroform): ν 1790 (C=O, β-lactam) and 1730 (C=O esters); ^{1}H-nmr: δ 5.88 (2H, dd, OCH_2O) and 5.82 (3H, s, H4), 4.69 (2H, s, OOCCH_2O), 2.27 (3H, s, =C(CH$_3$)CH_3), 2.17 (2H, t, CH_2CH$_3$), 2.17 (3H, s, OOCCH_3) and 2.12 (3H, s, OOCCH_3), 1.42 (3H, s, =C(CH_3)CH$_3$); 1.22 (9H, s, OOC(CH_3)$_3$), 1.13 (3H, t, CH$_2$CH_3).

Anal. Calcd. for $C_{22}H_{31}NO_{10}S$: C, 52.69; H, 6.23; N, 2.79; S, 6.39. Found: C, 52.73; H, 6.12; N, 2.78; S, 6.48.

(3*R*,4*R*)-1-[1-((2,2-Dimethyl-1-oxo)propoxy)methoxycarbonyl-2-methyl-1-propenyl]-3-ethyl-3-acetoxy-4-(2-chloro-1-oxoethyl)thio-2-azetidinone **7b**.

The title compound was obtained in 33% yield as a pale yellow oil using chloroacetyl chloride under the same reaction condition applied for compound **7a**; ir (deuteriochloroform): ν 1780 (C=O, β-lactam), 1750 and 1690 (C=O, esters); ^{1}H-nmr: 5.89 (2H, dd, OCH_2O), 5.89 (1H, s, H4), 4.17 (2H, s, OOCCH_2Cl), 2.27 (3H, s, OOCCH_3); 2.19 (3H, s, =C(CH$_3$)CH_3), 2.14 (3H, s, =C(CH_3)CH$_3$), 2.2 (2H, m, CH_2CH$_3$), 1.23 (9H, s, OOC(CH_3)$_3$), 1.15 (t, 3H, t, CH$_2$CH_3).

Anal. Calcd. for $C_{20}H_{28}ClNO_7S$: C, 52.00; H, 6.11; Cl, 7.67; N, 3.03; S, 6.94. Found: C, 51.88; H, 6.15; Cl, 7.49; N, 3.12; S, 7.01.

(4*R*)-1-[1-((2,2-Dimethyl-1-oxo)propoxy)methoxycarbonyl-2-methyl-1-propenyl]-3,3-dimethoxy-4-(2-chloro-1-oxoethyl)thio-2-azetidinone **7c**.

To a stirred suspension of phenylmercuric chloride (3.5 g, 11 mmoles) in dry acetonitrile (200 ml) was added 1,8-diazabicyclo-[5.4.0]undec-7-ene (1.5 g, 12 mmoles) dropwise over 15 minutes. The resulting mixture was stirred for 15 minutes at room tempeature and then cooled to 5°. A solution of **4e** (3.72 g, 10 mmoles) in dry acetonitrile (100 ml) was added and the resulting mixture was stirred for 1 hour at room temperature. Chloroacetyl chloride (2 ml, 20 mmoles), dissolved in anhydrous acetonitrile (20 ml) was added and the resulting mixture stirred for 2 hours. The reaction was filtered and concentrated to a small volume, ethyl acetate (100 ml) was added and the organic layer was extracted with water (100 ml) and three times with 5% sodium hydrogen carbonate (50 ml). The organic layer was dried over sodium sulfate, evaporated under reduced pressure and the oily residue purified by flash chromatography (cyclohexane-ethyl acetate). The title compound (4.1 g, 82%) was obtained as a light yellow oil; ir (deuteriochloroform): ν 1780 (β-lactam), 1750 (esters); ^{1}H-nmr: δ 5.8 (3H, m, OCH_2O + H4), 4.16 (2H, s, CH_2Cl), 3.63 (3H, s, α-OCH_3), 3.50 (3H, s, β-OCH_3), 2.27 (3H, s, =C(CH$_3$)CH_3), 1.96 (3H, s, =C(CH_3)CH$_3$), 1.22 (9H, s, OOC(CH_3)$_3$).

Anal. Calcd. for $C_{18}H_{26}ClNO_8S$: C, 47.84; H, 5.80; Cl, 7.84; N, 3.10; S, 7.09. Found: C, 47.80; H, 5.82; Cl, 7.70; N, 3.08; S, 7.21.

(5*R*,6*R*)-3-Acetoxymethyl-2-[(2,2-dimethyl-1-oxo)propoxy]methoxycarbonyl-6-ethyl-6-acetoxy-7-oxo-4-thia-1-azabicyclo[3.2.0]-hept-2-ene **1a**.

Intermediate **7a** (0.55 g, 1.1 mmoles), dissolved in dry methylene chloride, was cooled to −78°, with vigorous stirring, and ozone was bubbled in for 15 minutes until the solution turned light blue. The solvent was evaporated and an oily residue was obtained (515 mg). Anhydrous xylene (20 ml) was added and the resulting solution heated at 50°. A solution of triethyl phosphite (360 mg, 2.16 mmoles) in anhydrous xylene (2 ml) was added in 15 minutes and the resulting solution was heated at 110° for 8 hours then further 2 hours at reflux. The solvent was removed under vacuum and the residue was purified by flash chromatography (cyclohexane-ethyl acetate gradient from 98/2 to 9/1) to afford the title compound (10 mg, 2%) as a colourless oil; ir (deuteriochloroform): ν 1810 (β-lactam), 1750 (ester), 1580 (C=C); ^{1}H-nmr: δ 5.9 (3H, m, OCH_2O + H5), 5.3 (2H, CH_2O), 2.4 (2H, CH_2CH$_3$); 2.17 (3H, s, OOCCH_3), 2.09 (3H, s, OOCCH_3), 1.22 (9H, s, OOC(CH_3)$_3$), 1.1 (3H, t, CH$_3$CH_3).

Anal. Calcd. for $C_{19}H_{25}NO_9S$: C, 51.46; H, 5.68; N, 3.16; S, 7.23. Found: C, 51.32; H, 5.80; N, 3.12; S, 7.15.

(5*R*,6*R*)-3-(1-Methyltetrazol-5-yl)thiomethyl-2-[(2,2-dimethyl-1-oxo)propoxy]methoxycarbonyl-6-ethyl-6-acetoxy-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene **1c**.

Intermediate **7b** (2.25 g, 4.5 mmoles), dissolved in methylene chloride (50 ml), was cooled at −78° with stirring and ozone was bubbled in until the colourless solution turned light blue (1.5 hours). Nitrogen was bubbled in to remove excess of ozone, the solution was warmed to room temperature and the solvent removed under reduced pressure. The oily residue was dissolved in dry toluene (60 ml) and heated at 50°. A solution of triethyl phosphite (1.67 g, 8.9 mmoles) in dry toluene (10 ml) was added dropwise and the resulting mixture was heated at 90° for 1 hour then refluxed for 8 hours. The reaction mixture was cooled and the solvent removed under reduced pressure. The oily residue was submitted to a filtration on silica to remove polar materials (cyclohexane-ethyl acetate 9/1) to afford a crude mixture containing the unstable intermediate **1b** (1.860 g), half of this mixture (930 mg) was dissolved in dichloromethane (20 ml). An aqueous solution (20 ml) of 5-mercapto-1-methyltetrazole sodium salt (380 mg, 2.22 mmoles) was added followed by tetrabutylammonium bromide 71 mg, 0.222 mmoles). The resulting mixture was vigorously stirred for 3 hours, the reaction mixture was transferred into a separatory funnel and methylene chloride (50 ml) was added, the organic layer was separated and extracted twice with water (30 ml), dried over sodium sulphate and evaporated under reduced pressure. The oily residue was purified by flash chromatography (cyclohexane-ethyl acetate gradient from 9/1 to 7/3) to give the title compound (350 mg, 30% overall yield); ir (deuteriochloroform): ν 1810 (β-lactam), 1750 (C=O ester), 1580 (C=C and C=N); ^{1}H-nmr: δ 5.88 (2H, OCH_2O), 5.71 (1H, bs, H5), 4.85 and 4.45 (2H, d + d, CH_2S), 3.95 (3H, s, NCH_3), 2.3 (2H, m, CH_2CH$_3$), 2.14 (3H, s, OOCCH_3), 1.23 (9H, s, OOC(CH_3)$_3$), 1.08 (3H, t, CH$_3$CH_3).

Anal. Calcd. for $C_{19}H_{25}N_5O_8S_2$: C, 44.26; H, 4.89; N, 13.58; S, 12.44. Found: C, 44.12; H, 4.89; N, 13.50; S, 12.37.

(5*R*)-3-(1-Methyltetrazol-5-yl)thiomethyl-2-[(2,2-dimethyl-1-oxo)-propoxy]methoxycarbonyl-6,6-dimethoxy-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene **1e**.

Intermediate **7c** (2 g, 4.4 mmoles), dissolved in dry methylene chloride (70 ml), was cooled to −50° with vigorous stirring and ozone was bubbled in during 50 minutes until the colourless solution turned light blue. Nitrogen was then bubbled in and the solvent was evaporated under reduced pressure. The oily residue was dissolved in dry xylene (100 ml) and heated at 50° with stirring. Triethyl phosphite (1.5 g, 9 mmoles) was added dropwise (10 minutes) and the reaction mixture was heated at 110° for 1 hour and at 130° for 5 hours. The solvent was removed, after cooling,

under reduced pressure and the residue was dissolved in methylene chloride (50 ml), a solution of 5-mercapto-1-methyltetrazole sodium salt (0.77 g, 1 eq) and tetrabutylammonium bromide (0.2 g) in water (30 ml) was added and the resulting mixture was stirred for 3 hours. The organic layer was separated and washed twice with water (50 ml) then dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by flash chromatography (cyclohexane-ethyl acetate gradient from 8/2 to 1/1) to afford the title compound (0.7 g, 33%) as a colourless oil; ir (deuteriochloroform): ν 1805 (β-lactam); 1760-1740 (esters), 1585 (C=C penem); ^{1}H-nmr: δ 5.87 (2H, dd, OCH_2), 5.5 (1H, s, H5), 4.72 (2H, dd, CH_2S), 3.94 (3H, s, NCH_3), 3.47 (3H, s, OCH_3), 3.40 (3H, OCH_3), 1.25 (9H, s, OOC(CH_3)$_3$).

Anal. Calcd. for $C_{17}H_{23}N_5O_7S_2$: C, 43.12; H, 4.90; N, 14.79; S, 13.54. Found: C, 43.21; H, 4.80; N, 14.60; S, 13.22.

(5*R*,6*R*)-3-(1-Methyltetrazol-5-yl)thiomethyl-2-[(2,2-dimethyl-1-oxo)propoxy]methoxycarbonyl-6-ethyl-6-methoxy-7-oxo-[4-thia-1-azabicyclo[3.2.0]hept-2-ene **1g**.

To a suspension of phenylmercuric chloride (1.25 g, 4 mmoles) in dry acetonitrile (66 ml) cooled with a ice bath, a solution of 1,8-diazabicyclo[5.5.0]undec-7-ene (0.813 g, 5.74 mmoles) in acetonitile (15 ml) was added dropwise with stirring. The resulting mixture was stirred at room temperature for 30 minutes and then a solution of **4h** (1 g, 2.67 mmoles) in dry acetonitrile was added from a dropping funnel. The stirring was continued for 1 hour then bromoacetyl bromide (1.19 g, 5.9 mmoles) was added *via* a syringe. The reaction was stirred for 30 minutes then filtered. The filtrate was concentrated to small volume under reduced pressure, diluted with ethyl acetate (200 ml) and extracted with water (100 ml) followed by saturated ammonium chloride (100 ml) and 5% sodium hydrogen carbonate (100 ml). The residue obtained after evaporation of the dried organic phase over sodium sulfate was purified by flash chromatography (cyclohexane-ethyl acetate gradient from 9/1 to 7/3) a pale yellow oil (640 mg, 55%, 1.92 mmoles) (Rf = 0.4 cyclohexane-ethyl acetate 7/3) which was dissolved in dry methylene chloride (100 ml), cooled at −78° and ozone was bubbled in for 45 minutes until the reaction turned light blue. The excess of ozone was removed by flushing with nitrogen and the solution was warmed to room temperature and the solvent was removed under reduced pressure. Dry xylene was added (20 ml) and the solution was heated with stirring at 50° and triethyl phosphite (640 gm, 3.85 mmoles) was added dropwise over 10 minutes. The reaction was stirred at −110° for 2 hours, cooled and the solvent was removed under reduced pressure. The oily residue was dissolved in methylene chloride (10 ml) and a solution of 5-mercapto-1-methyltetrazole sodium salt (319 mg, 2.53 mmoles) in water (2 ml) was added followed by tetrabutylammonium bromide (322 mg). The reaction was stirred for 1.5 hours, then the organic layer was separated and extracted twice with water (10 ml) and then with brine (10 ml). The residue, after evaporation of the solvent, was purified by flash chromatography (cyclohexane-ethyl acetate gradient from 9/1 to 7/3) to afford the title compound as a colourless oil (140 mg, 18% overall); ir (deuteriochloroform): ν 1767 (β-lactam), 1576 (C=C); ^{1}H-nmr: δ 5.88 (2H, dd, OCH_2O), 5.66 (1H, s, H5), 4.68 (2H, dd, CH_2S), 3.96 (3H, s, NCH_3), 3.50 (3H, s, OCH_3), 2.00 (2H, m, CH_2CH$_3$), 1.20 (9H, s, OOC(CH_3)$_3$), 0.96 (3H, t, CH$_2$CH_3).

Anal. Calcd. for $C_{18}H_{25}N_5O_6S_2$: C, 45.85; H, 5.34; N, 14.85; S, 13.60. Found: C, 46.01; H, 5.34; N, 15.10; S, 13.37.

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