Synthesis of 2β-Azidomethylpenicillin-1,1-Dioxides and 3β-Azido-3α-methylcepham-1,1-Dioxides

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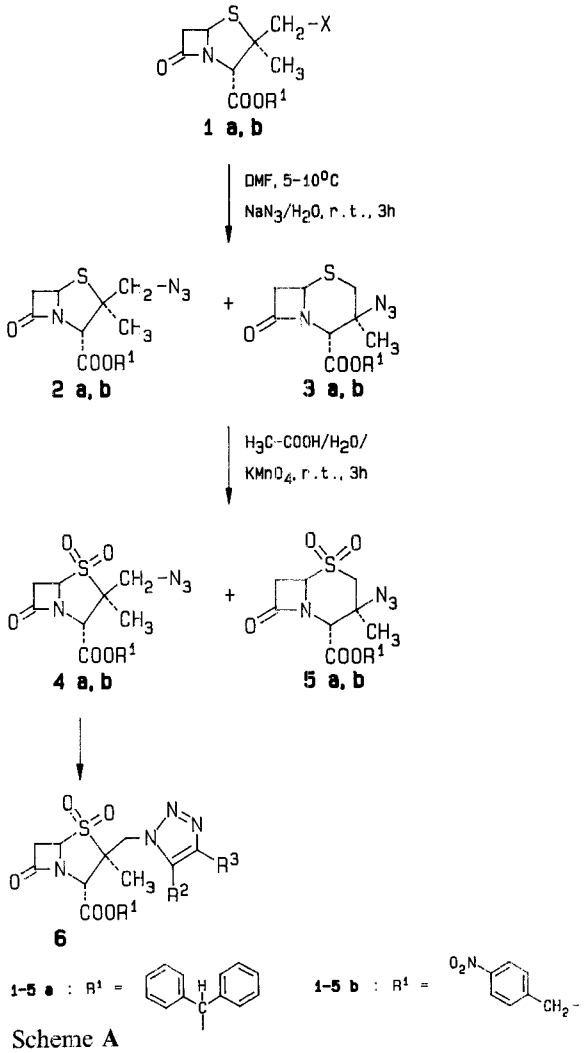
A convenient synthesis of the 2β-azidomethylpenicillin-1,1-dioxides, precursors of the active "YTR" class of β-lactamase inhibitors, is described starting with 6-aminopenicillanic acid (6-APA), which is converted to 6α-bromopenicillanic acid. Oxidation with peracetic acid in the presence of benzophenone hydrazone give benzhydryl 6α-bromopenicillanate-1-oxide in one step and reduction with zinc and acetic acid gave the 6,6-dihydropenicillanate-1-oxide. The unsymmetrical azetidinone disulfide was obtained by heating with 2-mercaptobenzothiazole, and reaction with copper(II) chloride or bromide gave the 2β-halomethylpenams. Reaction with sodium azide in aqueous dimethylformamide gave a mixture of the 2β-azidomethylpenam and the 3β-azidocepham. Oxidation with potassium permanganate gave a mixture of the 2β-azidomethylpenam-1,1-dioxide and the 3β-azidocepham-1,1-dioxide, which was easily separated by fractional crystallization.

In connection with our studies on the design and synthesis of β-lactamase inhibitors, we have had occasion to synthesize the 2β-azidomethylpenicillin-1,1-dioxides **4a, b** (Scheme A),



Scheme A

as precursors to the very active β-lactamase inhibitors – the 6,6-dihydro-2β-triazolylmethylpenicillin-1,1-dioxides **6**, exemplified by YTR-830[1-10]. This paper describes a convenient method for the preparation of the 6,6-dihydro-2β-azidomethyl-2α-methylpenam-1,1-dioxides, **4a, b** and the isomeric 7,7-dihydro-3β-azido-3α-methylcepham-1,1-dioxides **5a, b**. The preparation and biological activity of the 6,6-dihydro-2β-triazolylmethylpenicillin-1,1-dioxides **6** will be reported in a separate publication.

Among the methods described for the preparation of alkyl azides[11,12,13], the direct bimolecular nucleophilic displacement of the halide by azide ion constitutes one of the most convenient and general synthesis of aliphatic azides[12,13]. The patent literature contains only one example of a 2-azidomethylpenicillin, 2,2,2-trichloroethyl-2β-azidomethyl-2α-methyl-6-(2-phenylacetamido)-penam-3-carboxylate obtained in low yield (about 15%)[14]. We have studied the reaction of the 6,6-dihydro-2β-halomethyl-2α-methylpenam-3-carboxylates (**1a, b**; X = Cl or Br) with azides, as a route to the 2β-azidomethylpenicillins **2**. The 2β-halomethyl-2α-methylpenicillins **1** (X = Cl or Br) were prepared from 6,6-dihydropenicillin-1-oxides **11a, b** (see Scheme **C**).

Until recently, the most widely used procedure for the preparation of the 6,6-dihydropenicillins involved either tributyltin hydride reduction[15] of the 6α-bromopenicillanate or catalytic hydrogenation of 6α-bromopenicillins[16,17] and 6,6-dibromopenicillins[18,19]. The route employed by us for the preparation of 6,6-dihydropenicillin oxides **11** is summarized in Scheme **B**. The preparation of 6α-bromopenicillanic acid **(8)** using a range of co-solvents was investigated. Table 1 summarizes the data from these reactions. With methanol as co-solvent there was always the co-formation of the thiazine[20]. Ethanol was the choice of co-solvent (no thiazine being formed). Thus in the modified procedure using potassium bromide and 2.5 normal sulfuric acid (instead of 48% hydrobromic acid) and ethanol as co-solvent the yield of 6α-bromopenicillanic acid **(8)** was close to 90%.

The 6α-bromopenicillanic acid **(8)** was conveniently and efficiently converted in one step to the benzhydryl 6α-bromopenicillanate-1-oxide **(12a)** in 94% by reaction with peracetic acid and benzophenone hydrazone by a modified procedure[21]. Treatment of the benzhydryl 6α-bromopenicillanate-1-oxide **(12a)** with zinc and glacial acetic acid in acetonitrile gave benzhydryl 6,6-dihydropenicillanate-1-oxide **(11a)** in almost quantitative yield.

While the benzhydryl 6α-bromopenicillanate-1-oxide **(12a)** was reduced cleanly with zinc and acetic acid, we found that a

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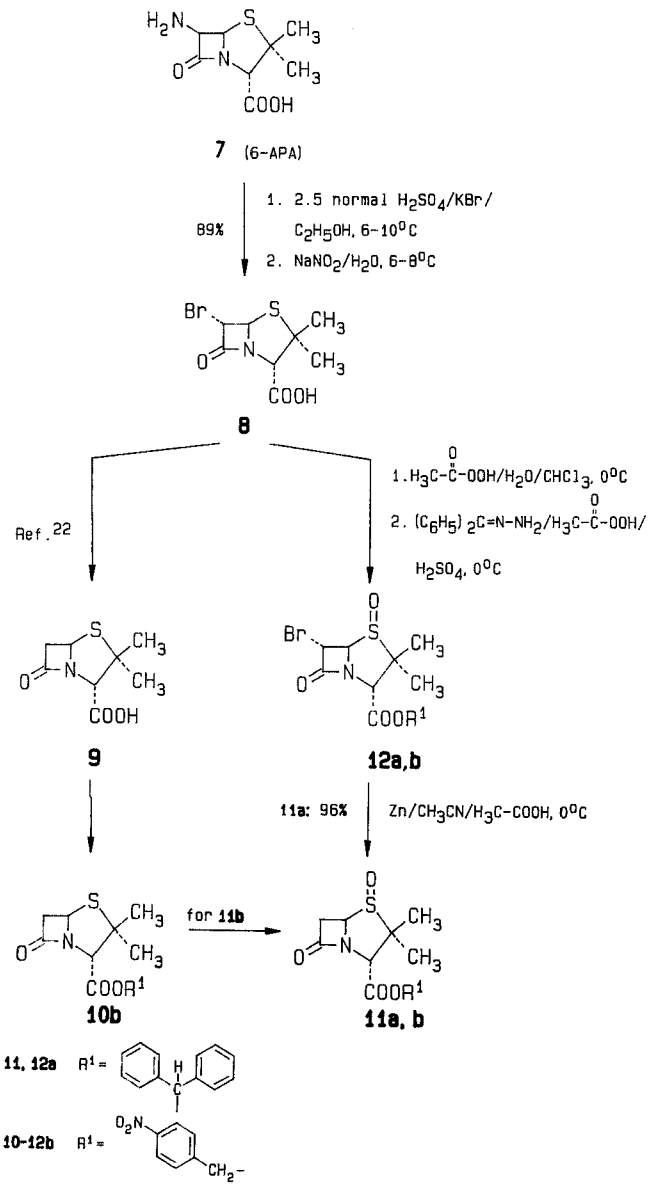
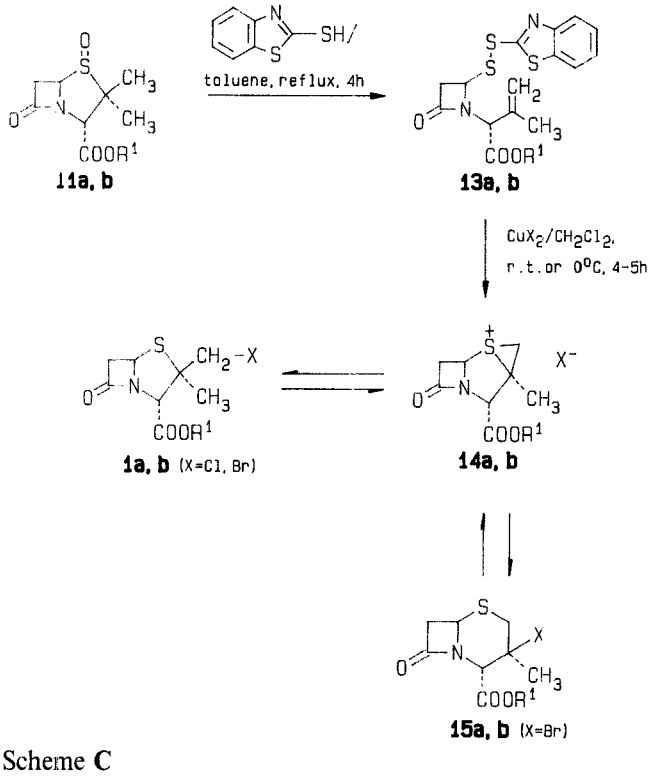


Scheme **B**

was not successful, and hence a different sequence[22] we used to prepare *p*-nitrobenzyl 6,6-dihydropenicillanate-1-oxide **(11b)**.

The 6,6-dihydropenicillin-1-oxides **11a, b** when heated with a stoichiometric amount of 2-mercaptobenzothiazole in a solvent such as toluene or dioxane, gave an essentially quantitative yield of the unsymmetrical azetidinone disulfides **13a, b** as pale yellow foam (Scheme **C**)[23]. Although 2-halomethylpenicillins **1a, b** have been prepared by reacting the unsymmetrical azetidinone disulfides **13a, b** with halogens (see Ref.[23]), we have found that a convenient method for carrying out these reactions is the heterogeneous reaction of a solution of **13** in solvents such as dichloromethane, with copper(II) chloride or bromide. When a solution of the



Scheme **C**

Table 1. Effect of Co-solvents on the Yield of **8** from **7**

Entry	Reagent	Co-solvent	Yield [%][a]
1	$HBr/NaNO_2$	CH_3OH	75
2	$HBr/NaNO_2$	$(H_3C)_2C=O$	75
3	$HBr/NaNO_2$	*i*-C_3H_7OH	59
4	$HBr/NaNO_2$	*t*-C_4H_9OH	42
5	$HBr/NaNO_2$	$H_3C-CO-C_4H_9$-*i*	70
6	$HBr/NaNO_2$	1,4-dioxane	78
7	$HBr/NaNO_2$	C_2H_5OH	77
8	KBr/2.5 normal $H_2SO_4/NaNO_2$	$CHCl_3$	62
9	KBr/2.5 normal $H_2SO_4/NaNO_2$	C_2H_5OH	89

[a] Yield of crude product.

similar reduction of the benzhydryl 6α-chloropenicillanate-1-oxide was extremely slow and incomplete (only about 35% reduction even after 72 h). A similar slow reduction of 6α-chloropenicillanates with tributyltin hydride has been reported[15]. The attempted reductive debromination of *p*-nitrobenzyl 6α-bromopenicillanate-1-oxide **(12b)** using zinc/acetic acid or tributyltin hydride in refluxing toluene unsymmetrical azetidinone disulfide **13a, b** in dichloromethane was stirred for 4 h at room temperature with copper(II) chloride, an essentially quantitative yield of the 2β-chloromethylpenicillin **1a** or **b** (X = Cl) was obtained as yellow foam. Under exactly the same conditions, copper(II) bromide gave a mixture of the 2β-bromomethylpenicillins, **1** (X = Br) and the 3β-bromo-3α-methylcephams **15** (X = Br).

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However, when this reaction with copper(II) bromide was run at 0°C instead of room temperature, a quantitative yield of the 2β-bromomethylpenicillins **1a, b** (X = Br) resulted; the formation of the kinetic product, the 2β-bromomethylpenicillins **1** being favoured at low temperatures, over that of the thermodynamic product, the 3β-bromo-3α-methylcephams **15** the reaction proceeding by way of the thiiranium intermediate **14** (X = Cl or Br).

The 2β-halomethylpenicillins **1a, b** (X = Cl, Br), on treatment with sodium azide in aqueous solvents such as acetone, acetonitrile, or dimethylformamide, gave a mixture of the 2β-azidomethylpenicillin, **2** and the 3β-azido-3α-methylcepham **3**. Dimethylformamide was found to be the best solvent for this reaction, resulting in the shortest reaction time (about 3 h). The temperature at which this reaction was run while affecting the rate of reaction, had no effect on the penam : cepham ratio, which was about 3:2 (see Table 2) – the ratio being determined from the ^{1}H-N.M.R. spectrum of the crude product.

Table 2. Influence of Temperature on the Rate of Formation of Azide

Compound	Solvent	Temperature	Time	Yield [%] of 1	2	3
1a (X = Cl)	DMF/H_2O	0°C	10 h	19	48	33
	DMF/H_2O	10–15°C	8 h	9	59	32
	DMF/H_2O	25°C	3 h	–	60–65	40–35

It was also found that the ratio of the penam **2**: cepham **3**, formed and the rate of the reaction was not dependent on the 2β-halo-(Br or Cl)-methylpenam **1** used. In both cases the ratio of **2**:**3** formed was 3:2, reaction being complete in 3 h.

This reaction of the 2β-halomethylpenams **1** with sodium azide to give the mixture of the 2β-azidomethylpenam **2** and the 3β-azido-3α-methylcepham **3** probably proceeds by way of the thiiranium azide **14** (X = N_3). Oxidation of the sulfur of **1** to the sulfoxide or sulfone would prevent the formation of a thiiranium type intermediate **14**. In fact, attempts to displace the halide group of the corresponding sulfoxide or sulfone of compound **1a** by azide, using exactly the same conditions, or even after longer reaction times or under gentle reflux at 40°C, were unsuccessful – only starting material or decomposition products being isolated. These reactions confirm the anchimeric assistance of the unshared electrons of the ring sulfur atom of compounds **1** for the nucleophilic displacement of the halide group. Attempts to prepare the 2β-azidomethylpenicillins **2** directly from the unsymmetrical azetidinone disulfide **13** using iodine azide was unsuccessful. Nitrogen was liberated probably by reduction of the sulfenyl azide intermediate by azide ion[24].

The separation of the 2β-azidomethylpenams **2** and the 3β-azido-3α-methylcephams **3** proved to be quite difficult. For our studies the most convenient procedure was to oxidize the isomeric mixture of **2** and **3** with potassium permanganate in acetic acid. The resulting mixture of the 2β-azidomethylpenicillin-1,1-dioxide **4a** and the 3β-azido-3α-methylcepham-1,1-dioxides **5a**, although difficult to separate by chromatography, was easily and efficiently separated by treatment with ether. The 2β-azidomethylpenicillin-1,1-dioxide **4a** was readily soluble in ether, while the 3β-azido-3α-methylcepham-1,1-dioxide **5a** was quite insoluble in ether. Similarly, in the case of the *p*-nitrobenzyl ester, the isomers **4b** and **5b** were readily separated by fractional crystallization using ether and chloroform (see Experimental Section). The assignment of structures of **4** and **5** were made from the ^{1}H-N.M.R. spectral data, and from the fact that compound **5** on treatment with pyridine gave the corresponding desacetoxycephem.

Melting points were determined on a Thomas-Hoover uni-melt melting point apparatus and are uncorrected. Microanalyses were performed by Department of Chemistry, University of Alberta. I.R. Spectra were recorded on a Nicolet DX FT-IR Spectrophotometer, only significant maxima are listed. ^{1}H-N.M.R. spectra were taken on Varian 60 MHz and Bruker AM-300 MHz spectrometers and are reported in parts per million downfield from TMS.

6α-Bromopenicillanic Acid (8):
2.5 Normal sulfuric acid (500 ml) is cooled with stirring to ~ 10°C; to this 6-aminopenicillanic acid (**7**; 43.2 g, 0.2 mol) is added in one portion followed by potassium bromide (120.2 g), then ethanol (95%, 400 ml) is added, the mixture is allowed to cool to 6–8°C, then a solution of sodium nitrite (21.2 g) in water (100 ml) is added dropwise within 1 h, the temperature of the mixture is maintained between 6–8°C and it is stirred at that temperature for 3.5 h. The mixture is extracted with chloroform (2 × 250 ml, 4 × 100 ml, 3 × 50 ml), all chloroform layers are combined and washed with 50% cold brine (2 × 250 ml), dried with sodium sulfate, and concentrated to give the desired compound as a sticky foam; yield: 49.96 g (89%).

I.R. (KBr): ν = 1788, 1731 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 9.85 (br. s, 1H, COOH); 5.43 (d, 1H, *J* = 1 Hz, 6β-H); 4.9 (d, 1H, *J* = 1 Hz, 5α-H); 4.63 (s, 1H, 3-H); 1.7 (s, 3H, CH_3); 1.58 ppm (s, 3H, CH_3).

Benzhydryl 6α-Bromopenicillanate-1-oxide (12a):
To a stirred and ice-cold mixture consisting of **8** (19.56 g, 0.0698 mol), chloroform (138 ml), and water (69 ml), peracetic acid (40%, 13.94 g, 0.0733 mol) is added dropwise over 30 min. The mixture is stirred at 0°C for 30 min more, benzophenone hydrazone (14.81 g, 0.0755 mol) and potassium iodide (1% aqueous solution, 4.6 ml) are added followed by peracetic acid (40%, 15.93 g, 0.0838 mol) over 30 min at 0°C followed by sulfuric acid (10%, 5.5 ml). The mixture is stirred at 0°C for 1 h, then at ambient temperature for 1 h. The chloroform layer is separated and the aqueous layer is back extracted with chloroform (2 × 50 ml). The combined organic layers are washed with cold water (200 ml), and stirred for 30 min with saturated sodium hydrogen carbonate (150 ml) at 10°C. The chloroform layer is washed with brine, dried with sodium sulfate, and concentrated to give the product as a pale yellow, hard foam [yield: 30.3 g (94%)] which is recrystallized from ethyl acetate/hexane to give a white solid; m.p. 65–70°C.

$C_{21}H_{20}BrNO_4S$	calc.	C 54.51	H 4.32	N 3.03	S 6.92
(462.3)	found	54.64	4.29	3.11	7.03

I.R. (KBr): ν = 1795, 1757 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 7.4 (m, $10H_{arom}$); 7.0 [s, 1H, $(C_6H_5)_2CH$]; 5.1, 5.0 (AB-q, 2H, *J* = 1 Hz, 5α-H and 6β-H); 4.65 (s, 1H, 3-H); 1.65 (s, 3H, CH_3); 0.9 ppm (s, 3H, CH_3).

Benzhydryl 6,6-Dihydropenicillanate-1-oxide (11a):
Zinc dust (10.72 g) is added over 15 min to a stirred and ice-cold solution of **12a** (15.19 g, 0.0328 mol) in acetonitrile (250 ml) and glacial acetic acid (35 ml) and the mixture is stirred in ice-bath for an additional 3 h, filtered through celite, washed with acetonitrile, and ether. The combined filtrates are concentrated under reduced pressure, poured into ice-cold water (500 ml), and extracted with chloroform (3 × 60 ml). The combined extracts are washed with water, stirred for 30 min with saturated sodium hydrogen carbonate, washed again with brine, dried with sodium sulfate, and concentrated to give the product as a pale yellow foam; [yield: 12 g (96%)] which is recrystallized from ethyl acetate/hexane to give a white solid; m.p. 145–148°C.

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$C_{21}H_{21}NO_4S$ (383.4) calc. C 65.72 H 5.47 N 3.65 S 8.34
found 65.82 5.49 3.69 8.38

I.R. (KBr): $\nu = 1797, 1759\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 7.3$ (m, $10H_{arom}$); 7.0 [s, 1H, $(C_6H_5)_2CH$]; 4.9 (t, 1H, $J = 3.5$ Hz, 5α-H); 4.6 (s, 1H, 3-H); 3.25 (d, 2H, $J = 3.5$ Hz, 6-H); 1.65 (s, 3H, CH_3); 0.9 ppm (s, 3H, CH_3).

Unsymmetrical Disulfides 13a and 13b:

Benzhydryl 6,6-dihydropenicillanate-1-oxide (**11a**; 11.49 g, 0.03 mol) and 2-mercaptobenzothiazole (5.0175, 0.03 mol) in toluene (100 ml) are stirred and heated under reflux, using a Dean-Stark trap. The reaction is followed by T.L.C. and is complete after 4 h. Toluene is removed under reduced pressure. For the complete removal of toluene, the sticky light brown residue is dissolved in a small volume of dichloromethane (15–20 ml) and precipitated by addition of a large volume of hexane under cooling and the hexane layers decanted off (repeated 3 times). The residue is dissolved in ether (250 ml) and cooled; the precipitated solid is filtered off, the filtrate is concentrated to give the desired compound **13a** as a sticky light yellow foam; yield: 15 g (94%).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 7.95–7.1$ (m, $14H_{arom}$); 6.88 [s, 1H, $(C_6H_5)_2CH$]; 5.34 (dd, 1H, $J = 2$ Hz, 4 Hz, 4-H); 5.1 4.9 (2 br.s, 2H, $C{=}CH_2$); 5.0 (s, 1H, CH—COO); 3.28 (t, 2H, CH_2—CO); 1.9 ppm (s, 3H, CH_3).

The unsymmetrical sulfide **13b** is prepared analogously from **11b** (2.0 g, 0.0056 mol). After complete removal of toluene, the viscous residue is dissolved in dichloromethane and precipitated with hexane to give **13b**; yield: 2.60 g (91%); m.p. 122–124°C.

$C_{22}H_{19}N_3O_5S_3$ (501.6) calc. C 52.69 H 3.79 N 8.38 S 19.16
found 52.78 3.99 8.15 19.16

I.R. (KBr): $\nu = 1774, 1741, 1516, 1347\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 8.4–7.35$ (m, $8H_{arom}$); 5.1, 4.93 (2s, 2H, $C{=}CH_2$); 5.35 (m, overlapping with a sharp s, 4H, H-4, CH—COO, $COOCH_2$); 3.45 (t, 2H, CH_2—CO); 1.98 ppm (s, 3H, CH_3).

These compounds are rapidly affected by silica, so that purification by chromatography is not possible. However, the compounds are pure enough for further reactions.

Benzhydryl 2β-Chloromethyl-2α-methyl-6,6-dihydropenicillanate (1a; X = Cl):

A mixture of **13a** (2.65 g, 5 mmol) and copper(II) chloride (0.8067 g), 6 mmol) in dichloromethane (40 ml) is stirred at room temperature for 4 h. The color of the heterogeneous mixture initially becomes darker (almost black), but after a while changes to greenish yellow. The mixture is filtered through Celite and washed thoroughly with dichloromethane. The filtrate is washed with aqueous sodium hydrogen carbonate, followed by brine (twice), and dried with sodium sulfate. The light yellow dichloromethane solution is rapidly filtered through a small bed of silica; removal of dichloromethane gives the desired product **1a**, as a light yellow foam, which is pure enough for further reaction; yield: 1.8 g (90%).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 7.38$ (m, $10H_{arom}$); 6.98 [s, 1H, $(C_6H_5)_2CH$]; 5.4 (dd, 1H, $J = 2$ Hz, 4 Hz, H-5); 5.14 (s, 1H, H-3); 3.6 (dd, 1H, $J = 4$ Hz, 16 Hz, H-6); 3.6 (s, 2H, CH_2Cl); 3.08 (dd, 1H, $J = 2$ Hz, 16 Hz, H-6); 1.33 ppm (s, 3H, CH_3).

***p*-Nitrobenzyl 2β-Chloromethyl-2α-methyl-6,6-dihydropenicillanate (1b; X = Cl):**

Prepared similarly from **13b** (5.0 g, 9.9 mmol). The compound solidifies on standing; crystallization from dichloromethane/hexane gives a white solid; yield: 3.32 g (90%); m.p. 108–110°C.

$C_{15}H_{15}ClN_2O_5S$ (370.5) calc. C 48.58 H 4.04 Cl 9.58 N 7.55 S 8.63
found 48.82 4.10 10.06 7.50 8.64

I.R. (KBr): $\nu = 1780, 1740\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 8.38$ (d, $2H_{arom}$); 7.65 (d, $2H_{arom}$); 5.48 (dd, 1H, $J = 2$ Hz, 4 Hz, H-5); 5.39 (s, 2H, $COOCH_2$); 5.18 (s, 1H, H-3); 3.75 (dd, 1H, $J = 4$ Hz, 16 Hz, H-6); 3.7 (s, 2H, CH_2Cl); 3.15 (dd, 1H, $J = 2$ Hz, 16 Hz, H-6); 1.55 ppm (s, 3H, CH_3).

***p*-Nitrobenzyl 2β-Bromomethyl-2α-methyl-6,6-dihydropenicillanate (1b; X = Br):**

A mixture of **13b** (2.0 g, 3.9 mmol) and powdered copper(II) bromide (0.96 g, 4.3 mmol) in dichloromethane (30 ml) is stirred at 0–5°C for 4–5 h. The color changes from dark green to greenish yellow. The reaction is followed by T.L.C. The mixture is rapidly filtered through Celite covered with a small bed of silica, while the filtration flask is placed in an ice-cold bath (0–5°C). Dichloromethane is removed under reduced pressure maintaining the bath temperature between 10–15°C. The viscous oil is pumped under high vacuum for 0.5–1 h to give the pure bromo compound **1b** as a light yellow foam; yield: 1.485–1.551 g (90–94%). All the operations are done rapidly and with proper cooling to prevent the formation of the corresponding cepham isomer **15b**.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 8.35$ (d, $2H_{arom}$); 7.65 (d, $2H_{arom}$); 5.5 (dd, 1H, $J = 2$ Hz, 4 Hz, H-5); 5.4 (s, 2H, $COOCH_2$); 5.24 (s, 1H, H-3); 3.74 (dd, 1H, $J = 4$ Hz, 16 Hz, H-6); 3.68 (s, 2H, CH_2Br); 3.2 (dd, 1H, $J = 2$ Hz, 16 Hz, H-6); 1.55 ppm (s, 3H, CH_3).

Benzhydryl 2β-Bromomethyl-2α-methyl-6,6-dihydropenicillanate (1a; X = Br):

Prepared similarly from **13a** (4.0 g, 7.5 mmol); yield: 3.08 g (92%).

I.R. ($CHCl_3$): $\nu = 1781, 1749\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 7.4$ (m, $10H_{arom}$); 6.98 [s, 1H, $(C_6H_5)_2CH$]; 5.45 (dd, 1H, $J = 2$ Hz, 4 Hz, H-5); 5.2 (s, 1H, H-3); 3.64 (dd, 1H, $J = 4$ Hz, 16 Hz, H-6); 3.58 (s, 2H, CH_2Br); 3.1 (dd, 1H, $J = 2$ Hz, 16 Hz, 6-H); 1.38 ppm (s, 3H, CH_3).

Benzhydryl 2β-Azidomethyl-2α-methyl-6,6-dihydropenicillanate (2a) and Benzhydryl 3β-Azido-3α-methyl-7,7-dihydrocephalosporanate (3a):

A solution of **1a** (X = Cl; 5 g, 12.4 mmol) in dimethylformamide (120 ml) is cooled with stirring to 5–10°C; to the cooled solution is added powdered sodium azide (4.83 g, 0.0744 mol), followed by water (40 ml). The mixture is stirred at room temperature for 3 h. A major portion of the dimethylformamide is removed in vacuo and the residue is diluted with ice-cold water (250 ml). The resultant mixture is extracted with ethyl acetate (3 × 100 ml). The combined organic extracts are washed with water (8 × 100 ml), and dried with sodium sulfate. Concentration and drying under high vacuum gives a residue weighing 4.5 g. T.L.C. analysis indicates two major components with very similar R_f values. A small amount (300 mg) of the penam isomer **2a** is separated in fairly pure form by very careful column chromatography over silica using chloroform/hexane (4:1) as eluting solvent.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 7.4$ (m, $10H_{arom}$); 7.0 [s, 1H, $(C_6H_5)_2CH$]; 5.42 (dd, 1H, $J = 2$ Hz, 4 Hz, H-5); 4.9 (s, 1H, H-3); 3.65 (dd, 1H, $J = 4$ Hz, 14 Hz, H-6); 3.5 (s, 2H, CH_2N_3); 3.15 (dd, 1H, $J = 2$ Hz, 14 Hz, H-6); 1.3 ppm (s, 3H, CH_3).

The mixture (penam:cepham) is directly oxidized with potassium permanganate in glacial acetic acid without prior separation.

Benzhydryl 2β-Azidomethyl-2α-methyl-6,6-dihydropenicillanate-1,1-Dioxide (4a) and Benzhydryl 3β-Azido-3α-methyl-7,7-dihydrocephalosporanate-1,1-Dioxide (5a):

The crude mixture (4.5 g, from the previous experiment) is dissolved in glacial acetic acid (230 ml). To this solution, water (30 ml) is added; potassium permanganate (4.17 g, 0.026 mol) is added portionwise over a period of 30 min. The mixture is stirred at room temperature until the oxidation is complete (usually 3 h) as indicated by the persistence of the dark purple color. The excess of permanganate is decomposed by the dropwise addition of hydrogen peroxide and the mixture poured into ice-cold water (200 ml). The precipitated solid is filtered off and dissolved in dichloromethane (100 ml). The aqueous layer is saturated with sodium chloride and back extracted with additional dichloromethane (2 × 50 ml). The combined organic extracts are washed with saturated sodium hydrogen carbonate (2 × 50 ml), followed by brine (2 × 50 ml), and dried with sodium sulfate. Concentration in vacuo gives the crude mixture (4 g) as a light yellow foam which is dissolved in ether (100 ml), refluxed (30 min), and cooled to 5–10°C, the precipitated white solid is pure **5a**; yield: 0.97 g (25%); m.p. 136–138°C.

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$C_{21}H_{20}N_4O_5S$	calc.	C 57.27	H 4.54	N 12.72	S 7.27
(440.5)	found	57.46	4.59	12.06	7.24

I.R. ($CHCl_3$): ν = 2140, 1800, 1745 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 7.35 (m, 10 H_{arom}); 6.96 [s, 1H, $(C_6H_5)_2CH$]; 4.96 (dd, 1H, J = 2 Hz, 4.5 Hz, H-6); 4.5 (s, 1H, H-4); 3.65 (dd, 1H, J = 2 Hz, 15 Hz, H-7); 3.34 (dd, 1H, J = 4.5 Hz, 15 Hz, H-7); 3.6 (d, 1H, J = 15 Hz, H-2); 3.16 (d, 1H, J = 15 Hz, H-2); 1.2 ppm (s, 3H, CH_3).

Concentration of the filtrate gives a sticky white foam which on crystallization from benzene/hexane affords pure **4a** as a white solid; yield: 2.522 g (65%); m.p. 88–90°C (softening at 60–65°C).

$C_{21}H_{20}N_4O_5S$	calc.	C 57.27	H 4.54	N 12.72	S 7.27
(440.5)	found	57.52	4.79	12.62	7.07

I.R. ($CHCl_3$): ν = 2135, 1810, 1760 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 7.35 (m, 10 H_{arom}); 6.96 [s, 1H, $(C_6H_5)_2CH$]; 4.65 (s, 1H, H-3); 4.56 (dd, 1H, J = 2.2 Hz, 3.7 Hz, H-5); 3.8 (AB-q, 2H, J = 13.5 Hz, CH_2N_3); 3.48 (dd, 1H, J = 3.7 Hz, 17 Hz, H-6); 3.39 (dd, 1H, J = 2.2 Hz, 17 Hz, H-6); 1.15 ppm (s, 3H, CH_3).

p-Nitrobenzyl 2β-Azidomethyl-2α-methyl-6,6-dihydropenicillanate-1,1-Dioxide (4b) and p-Nitrobenzyl 3β-Azido-3α-methyl-7,7-dihydrocephalosporanate-1,1-Dioxide (5b):

An analogous procedure is followed. The crude mixture is heated to reflux with a large volume of ether (150–200 ml); the ether soluble fraction is the pure penam isomer **4b** which is obtained as a white foam; yield: 60%; m.p. 40–45°C (sinters).

I.R. (KBr): ν = 2116, 1799, 1760, 1524, 1351 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 8.28 (d, 2 H_{arom}); 7.6 (d, 2 H_{arom}); 5.35 (AB-q, 2H, J = 13.2 Hz, $COOCH_2$); 4.68 (dd, 1H, J = 2.2 Hz, 4.4 Hz, H-5); 4.65 (s, 1H, H-3); 3.88 (AB-q, 2H, J = 13.2 Hz, CH_2N_3); 3.6 (dd, 1H, J = 4.4 Hz, 16.5 Hz, H-6); 3.5 (dd, 1H, J = 2.2 Hz, 16.5 Hz, H-6); 1.45 ppm (s, 3H, CH_3).

The ether insoluble portion on crystallization from chloroform affords the pure crystalline cepham isomer **5b**; yield: 32%; m.p. 200–204°C (decomp.).

$C_{15}H_{15}N_5O_7S$	calc.	C 44.00	H 3.66	N 17.11	S 7.82
(409.4)	found	44.00	3.68	16.18	6.96

I.R. (KBr): ν = 2118, 1781, 1739 cm^{-1}.

^{1}H-N.M.R. (acetone-d_6): δ = 8.3 (d, 2 H_{arom}); 7.85 (d, 2 H_{arom}); 5.53 (AB-q, 2H, J = 13 Hz, $COOCH_2$); 5.13 (dd, 1H, J = 2.1 Hz, 4.2 Hz, H-6); 4.53 (s, 1H, H-4); 3.75 (AB-q, 2H, J = 15 Hz, SO_2—CH_2); 3.55 (dd, 1H, J = 4.2 Hz, 15 Hz, H-7); 3.45 (dd, 1H, J = 2.1 Hz, 15 Hz, H-7); 1.55 ppm (s, 3H, CH_3).

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