fractions: 1, 28.0 mg (32.1%) **16**, mp 153–157 °C, contaminated by the trans cyclopropane, which was recrystallized from ether/pentane to yield 14.4 mg (16.5%) of cis cyclopropane, mp 171–173 °C; 2, 9.7 mg (10.5%) of the transcyclopropane, mp 164–174 °C. This fraction was combined with the solid from the fractional crystallization and recrystallized from ether/pentane to yield 41.4 mg (47.4%) of **17**, mp 179–182 °C.

Exploratory Sensitized Photochemistry of *trans*-1,2,2-Triphenyl-1-[(phenyldimethylsilyl)oxy]-3-(2,2-diphenylvinyl)cyclopropane (17). A solution of 50.5 mg (84.4 μmol, 4.69×10^{-4}) of **17** and 57.5 mg (293 μmol, 1.54×10^{-3} M) of xanthone in 180 mL of acetonitrile was photolyzed for 31 min through a Pyrex filter and a 2.0×10^{-2} M sodium metavanadate solution circulating through the cooling jacket of a 450-W Hanovia medium-pressure lamp. The photolysate was concentrated under vacuum to yield 111.4 mg of a mixture of sensitizer and vinylcyclopropanes. The NMR showed a 2.25:1 ratio of **17** to **16**. The mixture was subjected to a HPLC (50 × 0.95 cm silica column, 25% ether/pentane) to give fractions A1, 42.7 mg (84.6%) of the vinylcyclopropanes, and A2, 48.5 mg (247 μmol) of xanthone. Fraction A1 was fractionally crystallized to give 13.8 mg (27.4%) of **17** contaminated with the cis isomer. The filtrate was subjected to HPLC (1.5% ether/pentane to give the following) fractions: B1, 7.4 mg (14.7%) of the cis cyclopropane with a trace of the trans isomer present; B2, 19.0 mg (37.7%) of the trans cyclopropane, mp 178–180 °C. Fraction B2 and the solid that was fractionally crystallized were recrystallized from ether/pentane to yield 29.1 mg (57.6%) of trans cyclopropane, mp 179–180 °C.

Exploratory Direct Photolysis of 1,2,2,5,5-Pentaphenyl-4-penten-1-one (18). A solution of 94.1 mg (202 μmol, 1.12×10^{-3} M) of 1,2,2,5,5-pentaphenyl-4-penten-1-one in 180 mL of acetonitrile was photolyzed for 1 h 34 min through a Pyrex filter with a 450-W Hanovia medium-pressure lamp. The photolysate was concentrated under vacuum to yield 102.4 mg of a mixture whose NMR showed a 5.6:5.6:1 ratio of *cis*-1-hydroxy-1,2,2-triphenyl-3-(2,2-diphenylvinyl)cyclopropane (**14**) to *trans*-1-hydroxy-1,2,2-triphenyl-3-(2,2-diphenylvinyl)cyclopropane (**15**) to 1,2,2,5,5-pentaphenyl-4-penten-1-one (**18**). The mixture was subjected to HPLC (50 × 0.95 cm silica column, 15% ether/pentane) to give the following fractions: A1, 11.6 mg (16.0%) of impure 1,1,4,4-tetraphenyl-1,3-butadiene (**22**), which was recrystallized from ether/pentane to yield 7.0 mg (9.65%) of **22**, mp 196–199 °C (lit.[39] mp 200 °C); A2, 8.4 mg of unidentified aromatic material; A3, 16.2 mg of a mixture of compounds including the starting ketone; A4, 19.7 mg (21.0%) of **14**; A5, 15.8 mg (16.8%) of **15**. Fraction A3 was subjected to HPLC (4% ether/pentane) to give 6.2 mg (6.58%) of slightly impure **18**, which was recrystallized from ether/pentane to yield 4.2 mg (9.0 μmol, 4.56%) of the ketone, mp 169–171 °C.

Single Photon Counting. The apparatus and procedure have been described previously.[13a] The solvents were methylcyclohexane (Kodak Spectral Grade) and isopentane purified as described previously.[13a] Individual samples were prepared in a 4:1 methylcyclohexane–isopentane solution to give an optical density in the range 0.80–1.5, thoroughly degassed by at least four freeze–thaw cycles immediately before counting, and counted at 77 K until a minimum of 1500 counts in the maximum channel (512 channels total) were obtained. Data were collected at less than 5% of the 30–40-kHz lamp flash rate to ensure exclusion of double photon counting. In separate runs excitation was varied over the range 265–275 nm, and emission was monitored over the range 300–315 nm with an RCA 8850 photomultiplier. The decay rate was independent of excitation and emission wavelengths employed. A single exponential decay function was found in all cases. The data are reported as follows: lifetime at 77 K, 2.6 ns; lifetime at room temperature, 74 ps; rate of decay at 77 K, 3.8×10^8 s^{-1}; rate of decay at room temperature, 1.33×10^{10}; rate of reaction at room temperature, 9.31×10^7; number of runs, 4; and an estimated 10% error in rate.

Fluorescence Studies.[13a] The fluorescence spectrum was recorded in 4:1 methylcyclohexane–isopentane solution at 77 and 295 K under otherwise identical conditions. Details are given in the supplementary material.

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Registry No. 1, 21086-26-0; **2**, 27674-41-5; **3**, 114789-75-2; **4**, 114789-76-3; **5**, 114789-77-4; **6**, 114789-78-5; **7**, 114789-79-6; **8**, 114789-80-9; **9**, 7476-12-2; **10**, 451-40-1; **11**, 114789-81-0; **12**, 19692-28-5; **13**, 114789-82-1; **14**, 114789-83-2; **15**, 114789-84-3; **16**, 114789-85-4; **17**, 114819-59-9; **18**, 57365-26-1; **19**, 114789-86-5; **20**, 57694-83-4; **21**, 1733-63-7; **23**, 114789-87-6; **24**, 114789-88-7; **25**, 114789-89-8; **26**, 114789-90-1; **27**, 114789-91-2; **28**, 114789-92-3; **29**, 7498-88-6; **30**, 55004-95-0; Ph_2CHBr, 776-74-9; $Ph_2C{=}CHCH_2Br$, 4801-15-4.

Supplementary Material Available: Crystal data, positional parameters, interatomic distances, bond angles, anisotropic and isotropic temperature factors, and an ORTEP drawing for *cis*-1,2,2-triphenyl-1-[(phenyldimethylsilyl)oxy]-3-(2,2-diphenylvinyl)cyclopropane, general experimental information, and IR data for **3–9**, **11**, **13–20**, and **26–28** (13 pages). Ordering information is given on any current masthead page.

Synthesis of Benzhydryl 2α-(Chloromethyl)-2β-methyl-6,6-dihydropenam-3α-carboxylate 1,1-Dioxide: The 2α-Isomer of the Potent β-Lactamase Inhibitor BL-P2013

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In order to study the effect of stereochemical changes on the activity of an active group of β-lactamase inhibitors, the 2β-(substituted methyl)penam 1,1-dioxides, an investigation of the method for the preparation of 2α-(substituted methyl)penam was undertaken. The described 2α-(chloromethyl)penam 1β-sulfoxide **11** was conveniently obtained by the thermolytic rearrangement of the 2β-(chloromethyl)penam 1α-sulfoxide **10**. The preparation and β-lactamase inhibitory activity of the 2α-isomer of the active β-lactamase inhibitor BL-P2013 are reported.

The introduction of benzylpenicillin into clinical practice about 45 years ago was almost immediately followed by the discovery of resistant strains of pathogenic microorganisms. One of the major causes of bacterial resistance to the β-lactam antibiotics is the ability of these bacteria to produce β-lactamases that catalyze the hydrolysis of the β-lactam antibiotics to the inactive penicilloic acids. The

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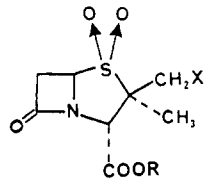
discovery that clavulanic acid[1] and sulbactam (CP-45,899)[2] are effective inhibitors of β-lactamases not only provided a new approach for the control of infectious diseases caused by penicillin-resistant microorganisms but also led to new insight into the nature of the active site of β-lactamases and into the mechanism of their action on penicillins. A variety of new inhibitors[3] that incorporate a β-lactam ring in their structures have been reported recently. Many of these compounds are relatively simple semisynthetic derivatives of 6-aminopenicillanic acid. One of these derivatives is 2β-(chloromethyl)-2α-methylpenam-3α-carboxylic acid 1,1-dioxide (BL-P2013),[3e] **1** (R = H, X = Cl), which demonstrates high β-lactamase inhibitory activity against a variety of bacterial β-lactamases.



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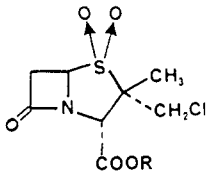


2

We had also previously prepared and investigated the same compound (BL-P2013), **1** (R = H, X = Cl), and the related more active 2β-(bromomethyl)-2α-methylpenam-3α-carboxylic acid 1,1-dioxide, **1** (R = H, X = Br),[3g] 2β-(azidomethyl)-2α-methylpenam-3α-carboxylic acid 1,1-dioxide, **1** (R = H, X = N_3);[3c] and 2β-(triazolylmethyl)-2α-methylpenam-3α-carboxylic acid 1,1-dioxide, **1** (R = H, X = 1,2,3-triazole).[3b] In continuation of this work and in order to determine the effect of stereochemical changes on activity, we have studied the synthesis of the 2α-isomer (**2**) of benzhydryl 2β-(chloromethyl)-2α-methyl-6,6-dihydropenicillanate 1,1-dioxide, **1** (R = $CHPh_2$, X = Cl). This paper reports a useful route for the synthesis of the compound **2** (R = $CHPh_2$) and the β-lactamase inhibitory activity of the corresponding sodium salt.

Results and Discussion

The 2α-(substituted methyl)penam system **4** was first reported by Spry[4] by the thermal epimerization of methyl 2β-(acetoxymethyl)-6β-acetamido 1α-sulfoxide **3**. Barton and co-workers[5] also utilized this concept for flipping the 2β-(acetoxymethyl)penam to the 2α-(acetoxymethyl)penam. The success of this transformation is dependent on the proper orientation of the sulfoxide and the C_2-substituted methyl group. Since the opening of the thiazolidine ring occurs stereospecifically by a cis [2,3] sigmatropic reaction, the sulfoxide and the unsubstituted methyl group at the C-2 position should be cis oriented (in this instance both should have the α-orientation) to give the desired sulfenic acid. The sulfenic acid forms an intramolecular hydrogen bond with the NH group of the 6β-amido side chain, forcing the recyclization to take place from the β-face of the molecule and thus controlling the stereochemistry of the transformation (Figure 1).

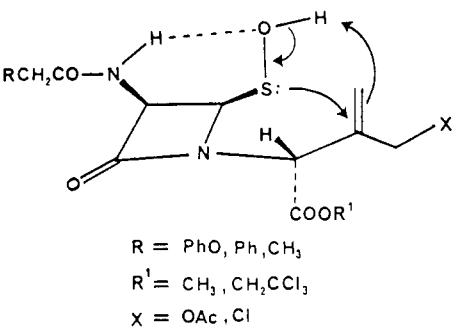
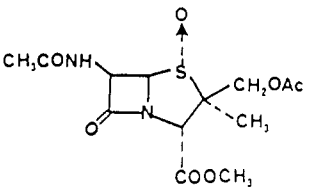


Figure 1.



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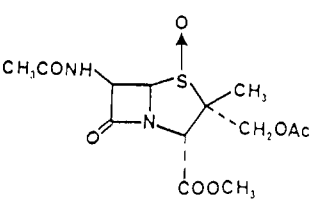

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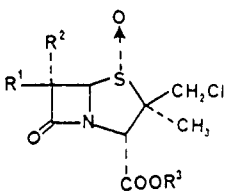

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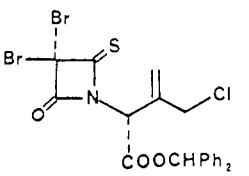

6

a, R^1 = Phth, R^2 = H, R^3 = CH_3

b, R^1 = R^2 = Br, R^3 = $CHPh_2$

During the isomerization, the stereospecific syn-elimination–addition mechanism involves only the 2α-methyl group, which by rotation about the C_2–C_3 bond and subsequent cyclization enters the 2β-position.

That the 6β-amido chain exerts a strong directing influence on the stereochemistry of this transformation through H-bonding with the sulfenic acid was further confirmed by refluxing methyl 2β-(chloromethyl)-6β-phthalimidopenicillanate 1α-sulfoxide (**5a**) in toluene for 1 h. Only starting material was recovered. It may be predicted that the 6,6-dibromopenam 1α-sulfoxide and 6β-phthalimidopenam 1α-sulfoxide, both of which lack the C-6 CONH proton, should behave similarly on thermolysis. However, we have found that when a solution of **5b** in benzene or carbon tetrachloride was refluxed for 15 min or even when compound **5b** was left at room temperature over a week, rearrangement to the thione **6** occurs. We have utilized the thermal epimerization approach for the synthesis of benzhydryl 2α-(chloromethyl)-2β-methyl-6,6-dihydropenicillanate 1,1-dioxide, **2** (R = $CHPh_2$) as summarized in Scheme I.

The 1α-sulfoxide **10** was prepared by a three-step process starting with 2β-(chloromethyl)-6β-(phenylacetamido)penicillanate **7** according to the procedure as de-

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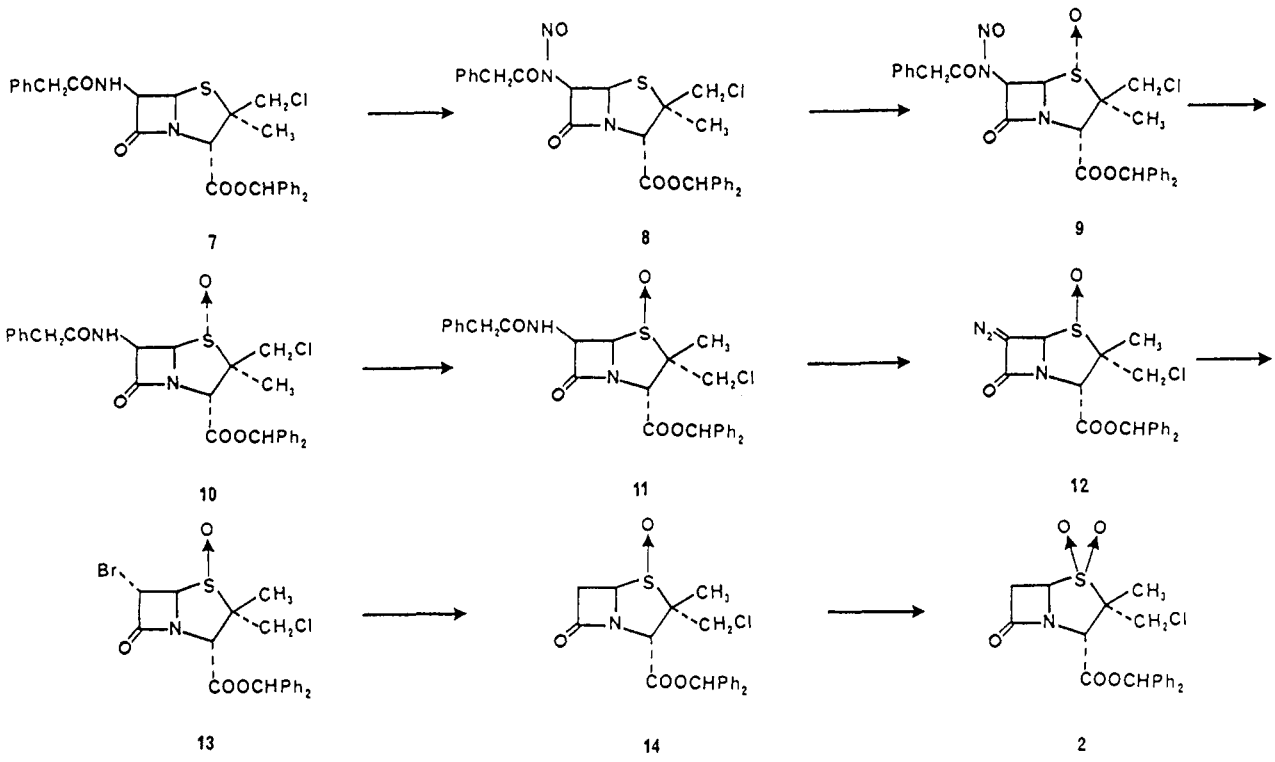
Scheme I



scribed in the literature.[6] Thus treatment of compound **7** with dinitrogen tetroxide in methylene chloride at 0 °C for 1 h gave the *N*-nitroso derivative **8**, which was oxidized with *m*-chloroperbenzoic acid at room temperature for 35 min to afford the *N*-nitroso sulfoxide **9**. Subsequent removal of the NO group by treatment with zinc and glacial acetic acid in methylene chloride at 0 °C for 1 h gave the desired 1α-sulfoxide **10** exclusively. On heating in toluene, the 1α-sulfoxide **10** was converted to the more stable 2α-(chloromethyl)penicillanate 1β-sulfoxide **11** in about 50% yield, after column chromatography. The sulfoxide **11** thus obtained was converted to its corresponding 6-diazo derivative,[7] **12**, in good yield (65%) by nitrosation with dinitrogen tetroxide followed by reflux of the intermediate *N*-nitroso derivative with pyridine for 3 h. The diazo compound **12** dissolved in ethyl acetate and cooled to 0 °C was treated with 2-fold excess of hydrogen bromide dissolved in ethyl acetate.

A brisk evolution of nitrogen ensued immediately. The resulting mixture was stirred at ice-temperature for 20 min. Workup and chromatography of the crude product on silica gel gave the 6α-bromo compound **13**. Removal of the bromine was accomplished[8] by treating with 2 molar equiv of zinc in glacial acetic acid at 10 °C for 2 h. Oxidation[9] of **14** with potassium permanganate in glacial acetic acid produced the desired sulfone **2**.

Based on the results obtained from NOE studies and aromatic solvent induced shift (ASIS) studies, complete and unambiguous assignments for both the isomers **1** and **2** have been made and are recorded in Table I. The α-configuration of the chloromethyl group at C-2 of compound **2** was established by measuring the internal nuclear Overhauser effect (NOE).[10] Upon irradiation of the low-field (2β) methyl protons at 99 ppm of compound **2**, the intensity of the H-3 singlet at 274 ppm increased by 30%. Because of proximity, only 2β-CH_3 protons are capable of relaxing H-3 and consequently the configuration at C-2 is as shown by **2**. Only negligible relaxation was observed for the H-3 signal upon irradiation of the 2α-CH_3 protons of compound **1** (R = $CHPh_2$, X = Cl). Saturation of the high-field (2α) methyl protons (78 ppm) increases the intensity of the H-3 peak (283 ppm) by only 3.6%.

In the case of compound **2**, the direction of benzene complexation should be from the β-face of the solute molecule; consequently it is anticipated that 2β-methyl and H-3 protons will experience strong shielding effects in benzene solution. The results in Table I indicate that the H-3 and 2β-methyl protons are more shielded (0.23 and 0.64 ppm, respectively) in **2**, while the H-3 and 2α-methyl protons in **1** (R = $CHPh_2$, X = Cl) are only marginally affected (0.18 and 0.12, respectively). This can probably be explained by the fact that the 2β-chloromethyl group and the bulky ester functionality at C-3 prevents the approach of benzene for association. Similarly, in the 2α-isomer, **2**, since the α-face is more crowded (relative to **1**), the H-5 proton experiences less shielding (0.69 ppm) due to poor association with the benzene molecules.

^{13}C NMR spectroscopy (Table II) was also useful for establishing the configuration at C-2 of compounds **2** and **1**. The ^{13}C signals were assigned by ^{13}C–^{1}H shift correlated 2D NMR.[11] On the basis of the steric proximity of 2α-CH_3 to the cis substituent at C-3 ($COOCHPh_2$), the 2α-CH_3 is expected to absorb at higher field than the 2β-CH_3 group.[12] Thus the CH_3 signal in **2** appears at δ_C 18.65 and that in **1** at 16.11.

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Table I. ^{1}H NMR Chemical Shift (in $CDCl_3$) and Aromatic Solvent Induced Shift (in C_6D_6) Values

compd		2-CH_3 α	2-CH_3 β	3β-H	5α-H	6-H α	6-H β	2β-CH_2Cl	2α-CH_2Cl	NOE[a]
1 (R = $CHPh_2$, X = Cl)	δ($CDCl_3$)	1.29		4.7	4.64, dd, J = 2.1, 3.7 Hz	3.53, dd, J = 3.7, 16.2 Hz	3.43, dd, J = 2.1, 16.2 Hz	3.88, 4.08, AB, J = 12 Hz		αMe-H_3 3.6%
	δ(C_6D_6)	1.17		4.52	3.64, dd, J = 2.0, 4.4 Hz	2.2, dd, J = 4.4, 16.2 Hz	2.77, dd, J = 2.0, 16.2 Hz	3.52, 3.62, AB, J = 12.5 Hz		
	Δ($CDCl_3$–C_6D_6)	+0.12		+0.18	+1.0	+1.33	+0.66			
2 (R = $CHPh_2$)	δ($CDCl_3$)		1.66	4.57	4.77, t, J = 2.9 Hz	3.47, d, J = 2.9 Hz			3.84[b]	βMe-H_3 30%
	δ(C_6D_6)		1.02	4.34	4.08, dd, J = 1.6, 4.44 Hz	2.15, dd, J = 4.4, 16.1 Hz	2.8, dd, J = 1.6, 16.1 Hz		3.5, 3.59, AB, J = 12 Hz	
	Δ($CDCl_3$–C_6D_6)		+0.64	+0.23	+0.69					

[a] Given as the percentage increase in integrated intensity on irradiation. All NOE experiments were carried out on nitrogen-sparged solutions in $CDCl_3$. [b] Appeared as a singlet.

Table II. ^{13}C Chemical Shift Assignments[a] for Compounds 1 and 2

carbon no.	1 (R = $CHPh_2$, X = Cl)	2 (R = $CHPh_2$)
2	66.15	67.55
3	61.27	61.06
5	63.29	65.18
6	39.95	39.09
7	165.58	165.88
$COOCHPh_2$	79.58	79.44
$COOCHPh_2$	169.61	170.28
2β-CH_3	44.84	18.65
2α-CH_3	16.11	44.33

[a] ^{13}C FT NMR spectra were determined with a Bruker AM-300 spectrometer operating at 75.47 MHz at 28 °C with $CDCl_3$ solutions containing TMS as an internal reference in 5-mm tubes.

Table III. β-Lactamase Activity[a]

compd	IC_{50}, μM
2 (R = Na)	57.5
BL-P2013	36.2

[a] Conditions: method, UV (λ_{max} at 233 nm) (ref 13 and 14); substrate, PCG (200 μM, Sigma); enzyme, penicillinase from *Bacillus cereus* (5000 units, 30 μL, Tokyo Kasei); preincubation, 30 °C, 5 min; incubation, 30 °C, 3 min.

Thus a convenient method for the preparation of the 2α-(substituted methyl)penam is by the thermolytic rearrangement of a 6β-amido-2β-(substituted methyl)penam 1α-sulfoxide. By this approach the 2α-isomer of an active β-lactamase inhibitor, BL-P2013, has now been made and the β-lactamase inhibitory activity of the sodium salt of compound **2** is determined. A comparative β-lactamase inhibitory activity data for both the isomers is reported in Table III. The data indicate that the 2α-isomer is not as active as the 2β-isomer.

Experimental Section

Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. The ^{1}H NMR spectra were recorded on either a Varian EM-360 or a Bruker AM-300 spectrometer and are reported in parts per million downfield from Me_4Si. Infrared spectra were recorded on a Nicolet DX FT-IR. Only significant maxima are reported. Microanalyses were performed by the Department of Chemistry, University of Alberta.

Benzhydryl 2β-(Chloromethyl)-2α-methyl-6β-(phenylacetamido)penam-3α-carboxylate 1α-Oxide (10). Nitrosation. To a stirred solution of benzhydryl 2β-(chloromethyl)-2α-methyl-6β-(phenylacetamido)penam-3α-carboxylate, **7** (10.0 g, 0.0187 mol), in dry methylene chloride (50 mL) was added 5.4 g (0.0658 mol) of anhydrous sodium acetate, and the mixture was cooled with an ice bath. Dinitrogen tetroxide (3 mL) was added in one portion and the mixture was stirred at ice temperature. After 0.5 h an additional portion of dinitrogen tetroxide (1.0 mL) was added and the mixture was stirred at ice temperature for a total period of 1 h. The mixture was diluted with methylene chloride and the excess dinitrogen tetroxide was destroyed by adding aqueous $NaHCO_3$ solution. The methylene chloride layer was separated out, washed with water followed by brine, dried (Na_2SO_4), and concentrated to about 250 mL. A sample had the following: IR ($CHCl_3$) 1802, 1747 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 3 H, CH_3), 3.63 and 4.30 (AB q, J = 12 Hz, 2 H, CH_2Cl), 4.52 (s, 2 H, $C_6H_5CH_2$), 5.14 (s, 1 H, 3-H), 5.57 and 5.68 (AB q, J = 4 Hz, 2 H, 5α-H + 6α-H), 7.0 (s, 1 H, $CHPh_2$), 7.4 (s, 15 H, Ar).

Oxidation. The NNO derivative 8, from the previous experiment, was directly oxidized with *m*-chloroperbenzoic acid (3.7965 g, 0.0187 mol, 85%). After being stirred at room temperature for 40 min, the mixture was cooled with ice, the precipitated solid was filtered off, and the filtrate was washed with aqueous $NaHCO_3$ (3 × 50 mL), water, and brine, dried (Na_2SO_4), and concentrated to about 60 mL. A sample had the following: IR ($CHCl_3$) 1806, 1752 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.08 (s, 3 H, CH_3),

4.03 (br s, 2 H, CH_2Cl), 4.48 (br s, 2 H, $C_6H_5CH_2$), 4.68 (d, J = 4 Hz, 1 H, 6-H), 5.03 (s, 1 H, 3-H), 6.03 (d, J = 4 Hz, 1 H, 5-H), 6.98 (s, 1 H $CHPh_2$), 7.34 (s, 15 H, Ar).

Reduction. To the solution of the (*R*)-sulfoxide **9** in methylene chloride (60 mL) was added 8 mL of glacial acetic acid, and the mixture was cooled with an ice bath; 9.0 g of zinc dust was added portionwise and the mixture was stirred at ice temperature for 1 h. Excess zinc was removed by filtration through a bed of Celite, the filtrate was washed with water, followed by aqueous $NaHCO_3$ solution and finally with brine, dried (Na_2SO_4), and concentrated under reduced pressure to give the desired (*R*)-sulfoxide (8.5 g). The compound was purified over silica column (deactivated with 10% water). Elution of the column with methylene chloride–ethyl acetate (70:30) gave the pure (*R*)-sulfoxide **10** as a light yellow foam (6.0 g, 58.25%): IR ($CHCl_3$) 1803, 1754, 1682 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12 (s, 3 H, CH_3), 3.64 (br s, 2 H, CH_2Cl), 3.98 (br s, 2 H, $C_6H_5CH_2$), 4.76 (d, J = 4.5 Hz, 1 H, 5-H), 4.92 (s, 1 H, 3-H), 5.19 (dd, J = 4.5, 8.0 Hz, 1 H, 6-H), 6.62 (d, J = 8.0 Hz, 1 H, NH), 7.0 (s, 1 H, $CHPh_2$), 7.4 (s, 15 H, Ar).

Benzhydryl 2α-(Chloromethyl)-2β-methyl-6β-(phenylacetamido)penam-3α-carboxylate 1β-Oxide (11). The (*R*)-sulfoxide **10** (6.0 g) in dry toluene (12 L) was heated at reflux under nitrogen for 30 min. Solvent was removed under reduced pressure and the residue was purified by silica column chromatography. Elution of the column with hexane–ethyl acetate (70:30) gave the isomeric (*S*)-sulfoxide **11** (3.0 g, 50%) as a white foam. Crystallization from ethyl acetate–hexane afforded a white solid: mp 125–128 °C dec; IR ($CHCl_3$) 3394, 1802, 1753, 1688, 1507 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.73 (s, 3 H, CH_3), 3.13 and 3.5 (AB q, J = 13 Hz, 2 H, CH_2Cl), 3.58 (s, 2 H, $C_6H_5CH_2$), 4.73 (s, 1 H, 3-H), 5.03 (d, J = 4.5 Hz, 1 H, 5-H), 6.0 (dd, J = 4.5, 9.0 Hz, 1 H, 6-H), 6.92 (s, 1 H, $CHPh_2$), 6.97 (d, J = 9.0 Hz, 1 H, NH), 7.29 (s, 15 H, Ar). Anal. Calcd for $C_{29}H_{27}N_2O_5SCl$: C, 63.21; H, 4.90; N, 5.08. Found: C, 63.54; H, 4.94; N, 5.08.

Benzhydryl 2α-(Chloromethyl)-2β-methyl-6-diazopenam-3α-carboxylate 1β-Oxide (12). To a stirred solution of the (*S*)-sulfoxide **11** (3.0 g, 0.005 44 mol) in dry methylene chloride (20 mL) was added 1.55 g (0.0189 mol) of anhydrous sodium acetate, and the mixture was cooled with an ice bath. Dinitrogen tetroxide (1.0 mL) was added and the mixture was stirred at ice temperature. After 0.5 h an additional portion of dinitrogen tetroxide (0.6 mL) was added and the mixture was stirred at ice temperature for a total period of 1 h. The mixture was diluted with methylene chloride and washed with aqueous $NaHCO_3$ solution to remove excess dinitrogen tetroxide. The methylene chloride layer was washed with water followed by brine, dried (Na_2SO_4), and concentrated to about 100 mL. A sample crystallized from methylene chloride–hexane had mp 108–110 °C.

To the methylene chloride solution (100 mL) from the previous step was added 0.5 mL of pyridine, and the mixture was heated to reflux gently under nitrogen for 3 h, cooled, washed with water, aqueous $NaHCO_3$ solution, and finally brine, dried (Na_2SO_4), and concentrated to give a dark brown viscous oil. The residue was dissolved in a small volume (ca. 2–3 mL) of methylene chloride and precipitated with hexane with stirring under ice cooling. The hexane layer was decanted off. This process was repeated twice and thus the pyridine was removed completely. The residual solution after evaporation in vacuo gave the diazo compound **12** as a brown foam (2.1 g, 87%): IR ($CHCl_3$) 2101, 1787, 1741 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.68 (s, 3 H, CH_3), 3.29 and 3.68 (AB q, J = 12 Hz, 2 H, CH_2Cl), 4.5 (s, 1 H, 3-H), 5.85 (s, 1 H, 5-H), 6.94 (s, 1 H, $CHPh_2$), 7.35 (s, 10 H, Ar).

Benzhydryl 2α-(Chloromethyl)-2β-methyl-6α-bromopenam-3α-carboxylate 1β-Oxide (13). To a stirred solution of benzhydryl 6-diazopenicillanate 1β-oxide, **12**, (2.1 g, 0.0047 mol) in 40 mL of anhydrous ethyl acetate at 0 °C was added dropwise a solution of hydrogen bromide in ethyl acetate (10 mL, 0.76 g, 0.0094 mol). A brisk evolution of nitrogen was observed. The mixture was stirred at 0 °C for 30 min, washed with 10% aqueous sodium thiosulfate solution and then with aqueous $NaHCO_3$ solution followed by brine, dried (Na_2SO_4), and concentrated. The dark brown residue was rapidly chromatographed over a short silica column with hexane–ethyl acetate (75:25). Concentration under reduced pressure gave pure compound **13** as a brown foam (1.5 g, 63.8%): ^1H NMR ($CDCl_3$) δ 1.72 (s, 3 H, CH_3), 3.32 and 3.66 (AB q, J = 13 Hz, 2 H, CH_2Cl), 4.73 (s, 1 H, 3-H), 5.14 (d, J = 2 Hz, 1 H), 5.20 (d, J = 2 Hz, 1 H), 7.0 (s, 1 H, $CHPh_2$), 7.4 (s, 10 H, Ar).

Benzhydryl 2α-(Chloromethyl)-2β-methyl-6,6-dihydropenam-3α-carboxylate 1β-Oxide (14). To a stirred solution of **13** (1.0 g, 0.002 mol) in 6 mL of acetonitrile at 0 °C was added 2 mL of glacial acetic acid. Zinc powder (0.262 g) was added in one portion and the mixture was stirred at 10 °C for 2 h. Excess zinc was removed by filtration through Celite; the filtrate was diluted with methylene chloride, washed successively with cold water, aqueous $NaHCO_3$ solution, and brine, dried (Na_2SO_4), and concentrated to a sticky light yellow foam. Short-column chromatography over silica with hexane–ethyl acetate (70:30) gave pure 6,6-dihydropenicillanate 1β-oxide, **14**, as a white foam (0.4 g, 47.6%). Crystallization from methylene chloride–ether gave an analytically pure sample: mp 132–134 °C dec; IR ($CHCl_3$) 1793, 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.75 (s, 3 H, CH_3), 3.28 and 3.64 (AB q, J = 13 Hz, 2 H, CH_2Cl), 3.30 (d, J = 3 Hz, 2 H, 6β-H + 6α-H), 4.7 (s, 1 H, 3-H), 5.02 (t, J = 3 Hz, 1 H, 5α-H), 7.0 (s, 1 H, $CHPh_2$), 7.38 (s, 10 H, Ar). Anal. Calcd for $C_{21}H_{20}NO_4SCl$: C, 60.35; H, 4.79; N, 3.35. Found: C, 60.63; H, 4.96; N, 3.25.

Benzhydryl 2α-(Chloromethyl)-2β-methyl-6,6-dihydropenam-3α-carboxylate 1,1-Dioxide (2). The (*S*)-sulfoxide **14** (0.3 g, 0.000 72 mol) was dissolved in 7 mL of glacial acetic acid, and 2 mL of water was added. To this mixture was added potassium permanganate (0.158 g, 0.009 mol) in one portion, and the mixture was stirred at room temperature for 2 h; excess permanganate was destroyed by dropwise addition of hydrogen peroxide. The mixture was poured into ice-cold water and extracted with methylene chloride. The aqueous phase was saturated with sodium chloride and extracted twice with methylene chloride. The combined organic extracts were washed with aqueous sodium bicarbonate solution, followed by brine, dried (Na_2SO_4), and rapidly filtered through a small bed of silica. Concentration of the filtrate gave pure 6,6-dihydropenicillanate 1,1-dioxide **2** as white solid (0.217 g, 69.5%). Crystallization from methylene chloride–ether gave an analytically pure sample as white needles: mp 130–132 °C dec; IR ($CHCl_3$) 1805, 1743 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.66 (s, 3 H, CH_3), 3.47 (d, J = 2.9 Hz, 2 H, 6β-H + 6α-H), 3.84 (s, 2 H, CH_2Cl), 4.57 (s, 1 H, 3-H), 4.77 (t, J = 2.9 Hz, 1 H, 5α-H), 7.0 (s, 1 H, $CHPh_2$), 7.4 (s, 10 H, Ar). Anal. Calcd for $C_{21}H_{20}NO_5SCl$: C, 58.13; H, 4.61; N, 3.23. Found: C, 58.31; H, 4.67; N, 3.09.

Sodium 2α-(Chloromethyl)-2β-methyl-6,6-dihydropenam-3α-carboxylate 1,1-Dioxide (2, R = Na). A mixture of compound **2** (R = $CHPh_2$) in ethyl acetate (10 mL), 0.5 M $NaHCO_3$ solution (0.25 mL), and water (10 mL) was hydrogenated in the presence of 10% Pd–C (10 mg) under 2–3 atm. The reaction mixture was filtered and the filtrate was concentrated to about 3 mL, which was purified over MCI gel to give the sodium salt (10 mg): mp 238–242 °C dec; IR (KBr) 1770, 1620 cm^{-1}; ^1H NMR (D_2O) δ 1.67 (s, 3 H, CH_3), 3.42 and 3.68 (dd, 2 H, 6-H), 3.94 and 4.2 (AB q, 2 H, 2α-CH_2), 4.42 (s, 1 H, 3-H), 5.04 (dd, 1 H, 5-H).

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Registry No. **2** (R = $CHPh_2$), 115095-93-7; **2** (R = Na), 115095-94-8; **2** (R = H), 115095-95-9; **7**, 51415-50-0; **8**, 64258-68-0; **9**, 64258-74-8; **10**, 64258-80-6; **11**, 115095-88-0; **11** (*N*-nitroso deriv), 115095-89-1; **12**, 115095-90-4; **13**, 115095-91-5; **14**, 115095-92-6; β-lactamase, 9073-60-3.