SYNTHESIS OF PENAMS FROM 1*H*-AZETIDINONES BY INTRAMOLECULAR CARBENOID INSERTION

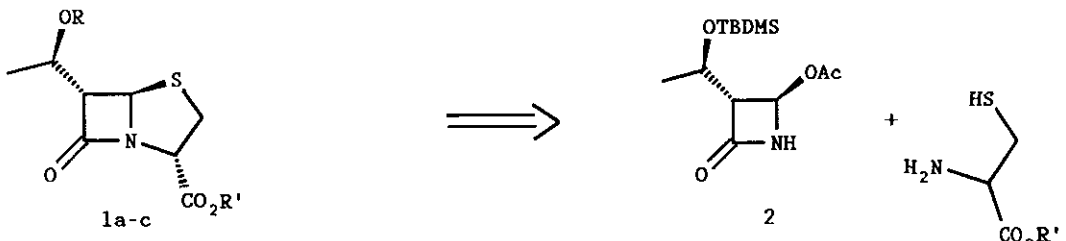
*Pierluigi Bissolino, Marco Alpegiani, Daniela Borghi, Ettore Perrone, and Giovanni Franceschi**

Farmitalia Carlo Erba R&D, Via C. Imbonati 29, 20146 Milano, Italy

Abstract- Construction of the penam ring system has been achieved by dirhodium tetraacetate cyclization of 4-thio-1*H*-azetidinone derivatives bearing an α-diazoester appendage. The sulfur atom of 4-thioethers interferes by reacting with the electrophilic metal carbene, but the corresponding sulfone and sulfoxides undergo the prescribed cyclization exclusively. Nmr studies on obtained bisnorpenams indicate pseudoequatorial puckering for the thiazolidine ring of the *S*-sulfoxide, while the parent sulfide and the *R*-sulfoxide exist as pseudoaxial conformers.

Though penicillins lacking the C-2 geminal methyl groups (bisnorpenams) have been described,[1~4] the preparation of derivatives possessing at C-6 the 1(*R*)-hydroxyethyl side chain proper of thienamycin and biologically active penems was never addressed. In a program devoted to new strategies for penem synthesis, the free bisnorpenam carboxylate (1c) and the protected sulfoxides (10), (11) were required in multigram quantities.[5,6] We have examined the intramolecular insertion of carbenoid species into the N-H bond of azetidinones, originally proposed by the Merck group for oxapenams[7] and carbapenems,[8] as a novel method for the construction of the penam ring system.[9] Here we wish to report the efficient synthesis of bisnorpenams (1a-c, 10, 11, 12) from the commercially available, optically active azetidinone (2) and cysteine.

The azetidinyl-4-thioether (3) was obtained by condensation of 2 with *N*-*tert*-butoxycarbonyl-L-cysteine (NaOMe in methanol, -10°C), and converted to the diazoester (6) (35% overall) by sequential esterification (*p*-nitrobenzyl bromide/NEt_3, DMF), *N*-Boc deblocking



1a-c

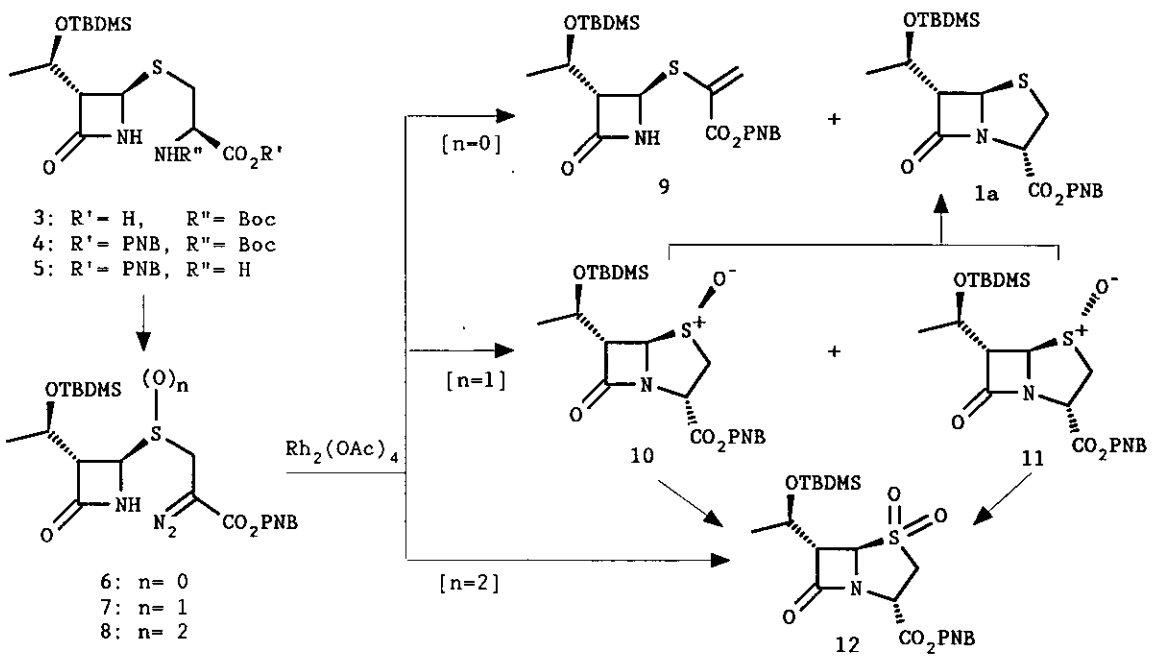
a: R= TBDMS, R'= PNB
b: R= H, R'= PNB
c: R= H, R'= Na

2

[*TBDMS= $SiMe_2t$-Bu; PNB= p-nitrobenzyl*]

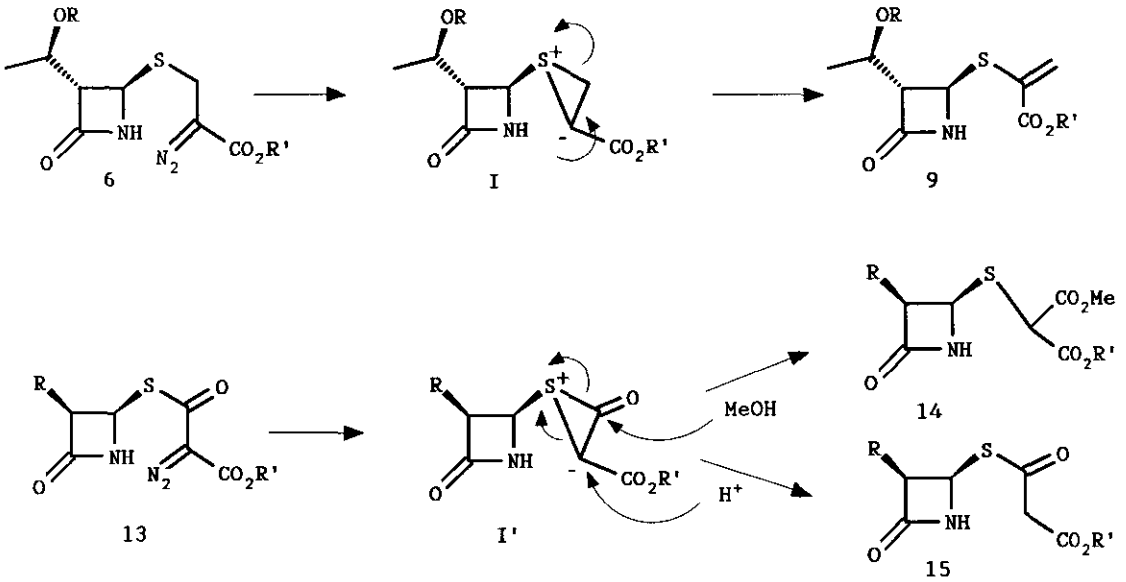
(TFA/anisole in CH_2Cl_2, 0°C), and diazotization (*tert*-butyl nitrite, cat. AcOH, refluxing CH_2Cl_2). Oxidation of diazo-sulfide (6) with 3-chloroperoxybenzoic acid (MCPBA) afforded, according to the experimental conditions, an inseparable mixture of the epimeric sulfoxides (7) (ca. 1.5:1) or the sulfone (8) in virtually quantitative yield.

Treatment of 6 with dirhodium tetraacetate (1% by weight; dry benzene under nitrogen, 2 h) resulted in the formation of the vinyl thioether (9; 68%), accompanied by a minor amount of the desired bisnorpenam (1a; single epimer, 5% isolated yield). Instead, rhodium-catalyzed cyclization of sulfoxidized diazoesters (7) and (8) occurred without detectable formation of rearranged azetidinone by-products; two epimeric penam sulfoxides (10, 25%; 11, 15%) and the penam sulfone (12; 50%), respectively, were isolated after flash chromatography. Reduction of the isomeric mixture of sulfoxides according to the method of Micetich[10] (phosphorus pentasulfide and pyridine in CH_2Cl_2) gave 1a (50%), while oxidation of individual epimers (MCPBA) afforded 12 (80% from 10, 75% from 11); both products were identical to samples isolated from direct cyclization of 6 and 8, respectively. Finally, conventional removal of the silyl and *p*-nitrobenzyl protecting groups of 1a provided the desired bisnorpenam (1c) *via* 1b (68% overall).



Details on the mechanism of the dirhodium tetraacetate cyclization are in part obscure; the likely intermediate is a mono-solvated, tetraacetate dirhodium-carbenoid species which undergoes a series of methatesis reactions.[11] However, the electrophilic metal carbene may also react with nucleophiles, including a pair of nonbonding electrons contributed by a Lewis base.[12] Thioethers, among other neutral nucleophilic species, are known to trap

carbenes. Electrophilic attack of a metal carbene to the sulfur atom of 4-thioazetidinones, preferential to insertion to the NH bond, has been observed by Kametani.[13] Intramolecularly, the presence of a thioether group in the β position of a developing carbene is known to be associated with preferential migration of that group.[14] Formation of the olefin (**9**) from the diazosulfide (**6**) is consonant with these precedents; oxidation at sulfur (compounds **7**, **8**) precludes this pathway and restores the prescribed cyclization. The intermediate responsible for the olefin product can be represented as the sulfur ylide (I). Similarly, sulfur ylide chemistry[13,15] (species I') may be used to describe the origin of the rearranged products (**14**, **15**; solvent THF and MeOH, respectively) obtained from **13** in an attempted penem synthesis.[16]



Structural analysis of the bisnorpenam products was carried out as follows. The (5*R*,6*S*,8*R*)-configuration is dictated by the hydroxyethyl side chain present in the azetidinone precursor (**2**), which addresses *trans* insertion of the thioether appendage by an SNl mechanism;[17] consistently, a small coupling constant characterized the β-lactam protons ($J_{5,6}$ = 1.7-2.9 Hz). The four protected bisnorpenams did not differ for the configuration at C-3, since oxidation of the sulfide (**1a**) with MCPBA ($CDCl_3$) gave the two sulfoxides (**10**, **11**; 1:1), slowly evolving to the single sulfone (**12**). NOESY analysis of **10** (400 MHz, $CDCl_3$) showed strong correlations for H-5 and one of the geminal proton (thence assigned as $H_{2\alpha}$), and for the other geminal proton ($H_{2\beta}$) and H-3; therefore, the C-3 configuration is *S*. The low-field resonance (δ 4.8-5.1 ppm) of H-3 in all of the four bisnorpenams is consonant with the *trans* relationships between H-3 and H-5 (expected range

δ 4.3-4.9; when these protons are *cis*, H-3 of penams resonates at 3.7-4.0 ppm).[2,18] On the other hand, strong NOEs between H-3 and $H_{2\beta}$, and minor ones between H-3 and $H_{2\alpha}$, were observed on the sulfide (1a) and the sulfoxide (11); concurrently, NOEs between H-5 and $H_{2\alpha}$ were minor. Thus, the NOESY experiments, beside allowing relative assignment of the geminal protons at C-2, were also suggestive of different geometries[19] adopted by the thiazolidine ring of the compounds (Figure 1). In particular the target product (1c), showing in D_2O NOEs similar to those observed for 1a in $CDCl_3$, was considered to adopt in water solution a "closed" (quasi-planar) conformation.[20]

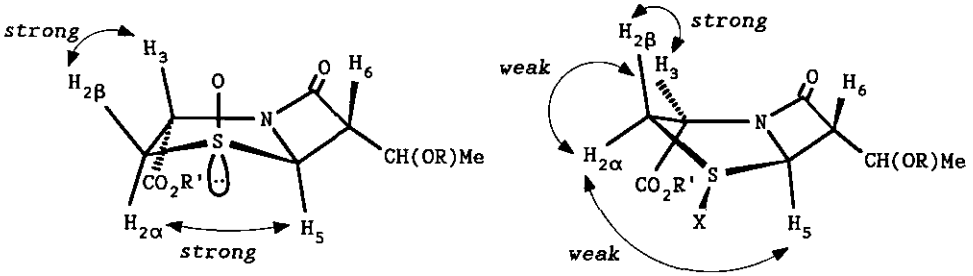


Figure 1. Possible thiazolidine ring conformations: open or pseudoequatorial (left), and closed or pseudoaxial (right). Arrows indicate relevant NOEs observed for 10 (left) and for 1a, 11 (right; X= lone pair or O, respectively).

Attribution of individual sulfoxide epimers was made after analysis of aromatic-solvent-induced shifts (ASIS; Table 1). Upon change of the solvent from $CDCl_3$ to C_6D_6, a distinct shielding effect on the α-oriented protons is expected on the (*R*)-oxide owing to preferential coordination of the aromatic solvent to the positive end of the S→O dipole; the reverse (shielding of the β-oriented protons) is anticipated for the (*S*)-oxide. In particular, a large positive differential ASIS for H-5 (compound 10 in Table 1) is diagnostic for the *S*-sulfoxide configuration.[21]

Table 1. ^1H nmr solvent shift data[(a)] for ring protons of 1a and its sulfoxides (10, 11)

		$H_{2\alpha}$	$H_{2\beta}$	$H_{3\beta}$	$H_{5\alpha}$	$H_{6\beta}$
ASIS, ppm:	1a	0.53	0.73	0.28	-0.06	0.16
	10	0.89	0.90	0.22	0.64	0.04
	11	0.60	1.19	0.54	0.10	0.75
Δ ASIS, ppm:	10	+0.36	+0.17	-0.06	+0.70	-0.12
	11	+0.07	+0.46	+0.26	+0.16	+0.59

([a]) In 2% w/v solution. ASIS= $\delta(CDCl_3)-\delta(C_6D_6)$; Δ ASIS= ASIS(sulfoxide)-ASIS(sulfide).

Having assigned the individual sulfoxide epimers and the individual C-2 protons in all of the four protected bisnorpenams (Table 2), support for the conformations predicted by NOESY spectroscopy (Figure 1) was sought by inspection of sulfoxide bond perturbation shifts and vicinal coupling constants ($J_{2,3}$). In penicillins and cephalosporins it is known that, without exceptions, protons located vicinal and *trans* diaxal to either a sulfoxide bond or a sulfur lone pair are shielded in the process sulfide → sulfoxide.[22] This condition is satisfied for H-5 and $H_{2\alpha}$ in the *S*-sulfoxide (10), adopting the open conformation as suggested by NOE results (Figure 1, left-hand structure). On the other hand, the anomalous behaviour of the *R*-sulfoxide (11) is evident. First, in this compound $H_{2\alpha}$ resonates at lower fields than $H_{2\beta}$, contrarily to what observed for the analogous C-2 protons in cephem *R*- and *S*-oxides (compounds known to exist in an "open" conformation).[23] Second, both $H_{2\alpha}$ and H_3 (but not H_5, owing to its *trans* diaxal relationship to the sulfur lone pair) are deshielded in the oxidation process 1a → 11. These two protons are located in the deshielding region of the *R*-sulfoxide bond[24] if the thiazolidine ring conformation is "closed", consistently with NOE results (Figure 1, right-hand structure). Inspection of vicinal *J* values further supports the conformational assignments. The stricking difference in $J_{2\alpha,3}$ existing between the pairs of compounds (1a), (11) (3.1 and 2.2 Hz, respectively) and (10), (12) (9.9 and 8.1 Hz) is coherent with differences in dihedral angles relative to the two proposed conformations.

Table 2. ^{1}H nmr chemical shift (δ ppm) and coupling constant (Hz) data[(a)]

	$H_{2\alpha}$	$H_{2\beta}$	$H_{3\beta}$	$H_{5\alpha}$	$H_{6\beta}$	$J_{2\alpha,2\beta}$	$J_{2\alpha,3}$	$J_{2\beta,3}$
sulfide (1a)	3.64	3.61	5.01	5.09	3.19	12.1	3.1	7.1
S-oxide (10)	3.29	3.78	5.06	4.84	3.60	14.4	9.9	6.5
R-oxide (11)	3.83	3.17	5.20	4.92	3.31	14.1	2.2	7.9
sulfone (12)	3.56	3.68	4.88	4.52	3.67	14.0	8.1	8.1

(a) In $CDCl_3$ solution.

In conclusion, a simple strategy for the synthesis of bisnorpenicillins has been devised. Its scope clearly extends to the preparation of 2-mono and 2,2-disubstituted penams, including classical penicillins, and thence is wider than that of Osborne[2] and its modifications.[3] Since the chirality at the pro-C_3 position is lost in the diazotization step, the use of enantiomerically pure cysteine derivatives is not necessary. On the other hand, an α-oriented side chain at azetidinone C-3 is important to achieve the desired (5*R*)-diastereoselection. Preparation of 5,6-*cis*-penams by this strategy would require an approach to the azetidinone thioether intermediates alternative to the displacement 2 → 3.

EXPERIMENTAL

The nmr spectra were taken at 200 MHz or 400 MHz on Varian VXR-200 and VXR-400S instruments. The ir spectra were obtained on a Perkin-Elmer 1420 spectrophotometer. The FD mass spectra were recorded on a Varian Mat 311/A instrument equipped with a combined EI/FI/FD ion source using benzonitrile activated emitters. Elemental analyses were performed on a Carlo Erba NA 1005 analyzer. Flash chromatography was done with Carlo Erba 60 silica gel (230-400 mesh) and elution was carried out with *n*-hexane : ethyl acetate mixtures (4:1 to 1:1 gradient). Prior concentration under reduced pressure, all organic extracts were washed with brine and dried over anhydrous sodium sulfate.

(3*S*,4*R*)-3-[(*R*)-1-*tert*-Butyldimethylsilyloxyethyl]-4-[(*R*)-2-*tert*-butoxycarbonylamino-2-(4-nitrobenzyloxycarbonyl)ethyl]thio-2-azetidinone (4).

A solution of di-*tert*-butyl dicarbonate (24 g, 0.11 mol) in dioxane (150 ml) was added to a solution of L-cysteine (12.1 g, 0.1 mol) and triethylamine (15.3 ml, 0.11 mol) in water (140 ml). The reaction mixture was stirred for 4 h and, after removal of most of the dioxane *in vacuo*, was washed with Et_2O (100 ml) and acidified to pH 2 with 37% HCl. Extraction with EtOAc (3 x 100 ml) and evaporation gave reagent-grade *N*-*tert*-butoxycarbonyl-L-cysteine (21 g, 95%) as a colourless oil. Ir ($CHCl_3$) υ_{max} 3440, 1715 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.44 (9H, s), 2.8-3.1 (2H, m), 4.60 (1H, m), 5.42 ppm (1H, m, exch. D_2O).

A solution of this reagent (21 g, ca. 95 mmol) in dry methanol (250 ml) at -10°C under nitrogen was treated with 95% sodium methoxide (10.8 g, 0.1 mol) and, after 5 min, with azetidinone (2) (Kanegafuchi Chemical Industry, Lot D8-005; 27.3 g, 95 mmol). After 30 min the reaction was quenched by addition of acetic acid (10 ml), most of the methanol was removed *in vacuo*, and the residue was partitioned between EtOAc (400 ml) and brine. Concentration to dryness of the organic layer yielded crude (3*S*,4*R*)-3-[(*R*)-1-*tert*-butyldimethylsilyloxyethyl]-4-[(*R*)-2-*tert*-butoxycarbonylamino-2-carboxyethyl]thio-2-azetidinone (compound 3; 34 g, 80% from 2) as a yellowish oil. Ir ($CHCl_3$) ν_{max} 3400, 1750, 1700 cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.04 (3H, s), 0.05 (3H, s), 0.85 (9H, s), 1.21 (3H, d, *J*= 6.3 Hz), 1.44 (9H, s), 3.0-3.1 (2H, m), 3.08 (1H, m), 4.22 (1H, dq, *J*= 3.6 and 6.3 Hz), 4.51 (1H, m), 4.79 (1H, d, *J*= 2.2 Hz), 5.64 (1H, br s), 7.17 ppm (1H, br s); FDms, m/z 449 $[M+H]^+$.

A solution of this intermediate (34 g, ca. 75 mmol) in anhydrous dimethylformamide (30 ml) was treated with triethylamine (11.6 ml, 83.4 mmol) and 4-nitrobenzyl bromide (18 g, 83.4 mmol). After stirring for 4 h, the mixture was diluted with CH_2Cl_2 (400 ml), washed with saturated aqueous $NaHCO_3$, and concentrated *in vacuo*. Purification of the residue by chromatography afforded the title compound (33.14 g, 74.5% from 2) as an oil. Ir ($CHCl_3$) ν_{max} 3400, 1760, 1710 cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.04 (3H, s), 0.06 (3H, s), 0.85 (9H, s), 1.21 (3H, d, *J*= 6.3 Hz), 1.44 (9H, s), 3.03 (1H, m), 2.9-3.2 (2H, m), 4.22 (1H, dq, *J*= 3.5 and 6.3 Hz), 4.60 (1H, m), 4.75 (1H, d, *J*= 2.4 Hz), 5.28 (2H, s), 5.35 (1H, d, *J*= 7.9 Hz), 6.36 (1H, br s), 7.52 and 8.24 ppm (4H, two d, *J*= 8.8 Hz); FDms, m/z 584 $[M+H]^+$.

(3*S*,4*R*)-3-[(*R*)-1-*tert*-Butyldimethylsilyloxyethyl]-4-[2-diazo-2-(4-nitrobenzyloxycarbonyl)-ethyl]thio-2-azetidinone (6).

Anisole (6.5 ml, 59 mmol) and the *N*-Boc derivative (4) (33.4 g, 56.9 mmol) were added sequentially to an ice-cooled solution of CH_2Cl_2-TFA 1:1 (200 ml). The mixture was stirred for about 30 min and then concentrated *in vacuo* to remove the excess of TFA. The residue was partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. Removal of the solvent from the organic extract left crude (3*S*,4*R*)-3-[(*R*)-1-*tert*-butyldimethylsilyloxyethyl]-4-[(*R*)-2-amino-2-(4-nitrobenzyloxycarbonyl)ethyl]thio-2-azetidinone (5) (24.8 g, ca. 90% yield) as a yellow oil.

This compound (24.8 g, 51.2 mmol) was dissolved in CH_2Cl_2 (300 ml) and heated at reflux temperature in the presence of *tert*-butyl nitrite (6.9 ml, 58 mmol) and acetic acid (0.55 ml, 9.7 mmol). After complete conversion (ca. 1.5 h, tlc monitoring), the reaction mixture was washed with 2 M aqueous $NaHCO_3$ and concentrated *in vacuo*. Purification by flash-chromatography afforded the title compound (16.45 g, 58.5% from 4) as a yellow oil. Ir ($CHCl_3$) ν_{max} 3400, 2100, 1775, 1695 cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.04 (3H, s), 0.05 (3H, s), 0.85 (9H, s), 1.20 (3H, d, *J*= 6.3 Hz), 3.07 (1H, dd, *J*= 3.8 and 2.4 Hz), 3.59 and 3.72 (2H, two d, *J*= 15.3 Hz); 4.22 (1H, dq, *J*= 3.8 and 6.3 Hz), 4.90 (1H, d, *J*= 2.4 Hz), 5.29 (2H, s), 6.37 (1H, br s), 7.50 and 8.23 ppm (4H, two d, *J*= 8.7 Hz); FDms, m/z 495 $[M+H]^+$.

(3*S*,4*R*)-3-[(*R*)-1-*tert*-Butyldimethylsilyloxyethyl]-4-[(*R,S*)-[2-diazo-2-(4-nitrobenzyloxy-carbonyl)ethyl]sulfinyl]-2-azetidinone (7).

A solution of diazosulfide (6) (14.33 g, 29 mmol) in CH_2Cl_2 (700 ml) was treated with 85% MCPBA (5.89 g, 29 mmol) under stirring for 30 min at -40°C. The reaction mixture was washed with 2 M aqueous $NaHCO_3$ and concentrated *in vacuo*. Chromatography of the residue afforded the title compound as an epimeric mixture at sulfur (ca. 1:1.5 by nmr integration; 13.3 g, 90%). Ir ($CHCl_3$) ν_{max} 2100, 1790, 1690 cm^{-1}; ^1H nmr ($CDCl_3$) δ [major isomer] 0.06 (3H, s), 0.07 (3H, s), 0.85 (9H, s), 1.26 (3H, d, *J*= 6.3 Hz), 3.57 (1H, dd, *J*= 2.5 and 2.7 Hz), 3.58 and 3.86 (2H, ABq, *J*= 15.1 Hz), 4.33 (1H, dq, *J*= 2.7 and 6.3 Hz), 4.43 (1H, m), 5.23 and 5.38 (2H, ABq, *J*= 15.0 Hz), 7.51 and 8.72 ppm (4H, two d, *J*= 8.7 Hz); δ [minor isomer], *inter alia*, 1.25 (3H, d, *J*= 6.3 Hz), 3.46 (1H, m), 3.70 and 3.80 (2H, ABq, *J*= 15.1 Hz), 4.55 (1H, d, *J*= 2.7 Hz), 5.32 ppm (2H, m); FDms, m/z 511 $[M+H]^+$.

(3*S*,4*R*)-3-[(*R*)-1-*tert*-Butyldimethylsilyloxyethyl]-4-[2-diazo-2-(4-nitrobenzyloxycarbonyl)-ethyl]sulfonyl-2-azetidinone (8).

A cooled solution (ice bath) of diazosulfide (6) (1 g, 2.02 mmol) in CH_2Cl_2 (50 ml) was treated under stirring with 85% MCPBA (1 g, 5 mmol). The ice bath was removed and after 30 min the reaction mixture was poured into 1 M aqueous $Na_2S_2O_5$. The organic layer was collected and washed with saturated aqueous $NaHCO_3$. Evaporation of the solvent and flash chromatography afforded the title diazosulfone (990 mg, 93%) as a foam. Ir ($CHCl_3$) ν_{max} 3400, 2120, 1800, 1695 cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.04 (3H, s), 0.05 (3H, s), 0.85 (9H, s), 1.20 (3H, d, *J*= 6.3 Hz), 3.65 (1H, dd, *J*= 2.0 and 2.2 Hz), 3.83 (1H, d, *J*= 16.0 Hz), 4.08 (1H, d, *J*= 16.0 Hz), 4.35 (1H, dq, *J*= 2.0 and 6.3 Hz), 4.75 (1H, d, *J*= 2.2 Hz), 5.23 (1H,

d, *J*= 13.1 Hz), 5.36 (1H, d, *J*= 13.1 Hz), 6.61 (1H, br s), 7.50 and 8.20 ppm (4H, two d, *J*= 8.7 Hz); FDms, m/z 527 $[M+H]^+$.

(3*S*,4*R*)-3-[(*R*)-1-tert-Butyldimethylsilyloxyethyl]-4-[1-(4-nitrobenzyloxycarbonyl)ethenyl]-thio-2-azetidinone (9).

A solution of diazosulfide (6) (1.33 g, 2.69 mmol) in dry benzene (40 ml) under nitrogen was treated with a catalytic amount of $Rh_2(OAc)_4$ (13 mg; ca. 1% by weight). Tlc monitoring revealed that the reaction was complete in ca. 2 h, and that two distinct products were present in the approximate ratio 10:1. The reaction mixture was filtered over celite and the filtrate was concentrated *in vacuo*. Fractionation by flash-chromatography afforded, in this order, the bisnorpenam (1a) (63 mg, 5%; see the pertinent heading), and the title compound (9) (850 mg, 68%) as a syrup. $[\alpha]_D$ + 87° (c 1, MeCN); ir ($CHCl_3$) ν_{max} 3400, 1770, 1730 cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.05 (3H, s), 0.06 (3H, s), 0.85 (9H, s), 1.20 (3H, d, *J*= 6.3 Hz), 3.14 (1H, dd, *J*= 2.5 and 3.5 Hz), 4.26 (1H, dq, *J*= 3.5 and 6.3 Hz), 4.99 (1H, d, *J*= 2.5 Hz), 5.34 (2H, s), 5.97 (1H, s), 6.37 (1H, br s), 6.60 (1H, s), 7.54 and 8.24 ppm (4H, two d, *J*= 8.5 Hz); FDms, m/z 467 $[M+H]^+$. Anal. Calcd for $C_{21}H_{30}N_2O_6SSi$: C, 54.07; H, 6.44; N, 6.01. Found: C, 54.47; H, 6.68; N, 5.94.

4-Nitrobenzyl (3*S*,5*R*,6*S*)-6-[(*R*)-1-*tert*-butyldimethylsilyloxyethyl]-3-(2,2-bisnor)penicillanate (1*S*)-oxide (10) and (1*R*)-oxide (11).

A solution of diazosulfoxide (7) (epimeric mixture; 13.3 g, 26.08 mmol) in 600 ml of dry benzene under nitrogen was treated with a catalytic amount of $Rh_2(OAc)_4$ (135 mg; 1% by weight). After 2 h, the reaction mixture was filtered over celite, the filtrate was concentrated *in vacuo*, and the residue was fractionated by flash-chromatography.

The first eluted product was 10 (3.14 g, 25%): $[\alpha]_D$ + 65° (c 0.3, MeCN); ir ($CHCl_3$) ν_{max} 1795, 1740 cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.03 (3H, s), 0.07 (3H, s), 0.82 (9H, s), 1.25 (3H, d, *J*= 6.2 Hz), 3.29 (1H, dd, *J*= 9.9 and 14.4 Hz), 3.60 (1H, dd, *J*=3.4 and 1.7 Hz), 3.78 (1H, dd, *J*= 14.4 and 6.5 Hz), 4.39 (1H, dq, *J*= 6.2 and 3.4 Hz), 4.84 (1H, d, *J*= 1.7 Hz), 5.06 (1H, dd, *J*= 9.9 and 6.5 Hz), 5.27 (2H, s), 7.52 and 8.24 ppm (4H, two d, *J*= 8.7 Hz); FDms, m/z 483 $[M+H]^+$.

The second eluted product was 11 (1.58 g, 15%): $[\alpha]_D$ + 101° (c 0.5, MeCN); ir ($CHCl_3$) ν_{max} 1795, 1760 cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.04 (3H, s), 0.07 (3H, s), 0.83 (9H, s), 1.28 (3H, d, *J*= 6.2 Hz), 3.17 (1H, dd, *J*= 14.1 and 7.9 Hz), 3.31 (1H, dd, *J*= 2.9 and 3.2 Hz), 3.83 (1H, dd, *J*= 2.2 and 14.1 Hz), 4.32 (1H, dd, *J*= 6.2 and 3.2 Hz), 4.92 (1H, d, *J*= 2.9 Hz), 5.20 (1H, dd, *J*=2.2 and 7.9 Hz), 5.28 (2H, s), 7.53 and 8.22 ppm (4H, two d, *J*= 8.7 Hz); FDms, m/z 483 $[M+H]^+$.

4-Nitrobenzyl (3*S*,5*R*,6*S*)-6-[(*R*)-1-*tert*-butyldimethylsilyloxyethyl]-3-(2,2-bisnor)penicillanate 1,1-dioxide (12).

-a) By cyclization of diazosulfone (8). Dirhodium tetraacetate (10 mg; 1% by weight) was added to a nitrogen-flushed solution of diazosulfone 8 (990 mg, 1.88 mmol) in dry benzene (30 ml). After stirring for 1 h, the reaction mixture was filtered over celite and the

resulting filtrate was evaporated to dryness. The title compound (470 mg, 50%) was isolated by flash chromatography as an amorphous solid.

-b) By oxidation of the bisnorpenicillanate (1S)-oxide (10). A solution of **10** (4.82 mg, 1 mmol) in CH_2Cl_2 (50 ml), cooled in an ice bath, was treated with 85% MCPBA (245 mg, 1.2 mmol). After few minutes the bath was removed, the reaction mixture was let stir at room temperature for 1 h, and eventually poured into 1 M aqueous $Na_2S_2O_5$. The organic layer was washed with saturated aqueous $NaHCO_3$ and evaporated *in vacuo*. Chromatography of the residue gave the title compound (395 mg, 80%).

-c) By oxidation of the bisnorpenicillanate (1R)-oxide (11). Starting from 482 mg (1 mmol) of **11**, the hereabove described procedure gave the title compound (370 mg, 75%). $[\alpha]_D$ + 47° (c 0.5, MeCN); ir ($CHCl_3$) ν_{max} 1805, 1755 cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.01 (3H, s), 0.05 (3H, s), 0.80 (9H, s), 1.23 (3H, d, *J*= 6.4 Hz), 3.56 (1H, dd, *J*= 8.1 and 14.0 Hz), 3.68 (1H, dd, *J*= 8.1 and 14.0 Hz), 3.67 (1H, dd, *J*= 1.9 and 3.0 Hz), 4.35 (1H, dd, *J*= 3.0 and 6.4 Hz), 4.52 (1H, d, *J*= 1.9 Hz), 4.88 (1H, t, *J*= 8.1 Hz), 5.24 (1H, d, *J*= 13.1 Hz), 5.32 (1H, d, *J*= 13.1 Hz), 7.52 and 8.23 ppm (4H, two d, *J*= 8.7 Hz); FDms, m/z 499 $[M+H]^+$.

4-Nitrobenzyl (3*S*,5*R*,6*S*)-6-[(*R*)-1-*tert*-butyldimethylsilyloxyethyl]-3-(2,2-bisnor)penicillanate (1a).

-a) By cyclization of diazosulfide (6). The title compound was obtained as a by-product (5% isolated yield) in the reaction leading to **9** (see above).

-b) By reduction of sulfoxides (10, 11). Pyridine (3.35 ml, 41.64 mmol) and phosphorus pentasulfide (2.31 g, 5.02 mmol) were sequentially added to a solution of the epimeric sulfoxides (**10**, **11**) (5.02 g, 10.41 mmol) in CH_2Cl_2 (100 ml). After stirring for 8 h, the insoluble residue was removed by filtration, washed with CH_2Cl_2 and discarded. The filtrate was washed with water and evaporated *in vacuo*. Following flash chromatography, the title compound (2.42 g, 50%) was obtained as an amorphous solid. Ir ($CHCl_3$) ν_{max} 1780-1740 (br) cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.03 (3H, s), 0.05 (3H, s), 0.83 (9H, s), 1.22 (3H, d, *J*= 6.3 Hz), 3.19 (1H, dd, *J*= 1.7 and 4.4 Hz), 3.61 (1H, dd, *J*= 7.1 and 12.1 Hz), 3.64 (1H, dd, *J*= 3.1 and 12.1 Hz), 4.22 (1H, dq, *J*= 4.4 and 6.3 Hz), 5.01 (1H, dd, *J*= 3.1 and 7.1 Hz), 5.09 (1H, d, *J*= 1.7 Hz), 5.25 (2H, s), 7.50 and 8.22 ppm (4H, two d, *J*= 8.6 Hz); FDms, m/z 467 $[M+H]^+$. Anal. Calcd for $C_{21}H_{30}N_2O_6SSi$: C, 54.07; H, 6.44; N, 6.01. Found: C, 54.45, H, 6.68, N, 5.87.

4-Nitrobenzyl (3*S*,5*R*,6*S*)-6-[(*R*)-1-hydroxyethyl]-3-(2,2-bisnor)penicillanate (1b).

Acetic acid (1.5 ml, 25.9 mmol) and tetrabutylammonium fluoride trihydrate (4.91 g, 15.6 mmol) were added to a solution of **1a** (2.42 g, 5.19 mmol) in THF (12 ml). The reaction mixture was let stand at room temperature for 20 h, then diluted with CH_2Cl_2 (100 ml), washed with saturated NaCl and dried. Removal of the solvent and chromatography gave the title compound (1.55 g, 85%) as an amorphous solid. $[\alpha]_D$ + 151° (c 1, MeCN); ir ($CHCl_3$) ν_{max} 1780, 1750 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.34 (3H, d, *J*= 6.3 Hz), 3.27 (1H, dd, *J*= 1.7 and 6.4 Hz), 3.52 (1H, dd, *J*= 4.4 Hz), 3.53 (1H, d, *J*= 5.7 Hz), 4.27 (1H, dd, *J*= 6.3 and 6.4 Hz), 5.04 (1H, dd, *J*= 4.4 and 5.7 Hz), 5.11 (1H, d, *J*= 1.7 Hz), 5.24 (1H, d, *J*= 14.0 Hz),

5.31 (1H, d, *J*= 14.0 Hz), 7.51 and 8.23 ppm (4H, two d, *J*= 8.7 Hz); FDms, m/z 353$[M+H]^+$.

(3*S*,5*R*,6*S*)-6-[(*R*)-1-hydroxyethyl]-3-(2,2-bisnor)penicillanic acid, sodium salt (1c). A mixture of the ester (1b) (1.46 g, 4.15 mmol) and 10% Pd/C (1.45 g) in THF (60 ml) and H_2O (15 ml) was hydrogenated under pressure (5 atm) for 2 h. The catalyst was filtered off and washed with THF. The filtrate was concentrated and the residue was taken up in a cooled mixture of EtOAc and water. Under vigorous stirring, the pH was adjusted to 7.0 with saturated $NaHCO_3$ solution and the organic layer was discarded. Acidification to pH 2.0 with 1 N hydrochloric acid and back-extraction with EtOAc gave a solution of the title acid, which was washed with brine and concentrated to a small volume (about 10 ml). Sodium 2-ethylhexanoate in isopropanol (2 N solution; 3.1 ml, 6.22 mmol) was added under stirring, and the mixture was diluted with isopropyl ether (100 ml). The precipitate was collected by filtration, washed with ether and dried to give the title compound (796 mg, 80%) as a white powder, mp 151-153 °C (decomp.). $[\alpha]_D$ + 299° (c 0.5, H_2O); ir (KBr) ν_{max} 1775, 1610 cm^{-1}; ^1H nmr (D_2O) δ 1.30 (3H, d, *J*= 6.4 Hz), 3.34 (1H, dd, *J*= 6.5 and 1.7 Hz), 3.50 (1H, dd, *J*= 11.4 and 4.2 Hz), 3.58 (1H, dd, *J*= 11.4 and 7.0 Hz), 4.26 (1H, dd, *J*= 6.4 and 6.5 Hz), 4.79 (1H, dd, *J*= 4.2 and 7.0 Hz), 5.09 ppm (1H, d, *J*=1.7 Hz); FABms, m/z 240 $[M+Na]^+$. Anal. Calcd for $C_8H_{10}NO_4NaS$: C, 40.17; H, 4.18; N, 5.86. Found: C, 40.34; H, 4.48; N, 5.62.

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