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AN EFFICIENT SYNTHESIS OF 2-SUBSTITUTED-THIO-6-HYDROXYETHYL-PENEM-3-CARBOXYLIC ACIDS *VIA* 2-THIOXOPENAMS

W. J. LEANZA,* FRANK DININNO,* DAVID A. MUTHARD, R. R. WILKENING, KENNETH J. WILDONGER, R. W. RATCLIFFE and B. G. CHRISTENSEN
Department of Synthetic Chemical Research, Merck Sharp & Dohme Research Laboratories, Rahway, NJ 07065, U.S.A.

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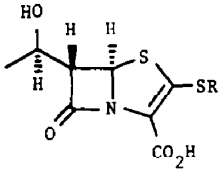
Abstract—Allyl and *p*-nitrobenzyl (5*R*, 6*S*)-6-[(*R*)-1-(t-butyldimethylsilyloxy)ethyl]-2-thioxopenam-3-carboxylates (**19**) were synthesized by base mediated cyclization of the corresponding 1-carboxylmethyl-4-phenoxy(thiocarbonyl)thio-2-azetidinones (**16**). The thioxopenams underwent alkylation and Michael reactions to produce 2-alkylthio- and 2-alkenylthio-penem derivatives **20** and **21**.

The penem class of bicyclic, β-lactam compounds occupies a unique position in the evolution of antibiotic substances. While not having a naturally occurring representative as yet, the penems can be viewed as a convergence of the classical penicillin and cephalosporin structures. The penems also share many structural and biological similarities with the naturally based, nonclassical, carbapenem family of antibiotics. Since the pioneering synthetic work of Woodward *et al.*[1] in 1976, several research groups have been involved in synthetic approaches to penem derivatives.[2] This effort has resulted in the preparation of a series of (5*R*,6*S*)-6-[(*R*)-1-hydroxyethyl]-2-substitutedthio-penem-3-carboxylic acids (**1**) in which the substitution pattern and the absolute configuration of the carbapenem antibiotic thienamycin (**2**)[3] have been retained. Many members of this series display highly desirable antibacterial properties and the simple analog where R is ethyl has been advanced by the Schering group as a broad spectrum, orally active, clinical candidate.[4]



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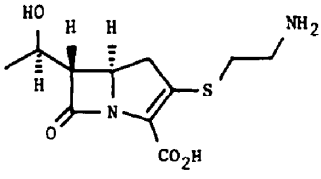

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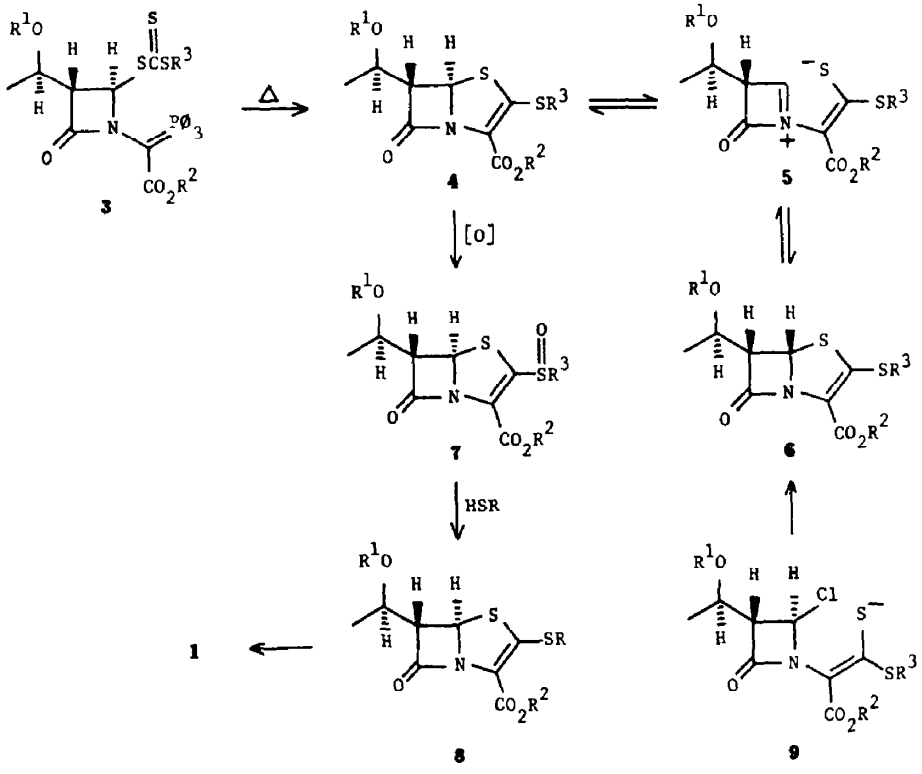
The most common synthetic approach to penem derivatives of type **1** initially focused on the method of Woodward *et al.* in which a suitably functionalized, stabilized phosphoranyl azetidinone **3** underwent an intramolecular thio-Wittig reaction at elevated temperatures to form the thiazoline ring of the bicyclic system (Scheme 1). The relative success of this transformation was found to be highly dependent on the choice of protecting groups R^1 and R^2 and, moreover, the resulting *trans* penem **4** was found[2a,e] to undergo thermal isomerization under the cyclization conditions, presumably *via* betaine intermediate **5**, to provide mixtures of **4** and the undesired *cis* penem **6**. Because of these deficiencies and the incompatibility of the Wittig process with certain functionalities embodied in the variations of R^3, some of us[5] and the Beecham group[6] found it convenient to prepare derivatives **8** in this series by an addition–elimination reaction of thiols to a C-2 sulfinyl substituted penem **7**. Thus, by optimizing a single Wittig reaction followed by selective oxidation and replacement of the exocyclic thio group, a number and variety of analogs were easily prepared.

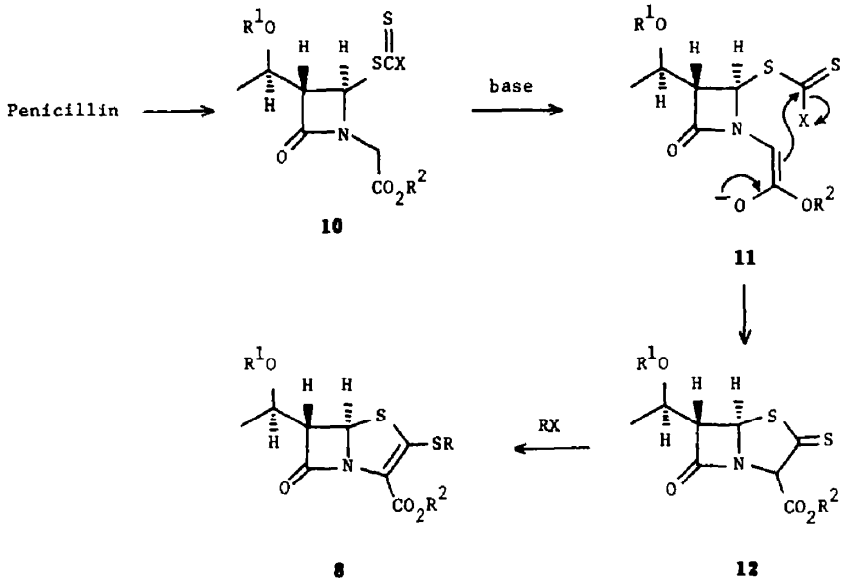
The Sankyo group reported[7] an alternative approach to the construction of the bicyclic ring system in which an appropriate lactam precursor was transformed *via* the key intermediate **9** in an S_N2 fashion to the *cis* fused penem **6**. Subsequent thermal equilibration gave an isomeric mixture from which the biologically more interesting *trans* penem **4** was separated.

The foregoing methods suffer at some point from a lack of versatility and, more importantly, from a loss of stereocontrol leading to the production of penem mixtures containing undesired isomers. We now wish to report a stereospecific route to the 6-hydroxyethyl *penam* nucleus which avoids these problems and is suitable for further elaboration to a variety of 2-alkylthio *penem* derivatives **1** having the desired absolute configuration of thienamycin. As indicated in Scheme 2, we envisioned that an ester enolate **11** generated from a suitably functionalized azetidinone **10** bearing a 4-dithiocarbonate substituent would undergo an intramolecular condensation[8] to provide the potentially valuable penem precursor 2-thioxopenam **12**. The derivatization of **12** by base mediated alkylation and Michael reactions would then afford the penem derivatives **8**. This method has the advantage that the proposed cyclization occurs under mild conditions with complete retention of configuration at the bridgehead position, thereby enabling an enantiospecific synthesis of penems from an azetidinone intermediate derived from penicillin.

The synthetic scheme was first investigated in the racemic series in which the required intermediate **16a** for the crucial cyclization reaction was obtained by adaptation of a Bristol process[9] to the N-carboalkoxymethyl azetidinone **14a**. The latter was obtained by alkylation of tritylthioazetidinone **13**



Scheme 1.



Scheme 2.

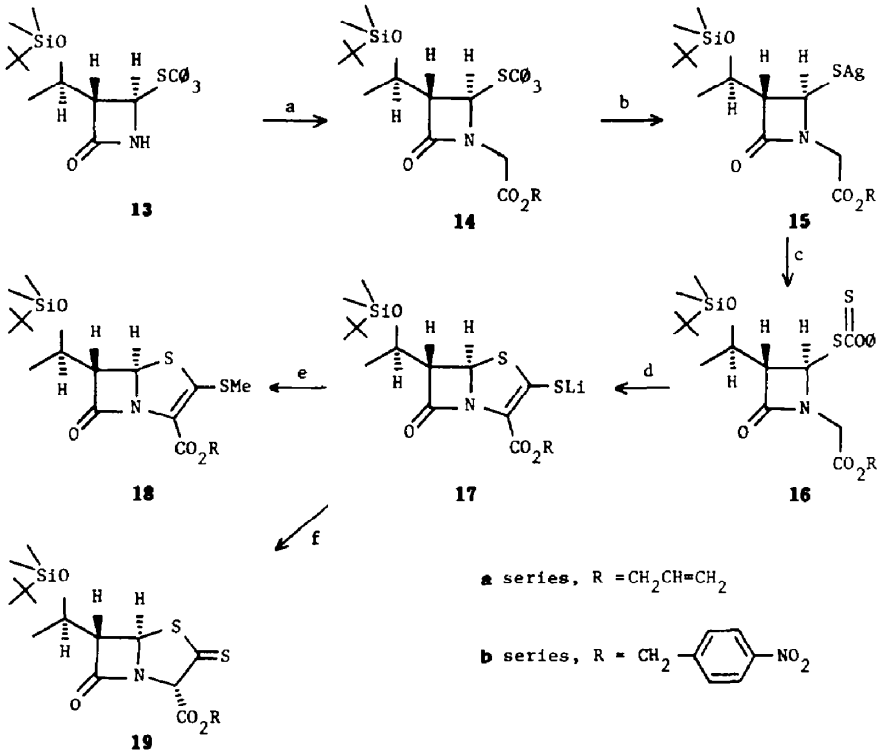
with allyl bromoacetate in benzene in the presence of powdered potassium hydroxide and 18-crown-6 according to the method of Yamazaki *et al.*[10] Because of loss of the bromo ester through self-condensation, it was found necessary to use 1.5 equiv of ester to obtain an 84% isolated yield. The trityl group of **14a** was cleaved with silver nitrate and pyridine in methanol, and the resulting silver thiolate **15a** was acylated with phenoxythiocarbonyl chloride[11] to give **16a** in 74% yield. Although the silver thiolate could be isolated as a foam following preparative plate-layer chromatography, it was more practical to acylate the crude product after removing nitrate salts by partitioning between water and methylene chloride.

Treatment of **16a** with 2–3 equivalents of lithium hexamethyldisilazide in THF solution containing 1,3-dimethyl-2-imidazolidinone at −78° led to a rapid displacement of the phenoxy group with formation of the bicyclic thiolate **17a**. The progress of the cyclization was conveniently monitored by UV spectroscopy in dioxane by observing the appearance and increase in the absorption maximum at 337 nm due to the thiolate. Further evidence for the thiolate intermediate **17a** was obtained by quenching the reaction mixture with excess methyl iodide to afford the methylthio penem **18a** in 58% yield. Alternatively, the reaction mixture was neutralized with dilute hydrochloric acid and the thioxopenam **19a** was isolated after chromatography in 81% yield.

The structural assignment of the thioxopenam was initially formulated on the basis of its spectroscopic properties. The IR spectrum exhibited a β-lactam CO absorption at 1790 cm^{-1} and a saturated ester CO absorption at 1750 cm^{-1}. The 200 MHz NMR spectrum in deuteriochloroform solution exhibited a single set of proton resonances indicative of stereochemical homogeneity and the absence of any enethiol tautomer. Pertinent resonances for H-5 and H-6 at δ 5.88 and 3.64 ppm and a $J_{5,6}$ value of 1.5 Hz signified retention of the *trans* stereochemistry about the β-lactam ring, and the appearance of a downfield, one proton singlet at δ 5.35 ppm was consistent for the H-3 assignment when considering the anisotropic influence of the thiocarbonyl group and similar, related systems.[12] Furthermore, the thermodynamically expected exo orientation of the 3-carboxyl group was inferred from the position of the H-3 resonance and from the absence of a four-bond "W" coupling to H-5. The UV spectrum of **19a** in dioxane proved interesting in that an initial measurement in dioxane solution provided an absorption maximum at 316 nm whereas aging of the solution for several minutes produced a new maximum at 345 nm. On the other hand, measurement in ethanol solution exhibited a "stable" maximum at 316 nm which shifted to 353 nm on addition of triethylamine.

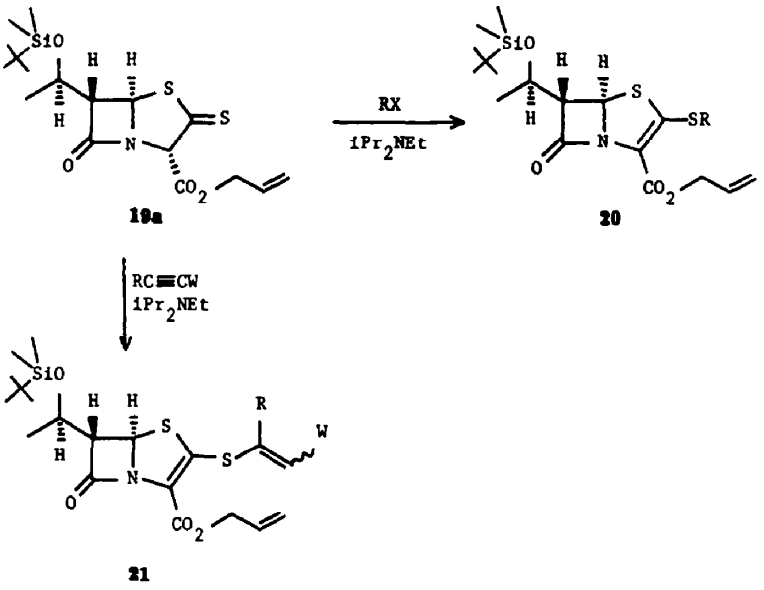
The transformations depicted in Scheme 3 were also conducted on substrates in which a *p*-nitrobenzyl ester was substituted for the allyl ester. In this series, the silver thiolate **15b** precipitated from the methanolic reaction mixture as a silver nitrate complex which was recovered by filtration. The solid decomposed when kept for several days at room temperature and it darkened rapidly in deuteriochloroform solution. Pure **15b** was obtained as a stable foam after aqueous workup. Thioacylation and cyclization as described previously provided the thioxopenam **19b**.[13] Alternatively, the thiolate intermediate **17b** could be alkylated *in situ* with excess methyl iodide to afford the 2-methylthiopenem **18b**. It is noteworthy that the cyclization reaction proceeded without interference from the base sensitive *p*-nitrophenyl group.

The chemistry of the thioxopenam intermediate



Conditions: a) $BrCH_2CO_2R$, KOH, 18-crown-6, ØH, RT; b) $AgNO_3$, C_5H_5N, MeOH, 0°; c) ClCSOØ, C_5H_5N, CH_2Cl_2, 0°; d) LiHMDS, THF, DMI, −78°; e) MeI; f) aq. HCl

Scheme 3.



was mainly explored in the allyl ester series and found to be applicable to the synthesis of a number of 2-substitutedthio penem derivatives. For example, **19a** was alkylated in the expected manner[13,14] with a variety of alkyl halides in the presence of diisopropylethylamine to afford the corresponding 2-alkylthio penems **20**. The reaction conditions developed for these alkylations reflected the relative reactivity of the alkyl halides and ranged from a few minutes at 0° to 5 hr at 80°. Table 1 provides several examples which were chosen to illustrate the scope of this reaction. In addition to alkylations, the thioxopenam **19a** was found to undergo Michael reactions with activated acetylenes to afford the penem derivatives **21** having an alkenylthio side chain, a moiety common to several carbapenem natural products[15] and thus far unreported in the penem literature. In agreement with observations from the Beecham group regarding related carbapenem chemistry,[16] the adducts **21** were dominated by the *Z*-olefin configuration that results from formal *trans* addition to the acetylene. While most reactions resulted in separable mixtures of olefin isomers, the reactions with cyanoacetylenes yielded only the *Z*-adducts. Several representative examples of this transformation are listed in Table 2.

In order to provide penems having the correct absolute configuration necessary for full antibacterial activity, an enantiospecific synthesis of the azetidinone intermediate **13** from 6-aminopenicillanic acid (**22**) was developed (Scheme 4). The foundation for this process lies in the work of DiNinno *et al.*[17]

Table 1. Alkylations of 2-thioxopenam **19a** to penems **20**

Alkyl Halide (equiv.)[a]	R	Time (h)	Solvent, T°C	Isolated Yield (%)
$ClCH_2COCH_3$ (1.5)	CH_2COCH_3	1	CH_2Cl_2, 0°	80
$BrCH_2CH_3$ (1.5)	CH_2CH_3	19	CH_2Cl_2, RT	76
$BrCH_2CH_2CH_3$ (1.5)	$CH_2CH_2CH_3$	1.5	DME, 60°	80
$BrCH(CH_3)CH_2CH_3$ (3.0)	$CH(CH_3)CH_2CH_3$[b]	0.5	DMF, 80°	77
$BrC(CH_3)_3$ (3.0)[c]	$C(CH_3)_3$	5	DME, 60°	30
$ClCH_2CH_2CH_2CH_3$ (1.5)	$CH_2CH_2CH_2CH_3$	21	DME, 60°	10
$ClCH_2CH_2CH_2CH_3$ (1.5)[d]	$CH_2CH_2CH_2CH_3$	5	DMF, 80°	70
ICH_2CN (1.0)	CH_2CN	0.2	CH_2Cl_2, 0°	75

[a]An equal equivalency of iPr_2NEt was added. [b]1:1 Mixture of diastereomers. [c]One equivalent of $AgOSO_2CF_3$ added. [d]One equivalent of KI added.

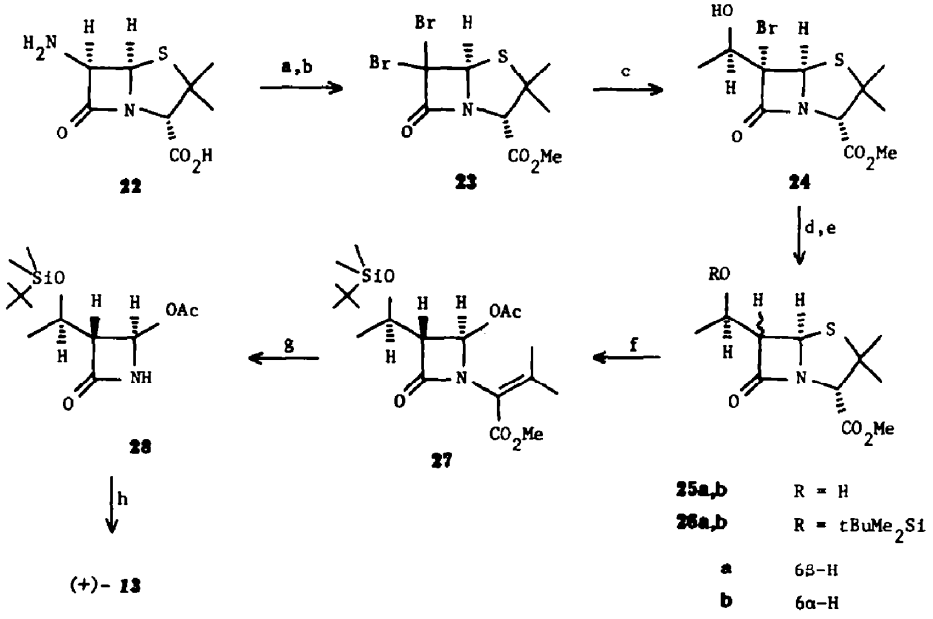
Table 2. Michael reactions of 2-thioxopenam **19a** to penems **21**

Acetylene[a]	R	W	Z/E	Time (h)	T°C	Isolated Yield (%)
$HC{\equiv}CCO_2CH_3$	H	CO_2CH_3	3	1	RT	94
$HC{\equiv}CCONH_2$	H	$CONH_2$	3	22	RT	60
$HC{\equiv}CCN$	H	CN	–[b]	0.25	0°	84
$CH_3C{\equiv}CCO_2CH_3$[c]	CH_3	CO_2CH_3	3	22	70°	30
$CH_3C{\equiv}CCN$	CH_3	CN	–[b]	24	RT	80

[a]All reactions were performed using 1.3 equivalents of acetylene and 0.5 equivalents of iPr_2NEt unless otherwise denoted. [b]Only the Z isomer was detected. [c]2.5 equivalents used.

which was subsequently examined in greater detail by researchers at Schering[2r] and Sankyo.[18] The present description (*vide supra*) embodies the latest improvements and addresses the critical debromination reaction which has plagued this route in the past.

Methyl 6,6-dibromopenicillanate (**23**) was readily obtained from **22** by diazotization-bromination[19] followed by esterification[20] of the crude dibromo acid. This material underwent metal halogen exchange with methylmagnesium bromide in THF at −78° to give an enolate intermediate which, on quenching with excess acetaldehyde, afforded a mixture of hydroxyethyl products in high yield.[17a] The major bromohydrin **24** having the desired *R* configuration at the OH bearing carbon was isolated in 66% yield by a combination of chromatography and crystallization. Our efforts to reductively debrominate **24** and the related benzyl ester[17] using either Zn–Ag couple or catalytic hydrogenation resulted in either low or irreproducible yields on scale-up. Consequently we studied the debromination in detail and found that simply stirring **24** with 3 molar equivalents of Zn in a mixture of diethyl ether and aqueous ammonium acetate[21] at room temperature afforded a 91 : 9 mixture of *trans* and *cis* isomers **25a** and **25b** in 92% yield. The mixture of alcohols was converted to



Conditions: a) Br_2, $NaNO_2$, H_2SO_4, H_2O–CH_2Cl_2, 5°; b) K_2CO_3, MeI, DMF, RT; c) MeMgBr, THF, −78° then MeCHO; d) Zn, Et_2O, aq. NH_4OAc, RT; e) $tBuMe_2SiCl$, ImH, DMF, RT; f) $Hg(OAc)_2$, HOAc, 90°; g) $KMnO_4$, $NaIO_4$, Me_2CO–buffer, RT; h) $Ø_3CSH$, NaH, DMF, 0°

Scheme 4.

the corresponding mixture of t-butyldimethylsilyl derivatives **26a** and **26b** and the thiazolidine ring was then disrupted using established procedures.[18] Treatment of **26** with mercuric acetate in acetic acid at 90° gave a mixture of acetoxyazetidinones consisting primarily of the major isomer **27** derived from **26a**. Oxidation of the mixture with a catalytic amount of potassium permanganate and sodium periodate in buffered acetone removed the N-isopropylidineacetate group to produce a mixture of azetidinones from which the major, crystalline isomer **28**[22] was isolated in 36–40% overall yield from **25**. The completion of the enantiospecific route to (+)-**13** was accomplished in 96% yield by stereospecific replacement of the acetoxy group of **28** with tritylmercaptan in DMF containing sodium hydride.

The diprotected penems **20** and **21**, which were prepared form either the racemic or optically active forms of azetidinone **13**, were unmasked as previously described[5] by sequential cleavage of the silyl and allyl groups. Desilylation was accomplished by the method of Just and Liak[23] in which the penem was treated with an excess of tetrabutylammonium fluoride in acetic acid buffered THF at ambient temperature. The removal of the allyl ester was then accomplished by the method of Jeffrey and McCombie[24] using catalytic tetrakistriphenylphosphinepalladium (0) and potassium 2-ethylhexanoate in methylene chloride, ethyl acetate, or THF solution. In general, the penem antibiotics obtained by this synthetic methodology were less potent than their carbapenem counterparts against a variety of bacterial strains, more stable to the renal dipeptidase dehydropeptidase-I[25] than the corresponding carbapenems, and in certain cases, more potent than the oral penem SCH 29,482 (**1**, R = Et). These and other biological findings will be reported in detail elsewhere.

EXPERIMENTAL

Mps were determined on a Thomas-Hoover capillary m.p. apparatus and are uncorrected. IR spectra were recorded on Perkin–Elmer 727B and 267 spectrophotometers and only selected absorptions are reported. UV spectra were recorded on a Perkin–Elmer 552A spectrophotometer and optical rotations were determined at room temp. using a Perkin–Elmer 241 polarimeter. The NMR spectra were recorded on Varian T-60, SC-300 and XL-200 spectrometers in either $CDCl_3$ soln with TMS as an internal standard or in D_2O soln with DSS as an internal standard. Chemical shifts are reported in ppm δ relative to the standards.

All reactions were performed under a positive atmosphere of N_2 with the aid of a Firestone valve (Ace Glass). The usual workup means partitioning of the mixture between EtOAc and ice-H_2O, separating the organic phase, washing it with sat. NaCl aq, drying over Na_2SO_4, filtering, and evaporating under reduced pressure. Plate layer chromatography (PLC) was performed on Analtech silica gel GF plates and column chromatography (CC) was conducted with E. Merck 60 silica gel. Reverse phase plate layer chromatography (RP–PLC) was performed on either 0.25 mm RPS–F preabsorbant or 0.5 mm RPS–F Analtech plates which were developed in the cold with 5–15% EtOH in H_2O.

The following solvents and/or reagents were distilled from CaH_2 prior to use: diisopropylethylamine (DIEA), hexamethyldisilazane (HMDS), and 1,3-dimethyl-2-imidazolidinone (DMI). Tetrahydrofuran (THF) was distilled from benzophenone ketyl prior to use. 2.9 M MeMgBr in Et_2O (Aldrich), 2.2 M n-BuLi in hexane (Alfa), 1 M tetrabutylammonium fluroide in THF (Aldrich), and 6-aminopenicillanic acid (Bristol–Meyers) were used as supplied. Allyl bromoacetate and *p*-nitrobenzyl bromoacetate were prepared from bromoacetic acid and the corresponding alcohol in benzene with azeotropic water removal *via* a Dean–Stark trap.

In the examples which follow, the experimental procedure is outlined for a given compound in the racemic allyl ester series followed by the pertinent data for the corresponding chiral material, and lastly by an accompanying set of data for the *p*-nitrobenzyl (PNB) ester series, all of which were obtained by the procedure described. Under *General Procedures*, only a specific example is provided and the experimental parameters in Table 1 and 2 should be consulted for any given compound. Selected NMR data for selected penems follows the experimental procedure.

Racemic (3S,4R)-3-[(R)-1-(*t-butyldimethylsilyloxy*)*ethyl*]-4-*triphenylmethylthio*-2-*azetidinone* (**13**). A mixture of 35.7 g (0.092 mol) of racemic (3*S*,4*R*) - 3 - [(*R*) - 1 - hydroxyethyl] - 4 - triphenylmethylthio - 2 - azetidinone,[9] 15.2 g (0.1 mol) of t-butyldimethylsilyl chloride, and 9.4 g (0.14 mol) imidazole in 200 ml of sieve dried DMF was stirred at room temp. for 24 hr. The mixture was partitioned between EtOAc and ice-H_2O and the organic phase separated, washed sequentially with ice-H_2O, cold dilute HCl, cold dilute $NaHCO_3$, ice-H_2O, and sat. NaCl aq, dried over Na_2SO_4, filtered, and evaporated under vacuum to a solid residue. Recrystallization from boiling Et_2O–petroleum ether (35–60°) gave 39.7 g (86%) of **13**. Concentration of the mother liquors and repetition of the above gave an additional 5.3 g (11%) of **13**: m.p. 94–95°; IR 1760 cm^{-1}; ^1H NMR ($CDCl_3$) δ −0.06 (s, $SiCH_3$), −0.01 (s, $SiCH_3$), 0.72 (s, Si-*t*-C_4H_9), 1.26 (d, J = 6 Hz, CH_3CH), 3.1 (app. t, J = 2 Hz, H3), 4.22 (m, CH_3CH), 4.36 (br. s, NH), 4.54 (d, J = 2 Hz, H4), 7.42 (m, aryl).

Chiral **13**. To a stirred suspension of 0.92 g (23.3 mmol) of 61% NaH dispersion in 20 ml of sieve dried DMF at 0° was added dropwise a soln of 6.44 g (23.3 mmol) trityl mercaptan in 35 ml DMF over a period of 0.5 hr. The mixture was stirred further for 10 min and then a soln of 6.1 g (21.2 mmol) of **28** in 20 ml DMF was added over 15 min. The mixture was stirred further at 0° for 45 min and then poured onto a mixture of sat. NH_4Cl aq and ice-H_2O and extracted thoroughly with Et_2O. The Et_2O extracts were washed twice with H_2O and then sat. NaCl aq, dried over Na_2SO_4, filtered, evaporated and dried under vacuum to give a solid residue. The residue was washed twice with petroleum ether to give 7.7 g crude product which upon recrystallization from boiling Et_2O–petroleum ether gave 6.44 g (60%) of **13**. The pet ether washings and the mother liquors were combined and purified by CC on 100 g of silica gel eluted with toluene, CH_2Cl_2, and CH_2Cl_2–EtOAc (10 : 1) to give an additional 3.8 g (36%) of **13**: m.p. 94–96.5°; $[\alpha]_D$ + 3.7(*c* 8, $CHCl_3$).

Racemic (3S,4R) - 1 - (*allyloxycarbonyl*)*methyl* - 3 - [(R) - 1 - *t* - *butyldimethylsilyloxyethyl*] - 4 - *triphenylmethylthio* - 2 - *azetidinone* (**14a**). To a stirred soln of 9.46 g (18.8 mmol) of **13** and 0.5 g (1.88 mmol) dicyclohexyl-18-crown-6 in 95 ml benzene at room temp. was added sequentially 1.74 g (31.0 mmol) powdered, fused KOH and a soln of 5.01 g (28.2 mmol) allyl bromoacetate in 50 ml benzene over 12 min. The resulting mixture was stirred under an atmosphere of N_2 and at room temp. for an additional 4.5 hr. The usual workup and purification by CC on 200 g silica gel eluted with CH_2Cl_2 and 95 : 5 CH_2Cl_2–EtOAc gave 9.5 g (84%) of **14a** as a colorless oil: IR (CH_2Cl_2) 1780, 1760 (sh) cm^{-1}; ^1H NMR ($CDCl_3$) δ −0.05 (s, $SiCH_3$), −0.01 (s, $SiCH_3$), 0.78 (s, Si-*t*-C_4H_9), 1.07 (d, J = 6.4 Hz, CH_3CH) 3.33 (s, NCH_2CO_2), 3.37 (dd, J = 2.6 and 5.3 Hz, H3), 4.1 (m, CH_3CH), 4.5 (m, H4 and CO_2CH_2), 5.25 (m, $=CH_2$), 5.8 (m, CH=), 7.4 (m, phenyl).

Chiral **14a**. $[\alpha]_D$ + 0.8(*c* 20, $CHCl_3$).

Racemic PNB ester **14b**. 68% yield; IR (film) 1775, 1760 (sh) cm^{-1}; ^1H NMR ($CDCl_3$) δ −0.07 (s, $SiCH_3$), −0.02 (s, $SiCH_3$), 0.74 (s, Si-*t*-C_4H_9), 1.09 (d, J = 6.4 Hz, CH_3CH), 3.07 and 3.46 (2d, J = 18 Hz, NCH_2CO_2), 3.41 (app. t,

J = 2.3 Hz, H3), 4.15 (m, CH_3CH), 4.54 (d, J = 2.3 Hz, H4), 5.15 (s, CO_2CH_2), 7.4 (m, phenyl and 2 aryl), 8.15 (d, J = 8.8 Hz, 2 aryl).

Racemic (3S,4R) - 1 - (*alloxycarbonyl*)*methyl* - 3 - [(R) - 1 - t - *butyldimethylsilyloxy*) - *ethyl*] - 4 - *phenoxy*-(*thiocarbonyl*)*thio* - 2 - *azetidinone* (**16a**). To a stirred soln of 0.92 g (1.53 mmol) of **14a** in 10 ml MeOH at 0° was added sequentially 0.2 ml (2.5 mmol) pyridine and 17 ml (2.04 mmol) 0.12 M $AgNO_3$ in MeOH soln. The mixture was stirred at 0° for 0.5 hr and concentrated under vacuum. The concentrate was partitioned between CH_2Cl_2 and H_2O and the organic phase separated, washed twice with H_2O, dried over $MgSO_4$, filtered, and evaporated. The residue of **15a** so obtained was dissolved in 30 ml CH_2Cl_2 and stirred at 0° while 0.15 ml pyridine and 0.22 ml (1.63 mmol) phenoxythiocarbonyl chloride[11] were added. After stirring at 0° for 20 min, the mixture was filtered through celite to remove the insoluble materials which were thoroughly washed with EtOAc. The filtrate was partitioned between EtOAc and ice-cold, dilute HCl aq. The organic phase was separated and after the usual workup and purification by CC on 80 g of silica gel eluted with CH_2Cl_2 there was obtained 0.60 g (79%) of **16a** as a yellow oil: IR (film) 1775, 1740 (sh) cm^{-1}; UV (dioxane) λ_{max} 283.5 nm; ^1H NMR ($CDCl_3$) δ 0.1 [s, $Si(CH_3)_2$], 0.9 (s, Si-*t*-C_4H_9), 1.32 (d, J = 6 Hz, CH_3CH), 3.35 (dd, J = 2.5 and 6 Hz, H3), 3.94 and 4.26 (2d, J = 18 Hz, NCH_2CO_2), 4.34 (m, CH_3CH), 4.5 (m, CO_2CH_2), 5.3 (m, $=CH_2$), 5.86 (m, H4 and CH=), 7.3 (m, phenyl).

A sample of intermediate **15a** was purified by PLC using 7 : 3 toluene–EtOAc as developing solvent: IR (film) 1760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.06 (s, $SiCH_3$), 0.08 (s, $SiCH_3$), 0.87 (s, Si-*t*-C_4H_9), 1.32 (d, J = 6 Hz, CH_3CH), 3.00 (dd, J = 1.8 and 4.2 Hz, H3), 3.96 and 4.28 (2d, J = 18 Hz, NCH_2CO_2), 4.24 (m, CH_3CH), 4.67 (d, J = 6 Hz, CO_2CH_2), 5.23 (d, J = 1.8 Hz, H4), 5.3 (m, $=CH_2$), 5.9 (m, CH=).

Chiral **16a**. $[\alpha]_D$ + 59.6 (*c* 13.6, $CHCl_3$).

Racemic PNB ester **16b**. 64% yield; IR (film) 1775, 1750 (sh) cm $^{-1}$; ^1H NMR ($CDCl_3$) δ 0.04 (s, $SiCH_3$), 0.07 (s, $SiCH_3$), 0.86 (s, Si-*t*-C_4H_9), 1.29 (d, J = 6 Hz, CH_3CH), 3.34 (dd, J = 2.8 and 6 Hz, H3), 3.99 and 4.29 (2d, J = 18 Hz, NCH_2CO_2), 4.3 (app. p, J = 6 Hz, CH_3CH), 5.17 (ABq, J = 13 Hz, CO_2CH_2), 5.84 (d, J = 2.8 Hz, H4), 7–8.2 (m, phenyl and aryl).

The intermediate **15b** used in the preparation of **16b** was obtained as a foam following the usual workup: IR (film) 1765, 1750 (sh) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.04 (s, $SiCH_3$), 0.07 (s, $SiCH_3$), 0.86 (s, Si-*t*-C_4H_9), 1.32 (d, J = 6 Hz, CH_3CH), 3.12 (dd, J = 1.6 and 4 Hz, H3), 4.04 and 4.19 (2d, J = 18 Hz, NCH_2CO_2), 4.22 (m, CH_3CH), 5.20 (d, J = 1.6 Hz, H4), 5.32 (s, CO_2CH_2), 7.59 and 8.27 (2 m, aryl). A sample of the $AgNO_3$ complex of **15b** which initially crystallized from the mixture had m.p. 85–87° (dec); Anal. ($C_{20}H_{29}N_2O_6SSiAg \cdot 0.5\,AgNO_3$) C, H, N, Ag.

Racemic allyl (3S,5R,6S) - 6 - [(R) - 1 - (t - *butyldimethylsilyloxyl*)*ethyl*] - 2 - *thioxopenam* - 3 - *carboxylate* (**19a**). To a stirred soln of 1.94 ml (9.21 mmol) hexamethyldisilazane in 80 ml anhydrous THF at 0° was added a soln of 4.2 ml (9.21 mmol) of 2.2 M n-BuLi in hexane. The mixture was stirred at 0° for 0.5 hr and 1.7 ml DMI was then added. To the stirred soln at −78° was added a soln of 1.66 g (3.3 mmol) of **16a** in 5.0 ml dry THF. The mixture was stirred at −78° for 5 min and poured into a mixture of EtOAc, ice-H_2O, and 2N HCl. After the usual workup and purification by CC on 25 g of silica gel eluted with CH_2Cl_2, there was obtained 1.08 g (81%) of **19a** as a red–orange oil that solidfied on refrigeration: IR (CH_2Cl_2) 1790, 1750 cm^{-1}; UV (EtOH) λ_{max} 316 nm, (EtOH–Et_3N) 353 nm; ^1H NMR ($CDCl_3$) δ 0.08 (s, $SiCH_3$), 0.1 (s, $SiCH_3$), 0.88 (s, Si-*t*-C_4H_9), 1.3 (d, J = 6 Hz, CH_3CH), 3.64 (dd, J = 1.5 and 3.5 Hz, H6), 4.36 (m, CH_3CH), 4.68 (m, CO_2CH_2), 5.35 (s, H3), 5.35 (m, $=CH_2$), 5.88 (d, J = 1.5 Hz, H5), 5.91 (m, CH=).

Chiral **19a**. m.p. 42–44°; $[\alpha]_D$ − 31.7 (*c* 3.5, $CHCl_3$).

Racemic PNB ester **19b**. 53% yield (DMI was omitted); IR (film) 1790, 1750 cm^{-1}; UV (MeOH) λ_{max} 272, 317, 353 nm; ^1H NMR ($CDCl_3$) δ 0.07 (s, $SiCH_3$), 0.1 (s, $SiCH_3$), 0.85 (s, Si-*t*-C_4H_9), 1.3 (d, J = 6 Hz, CH_3CH), 3.68 (dd, J = 1 and 4 Hz, H6), 4.37 (m, CH_3CH), 5.32 (s, CO_2CH_2), 5.42 (s, H3), 5.89 (d, J = 1 Hz, H5), 7.54 and 8.27 (2d, J = 8.5 Hz, aryl).

Racemic allyl (5R,6S) - 6 - [(R) - 1 - (t - *butyldimethylsilyloxy*)*ethyl*] - 2 - *methylthiopenem* - 3 - *carboxylate* (**18a**). To a soln of intermediate **17a**, prepared as described above from 18.1 mg (0.036 mmol) racemic **16a** in 0.4 ml THF and 0.42 ml (0.074 mmol) of a 0.175 M soln of lithium hexamethyldisiliazide in THF, was added 0.02 ml MeI. The mixture was allowed to warm from −78° to room temp., then diluted with CH_2Cl_2, washed with H_2O, dried over $MgSO_4$, filtered and evaporated under vacuum. The residue was purified by PLC using 9 : 1 toluene–EtOAc as developing solvent to afford 8.8 mg (58%) of **18a** as an oil: UV (dioxane) λ_{max} 256, 337 nm; ^1H NMR ($CDCl_3$) δ 1.26 (d, J = 6 Hz, CH_3CH), 2.52 (s, SCH_3), 3.66 (dd, J = 1.5 and 5.2 Hz, H6), 5.65 (d, J = 1.5 Hz, H5).

Racemic PNB ester **18b**. 65% yield; ^1H NMR ($CDCl_3$) δ 1.26 (d, J = 6 Hz, CH_3CH), 2.54 (s, SCH_3), 3.72 (dd, J = 1.5 and 4.5 Hz, H6), 5.67 (d, J = 1.5 Hz, H5).

General procedure for the alkylations of 2-thioxopenam **19a** *to penems* **20**. *Preparation of chiral allyl* (5R,6S)-6-[(R) - 1-(t - *butyldimethylsilyloxy*)*ethyl*] - 2 - *cyanomethylthiopenem* - 3 - *carboxylate* (**20**, R = CH_2CN)

To a stirred soln of 75.5 mg (0.19 mmol) chiral **19a** in 2 ml CH_2Cl_2 at 0° was added sequentially 24.3 mg (0.19 mmol) DIEA and 31.4 mg (0.19 mmol) iodoacetonitrile. The mixture was stirred at 0° for 10 min, and then partitioned between EtOAc, ice-H_2O and 2N HCl. After the usual workup and purification by PLC (one development with CH_2Cl_2), there was obtained 62.0 mg (75%) of the title penem; m.p. 91–92° (Et_2O–hexanes); $[\alpha]_D$ + 97.5 (*c* 2.49, $CHCl_3$); IR (CH_2Cl_2) 1799, 1712, 1684 cm^{-1}; UV (dioxane) λ_{max} 252.5, 338 nm; ^1H NMR ($CDCl_3$) δ 0.09 (s, $Si(CH_3)_2$), 0.9 (s, Si-*t*-C_4H_9), 1.28 (d, J = 6.5 Hz, CH_3CH), 3.69 and 3.76 (2d, J = 18 Hz, CH_2CN), 3.84 (dd, J = 1.5 and 4.5 Hz, H6), 4.3 (m, CH_3CH), 4.76 (m, CO_2CH_2), 5.3, 5.46, and 5.96 (3 m, $CH=CH_2$), 5.8 (d, J = 1.5 Hz, H5); MS, *m/e* 440 (M), 383, 143, 73.

Racemic penem **20**, R = CH_2COCH_3. ^1H NMR ($CDCl_3$) δ 1.23 (d, J = 6 Hz, CH_3CH), 2.34 (s, $COCH_3$), 3.7 (dd, J = 1.5 and 4.7 Hz, H6), 3.78 (ABq, J = 17.9 Hz, SCH_2CO), 5.64 (d, J = 1.5 Hz, H5).

Racemic penem **20**, R = $C(CH_3)_3$. ^1H NMR ($CDCl_3$) δ 1.26 (d, J = 6.1 Hz, CH_3CH), 1.48 [s, $C(CH_3)_3$], 3.7 (dd, J = 1.3 and 4.9 Hz, H6), 5.68 (d, J = 1.3 Hz, H5).

Racemic penem **20**, R = $CH(CH_3)CH_2CH_3$. ^1H NMR ($CDCl_3$) δ 1.02 (t, J = 7.2 Hz, CH_2CH_3), 1.26 (d, J = 6.1 Hz, CH_3CH–O), 1.38 and 1.43 (2d, J = 7 Hz, diastereomeric $SCHCH_3$), 1.7 (m, CH_2CH_3), 3.23 (m, SCH), 3.7 (dd, J = 1.2 and 5 Hz, H6), 5.64 (2d, J = 1.2 Hz, diastereomeric H5).

General procedure for the Michael reactions of 2-thioxopenam **19a** *to penems* **21**

Preparation of chiral allyl (5R,6S) - 6 - [(R) - 1 - (t - *butyldimethylsilyloxy*)*ethyl*] - 2 - [(Z) - 2 - *cyanovinylthio*]*penem* - 3 - *carboxylate* (**21**; R = H, W = CN). To a stirred soln of 94.3 mg (0.24 mmol) of chiral **19a** in 8 ml of sieve dried acetonitrile at 0° was added 20.5 μl (0.12 mmol) DIEA and 19.1 μl (0.3 mmol) cyanoacetylene.[26] The mixture was stirred at 0° for 15 min, and then partitioned between EtOAc and cold, dilute HCl aq. The organic phase was separated and worked up in the usual way. Purification by PLC (one development with 2% EtOAc in CH_2Cl_2) afforded 89.9 mg (84%) of the title penem: m.p. 122–123° (CH_2Cl_2–pet. ether); $[\alpha]_D$ + 333 (*c* 1, $CHCl_3$); IR (CH_2Cl_2) 2220, 1792, 1710 (sh), 1692 cm^{-1}; UV (dioxane) λ_{max} 269, 325 (sh), 342 nm; ^1H NMR ($CDCl_3$) δ 0.08 [s, $Si(CH_3)_2$], 0.88 (s, Si-*t*-C_4H_9), 1.26 (d, J = 6 Hz, CH_3CH), 3.79 (dd, J = 1.5 and 4.5 Hz, H6), 4.28 (m, CH_3CH), 4.76 (m, CO_2CH_2), 5.29, 5.44 and 5.94 (3 m, $CH=CH_2$), 5.56 (d,

J = 10 Hz, =CHCN), 5.71 (d, J = 1.5 Hz, H5), 7.42 (d, J = 10 Hz, SCH=); MS, *m/e* 452 (M), 395, 269, 253, 143.

Chiral penem **21**; R = H, W = $CONH_2$, *Z-Isomer*. $[\alpha]_D$ + 222 (*c* 1, $CHCl_3$); IR (CH_2Cl_2) 3500, 3390, 1780, 1690 (sh), 1670 cm^{-1}; UV (dioxane) λ_{max} 267, 342 nm; ^1H NMR ($CDCl_3$) δ 0.08 [s, $Si(CH_3)_2$], 0.88 (s, Si-*t*-C_4H_9), 1.26 (d, J = 6.5 Hz, CH_3CH), 3.74 (dd, J = 1.5 and 4.5 Hz, H6), 4.26 (m, CH_3CH), 4.74 (m, CO_2CH_2), 5.26 5.44 and 5.9 (3 m, $CH=CH_2$), 5.62 (d, J = 1.5 Hz, H5), 5.8 (br s, NH_2), 6.04 (d, J = 9.5 Hz, =CHCO), 7.26 (d, J = 9.5 Hz, SCH=).

Chiral penem **21**; R = H, W = $CONH_2$, E-*Isomer*. IR (CH_2Cl_2) 3500, 3400, 1790, 1680 (br) cm^{-1}; UV (dioxane) λ_{max} 267, 342 nm; ^1H NMR ($CDCl_3$) δ 0.06 [s, $Si(CH_3)_2$], 0.86 (s, Si-*t*-C_4H_9), 1.25 (d, J = 6.5 Hz, CH_3CH), 3.74 (dd, J = 1.5 and 4 Hz, H6), 4.26 (m, CH_3CH), 4.72 (m, CO_2CH_2), 5.26, 5.4 and 5.92 (3 m, $CH=CH_2$), 5.46 (br s, NH_2), 5.68 (d, J = 1.5 Hz, H5), 6.19 (d, J = 15 Hz, =CHCO), 7.79 (d, J = 15 Hz, SCH=).

Methyl (3S,5R,6S) - 6 - bromo - 6 - [(R) - 1 - *hydroxyethyl*]*penicillanate* (**24**). To a stirred soln of 13.00 g (34.8 mmol) of **23**[19,20] in 350 ml anhydrous THF at −78° was added dropwise 14.5 ml (42.1 mmol) of 2.9M MeMgBr in Et_2O soln. The soln was stirred an additional 40 min at −78° and then treated all at once with 9.7 ml (174.2 mmol) freshly distilled acetaldehyde. The soln was aged for 10 min and then quenched with 50 ml sat. NH_4Cl aq. After warming to room temp., the mixture was evaporated under vacuum to remove most of the THF and the residue was extracted with EtOAc. The combined EtOAc extracts were washed with sat. NaCl aq, dried over $MgSO_4$, filtered, and evaporated to provide 13.25 g of an oil. NMR analysis of this material indicated the presence of 72% of the desired isomer **24**, 19% of the 6β-bromo-6-[(*S*)-1-hydroxyethyl] isomer, 5% of the 6β-bromo-6-[(*R*)-1-hydroxyethyl] isomer, and 3% of the methyl ketone corresponding to **24**.

The crude product was chromatographed on a Waters Prep 500 instrument using a single silica gel cartridge which was eluted with 2% acetone in CH_2Cl_2 at 250 ml/min. The product fractions were located by TLC, combined, and evaporated to give 7.80 g (66%) of **24** as a white solid: m.p. 107.5–108° (hexane–EtOAc); $[\alpha]_D$ + 200(*c* 1.0, $CHCl_3$); IR (CH_2Cl_2) 3560, 1782, 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (d, J = 6.1 Hz, CH_3CH), 1.48 (s, CH_3), 1.66 (s, CH_3), 2.39 (d, J = 5.6 Hz, OH), 3.80 (s, OCH_3), 4.23 (dq, J = 5.6 and 6.1 Hz, CH_3CH), 4.53 (s, H3), 5.60 (s, H5); MS, *m/e* 337/339 (M), 258 (M–Br), 174; Anal. ($C_{11}H_{16}BrNO_4S$) C, H, N.

Methyl (3S,5R,6S) - 6 - [(R) - 1 - *hydroxyethyl*]*penicillanate* (**25a**) *and methyl* (3S,5R,6R) - 6 - [(R) - 1 - *hydroxyethyl*]*penicillanate* (**25b**). A soln of 7.30 g (21.6 mmol) of **24** in 216 ml Et_2O was treated with 108 ml of 1M NH_4OAc aq and 5.64 g (86.3 mmol) powdered Zn. The resulting mixture was stirred at room temp. for 50 min and then filtered through a sintered glass funnel. The Et_2O portion of the filtrate was separated from the aqueous portion which was twice more filtered and extracted with Et_2O. The combined Et_2O solution was washed with sat. NaCl aq, dried with $MgSO_4$, filtered, and evaporated under vacuum to provide 5.20 g (92%) of a 91 : 9 mixture of **25a** and **25b** as an oil: IR (CH_2Cl_2) 3605, 1775, 1752 cm^{-1}; MS, *m/e* 259 (M), 231, 173; major isomer **25a** had ^1H NMR ($CDCl_3$) δ 1.35 (d, J = 6.5 Hz, CH_3CH), 1.46 (s, CH_3), 1.64 (s, CH_3), 2.15 (d, J = 5.1 Hz, OH), 3.33 (dd, J = 1.7 and 6.5 Hz, H6), 3.77 (s, OCH_3), 4.28 (m, CH_3CH), 4.48 (s, H3), and 5.31 (d, J = 1.7 Hz, H5); minor isomer **25b** had ^1H NMR ($CDCl_3$) δ 1.23 (d, J = 6.1 Hz, CH_3CH), 1.48 (s, CH_3), 1.68 (s, CH_3), 3.51 (dd, J = 4.5 and 8.8 Hz, H6), 3.78 (s, OCH_3), 4.28 (m, CH_3CH), 4.48 (s, H3), 5.43 (d, J = 4.5 Hz, H5).

Methyl (3S,5R,6S) - 6 - [(R) - 1 - (t - *butyldimethylsilyloxy*)*ethyl*]*penicillanate* (**26a**) *and methyl* (3S,5R,6R) - 6 - [(R) - 1 - (t - *butyldimethylsilyloxy*)*ethyl*]*penicillanate* (**26b**). A soln of 5.10 g (19.7 mmol) of the alcohol mixture **25** in 20 ml sieve dried DMF was treated with 4.02 g (59.0 mmol) imidazole and 4.45 g (29.5 mmol) *t*-butyldimethylsilyl chloride. The resulting mixture was stirred at room temp. overnight, then diluted with 250 ml of Et_2O and washed with three 100 ml portions H_2O and 100 ml sat. NaCl aq. The Et_2O soln was dried over $MgSO_4$, filtered, and evaporated under vacuum to provide 7.05 g (96%) of a 91 : 9 mixture of **26a** and **26b** as a yellow oil: IR (CH_2Cl_2) 1772, 1751 cm^{-1}; MS, *m/e* 358 (M–CH_3), 316 (M–C_4H_9), 174; major isomer **26a** had ^1H NMR ($CDCl_3$) δ 0.06 (s, $SiCH_3$), 0.09 (s, $SiCH_3$), 0.87 (s, Si-*t*-C_4H_9), 1.23 (d, J = 6.2 Hz, CH_3CH), 1.45 (s, CH_3), 1.62 (s, CH_3), 3.23 (dd, J = 1.7 and 4.7 Hz, H6), 3.73 (s, OCH_3), 4.24 (dd, J = 4.7 and 6.2 Hz, CH_3CH), 4.43 (s, H3), 5.27 (d, J = 1.7 Hz, H5); minor isomer **26b** had ^1H NMR ($CDCl_3$) δ 3.75 (s, OCH_3), 4.40 (s, H3), 5.31 (d, J = 4.7 Hz, H5).

(3R,4R) - 4 - *Acetoxy* - 3 - [(R) - 1 - (t - *butyldimethylsilyloxy*)*ethyl*] - 1 - (1 - *methoxycarbonyl* - 2 - *methyl* - 1 - *propenyl*) - 2 - *azetidinone* (**27**). A soln of 7.05 g (18.9 mmol) of the O-silylated products **26** in 377 ml glacial AcOH was treated with 18.04 g (56.6 mmol) mercuric acetate, and the resulting mixture was heated with stirring in an oil bath maintained at *ca* 90° for 70 min. After cooling to room temp., the mixture was filtered to remove the white ppt which was washed with a small volume of EtOAc. The filtrate was evaporated under vacuum to a semi-solid residue which was mixed with 300 ml of EtOAc, filtered, and washed with an additional 50 ml EtOAc. The combined EtOAc soln was washed with water, sat. $NaHCO_3$ aq, water and sat. NaCl aq, dried over $MgSO_4$, filtered, and evaporated under vacuum to afford 6.47 g (86%) of an oil consisting mainly of **27**: IR (CH_2Cl_2) 1770, 1752, 1722 cm^{-1}; MS, *m/e* 399 (M), 342 (M–C_4H_9); major isomer **27** had ^1H NMR ($CDCl_3$) δ 0.08 (s, $SiCH_3$), 0.1 (s, $SiCH_3$), 0.88 (s, Si-*t*-C_4H_9), 1.31 (d, J = 6.2 Hz, CH_3CH), 1.93 (s, CH_3), 2.06 (s, CH_3CO_2), 2.21 (s, CH_3), 3.21 (dd, J = 1.4 and 6.1 Hz, H3), 3.78 (s, OCH_3), 4.23 (app. p, J = 6.2 Hz, CH_3CH), 6.28 (d, J = 1.4 Hz, H4).

In addition to containing *ca* 87% of the desired (3*R*,4*R*) isomer **27**, the crude product contained *ca* 9% of the (3*S*,4*S*) isomer, 4% of the (3*R*,4*S*) isomer, and less than 1% of the (3*S*,4*R*) isomer. The configuration of the side chain chiral center was *R* for all isomers. The *R*,*R* and *R*,*S* isomers are derived from the major bicyclic precursor **26a** with *ca* 96% retention of configuration at C4 while the *S*,*R* and *S*,*S* isomers are derived from **26b** with *ca* 96% inversion of configuration of C4. The minor isomers displayed the following characteristic resonances in the ^1H NMR ($CDCl_3$) spectrum: (3*S*,4*S*) δ 3.33 (dd, J = 1.4 and 4.7 Hz, H3), 6.20 (d, J = 1.4 Hz, H4); (3*R*,4*S*) δ 3.45 (dd, J = 4.5 and 8.1 Hz, H3), 6.32 (d, J = 4.5 Hz, H4).

(3R,4R) - 4 - *Acetoxy* - 3 - [(R) - 1 - (t - *butyldimethylsilyloxy*)*ethyl*] - 2 - *azetidinone* (**28**). A soln of 6.47 g (16.2 mmol) crude **27** in 323 ml acetone was added to a soln of 0.128 g (0.81 mmol) $KMnO_4$ and 19.05 g (89.05 mmol) sodium periodate in 162 ml water and 162 ml 0.1N pH 7 phosphate buffer. The resulting mixture was stirred overnight at room temp., then filtered and the filtrate concentrated under vacuum to one-half of its original volume. The residue was saturated with NaCl and extracted with several portions of EtOAc. The extracts were washed with sat. NaCl aq, dried with $MgSO_4$, filtered and evaporated under vacuum to provide 3.60 g (77%) of a somewhat tacky, amber colored solid.

The crude product was rapidly chromatographed on 50 g (3 × 14 cm column) of silica gel using 20% EtOAc in hexane as the eluting solvent. The product containing fractions (by TLC) gave 3.17 g of a white solid which was recrystallized from hexane to give 2.29 g (49%) of **28** as fluffy white needles: m.p. 107–108°; $[\alpha]_D$ + 50.0 (*c* 0.41, $CHCl_3$); IR (CH_2Cl_2) 3405, 1786, 1745 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.06 (s, $SiCH_3$), 0.08 (s, $SiCH_3$), 0.87 (s, Si-*t*-C_4H_9), 1.26 (d, J = 6.3 Hz, CH_3CH), 2.11 (s, CH_3CO_2), 3.19 (dd, J = 1.3 and 3.4 Hz, H3), 4.22 (dq, J = 3.4 and 6.3 Hz, CH_3CH), 5.84 (d, J = 1.3 Hz, H4), 6.52 (br s, NH); MS, *m/e* 230 (M–C_4H_9); Anal. ($C_{13}H_{25}NO_4Si$) C, H, N.

General procedures for the deblocking of diprotected penems **20** *and* **21**

Preparation of chiral potassium (5R,6S) - 2 - *cyanomethylthio* - 6 - [(R) - 1 - *hydroxyethyl*]*penem* - 3 - *carboxylate*. To a stirred soln of 297 mg (0.68 mmol) chiral **20** (R = CH_2CN) in 6 ml of THF at room temp. was added sequentially 386 μl (6.75 mmol) glacial AcOH and 2 ml (2 mmol) of a 1M solution of tetrabutylammonium fluoride in THF. The mixture was stirred at room temp. for 19.5 hr, and then partitioned between EtOAc, ice-H_2O, and $NaHCO_3$ aq. Separation of the organic phase followed by the usual workup and purification by PLC (one development with 2:1 CH_2Cl_2–EtOAc) afforded 185 mg (84%) of allyl (5*R*,6*S*) - 2 - cyanomethylthio - 6 - [(R) - 1 - hydroxyethyl]penem - 3 - carboxylate: m.p. 151–154° (EtOAc–hexanes); $[\alpha]_D$ + 89.9 (*c* 1.9, THF); IR (CH_2Cl_2) 3630, 1800, 1720 and 1690 cm^{-1}; UV (dioxane) λ_{max} 252.5, 338 nm; ^1H NMR ($CDCl_3$) δ 1.38 (d, J = 6.5 Hz, CH_3CH), 1.76 (d, J = 4.5 Hz, OH), 3.66 and 3.76 (2d, J = 18 Hz, SCH_2CN), 3.85 (dd, J = 1.5 and 7 Hz, H6), 4.3 (m, CH_3CH), 4.78 (m, CO_2CH_2), 5.3, 5.45 and 5.98 (3 m, $CH{=}CH_2$), 5.8 (d, J = 1.5 Hz, H5); MS, *m/e* 326 (M), 241.

To a stirred soln of 151 mg (0.46 mmol) of the above desilylated penem in 6 ml THF and 4 ml EtOAc at room temp. was added 12.1 mg (0.046 mmol) triphenylphosphine, 16 mg (0.014 mmol) tetrakistriphenylphosphinepalladium (0), and 1 ml (0.5 mmol) of a 0.5M soln of potassium 2-ethylhexanoate in EtOAc. The mixture was stirred at room temp. for 70 min then cooled in an ice-H_2O bath. The crude product was precipitated from the soln by addition of 20 ml Et_2O. The mixture was centrifuged and the supernatant decanted from the separated solid. The solid was washed similarly with EtOAc and then Et_2O and dried under vacuum. The tan powder was dissolved in 15 ml of H_2O and filtered through a H_2O-wet pad of celite which was thoroughly washed with H_2O. The filtrate was concentrated under vacuum and purified by RP-PLC to afford after extraction of the band with 4 : 1 acetonitrile–H_2O, washing with hexane, evaporation of the acetonitrile, and lyopilization, 112 mg (75%) of the title penem: $[\alpha]_D$ + 142 (*c* 0.4, H_2O); IR (Nujol) 3375 (br), 1780 (br), 1590 (br) cm^{-1}; UV (H_2O) λ_{max} 258, 321.5 nm; ^1H NMR (D_2O) δ 1.34 (d, J = 6.5 Hz, CH_3CH), 3.92 and 4.02 (2d, J = 17.5 Hz, SCH_2CN), 4.04 (br d, J = 6.5 Hz, H6), 4.3 (app. p, J = 6.5 Hz, CH_3CH), 5.82 (br s, H5).

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