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A Practical Conversion of an Azetidinone to Penem: Synthesis of Sch 34343

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Abstract: A synthesis of penems from azetidinone **1** is described in detail. This synthesis is used to prepare multikilo batches of (5R,6S)-2-[[-(carbamoyloxy)ethyl]thio]-6-[(R)-1-hydroxyethyl]penem-3-carboxylic acid **(10), (Sch 34343)**. It is practical as all chemical steps progress in high yields, and isolation of all unstable intermediates is avoided. The eight step conversion of (3S,4R)-3-[(R)-1-hydroxyethyl]-4-triphenylmethylthio-2-azetidinone **(1)** to penem **10** via intermediacy of stable, solid (3S,4R)-1-[[(allyloxy)carbonyl]methyl]-3[(R)-hydroxyethyl]-4-(argentiothio)-2-azetidinone **(4)**, and (3S,4R)-1-[[(allyloxy)carbonyl]methyl]-3-[(R)-1-hydroxyethyl]-4-ß-naphthoxy (thiocarbonyl)thio-2-azetidinone **(5)** is achieved in 43% yield.

In recent years, penems have become an important class of ß-lactam antibiotics. Several syntheses of penems have been reported in the literature.[1-5] A recent review that discusses the merits of these and other penem syntheses has been published.[6] Typically the preparation of penems involves the synthesis of an azetidinone followed by its conversion to the penem by thiazoline ring construction. Efficient large scale syntheses of appropriately substituted azetidinones from isocyanates,[7a] penicillin,[7b] and threonine[7c] (with some limitations[7d]) have become available. As a follow-up on the studies we have reported over the past few years in the form of communications or notes,[1,5,8a] we report here , in full details, a practical process for the conversion of azetidinones to penems. Since the penem syntheses are long, and since many intermediates are labile, a more efficient, practical synthesis of penems was required that avoided (i) all low yielding steps, and (ii) separate work-up/isolation/purification of each intermediate. Modifications/improvements of the above literature syntheses have led to a practical (five sequential reactions in high yields without the isolation of any intermediates) penem synthesis which is depicted below **(Scheme I)**. This process has been used to prepare multikilo batches of Sch 34343 **(10)** which were needed for extended biological and pharmaceutical studies.

The *N*-alkylation of azetidinone **1** with allyl iodoacetate **2** in acetonitrile using costly cesium carbonate has been described earlier.[1,5] Since potassium is closest to cesium in the alkali metal family, potassium carbonate was evaluated for the above reaction. Though hydrated potassium carbonate in acetonitrile led to a very slow *N*-alkylation reaction along with some decomposition, the use of anhydrous potassium carbonate gave partial conversion. This problem of incomplete reaction with anhydrous potassium carbonate

was overcome by using DMF as a cosolvent, which lead to complete reaction. In this reaction, the excess of iodoallyl acetate[9] was removed by treatment with triethylamine at the end of the reaction. This avoided the need for chromatographic purification of azetidinone **3**.

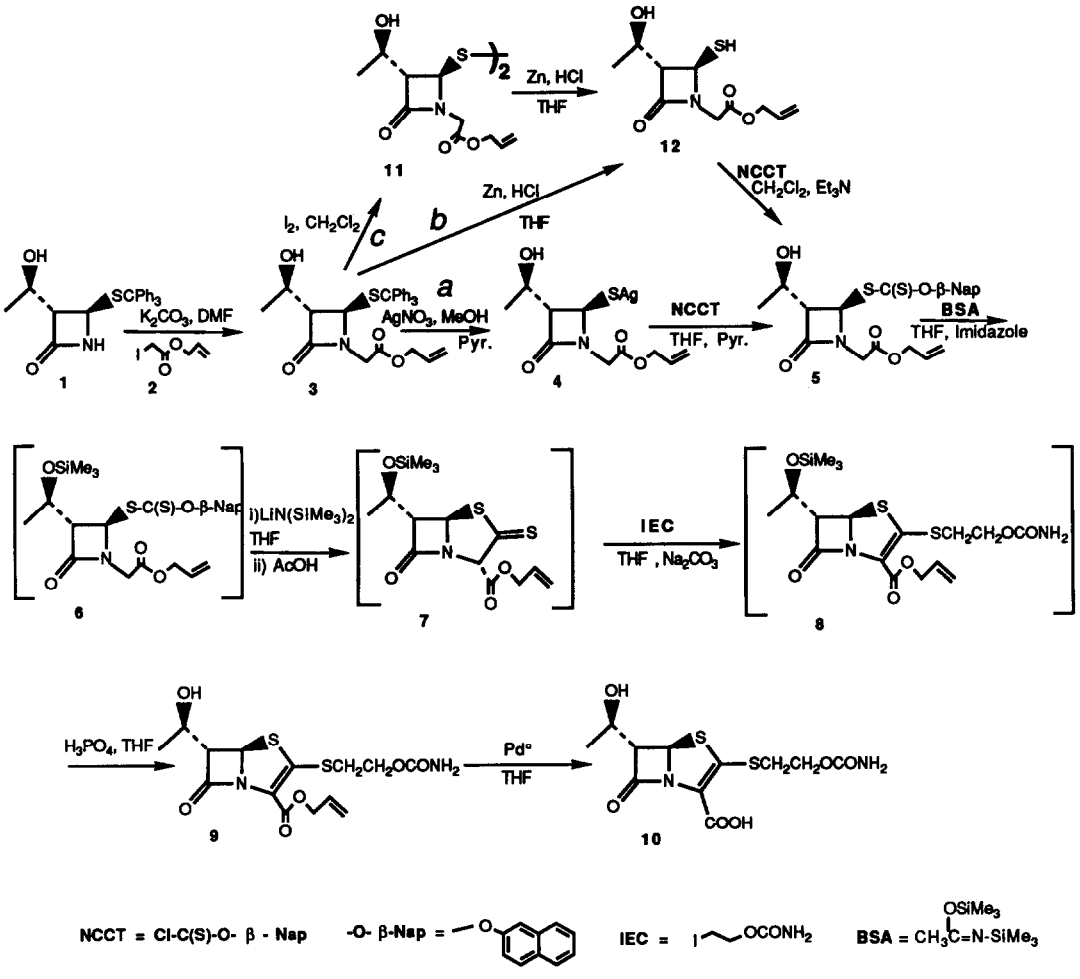
The deprotection of the trityl group with $AgNO_3$ has been reported in the literature.[10] The removal of the triphenylmethyl moiety from the unprotected secondary hydroxy azetidinone **3** was achieved in high yields using $AgNO_3$,[1] and the resultant product **4** precipitated out of the reaction mixture in essentially pure form.[11] This intermediate is stable and can be stored in the dark for prolonged periods. The protection of the secondary hydroxy group of the azetidinone at this stage was unnecessary as due to the very high affinity of silver for the halogens, the exclusive *S*-thionoacylation of **4** with previously reported,[5] easily purifiable *O*-2-naphthalenyl-carbonochloridothioate (NCCT), was achieved in excellent yields under neutral conditions without any *O*-thionoacylation of the secondary hydroxy group of **4**. It should be noted that with excess NCCT, and with warming of the reaction mixture, especially in the presence of a base, *O*-thionoacylation can result. This, in turn, would lead to olefin formation at the 3-position of the azetidinone via β-elimination. Azetidinone **5** is a stable, storable crystalline solid which has been used for the preparation of novel penems.[1] Since the conversion of **4** to **5** is very clean, purification of **5** is unnecessary. In fact, **5** prepared in THF was subjected to further reactions without isolation. Additionally, the protection of the hydroxy group of **5** with a tetrahydropyranyl moiety (DHP, PPTS) can be achieved in high yields to prepare the intermediate described previously[5] which can then be used to synthesize penems substituted with base sensitive functionalities.

Two additional avenues for the conversion of **3** to **5** were also explored. The first new route (path *b*) involved a direct reductive cleavage of the trityl moiety of **3**.[12] Here it was clear that with zinc, organic acids such as acetic acid or *p*-toluenesulfonic acid were less effective than HCl for the cleavage of **3** to **12**. In the cases of organic acids, changes in solvents, reaction temperatures, use of additional metal salts such as $CuCl_2$, or sonication did not improve the outcome significantly. The use of Zn/NH_4Cl with or without NH_4OAc also proved ineffective. For optimum yields, periodic alternative addition of Zn and HCl was superior to those cases where an excess of either or both was added in one portion. The conversion of thiol **12** to **5** required the addition of base. Pyridine, triethylamine, and N,N-dimethyl aniline gave a 30-60% yield for the two step conversion of **3** to **5** via **12**. Addition of catalysts such as 4-(dimethylamino)pyridine did not improve the results. It appeared that degradation of **12** competed with its conversion to **5**, limiting the yield of **5**.

It is known in the literature that I_2 can be used to cleave the trityl group of S-triphenylmethylcysteine.[13] In spite of the steric crowding around the trityl moiety of 3-substituted azetidinone **3**, treatment of **3** with I_2 resulted in detritylation affording the disulfide **11** (path *c*) in excellent yield. The reduction of this disulfide to thiol **12** was facile and near quantitative. Here, both Zn/HCl or Zn/acetic acid reduced the disulfide to thiol which was then converted to **5**. Both of these paths (*b* and *c*) proceed *via* thiol **12**, and lead to a lower overall yield for the conversion of **3** to **5** compared to path *a* where **4** is the intermediate. Thus, the latter path was preferred for the large scale preparation of **5**, and hence of Sch 34343, (**10**).

Next, a careful manipulation of reaction conditions lead to a one-pot, high-yielding conversion of the azetidinone **5** to the penem **9** avoiding the isolation of unstable intermediates. In view of its ease of removal and its compatibility with the rest of the chemistry, trimethylsilyl (TMS) was selected as a group of choice for protection of the hydroxy moiety of **5**. Of the mild, compatible silylating reagents evaluated, TMSCl proved to be nonpractical, and hexamethyldisilazane led to silylated product accompanied by decomposition products, whereas bis(trimethylsilyl)acetamide (BSA) led to only the silylated product (**6**), albeit very slowly (*ca.* 18 hr at room temperature for complete silylation). Addition of imidazole as a catalyst gave rapid and quantitative silylation with BSA. The byproduct, N-trimethylsilylacetamide, and the catalyst, imidazole, were tolerated in the cyclization step, and hence the isolation of

Scheme I



the labile *O*-silylated azetidinone **6** was unnecessary. Though the cyclization of the azetidinone **6** was possible either with NaH or lithium hexamethyldisilazane (LiHMDS), with NaH the reaction was slow, the yield was lower, and the use of DMF as a co-solvent with THF was necessary. With LiHMDS, a quantitative yield was realized within minutes at -40°. The need for isolation of this readily labile cyclized product was circumvented by neutralizing the excess base with the addition of a controlled amount of acetic acid. The thione (**7**) and β-naphthol, thus generated, remained in the organic phase during the aqueous wash[14] (only slight desilylation/decomposition could have taken place during this wash period as judged by the high overall yield for the four-step sequence). Since sulfur is a better nucleophile than oxygen, and since compound **7** is more acidic than ß-naphthol, just over one

molar equivalent of a weak base, Na_2CO_3, was used to convert **7** into its Na salt which then reacted with 2-iodoethylcarbamate in a slow but efficient manner. No *O*-alkylation of ß-naphthol was seen under these conditions avoiding the need for excess 2-iodoethylcarbamate. This eventually facilitated the isolation of stable allyl ester **9**. Desilylation of **8** proceeded very smoothly with citric acid or phosphoric acid in the presence of all the byproducts. Ester **9**, a crystalline solid,was readily separated from byproducts. This five-step sequence gave **9** in 62% yield, as a stable, crystalline solid. The deblocking of the allyl ester (**9-->10**) was carried out as described in the literature.[8] This progressed very smoothly resulting in a 95% yield of **10**. The problem of palladium contamination in the final product was alleviated by adding tri-*n*-butylphosphite[21] to the reaction mixture subsequent to the removal of the allyl group but prior to aqueous work-up.

In summary, a high yielding synthesis of penems from azetidinone **1** *via* stable intermediates **4** and **5** has been developed. This synthesis has been successfully used for the large scale preparation of the penem SCH 34343, **10**.

Experimental Section

The ^1H NMR spectra were recorded on a Varian FT-80 or Varian XL-200. Chemical shifts are expressed in parts per million downfield from Me_4Si, and coupling constants are recorded in Hertz. The infrared spectra were recorded on a Perkin-Elmer 1320 or Nicolet MX-IE FTIR spectrophotometer. The FAB mass spectra were recorded on a Finnigan MAT 312 instrument at 3kV and the electron impact mass spectra were recorded on a Varian MAT CH-5 spectrometer at 70 eV. Elemental microanalyses were conducted by Schering Analytical Services. Melting points were recorded on a Fisher-Johns hot-plate apparatus. Specific rotations were recorded on Jasco DIP-370 digital polarimeter. The term flash chromatography refers to the method described by Still.[15]

(3S,4R)-1-(Allyloxycarbonyl)methyl-3[(R)-1-hydroxyethyl]-4-triphenylmethyl-thio-2-azetidinone (3): To a stirred solution of of (3S,4R)-3-[(R)-1-hydroxyethyl]-4-triphenylmethylthio-2-azetidinone (**1**) (752.5 g, 1.93 mol) in DMF (1.75 L) under N_2 at rt, allyliodoacetate[9] (**2**) (317 mL, 567 g , 2.51 mol) was added followed by milled anhydrous K_2CO_3 (795 g, 5.75 mol). The reaction mixture was warmed to 50°-55° for 2.5 h, and then cooled to rt. Next Et_3N (120 mL) was added and the mixture was stirred for 0.5 h. The reaction mixture was then diluted with CH_2Cl_2 (3 L) and poured into water (5.25 L). The organic layer was separated, and the aqueous layer was reextracted with CH_2Cl_2 (750 mL). The combined organic extracts were washed with water (5.25 L, and 4.5 L), aqueous $NaHCO_3$ (4.5 L) and then filtered through celite. The celite cake was washed with CH_2Cl_2 (750 mL). The combined CH_2Cl_2 layer was concentrated *in vacuo* to give (HPLC corrected) 896 g (95.6% yield) of the product **3** as a gummy solid. This material was suitable for subsequent reactions.

An analytical sample was obtained by flash chromatography of a small amount of the crude product [silica gel, ether/petroleum ether (45:55)]. The white fluffy product thus obtained did not have a sharp melting point. NMR ($CDCl_3$): δ1.2 (d, 3H, J = 7 Hz, CH_3CH), 1.85 (d, 1H, J = 6 Hz, OH, exchanged with D_2O), 2.8 and 3.75 (d, 2H, J = 18 Hz, N-CH_2), 3.4 (d of d, 1H, J = 3 Hz and 6 Hz, H3), 3.95 (m, 1H, $CHCH_3$), 4.45 (m, 3H, H4 and $COOCH_2$), 5.25 (m, 2H, = CH_2), 5.75 (m, 1H, CH=), 7.05-7.45 (m, 15H, C_6H_5); $[\alpha]_D$ -123.4° (c:0.52, DMSO); IR (KBr): 3340, 1770, 1740 cm $^{-1}$; MS (CI, NH_3): m/e 488 $(M + H)^+$, 505 $(M + NH_4)^+$; Anal. calcd. for $C_{29}H_{29}N_1O_4S$: C, 71.47; H, 5.95; N, 2.87; S, 6.57. Found: C, 70.97; H, 6.16; N, 2.75; S, 6.43.

(3S,4R)-1-[[(Allyloxy)carbonyl]methyl]-3-[(R)-1-hydroxyethyl]-4-ß-naphthoxy-(thiocarbonyl)thio-2-azetidinone (5):

(Path *a*) *via* **(3S,4R)-1-[[(Allyloxy)carbonyl]methyl]-3[(R)-hydroxyethyl]-4-(argentiothio)-2-azetidinone** (4): A solution of $AgNO_3$ (1.08 kg, 6.36 mol) in CH_3OH (6 L) and pyridine (510 mL, 499 g, 6.31 mol), in the dark and under N_2, was slowly added to a solution of 3 (3.0 kg, 6.2 mol) in CH_3OH (6 L) at rt. The reaction mixture was stirred at rt for 2 h, and then filtered through filter press to separate 4. The precipitate was washed with H_2O (3X3 L) followed by acetone (2X3 L) and then dried. The mother liquor and acetone washes were concentrated *in vacuo* at rt to approximately 4.5 L volume. To this acetone (12 L) was added and then the mixture was stirred overnight in dark at rt. Additional 4 thus resulted was filtered and washed with H_20 (2X3 L) followed by acetone (2X3 L) and dried. This gave a total of 1.67 kg (76.6%) of 4 as a white solid.

The white solid thus obtained, 4, is of high purity, and had the following properties: mp 155-160° (decomp.). NMR (DMSO-d_6): δ 1.2 (d, 3H, J = 7Hz, CH_3CH), 2.95 (d of d, 1H, J = 2 and 7Hz, H3), 3.7-4.1 (m, 3H, CH_3CH and N-CH_2), 4.6 (d, 2H, J = 6Hz, $COOCH_2$), 5.0 (d, 1H, J = 1Hz, H4), 5.2 (m, 2H, $=CH_2$), 5.8 (m, 1H, CH=); IR (nujol) 3360, 1760, 1750 cm^{-1}. Anal. Calcd. for $C_{10}H_{14}NSAgO_4$: C, 34.12; H, 3.98; N, 3.98; S, 9.10; Ag, 30.64. Found: C, 33.95; H, 3.91; N, 3.88; S, 9.25; Ag, 30.05.

To a stirred mixture of 4 (740 g, 2.10 mol) in dry THF (4.4 L) and dry pyridine (17 mL, 16.6 g, 0.21 mol)) under N_2, *O*-2-naphthalenyl-carbonochloridothioate (NCCT), (488 g, 2.19 mol)) was added. The reaction mixture was heated to 40° for 0.5 h and then gently refluxed for 0.75 h. The reaction mixture was cooled to rt and then filtered through 160 g of Supercel. The Supercel cake was washed with THF (3X270 mL). The combined THF filtrate plus the washes weighed 4.8 kg. An HPLC analysis of this solution versus pure 5 (obtained as described below) indicated that this solution contained 850 g (93.5%) of 5. The THF solution of 5 obtained above was used for the subsequent reactions without purification.

An analytical sample of 5 was prepared by either chromatography (silica gel, methylene chloride/ethyl acetate, 4:1) or by crystallization from toluene-hexane to give a white solid, mp 76-78°. NMR ($CDCl_3$): δ1.42 (d, 3H, J = 7Hz, CH_3CH), 2.25 (br, 1H, OH, exchanged with D_2O), 3.4 (d of d, 1H, J = 3Hz and 6Hz, H3), 3.85 and 4.37 (2d, 2H, J = 18Hz, N-CH_2), 4.2-4.6 (m, 3H, $COOCH_2$ and CH_3CH), 5.17 (m, 2H, $=CH_2$), 5.75 (m, 1H, CH=), 5.9 (d, 1H, J = 2Hz, H4), 7.1 to 7.9 (m, 7H, ArH). IR (KBr): 3480, 1775, 1750 cm^{-1}; MS (FAB, thioglycerol) m/e 432 (m + 1). $[\alpha]_D$ + 115.5° (c: 0.48, DMSO); + 61.1° (c: 0.60, $CHCl_3$). Anal. Calcd. for $C_{21}H_{21}N_1S_2O_5$: C, 58.47; H, 4.87; N, 3.24; S, 14.87. Found: C, 58.25; H, 4.61; N, 3.10; S, 14.85.

(Path *b*): *via* **(3S,4R)-1-(Allyloxycarbonyl)methyl-3[(R)-1-hydroxyethyl]-4-sulfhydril-2-azetidinone** (12): To a solution of 3 (0.70 g, 1.44 mmol) in THF (10mL) at 0° under N_2, finely powdered zinc (0.38 g, 5.67 mmol) was added followed by a slow addition of methanolic HCl (9mL CH_3OH/1mL conc. HCl) until all the zinc dissolved (ca. 15mL). This procedure of Zn addition followed by a slow methanolic HCl addition was repeated one more time to complete the reaction as judged by tlc (silica gel, 20% EtOAc in CH_2Cl_2). To this cold reaction mixture cold (0°) CH_2Cl_2 (100mL) was added followed by ice (30 g) and degased sat. aqueous NaCl solution (5mL).The organic layer was separated and the aqueous layer was back-extracted with CH_2Cl_2. The combined organic layers were washed with degassed ice cold sat. NaCl solution until the aqueous layer was neutral. The organic layer was dried over anhyd. $MgSO_4$ and concentrated *in vacuo* to obtain 0.65 g (93%) of a white solid as a equimolar mixture of the title compound 12 and triphenylmethane, suitable for the next reaction as described below.

NMR ($CDCl_3$): δ 1.35(d,3H,J=7Hz,CH_3CH), 2.15(d,1H,J=10Hz,SH, exchanged with D_2O), 2.6(br,1H, OH, exchanged with D_2O), 3.17(d of d,1H,J=2Hz and 6Hz,H3), 3.77 and 4.2(2d,2H,J=18Hz,NCH_2), 4.3(m, 1H, CH_3CH), 4.6(d, 2H, J=7Hz, $COOCH_2$), 5.05(d of d,1H, J=2Hz and 10Hz,H4), 5.35(m, 2H, $=CH_2$), 5.95(m, 1H, CH=). No additional data were necessary on this compound as it was converted to known intermediate 5.

The mixture of **12** and triphenylmethane obtained above was taken up in CH_2Cl_2 (18mL) . The resultant solution was stirred and cooled to 0° and then NCCT (0.32 g, 1.44 mmol) followed by dry Et_3N (0.2 mL, 0.15 g, 1.44 mmol) was added. The reaction mixture was stirred for 50 min, diluted with CH_2Cl_2 (50mL), washed with distilled water (30mL) followed by 1:1 mixture of distilled water:saturated brine, dried over anhyd. $MgSO_4$ and concentrated *in vacuo* to give an off-white solid. To determine the yield[16] this solid was chromatographed (silica gel, CH_2Cl_2 followed by 5% EtOAc in CH_2Cl_2) to obtain 0.25 g (43.5%) of **5** as a white solid, identical to **5** obtained via path *a*.

(Path *c*): *via* **(3S,4R,5R,3'S,4'R,5'R)-4,4'-Dithiobis-1-(allyloxycarbonyl)methyl-3-[1-hydroxyethyl]-2-azetidinone (11):** To a stirred solution of **3** (0.44 g, 0.9 mmol) in CH_2Cl_2 (5mL) under N_2 at rt, I_2 (0.114 g, 0.045 mmol) was added. This mixture was stirred for 0.5h (complete reaction as indicated by tlc, silica gel/10% EtOAc in CH_2Cl_2) and then CH_3OH[17] (2 mL) was added. The resultant mixture was diluted with CH_2Cl_2 (30 mL), and washed with aqueous Na_2SO_3, dried over anhyd. Na_2SO_4, and concentrated *in vacuo* to give 0.37 g (78.7%) of mixture of title compound **11** plus triphenylmethane methylether as a yellow oil containing some solid. This mixture was used without purification for the next reaction as described below.

For the purpose of characterization, in a separate experiment, disulfide **11** was purified using silica gel flash column chromatography with CH_2Cl_2 changing to EtOAc as eluant.

NMR($CDCl_3$): δ1.38(d,6H,J=7.5Hz,CH_3CH), 2.84(br,2H,OH, exchanged with D_2O), 3.4,(d of d, 2H,J=3.5, and 7Hz,H3), 3.8 and 4.3(2d,4H,J=18Hz,NCH_2), 4.25(m,2H,CH_3CH), 4.65(d,4H,J=7.5Hz,$COOCH_2$), 5.05(d,2H,J=3Hz,H4), 5.3(m,4H,=$CH)_2$, 5.87(m, 2H,CH=). IR(Neat) 3460,2910,1755,1735 cm^{-1}. MS(FAB,thioglycerol) m/e 489(M^+), 490$(M+1)^+$.

To the above mixture of disulfide **11** and triphenylmethyl methylether in THF (5mL) under N_2, Zn (0.045 g, 0.68mM) was added. The reaction mixture was stirred vigorously and then conc. HCl in THF (1mL; conc. HCl:THF::1:9) was slowly added. The reaction mixture was stirred for 0.5h (complete reaction as indicated by tlc, silica gel/20% EtOAc in CH_2Cl_2), diluted with CH_2Cl_2 (30 mL), and washed with aliquots of distilled (degassed) water (3 to 4 X 10mL) until the aqueous layer was neutral. The organic layer was dried over anhyd. Na_2SO_4 and concentrated *in vacuo* to give 0.39 g (quantitative) of a white solid consisting of thiol **12** and triphenylmethyl methylether. This thiol was converted to **5** as described under path *b* using pyridine as base in place of triethylamine. The overall three-step yield from **3** to **5** via **11** was 27%.

Allyl (5R,6S)-2-(2-carbamoyloxyethylthio)-6-[(R)-1-hydroxethyl]penem-3-carboxylate (9): To a THF solution of **5** obtained as described above (i.e. 6.8 kg THF solution containing 1.2 kg, 2.78 mol of **5**), under N_2, bis(trimethylsilyl)acetamide (BSA) (824 mL, 678 g, 3.33 mol) was added followed by a catalytic amount of imidazole (4.8 g). The reaction mixture was stirred at rt for 15 min (complete silylation). Additional THF (13 L) was added to this and then it was cooled to -40°. To this cold solution 1.1 M lithium hexamethyldisilazide (LiHMDS) in hexane (8.7 L, 9.6 mol) was added over 1.5 h. The reaction mixture was stirred for ca. 15 min at -40°, and then glacial acetic acid (1.56 L) was added. At this stage cooling was discontinued, H_2O (12 L) was added (pH of the reaction mixture was 6.3 as judged by a pH meter) and then the organic layer was separated. To this was added iodoethylcarbamate (840 g, 3.90 mol) followed by Na_2CO_3 (270 g, 2.55 mol) dissolved in H_2O (7.2 L) to adjust the pH of the reaction between 7.5 and 8.0. The reaction mixture was stirred at rt for 20 h (complete S-alkylation). At this stage the organic layer was separated, diluted with H_2O (4.8 L) and then treated slowly with phosphoric acid (300 mL) until the pH was 1.9. The reaction mixture was stirred for an additional 2.5 h at rt (complete desilylation) and then adjusted to pH ≈7 by adding Na_2CO_3 (450 g). The organic layer was separated and concentrated to a volume of 4.8 L. To this hexanes (4.8 L) were added. The resultant slurry was stirred

for 0.5 h and filtered. The solid was washed with EtOAc (2 X 1.2 L) followed by CH_2Cl_2 (2 X 1.2 L) and then dried *in vacuo*. Additional product was obtained by further concentrating the mother liquor and the washes and then treating it with hexanes as described above. These two crops gave a total of 902 g of solid with HPLC purity of 84.5% (compared to pure **9**) representing a total of 762 g (74% [18] for four steps from **5**) of **9**. This crude **9** was purified by crystallization from CH_3CN (650 mL/ 100 g). The resultant crystals were washed thrice with EtOAc (16 mL/100 g) followed by twice with hexane (16 mL/100 g, to ensure a thorough removal of CH_3CN [19]) to obtain a 89% [20] recovery of **9** for the first crop of the crystallization step.

An analytical sample was prepared in a separate experiment by crystallization from CH_3CN, m.p. 152-152.5°. NMR (DMSO-d_6-$CDCl_3$) δ 1.17 (d, 3H, J = 7 Hz, CH_3CH), 3.15 (m, 2H, SCH_2), 3.65 (d of d, 1H, J = 1.5 Hz and 6Hz, H6), 3.8-4.3 (m, 3H, CH_3CH and CH_2OCO), 4.6 (m, 2H, $COOCH_2$), 5.1-5.4 (m, 2H, $=CH_2$), 5.65 (d, 1H, J = 1.5 Hz, H5), 5.75 (m, 1H, CH=), 6.45 (br., 2H, $OCONH_2$); IR (nujol): 3420, 3305, 1780, 1690, 1610 cm^{-1}; MS (FAB, thioglycerol) m/e 375 $(M + 1)^+$. $[\alpha]_D$ +188.9° (c: 0.46, DMSO). Anal. calcd. for $C_{14}N_{18}N_2O_6S_2$: C, 44.93; H, 4.81; N, 7.48; S, 17.13. Found: C, 44.88; H, 4.84; N, 7.44; S, 16.85.

(5R,6S)-2-[[-(Carbamoyloxy)ethyl]thio]-6-[(R)-1-hydroxyethyl]penem-3-carboxylic Acid (10): To a stirred suspension of **9** (364 g, 0.97 mol) in THF (3.64 L) under N_2 at rt, triphenylphosphine (36.4 g, 0.14 mol) and bis(triisopropyl-phosphite) palladium dichloride (12.0 g , 0.03 mol) were added. The reaction mixture was stirred for 15 min. and then a solution of sodium 2-ethylhexanoate (194.4 g, 1.18 mol) in THF was added to it. The reaction mixture was stirred for 0.5h (complete reaction as judged by tlc, silica gel/CH_2Cl_2:acetone:acetic acid::15:4:1) and tri-*n*-butyl phosphite (88 mL, 81 g, 0.32 mol) was added. After stirring for an additional 10 min, toluene (440 mL) followed by deionized H_2O (1.46 L) were added to the reaction mixture. To this conc. HCl (*ca.* 20 mL) was slowly added to adjust the pH to 7.7 (from pH 8.5). The aqueous layers were separated, and the organic layer was re-extracted with deionized H_2O (400 mL, and 110 mL). The combined aqueous layer was washed with CH_2Cl_2 (1.48 L, and 360 mL). Next the pH of the stirred aqueous phase was adjusted to ≈1.6 by a slow addition of conc. HCl (*ca.* 120 mL). The resultant slurry was stirred for 0.5 h and filtered. The product was washed thoroughly with water (4 X 146 mL) followed by EtOAc (3 X 146 mL) and dried *in vacuo* to obtain 310 g (95.6 %) of tan- colored **10**, m.p. 162.5-164°. This product was identical to the product obtained via the previously published procedure.[5] NMR (d_6-DMSO) δ1.15(d, 3H, J = 7Hz, CH_3CH), 3.13 (m, 2H, S-CH_2), 3.76(d of d, J = 1.5Hz, H6), 3.98(br, 1H, $CHCH_3$), 4.12(m, 2H, CH_2OCO), 5.68(d, 1H, J = 1.5Hz, H5), 6.55(br, 2H, NH_2); Anal. Calcd. for $C_{11}H_{14}O_6N_2S_2$: C,39.51; H4.22; N,8.38; S19.19. Found: C,39.33; H,4.21; N,8.43; S,19.26; IR(nujol) 3410, 3340, 1750, 1700, 1675 cm^{-1}; MS (FAB,thioglycerol) *m/e* 335(M=H); $[\alpha]_D^{26}$ =+208.7° (c 0.3,DMF)

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References and Notes

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11. The hydroxy-protected analogs of **4** reported previously [1-3] are not solids, and hence they do not crystallize out of the reaction mixture. In some cases their separation from triphenylmethyl byproducts was necessary.
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16. The chromatography was done to obtain pure **5**. Crude **5** along with triphenylmethane can be converted to **10**, with the crystallization of **9** during the process whereby most of the byproducts are removed.
17. A work-up without the use of CH_3OH results in the formation of triphenylmethanol in place of triphenylmethyl methylether. The subsequent reactions may be carried out without any complications to obtain a similar yield of **5**.
18. On a multikilo scale, a third crop representing an additional yield of 5.25% was obtained, raising the yield to 79% for this four-step sequence.
19. Contamination of **9** by CH_3CN interferes with Pd-catalyzed deblocking of the allyl ester. Hence it is important that almost all the CH_3CN be removed at this stage.
20. On a multikilo scale, an additional crop representing *ca.* 5% yield was obtained improving the crystallization step yield to 94%.
21. We thank Dr. Peter Kabasakalian for providing useful information towards the removal of Pd from the reaction mixture and/or the product.