HETEROARYLIUMTHIO SUBSTITUTED CARBAPENEM DERIVATIVES: SYNTHESIS AND *IN VITRO* ACTIVITY OF 1β-METHYL-2-(DIHYDROPYRROLOTRIAZOLIUMTHIO)CARBAPENEMS

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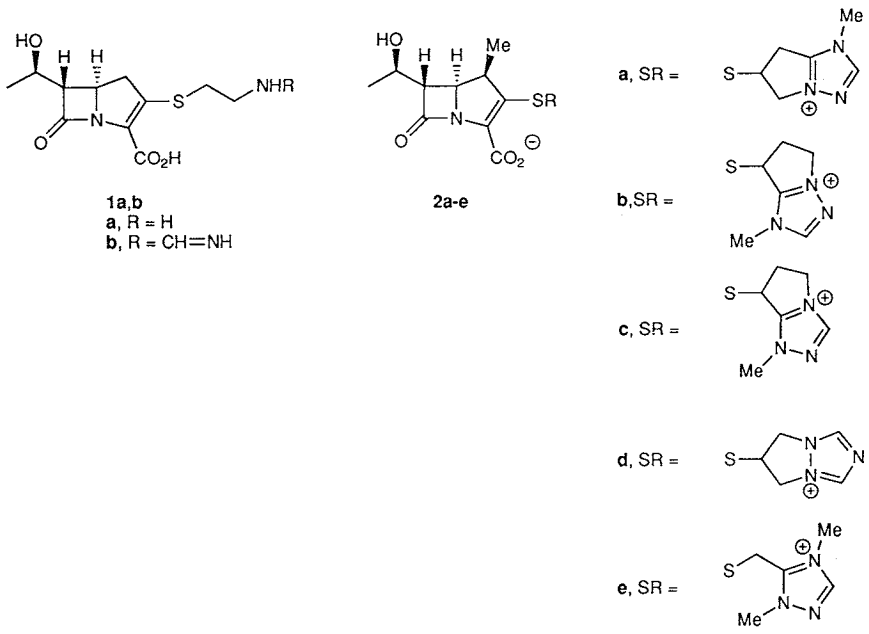
The syntheses of five thiols, including three dihydropyrrolotriazoliumthiol salts, 1,4-dimethyl-5-mercaptomethyl-1,2,4-triazolium trifluoromethanesulfonate, and 6-mercapto-6,7-dihydro-5*H*-pyrazolo[1,2-*a*][1,2,4]triazolium chloride; and the addition of these thiols to 4-nitrobenzyl (1*R*,5*R*,6*S*)-2-(diphenylphosphono)oxy-6-[1(*R*)-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylate and the subsequent hydrogenolysis of the addition products is described. The latter thiol provides a new route towards the preparation of L-627 (LJC 10,627). The compounds were evaluated *in vitro* against a panel of Gram-positive and Gram-negative bacteria and their antibacterial activities compared with imipenem. The compounds were measured for their hydrolytic stability to dehydropeptidase I (DHP-I) relative to imipenem. The five compounds generally had poorer Gram-positive and *Pseudomonas* activity than imipenem, although their Gram-negative activity was variably improved. The monocyclic triazolium analog was nearly comparable in overall activity to the four bicyclic heterarylium analogs evaluated, including L-627 (LJC 10,627). All compounds were more stable to DHP-I than imipenem, although minor differences existed among them.

The discovery of thienamycin[1,2], the first structurally elucidated carbapenem antibiotic, initiated the search for more stable analogs with increased potency. The search for more stable analogs focused upon improving chemical stability and also reducing susceptibility to mammalian dehydropeptidase, DHP-I, which rapidly metabolizes thienamycin rendering it inactive[3]. Increased potency against Gram-negative organisms, especially *Pseudomonas aeruginosa*, remained as an objective. Conversion of the primary amino group of thienamycin to the less nucleophilic *N*-formimidoyl derivative, imipenem[4], improved antibacterial potency and chemical stability, but did not reduce susceptibility to DHP-I. The discovery that 1β-methyl substituted carbapenems retain potency, are chemically stable, and significantly less susceptible to DHP-I was a significant advance in carbapenem chemistry[5]. The general observation that a basic or cationic substituent at the C-2 position is required for anti-pseudomonal activity has led to the preparation of a number of (aminoalkyl)thio and quaternary (heteroarylalkyl)thio deriviatives[6,7]. However, few examples exist of 1β-methyl-2-(heteroaryliumalkyl)thio carbapenems[8]. Recent papers reporting the chemistry[9], *in vitro* activity[10,11], and DHP-I susceptibility[12] of the dihydropyrazolotriazolium analog L-627 (LJC 10,627) highlight this effort. Herein we report the syntheses, antibacterial spectra, and DHP-I susceptibilities for an isomeric series of 1β-methyl-2-(dihydropyrrolotriazoliumthio)carbapenems (**2a**~**c**) and a 1β-methyl-2-(dimethyltriazoliummethylthio)carbapenem (**2e**). We also report a new preparation of L-627 (LJC 10,627) (**2d**) and compare its activity to the above mentioned carbapenems.

Chemistry

The synthetic strategy we envisioned had been developed in our laboratories and involved the addition of the appropriate thiol to a *p*-nitrobenzyl protected activated carbapenem in the presence of a hindered

Fig. 1.

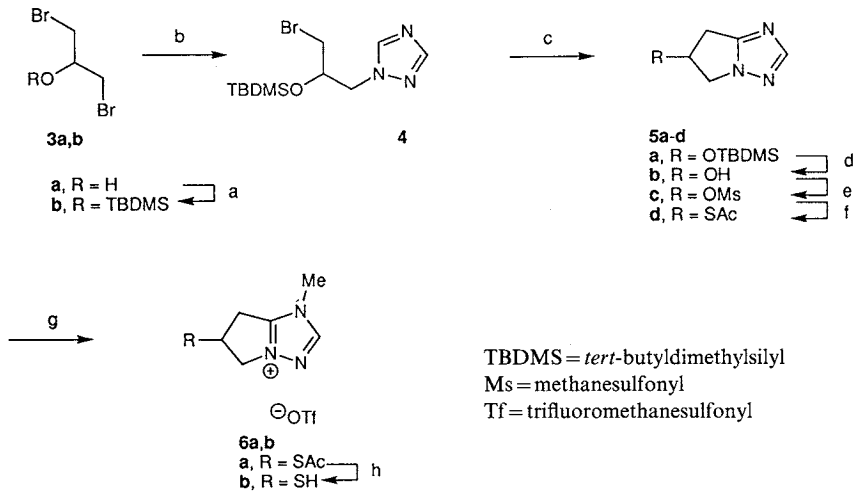


tertiary base[5,13]. Hydrogenolysis of the the resulting addition product provides the desired derivative. The syntheses of the requisite quaternary dihydropyrrolotriazolium thiols were envisioned as starting from 1,2,4-triazole. In the synthesis of the requisite thiol for the prepartion of L-627 (LJC 10,627), formation of the heteroarylium ring was planned as a final step, with the synthesis starting from a pyrrazolidine derivative.

The preparation of the requisite thiol for analog **2a** started from 1,3-dibromo-2-propanol (**3a**) which was O-silyated to give the silyl ether **3b.** Sodium triazole was allowed to react with **3b** to give the alkylated triazole **4**. Formation of the dihydropyrrolotriazole **5a** was effected by treating the bromotriazole **4** in THF and hexamethylphosphoramide with *n*-BuLi at −78°C and allowing the reaction to warm to room temperature. The silyl ether was removed using TFA in MeOH to provide **5b** as the TFA salt. The alcohol **5b** was mesylated to give **5c** which was allowed to react with potassium thiolacetate to give **5d**. The dihydropyrrolotriazole **5d** was alkylated with methyl triflate and the resulting thiolacetate salt **6a** was deacetylated with anhydrous HCl in MeOH to give the quaterinized thiol salt **6b**.

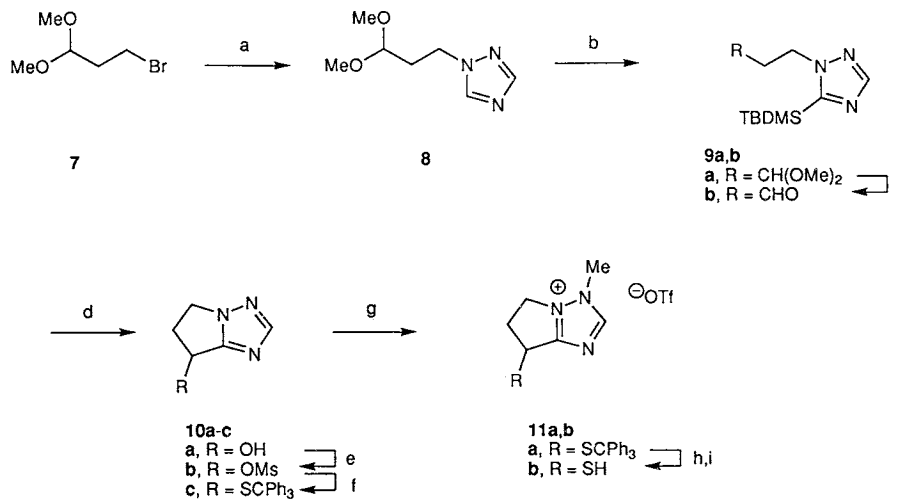
The thiol required for the preparation of **2b** was prepared beginning from the alkylation of sodium triazole with the 3-bromo-1,1-dimethoxypropane[14] (**7**) to provide **8**. The key step in the synthesis of the desired ring system was the intramolecular annelation of the triazolyl 5-position. By silylation at C-5 followed by a fluoride promoted intramolecular aldol reaction we hoped to achieve this goal[15]. The *N*-alkylated product **8** was lithiated using *n*-BuLi in THF at −78°C and silylated with *tert*-butyldimethylsilyl triflate to provide **9a**. Acetal cleavage using bromodimethylborane provided the aldehyde **9b** which was successfully desilylated with tetrabutylammonium fluoride to give the bicyclic intramolecular aldol product **10a**. The alcohol **10a** was converted to the mesylate **10b**, reacted with triphenylmethyl thiolate to give the tritylthio derivative **10c**, and quaternized with methyl triflate to give **11a**. The triflate salt **11a** was deblocked using silver nitrate in MeOH and the resulting silver thiolate treated with hydrogen sulfide to give the

Scheme 1.



(a) TBDMSCl, imidazole, CH_2Cl_2, Room temperature (RT); (b) sodium triazole, DMF, 70° to 100°C; (c) *n*-BuLi, hexamethylphosphoramide, THF, −78°C to RT; (d) TFA, RT; (e) MsCl, Et_3N, THF, 0°C; (f) KSAc, DMF, 50°C; (g) MeOTf, CH_2Cl_2, 0°C to RT; (h) HCl, MeOH, RT.

Scheme 2.

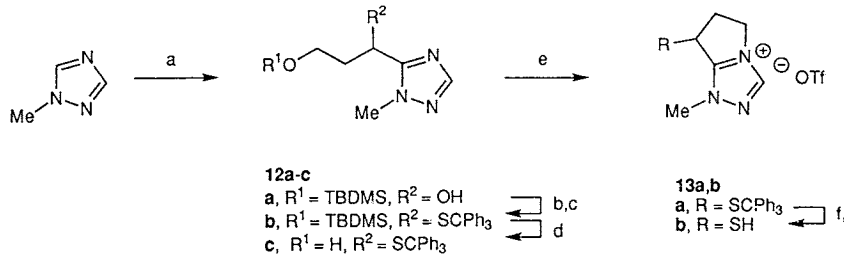


(a) Sodium triazole, MeOH, reflux; (b) *n*-BuLi, TBDMSOTf, THF, −78°C to RT; (c) Me_2BBr, CH_2Cl_2, −78°C; (d) *n*-Bu_4NF, THF, 0°C to RT; (e) MsCl, Et_3N, CH_2Cl_2, 0°C to RT; (f) Ph_3CLi, THF, 0°C to RT; (g) MeOTf, CH_2Cl_2, 0°C; (h) $AgNO_3$, MeOH; RT (i) H_2S, H_2O, RT.

thiol salt **11b**.

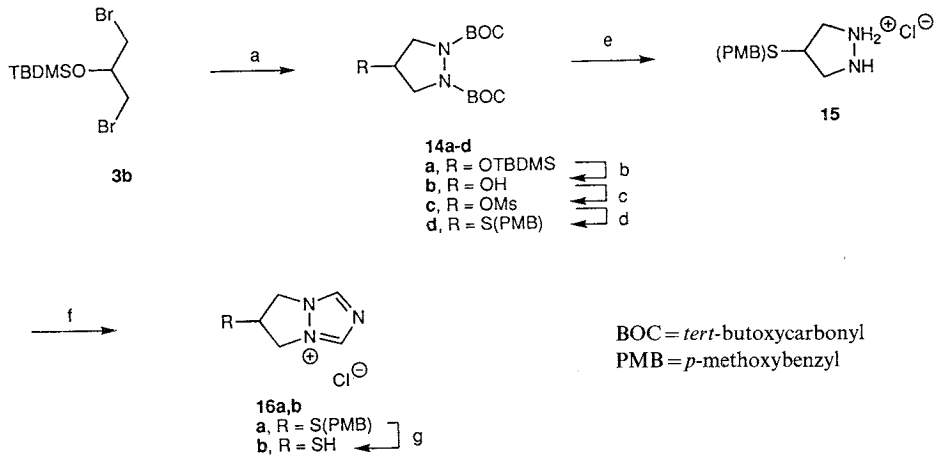
The requisite thiol for analog **2c** was prepared starting from the condensation of lithiated 1-methyl-1*H*-1,2,4-triazole with 3-(*tert*-butyldimethylsilyloxy)propanal[16] to give **12a**. The resulting alcohol was converted to the mesylate which was transformed into the tritylthio derivative **12b**. The silyl protection of **12b** was removed using tetrabutylammonium fluoride to provide the alcohol **12c**. Intramolecular cyclization was achieved by treating a solution of **12c** in dichloromethane containing 2,6-lutidine at 0°C

Scheme 3.



(a) *n*-BuLi, $TBDMSO(CH_2)_2CHO$, THF, −78°C to RT; (b) MsCl, Et_3N, CH_2Cl_2, 0°C; (c) Ph_3CSLi, THF, 0°C to RT; (d) *n*-Bu_4NF, AcOH, THF, 0°C to RT; (e) Tf_2O, 2,6-lutidine, CH_2Cl_2, 0°C; (f) $AgNO_3$, MeOH, RT; (h) H_2S, H_2O, RT.

Scheme 4.

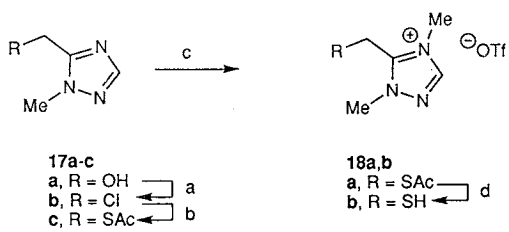


(a) (BOC)NHNH(BOC), NaH, DMF, RT; (b) *n*-Bu_4NF, AcOH, THF, 0° to 50°C; (c) MsCl, Et_3N, CH_2Cl_2, 0°C; (d) PMBSLi, THF, 0° to 60°C; (e) HCl, CH_2Cl_2, RT; (f) $MeOCH{=}NH_2Cl$, pH 9, water, 0° to 5°C; (g) TFA, TfOH, anisole, 0° to 5°C.

with triflic anhydride. The resulting bicyclic product **13a** was deblocked using silver nitrate/hydrogen sulfide as previously described to give the thiol salt **13b**.

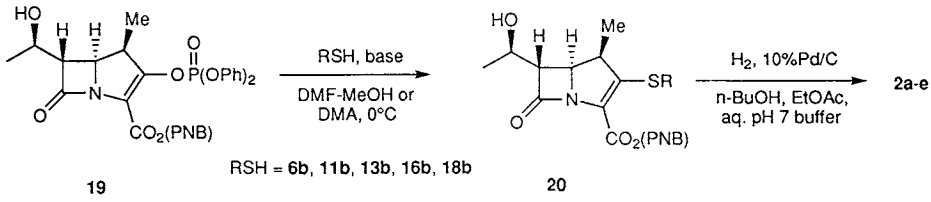
The preparation of the requisite thiol for analog **2d** started from the alkylation of 1,2-di(*tert*-butyloxycarbonyl)hydrazine[18] with 1,3-dibromo-2-(*tert*-butyldimethylsilyloxy)propane (**3b**) to provide pyrazolidine **14a**. The *tert*-butyldimethylsily protection was removed using tetrabutylammonium fluoride and the resulting pyrazolidine alcohol **14b** was mesylated to give **14c**. The mesylate **14c** was allowed to react with lithium *p*-methoxybenzyl thiolate to provide **14d**. The *tert*-butyloxycarbonyl protection of **14d** was removed using anhydrous hydrogen chloride

Scheme 5.



(a) $SOCl_2$, reflux; (b) KSAc, Et_3N, MeCN, RT; (c) MeOTf, CH_2Cl_2, 0°C; (d) TfOH, MeOH, RT.

Scheme 6.



to give the pyrazolidine hydrochloride salt **15**. The synthesis of the pyrazolo[1,2-*a*][1,2,4]triazolium ring system was accomplished following the observation that the reaction of a pyrazolidine substrate with ethyl formimidate hydrochloride under alkaline conditions affords a triazolium product[9]. Thus, the salt **15** was dissloved in water, basified, and treated with methyl formimidate hydrochloride while maintaining a pH of ~9. The product **16a** was isolated by chromatography on SP-207 resin. The *p*-methoxybenzyl group of **16a** was removed under acidic conditions to give the desired dihydropyrazolotriazolium thiol **16b**.

The requisite thiol for analog **2e** was prepared starting with the chlorination of 5-hydroxymethyl-1-methyl-1*H*-1,2,4-triazole[18] (**17a**) with thionyl chloride to give **17b**. The chloromethyl derivative **17b** reacted with potassium thiolacetate to give the thiolacetate **17c** which was quaternized with methyl trifluoromethanesulfonate to give **18a**. Deacetylation using trifluoromethanesulfonic acid in methanol provided the required thiol **18b**.

The thiols **6b**, **11b**, **13b**, **16b**, and **18b** were added to the carbapenem enol phosphate **19** in dimethylacetamide (DMF - MeOH in the case of **6b**) in the presence of a hindered base (diisopropylethylamine or triethylamine) to give the respective addition-elimination products **20**. Without isolation the products were hydrogenolyzed and the crude reduction products purified by ion exchange chromatography to provide the carbapenems **2a**~**e** as their internal zwitterions. Carbapenem derivatives **2a**~**c** were identified by ^{1}H NMR as diastereomeric mixtures and all, interestingly, had similar diastereomer ratios of ~3:2. No attempt was made to separate the diastereomeric products since the *in vitro* antibacterial activities of the mixture were unexciting (*vide supra*).

Biology

The *in vitro* activities of **2a**~**e** were determined by disc diffusiion assay[19] against a panel of Gram-positive and Gram-negative organisms using imipenem as an internal standard. Table 1 lists the antibacterial activities of **2a**~**e** and the DHP-I susceptibilities[20] of these compounds relative to imipenem (imipenem = 1.0) and also lists the estimated minimum inhibitory concentrations (MIC_{90}'s) derived using the Humphrey-Lightbrown equation[21]. Table 1 shows that the relative activities of **2a**~**e** against *Staphylococcus aureus* and *Enterococcus* were less than imipenem with generally comparable activity among the five derivatives. Against *Escherichia coli*, *Enterbacter*, and *Klebsiella* relative activity of the derivatives was greater than imipenem (with the exception of **2e** against *Klebsiella*). Analog **2b** stood out in its high activity against *Serratia* and analog **2a** did likewise against *Proteus*. Against *P. aeruginosa* all the analogs were less active than imipenem with the exception of **2c** which was comparable in activity to imipenem. Overall comparison of the bicyclic side chain derivatives **2a**~**d** showed no clear structure-activity relationship. The monocyclic quaternary derivative **2e** had activity comparable to the bicyclic derivatives **2a**~**d**, suggesting no clear advantage to quaternary bicyclic side chains. Furthermore, the comparable activities of **2d** and **2e** to that of the diastereomeric products **2a**~**c** suggests that resolution of the mixtures

Table 1. Relative antibacterial activity[a], estimated MIC_{90} (μg/ml)[b], and DHP-I susceptibility [c] of carbapenems **2a**~**e**.

Species	**2a**	**2b**	**2c**	**2d**	**2e**	**1b**[d]
Staphylococcus aureus (4)	0.4 (0.23)	0.4 (0.26)	0.4 (0.23)	0.3 (0.35)	0.3 (0.27)	0.09
Enterococcus (3)	0.8 (2.2)	0.6 (2.7)	0.5 (3.3)	0.7 (2.6)	0.5 (3.3)	1.8
Escherichia coli (5)	1.4 (0.18)	2.4 (0.10)	1.6 (0.15)	1.3 (0.19)	2.0 (0.13)	0.25
Enterobacter (6)	1.6 (0.75)	1.6 (0.75)	1.1 (1.1)	1.5 (0.79)	1.2 (1.0)	1.2
Klebsiella (5)	2.2 (0.22)	1.4 (0.37)	2.4 (0.21)	1.3 (0.37)	0.8 (0.62)	0.50
Serratia (2)	0.7 (2.8)	3.9 (0.51)	0.8 (2.5)	0.9 (2.1)	0.9 (2.1)	2.0
Proteus (5)	2.3 (1.7)	0.9 (4.7)	0.6 (7.1)	1.6 (2.5)	0.4 (9.2)	4.0
P. aeruginosa (4)	0.2 (22)	0.5 (7.7)	0.9 (4.4)	0.6 (6.9)	0.7 (6.1)	4.0
DHP-I	0.000	0.014	0.001	0.008	0.011	

[a] Agar Disc diffusion assay, see ref 19. Activities are reported as computed MIC indices relative to imipenem = 1.0 (*e.g.* 2.0 means twice as active). Species indices are the geometric means of the MIC's for the number of strains indicated in parentheses.

[b] Values in parentheses, see ref 21. MIC_{90} values for a compound are estimated by dividing the established MIC_{90} values for imipenem for the indicated species, by the relative index activities. The absolute MIC_{90} values for imipenem (**1b**) were determined by standard microtube dilution methods.

[c] DHP-I results are presented as multiples of swine kidney enzyme activity[20] times the activity with imipenem as substrate, which is given a value of 1.0. Imipenem has a DHP-I susceptibility = 0.9 × thienamycin.

[d] Absolute MIC_{90} values (μg/ml).

int their individual isomers would not lead to significant improvements in activity. L-627 (LJC 10,627) (**2d**) was never the analog of greatest relative activity against any of the eight species tested.

The literature (see footnotes 10 and 11 and references therein) reports the *in vitro* activity of L-627 (LJC10,627) (**2d**) to be generally twice that of imipenem against *P. aeruginosa*, while our assay shows L-627 (LJC 10,627) to be less active than imipenem. This discrepency is likely due to the limited number of *P. aeruginosa* strains (4) employed in our assay as compared to the indices derived from large numbers of strains as reported in the literature. Against other Gram-negative organisms the relative activity of L-627 (LJC 10,627) as compared to imipenem was similar to literature values.

The relative DHP-I susceptibility of derivatives **2a**~**e** is shown in the last row of Table 1. Although L-627 (LJC 10,627) (**2d**) has a very low susceptibility towards DHP-I, **2c** has a lower value and the susceptibility of **2a** appears negligible.

In summary, the data presented in Table 1 show *in vitro* activities of several heteroarylium 1β-methyl-2-SR side-chain replacement analogs that rival the relative potency of **2d**. The data presented suggests that further research into heteroarylium side chain replacement analogs may be warranted. The low DHP-I susceptibility of **2d** is also shared among the other quaternary analogs presented herein.

Experimental

General

IR spectra were recorded on a Perkin-Elmer Model 1420 spectrophometer and the UV spectra on a Perkin-Elmer 552A UV/VIS spectrophotometer. ^1H NMR spectra were recorded with a Varian XL-300 instrument and chemical shifts are reported in δ values (ppm) relative to internal standard TMS for solvents $CDCl_3$, DMSO-d_6, and CD_3OD, and unreferenced in D_2O. MS were obtained on a MAT 730 instrument. FAB was performed with Zenon gas at 8 kv using a matrix of dithioerythritol. Elemental microanalyses were performed in-house. Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Chromatography on a Waters Prep 500 LC employed PrepPak-500/silica gel cartridge eluted at flows of 250 ml/minute. Column chromatography was carried out on Silica Gel 60

(63~200 μm, E. Merck #7734). Ion exchange chromatography was performed using Bio-Rad AG 50W-X4 resin, sodium form, 200~400 mesh. Preparative TLC (PTLC) was carried out on Analtech silica gel GF Uniplates, 500 or 1,000 μm thick.

In Vitro Antibacterial Assay

The *in vitro* antibacterial activities were determined by a disc diffusion assay employing the Kirby-Bauer method[19], modified only by the used of an agar thickness of 0.2 cm. Imipenem was used as the internal standard. For maximum reproducibility, the inner, completely clear region of the zones of inhibition were measured. The zone sizes were converted to minimum inhibitory conecntrations (MIC's) using the Humphrey-Lightbrown equation[21], which takes into account the molecular weight of the antibiotic tested, the depth of the agar, the disc content, and the critical time. The critical time is the earliest time at which the zone of inhibition is constant. The critical time varies from species to species because of different growth rates and is experimentally determined for each strain. A panel of 34 strains representing both Gram-positive and Gram-negative species was used. For each species, at least one strain of typical antibiotic sensititivy is represented, while the remaining strains are selected for their resistance to beta-lactam antibiotics currently in use. The geometric means of the inhibitory concentrations for the strains of each species relative to that of imipenem are reported.

1,3-Dibromo-2-(*tert*-butyldimethylsilyloxy)propane (**3b**)

tert-Butyldimethylsilyl chloride (15.51 g, 0.103 mol) was added to a solution on imidazole (13.74 g, 0.202 mol) in dichloromethane (100 ml). The mixture was stirred at room temperature under a nitrogen atmosphere for 7 minutes, then treated with 1,3-dibromo-2-propanol (10.00 ml, 0.098 mol). After stirring an additional 2.5 hours at room temperature, the mixture was water (100 ml), 1 N hydrochloric acid (100 ml), water (100 ml), saturated aqueous sodium bicarbonate (100 ml) and brine, dried over magnesium sulfate, filtered, and evaporated under vacuum to an oil (34.39 g).

The crude product was distilled under reduced pressure through a 15 cm, vacuum-jacketed, Vigreux column to afford a clear liquid (24.93 g) bp 82~88°C (1.0~1.5 torr). This material was redistilled to give **3b** (17.90 g, 55%) as a clear liquid boiling at 100~101°C (8.8 torr). IR (film) ν_{max} 2950, 2930, 2890, 2855, 1470, 1460, 1430, 1415, 1355, 1250, 1215, 1185, 1125, 1085, 1050, 900, 835, 800, 770, 670 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.10 (s, two $SiCH_3$), 0.89 (s, $SiC(CH_3)_3$), 3.47 (m, two CH_2Br), 3.98 (p, SiOCH).

Anal Calcd for $C_9H_{20}OBr_2Si$: C 32.55, H 6.07, Br 48.11.
Found: C 32.79, H 5.80, Br 49.01.

1-(3-Bromo-2-*tert*-butyldimethylsilyloxypropyl)-1*H*-1,2,4-triazole (**4**)

Sodium hydride (0.64 g of a 60% dispersion in mineral oil, 16 mmol) was washed *in situ* with pentane (2 × 5 ml) under a nitrogen atmosphere and suspended in DMF (40 ml). The suspension was treated with a solution of 1*H*-1,2,4-triazole (1.00 g, 15 mmol) in DMF (10 ml) and after 30 minutes at room temperature treated with 1,3-dibromo-2-(*tert*-butyldimethylsilyloxy)propane (**3b**) (3.7 ml, 15 mmol). The mixture was heated in an oil bath at 70°C for 20 minutes and 100°C for 2.0 hours. After cooling the reaction mixture was evaporated under vacuum to a paste, mixed with EtOAc (70 ml), washed with water (4 × 50 ml) and brine, dried over magnesium sulate, filtered and evaporated under vacuum to a dark red oil (5.00 g).

The crude product was purified by gel chromatography on a Waters Prep 500 eluting with 1:1 EtOAc - hexane at 250 ml/minute. The appropriate fractions were combined and evaporated under vacuum to give the desired product (1.75 g) as an oil. The oil was distilled by Kugelrohr to give **4** as a clear oil (1.06 g, 23%), bp 210°C (0.2 torr). ^1H NMR ($CDCl_3$) δ 0.03 (s, two $SiCH_3$), 0.82 (s, $SiC(CH_3)_3$), 3.26~3.35 (m, CH_2Br), 4.19~4.28 (m, NCH_2), 4.34~4.44 (m, SiOCH), 7.94 (s, heteroaryl-H), 8.07 (s, heteroaryl-H). FAB-MS, *m/z* 320, 322 (M+H).

6-*tert*-Butyldimethylsilyloxy-6,7-dihydro-5*H*-pyrrolo[1,2-*b*][1,2,4]triazole (**5a**)

A solution of 1-(3-bromo-2-*tert*-butyldimethylsilyloxypropyl)-1*H*-1,2,4-triazole (**4**) (2.92 g, 9.11 mmol) in THF (60 ml) under a nitrogen atmosphere was cooled in a dry ice acetone bath to −78°C and then cold solution treated with a solution of *n*-butyllithium in hexane (2.5 M, 4.37 ml, 10.9 mmol) followed by hexamethylphosphoramide (2.24 ml, 18.22 mmol). After 80 minutes the solution was removed from the

bath to stir at room temperature. After stirring 40 minutes at room temperature the reaction was treated with AcOH and concentrated under vacuum to an oil (2.18 g).

The crude product was purified by silica gel chromatography on a Waters Prep 500 eluting with 7:3 EtOAc-hexane. The appropriate fractions were combined and evaporated under vacuum to give **5a** as a solid (0.77 g, 30%). ^{1}H NMR ($CDCl_3$) δ 0.13 (s, $Si(CH_3)_2$), 0.90 (s, $SiC(CH_3)_3$), 2.85 (dd, J=2.7, 16.7 Hz, C*H*H-Ar), 3.23 (dd, J=7.1, 16.7 Hz, CH*H*-Ar), 3.98 (dd, J=3.6, 11.3 Hz, NC*H*H), 4.34 (dd, J=6.5, 11.3 Hz, NCH*H*), 5.13 (m, SiOCH), 7.92 (s, heteroaryl-H). FAB-MS, m/z 240 (M+H).

6-Hydroxy-6,7-dihydro-5*H*-pyrrolo[1,2-*b*][1,2,4]triazole, Trifluoroacetic Acid Salt (**5b**)

A solution of 6-*tert*-butyldimethylsilyloxy-6,7-dihydro-5*H*-pyrrolo[1,2-*b*][1,2,4]triazole (**5a**) (200 mg, 0.84 mmol) in MeOH (1.6 ml) was stirred under a nitrogen atmosphere at room temperature and treated with TFA (8.0 ml). After stirring 16 hours the solution was evaporated under vacuum to give **5b** as an oil. ^{1}H NMR ($CDCl_3$) δ 3.01 (dd, C*H*H-aryl), 3.31 (dd, CH*H*-aryl), 4.09 (dd, C*H*H-N), 4.34 (dd, CH*H*-N), 4.69 (br s, OH), 5.17 (m, HOC*H*), 7.97 (s, heteroaryl-H).

6-Methanesulfonyloxy-6,7-dihydro-5*H*-pyrrolo[1,2-*b*][1,2,4]triazole (**5c**)

An ice-cold solution of curde 6-hydroxy-6,7-dihydro-5*H*-pyrrolo[1,2-*b*][1,2,4]triazole TFA salt (**5b**) (0.21 mmol) in THF (1.0 ml) was treated with triethylamine (116 μl, 0.84 mmol) followed by methanesulfonyl chloride (32 μl, 0.41 mmol). The mixture was stirred at 0°C for 45 minutes and then evaporated under vacuum. The residue was partitioned between EtOAc (8 ml) and water (2 ml) which was then saturated with sodium bicarbonate. The organic phase was recovered and washed with brine, dried with magnesium sulfate, filtered, and evaporated under vacuum to give **5c** as an oil (30.4 mg, 72%). ^{1}H NMR ($CDCl_3$) δ 3.13 (s, CH_3), 3.25 (dd, J=2.4, 17.8 Hz, C*H*H-aryl), 3.47 (dd, J=7.0, 17.8 Hz, C*H*H-aryl), 4.42 (dd, J=2.4, 12.9 Hz, C*H*HN), 4.54 (dd, J=6.1, 12.9 Hz, C*H*HN), 5.90 (m, OCH), 7.97 (s, heteroaryl-H).

6-Acetylthio-6,7-dihydro-5*H*-pyrrolo[1,2-*b*][1,2,4]triazole (**5d**)

A solution of 6-methanesulfonyloxy-6,7-dihydro-5*H*-pyrrolo[1,2-*b*][1,2,4]triazole (**5c**) (30 mg, 0.15 mmol) and potassium thiolacetate (19 mg, 0.17 mmol) in DMF (1.0 ml) under a nitrogen atmosphere was heated in a oil bath at 50°C for 2.5 hours. The reaction was evaporated under vacuum and the residue mixed with EtOAc (10 ml), washed with water (2×4 ml) and brine, dried over magnesium sulfate, filtered and evaporated under vaccum to a film (17.3 mg).

The crude product was purified by PTLC eluting with absolute EtOAc to give **5d** as a film (12.1 mg, 45%). ^{1}H NMR ($CDCl_3$) δ 2.40 (s, CH_3), 2.89~2.97 (m, C*H*H-aryl), 3.43~3.52 (m, CH*H*-aryl), 4.02~4.08 (m, C*H*HN), 4.62~4.73 (m, CH*H*N, SCH), 7.94 (s, heteroaryl-H).

6-Acetylthio-1-methyl-6,7-dihydro-5*H*-pyrrolo[1,2-*b*][1,2,4]triazolium Trifluoromethanesulfonate (**6a**)

A solution of 6-acetylthio-6,7-dihydro-5*H*-pyrrolo[1,2-*b*][1,2,4]triazole (**5d**) (12 mg, 0.066 mmol) in dichloromethane (0.5 ml) under a nitrogen atmosphere at 0°C was treated with methyl trifluoromethanesulfonate (8.0 μl, 0.071 mmol). After 70 minutes the reaction mixture was warmed to room temperature and evaporated under vacuum to give **6a** as a white solid. ^{1}H NMR (DMSO-d_6) δ 2.30 (s, CH_3CS), 3.12~3.36 (m, C*H*H-Aryl), 3.68 (s, CH_3), 3.64~3.82 (m, CH*H*-Aryl), 4.14~4.28 (m, C*H*HN), 4.60~4.76 (m, CH*H*N, SCH), 8.93 (s, heteroaryl-H). FAB-MS, m/z 198 (M+H).

6-Mercapto-1-methyl-6,7-dihydro-5*H*-pyrrolo[1,2-*b*][1,2,4]triazolium Trifluoromethanesulfonate (**6b**)

A solution of 6-acetyltio-1-methyl-6,7-dihydro-5*H*-pyrrolo[1,2-*b*][1,2,4]triazolium trifluoromethanesulfonate (**6a**) (0.174 mmol) in MeOH (0.50 ml) under a nitrogen atmosphere at 0°C was treated with acetyl chloride (35 μl, 0.50 mmol). After acetyl chloride addition, the reaction was stirred at room temperature for 16 hours and evaporated under vacuum to dryness to give **6b**. ^{1}H NMR (DMSO-d_6) δ 3.24 (dd, J=5.6, 17.7 Hz, C*H*H-Aryl), 3.76~3.92 (m, CH*H*-Aryl), 3.82 (s, CH_3), 4.24 (dd, J=5.8, 11.4 Hz, C*H*HN), 4.35~4.43 (m, SCH), 4.82 (dd, J=8.0, 11.3 Hz, CH*H*N), 9.05 (s, heteroaryl-H).

(1*R*,5*S*,6*S*)-6-(1(*R*)-Hydroxyethyl)-2-((1-methyl-6,7-dihydro-5*H*-pyrrolo[1,2-*b*][1,2,4]triazolium-6(*R*,*S*)-yl)thio)-1-methylcarbapen-2-em-3-carboxylate (**2a**)

A solution of 4-nitrobenzyl (1*R*,5*R*,6*S*)-2-(diphenylphosphono)oxy-6-(1(*R*)-hydroxyethyl)-1-methylcarbapen-2-em-3-carboxylate (**19**) (103 mg, 0.174 mmol) and 6-mercapto-1-methyl-6,7-dihydro-5*H*-pyrrolo[1,2-*b*][1,2,4]triazolium trifluoromethanesulfonate (**6b**) (0.174 mmol) in *N*,*N*-dimethylacetamide (0.87 ml) was stirred at 0°C under a nitrogen atmosphere and treated with *N*,*N*-diisopropylethylamine (61 μl, 0.348 mmol).

After 28 minutes the reaction solution was diluted *n*-butanol (3.5 ml), EtOAc (1.7 ml), water (3.5 ml), and 0.5 M pH 7.0 *N*-methylmorpholine - HCl buffer (1.7 ml), treated with 10% palladium on carbon (35 mg), and hydrogenated at 3.0 kg/cm^2 for 90 minutes on a Parr shaker. The mixture was filtered (0.2 μm Gelman Acrodisc) and the aqueous phase was recovered, washed with EtOAc (2 × *ca.* 3 ml), concentrated under vacuum to approximately 4 ml, and charged onto a column (1.5 cm × 29 cm) of Dowex 50-X4 ion exchange resin. The columm was eluted with deionized water in the cold room (4°C). Product containing fractions, as determined by UV spectroscopy, were concentrated under vacuum to approximately 4 ml volume and lyophilized to afford compound **2a** as an amorphous, fluffy, white solid (31.2 mg). IR (Nujol) ν_{max} 3380 (br), 1750, 1598 cm^{-1}. UV (0.05 M pH 7.0 MOPS buffer) λ_{max} nm(ε) 298 (6,120). UV (buffer + NH_2OH) $\lambda_{max\ ext}$ nm (ε_{ext}) 298 (5,870). ^{1}H NMR (D_2O) δ 1.30 ~ 1.40 (m, C*H*CH_3, C*H*CH_3), 2.97 ~ 3.15 (m), 3.45 ~ 3.69 (m), 4.10 (s, CH_3), 4.18 (s, CH_3), 4.29 ~ 4.61 (m), 8.76 (s, heteroaryl-H), 8.79 (s, heteroaryl-H).

1-(3,3-Dimethoxypropyl)-1*H*-1,2,4-triazole (**8**)

A solution of 1*H*-1,2,4-triazole (4.85 g, 70.2 mmol) in MeOH (60 ml) was treated with a solution of sodium methoxide in MeOH (5.5 M, 12.8 ml, 70.2 mmol) followed by 3-bromo-1,1-dimethoxypropane (**7**) (10.0 ml, 73.7 mmol). After heating at reflux for 4 hours the solution was allowed to cool to room temperature and concentrated under vacuum to an oil. The oil was mixed with dichloromethane (75 ml), filtered and concentrated under vacuum to an oil (16.71 g). The oil was short path distilled bp 86 ~ 90°C (2.5 torr) to give **8** as an oil (8.16 g, 67.9%). FAB-MS, *m*/*z* 172 (M + H). ^{1}H NMR ($CDCl_3$) δ 2.19 (dt, J = 5.5, 6.9 Hz, CH_2), 3.33 (s, two OCH_3), 4.27 (t, J = 6.9 Hz, NCH_2), 4.31 (t, J = 5.5 Hz, CH), 7.95 (aryl-H), 8.08 (aryl-H).

1-(3,3-Dimethoxypropyl)-5-*tert*-butyldimethylsilyl-1*H*-1,2,4-triazole (**9a**)

A solution of 1-(3,3-dimethoxypropyl)-1*H*-1,2,4-triazole (**8**) (3.62 g, 21.1 mmol) in THF (100 ml) under a nitrogen atmosphere and cooled to −78°C in a dry ice acetone bath was treated with a solution of *n*-butyllithium in hexane (2.5 M, 8.80 ml, 2.20 mmol). After 90 minutes at −78°C, the suspension was treated with *tert*-butyldimethylsilyl trifluoromethanesulfonate (5.00 ml, 22.0 mmol) and allowed to warm to room temperature. After stirring 16 hours the reaction solution was concentrated under vacuum to an oil. The oil was dissolved in EtOAc (75 ml) washed with 0.5 M, pH 7 phosphate buffer (50 ml), water (25 ml) and brine (25 ml), dried over magnesium sulfate, filtered, and evaporated under vacuum to an clear oil (8.47 g).

The crude product was short path distilled bp 110 ~ 120°C (0.75 torr) to afford the **9** as a clear colorless oil (3.40 g, 56%). ^{1}H NMR ($CDCl_3$) δ 0.43 (s, $Si(CH_3)_2$), 0.96 (s, $SiC(CH_3)_3$), 2.18 ~ 2.55 (m, CH_2), 3.36 (s, two OCH_3), 4.26 ~ 4.31 (m, NCH_2), 4.44 (t, J = 5.4 Hz, CH), 8.02 (s, heteroaryl-H). FAB-MS, *m*/*z* 286 (M + H), 254.

1-(3-Oxypropyl)-5-*tert*-butyldimethylsilyl-1*H*-1,2,4-triazole (**9b**)

A solution of 1-(3,3-dimethoxypropyl)-5-*tert*-butyldimethylsilyl-1*H*-1,2,4-triazole (**9a**) (2.01 g, 7.02 mmol) in dichloromethane (70 ml) under a nitrogen atmosphere was cooled to −78°C in an acetone dry ice bath and treated with bromodimethylborane (2.0 ml, 20.5 mmol). After 60 minutes the reaction solution was added to a stirred mixture of THF and saturated aqueous sodium bicarbonate (50 ml, 1 : 1 mixture). The mixture was concentrated under vacuum (approximately 25 ml), mixed with EtOAc (75 ml), and the organic phase recovered. The organic phase was washed with 10% aqueous potassium dihydrogen phosphate (50 ml), 1.0 M pH 7 phosphate buffer (50 ml) and brine, dried over magnesium sulfate, filtered and evaporated under vacuum to an oil (1.54 g, 91.7%).

The crude product was purified by silica gel chromatography eluting with 1 : 1 hexane - EtOAc. The product containing fractions were evaporated under vacuum to give **9b** as a clear colorless oil (1.124 g,

66.9%). ^{1}H NMR ($CDCl_3$) δ 0.44 (s, $Si(CH_3)_2$), 0.97 (s, $SiC(CH_3)$, 3.14 (t, J=6.9 Hz, $OHCCH_2$), 4.53 (t, J=6.9 Hz, NCH_2), 8.00 (s, aryl-H), 9.86 (s, CHO).

7-Hydroxy-6,7-dihydro-5*H*-pyrrolo[1,2-*b*][1,2,4]triazole (**10a**)

A solution of 1-(3-oxypropyl)-5-*tert*-butyldimethylsilyl-1*H*-1,2,4-triazole (**9b**) (821 mg, 3.43 mmol) in THF (30 ml) was cooled under a nitrogen atmosphere in an ice bath and treated with a solution of tetrabutylammonium fluoride in THF (1.0 M, 3.43 ml, 3.43 mmol). After 20 minutes the solution was removed from the ice bath to stir at room temperature for 30 minutes.

The reaction solution was concentrated under vacuum to an oil which was purified by silica gel chromatography eluting with 10% ethanol in EtOAc to provide **10a** as an oil (135 mg). ^{1}H NMR ($CDCl_3$) δ 2.64~2.78 (m, C*H*HCH$_2$N), 3.04~3.20 (m, CH*H*CH$_2$N), 4.08~4.20 (m, NC*H*H), 4.22~4.42 (m, NCH*H*), 5.24~5.34 (dd, C*H*OH), 8.02 (s, heteroaryl-H).

7-Methanesulfonyloxy-6,7-dihydro-5*H*-pyrrolo[1,2-*b*][1,2,4]triazole (**10b**)

A solution of 7-hydroxy-6,7-dihydro-5*H*-pyrrolo[1,2-*b*][1,2,4]triazole (**10a**) (135 mg, 1.08 mmol) in anhydrous dichloromethane (5.0 ml) under a nitrogen atmosphere was cooled in an ice bath and treated with methanesulfonyl chloride (250 μl, 3.23 mmol) and triethylamine (451 μl, 3.23 mmol) added dropwise over 2 minutes. The mixture was stirred at 0~5°C for 40 minutes and removed from the ice bath to stir at room temperature. After 40 minutes the mixture was evaporated under vacuum to dryness. The residue was dissolved in EtOAc and washed with 0.5 M pH 7 phosphate buffer (5 ml), water (5 ml), 10% aqueous potassium dihydrogen phosphate solution (5 ml) and brine, dried over magnesium sulfate, filtered, and exaporated under vacuum to provide **10b** as a solid (97 mg).

The crude product was purified by chromatography on a PTLC plate developed with EtOAc to give **10b** (17 mg). ^{1}H NMR ($CDCl_3$) δ 2.92~3.10 (m, C*H*HCH$_2$N), 3.10~3.36 (m, CH*H*CH$_2$N), 3.21 (s, CH_3), 4.06~4.46 (m, NCH_2), 6.00 (dd, J=2.4, 7.6 Hz, C*H*OMs), 8.06 (s, heteroaryl-H).

7-Triphenylmethylthio-6,7-dihydro-5*H*-pyrrolo[1,2-*b*][1,2,4]triazole (**10c**)

A suspension of triphenylmethyl mercaptan (28 mg, 0.100 mmol) in THF (0.25 ml) under a nitrogen atmosphere was cooled in an ice bath and treated with a solution of *n*-butyllithium in hexane (2.5 M, 37 μl, 0.092 mmol). After 5 minutes the resulting mixture was transferred to a flask under nitrogen containing ice cold 7-methanesulfonyloxy-6,7-dihydro-5*H*-pyrrolo[1,2-*b*][1,2,4]triazole (**10b**) (17 mg, 0.084 mmol) using an additional amount of THF in the transfer (0.5 ml). After 30 minutes the reaction was removed from the ice bath to stir at room temperature. After 2 hours the reaction was diluted with EtOAc (10 ml) and washed with 0.5 M pH 7 phosphate buffer (5 ml), water (5 ml) and brine, dried over magnesium sulfate, filtered, and evaporated under vacuum to an oil.

The crude product was purified by chromatography on a PTLC plate developed with EtOAc to give **10c** as an oil (20 mg). ^{1}H NMR ($CDCl_3$) δ 1.97~2.07 (m, CH_2CH$_2$N), 3.39~4.14 (m, NCH_2, SCH), 7.15~7.6 (m, phenyl), 8.01 (s, aryl-H).

1-Methyl-7-triphenylmethylthio-6,7-dihydro-5*H*-pyrrolo[1,2-*b*][1,2,4]triazolium Trifluoromethanesulfonate (**11a**)

A solution of 7-triphenylmethylthio-6,7-dihydro-5*H*-pyrrolo[1,2-*b*][1,2,4]triazole (**10c**) (20 mg, 0.052 mmol) in dichloromethane (0.5 ml) under a nitrogen atmosphere and cooled to 0°C was treated with methyl trifluoromethanesulfonate (6.5 μl, 0.057 mmol). After 40 minutes the reaction solution was removed from the ice bath and evaporated under vacuum to give **11a** as a film. ^{1}H NMR ($CDCl_3$) δ 2.34~2.54 (m, C*H*HCH$_2$N), 2.74~2.98 (m, CH*H*CH$_2$N), 3.70 (s, CH_3), 4.10~4.36 (m, CH_2N), 4.68 (dd, SCH), 7.2~7.6 (m, phenyl), 8.46 (s, heteroary-H).

7-Mercapto-1-methyl-6,7-dihydro-5*H*-pyrrolo[1,2-*b*][1,2,4]triazolium Trifluoromethanesulfonate (**11b**)

A solution of 1-methyl-7-triphenylmethylthio-6,7-dihydro-5*H*-pyrrolo[1,2-*b*][1,2,4]triazolium trifluoromethanesulfonate (**11a**) (0.052 mmol) in dichloromethane (160 μl), MeOH (520 μl), and pyridine (6.4 ml), was treated with a solution of silver nitrate in MeOH (0.105 M, 590 μl, 0.062 mmol). After stirring

20 minutes at room temperature the mixture was cooled in an ice bath and after 30 minutes at 0°C the mixture was centrifuged. The supernatant was decanted and the silver salt washed with additional MeOH. The recovered solid was suspended in water, bubbled with hydrogen sulfide for 1 minute, stirred at room temperature, and filtered (0.2 μm Gelman Acrodisc). The filtrate was adjusted to pH 7 with saturated aqueous sodium bicarbonate solution and evaporated under vacuum to dryness to give **11b**. ^{1}H NMR (D_2O) δ 2.48~2.60 (m, C*H*HCH$_2$N), 3.30~3.48 (m, CH*H*CH$_2$N), 3.90 (s, CH_3), 4.26~5.1 (m, CH, CH_2N), 8.58 (s, heteroaryl-H).

(1*R*,5*S*,6*S*)-6-(1(*R*)-Hydroxyethyl)-2-((1-methyl-6,7-dihydro-5*H*-pyrrolo[1,2-*b*][1,2,4]triazolium-7(*R*,*S*)-yl)thio)-1-methylcarbapen-2-em-3-carboxylate (**2b**)

An ice cold solution of 4-nitrobenzyl (1*R*,5*R*,6*S*)-2-(diphenylphosphono)oxy-6-(1(*R*)-hydroxyethyl)-1-methylcarbapen-2-em-3-carboxylate (**19**) (30 mg, 0.052 mmol) and 7-mercapto-1-methyl-6,7-dihydro-5*H*-pyrrolo[1,2-*b*][1,2,4]triazolium trifluoromethanesulfonate (**11b**) (0.052 mmol) in *N*,*N*-dimethylacetamide (0.5 ml) was stirred under a nitrogen atmosphere and treated with *N*,*N*-diisopropylethylamine (0.010 ml, 0.060 mmol). After stirring 15 minutes at 0°C the reaction was diluted with *n*-butanol (1.0 ml), EtOAc (0.5 ml), water (1.0 ml) and 0.5 M pH 7.0 *N*-methylmorpholine HCl buffer (0.5 ml), and mixed with 20% palladium on carbon (10 mg). The mixture was hydrogenated at 3.2 kg/cm^2 for 70 minutes on a Parr Shaker. The mixture was filtered (0.2 μm Gelman Acrodisc) and the aqueous phase recovered and washed with EtOAc (2×4 ml), evaporated under vacuum to approximately 3 ml, and charged onto a column (1.5 cm×21 cm) of Dowex 50-X4 ion exchange resin. The column was eluted with deionized water in a cold room (4°C) and fractions containing desired product, as determine by UV spectroscopy, concentrated under vacuum to approximately 2 ml volume, and lyophilized to afford **2b** as an amorphous, fluffy, white solid (14.4 mg). UV (0.05 M pH 7.0 MOPS buffer) λ_{max} nm 295, UV (buffer+NH_2OH) $\lambda_{max\,ext}$ nm 298. ^{1}H NMR (D_2O) δ 1.05~1.20 (m, C*H*CH_3, C*H*CH_3), 2.75~2.90 (m), 3.22~3.48 (m), 3.74 (s, CH_3), 3.82 (s, CH_3), 4.07~4.45 (m), 8.57 (s, heteroaryl-H), 8.59 (s, heteroaryl-H).

5-3(*tert*-Butyldimethylsilyloxy-1-hydroxypropyl)-1-methyl-1*H*-1,2,4-triazole (**12a**)

A solution of 1-methyl-1*H*-1,2,4-triazole (581 mg, 6.99 mmol) in THF (4.2 ml) under a nitrogen atmosphere in a dry ice acetone bath at −78°C was treated with a solution of *n*-butyllithium in hexane (2.5 M, 2.8 ml, 7.00 mmol) and stirred 16 hours at −78°C. The yellow-white reaction mixture was then treated with 4-(*tert*-butyldimethylsilyloxy)butyraldehyde (1.43 ml, 7.00 mmol) and allowed to warm to room temperature. After 4 hours at room temperature the reaction was treated with AcOH (400 μl, 7.00 mmol) and concentrated under vacuum to a paste. The residue was dissolved in EtOAc (10 ml) and washed with 0.5 M pH 7 phosphate buffer (2×4 ml), water and brine, dried over magnesium sulfate, filtered and evaporated under vacuum to an oil (1.219 mg).

The crude product was purified on a Waters Prep 500 eluting with EtOAc. The appropriate fractions were combined and evaporated under vacuum to give **12a** as an oil (343 mg, 18%). ^{1}H NMR ($CDCl_3$) δ 0.06 (s, Si(CH_3)$_2$), 0.88 (s, SiC(CH_3)$_3$), 2.02~2.26 (m, CH_2), 3.81~3.89 (m, C*H*HOSi), 3.96 (s, CH_3), 3.96~4.03 (m, CH*H*OSi), 5.12 (dd, J=3.6, 8.5 Hz, OCH), 7.76 (s, heteroaryl-H).

5-(3-*tert*-Butyldimethylsilyloxy-1-triphenylmethylthio-1-propyl)-1-methyl-1*H*-1,2,4-triazole (**12b**)

A solution of 5-(3-*tert*-butyldimethylsilyloxy-1-hydroxypropyl)-1-methyl-1*H*-1,2,4-triazole (**12a**) (343 mg, 1.26 mmol) in dichloromethane (5.0 ml) under a nitrogen atmosphere cooled in an ice bath at 0°C was treated with methanesulfonyl chloride (196 μl, 2.53 mmol) followed by triethylamine (352 μl, 2.53 mmol). After 40 minutes the reaction was then diluted with EtOAc (5 ml) and washed with 0.5 M pH 7 phosphate buffer (5 ml), water (5 ml) and brine, dried over anhydrous magnesium sulfate, filtered, and evaporated under vacuum to provide the crude mesylate as an oil (414 mg).

A suspension of triphenylmethyl mercaptan (360 mg, 1.30 mmol) in THF (2.0 ml) under a nitrogen atmosphere was cooled in an ice bath to 0°C and treated with a solution of *n*-butyllithium in hexane (2.5 M, 475 μl, 1.18 mmol). After 5 minutes the resulting mixture was transferred to a solution of the crude mesylate (414 mg, 1.18 mmol) in THF (2.75 ml) under a nitrogen atmosphere. The reaction was allowed to warm to room temperature, stirred 16 hours and evaporated under vacuum to an oil. The oil was mixed with EtOAc (10 ml), washed with 0.5 M pH 7 phosphate buffer (5 ml), water (5 ml) and brine, dried, over

magnesium sulfate, filtered, and evaporated under vacuum to an oil (657 mg).

The crude product was purified by PTLC developing with 3:1 hexane-EtOAc. Compound **12b** was isolated as a foam (424 mg, 63%). ^{1}H NMR ($CDCl_3$) δ 0.03 (s, $Si(CH_3)_2$), 0.80 (s, $SiC(CH_3)_3$), 2.01~2.18 (m, CH_2), 2.92~3.00 (m, SiOC*H*H), 3.24 (s, NCH_3), 3.42~3.49 (m, SiOCH*H*), 3.75 (dd, J=5.2, 10.9 Hz, SCH), 7.2~7.4 (m, phenyl), 7.84 (s, heteroaryl-H).

5-(3-Hydroxyl-1-triphenylmethylthio-1-propyl)-1-methyl-1*H*-1,2,4-triazole (**12c**)

A solution of 5-(3-*tert*-butyldimethylsilyloxy-1-triphenylmethylthio-1-propyl)-1-methyl-1*H*-1,2,4-triazole (**12b**) (424 mg, 0.800 mmol) in THF (2.4 ml) under a nitrogen atmosphere and cooled in an ice bath at 0°C was treated with AcOH (180 μl, 3.20 mmol) followed by a solution of tetrabutylammonium fluoride in THF (1.0 M, 1.6 ml, 1.60 mmol). After 60 minutes the solution was removed from the ice bath to stir at room temperature. After 2 hours at room temperature additional tetrabutylammonium fluoride in THF (1.0 M, 1.60 ml, 1.60 mmol) was added. After 4 hours at room temperature the solution was warmed in an oil bath at 45°C. After 7 hours additional tetrabutylammonium fluoride in THF (1.0 M, 1.60 ml, 1.60 mmol) was added. After a total reaction time of 8 hours the reaction was evaporated under vacuum to an oil, mixed with EtOAc (10 ml), washed with 1.0 M pH 7.0 phosphate buffer (6 ml), water (5 ml), 10% aqueous potassium dihydrogen phosphate (5 ml) and brine, dried over magnesium sulfate, filtered, and evaporated under vacuum to give **12c** as a foam (341 mg, 100%). ^{1}H NMR ($CDCl_3$) δ 1.75~1.86 (m, C*H*H), 1.94~2.04 (m, CH*H*), 3.11~3.19 (m, OC*H*H), 3.35 (s, NCH_3), 3.32~3.43 (m, OCH*H*), 3.65 (dd, J=5.2, 9.3 Hz, SCH), 7.1~7.4 (m, phenyl), 7.78 (s, heteroaryl-H).

1-Methyl-7-triphenylmethylthio-6,7-dihydro-5*H*-pyrrolo[2,1-*c*][1,2,4]triazolium Trifluoromethanesulfonate (**13a**)

A solution of 5-(3-hydroxy-1-triphenylmethylthio-1-propyl)-1-methyl-1*H*-1,2,4-triazole (**12c**) (333 mg, 0.800 mmol) in dichloromethane (8.0 ml) under a nitrogen atmosphere was cooled in an ice bath to 0°C and treated with 2,6-lutidine (93 μl, 0.800 mmol) followed by trifluoromethanesulfonic anhydride (150 μl, 0.880 mmol). After 2 hours the reaction solution evaporated under vacuum to afford **13a** as an oil. FAB-MS, m/z 298 (M^+). ^{1}H NMR ($CDCl_3$) δ 2.4~2.6 (m, C*H*H), 2.6~3.0 (m, CH*H*), 3.75 (s, NCH_3), 4.10~4.30 (m, NCH_2), 4.53 (dd, J=6.0, 8.6 Hz, SCH), 7.15~7.6 (m, phenyl), 8.39 (s, heteroaryl-H).

7-Mercapto-1-methyl-6,7-dihydro-5*H*-pyrrolo[2,1-*c*][1,2,4]triazolium Trifluoromethanesulfonate (**13b**)

A solution of 1-methyl-7-triphenylmethylthio-6,7-dihydro-5*H*-pyrrolo[2,1-*c*][1,2,4]triazolium trifluoromethanesulfonate (**13a**) (0.16 mmol) in dichloromethane (265 μl) and MeOH (0.8 ml) was treated with a solution of silver nitrate in MeOH (0.105 M, 1.8 ml, 0.19 mmol). After 15 minutes the mixture cooled in ice bath and stirred for 20 minutes. The mixture was filtered and the filter cake washed with MeOH (3×2 ml) and vacuum dried to afford the silver salt as a flesh colored solid (53.6 mg, 82%).

A suspension of the solid in water (2 ml) was bubbled with hydrogen sulfide for 2 minutes, stirred at room temperature 10 minutes, filtered (0.2 μm Gelman Acrodisc) and the filtrate concentrated to 1 ml. The solution was adjusted to pH 7 using sodium bicarbonate and evaporated under vacuum to give **13b** (37 mg). ^{1}H NMR (D_2O) δ 2.44~2.56 (m, CH_2), 3.30~3.45 (m), 3.96 (s, NCH_3), 4.23~4.59 (m), 8.49 (s, heteroary-H).

(1*R*,5*S*,6*S*)-6-(1(*R*)-Hydroxyethyl)-2-((1-methyl-6,7-dihydro-5*H*-pyrrolo[2,1-*c*][1,2,4]triazolium-7(*R*,*S*)-yl)thio)-1-methylcarbapen-2-em-3-carboxylate (**2c**)

A solution of 4-nitrobenzyl (1*R*,5*R*,6*S*)-2-(diphenylphosphono)oxy-6-(1(*R*)-hydroxyethyl)-1-methylcarbapen-2-em-3-carboxylate (**19**) (78 mg, 0.13 mmol) and 7-mercapto-1-methyl-6,7-dihydro-5*H*-pyrrolo-[2,1-*c*][1,2,4]triazolium trifluoromethanesulfonate (**13b**) (37 mg, 0.12 mmol) in *N*,*N*-dimethylacetamide (0.50 ml) was stirred at 0°C under a nitrogen atmosphere and treated with *N*,*N*-diisopropylethylamine (25 μl, 0.14 mmol).

After stirring at 0°C for 20 minutes the reaction solution was diluted with *n*-butanol (2.6 ml), EtOAc (1.3 ml), water (2.6 ml) and 0.5 M pH 7.0 *N*-methyl morpholine-HCl buffer (1.3 ml), treated with 10% palladium on carbon (23 mg), and hydrogenated at 3.2 kg/cm^2 on a Parr shaker. After 75 minutes the mixture was filtered (0.2 μm Gelman Acrodisc) to remove catalyst. The aqueous phase was recovered, and washed

with EtOAc (2 × *ca.* 4 ml), concentrated under vacuum to approximately 4 ml, and chromatographed on a column (1.5 cm × 20 cm) of Dowex 50-X4 ion exchange resin. The column was eluted with deionized water in a cold room (4°C) and product containing fractions, as determined by UV spectroscopy, concentrated under vacuum to approximately 4 ml volume. The solution was lyophilized to afford **2c** as an amorphous, fluffy, white solid (8.9 mg). IR (Nujol) ν_{max} 3380 (br), 1750, 1598 cm^{-1}. UV (0.05 M pH 7.0 MOPS buffer) λ_{max} nm (ε) 298 (6,120). UV (buffer + NH_2OH) $\lambda_{max\,ext}$ nm (ε_{ext}) 298 (5,870). ^1H NMR (D_2O) δ 1.30~1.40 (m, $CHCH_3$, $CHCH_3$), 2.97~3.15 (m), 3.45~3.69 (m), 4.10 (s, CH_3), 4.18 (s, CH_3), 4.29~4.61 (m), 8.76 (s, heteroaryl-H), 8.79 (s, heteroaryl-H).

1,2-Di(*tert*-butyloxycarbonyl)hydrazine

An ice-cold solution of anhydrous hydrazine (2.5 ml, 78.9 mmol) in 2-propanol (40 ml) was treated with di-*tert*-butyl dicarbonate (22 g, 101 mmol). After 30 minutes, additional di-*tert*-butyl dicarbonate (22 g, 101 mmol) was added over 5 minutes and the mixture was stirred for 90 minutes. The mixture was decanted to remove a clear, colorless solution which was evaporated under vacuum to a white paste. The paste was dissolved in bezene (100 ml), diluted with petroleum ether (200 ml) and let stand to crystallize. The solid was collected, washed with petroleum ether, and vacuum dried to afford 1,2-di(*tert*-butyloxycarbonyl)hydrazine (8.26 g, 45%) as fine white needles. MP 121~122°C. IR (CH_2Cl_2) ν_{max} 3420, 3060, 2980, 1730, 1480, 1365, 1230, 1150 cm^{-1}.

Anal Calcd for $C_{10}H_{20}N_2O_4$: C 51.71, H 8.68, N 12.06.
Found: C 52.00, H 8.39, N 12.22.

4-(*tert*-Butyldimethylsilyloxy)-1,2-di(*tert*-butyloxycarbonyl)pyrazolidine (**14a**)

Sodium hydride (0.74 g of a 60% dispersion in mineral oil, 18 mmol) was added to a solution of 1,2-di(*tert*-butyloxycarbonyl)hydrazine (4.08 g, 17.8 mmol) in anhydrous DMF (88 ml) and the mixture was stirred at room temperature under a nitrogen atmosphere for 1.75 hours. 2-(*tert*-Butyldimethylsilyloxy)-1,3-dibromopropane (**3**) (5.83 g, 17.6 mmol) was added and the mixture was stirred an additional 1.75 hours at room temperature. A second equivalent of sodium hydride in mineral oil (0.74 g, 18 mmol) was added and the resulting mixture was heated in an oil bath at 90°C for 2 hours. A third portion of sodium hydride in mineral oil (0.21 g, 5.3 mmol) was added and the mixture was stirred overnight at room temperature. A final portion of sodium hydride in mineral oil (0.28 g, 7.0 mmol) was added and the mixture was heated in an oil bath at 90°C for 1 hour. After cooling, the reaction mixture was evaporated under vacuum to an oil that was mixed with MeOH (5 ml) to decompose excess sodium hydride and reconcentrated. The residue in EtOAc (125 ml) was washed with water (2 × 100 ml), diluted with ethyl ether (50 ml), washed with more water (2 × 100 ml) and brine, dried over magnesium sulfate, filtered and evaporated under vacuum to a red oil (7.99 g).

The crude product was purified by on a Waters Prep 500 LC eluting with 6:1 hexane-EtOAc. The appropriate fractions were combined and evaporated under vacuum to give the pyrazolidine **14a** (3.29 g, 46.5%) as an oil. The product was distilled under vacuum, bp 126°C (0.3 torr). IR (film) ν_{max} 2950 (br), 2860, 1715 (br), 1470, 1460, 1365 (br), 1250, 1135, 1095, 1075 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.03 (s, $SiCH_3$), 0.04 (s, $SiCH_3$), 0.84 (s, $SiC(CH_3)_3$), 1.45 (s, two $CO_2C(CH_3)_3$), 3.09 (br d, NCH), 3.23 (d, NCH), 3.80 (dd, NCH), 3.90 (br s, NCH), 4.47 (m, SiOCH).

Anal Calcd for $C_{19}H_{38}N_2O_5Si$: C 56.68, H 9.51, N 6.96.
Found: C 56.56, H 9.51, N 7.00.

1,2-Di(*tert*-butyloxycarbonyl)-4-hydroxypyrazolidine (**14b**)

A solution of 4-(*tert*-butyldimethylsilyloxy)-1,2-di(*tert*-butyloxycarbonyl)pyrazolidine (**14a**) (2.79 g, 6.92 mmol) in anhydrous THF was stirred under a nitrogen atmosphere and cooled in an ice bath. Glacial acetic acid (0.80 ml, 13.8 mmol) and tetrabutylammonium fluoride (7.2 ml of a 1 M solution in THF, 7.2 mmol) were added. The solution was stirred at 0~5°C for 1 hour and then at room temperature for 2 hours. Additional acetic acid (0.80 ml, 13.8 mmol) and tetrabutylammonium fluoride in THF (3.6 ml, 3.6 mmol) were added and the solution was heated in an oil bath at 50°C for 4 hours. After stirring an additional 3 days at room temperature, the solution was evaporated under vacuum to an oil. The residue was taken up in EtOAc (50 ml), washed with saturated aqueous sodium bicarbonate (50 ml), water (2 × 50 ml)

and brine, dried over magnesium sulfate, and filtered. Evaporation of the solution at reduced pressure gave **14b** as a viscous oil (1.94 g, 97%). IR (film) ν_{max} 3440 (br), 2980, 2930, 1705 (br), 1365, 1245, 1135, 960, 850, 730 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.44 (s, two $C(CH_3)_3$), 3.09 (dd, NCH), 3.33 (d, NCH), 3.80 (dd, NCH), 3.98 (d, NCH), 4.56 (m, OCH). MS *m/z* 288, 215, 188, 173, 159, 132, 87.

MS (High resolution) Calcd for $C_{13}H_{24}N_2O_5$: *m/z* 288.1685.
Found: 288.1686.

1,2-Di(*tert*-butyloxycarbonyl)-4-(methanesulfonyloxy)pyrazolidine (**14c**)

An ice-cold solution of 1,2-di(*tert*-butyloxycarbonyl)-4-hydroxypyrazolidine (**14b**) (1.94 g, 6.73 mmol) in anhydrous dichloromethane (30 ml) and triethylamine (1.9 ml, 13.5 mmol) was treated with methanesulfonyl chloride (1.04 ml, 13.45 mmol) added dropwise over 2 minutes. The mixture was stirred at 0~5°C for 90 minutes then evaporated under vacuum. The residue was partitioned between water (50 ml) and EtOAc (50 ml). The organic phase was washed with saturated aqueous sodium bicarbonate (50 ml), water (50 ml) and brine, dried with magnesium sulfate, filtered, and evaporated under vacuum to provide **14c** (2.31 g, 93.5%) as an oil. R (CH_2Cl_2) ν_{max} 1735 (sh), 1720, 1695, 1365, 1170, 1135, 960, 905 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.45 (s, $C(CH_3)_3$), 1.47 (s, $C(CH_3)_3$), 3.02 (s, SO_2CH_3), 3.23 (dd, NCH), 3.60 (d, NCH), 4.04 (dd, NCH), 4.38 (d, NCH), 5.36 (m, SO_2OCH).

1,2-Di(*tert*-butyloxycarbonyl)-4-(*p*-methoxybenzylthio)pyrazolidine (**14d**)

A solution of 4-methoxy-α-toluenethiol (0.433 ml, 3.1 mmol) in anhydrous THF (6 ml) was cooled in an ice-bath and stirred under a nitrogen atmosphere while *n*-butyllithium in hexane (2.5 M, 1.1 ml, 2.73 mmol) was added dropwise over 2 minutes. The resulting solution was stirred at 0~5°C for 15 minutes, then added *via* cannula to an ice-cold, stirring solution of 1,2-di(*tert*-butyloxycarbonyl)-4-(methanesulfonyloxy)-pyrazolidine (**14c**) (0.91 g, 2.48 mmol) in anhydrous THF (6 ml). Additional THF (2 ml) was used to completely transfer the thiolate solution. The reaction mixture was room temperature for 3 days, then heated in an oil bath at 60°C for 2 hours. After cooling, the solution was evaporated under vacuum to an oil. The residue was dissolved in EtOAc (50 ml), washed with water (2 × 50 ml) and brine, dried over magnesium sulfate, and evaporated under vacuum to an oil (1.377 g).

The crude product was chromatographed on a Waters Prep 500 eluting with 5:1 hexane-EtOAc. The fractions eluting at 4.2~6.5 column volumes were concentrated under vacuum to provide **14d** (0.815 g, 77.3%) as an oil. IR (CH_2Cl_2) ν_{max} 1725, 1710, 1695, 1610, 1510, 1355, 1135, 905 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.43 (s, $C(CH_3)_3$), 1.46 (s, $C(CH_3)_3$, 3.05 (dd, NCH), 3.24 (m, SCH and NCH), 3.35 (dd, NCH), 3.67 (s, SCH), 3.78 (s, OCH_3), 3.99 (dd, NCH), 6.83 (m, two aryl-H), 7.20 (m, two aryl-H). FAB-MS *m/z* 425 (M+H), 369, 324, 313, 269, 121.

4-(*p*-Methoxybenzylthio)pyrazolidine Hydrochloride (**15**)

A solution of 1,2-di(*tert*-butyloxycarbonyl)-4-(*p*-methoxybenzylthio)pyrazolidine (**14d**) (693 mg, 1.63 mmol) in anhydrous dichloromethane (16 ml) was cooled in an ice bath under a nitrogen atmosphere. Anhydrous hydrogen chloride was bubbled into the solution for approximately one minute, then the flask was stoppered and the solution was stirred at 0~5°C for 30 minutes. The solution was evaporated under vacuum to a white solid which was washed with dichloromethane and vacuum dried to afford **15** (302 mg, 71.0%) as a white solid. MP 193~194°C. IR (Nujol) ν_{max} 1605, 1510, 1410, 1300, 1260, 1240, 1175, 1030 cm^{-1}. ^1H NMR (D_2O) δ 3.16 (dd, two NCH), 3.52 (dd, two NCH), 3.62 (m, SCH), 3.84 (s, OCH_3), 3.88 (s, SCH_2), 7.01 (m, two aryl H), 7.37 (m, two aryl H).

Anal Calcd for $C_{11}H_{17}N_2OSCl$: C 50.66, H 6.57, N 10.74.
Found: C 50.76, H 6.30, N 10.16.

6-(*p*-Methoxybenzylthio)-6,7-dihydro-5*H*-pyrazolo[1,2-*a*][1,2,4]triazolium Chloride (**16a**)

A solution of 4-(*p*-methoxybenzylthio)pyrazolidine hydrochloride (**15**) (320 mg, 1.23 mmol) in water (10 ml) and MeOH (5 ml) was cooled in an ice bath and the pH was brought to 9.0 by addition of 5 N sodium hydroxide. Solid methyl formimidate hydrochloride (2.05 g, 21.5 mmol) was added in one portion and the pH was readjusted to 9.0 by addition of 5 N sodium hydroxide. The resulting hazy solution was stirred at 0~5°C for 30 minutes, and then treated with a second portion of methyl formimidate hydrochloride

(2.05 g, 21.5 mmol) followed by addition of 5 N sodium hydroxide to adjust the pH to 9.0. The mixture was stirred an additional 30 minutes at 0~5°C, then acidified to pH 6 with 2 N hydrochloric acid and concentrated under vacuum to approximately one third the original volume. The aqueous solution was applied to a column of SP-207 resin (2.5 × 15 cm) which was eluted in a cold room (4°C), first with water (600 ml) and then with 50% aqueous MeOH to elute the desired product. The eluate was evaporated under vacuum to afford **16a** (205 mg, 56%) as a waxy solid. IR (film) ν_{max} 1610, 1510, 1300, 1245, 1175, 1025, 645 cm^{-1}. ^1H NMR (CD_3OD) δ 3.78 (s, OCH_3), 3.94 (s, SCH_2), 4.43 (m, SCH and two NCH), 4.84 (dd, two NCH), 6.91 (m, two aryl-H), 7.32 (m, two aryl-H), 8.98 (s, two heteroaryl-H). FAB-MS, *m/z* 262 (M−Cl), 121.

6-Mercapto-6,7-dihydro-5*H*-pyrazolo[1,2-*a*][1,2,4]triazolium Chloride (**16b**)

The 6-(*p*-methoxybenzylthio)-6,7-dihydro-5*H*-pyrazolo[1,2-*a*][1,2,4]triazolium chloride (**16a**) (200 mg, 0.672 mmol) was dissolved in TFA (2.59 ml, 33.6 mmol) under a nitrogen atmosphere. The solution was cooled in an ice bath and treated with anisole (0.365 ml, 3.36 mmol) followed by trifluoromethanesulfonic acid (0.30 ml, 3.36 mmol). The resulting solution was stirred at 0~5°C for one hour, and then evaporated under vacuum to a red oil. The oil was partitioned between EtOAc (7 ml) and water (8 ml), and the aqueous phase washed with additional EtOAc (2 × 7 ml) and briefly evaporated under vacuum to give a clear, colorless solution. The solution was applied to a column of SP-207 resin (2.6 cm × 11 cm) which was eluted in a cold room (4°C) with water (260 ml) and then with 50% aqueous MeOH. Fractions containing product were combined and evaporated under vacuum to afford the title compound (88 mg, 73.5%) as a clear oil. IR (film from MeOH) ν_{max} 3130, 1510, 1450, 1405, 1350, 1260, 1225, 1155, 1025, 975, 635 cm^{-1}. ^1H NMR (CD_3OD) δ 4.49 (dd, two NCH), 4.57 (p, SCH), 5.06 (dd, two NCH), 9.01 (s, two heteroaryl-H). FAB-MS, *m/z* 142 (M−Cl), 108.

(1*R*,5*S*,6*S*)-2-((6,7-Dihydro-5*H*-pyrazolo[1,2-*a*][1,2,4]triazolium-6-yl)thio)-6-(1(*R*)-hydroxyethyl)-1-methylcarbapen-2-em-3-carboxylate (**2d**)

An ice-cold solution of *p*-nitrobenzyl (1*R*,5*R*,6*S*)-2-(diphenylphosphono)oxy-6-(1(*R*)-hydroxyethyl)-1-methylcarbapen-2-em-3-carboxylate (**19**) (117 mg, 0.197 mmol) in DMF (0.80 ml) was stirred under a nitrogen atmosphere and treated with a solution of 6-mercapto-6,7-dihydro-5*H*-pyrazolo[1,2-*a*][1,2,4]-triazolium chloride (**16b**) (35 mg, 0.197 mmol) in MeOH (0.25 ml) followed by *N*,*N*-diisopropylethylamine (0.072 ml, 0.414 mmol). The resulting solution was stirred at 0~5°C for 10 minutes and then treated with additional *N*,*N*-diisopropylethylamine (0.018 ml, 0.10 mmol). After stirring an additional 15 minutes, the reaction mixture was evaporated under vacuum to a viscous gum containing the desired thiol addition product, *p*-nitrobenzyl (1*R*,5*S*,6*S*)-2-((6,7-dihydro-5*H*-pyrazolo[1,2-*a*][1,2,4]triazolium-6-yl)thio)-6-(1(*R*)-hydroxyethyl)-1-methylcarbapen-2-em-3-carboxylate.

A solution of the gum in *n*-butanol (4.0 ml) and EtOAc (2.0 ml) was diluted with water (4.0 ml) and 0.1 M pH 7.0 potassium phosphate buffer (2.0 ml), treated with 20% palladium hydroxide on carbon (35 mg), and hydrogenated at 3.2 kg/cm^2 for 2 hours on a Parr shaker. The mixture was filtered (0.2 μm Gelman Acrodisc) and the aqueous portion was separated, washed with EtOAc (2 × 5 ml), evaporated under vacuum to approximately 5 ml volume, and charged onto a column (1.4 cm × 24 cm) of Dowex 50-X4 ion exchange resin. The column was eluted with deionized water in a cold room (4°C). Product fractions, as determined by UV spectroscopy, were combined, concentrated under vacuum to approximately 5 ml volume, and lyophilized to afford **2d** as an amorphous, fluffy, white solid (17.1 mg). IR (Nujol) ν_{max} 3360 (br), 1750, 1595 cm^{-1}. UV (0.05 M pH 7.0 MOPS buffer) λ_{max} nm (ε) 293 (8,200). UV (buffer + NH_2OH) $\lambda_{max\,ext}$ nm (ε_{ext}) 293 (8,000). ^1H NMR (D_2O) δ 1.26 (d, 1-β-CH_3), 1.30 (d, $CHCH_3$), 3.41 (dq, H1), 3.54 (dd, H6), 4.27 (p, CH_3CHOH), 4.31 (dd, H5), 4.75 (m, two NCH), 4.99 (m, SCH), 5.08 (m, two NCH), 9.02 (s, heteroaryl-H), 9.04 (s, heteroaryl-H). FAB-MS, *m/z* 373 (M+Na), 351 (M+H).

5-Chloromethyl-1-methyl-1*H*-1,2,4-triazole Hydrochloride (**17b**)

5-Hydroxymethyl-1-methyl-1*H*-1,2,4-triazole (**17a**) (0.50 g, 4.42 mmol) was added in portions to ice-cold thionyl chloride (1.0 ml, 13.7 mmol) and the resulting mixture heated at reflux. After 20 minutes the excess thionyl chloride was removed under vacuum and the product recrystallized from hot EtOH, washed with cold EtOH and ether, and dried under vacuum to give **17b** as white crystals (502 mg, 68%).

The filtrate gave additional (125 mg, 17%) product. IR (Nujol) ν_{max} 3110, 3010, 2280 (br), 1850 (br) 1585, 1400, 1265, 960 cm^{-1}. ^1H NMR (200 MHz, D_2O) δ 4.03 (s, CH_3), 4.99 (s, CH_2), 8.42 (s, heteroaryl-H).

Anal Calcd for $C_4H_7N_3Cl_2$: C 28.59, H 4.20, N 25.01.
Found: C 28.73, H 4.16, N 25.00.

5-Acetylthiomethyl-1-methyl-1*H*-1,2,4-triazole (**17c**)

A suspension of 5-chloromethyl-1-methyl-1*H*-1,2,4-triazole hydrochloride (**17b**) (122 mg, 0.73 mmol) and KSAc (99 mg, 0.87 mmol) in anhydrous MeCN (1.5 ml) was treated with dicyclohexyl 18-crown-6 (~1 mg) and triethylamine (107 μl, 0.77 mmol). After stirring 4 hours at room temperature the mixture was filtered and the filtrate evaporated under vacuum. The residue was taken up in EtOAc (10 ml), washed with brine, dried over magnesium sulfate, filtered and evaporated under vacuum to give **17c** as an amber oil (114 mg, 91%). ^1H NMR (200 MHz, $CDCl_3$) δ 2.40 (s, $COCH_3$), 3.91 (s, CH_3), 4.26 (s, CH_2), 7.80 (s, heteroaryl-H).

5-Acetylthiomethyl-1,4-dimethyl-1,2,4-triazolium Trifluoromethanesulfonate (**18a**)

An ice-cold solution of 5-acetylthiomethyl-1-methyl-1*H*-1,2,4-triazole (**17c**) (97.4 mg, 0.57 mmol) in dichloromethane (0.6 ml) was treated with methyl trifluoromethanesulfonate (77 μl, 0.68 mmol). After 50 minutes the solution was evaporated under vacuum to give **18a** as a pale orange oil (189 mg, 99%). ^1H NMR (200 MHz, D_2O) δ 2.43 (s, $COCH_3$), 3.95 (s, CH_3), 4.14 (s, CH_3), 4.62 (s, CH_2), 8.72 (s, heteroaryl-H).

1,4-Dimethyl-5-mercaptomethyl-1,2,4-triazolium Trifluoromethanesulfonate (**18b**)

A solution of 5-acetylthiomethyl-1,4-dimethyl-1,2,4-triazolium trifluoromethanesulfonate (**18a**) (582 mg, 1.74 mmol) in MeOH (1.74 ml) was treated with trifluoromethanesulfonic acid (154 μl, 1.74 mmol) and the resulting solution left to stand in a capped flask. After 21 hours the solution was diluted with ether to precipitate an oil. The oil was triturated with ether and stripped with dichloromethane to give **18b** as an amber gum (391 mg, 77%). ^1H NMR (200 MHz, D_2O) δ 3.93 (s, CH_3), 4.08 (s, CH_3), 4.25 (s, CH_2), 8.72 (s, heteroaryl-H).

(1*R*,5*S*,6*S*)-6-(1(*R*)-hydroxyethyl)-2-(1,4-dimethyl-1,2,4-triazolium-5-methylthio)-1-methylcarbapen-2-em-3-carboxylate (**2e**)

A solution of 1,4-dimethyl-5-mercaptomethyl-1,2,4-triazolium trifluoromethanesulfonate (**18b**) (108 mg, 0.368 mmol) in dimethylacetamide (2.3 ml) was cooled to −20°C (dry ice-*i*-PrOH) under a nitrogen atmosphere and treated with solid 4-nitrobenzyl (1*R*,5*R*,6*S*)-2-(diphenylphosphono)oxy-6-(1(*R*)-hydroxyethyl)-1-methylcarbapen-2-em-3-carboxylate (146 mg, 0.245 mmol) (**19**) followed by a solution of *N*,*N*-diisopropylethylamine (64 μl, 0.368 mmol) in dimethylacetamide (0.15 ml) added dropwise over 6 minutes. The resulting solution was stirred at −20°C. After 30 minutes, the solution was diluted with *n*-butanol (12 ml), ethyl acetate (6 ml), water (12 ml) and 0.5 M pH 6.8 *N*-methyl morpholine hydrochloride buffer (6 ml), mixed with 20% palladium hydroxide on carbon (75 mg), and hydrogenated on a Parr shaker at 3.1 atmospheres hydrogen. After 90 minutes the mixture was filtered and the filtrate washed with dichloromethane and ether. The aqueous solution was concentrated under vacuum to *ca.* 5 ml and chromatographed on a column (1.5 × 33 cm) of Dowex 50-X4 ion exchange resin. The column was eluted with deionized water in a cold room (4°C). Fractions containing product, as determined by UV spectroscopy, were combined, concentrated under vacuum to *ca.* 5 ml, filtered (0.45 μm Gelman Acrodisc) and lyophilized to give **2e** as a white amorphous powder (32.9 mg). IR (Nujol) ν_{max} 3380 (br), 1760, 1610 cm^{-1}. UV (0.05 M pH 7.0 MOPS) λ_{max} nm (ε) 293 (5,950). UV (buffer + NH_2OH) $\lambda_{max\,ext}$ (ε_{ext}) 293 (5,650). ^1H NMR (200 MHz, D_2O) δ 1.19 (d, J=7.2 Hz, 1-CH_3), 1.29 (d, J=6.4 Hz, CH_3CHOH), 3.42 (dq, J=9.6, 7.2 Hz, H-1), 3.57 (dd, J=3.0, 5.8 Hz, H-6), 3.94 (s, NCH_3), 4.09 (s, NCH_3), 4.17~4.37 (m, H-5 and CH_3CHOH), 8.76 (s, heteroary-H).

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