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PENEMS CONTAINING AMINO ACID DERIVED SUBSTITUENTS AT C-2

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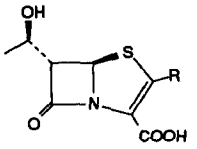
Abstract: Several penems of types **I** - **IV** containing side-chains at C-2 derived from D- or L-amino acids were synthesized. The *in-vitro* antibacterial spectrum of these compounds is influenced by the stereochemistry of the side-chain. In general, penems with side-chains derived from D-amino acids are more potent, particularly against gram-negative organisms, relative to the isomeric analogs.

Penems are potent broad spectrum synthetic ß-lactam antibiotics that have been investigated by several laboratories during the past decade. An important requirement for antibacterial activity in this class of compounds is a hydroxyethyl substituent (6*S*,8*R*) at C-6 along with a variety of side-chains at C-2.[1] We report here the syntheses and antibacterial activities of the following four types of penems **I-IV**which contain a C-2 substituent derived from D- or L-amino acids.



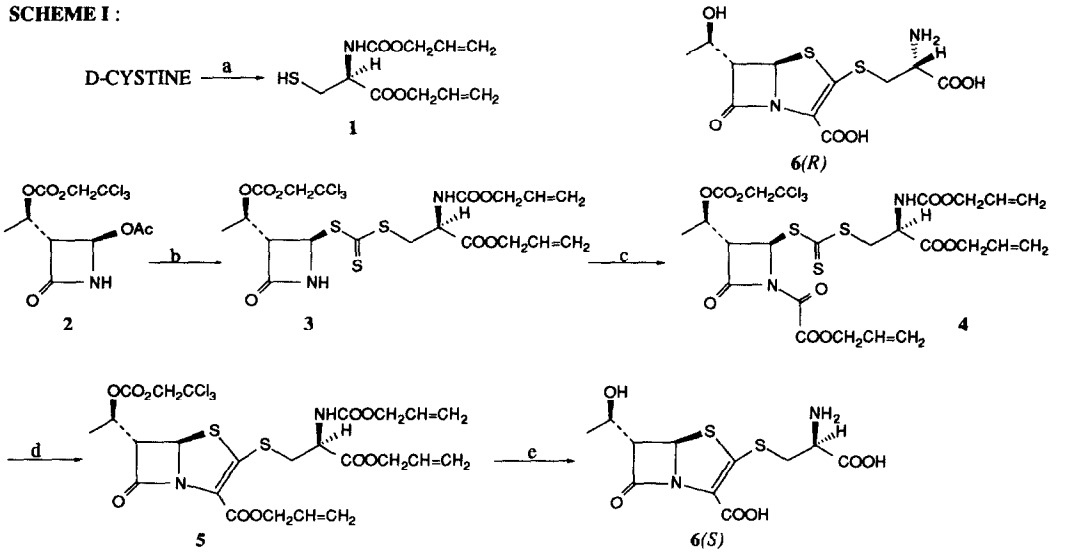
R = -S-$CH_2CH(NH_2)COOH$; -$(CH_2)_nCH(NH_2)COOH$
I **II**

-CH_2-S-$CH_2CH(NH_2)COOH$; -$CH(R')NH_2$
III **IV**

The synthetic sequence for compounds **I** is shown in Scheme I. *N*-Allyloxycarbonyl-D-cysteine allyl ester (**1**) obtained by zinc-dust reduction[2] of the D-cystine precursor[3] was converted to its sodium trithiocarbonate salt which was then reacted with the acetoxy azetidinone **2**[4] to afford **3** as a stable compound. Oxalimide cyclization[5] of **3** involving the intermediate **4** led to the formation of protected penem **5**. Removal of the trichloroethoxycarbonyl group with zinc-acetic acid followed by Pd^0-catalyzed deprotection of the three allyloxy groups under reductive conditions,[7] afforded the desired penem **6***(S)*.[8] The same reaction sequence was used to prepare the isomeric analog **6***(R)* starting from L-cystine. The isomeric penems **6***(S)* and **6***(R)*were found to be equipotent as antibacterials against gram-positive organisms; however, **6***(S)* was approximately thirty-fold more active than **6***(R)* against gram-negative organisms. Based on this observation, compounds II-IV were then prepared in order to explore the effect of replacing the sulfur atom linking the side-chains at C-2.

For the synthesis of penems II and III (Scheme II), the azetidinone silver thiolate **8** was found to be an useful advanced intermediate for preparing this series of related target structures; compound **8** was conveniently prepared from **2** by applying previously described methodology.[6] *N*-Allyloxycarbonyl-D-methionine (**7**)[3] was converted to a mixed anhydride and reacted with **8** to give the acylated phosphorane **9**.

SCHEME I :



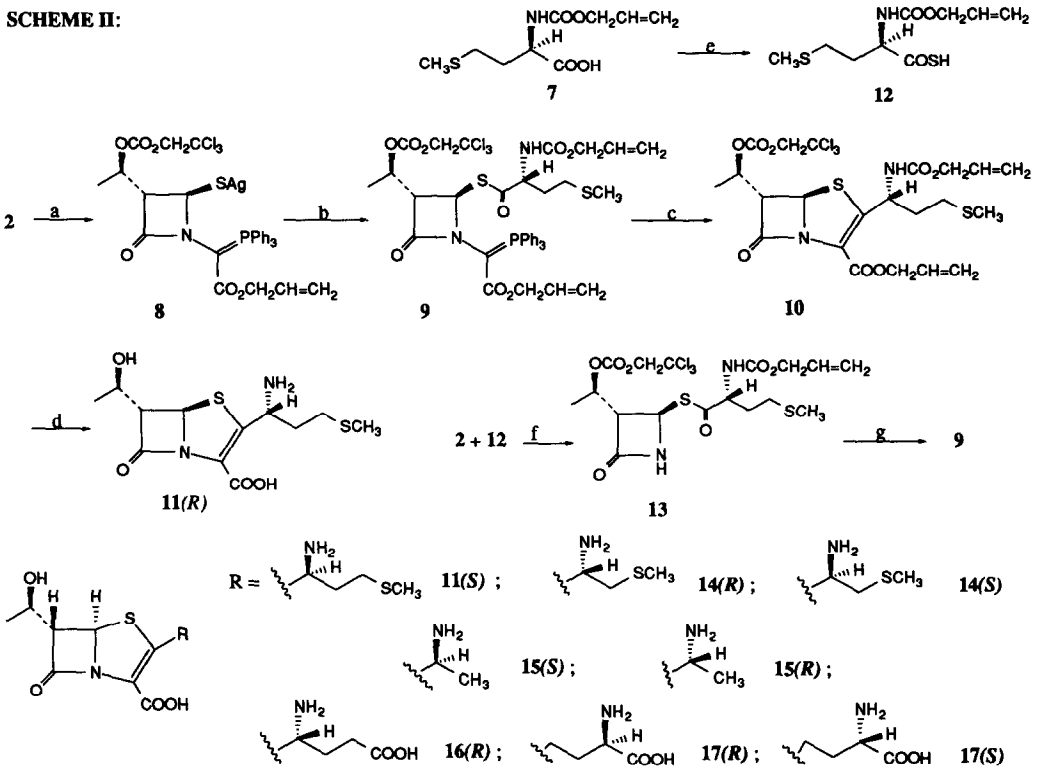
Reagents and conditions: (a) i. allyl chloroformate/4N NaOH/1 hr. (98%); ii. allyl bromide/Et_3N/Me_2CO/24 hrs. (92%) iii. Zn-dust/MeOH/0°C/conc.HCl/2 mins./extr. Et_2O; (b) **1** / CS_2/1N NaOH /added to **2** in EtOH/0°C/15 min/chrom. (23%); (c) allyl oxalyl chloride/ i-Pr_2NEt/CH_2Cl_2/$CaCO_3$/0°C; (d) $CHCl_3$ / $P(OEt)_3$ - syringe pump addition/reflux 17 hrs/chromat. (75%); (e) i. Zn dust/ THF-10%H_2O-50%AcOH/ -15°C/chromat. (54%) ii. $Pd(PPh_3)_4$ / pyridinium formate/ PPh_3/2 hrs. (79%)

Wittig cyclisation of **9** gave the protected penem **10**. Removal of the trichloroethoxycarbonyl group with zinc-acetic acid followed by Pd^0 deprotection of the allyloxy groups under ester-exchange conditions[9] afforded the desired penem **11***(R)*.[8] The isomeric penem **11***(S)* was obtained by using the same reaction sequence starting with *N*-allyloxycarbonyl-L-methionine. Similarly, compounds **14** - **17** were prepared from the corresponding protected amino acids. For compounds **16** and **17**, the final deprotection of the three allyloxy groups (step e.ii) was carried out with Pd^0-formate[7] as in compounds **6** and **21** (Schemes I and III); ester-exchange conditions[9] in this step for such compounds which contain multiple allyloxy-protective groups, led to incomplete de-allylation /or *N*-allylation products.

The thiol acid **12**[10]derived from *N*-allyloxycarbonyl-D-methionine was used in an alternative reaction sequence to prepare the phosphorane intermediate **9**. Reaction of the sodium salt of **12** with acetoxy azetidinone **2** afforded the intermediate **13** which was then converted to **9** using conventional methodology. This route was found useful to prepare selected compounds **III** on a larger scale.

Compounds **IV** were synthesized using the sequence shown in Scheme III. Azetidinone silver thiolate **8** was acylated with bromoacetyl bromide to afford the bromoacetyl phosphorane **18**. Displacement of the bromine with the thiolate anion of **1** afforded **19**. Wittig cyclization of **19** proceeded satisfactorily, however the resulting penem was not stable to zinc reduction conditions to remove the trichloroethoxycarbonyl group; reversing these steps by removing the trichloroethoxycarbonyl protective group prior to Wittig cyclization gave

SCHEME II:



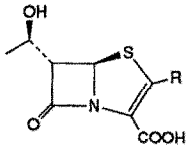
Reagents and conditions: (a) i. Ph_3CSH/K_2CO_3/acetonitrile/24 hrs./chromat. ii. allyl glyoxylate/CH_2Cl_2/trace Et_3N/1 hr.rt/0°C MsBr/Et_3N/1hr/chromat. iii. PPh_3/DMF/15 hrs./chromat. iv. CH_2Cl_2-MeOH-Pyr./0°C/aq $AgNO_3$/5 mins. (20% overall); (b) 7/THF/*i*-butyl chloroformate/pyr./-20°C/45 mins./chromat. (20%); (c) Benzene-reflux/18 hrs./chromat. (87%); (d) i. Zn-dust/THF-10% water-50% acetic acid/-15°C/3 hrs./chromat. (81%) ii. $Pd(PPh_3)_4$/2-ethylhexanoic acid-CH_2Cl_2/PPh_3/1 hr.(75%); (e) *i*-butyl chloroformate/THF-pyr./-15°C/30 min./H_2S; (f) THF-aq.$NaHCO_3$/24 hrs./chromat. (60%). (g) i. allyl glyoxylate/CH_2Cl_2/trace Et_3N/15 mins. ii. MsBr/CH_2Cl_2/Et_3N /-10°C/10 mins./chromat. iii. PPh_3/DMF/24 hrs./chromat.(48% overall)

the protected penem **20**. Pd^0-catalyzed de-allylation of **20** under reductive conditions[7] afforded the desired penem **21**(*S*). The isomeric **21**(*R*) was prepared from L-cystine by using the same sequence.

The *in-vitro* antibacterial activity of compounds I - IV is summarized in Tables **1** and **2**. Methodology for determining the minimum inhibitory concentrations (MIC values) has been described previously.[11] The data in Table **2** shows that compounds with side chains derived from D-amino acids are markedly more potent vs gram-negative organisms than are their L-diastereoisomers; on the other hand, the gram-positive activity is not significantly influenced by this stereochemistry (Table **1**). Replacement of the sulfur linkage at C-2 by a

Table 1. GRAM-POSITIVE *in-vitro* Antibacterial Activity* of Penems I - IV

Compound	Geometric Mean MICs µg/ml (*number of strains*)			GRAM-POSITIVE Geometric Mean MIC's µg/ml
	B. subtilis	*Staphyl.*	*Strept. faec.*	
6(S)	0.50 (1)	1.82 (12)	45.25 (4)	3.01
6(R)	2.83 (1)	1.94 (12)	128.00 (4)	4.00
11(S)	4.00 (1)	0.214 (18)	64.00 (2)	0.37
11(R)	0.125 (1)	0.070 (13)	8.02 (2)	0.13
14(S)	0.50 (1)	0.26 (18)	90.51 (2)	0.45
14(R)	0.125 (1)	0.099 (18)	16.02 (2)	0.18
15(S)	1.00 (1)	0.260 (18)	64.00 (2)	0.47
15(R)	---	0.229 (24)	---	0.29
16(R)	0.25 (1)	0.735 (18)	16.00 (2)	1.00
17(S)	2.00 (1)	2.33 (18)	90.51 (2)	3.40
17(R)	1.01 (1)	2.08 (18)	45.26 (2)	2.70
21(S)	0.25 (1)	0.852 (13)	16.00 (2)	1.10
21(R)	0.50 (1)	0.707 (18)	22.63 (2)	0.94
22	0.06 (1)	0.11 (18)	5.70 (2)	0.15
23	0.50 (1)	0.153 (18)	32.00 (2)	0.28
24	0.06 (1)	0.12 (18)	5.70 (2)	0.16



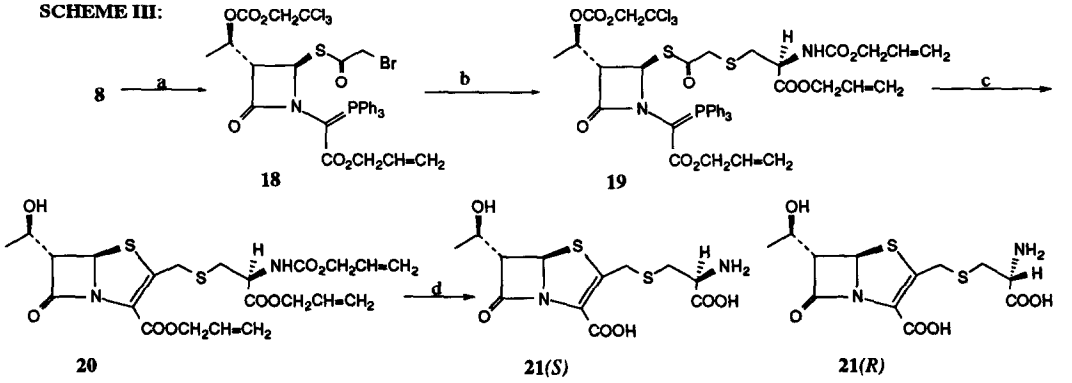
R = $-SCH_2CH_2OCONH_2$ (22) (Sch 34343)
$-CH_2NH_2$ (23) (CGP 31,608)
$-CH_2OCONH_2$ (24) (FCE 22101)

Table 2. GRAM-NEGATIVE *in-vitro* Antibacterial Activity* of Penems I - IV

Compound	Geometric Mean MICs in µg/ml (*number of strains*)								GRAM-NEGATIVE Geometric Mean MIC's µg/ml
	E. coli	*Enterobacter*	*Klebsiella*	*Morganella*	*Providencia*	*Salmonella*	*Sarcinea lut.*	*Serratia*	
6(S)	0.25 (13)	0.76 (5)	0.17 (12)	--	5.66 (12)	0.16 (5)	4.00 (1)	1.08 (9)	0.49
6(R)	6.46 (13)	16.00 (5)	4.00 (12)	--	42.71 (12)	5.28 (5)	4.00 (1)	17.28 (9)	16.00
11(S)	11.68 (11)	20.16 (3)	12.13 (10)	64.10 (1)	55.72 (5)	10.08 (3)	0.031 (1)	38.06 (4)	17.60
11(R)	0.441 (11)	1.00 (3)	0.50 (10)	4.00 (1)	5.28 (5)	0.397 (3)	0.125 (1)	2.83 (4)	0.88
14(S)	12.44 (11)	20.16 (3)	8.57 (10)	128.00 (1)	97.01 (5)	5.04 (3)	0.25 (1)	22.63 (4)	16.30
14(R)	0.707 (10)	2.00 (3)	0.595 (8)	2.00 (1)	9.19 (5)	0.794 (3)	2.00 (1)	2.83 (4)	1.33
15(S)	21.93 (11)	20.16 (3)	17.15 (10)	64.00 (1)	64.00 (5)	10.08 (5)	0.50 (1)	45.26 (4)	24.60
15(R)	11.68 (11)	10.08 (3)	9.85 (10)	32.00 (1)	55.72 (5)	5.04 (3)	--	26.91 (4)	14.29
16(R)	3.11 (11)	6.35 (3)	3.73 (10)	16.00 (1)	16.00 (5)	4.00 (2)	2.00 (1)	13.45 (4)	5.40
17(S)	9.67 (11)	16.00 (3)	12.13 (10)	64.00 (1)	55.72 (5)	11.31 (2)	8.00 (1)	45.26 (4)	17.30
17(R)	2.42 (11)	2.52 (3)	2.83 (10)	16.00 (1)	18.38 (5)	1.00 (3)	4.00 (1)	16.00 (4)	4.00
21(S)	0.284 (11)	0.63 (3)	0.308 (10)	2.00 (1)	2.00 (5)	0.25 (3)	0.50 (1)	1.68 (4)	0.51
21(R)	4.00 (11)	10.08 (3)	4.93 (10)	8.00 (1)	13.93 (5)	3.18 (3)	0.50 (1)	19.03 (4)	6.40
22	0.30 (11)	1.30 (3)	0.35 (10)	2.00 (1)	0.87 (5)	0.25 (3)	--	4.80 (4)	0.57
23	5.15 (11)	8.00 (3)	6.06 (10)	4.00 (1)	8.00 (5)	3.18 (3)	0.50 (1)	13.45 (4)	6.27
24	0.68 (11)	3.20 (3)	0.81 (10)	2.00 (1)	2.30 (5)	0.50 (3)	--	5.70 (4)	1.20

* Mueller-Hinton agar, 24 hrs.

SCHEME III:



Reagents and conditions: (a) $BrCH_2COBr/CH_2Cl_2/0^oC/45$ mins./chromat. (98%); (b) 1 /DMF/$Et_3N/0^oC/1$ hr./chromat. (72%); (c) i. Zn-dust/THF-10%water-50%acetic acid/-15^oC/45 mins./chromat. (82%) ii. Benzene-reflux/18 hrs./chromat. (68%); (d) $Pd(PPh_3)_4$/pyridinium formate-CH_2Cl_2/PPh_3/ 1 hr./chromat. (65%).

methylene group reduces the gram-negative activity as in **6***(S)* vs **17***(R)*, whereas a spacer methylene at C-2 maintains the activity as in **6***(S)* vs **21***(S)*. Diastereoisomeric penems **IV** derived from amino acids having no functionalities on the side chain, show only modest potency differences e.g. **15** vs **14**.[12] The presence of a carboxyl group, surprisingly,[13] does not have an adverse effect on the gram-negative activity of the compounds e.g. **6**, **16**, **17**, **21** vs **15** . From this series of penems, **11***(R)* has the highest potency against both groups of organisms. With the exception of **23**,[14] none of the compounds have significant activity against *Pseudomonas*. Included in the Tables are MIC values[15] for the reference penems Sch 34343 (**22**),[4] CGP 31608 (**23**)[14] and FCE 22101 (**24**).[16]

Acknowledgement: The authors thank Drs. B. Pramanick and M. Puar for spectroscopic data.

References and notes:

1. *For a review see* McCombie, S. W.; Ganguly, A. K.; *Medicinal Res. Reviews* **1988**, *8*, 393.
2. This reductive procedure is preferable since the reaction proceeds quantitatively; the thiol **1** is not stable and hence is carried thru the next step immediately.
3. The preparation of allyl protected amino acids used in Schemes I - III followed standard methodology for carbamate and ester formation.
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8. All new compounds gave mass spectral and spectroscopic data in accord with their assigned structures. Relevant data on selected compounds: **3***(S)* : $[\alpha]_D$ +139° (chloroform); IR: 5.60, 5.70, 5.80 μ; PMR ($CDCl_3$): δ 1.5 (d,3H, J = 6 Hz), 3.42 (dd, 1H, J = 2; 7 Hz), 5.65 (d, 1H, J = 2 Hz). **5***(S)* : $[\alpha]_D$ +111° (chloroform); IR: 5.58, 5.70, 5.80 μ; PMR ($CDCl_3$): δ 1.55 (d, 3H, J = 7 Hz), 3.45 (d, 2H, J = 5 Hz), 3.90 (dd, 1H, J = 2; 7 Hz), 5.65 (d, 1H, J = 2 Hz). **6***(S)* : $[\alpha]_D$ +123°(ethanol); IR(nujol): 5.60, 6.1 μ; PMR(d_6DMSO): δ 1.15 (d, 3H, J = 6 Hz), 3.75 (dd, 1H, J =1.5; 7 Hz), 5.68 (d, 1H, J = 1.5 Hz). **6***(R)* : $[\alpha]_D$ +118°; IR: 5.68, 6.0 μ. **9***(R)* : $[\alpha]_D$ +23°(chloroform); PMR($CDCl_3$): δ 4.22 (dd, 1H, J = 2;8 Hz), 5.61 (d,1H,J = 2 Hz). **10***(R)* : $[\alpha]_D$ +84°(chloroform); PMR($CDCl_3$): δ 1.54 (d, 3H, J = 7 Hz), 2.15 (s, 3H), 2.59 (m, 2H), 3.97 (dd, 1H, J = 1.5; 7 Hz), 4.85(s, 2H), 5.67 (d, 1H, J = 1.5 Hz). **11***(R)* : $[\alpha]_D$ +57° (water); IR: 5.65 μ; PMR(D_2O): δ 1.3 (d, 3H, J = 7 Hz), 2.13 (s, 3H), 2.68(m, 2H); 3.97 (dd,1H, J = 1.5, 7 Hz); 5.76 (d, 1H, J =1.5 Hz). **13***(R)* : $[\alpha]_D$ +76° (chloroform); MS: m/e 538; PMR($CDCl_3$): δ 1.45 (d, 3H, J = 7 Hz), 2.08 (s, 3H), 2.5 (m, 2H), 3.38 (dd,1H, J = 2, 7 Hz), 5.25 (d, 1H, J = 2 Hz). **17***(R)* : $[\alpha]_D$+105° (water); IR: 5.65 μ; PMR(D_2O): δ 1.27 (d, 3H, J = 6 Hz), 3.83 (dd, 1H, J = 2; 8 Hz), 5.61 (d, 1H, J = 2 Hz). **15***(R)* : $[\alpha]_D$ +61° (water); IR: 5.62 μ; PMR: δ 1.27 (d, 3H, J = 6 Hz), 1.52 (d, 3H, J =7 Hz), 3.92 (dd, 1H, J = 1.6; 6 Hz), 5.67 (d, 1H, J = 1.6 Hz). **16***(R)* : $[\alpha]_D$ +67° (water); IR: 5.61, 6.3 μ; PMR(D_2O): δ 1.27 (d, 3H, J = 7 Hz), 3.92 (dd, 1H, J = 1.9; 7 Hz), 5.71 (d, 1H, J = 1.9 Hz). **20***(S)* : PMR($CDCl_3$): δ 1.35 (d,3H, J = 6 Hz), 3.03 (m, 2H), 3.75 (dd,1H, J = 1.5;7 Hz), 4.0 (s, 2H), 4.25 (m,1H), 5.65 (d, 1H, J = 1.5 Hz). **21***(S)* : PMR: δ 1.21 (d, 3H, J = 6 Hz), 3.02 (m, 2H), 3.84 (dd, 1H, J = 1.6, 7 Hz), 3.88 (d, 1H, J =12 Hz), 4.15 (d, 1H, J = 12 Hz), 4.18 (m, 1H), 5.62 (d, 1H, J =1.5 Hz); MS (FABS): m/e 349 (M^++ 1).
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12. Analogs of **15***(S)* and **15***(R)* in which the C-6 substituent is a hydroxymethyl group, likewise, are not influenced by the C-2 stereochemistry.[14]
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