

163. (+)-(5*R*,6*S*)-2-(1'-Aminoalkyl)-6-(hydroxyalkyl)penem-3-carboxylic Acids

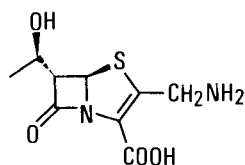
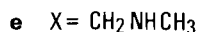
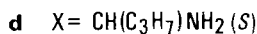
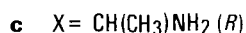
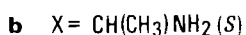
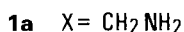
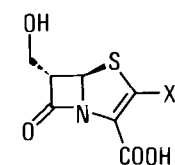
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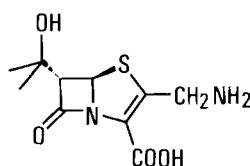
(21.VII.86)

In continuation of our work on penem antibiotics, novel chiral (5*R*,6*S*)-2-(1'-aminoalkyl)-6-(hydroxyalkyl)-derivatives **1** have been synthesized by two essentially different strategies. Whereas the starting materials for **1a–f**, azetidinones **2** and **5**, were obtained from chiral building blocks (6-aminopenicillanic acid and L-threonine, resp.), the one for **1g**, azetidinone **9**, was derived from racemic 4-acetoxyazetidinone and, as chiral auxiliary, (2*R*)-2-mercapto-propan-1-ol. The 2-aminomethyl derivatives **1a** (CGP 30779) and **1f** (CGP 31608) proved the most potent compounds in the antibacterial tests *in vitro* and showed a well-balanced spectrum of activity by comparison with that of established β -lactams.

Introduction. – The penems, which were initially considered insufficiently stable to exert any notable antibacterial activity [1], reached a high level of development by the end of their first decade [2–5]. In general, they are active against a broad spectrum of bacteria, excluding, however, *Pseudomonas aeruginosa*. Knowing that the older rules governing substituent requirements that apply to penicillins and cephalosporins are inoperative, and that antipseudomonal activity seems to be related – at least in the structurally close carbapenem series – to the presence of a basic substituent [6], we decided to assess the



1f



1g

minimal structural requirements for this activity in the 2-(aminoalkyl) series. The C(6) substituent was limited to the hydroxymethyl, (1*R*)-1-hydroxyethyl and 1-hydroxy-1-methylethyl groups first found in the isolated natural carbapenem derivatives [6] and attached to the β -lactam in a *trans*-configuration with respect to the condensed dihydrothiazolidine ring. These penems **1a–g** were synthesized by two essentially different strategies.

Synthesis. – For penems **1a–e**, the final (5*R*,6*S*)-configuration was attained by synthesis starting from 6-aminopenicillanic acid (*Scheme 1*). An intermediate silver (3*S*,4*R*)-

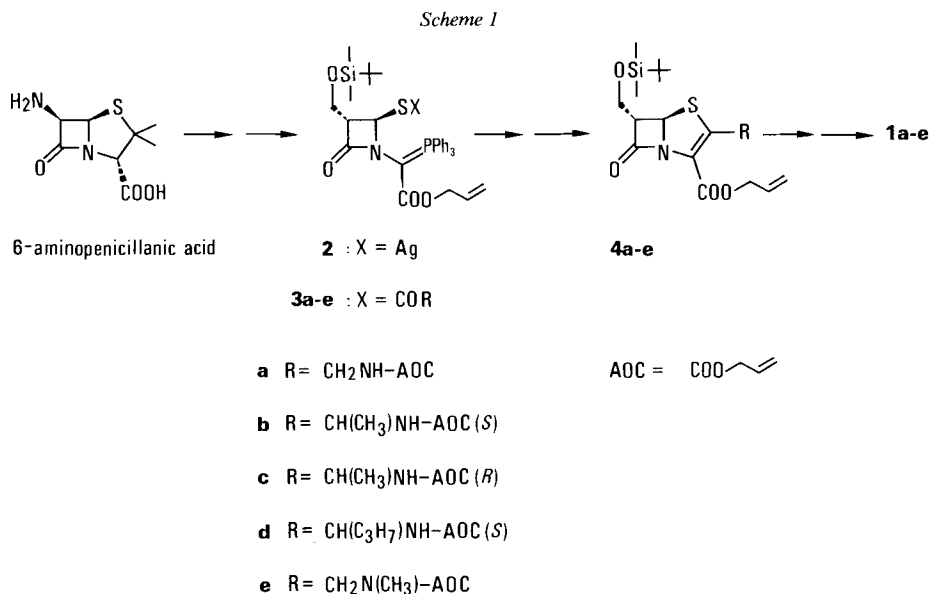


Table 1. Typical Reaction Conditions and Chemical Yields for the Syntheses of **1a–g**

Conversion ^{a)}	Conditions	Yield [%]
2 → 3a ^{b)}	AOC-Gly-Cl, pyridine, CH ₂ Cl ₂ , 0°, 30 min	63
3a → 4a ^{b)}	Toluene, reflux, 1.5 h	96
4a → 1a ^{b)}	a) Bu ₄ NF, AcOH, THF, r.t., 3 h b) Bu ₃ SnH, (PPh ₃) ₄ Pd ^{c)} , THF, r.t., 30 min	59 58
5 → 6	NaSCoCH ₂ NH-AOC, CH ₂ Cl ₂ /H ₂ O, pH 11.8, 0°, 1 h	65
6 → 7	AOC-COCl, (<i>i</i> -Pr) ₂ EtN, CH ₂ Cl ₂ , -15°, 20 min	90
13 → 14	AOC-COCl, (<i>i</i> -Pr) ₂ EtN, CH ₂ Cl ₂ , -15°, 20 min	82
7 → 8	P(OEt) ₃ , dioxane, 100°, 6 h	45
9 → 10	LiN(<i>i</i> -Pr) ₂ , THF, -70°, acetone, 45 min	83
10 → 11	<i>m</i> -ClC ₆ H ₄ COOH, CH ₂ Cl ₂ , -20 → 0°, 45 min	93.5
11 → 12	AcOH/H ₂ O, 120°, 2.5 h	52
12 → 13	NaSCoCH ₂ NH-AOC, acetone/H ₂ O, pH 8, 10°, 35 min	50
14 → 15	P(<i>i</i> -PrO) ₃ , 16 h, r.t.; dioxane, 10 h, 100°	97
15 → 1g	Dimedone, (PPh ₃) ₄ Pd ^{c)} , THF, r.t., 3 h	55

^{a)} Spectroscopic data are in full agreement with the proposed structures.

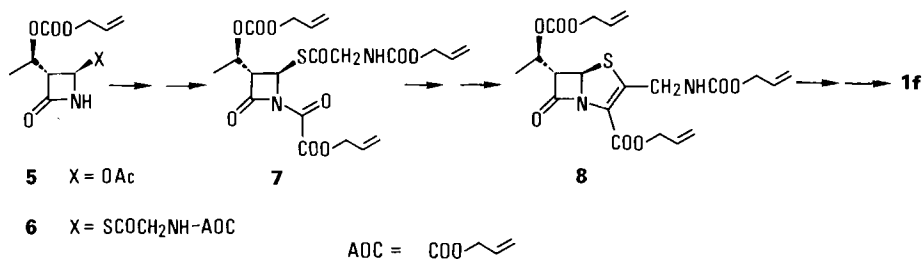
^{b)} **3b–e**, **4b–e**, and **1b–e**, respectively, were synthesized by analogy.

^{c)} Catalyst.

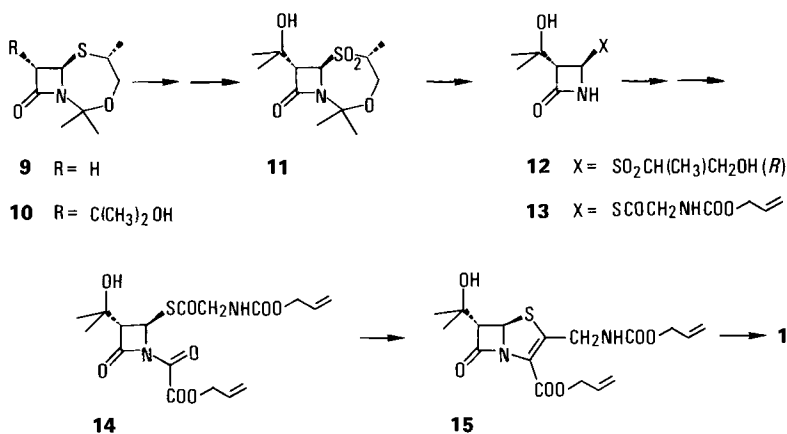
thiolate **2** [7] was acylated with various *N*-(allyloxycarbonyl)-protected α -amino-acid chlorides to provide the phosphoranes **3a-e**. The latter were converted *via* the standard Wittig reaction first described by Woodward [1] to penems **4a-e**. Initial deprotection of the OH group, followed by simultaneous deprotection of the NH₂ and COOH groups by way of a modified Pd-catalysed transallylation [8] yielded penems **1a-e** (reaction conditions and chemical yields are summarized in Table 1).

The homologous ((1'*R*)-hydroxyethyl)penem **1f** was synthesized in several steps from *L*-threonine by way of the (3*S*,4*R*)-azetidinone **5** [9] (Scheme 2). Substitution of the AcO group of **5** with sodium α -[*N*-(allyloxycarbonyl)amino]thioacetate with overall retention of configuration at C(4) gave the azetidinone **6**, which was converted by analogy with published procedures [10] *via* the oxamide **7** to the penem **8** and, after deprotection, to **1f**¹⁾.

Scheme 2



Scheme 3



The 6-(1'-hydroxy-1'-methylethyl)penem **1g** was prepared (Scheme 3) from the chiral bicyclic azetidinone **9** first synthesized by Pfaendler [12] from racemic 4-acetoxiazetidinone [13] and (2*R*)-2-mercaptopropan-1-ol [14] as chiral auxiliary. The generation of the enolate from the β -lactam **9** and subsequent quenching with acetone exclusively yielded the *trans*-configured 1'-hydroxy-1'-methylethyl derivative **10**. Oxidation to the

¹⁾ For racemic **1f**, see [11].

Table 2. Antibacterial Activity^{a)} of 2-(1'-Aminoalkyl)-6-(hydroxyalkyl)penem-3-carboxylic Acids **1a-g** in vitro (MIC; µg/ml) Compared with that of Ampicillin, Cefazidime, and Aztreonam

Test organism	1a CGP	1b CGP	1c CGP	1d CGP	1e CGP	1f CGP	1g CGP	Ampicillin	Cefazidime	Aztreonam
	30779	31073	31221	32357	31461	31608	38602			
<i>Staphylococcus aureus</i> 10B	0.1	0.1	0.1	0.05	0.05	0.05	64	0.1	4	> 128
<i>S. aureus</i> 2995 i ⁺ P ⁺	0.2	0.2	0.2	0.05	0.1	0.05	64	16	4	> 128
<i>S. aureus</i> A 124 (methicillin resistant) ^{b)}	1	1	0.5	0.5	0.5	0.05	–	4	64	> 128
<i>Streptococcus pyogenes</i> Aronson	1	1	0.5	1	0.2	0.2	> 128	0.05	0.2	32
<i>Neisseria meningitidis</i> 1316	0.5	2	0.5	1	1	0.2	16	0.05	0.05	0.02
<i>Haemophilus influenzae</i> NCTC 4560	0.5	16	16	32	8	1	64	0.5	0.2	0.1
<i>Escherichia coli</i> 205	0.5	64	16	64	4	4	> 128	4	0.1	0.05
<i>E. coli</i> 205 R + TEM	1	64	32	64	8	4	–	> 128	0.1	0.05
<i>Klebsiella pneumoniae</i> 327	1	16	16	32	2	1	> 128	32	0.1	0.02
<i>Enterobacter cloacae</i> P 99	2	32	16	64	2	0.5	> 128	> 128	4	0.5
<i>Morganella morganii</i> 1518	2	64	128	> 64	> 32	2	> 128	> 128	4	0.1
<i>Pseudomonas aeruginosa</i> ATCC 12055	0.2	32	64	> 64	16	0.2	64	16	0.5	0.5
<i>Clostridium perfringens</i> ^{c)}	8	32	16	64	16	1	> 128	0.25	0.06	32
<i>Bacteroides fragilis</i> L 01 ^{c)}	1	4	4	16	2	0.5	> 128	32	16	64

^{a)} Agar dilution method; DST Agar Oxoid, inoculum 10⁶ CFU/ml.

^{b)} MRSA; incubation at 30° for 48 h.

^{c)} Anaerobic incubation.

sulfone **11** and acid-catalysed ring opening to the azetidinone **12** finally afforded the penem **1g**, after the previously described sequence (**12**→**13**→**14**→**15**→**1g**). It should be noted that protection of the tertiary OH group during the entire reaction sequence is unnecessary.

Antibacterial Activity. – The antibacterial activities of the 2-(1'-aminoalkyl) derivatives **1a–g** *in vitro* against selected Gram-positive and Gram-negative bacteria are listed in Table 2. Structural requirements relating to the C(6) and C(2) substituents are documented by a substantial loss of antibacterial activity caused by an additional CH₃ group α to the OH group or by a similar effect confined, however, to the Gram-negative strains, observed after the introduction of a branched side-chain at C(2) α to the amino group (**1b–d** vs. **1a**). The 2-aminomethyl penems **1a** (CGP 30 779) and **1f** (CGP 31 608) proved to be the most interesting compounds in the series; by comparison with established β -lactam antibiotics (Table 2), they exhibit a well-balanced anti-bacterial spectrum, including activity against anaerobes and, especially, methicillin-resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Preliminary results of studies *in vivo* indicate that they exert a good therapeutic effect against experimental infections in mice. The ED₅₀²⁾ of penem **1f**, for instance, upon subcutaneous administration to mice infected with *Staphylococcus aureus* 10B or *Streptococcus pyogenes* ARONSON was 1.4 mg/kg (cumulative dose).

The authors express their gratitude to Mrs. G. Geiger and Mr. B. Staheli for their excellent assistance and to Mrs. J. Gysin for her skilful determinations of antibacterial activity.

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²⁾ Dose protecting 50% of animals from death.