Synthesis of 5,6-*cis*-Carbapenems Related to C-19393 H_2

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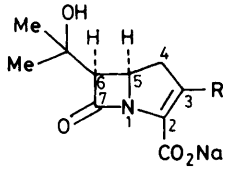
The synthesis of 6,7-*cis*-7-(1-hydroxy-1-methylethyl)-3-oxa-1-azabicyclo[4.2.0]octan-8-ones (3a, b), key intermediates for the preparation of the 5,6-*cis*-carbapenem antibiotic C-19393 H_2 {sodium (5*R*,6*R*)-3-[(*E*)-(2-acetamidoethenyl)-(*R*)-sulphinyl]-6-(1-hydroxy-1-methylethyl)-7-oxo-1-azabicyclo-[3.2.0]hept-2-ene-2-carboxylate} (1a) and its derivatives, was investigated. Sulphenylation of the 3-oxa-1-azabicyclo[4.2.0]octan-8-ones (2a, b), followed by the aldol reaction with acetone, gave the 7-(1-hydroxy-1-methylethyl)-7-sulphenyl derivatives (7a—e). Reductive desulphurization of compounds (7a—e) with an organotin hydride (tri-n-butyltin hydride or triphenyltin hydride) in the presence of a radical initiator gave rise to stereoselective formation of the *cis*-azetidinones (3a, b). A total synthesis of (±)-C-19393 H_2 (1a) and its derivatives having other substituents at the C(3) position, (1b—e), starting from (3a, b) *via* a carbene insertion reaction, is also described.

Since the discovery of thienamycin,[1] the carbapenem antibiotics have attracted much attention because of their novel chemical structures and potent antibacterial properties.

The recently discovered carbapenem antibiotic C-19393 H_2 (1a)[2a,†] is unique in that it has a 1-hydroxy-1-methylethyl moiety at the 6-position with the 5,6-*cis*-relative stereochemistry. The antibiotic (1a), and its derivatives obtained by chemical modification of compound (1a) at the C(3) position [*e.g.* compounds (1b—e)],[2c] possess not only a highly potent, broad-spectrum antibacterial activity, but also a strong β-lactamase inhibitory activity. It is also noteworthy that, in aqueous solution, compound (1a) is more stable than cephalosporin C and several other carbapenems (*e.g.* epithienamycin B and MM-17880).[2b] These attractive properties prompted us to undertake a synthesis of compound (1a) and its analogues in order to study the structure–activity relationships.

Syntheses of a few 5,6-*cis*-carbapenems [*i.e.* (±)-epithienamycin (A, B),[3] (±)-epi-PS-5[4]] have recently been reported. However, because of the limited applicability with regard to the substituent at the C(6) position, these processes appear to be inapplicable to the synthesis of compound (1a) and its analogues. The introduction of a substituent onto the C(6) position in the *cis*-configuration was the most important step for the exploration of a generally applicable synthesis of *cis*-carbapenems. In the aldol reaction of β-lactam enolates, which has vast utility for the introduction of a substituent onto the C-3 position of a β-lactam, thermodynamically favoured *trans*-β-lactams are preferentially formed.[5] In the original total synthesis of (±)-thienamycin,[6] the azetidinone with the hydroxyethyl side-chain in the *trans*-configuration was obtained in 89% yield by the aldol reaction of the bicyclic azetidinone (2a) with acetaldehyde; the *cis*-isomer was obtained as a minor product (9%). The aldol reaction of compound (2a) with acetone was also described in the patent literature [7] as giving the *cis*-azetidinone (3a), but only in poor yield (5%); the *trans*-isomer (4a) was the major product (42%).

The *cis*-azetidinones (3a, b) are of particular interest to us because they possess moieties of suitable functionality for the synthesis of compound (1a) and its analogues. In this paper we describe an efficient synthesis of the *cis*-azetidinones (3a, b) and the first total synthesis of (±)-C-19393 H_2 (1a) and its derivatives (1b—e) using compounds (3a, b) as key intermediates.



(1)

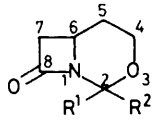
a; R = S(O)C(H)=CNHAc (*R*)

b; R = S(O)C(H)=CNHAc (*S*)

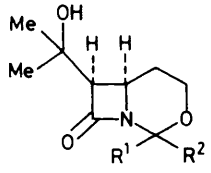
c; R = SC(H)=CNHAc

d; R = H

e; R = SCH_2CH_2NHAc



(2)



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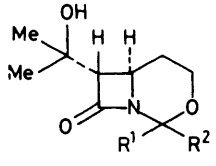


(4)

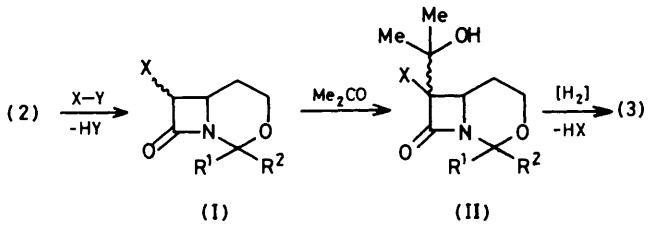
(2)–(4) a; $R^1 = R^2 = Me$

b; $R^1R^2 = -[CH_2]_5-$

Results and Discussion

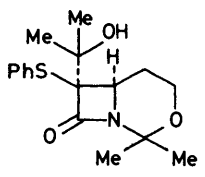
Taking into consideration previous findings that desulphurization of sulphenylated β-lactams with Raney nickel [8] and the reduction of 6-halogeno-[9] and 6-isocyano-penicillanates [10] with tri-n-butyltin hydride give thermodynamically unfavoured *cis*-β-lactams, we planned a possible synthetic route to the *cis*-azetidinones (3a, b) as illustrated in the Scheme. The key feature of this approach is the stereoselective reduc-

† The same structure has been proposed for carpetimycin A (M. Nakayama, A. Iwasaki, S. Kimura, T. Mizoguchi, S. Tanabe, A. Murakami, M. Okuchi, H. Itoh, Y. Saino, F. Kobayashi, and T. Mori, *J. Antibiot.*, 1980, **33**, 1388; M. Nakayama, S. Kimura, S. Tanabe, T. Mizoguchi, I. Watanabe, T. Mori, K. Miyahara, and T. Kawasaki, *ibid.*, 1981, **34**, 818).

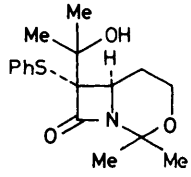


(I) (II)

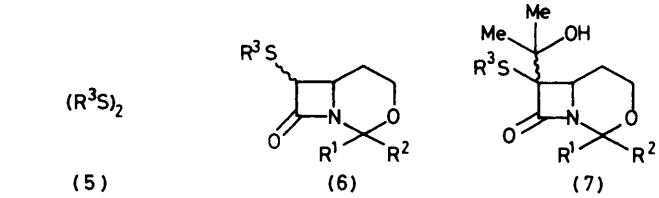
Scheme



(7a-i)
major isomer



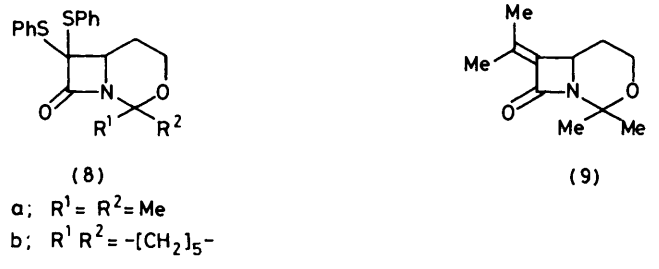
(7a-ii)
minor isomer



(5)
a; R^3 = Ph
b; R^3 = 2-pyridyl
c; R^3 = Me
d; R^3 = $Me_2NC(=S)$

(6)
a; R^1 = R^2 = Me, R^3 = Ph
b; R^1 = R^2 = Me, R^3 = 2-pyridyl
c; R^1 = R^2 = R^3 = Me
d; R^1 = R^2 = Me, R^3 = $Me_2NC(=S)$
e; R^1R^2 = $-[CH_2]_5-$, R^3 = Ph

(7)



(8)
a; R^1 = R^2 = Me
b; R^1R^2 = $-[CH_2]_5-$

(9)

tion of the intermediate (II) where X is an appropriate substituent easily introducible into the azetidinones (2a, b) and readily replaceable by a hydrogen atom. We found that organosulphur groups are very effective as the substituent X.

Sulphenylation of compound (2a) with diphenyl disulphide (5a) (1 equiv.) was carried out in tetrahydrofuran (THF) at −78 °C, using lithium di-isopropylamide (LDA) as a base, to obtain the mono-sulphenylated product (6a) * and the bis-sulphenylated product (8a). In this reaction the amount of the base (LDA) had a significant effect on the ratio of the products (6a) : (8a); *i.e.* when 1.2 equiv. of LDA were used, (6a) and (8a) were obtained in 46% and 21% yield, respectively, whereas with 2.1 equiv. of LDA, the mono-sulphenylated product (6a) was obtained in 89% yield, along with a small amount of (8a) (5%). These results are similar to those observed in the sulphenylation of 1-methylpyrrolidin-2-one and 1-methylpiperidin-2-one.[11] The stereochemistry of compound (6a) was confirmed as *trans* by the n.m.r. spectrum ($J_{6,7}$ 2 Hz).

The aldol reaction of the enolate of compound (6a) proceeded smoothly by treatment with acetone (excess) at −78 °C to give a mixture of the aldolization products (7a-i) and (7a-ii), which are separable by chromatography, in a ratio of 3.4 : 1 in 94% yield (Method A). Alternatively, compounds (7a-i) and (7a-ii) were more conveniently obtained in 79% yield directly from compound (2a) by successive treatment with LDA (2.2 equiv.), diphenyl disulphide (5a) (1 equiv.), and acetone (excess) at −78 °C in THF (Method B).†

The stereochemistry of compounds (7a-i) and (7a-ii) was confirmed as that shown in the Figure by a single-crystal *X*-ray analysis [12] of the minor product (7a-ii). This result is consistent with mechanistic considerations; the reagent (acetone) preferentially approaches the enolate of compound (6a) from the less hindered α-side of the molecule to give compound (7a-i) as the major product. The *X*-ray analysis of compound (7a-ii) also indicated that one methyl group of the $NCMe_2O$ moiety lies over the plane of the benzene ring; this causes an extraordinarily high shift of a methyl signal (δ 0.65) in the n.m.r. spectrum (Table 3).

The aldolization products (7a-i), (7a-ii) were then subjected to reductive desulphurization. However, desulphurization of compound (7a-i) with Raney nickel unexpectedly gave the *trans*-azetidinone (4a) as a major product (47%; m.p. 102—104 °C; $J_{6,7}$ 2 Hz) and the *cis*-isomer (3a) as a minor product (21%; m.p. 125—127 °C; $J_{6,7}$ 6 Hz) together with the isopropylidene lactam (9) (10%) after separation by chromatography.

Our attention was then directed to an organotin hydride reduction, since several kind of sulphides are reductively desulphurized with an organotin hydride.[13] When compound (7a-i) was heated with tri-n-butyltin hydride (3.3 equiv.) in the presence of azobisisobutyronitrile (AIBN) (0.2 equiv.) in acetone, reduction proceeded as expected to give, after chromatographic separation, the *cis*-azetidinone (3a) in 72% yield in preference to the *trans*-isomer (4a) (22%); formation of the isopropylidene lactam (9) was not observed.

The reduction was found to give the same products in almost the same ratio regardless of the stereochemistry of the C(7) substituents; *i.e.* compound (7a-ii) gave the isomers (3a) and (4a) in 71% and 22% yield, respectively. Thus we were able to use a mixture of compounds (7a-i) and (7a-ii), without prior separation of the isomers, for the desulphurization (Table 4, entry 3). These results indicate that the same intermediate (presumably a radical intermediate) is formed regardless of the C(7) stereochemistry of the starting materials, and the hydrogen transfer from the bulky tri-n-butyltin hydride takes place from the less hindered α-side of the molecule. It is also noteworthy that, for completion of the reduction, compound (7a-i) required more than 15 h reaction time, whereas its epimer (7a-ii) required only 5 h, suggesting that elimination of the phenylthio radical from (7a-ii), where the phenylthio-group is substituted in the less hindered α-side, is faster than that from (7a-i).

In order to examine this reductive desulphurization in more detail, the azetidinones (2a, b) were converted into the aldolization products (7a—e) using several disulphides (5a—d) by Method A and/or Method B described above. These results are summarized in Table 1—3. The aldolization products (7a—e) were subjected to desulphurization using an organotin hydride (Bu^n_3SnH or Ph_3SnH) in the presence of a

* All the β-lactams prepared in this study are racemic, but only one enantiomer is depicted for convenience.

† The ratio (7a-i):(7a-ii) (15:1) differed from that obtained in Method A. The reason has not yet been clarified.

Table 1. Sulphenylation of the 3-oxa-1-azabicyclo[4.2.0]octan-8-ones (2a,b)

Entry	Starting material	Disulphide	Product (6,7-stereochemistry)	Yield [a] (%)	M.p. (°C)	$\nu_{max.}$ [b] [(C=O) cm^{-1}]	δ(CDCl$_3$) 7-H, multiplicity, *J* (Hz)	Formula	Found (Required) % C	H	N
1	(2a)	(5a)	(6a) (*trans*)	89.3 (45.8)	49—51	1 740	3.95, d *J* 2	$C_{14}H_{17}NO_2S$	64.0 (63.85	6.4 6.5	5.2 5.3)
			(8a)	4.5 (21.2)	79—81	1 740		$C_{20}H_{21}NO_2S_2$	64.7 (64.7	5.8 5.7	3.9 3.8)
2	(2a)	(5b)	(6b) (*trans*)	74.9	oil	1 750	4.66, d *J* 2	$C_{13}H_{16}N_2O_2S$	(59.1	6.1	*c* 10.6)
3	(2a)	(5c)	(6c) (*trans*: *cis* = 3:1)	70.0	oil	1 740	*d*	$C_9H_{15}NO_2S$	(53.7	7.5	*c* 7.0)
4	(2a)	(5d)	(6d) (*trans*)	65.7	128—129	1 740	4.68, d *J* 1.5	$C_{11}H_{18}N_2O_2S$	48.3 (48.2	6.8 6.6	10.2 10.2)
5	(2b)	(5a)	(6e) (*trans*)	72.2	133—134	1 730	3.88, d *J* 2	$C_{17}H_{21}NO_2S$	67.2 (67.3	6.8 7.0	4.4 4.6)
			(6e) (*cis*)	2.9	133—135	1 725	4.60, d *J* 5	$C_{17}H_{21}NO_2S$	66.9 (67.3	7.0 7.0	4.7 4.6)
			(8b)	5.0	124—126	1 740		$C_{23}H_{25}NO_2S_2$	67.3 (67.1	6.2 6.1	3.9 3.9)

[a] In parentheses, yield estimated by reaction using 1:1:1.2 proportions of reagents (2):(5): base (LDA); others, 1:1:2.0—2.3. [b] Compounds (6a), (6d), (6e), (8a), and (8b) were measured in Nujol; (6b) and (6c) as neat liquids. [c] Not analyzed. [d] Overlapped with other signals.

Table 2. Preparation of the 7-(1-hydroxy-1-methylethyl)-7-sulphenylazetidinones (7a—e) from compound (2) and/or (6)

Entry	Starting material	Method [a]	Product	Ratio of isomers	Yield [b] (%)
1	(6a) [c]	A	(7a)	3.4:1 [d]	94
2	(2a)	B	(7a)	15:1 [d]	79
3	(6b) [c]	A	(7b)	2.3:1 [e]	80
4	(6c) [f]	A	(7c)	9.4:1 [d]	58
5	(6d) [c]	A	(7d)	3.0:1 [e]	60
6	(2a)	B	(7d)	3.0:1 [e]	35
7	(6e) [c]	A	(7e)	4.0:1 [e]	80

[a] Method, A, B; see Experimental section. [b] Combined yield of the isolated compounds. [c] *trans*-Isomer. [d] Determined for the separated isomers. [e] Determined for the unseparated isomers by n.m.r. [f] A *trans*: *cis* (3:1) mixture.

radical initiator (AIBN or *hν*). The results are summarized in Table 4.

In Table 4 the following results appear to be particularly noteworthy: (i) the *cis*-azetidinones were the predominant products in all the attempted reactions; (ii) the organosulphur groups (R^3S) had a noticeable effect on the rate of the reaction and the yield of the products; the following order of the ease of tin hydride-induced homolysis of the organosulphur groups was observed: [13b] Me_2NCSS > PhS > 2-pyridylthio > MeS; (iii) alteration of R^1 and R^2 groups had little effect on the reaction (entries 1, 7); (iv) photo-irradiation also initiated the reaction (entry 9); and (v) triphenyltin hydride seemed to be more effective than tri-n-butyltin hydride; the reaction was complete using only 2 mol equiv. of triphenyltin hydride and the *cis*/*trans* ratio was slightly increased (entries 3, 8).

Thus, an efficient and stereoselective synthesis of the *cis*-azetidinones (3a, b) with the 1-hydroxy-1-methylethyl moiety was achieved. We next attempted a total synthesis of (±)-C-19393 H_2 (1a) and its derivatives (1b—e), using compounds (3a, b) as key intermediates, *via* a carbene-insertion reaction.[14]

To apply the carbene-insertion reaction to the synthesis of the *cis*-carbapenems, conversion of compounds (3a, b) into an azetidinone with a *cis*-carboxymethyl moiety at the C(4) position [*e.g.* compounds (12) or (13)] was first investigated. In this reaction, protection of the hydroxy-group seemed to be crucial because of its *cis*-stereochemistry; *e.g.* Jones oxidation of compound (3a), without protection of the hydroxy-group, gave the lactone (11) instead of the desired carboxylic acid (12). Because of the large steric hindrance, however, protection of the hydroxy-group was difficult; the steric hindrance of the tertiary hydroxy-group is increased by the *cis*-substituent. Attempts to protect the hydroxy-group with a *p*-nitrobenzyloxycarbonyl or a t-butyldimethylsilyl group (groups currently used in β-lactam chemistry) failed. Protection was finally achieved by using (2-methoxyethoxy)methyl (MEM) chloride.[15]

Treatment of compound (3a) with MEM chloride (*ca.* 3 equiv.) in methylene dichloride at room temperature for 21 h gave the protected azetidinone (10a), Jones oxidation of which produced the carboxylic acid (13) [80% from (10a)] which was also obtained from compound (3b) *via* (10b) in 66% yield. The acid was then converted into the keto-ester (14) (82%) by successive treatment with *NN'*-carbonyldi-imidazole and the magnesium salt of the mono-*p*-nitrobenzyl ester of malonic acid.[16] Reaction of compound (14) with toluene-*p*-sulphonyl azide in the presence of triethylamine gave the diazo-ester (15) in 88% yield. Cleavage of the MEM group [15] was successfully effected by treating compound (15) with titanium tetrachloride (*ca.* 6 equiv.) in methylene dichloride at 0 °C for 1 h to afford compound (16) in 82% yield.

The carbene-insertion reaction of compound (16) in the presence of rhodium diacetate was carried out according to the reported procedure [14] to form the bicyclic β-lactam (17).* By treatment with diphenyl chlorophosphate in the presence of di-isopropylethylamine, compound (17) was transformed into the enol phosphate (18), which was used without isolation in the subsequent addition–elimination reaction with the thiol compounds *N*-acetylcysteamine and silver (*E*)-2-acetamidoethenethiolate.[3,17] Reaction of compound (18) with *N*-acetylcysteamine in the presence of di-isopropylethylamine afforded the protected carbapenem (19) in 44% yield from (16). Deprotection of compound (19) by hydrogenolysis using

* The bicyclic β-lactam (17) was obtained as a single stereoisomer. The stereochemistry at the C(2) position was assigned as shown in the formula from steric considerations and from results already obtained from similar compounds (*cf.*, ref. 14*a*).

Table 3. Properties of the 7-(1-hydroxy-1-methylethyl)-7-sulphenylazetidinones (7a—e)

Compound	M.p. (°C)	$\nu_{max.}$ (Nujol) [(C=O) cm^{-1}]	δ($CDCl_3$)	Formula	Found (Required) % C	H	N
(7a—i) [a]	95—97	1 725	1.33 and 1.40 (each 3 H, s), 1.56 (6 H, s), 1.70 (1 H, m), 2.30 (1 H, m), 2.7 (1 H, s), 3.7—4.1 (3 H, m), and 7.2—7.8 (5 H, m)	$C_{17}H_{23}NO_3S$ [b]	63.5 (63.5	7.25 7.2	4.45 4.4)
(7a—ii) [c]	188—189	1 720	0.65, 1.42, 1.58, and 1.68 (each 3 H, s), 1.75 (1 H, m), 2.4 (1 H, s), 2.92 (1 H, m), 3.4—3.8 (3 H, m), and 7.2—7.7 (5 H, m)	$C_{17}H_{23}NO_3S$ [d]	63.35 (63.5	7.1 7.2	4.5 4.4)
(7b) [e]	124—125	1 735	1.30, 1.40, 1.64, and 1.70 (each 0.9 H, s), 1.39, 1.41, 1.49, and 1.71 (each 2.1 H, s), 1.0—2.3 (2 H, m), 2.1 (1 H, s), 3.72 (2 H, m), 4.15 (1 H, m), 7.0—7.8 (3 H, m), and 8.3 (1 H, m)	$C_{16}H_{22}N_2O_3S$	59.5 (59.6	7.2 6.9	8.6 8.7)
(7c—i) [a]	95—97	1 720	1.27, 1.43, 1.48, and 1.72 (each 3 H, s), 1.8 (2 H, m), 2.35 (3 H, s), 2.5 (1 H, s), and 3.7—4.0 (3 H, m)	$C_{12}H_{21}NO_3S$	55.2 (55.6	8.0 8.2	5.5 5.4)
(7c—ii) [c]	oil	1 740	1.37, 1.47, 1.63, and 1.80 (each 3 H, s), 1.9 (2 H, m), 2.23 (3 H, s), 2.3 (1 H, s), 3.7—4.1 (3 H, m)	$C_{12}H_{21}NO_3S$	(55.6	8.2	5.4) [f]
(7d—i) [a]	124—126	1 750	1.45 (6 H, s), 1.60 and 1.72 (each 3 H, s), 2.2 (2 H, m), 3.47 (6 H, s), 3.9 (2 H, m), 4.3 (1 H, m), and 4.5 (1 H, s)	$C_{14}H_{24}N_2O_3S_2$	50.7 (50.6	7.4 7.3	8.55 8.4)
(7d—ii) [c]	166—167	1 740	1.37, 1.42, 1.52, and 1.72 (each 3 H, s), 2.2 (2 H, m), 3.50 (6 H, s), 3.8 (2 H, m), 4.2 (1 H, m), and 5.75 (1 H, s)	$C_{14}H_{24}N_2O_3S_2$	50.7 (50.6	7.4 7.3	8.3 8.4)
(7e) [g]	98—100	1 740	1.3—2.3 (18 H, m), 2.0 (1 H, s), 3.4—4.1 (3 H, m), and 7.2—7.7 (5 H, m)	$C_{20}H_{27}NO_3S$	66.5 (66.45	7.6 7.5	4.1 3.9)

[a] Major isomer. [b] *m/z* 321 (M^+). [c] Minor isomer. [d] *m/z* 321 (M^+). [e] A 2.3:1 isomeric mixture (n.m.r.). [f] Not analysed. [g] Presumably a mixture of isomers; the relative ratio could not be determined.

Table 4. Desulphurization of compounds (7a—e) with an organotin hydride

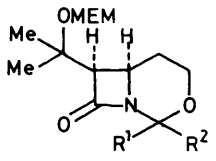
Entry	Starting material (7) (isomer ratio)	Reagent [a] (mol equiv.)	Initiator [b]	Reaction time [c] (h)	Product ratio [d] (3) :(4) (*cis*) :(*trans*)	Yield [e] (%)
1	(a-i)	B (3.3)	A	16	3.3:1	94
2	(a-ii)	B (3.3)	A	5	3.2:1	93
3	(a-i)–(a-ii) (3.4:1)	B (3.3)	A	16	3.7:1	94
4	(b-i)–(b-ii) (2.3:1)	B (3.3)	A	16	3.4:1	52 [f]
5	(c-i)	B (3.3)	A	17	3.7:1	28 [g]
6	(d-i)–(d-ii) (3:1)	B (2.5)	A	5	3.4:1	96
7	(e-i)–(e-ii) (4:1)	B (3.3)	A	14	3.7:1	94
8	(a-i)–(a-ii) (20:1)	P (2.0)	A	22	4.8:1	96
9	(a-i)–(a-ii) (20:1)	P (2.0)	*hν* [h]	6	4.3:1	93

[a] B, Bu^n_3SnH; P, Ph_3SnH. [b] A, AIBN (0.2 mol equiv.). [c] Entries 1—8, under reflux in acetone; entry 9, at room temperature in acetone. [d] Determined for the isolated isomers. [e] Combined yield of the isolated isomers. [f] Recovery of the starting material, 26%. [g] Recovery of the starting material, 68%. [h] A 300-W high-pressure mercury lamp was used.

10% palladium–charcoal in aqueous THF followed by purification by column chromatography (XAD-2 and Dianion HP-20), afforded the carbapenem sodium salt (1e) (55%).

A similar reaction of the enol phosphate (18) with silver (*E*)-2-acetamidoethenethiolate in the presence of sodium iodide afforded compound (20) [67% from (16)], which was deprotected to give the sodium salt (1c) (66%) by a similar procedure as described for (19).

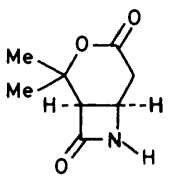
Oxidation of compound (1c) with *m*-chloroperbenzoic acid (1.2 equiv.) in water at 0 °C gave the two diastereoisomers of the corresponding sulphoxide which were successfully separated by chromatography on Diaion HP-20 to afford (±)-



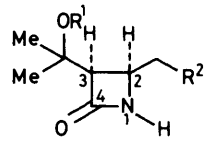
(10)

a; $R^1 = R^2 = Me$

b; $R^1R^2 = -[CH_2]_5-$



(11)



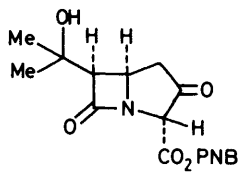
(12) $R^1 = H$, $R^2 = CO_2H$

(13) $R^1 = MEM$, $R^2 = CO_2H$

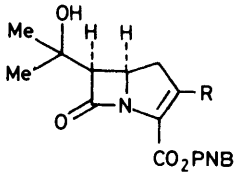
(14) $R^1 = MEM$, $R^2 = COCH_2CO_2PNB$

(15) $R^1 = MEM$, $R^2 = COC(=N_2)CO_2PNB$

(16) $R^1 = H$, $R^2 = COC(=N_2)CO_2PNB$



(17)



MEM = $CH_2OCH_2CH_2OMe$

PNB = $CH_2C_6H_4NO_2$-*p*

(18) R = $OP(=O)(OPh)_2$

(19) R = SCH_2CH_2NHAc

(20) R = $SC(=CHNHAc)H$

C-19393 H_2 (1a) which has the *R*-configuration at sulphur [2b,c] (53%), and its *S*-sulphoxide isomer (1b) [2c] (41%).

During the deprotection procedures used on compounds (19) and (20), the hydrogenolysis of the C(3)–S bond was observed to afford compound (1d) as a by-product in low yield.

The racemic *cis*-carbapenems (1a—e) prepared by the above method were identical (h.p.l.c. and i.r., u.v., and n.m.r. spectra) with the natural compound C-19393 H_2 and its derivatives,[2b,c] and showed, as expected, *ca.* 50% of the biological activity of the natural products in *in vitro* antibacterial tests.

Application of this synthetic process to the synthesis of 5,6-*cis*-carbapenems having various substituents at the C(3) and C(6) positions, and the antibacterial activity of the new 5,6-*cis*-carbapenems, will be reported elsewhere.

Experimental

M.p.s were determined using a Yanagimoto m.p. apparatus and are uncorrected. I.r. spectra were measured with a Hitachi 215 spectrophotometer for Nujol mulls unless otherwise stated. ^1H N.m.r. spectra were taken on a Varian T-60 (60 MHz), a Varian EM-390 (90 MHz), or a Varian XL-100 (100 MHz) spectrometer for solutions in $CDCl_3$ unless otherwise stated, with $SiMe_4$ as internal standard. U.v. spectra were taken with a Perkin-Elmer 450 or a Hitachi EPS-3T spectrophotometer, and mass spectra with a JEOL JMS-01SC mass spectrometer. H.p.l.c. data were obtained using a Waters LAC/GPC-202/660 equipment, and the analytical conditions were as follows: Radial Pak A; MeOH–0.02M phosphate buffer (p.b.) (pH 6.3); flow rate 2 ml min^{-1}. Extracted solutions were dried over sodium sulphate. All the β-lactams prepared are racemic.

Spiro{cyclohexane-1,2′-[3]-oxa-[1]-azabicyclo[4.2.0]octan}-8′-one * (2b).—A solution of 4-(2-hydroxyethyl)azetidin-2-one [6] (2.0 g, 17.3 mmol) and cyclohexanone (2.5 g, 25.5 mmol) in dry methylene dichloride (25 ml) was treated with BF_3–ether (47%) (0.2 ml, 1.98 mmol) at 25 °C. After being stirred for 1.5 h at 25 °C the mixture was concentrated and the residue was subjected to chromatography on silica gel. Elution with hexane–ethyl acetate (1 : 2 v/v) gave the *azetidinone* (2b) (1.8 g, 53.3%) as crystals, m.p. 71—72 °C (Found: C, 67.6; H, 8.9; H, 7.1. $C_{11}H_{17}NO_2$ requires C, 67.7; H, 8.8; N, 7.2%); $\nu_{max.}$ (KBr) 1 730 cm^{-1}; δ 1.38—2.40 (total 12 H, m, 6 × CH_2), 2.63 (1 H, dd, *J* 14 and 2 Hz, 7′-H), 3.01 (1 H, dd, *J* 14 and 5 Hz, 7′-H), 3.20—3.72 (1 H, m, 6′-H), and 3.74—3.79 (2 H, m, CH_2O).

Sulphenylation of the Azetidinones (2a, b).—A solution of 2,2-dimethyl-3-oxa-1-azabicyclo[4.2.0]octan-8-one (2a) [6] (4.65 g, 0.03 mol) in dry THF (30 ml) was added during 20 min at −78 °C to a solution of LDA, prepared from n-butyl-lithium (42 ml of 15% hexane solution, 0.067 mol) and di-isopropylamine (8.82 ml, 0.063 mol) in dry THF (140 ml) at −78 °C under nitrogen, and the mixture was then stirred for 10 min. To this enolate solution at −78 °C was added, during 25 min, a solution of diphenyl disulphide (5a) (6.54 g, 0.03 mol) in dry THF (30 ml). After being stirred for 10 min at −78 °C the reaction mixture was poured into ice-cooled saturated aqueous ammonium chloride. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined extracts were washed in turn with 0.5M-NaOH and water, dried, and evaporated to dryness. The residue was treated with di-isopropyl ether to give crystals of the *mono-sulphenylated azetidinone* (6a) (5.72 g). The mother liquor was concentrated and the residue was subjected to chromatography on silica gel. Elution with hexane–ethyl acetate (4 : 1 v/v) afforded the crystalline *bis-sulphenylated azetidinone* (8a) (0.50 g, 4.5%) and an additional crop of compound (6a) (1.33 g; combined yield 7.05 g, 89.4%). Properties of compounds (6a) and (8a) are listed in Table 1.

Similar sulphenylation reactions of the azetidinones (2a, b) with the disulphides diphenyl disulphide (5a), bis-(2-pyridyl) disulphide (5b), dimethyl disulphide (5c), and bis[(dimethyl-amino)thiocarbonyl] disulphide † (5d) were carried out. The results are summarized in Table 1.

(7R)- *and* (7S)-7-(1-*Hydroxy*-1-*methylethyl*)-2,2-*dimethyl*-7-*phenylthio*-3-*oxa*-1-*azabicyclo*[4.2.0]*octan*-8-*one* (7a-i) *and* (7a-ii).—*Method A. Aldol reaction of the mono-sulphenylated azetidinone* (6a). A solution of compound (6a) (3.95 g, 15 mmol) in dry THF (15 ml) was added at −78 °C to a solution of LDA, prepared from n-butyl-lithium (15 ml of 15% hexane solution, 24.0 mmol) and di-isopropylamine (3.16 ml, 22.5 mmol) in dry THF (80 ml) under nitrogen at −78 °C, and the mixture was then stirred for 10 min at −78 °C. To this

* Contrary to usual practice braces will be used, instead of the usual square brackets in the systematic names of spiro-compounds of this type, as an aid to clarity.

† Tetramethylthiuram disulphide.

enolate solution was added dry acetone (5 ml). After being stirred for 0.5 h at −78 °C the mixture was poured into a stirred solution of acetic acid (4 ml) and water (150 ml) at <5 °C. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined extracts were washed with water, dried, and concentrated. The residue was treated with di-isopropyl ether and hexane to give a crystalline mixture of compounds (7a-i) and (7a-ii) (2.4 : 1 by n.m.r.; 3.50 g, 72.7%). The filtrate was concentrated and the residue was subjected to chromatography on silica gel. Gradient elution with hexane–ethyl acetate (4 : 1 ⟶ 1 : 1 v/v) gave recovered starting material (6a) (0.16 g) and compound (7a-i) (1.0 g, 20.8%), both as crystals. A part of the aforementioned mixture (7a-i)–(7a-ii) (1.0 g) was subjected to chromatography on silica gel with hexane–ethyl acetate (4 : 1 ⟶ 1 : 1 v/v) as eluant. The mixture was separated, and work-up afforded compounds (7a-i) (0.7 g) and (7a-ii) (0.3 g) whose properties are listed in Table 3.

Method B. Direct preparation from the azetidinone (2a). A solution of compound (2a) (0.93 g, 6 mmol) in dry THF (6 ml) was added at −78 °C to a solution of LDA, prepared from n-butyl-lithium (8.4 ml of 15% hexane solution, 13 mmol) and di-isopropylamine (1.74 ml, 12 mmol) in dry THF (80 ml) under nitrogen at −78 °C, and the mixture was then stirred for 5 min at −78 °C. To this enolate solution was added a solution of diphenyl disulphide (5a) (1.31 g, 6 mmol) in dry THF (6 ml) during 15 min at −78 °C. After being stirred for 5 min at −78 °C the mixture was treated with dry acetone (2 ml) and was then stirred for 5 min and poured into a stirred mixture of saturated aqueous ammonium chloride and ethyl acetate at between −10 and −20 °C. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined extracts were washed in turn with 0.5M-NaOH and water, dried, and evaporated to dryness. The residue was treated with hexane to give a crystalline mixture of compounds (7a-i) and (7a-ii) (*ca.* 20 : 1 by n.m.r.) (1.36 g, 70.6%). The mother liquor was concentrated and the residue was subjected to chromatography on silica gel. Gradient elution with hexane–ethyl acetate (4 : 1 ⟶ 1 : 1 v/v) gave crystals of the following compounds: the bis-sulphenylated azetidinone (8a) (0.10 g, 4.5%), the mono-sulphenylated azetidinone (6a) (0.04 g, 2.5%), (7a-ii) (0.03 g, 1.5%), and (7a-i) (0.13 g, 6.7%).

The results of other aldol reactions by Method A and/or Method B are summarized in Tables 2 and 3.

Desulphurization of Compound (7a-i) *with Raney Nickel.*—A mixture of compound (7a-i) (128 mg, 0.4 mmol), Raney nickel (W-2) (3 ml), and acetone (10 ml) was stirred and refluxed for 2 min. The mixture was then filtered and the filtrate was concentrated. The residue was chromatographed on silica gel with hexane–ethyl acetate (1 : 1 v/v) as eluant to give the *isopropylideneazetidinone* (9) (8 mg, 10%), the cis-*azetidinone* (3a) (18 mg, 21%), and the trans-*azetidinone* (4a) (40 mg, 47%), all three as crystalline compounds. I.r. and n.m.r. spectra of compounds (3a) and (4a) were identical with those of the compounds obtained by the desulphurization of compounds (7a-i) and (7a-ii), respectively, with an organotin hydride (see below). Compound (9) had m.p. 107—108 °C (Found: C, 67.6; H, 8.5; N, 7.1. $C_{11}H_{17}NO_2$ requires C, 67.7; H, 8.8; N, 7.2%); $\nu_{max.}$ 1 720 cm^{-1}; δ 1.47, 1.77, 1.82, and 2.08 (each 3 H, s, Me), 1.8 (2 H, m, CH_2), and 3.8—4.1 (total 3 H, m, CHN and CH_2O).

Desulphurization of Compounds (7a-i) *and* (7a-ii) *with Tri-n-butyltin Hydride.*—A mixture of compounds (7a-i) and (7a-ii) (3.4 : 1) (20 g, 62 mmol), AIBN (2.0 g), tri-n-butyltin hydride (56.4 ml, 210 mmol), and acetone (500 ml) was refluxed for 16 h under nitrogen. The mixture was evaporated to dryness and the residue was dissolved in chloroform. After filtration to remove insoluble materials, the filtrate was concentrated and the residue was treated with di-isopropyl ether to give the crystalline *cis*-azetidinone (3a) (8.13 g, 61.3%). The mother liquor was concentrated and the concentrate was subjected to chromatography on silica gel. Elution with hexane–ethyl acetate (1 : 1 v/v) gave an additional crop of the *cis*-azetidinone (3a) (1.70 g, 12.8%) and the crystalline *trans*-azetidinone (4a) (2.63 g, 19.8%). *Compound* (3a) had m.p. 125—127 °C (Found: C, 61.7; H, 8.9; N, 6.7. $C_{11}H_{19}NO_3$ requires C, 61.9; H, 9.0; N, 6.6%); *m/z* 213 (M^+); $\nu_{max.}$ 3 450 and 1 720 cm^{-1}; δ 1.30, 1.43, 1.50, and 1.80 (each 3 H, s, Me), 1.9 (2 H, m, CH_2), 2.23 (1 H, s, OH), 3.27 (1 H, d, *J* 6 Hz, 7-H), and 3.7—4.1 (total 3 H, m, 6-H and CH_2O). *Compound* (4a) had m.p. 102—104 °C (Found: C, 62.1; H, 8.9; N, 6.5. $C_{11}H_{19}NO_3$ requires C, 61.9; H, 9.0; N, 6.6%); *m/z* 213 (M^+); $\nu_{max.}$ 3 450 and 1 720 cm^{-1}; δ 1.30, 1.37, 1.43, and 1.77 (each 3 H, s, Me), 1.9 (2 H, m, CH_2), 2.0 (1 H, s, OH), 2.91 (1 H, d, *J* 2 Hz, 7-H), and 3.5—4.1 (total 3 H, m, 6-H and CH_2O).

The results of other desulphurization reactions are summarized in Table 4. The data for both the cis-*azetidinone* (3b) and the trans-*azetidinone* (4b) are as follows: (3b); m.p. 153—154 °C (Found: C, 66.0; H, 9.1; N, 5.5. $C_{14}H_{23}NO_3$ requires C, 66.4; H, 9.15; N, 5.5%); $\nu_{max.}$ 3 500 and 1 720 cm^{-1}; δ 1.27 and 1.47 (each 3 H, s, Me), 1.3—3.0 (total 12 H, m, 6 × CH_2), 1.97 (1 H, s, OH), 3.18 (1 H, d, *J* 5 Hz, 7-H), and 3.6—3.9 (total 3 H, m, 6-H and CH_2O). (4b); m.p. 83—84 °C (Found: C, 66.4; H, 9.0; N, 5.7. $C_{14}H_{23}NO_3$ requires C, 66.4; H, 9.15; N, 5.5%); $\nu_{max.}$ 3 500 and 1 710 cm^{-1}; δ 1.27 and 1.33 (each 3 H, s, Me), 1.3—2.4 (total 12 H, m, 6 × CH_2), 2.0 (1 H, s, OH), 2.76 (1 H, d, *J* 2 Hz, 7-H), 3.5 (1 H, m, 6-H), and 3.8 (2 H, m, CH_2O).

Oxidation of the Azetidinone (3a).—To a stirred, cooled (0 °C) solution of the azetidinone (3a) (43 mg, 0.2 mmol) in acetone (2 ml) was added an 8N solution of Jones reagent (0.4 ml). After being stirred for 1.5 h at 0 °C the mixture was treated with isopropyl alcohol (0.2 ml) and was then stirred for 2 min and diluted with methylene dichloride. Filtration, followed by evaporation of the filtrate gave an oily residue which was dissolved in chloroform. The solution was washed with aqueous sodium chloride, dried, and evaporated to dryness. The residue was chromatographed on silica gel with ethyl acetate–methanol (10 : 1, v/v) as eluant to give the *lactone* (11) (26 mg, 76.5%) as crystals, m.p. 190—192 °C (Found: C, 56.4; H, 6.4; N, 8.1. $C_8H_{11}NO_3$ requires C, 56.8; H, 6.55; N, 8.3%); $\nu_{max.}$ 3 230, 1 750, and 1 720 cm^{-1}; δ [$(CD_3)_2SO$] 1.39 and 1.70 (each 3 H, s, Me), 2.62 (1 H, dd, *J* 16.5 and 1.5 Hz, C*H*H), 3.65 (1 H, dd, *J* 16.5 and 4 Hz, CH*H*), 3.45 (1 H, dd, *J* 6 and 1.5 Hz, CHCO, changed to doublet on addition of D_2O), 4.1 (1 H, m, CHN), and 8.2br (1 H, NH, exchanged with D_2O).

6,7-cis-7-[1-(2-*Methoxyethoxymethoxy*)-1-*methylethyl*]-2,2-*dimethyl*-3-*oxa*-1-*azabicyclo*[4.2.0]*octan*-8-*one* (10a).—A mixture of the azetidinone (3a) (7.00 g, 33 mmol), di-isopropylethylamine (18.92 ml, 109 mmol), (2-methoxyethoxy)methyl chloride (12.40 ml, 109 mmol), and methylene dichloride (130 ml) was kept at room temperature for 21 h under nitrogen. The mixture was then washed successively with water, 2% aqueous acetic acid, saturated aqueous sodium hydrogen carbonate, and water and was then dried. The mixture was evaporated to dryness to give the azetidinone (10a) (quantitative) as a pale-yellow oil which was used in the subsequent oxidation without further purification; $\nu_{max.}$ (neat) 1 750 cm^{-1}; δ 1.27, 1.35, 1.45, and 1.65 (each 3 H, s, Me), 1.9 (2 H, m, 5-H_2), 3.10 (1 H, d, *J* 5 Hz, 7-H), 3.30 (3 H, s, OMe), 3.3—3.9

(total 7 H, m, 3 × CH_2O and 6-H), and 4.78 (2 H, s, OCH_2O).

Similarly, from the azetidinone (3b) was prepared the protected spiroazetidinone (10b) (quantitative) as a pale-yellow oil; $\nu_{max.}$ (neat) 1 740 cm^{-1}; δ 1.27 and 1.47 (each 3 H, s, Me), 1.2—2.7 (total 12 H, m, 6 × CH_2), 3.13 (1 H, d, *J* 5 Hz, 7-H), 3.32 (3 H, s, OMe), 3.4—3.9 (total 7 H, m, 3 × CH_2O and 6-H), and 4.80 (2 H, s, OCH_2O).

cis-3-[1-(2-*Methoxyethoxymethoxy*)-1-*methylethyl*]-4-*oxoazetidine*-2-*acetic Acid* (13).—To a stirred, cooled (0 °C) solution of the azetidinone (10a) (10.0 g, 33 mmol) in acetone (330 ml) was added dropwise an 8N solution of Jones reagent (33 ml). After being stirred for 4 h at 0 °C the mixture was treated with a further quantity of 8N-Jones reagent (6.6 ml) and was then stirred for an additional 1.5 h at 0 °C. After the addition of isopropyl alcohol (16 ml) the mixture was stirred for 15 min at 0 °C and was then diluted with methylene dichloride (150 ml). The insoluble materials were filtered off and the filtrate was concentrated. The concentrate was dissolved in chloroform (200 ml) and the solution was washed with saturated aqueous sodium chloride (8 ml), dried, and evaporated to dryness to give the *acid* (13) (7.24 g, 80.1%) as crystals, m.p. 87—89 °C (Found: C, 52.5; N, 7.4; N, 5.2. $C_{12}H_{21}NO_6$ requires C, 52.35; H, 7.7; N, 5.1%); $\nu_{max.}$ (KBr) 3 500—2 800 1 765, and 1 730 cm^{-1}; δ 1.33 and 1.51 (each 3 H, s, Me), 2.7—3.4 (total 3 H, m, CH_2CO_2 and 3-H), 3.37 (3 H, s, OMe), 3.4—3.8 (4 H, m, OCH_2CH_2O), 4.0 (1 H, m, 2-H), 4.83 (2 H, s, OCH_2O), 7.2br (1 H, NH), and 8.6br (1 H, CO_2H).

Similar oxidation of the azetidinone (10b) (510 mg) also gave the acid (13) (270 mg, 65.6%) which was identical (m.p., i.r., and n.m.r. spectra) with the acid (13) obtained from compound (10a).

p-*Nitrobenzyl* cis-4-{3-[1-(2-*Methoxyethoxymethoxy*)-1-*methylethyl*]-4-*oxoazetidin*-2-*yl*}-3-*oxobutanoate* (14).—To a solution of the acid (13) (7.78 g, 28 mmol) in dry THF (230 ml) was added *NN'*-carbonyldi-imidazole (di-imidazol-2-yl ketone) (6.37 g, 39 mmol). After the mixture had been stirred for 6 h at room temperature under nitrogen, magnesium *p*-nitrobenzyl malonate [$Mg(O_2CCH_2CO_2CH_2C_6H_4NO_2$-*p*)$_2$] (14.0 g, 28 mmol) was added. The mixture was stirred for 17 h at room temperature under nitrogen and was then diluted with ethyl acetate and washed successively with dilute hydrochloric acid, water, saturated aqueous sodium hydrogen carbonate, and water. The organic phase was dried, the solvent was evaporated off, and the residue was chromatographed on silica gel. Elution with ethyl acetate gave the azetidinone (14) (10.50 g, 82.1%) as a pale-yellow oil; $\nu_{max.}$ (neat) 3 300 and 1 760—1 720 cm^{-1}; δ 1.30 and 1.48 (each 3 H, s, Me), 3.33 (3 H, s, OMe), 3.63 (2 H, s, $COCH_2CO$), 3.2—4.1 (total 7 H, m, 3-H, CH_2CO and OCH_2CH_2O), 4.2 (1 H, m, 2-H), 4.80 (2 H, s, OCH_2O), 5.27 (2 H, s, OCH_2Ar), 6.52br (1 H, NH), 7.53 (2 H, d, *J* 11 Hz, 2 × ArH), and 8.20 (2 H, d, *J* 11 Hz, 2 × ArH).

p-*Nitrobenzyl* cis-2-*Diazo*-4-{3-[1-(2-*methoxyethoxymethoxy*)-1-*methylethyl*]-4-*oxoazetidin*-2-*yl*}-3-*oxobutanoate* (15).—To a stirred, cooled (0 °C) solution of the azetidinone (14) (10.5 g, 23.2 mmol) in dry acetonitrile (300 ml) was added a solution of toluene-*p*-sulphonyl azide (5.48 g, 27.8 mmol) in dry acetonitrile and triethylamine (11.6 ml, 83.4 ml). After being stirred for 0.5 h at room temperature the mixture was diluted with ethyl acetate, washed with saturated aqueous sodium chloride, and dried. After evaporation of the solvent, the residue was chromatographed on silica gel. Elution with ethyl acetate gave the *protected diazo-azetidinone* (15) (9.80 g, 88.3%) as crystals, m.p. 97—99 °C (Found: C, 52.3; H, 5.4; N, 11.6. $C_{21}H_{26}N_4O_9$ requires C, 52.7; H, 5.5; N, 11.7%); $\nu_{max.}$ 3 360, 3 210, 2 140, 1 730, 1 705, and 1 640 cm^{-1}; δ 1.37 and 1.53 (each 3 H, s, Me), 3.37 (3 H, s, OMe), 3.3—4.0 (total 7 H, m, 3-H, CH_2CO, and OCH_2CH_2O), 4.2 (1 H, m, 2-H), 4.85 (2 H, s, OCH_2O), 5.40 (2 H, s, OCH_2Ar), 6.33br (1 H, NH), 7.57 (2 H, d, *J* 11 Hz, 2 × ArH), and 8.27 (2 H, d, *J* 11 Hz, 2 × ArH).

p-*Nitrobenzyl* cis-2-*Diazo*-4-[3-(1-*hydroxy*-1-*methylethyl*)-4-*oxoazetidin*-2-*yl*]-3-*oxobutanoate* (16).—To a stirred, cooled (0 °C) solution of the azetidinone (15) (1.00 g, 2.1 mmol) in methylene dichloride (42 ml) was added titanium tetrachloride (1.45 ml, 13.2 mmol) under nitrogen. After being vigorously stirred for 1 h at 0 °C, the mixture was poured into a stirred, cooled (0 °C) mixture of saturated aqueous potassium carbonate (50 ml) and methylene dichloride (50 ml). After the mixture had been filtered through Celite, the organic phase was separated and the aqueous phase was extracted with methylene dichloride. The combined extracts were washed successively with water, dilute hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and water and were then dried. The extracts were evaporated to dryness and the residue was treated with benzene to give the *diazo-azetidinone* (16) (0.80 g, 81.7%) as pale-yellow crystals (solvated with benzene), m.p. 90 °C (melted and re-solidified), 154—155 °C (decomp.) (Found: C, 58.6; H, 5.2; N, 11.8. $C_{17}H_{18}N_4O_7 \cdot C_6H_6$ requires C, 59.0; H, 5.2; N, 12.0%); $\nu_{max.}$ 3 400, 3 310, 2 130, 1 740, and 1 680 cm^{-1}; δ 1.30 and 1.51 (each 3 H, s, Me), 1.8 (1 H, s, OH), 3.2—3.7 (total 3 H, m, 3-H and CH_2-CO), 4.1 (1 H, m, 2-H), 5.36 (2 H, s, OCH_2Ar), 6.2br (1 H, NH), 7.55 (2 H, d, *J* 9 Hz, 2 × ArH), and 8.27 (2 H, d, *J* 9 Hz, 2 × ArH).

p-*Nitrobenzyl* 5,6-cis-6-(1-*Hydroxy*-1-*methylethyl*)-3,7-*dioxo*-1-*azabicyclo*[3.2.0]*heptane*-2-*carboxylate* (17).—A suspension of the diazo-azetidinone (16) (solvated with benzene) (1.17 g, 2.5 mmol) and a catalytic amount of rhodium(II) diacetate (60 mg) in dry benzene (125 ml) was heated at 78 °C for 45 min under nitrogen. After being cooled to room temperature the mixture was filtered through Celite and the filtrate was evaporated to dryness to give the 3-*oxocarbapenem* (17) (0.91 g, quantitative) as a foam which was used without purification for subsequent reactions; $\nu_{max.}$ (KBr) 3 500 and 1 780—1 720 cm^{-1}; δ 1.28 and 1.53 (each 3 H, s, Me), 1.9br (1 H, OH), 2.63 (1 H, dd, *J* 19 and 7 Hz, 4-H), 3.67 (1 H, d, *J* 6 Hz, 6-H), 3.96 (1 H, dd, *J* 19 and 10 Hz, 4-H), 4.25 (1H, m, 5-H), 4.70 (1H, s, 2-H), 5.30 (2 H, ABq, *J* 16 and 13 Hz, OCH_2Ar), 7.55 (2 H, d, *J* 9 Hz, 2 × ArH), and 8.27 (2 H, d, *J* 9 Hz, 2 × ArH). This foam was treated with benzene to afford crystals of (17) (solvated with ⅓ mol of benzene), m.p. 55—60 °C (softened) (Found: C, 58.7; H, 5.2; N, 7.0. $C_{17}H_{18}N_2O_7 \cdot \frac{1}{3}C_6H_6$ requires C, 58.8; H, 5.2; N, 7.2%).

p-*Nitrobenzyl* 5,6-cis-3-(2-*Acetamidoethylthio*)-6-(1-*hydroxy*-1-*methylethyl*)-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylate* (19).—To a stirred, cooled (0 °C) solution of the 3-oxocarbapenem (17), prepared from compound (16) (250 mg, 0.52 mmol), in dry acetonitrile (20 ml) under nitrogen were added di-isopropylethylamine (0.12 ml, 0.7 mmol) and diphenyl chlorophosphate (0.14 ml, 0.7 mmol). The mixture was stirred for 1.5 h at 0 °C and then di-isopropylethylamine (0.13 ml, 0.75 mmol) and *N*-acetylcysteamine (90 mg, 0.75 mmol) were added. After being stirred for 2 h at 0 °C, the mixture was treated with further quantities of di-isopropylethylamine (0.13 ml, 0.75 mmol) and *N*-acetylcysteamine (90 mg, 0.75 mmol), and was then stirred for 4 h at 0 °C and kept at −20 °C for 14 h. The mixture was diluted with ethyl acetate, washed with water, dried and evaporated to dryness. The residue was treated with ethyl acetate to give the *protected*

carbapenem (19) [110 mg, 43.7% from (16)] as crystals, m.p. 185—187 °C (Found: C, 53.6; H, 5.4; N, 8.9. $C_{21}H_{25}N_3O_7S\cdot 0.5H_2O$ requires C, 53.4; H, 5.55; N, 8.9%); $\nu_{max.}$ 3 380, 1 760, 1 700, and 1 650 cm^{-1}; $\lambda_{max.}$ (EtOH) 265 and 315 nm (ε 11 400 and 12 400); δ [$(CD_3)_2SO$] 1.19 and 1.35 (each 3 H, s, Me), 1.82 (3 H, s, COMe), 2.8—3.4 (total 5 H, m, 4-H and SCH_2CH_2N), 3.59 (1 H, d, *J* 6 Hz, 6-H), 4.0—4.3 (total 2 H, m, 5- and 4-H), 4.70 (1 H, s, OH), 5.37 (2 H, ABq, *J* 21 and 14 Hz, OCH_2Ar), 7.77 (2 H, d, *J* 8 Hz, 2 × ArH), 8.10br (1 H, NH), and 8.27 (2 H, d, *J* 8 Hz, 2 × ArH).

p-*Nitrobenzyl* 5,6-cis-3-[(E)-2-*Acetamidovinylthio*]-6-(1-*hydroxy*-1-*methylethyl*)-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylate* (20).—To a stirred, cooled (0 °C) solution of the 3-oxocarbapenem (17), prepared from (16) (234 mg, 0.5 mmol), in dry acetonitrile (25 ml) under nitrogen were added di-isopropylethylamine (0.12 ml, 0.7 mmol) and diphenylchlorophosphate (0.14 ml, 0.7 mmol), and the mixture was stirred for 1.5 h at 0 °C. To this mixture were added sodium iodide (750 mg, 5 mmol) and silver (*E*)-2-acetamidoethenethiolate (167 mg, 0.75 mmol). After being stirred for 2 h at 0 °C the mixture was filtered and the filtrate was evaporated to dryness. The residue was partitioned between ethyl acetate and aqueous sodium chloride, and insoluble materials were filtered off. The organic phase was separated, washed with water, dried, and evaporated to dryness. The residue was subjected to chromatography on Florisil. Elution with ethyl acetate–hexane (2 : 1 v/v) and then with ethyl acetate gave the *protected carbapenem* (20) [155 mg, 67.2% from (16)] as pale-yellow crystals, m.p. 182—183 °C (decomp.) (Found: C, 54.6; H, 5.3; N, 8.9. $C_{21}H_{23}N_3O_7S$ requires C, 54.7; H, 5.0; N, 9.1%); $\nu_{max.}$ (KBr) 1 760, 1 700, and 1 620 cm^{-1}; $\lambda_{max.}$ (MeOH) 229.5, 262, and 322.5 nm (ε 17 300, 16 900, and 17 100); δ [$(CD_3)_2SO$] 1.15 and 1.33 (each 3 H, s, Me), 1.93 (3 H, s, COMe), 2.9—3.3 (1 H, m, 4-H), 3.55 (1 H, d, *J* 6 Hz, 6-H), 3.9—4.3 (total 2 H, m, 4- and 5-H), 4.7br (1 H, OH), 5.37 (2 H, ABq, *J* 21 and 14 Hz, OCH_2Ar), 5.87 (1 H, d, *J* 14 Hz, SC*H*=CHN), 7.07 (1 H, dd, *J* 14 and 13 Hz, SCH=C*H*N), 7.75 (2 H, d, *J* 8 Hz, 2 × ArH), 8.20 (2 H, d, *J* 8 Hz, 2 × ArH), and 10.28 (1 H, d, *J* 13 Hz, NH).

Deprotection of the Protected Carbapenems (19), (20) *by Hydrogenolysis*.—(a) *Deprotection of* (19). A mixture of compound (19) (73 mg, 0.15 mmol) and 10% palladium–charcoal (100 mg) in THF (14 ml), pH 7.0 phosphate buffer, and water (7 ml) was stirred under hydrogen at room temperature. After a further quantity of 10% palladium–charcoal (50 mg) had been added the mixture was stirred for another 2 h under hydrogen. The catalyst was filtered off and washed with water. To the combined filtrate and washings was added sodium hydrogen carbonate (20 mg) and the THF was evaporated off. The aqueous phase was washed with ethyl acetate and concentrated under reduced pressure to *ca.* 4 ml. The concentrate was subjected to chromatography on Amberlite XAD-2 with water as eluant. The first fractions, having a u.v. absorption at 263 nm, were combined and lyophilized to give a powder which was rechromatographed on Diaion HP-20. Elution with water, followed by lyophilization of the eluate gave the carbapenem sodium salt (1d) (2 mg, 5%) as a powder; $\nu_{max.}$ (KBr) 1 750 cm^{-1}; δ (D_2O) 1.32 and 1.44 (each 3 H, s, Me), 2.8 (1 H, m, 4-H), 3.5 (1 H, m, 4-H), 3.73 (1 H, d, *J* 6 Hz, 6-H), 4.4 (1 H, m, 5-H), and 6.33 (1 H, t, *J* 3 Hz, 3-H); h.p.l.c. R_t 3.8 min (10% MeOH–p.b.).

The second fractions, having a u.v. absorption at 298 nm, were combined, lyophilized, and re-chromatographed on Diaion HP-20. Elution with water and then with 5% aqueous ethanol, followed by lyophilization, gave the carbapenem sodium salt (1e) (30 mg, 55%) as a powder; $\nu_{max.}$ (KBr) 1 745 and 1 640 cm^{-1}; $\lambda_{max.}$ (H_2O) 298 nm (ε 9 300); δ (D_2O) 1.33 and 1.44 (each 3 H, s, Me), 2.02 (3 H, s, COMe), 2.9—4.0 (total 6 H, m, SCH_2CH_2N and 4-H_2), 3.74 (1 H, d, *J* 6 Hz, 6-H), and 4.3 (1 H, m, 5-H); h.p.l.c. R_t 8.2 min (10% MeOH–p.b.). The carbapenems (1d, 1e) were identical (i.r., u.v., and n.m.r. spectra and h.p.l.c.) with the compounds obtained by hydrogenolysis of the natural antibiotic C-19393 H_2.[2c]

(*b*) *Deprotection of* (20). A mixture of the protected carbapenem (20) (150 mg, 0.33 mmol) and 10% palladium–charcoal (150 mg) in THF (15 ml) and water (15 ml) containing sodium hydrogen carbonate (36 mg) was stirred under hydrogen at room temperature for 4 h [during the hydrogenation, additional 10% palladium–charcoal (200 mg) was added]. The catalyst was filtered off and washed with water. The combined filtrate and washings were evaporated under reduced pressure to remove THF. The aqueous phase was washed with ethyl acetate and concentrated under reduced pressure to *ca.* 4 ml. The concentrate was subjected to chromatography on Diaion HP-20. The first fractions ($\lambda_{max.}$ 263 nm), which were eluted with water, were combined, lyophilized, and re-chromatographed on Diaion HP-20. Elution with water, followed by lyophilization, gave the carbapenem sodium salt (1d) (3 mg, 4%), identical (i.r., u.v., and n.m.r. spectra, and h.p.l.c.) with the compound obtained in (*a*) above.

The second fractions ($\lambda_{max.}$ 230 and 310 nm) (eluted with 5% aqueous EtOH) were combined and lyophilized to give the carbapenem sodium salt (1c) (75 mg, 66% as a powder); $\nu_{max.}$ (KBr) 1 745, 1 670, and 1 615 cm^{-1}; $\lambda_{max.}$ (H_2O), 230 and 310 nm (ε 13 800 and 15 500); δ (D_2O) 1.30 and 1.44 (each 3 H, s, Me), 2.09 (3 H, s, COMe), 3.02 (1 H, dd, *J* 18 and *10 Hz*, 4-H), 3.72 (1 H, d, *J* 6 Hz, 6-H), 3.75 (1 H, dd, *J* 18 and 9 Hz, 4-H), 4.3 (1 H, m, 5-H), 6.07 (1 H, d, *J* 13 Hz, SC*H*=CHN), and 7.14 (1 H, d, *J* 13 Hz, SCH=C*H*N); h.p.l.c. R_t 25.0 min (8% MeOH–p.b.). The carbapenem sodium salt (1c) was identical (i.r., u.v., and n.m.r. spectra, and h.p.l.c.) with the compound obtained by hydrogenation of the natural compound C-19393 H_2.[2c]

Oxidation of the Carbapenem Sodium Salt (1c) *with* m-*Chloroperbenzoic Acid*.—To a stirred, cooled (0—5 °C) solution of the carbapenem sodium salt (1c) (63 mg, 0.18 mmol) in water (8 ml) was added *m*-chloroperbenzoic acid (80% purity; 45 mg, 0.21 mmol) and the mixture was stirred for 0.5 h at 0—5 °C. After being washed with ethyl acetate, the mixture was treated with pH 7.0 phosphate buffer (0.5 ml) and was then concentrated under reduced pressure. The concentrate was subjected to chromatography on Diaion HP-20. Elution with water, followed by lyophilization, gave the two isomeric carbapenem sodium salts (1b) (26.5 mg, 41%) and (1a) (34.2 mg, 53%) as powders. The carbapenem (1b), which was eluted first, had $\nu_{max.}$ (KBr) 1 770, 1 690, and 1 620 cm^{-1}; $\lambda_{max.}$ (H_2O) 252 and 287 nm (ε 14 600 and 12 000); δ (D_2O) 1.34 and 1.45 (each 3 H, s, Me), 2.15 (3 H, s, COMe), 3.14 (1 H, dd, *J* 17 and 11 Hz, 4-H), 3.84 (1 H, d, *J* 6 Hz, 6-H), 3.84 (1 H, dd, *J* 17 and 8 Hz, 4-H), 4.6 (1 H, m, 5-H), 6.30 (1 H, d, *J* 14 Hz, SC*H*=CHN), and 7.55 (1 H, d, *J* 14 Hz, SCH=C*H*N); h.p.l.c. R_t 4.5 min (8% MeOH–p.b.); these data were identical with those of the authentic compound with the *S*-configuration at sulphur.[2c] The carbapenem salt (1a) had $\nu_{max.}$ (KBr) 1 770, 1 700, and 1 620 cm^{-1}; $\lambda_{max.}$ (H_2O) 244 and 290 nm (ε 14 900 and 12 800); δ (D_2O) 1.34 and 1.45 (each 3 H, s, Me), 2.15 (3 H, s, COMe), 3.05 (1 H, dd, *J* 17 and 11 Hz, 4-H), 3.81 (1 H, d, *J* 6 Hz, 6-H), 3.90 (1 H, dd, *J* 17 and 9 Hz, 4-H), 4.5 (1 H, m, 5-H), 6.39 (1 H, d, *J* 14 Hz, SC*H*=CHN), and 7.55 (1 H, d, *J* 14 Hz, SCH=C*H*N); h.p.l.c. R_t 11.5 min (8% MeOH–p.b.); these data were identical with those of the natural antibiotic C-19393 H_2 with the *R*-configuration at sulphur.[2b,c]

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