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SYNTHESIS AND BIOLOGICAL ACTIVITY OF TETRACYCLIC CARBAPENEMS

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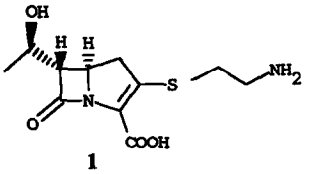
Abstract: The synthesis and biological activity of new tetracyclic carbapenem antibiotics **15**, **16** and **17** are described. Pharmacokinetic studies in the mouse have shown the pivaloyloxymethyl ester prodrug **18** to have oral activity.

Since the discovery of thienamycin **1**[1] in 1976, a number of other thienamycin derivatives of very high antibacterial potency have been found in nature, for example epithienamycins, olivanic acids,[2] carpetimycins,[3] asparenomycins,[4] pluracidomycins[5] and the carbapenems of the PS group,[6] and many total synthesis studies on thienamycin[7] and syntheses of novel carbapenems[8] have been published. Carbapenems generally possess a broad spectrum of activity against Gram-positive and Gram-negative bacteria. Formimidoylthienamycin or imipenem **2**,[9] in combination with cilastatin, is marketed as a drug for severe hospital infections.



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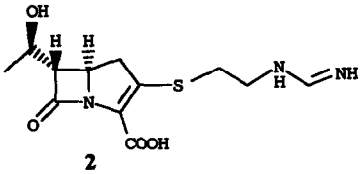
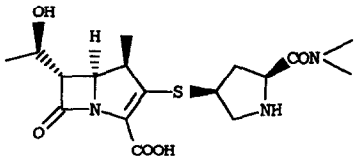


2

A disadvantage of imipenem is that it is rapidly degraded in the kidney by dehydropeptidase I (DHP-I),[10] and the metabolites formed cause nephrotoxicity. For clinical use, imipenem therefore had to be developed in a DHP-I-stable combination with cilastatin - a specific renal dehydropeptidase inhibitor. Dehydropeptidase-stable carbapenems are consequently a subject of therapeutic research.

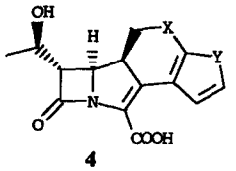
The introduction of a substituent into the 1-position of the carbapenem skeleton considerably improves the DHP-ase stability, as exemplified by meropenem **3**,[11] which can be administered as a single-entity drug without the additional use of a DHP-ase inhibitor.



3

Tricyclic carbapenems have already been described by Christensen,[12] Tamburini[13] and Perboni[14] and some tetracyclic thienamycin derivatives by Sendai[15] and Gerlach.[16]

The present study describes tetracyclic carbapenems of structure **4** which potentially should be more stable to DHP-ase I.



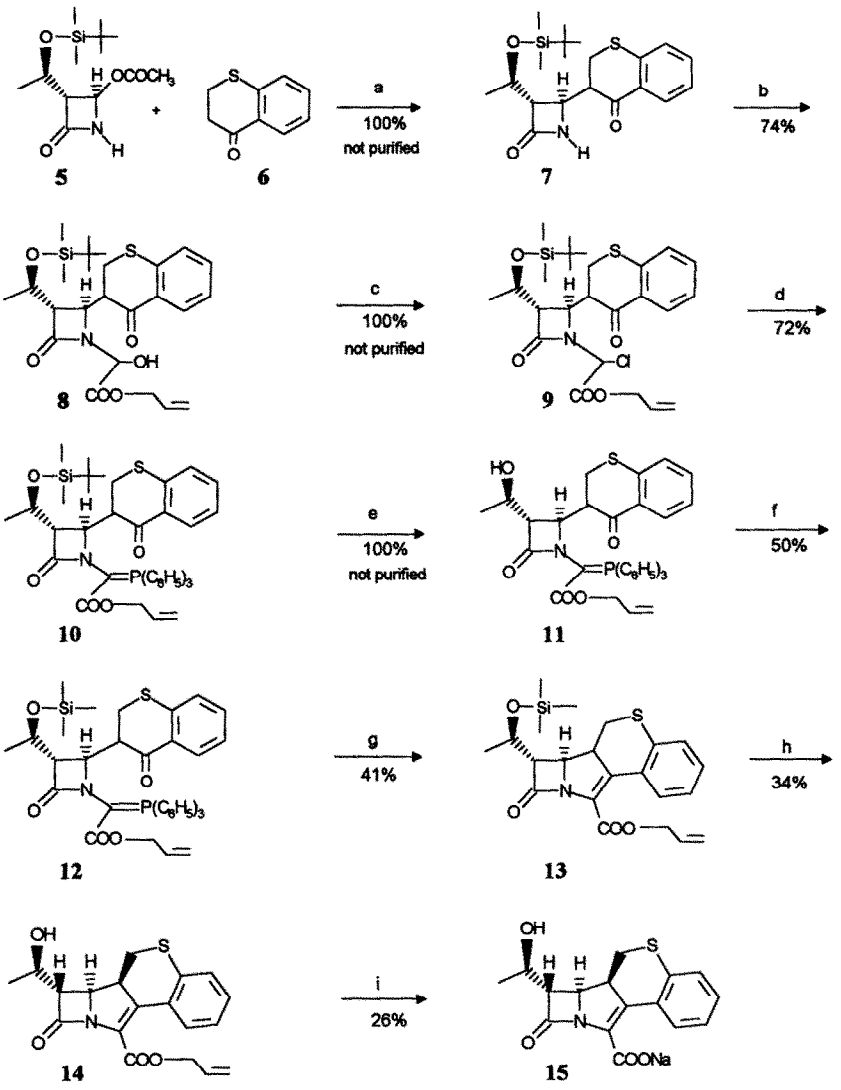
X = $-CH_2-$, $-CH_2CH_2-$
-O-, -S-
Y = -CH=CH-, -S-

4

Starting from the known enantiomerically pure azetidinone **5**,[17] the tetracyclic carbapenems were synthesized by a route shown in Scheme 1 using (1S,5S,6S)-6-[1(R)-1-hydroxyethyl]thiochromano-[3,4-a]- carbapen-2-em-3-carboxylic acid as an example.

Known methods[18] were used to carry out the C-C coupling of the 4-acetoxyazetidin-2-one **5** with the enolate of the thiochromanone **6** under basic catalysis and mild conditions to give a mixture of the α and ß isomers of the 4-(oxothiochroman-3-yl)azetidin-2-one **7**. This coupling could also be carried out under Lewis acid catalysis in CH_2Cl_2 in the presence of trimethylsilyl trifluoromethanesulphonate and triethylamine This was followed by the hydroxyalkylation of **7** with allyl glyoxylate monohydrate under reflux to give the allyl azetidin-1-yloxoacetate **8**, from which the phosphoranylidenemethylazetidin-2-one **10** was obtained after chlorination and reaction with triphenylphosphine.

As cyclization by means of the Wittig reaction resulted in undesired by-products at the stage of the tert-butyldimethylsilyloxyethyl derivative **10**, the tert-butyldimethylsilyl residue was replaced with the trimethylsilyl protecting group (TMS) in **12** and cyclization was then effected by an intramolecular Wittig reaction[19] to form the carbapenem skeleton **13**. After elimination of the TMS protecting group and chromatography on silica gel with toluene/ethyl acetate, the allyl ester **14** was obtained in the form of the isomerically pure 1S,5S,6S product. The configuration of both the isomers at C-1 of the carbapenem skeleton was derived from the 1-H/5-H couplings and the chemical shift of the ^{1}H-NMR signals of the C_5-azetidinone. The ^{1}H-NMR signals of the



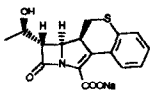
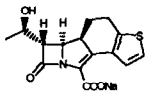
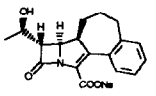
Scheme 1.

(a) HMDS-Li/THF, -78°C, N_2 or $CF_3SO_2Si(CH_3)_3/Et_3N$, -60°C, N_2; (b) $(HO)_2CH\text{-}COO\text{-}CH_2\text{-}CH{=}CH_2$, toluene, 2 h reflux, N_2; (c) $SOCl_2$, 2,6-lutidine, -20°C to room temp., 2 h; (d) Ph_3P/dioxane, 2,6-lutidine, room temp., silica gel chromatography in toluene/ethyl acetate; (e) 6 mol. HCl/CH_3OH, 2 h, room temp., N_2;

(f) 3 equiv. TMS-chloride/CH_2Cl_2, 3 equiv. Et_3N, 3 h, room temp., N_2, anhydrous work-up, silica gel chromatography in toluene/ethyl acetate; (g) xylene, hydroquinone, 5 h reflux; (h) pyridinium toluene-4-sulphonate, 45 min, room temp.; (i) $[Ph_3P]_4Pd(O)/Ph_3P$, 0.5 mol. $C_7H_{15}COONa$ in ethyl acetate, THF/CH_2Cl_2(1:1), preparative HPLC in water/acetonitrile.

C_5-atom of **14** are shifted to lower field by approx. 0.5 ppm relative to those of the R isomer and generally have a higher coupling constant.[15] Finally, saponification of the allyl ester **14**[20] gave the product **15**,[21] the sodium salt of which was purified on RP 18 (Hibar 250-25, Merck) with water containing acetonitrile as the eluent, in an overall yield of approx. 1 %.

Table 1: Antibacterial activity (MIC in µg/ml) of tetracyclic carbapenems compared with imipenem

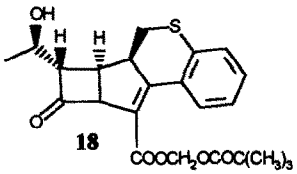
Organisms	 **15**	 **16**	 **17**	Imipenem **2**
E. coli Neumann	0.5	1	2	≤ 0.25
E. coli F 14	8	8	16	≤ 0.25
Klebs. 57 USA	4	4	1	≤ 0.25
Klebs. 63	2	4	16	≤ 0.25
Prot. morg. 932	1	2	16	0.5
Prot. vulg. N 6	≤ 0.25	≤ 0.25	1	0.5
Prot. rettg. 10007	2	4	16	2
Prot. mir. 1235	≤ 0.25	1	0.5	4
Serratia 16001	8	32	64	≤ 0.25
Serratia 16002	16	32	64	0.5
Enterob. cl. 5744	4	8	32	0.5
Acinetob. 14061	4	16	64	≤ 0 25
Psdm. aerug. F 41	128	128	128	2
Staph. aur. 133	≤ 0.25	1	0.5	≤ 0 25
Staph. 25455	≤ 0.25	1	0 5	≤ 0.25
Staph. 25470	8	32	128	32

MICs (Minimal Inhibitory Concentrations) were determined by the agar dilution technique on Isosensitest agar. Organisms from overnight cultures were diluted 1:500 and inoculated by a multipoint inoculator on the agar plates containing serial dilutions of the antibiotics.

The synthetic route described in Scheme 1 for the compound **15** was also chosen for the preparation of **16** and **17**.

Of the carbapenem derivatives represented, the compound **15** achieves the *in vitro* activity of imipenem **2** on Staphylococci, Streptococci and Proteus. Against Gram-negative bacteria such as E. coli, Klebsiella and Pseudomonas, **15** has a weaker activity than imipenem (see Table 1).

To improve the oral absorption, the pivaloyloxymethyl esters of the tetracyclic carbapenem derivatives were prepared. After oral administration of the pivaloyl ester **18** of the parent substance **15** to mice



18

(50 mg/kg), maximum serum levels of 7.1 μg/ml after 15 min and urine recovery values of 8.2% were measured. Thus the serum levels and recovery values are well above those of the parent substance **15**. The principle of the prodrug form, successfully established with cephalosporins,[22] could achieve therapeutic significance for carbapenems in the future.

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21. The analytical data are as follows·

    Compound **14**:

    ^{1}H-NMR ($CDCl_3$): 1.39 (d, 3H, $C\underline{H}_3$-CH), 2.44 (d, 1H, CH_3-CH-O$\underline{H}$), 3 02 (dd, 1H, S-CH_2-C$\underline{H}$), 3.25 (dd, 1H, 6-H), 3.22-3.41 (m, 2H, S-$C\underline{H}_2$-CH), 4.23-4.33 (m, 1H, CH_3-C$\underline{H}$), 4.40 (dd, 1H, 5-H, J = 10.6 Hz, 3.7 Hz), 4.68-4.86 (m, 2H, $C\underline{H}_2$-CH=CH_2), 5.22-5 40 (m, 2H, CH_2-CH=$C\underline{H}_2$), 5.89-6 01 (m, 1H, CH_2-C$\underline{H}$=CH_2), 6.98-7.20 (m, 3H, ArH), 7.53 (m, 1H, ArH).

    MS. m/z 358 (M+H).

    Compound **15**:

    ^{1}H-NMR (DMSO): 1.14 (d, 3H, $C\underline{H}_3$-CH), 3.10-3.50 (m, 3H, S-$C\underline{H}_2$-C$\underline{H}$), 3.60 (dd, 1H, 6-H), 4 25 (m, 1H, CH_3-C$\underline{H}$), 4.41 (dd, 1H, 5-H), 6 95-7.10 (m, 3H, ArH), 7.45 (m, 1H, ArH).

    FAB MS: m/z 362 (M+Na).
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