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Modification of natural products to improve their biological properties

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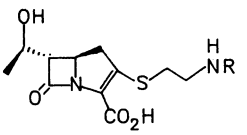
Abstract Natural products often do not possess the optimal properties for their use in human or animal medicine. The recent history of natural products would indicate that such optimization is likely. 2-Aryl-carbapenems were synthesized in an effort to improve upon the DHP-I susceptibility of the parent antibiotics. The synthesis of this class of compounds is described and they are indeed more DHP-I stable. However, it has not been possible to obtain meaningful anti-pseudomonal activity in this series.

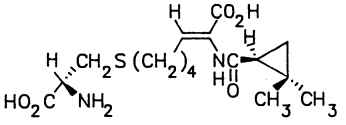
Nature produces many natural products that are antibiotics, pharmacological agents or are otherwise of interest in human or animal medicine. While their purpose in nature remains obscure in most instances, clearly they are not intended by the producing microorganism or plant source to be of utility for the treatment of disease states. Accordingly, it seems likely that the properties of natural products can be optimized for their projected use. The recent history of natural products has indicated that this is indeed the case.

Imipenem **1** (N-formimidoylthienamycin, MK-0787) (ref. 1) is an excellent example of this approach. The natural product, thienamycin **2**, while possessing extraordinary potency and breadth of spectrum, was too chemically unstable for clinical use (ref. 2). Imipenem was the result of a semi-synthetic analog program, is even more potent and is sufficiently stable for hospital use. A total synthesis was desired to produce imipenem commercially and to make analogs which could not be prepared by derivatization of the natural product. Totally synthetic analogs have been reported previously and this report details the synthesis of a new class of compounds.



1 R = CH=NH (imipenem)

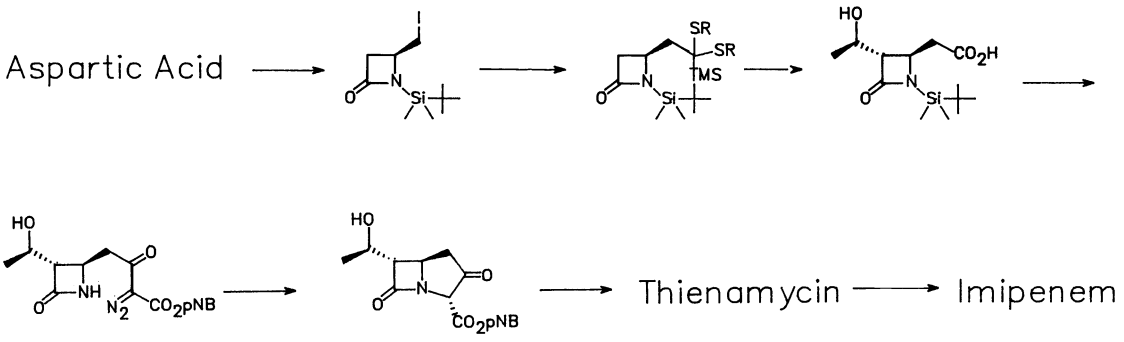
2 R = H (thienamycin)



3 cilastatin

While the first total synthesis of thienamycin (ref. 3) was deliberately not stereocontrolled in order to afford the unknown diastereomers of thienamycin, an enantiomerically stereoselective total synthesis (ref. 4) quickly followed that was the basis for its commercial production (ref. 5). Several key elements of that synthesis are shown in Scheme I. This synthesis has been used to make several different types of totally synthetic analogs (ref. 6).

Scheme I



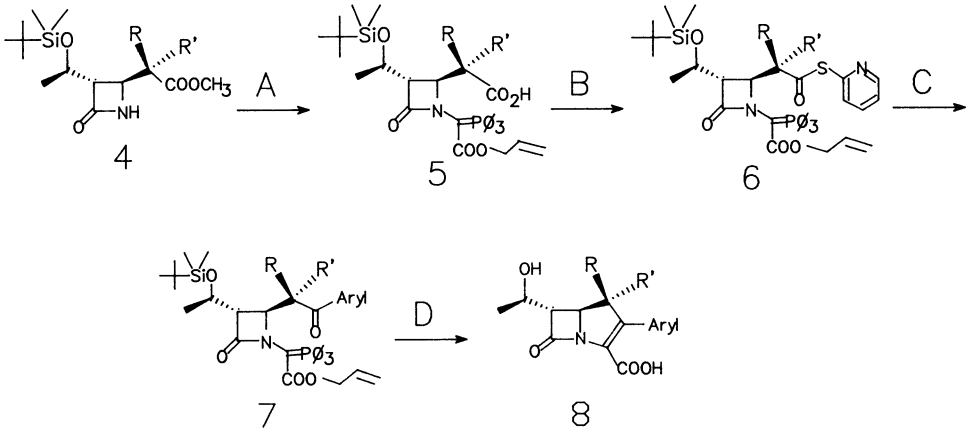
Imipenem showed yet another shortcoming. It was unstable to a kidney enzyme, renal dipeptidase I (or renal dehydropeptidase I, DHP-I) (ref. 7). This resulted in poor urinary levels of the antibiotic. Cilastatin, **3**, was developed during a medicinal chemical program to design an inhibitor of the DHP-I enzyme (ref. 8). **3** is an effective, safe inhibitor of the renal enzyme and an equal weight mixture of imipenem and cilastatin, sodium is used clinically. This mixture, Primaxin or Tienam, depending upon country of use, retains the potency, breadth of spectrum and stability of imipenem, but gives high urinary levels of the antibiotic. Two totally synthetic classes of analogs have been found that are DHP-I stable. They are the 1β-methyl- (ref. 9) and the 2-aryl- (ref. 10) analogs in the carbapenem series.

This report discusses more extensively on the 2-aryl class, as well as reporting the activities of those analogs having both functionalities.

The 1β-methylcarbapenems have proven to be the most interesting of the previously reported totally synthetic analogs. Biologically, these analogs have the interesting property of dramatically reducing DHP-I susceptibility while leaving the potency of the carbapenem nucleus unaffected. This series has been the focus of considerable synthetic effort and a stereoselective synthesis has been reported (ref. 11).

The critical ring-forming reaction in the thienamycin total synthesis is the insertion of the carbon bearing the diazo group into the NH bond of the azetidinone (ref. 12). Clearly, this chemistry is not as amenable for generating 2-arylcarbapenems. Instead, the crucial ring closure was designed to be effected by application of the Wittig reaction, originally used by Woodward (ref. 13) in his cephalosporin total synthesis and used by us in the carbapenem field (ref. 14). Another key assumption in our retrosynthetic analysis was the desire to use an intermediate as late as possible in the commercial synthesis of imipenem. Intermediate **4** was chosen. Its conversion to an arylketone **7** provides the final intermediate in the retrosynthetic analysis shown in Scheme II.

Scheme II



Reaction Conditions

A. 1) NaOH, CH_3OH/H_2O; 2) t-butyldimethylchlorosilane/imidazole, DMF; 3) allyl glyoxylate, toluene, Δ; 4) thionyl chloride/pyridine, THF, -40° to -20°C; 5) triphenyl phosphine, DMF, r.t.; 6) HCl.

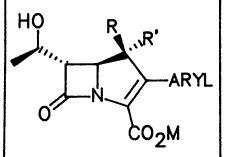
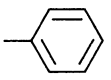
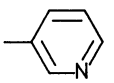
B. 2-pyridyl thiochloroformate/triethylamine, 0°C.

C. Grignard reagent, THF/ether, 0°.

D. 1) Δ, toluene or xylene; 2) tetra-n-butylammonium fluoride, HOAc, THF, r.t.; 3) tetrakis-triphenylphosphinepalladium, potassium 2-ethylhexanoate, triphenylphosphine, $EtOAc/CH_2Cl_2$.

The previously reported methyl esters **4a** (R=R'=H), **4b** (R=CH_3, R'=H) and **4c** (R=H, R'=CH_3) were converted to the t-butyldimethylsilyl esters via the intermediate acid in order to facilitate selective hydrolysis at a later stage of the synthesis. Conversion of **4** to the phosphoranylidene free acids **5** was effected by sequential reaction with allyl glyoxylate, thionyl chloride and triphenyl phosphine without isolation of any of the intermediates. A deliberate hydrolysis step was included in the case of **4a** and **4c**. Conversion of **5** to the activated pyridylthio esters **6** was readily accomplished by reaction with 2-pyridyl thiochloroformate. The conversion of the starting methyl esters **4** to **6** was effected in overall 15-44% yields.

TABLE I

	IMIPENEM M.I.C.* (MCG/ML)	ARYL R					
		R'	H	CH_3	H	CH_3	H
			H	H	H	H	CH_3
S. AUREUS	0.015		0.04	0.11	0.01	0.02	0.13
ENTEROCOCCUS	2.46		0.49	1.52	0.42	1.36	21
E. COLI	0.31		0.13	0.64	0.04	0.05	0.07
ENTEROBACTER	0.26		0.16	1.33	0.04	0.06	0.13
KLEBSIELLA	0.46		0.47	2.30	0.09	0.17	0.30
SERRATIA	0.68		0.11	1.03	0.03	0.05	0.05
PROTEUS	0.85		0.15	0.46	0.07	0.34	0.52
PSEUDOMONAS	0.36		57	71	26	41	68
DHP SUSCEPT.	1.0		0.18	0.24	0.32	0.79	0.10

*M.I.C. VALUES ARE DERIVED FROM ZONE DIAMETERS IN DISC DIFFUSION ASSAYS AND REPRESENT AVERAGES FOR SEVERAL DIFFERENT STRAINS OF EACH ORGANISM.

6 was the versatile synthetic intermediate desired in order to readily obtain a range of 2-arylcarbapenems. Reaction with an appropriate Grignard reagent afforded the corresponding aryl-ketone **7**. Yields ranged from 32-68%. Thermolysis of **7** readily afforded the protected carbapenem, which after desilylation (tetra-n-butylammonium fluoride/HOAc) and deesterification (ref. 15) gave the carbapenem **8**. It is interesting to note that the 1α-isomer is generated at lower temperatures than the other series investigated.

The antimicrobial activities of some representative analogs prepared by this sequence are given in Table I. Of primary interest is the effect of structural variation on DHP-I stability. It should be noted that the stability conferred by the 1β-methyl and 2-aryl groups is neither additive nor synergistic, but indeed is diminished by their combined presence. Indeed, the 1α-methyl variant is most stable when aryl is 3-pyridyl. Generally, a methyl group at C1 diminishes potency regardless of stereochemistry, while this diminution is less pronounced in the case of the 1β-methyl group. Finally, it has not been possible to restore meaningful anti-pseudomonal activity to the 2-aryl series despite the inclusion of basic groups in the 2-substituent. These results will be reported in detail elsewhere (ref. 16).

REFERENCES

1. W. J. Leanza, K. J. Wildonger, T. W. Miller and B. G. Christensen, J. Med. Chem. 22, 1435-1436 (1979).

2. (a) J. S. Kahan, F. M. Kahan, R. Goegelman, S. A. Currie, M. Jackson, E. O. Stapley, T. W. Miller, A. K. Miller, D. Hendlin, S. Mochales, S. Hernandez, H. B. Woodruff and J. Birnbaum, J. Antibiotics 32, 1-12 (1979). (b) G. Albers-Schonberg, B. H. Arison, O. E. Hensens, J. Hirshfield, K. Hoogsteen, E. Kaczka, R. E. Rhodes, J. S. Kahan, F. M. Kahan, R. W. Ratcliffe, E. Walton, L. J. Ruswinkle, R. B. Morin and B. G. Christensen, J. Amer. Chem. Soc. 100, 6491-6499 (1978).

3. S. M. Schmitt, D. B. R. Johnston and B. G. Christensen, J. Amer. Chem. Soc. 45, 1142-1148 (1980).

4. T. N. Salzmann, R. W. Ratcliffe, B. G. Christensen and F. A. Bouffard, ibid. 102, 6161-6163 (1980).

5. D. G. Melillo, I. Shinkai, T. Liu, K. Ryan and M. Sletzinger, Tetrahedron Letters 21, 2783-2786 (1980).

6. A. Andrus, F. Baker, F. A. Bouffard, L. D. Cama, B. G. Christensen, J. V. Heck, D. B. R. Johnston, W. J. Leanza, R. W. Ratcliffe, T. N. Salzmann, S. M. Schmitt, D. H. Shih, N. V. Shah, K. J. Wildonger and R. R. Wilkening, Recent Advances in the Chemistry of β-Lactam Antibiotics, p. 86, Royal Soc. Chem. (1985).

7. H. Kropp, J. G. Sondelof, R. Hajdu, and F. M. Kahan, Antimicrob. Agents Chemotherapy 22, 62-70 (1982).

8. D. W. Graham, W. T. Ashton, L. Barash, J. E. Brown, R. D. Brown, L. F. Canning, A. Chen, J. P. Springer and E. F. Rogers, submitted to J. Med. Chem.

9. D. H. Shih, F. Baker, L. Cama and B. G. Christensen, Heterocycles 21, 29-40 (1984).

10. L. D. Cama, K. J. Wildonger, R. N. Guthikonda, R. W. Ratcliffe and B. G. Christensen, Tetrahedron 39, 2531-2549 (1983).

11. L. M. Fuentes, I. Shinkai and T. N. Salzmann, J. Amer. Chem. Soc. 108, 4675-4676 (1986).

12. R. W. Ratcliffe, T. N. Salzmann and B. G. Christensen, Tetrahedron Letters 21, 31-34 (1980).

13. R. Scartazzini, H. Peter, H. Bickel, K. Heusler and R. B. Woodward, Helv. Chem. Acta 55, 408-417 (1972).

14. L. D. Cama and B. G. Christensen, J. Amer. Chem. Soc. 100, 8006-8007 (1978).

15. P. D. Jeffrey and S. W. McCombie, J. Org. Chem. 47, 587-590 (1982).

16. Ravindra Nath Guthikonda, L. D. Cama, M. Quesada, M. F. Woods, T. N. Salzmann, and B. G. Christensen, J. Med. Chem., in press.