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Synthesis and Antibacterial Activity of FR21818, a New, Potent 1β-Methylcarbapenem

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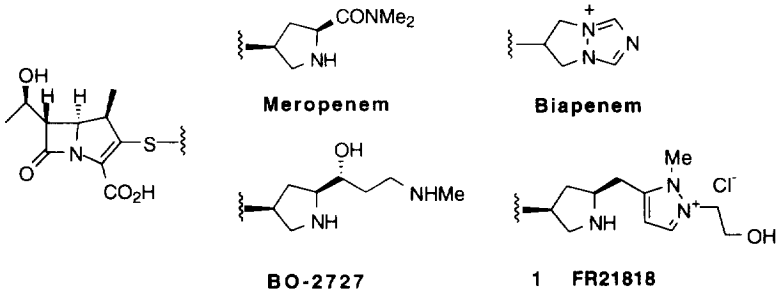
Abstract: The synthesis, *in vitro* antibacterial activity, and stability to renal dehydropeptidase I of FR21818, a new 1β-methyl carbapenem containing a novel pyrazoliomethyl pyrrolidine side chain at C-2 is described.

Introduction

Since the introduction of the imipenem-cilastatin combination into clinical practice[1], an intense effort to find new carbapenems with superior activity against a broader range of pathogens and improved stability against the renal dehydropeptidase DHP-1, has identified meropenem[2], biapenem[3], and BO-2727[4] as particularly effective. As part of our ongoing efforts to find a new carbapenem with superior activity compared to the carbapenems currently in development, or already marketed, we postulated that a combination of a high affinity for penicillin-binding proteins (PBP's) like meropenem[2c], with high outer membrane permeability of *Pseudomonas aeruginosa*, associated with the zwitterionic, non-basic biapenem[3c], would lead to agents with a broader spectrum of activity than either. Our design process involved the incorporation of quaternary salts of heterocycles onto a pyrrolidine ring. As a result of these efforts we have discovered FR21818 (**1**), a new 1β-methylcarbapenem, with a unique pyrazoliomethyl pyrrolidine side chain that has excellent, broad spectrum activity against Gram-positive and Gram-negative bacteria and good stability to DHP-I. In this communication, we wish to report the synthesis and preliminary biological evaluation of this new agent.

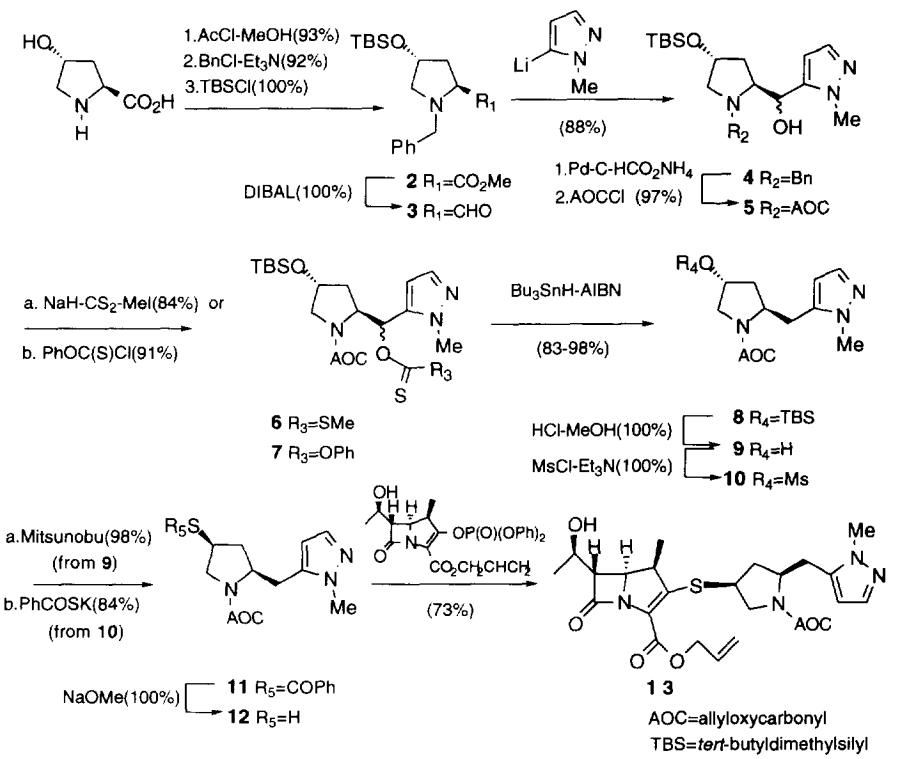


Synthesis

For the synthesis of FR21818 we required a convenient route to the thiol **12**, followed by coupling with a suitable C-2 activated carbapenem to afford protected carbapenem **13**, and elaboration to the final antibacterial agent *via* quaternary salt formation and deprotection. Scheme 1 summarizes our synthesis. Commercially available 4-hydroxyproline was converted in 4 high yielding steps to aldehyde **3**. It was necessary to protect the 4-hydroxy group in order to obtain differentiated hydroxyl groups after the coupling with 5-lithio-1-

methylpyrazole.[5] Alcohol **4** was thus produced as a 2:1 mixture of diastereoisomers by adding a THF solution of aldehyde **3** to the anion at -70°C, followed by warming to ambient temperature. It is noteworthy that we saw no evidence for epimerisation of **3**[6], and that the subsequent transformations after deoxygenation gave only single diastereoisomers. For reduction of the alcohol moiety it was necessary to first exchange the N-benzyl group for an allyloxycarbonyl group, followed by conversion to either xanthate **6** or thiocarbonate **7**. Reduction was effected by heating with Bu_3SnH-AIBN.[7] Desilylation of the resulting pyrazole **8** afforded alcohol **9** in quantitative yield which was then smoothly converted to the thiobenzoate **11** with clean inversion, by either Mitsunobu reaction with thiobenzoic acid[8], or *via* the mesylate **10** in a 2-step process. Hydrolysis of the thioester **11** occurred smoothly using NaOMe in acetonitrile at 0°C, and the resulting key thiol **12** was coupled with allyl (1R, 5R, 6S)-2-diphenylphosphoro-6-[(R)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylate[9] in the presence of $EtNPr^i_2$ in CH_3CN-CH_3CONMe_2 at 0-5°C to give a 73% isolated yield of key precursor **13**.

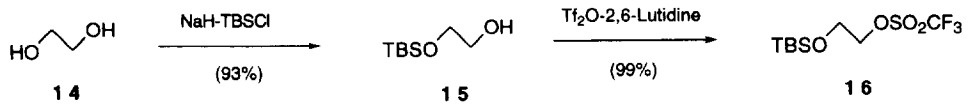
Scheme 1



Elaboration of **13** to FR21818 required introduction of a hydroxyethyl moiety to the pyrazole ring to form the quaternary salt. Reaction with bromo- or iodoethanol in a variety of solvents (CH_2Cl_2, $ClCH_2CH_2Cl$, DMF) and at various temperatures (rt-100°C) failed to afford any of the desired pyrazolium salt due to the low nucleophilicity of the pyrazole ring nitrogen atom. We were however, successful using the protected triflate **16**, conveniently prepared from ethylene glycol **14** in two high yielding steps *via* the known alcohol **15**[10] (scheme 2). Treatment of a solution of **13** in CH_2Cl_2 with **16** gave an essentially quantitative yield of salt **17**. We were unable to prepare the mono triflate of ethylene glycol bearing a free OH group, however triflate **16** was stable enough to be stored several weeks in the freezer (-30°C). Reaction with **13** was preferentially performed with a

small amount of solvent (3-4 v/w of **13**) to ensure fast reaction, although no problems were encountered with 20 v/w, even though 3 days were required for complete reaction. We believe that **16** will be useful for the introduction of a hydroxyethyl moiety to compounds bearing weakly nucleophilic nitrogen atoms in other areas.

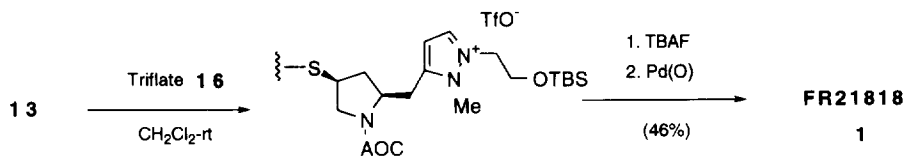
Scheme 2



14 **15** **16**

After quaternary salt formation, evaporation afforded the salt **17** which was then subjected to sequential deprotection[11] of the TBS group with TBAF, followed by a palladium-catalysed deprotection of both the AOC and allyl ester protecting groups, and finally by purification and passage through an Amberlyst column (Cl^- form) to give FR21818 as a white amorphous solid in 46% yield after lypholysation, from **13** (scheme 3).[12]

Scheme 3



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Biological Activity

In vitro antibacterial activity, stability to renal dehydropeptidase I, and urinary recovery of FR21818 in comparison to meropenem and biapenem are shown in Table 1.[13] FR21818 showed superior activity compared to the reference compounds against strains of *S.aureus*, although it was marginally weaker than meropenem against Gram-negative bacteria, with the exception of *Ps. aeruginosa* 26. The stability of FR21818 against recombinant[14] human renal dehydropeptidase I was superior to meropenem, although slightly weaker than the non-basic carbapenem biapenem, which is well known to be exceptionally stable.[3b] This data shows that FR21818 has a good balance of antibacterial activity, incorporating the desirable properties associated with both meropenem and biapenem. High urinary recovery in mice was observed, which indicates good stability to DHP I in an *in vivo* situation. Overall, FR21818 had a broad spectrum of activity and excellent stability to DHP I.

Table 1. *In vitro* Antibacterial Activity and DHP-I Stability of FR21818

	MIC (μg/ml)		
Bacteria	FR21818	Meropenem	Biapenem
S.aureus 209P JC-1	0.05	0.10	0.10
S.aureus 3004*[1]	6.25	25.0	25.0
E.coli NIHJ JC-2	0.20	<0.025	0.39
P.vulgaris IAM 1025	1.56	0.10	3.13
Ps.aeruginosa 26	0.20	0.20	0.20
DHP-I Stability*[2]	0.26	1.0	0.154
Urinary Recovery*[3]	68.9	25.0	70.68

*[1] Methicillin-Resistant Staphylococcus aureus(MRSA) *[2] DHP-I stability is given relative to meropenem

*[3] Recovery (%) in mice after s.c administration (20mg/kg)

Summary

In this communication, we have reported the discovery of FR21818 (**1**), a new, potent, 1β-methylcarbapenem antibacterial agent, that contains a basic pyrrolidine nitrogen atom and a quaternary pyrazolium salt with a hydroxyethyl substituent. Excellent antibacterial activity and stability to renal dehydropeptidase I make this compound a suitable candidate for further development. Future publications will report the *in vivo* protective activity, PBP affinity, and membrane permeability of **1**, as well as preliminary toxicological evaluation and detailed structure activity relationships.

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12. Selected spectroscopic data for FR21818 (**1**): ^{1}H NMR (200MHz, D_2O) 8.28 (d, 1H, J = 3.1 Hz), 6.85 (d, 1H, J = 3.1 Hz), 4.68-4.63 (m, 2H), 4.29-3.97 (m, 6H), 4.09 (s, 3H), 3.74 (dd, 1H, J = 6.6 and 12.5 Hz), 3.52-3.34 (m, 5H), 2.96-2.81 (m, 1H), 1.95-1.80 (m, 1H), 1.29 (d, 3H, J = 6.3 Hz), 1.23 (d, 3H, J = 7.2 Hz); IR (KBr) 1770.3, 1737.5; FAB-MS *m/z* 451 (M^+-Cl).

13. MIC's were determined by the agar dilution method using heart infusion agar after incubation at 37°C for 20 hours with an inoculum size of 10^6 cfu/ml. DHP-I stability was determined using recombinant human enzyme and is represented as the relative rate of hydrolysis compared to the control compound, meropenem (rate = 1.0).

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