Pergamon

Tetrahedron, Vol. 53, No. 2, pp. 539-556, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(96)00980-5

General and Efficient Synthesis of 2-Alkylcarbapenems: Synthesis of Dethiacarba Analogs of Clinically Useful Carbapenems *via* Palladium-Catalyzed Cross-Coupling Reaction

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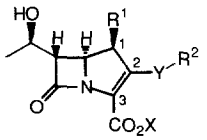
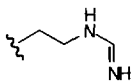
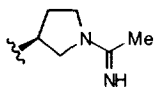
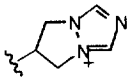
Abstract: Palladium-catalyzed cross-coupling reaction of carbapenem-2-yl triflate with alkylborane gave 2-alkylcarbapenem in good yield. The usefulness of this reaction was demonstrated by the synthesis of highly functionalized 2-alkylcarbapenems, dethiacarba analogs of imipenem, panipenem, biapenem, meropenem, and S-4661.Copyright © 1996 Elsevier Science Ltd

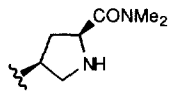
Carbapenems have been recognized as one of the most powerful and broad-spectrum antibiotics and have attracted much attention in the clinical field[1]. These compounds also attracted the interest of synthetic chemists due to the difficulty of constructing the highly strained bicyclic structure as well as controlling the stereochemistry[2]. Although several thousands of carbapenem derivatives have been synthesized so far, most are "natural type" carbapenems, in which the alkylthio side chain is connected to the C-2 position (Y = S, **1a–5a**). During our investigation, we were interested in synthesizing 2-alkylcarbapenems, in which the sulfur atom of "natural type" carbapenems is replaced by a carbon atom, i.e., a methylene group (Y = CH_2, **1b–5b**)[3]. Examination of such derivatives should provide valuable information on the role of the sulfur atom with respect to the antibacterial activity. Such work might also reveal novel unique features of 2-alkylcarbapenems not observed in "natural type" carbapenems.

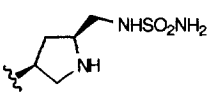


1a: Y = S (imipenem) **1b:** Y = CH_2 — R^1 = H — R^2 =  — X = H

2a: Y = S (panipenem) **2b:** Y = CH_2 — R^1 = H — R^2 =  — X = H

3a: Y = S (biapenem) **3b:** Y = CH_2 — R^1 = Me — R^2 =  — X= anion

4a: Y = S (meropenem) **4b:** Y = CH_2 — R^1 = Me — R^2 =  — X = H

5a: Y = S (S-4661) **5b:** Y = CH_2 — R^1 = Me — R^2 =  — X= H

Due to the lack of a general and efficient method for directly introducing a 2-alkyl group into the carbapemen skeleton[4], the C-2 side chain part was incorporated via carbon-carbon bond formation with monocyclic 2-azetidinone followed by construction of the carbapenem skeleton using Wittig intramolecular cyclization[5]. Although such methods might be reliable for the functionalized derivatives, the synthesis suffers the drawbacks that C-2 alkyl parts need to be incorporated early and that carbapenem skeleton synthesis must be done every time for a variety of C-2 substituents. Therefore, a new method of synthesizing various functionalized 2-alkylcarbapenems is highly desired, with the C-2 alkyl parts being introduced at the later stage of the synthesis from a common carbapenem intermediate.

Considering the mild reaction conditions suitable for the chemically labile carbapenem skeleton and the general applicability for alkenyl–alkyl coupling, a palladium-catalyzed cross-coupling reaction of enol triflates with alkylboranes seems to be quite attractive[6]. The requisite carbapenem-2-yl triflates[7] have been reported in literature and can be synthesized from a well-known, easy-to-prepare intermediate. The partner, alkylboranes, could be obtained from the corresponding olefinic compounds via a well-established hydroboration reaction[8]. Furthermore, the use of hydroboration would offer the additional advantage of a highly stereocontrolled reaction during the alkylborane synthesis. Herein we report the palladium-catalyzed cross-coupling reaction of carbapenem-2-yl triflates with alkylboranes derived via hydroboration and the synthesis of several 2-alkylcarbapenems (**1b-5b**), "dethiacarba" analogs of clinically useful carbapenems[9].

RESULTS AND DISCUSSION

Palladium-Catalyzed Cross-Coupling Reaction of Carbapenem-2-yl Triflates with Alkylboranes. The substrate carbapenem-2-yl triflate (**8a,b**) was obtained from carbapenam-2-one (**7a,b**) according to a known procedure. There are several excellent methods[2] for the synthesis of the precursor, carbapenam-2-one, including stereoselective synthesis of 1β-methyl derivatives (R^1 = Me). We prepared the diazoester

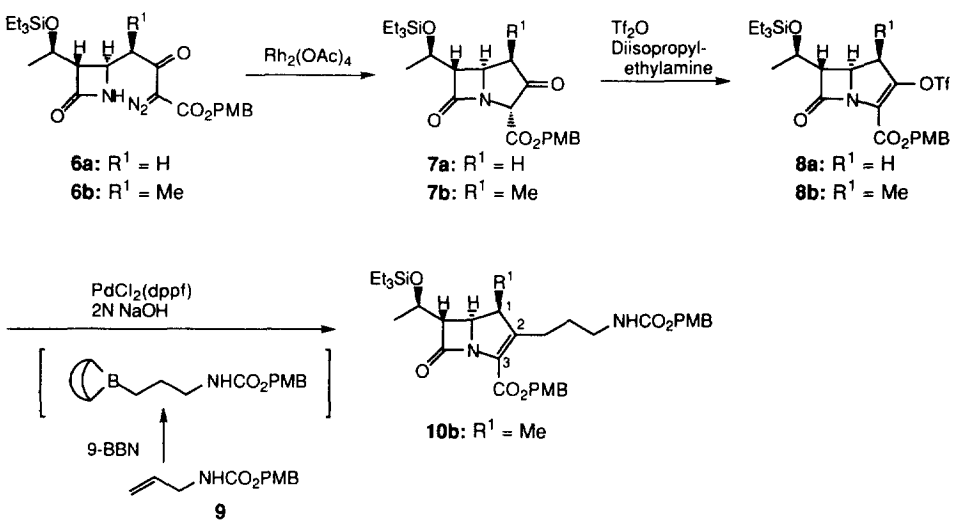


Table 1. Palladium-Catalyzed Cross-Coupling Reaction of Carbapenem-2-yl Triflate (**8b**) with Alkylborane Derived from Olefin (**9**)

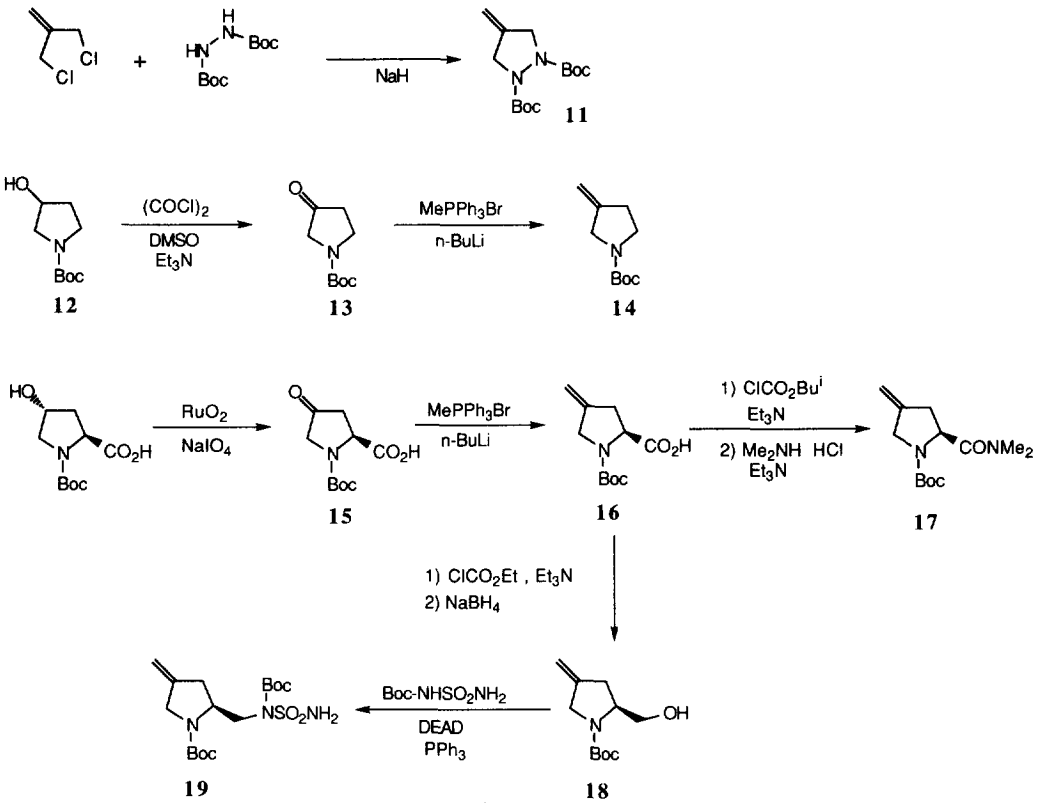
Entry	Catalyst	Solvent[a]	Reaction Condition[b]	Additive	Yield (**10b**, %)
1	$Pd(OAc)_2$	DMF	A	–	15
2	$Pd(PPh_3)_4$	DMF	A	–	21
3	$PdCl_2(PPh_3)_2$	DMF	A	–	33
4	$Pd_2Cl_2(allyl)_2$	DMF	A	–	43
5	$PdCl_2$(dppe)	DMF	A	–	13
6	$Pd(dba)_2$	DMF	A	–	49
7	$PdCl_2$(dppf)	DMF	A	–	49
8	$PdCl_2$(dppf)	DMF	B	–	60
9	$PdCl_2$(dppf)	DMF	B	KBr	54
10	$PdCl_2$(dppf)	DMF	B	LiBr	56
11	$PdCl_2$(dppf)	DMF	B	Et_4NBr	59
12	$PdCl_2$(dppf)	NMP	B	–	55
13	$PdCl_2$(dppf)	THF	B	–	66
14	$PdCl_2$(dppf)	dioxane	B	–	64

[a]1:1 mixture with THF. [b]Reaction Condition A: 25 °C, 3 h. B: 25 °C, 1 h, then 60 °C, 2 h.

(**6a,b**) from 4-acetoxy-2-azetidinone by alkylation of diazoester[10a] or by stereoselective intramolecular allylation[10d,e] followed by the established diazoester synthesis[10c]. The triflates (**8a,b**) were prepared[7] from diazoester (**6a,b**) just prior to use due to the instability of these intermediates.

In order to establish the reaction conditions for the cross-coupling reaction, a reaction of carbapenem-2-yl triflate (**8b**) with alkylborane derived from N-protected allylamine (**9**) was examined first. The presence of amine functionality was our minimal requirement for the C-2 side chain as it seems to be essential for antibacterial activity[1]. 4-Methoxybenzyl carbamate was selected as a protective group which could be cleaved by the $AlCl_3$-anisole method in the final step[11]. Furthermore, this olefinic compound (**9**) serves as the starting material for the synthesis of the dethiacarba analog (**1b**) of imipenem. For the hydroboration reaction of **9**, 9-BBN was selected as a reagent considering the ease of the reaction, its stereoselectivity, and its compatibility with the carbamate group in the olefinic compound.

Hydroboration of **9** was carried out in THF at r.t. for 2 h and the reaction mixture was used without further purification for the following coupling reaction. The generation of alkylborane under the reaction conditions was confirmed by the formation of the corresponding N-protected amino alcohol by usual oxidative workup of the mixture with alkaline hydroperoxide. The cross-coupling reaction of carbapenem-2-yl triflate (**8b**) with alkylborane proceeded readily to afford the product (**10b**) in the presence of various palladium catalysts and aqueous NaOH at r.t. or with heating (Table 1). Although all of the palladium catalysts investigated in this study gave the desired coupling product, $PdCl_2$(dppf) was found to be the most effective and use of $Pd(OAc)_2$, $Pd(PPh_3)_4$, or $PdCl_2$(dppe) resulted in lower yields. The effect of adding KBr, LiBr, or ammonium salt seemed to be small. Since the alkylborane was prepared in THF, all of the coupling reactions

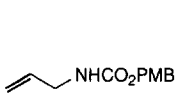
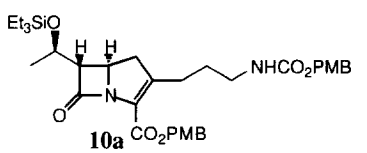
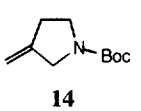
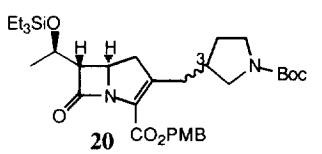
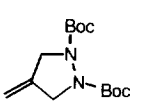
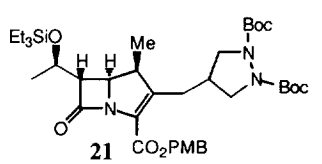
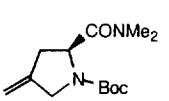
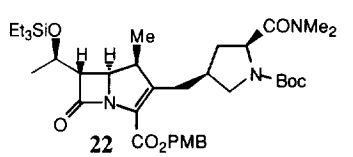
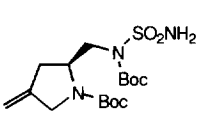
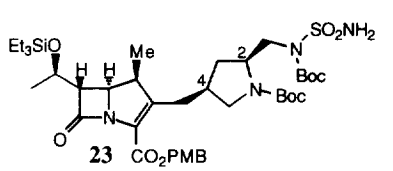


were carried out in the presence of THF solvent, and THF alone was found to be the most suitable solvent for this reaction.

Synthesis of Olefinic Compounds for Cross-Coupling Reaction. Having established an efficient method for introducing the C-2 alkyl side chain, we turned our attention to the synthesis of 2-alkylcarbapenems (**1b-5b**), i.e., dethiacarba analogs of clinically important carbapenems. From the above methodology, our next target was the synthesis of appropriately functionalized olefins (**11**, **14**, **17**, **19**) for the cross-coupling reactions. The synthetic strategy for **14**, **17**, and **19** involves oxidation of the hydroxyl group in the starting materials into ketone followed by Wittig olefination into exomethylene compounds. This strategy was attractive since such hydroxyl compounds are also intermediates for the synthesis of the corresponding thiols and 2-alkylthiocarbapenems. Therefore, switching from the synthesis of natural type 2-alkylthiocarbapenems to that of unnatural 2-alkylcarbapenems was expected to be quite easy. Racemic hydroxypyrrolidine (**12**) was employed for the preparation of achiral **14** while chiral *trans*-4-hydroxy-L-proline was used for the preparation of **17** and **19** since the stereochemistry of the pyrrolidine moiety is quite important for good antibacterial activity[1]. Oxidation of both hydroxyl compounds gave the desired ketones (**13**, **15**) in good yields, which were converted into exomethylene compounds (**14**,**16**) with methylene triphenylphosphorane. The 2-carboxyl group of pyrrolidine (**16**) was converted into carboxylic amide or sulfamide as given in literature[1d,e].

Palladium-Catalyzed Cross-Coupling Reaction of Triflates with Alkylboranes from Functionalized Olefinic Compounds. The prepared olefinic compounds were subjected to hydroboration with 9-BBN followed by palladium-catalyzed cross-coupling reactions of carbapenem-2-yl triflates (Table 2). In all cases, the desired coupling products were obtained in good yields under standard reaction conditions. Although when the hydroboration product is achiral, the coupling product should be a single isomer (Entry 1,3), cross-coupling reaction with racemic borane from prochiral olefin gave a mixture of two diastereomeric isomers (Entry 2). These isomers (**20**) were separated by chromatography (toluene / EtOAc) to give an isomer (34%) and a more polar isomer (37%). Since it has been shown that the absolute configuration of the pyrrolidine ring at the C-3 position greatly influences the antibacterial activity[1], the stereochemistry of the cross-coupling product (**20**) was determined from the following independent synthesis of structurally unambiguous carbapenem from chiral (*R*)-hydroxypyrrolidine.

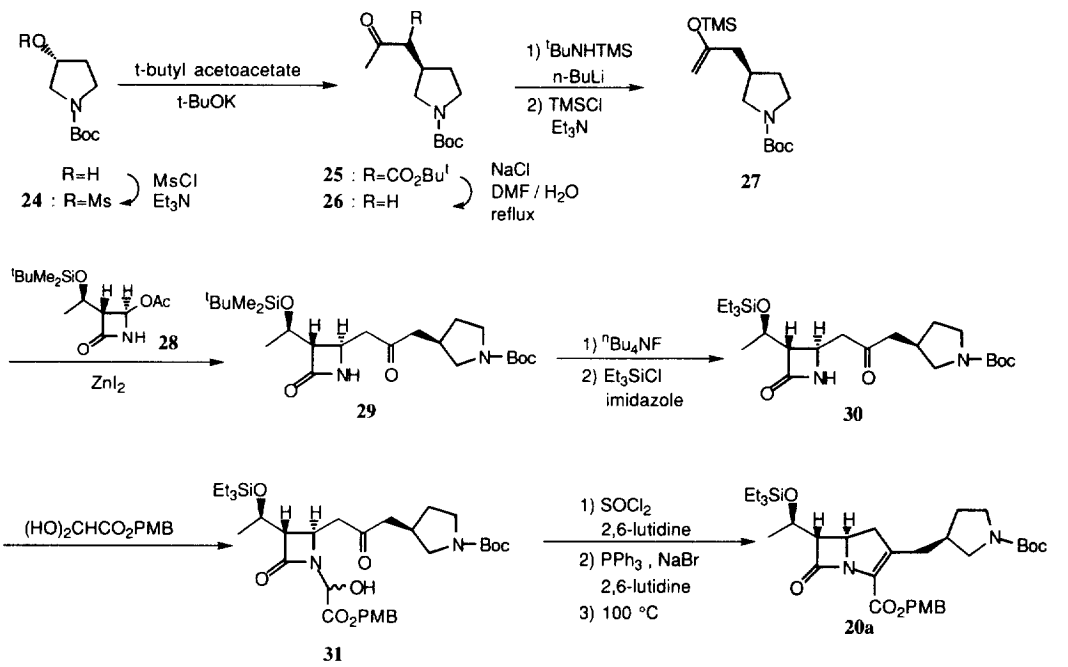
Table 2. Cross-Coupling Reactions of Triflates with Alkylboranes from Functionalized Olefinic Compounds

Entry	Triflate	Olefin	Product	Yield (%)
1	**8a**	 **9**	 **10a**	85
2	**8a**	 **14**	 **20**	71[a]
3	**8b**	 **11**	 **21**	66
4	**8b**	 **17**	 **22**	64
5	**8b**	 **19**	 **23**	62[b]

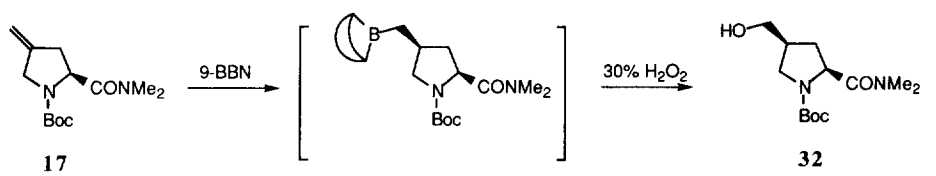
[a] isomer ratio 3*S* (**20a**) / 3*R* (**20b**) = 1 : 1

[b] isomer ratio 4*S* (**23a**) / 4*R* (**23b**) = 4 : 1

Alkylation of acetoacetate ester with mesylate (**24**) gave the desired product (**25**) via inversion of the configuration at the C-3 position[12]. After decarboxylation of the β-ketoester (**25**)[13], the methyl ketone (**26**) was converted into silyl enol ether (**27**)[14]. Introduction of this chiral pyrrolidine part into 4-acetoxyazetidin-2-one (**28**) was accomplished in the presence of ZnI_2[10a]. The protective silyl group at the hydroxyethyl side chain was replaced (**30**) and conventional construction of the carbapenem skeleton followed. The product (**20a**) having an *S*-configuration at the C-3 pyrrolidine ring was identical with the less polar isomer from the cross-coupling reaction. Thus, the isomer **20a** having the desired stereochemistry was used for the next deprotection reaction.



A cross-coupling reaction from the chiral olefinic compound (**17**) gave only one isomer (Entry 4). The stereochemistry of the product could be explained by the attack of 9-BBN from the less hindered side of the chiral olefin during hydroboration. The expected stereochemistry was confirmed by NOESY experiment of the alcohol (**32**) obtained by oxidative workup of the intermediate alkylborane (Figure 1). Since it is reasonable to expect that cross-coupling reaction and oxidative workup occurred from the identical intermediate alkylborane and both of the subsequent reactions should not interfere with the stereochemistry of the pyrrolidine ring system, the stereochemistry of the alcohol (**32**) should reflect that of the coupling product[15]. This *cis*-config-



uration of the pyrrolidine ring is quite attractive to us because its stereochemistry is the preferred one for better antibacterial activity. A similar olefinic compound (**19**) also gave a major and a minor cross-coupling product, with the former expected to be the *cis*-pyrrolidine derivative (Entry 5). It seems likely that the nitrogen-substituted methylene moiety at the C-2 position of **19** would have an insufficient steric effect on hydroboration compared with the N,N-dimethylcarbamoyl group of **17**.

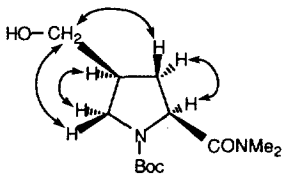


Figure 1. Results of NOESY Experiments for **32**

Synthesis and Antibacterial Activity of Dethiacarba Analogs of Clinically Useful Carbapenems. As a final step for the synthesis of dethiacarba analogs (**1b-5b**) of clinically useful carbapenems, functionalized 2-alkylcarbapenems (**10a**, **20a**, **21**, **22**, **23a**) with the suitable stereochemistry of the pyrrolidine part were then converted into the final products by deprotection and N-functionalization. In all cases, deprotection with $AlCl_3$ / anisole[11] proceeded readily and the reaction mixture was used without purification for the subsequent functionalization of the amino group[1a-c] (Table 3).

Table 3. Deprotection and N-Functionalization of 2-Alkylcarbapenems

Entry	Coupling product	Reagent	Product	Yield (%)
1	**10a**	1) $AlCl_3$, anisole 2) Ethyl formimidate·HCl	**1b**	52
2	**20a**	1) $AlCl_3$, anisole 2) Ethyl acetimidate·HCl	**2b**	40
3	**21**	1) $AlCl_3$, anisole 2) Ethyl formimidate·HCl	**3b**	32
4	**22**	$AlCl_3$, anisole	**4b**	47
5	**23a**	$AlCl_3$, anisole	**5b**	61

The *in vitro* antibacterial activity of dethiacarba analogs (**1b-5b**) against selected Gram-positive and Gram-negative bacteria are summarized in Table 4. For comparison, the MIC (minimum inhibitory concentration, μg/ml) values of each parent carbapenem (**1a-5a**) are also listed. These dethiacarba analogs prepared in this study showed excellent antibacterial activity against Gram-positive as well as Gram-negative strains including *Pseudomonas aeruginosa*. Comparison of the activity of 2-alkylcarbapenems with those of the parent thia analogs shows that their activities are almost similar against Gram-positive strains such as *Staphylococcus aureus* but except for **3b**, most of the dethiacarba analogs showed reduced activity against *E. coli* and *Pseudomonas aeruginosa*.. The retained antibacterial activity of **3b** and large differences of activity against *Pseudomonas aeruginasa* (0.8 – 100 μg/ml) among **1b-5b** suggest that 2-alkylcarbapenems have a different

Table 4. *In vitro* Antibacterial Activity of 2-Alkylcarbapenems (**1b-5b**) and Thia Analogs (**1a-5a**)

	MIC (μg/ml)									
Organism*	**1b**	**1a**	**2b**	**2a**	**3b**	**3a**	**4b**	**4a**	**5b**	**5a**
S. a.	0.02	0.01	0.1	0.02	0.05	0.05	0.2	0.1	0.05	0.03
E. c.	0.4	0.1	1.6	0.1	0.05	0.05	0.1	0.03	0.1	0.03
P. a.	12.5	1.6	100	3.1	0.8	0.4	1.6	0.1	3.1	0.1

* *S. a.*, *Staphylococcus aureus* Smith ; *E.c.*, *Escherichia coli* NIHJ JC-2 ; *P. a.*, *Pseudomonas aeruginosa* SR 24

structure-activity relationships from the thia analogs and have the potential to be excellent antibiotics provided that a suitable C-2 side chain can be selected.

CONCLUSION

We have established a convenient synthetic method for 2-alkyl substituted carbapenems via palladium-catalyzed cross-coupling reaction of carbapenem-2-yl triflates with alkylboranes, the latter being derived by hydroboration of appropriate olefins. This method makes it possible to synthesize 2-alkylcarbapenems (**1b-5b**), dethiacarba analogs of clinically useful carbapenems. Although some of the 2-alkylcarbapenems showed reduced activity compared with those of the parent thia analogs, one compound had comparable activity, indicating the potential of 2-alkylcarbapenems for being excellent antibiotics. The success of the present synthesis demonstrates the usefulness of this cross-coupling reaction for preparing functionalized 2-alkylcarbapenems.

EXPERIMENTAL

General: Reagents were used as supplied unless otherwise noted. Reactions were carried out under nitrogen using dry solvents. Solvents were dried over molecular sieves before use. Silica gel (E. Merck, 230–400 mesh) was used for column chromatography. Infrared (IR) spectra were recorded on a Hitachi 260-10 spectrophotometer. Proton and carbon nuclear magnetic resonance (^{1}H NMR / ^{13}C NMR) spectra were obtained on a Varian VXR-200 (200 MHz / 50 MHz) or Gemini-300 (300 MHz / 75 MHz) spectrometer. Chemical shifts are expressed in ppm downfield from tetramethylsilane (TMS) in $CDCl_3$, or DOH (δ 4.80) in D_2O as an internal standard. Mass spectra (MS) were obtained on a Hitachi M-90 (SIMS) mass spectrometer.

(3*S*,4*R*)-4-(3-Diazo-3-(4-methoxybenzyloxycarbonyl)-2-oxopropyl)-3-[(1*R*)-1-(triethylsilyloxy)ethyl]-azetidin-2-one (6a). Compound **6a** was prepared by triethylsilyl protection of the azetidinone derivative which was synthesized in a similar way as in reference[10a]: viscous pale yellow oil; IR ($CHCl_3$) 3408, 2138, 1755, 1711, 1646 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.59 (q, *J* = 8.0 Hz, 6H), 0.94 (t, *J* = 8.0 Hz, 9H), 1.23 (d, *J* = 6.0 Hz, 3H), 2.85 (dd, *J* = 5.4 Hz, 2.4 Hz, 1H), 2.99 (dd, *J* = 18.0 Hz, 10.0 Hz, 1H), 3.40 (dd, *J* = 18.0 Hz, 3.3 Hz, 1H), 3.82 (s, 3H), 4.00 (dt, *J* = 9.6 Hz, 2.7 Hz, 1H), 4.19 (quint, *J* = 6.0 Hz, 1H), 5.21 (s, 2H), 6.02 (br s, 1H), 6.91 (d, *J* = 8.7 Hz, 2H), 7.31 (d, *J* = 8.7 Hz, 2H). Anal. Calcd for $C_{23}H_{33}N_3O_6Si$: C, 58.08; H, 6.99; N, 8.83. Found: C, 58.04; H, 6.99; N, 8.83.

(3*S*,4*R*)-4-[(1*R*)-1-Methyl-3-diazo-3-(4-methoxybenzyloxycarbonyl)-2-oxopropyl]-3-[(1*R*)-1-(triethylsilyloxy)ethyl]azetidin-2-one (6b). Compound **6b** was prepared by triethylsilyl protection of the azetidinone derivative which was synthesized in a similar way as in references[10b-d]: white powder; IR ($CHCl_3$) 3404, 2138, 1755, 1709, 1645 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.59 (q, *J* = 8.0 Hz, 6H), 0.94 (t, *J* = 8.0 Hz, 9H), 1.16 (d, *J* = 6.8 Hz, 3H), 1.21 (d, *J* = 6.2 Hz, 3H), 2.91–2.99 (m, 1H), 3.77–4.02 (m, 2H), 3.82 (s, 3H), 4.17 (dq, *J* = 6.2 Hz, 4.8 Hz, 1H), 5.20 (s, 2H), 5.88 (br, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 7.31 (d, *J* = 8.8 Hz, 2H). Anal. Calcd for $C_{24}H_{35}N_3O_6Si$: C, 58.87; H, 7.20; N, 8.58. Found: C, 58.94; H, 7.23; N, 8.57.

General Procedure for the Synthesis of Enol Triflates (8a,b). To a solution of diazo derivative (**6a,b,** 0.77 mmol) in benzene (7 ml) was added a catalytic amount of $Rh_2(OAc)_4$ (1.7 mg, 0.0038 mmol, 0.5 mol %), and the mixture was refluxed for 30 min. After being cooled to r.t., evaporation of the solvent gave a crude 2-oxocarbapenam (**7a,b**). To a solution of this product in CH_2Cl_2 (7 ml) were added N,N-diisopropylethylamine (160 μl, 0.92 mmol, 1.2 eq) and trifluoromethanesulfonic anhydride (142 μl, 0.84 mmol, 1.1 eq) at -78 °C. After 30 min, the reaction mixture was poured into saturated aqueous $NaHCO_3$ and EtOAc, and extracted with EtOAc. The extracts were washed with water and brine and dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded a crude enol triflate, (**8a,b**) which was essentially pure by ^1H-NMR analysis. It was used for the next reaction without further purification.

4-Methoxybenzyl (5*R*,6*S*)-6-[(1*R*)-1-(Triethylsilyloxy)ethyl]-2-trifluoromethanesulfonyloxycarbapen-2-em-3-carboxylate (8a): a viscous pale yellow oil; IR ($CHCl_3$) 1793, 1726 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.59 (q, *J* = 8.0 Hz, 6H), 0.94 (t, *J* = 8.0 Hz, 9H), 1.25 (d, *J* = 6.3 Hz, 3H), 3.03–3.21 (m, 2H), 3.27 (dd, *J* = 5.4 Hz, 3.0 Hz, 1H), 3.80 (s, 3H), 4.16–4.28 (m, 2H), 5.25 (s, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 7.36 (d, *J* = 8.7 Hz, 2H).

4-Methoxybenzyl (1*R*,5*R*,6*S*)-1-Methyl-6-[(1*R*)-1-(triethylsilyloxy)ethyl]-2-trifluoromethanesulfonyloxycarbapen-2-em-3-carboxylate (8b): a viscous pale yellow oil; IR ($CHCl_3$) 1787, 1727 cm^{-1}; ^1H NMR(200 MHz, $CDCl_3$) δ 0.59 (q, *J* = 8.0 Hz, 6H), 0.94 (t, *J* = 8.0 Hz, 9H), 1.24 (d, *J* = 6.4 Hz, 3H), 1.26 (d, *J* = 7.2 Hz, 3H), 3.33 (dq, *J* = 11.0 Hz, 7.2 Hz, 1H), 3.35 (dd, *J* = 6.0 Hz, 3.4 Hz, 1H), 3.80 (s, 3H), 4.24 (quint, *J* = 6.0 Hz, 1H), 4.27 (dd, *J* = 11.0 Hz, 3.4 Hz, 1H), 5.21 and 5.29 (ABq, *J* = 11.9 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 7.37 (d, *J* = 8.8 Hz, 2H).

N-(4-Methoxybenzyloxycarbonyl)-2-propenylamine (9). To an ice-cooled solution of allylamine (5.00 g, 0.088 mol) and Et_3N (14.6 ml, 0.105 mol) in CH_2Cl_2 (200 ml) was added S-(4-methoxybenzyloxycarbonyl)-4,6-dimethyl-2-mercaptopyrimidine (31.98 g, 0.105 mol), and the solution was stirred with ice-cooling for 5 h. After being concentrated, water and EtOAc were added to the residue, and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification of the residue by silica gel column chromatography gave **9** (14.5 g, 75%) as a colorless oil: IR ($CHCl_3$) 3442, 1714 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.70–3.90 (m, 2H), 3.81 (s, 3H), 4.62–4.88 (br, 1H), 5.05 (s, 2H), 5.07–5.25 (m, 2H), 5.72–5.96 (m, 1H), 6.89 (d, *J* = 8.6 Hz, 2H), 7.31 (d, *J* = 8.6 Hz, 2H). Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 64.80; H, 6.87; N, 6.38.

General Procedure for Palladium-Catalyzed Cross-Coupling Reaction. To an ice-cooled solution of olefinic compound (0.51 mmol) in THF (0.5 ml) was added a solution of 9-BBN (0.5 M in THF, 1.54 ml, 0.77 mmol, 1.5 eq), and the reaction mixture was stirred at r.t. for 2 h. To this was added with ice-cooling a solution of enol triflate (prepared from 0.77 mmol of **6**, 1.5 eq) in THF (2 ml) followed by palladium catalyst (5 mol %) and 2N NaOH aqueous solution (0.26 ml, 0.52 mmol, 1 eq). The reaction was carried out as indicated in Table 1 or heated to 60 °C for 2 h. The mixture was poured into water and EtOAc, and extracted with EtOAc. The extracts were washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*.

Purification of the residue by silica gel column chromatography afforded the cross-coupling product.

4-Methoxybenzyl (1*S*,5*R*,6*S*)-2-[3-(4-methoxybenzyloxycarbonyl)aminopropyl]-1-methyl-6-[(1*R*)-1-(triethylsilyloxy)ethyl]carbapen-2-em-3-carboxylate (10b): a viscous colorless oil; IR ($CHCl_3$) 3438, 1765, 1709 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.58 (q, *J* = 8.0 Hz, 6H), 0.94 (t, *J* = 8.0 Hz, 9H), 1.10 (d, *J* = 7.4 Hz, 3H), 1.26 (d, *J* = 6.2 Hz, 3H), 1.45–1.83 (m, 2H), 2.04–2.24 (m, 1H), 2.80–3.30 (m, 4H), 3.16 (dd, *J* = 6.6 Hz, 3.0 Hz, 1H), 3.78 (s, 3H), 3.80 (s, 3H), 4.07 (dd, *J* = 10.2 Hz, 3.0 Hz, 1H), 4.20 (quint, *J* = 6.4 Hz, 1H), 4.97 (br, 1H), 5.03 (s, 2H), 5.16 and 5.21 (ABq, *J* = 12.2 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 7.31 (d, *J* = 8.8 Hz, 2H), 7.37 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 4.9, 6.8, 15.3, 22.6, 24.1, 28.4, 40.4, 41.8, 55.1, 55.2, 55.8, 60.0, 66.2, 66.3, 66.5, 113.8, 113.9, 127.1, 127.7, 128.8, 129.9, 130.0, 152.4, 156.6, 159.5, 161.7, 174.6; HRMS Calcd for $C_{36}H_{50}N_2O_8SiNa$ $[M+Na]^+$ 689.3232, Found 689.3238.

1,2-Bis(*tert*-butoxycarbonyl)-4-methylenepyrazolidine (11). To a solution of 1,2-di-*tert*-butoxycarbonylhydrazine (5.00 g, 21.5 mmol) in DMF (100 ml) was added at r.t. 60% NaH (947 mg, 23.7 mmol) portionwise, and the mixture was stirred for 1 h. After addition of 3-chloro-2-chloromethyl-1-propene (3.74 ml, 32.3 mmol), the reaction mixture was stirred for 1 h, and 60% NaH (947 mg, 23.7 mmol) was added again. After being stirred for 30 min, the solution was heated to 90 °C for 4 h. The reaction mixture was poured into water and EtOAc, and extracted with EtOAc. The extracts were washed with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by silica gel column chromatography to give **11** (5.12 g, 84%) as a white powder: IR ($CHCl_3$) 1691 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.48 (s, 18H), 3.84 (br d, *J* = 15 Hz, 2H), 4.44 (br d, *J* = 15 Hz, 2H), 5.07 (quint, *J* = 2.4 Hz, 2H). Anal. Calcd for $C_{14}H_{24}N_2O_4$: C, 59.14; H, 8.51; N, 9.85. Found: C, 58.86; H, 8.48; N, 9.95.

1-*tert*-Butoxycarbonyl-3-hydroxypyrrolidine (12). To a solution of 3-hydroxypyrrolidine (5.32 g, 61 mmol) in CH_2Cl_2 (80 ml) was added at r.t. a solution of di-*tert*-butyl dicarbonate (13.33 g, 61 mmol) in CH_2Cl_2 (40 ml). After being stirred for 1.5 h, the mixture was poured into water and CH_2Cl_2, and aqueous layer was extracted with CH_2Cl_2. The extracts were washed with water, dried over $MgSO_4$, and concentrated *in vacuo*. Purification of the residue by silica gel column chromatography gave **12** (11.21 g, 98%) as a white powder: IR ($CHCl_3$) 3398, 1677 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.46 (s, 9H), 1.84–2.23 (m, 2H), 2.84 (br, 1H), 3.26–3.56 (m, 4H), 4.44 (br s, 1H). Anal. Calcd for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48. Found: C, 57.49; H, 9.00; N, 7.47.

1-*tert*-Butoxycarbonyl-3-oxopyrrolidine (13). To a solution of DMSO (9.1 ml, 0.13 mol) in CH_2Cl_2 (100 ml) was added oxalyl chloride (5.6 ml, 0.064 mol) at -78 °C. After 30 min, a solution of **12** (10.0 g, 0.053 mol) in CH_2Cl_2 (50 ml) was added. After being stirred at that temperature for 1 h, Et_3N (22 ml, 0.16 mol) was added, and the reaction mixture was stirred for additional 1 h. The mixture was poured into saturated aqueous $NaHCO_3$ and EtOAc, and extracted with EtOAc. The organic layers were washed with brine, dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by silica gel column chromatography to give **13** (9.61 g, 97%) as a white powder: IR ($CHCl_3$) 1759, 1691 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.49 (s, 9H), 2.59 (t, *J* = 8.1 Hz, 2H), 3.75 (s, 2H), 3.78 (t, *J* = 8.1 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.4, 36.9, 42.3, 52.6, 80.1, 154.3, 211.0; HRMS Calcd for $C_9H_{15}NO_3$ 185.1051, Found 185.1061.

1-*tert*-Butoxycarbonyl-3-methylenepyrrolidine (14). To a solution of methyltriphenylphosphonium bromide (51.81 g, 0.145 mol) in THF (250 ml) was added at -78 °C a solution of *n*-butyllithium (1.6 M in hexane, 82 ml, 0.131 mol), and the mixture was stirred at the same temperature for 2 h. To this was added a solution of **13** (8.14 g, 0.044 mol) in THF (70 ml), and the reaction mixture was refluxed for 4 h. After being cooled to r.t., the reaction mixture was poured into water and CH_2Cl_2, and extracted with CH_2Cl_2. The extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by

silica gel column chromatography to give **14** (6.43 g, 80%) as a colorless oil: IR ($CHCl_3$) 1682 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.47 (s, 9H), 2.55 (br t, J = 6.9 Hz, 2H), 3.37–3.55 (m, 2H), 3.92 (br s, 2H), 4.91–5.02 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.5, 31.6, 32.2, 45.5, 45.9, 50.3, 79.2, 106.6, 145.2, 146.0, 154.4; HRMS Calcd for $C_{10}H_{17}NO_2$ 183.1258, Found 183.1256.

1-*tert*-Butoxycarbonyl-4-oxo-L-proline (15). To an ice-cooled solution of 1-*tert*-butoxycarbonyl-4-(*R*)-hydroxy-L-proline (20.0 g, 86.5 mmol) in EtOAc (280 ml) were added a saturated aqueous solution of sodium metaperiodate (495 ml) and ruthenium oxide (11.5 mg, 0.086 mmol, 0.1 mol %), and the solution was stirred at r.t. for 6 h. After separation of organic layer, aqueous layer was extracted with EtOAc. The combined organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was triturated with ether to give **15** (13.3 g, 67%) as a white powder: IR($CHCl_3$) 1765, 1724, 1699 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.46 (s, 9H), 2.45–2.64 (m, 1H), 2.97–3.21 (m, 1H), 3.68–3.97 (m, 2H), 4.60–4.79 (m, 1H). Anal. Calcd for $C_{10}H_{15}NO_5$: C, 52.40; H, 6.60; N, 6.11. Found: C, 52.05; H, 6.51; N, 6.08.

1-*tert*-Butoxycarbonyl-4-methylene-L-proline (16). To a solution of methyltriphenylphosphonium bromide (51.43 g, 0.144 mol) in THF (400 ml) was added at -78 °C a solution of *n*-butyllithium (1.69 M in hexane, 77 ml, 0.130 mol), and the reaction mixture was allowed to warm to r.t.. After addition of a solution of **15** (10.00 g, 0.0436 mmol) in THF (70 ml), the solution was refluxed overnight. The reaction mixture was cooled in an ice-bath, and water was added followed by saturated aqueous $NaHCO_3$ and ether. The aqueous layer was washed with ether, acidified with conc. HCl, and extracted with ether. The extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford **16** (9.9 g, quant. yield) as a pale yellow foam: IR ($CHCl_3$) 1721, 1693 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.43 (s, 9H x 2/5), 1.49 (s, 9H x 3/5), 2.60–3.14 (m, 2H), 3.98–4.14 (m, 2H), 4.34–4.58 (m, 1H), 5.03 (br s, 2H); HRMS Calcd for $C_{11}H_{18}NO_4$ $[M+H]^+$ 228.1234, Found 228.1234.

(2*S*)-1-*tert*-Butoxycarbonyl-2-(N,N-dimethylcarbamoyl)-4-methylenepyrrolidine (17). To a solution of **16** (2.45 g, 10.8 mmol) in CH_2Cl_2 (50 ml) were added Et_3N (1.80 ml, 12.9 mmol) and isobutyl chloroformate (1.54 ml, 11.9 mmol) at -20 °C. After being stirred for 1 h, dimethylamine hydrochloride (1.76 g, 21.6 mmol) and Et_3N (4.5 ml, 32.3 mmol) were added to the reaction mixture and it was stirred with ice-cooling for 2 h. The mixture was poured into 1N HCl and EtOAc, and extracted with EtOAc. The extracts were washed with 1N HCl, saturated aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. After evaporation, the residue was purified by silica gel column chromatography to give **17** (1.08 g, 39%) as a viscous pale yellow oil: IR ($CHCl_3$) 1686, 1654 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.41 (s, 9H x 1/3), 1.47 (s, 9H x 2/3), 2.40–2.60 (m, 1H), 2.81–3.03 (m, 1H), 2.95 (s, 3H x 2/3), 2.97 (s, 3H x 1/3), 3.06 (s, 3H x 1/3), 3.08 (s, 3H x 2/3), 3.99–4.31 (m, 2H), 4.71 (dd, J = 9.4 Hz, 3.3 Hz, 1H x 1/3), 4.85 (dd, J = 9.4 Hz, 2.2 Hz, 1H x 2/3), 4.92–5.07 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.3, 28.5, 35.8, 35.9, 36.4, 36.9, 51.2, 51.3, 56.3, 56.6, 79.7, 79.8, 107.3, 107.5, 143.1, 144.2, 153.9, 154.5, 171.9, 172.3; HRMS Calcd for $C_{13}H_{23}N_2O_3$ $[M+H]^+$ 255.1708, Found 255.1709.

(2*S*)-1-*tert*-Butoxycarbonyl-2-hydroxymethyl-4-methylenepyrrolidine (18). To a solution of **16** (2.80 g, 12.3 mmol) in THF (25 ml) were added Et_3N (3.4 ml, 24 mmol) and ethyl chloroformate (1.77 ml, 18.5 mmol) at -20 °C, and the solution was stirred for 30 min. After filtration of the reaction mixture, an aqueous solution (50 ml) of $NaBH_4$ (1.40 g, 37.0 mmol) was added to the filtrate, and the reaction mixture was stirred for 1 h. The solution was poured into water and EtOAc, and extracted with EtOAc. The extracts were washed with water and brine, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by silica gel column chromatography to afford **18** (1.67 g, 64%) as a viscous pale yellow oil: IR ($CHCl_3$) 3378, 1672 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.48 (s, 9H), 2.15–2.85 (m, 2H), 3.60 (t, J = 5.3 Hz, 2H), 3.81–4.30 (m, 3H), 4.98 (br s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.5, 34.9, 51.4, 59.4, 66.1, 80.3, 107.4, 144.1, 156.2; HRMS Calcd for $C_{11}H_{20}NO_3$ $[M+H]^+$ 214.1442, Found 214.1446.

(2*S*)-1-*tert*-Butoxycarbonyl-2-[N-(*tert*-butoxycarbonyl)-N-sulfamoylaminomethyl]-4-methylenepyrrolidine (19). To a solution of **18** (1.27 g, 5.95 mmol) in THF (25 ml) were added N-*tert*-butoxycarbonylsulfamide (1.40 g, 7.15 mmol), triphenylphosphine (1.56 g, 5.95 mmol) and diethyl azodicarboxylate (0.94 ml, 5.95 mmol), and the mixture was stirred at r.t. for 5 h. The reaction mixture was poured into water and EtOAc, and extracted with EtOAc. The extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography gave **19** (2.06 g, 88%) as a white powder: IR ($CHCl_3$) 3362, 3190, 1708, 1673 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.43 (s, 9H), 1.51 (s, 9H), 2.13 (d, *J* = 15.2 Hz, 1H), 2.60–2.81 (m, 1H), 3.49–3.90 (m, 3H), 4.02–4.20 (m, 1H), 4.50–4.68 (m, 1H), 5.05 (br s, 2H), 5.18 (br s, 2H). Anal. Calcd for $C_{16}H_{29}N_3O_6S$: C, 49.09; H, 7..47; N, 10.73; S, 8.19. Found: C, 48.86; H, 7.35; N, 10.67; S, 8.09.

4-Methoxybenzyl (5*R*,6*S*)-2-[3-(4-methoxybenzyloxycarbonyl)aminopropyl]-6-[(1*R*)-1-(triethylsilyloxy)ethyl]carbapen-2-em-3-carboxylate (10a): 85% yield (1.50 g) as a viscous colorless oil; IR ($CHCl_3$) 3442, 1772, 1710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.59 (q, *J* = 8.0 Hz, 6H), 0.94 (t, *J* = 8.0 Hz, 9H), 1.26 (d, *J* = 6.0 Hz, 3H), 1.57–1.74 (m, 2H), 2.58–2.69 (m, 2H), 2.81 (d, *J* = 9.0 Hz, 2H), 3.05 (dd, *J* = 6.6 Hz, 2.7 Hz, 1H), 3.04–3.19 (m, 2H), 3.78 (s, 3H), 3.80 (s, 3H), 4.06 (dt, *J* = 9.0 Hz, 2.7 Hz, 1H), 4.18 (quint, *J* = 6.3 Hz, 1H), 5.03 (s, 2H), 5.00–5.15 (br, 1H), 5.16 and 5.21 (ABq, *J* = 12.3 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 7.31 (d, *J* = 8.7 Hz, 2H), 7.36 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 4.9, 6.8, 22.6, 25.4, 27.7, 40.1, 40.3, 52.3, 55.1, 66.2, 66.4, 66.8, 113.8, 127.7, 128.9, 129.8, 129.9, 149.4, 156.6, 159.5, 161.5, 176.5; HRMS Calcd for $C_{35}H_{48}N_2O_8SiNa$ $[M+Na]^+$ 675.3075, Found 675.3076.

4-Methoxybenzyl (5*R*,6*S*)-2-[(3*S*)-[1-(*tert*-Butoxycarbonyl)pyrrolidin-3-yl]-methyl]-6-[(1*R*)-1-(triethylsilyloxy)ethyl]carbapen-2-em-3-carboxylate (20a): 34% yield (113 mg) as a viscous colorless oil, less polar isomer (toluene / EtOAc); IR ($CHCl_3$) 1772, 1710, 1679 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.59 (q, *J* = 7.8 Hz, 6H), 0.94 (t, *J* = 7.8 Hz, 9H), 1.27 (d, *J* = 6.3 Hz, 3H), 1.40–1.64 (m, 1H), 1.46 (s, 9H), 1.82–1.97 (m, 1H), 2.18–2.38 (m, 1H), 2.70–2.98 (m, 3H), 2.82 (d, *J* = 6.2 Hz, 2H), 3.01–3.11 (m, 1H), 3.14–3.31 (m, 1H), 3.33–3.58 (m, 2H), 3.80 (s, 3H), 4.01–4.14 (m, 1H), 4.19 (quint, *J* = 6.3 Hz, 1H), 5.17 and 5.21 (ABq, *J* = 12.3 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 7.37 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 4.9, 6.8, 22.7, 28.5, 30.9, 31.5, 31.6, 37.0, 37.8, 40.7, 40.8, 45.2, 45.4, 50.9, 51.2, 52.5, 55.2, 66.3, 66.5, 66.6, 66.9, 67.0, 79.1, 113.8, 127.6, 127.7, 128.3, 129.8, 129.9, 147.4, 147.6, 154.5, 159.6, 161.2, 176.4; HRMS Calcd for $C_{33}H_{50}N_2O_7SiNa$ $[M+Na]^+$ 637.3283, Found 637.3288.

4-Methoxybenzyl (5*R*,6*S*)-2-[(3*R*)-[1-(*tert*-Butoxycarbonyl)pyrrolidin-3-yl]-methyl]-6-[(1*R*)-1-(triethylsilyloxy)ethyl]carbapen-2-em-3-carboxylate (20b): 37% yield (125 mg) as a viscous colorless oil, more polar isomer (toluene / EtOAc); IR ($CHCl_3$) 1773, 1710, 1679 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.59 (q, *J* = 7.8 Hz, 6H), 0.94 (t, *J* = 7.8 Hz, 9H), 1.27 (d, *J* = 6.3 Hz, 3H), 1.40–1.80 (m, 1H), 1.46 (s, 9H), 1.81–1.97 (m, 1H), 2.18–3.01 (m, 6H), 3.02–3.12 (m, 1H), 3.14–3.31 (m, 1H), 3.31–3.60 (m, 2H), 3.80 (s, 3H), 4.01–4.14 (m, 1H), 4.19 (quint, *J* = 6.3 Hz, 1H), 5.16 and 5.23 (ABq, *J* = 12.2 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 7.37 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 4.9, 6.8, 22.7, 28.5, 30.9, 31.4, 31.6, 37.2, 37.9, 40.9, 45.1, 45.4, 51.1, 51.3, 52.4, 52.5, 55.2, 66.4, 66.6, 67.0, 79.2, 113.9, 127.7, 128.3, 129.9, 147.5, 154.5, 159.6, 161.3, 176.4; HRMS Calcd for $C_{33}H_{50}N_2O_7SiNa$ $[M+Na]^+$ 637.3283, Found 637.3287.

4-Methoxybenzyl (1*S*,5*R*,6*S*)-2-[[1,2-Bis(*tert*-butoxycarbonyl)pyrazolidin-4-yl]-methyl]-1-methyl-6-[(1*R*)-1-(triethylsilyloxy)ethyl]carbapen-2-em-3-carboxylate (21): 66% yield (2.00 g) as a viscous colorless oil; IR ($CHCl_3$) 1769, 1710, 1686 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.59 (q, *J* = 8.0 Hz, 6H), 0.94 (t, *J* = 8.0 Hz, 9H), 1.09 (d, *J* = 7.2 Hz, 3H), 1.26 (d, *J* = 6.0 Hz, 3H), 1.48

(s, 18H), 1.98–2.15 (m, 1H), 2.43–2.61 (m, 1H), 2.76–3.64 (m, 5H), 3.16 (dd, J = 6.6 Hz, 3.0 Hz, 1H), 3.74–4.16 (m, 2H), 3.80 (s, 3H), 4.21 (quint, J = 6.3 Hz, 1H), 5.16 and 5.23 (ABq, J = 12.3 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 7.38 (d, J = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 5.0, 6.8, 15.4, 22.6, 28.3, 28.7, 28.9, 38.7, 42.0, 42.2, 51.7, 52.0, 55.2, 55.7, 60.1, 66.2, 66.7, 81.2, 113.9, 127.6, 128.1, 130.0, 149.0, 149.2, 155.9, 156.2, 159.7, 161.3, 174.2; HRMS Calcd for $C_{38}H_{59}N_3O_9SiNa$ $[M+Na]^+$ 752.3914, Found 752.3913.

4-Methoxybenzyl (1*S*,5*R*,6*S*)-2-[[(2*S*, 4*S*)-1-(*tert*-Butoxycarbonyl)-2-(N,N-dimethylcarbamoyl)pyrrolidin-4-yl]methyl]-1-methyl-6-[(1*R*)-1-(triethylsilyloxy)-ethyl]carbapen-2-em-3-carboxylate (22): 64% yield (229 mg) as a viscous colorless oil; IR ($CHCl_3$) 1769, 1683, 1655 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.59 (q, J = 7.8 Hz, 6H), 0.94 (t, J = 7.8 Hz, 9H), 1.10 (d, J = 7.2 Hz, 3H), 1.26 (d, J = 6.2 Hz, 3H), 1.39 (s, 9H x 1/2), 1.45 (s, 9H x 1/2), 1.45–1.75 (m, 1H), 1.98–2.46 (m, 3H), 2.88–3.23 (m, 4H), 2.98 (s, 3H), 3.04 (s, 3H x 1/2), 3.09 (s, 3H x 1/2), 3.56–3.85 (m, 1H), 3.80 (s, 3H), 4.01–4.30 (m, 2H), 4.41–4.66 (m, 1H), 5.10–5.29 (m, 2H), 6.89 (d, J = 8.6 Hz, 2H), 7.39 (d, J = 8.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 5.0, 6.8, 15.4, 22.6, 28.3, 28.5, 29.1, 29.4, 35.8, 36.0, 36.1, 36.6, 36.9, 37.0, 37.3, 38.0, 42.1, 42.5, 51.8, 52.4, 55.2, 55.6, 55.8, 56.3, 56.6, 60.0, 60.1, 66.1, 66.2, 66.6, 66.7, 79.6, 79.7, 113.9, 127.5, 127.6, 127.7, 130.0, 150.1, 150.3, 153.4, 154.1, 159.5, 159.6, 161.2, 161.3, 172.2, 172.4, 174.4, 174.5; HRMS Calcd for $C_{37}H_{57}N_3O_8SiNa$ $[M+Na]^+$ 722.3809, Found 722.3808.

4-Methoxybenzyl (1*S*,5*R*,6*S*)-2-[[(2*S*, 4*S*)-1-(*tert*-Butoxycarbonyl)-2-[N-(*tert*-butoxycarbonyl)-N-sulfamoylaminomethyl]pyrrolidin-4-yl]methyl]-1-methyl-6-[(1*R*)-1-(triethylsilyloxy)ethyl]carbapen-2-em-3-carboxylate (23a): 49% yield (525 mg) as a viscous colorless oil, polar isomer (toluene / EtOAc); IR ($CHCl_3$) 3360, 3188, 1769, 1710, 1668 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.59 (q, J = 8.0 Hz, 6H), 0.94 (t, J = 8.0 Hz, 9H), 1.12 (d, J = 7.5 Hz, 3H), 1.27 (d, J = 6.0 Hz, 3H), 1.42 (s, 9H), 1.51 (s, 9H), 1.40–1.70 (m, 1H), 2.08–2.35 (m, 3H), 2.63–2.80 (m, 1H), 3.03 (dq, J = 10.2 Hz, 7.5 Hz, 1H), 3.10–3.25 (m, 1H), 3.18 (dd, J = 6.2 Hz, 3.0 Hz, 1H), 3.49–3.63 (m, 1H), 3.67–3.83 (m, 2H), 3.80 (s, 3H), 4.12 (dd, J = 10.2 Hz, 3.0 Hz, 1H), 4.21 (quint, J = 6.2 Hz, 1H), 4.32–4.51 (m, 1H), 5.16 and 5.22 (ABq, J = 12.2 Hz, 2H), 6.11 (br s, 2H), 6.89 (d, J = 8.7 Hz, 2H), 7.39 (d, J = 8.7 Hz, 2H). Anal. Calcd for $C_{40}H_{64}N_4O_{11}SSi$: C, 57.39; H, 7.71; N, 6.69; S, 3.83. Found: C, 57.45; H, 7.62; N, 6.41; S, 3.76.

4-Methoxybenzyl (1*S*,5*R*,6*S*)-2-[[(2*S*, 4*R*)-1-(*tert*-Butoxycarbonyl)-2-[N-(*tert*-butoxycarbonyl)-N-sulfamoylaminomethyl]pyrrolidin-4-yl]methyl]-1-methyl-6-[(1*R*)-1-(triethylsilyloxy)ethyl]carbapen-2-em-3-carboxylate (23b): 13% yield (134 mg) as a viscous colorless oil, less polar isomer (toluene / EtOAc); IR ($CHCl_3$) 3360, 3188, 1768, 1711, 1672 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.60 (q, J = 8.0 Hz, 6H), 0.95 (t, J = 8.0 Hz, 9H), 1.11 (d, J = 7.2 Hz, 3H), 1.27 (d, J = 6.0 Hz, 3H), 1.42 (s, 9H), 1.50 (s, 9H), 1.40–1.70 (m, 2H), 2.14 (dd, J = 13.8 Hz, 6.0 Hz, 1H), 2.37–2.54 (m, 1H), 2.97 (dq, J = 10.2 Hz, 7.2 Hz, 1H), 3.00–3.23 (m, 2H), 3.17 (dd, J = 6.2 Hz, 3.0 Hz, 1H), 3.37–3.70 (m, 3H), 3.80 (s, 3H), 4.11 (dd, J = 10.2 Hz, 3.0 Hz, 1H), 4.22 (quint, J = 6.2 Hz, 1H), 4.28–4.41 (m, 1H), 5.14 and 5.25 (ABq, J = 12.0 Hz, 2H), 6.13 (br s, 2H), 6.88 (d, J = 8.7 Hz, 2H), 7.38 (d, J = 8.7 Hz, 2H). Anal. Calcd for $C_{40}H_{64}N_4O_{11}SSi$: C, 57.39; H, 7.71; N, 6.69; S, 3.83. Found: C, 57.47; H, 7.70; N, 6.39; S, 3.61.

(3*R*)-(1-*tert*-Butoxycarbonyl)-3-methanesulfonyloxypyrrolidine (24). To an ice-cooled solution of (3*R*)-(1-*tert*-Butoxycarbonyl)-3-hydroxypyrrolidine (3.00 g, 16.0 mmol) in CH_2Cl_2 (50 ml) were added Et_3N (2.87 ml, 20.8 mmol) and methanesulfonyl chloride (1.49 ml, 19.2 mmol), and the solution was stirred with ice-cooling for 20 min. The reaction mixture was poured into water and EtOAc, and extracted with EtOAc. The extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was

purified by silica gel column chromatography to give **24** (4.23 g, quant. yield) as a colorless oil: IR ($CHCl_3$) 1686 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.47 (s, 9H), 1.99–2.41 (m, 2H), 3.05 (s, 3H), 3.36–3.79 (m, 4H), 5.21–5.33 (m, 1H); HRMS Calcd for $C_{10}H_{19}NO_5S$ $[M]^+$ 265.0983 ; Found 265.0998.

(3*R*)-1-(*tert*-Butoxycarbonyl)-3-[1-(*tert*-butoxycarbonyl)-2-oxopropyl]-pyrrolidine (25). *t*-Butyl acetoacetate (15.5 ml, 0.094 mol) was added at r.t. to a solution of potassium *tert*-butoxide (8.76 g, 0.078 mol) in *tert*-butanol (200 ml). After addition of THF (200 ml), a solution of **24** (13.8 g, 0.052 mol) in THF (50 ml) was added, and the reaction mixture was refluxed overnight. After being cooled to r.t., EtOAc and 1N HCl were added and extracted with EtOAc. The extracts were washed with water and brine, and dried over $MgSO_4$. After evaporation, the residue was purified by silica gel column chromatography to give **25** (6.18 g, 36%) as a colorless oil: IR ($CHCl_3$) 1733, 1709, 1681 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 9H), 1.48 (s, 9H), 1.40–1.71 (m, 1H), 1.93–2.13 (m, 1H), 2.24 (s, 3H), 2.69–3.08 (m, 2H), 3.18–3.71 (m, 4H); HRMS Calcd for $C_{17}H_{29}NO_5SNa$ $[M+Na]^+$ 350.1942 ; Found 350.1943.

(3*R*)-1-(*tert*-Butoxycarbonyl)-3-(2-oxopropyl)pyrrolidine (26). To a solution of **25** (1.10 g, 3.36 mmol) in DMF (6 ml) were added at r.t. sodium chloride (210 mg) and water (0.12 ml), and the mixture was refluxed for 9 h. After being cooled to r.t., the reaction mixture was poured into water and EtOAc, and extracted with EtOAc. The extracts were washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification of the residue by silica gel column chromatography gave **26** (700 mg, 92 %) as a colorless oil: IR ($CHCl_3$) 1712, 1677 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.36–1.57 (m, 1H), 1.45 (s, 9H), 1.96–2.21 (m, 1H), 2.16 (s, 3H), 2.42–2.67 (m, 3H), 2.74–2.97 (m, 1H), 3.19–3.52 (m, 2H), 3.52–3.67 (m, 1H); HRMS Calcd for $C_{12}H_{22}NO_3$ $[M+H]^+$ 228.1599, Found 228.1599.

(3*R*)-1-(*tert*-Butoxycarbonyl)-3-(2-trimethylsilyloxy-2-propen-1-yl)pyrrolidine (27). To a solution of N-*tert*-butyltrimethylsilylamine (4.0 ml, 0.021 mol) in THF (50 ml) was added a solution of *n*-butyllithium (1.61 M in hexane, 13 ml, 0.021 mol) at -78 °C, and the reaction mixture was stirred at r.t. for 20 min. To this solution were added chlorotrimethylsilane (5.3 ml, 0.042 mol) and a solution of **26** (3.19 g, 0.014 mol) in THF (30 ml) at -78 °C. After 30 min, Et_3N (23 ml, 0.165 mol) was added. The reaction mixture was stirred for 30 min, poured into saturated aqueous $NaHCO_3$ and EtOAc, and extracted with EtOAc. The extracts were washed with water and brine, and dried over $MgSO_4$. After evaporation, the residue was purified by silica gel column chromatography to give **27** (3.70 g, 88 %) as a colorless oil: IR ($CHCl_3$) 1676 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.21 (s, 9H), 1.38–1.73 (m, 1H), 1.46 (s, 9H), 1.85–2.15 (m, 3H), 2.22–2.49 (m, 1H), 2.78–3.04 (m, 1H), 3.14–3.63 (m, 3H), 4.05 (s, 2H); HRMS Calcd for $C_{15}H_{29}NO_3SiNa$ $[M+Na]^+$ 322.1812, Found 322.1811.

(3*S*,4*R*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-4-[3-[(3*R*)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl]-2-oxopropyl]azetidin-2-one (29). Zinc iodide (1.18 g, 3.78 mmol) was added to an ice-cooled solution of 4-acetoxyazetidinone **28** (3.55 g, 12.0 mmol) and **27** (3.7 g, 12.0 mmol) in acetonitrile (40 ml). The reaction mixture was stirred at r.t. overnight, and poured into saturated aqueous $NaHCO_3$ and EtOAc. After extraction, the combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give **29** (3.388 g, 60%) as a viscous colorless oil: IR ($CHCl_3$) 3408, 1756, 1712, 1680 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.065 (s, 3H), 0.073 (s, 3H), 0.87 (s, 9H), 1.21 (d, J = 6.3 Hz, 3H), 1.36–1.58 (m, 1H), 1.46 (s, 9H), 1.94–2.19 (m, 1H), 2.42–2.71 (m, 4H), 2.73–2.96 (m, 2H), 2.76 (dd, J = 5.4 Hz, 2.4 Hz, 1H), 3.20–3.67 (m, 3H), 3.95 (dt, J = 9.9 Hz, 2.4 Hz, 1H), 4.18 (quint, J = 6.0 Hz, 1H), 6.03 (br, 1H); HRMS Calcd for $C_{23}H_{42}N_2O_5SiNa$ $[M+Na]^+$ 477.2758, Found 477.2755.

(3*S*,4*R*)-4-[3-[(3*R*)-1-(*tert*-Butoxycarbonyl)pyrrolidin-3-yl]-2-oxopropyl]-3-[(1*R*)-1-(triethylsilyloxy)ethyl]azetidin-2-one (30). To an ice cooled solution of **29** (3.19 g, 7.0 mmol) in THF (20 ml) were added acetic acid (2.01 ml, 35 mmol) and a solution of tetrabutylammonium fluoride (1 M in

THF, 28 ml, 28 mmol). The reaction mixture was stirred at r.t. overnight and poured into saturated aqueous $NaHCO_3$ and EtOAc. The aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. To an ice-cooled solution of this residue in DMF (25 ml) were added imidazole (510 mg, 7.5 mmol) and triethylchlorosilane (1.01 ml, 6.0 mmol). The reaction mixture was stirred for 30 min, and poured into 10% H_3PO_4 and EtOAc. The aqueous layer was extracted with EtOAc. The combined organic layer was washed with 10% H_3PO_4, saturated aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. After removal of the solvent, purification of the residue by silica gel column chromatography gave **30** (1.42 g, 45%) as a viscous colorless oil: IR ($CHCl_3$) 3408, 1756, 1712, 1678 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.60 (q, J = 7.8 Hz, 6H), 0.95 (t, J = 7.8 Hz, 9H), 1.24 (d, J = 6.0 Hz, 3H), 1.37–1.58 (m, 1H), 1.46 (s, 9H), 1.96–2.16 (m, 1H), 2.41–2.71 (m, 4H), 2.72–2.98 (m, 2H), 2.75 (dd, J = 6.0 Hz, 2.4 Hz, 1H), 3.19–3.67 (m, 3H), 3.93 (dt, J = 9.9 Hz, 2.4 Hz, 1H), 4.17 (quint, J = 6.0 Hz, 1H), 6.07 (s, 1H); HRMS Calcd for $C_{23}H_{42}N_2O_5SiNa$ $[M+Na]^+$ 477.2758, Found 477.2755.

(3*S*,4*R*)-4-[3-[(3*R*)-1-(*tert*-Butoxycarbonyl)pyrrolidin-3-yl]-2-oxopropyl]-1-[(1*RS*)-hydroxy(4-methoxybenzyloxycarbonyl)methyl]-3-[(1*R*)-1-(triethylsilyloxy)ethyl]azetidin-2-one (31). A solution of **30** (500 mg, 1.10 mmol) and 4-methoxybenzyl glyoxylate (257 mg, 1.20 mmol) in toluene (10 ml) was refluxed with azeotropic removal of water for 5 h. After being cooled to r.t., water and EtOAc was added to this and extracted. The combined organic layer was washed with brine, and dried over $MgSO_4$. After concentration, the residue was purified by silica gel column chromatography (toluene / EtOAc) to afford **31** (660 mg, 92%, a mixture of two diastereomers) as a viscous pale yellow oil: less polar isomer; IR ($CHCl_3$) 3494, 1749, 1680 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.56 (q, J = 7.8 Hz, 6H), 0.92 (t, J = 7.8 Hz, 9H), 1.23 (d, J = 6.0 Hz, 3H), 1.30–1.54 (m, 1H), 1.46 (s, 9H), 1.93–2.13 (m, 1H), 2.23–2.58 (m, 3H), 2.58–2.95 (m, 3H), 2.76 (dd, J = 6.6 Hz, 2.7 Hz, 1H), 3.16–3.65 (m, 3H), 3.81 (s, 3H), 4.03–4.17 (m, 2H), 4.54 (br t, J = 10.4 Hz, 1H), 5.00–5.20 (m, 2H), 5.40 (br d, J = 10.4 Hz, 1H), 6.88 (d, J = 8.7 Hz, 2H), 7.30 (d, J = 8.7 Hz, 2H); HR-MS Calcd for $C_{33}H_{52}N_2O_9SiNa$ $[M+Na]^+$ 671.3336, Found 671.3334. polar isomer; IR ($CHCl_3$) 3498, 1749, 1678 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.53 (q, J = 8.0 Hz, 6H), 0.91 (t, J = 8.0 Hz, 9H), 1.24 (d, J = 6.0 Hz, 3H), 1.32–1.58 (m, 1H), 1.46 (s, 9H), 1.93–2.12 (m, 1H), 2.35–2.65 (m, 3H), 2.70–3.06 (m, 4H), 3.16–3.61 (m, 3H), 3.81 (s, 3H), 3.99–4.13 (m, 2H), 5.22 and 5.26 (ABq, J = 12.0 Hz, 2H), 5.49 (d, J = 6.0 Hz, 1H), 6.89 (d, J = 8.7 Hz, 2H), 7.34 (d, J = 8.7 Hz, 2H); HRMS Calcd for $C_{33}H_{52}N_2O_9SiNa$ $[M+Na]^+$ 671.3336, Found 671.3333.

4-Methoxybenzyl (5*R*,6*S*)-2-[(3*S*)-1-(*tert*-Butoxycarbonyl)pyrrolidin-3-yl]methyl-6-[(1*R*)-1-(triethylsilyloxy)ethyl]carbapen-2-em-3-carboxylate (20a). To a solution of **31** (660 mg, 1.02 mmol) in THF (5 ml) were added 2,6-lutidine (0.355 ml, 3.05 mmol) and thionyl chloride (83 μl, 1.12 mmol) at -40 °C. The solution was stirred for 30 min, poured into ice-cooled water and EtOAc, and extracted with EtOAc. The extracts were washed with brine, dried over $MgSO_4$, and concentrated. To a solution of this residue in DMF (5 ml) were added triphenylphosphine (293 mg, 1.12 mmol), 2,6-lutidine (142 μl, 1.22 mmol) and NaBr (115 mg, 1.12 mmol) at r.t. The reaction mixture was stirred for 3 h, poured into ice-cooled water and EtOAc. After extraction, the combined organic layer was washed with water and brine, dried over $MgSO_4$, and evaporated. A solution of the residue in toluene (30 ml) was heated to 100 °C for 5 h. After being cooled to r.t., the reaction mixture was concentrated, and purified by silica gel column chromatography to give **20a** (311 mg, 50%). Spectroscopic data of this compound were identical with those of the less polar isomer obtained by the cross-coupling reaction.

(2*S*, 4*S*)-1-(*tert*-Butoxycarbonyl)-2-(N,N-dimethylcarbamoyl)-4-hydroxymethylpyrrolidine (32). To an ice-cooled solution of **17** (125 mg, 0.49 mmol) in THF (2 ml) was added a solution of 9-BBN (0.5 M in THF, 1.18 ml, 0.59 mmol), and the reaction mixture was stirred at r.t. for 2 h. With cooling in an ice-bath, 2N NaOH (0.29 ml, 0.58 mmol) and 30% H_2O_2 (0.181 ml, 1.77 mmol) were added to this. The

reaction mixture was stirred at r.t. for 1 h, and poured into water and EtOAc. The aqueous layer was extracted with EtOAc and the combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated. Purification of the residue by silica gel column chromatography gave **32** (85 mg, 64 %) as a viscous colorless oil: IR ($CHCl_3$) 3404, 1681, 1652 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 9H x 1/2), 1.45 (s, 9H x 1/2), 1.71 (m, 1H, H-3), 2.38 (m, 1H, H-3), 2.48 (m, 1H, H-4), 2.97 (s, 3H), 3.07 (s, 3H x 1/2), 3.12 (s, 3H x 1/2), 3.35 (m, 1H, H-5), 3.65 (d, *J* = 5.6 Hz, 2H), 3.72 (m, 1H, H-5), 4.58 (t, *J* = 7.6 Hz, 1/2H, H-2), 4.68 (dd, *J* = 6.0 Hz, 8.8 Hz, 1/2H, H-2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.3, 28.5, 32.4, 33.2, 36.0, 36.1, 37.0, 37.1, 40.1, 40.6, 49.5, 49.9, 56.2, 56.5, 63.9, 64.2, 79.7, 153.7, 154.4, 173.0, 173.1; HRMS Calcd for $C_{13}H_{24}N_2O_4$ $[M]^+$ 272.1734, Found 272.1734.

(5*R*,6*S*)-2-[3-(N-Formimidoyl)aminopropyl]-6-[(1*R*)-1-hydroxyethyl]carbapen-2-em-3-carboxylic Acid (1b). A solution of $AlCl_3$ (460 mg, 3.45 mmol) in anisole (1.66 ml) was added to a solution of **10a** (500 mg, 0.766 mmol) in CH_2Cl_2 (7 ml) and nitromethane (7 ml) at -50 °C, and the mixture was allowed to warm to -10 °C over 1/2 h. The reaction mixture was diluted with CH_2Cl_2, an aqueous solution (14 ml) of $NaHCO_3$ (869 mg, 10.34 mmol) was added, and the reaction mixture was stirred with ice-cooling for 10 min. After filtration with Hyflo Super Cel®, the aqueous layer was concentrated to *ca.* half volume. To this aqueous solution was added 0.1M phosphate buffer (pH 7.0, 20 ml), and ethyl formimidate hydrochloride (420 mg, 3.83 mmol) was added portionwise with ice-cooling while the pH of the mixture was maintained to pH 8.5 by adding 1N NaOH. The pH of the solution was adjusted to pH 7 by adding 1N HCl, and most of water was removed by evaporation. After purification of the residue by HP-20SS column chromatography, the fractions containing the product were concentrated and lyophilized to give **1b** (112 mg, 52 %) as a white powder: IR (KBr) 3373, 1754, 1715, 1578 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.27 (d, *J* = 6.3 Hz, 3H), 1.71–1.91 (m, 2H), 2.46–2.75 (m, 2H), 2.87 (d, *J* = 9.0 Hz, 2H), 3.21–3.42 (m, 3H), 4.11 (dt, *J* = 9.0 Hz, 2.4 Hz, 1H), 4.20 (quint, *J* = 6.3 Hz, 1H), 7.75 (s, 1H); UV (H_2O) ν_{max} 267 nm (ε 4500). Anal. Calcd for $C_{13}H_{19}N_3O_4 \cdot 2.1H_2O$: C, 48.93; H, 7.33; N, 13.17. Found: C, 48.87; H, 7.03; N, 13.09.

(5*R*,6*S*)-2-[(3*S*)-1-Acetimidoylpyrrolidin-3-yl]methyl-6-[(1*R*)-1-hydroxyethyl]carbapen-2-em-3-carboxylic Acid (2b). A solution of $AlCl_3$ (195 mg, 1.46 mmol) in anisole (0.71 ml) was added to a solution of **20a** (200 mg, 0.325 mmol) in CH_2Cl_2 (3 ml) and nitromethane (3 ml) at -50 °C, and the mixture was allowed to warm to 0 °C over 1/2 h. The reaction mixture was diluted with CH_2Cl_2, an aqueous solution (8 ml) of $NaHCO_3$ (369 mg, 4.39 mmol) was added, and the reaction mixture was stirred with ice-cooling for 10 min. After filtration with Hyflo Super Cel®, the aqueous layer was concentrated to *ca.* half volume. To this aqueous solution was added 0.1M phosphate buffer (pH 7.0, 20 ml), and ethyl acetimidate hydrochloride (201 mg, 1.63 mmol) was added portionwise with ice-cooling while the pH of the mixture was maintained to pH 8.5 by adding 1N NaOH. The pH of the solution was adjusted to pH 7 by adding 1N HCl, and most of water was removed by evaporation. After purification of the residue by HP-20SS column chromatography, the fractions containing the product were concentrated and lyophilized to give **2b** (42 mg, 40%) as a white powder: IR (KBr) 3371, 1761, 1683, 1581 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.28 (d, *J* = 6.0 Hz, 3H), 2.22 (s, 3H x 1/2), 2.24 (s, 3H x 1/2), 1.56–4.06 (m, 12H), 4.13 (m, 1H), 4.22 (quint, *J* = 6.3 Hz, 1H); UV (H_2O) ν_{max} 255 nm (ε 3000); HRMS Calcd for $C_{16}H_{24}N_3O_4$ $[M+H]^+$ 322.1765, Found 322.1762.

(1*S*,5*R*,6*S*)-2-[(6,7-Dihydro-5*H*-pyrazolo[1,2-*a*][1,2,4]triazolium-6-yl)methyl]-6-[(1*R*)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylate (3b). A solution of $AlCl_3$ (548 mg, 4.11 mmol) in anisole (2.0 ml) was added to a solution of **21** (500 mg, 0.685 mmol) in CH_2Cl_2 (6 ml) and nitromethane (6 ml) at -50 °C, and the mixture was allowed to warm to 0 °C over 1/2 h. The reaction mixture was diluted with CH_2Cl_2, an aqueous solution (16 ml) of $NaHCO_3$ (1.04 g, 12.3 mmol) was added, and the solution was stirred with ice-cooling for 10 min. After filtration with Hyflo Super Cel®, the aqueous layer was

concentrated to *ca.* half volume. To this aqueous solution was added 0.1M phosphate buffer (pH 7.0, 15 ml), and ethyl formimidate hydrochloride (600 mg, 5.48 mmol) was added portionwise with ice-cooling while the pH of the mixture was maintained to pH 8.5 by adding 1N NaOH. The pH of the solution was adjusted to pH 7 by adding 1N HCl, and most of water was removed by evaporation. After purification of the residue by HP-20SS column chromatography, the fractions containing the product were concentrated and lyophilized to give **3b** (73 mg, 32%) as a white powder: IR (KBr) 3411, 1748, 1588 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.13 (d, *J* = 7.5 Hz, 3H), 1.29 (d, *J* = 6.6 Hz, 3H), 2.56 (dd, *J* = 14.1 Hz, 5.4 Hz, 1H), 3.18 (dq, *J* = 9.8 Hz, 7.5 Hz, 1H), 3.29 (dd, *J* = 14.1 Hz, 10.5 Hz, 1H), 3.41 (dd, *J* = 6.3 Hz, 2.6 Hz, 1H), 3.70–3.89 (m, 1H), 4.17 (dd, *J* = 9.8 Hz, 2.6 Hz, 1H), 4.24 (quint, *J* = 6.3 Hz, 1H), 4.33 (dd, *J* = 12.3 Hz, 6.6 Hz, 1H), 4.50 (dd, *J* = 12.3 Hz, 6.6 Hz, 1H), 4.76 (dd, *J* = 12.3 Hz, 7.2 Hz, 1H), 4.88 (dd, *J* = 12.3 Hz, 7.2 Hz, 1H), 8.95 (s, 1H), 8.96 (s, 1H); UV (H_2O) ν_{max} 268 nm (ε 5600). Anal. Calcd for $C_{16}H_{20}N_4O_4 \cdot 2.8H_2O$: C, 50.20; H, 6.74; N, 14.64. Found: C, 50.17; H, 6.59; N, 14.62.

(1*S*,5*R*,6*S*)-2-[[(2*S*,4*S*)-2-(N,N-Dimethylcarbamoyl)pyrrolidin-4-yl]methyl]-6-[(1*R*)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylic Acid (4b). A solution of $AlCl_3$ (180 mg, 1.35 mmol) in anisole (0.65 ml) was added to a solution of **22** (210 mg, 0.30 mmol) in CH_2Cl_2 (2 ml) and nitromethane (2 ml) at -50 °C, and the solution was allowed to warm to -15 °C over 1/2 h. The reaction mixture was poured into an aqueous solution (5 ml) of sodium acetate (554 mg, 6.75 mmol), and stirred with ice-cooling for 10 min. After filtration with Hyflo Super Cel®, the aqueous layer was washed with CH_2Cl_2 and most of water was removed by evaporation. After purification of the residue by CHP-20P column chromatography, the fractions containing the product were concentrated and lyophilized to give **4b** (51 mg, 47 %) as a white powder: IR (KBr) 3430, 1753, 1655, 1595 cm^{-1}; ^1H NMR (200 MHz, D_2O) δ 1.07 (d, *J* = 7.6 Hz, 3H), 1.26 (d, *J* = 6.2 Hz, 3H), 1.45–1.75 (m, 1H), 2.23 (dd, *J* = 13.6 Hz, 5.0 Hz, 1H), 2.55–2.86 (m, 2H), 2.92–3.20 (m, 3H), 2.97 (s, 3H), 3.05 (s, 3H), 3.35 (dd, *J* = 6.4 Hz, 2.8 Hz, 1H), 3.35–3.54 (m, 1H), 4.11 (dd, *J* = 9.4 Hz, 2.8 Hz, 1H), 4.21 (quint, *J* = 6.2 Hz, 1H), 4.72 (t, *J* = 8.2 Hz, 1H); UV(H_2O) ν_{max} 269 nm (ε 4600); HR-MS Calcd for $C_{18}H_{28}N_3O_5$ $[M+H]^+$ 366.2028, Found 366.2030. Anal. Calcd for $C_{18}H_{27}N_3O_5 \cdot 2.7H_2O$: C, 52.21; H, 7.89; N, 10.15. Found: C, 52.29; H, 7.78, N, 10.25.

(1*S*,5*R*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-1-methyl-2-[[(2*S*,4*S*)-2-(sulfamoylaminomethyl)-pyrrolidin-4-yl]methyl]carbapen-2-em-3-carboxylic Acid (5b). A solution of $AlCl_3$ (176 mg, 1.32 mmol) in anisole (0.65 ml) was added to a solution of **23a** (184 mg, 0.22 mmol) in CH_2Cl_2 (2 ml) and nitromethane (2 ml) at -50 °C, and the solution was allowed to warm to 0 °C over 1/2 h. The reaction mixture was diluted with CH_2Cl_2, an aqueous solution (5 ml) of $NaHCO_3$ (332 mg, 3.96 mmol) was added, and the reaction mixture was stirred with ice-cooling for 10 min. After filtration with Hyflo Super Cel®, the aqueous layer was washed with CH_2Cl_2 and most of water was removed by evaporation. The residue was purified by CHP-20P column chromatography, and the fractions containing the product were concentrated and lyophilized to give **5b** (54 mg, 61%) as a white powder: IR (KBr) 3384, 1748, 1585 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.09 (d, *J* = 7.2 Hz, 3H), 1.28 (d, *J* = 6.3 Hz, 3H), 1.38–1.74 (m, 2H), 2.24–3.62 (m, 9H), 3.76–3.92 (m, 1H), 4.13 (dd, *J* = 9.4 Hz, 2.7 Hz, 1H), 4.23 (quint, *J* = 6.3 Hz, 1H); UV(H_2O) ν_{max} 268 nm (ε 3700); HRMS Calcd for $C_{16}H_{26}N_4O_6SNa$ $[M+Na]^+$ 425.1469, Found 425.1475. Anal. Calcd for $C_{16}H_{26}N_4O_6S \cdot 2.1H_2O$: C, 43.65; H, 6.91; N, 12.72; S, 7.28. Found: C, 43.88; H, 6.73, N, 12.47; S, 6.96.

Acknowledgements: We wish to thank Dr. Y. Terui for the NMR measurement, Dr. Y. Ikenishi for the mass spectroscopy determination, and Dr. S. Sasaki for conducting the antibacterial assay.

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(*Received in Japan* 26 *September* 1996; *accepted* 21 *October* 1996)