Efficient synthesis of 1β-methylcarbapenems based on the counter-attack strategy

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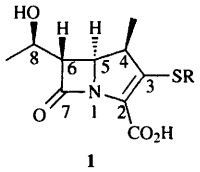
A seven-step efficient synthesis of 1β-methylcarbapenems 1 from the acetoxyazetidinone 6 is described. The Reformatsky reaction of 3-(2-bromopropionyl)-1,3-benzoxazinone 7 with compound 6 gave an adduct 8 in 96% yield with high β-selectivity (β:α = 92:8). Compound 8 was transformed in three steps into the side-chain thiol esters 12a–e in good yields. The chlorotrimethylsilane-mediated Dieckmann-type cyclisation of thioesters 12b–e followed by counter-attack of the liberated thiolate anion 18 yielded the C-2 alkylthio- or arylthio-substituted 1β-methylcarbapenems 19b–e in a one-pot procedure. The synthesis of 1β-methylcarbapenems 1 was demonstrated by a simple cleavage of the silyl ether and allyl ester of compound 19b to afford target compound 1b in high yield.

Introduction

The antibiotic 1β-methylcarbapenems **1** have recently attracted considerable attention as some of the most promising β-lactam antibiotics due to their chemical and metabolic stabilities as well as their having potent antimicrobial activities.[1] Owing to the lack of practical fermentation methods, various synthetic efforts have been initiated to construct the bicyclic ring skeleton with four contiguous stereogenic centres.[2] As a result of this effort, practical industrial syntheses have been developed. Any improvement, however, to optimise the current technology would be desirable.



1

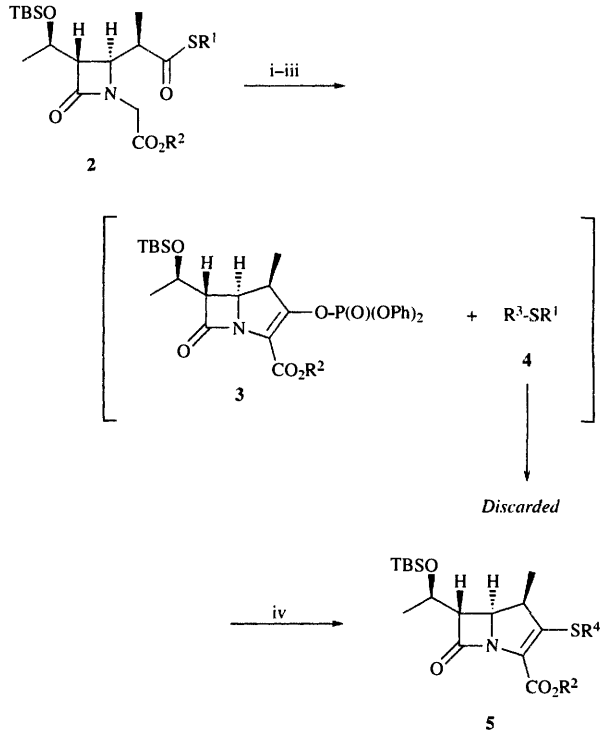
R: alkyl, aryl

Systematic azabicyclo[3.2.0]heptene numbering scheme

The Dieckmann-type cyclisation of thioester **2** has been employed as one of the major processes to construct the 1β-methylcarbapenem skeleton (Scheme 1).[2a,b] In these syntheses, an active thioester such as a 2-pyridyl thioester[2a] or a phenyl thioester[2b] **2** (R^1 = 2-pyridyl, phenyl) has been utilised to effect the smooth intramolecular addition of the enolate anion to the carbonyl group of the thioester. The liberated thiolate anion was then inactivated and removed as its sulfide **4** by treatment with various alkyl halides (R^3X). Addition of the side-chain thiol (R^4SH) was then necessary to effect the condensation after formation of the enol phosphate **3**.

From the point of view of atom economy[3] and environmental problems, an efficient synthetic method should involve the smallest number of steps and reagents as well as a high overall yield. A '*counter-attack reagent*'[4] can fulfil the requirements. A counter-attack reagent refers to a compound which accomplishes two or more consecutive transformations in one flask to afford the desired product.

Our approach to an economical synthesis of the 1β-methylcarbapenems **1** is based on the counter-attack strategy (see Scheme 4). In this strategy, the thiolate anion **18**, generated by the Dieckmann-type cyclisation, should counter-attack the enol phosphate **16**. The result would be the isolation of carbapenem **19** in a one-pot procedure. Described herein is the successful synthesis of the 1β-methylcarbapenem **1** accomplished by the modified Dieckmann-type cyclisation of a side-chain thiol ester **12**.[5]

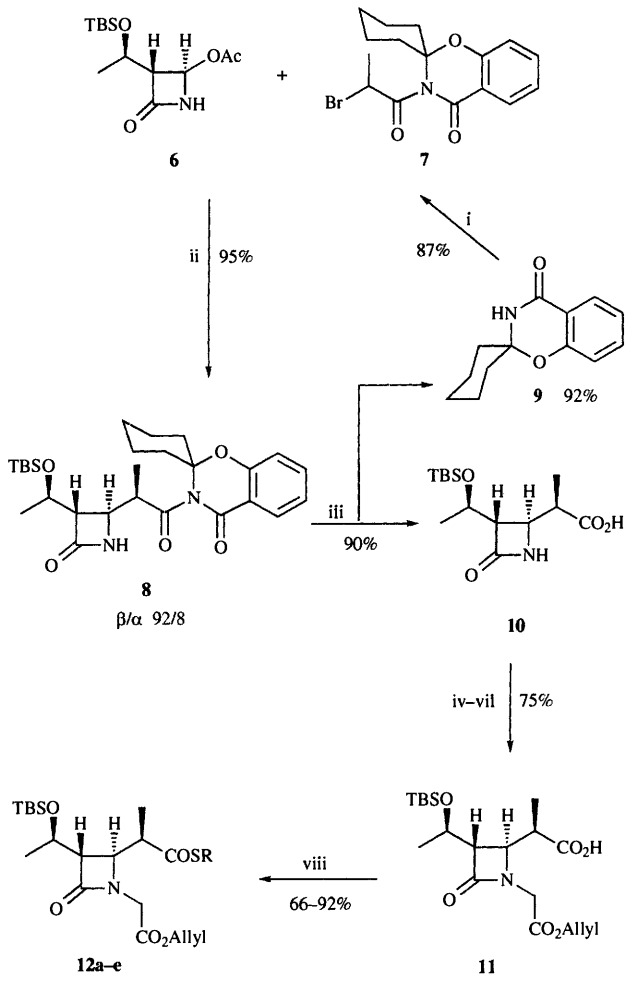


Scheme 1 *Reagents:* i, NaN(TMS); ii, R^3X; iii, $ClP(O)(OPh)_2$; iv, R^4SH, Pr^i_2EtN

Results and discussion

Synthesis of the thioesters 12a–e

A simple synthesis of the thioesters **12a–e**, substrates for the Dieckmann-type cyclisation, was first examined. We decided that condensation of side-chain thiols should be undertaken in the last step of the reaction sequence as shown in Scheme 2. This would avoid the possibility of ruining of labile functional groups and/or jeopardising asymmetric centres. A key



Scheme 2 *Reagents and conditions:* i, Me(Br)CHCOBr, pyridine, toluene, 25 °C, 17 h; ii, Zn, THF, reflux, 20 min; iii, H_2O_2, LiOH, THF, 0 °C, 10 min; iv, TBSCl, NaH, THF, 0 °C, 1 h; v, $BrCH_2CO_2Allyl$, $NaN(TMS)_2$, THF, −50 °C, 30 min; vi, aq. K_2CO_3, 25 °C, 10 min; vii, aq. HCl; viii, RSH, DCC, DMAP (cat.), benzene, 25 °C, 17 h

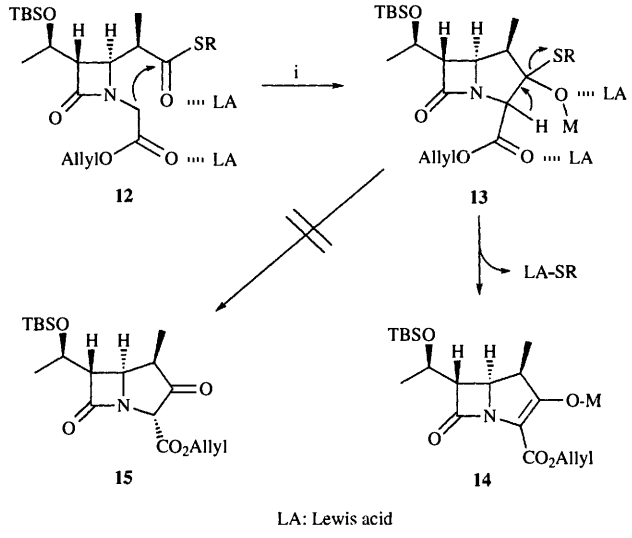
intermediate, azetidinone derivative **10**, was efficiently synthesized according to our previously reported procedure.[2h] Commercially available acetoxyazetidinone **6** was allowed to react with 3-(2-bromopropionyl)-1,3-benzoxazinone **7** in the presence of zinc dust in refluxing tetrahydrofuran (THF) to afford the coupled product **8** in 96% yield with a high β-selectivity (β:α = 92:8).† Recrystallisation of the crude product from aq. ethanol gave diastereomerically pure β-isomer **8** in 75% yield based on lactam **6**. Simple removal of the auxiliary of compound **8** was effected by employing the Evans conditions.[6] Compound **8** was treated with lithium hydroxide and hydrogen peroxide in aq. THF to give the desired carboxylic acid **10** in 90% yield together with the recovered auxiliary **9** in 92% yield. The physicochemical properties of product **10** were in complete agreement with the literature values.[7] Since compound **10** has been utilised as a key intermediate in other routes to 1β-methylcarbapenems,[2] our synthesis of compound **10** provides convenient access not only to the present target but to the previously reported analogues as well.

N-Alkylation of compound **10** was carried out by temporarily blocking the carboxy group as the silyl ester[8] followed by treatment with allyl bromoacetate in the presence of sodium bis(trimethylsilyl)amide. After *in situ* cleavage of the silyl ester by aq. potassium carbonate, the desired carboxylic acid **11** was obtained in good yield (overall 75% in three chemical transformations). Condensation of carboxylic acid **11** with the side-chain thiols was conducted with the use of dicyclohexylcarbodiimide (DCC) and catalytic 4-(dimethylamino)pyridine (DMAP) in benzene to give the desired thioesters **12a–e** in good yield (see Table 2).

Ring construction based on the counter-attack strategy

Although the Dieckmann-type cyclisation has previously been accomplished only by the use of an active thioester such as a phenyl thioester or 2-pyridyl thioester,[2a,b] the cyclisation of relatively less reactive substrates including alkyl thioesters should also be investigated to expand our synthetic methodology. Thus, the Dieckmann-type cyclisation of *tert*-butyl thioester **12a**, prepared with non-nucleophilic 2-methylpropane-2-thiol, was first examined.

We expected addition of a Lewis acid to the reaction mixture might accelerate the cyclisation and would simultaneously trap the liberated thiolate anion as shown in Scheme 3. The reaction



LA: Lewis acid

Scheme 3 *Reagent:* i, M–base

was conducted according to Meyers' protocol to protect the 1β-methyl group from epimerisation.[2a] Thus, two mole equivalents of sodium bis(trimethylsilyl)amide were rapidly added to compound **12a** at −30 °C followed by the Lewis acid. This would ensure an instantaneous formation of the enolate **14** from the thioester **12** *via* the tetrahedral intermediate **13**.‡ Then, after addition of one mole equivalent of diphenyl chlorophosphate at the same temperature, the reaction mixture was stirred at 0 °C for 2 h. By this procedure, the desired enol phosphate **16** was obtained in good yield from the less reactive substrate **12a** (Table 1, Entries 1–3). The Lewis acids including chlorotrimethylsilane§ probably accelerated the cyclisation by coordination to the thioester carbonyl group.¶ Moreover, the Lewis acids simultaneously trapped the liberated thiolate anion to permit phosphorylation of the enolate anion rather than attack by the thiolate anion. There is the possibility for epimerisation of the 1β-methyl group in these reactions. No 1α-methyl isomer of enol phosphate **16** was detected in the reaction mixture.‖

† The detailed mechanism of the reaction is now under investigation and will be reported elsewhere in due course.

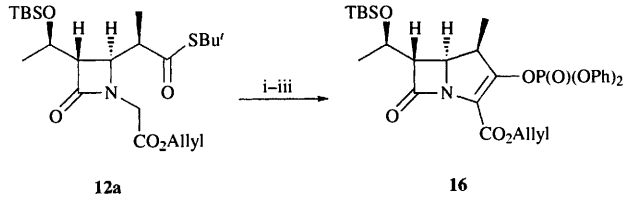
‡ The epimerisation of the 1β-methyl group was suggested to take place by formation of the ketone derivative **15** from the tetrahedral intermediate **13** and abstraction of its methine proton.[2a,b]

§ The Lewis acid-like behaviour of chlorotrimethylsilane was reported as well in other reactions.[9]

¶ The acceleration of the reaction by coordination of a Lewis acid to the carbonyl group was reported in the Michael addition of organocuprates to enones in the presence of boron trifluoride–diethyl ether.[10]

‖ The β-methyl enol phosphate was reported to be exclusively formed by the phosphorylation of a mixture of α- and β-methyl enolates.[2a,b]

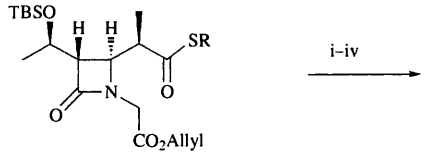
Table 1



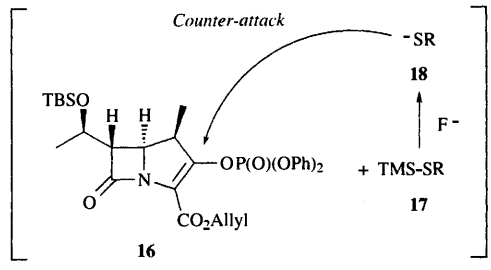
12a 16

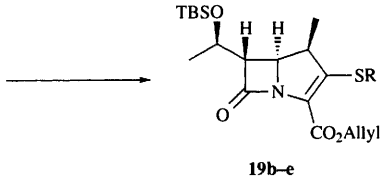
Entry[a]	Additive	Equiv./**12a**	Yield (%)[b]
1	$B(OMe)_3$	1.0	53
2	ZnI_2	0.5	76
3	TMSCl	1.0	85
4	MeI	1.0	66
5	none	0	5

[a] The reactions were conducted on a 1 mmol scale. [b] Isolation yields.



12b–e





19b–e

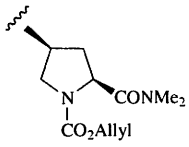
Scheme 4 *Reagents and conditions:* i, $NaN(TMS)_2$, THF, −30 °C, 5 min; ii, TMSCl, −30 °C, 5 min; iii, $ClP(O)(OPh)_2$, 0 °C, 2 h; iv, tetrabutylammonium fluoride, DMF, 5 °C, 72 h

Inspection of Table 1 reveals that chlorotrimethylsilane is the Lewis acid of choice (85%, Entry 3).

As a control experiment, the reaction was performed both in the presence of iodomethane, a previously employed thiolate anion scavenger,[2a,b] and in the absence of additives (Table 1, Entries 4 and 5). As expected, a dramatic decrease in yield was observed. This result can be explained by incomplete cyclisation and/or epimerisation to the α-isomer. In the case of the reaction without any additives (Table 1, Entry 5), phosphorylation of the thiolate anion rather than the enolate anion occurred to give a poor yield of product **16**.

We next turned our attention to the counter-attack of the liberated thiolate anion. In the case of chlorotrimethylsilane used as the additive, the thiolate anion was expected to be protected as silyl ether **17** as shown in Scheme 4. After *in situ* formation of the enol phosphate **16**, tetrabutylammonium fluoride (TBAF) was added to liberate the thiolate anion **18**. An aprotic polar solvent, *N*,*N*-diethylformamide (DMF), was added to accelerate the condensation of anion **18** with

Table 2

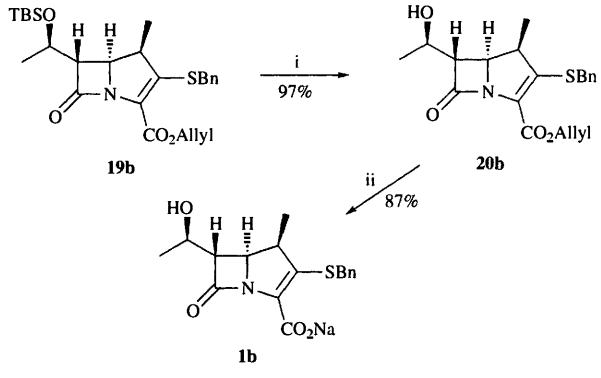
Entry		R	Yield (%)[a] **12**	**19**
1	**a**	Bu^t	92	*b*
2	**b**	Bn	79	62
3	**c**	Cyclopentyl	66	55
4	**d**	Ph	86	52
5	**e**		quant.	58

[a] Isolation yield. [b] Enol phosphate **16** was obtained in 85% yield (see Table 1). Compound **19a** was not detected in the reaction mixture.

phosphate **16**. By this one-pot procedure, the desired coupling products **19b–e** were obtained in from 52 to 62% yield based on the thioesters **12b–e** (Table 2). It should be noted that the reaction was applicable not only to the synthesis of simple alkylthio and arylthio derivatives **19b,c,d** but also to the synthesis of compound **19e** with labile substituents and chiral centres. The physicochemical properties of compound **19e** obtained by the present method were identical with those of an authentic sample prepared independently by the condensation of the thiol with the enol phosphate **16**.

Removal of the protective groups

Simple removal of the protecting groups of 1β-methylcarbapenems is essential for a successful process. Failure to develop an efficient deprotection procedure forces one to change the ring-construction methods and/or to add extra steps for exchanging protecting groups.[2b] We have already developed an efficient deprotection method for hydroxy- and carboxy-protecting groups of 1β-methylcarbapenems. The procedures were applied to the intermediate **19b**, as represented, to complete our synthetic scheme (Scheme 5). The *tert*-butyl dimethyl-



Scheme 5 *Reagents and conditions:* i, $NH_4F{\cdot}HF$, DMF, NMP, 20 °C, 72 h; ii, $Pd(OAc)_2$, $P(OEt)_3$, dimedone, $NaHCO_3$, THF, 1 h

silyl (TBS) ether group of compound **19b** was effectively cleaved by the use of ammonium bifluoride in a mixed solvent of DMF and *N*-methylpyrrolidone (NMP) to give the alcohol **20b** in 97% yield.[11] Cleavage of the allyl ester **20b** with palladium acetate was efficiently realised in an aqueous medium to give the final target of 1β-methylcarbapenem **1b** in 87% yield.[11]

Conclusions

The antibiotic 1β-methylcarbapenems **1** were synthesized in seven steps from the acetoxyazetidinone **6** by a combination of efficient reaction sequences involving (i) highly stereoselective formation of the 1β-methyl group by the novel 1,3-benzoxazinone auxiliary-mediated Reformatsky reaction; (ii) the ring construction based on the modified Dieckmann-type

cyclisation with concomitant counter-attack of the side-chain thiol; and (iii) effective removal of the hydroxy and carboxy protective groups by the use of easily accessible reagents under mild conditions. The counter-attack strategy provides easier access to a wide range of 1β-methylcarbpenems in a convergent manner. The simple operation and higher overall yield of the present process may permit a multi-scale synthesis of various 1β-methylcarbapenems of ongoing pharmaceutical interest.

Experimental

IR spectra were recorded on a Perkin-Elmer 1640 infrared spectrophotometer and are reported as $\nu_{max}(cm^{-1})$. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-200 (200 MHz and 50 MHz, respectively) spectrometer and are reported in δ-values, with *J* values in Hz. Mass spectra were taken on an Hitachi M-2000A spectrometer at an ionising potential of 70 eV. Microanalyses were performed by a Perkin-Elmer 2400 Series II CHNS/O Analyser. Optical rotations were measured on a Perkin-Elmer 243 polarimeter, and $[\alpha]_D$-values are given in 10^{-1} deg cm^2 g^{-1}. TLC was performed on E. Merck 0.25 mm pre-coated glass-backed plates (60 F_{254}). Development was accomplished using either 20% phosphomolybdic acid in ethanol–heat or visualisation by UV light where feasible. Flash chromatography was accomplished using Kieselgel 60 (230–400 mesh, E. Merck).

All solvents were distilled and dried according to standard procedures prior to use. THF was distilled from sodium–benzophenone ketyl. The acetoxyazetidinone **6** was supplied by Kanegafutikagakukogyo Co., Ltd. Zinc dust was supplied by E. Merck and used without further purification.

3-(2-Bromopropionyl)spiro-[2,3-dihydro-4*H*-1,3-benzoxazine-2,1′-cyclohexan]-4-one 7

To a suspension of spiro-[2,3-dihydro-4*H*-1,3-benzoxazine-1,2′-cyclohexan]-4-one[2i] **9** (140 g, 0.644 mol) in a mixture of pyridine (61.1 g, 0.773 mol) and toluene (700 cm^3) was added 2-bromopropionyl bromide (168 g, 0.773 mol) at 5–15 °C and the mixture was stirred at the same temperature for 30 min, then at 25 °C for 17 h. The reaction mixture was poured into water (700 cm^3) and the organic layer was washed successively with saturated aq. $NaHCO_3$ (100 cm^3) and saturated aq. NaCl (60 cm^3), dried over anhydrous $MgSO_4$, and evaporated *in vacuo*. The residue was dissolved in propan-2-ol (60 cm^3) at 50–55 °C and gradually cooled to 10 °C and stirred at the same temperature for 1 h. The crystals were collected and washed with propan-2-ol (140 cm^3) and dried at 40 °C for 17 h to afford *compound* **7** (197.3 g, 87%) as crystals, mp 74–75 °C (Found: C, 54.5; H, 5.3; N, 4.0. $C_{16}H_{18}BrNO_3$ requires C, 54.56; H, 5.15; N, 3.98%); ν_{max}(KBr)/cm^{-1} 1723, 1682 and 1613; δ_H(200 MHz; $CDCl_3$) 1.20–2.50 (m, 10 H, cyclohexyl), 1.92 (d, *J* 6.6, 3 H, Me), 5.14 (q, *J* 6.6, 1 H, methine), 7.00–7.15 (m, 2 H, Ph), 7.50–7.60 (m, 1 H, Ph) and 7.90–7.95 (m, 1 H, Ph); *m/z* (SIMS) 353 ($M^+ + 1$).

3-[(2*R*)-2-{(2*R*,3*S*)-3-[(1*R*)-1-(*tert*-Butyldimethylsiloxy)ethyl]-4-oxoazetidin-2-yl}propionyl]spiro[2,3-dihydro-4*H*-1,3-benzoxazine-2,1′-cyclohexan]-4-one 8

A mixture of the acetoxyazetidinone **6** (5.0 g, 17.4 mmol) and zinc dust (3.4 g, 52 mmol) in THF (50 cm^3) was heated to 65 °C for 5 min and a solution of the bromide **7** (9.2 g, 26.1 mmol) in THF (20 cm^3) was added portionwise for 15 min. After being refluxed for 5 min, the mixture was cooled and poured into phosphate buffer (0.2 M, K_2HPO_4–H_3PO_4, pH 7.0; 200 cm^3) and extracted with CH_2Cl_2 (1 × 200 cm^3, 2 × 50 cm^3). The combined extracts were washed with saturated aq. NaCl (200 cm^3), dried over anhydrous $MgSO_4$, and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (hexane–EtOAc 4:1) to afford *compound* **8** (8.27 g, 95%) as a mixture of β- and α-isomer (β:α 92:8; estimated by HPLC, Capcellpack C_{18} SG-120, Shiseido, 4.6 × 150 mm; CH_3CN–water 70:30, 1 cm^3 min^{-1}; 40 °C; 254 nm. Retention time: β-isomer, 12.3 min; α-isomer, 14.1 min); δ_H(200 MHz; $CDCl_3$) 0.07 (s, 6 H, $SiMe_2$), 0.87 (s, 9 H, SiBu′), 1.22 (d, *J* 6.3, 3 H, Me), 1.26 (d, *J* 7.1, 3 H, Me), 1.50–2.50 (m, 10 H, cyclohexyl), 2.75–2.85 (m, 1 H, α, C*H*Me), 3.18–3.22 (m, 1 H, β, C*H*Me), 3.48–3.62 (m, 1 H, CHC=O), 3.80–3.95 (m, 1 H, α, CH–O), 4.01–4.05 (m, 1 H, β, CH–O), 4.18–4.24 (m, 1 H, CH–N), 5.93 (s, 1 H, β, NH), 6.10 (s, 1 H, α, NH), 6.97–7.03 (m, 1 H, ArH), 7.07–7.16 (m, 1 H, ArH), 7.49–7.59 (m, 1 H, ArH) and 7.90–7.96 (m, 1 H, ArH).

A pure sample of compound **8** was obtained as follows: the crude residue obtained by evaporation of the extracts was dissolved in a mixed solvent of EtOH and water (65:35) (175 cm^3) at 90–95 °C. The mixture was gradually cooled to 25 °C for 1 h and was stirred at 5–10 °C for 1 h. The crystals formed were collected, and washed with a cooled, mixed solvent of EtOH and water (65:35) (20 cm^3) and dried at 40 °C for 17 h to afford pure *compound* **8** (6.52 g, 74.9% based on **6**) as crystals, mp 155.5–156.5 °C (Found: C, 64.55; H, 7.9; N, 6.0. $C_{27}H_{40}N_2O_5Si$ requires C, 64.77; H, 8.05; N, 5.59%); $[\alpha]_D^{25}$ +39.2 (*c* 1.01, MeOH); ν_{max}(KBr)/cm^{-1}1760, 1717, 1687 and 1613; δ_H(200 MHz; $CDCl_3$) 0.07 (s, 6 H, $SiMe_2$), 0.87 (s, 9 H, SiBu′), 1.22 (d, *J* 6.3, 3 H, Me), 1.26 (d, *J* 7.1, 3 H, Me), 1.50–2.50 (m, 10 H, cyclohexyl), 3.18–3.22 (m, 1 H, C*H*Me), 3.48–3.62 (m, 1 H, CH–C=O), 4.01–4.05 (m, 1 H, CH–O), 4.18–4.24 (m, 1 H, CH–N), 5.93 (s, 1 H, NH), 6.97–7.03 (m, 1 H, ArH), 7.07–7.16 (m, 1 H, ArH), 7.49–7.59 (m, 1 H, ArH) and 7.90–7.96 (m, 1 H, ArH); δ_C(50 MHz; $CDCl_3$) 183.2, 168.5, 163.4 and 155.3 (4 s), 136.0, 128.3, 122.4 and 117.3 (4 d), 117.3 and 95.2 (2 s), 65.4, 61.3, 51.6 and 45.9 (4 d), 33.1 (2 t), 25.8 (q), 24.3 (t), 22.6 (q), 22.4 and 22.3 (2 t), 18.0 (s), 13.1 (q) and −4.2 (q); *m/z* (SIMS) 501 ($M^+ + 1$).

(2*R*)-2-{(2*S*,3*S*)-3-[(1*R*)-1-(*tert*-Butyldimethylsiloxy)ethyl]-4-oxoazetidin-2-yl}propionic acid 10

To a solution of compound **8** (500 mg, 1 mmol) in a mixture of THF (15 cm^3) and water (5 ml) were added H_2O_2 (30%; 0.9 cm^3, 8 mmol) and $LiOH·H_2O$ (84 mg, 2 mmol) at 10 °C. After stirring of this mixture at 10 °C for 1 h, aq. $Na_2SO_3·7H_2O$ (970 mg in 5 cm^3) was added and the mixture was extracted with $CHCl_3$ (50 cm^3). The extracts were washed with water (50 cm^3), dried over anhydrous $MgSO_4$, and evaporated to give the 1,3-benzoxazinone **9** (200 mg, 92%). The aqueous layer was acidified by 10% aq. HCl (pH 1.0) at 5 °C and extracted with EtOAc (3 × 20 cm^3). The combined extracts were washed with water (50 cm^3), dried over anhydrous $MgSO_4$, and evaporated. The crystals formed were collected by addition of hexane to give *carboxylic acid* **10** (270 mg, 90%) as crystals, mp 146–147 °C (lit.,[7] 147 °C) (Found: C, 55.7; H, 9.0; N, 4.7. Calc. for $C_{14}H_{27}NO_4Si$: C, 55.78; H, 9.03; N, 4.65%); $[\alpha]_D^{25}$ −33.1 (*c* 1.0, MeOH) {lit.,[7] $[\alpha]_D^{20}$ −32.4 (*c* 0.17, MeOH)}; ν_{max}(KBr)/cm^{-1} 3266 and 1720; δ_H(200 MHz; $CDCl_3$) 0.07 (s, 6 H, $SiMe_2$), 0.87 (s, 9 H, SiBu′), 1.20 (d, *J* 6.3, 3 H, Me), 1.27 (d, *J* 7.1, 3 H, Me), 2.67–2.85 (m, 1 H, C*H*Me), 3.00–3.05 (m, 1 H, CHC=O), 3.90–3.97 (m, 1 H, CH–O), 4.12–4.30 (m, 1 H, CH–N) 6.07 (br s, 1 H, NH); δ_C(50 MHz; $CDCl_3$) 178.1 and 169.3 (2 s), 65.3, 61.3, 51.9 and 41.9 (4 d), 25.8 and 22.5 (2 q), 18.0 (s) and 12.2 and −4.3 (2 q); *m/z* (SIMS) 302 ($M^+ + 1$).

(2*R*)-2-{(2*S*,3*S*)-1-Allyloxycarbonylmethyl-3-[(1*R*)-1-(*tert*-butyldimethylsiloxy)ethyl]-4-oxoazetidin-2-yl}propionic acid 11

To a solution of acid **10** (6 g, 19.9 mmol) in THF (250 cm^3) was added NaH (60% in oil; 0.796 g, 19.9 mmol) at 10 °C. After stirring of the mixture at 10 °C for 20 min, *tert*-butyldimethylsilyl chloride (TBSCl) (3 g, 19.9 mmol) was added and the mixture was stirred at 25 °C for 1 h. To the suspension was added allyl bromoacetate (3.6 g, 19.9 mmol) followed by $NaN(TMS)_2$ (1 M in THF; 20 cm^3, 20 mmol) at −50 °C. After being stirred at −50 °C for 1 h, the mixture was warmed up to 25 °C and aq. K_2CO_3 (2.8 g, 20 mmol in 30 cm^3) was added. The

mixture was stirred at 25 °C for 15 min and was acidified to pH 4 by addition of conc. HCl (4.2 g, 20 mmol) followed by 1 M aq. HCl at 5 °C. The resulting organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (100 cm^3). The combined extracts were dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography ($CHCl_3$ to $CHCl_3$–MeOH 98:2) to afford *acid ester* **11** (6.02 g, 75%) as an oil (Found: C, 57.25; H, 8.6; N, 3.3. $C_{19}H_{33}NO_6Si$ requires C, 57.11; H, 8.33; N, 3.51%); ν_{max}(KBr)/cm^{-1} 1748; δ_H(200 MHz; $CDCl_3$) 0.0 (s, 3 H, SiMe), 0.02 (s, 3 H, SiMe), 0.90 (s, 9 H, SiBu^t), 1.11–1.21 (m, 6 H, Me), 2.78–2.89 (m, 1 H, C*H*Me), 2.97–3.01 (m, 1 H, CH–C=O), 3.84 (d, *J* 18, 1 H, CH–O), 4.05–4.23 (m, 3 H, CH_2N, CH–N), 4.54–4.57 (m, 2 H, CH_2–C=), 5.16–5.31 (m, 2 H, $=CH_2$), 5.74–5.94 (m, 1 H, CH=) and 10.10 (br s, 1 H, CO_2H); *m/z* (SIMS) 400 ($M^+ + 1$).

Typical procedure for the synthesis of thioesters: *S*-benzyl (2*R*)-2-{(2*S*,3*S*)-1-allyloxycarbonylmethyl-3-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-4-oxoazetidin-2-yl}thiopropionate 12b

To a solution of compound **11** (2 g, 5 mmol) in benzene (40 cm^3) were added DCC (1.09 g, 5.3 mmol) and 4-(dimethylamino)pyridine (DMAP) (61 mg, 0.5 mmol) at 10 °C. After stirring of this mixture at 25 °C for 30 min, toluene-α thiol (658 mg, 5.3 mmol) was added and the mixture was stirred at 25 °C for 17 h. The solid formed was filtered off and the filtrate was washed with water, dried over anhydrous $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (hexane–EtOAc 10:1) to afford oily *thioester* **12b** (2.004 g, 79.1%) (Found: C, 61.7; H, 7.75; N, 3.0. $C_{26}H_{39}NO_5SSi$ requires C, 61.74; H, 7.77; N, 2.77%); ν_{max}(KBr)/cm^{-1} 1767; δ_H(200 MHz; $CDCl_3$) 0.064 (s, 3 H, SiMe), 0.075 (s, 3 H, SiMe), 0.87 (s, 9 H, SiBu^t), 1.21–1.26 (m, 6 H, Me), 2.98–3.11 (m, 2 H, C*H*Me, CH–C=O), 3.82–4.26 (m, 6 H, CH–N, CH–O, CH_2N, CH_2–Ph), 4.60–4.63 (m, 2 H, CH_2–C=), 5.23–5.38 (m, 2 H, $=CH_2$), 5.81–6.01 (m, 1 H, CH=) and 7.20–7.34 (m, 5 H, Ph); *m/z* (SIMS) 506 ($M^+ + 1$).

***S*-*tert*-Butyl (2*R*)-2-{(2*S*,3*S*)-1-allyloxycarbonylmethyl-3-[(1*R*)-1-(*tert*-butyldimethylsiloxy)ethyl]-4-oxoazetidine-2-yl}-thiopropionate 12a**

Compound **12a** (4.35 g, 92%) was obtained as an oil from acid **11** (4.0 g, 10 mmol) (Found: C, 58.8; H, 8.75; N, 3.0. $C_{23}H_{41}NO_5SSi$ requires C, 58.56; H, 8.76; N, 2.97%); ν_{max}(KBr)/cm^{-1} 1770; δ_H(200 MHz; $CDCl_3$) 0.086 (s, 6 H, $SiMe_2$), 0.88 (s, 9 H, SiBu^t), 1.17–1.27 (m, 6 H, Me), 1.44 (s, 9 H, SBu^t), 2.84–3.03 (m, 2 H, C*H*Me, CH–C=O), 3.35–4.32 (m, 4 H, CH–O, CH–N, CH_2N), 4.57–4.67 (m, 2 H, CH_2–C=), 5.20–5.40 (m, 2 H, $=CH_2$) and 5.80–6.02 (m, 1 H, CH=); *m/z* (SIMS) 472 ($M^+ + 1$).

***S*-Cyclopentyl (2*R*)-2-{(2*S*,3*S*)-1-allyloxycarbonylmethyl-3-[(1*R*)-1-(*tert*-butyldimethylsiloxy)ethyl]-4-oxoazetidin-2-yl}-thiopropionate 12c**

Compound **12c** (1.606 g, 66.3%) was obtained from acid **11** (2 g, 5.00 mmol) (Found: C, 59.7; H, 8.5; N, 3.3. $C_{24}H_{41}NO_5SSi$ requires C, 59.58; H, 8.54; N, 2.90%); ν_{max}(KBr)/cm^{-1} 1769; δ_H(200 MHz; $CDCl_3$) 0.082 (s, 6 H, $SiMe_2$), 0.88 (s, 9 H, SiBu^t), 1.20–1.27 (m, 6 H, Me), 1.38–1.78 (m, 6 H, cyclopentyl), 1.99–2.17 (m, 2 H, cyclopentyl), 2.93–3.05 (m, 2 H, C*H*Me, CH–C=O), 3.65–3.76 (m, 1 H, CH–S), 3.86–4.29 (m, 4 H, CH–O, CH–N, CH_2N), 4.61–4.65 (m, 2 H, CH_2–C=), 5.23–5.39 (m, 2 H, C=CH_2) and 5.82–6.01 (m, 1 H, CH=); *m/z* (SIMS) 484 ($M^+ + 1$).

***S*-Phenyl (2*R*)-2-{(2*S*,3*S*)-1-allyloxycarbonylmethyl-3-[(1*R*)-1-(*tert*-butyldimethylsiloxy)ethyl]-4-oxoazetidin-2-yl}thio propionate**

Compound **12d** (1.06 g, 86%) was obtained from acid **11** (1.0 g, 2.5 mmol) (Found: C, 59.7; H, 8.5; N, 3.3. $C_{25}H_{37}NO_5SSi$ requires C, 61.06; H, 7.59; N, 2.85%); ν_{max}(KBr)/cm^{-1} 1768; δ_H(200 MHz; $CDCl_3$) 0.02 (s, 3 H, SiMe), 0.11 (s, 3 H, SiMe), 0.90 (s, 9 H, SiBu^t), 1.25–1.33 (m, 6 H, Me), 3.00–3.22 (m, 2 H, C*H*Me, CH–C=O), 3.90 (d, *J* 18, 1 H, CH–O), 4.13–4.30 (m, 3 H, CH–N, CH_2N), 4.58–4.60 (m, 2 H, CH_2–C=), 5.19–5.34 (m, 2 H, $=CH_2$), 5.77–5.97 (m, 1 H, CH=) and 7.35–7.44 (m, 5 H, Ph); *m/z* (SIMS) 492 ($M^+ + 1$).

***S*-(1-Allyloxycarbonyl-5-dimethylcarbamoylpyrrolidin-3-yl) (2*R*)-2-{(2*S*,3*S*)-1-allyloxycarbonylmethyl-3-[(1*R*)-1-(*tert*-butyldimethylsiloxy)ethyl]-4-oxoazetidin-2-yl}thiopropionate**

Compound **12e** (6.39 g, quant.) was obtained from acid **11** (4.0 g, 10 mmol) (Found: C, 56.7; H, 8.0; N, 6.3. $C_{30}H_{49}N_3O_8SSi$ requires C, 56.31; H, 7.72; N, 6.57%); ν_{max}(KBr)/cm^{-1} 1766, 1700 and 1655; δ_H(200 MHz; $CDCl_3$) 0.06 (s, 3 H, SiMe), 0.08 (s, 3 H, SiMe), 0.87 (s, 9 H, SiBu^t), 1.18–1.50 (m, 6 H, Me), 1.75–2.00 [m, 1 H, CH_2CH(N)CO], 2.60–2.77 [m, 1 H, CH_2CH(N)CO], 2.95–3.27 (m, 7 H, CH–N, NMe_2), 3.35–3.50 (m, 1 H, CH–C=O), 3.80–4.30 [m, 7 H, CH–N, CH–O, CH_2N–CH(CO), CH_2N], 4.50–4.80 (m, 5 H, CH_2–C=, CH–S), 5.12–5.43 (m, 4 H, $=CH_2$) and 5.27–6.02 (m, 2 H, –CH=); *m/z* (SIMS) 640 ($M^+ + 1$).

Typical procedure for the Lewis acid-promoted Dieckmann-type cyclisation: the synthesis of allyl (4*R*,5*R*,6*S*)-6-[(1*R*)-1-(*tert*-butyldimethylsiloxy)ethyl]-3-diphenylphosphoryl-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate 16 by the use of chlorotrimethylsilane

To a solution of compound **12a** (147.1 g, 0.312 mol) in THF (1300 ml) was added $NaN(TMS)_2$ (1 M in THF; 624 cm^3, 0.624 mol) at −30 °C followed by TMSCl (33.9 g, 0.312 mol) at the same temperature. After stirring of the mixture for 5 min, diphenyl chlorophosphate (92.2 g, 0.343 mol) was added at −30 °C and the mixture was stirred at 0 °C for 2.5 h. The mixture was poured into phosphate buffer (pH 7.0, 0.2 M, K_2HPO_4–H_3PO_4; 2000 cm^3) and extracted with EtOAc (2 × 1000 cm^3). The combined extracts were washed successively with water (2 × 1000 cm^3) and brine (1000 cm^3), dried over anhydrous $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (hexane–EtOAc 4:1) to afford *compound* **16** (162.7 g, 85.0%) as a viscous oil (Found: C, 60.8; H, 6.8; N, 2.55. $C_{31}H_{40}NO_8PSi$ requires C, 60.67; H, 6.57; N, 2.28%); ν_{max}(KBr)/cm^{-1} 2931, 1786, 1718, 1638 and 1591; δ_H(200 MHz; $CDCl_3$) 0.07 (s, 6 H, $SiMe_2$), 0.88 (s, 9 H, SiBu^t), 1.18 (d, *J* 7.5, 3 H, Me), 1.22 (d, *J* 6.3, 3 H, Me), 3.20–3.30 (m, 1 H, C*H*Me), 3.30–3.50 (m, 1 H, CH–C=O), 4.00–4.30 (m, 2 H, CH–N, CH–O), 4.64 (d, *J* 5.4, 2 H, CH_2–C=), 5.10–5.40 (m, 2 H, $=CH_2$), 5.75–5.95 (m, 1 H, CH=) and 7.10–7.40 (m, 10 H, Ph); *m/z* (SIMS) 614 ($M^+ + 1$). The synthesis of *compound* **16** from thioester **12a** by the use of other Lewis acids was conducted using the similar procedure described above. The yields obtained are listed in Table 1.

Typical procedure for the synthesis of 1β-methylcarbapenems: allyl (4*R*,5*S*,6*S*)-3-benzylthio-6-[(1*R*)-1-(*tert*-butyldimethylsiloxy)ethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate 19b

To a solution of thioester **12b** (506 mg, 1 mmol) in THF (5 ml) was added $NaN(TMS)_2$ (1 M in THF; 2.2 cm^3, 2.2 mmol) at −30 °C for 1 min. After stirring of the mixture for 5 min, TMSCl (0.14 cm^3, 1.1 mmol) was added at −30 °C and the mixture was stirred at the same temperature for 5 min. Diphenyl chlorophosphate (0.22 cm^3, 1.05 mmol) was then added at −30 °C and the mixture was stirred at 0 °C for 2 h. To this mixture was added TBAF (1 M in THF; 1 cm^3, 1.0 mmol) at 0 °C followed by DMF (5 cm^3). The reaction mixture was stored in a refrigerator (5 °C) for 72 h and poured into water and extracted with EtOAc (2 × 30 cm^3). The combined extracts were washed with water (3 × 30 cm^3), dried over anhydrous $MgSO_4$, and evaporated *in vacuo*. The residue was purified by reversed-

phase Lober column chromatography (RP-8, E. Merck) using a mixed solvent of CH_3CN and water (2:1) as eluent to afford *compound* **19b** (302 mg, 62%) as crystals, mp 65–66 °C (Found: C, 64.25; H, 7.5; N, 3.0. $C_{26}H_{37}NO_4SSi$ requires C, 64.03; H, 7.65; N, 2.87%); ν_{max}(KBr)/cm^{-1} 1760 and 1670; δ_H(200 MHz; $CDCl_3$) 0.061 (s, 3 H, SiMe), 0.068 (s, 3 H, SiMe), 0.872 (s, 9 H, SiBu^t), 1.22–1.26 (m, 6 H, Me), 3.16–3.18 (m, 1 H, C*H*Me), 3.28–3.32 (m, 1 H, CH–C=), 4.04–4.08 (m, 3 H, CH–O, benzyl), 4.17–4.23 (m, 1 H, CH–N), 4.65–4.71 (m, 2 H, CH_2–C=), 5.21–5.24 (m, 1, =CH_2), 5.41–5.46 (m, 1 H, =CH_2), 5.90–5.99 (m, 1 H, CH=) and 7.25–7.35 (m, 5 H, Ph); *m/z* (SIMS) 488 (M^+ + 1).

Allyl (4*R*,5*S*,6*S*)-6-[(1*R*)-1-(*tert*-butyldimethylsiloxy)ethyl]-3-cyclopentylthio-4-methyl-7-oxo-azabicyclo[3.2.0]hept-2-ene-2-carboxylate 19c

Compound **19c** (256 mg, 55%) was obtained from thioester **12c** (484 mg, 1 mmol), mp 86–88 °C (Found: C, 62.0; H, 8.2; N, 2.9. $C_{24}H_{39}NO_4SSi$ requires C, 61.89; H, 8.44; N, 3.01); ν_{max}(KBr)/cm^{-1} 1777 and 1703; δ_H(200 MHz; $CDCl_3$) 0.082 (s, 6 H, SiMe), 0.89 (s, 9 H, SiBu^t), 1.23–1.27 (m, 6 H, Me), 1.50–1.90 (m, 6 H, cyclopentyl), 1.90–2.20 (m, 2 H, cyclopentyl), 3.15–3.60 (m, 3 H, CHMe, CH–C=O, CH–S), 4.05–4.30 (m, 2 H, CH–N, CH–O), 5.20–5.50 (m, 2 H, =CH_2) and 5.80–6.06 (m, 1 H, CH=); *m/z* (SIMS) 466 (M^+ + 1).

Allyl (4*R*,5*S*,6*S*) -6-[(1*R*)-1-(*tert*-butyldimethylsiloxy)ethyl]-4-methyl-7-oxo-3-phenylthio-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate 19d

Compound **19d** (246 mg, 52%) was obtained from thioester **12d** (492 mg, 1 mmol); mp 82–85 °C (Found: C, 63.6; H, 7.5; N, 2.98. $C_{25}H_{35}NO_4SSi$ requires C, 63.38; H, 7.45; N, 2.96%); ν_{max}(KBr)/cm^{-1} 1780; δ_H(200 MHz; $CDCl_3$) 0.057 (s, 6 H, $SiMe_2$), 0.86 (s, 9 H, SiBu^t), 0.94 (d, *J* 7.3, 3 H, Me), 1.18 (d, *J* 6.2, 3 H, Me), 2.92–3.17 (m, 2 H, C*H*Me, CH–C=O), 4.10–4.25 (m, 2 H, CH–N, CH–O), 4.71–4.89 (m, 2 H, CH_2–C=), 5.23–5.30 (m, 1 H, =CH_2), 5.43–5.52 (m, 1 H, =CH_2), 5.89–6.09 (m, 1 H, CH=) and 7.37–7.56 (m, 5 H, Ph); *m/z* (SIMS) 474 (M^+ + 1).

Allyl (4*R*,5*S*,6*S*)-3-[(1-allyloxycarbonyl-5-dimethylcarbamoylpyrrolidin-3-yl)thio]-6-[1-(*tert*-butyldimethylsiloxy)ethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate 19e

Compound **19e** (361 mg, 58%) was obtained from substrate **12e** (640 mg, 1 mmol) as an oil (Found: C, 58.1; H, 7.4; N, 7.0. $C_{30}H_{47}N_3O_7SSi$ requires C, 57.94; H, 7.62; N, 6.76%); ν_{max}(KBr)/cm^{-1} 1776, 1710 and 1650; δ_H(200 MHz; $CDCl_3$) 0.085 (s, 6 H, $SiMe_2$), 0.89 (s, 9 H, SiBu^t), 1.24–1.27 (m, 6 H, Me), 1.85–2.07 [m, 1 H, $CH_2C(N)CO$], 2.55–2.80 (m, 1 H, $CH_2C(N)CO$], 2.95–3.12 (m, 6 H, NMe_2), 3.16–3.35 (m, 2 H, C*H*Me, CH–C=O), 3.37–3.75 (m, 2 H, CH_2N), 3.97–4.30 [m, 3 H, CH–N, CH–O, CH(N)CO], 4.50–4.85 (m, 5 H, CH–S, CH_2–C=), 5.12–5.50 (m, 4 H, =CH_2) and 5.75–6.07 (m, 2 H, CH=); *m/z* (SIMS) 622 (M^+ + 1).

Allyl (4*R*,5*S*,6*S*)-3-benzylthio-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylate 20b

To a solution of compound **19b** (1 g, 2.05 mmol) in DMF (8 cm^3) containing *N*-methylpyrrolidone (NMP) (3 cm^3) was added NH_4F·HF (469 mg, 8.2 mmol) at 20 °C and the mixture was stirred at the same temperature for 72 h before being diluted with water and extracted with EtOAc (2 × 20 cm^3). The extracts were washed with water, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography to afford compound **20b** (739 mg, 96.5%) in an oil (Found: C, 64.8; H, 6.3; N, 3.8. $C_{20}H_{23}NO_4SSi$ requires C, 64.32; H, 6.21; N, 3.75%); ν_{max}(Nujol)/cm^{-1} 3507, 1776 and 1700; δ_H(200 MHz; $CDCl_3$) 1.25 (d, *J* 7.3, 3 H, Me), 1.34 (d, *J* 6.3, 3 H, Me), 1.90 (br, 1 H, OH), 3.19–3.44 (m, 2 H, C*H*Me, CH–C=O), 4.07–4.24 (m, 4 H, CH–N, CH–O, benzyl), 4.63–4.88 (m, 2 H, CH_2–C=), 5.22–5.49 (m, 2 H, =CH_2), 5.90–6.04 (m, 1 H, CH=), 7.27–7.36 (m, 5 H, Ph); *m/z* (SIMS) 374 (M^+ + 1).

Sodium (4*R*,5*S*,6*S*)-3-benzylthio-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate 1b

To a solution of $NaHCO_3$ (47 mg, 0.56 mmol) and dimedone (47 mg, 0.34 mmol) in water (0.6 ml) were successively added THF (4.5 cm^3), $P(OEt)_3$ (0.033 cm^3, 0.19 mmol) and $Pd(OAc)_2$ (6.1 mg, 0.027 mmol) under N_2. After being stirred for 3 min, the mixture was treated with compound **20b** (208 mg, 58 mmol) and the mixture was stirred at 35–37 °C for 1 h. The mixture was diluted with water (30 cm^3) and washed with CH_2Cl_2 (3 × 30 cm^3). The aqueous phase was separated, and evaporated at <35 °C. The residue was purified by reversed-phase Lober column chromatography (RP-8, E. Merck) using a mixed solvent of CH_3CN:H_2O 1:1. The fractions containing compound **1b** were combined and CH_3CN was removed by evaporation. The aqueous solution was freezedried to afford the salt **1b** (172 mg, 86.9%) as a powder; ν_{max}(Nujol)/cm^{-1} 3384, 1750 and 1591; δ_H(200 MHz; D_2O) 1.17 (d, *J* 7.2, 3 H, Me), 1.28 (d, *J* 6.4, 3 H, Me), 3.30–3.46 (m, 2 H, C*H*Me, CH–C=), 3.92–4.27 (m, 4 H, CH–N, CH–O, benzyl) and 7.31–7.46 (m, 5 H, Ph); δ_C(50 MHz; D_2O) 179.1, 145.1, 140.6, 134.0 and 131.9 (5 s), 131.7 (2 d), 130.3 (d), 68.0, 61.0, 58.7 and 45.1 (4 d), 38.3 (t) and 22.9 and 18.7 (2 q); *m/z* (SIMS) 355 (M^+).

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