Pergamon

Tetrahedron, Vol. 53, No. 44, pp. 15011-15028, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)01053-3

The Synthesis of 4-Aminocarbonylmethoxy Trinems

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Abstract: The synthesis of 4-aminocarbonylmethoxy trinems was accomplished through Lewis acid catalysed opening of an epoxide intermediate with allyl glycolate, followed by deallylation, activation of the free acid *via* the 2-pyridyl thiolester and reaction with a series of trimethylsilylamines. An alternative route involving a rhodium-catalysed diazoacetate insertion was also successfully exploited.

Recently, the trinem antibiotics have been the subject of considerable interest owing to their broad spectrum antibacterial activity, resistance to β-lactamases and stability to renal dehydropeptidases, a potential problem for the penem and carbapenem classes of antibiotics. Currently, the (4*S*)-methoxytrinem sanfetrinem **1**, and its orally active ester pro-drug sanfetrinem cilexetil **2** (Figure 1) are in Phase II clinical trials.[1,2]

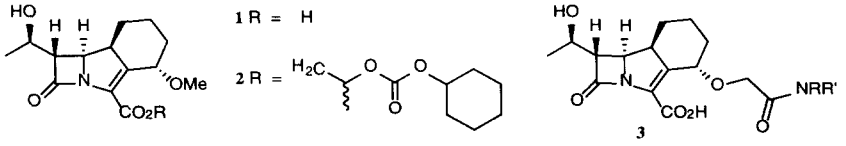


Figure 1

Following the very promising results obtained with sanfetrinem and as part of a program aimed at further modulating the antibacterial activity of the class, the synthesis of a series of 4-aminocarbonylmethoxy derivatives **3** has been studied and is described in this paper.[3]

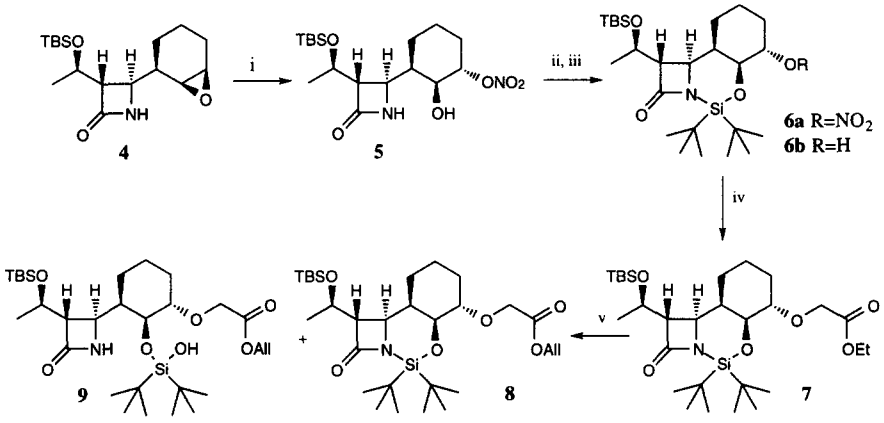
Previous studies have shown that epoxide **4** reacts with ceric ammonium nitrate (CAN) in acetonitrile to give the nitrate ester **5** in moderate yields (Scheme 1).[4,5] Simultaneous protection of the azetidinone nitrogen and the hydroxyl as the cyclic bis-*tert*-butylsilyl derivative **6a** was then accomplished, followed by hydrogenolysis to afford secondary alcohol **6b**.

Rhodium-carbenoid insertion on alcohol 6b

This synthetic route was easily scaled up, and with gram quantities of alcohol **6b** in hand the formation of a glycolic acid derivative, through carbenoid insertion into the O-H group, was considered an attractive approach to the desired series of derivatives. The rhodium catalysed reaction of ethyl diazoacetate[6] to give compound **7** was therefore investigated.

The reaction of intermediate **6b** with ethyl diazoacetate in CH_2Cl_2 using $Rh_2(OAc)_4$ as catalyst proceeded smoothly and in good yield, without the necessity of using the alcohol as the solvent, although very slow addition of the diazo acetate was necessary in order to minimise formation of dimers derived from the carbenoid intermediate, which also affected the ease of purification of the desired product **7**.

In order to avoid basic hydrolytic conditions on a sensitive substrate such as the trinem skeleton, we wished to introduce an ester group which was removable under milder conditions. Transesterification was therefore accomplished by the reaction of compound **7** in anhydrous allyl alcohol in the presence of catalytic amounts of potassium *tert*-butoxide (Scheme 1).



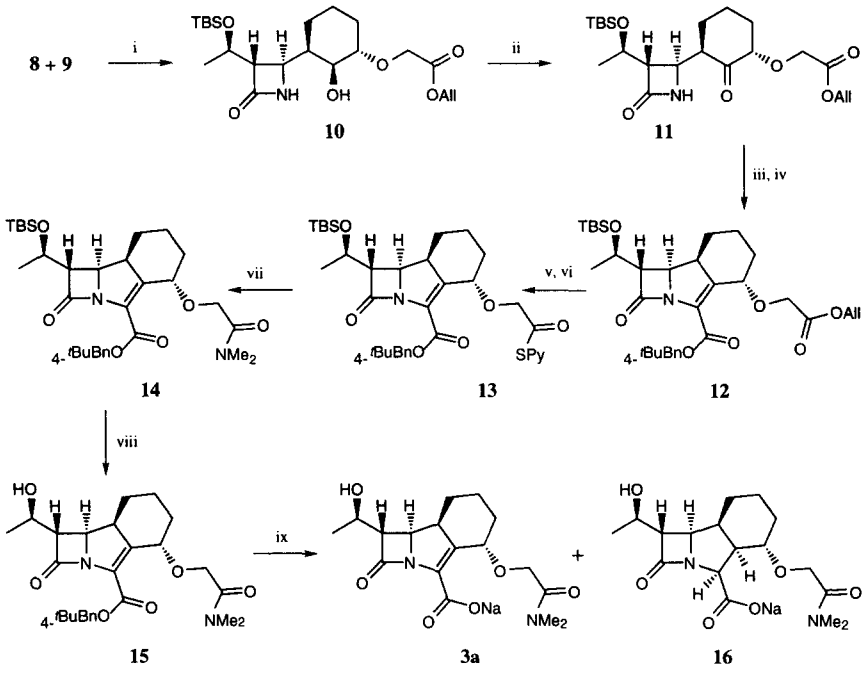
Reagents and Conditions: i) CAN, MeCN, 53%; ii) $(TfO)_2Si(^tBu)_2$, 2,6-lutidine, CH_2Cl_2, 79%; iii) H_2, Pd/C, AcOEt, 92%; iv) $Rh_2(OAc)_4$, N_2CHCO_2Et, CH_2Cl_2, 72%; v) allyl alcohol, ^tBuOK, 60%

Scheme 1

Along with the desired fully protected allyl ester **8**, variable amounts of the monodeprotected silanol **9** were obtained, but formation of this by-product did not constitute a problem as full deprotection to give alcohol **10** was obtained by treatment of the mixture with Bu_4NF buffered with AcOH (Scheme 2).[7] After Swern oxidation and formation of the trinem 4-*t*butylbenzyl ester[8] *via* the 'oxo-oxo' cyclisation route,[9] removal of the allyl group[10] was accomplished to give the acid, which was then activated as its 2-pyridyl thiolester **13**. Reaction with *N*-trimethylsilyldimethylamine afforded the required amide **14** in good yield,[11,12] either on the isolated pyridyl thiolester or through a one-pot procedure. Even when a large excess of the amine was used, no products derived from opening of the ß-lactam ring were isolated, thus proving the efficacy of this methodology also on the sensitive trinem nucleus.

After silyl removal with tetrabutylammonium bromide and caesium fluoride, compound **15** was submitted to catalytic hydrogenation in the presence of one molar equivalent of sodium ethyl hexanoate. The hydrogenation step was difficult to optimise and always afforded a mixture of the desired compound **3a** and the corresponding over-reduced product **16** in variable amounts. As the use of

different catalysts and reaction conditions did not lead to any significant improvement,[13] the 4-*tert*-butylbenzyl ester was replaced with the allyl group in a different route to the class (*vide infra*).

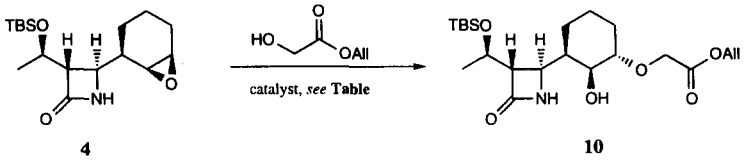


Reagents and Conditions: i) Bu_4NF, AcOH, THF, 55%; ii) Swern oxidation, 90%; iii) 4-^{t}BuBnOCOCOCl, Et_3N, CH_2Cl_2; iv) $P(OEt)_3$, xylene, 70% (2 steps); v) $Pd(PPh_3)_4$, Na 2-ethylhexanoate, buffer pH=3; vi) PPh_3, $(PyS)_2$, MeCN, 50% (2 steps); vii) Me_3SiNMe_2, MeCN, 78%; viii) Bu_4NBr, CsF, AcOH, THF, 44%; ix) H_2, Pd/C, Et_3N, *i*PrOH

Scheme 2

Metal salt-promoted alcoholysis of epoxide 4

In the search for a more versatile synthesis, the possibility of obtaining the advanced intermediate **10** by the ring opening of epoxide **4**[14] with allyl glycolate,[15] as illustrated in Scheme 3, was considered.



Scheme 3

Nucleophilic ring opening reactions of epoxides with alcohols in the presence of either acid or base have been extensively studied and recently some efficient methodologies under mild conditions have appeared in the literature. In particular, an extremely mild epoxide opening reaction catalysed by

$LiClO_4$, $Mg(ClO_4)_2$ and $Zn(OTf)_2$ has been published,[16] where the alcohol can be used either as the reaction solvent or in stoichiometric amount when performing the reaction in an aprotic solvent such as acetonitrile. This methodology has been applied to **4** and the results obtained using different metal salts are reported in the Table. Using allyl glycolate as solvent in the presence of variable quantities of CuCl, $LiClO_4$ and TMSOTf the reaction failed (Entries 1-3), whereas better results were obtained with the use of $Mg(ClO_4)_2$, $Sn(OTf)_2$ and $Zn(OTf)_2$. The reaction was optimised in terms of amount of Lewis acid and the best results were obtained with the use of 0.9 equivalents of $Sn(OTf)_2$ and 10 equivalents of allyl glycolate (Entry 10) and running the reaction at 0°C for 20 minutes. Under these conditions compound **10** could be isolated from the reaction mixture in an acceptable yield (40%). Attempts to further improve the efficiency of the process by changing different parameters were unsuccessful. When for example acetonitrile was used as the solvent in the presence of smaller amounts of the allyl glycolate, no reaction was observed.

Entry	Catalyst (eq.)	Temp.	Time	Alcohol (eq.)	Yields
1	CuCl (1.2)	55°C	4 hrs	10	--
2	$LiClO_4$ (1.2)	55°C	4 hrs	10	--
3	TMSOTf(1.2)	0°C	10 min	10	--
4	$Mg(ClO_4)_2$(2)	80°C	4 hrs	10	22%
5	$Zn(OTf)_2$ (1)	80°C	3 hrs	10	20%
6	$Zn(OTf)_2$ (1)	25°C	24 hrs	10	--
7	$Sn(OTf)_2$ (0.3)	25°C	1 hrs	10	30%
8	$Sn(OTf)_2$ (0.9)	25°C	10 min	20	decomp
9	$Sn(OTf)_2$ (0.9)	0°C	10 min	25	20%
10	$Sn(OTf)_2$ (0.9)	0°C	20 min	10	40%
11	$Sn(OTf)_2$ (0.9)	0°C	30 min	10	32%
12	$Sn(OTf)_2$ (1)	0°C	10 min	10	25%

Table

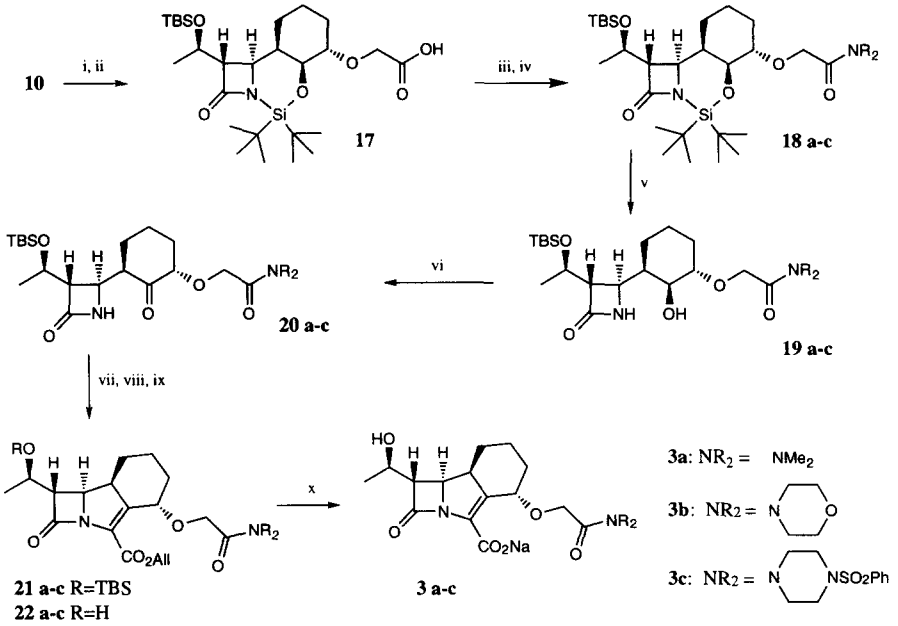
Although the isolated yields should not be considered as completely satisfactory, the great reduction in the number of steps with respect to the previous diazo insertion route proved to be of great advantage, and no attempts to further improve the reaction conditions were made.

To avoid the problems encountered in the hydrogenation step of the original route, it was decided to replace the benzyl ester with an allyl group, easily removed under Pd(0) catalysis in the last step of the process.[17] The synthetic route was therefore modified as shown in Scheme 4, to have the amide bond in place before ring closure to the trinem system.

In view of a possible intramolecular reaction of the free secondary hydroxyl group with the activated acid to form a 6-membered lactone, it was decided to work on a fully protected derivative of **10**. Thus, intermediate **10** was converted to **8** and subsequently deallylated under standard conditions. The crude acid **17** was treated with 2,2'-dipyridyldisulphide and triphenyl phosphine to give the corresponding pyridyl thiolester. This was then reacted with a series of *N*-trimethylsilylamines (Scheme

4), which were either commercially available or prepared following known literature procedures,[18] to give the desired amides **18a-c** in good yield.

Deprotection of the cyclic di-*tert*-butylsilyl protecting group was performed with TBAF and acetic acid in THF at room temperature to efficiently afford the secondary alcohol derivatives **19a-c** which were then transformed into the alkoxyketones in good yields **20a-c** through Swern oxidation.



Reagents and Conditions: i) $(TfO)_2Si(^tBu)_2$, 2,6-lutidine, CH_2Cl_2,; ii) $Pd(PPh_3)_4$, Na 2-ethyl hexanoate, buffer pH=3; iii) PPh_3, $(PyS)_2$, CH_2Cl_2; iv) Me_3SiNR_2, CH_2Cl_2, 60-80%; v) Bu_4NF, AcOH, THF, 65-80%; vi) Swern oxidation, 50-70%; vii) $ClCOCO_2All$, Et_3N, CH_2Cl_2; viii) $P(OEt)_3$, xylene, 35-50%; ix) Bu_4NBr, CsF, AcOH, THF, 40-50%; x) $Pd(PPh_3)_4$, Na 2-ethyl hexanoate, THF, 35-46%

Scheme 4

The trinem skeleton was then assembled following standard methodologies and the cyclised products **21a-c** were isolated by flash chromatography. The protecting group on the hydroxyethyl side-chain was removed in 40-45% yield with Bu_4NBr and CsF in THF to give **22a-c** and finally Pd(0) catalysed removal of the allyl group in the presence of one equivalent of sodium ethylhexanoate afforded the target amides **3 a-c** as the corresponding sodium salts.

In conclusion, two different synthetic routes have allowed us to obtain the desired compounds, the biological activity of which will be reported elsewhere.

Acknowledgements

The authors would like to thank the members of the NMR Spectroscopy, Mass Spectrometry and Analytical Sciences laboratories for their help with this work.

Experimental

All reactions were performed in oven-dried glassware under a positive pressure of nitrogen. Unless otherwise noted, starting materials were obtained from commercial suppliers and used without further purification.

Tetrahydrofuran (THF) was distilled from Na/benzophenone ketyl; dichloromethane (CH_2Cl_2) was distilled from CaH_2. Organic extracts were dried over Na_2SO_4 and filtered before removal of solvent under reduced pressure. ^{1}H-NMR spectra were recorded on Bruker AC 200F (200 MHz), Varian VXR5000S (300 MHz), Varian Unity (400 MHz) spectrometers and are reported in parts per million (ppm) with reference to the residual chloroform signal (7.26 ppm). Coupling constants (*J*) are reported in Hertz. IR spectra were recorded on a Bruker IFS48 instrument. Low resolution mass spectra (LRMS) were performed on a triple quadrupole instrument (Micromass VG Quattro), and high resolution mass spectra (HRMS) were obtained on a trisector instrument (Micromass VG Autospec). Both LRMS and HRMS were obtained under positive FAB ionisation, therefore the values refer to the protonated molecules. HPLC analysis was performed on a Perkin Elmer 410 using a diode array UV detector HP 1040M Series II. Elemental analyses were performed on a Carlo Erba CHNS-O EA-1108. Melting points (mp.) are uncorrected and were determined on a Buchi 510 apparatus. Analytical thin layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} plates (0.25mm); and visualised under UV light (254 nm) and/or ethanolic phosphomolybdic acid solution. Flash chromatography was performed using Merck silica gel 60 (230-400 mesh).

(3*S*, 4*R*) 3-[(1*R*) 1-(*t*-Butyldimethylsilyloxy)ethyl]-4-[(1*S*, 2*S*, 3*R*)-(2-hydroxy)-(1-nitroxy)cyclohex-3-yl] azetidin-2-one 5. Ceric ammonium nitrate (3.02 g, 5.52 mmol) was added to a solution of intermediate **4** (2.7 g, 8.29 mmol) in anhydrous acetonitrile (60 ml). The red suspension was stirred at room temperature for 20 hours, then the solvent was evaporated *in vacuo* and the residue taken in with ethyl acetate (50 ml). The resulting white precipitate was removed by filtration washing with ethyl acetate. The organic layers were washed with a 5% solution of sodium hydrogen carbonate (30 ml) and brine (3x20 ml). The crude yellow oil was purified by flash chromatography (ethyl acetate:cyclohexane 6:4) to afford the title compound **5** as a white solid (yield=53%). mp.:105-108°C. ^{1}H-NMR ($CDCl_3$, 300MHz): 6.14 (bs, 1H); 5.1-5.0 (m, 1H); 4.2-4.1 (m, 1H); 4.1-3.9 (m, 1H); 3.63 (dd, 1H, *J*= 2.2; 6.3); 2.96 (dd, 1H, *J*= 6.6; 1.2); 2.8-2.4 (bs, 1H); 2.04-1.4 (m, 7H); 1.28 (d, 3H, *J*= 6.3); 0.88 (s, 9H); 0.1 (s, 3H); 0.09 (s, 3H). IR ($CDCl_3$)ν_{max}: 3610, 3416, 1755, 1636, 1277 cm^{-1}. LRMS (*m/z*): 389 $[M+H]^+$, 331, 228, 189, 159. HRMS: Calcd. for $C_{17}H_{33}N_2O_6Si$: 389.210791; found MH^+ 389.20864.

(1*S*, 6*S*, 7*R*, 8*R*, 12*S*) 2-Oxa-4-aza-3-sila-6-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-3,3-di-*tert*-butyl-12-(nitroxy)tricyclo [6.4.0.0^{4,7}]dodecane 6a

2,6-lutidine (1.35 ml, 11.6 mmol), followed by $(TfO)_2Si(tert\text{-butyl})_2$ (1.83 ml, 5.02 mmol) were added to a cooled (0°C) solution of intermediate **5** (1.5 g, 3.86 mmol) in anhydrous dichloromethane (25 ml). The reaction mixture was stirred overnight at 5°C, then the solvent was evaporated *in vacuo* and the crude residue was purified by flash chromatography (eluant cyclohexane/ethyl acetate 9:1) to afford the title compound **6a** as white powder (yield=79%). mp.: 128-130°C. ^{1}H-NMR ($CDCl_3$, 200MHz): 5.17-

5.13 (m, 1H); 4.49-4.40 (m, 1H); 4.30-4.20 (m, 1H); 3.98 (t, 1H, *J*= 3.1); 3.12 (t, 1H, *J*= 3.4); 1.90-1.84 (m, 2H); 1.78-1.40 (m, 5H); 1.18 (d, 3H, *J*= 6); 1.12 (s, 9H); 1.09 (s, 9H); 0.90 (s, 9H); 0.07 (s, 3H); 0.05 (s, 3H). IR (nujol)ν_{max}: 1738, 1635 cm^{-1}. Elem. Anal.: Calcd for $C_{25}H_{48}N_2O_6Si_2$: C 56.77; H 9.17; N 5.30; found C 57.22; H 9.51; N 5.45.

(1*S*, 6*S*, 7*R*, 8*R*, 12*S*) 2-Oxa-4-aza-3-sila-6-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-3,3-di-*tert*-butyl-12-(hydroxy)tricyclo [6.4.0.0^{4,7}]dodecane 6b

Palladium (10% on carbon, 0.4 g) was added to a stirred solution of intermediate **6a** (1.6 g, 3.03 mmol) in ethyl acetate (50 ml) and the reaction mixture was stirred under hydrogen at atmospheric pressure for 2 hours. The catalyst was removed by filtration on Celite®, washing with ethyl acetate (2x15 ml) and the solvent was evaporated *in vacuo* to give the title compound **6b** as a white foam (yield=92%).
^{1}H-NMR ($CDCl_3$, 300MHz): 4.28-4.16 (m, 2H); 4.0-3.92 (m, 2H); 3.23 (t, 1H, *J*= 3.6); 2.1-2.0 (m, 1H); 1.85-1.75 (m, 1H); 1.65-1.50 (m, 3H); 1.48-1.38 (m,1H); 1.40 (d, 1H, *J*=3.9); 1.15 (d, 3H, *J*=6.3); 1.12 (s, 9H); 0.86 (s, 9H); 0.07 (s, 3H); 0.05 (s, 3H). IR ($CDCl_3$)ν_{max}: 1738 cm^{-1}. LRMS (*m/z*): 484 $[M+H]^+$, 426, 284, 199, 159. Elem. Anal.: Calcd for $C_{25}H_{49}NO_4Si_2$: C 62.04; H 10.23; N 2.90; found C 62.12; H 10.1; N 2.84.

(1*S*, 6*S*, 7*R*, 8*R*, 12*S*) 2-Oxa-4-aza-3-sila-6-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-3,3-di-*tert*-butyl-12-(ethoxycarbonylmethoxy)tricyclo [6.4.0.0^{4,7}]dodecane 7

A catalytic amount of $[Rh_2(OAc)]_4$ was added to a stirred solution of intermediate **6b** (1.15 g, 2.4 mmol) in anhydrous dichloromethane (5 ml) . To the resulting solution ethyl diazoacetate (1.5 ml, 14.4 mmol) was added dropwise at room temperature over 6 hours. Then, the solvent was evaporated *in vacuo* and the crude residue was purified by flash chromatography (eluant cyclohexane/ethyl acetate 98:2) to give the title compound **7** as a yellow oil (yield=72%). ^{1}H-NMR ($CDCl_3$, 300MHz): 4.40-4.35 (m, 1H); 4.3-4.15 (m, 3H); 4.11 (d, 2H, *J*= 9); 4.01 (t, 1H, *J*= 3.4); 3.61 (s, 1H); 3.24 (t, 1H, *J*= 3.3); 2.1-2.0 (m, 1H); 1.8-1.6 (m, 5H); 1.5-1.4 (m, 1H); 1.36-1.2 (m, 6H); 1.13 (s, 9H); 1.09 (s, 9H); 0.88 (s, 9H); 0.08 (s, 3H); 0.07 (s, 3H). IR ($CDCl_3$)ν_{max}: 1736 cm^{-1}.

(1*S*, 6*S*, 7*R*, 8*R*, 12*S*) 2-Oxa-4-aza-3-sila-6-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-3,3-di-*tert*-butyl-12-(allyloxycarbonylmethoxy)tricyclo [6.4.0.0^{4,7}]dodecane 8

Ethyl ester **7** (1.2 g, 2.1 mmol) was dissolved in allyl alcohol (10 ml) and cooled at -20°C. A catalytic amount of potassium *tert*-butoxide was added and the reaction mixture was allowed to warm to room temperature over 2 hours. A saturated solution of ammonium chloride (10 ml) was then added followed by ethyl acetate (30 ml); the organic layer was separated, washed with brine (2x15ml), dried over sodium sulphate and evaporated under reduced pressure to afford an oily residue which was purified by flash chromatography (eluant cyclohexane/ethyl acetate in gradient from 95:5 to 7:3). The title compound **8** was obtained as a colourless oil (yield=60%). Compound **9** was also isolated as a white foam in 15% yield. ^{1}H-NMR ($CDCl_3$, 300MHz); Compound **8**: 6.00-5.82 (m, 1H); 5.40-5.16 (m, 2H); 4.7-4.6 (m, 2H); 4.4-4.34 (m, 1H); 4.24-4.18 (m, 1H); 4.14 (d, 2H, *J*= 9.3); 4.0-3.96 (m, 1H); 3.63-3.6 (m, 1H); 3.23 (t, 1H, *J*= 3.6); 2.10-2.00 (m, 1H); 1.80-1.50 (m, 3H); 1.13 (s, 9H); 1.09 (s, 9H); 1.14 (d, 3H, *J*= 6.3); 0.88 (s, 9H); 0.08 (s, 3H); 0.07 (s, 3H). IR ($CDCl_3$): 1736 cm^{-1}. LRMS (*m/z*): 582 $[M+H]^+$, 524, 159. Compound **9**: 5.95 (s, 1H); 6.00-5.84 (m, 1H); 5.38-5.24 (m, 2H); 4.65 (d, 2H, *J*= 6); 4.29 (t,

1H, *J*= 3.6); 4.24-4.21 (m, 1H); 4.20 (d, 1H, *J*= 16.6); 4.04 (d, 1H, *J*= 16.6); 3.98-3.96 (m, 1H); 3.68-3.66 (m, 1H); 3.03 (bs, 1H); 2.95 (t, 1H, *J*= 2.7); 2.12-2.02 (m, 1H); 1.86-1.38 (m, 6H); 1.22 (d, 3H, *J*= 6.3); 1.05 (s, 9H); 1.02 (s, 9H); 0.87 (s, 9H); 0.07 (s, 6H). IR ($CDCl_3$)ν_{max}: 1749 cm^{-1}. LRMS (*m/z*): 600 $[M+H]^+$, 584, 542, 484, 400, 284.

From alcohol ***8***: 2,6-Lutidine (0.97 ml, 8.3 mmol), followed by $(TfO)_2Si(tert\text{-butyl})_2$ (1.31 ml, 3.60 mmol) was added to a cooled (0°C) solution of intermediate **8** (1.22 g, 2.77 mmol) in anhydrous dichloromethane (25 ml). The reaction mixture was stirred overnight at 5°C, then the solvent was evaporated *in vacuo* and the crude residue was purified by flash chromatography (eluant cyclohexane/ethyl acetate 9:1) to afford the title compound as a white foam in 79% yield.

(3*S*,4*R*) 3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-4-[(1*R*, 2*S*, 3*S*)-3-(allyloxycarbonylmethoxy)-2-hydroxycyclohexyl]azetidin-2-one 10.

A 1.1M solution of tetrabutylammonium fluoride in THF (3.0 ml, 3.3 mmol) followed by glacial acetic acid (188 µl, 3.3 mmol) was added to a solution of **8** (0.9 g, 1.5 mmol) in anhydrous tetrahydrofuran (45 ml). The mixture was stirred at room temperature for 2 hours, then it was diluted with a 5% solution of sodium hydrogen carbonate (25 ml) and ethyl acetate (30 ml). The organic layer was washed with saturated brine (2x20 ml), dried over sodium sulphate and evaporated *in vacuo* to give an oily residue that was purified by flash chromatography (eluant cyclohexane/ethyl acetate; gradient from 8:2 to 65:35). The title compound **10** was isolated as a pale yellow solid (yield=55%). mp.: 76-78°C.

Intermediate **9** (0.18 g, 0.3 mmol) was submitted to the same reaction conditions to give compound **10**. ^{1}H-NMR ($CDCl_3$, 400MHz) : 6.0-5.82 (m, 1H); 5.90 (s, 1H); 5.4-5.2 (m, 2H); 4.65-4.62 (m, 2H); 4.19 (d, 1H, *J*= 16.5); 4.08 (d, 1H, *J*= 16.5); 4.3-4.0 (m, 1H); 3.95-3.93 (m, 1H); 3.66 (dd, 1H, *J*= 1.9, 7); 3.51-3.49 (m, 1H); 3.01 (d, 1H, *J*= 3); 2.18-2.12 (m, 1H); 2.0-1.9 (m, 1H); 1.8-1.4 (m, 6H); 1.26 (d, 3H, *J*= 6); 0.88 (s, 9H); 0.09 (6H). IR ($CDCl_3$)ν_{max}: 1751; 3406 cm^{-1}. LRMS (*m/z*): 442 $[M+H]^+$, 426, 384, 242, 159. Elem. Anal.: Calcd for $C_{22}H_{39}NO_6Si$: C 59.82, H 8.92, N 3.17; found: C 59.44, H 8.67, N 3.11.

Via epoxide opening: To a cooled (0°C) suspension of intermediate **4** (3 g, 9.2 mmol) in allyl glycolate (10.3 ml, 92 mmol) $Sn(OSO_2CF_3)_2$ (3.45 g, 8.28 mmol) was added and the reaction mixture was stirred for 20 minutes. Diethyl ether (50 ml) was then added followed by a saturated solution of sodium hydrogen carbonate (20 ml). The organic layer was filtered on Celite®, washed with brine (3x30 ml), dried over sodium sulphate and evaporated *in vacuo* to give an oily residue that was purified by flash chromatography (eluant diethyl ether/petroleum ether gradient from 85:15 to 9:1). The title compound **10** was obtained as a pale yellow solid (yield=40%).

(3*S*,4*R*) 3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl] -4-[(1*R*, 3*S*)-3-(allyloxycarbonylmethoxy) -2-oxocyclohexyl]azetidin-2-one 11

Oxalyl chloride (424 µl, 4.86 mmol) was added dropwise to a cooled solution (-78°C) of dimethyl sulphoxide (690 µl, 9.72 mmol) in anhydrous dichloromethane (10 ml). After 20 minutes at -78°C a solution of alcohol **10** (0.87 g, 1.97 mmol) in anhydrous dichloromethane (20 ml) was added maintaining the temperature below -60°C. The mixture was stirred for 30 minutes, then triethylamine

(1.37 ml, 9.82 mmol) was added. The reaction mixture was allowed to warm at -20°C and stirred for further 2 hours. A 10% solution of hydrochloric acid (10 ml) was then added followed by dichloromethane (20 ml). The organic layer was separated, diluted with a saturated solution of sodium bicarbonate and washed with brine (3x10 ml). The solvent was dried over sodium sulphate and evaporated *in vacuo* to give an oily residue which was purified by flash chromatography (eluant cyclohexane/ethyl acetate 8:2) to afford the title compound **11** as a white foam (yield=90%). ^{1}H-NMR ($CDCl_3$, 400MHz) : 5.95-5.86 (m, 1H); 5.77 (bs, 1H); 5.34-5.24 (m, 2H); 4.63-4.59 (m, 2H); 4.20-4.12 (m, 1H); 4.1 (d, 2H*J*= 13.2); 4.03 (t, 1H, *J*= 3.3); 3.72 (t, 1H, *J*= 3.3); 3.36-3.24(m, 1H); 2.96 (dd, 1H, *J*= 2.5, 4.6); 2.33-2.28 (m, 1H); 2.182.0 (m, 3H); 1.8-1.5 (m, 2H); 1.24 (d, 3H, *J*= 6.3); 0.87 (s, 9H); 0.08 (s, 9H); 0.07 (s, 6H). IR ($CDCl_3$)ν_{max}: 3418; 1755;1720 cm^{-1}. LRMS (*m/z*): 440 $[M+H]^+$, 424, 382, 240, 159.

4-*tert*-Butylbenzyl (4*S*, 8*S* , 9*R* , 10*S*) 4-(allyloxycarbonylmethoxy)-10-[(1*R*)-(1-*tert*-butyldimethylsilyloxy)ethyl]-11-oxo-1-azatricyclo[7.2.0.0.^{3,8}] undec-2-ene-2-carboxylate 12

4-*tert*-Butylbenzyl oxalylchloride (3.7 g, 14.5 mmol) followed by triethylamine (3.0 ml, 21.8 mmol) were added to a cooled solution (0°C) of intermediate **11** (1.6 g, 3.6 mmol) in anhydrous xylene (10 ml). The reaction mixture was treated after 30 minutes with a 5% solution of sodium hydrogen carbonate (10 ml); the organic layer separated and washed with brine (3x10 ml), dried over sodium sulphate and evaporated under reduced pressure to give an oily residue. The latter was dissolved in anhydrous xylene (10 ml), and triethyl phosphite (6 ml, 35 mmol) and a catalytic amount of hydroquinone were added. The mixture was heated at 120°C for 4 hours, then the solvent was evaporated under reduced pressure and the crude oil was purified by flash chromatography (eluant cyclohexane/ethyl acetate 9:1) to afford the title compound **12** as a white oil (yield=70%). ^{1}H-NMR ($CDCl_3$, 400MHz): 7.50-7.24 (m, 5H); 5.96-5.80 (m, 1H); 5.36-5.14 (m, 5H); 4.61-4.58 (m, 2H); 4.23-4.11 (m, 1H); 4.16 (dd, 1H, *J*= 11.4, 3.3); 4.01 (s, 2H); 3.34-3.20 (m, 1H); 3.20 (dd, 1H, *J*= 5.4, 6.0); 2.24-2.10 (m, 1H); 2.02-1.78 (m, 2H); 1.78-1.20 (m, 3H); 1.20 (d, 3H, *J*= 6.3); 0.87 (s, 9H); 0.06 (s, 3H); 0.05 (m, 6H). IR ($CDCl_3$)ν_{max}: 1771; 1720 cm^{-1}. LRMS (*m/z*): 626 $[M+H]^+$, 568, 310, 159.

4-*tert*-Butylbenzyl (4*S*, 8*S*, 9*R*, 10*S*) 4-((2'-pyridylthio)carbonylmethoxy)-10-[(1*R*)-(1-*tert*-butyldimethylsilyloxyethyl)]-11-oxo-1-azatricyclo[7.2.0.0.^{3,8}] undec-2-ene-2-carboxylate 13

Triphenylphosphine (16 mg, 0.06 mmol) was added to a solution of intermediate **12** (0.360 g, 0.63 mmol) in anhydrous tetrahydrofuran (8 ml). Sodium 2-ethylhexanoate (1.26 ml of a 0.5M solution in ethyl acetate) and tetrakis(triphenylphosphine)palladium (16 mg) in anhydrous tetrahydrofuran (1 ml) were then added and the resulting mixture was stirred for 2 hours. Diethyl ether (6 ml) and petroleum ether (4 ml) were added to precipitate a solid which was separated by centrifugation and washed with diethyl ether (10 ml). This procedure was repeated three times. The white sodium salt was suspended in dichloromethane and washed with a buffered solution (pH=3; 2x10 ml). The organic layer was separated, washed with brine (2x10 ml), dried over sodium sulphate and evaporated under reduced pressure to give the free carboxylic acid as a pale yellow oil. The crude carboxylic acid (0.49 g, 0.83 mmol) was dissolved in anhydrous acetonitrile (10 ml). Triphenylphosphine (0.213 g, 0.81 mmol) and 2,2'-dipyridyl disulphide (0.179 g, 0.81 mmol) were added portionwise to the solution over 1hour,

monitoring the disappearance of the starting material by TLC (cyclohexane/ethyl acetate 1:1). After stirring at room temperature for 2hours, the solvent was evaporated *in vacuo* and the residue was purified by flash chromatography (eluant cyclohexane/ethyl acetate from 8:2 to 6:4) to afford the title compound as a yellow oil (yield=50%). ^{1}H-NMR ($CDCl_3$, 400MHz): 7.77-7.57 (m, 4H); 7.40-7.30 (m, 4H); 5.28-5.26 (m, 1H); 5.23 (d, 2H, *J*= 6.6); 5.19 (d, 1H, *J*= 9.3); 5.13 (t, 2H, *J*= 2.1); 4.25-4.08 (m, 4H); 3.38-3.28 (m, 1H); 3.23 (dd, 1H, *J*= 5.7, 3.3); 2.25-2.20 (m, 1H); 2.02-1.98 (m, 1H); 1.86-1.82 (m, 1H); 1.76-1.70 (m, 1H); 1.55-1.50 (m, 1H); 1.41-1.35 (m, 1H); 1.29 (s, 9H); 1.21 (d, 3H, *J*= 6.3); 0.87 (s, 9H); 0.07 (s, 3H); 0.06 (s, 3H). IR ($CDCl_3$)ν_{max}: 1780; 1713; 1570 cm^{-1}. LRMS (*m/z*): 679 $[M+H]^+$, 510, 310, 159.

4-*tert*-Butylbenzyl (4*S*, 8*S*, 9*R*, 10*S*) 4-(dimethylaminocarbonylmethoxy)-10-[(1*R*)-(1-*tert*-butyldimethylsilyloxyethyl)] -11-oxo-1-azatricyclo[7.2.0.0.^{3,8}] undec-2-ene-2-carboxylate 14

N- Trimethylsilyldimethylamine (70 µl, 0.44 mmol) was added dropwise to a stirred solution of thioester **13** (0.2 g, 0.29 mmol) in anhydrous acetonitrile (10 ml) and the reaction mixture was stirred at room temperature for 10 minutes. The solvent was removed *in vacuo* and the residue was diluted with ethyl acetate (20 ml) and washed with a 0.1N solution of hydrochloric acid (10ml). The organic phase was separated and washed with brine (2x15 ml), dried over sodium sulphate and evaporated *in vacuo* to give an oily residue which was purified by flash chromatography (eluant cyclohexane/ethyl acetate 3:7) to afford the title compound **14** as a white foam (yield=78%). ^{1}H-NMR ($CDCl_3$, 400MHz): 7.40-7.30 (m, 4H); 5.27 (d, 1H, *J*= 9.3); 5.19 (d, 1H, *J*= 9.3); 5.13 (t, 2H, *J*= 2.1); 4.25-4.15 (dt, 1H, *J*= 4.5); 4.14 (dd, 1H, *J*= 2.7, 8.1); 4.01 (s, 2H); 3.31-3.24 (m, 1H); 3.21 (dd, 1H, *J*= 2.4, 4.5); 2.91 (s, 3H); 2.86 (s, 3H); 2.22-2.10 (m, 1H); 1.94- 1.80 (m, 2H); 1.67-1.60 (m, 1H); 1.60-1.24 (m, 2H); 1.21 (d, 3H*J*= 6.3); 0.87 (s, 9H); 0.07 (s, 6H). IR ($CDCl_3$)ν_{max}: 1774; 1720-1713; 1659 cm^{-1}. LRMS (*m/z*): 613 $[M+H]^+$, 510, 334, 147.

4-*tert*-Butylbenzyl (4*S*, 8*S*, 9*R*, 10*S*) 4-(dimethylaminocarbonylmethoxy)-10-[(1*R*) 1-hydroxyethyl)] -11-oxo-1-azatricyclo[7.2.0.0.^{3,8}] undec-2-ene-2-carboxylate 15

Tetrabutylammonium bromide (0.379 g, 1.17 mmol) was added to a solution of **14** (0.12 g, 0.196 mmol) in anhydrous tetrahydrofuran (10 ml) followed by glacial acetic acid (78 µl, 1.37 mmol) and caesium fluoride (0.179 g, 1.17 mmol). The reaction mixture was stirred at 40°C for 24 hours, then it was diluted with ethyl acetate (15 ml) and washed with a 5% solution of sodium hydrogen carbonate (2x5 ml), and saturated brine (2x5 ml), dried over sodium sulphate and evaporated *in vacuo* to give an oily residue that was purified by flash chromatography (eluant cyclohexane/ethyl acetate gradient from 8:2 to 65:35). The title compound **15** was isolated as a colourless oil (yield=44%). ^{1}H-NMR ($CDCl_3$, 400MHz): 7.39-7.37 (m, 4H); 5.33 (d, 1H, *J*= 9.3); 5.18 (d, 1H, *J*= 9.3); 5.13 (t, 1H, *J*= 2.1); 4.25-4.21 (m, 1H); 4.19 (dd, 1H, *J*= 2.5, 7.9); 4.00 (s, 2H); 3.4-3.34 (m, 1H); 3.26 (dd, 1H, *J*= 2.5, 4.5); 2.91 (s, 3H); 2.84 (s, 3H); 2.18-2.15 (m, 1H); 2.00-1.82 (m, 2H); 1.78 (d, 1H, *J*= 3.6); 1.68-1.62 (m, 1H); 1.52-1.20 (m, 2H); 1.31 (d, 3H, *J*= 6.3); 1.30 (s, 9H). IR ($CDCl_3$)ν_{max}: 1776;1720; 1659 cm^{-1}. LRMS (*m/z*): 499 $[M+H]^+$, 396, 352, 204.

Sodium (4*S*, 8*S*, 9*R*, 10*S*) 4-(dimethylaminocarbonylmethoxy)-10-[(1*R*) 1-hydroxyethyl)] -11-oxo-1-azatricyclo[7.2.0.0.^{3,8}] undec-2-ene-2-carboxylate 3a

Triethylamine (18 µl, 0.13 mmol) and palladium (10% on carbon) (14 mg) were added to a solution of ester **15** (0.055 g, 0.11 mmol) in isopropanol (6 ml). The mixture was stirred under hydrogen at atmospheric pressure for 30 minutes. The catalyst was removed by filtration on Celite® and washed with acetone (2x5 ml). The solvent was evaporated *in vacuo* and the oily residue was diluted with diethyl ether (5 ml) and treated with a solution of sodium 2-ethylhexanoate (115 µl of a 0.5M solution in ethyl acetate). The precipitated solid was separated by centrifugation and washed with diethyl ether (4ml). This procedure was repeated three times. The sodium salt was purified by preparative HPLC to give 0.02 g of the title compound. ^{1}H-NMR (D_2O, 400MHz): 4.90-4.88 (m, 1H); 4.08-3.99 (m, 2H); 4.01 (s, 2H); 3.29-3.27 (m, 1H); 3.08-3.0 (m, 1H); 2.81 (s, 3H); 2.77 (s, 3H); 1.92 (m, 1H); 1.9-1.30 (m, 4H); 1.2 (m, 1H); 1.11 (d, 3H, *J*= 6). IR (nujol)ν_{max}: 1761; 1636; 1583 cm^{-1}. LRMS (*m/z*): 375 [MH$^+$]; 353 [MH$^+$-Na]. HPLC R_t= 16 minutes (Column: Lichrosphere C18 S5 25x0.4cm; λ= 225 nm; T=23°C; eluent MeCN/10µM phosphate buffer pH=7.4 10/90).

Sodium (2*S*, 3*R*, 4*S*, 8*S*, 9*R*, 10*S*) 4-(dimethylaminocarbonylmethoxy)-10-[(1*R*) 1-hydroxyethyl)] -11-oxo-1-azatricyclo[7.2.0.0.^{3,8}] undecane-2-carboxylate 16 ^{1}H-NMR (D_2O,400MHz): 4.17-4.16 (m, 2H); 4.1-4.09 (m, 1H); 3.82 (d, 1H, *J*= 10.2); 3.75 (bs, 1H); 3.63 (dd, 1H, *J*= 6, 1.8); 3.08-3.06 (m, 1H); 2.94 (s, 1H); 2.87 (s, 3H); 2.80 (s, 3H); 2.20-1.90 (m, 1H); 1.80-1.0 (m, 5H); 1.25 (m, 1H); 1.11 (d, 3H, *J*= 6). IR (nujol)ν_{max}: 1761;1636; 1583 cm^{-1}. LRMS (*m/z*): 377 [MH$^+$] ; 355 [MH$^+$-Na].

(1*S*, 6*S*, 7*R*, 8*R*, 12*S*) 2-Oxa-4-aza-3-sila-6-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-3,3-di-*tert*-butyl-12-(carboxymethoxy)tricyclo [6.4.0.0^{4,7}]dodecane 17

Triphenylphosphine (58 mg, 0.22 mmol) was added to a solution of **8** (1.28 g 2.2 mmol) in anhydrous tetrahydrofuran (25 ml). A solution of sodium 2-ethylhexanoate (4.4 ml of a 0.5M solution in ethyl acetate) and tetrakis(triphenylphosphine)palladium (64 mg) in anhydrous tetrahydrofuran (5 ml) were added and the resulting mixture was stirred for 12 hours. The solvent was evaporated *in vacuo* and the residue was dissolved in ethyl acetate (30 ml) and washed with a buffer solution (pH=3; 3x15 ml). The organic layer was separated, washed with brine (2x20 ml), dried over sodium sulphate and evaporated in vacuo to give the carboxylic acid **17**. The compound was no further purified because of its low stability and used, as crude, for the next amidation step.

General procedure for the synthesis of amides 18a-c

Triphenylphosphine and 2,2'-dipyridyl disulphide (0.993g, 4.49 mmol) were added portionwise over one hour to a stirred solution of intermediate **17** (1 g, 2.2 mmol) in anhydrous dichloromethane (20 ml) were added (1.18g, 4.49 mmol), monitoring the disappearance of the starting material by TLC (cyclohexane/ethyl acetate 1:1). The *N*-trimethylsilylamine (2.64 mmol) was added and the reaction mixture was stirred at room temperature for 1hour; the solvent was evaporated *in vacuo* and the oily residue was purified by flash chromatography.

(1*S*, 6*S*, 7*R*, 8*R*, 12*S*) 2-Oxa-4-aza-3-sila-6-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-3,3-di-*tert*-butyl-12-(dimethylaminocarbonylmethoxy)tricyclo [6.4.0.0^{4,7}]dodecane 18a

Prepared following the general procedure; purified by flash chromatography (eluant cyclohexane/ethyl acetate gradient from 8:2 to 7:3) and obtained as a yellow solid (yield=76%). mp.: 101-103°C ^{1}H-NMR ($CDCl_3$, 300MHz): 4.35-4.33 (m, 1H); 4.24-4.22 (m, 1H); 4.23 (d, 1H, *J*= 13.3); 4.12 (d, 1H, *J*= 13.3);

3.97 (t, 1H, *J*= 3.3); 3.66-3.64 (m, 1H); 3.23 (d, 1H, *J*= 3.6); 3.04 (s, 3H); 2.96 (s, 3H); 2.06-1.8 (m, 1H); 1.84-1.24 (m, 6H); 1.14 (d, 3H, *J*= 5.4); 1.12 (s, 9H); 1.08 (s, 9H); 0.87 (s, 9H); 0.15 (s, 3H); 0.08 (s, 3H). IR (nujol)ν_{max}: 1745; 1653 cm^{-1}. LRMS (*m/z*): 569 [MH$^+$], 511, 236. Elem. Anal.: Calcd for $C_{29}H_{56}N_2O_5Si_2$: C 61.21, H 9.94, N 4.92; found: C 61.05, H 9.87, N 4.68.

(1*S*, 6*S*, 7*R*, 8*R*, 12*S*) 2-Oxa-4-aza-3-sila-6-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-3,3-di-*tert*-butyl-12-(4'-morpholinylcarbonylmethoxy)tricyclo [6.4.0.0^{4,7}]dodecane 18b

Prepared following the general procedure; purified by flash chromatography (eluant cyclohexane/ethyl acetate gradient from 8:2 to 7:3). Yellow oil (yield=40%). ^{1}H-NMR ($CDCl_3$, 400MHz):4.32 (t, 1H, *J*= 2.8); 4.24-4.21 (m, 1H); 4.22 (d, 1H, *J*= 13.3); 4.14 (d, 1H, *J*= 13.3); 3.95 (t, 1H, *J*= 3.3); 3.75-3.5 (m, 9H); 3.22 (dd, 1H, *J*= 3.2, 4); 1.99-1. 95 (m, 1H); 1.8-1.5 (m, 5H); 1.44-1.41 (m, 1H); 1.15 (d, 3H, *J*= 6.4); 1.12 (s, 9H); 1.08 (s, 9H); 0.88 (s, 9H); 0.08 (s, 3H); 0.07 (s, 3H). IR ($CDCl_3$)ν_{max}: 1776; 1649 cm^{-1}. LRMS (*m/z*): 612 [M+ 2H]$^+$, 553, 466.

(1*S*, 6*S*, 7*R*, 8*R*, 12*S*) 2-Oxa-4-aza-3-sila-6-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-3,3-di-*tert*-butyl-12-(1'-phenylsulphonylpiperazin-4'-ylcarbonylmethoxy)tricyclo [6.4.0.0^{4,7}]dodecane 18c

Prepared following the general procedure; purified by flash chromatography (eluant cyclohexane/ethyl acetate gradient from 8:2 to 7:3). White solid (yield=60%). mp.:121-124°C ^{1}H-NMR ($CDCl_3$, 300MHz): 7.76-7.72 (m, 2H); 7.66-7.52 (m, 3H); 4.26-4.18 (m, 2H); 4.10 (dd, 2H, *J*= 13.2, 17.4); 3.93 (t, 1H, *J*= 3.3); 3.75-3.62 (m, 4H); 3.57-3.56 (m, 1H); 3.21 (t, 1H, *J*= 3.3); 3.1-3.0 (m, 4H); 1.92-1.88 (m, 1H); 1.8-1.4 (m, 6H); 1.14 (d, 3H, *J*= 6.3); 1.11 (s, 9H); 1.06 (s, 9H); 0.88 (s, 9H); 0.09 (s, 3H); 0.07 (s, 3H). IR (nujol)ν_{max}: 1744; 1659 cm^{-1}. LRMS (*m/z*): 750 [M+H]$^+$; 692. Elem. Anal.: Calcd for $C_{36}H_{63}N_3O_7Si_2S$: C 58.56, H 8.62, N 5.69; found: C 58.23, H 8.54, N 5.70.

(3*S*, 4*R*) 3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-4-[(1*R*, 2*S*, 3*S*)-3-(dimethylaminocarbonylmethoxy)-2-hydroxycyclohexyl]azetidin-2-one 19a

A solution of **18a** (0.99 g, 1.74 mmol) in anhydrous tetrahydrofuran (58 ml) was treated with a 1.1M solution of tetrabutylammonium fluoride (3.42 ml, 3.76 mmol) and glacial acetic acid (215 µl). The reaction mixture was stirred for 1 hour, then it was diluted with a 5% solution of sodium hydrogen carbonate and extracted with ethyl acetate (2x25 ml). The collected organic layers were washed with brine (3x20 ml), dried over sodium sulphate and evaporated under reduced pressure. The crude residue was purified by flash chromatography (ethyl acetate) to afford the title compound as a yellow oil (yield=75%). ^{1}H-NMR ($CDCl_3$, 300MHz): 5.81 (bs, 1H); 4.26 (d, 1H, *J*= 14.4); 4.24-4.17 (m, 1H); 4.10 (d, 1H, *J*= 14.4); 3.94-3.86 (m, 1H); 3.70 (dd, 1H, *J*= 2.1, 7.5); 3.48-3.43 (m, 1H); 3.04-3.03 (m, 1H); 2.99 (s, 3H); 2.95 (s, 3H); 2.89 (bs, 1H); 1.971.94 (m, 1H); 1.74-1.73 (m, 1H); 1.7-1.5 (m, 5H); 1.26 (d, 3H, *J*= 6.3); 0.88 (s, 9H); 0.08 (s, 3H); 0.04 (s, 3H). IR (nujol)ν_{max}: 1761;1734;3500 cm^{-1}. LRMS (*m/z*): 429 [M+H]$^+$, 159. HRMS: Calcd for $C_{21}H_{41}N_2O_5Si$:429.278476; found: 429.275240.

(3*S*, 4*R*) 3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-4-[(1*R*, 3*S*)-3-(dimethylaminocarbonylmethoxy)-2-oxocyclohexyl]azetidin-2-one 20a

Oxalyl chloride (298 µl, 3.41 mmol) was added dropwise to a cooled solution (-78°C) of dimethyl sulphoxide (447 µl, 6.29 mmol) in anhydrous dichloromethane (10 ml) and the mixture was stirred for

20 minutes at -78°C. A solution of **19a** (0.550 g, 1.28 mmol) in anhydrous dichloromethane (15 ml) was added maintaining the temperature below -60°C. The mixture was stirred for 30 minutes, then triethylamine (895µl, 6.42 mmol) was added. The reaction mixture was allowed to warm at -20°C and stirred for further 2 hours. The reaction was stopped by addition of a 10% solution of hydrochloric acid (10 ml) followed by dichloromethane (10 ml). The organic layer was separated, washed with a saturated solution of sodium bicarbonate and then with brine (3x15 ml). The solvent was dried over sodium sulphate and evaporated under reduced pressure to give an oily residue which was purified by flash chromatography (eluant ethyl acetate/methanol 98:2) to afford the title compound as a white foam (yield=40%). ^{1}H-NMR ($CDCl_3$, 200MHz): 5.8 (s, 1H); 4.25-4.10 (m, 1H); 4.28-4.05 (m, 2H); 4.03 (dd, 1H, *J*= 1.9, 3.8); 3.75 (t, 1H, *J*= 2.9); 3.35-3.25 (m, 1H); 3.02-2.95 (m, 1H); 2.93 (s, 3H); 2.91 (s, 3H); 2.35-2.25 (m, 1H); 2.15-2.0 (m, 1H); 1.75-1.45 (m, 4H); 1.22 (d, 3H, *J*= 6.2); 0.87 (s, 9H); 0.07 (s, 3H); 0.06 (s, 3H).

Allyl (4*S* , 8*S* , 9*R* , 10*S*) 4-(dimethylaminocarbonylmethoxy)-10-[(1*R*) (1-*tert*-butyldimethylsilyloxy)ethyl] -11-oxo-1-azatricyclo[7.2.0.0.^{3,8}] undec-2-ene-2-carboxylate 21a

A cooled solution (0°C) of **20a** (0.220 g, 0.52 mmol) in anhydrous dichloromethane (10 ml) was treated with allyl oxalylchloride (281 µl, 2.08 mmol) followed by triethylamine (435 µl, 3.12 mmol). After 30 minutes the reaction mixture was diluted with a 10% solution of hydrochloric acid (10 ml) and dichloromethane (10 ml) was added. The organic layer was separated, washed with a 5% solution of sodium hydrogen carbonate (2x5 ml) and brine (3x10 ml), dried over sodium sulphate and evaporated under reduced pressure to give an oily residue which was dissolved in anhydrous xylene (10 ml). Triethyl phosphite (446 µl, 2.6 mmol) and a catalytic amount of hydroquinone were added and the mixture was heated at 140°C for 4 hours. The solvent was evaporated and the crude oil was purified by flash chromatography (eluant cyclohexane/ethyl acetate from 6:4 to 4:6) to afford the title compound as a yellow oil (yield=44%). ^{1}H-NMR ($CDCl_3$, 200MHz): 6.1-5.85 (m, 1H); 5.45-5.20 (m, 2H); 5.25 (t, 1H, *J*= 3.3); 4.7-4.65 (m, 2H); 4.25-4.0-4.2 (m, 5H); 3.2 (dd, 1H, *J*= 3.3, 6); 2.96 (s, 3H); 2.94 (s, 3H); 2.25-2.15 (m, 1H); 1.9-1.6 (m, 5H); 1.21 (d, 3H, *J*= 6.2); 0.88 (s, 9H); 0.07 (s, 6H).

Allyl (4*S*, 8*S*, 9*R*, 10*S*) 4-(dimethylaminocarbonylmethoxy)-10-[(1*R*) 1-hydroxyethyl] -11-oxo-1-azatricyclo[7.2.0.0.^{3,8}] undec-2-ene-2-carboxylate 22a

A solution of **21a** (0.105 g, 0.21 mmol) in anhydrous THF (10 ml) was treated with glacial acetic acid (84 µl, 1.45 mmol), caesium fluoride (0.189 g, 1.24 mmol) and tetrabutylammonium bromide (0.401 g, 1.24 mmol). The reaction mixture was heated at 45°C for 20 hours, then a 5% solution of sodium hydrogen carbonate (20 ml) was added followed by ethyl acetate (25 ml); the organic layer was separated, washed with saturated brine (2x15 ml), dried over sodium sulphate and evaporated under reduced pressure to give an oily residue that was purified by flash chromatography (ethyl acetate/MeOH 95:5) to afford the title compound as a pale yellow oil (0.045g, yield=55%). ^{1}H-NMR ($CDCl_3$, 400 MHz): 6.0-5.93 (m, 1H); 5.46-5.24 (m, 2H); 5.14 (t, 1H, *J*= 2.8); 4.85-4.64 (m, 2H); 4.25-4.23 (m, 1H); 4.20 (dd, 1H, *J*= 3.2, 10.4); 4.06 (dd, 2H, *J*= 13.6, 16.8); 3.39-3.31 (m, 1H); 3.26 (dd, 1H, *J*= 3.2, 6.4): 2.95 (s, 3H); 2.94 (s, 3H); 2.21-2.17 (m, 1H); 2.00-1.84 (m, 2H); 1.80-1.42 (m, 3H); 1.42-1.28 (m, 1H); 1.31 (d, 3H, *J*= 6.4). IR ($CDCl_3$)ν_{max}: 1776; 1720; 1659-1649 cm^{-1}. LRMS (*m/z*): 393 $[M+H]^+$. HRMS: Calcd for $C_{20}H_{29}N_2O_6$: 393.2025562; found: 393.20623.

Sodium (4*S*, 8*S*, 9*R*, 10*S*) 4-(dimethylaminocarbonylmethoxy)-10-[(1*R*) 1-hydroxyethyl] -11-oxo-1-azatricyclo[7.2.0.0.^{3,8}] undec-2-ene-2-carboxylate 3a

A solution of **22a** (0.013 g, 0.033 mmol) in anhydrous tetrahydrofuran (1 ml) was treated with triphenylphosphine (0.87 mg, 0.033 mmol) followed by a solution of sodium 2-ethylhexanoate (66 µl of a 0.5M solution in ethyl acetate) and tetrakis(triphenylphosphine)palladium (0.95 mg) in anhydrous tetrahydrofuran (0.5 ml). The resulting mixture was stirred for 1hour; then diethyl ether (1 ml) and petroleum ether (1 ml) were added to precipitate a solid which was separated by centrifugation and washed with diethyl ether (2 ml). This procedure was repeated for three times to give the title compound as white solid (10mg, 81%).

(3*S*, 4*R*) 3-[(1*R*) - 1 - (*tert*-Butyldimethylsilyloxy)ethyl]-4-[(1*R*, 2*S*, 3*S*)-3-(4'morpholinylcarbonylmethoxy) -2- hydroxycyclohexyl]azetidin-2-one 19b

To a solution of **18b** (1.2 g, 1.96 mmol) in anhydrous tetrahydrofuran (65 ml) a 1.1M solution of tetrabutylammonium fluoride (3.94 ml, 4.33 mmol) and glacial acetic acid (250 µl, 4.37 mmol) were added. The reaction mixture was stirred for 1 hour, then diluted with a 5% solution of sodium hydrogen carbonate and extracted with ethyl acetate (2x25 ml). The collected organic layers were washed with brine (3x20 ml), dried over sodium sulphate and evaporated under reduced pressure. The crude residue was purified by flash chromatography (eluant ethyl acetate/MeOH 9:1) to afford the title compound as a yellow oil (0.810 g, 88%). ^{1}H-NMR ($CDCl_3$, 300MHz): 5.90 (s, 1H); 4.21-4.18 (m, 1H); 4.24 (d, 1H, *J*= 13.9); 4.12 (d, 1H, *J*= 13.9); 3.91-3.89 (m, 1H); 3.7-3.59 (m, 1H); 3.72-3.64 (m, 4H);3.6-3.45 (m, 4H); 2.98 (dd, 1H, *J*= 1.2, 5.4); 2.57 (bs, 1H); 1.92-1.85 (m, 1H); 1.8-1.6 (m, 2H); 1.6-1.4 (m, 4H); 1.26 (d, 3H, *J*= 6); 0.88 (s, 9H); 0.08 (s, 6H). IR (nujol)ν_{max}: 3500-3300; 1776; 1740 cm^{-1}. LRMS (*m/z*): 471 [M+H]$^+$, 413, 159. Elem. Anal.: Calcd for $C_{23}H_{42}N_2O_6Si$ C 58.68; H 9.01; N 5.95; found C 58.75; H 9.11; N 5.62.

(3*S*, 4*R*) 3-[(1*R*) - 1 - (*tert*-Butyldimethylsilyloxy)ethyl] -4-[(1*R*, 3*S*)-3-(4'-morpholinylcarbonylmethoxy) -2-oxocyclohexyl]azetidin-2-one 20b

Oxalyl chloride (366ml, 4.19 mmol) was added dropwise to a cooled solution (-78°C) of dimethyl sulphoxide (592 µl, 8.34 mmol) in anhydrous dichloromethane (15 ml). Mixture was stirred at -78°C for 20 minutes and a solution of **19b** (0.800 g, 1.7 mmol) in anhydrous dichloromethane (15 ml) was added maintaining the temperature below -60°C. The mixture was stirred for 30 minutes, then triethylamine (1.18 ml, 8.46 mmol) was added and the reaction mixture was allowed to warm at -20°C and stirred for further 2 hours. A 10% solution of hydrochloric acid (15 ml) was then added followed by dichloromethane (10 ml). The organic layer was separated, diluted with a saturated solution of sodium bicarbonate and washed with brine (3x15 ml). The solvent was dried over sodium sulphate and evaporated under reduced pressure to give an oily residue which was purified by flash chromatography (eluant ethyl acetate/cyclohexane 9:1) to afford the title compound as a white foam (yield=40%). ^{1}H-NMR ($CDCl_3$, 400 MHz): 5.79 (bs, 1H); 4.22-4.1 (m, 1H); 4.04-4.02 (m, 1H); 3.74 (t, 1H, *J*= 3.6); 3.68-3.66 (m, 6H); 3.58-3.56 (m, 2H); 3.40-3.38 (m, 1H); 3.24-3.20 (m, 1H); 2.99-2.97 (m, 1H); 2.32-2.24 (m, 1H); 2.16-1.96 (m, 2H); 1.84-1.7 (m, 2H); 1.6-1.58 (m, 1H); 1.23 (d, 3H, *J*= 6.4); 0.88 (s, 9H); 0.08 (s, 3H); 0.07 (s, 3H). IR (nujol)ν_{max}: 1753; 1696 cm^{-1}. LRMS (*m/z*): 469 [M+H]$^+$, 411, 159.

Allyl (4*S*, 8*S* , 9*R* , 10*S*) 4-(4'-morpholinylcarbonylmethoxy)-10-[(1*R*) (1-*tert*-butyldimethylsilyloxy)ethyl] -11-oxo-1-azatricyclo[7.2.0.0.3,8] undec-2-ene-2-carboxylate 21b

Allyl oxalylchloride (300 µl, 2.22 mmol) was added to a cooled solution (0°C) of **20b** (0.260 g, 0.55 mmol) in anhydrous dichloromethane (10 ml), followed by triethylamine (440 µl, 3.16 mmol). After 30 minutes the reaction mixture was diluted with a 10% solution of hydrochloric acid (10 ml) and dichloromethane (10 ml). The organic layer was separated, washed with a 5% solution of sodium hydrogen carbonate (2x5 ml) and saturated brine (3x10 ml), dried over sodium sulphate and evaporated under reduced pressure to give an oily residue that was dissolved in anhydrous xylene (10ml). Triethyl phosphite (476 µl, 2.77 mmol) and a catalytic amount of hydroquinone were added and the mixture was heated at 140°C for 4 hours, then the solvent was evaporated and the crude oil was purified by flash chromatography (eluant cyclohexane/ethyl acetate from 6:4 to 4:6) to afford the title compound as a yellow oil (yield=44%). ^{1}H-NMR ($CDCl_3$, 400 MHz): 5.99-5.90 (m, 1H); 5.46-5.40 (m, 1H); 5.27-2.24 (m, 1H); 5.15-5.13 (m, 1H); 4.82-4.66 (m, 2H); 4.24-4.10 (m, 2H); 4.07 (s, 2H); 3.74-3.44 (m, 8H); 3.27-3.23 (m, 1H); 3.21 (dd, 1H, *J*= 3.2, 6); 2.16-2.12 (m, 1H); 1.90-1.82 (m, 2H); 1.69-1.64 (m, 1H); 1.50-1.46 (m, 1H); 1.4-1.3 (m, 1H); 1.22 (d, 3H, *J*= 6); 0.88 (s, 9H); 0.08 (s, 6H). IR (nujol)ν_{max}: 1769; 1709; 1645 cm^{-1}. LRMS (*m/z*): 549 $[M+H]^+$, 491, 419. HRMS: Calcd for $C_{28}H_{45}N_2O_7Si$: 549.29961; found: 549.29932.

Allyl (4*S*, 8*S*, 9*R*, 10*S*) 4-(4'-morpholinylcarbonylmethoxy)-10-[(1*R*) (1-hydroxyethyl] -11-oxo-1-azatricyclo[7.2.0.0.3,8] undec-2-ene-2-carboxylate 22b

A solution of **21b** (0.06 g, 0.11 mmol) in anhydrous THF (10ml) was treated sequentially with glacial acetic acid (44 µl, 0.77 mmol), caesium fluoride (0.100 g, 0.65 mmol) and tetrabutylammonium bromide (0.212 g, 0.65 mmol). The reaction mixture was heated at 45°C for 20 hours, then a 5% solution of sodium hydrogen carbonate (20 ml) was added followed by ethyl acetate (25 ml); the organic layer was separated, washed with brine (2x15 ml), dried over sodium sulphate and evaporated under reduced pressure to give an oily residue that was purified by flash chromatography (ethyl acetate/MeOH 95:5) to afford the title compound as a pale yellow oil (yield=55%). ^{1}H-NMR ($CDCl_3$, 400MHz): 6.1-5.91 (m, 1H); 5.46-5.40 (m, 1H); 5.29-5.25 (m, 1H); 5.15 (t, 1H, *J*= 2.8); 4.84-4.64 (m, 2H); 4.27-4.19 (m, 1H); 4.20 (dd, 1H, *J*= 3.2, 10.4); 4.07 (s, 2H); 3.68-3.64 (m, 4H); 3.61-3.59 (m, 2H); 3.45-3.42 (m, 2H); 3.34-3.26 (m, 1H); 3.26 (dd, 1H, *J*= 3.2, 6); 2.17-2.13 (m, 1H); 1.96-1.82 (m, 2H); 1.74 (d, 1H, *J*= 4.4); 1.72-1.68 (m, 1H); 1.54-1.44 (m, 2H); 1.38 (dd, 1H, *J*= 6.4); 1.32 (d, 3H). IR (nujol)ν_{max}: 1750-1700, 1640 cm^{-1}.

Sodium (4*S*, 8*S* , 9*R* , 10*S*) 4-(4'-morpholinylcarbonylmethoxy)-10-[(1*R*) (1-*tert*-butyldimethylsilyloxy) ethyl] -11-oxo-1-azatricyclo[7.2.0.0.3,8] undec-2-ene-2-carboxylate 3b

A solution of **22b** (0.015 g, 0.034 mmol) in anhydrous tetrahydrofuran (1 ml) was treated with triphenylphosphine (0.91 mg, 0.003 mmol), sodium 2-ethylhexanoate (69 µl of a 0.5M solution in ethyl acetate) and tetrakis(triphenylphosphine)palladium (1 mg). The resulting mixture was stirred for 1hour; then diethyl ether (1 ml) and petroleum ether (1 ml) were added to precipitate a solid which was separated by centrifugation and washed with diethyl ether (2 ml). This procedure was repeated three times to give the title compound as a white solid (10 mg, 78%). ^{1}H-NMR (D_2O, 400MHz):4.9 (t, 1H, *J*=

3.2); 4.07-3.98 (m, 2H); 4.03 (dd, 2H, *J*= 16.8, 17.4); 3.62-3.52 (m, 4H); 3.41-3.38 (m, 2H); 3.31-3.28 (m, 2H); 3.27 (dd, 1H, *J*= 3.2, 6); 3.07-3.0 (m, 1H); 1.93-1.88 (m, 1H); 1.72-1.68 (m, 1H); 1.62-1.5 (m, 2H); 1.46-1.40 (m, 1H); 1.21-1.17 (m, 1H); 1.09 (d, 3H, *J*= 6.4). IR (nujol)ν_{max} : 1750-1700 cm^{-1}. MS (*m/z*) : 417, 439, 179. HPLC R_t = 7.6 minutes (Column Lichrosphere C18 S5 25x0.4cm; λ= 225 nm; T=23°C; eluent MeCN/10μM phosphate buffer pH=7.4 10/90).

(3*S*, 4 *R*) 3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-4-[(1*R* , 2*S* , 3*S*)-3-(1'-phenylsulphonylpiperazin-4'-ylcarbonylmethoxy) -2- hydroxycyclohexyl]azetidin-2-one 19c

A solution of **18c** (1.08 g, 1.47 mmol) in anhydrous tetrahydrofuran (50 ml) a 1.1M solution of tetrabutylammonium fluoride (2.95 ml, 3.23 mmol) and glacial acetic acid (185 μl, 3.23 mmol). The reaction mixture was stirred for 1 hour, then diluted with a 5% solution of sodium hydrogen carbonate and extracted with ethyl acetate (2x20 ml). The collected organic layers were washed with brine (3x20 ml), dried over sodium sulphate and evaporated under reduced pressure. The crude residue was purified by flash chromatography (eluant ethyl acetate/cyclohexane 9:1) to afford the title compound as yellow oil (0.750 g, 83%). ^{1}H-NMR ($CDCl_3$, 400MHz): 7.76-7.34 (m, 2H); 7.66-7.62 (m, 1H); 7.59-7.54 (m, 2H); 5.82 (bs, 1H); 4.19-4.09 (m, 1H); 4.15 (d, 1H, *J*= 13.8); 4.05 (d, 1H, *J*= 13.8); 3.86-3.83 (m, 1H); 3.78-3.6 (m, 4H); 3.61 (dd, 1H, *J*= 2, 7.2); 3.44-3.41 (m, 1H); 3.1-2.94 (m, 4H); 2.93 (dd, 1H, *J*= 2, 5.6); 2.37 (bs, 1H); 1.79-1.77 (m, 1H); 1.70-1.66 (m, 1H); 1.49-1.34 (m, 4H); 1.25 (d, 3H, *J*= 7.2); 0.87 (s, 9H); 0.08 (s, 6H). IR (nujol)ν_{max}: 1753, 1655, 1358-1171 cm^{-1}. LRMS (*m/z*): 610 $[M+H]^+$, 552, 159. HRMS: Calcd for $C_{29}H_{48}N_3O_7Si$: 610.29823; found: 610.29776.

(3*S*,4*R*) 3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl] -4-[(1*R*, 3*S*)-3-(1'phenylsulphonylpiperazin-4'-ylcarbonylmethoxy) -2-oxocyclohexyl]azetidin-2-one 20c

Oxalyl chloride (260 μl, 2.98 mmol) was added dropwise to a cooled solution (-78°C) of dimethyl sulphoxide (427 μl, 6.0 mmol) in anhydrous dichloromethane (15 ml). Mixture was stirred at -78°C for 20 minutes and a solution of **19c** (0.720 g, 1.2 mmol) in anhydrous dichloromethane (15 ml) was added maintaining the temperature below -60°C. The mixture was stirred for 30 minutes, then triethylamine (0.84 ml, 6.0 mmol) was added and the reaction mixture was allowed to warm at -20°C and stirred for further 2 hours. A 10% solution of hydrochloric acid (15 ml) was then added followed by dichloromethane (10 ml). The organic layer was separated, diluted with a saturated solution of sodium bicarbonate and washed with brine (3x15 ml). The solvent was dried over sodium sulphate and evaporated under reduced pressure to give an oily residue which was purified by flash chromatography (eluant ethyl acetate/cyclohexane 9:1) to afford the title compound as a white foam (0.35 g, 50%). ^{1}H-NMR ($CDCl_3$, 300MHz): 7.76-7.28 (m, 2H); 7.68-7.60 (m, 1H); 7.60-7.56 (m, 2H); 5.72 (bs, 1H); 4.21-4.14 (m, 1H); 4.09 (dd, 1H, *J*= 19.8, 14.2); 3.98 (dd, 1H, *J*= 2.1, 4.5); 3.66-3.60 (m, 3H); 3.50-3.44 (m, 2H); 3.17-3.13 (m, 1H); 3.04-2.98 (m, 4H); 2.93 (dd, 1H,. *J*= 2.1, 4.5); 2.2-2.18 (m, 1H); 2.1-1.9 (m, 2H); 1.8-1.34 (m, 3H); 1.19 (d, 3H, *J*= 6.6); 0.87 (s, 9H); 0.08 (s, 3H); 0.06 (s, 3H). IR (nujol)ν_{max}: 1757, 1717, 1653, 1358-1171 cm^{-1}. LRMS (*m/z*): 680 $[M+H]^+$, 630, 550, 159.

Allyl (4*S*, 8*S*, 9*R*, 10*S*) 4-(1'phenylsulphonylpiperazin-4'-ylcarbonylmethoxy)-10-[(1*R*) (1-*tert*-butyldimethylsilyloxy)ethyl] -11-oxo-1-azatricyclo[7.2.0.0.^{3,8}] undec-2-ene-2-carboxylate 21c

Allyl oxalylchloride (286 µl, 2.12 mmol) was added to a cooled solution (0°C) of **20c** (0.320 g, 0.53 mmol) in anhydrous dichloromethane (10 ml), followed by triethylamine (440 µl, 3.16 mmol). After 30 minutes the reaction mixture was diluted with a 10% solution of hydrochloric acid (10 ml) and dichloromethane (10 ml). The organic layer was separated, washed with a 5% solution of sodium hydrogen carbonate (2x5 ml) and saturated brine (3x10 ml), dried over sodium sulphate and evaporated under reduced pressure to give an oily residue that was dissolved in anhydrous xylene (10ml). Triethyl phosphite (454 µl, 2.64 mmol) and a catalytic amount of hydroquinone were added and the mixture was heated at 140°C for 4 hours, then the solvent was evaporated and the crude oil was purified by flash chromatography (eluant cyclohexane/ethyl acetate from 6:4 to 4:6) to afford the title compound as a yellow oil (0.90g, 44%). ^{1}H-NMR ($CDCl_3$, 400MHz): 7.76-7.73 (m, 2H); 7.66-7.61 (m, 1H); 7.58-7.54 (m, 2H); 5.95-5.86 (m, 1H); 5.44-5.39 (m, 1H); 5.26-5.22 (m, 1H); 5.07 (t, 1H, *J*= 2.8); 4.80-4.60 (m, 2H); 4.22-4.15 (m, 1H); 4.13 (dd, 1H, *J*= 3.2, 10.4); 3.99 (s, 2H); 3.71-3.69 (m, 2H); 3.58-3.52 (m, 2H); 3.19 (dd, 1H, *J*= 3.2, 5.6); 3.18-3.10 (m, 1H); 3.06-2.96 (m, 4H); 2.08-2.0 (m, 1H); 1.84-1.30 (m, 5H); 1.19 (d, 3H, *J*= 6); 0.87 (s, 9H); 0.08 (s, 6H). IR (nujol)ν_{max}: 1776, 1720, 1653, 1358-1171 cm^{-1}. LRMS (*m/z*):688 $[M+H]^+$, 404, 246.

Allyl (4*S*, 8*S*, 9*R*, 10*S*) 4-(1'-phenylsulphonylpiperazin-4'-ylcarbonylmethoxy)-10-[(1*R*) (1-hydroxyethyl] -11-oxo-1-azatricyclo[7.2.0.0.^{3,8}] undec-2-ene-2-carboxylate 22c

A solution of **21c** (0.09 g, 0.13 mmol) in anhydrous THF (10 ml) was treated sequentially with glacial acetic acid (54 µl, 0.94 mmol), caesium fluoride (0.120 g, 0.78 mmol) and tetrabutylammonium bromide (0.253 g, 0.78 mmol). The reaction mixture was heated at 45°C for 20 hours, then a 5% solution of sodium hydrogen carbonate (20 ml) was added followed by ethyl acetate (25 ml); the organic layer was separated, washed with brine (2x15 ml), dried over sodium sulphate and evaporated under reduced pressure to give an oily residue that was purified by flash chromatography (ethyl acetate/MeOH 95:5) to afford the title compound as a pale yellow oil (0.025 g, 33%). ^{1}H-NMR ($CDCl_3$, 400MHz): 7.76-7.73 (m, 2H); 7.66-7.61 (m, 1H); 7.59-7.53 (m, 2H); 5.98-5.88 (m, 1H); 5.44-5.38 (m, 1H); 5.28-5.22 (m, 1H); 5.06 (t, 1H, *J*= 2.8); 4.78- 4.58 (m, 2H); 4.28-4.20 (m, 1H); 4.16 (dd, 1H, *J*= 3.2, 10.4); 3.99 (dd, 2H, *J*= 14.4, 1.2); 3.70-3.64 (m, 2H); 3.56-3.50 (m, 2H); 3.24 (dd, 1H, *J*= 3.2, 6); 3.22-3.16 (m, 1H); 3.06-2.98 (m, 4H); 2.08-2.02 (m, 1H); 1.90-1.70 (m, 2H); 1.70-1.60 (m, 1H); 1.68 (d, 1H, *J*= 4.8); 1.50-1.30 (m, 2H); 1.31 (d, 3H, *J*= 6.4). IR (nujol)ν_{max}: 1776, 1720 cm^{-1}. LRMS (*m/z*): 574 $[M+H]^+$, 307. HRMS: Calcd for $C_{28}H_{35}N_3O_8S$: 574.22231; found: 574.22198.

Sodium (4*S*, 8*S*, 9*R*, 10*S*) 4-(1'-phenylsulphonylpiperazin-4'-ylcarbonylmethoxy)-10-[(1*R*) (1-*tert*-butyldimethylsilyloxy) ethyl] -11-oxo-1-azatricyclo[7.2.0.0.^{3,8}] undec-2-ene-2-carboxylate 3c

A solution of **22c** (0.023 g, 0.04 mmol) in anhydrous tetrahydrofuran (1 ml) was treated with triphenylphosphine (0.1 mg, 0.004 mmol), sodium 2-ethylhexanoate (80 µl of a 0.5M solution in ethyl acetate) and tetrakis(triphenylphosphine)palladium (1.2 mg). The resulting mixture was stirred for 1 hour; then diethyl ether (1 ml) and petroleum ether (1 ml) were added to precipitate a solid which was separated by centrifugation and washed with diethyl ether (2 ml). This procedure was repeated three times to give the title compound as a white solid (15mg, 78%). ^{1}H-NMR (D_2O, 300MHz): 7.70-7.48 (m, 5H); 4.86-4.84 (m, 1H); 4.08-3.95 (m, 2H); 3.98-3.92 (m, 2H); 3.94 (dd, 1H, *J*= 3.3, 9.9); 3.52-3.36 (m,

5H); 4.86-4.84 (m, 1H); 4.08-3.95 (m, 2H); 3.98-3.92 (m, 2H); 3.94 (dd, 1H, *J*= 3.3, 9.9); 3.52-3.36 (m, 4H); 3.25 (dd, 1H, *J*= 3.3, 6.3); 2.98-2.84 (m, 5H); 1.90-1.80 (m, 1H); 1.70-1.60 (m, 1H); 1.60-1.10 (m, 4H); 1.09 (d, 3H, *J*= 6.3). IR (nujol)n_{max}: 3433, 1759, 1657-1631 cm^{-1}. MS (*m/z*): 556 $[M+H]^+$,, 534, 176. HPLC R_t= 5.42 minutes.(Column Lichrosphere C18 S5 25x0.4cm; λ= 225nm; T=23°C; eluent MeCN/10μM phosphate buffer pH=7.4 23/77).

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(*Received in UK* 9 *July* 1997; *revised* 22 *August* 1997; *accepted* 28 *August* 1997)