Synthesis of esters of the potent anti-bacterial trinems† and analogues

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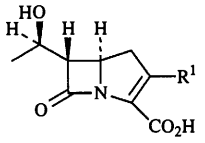
Coupling the silyl enol ether 5 and the β-lactam 9 (R = Me_3Si) affords the ketones 13a–d. Compounds 13a, 13c and 13d are converted into the tricyclic lactams 16–20, 23–25. (Chemoenzymatic synthesis of optically pure silyl enol ether 5 gave access to homochiral lactams 23–25.) In addition the ketoazetidinones 13 are protected as the 1,3-oxazanes 30. A hydroxyethyl moiety is introduced into these oxazanes at C-11 with the desired stereochemistry using the Bouffard methodology, to afford the alcohols 32. Formation of the corresponding nitrobenzyl carbonate, deprotection and oxidation furnishes the ketones 35a and 35b, which are subsequently converted into the trinems 41a and 41b, respectively.

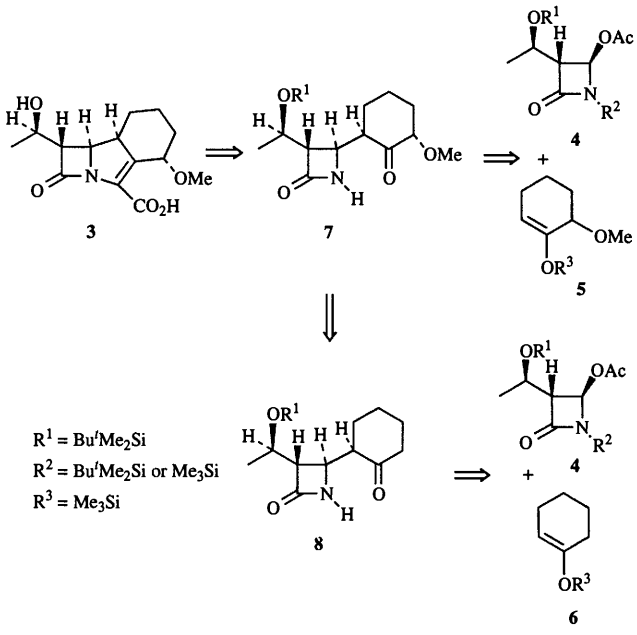
Introduction and background information

Following the discovery and development of penicillins and cephalosporins, intensive efforts were made to find related compounds with enhanced anti-microbial action. This search was rewarded with the discovery of two new classes of compounds, namely penems and carbapenems, following the isolation and identification of thienamycin **1**.[1] Modifications of the bicyclic framework of the thienamycin provided imipenem **2** and meropenem, commercially important anti-bacterial substances. A resurgence of interest in this field came as a result of the discovery of a new class of β-lactam antibiotics, the trinems, by Glaxo Wellcome laboratories, and a member of this class, the 4-methoxytrinem **3**, is currently under clinical evaluation. This tricyclic lactam shows very impressive anti-bacterial activity, with excellent potency being displayed against Gram-positive and many Gram-negative bacteria.[2] Syntheses of trinem **3** have been described that involve the coupling of 4-acetoxy-3-[1-(*tert*-butyldimethylsilyloxy)ethyl]azetidin-2-one **4**

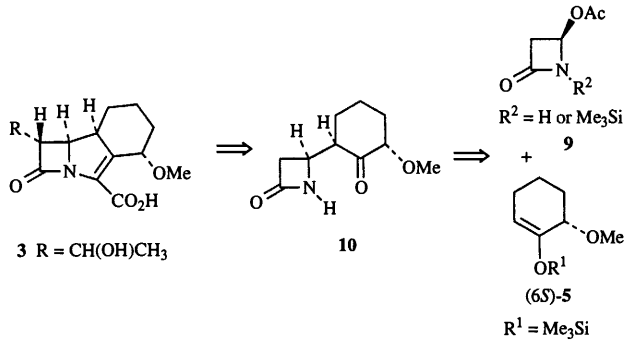


1 $R^1 = SCH_2CH_2NH_2$
2 $R^1 = SCH_2CH_2N{=}CH(NH_2)$

with the silyl enol ethers **5** or **6** to give the ketoazetidinones **7** or **8** respectively (as mixtures with corresponding stereoisomers) (Scheme 1).[3] Stereocontrol in this key step is offered by the hydroxyethyl side chain. As an alternative route to analogues of trinem **3** we investigated the coupling of the homochiral silyl enol ether (6*S*)-**5** with the simple azetidinone **9** having in mind the methoxy ketone **10** as the key intermediate (Scheme 2). It was planned that other substituents on the β-lactam ring could be introduced at a later stage with stereocontrol offered by the cyclohexane moiety. In this approach it was envisaged that stereochemical control would be relayed from the methoxy group in the six-membered ring to the β-lactam unit. The results of our investigations along these lines are outlined below.



Scheme 1



Scheme 2

† In earlier publications trinems were referred to as tribactams.
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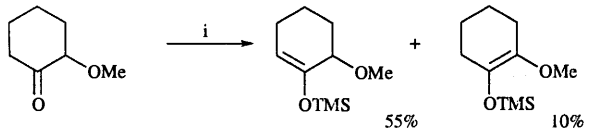
Results and discussion

Preparation of 6-methoxy-1-trimethylsilyloxycyclohexene 5 and coupling with 4-acetoxyazetidin-2-one 9 (R = $SiMe_3$)

6-Methoxy-1-trimethylsilyloxycyclohexene **5** is reported to be the major isomer obtained when 2-methoxycyclohexanone **11** is deprotonated using lithium diisopropylamide (LDA) in diethyl ether at low temperature and quenched with trimethylsilyl chloride.[4] Another reported procedure, using LDA as the base in tetrahydrofuran, gave 1-methoxy-2-trimethylsilyloxycyclohexene **12** as the major isomer.[5] In our hands, under a range of conditions using LDA, lithium *N*-isopropylcyclohexylamide (LICA) or lithium 2,2,6,6-tetramethylpiperide (LITMP) as the base, the two silyl enol ethers were obtained in approximately equal amounts. However treatment of 2-methoxycyclohexanone **11** with ethyl trimethylsilylacetate and a catalytic amount of tetrabutylammonium fluoride (TBAF) gave a mixture of the silyl enol ethers **5** and **12** in the ratio 5.5 : 1 (Scheme 3). The two isomers were readily separated by chromatography.



11 **5** **12**

Scheme 3 *Reagents and conditions:* i, $TMSCH_2CO_2Et$, TBAF on silica, THF, −20 °C

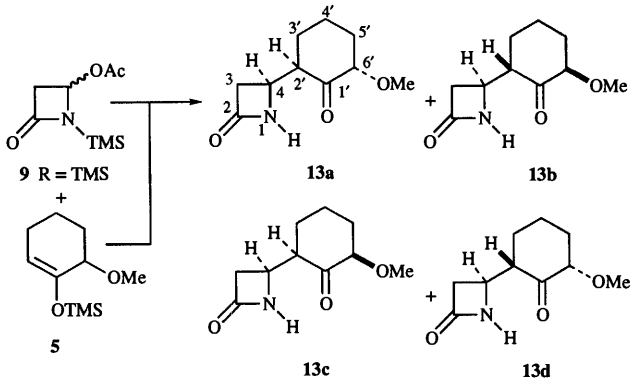
The *N*-silylated azetidin-2-one **9** (R = $SiMe_3$) was prepared by treatment of 4-acetoxyazetidin-2-one **9** (R = H) with trimethylsilyl chloride.[6] Coupling of the lactam **9** (R = $SiMe_3$) with the silyl enol ether **5** was investigated under a variety of conditions as summarised in Table 1. It was found that isomers **13a** and **13b**, in which the β-lactam ring and the methoxy group are *trans*-orientated, are less polar than isomers **13c** and **13d** in which these groups are *cis*. Hence the two pairs of isomers could be readily separated by chromatography. Other protecting groups (*e.g. N-tert*-butyldimethylsilyl) on the β-lactam nitrogen were investigated for the coupling reactions but these starting materials gave lower yields of coupled products. Similarly the unprotected lactam gave poor yields in the coupling process.[7] Hence the best conditions for this coupling were found to involve the use of a trimethylsilyl (TMS) protecting group on the β-lactam and zinc iodide or zinc chloride as the catalyst. However, little stereoselectivity was observed.

Formation of the trinem ring system (in racemic form)

There are two general methods for the conversion of ketoazetidinones into trinems. The first involves an intramolecular Wittig reaction of a phosphorane.[8] The second involves heating an oxalimide with triethyl phosphite.[9] Treatment of the mixture of ketoazetidinones **13a** and **13b** with benzyl glyoxylate gave the alcohols **14** in 74% yield. Reaction of the alcohols **14** with thionyl chloride followed by triphenylphosphine in tetrahydrofuran, using 2,6-lutidine as base, gave the phosphoranes **15** in 36% yield. The phosphoranes **15** underwent intramolecular Wittig reaction on heating in refluxing toluene, containing a single crystal of hydroquinone, to give the trinem **16** in 40% yield (Scheme 4).

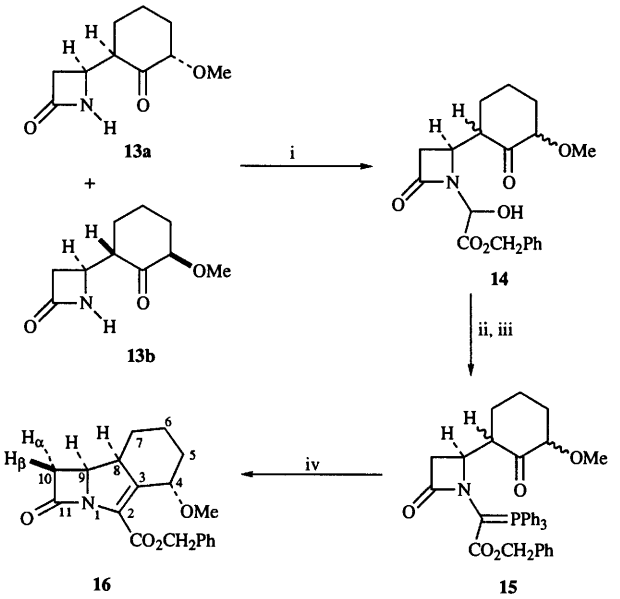
The stereochemistry of compound **16** was confirmed by NMR data. Coupling constants indicated the six-membered ring to be in an approximately 'chair' conformation with the proton 4-H in an equatorial situation. Pre-irradiation of 4-H resulted in enhancement of 5-H_{ax}, 5-H_{eq} and the methoxy signal. Pre-irradiation of 9-H resulted in strong enhancement of 8-H and 10-H_α. Pre-irradiation of 5-H_{eq} resulted in enhancement of 5-H_{ax} and 8-H, while pre-irradiation of 10-H_β resulted in enhancement of 10-H_α (strong), 7-H_{ax} and 9-H (weak). Note that the trinem **17** resulting from the cyclisation of the ketoazetidinone **13b** was not isolated.

Table 1 Reaction of 4-acetoxy-1-trimethylsilylazetidin-2-one **9** (R = $SiMe_3$) with 6-methoxy-1-trimethylsilyloxycyclohexene **5**

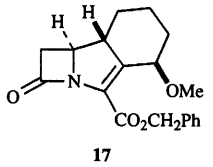


Silyl enol ether **5** (equiv.)	Catalyst	Catalyst (equiv.)	Solvent	*T*/°C	Combined yield of isomers **13**
1.2	$SnCl_4{\cdot}Et_2O$	1	CH_2Cl_2	0 to 25	—[a]
2	$SnCl_4{\cdot}Et_2O$	1	CH_2Cl_2	0 to 25	—[a]
1.2	$SnCl_4{\cdot}Et_2O$	2.2	CH_2Cl_2	0 to 25	—[a]
1.2	$SnCl_4{\cdot}PPh_3$	1.15	CH_2Cl_2	25	—[a]
1.2	$SnCl_4$	1.2	MeCN	−10 to 0	—[b]
1.2	ZnI_2	1	CH_2Cl_2	25	50%[c]
1.2	$ZnCl_2$	1	CH_2Cl_2	25	55%[d]
1.2	TMSOTf	0.05	CH_2Cl_2	−78 to 25	15%[e]
2.5	$SnCl_4{\cdot}Et_2O$	1.5	CH_2Cl_2	25	—[a]

[a] Starting azetidinone decomposed. [b] 4-Methoxyazetidin-2-one isolated in 27% yield. [c] **13a** and **13b**, 24%, ratio 1 : 1.6, major isomer not known; **13c** and **13d**, 26%, ratio 1 : 1.6, major isomer not known. [d] **13a** and **13b**, 30%, ratio **1** : 1.6, major isomer not known; **13c** and **13d**, 25%, ratio 1 : 1.2, major isomer not known. [e] **13a** and **13b**, 4%, ratio 1 : 1.1, major isomer not known; **13c** and **13d**, 11%, ratio 2.5 : 1, major isomer not known. Also obtained 4-methoxyazetidin-2-one, 7% and 4-acetoxyazetidin-2-one **9** (R = H), 41%.



Scheme 4 *Reagents and conditions:* i, $HCOCO_2CH_2Ph$, C_6H_6, reflux; ii, $SOCl_2$, 2,6-lutidine, THF; iii, PPh_3, 2,6-lutidine, THF; iv, PhMe, reflux



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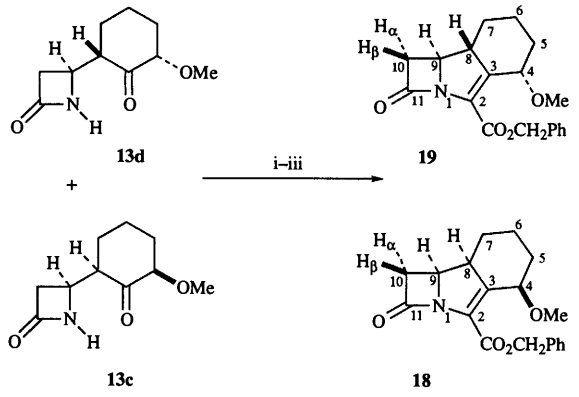
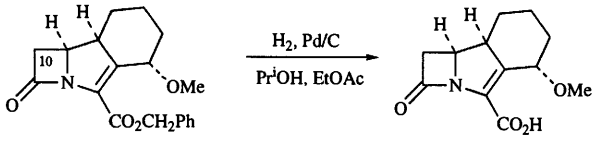
Similarly, cyclisation of the mixture of ketoazetidinones **13c** and **13d** gave pure samples of the trinems **18** and **19**, ratio (6:5) (Scheme 5).



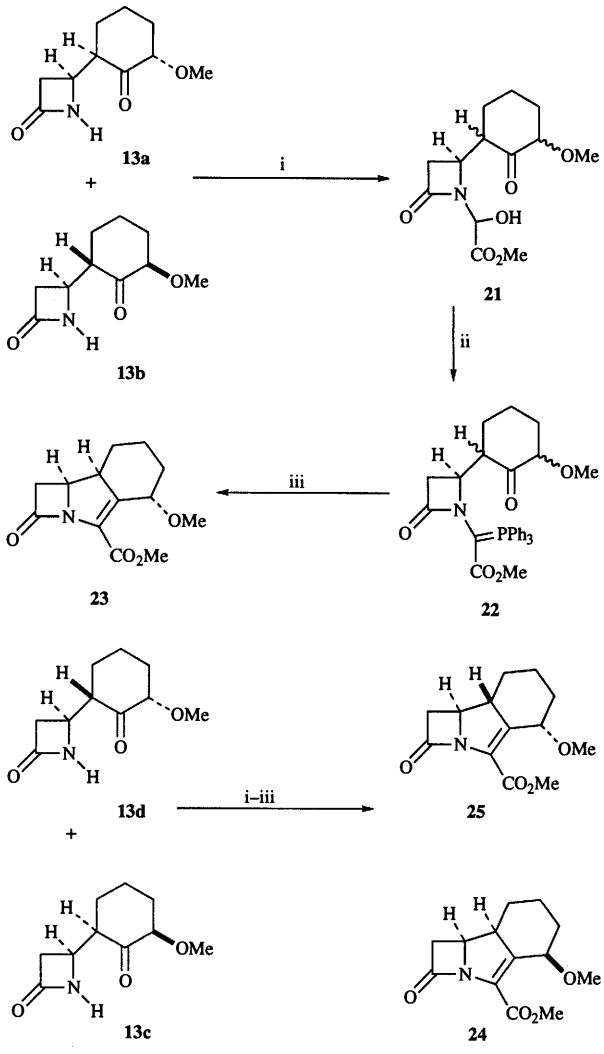
Scheme 5 *Reagents and conditions:* i, $HCOCO_2CH_2Ph$, 76%; ii, $SOCl_2$ then PPh_3, 55%; iii, PhMe, reflux, 42%

The relative stereochemistries were again confirmed by NOE data.§ Hydrogenolysis of the benzyl ester **16** catalysed by palladium on charcoal gave the acid **20** as a beige solid in nearly



quantitative yield. Compound **20** appeared unstable at ambient temperature, turning pink on standing.

The methyl esters **23–25** were prepared also: thus reaction of the ketoazetidinones **13a** and **13b** with methyl glyoxylate gave the alcohols **21** in good yield. The alcohols **21** were converted into the phosphoranes **22** (31%) under the usual conditions. Heating the phosphoranes **22** in refluxing toluene gave the trinem **23** in 38% yield (Scheme 6). Similarly, the ketoazetidinones **13c** and **13d** were converted into the trinems **24** and **25** (overall yield 17%, ratio of **24**:**25**, 1:1) (Scheme 6). The methyl esters **23–25** showed very similar NMR spectra to the corresponding benzyl esters **16**, **18** and **19**.

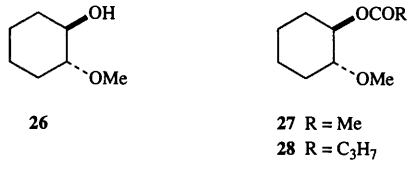


Scheme 6 *Reagents and conditions:* i, $HCOCO_2Me$, C_6H_6, reflux (66–70%); ii, $SOCl_2$, 2,6-lutidine, THF then PPh_3, 2,6-lutidine, THF (31–52%); iii, PhMe, reflux (38–51%)

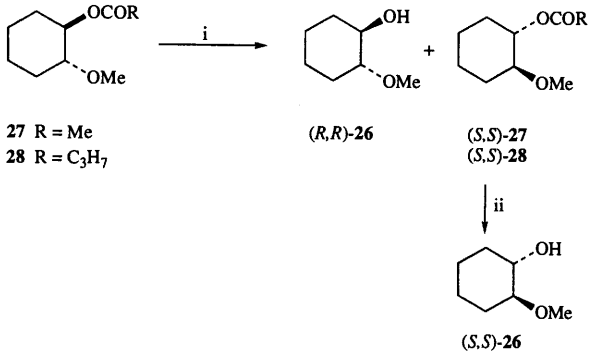
Synthesis of the trinems 23–25 in homochiral form

trans-2-Methoxycyclohexanol **26** was prepared in 81% yield by heating cyclohexene oxide in refluxing methanol containing a catalytic amount of concentrated sulfuric acid.[10] The alcohol **26** was converted into the acetate **27** or the butanoate **28** by treatment with the corresponding anhydride, pyridine and a catalytic amount of 4-dimethylaminopyridine (94–96% yield).

Hydrolysis of the racemic cyclohexyl butanoate **28**[11] using *Pseudonomas fluorescens* lipase (PFL) in 0.1 mol l^{-1}, pH = 7 phosphate buffer (with the addition of 2 mol l^{-1} aqueous sodium hydroxide to maintain the pH constant at 7) gave the (*R*,*R*)-alcohol **26** in 48% yield and the (*S*,*S*)-ester **28** in 47% yield. The (*S*,*S*)-ester was hydrolysed chemically using aqueous sodium hydroxide to give the (*S*,*S*)-alcohol **26** which exhibited a single peak when subjected to gas chromatography using a chiral stationary phase (Scheme 7).



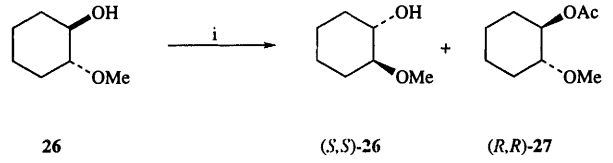
The enzymatic resolution was repeated on the acetate **27** because the preparation of the acetate was much more



Scheme 7 *Reagents and conditions:* i, PFL, 0.1 mol l^{-1} phosphate buffer, NaOH; ii, NaOH, MeOH

§ Pre-irradiation of 4-H of compound **19** showed enhancement of 5-H_{eq}, 8-H and the methoxy signal. Pre-irradiation of 9-H showed enhancement of 10-H_α and 7-H_{ax}. Pre-irradiation of 8-H showed enhancement of 4-H and 7-H_{eq}. Pre-irradiation of 10-H_α showed enhancement of 10-H_β and 9-H. Likewise, pre-irradiation of 9-H of compound **18** showed enhancement of 10-H_α and 8-H (strong). Pre-irradiation of 4-H showed enhancement of 5-H_{eq}, 8-H, 6-H_{ax} and the methoxy signal. Pre-irradiation of 8-H showed enhancement of 4-H, 9-H and 7-H_{eq}. Pre-irradiation of 10-H_β showed enhancement of 10-H_α, 7-H_{eq} and 7-H_{ax}

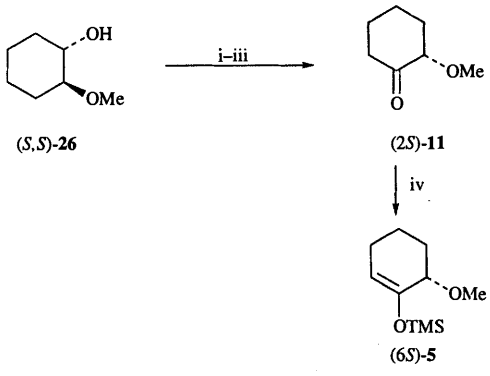
convenient than that of the butanoate. Equally good results were obtained using the acetate. A problem with this whole procedure is that three steps are required to obtain the (*S*,*S*)-alcohol since the (*S*,*S*)-ester is not affected by the enzyme and therefore has to be hydrolysed chemically. However we anticipated that it should be possible to enzymatically esterify the (*R*,*R*)-alcohol leaving the (*S*,*S*)-alcohol unreacted, so as to obtain the required homochiral material in one step. Indeed, treatment of the racemic alcohol **26** with vinyl acetate catalysed by *Pseudonomas fluorescens* lipase in dry tetrahydrofuran containing triethylamine resulted in formation of the (*R*,*R*)-acetate **27** in 48% yield, leaving the (*S*,*S*)-alcohol **26** in 44% yield (Scheme 8).



26 (*S*,*S*)-**26** (*R*,*R*)-**27**

Scheme 8 *Reagents and conditions:* i, vinyl acetate, PFL, Et_3N, THF

The (*S*,*S*)-alcohol **26** was oxidised to the ketone (−)-(2*S*)-**11** under Swern conditions. The ketone was converted into the silyl enol ether (−)-(6*S*)-**5** under the same conditions used to produce the racemic material (Scheme 9).



(*S*,*S*)-**26** (2*S*)-**11** (6*S*)-**5**

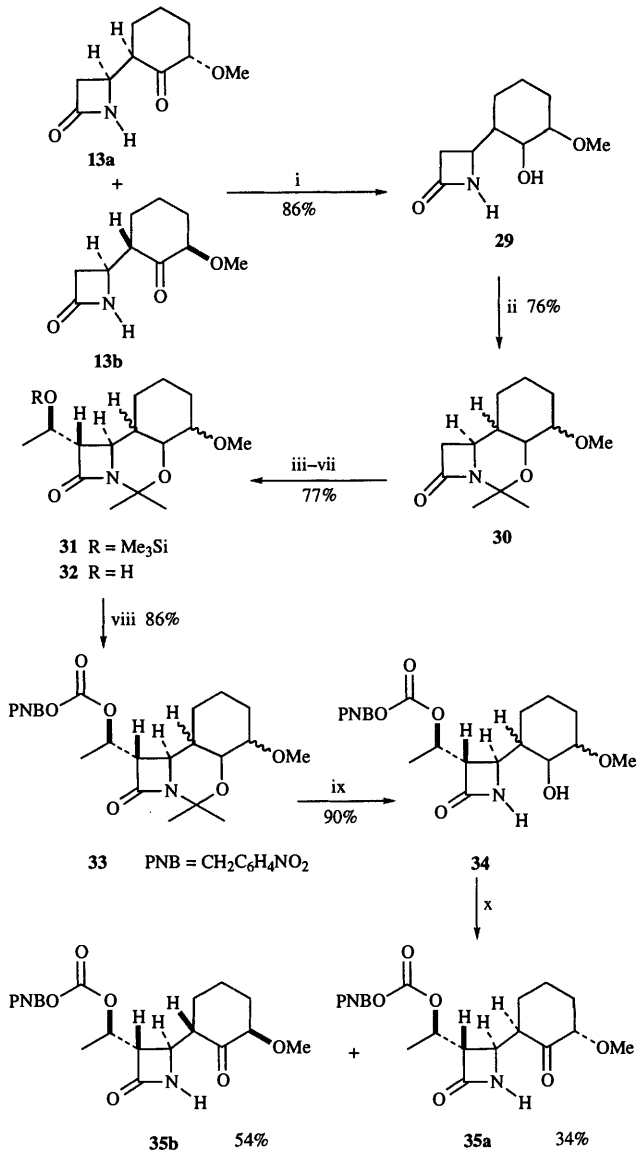
Scheme 9 *Reagents and conditions:* i, $(COCl)_2$, DMSO, CH_2Cl_2; ii, Et_3N; iii, H_2O; iv, $Me_3SiCH_2CO_2Et$, TBAF on silica, THF

The silyl enol ether (−)-(6*S*)-**5** was coupled to the acetoxyazetidinone **9** (R = $SiMe_3$) using zinc chloride catalysis to give the (6′*S*)-ketoazetidinones **13a–d** in a combined yield of 53%. The (6′*S*,2′*R*,4*S*)-ketoazetidinone **13a** was cyclised under the same conditions used for the racemic material to give the trinem (+)-(4*S*,8*S*,9*S*)-**23** (overall yield 7.7%). Chiral shift NMR experiments using [Eu(hfc)$_3$] showed the presence of only one enantiomer. The (6′*S*,2′*S*,4*R*)-ketoazetidinone **13c** and the (6′*S*,2′*S*,4*S*)-ketoazetidinone **13d** were similarly cyclised to give the (4*S*,8*R*,9*R*)-trinem (−)-(4*S*,8*R*,9*R*)-**24** (6.6%) and the trinem (+)-(4*S*,8*R*,9*S*)-**25** (7.3%). Again, chiral shift NMR experiments using [Eu(hfc)$_3$] showed only one enantiomer of the product.

Introduction of the hydroxyethyl side chain

The next phase of the work concentrated on the introduction of a hydroxyethyl side-chain onto the β-lactam ring, adjacent to the carbonyl group. These investigations involved the use of racemic material.

Attempts to functionalise the trinem **16** at C-10 by deprotonation, followed by quenching with acetaldehyde led only to decomposition. Hence it was necessary to introduce the required hydroxyethyl group prior to cyclisation to the trinem. After some experimentation the hydroxyethyl group was introduced with the correct stereochemistry using the methodology shown in Scheme 10. The ketoazetidinones **13a** and **13b** were reduced using sodium borohydride in ethanol to

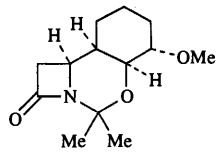


Scheme 10 *Reagents and conditions:* i, $NaBH_4$, EtOH, 0 °C; ii, 2,2-dimethoxypropane, BF_3·Et_2O, CH_2Cl_2; iii, LDA, THF, −78 °C; iv, $MeCOSiMe_3$, −78 °C; v, Bu^{t}OK, Bu^{t}OH, −78 °C to 0 °C; vi, NH_4Cl (aq); vii, TBAF, AcOH, THF, room temp.; viii, *p*-nitrobenzyl chloroformate, DMAP, CH_2Cl_2, room temp.; ix, TFA, H_2O, room temp.; x, DMSO, $(COCl)_2$, −60 °C, then Et_3N, −60 °C to room temp.

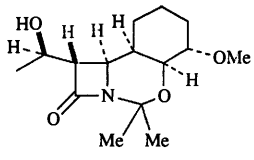
give an inseparable mixture of alcohols **29** which were protected as the 1,3-oxazanes **30** upon treatment with 2,2-dimethoxypropane catalysed by boron trifluoride–diethyl ether.[12] Whilst the mixture of oxazanes was used in the synthesis work, one major component of the mixture, compound **30a**, was isolated by chromatography and characterised by NMR (see Experimental section).

The hydroxyethyl group was incorporated at C-11 using the Bouffard methodology.[13] Thus deprotonation at C-11 using lithium diisopropylamide and quenching with acetyl trimethylsilane gave an intermediate alkoxysilane which underwent rearrangement upon treatment with potassium *tert*-butoxide in *tert*-butyl alcohol to give the silyloxyethyl compounds **31**. Deprotection was effected using tetrabutylammonium fluoride and acetic acid in tetrahydrofuran to give the hydroxyethyl compounds **32**. From this mixture a sample of compound **32a** was obtained by careful chromatography and characterised by NMR spectroscopy (see Experimental section).

The mixture of alcohols **32** were protected as the *p*-nitrobenzyl carbonates **33** by treatment with an excess of *p*-nitrobenzyl chloroformate and 4-dimethylaminopyridine in

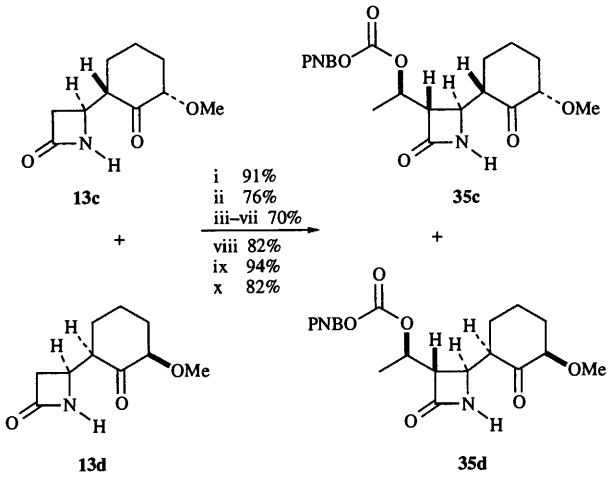


30a



32a

dichloromethane.[14] Deprotection of the 1,3-oxazanes was readily achieved by stirring at room temperature in aqueous trifluoroacetic acid[15] to give the β-lactams **34** in 90% yield. Oxidation under Swern conditions[16] afforded the ketoazetidinones **35** which could be separated by chromatography to give the (2′*S*,6′*R*)-isomer **35b** in 54% yield and the (2′*R*,6′*S*)-isomer **35a** in 34% yield. The methoxy ketones **13c** and **13d** were converted into a mixture of the (2′*S*,6′*S*)-ketoazetidinone **35c** and the (2′*R*,6′R)-ketoazetidinone **35d** using the same methodology (Scheme 11). Separation of the isomers **35c** and **35d** was not achieved.



Scheme 11 See Scheme 10 for reagents and conditions

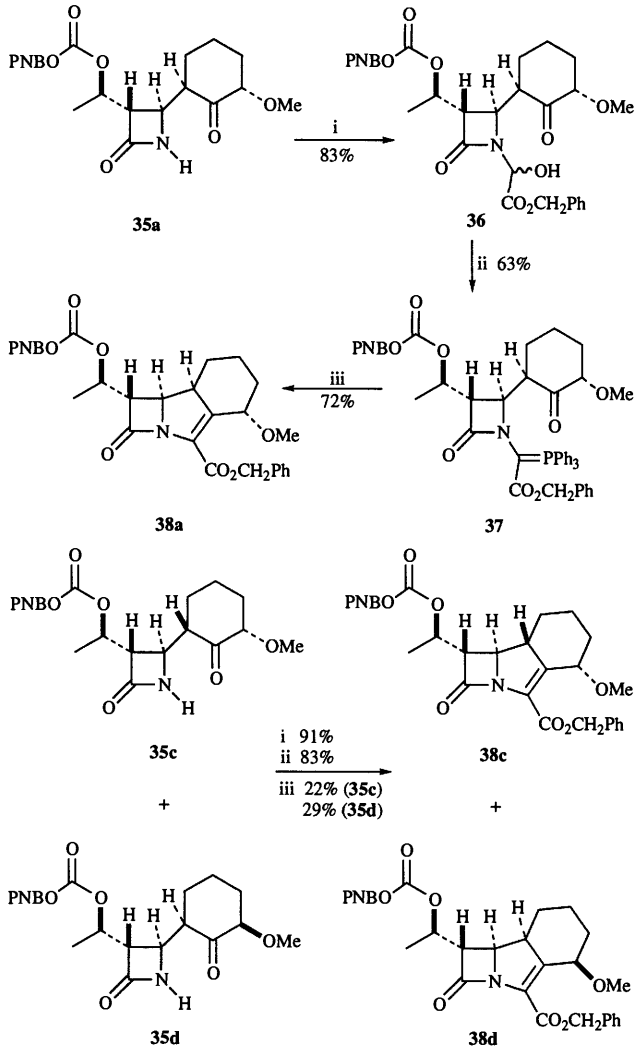
Reaction of the ketoazetidinone **35a** with benzyl glyoxylate afforded the alcohols **36** in 83% yield (Scheme 12). The alcohols were converted into the phosphoranes **37** in (63% yield) by treatment with thionyl chloride followed by triphenylphosphine. Upon heating in toluene, the phosphoranes smoothly underwent an intramolecular Wittig reaction to give the trinem **38a** in 72% yield. Similarly the ketoazetidinones **35c** and **35d** were converted into the trinems **38c** and **38d** which were separable by chromatography.

The trinem **38b** was not prepared using the phosphorane route. Instead reaction of the ketoazetidinone **35b** with benzyl oxalyl chloride and triethylamine in dichloromethane gave the crude oxalimide **39** which was cyclised to the trinem **38b** in 57% yield upon heating in xylene containing an excess of triethyl phosphite (Scheme 13).

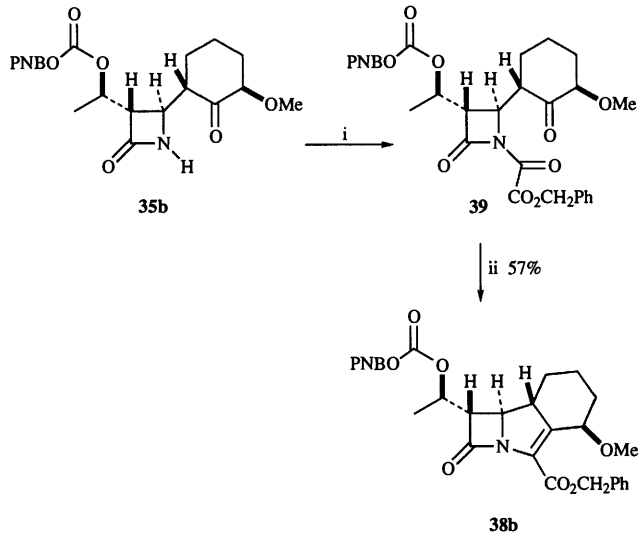
The methyl esters **40a** and **40b** were also prepared by the oxalimide route (Scheme 14) and the *p*-nitrobenzyl carbonate was removed by hydrogenation to give the alcohols **41a** and **41b**.

Conclusions

This synthetic route to the trinems relaying chirality from the methoxy group to the left hand side of the molecule (as conventionally drawn) complements other synthetic routes which utilised the initially installed hydroxyethyl group as the unit which dictates the relative stereochemistry of chiral centres as they are introduced across the molecule. These studies also

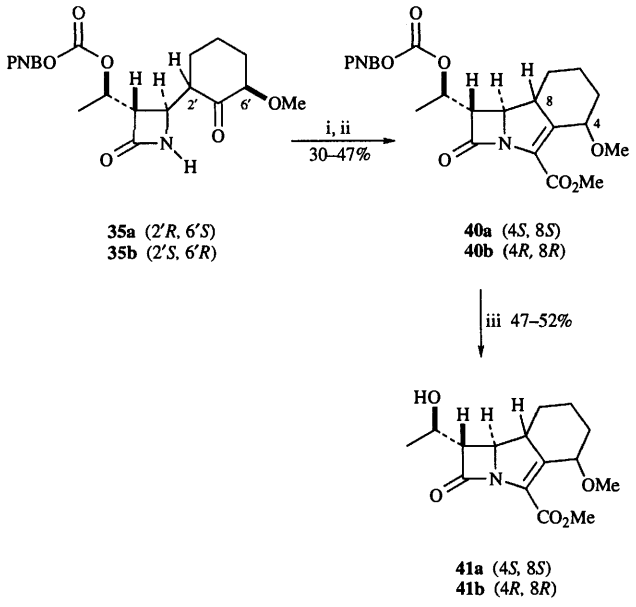


Scheme 12 *Reagents and conditions:* i, $HCOCO_2CH_2Ph$, C_6H_6, reflux; ii, $SOCl_2$, 2,6-lutidine, THF, −15 °C, then PPh_3, 2,6-lutidine, THF, 60 °C; iii, toluene or xylene, catalytic hydroquinone, reflux



Scheme 13 *Reagents and conditions:* i, $ClCOCO_2CH_2Ph$, Et_3N, CH_2Cl_2, 0 °C; ii, $P(OEt)_3$, xylene, reflux

complement our other recently reported work in this area, namely the construction of the trinem system using radical-controlled reactions[17] and the preparation of fluorine-containing trinems.[18]



Scheme 14 *Reagents and conditions:* i, $ClCOCO_2Me$, Et_3N, CH_2Cl_2, 0 °C; ii, $P(OEt)_3$, xylene, reflux; iii, H_2, Pd/C, EtOAc, Pr^iOH

Experimental

IR spectra were recorded either on a Perkin-Elmer 881 spectrometer or a 1FS48 Bruker (FT) spectrometer. ^1H NMR spectra were recorded on a Hitachi Perkin-Elmer spectrometer operating at 60 MHz; a Bruker AM 250 spectrometer operating at 250 MHz or a Bruker AC 300 spectrometer operating at 300 MHz. 400 MHz spectra were recorded at Glaxo, Verona on a Varian 400 unity spectrometer. ^{13}C NMR spectra were recorded on a Bruker AM 250 spectrometer operating at 62.9 MHz, or a Bruker AC 300 spectrometer operating at 75.5 MHz. All chemical shifts (δ) are reported in parts per million (ppm) and the coupling constants (J) are quoted in Hz. Mass spectra were recorded on a Kratos Profile instrument or by SERC Mass Spectrometry Centre, Swansea. Unless otherwise indicated, spectra were recorded in the electron impact mode. Optical rotations were measured on an AA-1000 polarimeter. The mps were determined on a capillary apparatus and are uncorrected. Light petroleum refers to the fraction of bp 40–60 °C and was distilled prior to use. Ethyl acetate was distilled prior to use. Ether and tetrahydrofuran (THF) were distilled from sodium using benzophenone ketyl radical as indicator. Dichloromethane was distilled from calcium hydride. Dimethyl sulfoxide was distilled from barium oxide and stored over 4 Å molecular sieves under nitrogen. Benzene and toluene were dried over sodium wire. TLC was performed using pre-coated glass plates (Merck silica gel 60F 254). The plates were visualised using UV light (254 nm) and/or phosphomolybdic acid in ethanol, or ninhydrin in ethanol–hydrochloric acid. Flash chromatography was performed using Merck silica 60 (40–63 μm). Ether refers to diethyl ether. 2,6-Lutidine = dimethylpyridine.

6-Methoxy-1-trimethylsilyloxycyclohexene 5

Ethyl trimethylsilylacetate (644 mg, 4.0 mmol) in dry tetrahydrofuran (1 ml) was added to a suspension of tetrabutylammonium fluoride (TBAF) on silica (1 mmol g^{-1}, 100 mg) in dry tetrahydrofuran (0.5 ml) with stirring at room temperature under nitrogen. The mixture was cooled to −20 °C and a solution of 2-methoxycyclohexanone **11** (429 mg, 3.35 mmol) in dry tetrahydrofuran (1.5 ml) was added dropwise. The mixture was stirred for 1 h at −20 °C and then filtered through Celite, washing with cold light petroleum. The organic phase was washed with saturated aqueous sodium hydrogen carbonate, water and brine, then dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed [ether–light petroleum (1:20)] to give (i) *1-methoxy-2-trimethylsilyloxycyclohexene* **12** (69 mg, 10%), ν_{max}(film)/cm^{-1} 1693, 1248, 1215, 923 and 853; δ_H(400 MHz, $CDCl_3$), 0.19 (9 H, s), 1.52–1.76 (4 H, m), 2.00–2.18 (4 H, m) and 3.51 (3 H, s); and (ii) the *title compound* **5** (367 mg, 1.83 mmol), ν_{max}(film)/cm^{-1} 1662, 1199 and 843; δ_H(400 MHz, $CDCl_3$), 0.25 (9 H, s) 1.44–1.70 (2 H, m), 1.84–2.14 (3 H, m), 3.4 (3 H, s), 3.49 (1 H, m) and 4.97 (1 H, m).

4-(6'-Methoxy-1'-oxocyclohexan-2'-yl)azetidin-2-one 13

A solution of the acetoxyazetidinone **9** (R = TMS) (3.25 g, 16.13 mmol) in dry dichloromethane (25 ml), followed by a solution of the silyl enol ether **5** (3.88 g, 19.36 mmol) in dry dichloromethane (25 ml), was added to a suspension of anhydrous zinc chloride (2.20 g, 16.13 mmol) in dry dichloromethane (25 ml) at room temperature under nitrogen. The mixture was stirred for 18 h and then poured into saturated aqueous sodium hydrogen carbonate and extracted with dichloromethane. The organic extracts were washed with water, 5% aqueous potassium fluoride, water and brine, then dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed [ether–methanol (95:5)] to give the *title compound* **13** as a mixture of isomers (i) **13a,b** (944 mg, 30%) (Found: M^+, 197.1052. $C_{10}H_{15}NO_3$ requires M, 197.1052); ν_{max}($CHCl_3$)/cm^{-1} 3427, 1764 and 1714; δ_H(250 MHz, $CDCl_3$) 1.18–1.68 (m), 1.83–2.27 (m), 2.49–2.59 (m), 2.76–2.97 (m), 3.00 (1 H, dd, J 5.0, 2.5), 3.04–3.10 (m), 3.14 (1 H, dd, J 5.0, 2.5), 3.22 (3 H, s), 3.23 (3 H, s), 3.47–3.52 (m), 3.61 (1 H, ddd, J 9, 6, 2.5), 3.79 (1 H, m), 6.29 (1 H, br s) and 6.44 (1 H, br s); δ_C(62.9 MHz, $CDCl_3$) 18.93, 18.99, 30.04, 30.55, 33.44, 33.51, 41.99, 42.40, 46.96, 47.02, 50.44, 51.96, 56.88 (OMe, both isomers), 83.48, 83.63, 167.23, 167.99, 212.29 and 212.71; m/z 197 (M^+, 3%), 180 (30), 169 (12), 155 (14), 126 (13), 109 (20), 94 (33), 85 (74), 80 (45) and 71 (100); and (ii) **13c,d** (788 mg, 25%) (Found: M^+, 197.1052. $C_{10}H_{15}NO_3$ requires M, 197.1052); ν_{max}($CHCl_3$)/cm^{-1} 3427, 1765 and 1722; δ_H(250 MHz, $CDCl_3$) 1.20–1.83 (m), 1.85–2.16 (m), 2.30–2.62 (m), 3.01 (1 H, dd, J 5.0, 2.5), 3.07 (1 H, m), 3.14 (1 H, dd, J 5.0, 2.5), 3.39 (s, OMe, both isomers), 3.62–3.80 (m), 3.87 (1 H, m), 6.24 (1 H, br s) and 6.39 (1 H, br s); δ_C(62.9 MHz, $CDCl_3$) 22.58, 22.73, 29.46, 30.36, 34.41, 34.54, 42.11, 42.40, 46.79, 46.90, 53.40, 55.17, 57.96 (OMe, both isomers), 84.19, 84.38, 167.12, 168.02, 208.71 and 209.11; m/z 197 (M^+, 7%), 169 (23), 153 (16), 139 (45), 126 (27), 109 (40), 94 (48), 86 (100) and 71 (60).

Benzyl 4-methoxy-11-oxo-1-azatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate 16

A mixture of the ketoazetidinones **13a,b** (944 mg, 4.79 mmol) and benzyl glyoxylate (1.18 g, 7.19 mmol) in dry benzene (25 ml) was heated under reflux for 12 h. The solvent was evaporated and the residue chromatographed [ethyl acetate–light petroleum (2:1)] to give the *alcohols* **14** (1.274 g, 74%), ν_{max}(film)/cm^{-1} 3417 (br) and 1744. A stirred solution of the alcohols **14** (1.274 g, 3.53 mmol) and 2,6-lutidine (1.23 ml, 10.59 mmol) in dry tetrahydrofuran (40 ml) under nitrogen was cooled to −15 °C. Thionyl chloride (0.77 ml, 10.59 mmol) in dry tetrahydrofuran (10 ml) was added dropwise. The mixture was stirred for 30 min and then evaporated. Dry toluene (20 ml) was added to the residue, the mixture was evaporated and this process was repeated once more (in order to completely remove thionyl chloride from the residue). The residue was dissolved in dry tetrahydrofuran (40 ml). 2,6-Lutidine (0.82 ml, 7.06 mmol) and triphenylphosphine (1.85 g, 7.06 mmol) were added and the mixture was stirred under nitrogen at 60 °C for 8 h. After allowing to cool to room temperature, the mixture was partitioned between ethyl acetate and water. The ethyl acetate layer was washed with brine and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed (ethyl acetate) to give the *phosphoranes* **15** (768 mg, 36%), ν_{max}(film)/cm^{-1} 1743 and 1620. The phosphoranes **15** (543 mg, 0.90 mmol) were dissolved in dry toluene (50 ml) containing a

single crystal of hydroquinone. The solution was heated under reflux under nitrogen for 24 h. The solvent was evaporated and the residue chromatographed [ethyl acetate–light petroleum (1:1)] to give the *title compound* **16** (116 mg, 40%), mp 100–102 °C (Found: M^+, 327.1471. $C_{19}H_{21}NO_4$ requires *M*, 327.1471); $\nu_{max}(CHCl_3)/cm^{-1}$ 1779, 1715 and 1631; δ_H(400 MHz, $CDCl_3$) 1.35 (1 H, qd, *J* 12, 3.5, 7-H_{ax}), 1.44 (1 H, tt, *J* 13, 3.5, 5-H_{ax}), 1.66 (1 H, m, 6-H_{eq}), 1.81 (1 H, tt, *J* 13, 3.5, 6-H_{ax}), 1.87 (1 H, m, 7-H_{eq}), 2.06 (1 H, m, 5-H_{eq}), 3.02 (1 H, dd, *J* 16.6, 3.1, 10-H_β), 3.21 (1 H, m, 8-H), 3.22 (3 H, s, OMe), 3.30 (1 H, dd, *J* 16.6, 5.8, 10-H_α), 4.20 (1 H, m, 9-H), 4.96 (1 H, t, *J* 3.0, 4-H), 5.23 (1 H, d, *J* 12.5, PhC*H*), 5.35 (1 H, d, *J* 12.5, PhC*H*) and 7.30–7.50 (5 H, m, Ph); δ_C(75.5 MHz, $CDCl_3$) 20.20, 30.19, 32.47, 39.32, 44.39, 51.37, 56.16, 66.98, 72.46, 126.26, 128.10, 128.26, 128.55, 135.41, 150.42, 161.06 and 175.60; *m/z* 327 (M^+, 12%), 149 (90) and 91 (100).

Benzyl 4-methoxy-11-oxo-1-azatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate 18, 19

A mixture of the ketoazetidinones **13c,d** (788 mg, 4.00 mmol) and benzyl glyoxylate (985 mg, 6.00 mmol) in dry benzene (20 ml) was heated under reflux for 12 h. The solvent was evaporated and the residue chromatographed (ethyl acetate) to give the *alcohols* **14** (1.102 g, 76%), ν_{max}(film)/cm^{-1} 3409 (br) and 1755. The alcohols **14** (1.102 g, 3.05 mmol) were converted into the *phosphoranes* **15** (1.01 g, 55%) using the usual procedure [$\nu_{max}(CHCl_3)/cm^{-1}$ 1727 and 1625]. The phosphoranes **15** (541 mg, 0.89 mmol) were dissolved in dry toluene (50 ml) containing a single crystal of hydroquinone. The solution was heated under reflux under nitrogen for 48 h. The solvent was evaporated and the residue chromatographed [ethyl acetate–light petroleum (2:3)] to give the *title compounds*, (i) **19** (56 mg, 19%) mp 88–90 °C (Found: M^+, 327.1479. $C_{19}H_{21}NO_4$ requires *M*, 327.1471); ν_{max}(Nujol)/cm^{-1} 1776 and 1730; δ_H(400 MHz, $CDCl_3$) 1.27–1.43 (3 H, m, 5-H_{ax}, 6-H_{ax} and 7-H_{ax}), 1.87–2.08 (3 H, m, 5-H_{eq}, 6-H_{eq} and 7-H_{eq}), 2.90 (1 H, m, 8-H), 2.92 (1 H, dd, *J* 16, 3.2, 10-H_β), 3.23 (3 H, s, OMe), 3.40 (1 H, dd, *J* 16, 5.6, 10-H_α), 3.81 (1 H, m, 9-H), 3.91 (1 H, dd, *J* 8.4, 5.7, 4-H), 5.23–5.33 (2 H, m, PhCH_2) and 7.28–7.46 (5 H, m, Ph); δ_C(75.5 MHz, $CDCl_3$) 22.05, 30.55, 31.50, 44.11, 49.86, 56.29, 57.26, 67.10, 76.43, 126.04, 128.14, 128.34, 128.46, 135.59, 141.43, 161.93 and 176.72; *m/z* 327 (M^+, 9%), 151 (29), 138 (43) and 91 (100); and (ii) **18** (68 mg, 23%), mp 71–73 °C (Found: M^+, 327.1465. $C_{19}H_{21}NO_4$ requires *M*, 327.1471); ν_{max}(Nujol)/cm^{-1} 1763 and 1732; δ_H(400 MHz, $CDCl_3$) 1.25–1.53 (3 H, m, 5-H_{ax}, 6-H_{ax} and 7-H_{ax}), 1.79 (1 H, m, 7-H_{eq}), 1.97 (1 H, m, 6-H_{eq}), 2.18 (1 H, m, 5-H_{eq}), 2.77 (1 H, m, 8-H), 3.01 (1 H, dd, *J* 16.6, 3.3, 10-H_β), 3.19 (3 H, s, OMe), 3.23 (1 H, dd, *J* 16.6, 5.8, 10-H_α), 3.91 (1 H, dd, *J* 10.3, 4.8, 4-H), 4.23 (1 H, m, 9-H), 5.22–5.34 (2 H, m, PhCH_2) and 7.28–7.48 (5 H, m, Ph); δ_C(75.5 MHz, $CDCl_3$) 23.84, 29.38, 33.50, 38.86, 40.05, 51.81, 57.49, 67.15, 79.06, 123.56, 128.07, 128.38, 128.40, 135.67, 141.23, 162.71 and 175.46; *m/z* 327 (M^+, 8%), 151 (45) and 91 (100).

Methyl 4-methoxy-11-oxo-1-azatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate 23

A mixture of the ketoazetidinones **13a,b** (418 mg, 2.12 mmol) and methyl glyoxylate (280 mg, 3.18 mmol) in dry benzene (10 ml) was heated under reflux for 12 h. The solvent was evaporated and the residue chromatographed (ethyl acetate) to give the *alcohols* **21** (426 mg, 70%), ν_{max}(film)/cm^{-1} 3421 (br) and 1742. The alcohols **21** (383 mg, 1.34 mmol) were converted into the *phosphoranes* **22** (217 mg, 31%) using the usual procedure, [ν_{max}(film)/cm^{-1} 1736 and 1616]. The phosphoranes **22** (200 mg, 0.38 mmol) were dissolved in dry toluene (20 ml) containing a single crystal of hydroquinone. The solution was heated under reflux under nitrogen for 24 h. The solvent was evaporated and the residue chromatographed [ethyl acetate–light petroleum (1:1)] to give the *title compound* **23** (36 mg, 38%), mp 102–103 °C (Found: M^+, 251.1151. $C_{13}H_{17}NO_4$ requires *M*, 251.1158); $\nu_{max}(CHCl_3)/cm^{-1}$ 1774, 1716 and 1630; δ_H(300 MHz, $CDCl_3$) 1.25–1.52 (2 H, m), 1.62–1.70 (1 H, m), 1.77–1.93 (2 H, m), 2.04–2.13 (1 H, m), 3.02 (1 H, dd, *J* 17, 3.3, 10-H_β), 3.20 (1 H, m, 8-H), 3.26 (3 H, s, OMe), 3.30 (1 H, dd, *J* 17, 6.0, 10-H_α), 3.86 (3 H, s, CO_2Me), 4.20 (1 H, m, 9-H) and 4.97 (1 H, t, *J* 3.3, 4-H); *m/z* 251 (M^+, 71%), 223 (24), 208 (20), 191 (50), 178 (86) and 164 (100).

Methyl 4-methoxy-11-oxo-1-azatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate 24, 25

A mixture of the ketoazetidinones **13c,d** (260 mg, 1.32 mmol) and methyl glyoxylate (174 mg, 1.98 mmol) in dry benzene (7 ml) was heated under reflux for 5 h. The solvent was evaporated and the residue chromatographed (ethyl acetate) to give the *alcohols* **21** (249 mg, 66%), ν_{max}(film)/cm^{-1} 3418 (br) and 1749. The alcohols **21** (222 mg, 0.78 mmol) were converted into the *phosphoranes* **22** (213 mg, 52%) using the usual procedure [$\nu_{max}(CHCl_3)/cm^{-1}$ 1723 and 1613]. The phosphoranes **22** (191 mg, 0.36 mmol) were dissolved in dry toluene (20 ml) containing a single crystal of hydroquinone. The solution was heated under reflux under nitrogen for 48 h. The solvent was evaporated and the residue chromatographed [ethyl acetate–light petroleum (1:1)] to give the *title compounds*, (i) **25** (24 mg, 26%), mp 116–118 °C (Found: M^+, 251.1144. $C_{13}H_{17}NO_4$ requires *M*, 251.1158); $\nu_{max}(CHCl_3)/cm^{-1}$ 1773 and 1729; δ_H(300 MHz, $CDCl_3$) 1.25–1.43 (3 H, m), 1.89 (1 H, m), 1.99–2.14 (2 H, m), 2.90 (1 H, m, 8-H), 2.92 (1 H, dd, *J* 17, 3, 10-H_β), 3.39 (3 H, s, OMe), 3.41 (1 H, dd, *J* 17, 5.7, 10-H_α), 3.81 (1 H, m, 9-H), 3.84 (3 H, s, CO_2Me) and 3.93 (1 H, m, 4-H); *m/z* 251 (M^+, 51%), 223 (28), 208 (39), 194 (40), 164 (37), 151 (92), 138 (84), 122 (57), 97 (57), 79 (60) and 69 (100); and (ii) **24** (23 mg, 25%) as a colourless oil (Found: M^+, 251.1149. $C_{13}H_{17}NO_4$ requires *M*, 251.1158); ν_{max}(film)/cm^{-1} 1773 and 1736; δ_H(300 MHz, $CDCl_3$) 1.24–1.51 (3 H, m), 1.75–1.84 (1 H, m), 1.95–2.04 (1 H, m), 2.14–2.22 (1 H, m), 2.72–2.82 (1 H, m, 8-H), 3.01 (1 H, dd, *J* 17, 3, 10-H_β), 3.24 (1 H, dd, *J* 17, 6, 10-H_α), 3.34 (3 H, s, OMe), 3.84 (3 H, s, CO_2Me), 3.88–3.96 (1 H, m, 4-H) and 4.19–4.26 (1 H, m, 9-H); *m/z* 251 (M^+, 45%), 236 (29), 192 (68), 178 (100) and 151 (70).

***trans*-2-Methoxycyclohexyl acetate 27**

A mixture of *trans*-2-methoxycyclohexanol **26** (3.72 g, 28.57 mmol), acetic anhydride (4.0 ml, 42.9 mmol), pyridine (3.5 ml, 42.9 mmol) and 4-dimethylaminopyridine (280 mg, 2.3 mmol) in dichloromethane (25 ml) was stirred at room temperature for 20 h. The reaction mixture was partitioned between ether and dilute hydrochloric acid. The ether layer was washed with water, saturated aqueous sodium hydrogen carbonate, water and brine, then dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed [ether–light petroleum (2:1)] to give the *title compound* **27** (4.63 g, 94%), ν_{max}(film)/cm^{-1} 1731 and 1239; δ_H(60 MHz, $CDCl_3$) 1.3–2.4 (8 H, m), 2.25 (3 H, s), 3.1–3.4 (1 H, m), 3.55 (3 H, s) and 4.8–5.2 (1 H, m).

***trans*-2-Methoxycyclohexyl butanoate 28**

A mixture of *trans*-2-methoxycyclohexanol **26** (2.57 g, 19.74 mmol), butyric anhydride (4.8 ml, 29.61 mmol), pyridine (2.4 ml, 29.61 mmol) and 4-dimethylaminopyridine (195 mg, 1.6 mmol) in dichloromethane (20 ml) was stirred at room temperature for 18 h. The reaction mixture was partitioned between ether and dilute hydrochloric acid. The ether layer was washed with water, saturated aqueous sodium hydrogen carbonate, water and brine, then dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed [ether–light petroleum (2:1)] to give the *title compound* **28** (3.78 g, 96%), ν_{max}(film)/cm^{-1} 1730 and 1183; δ_H(60 MHz, $CDCl_3$) 1.05 (3 H, t, *J* 8), 1.30–2.25 (10 H, m), 2.35 (2 H, q, *J* 7), 3.15–3.50 (1 H, m), 3.55 (3 H, s) and 4.80–5.20 (1 H, m).

Hydrolysis of *trans*-2-methoxycyclohexyl acetate 27

Racemic acetate **27** (1.00 g, 5.81 mmol) was dissolved in phosphate buffer (0.1 mol l^{-1}, pH = 7, 20 ml). *Pseudomonas fluorescens* lipase (100 mg) was added and the mixture stirred vigorously for 66 h, keeping the pH constant at 7 by the dropwise addition of 2 mol l^{-1} aqueous sodium hydroxide. The mixture was extracted with dichloromethane. The organic extracts were washed with brine and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed [ether–light petroleum (2:1)] to give (S,S)-*acetate* **27** (473 mg, 47%); and (R,R)-*alcohol* **26** (309 mg, 41%); $[\alpha]_D^{25}$ −71.9 (*c* 2, CH_2Cl_2) {lit.,[11] $[\alpha]_D^{20}$ −69.3 (*c* 2, CH_2Cl_2)}. Alkaline hydrolysis of (*S,S*)-acetate **27** gave (S,S)-*alcohol* **26** (339 mg, 95%); $[\alpha]_D^{25}$ +68.5 (*c* 2, CH_2Cl_2) {lit.,[11] $[\alpha]_D^{20}$ +69.7 (*c* 2, CH_2Cl_2)}.

Hydrolysis of *trans*-2-methoxycyclohexyl butanoate 28

Similarly, treatment of the racemic butanoate **28** (1.51 g, 7.53 mmol) in phosphate buffer (0.1 mol l^{-1}, pH = 7, 30 ml) with *Pseudomonas fluorescens* lipase (150 mg) for 48 h gave (*S,S*)-ester **28** (713 mg, 47%); and (R,R)-*alcohol* **26** (430 mg, 44%); $[\alpha]_D^{28}$ −73.2 (*c* 2, CH_2Cl_2). Alkaline hydrolysis of (*S,S*)-ester **28** gave (S,S)-*alcohol* **26** (432 mg, 44%); $[\alpha]_D^{28}$ +70.6 (*c* 2, CH_2Cl_2).

Esterification of *trans*-2-methoxycyclohexanol 26

Racemic alcohol **26** (1.50 g, 11.52 mmol) was dissolved in dry tetrahydrofuran (30 ml). Vinyl acetate (7.5 ml, 80 mmol), triethylamine (1.2 ml, 8.6 mmol) and *Pseudomonas fluorescens* lipase (250 mg) were added. The mixture was stirred at room temperature for 5 days and then filtered through Celite washing with ethyl acetate. The solvent was evaporated and the residue chromatographed [ether–light petroleum (2:1)] to give (R,R)-*acetate* **27** (955 mg, 48%); and (S,S)-*alcohol* **26** (663 mg, 44%); $[\alpha]_D^{26}$ +72.5 (*c* 2, CH_2Cl_2).

(*S*)-2-Methoxycyclohexanone 11

Dimethyl sulfoxide (3.24 ml, 45.72 mmol) in dry dichloromethane (10 ml) was added dropwise to a stirred solution of oxalyl chloride (1.83 ml, 20.95 mmol) in dichloromethane (40 ml) at −60 °C under nitrogen. After 5 min, (*S,S*)-alcohol **26** (2.48 g, 19.05 mmol) in dry dichloromethane (10 ml) was added dropwise over 10 min maintaining the temperature at −50 to −60 °C. After another 15 min, triethylamine (13.3 ml, 95 mmol) was added dropwise keeping the temperature below −50 °C. Stirring was continued for 5 min after which the mixture was allowed to warm to room temperature. Water (100 ml) was added and the mixture extracted with dichloromethane. The organic extracts were washed with 1% aqueous hydrochloric acid (until no longer basic), water, 5% aqueous sodium carbonate, water and brine then dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed [ether–light petroleum (2:1)] to give the *title compound* (2*S*)-**11** (1.90 g, 78%); $[\alpha]_D^{23}$ −113.1 (*c* 2, CH_2Cl_2); ν_{max}(film)/cm^{-1} 1718; δ_H(400 MHz, $CDCl_3$), 1.8–1.6 (3 H, m), 2.0–1.84 (2 H, m), 2.55 (1 H, m), 3.42 (3 H, s) and 3.75 (1 H, m).

(*S*)-6-Methoxy-1-trimethylsilyloxycyclohexene 5

(*S*)-2-Methoxycyclohexanone **11** (2.30 g, 17.94 mmol) was reacted using the same procedure described for racemic ketone to give the *title compound* (6*S*)-**5** (1.96 g, 55%); $[\alpha]_D^{24}$ −78.8 (*c* 2, CH_2Cl_2).

(6′*S*)-4-(6′-Methoxy-1′-oxocyclohexan-2′-yl)azetidin-2-one 13

The silyl enol ether (6*S*)-**5** (1.762 g, 8.80 mmol) underwent reaction with the *N*-silylacetoxyazetidinone **9** (R = TMS) (1.61 g, 8.00 mmol) under the same conditions described for the racemic material to give the *title compound* **13** as a mixture of isomers, (i) (6′*S*,2′*R*,4*S*)-**13a** and (6′*S*,2′*R*,4*R*)-**13b** (475 mg, 30%); $[\alpha]_D^{26}$ −6.8 (*c* 2, CH_2Cl_2) and (ii) (6′*S*,2′*S*,4*R*)-**13c** and (6′*S*,2′*S*,4*S*)-**13d** (363 mg, 23%); $[\alpha]_D^{26}$ −42.1 (*c* 2, CH_2Cl_2).

Methyl (4*S*,8*S*,9*S*)-4-methoxy-11-oxo-1-azatricyclo[7.2.0.0^{3,8}]-undec-2-ene-2-carboxylate 23

A mixture of the ketoazetidinones (6′*S*,2′*R*,4*S*)-**13a** and (6′*S*,2′*R*,4*R*)-**13b** (447 mg, 2.27 mmol) underwent reaction with methyl glyoxalate (300 mg, 3.40 mmol) under the usual conditions to give the *alcohols* **21** (376 mg, 58%). The alcohols were converted into the *phosphoranes* **22** (237 mg, 34%) using the usual conditions. The phosphoranes were dissolved in dry toluene (25 ml) containing a single crystal of hydroquinone. The solution was heated under reflux under nitrogen for 24 h to give the *title compound* **23** (44 mg, 39%); $[\alpha]_D^{25}$ +120.5 (*c* 2, CH_2Cl_2).

Methyl (4*S*,8*R*,9*R*)- and (4*S*,8*R*,9*S*)-4-methoxy-11-oxo-1-aza-tricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate 24 and 25

A mixture of the ketoazetidinones (6′*S*,2′*S*,4*R*)-**13c** and (6′*S*,2′*S*,4*S*)-**13d** (345 mg, 1.75 mmol) underwent reaction with methyl glyoxalate (231 mg, 2.62 mmol) under the usual conditions to give the *alcohols* **21** (288 mg, 58%). The alcohols were converted into the *phosphoranes* **22** (306 mg, 57%) using the usual conditions. The phosphoranes were dissolved in dry toluene (40 ml) containing a single crystal of hydroquinone. The solution was heated under reflux under nitrogen for 30 h to give the *title compounds* (i) (4*S*,8*R*,9*S*)-**25** (37 mg, 25%); $[\alpha]_D^{29}$ +22.9 (*c* 2, CH_2Cl_2); and (*ii*) (4*S*,8*R*,9*R*)-**24** (32 mg, 22%); $[\alpha]_D^{29}$ −146.7 (*c* 2, CH_2Cl_2).

2,2-Dimethyl-5-methoxy-12-oxo-3-oxa-1-azatricyclo[8.2.0.0^{4,9}]-dodecane 30

The mixture of ketoazetidinones **13a,b** (1.27 g, 6.44 mmol) was dissolved in absolute ethanol (15 ml) and the solution cooled to 0 °C. Sodium borohydride (244 mg, 6.44 mmol) was added and the mixture was stirred for 1 h. The reaction mixture was quenched with saturated ammonium chloride and extracted with dichloromethane. The combined extracts were dried ($MgSO_4$) and evaporated. The residue was filtered through a short column of silica, eluting with ethyl acetate, to give the *alcohols* **29** (1.11 g, 86%) as a mixture of isomers (Found: M^+, 199.1204. $C_{10}H_{17}NO_3$ requires *M*, 199.1208); ν_{max}($CHCl_3$)/cm^{-1} 3562, 3426 and 1737; *m/z* 199 (M^+, 2%), 138 (24), 124 (26), 112 (33) and 83 (100). A mixture of the alcohols **29** (1.11 g, 5.55 mmol) and 2,2-dimethoxypropane (1.16 g, 11.11 mmol) was dissolved in dry dichloromethane (20 ml). Boron trifluoride diethyl ether complex (0.07 ml, 0.55 mmol) was added and the mixture was stirred at room temperature for 5 h. The mixture was partitioned between water and dichloromethane and the aqueous phase was extracted with dichloromethane. The combined organic extracts were washed with brine and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed [ethyl acetate–light petroleum (1:1)] to give the *title compound* (1.02 g, 76%) as a mixture of isomers (Found: M^+, 239.1515. $C_{13}H_{21}NO_3$ requires *M*, 239.1521); ν_{max}(film)/cm^{-1} 1755; *m/z* 239 (M^+, 6%), 224 (27), 182 (32) and 84 (100). Chromatography over silica provided a sample of compound **30a**; δ_H(400 MHz) 3.85 (1 H, m), 3.60 (1 H, m), 3.42 (3 H, s), 3.40 (1 H, m), 2.78–2.95 (2 H, m), 2.51 (1 H, m), 2.04 (1 H, m), 1.40–1.80 (3 H, m), 1.69 and 1.42 (2 × 3 H, 2 × s), 1.22 (2 H, m).

2,2-Dimethyl-11-(1-hydroxyethyl)-5-methoxy-12-oxo-3-oxa-1-azatricyclo[8.2.0.0^{4,9}]dodecane 32

The acetonide **30** (610 mg, 2.55 mmol) was dissolved in dry tetrahydrofuran (10 ml) under nitrogen. The solution was cooled to −78 °C. A solution of lithium diisopropylamide (LDA) was prepared by addition of butyllithium (1.6 mol l^{-1}; 1.83 ml) to diisopropylamine (0.43 ml, 3.06 mmol) in tetrahydrofuran (10 ml) under nitrogen at 0 °C. The LDA solution was added dropwise to the acetonide and the resulting mixture was stirred for 30 min. Acetyltrimethylsilane (341 mg, 2.93 mmol) in tetrahydrofuran (5 ml) was added. After a further 30 min, a solution of potassium *tert*-butoxide (329 mg, 2.93

mmol) in *tert*-butyl alcohol (3 ml) was added. The mixture was allowed to warm to 0 °C, poured into saturated aqueous ammonium chloride and extracted with dichloromethane. The combined extracts were washed with brine, dried ($MgSO_4$) and evaporated. The residue was dissolved in dry tetrahydrofuran (15 ml). TBAF (1 mol l^{-1} in THF; 2.8 ml) and acetic acid (168 mg, 2.8 mmol) were added and the mixture was stirred at room temperature for 1 h. Saturated aqueous sodium hydrogen carbonate was added and the mixture was extracted with dichloromethane. The combined extracts were washed with brine, dried ($MgSO_4$) and evaporated. The residue was chromatographed [ethyl acetate–light petroleum (3:1)] to give the *title compounds* **32** (557 mg, 77%) as a mixture of isomers (Found: M^+, 283.1773. $C_{15}H_{25}NO_4$ requires M, 283.1784); ν_{max}(film)/cm^{-1} 3447 and 1756; m/z 283 (M^+, 3%), 268 (24), 111 (51) and 84 (100). Chromatography over silica provided a pure sample of compound **32a**; δ_H(400 MHz), 4.14 (1 H, m), 3.83 (1 H, dd, J 8.8, 2.2), 3.60 (1 H, m), 3.41 (3 H, s), 3.40 (1 H, t, J 2.5), 3.12 (1 H, dd, J 5.2, 2.2), 2.52 (1 H, m), 2.04 (1 H, m), 1.30–1.80 (3 H, m), 1.65 (3 H, s), 1.43 (3 H, s), 1.26 (3 H, d, 6.4) and 1.24 (2 H, m).

2,2-Dimethyl-11-[1-(*p*-nitrobenzylcarbonato)ethyl]-5-methoxy-12-oxo-3-oxa-1-azatricyclo[8.2.0.0^{4,9}]dodecane 33¶

A mixture of the alcohols **32** (930 mg, 3.28 mmol), 4-dimethylaminopyridine (801 mg, 6.56 mmol) and *p*-nitrobenzyl-chloroformate (1.41 g, 6.56 mmol) in dry dichloromethane (15 ml) was stirred at room temperature for 12 h. The mixture was diluted with dichloromethane (30 ml), washed with dilute hydrochloric acid (0.25 mol l^{-1}), water and brine, then dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed [ethyl acetate–light petroleum (1:1)] to give the *title compounds* **33** (1.30 g, 86%) as a mixture of isomers (Found: MH^+, 463.2070. $C_{23}H_{30}N_2O_8$ requires MH, 463.2080); ν_{max}(film)/cm^{-1} 1755, 1526, 1349 and 1260; m/z (CI, NH_3) 463 (MH^+, 100%) and 284 (50).

3-[1-(*p*-Nitrobenzylcarbonato)ethyl]-4-(1′-hydroxy-6′-methoxycyclohexan-2′-yl)azetidin-2-one 34

A solution of the acetonides **33** (1.30 g, 2.81 mmol) in trifluoroacetic acid (6 ml) and water (3 ml) was stirred at room temperature for 1 h. The solution was diluted with water and extracted with dichloromethane. The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate, water and brine then dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed [ethyl acetate–light petroleum (4:1)] to give the *title compound* **34** (1.07 g, 90%) as a mixture of isomers (Found: MH^+, 423.1767. $C_{20}H_{26}N_2O_8$ requires MH, 423.1767); ν_{max}($CHCl_3$)/cm^{-1} 3555, 3423, 1765, 1524, 1351 and 1263; m/z (CI, NH_3) 423 (MH^+, 25%), 244 (100) and 226 (73).

(3*S*,4*R*)-3-[(*R*)-1-(*p*-Nitrobenzylcarbonato)ethyl]-4-[(2′*S*,6′*R*)-6′-methoxy-1′-oxocyclohexan-2′yl]azetidin-2-one 35b and (3*S*,4*R*)-3-[(*R*)-1-(p-nitrobenzylcarbonato)ethyl]-4-[(2′*R*,6′*S*)-6′-methoxy-1′-oxocyclohexan-2′-yl]azetidin-2-one 35a

A solution of dimethyl sulfoxide (472 mg, 6.05 mmol) in dry dichloromethane (2 ml) was added dropwise to a stirred solution of oxalyl chloride (352 mg, 2.77 mmol) in dry dichloromethane (3 ml) at −60 °C under nitrogen. After 5 min, a solution of the alcohols **34** (1.07 g, 2.52 mmol) in dry dichloromethane (5 ml) was added dropwise over 10 min maintaining the temperature at −50 to −60 °C. After another 15 min, triethylamine (1.75 ml, 12.6 mmol) was added dropwise keeping the temperature below −50 °C. Stirring was continued for 5 min after which the mixture was allowed to warm to room temperature. Water (50 ml) was added and the mixture was extracted with dichloromethane. The combined organic extracts were washed with 1% aqueous hydrochloric acid (until no longer basic), water, 5% aqueous sodium carbonate, water and brine, then dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed to give the *title compounds* (i) **35b** (576 mg, 54%), mp 140–141 °C (Found: MH^+, 421.1611. $C_{20}H_{24}N_2O_8$ requires MH, 421.1611); ν_{max}($CHCl_3$)/cm^{-1} 3426, 1760, 1718, 1523, 1352 and 1261; δ_H(300 MHz, $CDCl_3$) 1.12–1.24 (1 H, m), 1.42 (3 H, d, J 7), 1.50–1.64 (2 H, m), 1.90–2.10 (2 H, m), 2.22 (1 H, m), 2.85 (1 H, m), 2.94 (1 H, dd, J 8, 2.5), 3.22 (3 H, s), 3.50 (1 H, t, J 3), 3.58 (1 H, dd, J 10, 2.5), 5.08 (1 H, m), 5.21 (2 H, s), 6.28 (1 H, s), 7.50 (2 H, m) and 8.20 (2 H, m); δ_C(75.5 MHz, $CDCl_3$) 18.58, 18.99, 30.83, 33.34, 51.40, 51.72, 56.91, 60.28, 67.93, 73.11, 83.39, 123.81, 128.47, 142.32, 147.91, 154.07, 165.52 and 212.55; m/z (CI, NH_3) 421 (MH^+, 76%), 259 (38), 242 (96), 224 (90), 206 (100), 156 (75), 122 (76) and 106 (56); and (ii) **35a** (366 mg, 34%) as a colourless oil (Found: MH^+, 421.1611. $C_{20}H_{24}N_2O_8$ requires MH 421.1611); ν_{max}($CHCl_3$)/cm^{-1} 3421, 1766, 1520, 1351 and 1267; δ_H(300 MHz, $CDCl_3$) 1.40 (3 H, d, J 7), 1.43 (1 H, m), 1.54–1.64 (2 H, m) 1.99 (1 H, m), 2.08 (1 H, m), 2.28 (1 H, m), 2.97 (2 H, m), 3.21 (3 H, s), 3.48 (1 H, t, J 3), 3.83 (1 H, dd, J 7, 2.5), 5.11 (1 H, m), 5.21 (2 H, s), 6.02 (1 H, s), 7.51 (2 H, m) and 8.14 (2 H, m); δ_C(75.5 MHz, $CDCl_3$) 18.10, 19.01, 29.99, 33.40, 49.76, 51.09, 56.85, 59.55, 67.91, 72.99, 83.88, 123.70, 128.39, 142.56, 147.78, 154.18, 166.68 and 211.87; m/z (CI, NH_3) 421 (MH^+, 100%), 241 (41), 224 (59), 206 (79), 181 (45) and 156 (39).

(3*S*,4*R*)-3-[(*R*)-1-(*p*-Nitrobenzylcarbonato)ethyl]-4-[(2′*R*,6′*R*)-6′-methoxy-1′-oxocyclohexan-2′-yl]azetidin-2-one 35c and (3*S*,4*R*)-3[(*R*)-1-(*p*-nitrobenzylcarbonato)ethyl]-4-[(2′*S*,6′*S*)-6′-methoxy-1′-oxocyclohexan-2′-yl]azetidin-2-one 35d

The *title compounds* **35c,d** were prepared as an inseparable mixture of isomers from the mixture of ketoazetidinones **13c,d** using the same procedures detailed above (Found: MH^+, 421.1611. $C_{20}H_{24}N_2O_8$ requires MH, 421.1611); ν_{max}($CHCl_3$)/cm^{-1} 3423, 1767, 1523, 1351, 1266 and 1202; δ_H(250 MHz, $CDCl_3$) 1.20–2.15 (18 H, m, both isomers), 2.45–2.60 (4 H, m, both isomers), 2.93 (1 H, dd, J 8, 2.5), 3.05 (1 H, dd, J 7.5, 2.5), 3.42 (3 H, s), 3.43 (3 H, s), 3.64 (1 H, dd, J 10, 2.5), 3.75 (2 H, m), 3.99 (1 H, dd, J 5, 2.5), 5.02–5.18 (2 H, m, both isomers), 5.25 (4 H, m, both isomers), 7.55 (4 H, m, both isomers) and 8.23 (4 H, m, both isomers); m/z (CI, NH_3) 421 (MH^+, 4%), 242 (49), 224 (100) and 206 (61).

Benzyl (4*S*,8*S*,9*R*,10*S*)-4-methoxy-10-[(*R*)-1-(*p*-nitrobenzylcarbonato)ethyl]-11-oxo-1-azatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate 38a

A mixture of the ketoazetidinone **35a** (285 mg, 0.68 mmol) and benzyl glyoxylate (222 mg, 1.36 mmol) in dry benzene (5 ml) was heated under reflux for 2.5 h. The solvent was evaporated and the residue chromatographed (ether) to give the *alcohols* **36** (330 mg, 83%), ν_{max}(film)/cm^{-1} 3424, 1764, 1524, 1349 and 1263. A stirred solution of the alcohols **36** (330 mg, 0.56 mmol) and 2,6-lutidine (182 mg, 1.70 mmol) in dry tetrahydrofuran (15 ml) under nitrogen was cooled to −15 °C. Thionyl chloride (202 mg, 1.70 mmol) in dry tetrahydrofuran (1 ml) was added dropwise. The mixture was stirred for 30 min and then evaporated. Toluene (20 ml) was added to the residue, the mixture was evaporated and this process was repeated once more (in order to completely remove thionyl chloride from the residue). The residue was dissolved in dry tetrahydrofuran (10 ml). 2,6-Lutidine (121 mg, 1.13 mmol) and triphenylphosphine (296 mg, 1.13 mmol) were added and the mixture was stirred under nitrogen at 60 °C for 8 h. After allowing to cool to room temperature, the mixture was partitioned between ethyl acetate and water. The ethyl acetate layer was washed with brine and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed (ethyl acetate) to give the *phosphoranes* **37** (297 mg, 63%), ν_{max}($CHCl_3$)/cm^{-1} 1742, 1710, 1521, 1438, 1350

¶ The IUPAC name for the carbonato prefix is oxycarbonyloxy.

and 1265. The phosphoranes **37** (297 mg, 0.36 mmol) were dissolved in dry toluene (30 ml) and a single crystal of hydroquinone was added. The solution was heated under reflux under nitrogen for 12 h. The solvent was evaporated and the residue chromatographed [(ethyl acetate–light petroleum (1:1)] to give the *title compound* **38a** (141 mg, 72%) (Found: M^+, 550.1970. $C_{29}H_{30}N_2O_9$ requires *M*, 550.1951); ν_{max}($CHCl_3$)/cm^{-1} 1778, 1747, 1717, 1630, 1609, 1521, 1350 and 1263; δ_H(300 MHz, $CDCl_3$) 1.30–1.42 (2 H, m), 1.44 (3 H, d, *J* 7), 1.60–1.66 (1 H, m), 1.79–1.86 (2 H, m), 2.02–2.08 (1 H, m), 3.16–3.24 (1 H, m), 3.19 (3 H, s), 3.40 (1 H, dd, *J* 7, 3), 4.17 (1 H, dd, *J* 10, 3), 4.93 (1 H, t, *J* 3), 5.12–5.21 (2 H, m), 5.24 (2 H, s), 5.37 (1 H, d, *J* 12), 7.29–7.47 (5 H, m), 7.53 (2 H, d, *J* 8) and 8.22 (2 H, d, *J* 8); δ_C(75.5 MHz, $CDCl_3$) 18.44, 20.13, 30.52, 32.49, 44.03, 55.58, 56.10, 57.62, 67.03, 68.05, 72.28, 72.96, 123.83, 126.04, 128.12, 128.29, 128.45, 128.54, 135.34, 142.19, 147.94, 149.50, 154.04, 160.76 and 172.92; *m/z* 550 (M^+, 1%), 519 (2), 353 (18), 262 (44) and 83 (100).

Benzyl (4*R*,8*R*,9*R*,10*S*)-4-methoxy-10-[(*R*)-1-(*p*-nitrobenzyl-carbonato)ethyl]-11-oxo-1-azatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate 38b

A mixture of the ketoazetidinone **35b** (77 mg, 0.18 mmol), benzyl oxalyl chloride (109 mg, 0.55 mmol) and triethylamine (56 mg, 0.55 mmol) in dry dichloromethane (3 ml) was stirred at 0 °C for 1 h. The mixture was partitioned between water and dichloromethane. The dichloromethane extracts were washed with aqueous sodium hydrogen carbonate, water and brine, then dried ($MgSO_4$). The solvent was evaporated and the residue dissolved in dry xylene (5 ml). Triethyl phosphite (0.16 ml, 0.92 mmol) was added and the mixture was heated under reflux under nitrogen for 12 h. The solvent was evaporated and the residue chromatographed [ethyl acetate–light petroleum (1:1)] to give the *title compound* **38b** (57 mg, 57%) (Found: MH^+, 551.2063. $C_{29}H_{30}N_2O_9$ requires *MH*, 551.2030); ν_{max}($CHCl_3$)/cm^{-1} 1785, 1751, 1724, 1524, 1383 and 1351; δ_H(300 MHz, $CDCl_3$) 1.30–1.40 (2 H, m), 1.45 (3 H, d, *J* 7), 1.48–1.56 (1 H, m), 1.66–1.74 (1 H, m), 2.00–2.08 (2 H, m), 3.15 (1 H, m), 3.20 (3 H, s), 3.36 (1 H, dd, *J* 7.5, 3), 3.70 (1 H, dd, *J* 7.5, 3), 4.82 (1 H, m), 5.14 (1 H, m), 5.21 (2 H, s), 5.29 (2 H, s), 7.29–7.45 (5 H, m), 7.50 (2 H, d, *J* 8) and 8.18 (2 H, d, *J* 8); δ_C(75.5 MHz, $CDCl_3$) 18.52, 19.04, 31.84, 34.14, 46.44, 56.13, 59.66, 63.22, 67.07, 68.03, 70.91, 72.82, 123.82, 127.55, 128.17, 128.30, 128.44, 128.55, 135.27, 142.24, 147.53, 147.93, 154.04, 160.70 and 174.17; *m/z* (FAB, NOBA) 551 (MH^+, 100%), 254 (40) and 149 (40).

Benzyl (4*S*,8*R*,9*R*,10*S*)-4-methoxy-10-[(*R*)-1-(*p*-nitrobenzyl-carbonato)ethyl]-11-oxo-1-azatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate 38c and benzyl (4*R*,8*S*,9*R*,10*S*)-4-methoxy-10-[(*R*)-1-(*p*-nitrobenzylcarbonato)ethyl]-11-oxo-1-azatricyclo-[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate 38d

A mixture of the ketoazetidinones **35c,d** (427 mg, 1.02 mmol) and benzyl glyoxylate (335 mg, 2.04 mmol) in dry benzene (10 ml) was heated under reflux for 12 h. The solvent was evaporated and the residue chromatographed [ether–methanol (97:3)] to give the *alcohols* **36** (538 mg, 90%), ν_{max}(film)/cm^{-1} 3436, 1755, 1524, 1349 and 1263. The alcohols **36** (538 mg, 0.92 mmol) were converted into the *phosphoranes* **37** (637 mg, 83%) using the usual procedure, ν_{max}($CHCl_3$)/cm^{-1} 1734, 1634, 1524, 1351 and 1265. The phosphoranes **37** (637 mg, 0.77 mmol) were dissolved in dry xylene (50 ml) and a single crystal of hydroquinone was added. The solution was heated under nitrogen at 130 °C for 15 h. The solvent was evaporated and the residue chromatographed [ethyl acetate–light petroleum (1:1)] to give the *title compounds* (i) **38c** (94 mg, 22%), mp 149–150 °C (Found: MH^+, 551.2041. $C_{29}H_{30}N_2O_9$ requires *MH*, 551.2030); ν_{max}($CHCl_3$)/cm^{-1} 1780, 1746, 1611, 1524, 1351 and 1265; δ_H(300 MHz, $CDCl_3$) 1.24–1.36 (3 H, m), 1.42 (3 H, d, *J* 7), 1.82–1.96 (2 H, m), 2.07 (1 H, m), 2.90 (1 H, m), 3.21 (3 H, s), 3.33 (1 H, dd, *J* 7.5, 3), 3.77 (1 H, dd, *J* 7.5, 3), 3.86 (1 H, m), 5.11 (1 H, m), 5.22 (2 H, s), 5.25 (2 H, dd), 7.26–7.45 (5 H, m), 7.53 (2 H, d, *J* 8) and 8.24 (2 H, d, *J* 8); δ_C(75.5 MHz, $CDCl_3$) 18.51, 22.06, 30.66, 31.47, 49.13, 57.24, 60.25, 62.70, 67.18, 68.02, 72.78, 76.46, 123.83, 125.61, 128.17, 128.33, 128.45 (2 overlapping signals), 135.49, 140.54, 142.28, 147.92, 153.99, 162.56 and 173.93; *m/z* (FAB, NOBA) 551 (MH^+, 89%), 519 (100), 475 (32), 254 (20) and 149 (26); and (ii) **38d** (121 mg, 29%) as a colourless oil (Found: MH^+, 551.2030. $C_{29}H_{30}N_2O_9$ requires *MH*, 551.2030); ν_{max}($CHCl_3$)/cm^{-1} 1780, 1746, 1611, 1524, 1351 and 1267; δ_H(250 MHz, $CDCl_3$) 1.25–1.38 (3 H, m), 1.44 (3 H, d, *J* 7), 1.74 (1 H, m), 1.95 (1 H, m), 2.16 (1 H, m), 2.78 (1 H, m), 3.21 (3 H, s), 3.42 (1 H, dd, *J* 7, 3.5), 3.89 (1 H, dd, *J* 10, 5), 4.19 (1 H, dd, *J* 10, 3.5), 5.12 (1 H, m), 5.23 (2 H, s), 5.26 (2 H, m), 7.28–7.45 (5 H, m), 7.54 (2 H, m) and 8.22 (2 H, m); δ_C(62.9 MHz, $CDCl_3$) 18.38, 23.68, 29.52, 33.15, 47.42, 56.12, 57.39, 57.50, 67.26, 68.08, 72.90, 78.73, 123.68, 123.90, 128.19, 128.47, 128.54 (2 overlapping signals), 135.68, 139.86, 142.39, 148.08, 154.13, 162.71 and 173.11; *m/z* (CI, NH_3) 551 (MH^+, 38%), 519 (100) and 339 (87).

Methyl (4*R*,8*R*,9*R*,10*S*)-4-methoxy-10-[(*R*)-1-hydroxyethyl)]-11-oxo-1-azatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate 41b

A mixture of the ketoazetidinone **35b** (102 mg, 0.24 mmol), methyl oxalyl chloride (89 mg, 0.73 mmol) and triethylamine (74 mg, 0.73 mmol) in dry dichloromethane (5 ml) was stirred at 0 °C for 1 h. The mixture was partitioned between water and dichloromethane. The dichloromethane extracts were washed with aqueous sodium hydrogen carbonate, water and brine, then dried ($MgSO_4$). The solvent was evaporated and the residue dissolved in dry xylene (5 ml). Triethyl phosphite (0.21 ml, 1.21 mmol) was added and the mixture was heated under reflux under nitrogen for 24 h. The solvent was evaporated and the residue chromatographed [ethyl acetate–light petroleum (2:3)] to give *methyl* (4R,8R,9R,10S)-4-*methoxy*-10-[(R)-1-(p-*nitrobenzylcarbonato*)*ethyl*]-11-*oxo*-1-*azatricyclo*[7.2.0.0^{3,8}]-*undec*-2-*enecarboxylate* **40b** (54 mg, 47%), ν_{max}($CHCl_3$)/cm^{-1} 1785, 1750, 1723, 1624, 1610, 1523, 1351 and 1264; δ_H(250 MHz, $CDCl_3$) 1.21–1.73 (4 H, m), 1.45 (3 H, d, *J* 7), 2.05 (2 H, m), 3.16 (1 H, m), 3.27 (3 H, s), 3.36 (1 H, dd, *J* 7, 3), 3.72 (1 H, dd, *J* 7, 3), 3.85 (3 H, s), 4.85 (1 H, m), 5.17 (1 H, m), 5.26 (2 H, s), 7.57 (2 H, d, *J* 8) and 8.26 (2 H, d, *J* 8); δ_C(62.9 MHz, $CDCl_3$) 18.50, 19.08, 31.94, 34.20, 46.44, 52.22, 56.18, 59.80, 63.30, 68.09, 70.98, 72.91, 123.92, 127.54, 128.54, 142.35, 147.60, 148.12, 154.17, 161.42 and 174.40. The *p*-nitrobenzyl carbonate **40b** (40 mg, 0.084 mmol) and palladium on carbon (10%, 8 mg) in ethyl acetate (2 ml) and isopropanol (2 ml) were stirred under an atmosphere of hydrogen for 30 min. The mixture was filtered through Celite, evaporated and chromatographed [ethyl acetate–light petroleum (3:2)] to give the *title compound* **41b** (13 mg, 52%), ν_{max}($CHCl_3$)/cm^{-1} 3620, 3543, 1778, 1722, 1633, 1325 and 1296; δ_H(250 MHz, $CDCl_3$) 1.28–1.62 (3 H, m), 1.33 (3 H, d, *J* 7), 1.74 (1 H, tt, *J* 14, 3), 1.94 (1 H, br s), 2.12 (2 H, m), 3.14 (1 H, m), 3.20 (1 H, dd, *J* 6.5, 3), 3.28 (3 H, s), 3.75 (1 H, dd, *J* 7, 3), 3.87 (3 H, s), 4.24 (1 H, m) and 4.88 (1 H, m).

Methyl (4*S*,8*S*,9*R*,10*S*)-4-methoxy-10-[(*R*)-1-hydroxyethyl)]-11-oxo-1-azatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate 41a

A mixture of the ketoazetidinone **35a** (51 mg, 0.12 mmol), methyl oxalyl chloride (45 mg, 0.36 mmol) and triethylamine (37 mg, 0.36 mmol) in dry dichloromethane (2 ml) was stirred at 0 °C for 1 h. The mixture was partitioned between water and dichloromethane. The dichloromethane extracts were washed with aqueous sodium hydrogen carbonate, water and brine, then dried ($MgSO_4$). The solvent was evaporated and the residue dissolved in dry xylene (5 ml). Triethyl phosphite (0.10 ml, 0.61 mmol) was added and the mixture was heated under reflux under nitrogen for 16 h. The solvent was evaporated and the residue chromatographed [ethyl acetate–light petroleum (1:1)] to give *methyl* (4S,8S,9R,10S)-4-*methoxy*-10-[(R)-1-(p-

nitrobenzylcarbonato)ethyl]-11-*oxo*-1-*azatricyclo*[7.2.0.0^{3,8}]-*undec*-2-*ene*-2-*carboxylate* **40a** (17 mg, 30%), $\nu_{max}(CHCl_3)/cm^{-1}$ 1783, 1750, 1725, 1636, 1610, 1522, 1351 and 1269; δ_H(250 MHz, $CDCl_3$) 1.25–1.68 (3 H, m), 1.43 (3 H, d, *J* 7), 1.84 (2 H, m), 2.08 (1 H, m), 3.20 (1 H, m), 3.24 (3 H, s), 3.39 (1 H, dd, *J* 7.5, 3), 3.86 (3 H, s), 4.17 (1 H, dd, *J* 10, 3), 4.95 (1 H, m), 5.18 (1 H, m), 5.28 (2 H, s), 7.53 (2 H, d, *J* 8) and 8.24 (2 H, d, *J* 8). The *p*-nitrobenzyl carbonate **40a** (17 mg, 0.036 mmol) and palladium on carbon (10%, 4 mg) in ethyl acetate (1 ml) and isopropanol (1 ml) were stirred under an atmosphere of hydrogen for 20 min. The mixture was filtered through Celite, evaporated and chromatographed to give the *title compound* **41a** (5 mg, 47%), $\nu_{max}(CHCl_3)/cm^{-1}$ 3619, 1774, 1721 and 1636; δ_H(250 MHz, $CDCl_3$) 1.33 (3 H, d, *J* 7), 1.35–1.94 (6 H, m), 2.08 (1 H, m), 3.18–3.32 (2 H, m), 3.26 (3 H, s), 3.84 (3 H, s), 4.20 (1 H, dd, *J* 10, 3), 4.24 (1 H, m) and 4.97 (1 H, t, *J* 3).

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