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SYNTHESIS OF THE β-LACTAM ANTIBIOTIC (+)-THIENAMYCIN VIA AN INTERMEDIATE π-ALLYLTRICARBONYLIRON LACTONE COMPLEX

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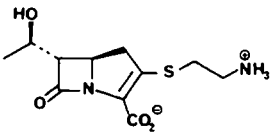
Abstract—The π-allyltricarbonyliron lactone complex (**7**), formed by reaction of *E*-1,2-epoxy-2-methyl-6,6-dimethoxyhex-3-ene (**5**) with co-ordinatively unsaturated iron carbonyl species, was reacted with benzylamine to give a lactam complex (**8**) by an S_N'-like mechanism. This complex upon oxidation with Ce(IV) afforded *cis*-3-isopropenyl-4-[(2',2'-dimethoxy)ethyl]-*N*-benzylazetidin-2-one (**9**) which was chemically modified into *trans*-3-(1'-hydroxyethyl)-4-[(2',2-dimethoxy)ethyl]azetidin-2-one (**13**), a key intermediate previously used in the synthesis of the antibiotic thienamycin. Similar reaction with (*S*)-(−)-α-methylbenzylamine afforded a separable mixture of diastereoisomeric iron lactam complexes (**16** and **17**). These complexes could be individually converted to the corresponding optically active β-lactam derivatives (**27** and **28**) and, hence, are precursors for the synthesis of either natural (+)-thienamycin or unnatural (−)-thienamycin.

While the importance of β-lactam antibiotics has been recognized for many years, the recent discovery of structurally new types of compound[1–4] has generated a flood of interest in their methods of synthesis. Typical examples of such compounds are illustrated by structures **1**–**4**. Of the many novel routes to the azetidinone ring inherent in these systems, the use of iron carbonyl complexes is an attractive and growing area of study.[5] Here we describe in full the use of a π-allyltricarbonyliron lactone complex[6] as a precursor for the synthesis of (+)-thienamycin (**1**), one of the more important members of this class owing to its exceptionally high and broad-spectrum antibacterial activity.



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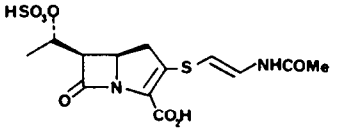

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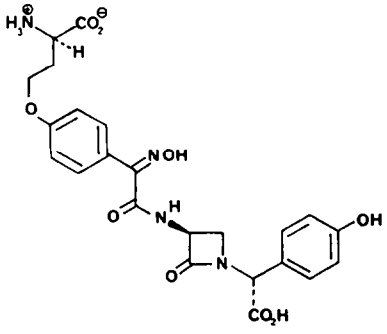

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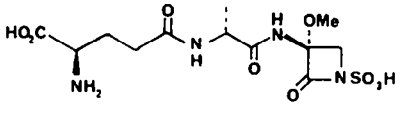
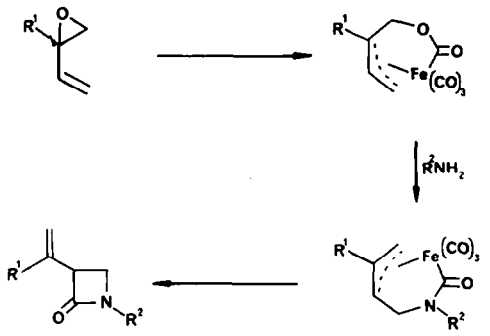


(4)

The route utilizes the reaction of vinyl epoxides with co-ordinatively unsaturated iron carbonyl species to afford π-allyltricarbonyliron lactone complexes.[7] These in turn react with amines to give the corresponding lactam complexes by an overall S_N'-like reaction.[8] The complexes undergo oxidation with ceric ammonium nitrate to afford β-lactam derivatives with control of stereochemical integrity (Scheme 1).[8c] The route is novel in that the final bond of the azetidinone ring is formed between the carbonyl group and C-3 in contrast to more commonly employed strategies for β-lactam synthesis. In addition, the route offers a regiochemical alternative to the well established chlorosulphonylisocyanate (CSI) addition to alkenes to afford β-lactams.[9] Clearly, by an appropriate choice of functional groups one should be able to construct relatively challenging molecules.

Before embarking upon a synthesis of **1** in its optically pure natural (+)-form,[10] we chose to study a route which would provide racemic material in order to define the initial synthetic parameters. Preparation of the necessary substituted vinyl epoxide (**5**) was achieved in 55% overall yield by reaction of 3,3-dimethoxypropanal with dimethyl-(2-oxopropyl)phosphonate, to



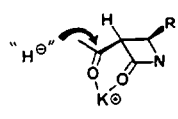
Scheme 1.

give the enone **6**, followed by methylenation with dimethylsulphonium methylide[11] in the normal way. Conversion of **5** to the tricarbonyliron lactone complex **7** was possible in one of two ways, either by treatment with $Fe(CO)_5$ under photolysis conditions (90%) or, more conveniently, by reaction with $Fe_2(CO)_9$ in tetrahydrofuran (84%).[12] The structure of **7** was in accord with previous examples and gave a fully consistent 250 MHz ^{1}H-NMR spectrum. Complex **7** reacted with benzylamine (10 equivalents) in the presence of $ZnCl_2$ to give the ferrilactam complex (**8**) as the major product (57%). Once again the high field ^{1}H-NMR spectrum of **8** was consistent with the structural assignment and was also in accord with related complexes. Oxidation of lactam complex **8** with ceric ammonium nitrate (MeOH, −30°) gave β-lactam **9** (64%) together with the corresponding δ-lactam **10** (24%). The *cis* arrangement of functional groups in **9** was clearly indicated by the coupling constant (5.9 Hz) for H-3–H-4.[13] Low temperature ozonolysis of the isopropenyl side chain of **9** followed by reductive work-up with dimethylsulphide afforded the 3-acetyl substituted β-lactam **11** after rapid epimerization of the C-3 centre during chromatography on silica gel. The H-3–H-4 coupling constant for **11** of 2.2 Hz denoted the *trans* relationship of appending functional groups.[13] Reduction of the acetyl group in **11** could be achieved with high stereoselectivity using potassium tri-sec-butylborohydride† (K-Selectride) in diethyl ether at room temperature to predominantly give the diastereoisomer **12** (74%). Debenzylation of **12** using sodium in liquid ammonia quantitatively provided the parent β-lactam **13**. Alternatively, debenzylation of **9** in a similar fashion gave lactam **14** as a 1 : 1 mixture of *cis* and *trans* isomers. Upon ozonolysis of this mixture followed by base-induced epimerization, a single β-lactam was afforded in 80% yield to which we assign the structure **15**, based on its spectral data (Scheme 2). The above model studies, therefore, constituted a way in which tricarbonyliron lactone may be used in the preparation of β-lactams containing chemically modifiable side chains for thienamycin synthesis.

Reaction of the lactone complex **7** with the chiral amine (*S*)-(−)-α-methylbenzylamine, mediated by $ZnCl_2$·TMEDA, proceeded slowly to give two readily separable diastereoisomeric ferrilactam complexes (**16** and **17**) in 29% and 30% yields, respectively. It was not possible to deduce the absolute configurations of these diastereoisomers using spectroscopic techniques, including nuclear Overhauser effect difference studies, presumably because the cognate chiral benzylic centre is remote from the rest of the molecule. Their structures could not be solved by a crystallographic determination since, in contrast to other lactam complexes (D. M. Hollinshead, S. V. Ley and D. J. Williams, unpublished) both diastereoisomers were non-crystalline. Assignment of the structures was finally achieved by subsequent chemical transformations. The slower reaction of the chiral amine vs benzylamine with **7**, reflects the greater steric requirements in the S_N2' reaction of the bulky amine at C-4 of the complex bearing the dimethoxyethyl substituent. Furthermore, a lowered yield of the lactam complexes (**16** and **17**) was observed owing to concomitant formation of the diene complex **18** (16%) presumably via slow decarboxylation of the ferrilactone **7** under the reaction conditions. The identity of **18** was evident from its high field ^{1}H-NMR spectrum, which exhibited a very high field resonance for the *syn* dienic H-4 and one of the proximate diastereotopic methylene protons at C-1′ (δ 0.38 and 0.77, respectively), due to the shielding effect of the tricarbonyliron moiety. The *syn,syn* nature of the diene was evidenced by a *cis* coupling constant of 8.4 Hz for H-1–H-2. Decarboxylation of π-allyltricarbonyliron lactone complexes has been noted previously.[7f] Independent oxidation of the diastereoisomers (**16** and **17**) with ceric ammonium nitrate gave the *cis* fused β-lactams (**19** and **20**) in 87% and 88% yields, respectively. The *cis* stereochemical assignment was indicated by the large coupling constant (6 Hz) for the vicinal H-3 and H-4. A small amount of the corresponding δ-lactam products (**21** and **22**) accompanied formation of the β-lactams, but were only characterized on the basis of their mass spectral data and IR spectra (ν_{max} 1690 cm^{-1}).

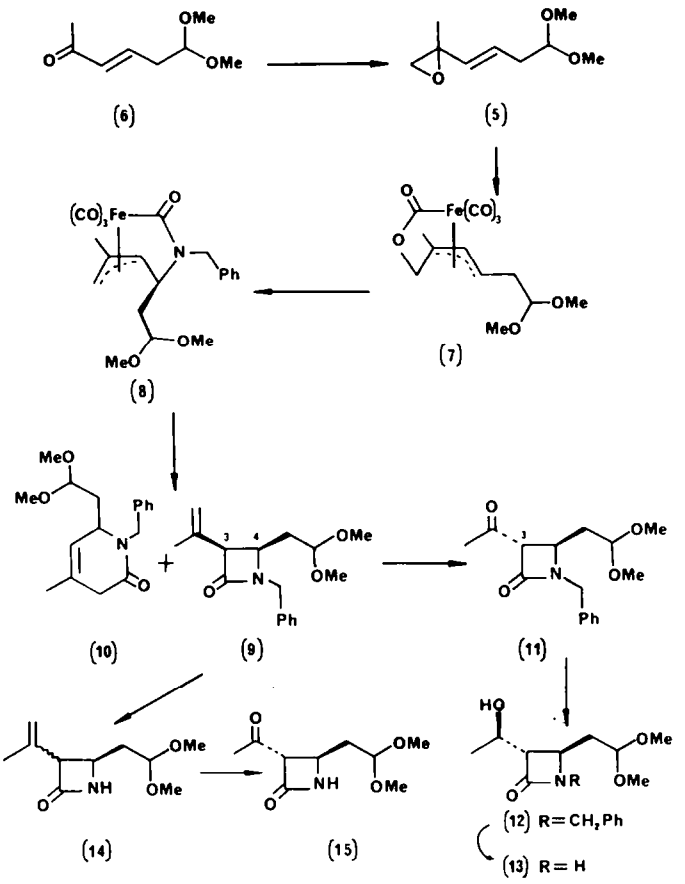
Ozonolysis of the isopropenyl substituted β-lactams (**19** and **20**) proceeded smoothly to give their 3-acetyl derivatives (**23** and **24**), each in 81% yield. As previously observed, the initially formed *cis*-azetidinone rapidly epimerized to give the thermodynamically more stable *trans* product upon chromatography on a short column of silica gel. The *trans* assignment was based on the vicinal H-3–H-4 coupling constants of 2.5 and 3 Hz for **23** and **24**, respectively.

In studies directed towards stereospecific reduction of 3-acetyl azetidinones to give hydroxyethyl derivatives, the bulky hydride reagent K-Selectride, was found to be the method of choice for the creation of the desired *erythro* side chain found in thienamycin.[14,15] The stereochemical course of the reduction is believed to result from co-ordination of the potassium cation to the two carbonyl groups, followed by hydride delivery to the least hindered face of the acetyl function. Using the more covalent lithium cation as in L-Selectride, a reversal in selectivity was observed.[14–16]



Treatment of the β-lactams **23** and **24** with K-Selectride (Et_2O, 0°) gave the *trans-erythro*-

† For a more detailed discussion of the use of this reducing reagent see later.



Scheme 2.

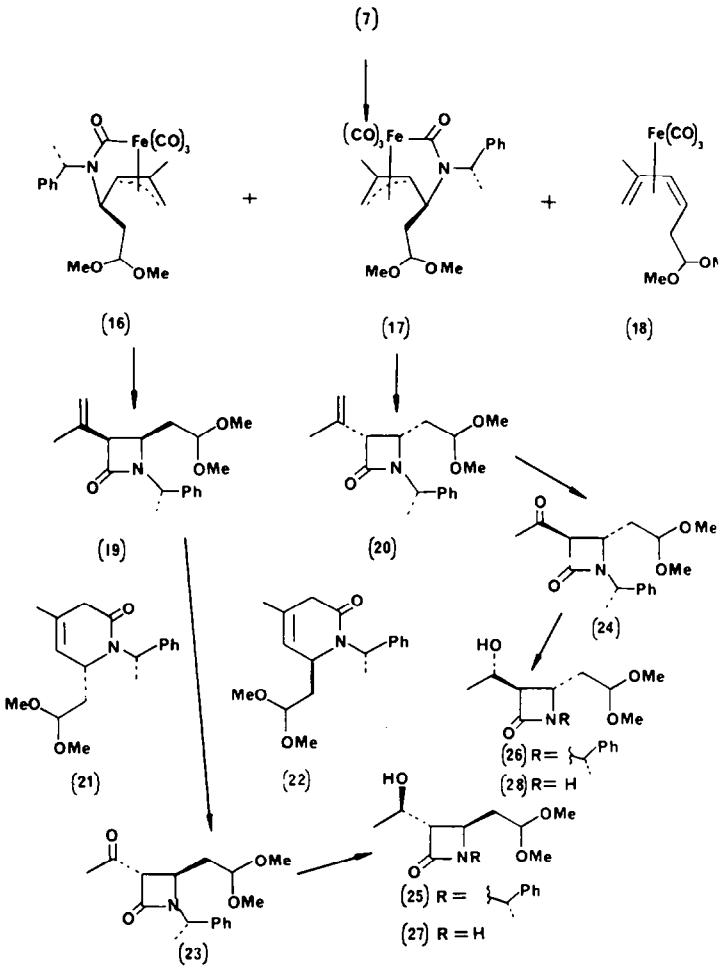
hydroxyethyl derivatives **25** and **26** in good yield. Disappointingly, the observed selectivity of 1′(*R*)–1′(*S*) for **25** and 1′(*S*)–1′(*R*) for **26** was 11:2, which was somewhat lower than that reported in other systems.[14,16] However, treatment of **23** with K-Selectride under the same conditions, but in the presence of KI gave an acceptable ratio of 9:1 for 1′(*R*)–1′(*S*). In the original study involving stereospecific reduction of the acetyl side chain, the addition of KI was found to give little change in overall selectivity, but facilitated isolation of the polar azetidinones.[14] Conversely, in the systems described here, the pre-addition of finely powdered KI was essential to achieve the selectivity in the reduction step: conducting the reaction without prior chelation of KI resulted in a lower 11:2 ratio.

Reductive removal of the benzylic protecting group from **25** and **26** was cleanly effected using sodium in liquid ammonia to give the desired enantiomeric hydroxyethyl β-lactams (**27** and **28**)† in excellent yields (Scheme 3). The enantiomers exhibited identical ^{1}H-NMR, ^{13}C-NMR, IR and mass spectra. The ^{1}H-NMR and IR data agreed well with that reported by Kametani *et al.*[17] The optical rotations of $[\alpha]_D^{22} + 11.4°$ and $-10.7°$ are presumed to be slightly different due to the low, but varying amounts of contaminants epimeric at C-1.

The absolute configurations of the two enantiomers were determined at this stage by their conversion into diastereoisomeric α-methoxy-α-(trifluoromethyl)-phenylacetyl (MTPA) esters according to Dale and Mosher's NMR configuration–correlation method.[18] Acylation of each of the enantiomeric azetidinones (**27** and **28**) with (*R*)-(+)-MTPA and *S*-(−)-MTPA chlorides (cleanly prepared from the corresponding acid using oxalyl chloride and catalytic DMF[19]) gave the four possible diastereoisomeric esters (**29a**, **29b** and **30a**, **30b**) of which two pairs are enantiomers, exhibiting identical properties. (Table 1).

Dale and Mosher's[18] model predicts that a derivative of (*R*)-(+)-MTPA would exhibit an upfield shift for the Me-2′ resonance and a corresponding downfield shift for the H-3, H-4 and CF_3 resonances relative to an (*S*)-(−)-MTPA derivative if the hydroxyl bearing carbon has the *R*-configuration. Examination of the high field ^{1}H-NMR spectra of the diastereoisomeric esters of **27** and **28** shows this to be the case and their structures are assigned accordingly. Support for applying Dale and Mosher's[18] method to a β-lactam possessing a hydroxyethyl substituent comes from similar derivatization experiments utilizing the penam **31** and the thienamycin derivative **32**. The side

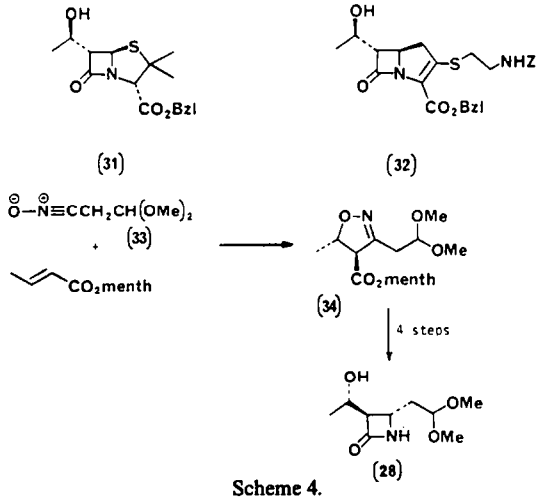
† Both contaminated by small quantities of their corresponding 1′-epimers.



Scheme 3.

Table 1. NMR chemical shifts for (*R*)-(+)-MTPA esters of the *trans*-azetidinones **27** and **28**

Me-2′	H-3	$(MeO)CCF_3$	H-4	$CH(OMe)_2$	CHOH
1.41	3.03	3.51	3.66	4.39	5.45
1.50	2.98	3.54	3.52	4.31	5.45

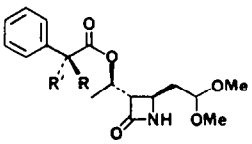


Scheme 4.

chains of both compounds were shown to have the *R*-configuration.[1,20] Further evidence to substantiate the absolute configurations assigned to **27** and **28** is provided by the work of Kametani *et al.*, in which they report a low (16–20%) asymmetric induction in the 1,3-dipolar cycloaddition between the nitrile oxide **33** and (−)-menthyl crotonate.[21] The diastereoisomeric mixture of *trans*-isoxazolines (**34**) was converted in fairly low yield to a mixture of enantiomeric *trans*-β-lactams showing slight predominance of the *un*natural enantiomer **28** (Scheme 4). The enantiomeric excess was determined by conversion into the diastereoisomeric MTPA esters from (*S*)-(−)-α-methoxyl-α-(trifluoromethyl)phenylacetic acid chloride and measuring the signal ratio of the two diastereoisomers by ^{1}H-NMR. The ^{1}H-NMR data assigned to the major isomer agreed closely with that obtained for the diastereoisomeric ester **30b**, derived from **28** and (*S*)-(−)-MTPA, confirming that this was indeed the *un*natural enantiomer.

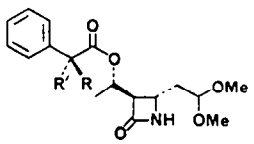
Since the racemic lactam **13** has been converted to protected (±)-thienamycin in eight steps using an adaption of the Merck route,[21] similar reactions using **27** would afford thienamycin (**1**) in its naturally occurring (+)-form; the present work, therefore, constitutes a formal total synthesis.

The novel route described above is reasonably short



(29a) R=CF$_3$ R=OMe

(29b) R=OMeR=CF$_3$



(30a) R=CF$_3$ R=OMe

(30b) R=OMe R=CF$_3$

and may be further modified and developed for the synthesis of a wide range of β-lactam antibiotics.

EXPERIMENTAL

M.ps were determined using a Kofler hot-stage apparatus and are uncorrected. IR spectra were recorded with a Perkin–Elmer 298 spectrometer for solns in $CHCl_3$ unless otherwise stated. ^{1}H-NMR spectra were recorded at 60 MHz using a Bruker WH250 spectrometer for solns in $CDCl_3$ with TMS as internal standard. Mass spectra were obtained using a V.G. Micromass 7070 B spectrometer. Solvents were dried using standard methods. Optical rotation measurements were conducted using a Perkin–Elmer 141 polarimeter at ambient temp. Chromatography was performed on MN-silica gel 60 (230–400 mesh) under pressure.

Preparation of 3,3-*dimethoxypropanal.* A suspension of anhyd. K_2CO_3 (0.51 g, 3.7 mmol) in MeOH (70 ml) was stirred with propynal (2 g, 37 mmol) at 0° and the reaction was warmed slowly to room temp. over 2 hr. The red mixture was diluted with CH_2Cl_2 (150 ml) and washed with H_2O (50 ml) and brine (50 ml) and then dried. After warming with decolourizing charcoal and filtration through a Celite pad, removal of solvent and distillation under reduced pressure gave 3,3-dimethoxypropanal (2.4 g, 55%), b.p. 55°/37 mmHg; IR ν_{max} cm^{-1}: 2800, 1725 and 1620; ^{1}H-NMR (60 MHz): δ 2.68 (2H, dd, J = 5.5 and 2.5 Hz, CH_2), 3.36 (6H, s, OMe), 4.79 [1H, t, J = 5.5 Hz, $CH(OMe)_2$] and 9.70 (1H, t, J = 2.5 Hz, CHO); MS: *m/z* (%) 118 $[M]^+$ (<1), 87 $[M-OMe]^+$ (10), and 75 (60). (Found: C, 50.92; H, 8.32%; $[M]^+$ 118.0630. $C_5H_{10}O_3$ requires: C, 50.84; H, 8.53%; $[M]^+$ 118.0629.)

Preparation of E-6,6-*Dimethoxyhex-3-en-2-one* (**6**). A suspension of finely ground anhyd K_2CO_3 (2.34 g, 17 mmol), 3,3-dimethoxypropanal (2.0 g, 17 mmol) and dimethyl-(2-oxoprop-1-yl)phosphonate (3.9 g, 24 mmol) were stirred in dry C_6H_6 (55 ml) at 0° for 1 hr. A similar quantity of K_2CO_3 was added and the reaction allowed to warm to room temp. After stirring for a further 4 hr, the reaction was diluted with Et_2O (120 ml) then washed with H_2O (25 ml), brine (2 × 30 ml) and dried. Chromatography (50% Et_2O–40:60 petrol) gave *E*-6,6-dimethoxyhex-3-en-3-one, **6** (2.24 g, 84%) as a mobile liquid, b.p. 70°/0.8 mmHg; IR ν_{max} cm^{-1} 2940, 2840, 1690, 1645, 1450, 1360, 1190, 1120, 1070, 975 and 920; ^{1}H-NMR (250 MHz): δ 2.21 (3H, s, COMe), 2.50 (2H ddd, J = 6.5, 5 and 1.5 Hz, Me), 4.43 [1H, t, J = 5 Hz, $CH(OMe)_2$], 6.08 (1H, dt, J = 15.5 and 1.5 Hz, H-3) and 6.69 (1H, dt, J = 15.5 and 6.5 Hz, H-4); MS: *m/z* (%) 127 $[M-OMe]^+$ (11) and 75 (100). (Found: C, 60.49; H, 8.78%; $[M-OMe]^+$ 127.0755. $C_8H_{14}O_2$ requires: C, 60.74, H, 8.92%; $[M-OMe]^+$ 127.0759.)

Preparation of E-1,2-*epoxy*-2-*methyl*-6,6-*dimethoxyhex*-3-*ene* (**5**). To NaH (562 mg of a 50% dispersion in mineral oil, 11.7 mmol) under Ar, dry DMSO (6 ml) was added and the mixture heated to 70° for 0.75 hr until H_2 evolution had ceased. The homogeneous soln was cooled to room temp. and diluted with THF (24 ml). After further cooling (−17°), DMSO (10 ml) then **6** (456 mg; 2.88 mmol) in THF (9 ml) were added to the vigorously stirred soln. The reaction was stirred at this temp. for 35 min before warming to room temp. H_2O (150 ml) was added and the reaction was extracted with Et_2O (2 × 150 ml). The combined Et_2O extracts were washed with H_2O (2 × 30 ml) then brine (2 × 40 ml) and dried. Removal of solvent furnished a mobile liquid which was chromatographed on Florisil (10% Et_2O–40:60 petrol) to give *E*-1,2-epoxy-2-methyl-6,6-dimethoxyhex-3-ene, **5** (324 mg, 66%), as a mobile liquid; IR ν_{max} cm^{-1}: 2835, 1440, 1360, 1120 and 970; ^{1}H-NMR (250 MHz): δ 1.46 (3H, s, Me), 2.39 (2H, ddt, J = 7, 5.5 and 1.5 Hz, CH_2), 2.74 (1H, d, J_{AB} = 6 Hz, CH_2O), 2.82 (1H, d, J_{AB} = 6 Hz, CH_2O), 3.34 (6H, s, OMe), 4.39 [1H, t, J = 5.5 Hz, $CH(OMe)_2$], 5.36 (1H, dt, J = 16 and 1.5 Hz, H-3) and 5.76 (1H, dt, J = 16 and 7 Hz, H-4); MS: *m/z* (%) 171 $[M-H]^+$ (<1), 141 $[M-OMe]^+$ and 75 (100). (Found: C, 62.52; H, 9.46%; $[M-H]^+$ 171.1024. $C_9H_{16}O_3$ requires: C, 62.77; H, 9.36%; $[M-H]^+$ 171.1021.) There was 63 mg (15%) of the starting material remaining.

Preparation of 2-4-η^3-[1-*formyloxy*-(6,6-*dimethoxy*-2-*methylhex*-3-*en*-2-*yl*)]*tricarbonyliron* (**7**). Pentacarbonyliron (2.9 ml, 22 mol) with **5** (630 mg, 3.66 mmol) in dry, degassed C_6H_6 (350 ml) were photolysed in the usual manner whilst following the progress of reaction by TLC (80% Et_2O–40:60 petrol). After 11.5 min, the reaction was filtered, frozen and freeze-dried. The residue was filtered through a Celite pad and chromatographed (80% Et_2O–40:60 petrol) to give 2-4-η^3-[1-formyloxy-(6,6-dimethoxyhex-3-en-2-yl)]tricarbonyliron, **7** (1.13 g, 90.5%), as a viscous yellow oil which slowly crystallized in the fridge, m.p. 51–52°; IR ν_{max} cm^{-1}: 2080, 2010, 1665 and 1120; ^{1}H-NMR (250 MHz): δ 1.98 (1H, ddd, J = 14, 9 and 6.5 Hz, H-5), 2.11 (3H, s, Me-2), 2.55 (1H, ddd, J = 14, 4.5 and 4.5 Hz, H-5), 3.39 (3H, s, OMe), 3.42 (3H, s, OMe), 3.64 (1H, ddd, J = 12.9 and 4.5 Hz, H-4), 3.88 (1H, dd, J = 12 and 1.5 Hz, H-1), 4.48 [1H, dd, J = 6 znd 4.5 Hz, $CH(OMe)_2$] and 5.83 (1H, d, J = 12 Hz, H-3); MS: *m/z* (%) 340 $[M]^+$ (<1), 240, 212, 101 and 75 (100). (Found: C, 45.72; H, 4.53%. $C_{14}H_{16}FeO_7$ requires: C, 45.91; H, 4.74%.)

Alternatively, **5** (1.07 g, 6.18 mmol) was stirred with $Fe_2(CO)_9$ (3.37 g, 9.3 mmol) in THF (100 ml) for 1 hr.[12] Solvent was removed and the residue transferred to a column and eluted with C_6H_6 to remove non-polar by-products, then 30% Et_2O–C_6H_6 to provide the pure ferrilactone complex **7** (1.77 g, 84%), identical to material prepared as above.

Preparation of 2-4-η^3-{1-[*formyl*(*benzylamino*)] - 1 - (2′,2′ - *dimethoxyethyl*) - 3 - *methylbut* - 3 - *en* - 2 - *yl*}*tricarbonyliron* (**8**). A soln of benzylamine (3.2 g, 30 mmol) in Et_2O (50 ml) was added to a stirred soln of complex **7** (0.99 g, 2.9 mmol) and $ZnCl_2$ (25 ml, 7.25 mmol soln in Et_2O) in THF (50 ml) under Ar at room temp. After 6 hr the mixture was worked-up by pouring into dilute citric acid soln, extracting with Et_2O and drying over Na_2SO_4. After removal of the solvent, the residue was subjected to chromatography (50% Et_2O–40:60 petrol) to give complex **8** (0.72 g, 57%); IR ν_{max} cm^{-1}: 3020, 2986, 2960, 2850, 2080, 2020, 1565, 1180, 1120 and 1050; ^{1}H-NMR (250 MHz): δ 1.32 (1H′, m, H-1′), 2.03 (3H, s, Me), 2.20 (1H, ddd, J = 11.8, 7.3 and 4.1 Hz, H-1′), 2.87 (1H, br s, H-4′), 3.08 (3H, s, OMe), 3.31 (3H, s, OMe), 3.52 (1H, ddd, J = 9.2, 6.2 and 4.1 Hz, H-1′), 3.54 (1H, d, J_{AB} = 15.2 Hz, $PhCH_2$), 3.62 (1H, br s, H-4), 4.42 (1H, dd, J = 6.2 and 1.4 Hz, H-2), 4.55 [1H, dd, J = 7.3 and 4.1 Hz, $CH(OMe)_2$], 5.00 (1H, d, J_{AB} = 15.2 Hz, $PhCH_2$) and 7.12–7.35 (5H, m, Ph); MS: *m/z* (%) 289 $[M-Fe(CO)_3]^+$ (3), 200 (38) and 75 (100). (Found: $[M-3CO]^+$ 345.1033. $C_{17}H_{23}FeNO_3$ requires: 345.1027.)

Preparation of cis - 4 - [(2′,2′ - *dimethoxy*)*ethyl*] - 3 - (2′ - *propenyl*) - N - *benzylazetidin*-2-*one* (**9**) *and* 3,6 - *dihydro* - 4 - *methyl* - N - *benzyl* - 2 - *pyridone* (**10**). A soln of **8** (0.68 g, 1.59 mmol) in MeOH (35 ml) was oxidized at −30° by adding a soln of ceric ammonium nitrate (8.66 g, 15.8 mmol) in MeOH (70 ml). After allowing to warm to room temp over 1 hr the solvent was removed under reduced pressure and the residue partitioned between Et_2O (100 ml) and H_2O (20 ml). The organic layer was washed with brine and removal of the solvent gave a residue which was subjected to chromatography (50% Et_2O–40:60 petrol) to give *cis*-4-[(2′,2′-dimethoxy)ethyl] - 3 - 2′ - (2′-propenyl)-*N*-benzylazetidin-2-one, **9** (0.24 g, 64%), as a colourless oil; IR ν_{max} cm^{-1}: 2970,

2930, 1750, 1645, 1450 and 1390; ^{1}H-NMR (250 MHz) δ: 1.76 (3H, s, Me), 1.77 (2H, m, H-1'), 3.18 (3H, s, OMe), 3.22 (3H, s, OMe), 3.77 (1H, dd, J = 11.6 and 5.9 Hz, H-4), 3.87 (1H, d, J = 5.9 Hz, H-3), 4.23 [1H, t, J = 5.9 Hz, $CH(OMe)_2$], 4.26 (1H, d, J_{AB} = 15.6 Hz, CH_2Ph), 4.62 (1H, d, J_{AB} = 15.6 Hz, CH_2Ph), 5.03 (1H, br s, $=CH_2$), 5.15 (1H, br s, $=CH_2$) and 7.24–7.38 (5H, m, Ph), and 3,6-dihydro-4-methyl-*N*-benzyl-2-pyridone, **10** (0.11 g, 24%), as a colourless oil; IR ν_{max} cm^{-1}: 2920, 1645 and 1125; ^{1}H-NMR (60 MHz): δ 1.7 (3H, s, Me), 1.85 (2H, m CH_2), 2.85 (2H, m, H-3), 3.25 (6H, s, OMe), 3.85 (1H, d, J = 15 Hz, $PhCH_2$), 3.75 (1H, m, H-6), 4.3 [1H, t, J = 6 Hz, $CH(OMe)_2$], 5.35 (1H, d, J = 15 Hz, $PhCH_2$), 5.4 (1H, m, H-5) and 7.22–7.38 (5H, m, Ph). (Found: [M]$^+$ 289.1671. $C_{17}H_{23}NO_3$ requires: 289.1678.)

Preparation of trans-3-*acetyl*-4-[(2',2'-*dimethoxy*)*ethyl*]-N-*benzylazetidin*-2-*one* (**11**). A soln of **9** (46 mg, 0.159 mmol) in CH_2Cl_2 (5 ml) was treated with O_3 at −78°. After 1 hr, the mixture was purged with N_2, treated with Me_2S (excess) and warmed to room temp. The mixture was stirred for 1 hr evaporated under reduced pressure and the residue subjected to chromatography (Et_2O) to give *trans*-3-acetyl-4-[(2',2'-dimethoxy)ethyl]-*N*-benzylazetidin-2-one, **11** (39 mg, 84%) as a colourless oil, IR ν_{max} cm^{-1}: 2930, 2830, 1755, 1715, 1415, 1360 and 1190; ^{1}H-NMR (250 MHz): δ 1.70 (1H, ddd, J = 13.8, 8.6 and 6.3 Hz, H-1'), 1.95 (1H, ddd, J = 13.8, 4.9 and 4.5 Hz, H-1'), 2.32 (3H, s, Me), 3.23 (3H, s, OMe), 3.96 (1H, ddd, J = 8.6, 4.5 and 2.2 Hz, H-4), 4.02 (1H, d, J = 2.2 Hz, H-3), 4.18 (1H, d, J_{AB} = 15.2 Hz, CH_2Ph), 4.57 (1H, d, J_{AB} = 15.2 Hz, CH_2Ph), 4.27 (1H, dd, J = 6.3 and 4.9 Hz, H-2') and 7.22–7.40 (5H, m, Ph).

Preparation of trans-4-[(2',2'-*dimethoxy*)*ethyl*-3-(1'-*hydroxyethyl*)-*N*-*benzylazetidin*-2-*one* (**12**). A soln of K-Selectride (0.58 ml of a 0.5 M soln in THF) was added to a stirred soln of **11** (35 mg, 0.12 mmol) in Et_2O (1.2 ml) under Ar at room temp. After 24 hr the mixture was treated with H_2O and extracted with EtOAc. The extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give a residue which was subjected to chromatography (Et_2O) to give *trans*-4-[(2',2'-dimethoxy)ethyl]-3-(1'-hydroxyethyl)-*N*-benzylazetidin-2-one, **12** (26 mg, 74%); IR ν_{max} cm^{-1}: 3450, 2940, 2920, 2860, 1750, 1370 and 1050; ^{1}H-NMR (250 MHz): δ 1.33 (3H, d, J = 6.2 Hz, Me), 1.71 (1H, ddd, J = 14.0, 9.5 and 9.3 Hz, H-1'), 2.02 (1H, ddd, J = 14.0, 5.3 and 4.2 Hz, H-1'), 2.56 (1H, br s, OH), 2.94 (1H, dd, J = 7.8 and 2.0 Hz, H-3), 3.23 (3H, s, OMe), 3.26 (3H, s, OMe), 3.54 (1H, ddd, J = 9.5, 4.2 and 2.0 Hz, H-4), 4.40 [1H, t, J = 5.3 Hz, $CH(OMe)_2$], 4.14 (1H, d, J = 14.9 Hz, CH_2Ph), 4.63 (1H, d, J = 14.9 Hz, CH_2Ph) and 7.24–7.39 (5H, m, Ph).

Preparation of trans-4-[(2',2'-*dimethoxy*)*ethyl*]-3-(1'-*hydroxyethyl*)*azetidin*-2-*one* (**13**). Compound **12** (8 mg, 0.027 mmol) was reacted with Na (*ca* 5 mg) and EtOH (50 μl) in liquid ammonia (10 ml) at −78°. Ammonia was evaporated and the residue treated with sat. NH_4Cl and extracted with Et_2O (2 × 10 ml). Removal of the solvent gave *trans*-4-[(2',2'-dimethoxy)ethyl]-3-(1'-hydroxyethyl)azetidin-2-one, **13** (6 mg), ^{1}H-NMR (250 MHz): δ 1.29 (3H, d, J = 6.5 Hz, Me), 1.98 (2H, m, H-1'), 2.87 (1H, dd, J = 7 and 2.5 Hz, H-3), 3.34 (6H, s, OMe), 3.74 (1H, dt, J = 6.5 and 2.5 Hz, H-4), 4.15 (1H, dq, J = 7 and 6.5 Hz, CHOH), 4.48 [1H, t, J = 5 Hz, $CH(OMe)_2$], 5.47 (1H, br s, OH) and 6.08 (1H, br s, NH).

Preparation of 4-[(2',2'-*dimethoxy*)*ethyl*]-3-(2'-*propenyl*)*azetidin*-2-*one* (**14**). Na metal (*ca* 6 equivalents) was added in small pieces to a soln of **9** (47 mg, 0.16 mmol) in liquid ammonia (20 ml), EtOH (6 equivalents) and Et_2O (5 ml) at −78° until a blue colour persisted. Ammonia was removed by evaporation under a stream of N_2, H_2O was added and the residue extracted with EtOAc. After removal of the solvent the residue was subjected to chromatography (Et_2O) to give 4-[(2'-2'-dimethoxy)ethyl]-3-(2'-propenyl)azetidin-2-one (**14**) (32 mg, 100%) as a 1:1 mixture of *cis–trans* C-3 isomers, IR ν_{max} cm^{-1}: 3280, 2910, 1750, 1450 and 1380; ^{1}H-NMR (250 MHz): δ 1.74 and 1.81 (3H, s, Me), 1.75 and 2.02 (2H, m, H-1'), 3.35 (6H, s, OMe), 3.35 and 3.45 (1H, m, H-3), 3.54 and 3.88 (1H, m, H-4), 4.47 [1H, m, $CH(OMe)_2$], 4.95 and 5.07 (2H, m, $=CH_2$) and 6.28 and 6.35 (1H, br s, NH).

Preparation of trans-3-*acetyl*-4-[(2',2'-*dimethoxy*)*ethyl*]*azetidin*-2-*one* (**15**). The *cis–trans* azetidinones **14** (50 mg, 0.25 mmol) were treated with O_3 at −78° and worked-up in the usual way to give a crude mixture of 3-acetyl derivatives, which were stirred with K_2CO_3 in wet Et_2O for 15 min. Removal of the solvent gave a residue which was subjected to chromatography on Florosil (Et_2O) to give *trans*-3-acetyl-1-[(2',2'-dimethoxy)ethyl]azetidin-2-one, **15** (40 mg, 80%), IR ν_{max} cm^{-1}: 3250, 2920, 2830, 1770, 1715 and 1370; ^{1}H-NMR (250 MHz): δ 1.96 (2H, m, H-1'), 2.32 (3H, s, MeCO), 3.34 (3H, s, OMe), 3.36 (3H, s, OMe), 3.91 (1H, d, J = 2.6 Hz, H-3), 4.11 (1H, dt, J = 2.6 and 6.4 Hz, H-4), 4.46 [1H, t, J = 5.1 Hz, $CH(OMe)_2$] and 6.33 (1H, br s, NH).

Preparation of Z- *and* E-2-4-η^3-{1-[*formyl*((1'S)-*phenylethyl*)*amino*]-1-(2',2'-*dimethoxyethyl*)-3-*methylbut*-3-*en*-2-*yl*}*tricarbonyliron* (**16** and **17**). $ZnCl_2 \cdot$ TMEDA (1.53 g, 6.06 mmol) was suspended in a stirred soln of complex **7** (1.03 g, 3.03 mmol) in Et_2O–THF (1:1, 10 ml) under Ar and (*S*)-(−)-α-methylbenzylamine (1.4 ml, 11.7 mmol) was added in small amounts over 2 hr. The reaction was followed by TLC (75% Et_2O–40:60 petrol) until all the starting material had been consumed (7 hr). The mixture was diluted with Et_2O (50 ml) and poured into 10% citric acid soln (20 ml) and extracted with Et_2O (150 ml). The Et_2O phase was washed with H_2O (2 × 30 ml) then 5% $NaHCO_3$ aq (30 ml) and brine (2 × 30 ml). The soln was dried, solvent evaporated and the residue carefully chromatographed (5%–40% Et_2O–40:60 petrol to give *E*-η^4-[1-(2',2'-dimethoxyethyl)-3-methylbuta-1,3-dienyl]tricarbonyliron, **18** (144 mg, 16%), as a brown oil, IR ν_{max} cm^{-1}: 2910, 2830, 2035, 1970, 1445, 1360 and 1115; ^{1}H-NMR (250 MHz): δ 0.38 (1H, d, J = 2.5 Hz, H-4'), 0.77 (1H, dm, J = 6.9 Hz, H-1'), 1.78 (1H, m, H-4), 1.79 (1H, ddd, J = 11.6, 7.3 and 4.3 Hz, H-1'), 2.01 (1H, m, H-1), 2.16 (3H, s, Me-3), 3.33 (3H, s, OMe), 4.29 [1H, dd, J = 6.9 and 4.3 Hz, $CH(OMe)_2$] and 5.15 (1H, d, J = 8.4 Hz, H-2); MS: *m/z* (%) 268 [M−CO]$^+$, 240 [M−2CO]$^+$ and 212 [M−3CO]$^+$ (100). (Found: C, 48.40; H, 5.75%; [M−CO]$^+$ 268.0389. $C_{11}H_{16}FeO_4$ requires: C, 48.68; H, 5.45%; [M−CO]$^+$ 268.0398.) Further elution gave *Z*-2-4-η^3-{1-[formyl(1'*S*)-phenylethyl)amino]-1-(2',2'-dimethoxyethyl)-3-methylbut-3-en-2-yl}tricarbonyliron, **16** (389 mg, 29%), as a yellow oil, IR ν_{max} cm^{-1}: 2070, 2010, 2000, 1570 and 1045; ^{1}H-NMR (250 MHz): δ 0.79 (1H, ddd, J = 13, 11.5 and 3.5 Hz, H-1'), 1.15 (3H, d, J = 7 Hz, Me), 1.80 (1H, ddd, J = 13, 7.5 and 5.5 Hz, H-1'), 2.01 (3H, s, Me-3), 2.88 (1H, d, J = 1.5 Hz, H-4), 3.16 (3H, s, OMe), 3.28 (3H, s, OMe), 3.66 (1H, dd, J = 1.5 and 1.5 Hz, H-4'), 3.94 (1H, ddd, J = 11.5, 6.5 and 3.5 Hz, H-1'), 4.44 (1H, dd, J = 6.5 and 1.5 Hz, H-2), 4.52 [1H, dd, J = 7.5 and 3.5 Hz, $CH(OMe)_2$], 5.45 (1H, q, J = 7 Hz, PhCH) and 7.12–7.28 (5H, m, Ph); MS: *m/z* (%) 415 [M−CO]$^+$ (1), 387 [M−2CO]$^+$, 359 [M−3CO]$^+$, 303 and 214. (Found: C, 56.71; H, 5.83; N, 3.25%. $C_{21}H_{24}NO_6Fe$ requires: C, 56.90; H, 5.68; N, 3.16%.) Also produced was *E*-2-4-η^3-{1-[formyl((1'*S*)-phenylethyl)amino]-1-(2',2'-dimethoxyethyl)-3-methylbut-3-en-2-yl}tricarbonyliron, **17** (410 mg, 30%), as a yellow oil, IR ν_{max} cm^{-1}: 2930, 2065, 2010, 1990, 1570, 1365 and 1120; ^{1}H-NMR (250 MHz): δ 1.25 (1H, ddd, J = 12.5, 11.5 and 3 Hz, H-1'), 1.37 (3H, d, J = 7 Hz, Me), 2.01 (3H, s, Me-3), 2.03 (1H, ddd, J = 12.5, 8 and 4 Hz, H-1'), 2.66 (3H, s, OMe), 2.79 (1H, d, J = 1.5 Hz, H-4'), 3.24 (3H, s, OMe), 3.45 (1H, dd, J = 11.5, 6.5 and 4 Hz, H-1'), 3.68 (1H, dd, J = 1.5 and 1.5 Hz, H-4), 4.37 (1H, dd, J = 6.5 and 1.5 Hz, H-2), 4.47 [1H, dd, J = 8 and 3 Hz, $CH(OMe)_2$], 5.46 (1H, q, J = 7 Hz, PhCH) and 7.17–7.38 (5H, m, Ph). (Found: C, 57.15; H, 5.90; N, 3.13%. $C_{21}H_{24}NO_6Fe$ requires: C, 56.90; H, 5.68; N, 3.16%.)

Preparation of (4S)-(2',2'-*dimethoxyethyl*)-(3R)-(2'-*propenyl*)-1-[(1'S)-*phenylethyl*]*azetidin*-2-*one* (**19**). To a cooled (−30°) soln of complex **16** (486 mg, 110 mmol) in MeOH (25 ml), a soln of ceric ammonium nitrate (3.01 g, 5.5 mmol) in MeOH (25 ml) was added with stirring. The reaction was allowed to warm slowly to room temp over 2.5 hr. After removal of solvent, the residue was partitioned between CH_2Cl_2 (120 ml) and 3% $NaHCO_3$ aq (60 ml). The organic phase was washed with H_2O then brine and dried. Chromatography (60% Et_2O–40:60 petrol) gave **21** (37 mg,

12%) as an oil, IR ν_{max} cm^{-1}: 2930, 2830, 1690, 1635, 1445, 1380, 1365, 1290, 1110 and 1050; MS: *m/z* (%) $[M]^+$ (< 1), 198 (33), 164 (90) and 105 (100). (Found: $[M]^+$ 303.1839. $C_{18}H_{25}NO_3$ requires: 303.1834.) Also produced was (4*S*)-(2',2'-dimethoxyethyl) - (3*R*) - (2') - propenyl) - 1 - [(1'*S*)-phenylethyl]azetidin-2-one, **19** (292 mg, 87.5%), as a syrup, $[\alpha]_D^{22}$ + 30.7° (c, 0.2 in $CHCl_3$); IR ν_{max} cm^{-1}: 3020, 2930, 2830, 1730, 1375, 1255 and 1185; ^{1}H-NMR (250 MHz): δ 1.66 (2H, dd, J = 6 and 6 Hz, H-1'), 1.72 (3H, d, J = 7.5 Hz, Me), 1.78 (3H, br s, Me), 3.12 (3H, s, OMe), 3.19 (3H, s, OMe), 3.67 (1H, dd, J = 6 and 6 Hz, H-4), 3.81 (1H, br d, J = 6 Hz, H-3), 4.03 [1H, t, J = 6 Hz, $CH(OMe)_2$], 4.82 (1H, q, J = 7.5 Hz, PhCH), 5.02 (1H, br s, $=CH_2$), 5.14 (1H, t, J = 1.5 Hz, $=CH_2$) and 7.24–7.40 (5H, m, Ph); MS: *m/z* (%) 303 $[M]^+$ (1), 271 $[M-MeOH]^+$, 245, 214 and 124 (100). (Found: C, 71.00; H, 8.49; N, 4.51%; $[M^+]$ 303.1827. $C_{18}H_{25}NO_3$ requires: C, 71.26; H, 8.31; N, 4.26%; $[M]^+$ 303.1834.)

Preparation of (4*R*) - (2',2' - *dimethoxyethyl*) - (3*S*) - (2' - *propenyl*) - 1 - [(1'*S*) - *phenylethyl*]*azetidin* - 2 - *one* (**20**). A stirred soln of **17** (637 mg, 1.42 mmol) in MeOH (25 ml) was cooled to −30° and ceric ammonium nitrate (3.49 g, 7.2 mmol) in MeOH (30 ml) added over 10 min. The reaction was warmed to room temp over 2 hr and solvent evaporated. The residue was partitioned between CH_2Cl_2 (200 ml) and 3% $NaHCO_3$ aq (100 ml), and the organic phase washed with H_2O then brine and dried. Chromatography (55% Et_2O–40:60 petrol) afforded β-lactam **20** (379 mg, 88%) as a colourless oil, $[\alpha]_D^{22}$ −31.0° (c, 1.5 in $CHCl_3$); IR ν_{max} cm^{-1}: 2930, 2874, 1725, 1445, 1380, 1350, 1110, 1040 and 905; ^{1}H-NMR (250 MHz): δ 1.69 (3H, d, J = 7 Hz, Me), 1.76 (2H, m, H-1'), 1.78 (3H, s, Me), 3.08 (3H, s, OMe), 3.18 (3H, s, OMe), 3.70 (1H, dd, J = 6.5 and 6 Hz, H-4), 3.81 (1H, d, J = 6 Hz, H-3), 4.13 [1H, t, J = 6 Hz, $CH(OMe)_2$], 4.80 (1H, q, J = 7 Hz, PhCH), 5.00 (1H, br s, $=CH_2$), 5.14 (1H, br t, J = 1.5 Hz, $—CH_2$) and 7.25–7.37 (5H, m, Ph); MS: *m/z* (%) 304 $[M+H]^+$ (< 1), 271 $[M-OMe]^+$, 245, 222, 124 and 105 (100). (Found: $[M-OMe]^+$ 271.1588. $C_{17}H_{21}NO_2$ requires: 271.1572.) The pyridone, **22** (3 mg, < 1%), IR ν_{max} cm^{-1}: 1690: $[M]^+$, 303 was also isolated from this reaction, but not fully characterized.

Preparation of (3*S*) - acetyl - (4*R*) - (2',2' - *dimethoxyethyl*) - 1 - [(1'*S*) - *phenylethyl*]*azetidin* - 2 - *one* (**23**). A soln of the β-lactam **19** (271 mg, 0.89 mmol) in CH_2Cl_2 (10 ml) was cooled to −78° and treated with a stream of dry O_3 until TLC (70% Et_2O–40:60 petrol) showed no further reaction. An excess of Me_2S was added and the reaction allowed to warm to room temp. After 1 hr, solvent was removed with a stream of N_2 and the residue chromatographed (80% Et_2O–40:60 petrol) to give (3*S*) - acetyl - (4*R*) - (2',2' - dimethoxyethyl) - 1 - [(1'*S*) - phenylethyl]azetidin - 2 - one, **23** (219 mg, 81%), as a colourless oil, $[\alpha]_D^{22}$ + 16.6° (c, 2.0 in $CHCl_3$); IR ν_{max} cm^{-1}: 2960, 2830, 1745, 1710, 1445, 1360 and 1120; ^{1}H-NMR (250 MHz): δ 1.54 (1H, dd, J = 14.6 and 2.5 Hz, H-1'), 1.71 (3H, d, J = 7 Hz, Me), 1.78 (1H, ddd, J = 14, 5 and 4 Hz, H-1'), 2.31 (3H, s, COMe), 3.20 (3H, s, OMe), 3.21 (3H, s, OMe), 3.95 (1H, ddd, J = 5, 2.5 and 2.5 Hz, H-4), 3.97 (1H, d, J = 2.5 Hz, H-3) 4.18 [1H, dd, J = 6 and 4.5 Hz, $CH(OMe)_2$], 4.81 (1H, q, J = 7 Hz, PhCH) and 7.25–7.40 (5H, m, Ph); MS: *m/z* (%) 305 $[M]^+$ (1), 273 $[M-MeOH]^+$ (18), 216 (10), 95 (100). (Found: C, 66.88; H, 7.78; N, 4.42%; $[M-MeOH]^+$ 273.1368. $C_{17}H_{23}NO_4$ requires: C, 68.86; H, 7.59; N, 4.59%; $[M-MeOH]^+$ 273.1365.)

Preparation of (3*R*) - *acetyl* - (4*S*) - (2',2' - *dimethoxyethyl*) - 1 - [(1'*S*) - *phenylethyl*]*azetidin* - 2 - *one* (**24**). The azetidinone **20** (354 mg, 1.16 mmol) in CH_2Cl_2 (25 ml) at −78° was treated with a stream of dry O_3 until a faint blue colour persisted. The reaction was treated with excess Me_2S and a trace of MeOH, and allowed to cool to room temp. After 2 hr, removal of solvent gave a single diastereoisomeric acyl β-lactam which was transformed upon passage down a silica column with 70% Et_2O–40:60 petrol, to give (3*R*) - acetyl - (4*S*) - (2',2' - dimethoxyethyl) - 1 - [(1'*S*) - phenylethyl]azetidin - 2 - one, **24** (286 mg, 81%), as a colourless oil, $[\alpha]_D^{22}$ −34.1° (c, 1.1 in $CHCl_3$); IR ν_{max} cm^{-1}: 2940, 2840, 1745, 1710, 1450, 1360, 1120 and 1040; ^{1}H-NMR (250 MHz): δ 1.66 (3H, d, J = 7 Hz, Me), 1.67 (1H, ddd, J = 14, 10.5 and 6 Hz, H-1'), 1.94 (1H, ddd, J = 14, 5 and 4 Hz, H-1'), 2.28 (3H, s, COMe), 3.21 (3H, s, OMe), 3.22 (3H, s, OMe), 3.89 (1H, ddd, J = 10.5, 4 and 3 Hz, H-4), 3.95 (1H, d, J = 3 Hz, H-3), 4.22 [1H, dd, J = 6 and 5 Hz, $CH(OMe)_2$], 4.79 (1H, q, J = 7 Hz, PhCH) and 7.28–7.42 (5H, m, Ph); MS: *m/z* (%) 305 $[M]^+$ (< 1), 273 $[M-MeOH]^+$, 216, 168, 127 and 105 (100). (Found: C, 67.13; H, 7.77; N, 4.44%; $[M-MeOH]^+$ 273.1355. $C_{17}H_{23}NO_4$ requires: C, 66.86; H, 7.59; N, 4.59%; $[M-MeOH]^+$ 273.1365.)

Preparation of (4*R*) - (2',2' - *dimethoxyethyl*) - (3*S*) - [(1'*R*) - *hydroxyethyl*] - 1 - [(1'*S*) - *phenylethyl*]*azetidin* - 2 - *one* (**25**). A soln of **23** (219 mg, 0.72 mmol) with finely powdered KI (141 mg, 0.85 mmol) in Et_2O (7 ml) was stirred for 0.5 hr under Ar before cooling to 0° and adding K-Selectride (1.73 ml of a 1 M soln in THF). The reaction was maintained at 0° for 1 hr before quenching with H_2O. The solvents were evaporated and the residue was chromatographed (30% EtOAc–Et_2O) to give the starting ketone, **23** (30 mg, 14%) and **25** (158 mg, 71%) as a 9:1 mixture of epimers at C-1', IR ν_{max} cm^{-1}: 3470, 2960, 2935, 1740, 1450, 1380, 1125 and 1055; ^{1}H-NMR (250 MHz): δ 1.33 (3H, d, J = 6.5 Hz, Me), 1.53 (1H, ddd, J = 13, 10 and 5 Hz, H-1'), 1.72 (3H, d, J = 7 Hz, Me), 1.82 (1H, ddd, J = 13, 5.5 and 4 Hz, H-1'), 2.66 (1H, br s, OH), 2.85 (1H, dd, J = 7.5 and 1.5 Hz, H-3), 3.19 (3H, s, OMe), 3.23 (3H, s, OMe), 3.53 (1H, ddd, J = 10, 4 and 1.5 Hz, H-4), 4.06 (1H, dq, J = 7.5 and 6.5 Hz, CHOH), 4.32 [1H, dd, J = 5.5 and 5 Hz, $CH(OMe)_2$], 4.72 (1H, q, J = 7 Hz, PhCH) and 7.28–7.38 (5H, m, Ph); ^{13}C-NMR (22.5 MHz): δ 19.0 (q, Me), 35.3 (t, CH_2), 52.3 (q, OMe), 52.3 (d, d, NCH and C-4), 53.5 (q, OMe), 62.7 (d, C-3), 66.4 (d, CHOH), 102.1 [d, $CH(OMe)_2$] and 167.1 (s, C-2); MS: *m/z* (%) 308 $[M+H]^+$ (1), 275 $[M-MeOH]^+$, 218, 146 and 105. (Found: $[M-MeOH]^+$ 275.1502. $C_{16}H_{21}NO_3$ requires: 275.1521.)

Preparation of (4*S*) - (2',2' - *dimethoxyethyl*) - (3*R*) - [(1'*S*) - *hydroxyethyl*] - 1 - [(1'*S*) - *phenylethyl*]*azetidin* - 2 - *one* (**26**). K-Selectride (676 μl of a 1 M soln in THF) was added under Ar to a stirred soln of **24** (78 mg, 0.26 mmol) and KI (943 mg, 0.26 mmol) in Et_2O (2 ml) at 0°. After stirring for 0.75 hr at room temp, the excess reagent was quenched with H_2O at 0° and the solvents evaporated. The residue was chromatographed (3% MeOH—$CHCl_3$) to give the starting ketone, **24** (7 mg, 9%) and **26** (69 mg, 85%) as a mixture (11:2) of C-1' epimers, IR ν_{max} cm^{-1}: 3500, 2980, 1750, 1475, 1400, 1120 and 1040; ^{1}H-NMR (250 MHz): δ 1.29 (3H, d, J = 6.5 Hz, Me), 1.64 (3H, d, J = 7.4 Hz, Me), 1.69 (1H, ddd, J = 14, 10.5 and 5 Hz, H-1'), 2.02 (1H, ddd, J = 14, 6.5 and 3.5 Hz, H-1'), 2.79 (1H, br s, OH), 2.83 (1H, dd, J = 8 and 2.5 Hz, H-3), 3.17 (3H, s, OMe), 3.26 (3H, s, OMe), 3.40 (1H, ddd, J = 10.5, 3.5 and 2.5 Hz, H-4), 3.98 (1H, dq, J = 8 and 6.5 Hz, CHOH), 4.37 [1H, dd, J = 6.5 and 5 Hz, $CH(OMe)_2$], 4.88 (1H, q, J = 7.5 Hz, PhCH) and 7.26–7.39 (5H, m, Ph); ^{13}C-NMR (62.5 MHz): δ 19.7 (q, Me), 21.3 (q, Me), 36.7 (t, CH_2), 52.3 (q, OMe), 52.5 (d, d, NCH and C-4), 53.4 (q, OMe), 62.6 (d, C-3), 66.2 (3, CHOH), 102.1 [d, $CH(OMe)_2$] and 167.1 (s, C-2); MS: *m/z* (%) 308 $[M+H]^+$ (1), 275 $[M-MeOH]^+$, 221, 146 and 105. (Found: $[M-MeOH]^+$ 275.1502. $C_{16}H_{21}NO_3$ requires: 275.1521.)

Preparation of (4*R*) - (2',2' - *dimethoxyethyl*) - (3*S*) - [(1'*R*) - *hydroxyethyl*]*azetidin* - 2 - *one* (**27**). Clean Na (40 mg, 1.73 mmol) was added to EtOH (200 ml) and liquid ammonia (100 ml) at −78° and the blue soln stirred for 5 min before addition of β-lactam **25** (158 mg, 0.51 mmol) in THF (2 ml). The reaction was stirred for a further 10 min and solid NH_4Cl (300 mg, 5.7 mmol) added. Ammonia was evaporated under a stream of N_2 and the residue diluted with CH_2Cl_2, filtered and solvent removed to provide **27** (86 mg, 83%) as a syrup, $[\alpha]_D^{22}$ + 11.4° (c, 1.3 in $CHCl_3$); IR ν_{max} cm^{-1}: 3440, 3400, 2910, 2825, 1750, 1445, 1370, 1125 and 1065; ^{1}H-NMR (250 MHz): δ 1.29 (3H, d, J = 7 Hz, Me), 1.98 (2H, dd, J = 6.5 and 5 Hz, H-1'), 2.87 (1H, dd, J = 7 and 2.5 Hz, H-3), 3.34 (6 H, s, OMe), 3.74 (1H, dt, J = 6.5 and 2.5 Hz, H-4), 4.15 (1H, dq, J = 7 and 6.5 Hz, CHOH), 4.48 [1H, t, J = 5 Hz, $CH(OMe)_2$], 5.31 (1H, s, OH) and 6.59 (1H, br s, NH); ^{13}C-NMR (62.5 MHz): δ 21.2 (q, Me), 37.3 (t, CH_2), 47.5 (d, C-4), 53.0 (q, OMe), 53.1 (q, OMe), 63.7 (d, C-3), 64.7 (d, CHOH), 102.7 [d, $CH(OMe)_2$] and 168.8 (s, C-2); MS: *m/z* (%) 204 $[M+H]^+$ (< 1), 172 $[M-MeOH]^+$, and 85, identical to previously synthesized material.

Preparation of (4*S*) - (2',2' - *dimethoxyethyl*) - (3*R*) - [(1'*S*) - *hydroxyethyl*]*azetidin* - 2 - *one* (**28**). Na (42 mg, 1.83 mmol) was

added to a stirred soln of EtOH (200 μl) and liquid ammonia (100 ml) at −78. After 10 min, the β-lactam, **26** (184 mg, 0.60 mol), was added to the blue soln and stirred for a further 10 min before quenching with solid NH_4Cl (300 mg, 5.7 mmol). Ammonia was evaporated under a stream of N_2 and the residue diluted with CH_2Cl_2 and filtered to give the deprotected **28** (122 mg, 100%) as a syrup, $[\alpha]_D^{22} - 10.7°$ (c, 0.8 in $CHCl_3$), with identical ^{1}H-NMR and IR spectra to **27** above.

Preparation of (4R) - (2',2' - *dimethoxyethyl*) - (3S) - {(1'R) - [(1"R) - α - *methoxy* - α - *trifluoromethylphenylacetyl*]*oxyethyl*}*azetidin* - 2 - *one* (**29a**). A soln of (*R*) - α - methoxy - α - trifluoromethylphenylacetyl chloride (22 mg, 0.10 mmol) in CH_2Cl_2 (100 μl) was added to a stirred soln of **27** (19.5 mg, 0.09 mmol) and *N,N*-4-dimethylaminopyridine (22 mg, 0.21 mmol) in CH_2Cl_2 (3 ml) under Ar at 0°. The mixture was stirred for 1 hr at room temp and solvent evaporated. The residue was diluted with CH_2Cl_2–C_6H_6 (1 : 3), washed with sat. $KHSO_4$ aq and dried. Chromatography ($CHCl_3$) provided **29a** (18.5 mg, 49%) as a syrup, ^{1}H-NMR (250 MHz): δ 1.41 (3H, d, J = 6.5 Hz, Me), 1.89 (2H, dd, J = 8.5 and 6 Hz, H-1'), 3.03 (1H, dd, J = 6.5 and 2.5 Hz, H-3), 3.31 (3H, s, OMe), 3.51 (3H, s, OMe), 3.66 (1H, ddd, J = 8.5, 5.5 and 2.5 Hz, H-4), 4.39 [1H, dd, J = 6 and 5 Hz, $CH(OMe)_2$], 5.45 (1H, dq, J = 6.5 and 6.5 Hz, CHOH) and 7.36–7.58 (5H, m, Ph).

Preparation of (4S) - (2',2' - *dimethoxyethyl*) - (3R) - {(1'S) - [(1"R) - α - *methoxy* - α - *trifluoromethylphenylacetyl*]-*oxyethyl*}*azetidin-2-one* (**30a**). To a stirred soln of **28** (9.5 mg, 0.04 mmol) and *N,N*-4-dimethylaminopyridine (12 mg, 0.10 mmol) in CH_2Cl_2 (1.5 ml) was added a soln of (*R*) - α - methoxy - α - trifluoromethylphenylacetyl chloride (11 mg, 0.05 mmol) in CH_2Cl_2 (50 μl) at 0° under Ar. The mixture was stirred for 1 hr at room temp and the solvent evaporated. The residue was diluted with CH_2Cl_2–C_6H_6 (1 : 3) and washed with sat $KHSO_4$ aq then dried. Chromatography ($CHCl_3$) gave **30a** (16 mg, 95%) as a syrup, ^{1}H-NMR (250 MHz): δ 1.50 (3H, d, J = 6.4 Hz, Me), 1.75 (2H, dd, J = 6.2 and 5.3 Hz, H-1'), 2.98 (1H, dd, J = 8.1 and 2.5 Hz, H-3), 3.31 (6H, s, OMe), 3.52 (1H, m, H-4), 2.54 (3H, br s, OMe), 4.31 [1H, t, J = 5.3 Hz, $CH(OMe)_2$], 5.45 (1H, dq, J = 8.1 and 6.4 Hz, CHOH), 6.13 (1H, br s, NH) and 7.31–7.66 (5H, m, Ph).

In the same manner, the diastereoisomeric **29b** and **30b** were prepared from (*S*) - (−) - α - methyl - α - trifluoromethylphenylacetyl chloride and the azetidinones (**27** and **28**), respectively, each in 85% yield. The ^{1}H-NMR spectrum of **29b** was found to be identical with that obtained for **30a** above and the ^{1}H-NMR spectrum of **30b** matched that of **29a** above.

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