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Studies towards the Synthesis of (+)-Ptilomycalin A; Stereoselective *N*-Acyliminium Ion Coupling Reactions to Enantiopure C-2 Substituted Lactams

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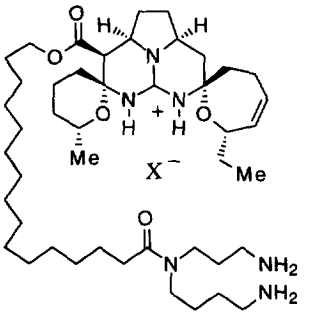
Abstract: Highly stereoselective *N*-acyliminium ion coupling reactions of β-ketoester derived silyl enol ethers with enantiopure lactams derived from (*S*)-malic acid are reported. This reaction type is applied in the synthesis of the enantiopure C-2 substituted lactam **27**, a plausible intermediate in a projected synthesis of ptilomycalin A.

INTRODUCTION

The complex guanidine alkaloid ptilomycalin A[1] was first reported in 1989 after its isolation from the Caribbean sponge *Ptilocaulus spiculifer* and from a Rea Sea sponge of the genus *Hemimycale*. In addition, this guanidine was recently obtained from the Caribbean sponge *Batzella* sp.[2] and from the New Caledonian starfish *Fromia monilis*[3]. With the recent discovery of several related guanidine alkaloids[3,4,5], ptilomycalin A has become a member of a remarkable family of guanidine alkaloids found in several species of warm water sponges. These include the crambescidins[4], the crambescins[5] and the batzelladines[2]. Substantial cytotoxic, antiviral and antifungal activities have been described for ptilomycalin A[1,3] and several of the related guanidines[2,3,4,5].

The absolute stereochemistry of ptilomycalin A has recently been established by Overman and co-workers[6] via an enantioselective total synthesis of (-)-ptilomycalin A, and is shown in Scheme 1. Ptilomycalin A consists of a structurally unique guanidine core and a spermidine unit linked together by a ω-hydroxy fatty acid spacer. A number of different approaches have been reported for the construction of the pentacyclic guanidine moiety[6,7], which reflect the current synthetic interest in these guanidine alkaloids.



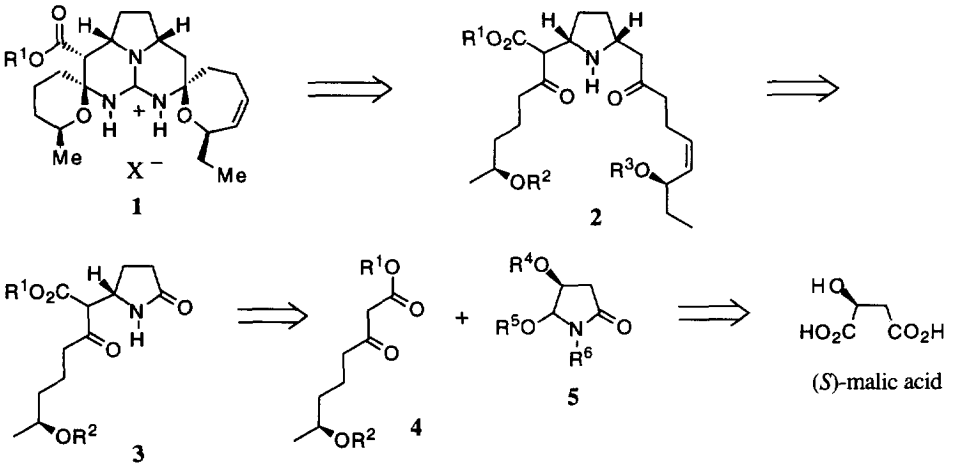
(-)-ptilomycalin A

We were intrigued by the possibility of an efficient synthetic approach to the pentacyclic core of ptilomycalin A based on a stereoselective *N*-acyliminium ion[8] coupling reaction of an enantiopure C-2 substituted lactam. In view of our previous studies[9], (*S*)-malic acid was selected as starting material for the construction of an enantiopure *N*-acyliminium ion precursor, although it recently became apparent that this approach will lead to the unnatural enantiomer of ptilomycalin A[6].

The retrosynthetic analysis of the pentacyclic core of (+)-ptilomycalin A put forward in 1990 is outlined in Scheme 1. The 2,5-disubstituted pyrrolidine **2** was deemed a viable precursor to the pentacyclic guanidine **1**. The key steps in the projected total synthesis consist of the coupling of the appropriate side-chains to the central

pyrrolidine in a stereocontrolled way. The synthetic approach to the monosubstituted lactam **3** was based on an intermolecular *N*-acyliminium ion coupling of β-ketoester **4** and lactam **5**, the latter obtained from (*S*)-malic acid.

This paper presents our investigations on stereoselective *N*-acyliminium ion coupling reactions of silyl enol ethers for the synthesis of enantiopure C-2 substituted lactams[10].

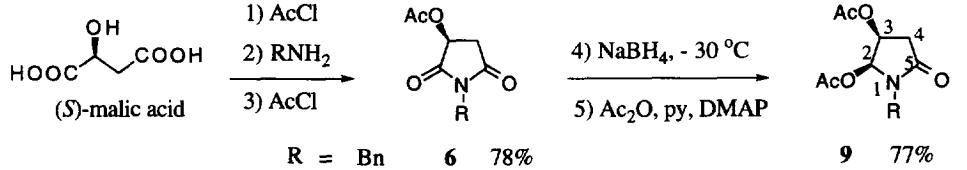


Scheme 1. Retrosynthetic Analysis.

RESULTS AND DISCUSSION

Synthesis of enantiopure N-acyliminium ion precursors

(*S*)-Malic acid has proven to be a useful precursor for *N*-acyliminium ion reactions leading to enantiopure pyrrolidine derivatives.[8,9] So far, silyl enol ethers have not received much attention as nucleophiles in the reaction with the (*S*)-malic acid derived cationic intermediate. Our investigations began with a systematic study of different *N*-protecting groups and silyl enol ethers. Starting from (*S*)-malic acid, three enantiopure *N*-acyliminium ion precursors were prepared (Scheme 2). (*S*)-Malic acid was successively treated with acetyl chloride, an amine and acetyl chloride[11] to afford the imides **6**, **7**, and **8** in good yields. Regio- and stereoselective reductions of the imides were accomplished by reaction with excess $NaBH_4$ in ethanol at -30 °C for 15 min to give the *cis*-products. For the reduction of the *N*-4-methoxybenzyl imide **8**, the use of THF as a cosolvent appeared crucial. In this way precipitation of **8** at -35 °C could be prevented, and a selective reduction was achieved. After acylation of the alcohols with acetic anhydride, the desired enantiopure *N*-acyliminium ion precursors were obtained in good yields. The stereochemistry of the bisacetoxylactams **9**, **10** and **11** followed from the ^1H NMR vicinal coupling constants of 5.3 Hz between H-2 and H-3[12].

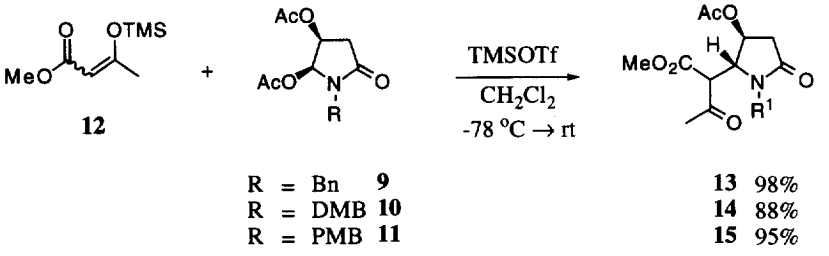


R = Bn	**6**	78%	**9**	77%
R = DMB	**7**	93%	**10**	73%
R = PMB	**8**	93%	**11**	68%

Scheme 2. Synthesis of the *N*-acyliminium ion precursors.

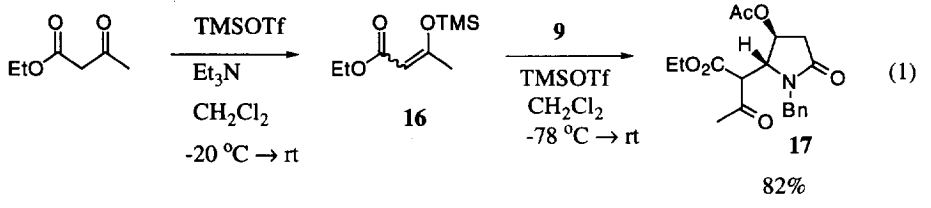
N-Acyliminium ion coupling reactions with silyl enol ethers

For initial screening experiments methyl 3-trimethylsiloxy-2-butenoate (**12**) was selected, which is commercially available as a technical 90:10 mixture of *E* and *Z*-isomers. Scheme 3 shows the results of the coupling reactions of **12** with *N*-acyliminium ion precursors **9**, **10** and **11**. The yields of the coupling reactions were excellent in all cases. Determination of stereochemistry at C-2 was not straightforward, as the coupling products **13-15** were obtained as mixtures of keto and enol tautomers, leading to complex NMR spectra. This problem was solved by chemical modification (*vide infra*), and showed the exclusive formation of 2,3-*trans*-disubstituted lactams.



Scheme 3. Coupling reactions with methyl 3-trimethylsiloxy-2-butenoate.

The coupling reaction was also performed with a silyl enol ether prepared in situ (eq 1). This procedure represents conditions that will be applied in the synthesis of **3** (Scheme 1). First, the silyl enol ether of ethyl acetoacetate **16** was prepared with one equivalent of TMSOTf as the silylating agent in the presence of triethylamine[13]. After cooling to -78 °C, **9** and a second equivalent of TMSOTf as the Lewis acid were added. In this way, the desired coupling product **17** was obtained in 82% yield.

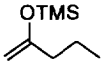
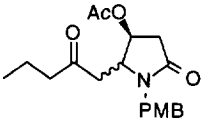
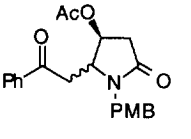
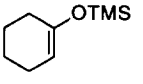
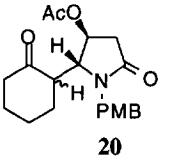
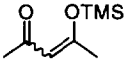
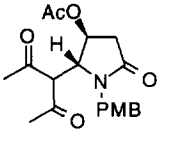


The NMR spectra of the coupled products **13-15** and **17** are very compex because of keto-enol tautomerism. For each of these compounds, keto- and enol tautomers were observed in different ratios. Moreover, in some cases these ratios changed in time. Characteristic signals for the enol-tautomers appear in ^1H NMR at 1.4-1.7 ppm (CH_3C=C) and 8-13 ppm (enol-OH), and in ^{13}C NMR at 18-19 ppm (*C*H_3C=C) and 93-97 ppm (CH_3C=*C*). Characteristic signals for the keto-tautomers appear in ^{13}C NMR at 29-31 ppm (*C*H_3CO) and 199-202 ppm (C=O). In all cases the keto isomers showed two diastereomers as expected. For the enol tautomers only the signals of the *Z*-enol were observed separately. Interpretation of the spectra was facilitated by the discovery that compound **15** gave a solid after neat storage at 4 °C for about one year. NMR spectra of this compound revealed the presence of one isomer, viz. only the *Z*-enol, which was inferred from the chemical shift of the alkene methyl group[14].

In order to study the scope and limitations of coupling reactions with the enantiopure *N*-acyliminium ion precursor **11**, several silyl enol ethers were tested for their reactivity (Table 1). Entries 1-3 describe reactions with silyl enol ethers derived from ketones. Coupling of the kinetic silyl enol ether of 2-pentanone afforded **18** as

a 25:75 mixture of *cis*- and *trans*-isomers in a yield of only 53%. Coupling of **11** with α-trimethylsiloxystyrene produced **19** in 71% yield as a 12:88 mixture of *cis*- and *trans*-isomers. The silyl enol ether of cyclohexanone gave a stereoselective coupling reaction with **11** with respect to C-2: only *trans*-**20** was obtained as a 75:25 mixture of diastereomers in 84% yield. Entry 4 presents a coupling reaction with a silyl enol ether derived from a β-diketone, which was made in situ by treatment of the β-diketone with TMSOTf and Et_3N, (cf. Scheme 3). Reaction of **11** with the silyl enol ether of 2,4-pentanedione provided **21** in good yield as a single product.

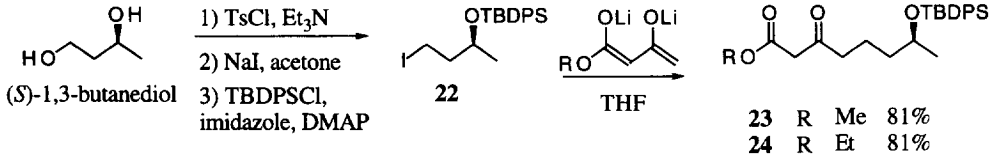
Table 1. Reactions of **11** with Silyl Enol Ethers.

entry	silyl enol ether	product	yield
1	 (1.3 equiv)	 **18**	53% *cis/trans* = 25:75
2	 (1.1 equiv)	 **19**	71% *cis/trans* =12:88
3	 (1.1 equiv)	 **20**	84% 75:25 mixture of diastereomers
4	 (1.1 equiv, made in situ)	 **21**	82%

Reagents and conditions: TMSOTf (1.1 equiv), CH_2Cl_2, -78 °C 1h, rt, 1-1.75 h.

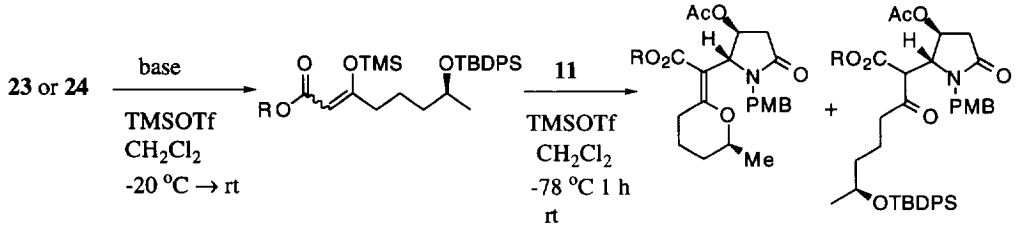
In summary, the enantiopure *N*-acyliminium ion precursor **11** has proven useful in coupling reactions with silyl enol ethers derived from various β-ketoesters, ketones and a β-diketone. Highest stereoselectivity with respect to the lactam ring is obtained for the more sterically demanding nucleophiles. This is in line with earlier reported coupling reactions with allylsilanes[9]. The formation of the *trans*-products as the major compounds obtained may be explained by the possible anchimeric stabilization of the cation by the acetoxy function, thus favouring *trans* addition of the nucleophile[12,15]. *Cis*-stereoselectivity has been observed for Lewis acid induced coupling reactions with allylsilanes and allylstannanes in the case of C-3 silyloxy[15]- and benzyloxy[16] substituents.

With these results in hand, we embarked upon the synthesis of lactam **3**. The syntheses of the enantiopure β-ketoesters **23** and **24**, used in the *N*-acyliminium ion coupling reactions are outlined in Scheme 4 and started with (*S*)-1,3-butanediol. Selective tosylation of the primary hydroxyl group was accomplished by reaction of the diol with *p*-toluenesulphonyl chloride in the presence of triethylamine at low temperature[17]. The corresponding tosylate was converted into the iodide by a reaction with sodium iodide[18] in refluxing acetone to give (*S*)-1-iodobutan-3-ol in 73% overall yield. Now, the *tert*-butyldiphenylsilyl (TBDPS) group was chosen as a protecting group for the secondary alcohol, as this protecting group allows the use of both basic and (Lewis) acidic reaction conditions, combined with easy removal[19]. The optimized procedure for the protection proved to be reaction of **22** with *tert*-butyldiphenylsilyl chloride in CH_2Cl_2 in the presence of imidazole and a catalytic amount of DMAP[20] to give the iodide **22** in 92% yield. Reaction of the iodide **22** with the dianion of methyl or ethyl acetoacetate[21] furnished the desired β-ketoesters **23** and **24** both in 81% yield. Independently, the groups of Overman[6] and Snider[7b] have also reported syntheses of similar compounds.



Scheme 4. Synthesis of the enantiopure β-ketoesters.

The stereoselective coupling reactions (Scheme 5) were carried out with the silyl enol ethers prepared in situ. Thus, the silyl enol ether was generated by treatment with one equivalent of TMSOTf as the silylating agent in the presence of one equivalent of triethylamine[13]. After cooling the mixture to -78 °C, lactam **11** and a second equivalent of TMSOTf as the Lewis acid were added. In this way, lactam **25** containing a tetrahydropyran ring was obtained in 73% yield as the sole product. The trans substitution pattern for the lactam ring[12] was inferred from the H-2-H-3 vicinal coupling constant of 2.0 Hz. The formation of the tetrahydropyran ring in **25** may be explained by assuming Lewis acid-catalysed cyclisation of the silyl ether onto the β-ketoester in the coupled product **26**, followed by silyl transfer and elimination to the cyclic enol ether. Alternatively, the secondary alcohol might be deprotected first, although the TBDPS group is known to be stable in the presence of Lewis acids[19].



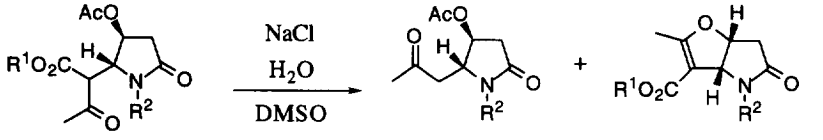
	R	base	products	
23	Me	Et_3N (1.0 equiv)	**25** 73%	-
23	Me	iPr_2EtN (2.0 equiv)	-	**26** 74%
24	Et	iPr_2EtN (2.0 equiv)	-	**27** 75%

Scheme 5. Stereoselective *N*-acyliminium ion couplings with enantiopure β-ketoesters.

To prevent the loss of the TBDPS protecting group and subsequent ring closure to the cyclic enol ether, the *N*-acyliminium ion reaction was performed in the presence of extra base. Thus, the silyl enol ethers of **23** and **24** were prepared in situ with one equivalent of TMSOTf in the presence of *two* equivalents of diisopropylethylamine. After cooling to -78 °C, the lactam **11** and a second equivalent of TMSOTf were added. Indeed, the desired lactams **26** and **27** were now obtained in good yields (Scheme 5) without a trace of the cyclic enol ethers. Determination of the stereochemistry on C-2 was not straightforward, as the coupling products **26** and **27** occurred as mixtures of keto and enol tautomers leading to complex NMR-spectra. Based on the results of the model studies described above, and the *trans* selectivity in the formation of **25**, it was assumed that both **26** and **27** are *trans*-isomers. In the case of **27**, this *trans*-substitution pattern was proven after deprotection of the lactam (*vide infra*).

Derivatization reactions

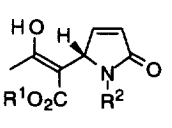
Chemical modification of the products **13-15** and **17** was studied, in order to obtain derivatives which would allow unambiguous assignment of their stereochemistry. First, decarboxylation reactions were investigated, as this would eliminate the interfering ester group (eq 2). Standard conditions for decarboxylation of β-ketoesters were employed[22]. Surprisingly, these conditions did not only give the decarboxylated products **28** and **30**, but also the bicyclic systems **29**, **31** and **32** were produced. A striking difference in reactivity between the methyl ester and ethyl ester was observed. In the case of the methyl esters, the bicyclic product was obtained as the major product. In the decarboxylated products, the stereochemistry followed from the ^{1}H NMR vicinal coupling constants between H-2 and H-3, which is reported to be 0-1 Hz for the *trans*-product and 5-6 Hz for the *cis*-product[12]. In this case H-2 and H-3 clearly show a *trans*-relationship with no vicinal coupling being observed.



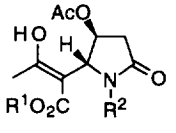
(2)

	R^1	R^2				
13	Me	Bn	**28**	9%	**29**	75%
15	Me	PMB	**30**	17%	**31**	64%
17	Et	Bn	**28**	57%	**32**	24%

Two possible mechanisms for the formation of the bicyclic product can be distinguished, viz. an elimination-addition process and a direct S_N2 type substitution. In the former process, elimination of acetic acid leads to intermediate **33**, which then undergoes an intramolecular 1,4-addition to the enone system. In the latter mechanism, the enol **34**, which is favourably *trans*-oriented, substitutes the acetoxy group in an S_N2 type process. Although neither of these pathways can be excluded at present, the former seems more reasonable.



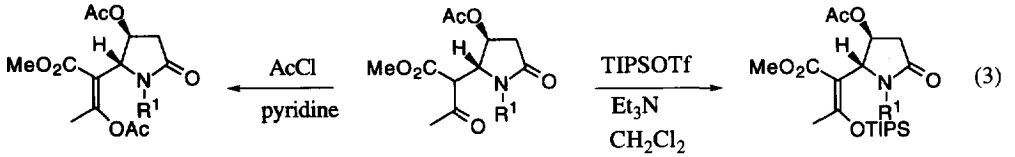
33



34

As the decarboxylation reaction of the β-ketoester did not produce one single product, other derivatization methods were investigated. In order to trap the β-ketoester in a fixed enol configuration, compound **15** was treated with TIPSOTf and Et_3N. In this way, a 66:33 mixture of *E* and *Z* silyl enol ethers was obtained in good

yield. The vicinal coupling constants between H-2 and H-3 were 1.7 and 1.3 Hz for the *E* and *Z* silyl enol ethers, respectively, indicative of a *trans*-substitution pattern for the lactam ring. The *E*/*Z* geometry of the enol compounds was inferred from the chemical shift of the alkene methyl group[14].



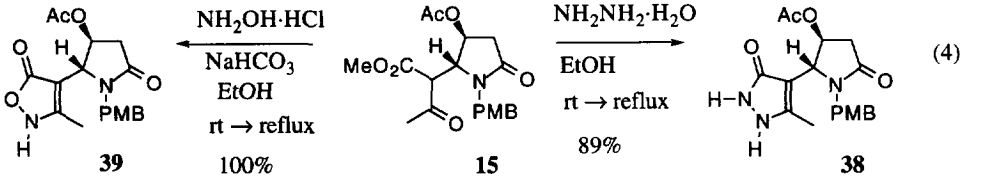
(3)

36 87% R = DMB **14** **35** 90%
37 84% R = PMB **15**

E/*Z* = 66:33

Remarkably, treatment of **14** and **15** with acetyl chloride in pyridine at 0 °C (eq 3) produced exclusively the *E*-enol acetates **36** and **37** in good yield. The vicinal coupling constant between H-2 and H-3 was 1.9 Hz in both **36** and **37**, again clearly indicating *trans*-substitution.

Further proof of the stereochemistry of **15** was obtained by treatment of this compound with hydrazine and hydroxylamine[23] under carefully controlled conditions. In both cases the mixture was first stirred at rt and then heated in refluxing ethanol, giving the pyrazole- and isoxazole-substituted lactams **38** and **39** in excellent yields as single isomers. A singlet was observed for H-2 in the ^{1}H NMR spectra of both **38** and **39**, clearly indicating the *trans*-substitution pattern of the lactam ring.



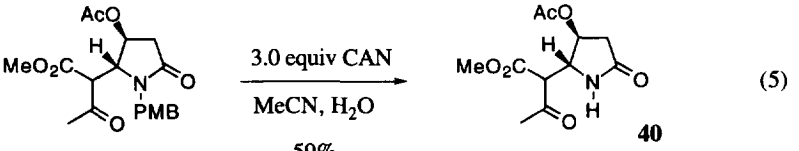
(4)

39 100% **15** 89% **38**

$[\alpha]_D$ +49.0 (*c* 1.0, MeOH) $[\alpha]_D$ +59.0 (*c* 1.0, $CHCl_3$)

N-Deprotection of the lactam

Three different *N*-protecting groups have been used in the synthesis of enantiopure C-2 substituted lactams **13**-**15**. In the proposed synthesis of ptilomycalin A (Scheme 1) the *N*-protecting group in the β-ketoester substituted lactam has to be removed. First, the deprotection of the *N*-benzyl substituted lactam **13** was investigated. Despite several attempts, the *N*-benzyl group could not be selectively removed. Next, the deprotection of the *N*-3,4-dimethoxybenzyl substituted lactam **14** was investigated. Reaction of **14** with DDQ produced only starting material, while treatment with cerium ammonium nitrate (CAN) did not give a selective removal of the *N*-3,4-dimethoxybenzyl group.



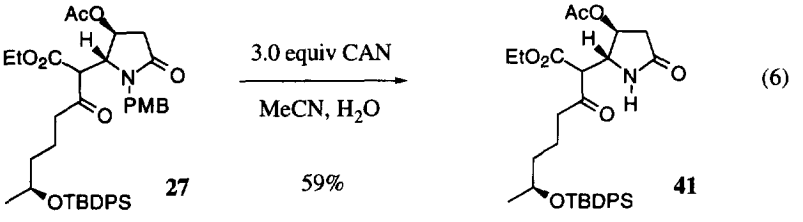
(5)

15 **40**

$[\alpha]_D$ -41.4 (*c* 0.9, $CHCl_3$)

Better results were obtained in the removal of the 4-methoxybenzyl group as the *N*-protecting group. Treatment of β-ketoester **15** with CAN[24] gave the desired deprotected lactam **40** (eq 5). NMR analysis of this product was easy, because it consisted of only two stereoisomers, both keto tautomers. These tautomers are probably stabilized by efficient hydrogen bonding to the amide NH. A similar difference in reactivity between the *N*-benzyl, *N*-3,4-dimethoxybenzyl and *N*-4-methoxybenzyl groups was reported by Smith and co-workers[25] in their synthesis of latrunculin B.

The deprotection of **27** with three equivalents of CAN produced the desired lactam **41** in 59% yield (eq 6). NMR showed the presence of only two keto tautomers, probably because of favourable hydrogen bonding of the carbonyl group to the lactam NH. The vicinal coupling constant between H-2 and H-3 was 0 Hz, clearly indicating a *trans*-substitution pattern of the lactam ring. In conclusion, the enantiopure lactam **41** was obtained via a stereoselective *N*-acyliminium ion coupling reaction of lactam **11** and the β-ketoester **24**.

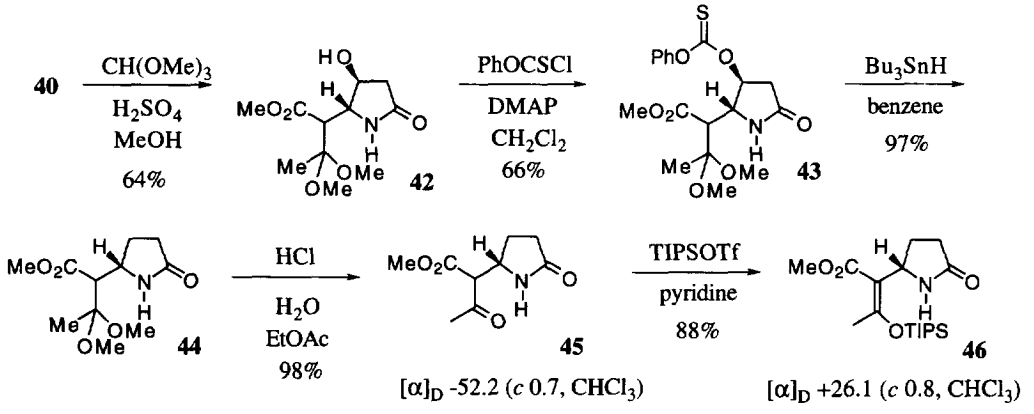


(6)

$[\alpha]_D$ -16.6 (*c* 0.96, $CHCl_3$)

Removal of the directing acetoxy group

In the intermolecular *N*-acyliminium ion coupling reactions of lactams **9-11**, the C-3 acetoxy group in the precursors was used efficiently to direct the C-C bond formation at C-2. In the proposed synthesis of ptilomycalin A (Scheme 1), the C-3 acetoxy group in the C-2,C-3 *trans*-disubstituted lactam thus obtained has to be removed eventually. A practical method to remove a secondary alcohol is the Barton deoxygenation method[26], which involves reduction of the corresponding thiocarbonate with Bu_3SnH in a radical process. It appeared necessary to protect the β-ketoester during this process[27]. Treatment of **40** with trimethyl orthoformate in methanol in the presence of a catalytic amount of H_2SO_4 afforded the desired dimethoxy acetal **42** (see Scheme 6). Under these conditions the acetoxy group was hydrolyzed, allowing conversion to the thiocarbonate. Thus, reaction of **42** with phenyl chlorothionoformate gave the thiocarbonate **43** in 66%. Reductive removal of the thiocarbonate group with Bu_3SnH in refluxing benzene proceeded in high yield to give the acetal **44**.



$[\alpha]_D$ -52.2 (*c* 0.7, $CHCl_3$)

$[\alpha]_D$ +26.1 (*c* 0.8, $CHCl_3$)

Scheme 6. Removal of the directing acetoxy group.

Deprotection of the acetal **44** was accomplished under carefully controlled conditions. Treatment with 0.1M aqueous HCl and ethyl acetate in a two phase system gave the desired C-2 substituted lactam **45** in 98% yield as a 1:1 mixture of the two keto isomers. For the determination of the enantiomeric purity of **45** the β-ketoester was trapped in a fixed enol configuration. Reaction of **45** with TIPSOTf in pyridine selectively gave the *E*-enol ether **46** as a single isomer. The enantiomeric purity of **46** was established by using $Eu(hfc)_3$ as the chiral shift reagent in ^1H NMR. In the case of **46**, ^1H NMR did not reveal the presence of even a trace of the enantiomer. In contrast, rac-**46** which was prepared from succinimide clearly showed double signals in its ^1H NMR spectrum in the presence of $Eu(hfc)_3$. Thus, an efficient route has been developed for the conversion of the *N*-acyliminium ion coupling product **15** to the enantiopure C-2 monosubstituted lactam **45**.

In conclusion, a successful synthesis of an enantiopure C-2 monosubstituted lactam has been achieved starting from (*S*)-malic acid. In this synthesis a stereoselective *N*-acyliminium ion coupling reaction is the key step. The use of the silyl enol ether of a β-ketoester as the nucleophile results in a high yield and stereoselectivity. Furthermore, it has been shown that the 4-methoxybenzyl group is a suitable protecting group for the lactam in this *N*-acyliminium ion reaction. Lactam **15** obtained from the *N*-acyliminium ion coupling was further elaborated towards the enantiopure C-2 substituted lactam **45**. In addition, coupling of the enantiopure β-ketoester **24** with lactam **11** selectively produced the *trans*-substituted lactam **27**, which might serve as a useful intermediate in the synthesis of (+)-ptilomycalin A. Further synthetic studies towards ptilomycalin A based on this approach will be reported in due course.

EXPERIMENTAL

General information. All reactions were carried out under an inert atmosphere of dry nitrogen, unless described otherwise. Standard syringe techniques were applied for transfer of dry solvents. Infrared (IR) spectra were obtained from $CHCl_3$ solutions, using a Perkin-Elmer 298 spectrophotometer or a Bruker IFS 28 FT-spectrophotometer and wavelengths are reported in cm^{-1} Proton nuclear magnetic resonance (^1H NMR) spectra were determined in $CDCl_3$ (unless indicated otherwise) using a Bruker AC 200 (200 MHz), a Bruker WM 250 (250 MHz), a Bruker AMX 300 (300 MHz) or a Bruker AMX 400 (400 MHz) spectrometer. The latter machines were also used for ^{13}C NMR (APT) spectra (50, 63, 75 and 100 MHz resp.) in $CDCl_3$ (unless indicated otherwise). Chemical shifts are given in ppm down field from tetramethylsilane. The relatively slow rotation about the C-N bond in some compounds caused substantial line broadening and sometimes the appearance of double signals in ^1H NMR and ^{13}C NMR spectra. For convenience, both spectra at room temperature and elevated temperature are given. Electron impact (EI) mass spectrometry was carried out using a JEOL JMS SX/SX102A four-sector mass spectrometer, coupled to a JEOL MS-MP7000 data system. The samples were introduced via the direct insertion probe into the ion source. During the high resolution EIMS measurements a resolving power of 5000 (10% valley definition) was used. Fast atom bombardment (FAB) mass spectrometry was carried out using a JEOL JMS SX/SX102A four-sector mass spectrometer, coupled to a JEOL MS-MP7000 data system. The samples were loaded in a matrix solution (glycerol, thioglycerol, nitrobenzylalcohol) onto a stainless steel probe and bombarded with xenon atoms with an energy of 3 KeV. During the high resolution FABMS measurements a resolving power of 5000 (10% valley definition) was used. Elemental analyses were performed by Dornis u. Kolbe Mikroanalytisches Laboratorium, Mülheim a.d. Ruhr, Germany. Optical rotations were measured with a Perkin-Elmer 241 polarimeter in a 1 dm cell in the indicated solvents. R_f values were obtained by using thin-layer chromatography (TLC) on silica gel-coated plastic sheets (Merck silica gel 60 F_{254}) with the indicated solvent(mixture). Chromatographic purification refers to flash chromatography[28] using the indicated solvent (mixture) and Merck silica gel 60 (230-400 mesh) or Janssen Chimica silica gel (0.030-0.075 mm). Melting and boiling points are uncorrected. CH_2Cl_2 and MeCN were distilled from P_2O_5 and stored over MS 3 Å under an atmosphere of dry nitrogen. Benzene and toluene were distilled from P_2O_5 and stored over sodium-wire. Dry THF and Et_2O were distilled from sodium benzophenone ketyl prior to use. DMSO, DMF, MeOH and EtOH were dried and distilled from CaH_2 and stored over MS 3 or 4 Å. Et_3N and pyridine were dried and distilled from KOH pellets. Ratios of mixtures of diastereomers were determined by peak integration in the

^{1}H NMR spectra. 2-Trimethylsiloxy-1-pentene was prepared according to a literature procedure[29]. (*S*)-Malic acid, (*S*)-1,3-butanediol, methyl and ethyl acetoacetate, methyl 3-trimethylsiloxy-2-butenoate, 2,4-pentanedione, α–trimethylsiloxystyrene, 1-(trimethylsiloxy)-cyclohexene and 1,3-cyclohexanedione were commercially available.

Acetic Acid (3*S*)-1-Benzyl-2,5-dioxo-pyrrolidin-3-yl Ester (6). A suspension of (*S*)-malic acid (22.36 g, 167 mmol) in 125 mL of acetyl chloride was heated at reflux for 2 h. The resulting mixture was concentrated in vacuo to give a white solid, which was dissolved in 170 mL of THF. Benzylamine (17.89 g, 167 mmol) was added, the mixture was stirred at room temperature for 4 h and thoroughly concentrated in vacuo. Acetyl chloride was added (150 mL) and the mixture was heated at reflux for 18 h. After concentration in vacuo, recrystallisation (EtOH) afforded **6** (32.2 g, 131 mmol, 78%) as white crystals, mp 61-62.5 °C. R_f 0.8 (EtOAc). $[\alpha]_D$ -25.8 (*c* 1.2, $CHCl_3$). IR 3020, 2940, 1785, 1710, 1495, 1395, 690. ^{1}H NMR (400 MHz) 2.13 (s, 3H, CH_3), 2.64 (dd, *J* = 4.8, 18.3 Hz, 1H, H-4), 3.12 (dd, *J* = 8.7, 18.3 Hz, 1H, H-4'), 4.63-4.71 (m, 2H, CH_2N), 5.41 (dd, *J* = 4.8, 8.7 Hz, 1H, H-3), 7.25-7.38 (m, 5H, Ar-H). ^{13}C NMR (100 MHz) 20.47 (CH_3), 35.69 (C-4), 42.64 (CH_2N), 67.45 (C-3), 128.13, 128.70 and 128.87 (Ar-CH), 135.11 (Ar-C), 169.76, 172.87 and 173.16 (3× C=O). HRMS calculated for $C_{13}H_{13}NO_4$ 247.0845, found 247.0843. Anal. found: C, 63.06; H, 5.42; N, 5.71. Calculated for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.66.

Acetic Acid (3*S*)-2,5-Dioxo-tetrahydrofuran-3-yl Ester. A suspension of (*S*)-malic acid (25 g, 186 mmol) in 135 mL of acetyl chloride was heated at reflux for 2 h. The resulting mixture was concentrated in vacuo to give the title compound (29.5 g, 186 mmol, 100%) as a white solid, mp 51-52 °C. $[\alpha]_D$ -22.9 (*c* 1.1, $CHCl_3$). IR 3010, 2930, 1870, 1800, 1750, 1220. ^{1}H NMR (400 MHz) 2.13 (s, 3H, CH_3), 2.97 (dd, *J* = 6.2, 18.9 Hz, 1H, H-4), 3.35 (dd, *J* = 9.6, 18.9 Hz, 1H, H-4'), 5.48 (dd, *J* = 6.2, 9.6 Hz, 1H, H-3). ^{13}C NMR (75 MHz) 20.12 (CH_3), 34.97 (C-4), 67.70 (C-3), 166.91, 168.20 and 169.96 (3× C=O). HRMS calculated for $C_6H_7O_5$ 159.0298, found 159.0294.

Acetic Acid (3*S*)-1-(3,4-Dimethoxy-benzyl)-2,5-dioxo-pyrrolidin-3-yl Ester (7). To a solution of the crude product of the previous synthesis (3.7 g, 23.4 mmol) in 25 mL of THF was added 3,4-dimethoxy-benzylamine (3.6 mL, 23.9 mmol). The mixture was stirred at room temperature for 18 h and concentrated in vacuo. Acetyl chloride was added (30 mL) and the mixture was heated at reflux for 18 h. After concentration in vacuo, flash chromatography (EtOAc/hexanes 1:2, then 1:1) afforded **7** (6.7 g, 21.7 mmol, 93%) as a viscous yellow oil. R_f 0.35 (EtOAc/hexanes 1:1). $[\alpha]_D$ -18.9 (*c* 1.1, $CHCl_3$). IR 3010, 2955, 2930, 2830, 1750, 1715, 1590, 1510, 810. ^{1}H NMR (200 MHz) 2.13 (s, 3H, CH_3), 2.62 (dd, *J* = 4.8, 18.3 Hz, 1H, H-4), 3.11 (dd, *J* = 8.7, 18.3 Hz, 1H, H-4'), 3.82 (s, 3H) and 3.84 (s, 3H, 2× CH_3O), 4.59 (s, 2H, CH_2N), 5.39 (dd, *J* = 4.8, 8.7 Hz, 1H, H-3), 6.70-6.80 (m, 1H, Ar-H), 6.90-7.00 (m, 2H, Ar-H). ^{13}C NMR (75 MHz) 20.39 (CH_3), 35.54 (C-4), 42.33 (CH_2N), 55.76 and 55.80 (2× CH_3O), 67.47 (C-3), 110.95, 112.13 and 121.40 (Ar-CH), 127.71 (Ar-C-1), 148.77 and 148.81 (Ar-C-3 and Ar-C-4), 169.70, 172.96 and 173.26 (3× C=O). HRMS calculated for $C_{15}H_{17}NO_6$ 307.1056, found 307.1092.

Acetic Acid (3*S*)-1-(4-Methoxy-benzyl)-2,5-dioxo-pyrrolidin-3-yl Ester (8). To a solution of acetic acid (3*S*)-2,5-dioxo-tetrahydrofuran-3-yl ester (14.26 g, 90.2 mmol) in 75 mL of THF was added 4-methoxybenzylamine (13.0 mL, 99.5 mmol). The mixture was stirred at room temperature for 18 h and concentrated in vacuo. Acetyl chloride was added (65 mL) and the mixture was heated at reflux for 18 h. After concentration in vacuo, flash chromatography (EtOAc/hexanes1:2) afforded **8** (23.35 g, 84.2 mmol, 93%) as an orange oil. R_f 0.25 (EtOAc/hexanes 1:2). $[\alpha]_D$ -32.1 (*c* 1.0, $CHCl_3$). IR 3010, 2950, 2830, 1785, 1745, 1710, 1610, 1580, 1510, 1240, 840. ^{1}H NMR (200 MHz) 2.12 (s, 3H, CH_3), 2.59 (dd, *J* = 4.8, 18.3 Hz, 1H, H-4), 3.09 (dd, *J* = 8.7, 18.3 Hz, 1H, H-4'), 3.75 (s, 3H, CH_3O), 4.59 (s, 2H, CH_2N), 5.39 (dd, *J* = 4.8, 8.7 Hz, 1H, H-3), 6.80 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.30 (d, *J* = 8.7Hz, 2H, Ar-H). ^{13}C NMR (75 MHz) 20.43 (CH_3), 35.62 (C-4), 42.00 (CH_2N), 55.15 (CH_3O), 67.46 (C-3), 113.92 (2× Ar-CH), 127.40 (Ar-C-1), 130.37 (2×

Ar-CH), 159.34 (Ar-C-4), 169.75, 173.02 and 173.26 (3× C=O). HRMS calculated for $C_{14}H_{15}NO_5$ 277.0950, found 277.0915.

Acetic Acid (2*S*,3*S*)-1-Benzyl-2-hydroxy-5-oxo-pyrrolidin-3-yl Ester. To a solution of **6** (29.6 g, 120 mmol) in 750 mL of EtOH was added at -35 °C $NaBH_4$ (25 g, 658 mmol). The resulting suspension was stirred at -30 °C for 15 min. The mixture was poured out into a saturated aqueous solution of $NaHCO_3$ (400 mL) and was extracted with CH_2Cl_2 (3 times 400 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give the title compound (24.5 g, 98.3 mmol, 85%) as a white solid. Recrystallisation (EtOAc) gave white crystals, mp 144-145 °C. R_f 0.5 (EtOAc). $[\alpha]_D$ -54.2 (*c* 0.89, $CHCl_3$). IR 3590, 3560, 3380, 3000, 2930, 1735, 1690, 1235, 695. ^{1}H NMR (200 MHz) 2.11 (s, 3H, CH_3), 2.55-2.80 (m, 2H, 2× H-4), 3.20 (d, *J* = 8.0 Hz, 1H, OH), 4.16 (d, *J* = 14.7 Hz, 1H, CH_2N), 4.89 (d, *J* = 14.7 Hz, 1H, CH_2N), 5.05-5.20 (m, 2H, H-2 and H-3), 7.20-7.40 (m, 5H, Ar-H). ^{13}C NMR (100 MHz) 20.69 (CH_3), 34.71 (C-4), 43.45 (CH_2N), 67.74 (C-3), 80.72 (C-2), 127.76, 128.38 and 128.73 (Ar-CH), 135.97 (Ar-C), 170.57 and 171.11 (2× C=O). HRMS calculated for $C_{13}H_{15}NO_4$ 249.1001, found 249.1015. Anal. found: C, 62.49; H, 6.12; N, 5.70. Calculated for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62.

Acetic Acid (2*S*,3*S*)-2-Acetoxy-1-benzyl-5-oxo-pyrrolidin-3-yl Ester (9). To a solution of the product of the previous synthesis (10.0 g, 40.1 mmol) in 100 mL of pyridine were added acetic anhydride (19 mL, 200 mmol) and DMAP (892 mg, 7.3 mmol). After stirring at room temperature for 3 h, the mixture was concentrated in vacuo. Toluene (20 mL) was added and the mixture was concentrated in vacuo (this procedure was repeated 3 times). Flash chromatography (EtOAc) afforded **9** (10.6 g, 36.4 mmol, 91%) as a white solid. Recrystallisation (EtOAc/hexanes 2:1) gave a sample of **9** as white crystals, mp 94 °C. R_f 0.7 (EtOAc). $[\alpha]_D$ -51 (*c* 1.0, $CHCl_3$). IR 3030, 3000, 2930, 1740, 1710, 1240, 695. ^{1}H NMR (400 MHz) 1.92 (s, 3H), and 2.02 (s, 3H, 2× CH_3), 2.65 (dd, *J* = 8.9, 16.6 Hz, 1H, H-4), 2.77 (dd, *J* = 8.3, 16.6 Hz, 1H, H-4'), 4.23 (d, *J* = 14.8 Hz, 1H, CH_2N), 4.68 (d, *J* = 14.8 Hz, 1H, CH_2N), 5.23-5.29 (m, 1H, H-3), 6.26 (d, *J* = 5.3 Hz, 1H, H-2), 7.23-7.33 (m, 5H, Ar-H). ^{13}C NMR (100 MHz) 20.42 and 20.48 (2× CH_3), 33.87 (C-4), 44.66 (CH_2N), 66.01 (C-3), 81.40 (C-2), 127.88, 128.36 and 128.74 (Ar-CH), 135.84 (Ar-C), 169.78, 170.03 and 171.41 (3× C=O). HRMS calculated for $C_{15}H_{17}NO_5$ 291.1106, found 291.1083. Anal. found: C, 61.75; H, 5.89. Calculated for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88.

Acetic Acid (2*S*,3*S*)-1-(3,4-Dimethoxy-benzyl)-2-hydroxy-5-oxo-pyrrolidin-3-yl Ester. To a solution of **7** (2.37 g, 7.71 mmol) in 60 mL of EtOH was added at -35 °C $NaBH_4$ (1.7 g, 45 mmol). The resulting suspension was stirred at -30 °C for 15 min. The mixture was immediately poured out into a saturated aqueous solution of $NaHCO_3$ (80 mL) and extracted with CH_2Cl_2 (3 times 100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo . Flash chromatography (EtOAc/hexanes 3:1, then EtOAc) afforded the title compound (1.97 g, 6.36 mmol, 83%) as a white solid. Recrystallisation (EtOAc) gave crystals, mp 106-107 °C. R_f 0.4 (EtOAc). $[\alpha]_D$ -59.9 (*c* 0.88, $CHCl_3$). IR 3560, 3360, 3000, 2955, 2930, 2830, 1735, 1690, 1585, 1510, 1235, 805. ^{1}H NMR (400 MHz) 2.05 (s, 3H, CH_3), 2.57-2.68 (m, 2H, 2× H-4), 3.79 (s, 6H, 2× CH_3O), 4.02 (d, *J* = 14.5 Hz, 1H, CH_2N), 4.77 (d, *J* = 14.5 Hz, 1H, CH_2N), 5.02-5.12 (m, 2H, H-2 and H-3), 6.72-6.79 (m, 3H, Ar-H) (OH not observed). ^{13}C NMR (75 MHz) 20.61 (CH_3), 34.68 (C-4), 43.20 (CH_2N), 55.81 and 55.85 (2× CH_3O), 67.67 (C-3), 80.56 (C-2), 111.13, 111.77 and 120.90 (Ar-CH), 128.41 (Ar-C-1), 148.60 and 149.07 (Ar-C-3 and Ar-C-4), 170.48 and 170.98 (2× C=O). HRMS calculated for $C_{15}H_{19}NO_6$ 309.1212, found 309.1265. Anal. found: C, 58.12; H, 6.25; N, 4.48. Calculated for $C_{15}H_{19}NO_6$: C, 58.25; H, 6.15; N, 4.53.

Acetic Acid (2*S*,3*S*)-2-Acetoxy-1-(3,4-dimethoxy-benzyl)-5-oxo-pyrrolidin-3-yl Ester (10). To a solution of product of the previous synthesis (1.16 g, 3.74 mmol) in mL of pyridine were added acetic anhydride (1.8 mL, 19 mmol) and DMAP (68 mg, 0.56 mmol). After stirring at room temperature for 3.5 h, the mixture was concentrated in vacuo. Toluene (2 mL) was added and the mixture was concentrated in vacuo (this

procedure was repeated 3 times). Flash chromatography (EtOAc) afforded **10** (1.16 g, 3.30 mmol, 88%) as a colourless oil. R_f 0.65 (EtOAc). $[\alpha]_D$ -35.4 (*c* 0.92, $CHCl_3$). IR 3000, 2955, 2930, 2830, 1740, 1710, 1585, 1510, 1235. ^1H NMR (400 MHz) 1.90 (s, 3H), and 1.96 (s, 3H, 2× CH_3), 2.58 (dd, *J* = 8.9, 16.7 Hz, 1H, H-4), 2.70 (dd, *J* = 8.3, 16.7 Hz, 1H, H-4'), 3.78 (s, 6H, 2× CH_3O), 4.06 (d, *J* = 14.6 Hz, 1H, CH_2N), 4.58 (d, *J* = 14.6 Hz, 1H, CH_2N), 5.14-5.19 (m, 1H, H-3), 6.21 (d, *J* = 5.3 Hz, 1H, H-2), 6.73 (s, 3H, Ar-H). ^{13}C NMR (75 MHz) 20.40 and 20.57 (2× CH_3), 33.92 (C-4), 44.53 (CH_2N), 55.84 (2× CH_3O), 66.01 (C-3), 81.16 (C-2), 111.12, 111.64 and 120.96 (Ar-CH), 128.27 (Ar-C-1), 148.73 and 149.08 (Ar-C-3 and Ar-C-4),169.78, 170.08 and 171.33 (3× C=O). HRMS calculated for $C_{17}H_{21}NO_7$ 351.1318, found 351.1361.

Acetic Acid (2*S*,3*S*)-2-Hydroxy-1-(4-methoxy-benzyl)-5-oxo-pyrrolidin-3-yl Ester. To a solution of **8** (20.1 g, 72.4 mmol) in a mixture of 554 mL of EtOH and 46 mL of THF was added at -35 °C $NaBH_4$ (13.7 g, 360 mmol). The resulting suspension was stirred at -30 °C for 20 min. The mixture was immediately poured out into a saturated aqueous solution of $NaHCO_3$ (900 mL) and extracted with CH_2Cl_2 (3 times 900 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo . Recrystallisation (EtOAc) afforded the title compound (13.6 g, 48.8 mmol, 68%) as white crystals, mp 152-153 °C. $[\alpha]_D$ -82.7 (*c* 1.03, $CHCl_3$). $[\alpha]_D$ -84.0 (*c* 0.50, MeOH). IR 3560, 3350, 3000, 2950, 2930, 2830, 1730, 1685, 1505, 1240, 840. ^1H NMR (200 MHz) 2.12 (s, 3H, CH_3), 2.50-2.80 (m, 2H, 2× H-4), 2.87 (d, *J* = 8.1 Hz, 1H, OH), 3.78 (s, 3H, CH_3O), 4.11 (d, *J* = 14.5 Hz, 1H, CH_2N), 4.82 (d, *J* = 14.5 Hz, 1H, CH_2N), 5.05-5.20 (m, 2H, H-2 and H-3), 6.84 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.22 (d, *J* = 8.7 Hz, 2H, Ar-H). ^{13}C NMR (63 MHz) 20.67 (CH_3), 35.12 (C-4), 43.10 (CH_2N), 55.27 (CH_3O), 67.70 (C-3), 80.80 (C-2), 114.19 (2× Ar-CH), 128.07 (Ar-C-1), 129.85 (2× Ar-CH), 159.27 (Ar-C-4), 170.12 and 170.35 (2× C=O). HRMS calculated for $C_{14}H_{17}NO_5$ 279.1107, found 279.1136. Anal. found: C, 60.08; H, 6.13; N, 5.03. Calculated for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.14; N, 5.02.

Acetic Acid (2*S*,3*S*)-2-Acetoxy-1-(4-methoxy-benzyl)-5-oxo-pyrrolidin-3-yl ester (11). To a solution of product of the previous synthesis (13.77 g, 49.3 mmol) in 125 mL of pyridine were added acetic anhydride (23.5 mL, 249 mmol) and DMAP (900 mg, 7.3 mmol). After stirring at room temperature for 18 h, the mixture was concentrated in vacuo. Toluene (50 mL) was added and the mixture was concentrated in vacuo (this procedure was repeated twice). Flash chromatography (EtOAc) afforded **11** (15.85 g, 49.3 mmol, 100%) as a light yellow solid. Recrystallisation gave a sample of **11**, mp 73.5 °C. R_f 0.6 (EtOAc). $[\alpha]_D$ -52.1 (*c* 1.1, $CHCl_3$). IR 3000, 2960, 2930, 2830, 1740, 1710, 1605, 1580, 1510, 1240, 840. ^1H NMR (200 MHz) 1.95 (s, 3H), and 2.02 (s, 3H, 2× CH_3), 2.62 (dd, *J* = 9.0, 16.6 Hz, 1H, H-4), 2.72 (dd, *J* = 8.3, 16.6 Hz, 1H, H-4'), 3.77 (s, 3H, CH_3O), 4.11 (d, *J* = 14.6 Hz, 1H, CH_2N), 4.65 (d, *J* = 14.6 Hz, 1H, CH_2N), 5.17-5.28 (m, 1H, H-3), 6.23 (d, *J* = 5.3 Hz, 1H, H-2), 6.82 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.16 (d, *J* = 8.6 Hz, 2H, Ar-H). ^{13}C NMR (75 MHz) 20.41 and 20.54 (2× CH_3), 33.91 (C-4), 43.96 (CH_2N), 55.23 (CH_3O), 65.99 (C-3), 81.24 (C-2), 114.07 (2× Ar-CH), 127.88 (Ar-C-1), 129.75 (2× Ar-CH), 159.24 (Ar-C-4), 169.77, 170.05 and 171.29 (3× C=O). HRMS calculated for $C_{16}H_{19}NO_6$ 321.1212, found 321.1206. Anal. found: C, 59.75; H, 5.99; N, 4.41. Calculated for $C_{16}H_{19}NO_6$: C, 59.81; H, 5.96; N, 4.36.

(2*R*,3*S*)-2-(3-Acetoxy-1-benzyl-5-oxo-pyrrolidin-2-yl)-3-oxo-butyric Acid Methyl Ester (13). To a solution of methyl 3-trimethylsiloxy-2-butenoate (315 µL, 1.61 mmol) in 4.8 mL of CH_2Cl_2 were added at -78 °C **9** (420 mg, 1.44 mmol) in 1.6 mL of CH_2Cl_2 and TMSOTf (290 µL, 1.61 mmol) in succession. After stirring at -78 °C for 1h, the solution was allowed to warm to room temperature and was stirred for an additional 45 min. The mixture was poured out into a saturated aqueous solution of $NaHCO_3$ (25 mL) and extracted with CH_2Cl_2 (3 times 25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (EtOAc) afforded **13** (490.5 mg, 1.41 mmol, 98%) as a colourless oil. R_f 0.6 (EtOAc). $[\alpha]_D$ +7.4 (*c* 1.0, $CHCl_3$). IR 3660, 3440, 3020, 3000, 2950, 1730, 1680, 1600, 1440, 1230, 695. ^1H NMR (300 MHz, mixture of keto and enol isomers, assignment with C-H correlation) 1.59-5.33 (m, 15.8H, including: 2.42 (dd, *J* = 5.7, 18.2 Hz) and 2.48 (dd, *J* = 3.0, 18.1 Hz, H-4 2 isomers), 3.05 (dd, *J* = 7.5, 18.1 Hz) and 3.20

(dd, J = 7.2, 18.1 Hz, H-4' 2 isomers), and characteristic signal for enol: 1.59 (s, CH_3C=C)), 7.13-7.36 (m, 5H, Ar-H), 8.97 (s, 0.2H, enol-H). ^{13}C NMR (100 MHz, mixture of keto and enol isomers, assignment with C-H correlation) 18.66 (CH_3C=C), 20.80 and 20.89 (CH_3COO), 29.75 and 29.89 (CH_3CO), 35.77, 37.34, 37.62 and 38.11 (C-4), 43.01, 43.96, 44.92 and 45.55 (CH_2N), 51.93, 52.81 and 52.98 (CH_3O), 59.06, 59.37, 59.47, 62.71, 62.92, 64.35, 69.53, 70.45, 72.96, 73.63 and 85.74 (C-2, C-3 and $CH(CO)_2$), 96.38 (C=CCH_3), 127.21, 127.44, 127.62, 127.74, 127.84, 127.89, 129.99, 128.03, 128.25, 128.34, 128.53, 128.70 and 128.79 (Ar-CH), 135.64, 136.01, 136.26 and 136.44 (Ar-C), 167.19, 167.47, 169.99, 170.43, 171.76, 172.27, 173.00, 173.38 and 177.28 (3× C=O), 199.74 and 200.53 (C=O ketone). HRMS calculated for $C_{18}H_{21}NO_6$ 347.1369, found 347.1371.

(2*R*,3*S*)-2-[3-Acetoxy-1-(3,4-dimethoxy-benzyl)-5-oxo-pyrrolidin-2-yl]-3-oxo-butyric Acid Methyl Ester (14). To a solution of **10** (464.8 mg, 1.32 mmol) in 4.5 mL of CH_2Cl_2 were added at -78 °C methyl 3-trimethylsiloxy-2-butenoate (285 µL, 1.46 mmol) and TMSOTf (265 µL, 1.47 mmol), successively. The solution was stirred at -78 °C for 1 h, and was then allowed to warm to room temperature. After stirring for an additional 1.5 h, the mixture was poured out into a saturated aqueous solution of $NaHCO_3$ (25 mL) and extracted with CH_2Cl_2 (3 times 25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (EtOAc) afforded **14** (477 mg, 1.17 mmol, 88%) as a colourless oil. R_f 0.30 (EtOAc). $[\alpha]_D$ +6.7 (*c* 1.14, $CHCl_3$). IR 3000, 2950, 2830, 1740, 1685, 1600, 1510, 1250. ^1H NMR (200 MHz, mixture of keto and enol isomers) 1.60-5.36 (m, 21.9H, including: 2.39 (dd, J = 3.4, 18.1 Hz, H-4), 3.06 (dd, J = 6.8, 18.4 Hz) and 3.25 (dd, J = 7.4, 18.1 Hz, H-4' 2 isomers), and characteristic signal for enol: 1.65 (s) and 1.69 (s, 2× CH_3C=C)), 6.65-7.30 (m, 3H, Ar-H), 8.8 (s, 0.1H, enol-H). ^{13}C NMR (75 MHz, mixture of keto and enol isomers) 18.87 (C=CCH_3), 20.80 and 20.88 (CH_3COO), 29.79 and 30.00 (CH_3CO), 37.46, 37.75, 38.16 and 38.64 (C-4), 43.57, 44.64 and 45.31 (CH_2N), 51.94, 52.74 and 52.97 (CH_3OCO), 55.84 (2× CH_3O), 58.87, 59.17, 62.56, 62.83, 64.38, 69.47, 69.91, 70.38 and 72.98 (C-2, C-3 and $CH(CO)_2$), 93.13 and 96.41 (C=CCH_3), 110.87, 111.02, 111.13, 120.25, 120.30 and 120.40 (Ar-CH), 128.07, 128.43, 128.94 and 136.44 (Ar-C-1), 148.46, 148.57, 148.68, 149.22 and 149.33 (Ar-C-3 and Ar-C-4), 167.19, 167.54, 169.75, 169.94, 170.35, 172.10, 172.87, 173.32 and 177.24 (3× C=O), 199.78 and 200.57 (C=O ketone). HRMS calculated for $C_{20}H_{25}NO_8$ 407.1580, found 407.1538.

(2*R*,3*S*)-2-[3-Acetoxy-1-(4-methoxy-benzyl)-5-oxo-pyrrolidin-2-yl]-3-oxo-butyric Acid Methyl Ester (15). To a solution of **11** (4.8 g, 14.9 mmol) in 50 mL of CH_2Cl_2 were added at -78 °C methyl 3-trimethylsiloxy-2-butenoate (3.2 mL, 16.4 mmol) and TMSOTf (3.0 mL, 16.6 mmol), successively. The solution was stirred at -78 °C for 1 h, and was then allowed to warm to room temperature. After stirring for an additional 1 h, the mixture was poured out into a saturated aqueous solution of $NaHCO_3$ (100 mL) and extracted with CH_2Cl_2 (3 times 120 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (EtOAc/hexanes 1:1) afforded **15** (5.33 g, 14.1 mmol, 95%) as a light yellow oil. R_f 0.6 (EtOAc). $[\alpha]_D$ +57.4 (*c* 1.3, $CHCl_3$). IR 3000, 2950, 2830, 1740, 1715, 1680, 1605, 1510, 1240. ^1H NMR (400 MHz, mixture of keto and enol isomers) 1.57-5.25 (m, 18.6H, including: 2.27 (dd, J = 6.6, 18.1 Hz) and 2.38 (dd, J = 2.7, 18.0 Hz, H-4), 2.95 (dd J = 8.2, 18.0 Hz) and 3.08 (dd, J = 7.2, 18.0 Hz, H'-4), and characteristic signal for enol: 1.57 (s, CH_3C=C), 6.74-6.78 (m, 2H, Ar-H), 6.96-7.10 (m, 2H, Ar-H), 13.05 (s, 0.4H, enol-OH). ^{13}C NMR (100 MHz, mixture of keto and enol isomers) 18.78 (CH_3C=C), 20.79 and 20.87 (CH_3COO), 29.76 and 29.96 (CH_3CO), 36.42 37.37, 37.69 and 38.13 (C-4), 43.25, 44.24 and 44.84 (CH_2N), 51.89, 52.75 and 52.93 (CH_3OCO), 55.20 (CH_3O), 58.67, 59.00, 59.31, 62.54, 62.68, 64.08, 69.47, 70.43 and 72.9 (C-2, C-3 and $CH(CO)_2$), 96.47 (C=CCH_3), 114.03 and 114.10 (Ar-CH), 127.56, 127.99 and 128.40 (Ar-C-1), 129.15, 129.20, 129.37 and 129.49 (Ar-CH), 159.02, 159.16 and 159.21 (Ar-C-4), 167.23, 167.50, 169.79, 169.96, 171.79, 172.03, 172.77, 173.16 and 177.15 (3× C=O), 199.77 and 200.54 (C=O ketone). HRMS calculated for $C_{19}H_{23}NO_7$ 377.1475, found 377.1449. After storage of neat **15** at 4 °C for one year, a white solid was formed and NMR showed the formation of pure *Z*-enol tautomer. ^1H NMR (400 MHz) 1.59 (s, 3H, CH_3C=C), 1.97 (s, 3H, CH_3COO), 2.40 (dd, J = 2.9, 18.0 Hz, 1H, H-4), 2.97 (dd, J = 8.5, 18.0

Hz, 1H, H'-4), 3.59-3.71 (m, 7H, 2× CH_3O and CH_2N; characteristic signals for CH_3O: 3.64 (s) and 3.71 (s)), 4.09 (s, 1H, H-2), 4.80 (d, J = 14.9 Hz, 1H, CH_2N), 4.99-5.02 (m, 1H, H-3), 6.77 (d, J = 8.5 Hz, 2H, Ar-H), 7.01 (d, J = 8.5 Hz, 2H, Ar-H), 13.08 (s, 1H, OH). ^{13}C NMR (100 MHz) 18.77 (CH_3C=C), 20.87 (CH_3COO), 38.13 (C-4), 43.25 (CH_2N), 51.90 (CH_3OCO), 55.19 (CH_3OAr), 62.54 and 72.97 (C-2 and C-3), 96.46 (C=COH), 114.02 (Ar-CH), 127.99 (Ar-C-1), 129.15 (Ar-CH), 159.01 (Ar-C-4), 170.39, 171.79, 172.04 and 177.15 (C=COH and 3× C=O).

(2*R*,3*S*)-2-(3-Acetoxy-1-benzyl-5-oxo-pyrrolidin-2-yl)-3-oxo-butyric Acid Ethyl Ester (17). To a solution of freshly distilled ethyl acetoacetate (67 mg, 0.52 mmol) in 1.5 mL of CH_2Cl_2 were added at -20 °C Et_3N (75 µL, 0.54 mmol) and TMSOTf (95 µL, 0.53 mmol) in succession. After stirring at room temperature for 1.5 h, the solution was cooled to -78 °C and **9** (134 mg, 0.46 mmol) in 0.5 mL of CH_2Cl_2 and TMSOTf (95 µL, 0.53 mmol) were added successively. The mixture was stirred at -78 °C for 1 h. After warming to room temperature, the mixture was stirred for an additional 18 h, poured out into a saturated aqueous solution of $NaHCO_3$ (25 mL) and extracted with CH_2Cl_2 (3 times 25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (EtOAc) afforded **17** (137.0 mg, 0.38 mmol, 82%) as a colourless oil. R_f 0.7 (EtOAc). $[\alpha]_D$ +13.9 (c 1.0, $CHCl_3$). IR 3650, 3450, 2990, 2930, 1735, 1680, 1630, 1240, 695. ^1H NMR (200 MHz, mixture of keto and enol isomers) 1.17-5.34 (m, 17.8H, including characteristic signal for enol: 1.55 (s, CH_3C=C), 7.12-7.26 (m, 5H, Ar-H), 8.79 (s, 0.2H, enol-H). ^{13}C NMR (63 MHz, mixture of keto and enol isomers) 13.77 and 13.91 (CH_3CH_2), 18.56 (CH_3C=C), 20.68 and 20.77 (CH_3COO), 29.56 and 29.71 (CH_3CO), 37.31, 37.62 and 38.18 (C-4), 43.82, 44.78 and 45.41 (CH_2N), 59.46 and 59.52 (CH), 61.03, 61.98 and 62.16 (CH_3CH_2O), 62.57, 62.75, 63.86, 69.43, 70.64 and 72.90 (CH), 96.49 (C=CCH_3), 127.46, 127.54, 127.66, 127.75, 127.88, 127.94, 128.19, 128.55, 128.61 and 128.63 (Ar-CH), 135.58, 135.95 and 136.39 (Ar-C), 166.64, 166.95, 169.60, 169.79, 170.20, 171.39, 171.99, 172.76, 173.12 and 177.08 (3× C=O), 199.63 and 200.36 (C=O ketone). HRMS calculated for $C_{19}H_{23}NO_6$ 361.1525, found 361.1520.

Acetic Acid (2*R*,3*S*)-1-(4-Methoxy-benzyl)-5-oxo-2-(2-oxo-pentyl)-pyrrolidin-3-yl Ester (18) and the (2*S*,3*S*)-isomer. To a solution of **11** (270 mg, 0.835 mmol) in 2 mL of CH_2Cl_2 were added at -78 °C 2-(trimethylsiloxy)-1-pentene (172 mg, 1.09 mmol) and TMSOTf (166 µL, 0.91 mmol), successively. The solution was stirred at -78 °C for 1 h, and was then allowed to warm to room temperature. After stirring for an additional 1.5 h, the mixture was poured out into a saturated aqueous solution of $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (4 times 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (EtOAc/hexanes 2:1) afforded **18** (153.1 mg, 0.441 mmol, 53%) as a light yellow oil. R_f 0.3 (EtOAc/hexanes 2:1). $[\alpha]_D$ -6.0 (c 1.1, $CHCl_3$). IR 3020, 3000, 2960, 2930, 2900, 2870, 2830, 1735, 1680, 1600, 1580, 1505, 1240, 840. ^1H NMR (400 MHz, 1:3 mixture of *cis* and *trans* isomers) 0.69-0.85 (m, 3H, CH_3), 1.37-1.52 (m, 2H, CH_3CH_2), 1.93 (s) and 1.95 (s, 3H, CH_3CO), 1.97-2.25 (m, 2H, $CH_3CH_2CH_2$), 2.30 (d, J = 18.1 Hz, 0.25H, H-4 *cis*), 2.40 (d, J = 18.1 Hz, 0.75H, H-4 *trans*), 2.45-2.70 (m, 2H, CH_2CO), 2.74 (dd, J = 7.0, 17.6 Hz, 0.25H, H-4'*cis*), 2.98 (dd, J = 7.0, 18.0 Hz, 0.75H, H-4'*trans*), 3.73 (s) and 3.74 (s, 3H, CH_3O), 3.70-3.75 (m, 0.75H, H-2 *trans*), 4.02 (d, J = 15.1 Hz, 0.25H, CH_2N), 4.12-4.18 (m, 0.25H, H-2 *cis*), 4.18 (d, J = 15.0 Hz, 0.75H, CH_2N), 4.47 (d, J = 15.0 Hz, 0.75H, CH_2N), 4.60 (d, J = 15.1 Hz, 0.25H, CH_2N), 4.94 (d, J = 6.8 Hz, 0.75H, H-3 *trans*), 5.26-5.39 (m, 0.25H, H-3 *cis*), 6.77-6.83 (m, 2H, ArH), 7.00-7.16 (m, 2H, Ar-H). ^{13}C NMR (100 MHz, mixture of *cis* and *trans* isomers) 13.47 and 13.57 (CH_3CH_2), 16.71 and 16.89 (CH_3CH_2), 20.70 and 20.85 (CH_3CO), 36.83, 37.40, 41.15, 43.29, 43.87, 44.35, 44.87 and 44.91 (4× CH_2), 55.20 and 55.92 (CH_3O), 60.76, 68.06, 72.16 and 73.67 (C-2 and C-3), 113.91, 114.00 and 114.15 (Ar-CH), 128.16 and 128.34 (Ar-C-1), 129.89 129.19 and 129.42 (Ar-CH), 159.42 (Ar-C-4), 169.59, 170.50, 172.01 and 172.32 (2× C=O), 207.13 and 207.27 (C=O ketone). HRMS-FAB $[M+H]^+$ calculated for $C_{19}H_{26}NO_5$ 348.1811, found 348.1829.

Acetic Acid (2*R*,3*S*)-1-(4-Methoxy-benzyl)-5-oxo-2-(2-oxo-2-phenyl-ethyl)-pyrrolidin-3-yl Ester (19) and the (2*S*,3*S*)-isomer. To a solution of **11** (275 mg, 0.856 mmol) in 3 mL of CH_2Cl_2 were added at -78 °C 1-phenyl-1-trimethylsiloxyethylene (195 μL, 0.95 mmol) and TMSOTf (170 μL, 0.94 mmol), successively. The solution was stirred at -78 °C for 1 h, and was then allowed to warm to room temperature. After stirring for an additional 1.5 h, the mixture was poured out into a saturated aqueous solution of $NaHCO_3$ (10 mL) and was extracted with CH_2Cl_2 (4 times 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (EtOAc/hexanes 1:1 then 3:1) gave two fractions. The first fraction consisted of a 1:2 mixture of *cis* and *trans* **19** (85.1 mg, 0.22 mmol, 26%) as a light yellow oil. The second fraction consisted of pure *trans* **19** (148.1 mg, 0.39 mmol, 45%) as a light yellow oil. R_f 0.35 (EtOAc/hexanes 3:1). Data for *trans*-**19**: $[\alpha]_D$-15.9 (*c* 1.09, $CHCl_3$). IR 3000, 2950, 2825, 1730, 1670, 1600, 1505, 1240, 840. ^{1}H NMR (400 MHz) 2.00 (s, 3H, CH_3), 2.49 (dd, *J* = 1.4, 18.0 Hz, 1H, H-4), 3.06-3.26 (m, 3H, H-4" and CH_2CO), 3.69 (s, 3H, CH_3O), 3.97 (dt, *J* = 1.0, 5.5 Hz, 1H, H-2), 4.18 (d, *J* = 15.0 Hz, 1H, CH_2N), 4.65 (d, *J* = 15.0 Hz, 1H, CH_2N), 5.09 (d, *J* = 6.9 Hz, 1H, H-3), 6.71-6.75 (m, 2H, ArH), 7.10-7.12 (m, 2H, Ar-H), 7.39-7.43 (m, 2H, Ar-H), 7.53-7.57 (m, 1H, Ar-H), 7.74-7.76 (m, 2H, Ar-H). ^{13}C NMR (100 MHz) 20.73 (CH_3), 36.81 and 39.10 (C-4 and CH_2O), 44.13 (CH_2N), 54.95 (CH_3O), 66.68 (C-2), 72.03 (C-3), 113.82 (Ar-CH), 127.70, 128.42 and 129.04 (Ar-CH), 127.93 (Ar-C), 133.34 (Ar-CH), 135.99 (Ar-C), 158.82 (Ar-C-4), 170.30 and 172.14 (2× C=O), 196.25 (C=O ketone). HRMS calculated for $C_{22}H_{23}NO_5$ 381.1576, found 381.1547. Characteristic signals for *cis*-**19**: ^{1}H NMR (400 MHz, mixture of *cis* and *trans* isomers) 1.72 (s, 3H, CH_3), 2.82 (dd, *J* = 7.2, 17.70 Hz, 1H, H-4), 3.73 (s, 3H, CH_3O), 4.37-4.41 (m, 1H, H-2), 4.78 (d, *J* = 15.1 Hz, 1H, CH_2N), 5.40-5.48 (m, 1H, H-3), 6.70-6.78 (m, 2H, ArH), 7.78-7.82 (m, 2H, Ar-H).^{13}C NMR (100 MHz, mixture of *cis* and *trans* isomers) 20.48 (CH_3), 36.17 and 37.45 (C-4 and CH_2O), 43.97 (CH_2N), 56.67 and 67.79 (C-2 and C-3), 114.21 (Ar-CH), 136.31 (Ar-C), 159.15 (Ar-C-4), 169.60 and 171.93 (2× C=O), 196.71 (C=O ketone).

Acetic acid (2*R*,3*S*)-1-(4-methoxy-benzyl)-5-oxo-2-(2-oxo-cyclohexyl)-pyrrolidin-3-yl ester (20). To a solution of **11** (274 mg, 0.853 mmol) in 3 mL of CH_2Cl_2 were added at -78 °C 1-(trimethylsiloxy)-cyclohexene (180 μL, 0.94 mmol) and TMSOTf (250 μL, 1.4 mmol), successively. The solution was stirred at -78 °C for 1 h, and then allowed to warm to room temperature. After stirring for an additional 1 h, the mixture was poured out into a saturated aqueous solution of $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (4 times 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (EtOAc/hexanes 3:1) afforded **20** (258.9 mg, 0.72 mmol, 84%) as a colourless oil. R_f 0.4 (EtOAc/hexanes 3:1). $[\alpha]_D$ +4.6 (*c* 0.91, $CHCl_3$). IR 3010, 2990, 2950, 2930, 2860, 1735, 1705, 1675, 1605, 1510, 1240. ^{1}H NMR (400 MHz, C_6D_6, 1:3 mixture of diastereomers) 0.62-1.60 (m, 10H) and 2.04-2.47 (m, 3H, CH_3, $CH_2CH_2CH_2$, CH_2CO, H-4 and CHCO), 2.59 (dd, *J* = 6.6, 18.2 Hz, 0.25H) and 2.85 (dd, *J* = 7.2, 18.0 Hz, 0.75H, H-4'), 3.25 (s) and 3.27 (s, 3H, CH_3O), 4.01 (d, *J* = 2.1 Hz, 0.75H, H-2), 3.14 (d, *J* = 14.9 Hz, 0.25H, CH_2N), 4.21 (d, *J* = 14.9 Hz, 0.75H, CH_2N), 4.29 (s, 0.75H, H-2), 4.48 (d, *J* = 14.9 Hz, 0.25H, CH_2N), 4.67 (d, *J* = 14.7 Hz, 0.75H, CH_2N), 4.83 (d, *J* = 7.1 Hz, 0.75H) and 5.13 (d, *J* = 6.6 Hz, 0.25H, H-3), 6.69-6.96 (m, 2H, Ar-H), 7.35-7.41 (m, 2H, Ar-H). ^{1}H NMR (400 MHz, $CDCl_3$, 1:3 mixture of diastereomers) 1.17-2.64 (m, 13H, CH_3, $CH_2CH_2CH_2$, CH_2CO, H-4 and CHCO), 2.73 (dd, *J* = 6.8, 18.4 Hz, 0.25H) and 3.11 (dd, *J* = 7.3, 18.1 Hz, 0.75H, H-4'), 3.74-3.77 (m, 3.75H, CH_3O and H-2), 4.06 (d, *J* = 3.3 Hz, 0.25H, H-2), 4.17-4.24 (m, 1H, CH_2N), 4.52 (d, *J* = 15.0 Hz, 0.75H, CH_2N), 4.60 (d, *J* = 15.0 Hz, 0.25H, CH_2N), 4.99 (d, *J* = 6.7 Hz, 0.25H) and 5.03 (d, *J* =7.3 Hz, 0.75H, H-3), 6.79-6.84 (m, 2H, Ar-H), 7.09-7.17 (m, 2H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$, mixture of diastereomers, assignment with C-H correlation) 20.80 and 20.99 (CH_3C), 24.62, 24.76, 26.73, 26.78, 27.15 and 28.85 ($CH_2CH_2CH_2$), 38.06 and 38.77 (C-4), 41.92 (CH_2CO), 44.44 and 45.01 (CH_2N), 50.08 and 51.48 (CH_3CO), 55.24 (CH_3OAr), 62.92 and 64.67 (C-2), 69.44 and 71.17 (C-3), 113.82 and 114.09 (Ar-CH), 128.19 and 128.77 (Ar-C-1), 129.22 and 129.48 (Ar-CH), 158.96 and 159.20 (Ar-C-4), 170.23, 172.53, and 173.25 (2× C=O), 209.46 and 209.67 (C=O ketone). HRMS calculated for $C_{20}H_{25}NO_5$ 359.1733, found 359.1718.

Acetic Acid (2*R*,3*S*)-2-Acetoxy-1-(4-methoxy-benzyl)-5-oxo-pyrrolidin-3-yl Ester (21). To a solution of freshly distilled 2,4-pentanedione (100 µL, 0.97 mmol) in 1.0 mL of CH_2Cl_2 were added at -20 °C Et_3N (140 µL, 1.01 mmol) and TMSOTf (195 µL, 1.08 mmol). After stirring at room temperature for 1.5 h, the solution was cooled to -78 °C and **11** (283.4 mg, 0.88 mmol) in 0.75 mL of CH_2Cl_2 and TMSOTf (195 µL, 1.08 mmol) were added in succession. The mixture was stirred at -78 °C for 1 h. After warming to room temperature, the mixture was stirred for an additional 1.75 h, poured out into a saturated aqueous solution of $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 times 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (EtOAc/hexanes 4:1) afforded **21** (260 mg, 0.72 mmol, 82%) as a yellow solid. R_f0.5 (EtOAc/hexanes 4:1). Recrystallisation (EtOAc/hexanes 3:1) gave a sample of **21** as light yellow crystals, mp 128-128.5 °C. $[\alpha]_D$ -61.2 (*c* 0.94, $CHCl_3$). IR 3020, 3000, 2950, 2930, 2830, 1730, 1685, 1605, 1580, 1505, 1240. ^{1}H NMR (400 MHz) 1.92 (s, 3H), 1.94 (s, 3H) and 2.09 (s, 3H, 3× CH_3CO), 2.36 (d, *J* = 18.1 Hz, 1H, H-4), 3.05 (dd, *J* = 6.6, 18.1 Hz, 1H, H-4'), 3.76 (s, 3H, CH_3O), 3.92 (d, *J* = 6.1 Hz, 1H) and 3.97 (d, *J* = 6.1 Hz, 1H, H-2 and $CH(CO)_2$), 4.16 (d, *J* = 15.1 Hz, 1H, CH_2N), 4.58 (d, *J* = 15.1 Hz, 1H, CH_2N), 5.07 (d, *J* = 6.4 Hz, 1H, H-3), 6.83 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.13 (d, *J* = 8.5 Hz, 2H, Ar-H). ^{13}C NMR (100 MHz) 20.78 (CH_3COO), 30.03 and 30.70 (2× CH_3CO), 37.25 (C-4), 45.00 (CH_2N), 55.27 (CH_3O), 63.26, 68.10 and 70.16 (C-2, C-3 and $CH(CO)_2$), 114.19 (Ar-CH), 127.92 (Ar-C-1), 129.43 (Ar-CH), 159.30 (Ar-C-4), 169.99 and 172.95 (2× C=O), 201.25 and 201.80 (2× C=O ketone). HRMS calculated for $C_{19}H_{23}NO_6$ 361.1525, found 361.1519. Anal. found: C, 62.99; H, 6.45; N, 3.84. Calculated for $C_{19}H_{23}NO_6$: C, 63.15; H, 6.41; N, 3.88.

Toluene-4-sulfonic Acid (*S*)-3-Hydroxy-butyl Ester. To a solution of (*S*)-1,3-butanediol (5.0 g, 55.5 mmol) in 20 mL of CH_2Cl_2 was added at -20 °C Et_3N (9.7 mL, 69 mmol). The reaction mixture was stirred at -20 °C while a solution of tosyl chloride (10.6 g, 55.5 mmol) in 20 mL of CH_2Cl_2 was added dropwise over a period of 4 h. After stirring at -20 °C for 3 h, the mixture was allowed to warm to room temperature. After stirring for an additional 36 h, the mixture was poured out into 20 mL of water. The organic layer was successively washed with 20 mL of a 10% aqueous solution of HCl, 20 mL of a saturated aqueous solution of $NaHCO_3$ and 20 mL of water . The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give the title compound (12.6 g, 51.6 mmol, 93%) as a colourless oil. $[\alpha]_D$ +15.0 (*c* 0.9, $CHCl_3$). Lit.[30] $[\alpha]_D$ -20.5 (*c* 2.32, EtOH). IR 3590, 3540, 3020, 2960, 2920, 1590, 1350, 1170. ^{1}H NMR (400 MHz) 1.18 (d, *J* = 6.3 Hz, 3H, CH_3CHOH), 1.65-1.73 (m, 1H), 1.78-1.86 (m, 1H), 2.45 (s, 3H, Ar-CH_3), 3.91-3.99 (m, 1H), 4.08-4.14 (m, 1H), 4.20-4.26 (m, 1H), 7.34 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.79 (d, *J* = 8.2 Hz, Ar-H). ^{13}C NMR (100 MHz) 21.62 (CH_3CHOH), 23.58 (Ar-CH_3), 37.85 (CH_2), 64.10 (CHOH), 67.80 (CH_2O), 127.87 and 129.86 (Ar-CH), 132.96 and 144.83 (Ar-C). HRMS-FAB $[M+H]^+$ calculated for $C_{11}H_{17}O_4S$ 245.0848, found 245.0820.

(*S*)-4-Iodo-butan-2-ol. To a solution of the above product (12.5 g, 51.1 mmol) in 200 mL of acetone was added sodium iodide (30.6 g, 204 mmol). The mixture was heated at reflux for 1 h, poured out into 100 mL of water, and extracted with toluene (130 and 100 mL). The combined organic layers were washed with 160 mL of a saturated aqueous solution of $Na_2S_2O_5$ and 160 mL of water. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. Kugelrohr destillation afforded the title compound (8.07 g, 40.4 mmol, 79%) as a light yellow oil. $[\alpha]_D$ +30.3 (*c* 1.5, $CHCl_3$). Lit. $[\alpha]_D$ +22 (*c* 1.9, C_6H_6)[31]. IR 3600, 3420, 3000, 2960, 2930, 2880. ^{1}H NMR (400 MHz) 1.21 (d, *J* = 6.2 Hz, 3H, CH_3), 1.89-1.95 (m, 3H, CH_2 and OH), 3.26 (t, *J* = 6.8 Hz, 2H, CH_2I), 3.91 (m, 1H, C*H*OH). ^{13}C NMR (100 MHz) 2.71 (CH_2I), 23.07 (CH_3), 42.10 (CH_2), 67.67 (CHOH). HRMS calculated for C_4H_9OI 199.9699, found 199.9727.

(*S*)-3-*tert*-Butyldiphenylsiloxy-1-iodobutane (22). To a solution of the above product (7.3 g, 36.4 mmol) in 80 mL of CH_2Cl_2 were added imidazole (6.2 g, 91 mmol), TBDPSCl (10.6 mL, 40.7 mmol) and DMAP (0.67 g, 5.5 mmol). The mixture was stirred at room temperature for 17 h, poured out into 25 mL of water, and extracted with CH_2Cl_2 (3 times 50 mL). The combined organic layers were dried ($MgSO_4$) and

concentrated in vacuo. Flash chromatography (EtOAc/hexanes 1:20) afforded **22** (14.8 g, 33.6 mmol, 92%) as a colourless oil. R_f 0.5 (EtOAc/hexanes 1:20). $[\alpha]_D$ -5.7 (*c* 1.0, $CHCl_3$). Lit. $[\alpha]_D$ +6.9 (*c* 2.5, $CHCl_3$) for (*R*)-**22**[7b]. IR 3060, 3000, 2980, 2930, 2880, 2850. ^1H NMR (400 MHz) 1.07-1.09 (m, 12H, $(CH_3)_3C$ and $CH_3CHOTBDPS$), 1.92-2.01 (m, 1H), 2.05-2.13 (m, 1H), 3.24 (t, *J* = 7.6 Hz, 2H, CH_2I), 3.91-3.98 (m, 1H, CHOTBDPS), 7.38-7.48 (m, 6H, Ar-H), 7.70-7.75 (m, 4H, Ar-H). ^{13}C NMR (100 MHz) 2.40 (CH_2I), 19.32 ($(CH_3)_3C$), 22.96 (CH_3), 27.06 ($(CH_3)_3C$), 43.52 (CH_2), 69.80 (CHOTBDPS), 127.50, 127.68, 129.57 and 129.73 (Ar-CH), 133.83 and 134.48 (Ar-C), 135.89 (Ar-CH). MS (EI) 381 (98, M-C_4H_9), 308 (100), 199 (18). HRMS (M^+-C_4H_9) calculated for $C_{16}H_{18}OISi$ 381.0172, found 381.0157.

(*S*)-7-*tert*-Butyldiphenylsiloxy-3-oxo-octanoic Acid Methyl Ester (23). To a solution of diisopropyl amine (14.9 mL, 105 mmol) in 125 mL of THF was added at 0 °C 68 mL of a 1.6 M solution of BuLi in hexane (109 mmol). After stirring for 10 min at 0 °C, freshly distilled methyl acetoacetate (5.5 mL, 51.3 mmol) was added and the solution was stirred at 0 °C for 1 h. A solution of **22** (15.0 g, 34.2 mmol) in 25 mL of THF was added dropwise, and the mixture was allowed to warm to room temperature. After stirring at room temperature for 45 min, the mixture was diluted with 300 mL of hexane and was successively washed with 100 mL of a saturated aqueous solution of NH_4Cl and 100 mL of brine (twice). The organic layer was dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (EtOAc/hexanes 1:9) afforded **23** (11.8 g, 27.7 mmol, 81%) as a colourless oil. R_f 0.2 (EtOAc/hexanes 1:9). $[\alpha]_D$ -16.3 (*c* 1.1, $CHCl_3$). Lit. $[\alpha]_D$ +17.4 (*c* 0.95, $CHCl_3$) for (*R*)-**23**[7b]. IR 3060, 3000, 2950, 2920, 2880, 2850, 1740, 1710. ^1H NMR (400 MHz, mixture of keto and enol isomers) keto: 1.10-1.12 (m, 12H, $(CH_3)_3C$ and $CH_3CHOTBDPS$), 1.39-1.70 (m, 4H, CH_2CH_2), 2.42 (t, *J* = 7.3 Hz, 2H, CH_2CH_2C=O), 3.39 (s, 2H, $CH_2(CO)_2$), 3.72 (s, 3H, CH_3O), 3.86-3.93 (m, 1H, CHOTBDPS), 7.37-7.46 (m, 6H, Ar-H), 7.71-7.74 (m, 4H, Ar-H). Characteristic signals enol: 2.11 (t, *J* = 7.3 Hz, 2H, CH_2CH_2C=O), 4.96 (s, 1H, C*H*=COH), 12.08 (s, 1H, C=COH). ^{13}C NMR (100 MHz, mixture of keto and enol isomers) keto: 19.15 and 19.27 ($(CH_3)_3C$ and CH_2), 23.18 (CH_3), 27.08 ($(CH_3)_3C$), 38.55 (CH_2), 42.88 (CH_2), 48.87 (CH_2), 52.20 (CH_3O), 69.10 (CHOTBDPS), 127.49, 127.60, 129.52, 129.60 (Ar-CH), 134.38 and 134.71 (Ar-C), 135.87 and 135.88 (Ar-C), 167.59 (C=O), 202.40 (C=O ketone). Characteristic signals enol: 19.61 and 21.84 ($(CH_3)_3C$ and CH_2), 34.90 (CH_2), 38.60 (CH_2), 51.00 (CH_3O), 88.70 (*C*H=COH), 173.04 and 178.79 (C=O and C=*C*OH). MS (EI) 369 (100, M^+-C_4H_9), 291(75), 262 (40), 213 (55). HRMS (M^+-C_4H_9) calculated for $C_{21}H_{25}O_4Si$ 369.1522 found 369.1528.

(*S*)-7-*tert*-Butyldiphenylsiloxy-3-oxo-octanoic Acid Ethyl Ester (24). To a solution of diisopropyl amine (6.78 g, 67.0 mmol) in 150 mL of THF was added at 0 °C 43 mL of a 1.6 M solution of BuLi in hexane (69 mmol). After stirring for 10 min at 0 °C, freshly distilled ethyl acetoacetate (4.1 mL, 32.4 mmol) was added and the solution was stirred at 0 °C for 1 h. A solution of **22** (9.5 g, 21.7 mmol) in 25 mL of THF was added dropwise, and the mixture was allowed to warm to room temperature. After stirring at room temperature for 45 min, the mixture was poured out into a 10% aqueous HCl solution (45 mL) and extracted with Et_2O (100 mL and twice 60 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (EtOAc/hexanes 1:9) afforded **24** (7.70 g, 17.5 mmol, 81%) as a colourless oil. R_f 0.2 (EtOAc/hexanes 1:9). $[\alpha]_D$ -12.1 (*c* 1.3, $CHCl_3$). IR 3060, 3000, 2960, 2915, 2890, 2855, 1735, 1710, 1110, 700. ^1H NMR (400 MHz, mixture of keto and enol isomers) keto: 1.06-1.08 (m, 12H, $(CH_3)_3C$ and $CH_3CHOTBDPS$), 1.20 (t, *J* = 7.1 Hz, 3H, CH_3CH_2), 1.37-1.54 (m, 2H), 1.55-1.67 (m, 2H), 2.40 (t, *J* = 7.3 Hz, 2H, CH_2CH_2C=O), 3.36 (s, 2H, $CH_2(CO)_2$), 3.81-3.88 (m, 1H, CHOTBDPS), 4.18 (q, *J* = 7.2 Hz, 2H, CH_3CH_2O), 7.35-7.45 (m, 6H, Ar-H), 7.67-7.70 (m, 4H, Ar-H). characteristic signals enol: 2.09 (t, *J* = 7.3 Hz, 2H, CH_2CH_2C=O), 4.91 (s, 1H, C*H*=COH), 12.08 (s, 1H, C=COH). ^{13}C NMR (100 MHz, mixture of keto and enol isomers) keto: 19.15 and 19.27 ($(CH_3)_3C$ and CH_2), 23.18 (CH_3), 27.08 ($(CH_3)_3C$), 38.55 (CH_2), 42.88 (CH_2), 48.87 (CH_2), 52.20 (CH_3O), 69.10 (CHOTBDPS), 127.49, 127.60, 129.52, 129.60 (Ar-CH), 134.38 and 134.71 (Ar-C), 135.87 and 135.88 (Ar-C), 167.59 (C=O), 202.40 (C=O ketone). Characteristic signals enol: 19.61 and 21.84 ($(CH_3)_3C$ and CH_2), 34.90 (CH_2), 38.60 (CH_2), 51.00 (CH_3O),

88.70 (*C*H=COH), 173.04 and 178.79 (C=O and C=*C*OH). MS (EI) 383 (49, M^+-C_4H_9), 311 (40), 199 (100). HRMS (M^+-C_4H_9) calculated for $C_{22}H_{27}O_4Si$ 383.1679 found 383.1678.

[3-Acetoxy-1-(4-methoxy-benzyl)-5-oxo-pyrrolidin-2-yl]-(6-methyl-tetrahydropyran-2-ylidene)-acetic Acid Methyl Ester (25). To a solution of **23** (104 mg, 0.244 mmol) in 0.9 mL of CH_2Cl_2 were added at -20 °C Et_3N (34 µL, 0.244 mmol) and TMSOTf (46 µL, 0.25 mmol) in succession. After stirring at room temperature for 1.5 h, the solution was cooled to -78 °C and **11** (77 mg, 0.24 mmol) in 0.2 mL of CH_2Cl_2 and TMSOTf (46 µL, 0.25 mmol) were added successively. The mixture was stirred at -78 °C for 1 h. After warming to room temperature, the mixture was stirred for an additional 18 h, poured out into a saturated aqueous solution of $NaHCO_3$ (3 mL) and extracted with CH_2Cl_2 (3 times 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (EtOAc) afforded **25** (75 mg, 0.174 mmol, 73%) as a colourless oil. R_f 0.7 (EtOAc). $[\alpha]_D$ +18.9 (*c* 1.2, $CHCl_3$). IR 2990, 2950, 2830, 1735, 1670, 1600, 1510, 1240. ^{1}H NMR (400 MHz) 1.09 (d, *J* = 6.2 Hz, 3H, CH_3), 1.31-1.39 (m, 1H), 1.60-1.94 (m, 3H), 1.97 (s, 3H, CH_3C=O), 2.36 (dd, *J* = 2.5, 18.0 Hz, 1H, H-4), 2.70-2.78 (m, 1H), 2.95-3.06 (m, 2H), 3.58 (CH_3OCO), 3.74 (CH_3OAr), 3.74-3.78 (m, 1H, CH_2N), 3.92-3.97 (m, 1H, CH_3CHO), 4.68 (d, *J* = 14.7 Hz, 1H, CH_2N), 4.75 (d, *J* = 2.0 Hz, 1H, H-2), 5.13 (dt, *J* = 8.3, 2.3 Hz, 1H, H-3), 6.78 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.09 (d, *J* = 8.6 Hz, 2H, Ar-H). ^{13}C NMR (100 MHz) 17.98 (CH_2), 20.99 and 21.11 (CH_3CH and CH_3CO), 25.07 (CH_2), 29.77 (CH_2), 38.75 (C-4), 43.57 (CH_2N), 51.09 (CH_3OCO), 55.23 (CH_3OAr), 61.26, 72.92 and 74.46 (C-2, C-3 and CH_3CHO), 104.30 (C=C), 113.58 (Ar-CH), 128.96 (Ar-C-1), 129.53 (Ar-CH), 158.79 (Ar-C-4), 167.63, 170.218, 171.61 and 172.44 (C=C and 3× C=O). HRMS-FAB $[M+H]^+$ calculated for $C_{23}H_{30}NO_7$ 432.2022 found 432.1992.

2-[3-Acetoxy-1-(4-methoxy-benzyl)-5-oxo-pyrrolidin-2-yl]-7-*tert*-butyldiphenylsiloxy-3-oxo-octanoic Acid Methyl Ester (26). To a solution of **23** (91.7 mg, 0.215 mmol) in 0.5 mL of CH_2Cl_2 were added at -20 °C iPr_2EtN (73 µL, 0.42 mmol) and TMSOTf (40 µL, 0.22 mmol) in succession. After stirring at room temperature for 1.5 h, the solution was cooled to -78 °C and **11** (69.6 mg, 0.216 mmol) in 0.5 mL of CH_2Cl_2 and TMSOTf (40 µL, 0.22 mmol) were added successively. The mixture was stirred at -78 °C for 1 h. After warming to room temperature, the mixture was stirred for an additional 2 h, poured out into a saturated aqueous solution of $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (4 times 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (EtOAc/hexanes 1:6, then 1:1) afforded two fractions. The first fraction consisted of **23** (13.6 mg, 0.032 mmol, 15%) as a light yellow oil. The second fraction consisted of **26** (110.2 mg, 0.160 mmol, 74%) as a colourless oil. R_f 0.25 (EtOAc/hexanes 1:1). $[\alpha]_D$ -4.8 (*c* 1.1, $CHCl_3$). IR 3010, 2961, 2932, 2859, 1743, 1687, 1611, 1513, 1249. ^{1}H NMR (400 MHz, mixture of keto and enol tautomers) 1.00-1.04 (m, 12H, $(CH_3)_3C$ and $CH_3CHOTBDPS$), 1.26-5.34 (m, 22.9H including: characteristic signal for CH_3COO: 1.98 (s); 3.02 (dd, *J* = 7.0, 18.2 Hz) and 3.20 (dd, *J* = 7.2, 18.1 Hz, H'-4), characteristic signals for CH_3O: 3.64 (s), 3.70 (s), 3.73 (s) and 3.78 (s); 4.02 (d, *J* = 15.1 Hz) and 4.32 (d, *J* = 15.1 Hz) and 4.43 (d, *J* = 15.1 Hz) and 4.78 (d, *J* = 15.1 Hz, CH_2N), 5.30 (d, *J* = 6.9 Hz, H-3)), 6.80-6.86 (m, 2H, Ar-H), 7.14-7.18 (m, 2H, Ar-H), 7.34-7.43 (m, 6H, Ar-H), 7.65-7.67 (m, 4H, Ar-H), 13.23 (s, 0.1H, enol-OH). ^{13}C NMR (100 MHz, mixture of keto and enol tautomers) 18.76, 18.85 and 19.23 (CH_2 and $(CH_3)_3C$), 20.54 and 20.87 (CH_3COO), 22.24 (CH_2), 23.06 ($CH_3CHOTBDPS$), 27.01 ($(CH_3)_3C$), 31.89, 37.49, 37.75, 38.32, 38.49, 38.82, 42.74, 42.93, 43.39, 44.38 and 44.95 (C-4, CH_2N, CH_2C=O and $CH_2CHOTBDPS$), 51.97, 52.77 and 52.92 (CH_3OCO), 55.20 and 55.25 (CH_3OAr), 58.30, 58.73, 61.80, 62.64, 64.44, 69.00, 69.09, 69.15, 69.65, 70.44 and 72.97 (C-3, C-2,$CH(C=O)_2$ and $CH_3CHOTBDPS$), 96.36 (*C*=COH), 114.03 and 114.12 (Ar-CH), 127.42, 127.52 (Ar-CH), 127.67, 128.28 and 128.54 (Ar-C-1), 129.18, 129.25, 129.42, 129.45, 129.48 and 129.53 (Ar-CH), 134.35, 134.62 and 134.69 (Si-Ar-C), 135.82 (Ar-CH), 159.03, 159.21 and 159.26 (Ar-C-4), 167.34, 167.43, 169.77, 169.95, 172.03, 171.87, 173.24 and 180.09 (3× C=O), 201.82 and 202.49 (C=O ketone). MS (EI) 630 (13, M^+-C_4H_9), 570 (32), 369 (29). HRMS (M^+-C_4H_9) calculated for $C_{35}H_{240}NO_8Si$ 630.2513 found 630.2493.

2-[3-Acetoxy-1-(4-methoxy-benzyl)-5-oxo-pyrrolidin-2-yl]-7-*tert*-butyldiphenylsiloxy-3-oxo-octanoic Acid Ethyl Ester (27). To a solution of **24** (116 mg, 0.263 mmol) in 0.75 mL of CH_2Cl_2 were added at -20 °C iPr_2EtN (92 µL, 0.53 mmol) and TMSOTf (50 µL, 0.28 mmol) in succession. After stirring at room temperature for 1.5 h, the solution was cooled to -78 °C and **11** (85.1 mg, 0.265 mmol) in 0.5 mL of CH_2Cl_2 and TMSOTf (50 µL, 0.28 mmol) were added successively. The mixture was stirred at -78 °C for 1 h. After warming to room temperature, the mixture was stirred for an additional 2.5 h, poured out into a saturated aqueous solution of $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (4 times 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (EtOAc/hexanes 1:6, then 1:1) afforded two fractions. The first fraction consisted of **24** (20.9 mg, 0.047 mmol, 18%) as a light yellow oil. The second fraction consisted of **27** (138.5 mg, 0.197 mmol, 75%) as a colourless oil. R_f 0.25 (EtOAc/hexanes 1:1). $[\alpha]_D$ +3.7 (*c* 1.1, $CHCl_3$). IR 3012, 2964, 2933, 2859, 1742, 1685, 1612, 1513, 1249. ^1H NMR (400 MHz, mixture of keto and enol tautomers) 0.99-1.04 (m, 12H, $(CH_3)_3C$ and $CH_3CHOTBDPS$), 1.09-5.34 (m, 24.9H including: characteristic signals for CH_3COO: 1.97 (s), 1.98 (s) 2.00 (s) and 2.03 (s); 3.19 (dd, J = 7.1, 18.1 Hz, H'-4), 4.30 (d, J = 15.0 Hz) and 4.46 (d, J = 15.0 Hz, CH_2N), characteristic signals for CH_3OAr: 3.74 (s), 3.77 (s) and 3.78 (s); 5.31 (d, J = 6.9 Hz, H-3)), 6.79-6.87 (m, 2H, Ar-H), 7.12-7.22 (m, 2H, Ar-H), 7.33-7.43 (m, 6H, Ar-H), 7.64-7.67 (m, 4H, Ar-H), 13.34 (s, 0.1H, enol-OH). ^{13}C NMR (100 MHz, mixture of keto and enol tautomers) 13.91, 13.99 and 14.17 (CH_3CH_2), 18.80, 18.86 and 19.22 (CH_2 and $(CH_3)_3C$), 20.70, 20.79, 20.87 and 21.01 (CH_3COO), 22.24 (CH_2), 23.03 ($CH_3CHOTBDPS$), 27.00 ($(CH_3)_3C$), 31.89, 35.72, 37.58, 37.87, 38.40, 38.65, 38.82, 42.68, 42.75, 42.90, 43.32, 44.34 and 44.91 (C-4, CH_2N, $CH_2C{=}O$ and $CH_2CHOTBDPS$), 55.20 and 55.24 (CH_3OAr), 58.68, 58.80, 61.76, 62.60 (C-2 and $CH(C{=}O)_2$), 60.36, 61.21, 62.07 and 62.25 (CH_3CH_2O), 64.15 (CH), 69.01, 69.09, 69.18, 69.62, 70.64, 72.99 and 73.90 (C-3 and $CH_3CHOTBDPS$), 96.47 ($C{=}COH$), 114.05, 114.09 and 114.15 (Ar-CH), 127.41, 127.51 (Ar-CH), 127.63, 128.11, 128.19 and 128.53 (Ar-C-1), 129.25, 129.43, 129.52, 129.55 and 129.86 (Ar-CH), 134.32, 134.34, 134.63 and 134.68 (Si-Ar-C), 135.82 (Ar-CH), 158.18, 159.24 (Ar-C-4), 166.91, 167.03, 169.76, 169.95, 170.52, 171.77, 172.92, 173.30 and 180.08 (3× C=O), 201.94 and 202.56 (C=O ketone). MS (EI) 644 (10, M^+-C_4H_9), 584 (87), 121 (100). HRMS (M^+-C_4H_9) calculated for $C_{36}H_{42}NO_8Si$ 644.2680 found 644.2698.

Decarboxylation of 13. To a solution of **13** (80.5 mg, 0.23 mmol) in 2.5 mL of DMSO were added NaCl (16.9 mg, 0.29 mmol) and water (20 µL, 1.1 mmol). The mixture was heated at 100 °C for 5 h. Water (10 mL) was added and the mixture was extracted with CH_2Cl_2 (4 times 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (EtOAc/hexanes 1:2, then 3:1) afforded two fractions. The first fraction consisted of **(3a*R*,6a*R*)-4-benzyl-2-methyl-5-oxo-3a,5,6,6a-tetrahydro-4*H*-furo[3,2-b]pyrrole-3-carboxylic acid methyl ester (29)** (49.9 mg, 0.17 mmol, 75%) as a colourless oil. R_f 0.25 (EtOAc/hexanes 1:2). $[\alpha]_D$ +79 (*c* 0.90, $CHCl_3$). IR 2990, 2940, 1680, 1625, 1435, 695. ^1H NMR (200 MHz, $CDCl_3$) 2.20 (s, 3H, $CH_3C{=}C$), 2.83-2.86 (m, 2H, 2× H-6), 3.65 (s, 3H, CH_3O), 4.25 (d, J = 15.0 Hz, 1H, CH_2N), 4.82 (d, J = 15.1 Hz, 1H, CH_2N), 4.86-5.06 (m, 2H, H-3a and H-6a), 7.27 (s, 5H, Ar-H). ^1H NMR (200 MHz, C_6D_6) 1.88 (s, 3H, $CH_3C{=}C$), 2.11 (dd, J = 7.3, 18.2 Hz, 1H, H-6), 2.49 (d, J = 18.3 Hz, 1H, H-6'), 3.32 (s, 3H, CH_3O), 4.07 (t, J = 7.2 Hz, 1H, H-6a), 4.22 (d, J = 14.8 Hz, 1H, CH_2N), 4.47 (d, J = 7.3 Hz, 1H, H-3a), 4.94 (d, J = 14.8 Hz, 1H, CH_2N), 7.04-7.30 (m, 5H, Ar-H). ^{13}C NMR (63 MHz) 14.66 ($CH_3C{=}C$), 37.02 (C-6), 44.61 (CH_2N), 50.97 (CH_3O), 64.46 and 79.26 (C-3a and C-6a), 104.50 (C-3), 127.18, 127.68, 128.07, 128.28 and 128.57 (Ar-CH), 137.07 (Ar-C), 165.42 (C-2), 171.83 and 173.56 (2× C=O). HRMS calculated for $C_{16}H_{17}NO_4$ 287.1158, found 287.1162. The second fraction consisted of **acetic acid (2*R*,3*S*)-1-benzyl-5-oxo-2-(2-oxo-propyl)-pyrrolidin-3-yl ester (28)** (6.1 mg, 0.021 mmol, 9%). R_f 0.15 (EtOAc). $[\alpha]_D$ -25.1 (*c* 1.0, $CHCl_3$). IR 3020, 2990, 2920, 1720, 1680, 1240, 695. ^1H NMR (200 MHz) 1.85 (s, 3H), and 1.99 (s, 3H, 2× CH_3CO), 2.47 (dd, J = 1.1, 18.1 Hz, 1H, H-4), 2.55-2.75 (m, 2H, CH_2CO), 3.03 (dd, J = 7.0, 18.0 Hz, 1H, H-4'), 3.77 (t, J = 5.0 Hz, 1H, H-2), 4.32 (d, J = 15.2 Hz, 1H, CH_2N), 4.55 (d, J = 15.2 Hz, 1H, CH_2N), 4.95 (d, J = 6.9 Hz, 1H, H-3), 7.17-7.33 (m, 5H, Ar-H). ^{13}C NMR (63 MHz) 20.87 (CH_3COO), 30.11 (CH_3CO), 36.78 (C-4), 44.40 and 45.03

(CH_2N and CH_2CO), 60.81 (C-2), 72.14 (C-3), 127.62, 127.91 and 128.69 (Ar-CH), 136.41 (Ar-C), 170.46 and 172.34 (2× C=O), 204.83 (C=O ketone). HRMS calculated for $C_{16}H_{19}NO_4$ 289.1314, found 289.1319.

Decarboxylation of 15. To a solution of **15** (253 mg, 0.67 mmol) in 6 mL of DMSO were added NaCl (50 mg, 0.86 mmol) and water (60 µL, 3.3 mmol). The mixture was heated at 100 °C for 18 h. Water (12 mL) was added and the mixture was extracted with CH_2Cl_2 (4 times 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (EtOAc/hexanes 1:1, then 3:1) afforded two fractions. The first fraction consisted of **(3a*R*,6a*R*)-4-(4-methoxy-benzyl)-2-methyl-5-oxo-3a,5,6,6a-tetrahydro-4*H*-furo[3,2-b]pyrrole-3-carboxylic acid methyl ester (31)** (136.4 mg, 0.43 mmol, 64%) as a colourless oil. R_f 0.3 (EtOAc/hexanes 1:1). $[\alpha]_D$ +90.5 (*c* 1.1, $CHCl_3$). IR 2995, 2940, 2830, 1675, 1625, 1505, 1240, 8405. ^1H NMR (400 MHz, $CDCl_3$) 2.18 (s, 3H, CH_3C=C), 2.78-2.80 (m, 2H, 2× H-6), 3.68 (s, 3H) and 3.75 (s, 3H, 2× CH_3O), 4.11 (d, *J* = 14.7 Hz, 1H, CH_2N), 4.77 (d, *J* = 14.7 Hz, 1H, CH_2N), 4.89 (d, *J* = 7.2 Hz, 1H, H-3a), 4.99-5.04 (m, 1H, H-6a), 6.80 (d *J* = 8.7 Hz, 2H, Ar-H), 7.23 (d *J* = 8.6 Hz, 2H, Ar-H). ^{13}C NMR (100 MHz) 14.73 (CH_3C=C), 37.08 (C-6), 43.83 (CH_2N), 51.06 (CH_3OCO), 55.18 (CH_3OAr), 64.14 and 79.23 (C-3a and C-6a), 104.53 (C-3), 113.70 and 129.23 (Ar-CH), 129.29 (Ar-C-1), 158.82 (Ar-C-4), 165.60 (C-2), 171.70 and 173.65 (2× C=O). HRMS-FAB $[M + H]^+$ calculated for $C_{17}H_{20}NO_5$ 318.1341, found 318.1336. The second fraction consisted of **acetic acid (2*R*,3*S*)-1-(4-methoxy-benzyl)-5-oxo-2-(2-oxo-propyl)-pyrrolidin-3-yl ester (30)** (37.3 mg, 0.117 mmol, 17%) as a colourless oil. R_f 0.15 (EtOAc/hexanes 1:1). $[\alpha]_D$ -13.1 (*c* 0.44, $CHCl_3$). IR 3020, 2990, 2920, 2820, 1730, 1715, 1680, 1605, 1505, 1240. ^1H NMR (400 MHz) 1.89 (s, 3H), and 1.98 (s, 3H, 2× CH_3CO), 1.96 (s, 3H, CH_3COO), 2.44 (dd, *J* = 1.5, 17.9 Hz, 1H, H-4), 2.60-2.75 (m, 2H, CH_2CO), 2.99 (dd, *J* = 7.0, 17.9 Hz, 1H, H-4'), 3.73-3.77 (m, 1H, H-2) , 3.77 (s, 3H, CH_3O), 4.22 (d, *J* = 15.1 Hz, 1H, CH_2N), 4.52 (d, *J* = 15.1 Hz, 1H, CH_2N), 4.95-4.97 (m, 1H, H-3), 6.80-6.84 (m, 2H, ArH), 7.11-7.13 (m, 2H, Ar-H).^{13}C NMR (100 MHz) 20.89 (CH_3COO), 30.20 (CH_3CO), 36.80 (C-4), 44.33 and 44.35 (CH_2N and CH_2CO), 55.25 (CH_3O), 60.59 (C-2), 72.10 (C-3), 114.05 (Ar-CH), 128.34 (Ar-C-1), 129.22 (Ar-CH), 159.11 (Ar-C-4), 170.53 and 172.22 (2× C=O), 204.97 (C=O ketone). HRMS calculated for $C_{17}H_{21}NO_5$ 319.1420, found 319.1416.

Decarboxylation of 17. To a solution of **17** (107.9 mg, 0.30 mmol) in 3 mL of DMSO were added NaCl (21.8 mg, 0.37 mmol) and water (27 µL, 1.5 mmol). The mixture was heated at 100 °C for 18 h. Water (10 mL) was added and the mixture was extracted with CH_2Cl_2 (4 times 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (EtOAc/hexanes 4:1, then EtOAc) afforded two fractions. The first fraction consisted of **(3a*R*,6a*R*)-4-benzyl-2-methyl-5-oxo-3a,5,6,6a-tetrahydro-4*H*-furo[3,2-b]pyrrole-3-carboxylic acid ethyl ester (32)** (21.2 mg, 0.070 mmol, 24%) as a colourless oil. R_f 0.4 (EtOAc/hexanes 4:1). $[\alpha]_D$ +63.8 (*c* 1.0, $CHCl_3$). IR 2990, 2920, 1680, 1625, 695. ^1H NMR (200 MHz, $CDCl_3$) 1.22 (t, *J* = 7.1 Hz, 3H, CH_3CH_2), 2.20 (s, 3H, CH_3C=C), 2.80-2.90 (m, 2H, 2× H-6), 4.00-4.23 (m, 2H, CH_3CH_2), 4.31 (d, *J* = 15.0 Hz, 1H, CH_2N), 4.80 (d, *J* = 15.0 Hz, 1H, CH_2N), 4.90-5.10 (m, 2H, H-3a and H-6a), 7.19-7.33 (m, 5H, Ar-H). ^{13}C NMR (63 MHz) 14.30 and 14.76 (CH_3CH_2 and CH_3C=C), 37.08 (C-6), 44.63 (CH_2N), 59.99 (CH_3CH_2), 64.61 and 79.20 (C-3a and C-6a), 104.91 (C-3), 127.14, 127.74, 128.30 and 128.70 (Ar-CH), 137.19 (Ar-C), 165.13 (C-2), 171.74 and 173.10 (2× C=O). The second fraction consisted of **28** (49.0 mg, 0.17 mmol, 57%) as a colourless oil.

(2*R*,3*S*)-*E*- and *Z*-2-[3-Acetoxy-1-(4-methoxy-benzyl)-5-oxo-pyrrolidin-2-yl]-3-triisopropyl-siloxy-but-2-enoic Acid Methyl Ester (35). To a solution of **15** (188.0 mg, 0.498 mmol) in 1.5 mL of CH_2Cl_2 were added at 0 °C Et_3N (83 µL, 0.60 mmol) and TIPSOTf (160 µL, 0.59 mmol), successively. The solution was stirred at 0 °C for 0.5 h, and then allowed to warm to room temperature. After stirring for an additional 5 h, the mixture was poured out into a saturated aqueous solution of $NaHCO_3$ (6 mL) and was extracted with CH_2Cl_2 (4 times 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (EtOAc/hexanes 1:1, then 2.5:1) afforded **35** (240.3 mg, 0.450 mmol, 90%) as a

colourless oil. R_f 0.3 (EtOAc/hexanes 1:1). $[\alpha]_D$ +60.9 (*c* 1.0, $CHCl_3$). IR 3000, 2940, 2860, 1735, 1675, 1600, 1505, 1240, 840. Major isomer (*E*): ^{1}H NMR (400 MHz, 2:1 mixture of *E*- and *Z*-isomers) 0.89-1.22 (m, 21H, 3× $CH_3CH_2CH_2$), 1.95 (s, 3H, CH_3CO), 2.26 (s, 3H, CH_3C=C), 2.29-2.39 (m, 1H, H-4), 3.07-3.15 (m, 1H, H-4'), 3.57 (s, 3H, CH_3OCO), 3.73 (s, 3H, CH_3OAr), 3.85 (d, *J* = 15.0 Hz, 1H, CH_2N), 4.62 (d, *J* = 15.0 Hz, 1H, CH_2N), 5.05 (d, *J* = 1.7 Hz, 1H, H-2), 5.16-5.18 (m, 1H, H-3), 6.74 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.03 (d, *J* = 8.5 Hz, 2H, Ar-H). ^{13}C NMR (100 MHz, mixture of 2 isomers) 13.17 (CH_3CH), 17.77 (CH_3CH), 20.87 and 22.24 (CH_3C=C andCH_3CO), 39.14 (C-4), 43.53 (CH_2N), 51.12 (CH_3OCO), 55.19 (CH_3OAr), 60.31 (C-2), 73.08 (C-3), 108.49 (C=CCO), 113.76 (Ar-CH), 128.70 (Ar-C-1), 128.81 (Ar-CH), 158.83 (Ar-C-4), 160.20, 167.42 and 172.85 (3× C=O). Characteristic signals minor isomer (*Z*): ^{1}H NMR (400 MHz, 2:1 mixture of *E*- and *Z*-isomers): 1.61 (s, 3H, CH_3C=C), 1.97 (s, 3H, CH_3COO), 3.62 (s, 3H, CH_3OCO), 3.63-3.69 (m, 1H, CH_2N), 3.75 (s, 3H, CH_3OAr), 3.97 (d, *J* = 1.3 Hz, 1H, H-2), 4.99 (d, *J* = 14.9 Hz, 1H, CH_2N), 5.22 (d, *J* = 7.6 Hz, 1H, H-3), 6.80 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.08 (d, *J* = 8.5 Hz, 2H, Ar-H). ^{13}C NMR (100 MHz, mixture of 2 isomers) 13.22 (CH_3CH), 19.92 and 20.93 (CH_3C=C andCH_3CO), 37.82 (C-4), 43.12 (CH_2N), 51.30 (CH_3OCO), 64.16 (C-2), 73.15 (C-3), 108.40 (C=CCO), 113.92 (Ar-CH), 128.12 (Ar-C-1), 129.25 (Ar-CH), 158.97 (Ar-C-4). HRMS-FAB $[M+H]^+$ calculated for $C_{28}H_{44}NO_7Si$ 534.2887, found 534.2864.

(2*R*,3*S*)-*E*-3-Acetoxy-2-[3-acetoxy-1-(3,4-dimethoxy-benzyl)-5-oxo-pyrrolidin-2-yl]-but-2-enoic Acid Methyl Ester (36). To a solution of **14** (50.0 mg, 0.123 mmol) in 100 µL of pyridine was added at 0 °C acetyl chloride (20 µL, 0.28 mmol). The mixture was stirred at room temperature for 3 h. Diethyl ether (5 mL) was added and the mixture was poured out into a saturated aqueous solution of $CuSO_4$ (7.5 mL). The water layer was extracted with Et_2O (3 times 10 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (EtOAc) afforded **36** (48.3 mg, 0.107 mmol, 87%) as a colourless oil. R_f0.4 (EtOAc). $[\alpha]_D$ +47.5 (*c* 0.87, $CHCl_3$). IR 3010, 2990, 2950, 2830, 1760, 1735, 1680, 1510, 1240. ^{1}H NMR (400 MHz) 1.94 (s, 3H) and 1.97 (s, 3H, 2× CH_3COO), 2.23 (s, 3H, CH_3C=C), 2.37 (dd, *J* = 2.3, 18.1 Hz, 1H, H-4), 3.08 (dd, *J* = 7.0, 18.0 Hz, 1H, H-4'), 3.64 (s, 3H, CH_3OCO), 3.71 (d, *J* 14.5 Hz, 1H, CH_2N), 3.83 (s) and 3.84 (s, 6H, 2× CH_3OAr), 4.37 (d, *J* = 1.9 Hz, 1H, H-2), 4.75 (d, *J* = 14.8 Hz, 1H, CH_2N), 5.17 (dt, *J* = 2.0, 7.9 Hz, 1H, H-3), 6.70-6.77 (m, 3H, Ar-H). ^{13}C NMR (100 MHz) 19.98, 20.48 and 20.79 (2× CH_3COO and CH_3C=C), 38.19 (C-4), 44.05 (CH_2N), 52.03 (CH_3OCO), 55.81 and 55.90 (2× CH_3OAr), 61.54 (C-2), 72.01 (C-3), 110.90 and 111.58 (Ar-CH), 118.95 (C=CCO), 120.78 (Ar-CH), 128.42 (Ar-C-1), 148.40 and 148.97 (Ar-C-3 and Ar-C-4), 159.99 (C=COAc), 165.80, 167.35, 169.90, and 172.46 (4× C=O). HRMS-FAB $[M+H]^+$ calculated for $C_{22}H_{28}NO_9$ 450.1764; found 450.1826.

(2*R*,3*S*)-*E*-3-Acetoxy-2-[3-acetoxy-1-(4-methoxy-benzyl)-5-oxo-pyrrolidin-2-yl]-but-2-enoic Acid Methyl Ester (37). To a solution of **15** (436.2 mg, 1.16 mmol) in 2 mL of pyridine was added at 0 °C acetyl chloride (125 µL, 1.76 mmol). The mixture was stirred at room temperature for 3 h. Diethyl ether (10 mL) was added and the mixture was poured out into a saturated aqueous solution of $CuSO_4$ (15 mL). The water layer was extracted with Et_2O (3 times 15 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (EtOAc) afforded **37** (406.2 mg, 0.97 mmol, 84%) as a colourless solid. Recrystallisation (EtOAc) gave a sample of **37** as colourless crystals, mp. 66-69 °C. R_f0.6 (EtOAc). $[\alpha]_D$ +64.8 (*c* 1.0, $CHCl_3$). IR 3010, 2990, 2950, 2830, 1760, 1735, 1680, 1605, 1580, 1505, 1240, 840. ^{1}H NMR (400 MHz) 1.92 (s, 3H) and 1.94 (s, 3H, 2× CH_3COO), 2.21 (s, 3H, CH_3C=C), 2.34 (dd, *J* = 2.3, 18.1 Hz, 1H, H-4), 3.04 (dd, *J* = 8.1, 18.1 Hz, 1H, H-4'), 3.63 (s, 3H, CH_3OCO), 3.68 (d, *J* = 14.8 Hz, 1H, CH_2N), 3.73 (s, 3H, CH_3OAr), 4.35 (d, *J* = 1.9 Hz, 1H, H-2), 4.74 (d, *J* = 14.9 Hz, 1H, CH_2N), 5.13 -5.16 (m, 1H, H-3), 6.78 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.07 (d, *J* = 8.6 Hz, 2H, Ar-H). ^{13}C NMR (100 MHz) 19.93, 20.45 and 20.76 (2× CH_3COO and CH_3C=C), 38.15 (C-4), 43.62 (CH_2N), 51.99 (CH_3OCO), 55.20 (CH_3OAr), 61.43 (C-2), 71.92 (C-3), 113.77 and 114.01 (Ar-CH), 118.84 (C=CCO), 127.92 (Ar-C-1), 129.62 and 129.90 (Ar-CH), 158.98 and 160.07 (C=COAc and Ar-C-4), 165.76, 167.32, 169.92, and 172.38 (4× C=O). HRMS calculated

for $C_{21}H_{25}NO_8$ 419.1580, found 419.1534. Anal. found: C, 60.09; H, 6.11; N, 3.33. Calculated for $C_{21}H_{25}NO_8$: C, 60.14; H, 6.01; N, 3.34.

Acetic Acid (2*R*,3*S*)-1-(4-Methoxy-benzyl)-2-(5-methyl-3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl)-5-oxo-pyrrolidin-3-yl Ester (38). To a solution of **15** (176 mg, 0.466 mmol) in 0.5 mL of EtOH was added $N_2H_4 \cdot H_2O$ (24 μL, 0.49 mmol). After stirring at room temperature for 6 h, the mixture was heated at reflux for 18 h and then concentrated in vacuo. Flash chromatography of the residue (EtOAc, then EtOAc/MeOH 9:1, then 4:1) afforded **38** (148.9 mg, 0.414 mmol, 89%) as a white solid. R_f 0.25 (EtOAc/MeOH 9:1). Recrystallisation (EtOAc/MeOH) gave a sample of **38** as colourless crystals, mp. 90.5-92.0 °C. $[\alpha]_D$ +59.0 (*c* 1.0, $CHCl_3$). IR 3460, 3200, 3000, 2960, 2930, 2830, 1760, 1735, 1670, 1610, 1510, 1240, 830. ^1H NMR (400 MHz) 1.95 (s, 3H) and 2.00 (s, 3H, CH_3COO and CH_3C=C), 2.53 (d, *J* = 17.5 Hz, 1H, H-4), 3.36 (dd, *J* = 6.8, 17.5 Hz, 1H, H-4'), 3.54 (d, *J* = 14.9 Hz, 1H, CH_2N), 3.78 (s, 3H, CH_3OAr), 4.13 (s, 1H, H-2), 5.01 (d, *J* = 15.0 Hz, 1H, CH_2N), 5.12 (d, *J* = 6.7 Hz, 1H, H-3), 6.78-6.86 (m, 2H, Ar-H), 7.03-7.06 (m, 2H, Ar-H), 9.20 (br s, 2H, 2× NH). ^{13}C NMR (100 MHz) 9.89 (CH_3C=C), 21.01 (CH_3COO), 37.91 (C-4), 43.26 (CH_2N), 55.25 (CH_3OAr), 58.84 (C-2), 73.46 (C-3), 96.63 (CH_3C=*C*), 114.01 (Ar-CH), 127.85 (Ar-C-1), 129.20 (Ar-CH), 140.60 (CH_3C=C), 159.02 (Ar-C-4), 160.87, 170.54 and 173.13 (3× C=O). HRMS calculated for $C_{18}H_{21}N_3O_5$ 359.1481, found 359.1488. Anal. found: C, 59.88; H, 5.95; N, 11.73 Calculated for $C_{18}H_{21}N_3O_5$: C, 60.16; H, 5.89; N, 11.69.

(2*R*,3*S*)-Acetic Acid 1-(4-Methoxy-benzyl)-2-(3-methyl-5-oxo-2,5-dihydro-isoxazol-4-yl)-5-oxo-pyrrolidin-3-yl Ester (39). To a solution of **15** (211.5 mg, 0.56 mmol) in 0.6 mL of EtOH were added $NaHCO_3$ (94 mg, 1.1 mmol) and $NH_2OH \cdot HCl$ (41 mg, 0.59 mmol). After stirring at room temperature for 2 h, the mixture was heated at reflux for 18 h and then concentrated in vacuo. Flash chromatography of the residue (EtOAc/MeOH 3:1) afforded **39** (200.8 mg, 0.56 mmol, 100%) as a light yellow viscous oil. R_f 0.1 (EtOAc/MeOH 3:1). $[\alpha]_D$ +49 (*c* 0.99, MeOH). IR 3380, 2990, 2960, 2830, 1735, 1660, 1510, 1240, 830. ^1H NMR (400 MHz, $CDCl_3$ + 3 drops of CD_3OD) 1.70 (s, 3H, CH_3C=C), 1.89 (s, 3H, CH_3COO), 2.33 (d, *J* = 17.5 Hz, 1H, H-4), 3.09 (dd, *J* = 6.5, 17.5 Hz, 1H, H-4'), 3.42 (d, *J* = 14.9 Hz, 1H, CH_2N), 3.70 (s, 3H, CH_3OAr), 3.82 (br s, 1H, NH), 3.88 (s, 1H, H-2), 4.82 (d, *J* = 14.9 Hz, 1H, CH_2N), 4.90 (d, *J* = 6.4 Hz, 1H, H-3), 6.67-6.74 (m, 2H, Ar-H), 6.93-6.95 (m, 2H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$ + 3 dr CD_3OD) 10.85 (CH_3C=C), 20.76 (CH_3COO), 37.95 (C-4), 42.89 (CH_2N), 55.11 (CH_3OAr), 59.41 (C-2), 73.72 (C-3), 78.83 (CH_3C=*C*), 113.81 and 113.90 (Ar-CH), 127.63 (Ar-C-1), 129.03 and 129.18 (Ar-CH), 158.94 (Ar-C-4), 161.58 (CH_3C=C), 170.89, 173.83 and 175.38 (3× C=O). HRMS-FAB $[M+Na]^+$ calculated for $C_{18}H_{21}N_2O_6Na$ 383.1219, found 383.1218.

(2*R*,3*S*)-2-(3-Acetoxy-5-oxo-pyrrolidin-2-yl)-3-oxo-butyric Acid Methyl Ester (40). To a solution of **15** (5.33 g, 14.1 mmol) in a 7:3 mixture of acetonitrile and water (100 mL) was added CAN (23.2 g, 42.3 mmol). After stirring at room temperature for 12 min, the mixture was poured out into a saturated aqueous solution of $NaHCO_3$ (400 mL) and was extracted with CH_2Cl_2 (5 times 300 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (EtOAc/hexanes 3:1, then EtOAc/MeOH 95:5) afforded **40** (2.13 g, 8.3 mmol, 59%) as an orange oil. R_f 0.3 (EtOAc/MeOH 95:5). $[\alpha]_D$ -41.4 (*c* 0.92, $CHCl_3$). IR 3650, 3430, 3000, 2950, 2830, 1730, 1715, 1700, 1240. ^1H NMR (200 MHz, 1:1 mixture of 2 diastereomers) 2.05 (s) and 2.06 (s, 3H, CH_3CO), 2.25 (s) and 2.31 (s, 3H, CH_3CO), 2.31-2.39 (m, 1H, H-4), 2.79 (dd, *J* = 7.5, 18.2 Hz, 1H, H-4'), 3.66 (d, *J* = 8.5 Hz, 0.5H), 3.76 (s) and 3.80 (s, 3H, CH_3O), 3.95-4.11 (m, 1.5H), 5.16 -5.23 (m, 1H, H-3), 6.43 (br s, 0.5H, NH), 6.48 (br s, 0.5H, NH). ^{13}C NMR (100 MHz, mixture of 2 diastereomers) 20.81 (CH_3COO), 29.73 and 30.20 (2× CH_3CO), 35.98 and 36.04 (C-4), 53.02 and 53.12 (CH_3O), 59.36, 59.49, 61.17 and 62.22 (C-2 and $CH(CO)_2$), 71.48 and 72.20 (C-3),167.29, 167.44, 170.24, 170.72 and 174.59 (2× C=O), 200.65 and 201.58 (C=O ketone). MS(EI): 197 (38, M^+-COOMe), 155 (100), 142 (26), 123 (49). HRMS (M^+-COOMe) calculated for $C_9H_{11}NO_4$ 197.0618, found 197.0678.

2-(3-Acetoxy-5-oxo-pyrrolidin-2-yl)-7-*tert*-butyldiphenylsiloxy-3-oxo-octanoic Acid Ethyl Ester (41). To a solution of **27** (498 mg, 0.71 mmol) in a 7:3 mixture of acetonitrile and water (4.4 mL) was added CAN (1.17 g, 2.14 mmol). After stirring at room temperature for 12 min, the mixture was poured out into a saturated aqueous solution of $NaHCO_3$ (20 mL) and was extracted with CH_2Cl_2 (5 times 40 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (EtOAc/hexanes 1:5, 1:3, 1:1, 2:1) afforded **41** (265.5 mg, 0.45 mmol, 59%) as a colourless oil. R_f 0.3 (EtOAc/hexanes 2:1). $[\alpha]_D$ -16.6 (*c* 0.96, $CHCl_3$). IR 3434, 3073, 3014, 2966, 2932, 2858, 1741, 1704, 1211. ^1H NMR (400 MHz, 1:1 mixture of diastereomers) 1.00-1.06 (m, 12H, $(CH_3)_3C$ and $CH_3CHOTBDPS$), 1.21-1.28 (m, 3H, CH_3CH_2O), 1.29-1.63 (m, 4H, $CH_2CH_2CHOTBDPS$), 2.06 (s, 3H, CH_3COO), 2.31-2.61 (m, 3H, $CH_2C{=}O$ and H-4), 2.78 (dd, J = 7.9, 18.2 Hz, 0.5H) and 2.79 (dd, J = 7.1, 18.2 Hz, 0.5H, H'-4), 3.53 (d, J = 8.7 Hz, 0.5H), 3.79-3.87 (m, 1H, CHOTBDPS), 3.89 (d, J = 4.8 Hz, 0.5H), 3.97 (d, J = 4.7 Hz, 0.5H), 4.09 (d, J = 8.8 Hz, 0.5H), 4.16-4.24 (m, 2H, CH_3CH_2O), 5.17 (d, J = 7.1 Hz, 0.5H) and 5.21 (d, J = 7.8 Hz, 0.5H, H-3), 6.09 (br s, 0.5H) and 6.16 (br s, 0.5H, NH), 7.35-7.44 (m, 6H, Ar-H), 7.61-7.67 (m, 4H, Ar-H). ^{13}C NMR (100 MHz, mixture of 2 diastereomers) 13.93 and 14.00 (CH_3CH_2), 18.85, 19.03 and 19.22 (CH_2 and $(CH_3)_3C$), 20.83 (CH_3COO), 23.03 ($CH_3CHOTBDPS$), 26.99 ($(CH_3)_3C$), 35.93 and 36.01 (C-4), 38.38 and 38.48 (CH_2), 42.42 and 43.29 (CH_2), 59.17, 59.59, 60.38 and 61.93 (C-2 and $CH(C{=}O)_2$), 62.29 and 62.40 (CH_3CH_2O), 68.91, 69.14, 71.51 and 72.31 (C-3 and $CH_3CHOTBDPS$), 127.41, 127.52, 129.46 and 129.53 (Ar-CH), 134.35 and 134.65 (Ar-C), 135.82 (Ar-CH), 166.75, 167.05, 170.69, 174.05 and 174.16 (3× C=O), 202.06 and 202.89 (C=O ketone). MS (EI) 524 (27, M^+-C_4H_9), 464 (31), 383 (100). HRMS (M^+-C_4H_9) calculated for $C_{28}H_{34}NO_7Si$ 524.2105 found 524.2132.

(2*R*,3*S*)-2-(3-Hydroxy-5-oxo-pyrrolidin-2-yl)-3,3-dimethoxy-butyric Acid Methyl Ester (42). To a solution of **40** (625 mg, 2.4 mmol) in 6 mL of MeOH was added trimethyl orthoformate (0.53 mL, 4.8 mmol). The solution was acidified to pH 2 with a 2M H_2SO_4/MeOH solution. After stirring for 3 days, the mixture was poured out into a saturated aqueous solution of $NaHCO_3$ (40 mL), and was extracted with EtOAc (4 times 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (EtOAc, then EtOAc/MeOH 95:5) afforded **42** (401 mg, 1.53 mmol, 64%) as a light yellow oil. R_f 0.3 (EtOAc/MeOH 95:5). $[\alpha]_D$ +4.1 (*c* 1.1, $CHCl_3$). IR 3420, 3000, 2950, 2830, 1700, 1230. ^1H NMR (400 MHz, 1:1 mixture of 2 diastereomers) 1.45 (s, 1.5H) and 1.48 (s, 1.5H, CH_3), 2.34 (dd, J = 6.5, 17.0 Hz, 1H, H-4), 2.61 (dd, J = 7.8, 17.1 Hz, 1H, H-4'), 2.91 (d, J = 10.4 Hz, 0.5H) and 3.03 (d, J = 9.1 Hz, 0.5H, $CHCO_2Me$), 3.17 (s), 3.20 (s), 3.23 (s) and 3.25 (s, 6H, 2× CH_3O), 3.43-3.66 (m, 0.5H, OH), 3.70 (s) and 3.72 (s, 3H, CH_3OCO), 3.70-3.88 (m, 1H, H-2), 4.10-4.15 (m, 0.5H) and 4.30-4.40 (m, 0.5H, H-3), 6.17 (br s, 0.5H, NH), 6.34 (br s, 0.5H, NH). ^{13}C NMR (100 MHz, mixture of 2 diastereomers) 18.42 and 18.74 (CH_3), 38.72 and 38.94 (C-4), 48.10, 48.39, 48.41 and 48.66 (2× CH_3O), 52.18 and 52.24 (CH_3OCO), 54.46 and 54.84($CHCO_2Me$), 61.27 and 61.72 (C-2), 71.17 and 71.73 (C-3), 101.36 and 101.87(CH_3C), 170.71, 170.75, 174.52 and 175.56 (2× C=O). MS(EI): 230 (19, $[M\text{-}OMe]^+$), 197 (25), 170 (85), 155 (45). HRMS $[M\text{-}OMe]^+$ calculated for $C_{10}H_{16}NO_5$ 230.1029, found 230.1023.

(2*R*,3*S*)-3,3-Dimethoxy-2-(5-oxo-3-phenoxythiocarbonyloxy-pyrrolidin-2-yl)-butyric Acid Methyl Ester (43). To a solution of **42** (103.2 mg, 0.395 mmol) in 0.5 mL of CH_2Cl_2 were added at 0 °C DMAP (101 mg, 0.83 mmol) and phenyl chlorothionoformate (68 µL, 0.49 mmol). The mixture was stirred at 0 °C for 2 h, and concentrated in vacuo. Flash chromatography (EtOAc/hexanes 3:1) afforded two fractions. The first fraction consisted of **43** (103.1 mg, 0.259 mmol, 66%) as a colourless oil. R_f 0.3 (EtOAc/hexanes 3:1). $[\alpha]_D$ +20.1 (*c* 0.71, $CHCl_3$). IR 3420, 2990, 2960, 2830, 1700, 1290, 1190. ^1H NMR (400 MHz, 45:55 mixture of 2 diastereomers) 1.48 (s) and 1.51 (s, 3H, CH_3), 2.46-2.52 (m, 1H, H-4), 2.88-3.00 (m, 1H, H-4'), 3.10 (d, J = 9.5 Hz, 0.5H, $CHCO_2Me$), 3.16-3.24 (m, 6.5H, 2× CH_3O and $CHCO_2Me$), 3.73 (s) and 3.74 (s, 3H, CH_3OCO), 4.18 (dd, J = 3.6, 9.5 Hz, 0.45H, H-2), 4.25 (d, J = 7.5 Hz, 0.55H, H-2), 5.62-5.66 (m, 0.45H, H-3), 5.96 (dd, J = 2.3, 4.6 Hz, 0.55H, H-3), 6.26 (br s, 0.55H, NH), 6.42 (br s, 0.45H, NH), 7.08 (d, J = 7.8 Hz, 2H, Ar-H), 7.76-7.29 (m, 1H, Ar-H), 7.40-7.42 (m, 2H, Ar-H). ^{13}C NMR (100 MHz, mixture

of 2 diastereomers) 18.71 and 18.81 (CH_3), 36.11 and 36.19 (C-4), 48.16, 48.45, 48.68 and 48.76 (2× CH_3O), 52.07 (CH_3OCO), 54.19 , 55.01, 58.20 and 58.70 (*C*HCO$_2$Me and C-2), 81.43 and 81.68 (C-3), 101.07 and 101.81 (CH_3*C*), 121.63, 121.66, 126.60, 126.62 and 129.48 (Ar-CH), 153.39 (Ar-C), 169.50, 170.22, 172.60 and 173.66 (2× C=O), 193.76 and 193.82 (C=S). HRMS calculated for $C_{18}H_{24}NO_7S$ 398.1273, found 398.1295. The second fraction consisted of **3,3-dimethoxy-2-(5-oxo-4,5-dehydro-1H-pyrrol-2-yl)-butyric acid methyl ester** (14.3 mg) as a colourless oil still containing solvent according to ^{1}H NMR. Attempts to purify this compound by prolonged evaporation failed and gave decomposition. R_f 0.2 (EtOAc/hexanes 3:1). ^{1}H NMR (400 MHz, contaminated with EtOAc and hexanes) 1.43 (s, 3H, CH_3), 3.02 (s, 2H, H-4), 3.23 (s) and 3.24 (s, 6H, 2× CH_3O), 3.75 (s, 3H, CH_3OCO), 3.80 (s, 1H, *C*HCO$_2$Me), 5.08 (s, 1H, H-3), 7.45 (br s, 1H, NH).

(2*S*)-3,3-Dimethoxy-2-(5-oxo-pyrrolidin-2-yl)-butyric Acid Methyl Ester (44). To a solution of **43** (323.6 mg, 0.814 mmol) in 16 mL of benzene were added at 80 °C AIBN (14 mg, 0.085 mmol) and Bu_3SnH (440 µL, 1.66 mmol). The mixture was heated at reflux for 30 min. Flash chromatography (EtOAc/hexanes 1:2, EtOAc and EtOAc/MeOH 95:5) afforded **44** (192.9 mg, 0.79 mmol, 97%) as a colourless oil. R_f 0.3 (EtOAc/MeOH 95:5). $[\alpha]_D$ +3.1 (*c* 1.0, $CHCl_3$). IR 3420, 2990, 2960, 2830, 1725, 1685. ^{1}H NMR (400 MHz, 40:60 mixture of 2 diastereomers) 1.40 (s) and 1.44 (s, 3H, CH_3), 1.60-1.70 (m, 0.4H), 2.05-2.33 (m, 3.6H), 2.88 (d, *J* = 10.3 Hz, 0.4H, *C*HCO$_2$Me), 2.96 (d, *J* = 8.3 Hz, 0.6H, *C*HCO$_2$Me), 3.18 (s), 3.19 (s), 3.20 (s) and 3.21 (s, 6H, 2× CH_3O), 3.69 (s) and 3.70 (s, 3H, CH_3OCO), 3.79-4.02 (m, 1H, H-2), 5.28 (br s, 0.6H, NH), 5.90 (br s, 0.4H, NH). ^{13}C NMR (100 MHz, mixture of 2 diastereomers) 18.40 and 18.64 (CH_3), 26.30, 26.93, 29.72 and 29.83 (C-3 and C-4), 48.14, 48.26, 48.43 and 48.49 (2× CH_3O), 51.93 and 52.07 (CH_3OCO), 52.84, 53.36, 56.27 and 56.30 (*C*HCO$_2$Me and C-2), 101.07 and 101.96 (CH_3*C*), 170.23, 171.31, 177.19 and 177.83 (2× C=O). HRMS-FAB $[M+H]^+$ calculated for $C_{11}H_{20}NO_5$ 246.1342, found 246.1325.

(2*S*)-2-(5-Oxo-pyrrolidin-2-yl)-3-oxo-butyric Acid Methyl Ester (45). To a solution of **44** (98.2 mg, 0.40 mmol) in 1.0 mL of EtOAc was added 2 mL of a 0.1 M aqueous solution of HCl. The mixture was stirred vigorously for 2.5 h, neutralized to pH 7 with a 1 M aqueous NaOH solution and was extracted with EtOAc (5 times 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (EtOAc/MeOH 9:1) afforded **45** (77.8 mg, 0.39 mmol, 98%) as a colourless oil. R_f 0.25 (EtOAc/MeOH 9:1). $[\alpha]_D$ -52.2 (*c* 0.69, $CHCl_3$). IR 3425, 2990, 2940, 2830, 1735, 1690. ^{1}H NMR (400 MHz, 1:1 mixture of 2 diastereomers) 1.73-1.83 (m, 1H), 2.24-2.36 (m, 6H, including CH_3CO), 3.51 (d, *J* = 9.4 Hz, 0.5H) and 3.58 (d, *J* = 8.5 Hz, 0.5H, $CH(CO)_2$), 3.76 (s) and 3.78 (s, 3H, CH_3O), 4.19-4.24 (m, 1H, H-2), 6.24 (br s) and 6.29 (br s, 1H, NH). ^{13}C NMR (100 MHz, mixture of 2 diastereomers, assignment with C-H correlation) 24.69, 24.96, 29.02 and 29.18 (C-3 and C-4), 29.58 and 30.65 (CH_3), 52.33, 52.44 (C-2), 52.89, 53.00 (CH_3O), 64.30 and 65.36 (*C*H(CO)$_2$), 167.45, 168.05, 177.58 and 177.61 (2× C=O), 200.92 and 201.50 (C=O ketone). HRMS calculated for $C_9H_{13}NO_4$ 199.0845, found 199.0829.

(2*R*)-2-(5-Oxo-pyrrolidin-2-yl)-3-triisopropylsiloxy-but-2-enoic Acid Methyl Ester (46). To a suspension of **45** (34.2 mg, 0.172 mmol) in 0.5 mL of pyridine was added TIPSOTf (56 µL. 0.21 mmol). The mixture was stirred at room temperature for 18 h, and concentrated in vacuo. Toluene was added (2 mL) and the mixture was concentrated in vacuo (this procedure was repeated 3 times). Flash chromatography (EtOAc/hexanes 3:1, then 5:1) afforded **46** (53.7 mg, 0.151 mmol, 88%) as a light yellow oil. R_f 0.25 (EtOAc/hexanes 3:1). $[\alpha]_D$ +26.1 (*c* 0.82, $CHCl_3$). IR 3430, 2990, 2940, 2860, 1680, 1590. ^{1}H NMR (400 MHz) 1.09 (d, *J* = 6.7 Hz, 18H, 6× CH_3-TIPS), 1.17-1.28 (m, 3H, 3× CH-TIPS), 2.04-2.11 (m, 1H), 2.25 (s, 3H, CH_3C=C), 2.26-2.51 (m, 3H), 3.71 (s, 3H, CH_3O), 5.10-5.14 (m, 1H, H-2), 5.27 (br s, 1H, NH). ^{13}C NMR (100 MHz) 13.28 and 17.89 ((CH_3)$_2$CH), 21.84 (CH_3C=C), 26.25 and 30.05 (C-3 and C-4), 49.69 (C-2), 51.22 (CH_3O), 113.39 (C=*C*CO), 162.46, 168.46 and 178.46 (2× C=O and C=*C*OTIPS). HRMS-FAB $[M+H]^+$ calculated for $C_{18}H_{34}NO_4Si$ 356.2257, found 356.2234. The ee of (+)-**46** was determined as follows. A solution of tris[3-

(heptafluoropropyl hydroxymethylene)-(+)-camphorato]europium (III) ($Eu(hfc)_3$) (40 mg) in 0.5 mL of $CDCl_3$ was added in increments to a solution of (±)-**46** (circa 8 mg, prepared from succinimide) in 0.5 mL of $CDCl_3$. After addition of 350 μL of the $Eu(hfc)_3$ solution, the ^1H NMR (400 MHz) spectrum of this mixture showed clear separation of the two singlets for $CH_3C{=}C$ of the two enantiomers (at 2.55 and 2.70 ppm). Integration of these two singlets showed a clear 1:1 ratio for (±)-**46**. In the case of (+)-**46**, ^1H NMR (400 MHz) did not reveal the presence of any of the enantiomeric product. Therefore, the ee was determined to be ≥ 97%.

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