Intramolecular Opening of β-Lactams with Amines as a Strategy Toward Enzymatically or Photochemically Triggered Activation of Lactenediyne Prodrugs

Luca Banfi,*[a] Giuseppe Guanti,*[a] and Marcello Rasparini[a]

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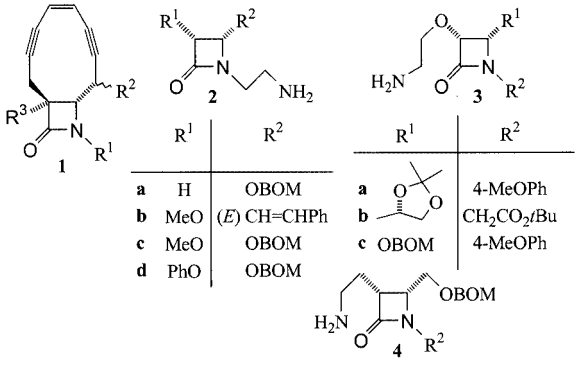
In order to develop a general strategy for selective activation of designed enediyne prodrugs belonging to the "lactenediyne" family, we studied the scope of intramolecular transamidation of simple monocyclic β-lactams bearing a tethered amine. The effect of substituents, of reaction media, and of the type of tether, on the rate of transamidation is disclosed. The possibility of triggering the transamidation event under mild conditions by the action of suitable enzymes or UV light was demonstrated on model monocyclic β-lactams. Finally, the strategy of intramolecular opening of the β-lactam leading to a larger seven-membered ring was employed on a lactenediyne, demonstrating that ring enlargement could unleash the reactivity of the enediyne moiety.

Introduction

We have recently reported the synthesis of various members of a new family of artificial enediynes (lactenediynes)[1−3] characterized by the fusion of a β-lactam with a ten-membered enediyne ring. These compounds have been designed to be structurally simpler than natural enediyne antibiotics,[4] and to be endowed with a triggering mechanism amenable to selective control. The most useful representatives of this family have the general formula **1** (Scheme 1). We have already proved that in these compounds the β-lactam unit acts as a very efficient safety lock, completely preventing Bergman cycloaromatization of the enediyne. On the other hand, removing this constraint results in a reactive monocyclic enediyne, which cyclizes rapidly to a reactive diradical. Opening of the four-membered ring may, therefore, represent the triggering event that converts a stable prodrug into a reactive, cytotoxic drug.

In the absence of activating substituents, the β-lactam unit is quite stable under physiological conditions. It is necessary, therefore, to find a way to induce its opening under mild conditions. Optimally, the triggering event should be initiated by the action of a suitable enzyme or by UV light. In this way, it would be possible, in principle, to effect prodrug activation selectively within tumor cells.

There are three alternative strategies that exploit enzymes for prodrug activation: prodrug monotherapy (PMT),[5,6] antibody-directed enzyme prodrug therapy (ADEPT),[7]



Scheme 1

and gene-directed enzyme prodrug therapy (GDEPT). Photochemically directed prodrug therapy (PDPT) may also be used to direct the cytotoxic effects with site selectivity. We feel that designed enediynes can be ideal candidates for these four strategies, although by now only a few examples of artificial enediynes equipped with enzymatic[8] or photochemical[9,10] triggers have been reported.

We thought that a good way to achieve our goals would be to tether a nucleophile, in particular an amino group, to the lactenediyne in order to make intramolecular opening of the β-lactam unit feasible under mild conditions. Since several enzymatically or photochemically removable amine protecting groups are known, accomplishing such a strategy definitely seems workable. Intramolecular opening of the β-lactam unit in lactenediynes **1** does not lead to monocyclic enediynes, but to *ortho*-fused or spiro-bicyclic systems. Because of the different nature of the newly formed fused heterocyclic rings, however, no longer are they expected to be

[a] Dipartimento di Chimica e Chimica Industriale dell'Università di Genova
Via Dodecaneso 31, 16146 Genova, Italy
E-mail: banriv@chimica.unige.it
guanti@chimica.unige.it

stabilizing against cycloaromatization. Preliminary molecular mechanics calculations, performed using the simplified approach proposed by Maier,[11] corroborated this hypothesis.

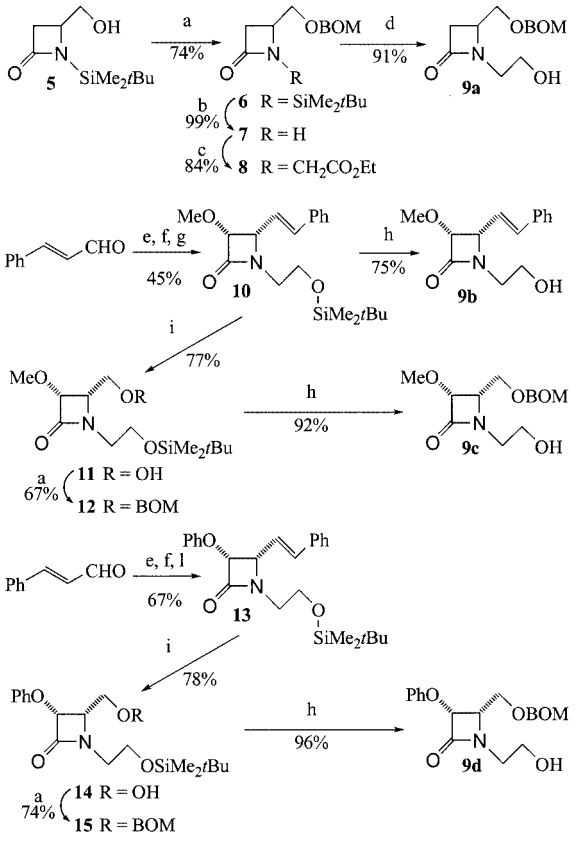
At the outset of this work very little was known on the intramolecular nucleophilic opening of simple monocyclic β-lactams.[12] For this reason, we decided to explore the whole strategy on model compounds. In a preliminary communication we have already described some results concerning the effect of the type of tether, of substituents, and of reaction media, on the rate of transamidation.[13] We now report in full the preparation of those and other model compounds, the results of transamidation, and the conjugation of these model compounds with enzymatically or photochemically removable protecting groups.

Finally, we report the first application of the strategy on a simple lactenediyne, demonstrating that ring enlargement removes all of the steric constraints that inhibit cycloaromatization.

Preparation of Model Amines

To gain some insight on the influence that structural changes have on the rate of transamidation reactions, we prepared a series of model monocyclic β-lactams having an amino group tethered either at N-1 (**2a**−**d**) or at C-3. In these compounds the amine is connected to the β-lactam through either an oxygenated chain (**3a**−**c**) or an alkyl chain (**4**). All the compounds were prepared in racemic form. They are depicted in Scheme 1 (BOM = $PhCH_2OCH_2$). Although the amino group could be also tethered, in principle, to C-4, we chose not to study this type of compound for two reasons: a) We expected that stereoselective synthesis of *trans*-lactenediynes, disubstituted at position 4 of the β-lactam unit, would be problematic. b) The transition state for a transamidation reaction in this case would be (again at the lactenediyne level) a bridged tricyclic ring instead of an *ortho*-fused tricyclic ring and, thus, we foresaw the intramolecular reaction as being more difficult.

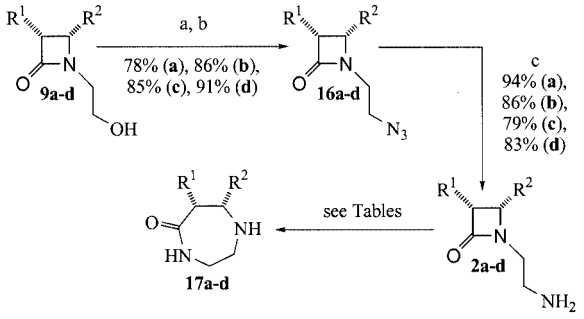
Amines **2a**−**d** were prepared in every case from the corresponding alcohols **9a**−**d** through azides **14a**−**d** (Scheme 3). The syntheses of alcohols **9a**−**d** are in turn described in Scheme 2. Compound **9a** was prepared from known azetidinone **5**.[2] After protection of the hydroxy unit as a benzyloxymethoxy ether and *N*-desilylation, the required side chain was introduced by base-mediated alkylation of the nitrogen atom with ethyl bromoacetate. This reaction was carefully optimized by varying the bromoacetate and base employed. Good yields were obtained with either *t*BuOK, $NaN(SiMe_3)_2$ or by the phase-transfer methodology described by Reuschling.[14] As for the ester, we found that ethyl or *tert*-butyl bromoacetates definitely gave better yields than benzyl bromoacetate. In order to facilitate subsequent reduction, we eventually chose the ethyl ester. Reduction of **8** with calcium borohydride gave **9a**. This reagent is ideal in this case because the reaction medium is not basic, provided that $CaCl_2$ is used in slight excess, and thus intramolecular β-lactam opening by the alcohol is avoided. Compounds **9b**−**d** were prepared in a completely different way, starting from the imine formed between cinnamaldehyde and 2-[(*tert*-butyldimethylsilyl)oxy]ethanamine.[15] Staudinger condensations with methoxyacetyl and phenoxyacetyl chlorides furnished azetidinones **10** and **13**, respectively. Compound **10** was converted by desilylation to the 4-styrylazetidinone **9b** or, through ozonolysis, protection, and desilylation, to **9c**. The synthesis of **9d** from **13** was carried out similarly to that of **9c**.



Scheme 2. a) BOMCl, $EtNiPr_2$; b) nBu_4NF, THF, −40 °C; c) KOH, $BrCH_2CO_2Et$; d) $Ca(BH_4)_2$, THF/H_2O, −20 °C; e) $HOCH_2CH_2NH_2$; f) $Me_2tBuSiCl$, Et_3N; g) $MeOCH_2COCl$, Et_3N, CH_2Cl_2, −78 °C → room temp.; h) HF, H_2O/CH_3CN; i) O_3, then $Me_2S{\cdot}NaBH_4$; l) $PhOCH_2COCl$, Et_3N, CH_2Cl_2, −78 °C → room temp.

All of these alcohols were transformed into the corresponding azides **16a**−**d** by substitution of their corresponding mesylates (Scheme 3). Finally, reduction with triphenylphosphane[16] gave the free amines **2a**−**d**, which were purified by chromatography [$CHCl_3$/MeOH/iPr_2NH]. Interestingly, some of these amines (**2a** and **2d**) tend to give two spots by TLC, but they cannot be separated by column chromatography. Treatment with an acylating agent (e.g., Ac_2O in pyridine) provokes the disappearance of both spots, and affords the expected acetamides in high yields. Therefore, we think that the presence of the two spots reflects an equilibrium between a free amine and its product of addition to the β-lactam carbonyl group (a sort of hemi-

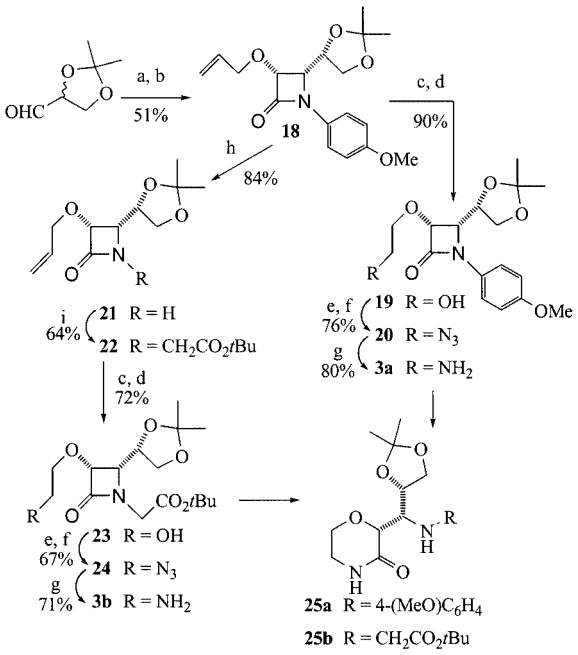
aminal). This fact, however, could not be proved by ^{1}H NMR spectroscopy because the spectra were quite complex. On standing, amines **2a**−**d** tended to afford less-polar products, giving negative Fluram™ tests,[17] identified as the seven-membered azalactams **17a**−**d**. This transformation is clearly faster for oxygenated compounds **2c**−**d**. In the case of **2d** in particular, **17d** is already visible in the crude mixture derived from azide reduction. After the intramolecular transamidation process was completed as described below, the rearranged azalactams **17a**−**d** were easily identified by IR, ^{13}C NMR and ^{1}H NMR spectroscopies. In the IR spectrum, the β-lactam carbonyl signal that had appeared at about 1740 cm^{-1} was replaced by a signal at 1660 cm^{-1}. In the ^{13}C NMR spectrum, the carbonyl group's signal was shifted downfield by about 8−9 ppm relative to that of the β-lactam. In the ^{1}H NMR spectrum, the coupling constants between 3-H and 4-H (β-lactam numbering) changed: the *cis* one went from 4−5 Hz to nearly 0 Hz, while the *trans* one (present only in the case of **2a**−**17a**) went from 2.2 to 9.8 Hz. Moreover, the signal(s) of 3-H proton(s) was (were) shifted upfield by about 0.5 ppm.



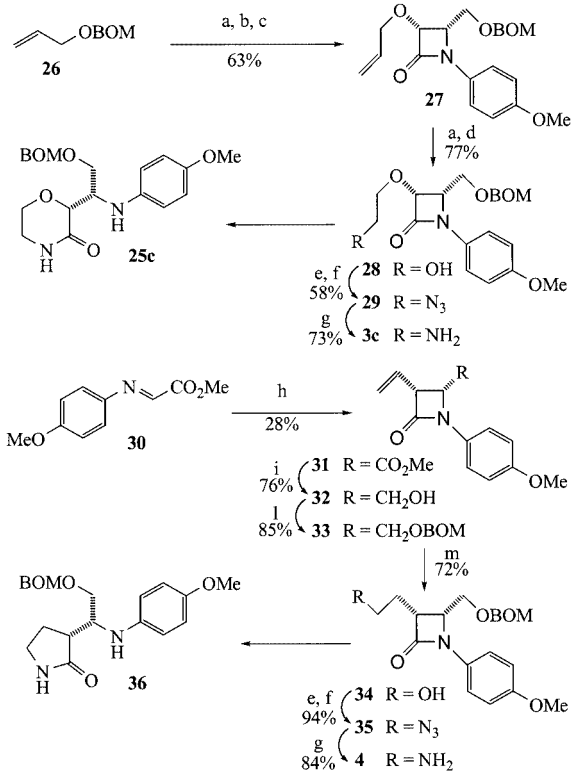
Scheme 3. a) MsCl, Et_3N, CH_2Cl_2, −30 °C; b) NaN_3, DMF, 50−60 °C; c) Ph_3P, H_2O/THF, room temp.

Amines **3a**,**b** (Scheme 4) were prepared in racemic form as shown in Scheme 4. Again, in this case the first step was a Staudinger reaction[18] between an imine of glyceraldehyde acetonide and allyloxyacetyl chloride. As already reported, this reaction afforded racemic **18** as a single diastereoisomer from among the four possible ones. Ozonolysis of **18**, followed by in situ $NaBH_4$ reduction, afforded alcohol **19** in unsatisfactory yields, because intramolecular opening of the lactam by the hydroxy group occurred, followed by reduction of the resulting lactone. We then discovered that an excellent yield of **19** could be achieved by reduction of the ozonolysis product with Me_2S to form the aldehyde that then was reduced with BH_3. Transformation into the amine **3a** was then realized as outlined above. To evaluate the effect of an electron-withdrawing substituent bonded to the nitrogen atom, we also replaced the anisyl group with a *tert*-butoxycarbonylmethyl group to give **22**. Ozonolysis/reduction and the usual functional group transformations gave **3b**.

The synthesis of amine **3c** followed a very similar approach (Scheme 5). In this case the required imine was prepared from benzyloxymethoxyacetaldehyde, in turn obtained by ozonolysis of ether **26**.



Scheme 4. a) *p*-Anisidine, mol. sieves; b) allyloxyacetyl chloride, CH_2Cl_2, Et_3N, −20 °C to room temp.; c) O_3, CH_2Cl_2/MeOH, then Me_2S; d) BH_3·THF; e) MsCl, Et_3N, CH_2Cl_2, −30 °C; f) NaN_3, DMF, 50−60 °C; g) Ph_3P, H_2O/THF, room temp.; h) $Ce(NH_4)_2(NO_3)_6$; i) *t*BuOK, $BrCH_2CO_2tBu$, nBu_4NI



Scheme 5. a) O_3, CH_2Cl_2/MeOH, then Me_2S; b) *p*-anisidine, mol. sieves; c) allyloxyacetyl chloride, CH_2Cl_2, Et_3N, −20 °C to room temp.; d) BH_3·THF; e) MsCl, Et_3N, CH_2Cl_2, −30 °C; f) NaN_3, DMF, 50−60 °C; g) Ph_3P, H_2O/THF, room temp.; h) crotonyl chloride, Et_3N, CH_2Cl_2, reflux; i) $Ca(BH_4)_2$, THF/EtOH; l) BOMCl, $EtNiPr_2$; m) 9-BBN, THF, room temp.; then $KHCO_3$, H_2O_2

Compounds **3a**−**c** also showed the same phenomenon of the double spot on TLC plates that was seen with **2a** and **2d**. On standing in solution, compounds **3a**−**c** were slowly converted into morpholinones **25a**−**c**. The rearranged azalactams **25a**−**c** could be easily identified by IR, ^{13}C NMR and ^{1}H NMR spectroscopies. In the IR spectra, the β-lactam carbonyl groups' signals that had appeared at about 1740 cm^{-1} were replaced by signals at 1670 cm^{-1}. In the ^{13}C NMR spectra, the carbonyl groups' peaks were shifted downfield by about 4 ppm relative to those of the β-lactams. In the ^{1}H NMR spectra, the coupling constants between 3-H and 4-H (β-lactam numbering) went from 4−5 Hz to nearly 0 Hz. Finally, the 3-H protons were shifted upfield by about $\delta = 0.4$ ppm.

For the synthesis of **4** (Scheme 5), we condensed crotonyl chloride with imine **30**. Although this reaction was reported to give a 60% yield,[19] in our hands the method was less efficient. Nevertheless, the adduct **31** was reduced with calcium borohydride in good yield to give the alcohol **32**. It is worth noting that the same reduction conditions failed when applied to the similar 3-(allyloxy)-4-(methoxycarbonyl)-1-(4-methoxyphenyl)-2-azetidinone, which led instead to reduction also of the β-lactam unit. It seems that the 3-alkoxy substituent activates the β-lactam toward reduction. Reduction of **31** with $NaBH_4$ in THF/EtOH/H_2O produced a mixture of **32** and of the *trans* isomer, probably because of enolization at the carbon atom α to the methyl ester. To avoid this isomerization, it is important to use a slight excess of $CaCl_2$ in the preparation of $Ca(BH_4)_2$.[20] After protection as the BOM ether, the double bond in **33** was smoothly hydroborated with 9-BBN to give the alcohol **34**, which was finally converted into amine **4** through the usual protocol.

Compound **4** also underwent rearrangement, albeit more slowly, to the pyrrolidinone **36**. In the IR spectrum, the carbonyl group's signal moved from the position of a typical β-lactam (1740 cm^{-1}) to 1692 cm^{-1}, while in the ^{13}C NMR spectrum, the signal of the carbonyl group was shifted downfield by about 10 ppm.

Studies on the Rate of Intramolecular Transamidation of Model Amines

The half-lives of amines **2a**−**d**, **3a**−**c** and **4** were examined in 96% EtOH as solvent (Table 1) by taking aliquots of the solutions and analysing them by ^{1}H NMR spectroscopy. Although in aprotic solvents the reaction rate was in some cases slightly higher,[13] we preferred a protic solvent because of its greater similarity to in vivo conditions. In all cases, the reactions were driven to completion after an appropriate time, indicating that the equilibrium was shifted to the right. The collected results show that the nature of the substituent can be important in accelerating the reaction. For example, in the case of lactams **2a**−**d**, where the amino group is tethered to the nitrogen atom, an OR group at C-3 causes an increase in the rate, with the phenoxy group being more activating than the methoxy one. An unsaturated substituent at C-4 also has an activating effect. As for the lactams **3a**−**c**, with the amino unit tethered at C-3, the *tert*-butoxycarbonylmethyl group was more activating than an aryl group, despite the higher basicity of the leaving group. This result suggests that the leaving group probably is not the amide anion, and that protonation of the lactam nitrogen atom before opening of the ring may be required for a fast reaction rate.[21]

The lower reactivity of amines **3a** and **3c** compared to **2b**−**d** is somewhat surprising, since they have an oxygenated substituent at C-3 and an aryl group at the nitrogen atom (which is expected to be more activating than an alkyl group). This observation may depend on stereoelectronic factors: if the activation by the oxygen atom in compounds

Table 1. Rate of intramolecular transamidation of amines **2a**−**d**, **3a**−**c** and **4** in 96% EtOH

Entry	Starting amine	Rearranged lactam	Additives	Conc. [M]	Temp. [°C]	$t_{1/2}$ [h][a]
1	**2a**	**17a**	none	$1.1\cdot10^{-2}$	60	136
2	**2b**	**17b**	none	$1.1\cdot10^{-2}$	60	8
3	**2b**	**17b**	none	$1.1\cdot10^{-2}$	40	55
4	**2c**	**17c**	none	$1.1\cdot10^{-2}$	60	25
5	**2c**	**17c**	none	$1.1\cdot10^{-2}$	40	90
6	**2d**	**17d**	none	$1.1\cdot10^{-2}$	60	8
7	**2d**	**17d**	none	$1.1\cdot10^{-2}$	40	50
8	**3a**	**25a**	none	$1.1\cdot10^{-2}$	60	130
9	**3b**	**25b**	none	$1.1\cdot10^{-2}$	60	22
10	**3c**	**25c**	none	$1.1\cdot10^{-2}$	60	120
11	**4**	**36**	none	$1.1\cdot10^{-2}$	60	204
12	**2a**	**17a**	none	10^{-1}	60	130
13	**2a**	**17a**	0.1 M Et_3N	$1.1\cdot10^{-2}$	60	130
14	**2a**	**17a**	0.1 M Et_3N/0.05 M AcOH	$1.1\cdot10^{-2}$	60	8
15	**2a**	**17a**	0.1 M Et_3N/0.05 M AcOH	$1.1\cdot10^{-2}$	40	33
16	**2d**	**17d**	0.1 M Et_3N/0.05 M AcOH	$1.1\cdot10^{-2}$	40	3

[a] $t_{1/2}$ was determined by ^{1}H NMR spectroscopy (see Exp. Sect.).

3 depends on the spatial arrangement of its nonbonding electron pairs, intramolecular transamidation of amines **3a**–**c** may force the electron pairs into an unfavourable position. Another explanation is that the oxygen atom in the β-position lower the basicity of the amine. To check this hypothesis we prepared amine **4**, in which the tether does not contain an oxygen atom, but its reactivity was found to be even lower than that of **3a** and **3c**.

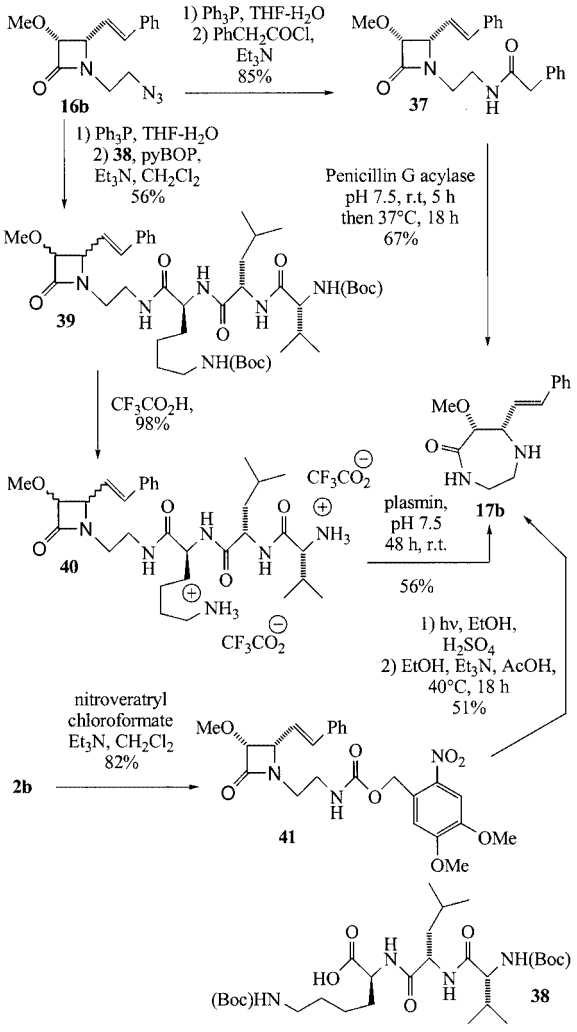
As expected, the effect of concentration on rate was negligible (compare Entry 12 with Entry 1). Also, a basic additive (Et_3N) had no effect. On the contrary, we observed a dramatic accelerating effect brought about by a near-neutral buffer (compare Entry 14 with Entry 1 and Entry 16 with Entry 7). This observation indicates once again that protonation of the leaving nitrogen atom is likely to be of great importance in the mechanism. Surprisingly, the effect of buffer on amine **3a** was less significant than on other lactams.[13]

In conclusion, the collected data allowed us to demonstrate the possibility of intramolecular opening of the lactam to give a larger ring under conditions similar to those that may be present in the cell. Although the rate of transamidation still seems too low in ethanol alone, the dramatic effect of buffer is promising in view of in vivo applications. Compounds with the amine tethered to the nitrogen atom and having an alkoxyl group at C-3 have been singled out as good candidates for implementing this strategy at the lactenediyne level.

Control of Transamidation by Blocking the Amines with an Enzymatically or Photochemically Removable Protecting Group

To induce selective intramolecular opening of the β-lactam ring of the lactenediynes within the tumor cells or in their neighbourhood, we planned to block the amino unit with enzymatically or photochemically removable protecting groups. Again, in this case we first carried out a preliminary study on a model compound lacking the enediyne moiety, represented by amine **2b**. It was converted, as shown in Scheme 6, into three protected derivatives: **37**, **40** and **41**. The best yields of these compounds were obtained by not isolating the amine **2b** chromatographically, but by directly acylating the crude product of the reduction of azide **16b** with PPh_3.

Phenylacetamide **37** was prepared to exploit Penicillin G acylase as the initiator of the cascade of events leading to intramolecular β-lactam opening. This is a cheap, non-endogenous enzyme that is perfectly suited for Antibody-Directed Enzyme Prodrug Therapy (ADEPT). The enzyme is generally active in the hydrolysis of esters[22,23] and amides[23,24] of phenylacetic acid, and has been used previously in the activation of antitumor prodrugs.[25] The enzymatic deprotection of **37** was carried out in aqueous TRIS buffer (pH = 7.5) containing 10% MeOH (used to partially solubilize the substrate). The hydrolysis reaction was complete in 5 h, indicating that **37** is a good substrate for the enzyme.



Scheme 6

At this point, TLC showed the presence of both amine **2b** and azalactam **17b**. On stirring overnight at 37 °C, complete conversion of **2b** into **17b** occurred and the latter was isolated in good yield.

Plasmin is a serine protease that has been found to be particularly abundant on the surface of tumor cells with high metastatic potential.[26] It was, therefore, suggested as an ideal candidate for the development of a Prodrug Monotherapy (PMT) approach to selective delivery of antitumor agents to cancer cells.[5,27] Plasmin is an endopeptidase that is selective for breaking the peptide bond at a lysine site. Tripeptide **38**, therefore, is a well-suited protecting group to be cleaved by plasmin: the terminal D-valine unit is important to avoid the action of exopeptidases. The synthesis of Boc-protected tripeptide **38** was carried out as described previously.[5] We also prepared the analogous Fmoc-protected derivative, but we had trouble coupling it with **2b** and in chromatographic purification (in part, because of the high insolubility of these Fmoc derivatives).

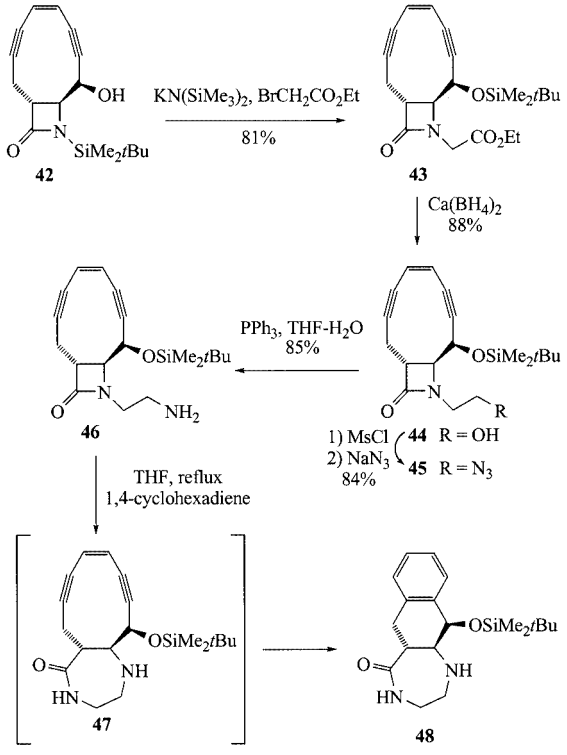
After coupling **2b** with **38**, the protecting groups were smoothly removed by CF_3CO_2H. Reaction of the resulting

salt **40** with plasmin took place at room temperature in buffer of pH = 7.5. In this case the reaction was slower than that with Penicillin G acylase and, as a result, we isolated the rearranged azalactam **17b** directly.

Finally, we also protected the amino group of **2b** as the nitroveratryl urethane **41**. This group is known to be removable by irradiation at 350 nm.[10,28] Compound **41** disappeared after several hours (depending on the molar amount and on the overall lamp power) when it was irradiated at 350 nm at room temperature in ethanol. The yields, however, of either the amine **2b** or the azalactam **17b** were poor. These low yields were probably due to reaction of the free amine with the nitrosoaldehyde derived from the protecting group. To circumvent this problem, we carried out the deblocking in the presence of semicarbazide or H_2SO_4.[29] The yields in these cases turned out to be quite good, as determined by phenylacetylation of the resulting crude **2b** to afford the corresponding phenylacetamide in 65−75% yield. The most convenient additive is H_2SO_4. The ammonium salt of **2b** is stable against transamidation and it can be purified from the byproducts by simple extraction. On addition of a base, the amine **2b** can be extracted into $CHCl_3$. Stirring of this solution at 40 °C led to complete conversion of **2b** into azalactam **17b**.

First Application of the Intramolecular Transamidation Reaction to Lactenediynes

The study described above on model compounds has demonstrated the feasibility of triggering, with suitable enzymes or UV light, the intramolecular opening of a monocyclic β-lactam under mild conditions (pH = 7.5, temperature ca. 37 °C). We still had to check, however, that ring enlargement to a more flexible seven-membered azalactam really does remove the "safety lock" provided by the β-lactam, thus allowing enediyne cycloaromatization to occur. Preliminary force-field calculations had suggested that this process was likely to happen, but we obviously needed more solid experimental proof. Therefore, we prepared amine **46**, starting from the previously described lactenediyne **42** (Scheme 7). The first step of this synthesis is interesting. On treating with a base such as $KN(SiMe_3)_2$ or NaH, a fast, quantitative migration of the silyl group occurs from the nitrogen atom to the oxygen atom. The resulting anion at the nitrogen atom can be alkylated in situ with ethyl bromoacetate. In just one step, therefore, we have succeeded in protecting the hydroxy group, deblocking the nitrogen atom, and then alkylating it. The following steps are similar to those applied to the model compounds. Amine **46** was purified by chromatography and can be stored in a freezer as the stable hydrochloride salt. On warming the free amine in THF at reflux in the presence of the hydrogen donor 1,4-cyclohexadiene, the amine slowly disappears and gives rise to two new spots (TLC). Small quantities (< 1 mg) of the less-polar one were isolated by fast preparative TLC and analyzed by ^{1}H NMR spectroscopy. This compound, which still possesses the enediyne group and, therefore, is most likely azalactam **47**, is always present in minimal quantities throughout the reaction; the main product is the cycloaromatized compound **48**. The latter compound was isolated in moderate yield (45%) after completion of the reaction (4 d). Its structure was easily identified, by ^{1}H and ^{13}C NMR spectroscopy, by the absence of the ethylenic protons and carbon atoms and of the acetylenic carbon atoms typical of the enediyne moiety, and by the presence of aromatic protons and carbon atoms. The fact that intramolecular transamidation had occurred was demonstrated by: a) the carbonyl group's appearance at 1663 cm^{-1} in the IR spectrum; b) the signal at δ = 179.04 ppm in the ^{13}C NMR spectrum for the carbonyl group; c) the presence of an amide NH unit in both ^{1}H NMR and IR spectra. The half-life of **46** under these conditions was estimated to be about 24 h. At 40 °C the reaction was obviously slower. At this temperature, however, **47** was only ever present in small quantities, indicating that cycloaromatization is faster than intramolecular transamidation. The reactivity of **46** towards transamidation seems somewhat lower than that of the model compound **2a**. Structural modifications, such as, for example, the introduction of an alkoxy group at C-3, are expected to increase its reactivity. We have recently completed the total synthesis of lactenediynes endowed with this feature.[3,15]



Scheme 7

Conclusions

A thorough study on the intramolecular transamidation of model β-lactams bearing an amino group tethered at

either N-1 or C-3 has been carried out, showing interesting structure−reactivity relationships and the important effects of solvent and buffer. Protection of this amine with enzymatically or photochemically removable groups allows the selective triggering of intramolecular β-lactam opening. Finally, applying the same concepts to a lactenediyne, we have demonstrated that, upon ring enlargement, the heterocycle *trans*-fused with the enediyne ring is no longer able to act as a "safety lock" (i.e., it no longer prevents cycloaromatization).

These results open the way to the implementation of these concepts in the development of new lactenediyne prodrugs whose activity against DNA may be triggered by a suitable enzyme or by UV light. Studies towards this important goal are in progress.

Experimental Section

General Remarks: ^{1}H and ^{13}C NMR spectra were taken in $CDCl_3$ at 200 MHz and 50 (or 20) MHz, respectively. Chemical shifts are reported in ppm (δ scale), using TMS as an internal standard. Coupling constants are reported in Hz. In ABX systems, the proton A is considered downfield and B upfield. Peak assignment in the ^{13}C NMR spectra was also made on the basis of DEPT or off-resonance experiments. GC-MS was carried out with an HP-5971A instrument, with an HP-1 column (12 m long, 0.2 mm diameter), electron impact at 70 eV, a mass temperature of about 167 °C, and starting the spectral range from m/z = 33. Analyses were performed with a constant He flow of 0.9 mL/min, starting at 100 °C for 2 min (unless otherwise noted) and then raising the temperature by 20 °C/min. Values of R_t were measured in minutes from injection. IR spectra were measured as $CHCl_3$ solutions. TLC analyses were carried out on silica gel plates, which were scrutinized by UV or by dipping into a solution of $(NH_4)_4MoO_4{\cdot}4H_2O$ (21 g) and $Ce(SO_4)_2{\cdot}4H_2O$ (1 g) in H_2SO_4 (31 mL) and H_2O (469 mL) and warming. In the case of primary amines, the spots were also developed with the Fluram™ reagent.[17] Values of R_f were measured after an elution of 7−9 cm. Column chromatographies were carried out on 220−400 mesh silica gel by using the "flash" methodology. All reactions employing dry solvents were carried out under nitrogen (or argon, where indicated). During extractions, the aqueous phases were always reextracted twice with the indicated organic solvent. Organic extracts were always dehydrated with Na_2SO_4 and filtered before concentration to dryness. Abbreviations used: PE = petroleum ether, boiling range 40−60 °C; THF = tetrahydrofuran; DMF = dimethylformamide; BOM = benzyloxymethyl; pyBOP = (benzotriazol-1-yloxy)tris(pyrrolidino)phosphonium hexafluorophosphate.

***rac*-4-[(Benzyloxymethoxy)methyl]-1-(*tert*-butyldimethylsilyl)-azetidin-2-one (6):** A solution of alcohol **5**[2] (2.510 g, 11.65 mmol) in dry CH_2Cl_2 (40 mL) was cooled to 0 °C and treated in sequence with *N*-ethyldiisopropylamine (3.00 mL, 17.52 mmol) and freshly distilled benzyl chloromethyl ether (2.5 mL, 18.0 mmol). After 10 min, the cooling bath was removed and the solution stirred for 5 h at room temp. After addition of diethylamine (1.21 mL, 11.65 mmol) and stirring for 15 min, the mixture was poured into saturated aqueous NH_4Cl and extracted with Et_2O. Concentration and chromatography of the crude product (PE/EtOAc, 70:30 to 50:50 + 1% Et_3N) gave pure **6** as a slightly yellow oil (2.894 g, 74%). R_f = 0.55 (PE/EtOAc, 70:30). $C_{18}H_{29}NO_3Si$ (335.51): calcd. C 64.44, H 8.71, N 4.17; found C 64.5, H 8.75, N 4.1. GC-MS: R_t = 9.55, m/z = 278 [$M^{+\cdot}$ − 57] (2.3), 248 (3.3), 206 (16.7), 158 (4.5), 100 (10.0), 91 (100.0), 75 (3.9), 73 (10.1), 65 (4.4), 57 (6.8), 41 (7.3). ^{1}H NMR: δ = 0.23 and 0.24 (2 s, 2 × 3 H, CH_3Si), 0.96 [s, 9 H, (CH_3)$_3$C], 2.78 (dd, J = 2.0, 15.2 Hz, 1 H, CHHC=O), 3.13 (dd, J = 5.4, 15.2 Hz, 1 H, CHHC=O), 3.56−3.76 (m, 3 H, CHN and CH_2O), 4.61 (s, 2 H, PhCH_2), 4.77 (s, 2 H, OCH_2O), 7.30−7.43 (m, 5 H, aromatics) ppm.

***rac*-4-[(Benzyloxymethoxy)methyl]azetidin-2-one (7):** A solution of alcohol **6** (2.620 g, 7.81 mmol) in dry THF (40 mL) was cooled to −40 °C and treated with a solution of nBu$_4$NF·3H$_2$O in THF (1 M, 23.4 mL, 23.4 mmol). After 1 h, the reaction was complete and was quenched at −40 °C with saturated aqueous NH_4Cl. Extraction with Et_2O gave, after concentration and chromatography (PE/EtOAc, 30:70 to 20:80), pure **7** as a slightly yellow oil (1.708 g, 99%). R_f = 0.27 (PE/EtOAc, 30:70). $C_{12}H_{15}NO_3$ (221.25): calcd. C 65.14, H 6.83, N 6.33; found C 65.3, H 7.05, N 6.2. GC-MS: R_t = 7.93, m/z = 190 [$M^{+\cdot}$ − 31] (0.2), 120 (29.5), 119 (9.8), 108 (12.0), 91 (100.0), 72 (8.4), 70 (12.8), 65 (10.4), 43 (19.7), 41 (7.6), 39 (5.3). ^{1}H NMR: δ = 2.65 (ddd, J = 1.5, 2.4, 14.8 Hz, 1 H, CHHC=O), 3.04 (ddd, J = 1.9, 4.9, 14.8 Hz, 1 H, CHHC=O), 3.56 (dd, J = 8.5, 11.2 Hz, 1 H CHHO), 3.75−3.86 (m, 2 H, CHN and CHHO), 4.61 (s, 2 H, PhCH_2), 4.79 (s, 2 H, OCH_2O), 5.99 (br. s, 1 H, NH), 7.30−7.43 (m, 5 H, aromatics) ppm. ^{13}C NMR (20 MHz): δ = 40.52 (*C*H$_2$), 46.92 (*C*H), 69.92 (*C*H$_2$O), 70.80 (*C*H$_2$O), 95.17 (O*C*H$_2$O), 127.84, 128.53 (aromatics), 137.51 (quat. aromatic), 167.50 (*C*=O) ppm. IR: $\tilde{\nu}_{max}$ = 3416, 3003, 2950, 2890, 2870, 1762 (s), 1604, 1494, 1453, 1412, 1361, 1337, 1167, 1109, 1037 cm^{-1}.

Ethyl *rac*-{2-[(Benzyloxymethoxy)methyl]-4-oxoazetidin-1-yl}acetate (8): A solution of azetidinone **7** (1.00 g, 4.52 mmol) in dry THF (30 mL) was cooled to 0 °C and treated with nBu$_4$NBr (154 mg, 0.48 mmol), powdered KOH (85%, 348 mg, 5.27 mmol) and ethyl bromoacetate (0.60 mL, 5.41 mmol). After 75 min, the reaction was complete and was quenched with saturated aqueous NH_4Cl. Extraction with Et_2O (2 ×) and EtOAc gave, after concentration and chromatography (PE/EtOAc, 50:50 to 40:60), pure **8** as an oil (1.171 g, 84%). R_f = 0.41 (PE/EtOAc, 50:50). $C_{16}H_{21}NO_5$ (307.34): calcd. C 62.53, H 6.89, N 4.56; found C 62.35, H 6.9, N 4.5. GC-MS: R_t = 9.55; m/z = 307 [$M^{+\cdot}$] (0.1), 234 (0.5), 200 (9.3), 174 (5.7), 156 (9.7), 129 (6.6), 120 (13.2), 114 (7.5), 91 (100.0), 86 (11.3), 65 (5.6), 56 (5.6), 55 (4.5), 41 (7.2). ^{1}H NMR: δ = 1.28 (t, J = 7.1 Hz, 3 H, CH_3), 2.71 (dd, J = 2.6, 14.6 Hz, 1 H, CHHC=O), 3.08 (dd, J = 5.2, 14.6 Hz, 1 H, CHHC=O), 3.68 and 3.83 (AB part of ABX system, J_{AB} = 10.4 Hz, J_{AX} = 3.4 Hz, J_{BX} = 7.6 Hz, 2 H, CH_2O), 3.86 (d, J = 18.0 Hz, 1 H, CHHCO$_2$Et), 4.00 (m$_c$, 1 H, CHN), 4.18 (d, J = 18.0 Hz, 1 H, CHHCO$_2$Et), 4.19 (q, J = 7.2 Hz, 2 H, CH_2CH$_3$), 4.59 (s, 2 H, PhCH_2), 4.75 (s, 2 H, OCH_2O), 7.30−7.43 (m, 5 H, aromatics) ppm.

***rac*-4-[(Benzyloxymethoxy)methyl]-1-(2-hydroxyethyl)azetidin-2-one (9a):** A suspension of finely ground $CaCl_2$ (388 mg, 3.48 mmol) in dry THF (20 mL) and dry EtOH (10 mL) was cooled to −20 °C and treated with $NaBH_4$ (240 mg, 6.40 mmol). After 15 min, a solution of ester **8** (357 mg, 1.16 mmol) in dry THF (10 mL) was added. After 3.5 h, the reaction was complete and was quenched by the slow addition of saturated aqueous NH_4Cl. Most of the THF and EtOH were evaporated and the mixture was extracted three times with EtOAc. After concentration and chromatography (PE/EtOAc, 30:70 to EtOAc/MeOH, 95:5) pure **9a** was obtained as an oil (281 mg, 91%). R_f = 0.27 (PE/EtOAc, 30:70). $C_{14}H_{19}NO_4$ (265.31): calcd. C 63.38, H 7.22, N 5.28; found C 63.6, H 7.4, N 5.0. GC-MS: R_t = 9.31; m/z = 234 [$M^{+\cdot}$ − 31] (1.5), 204 (2.1), 144 (2.4), 132 (5.6), 120 (7.9), 114 (14.8), 91 (100.0), 72 (20.4), 65 (5.4),

45 (10.2), 41 (6.8). ^{1}H NMR: δ = 1.80 (br. s, 1 H, O*H*), 2.70 (dd, *J* = 2.2, 14.6 Hz, 1 H, C*H*HC=O), 2.99 (dd, *J* = 4.6, 14.6 Hz, 1 H, C*H*HC=O), 3.30−3.42 (m, 2 H, CH_2N), 3.64−3.90 (m, 5 H, CH_2O and C*H*N), 4.61 (s, 2 H, PhCH_2), 4.79 (s, 2 H, OCH_2O), 7.30−7.43 (m, 5 H, aromatics) ppm. ^{13}C NMR (20 MHz): δ = 38.65 and 46.71 (*C*H_2), 51.35 (*C*HN), 60.44, 68.43, 69.96 (*C*H_2), 94.98 (O*C*H_2O), 127.69, 128.42 (aromatic *C*H), 137.33 (quat. aromatic), 167.66 (*C*=O) ppm. IR: $\tilde{\nu}_{max}$ = 3668, 3603, 3430, 3085, 3036, 2995, 2943, 2888, 1741 (s), 1602, 1453, 1402, 1379, 1344, 1331, 1193, 1168, 1147, 1113, 1050, 944 cm^{-1}.

(3*R,4*S**)-1-(2-Hydroxyethyl)-3-methoxy-4-(2-phenylethenyl)-azetidin-2-one (9b):** A solution of silyl ether **10**[15] (4.50 g, 12.45 mmol) in CH_3CN (40 mL) was cooled to −20 °C and treated with 40% aqueous HF (2 mL, 45.18 mmol). The solution was stirred at −20 °C for 1 h, at −10 °C for 5 h, and at 0 °C for 3 h. Then the mixture was poured cautiously into a suspension of $NaHCO_3$ (12.6 g, 150 mmol) in 100 mL of H_2O. Extraction with EtOAc, followed by washing with saturated aqueous NaCl, concentration, and chromatography (EtOAc to EtOAc/MeOH, 95:5) gave pure **9b** as a white solid (2.31 g, 75%). An analytical pure sample was obtained by trituration with Et_2O/PE. R_f = 0.31 (EtOAc). M.p. 78.2−79.4 °C. $C_{14}H_{17}NO_3$ (247.29): calcd. C 68.00, H 6.93, N 5.66; found C 67.9, H 7.0, N 5.6. GC-MS: R_t = 8.98; *m*/*z* = 247 [M$^{+\cdot}$] (3.3), 216 (28.9), 215 (6.7), 188 (7.5), 176 (21.2), 172 (5.3), 163 (23.4), 160 (58.5), 159 (45.7), 156 (26.4), 145 (18.3), 144 (21.7), 140 (13.7), 129 (38.8), 128 (33.3), 127 (16.3), 121 (5.9), 117 (46.1), 116 (19.4), 115 (100.0), 91 (37.5), 85 (7.3), 77 (13.6), 72 (11.6), 65 (9.1), 51 (13.0), 45 (34.8), 44 (12.0), 42 (12.0), 39 (15.7). ^{1}H NMR: δ = 3.10−3.45 (m, 2 H, CH_2N), 3.46 (s, 3 H, OCH_3), 3.74−3.90 (m, 3 H, CH_2O*H*), 4.35 (dd, *J* = 4.4, 9.1 Hz, 1 H, C*H*N), 4.64 (d, *J* = 4.4 Hz, 1 H, C*H*OMe), 6.24 (dd, *J* = 9.1, 16.0 Hz, 1 H, C*H*=CHPh), 6.75 (d, *J* = 16.0 Hz, 1 H, PhC*H*), 7.20−7.50 (m, 5 H, aromatics) ppm. ^{13}C NMR: δ = 45.41 (*C*H_2N), 58.62 (*C*H_3O), 59.90 (*C*HN), 61.65 (*C*H_2OH), 84.70 (*C*HOMe), 122.61 (*C*=CHPh), 126.72, 128.46, 128.68 (aromatic *C*H), 135.78 (aromatic quat.), 137.07 (Ph*C*H=), 167.66 (*C*=O) ppm. IR: $\tilde{\nu}_{max}$ = 3402 (broad), 2994, 2928, 2832, 1739 (s), 1599, 1403, 1346, 1250, 1145, 1052, 995, 968 cm^{-1}.

(3*R,4*S**)-1-[2-(*tert*-Butyldimethylsilyloxy)ethyl]-4-(hydroxymethyl)-3-methoxyazetidin-2-one (11):** A solution of azetidinone **10**[15] (700 mg, 1.94 mmol) in dry CH_2Cl_2 (9 mL) and dry MeOH (13.4 mL) was ozonized at −78 °C until a grey-blue color persisted. The solution was treated with Me_2S (0.50 mL) and, after 10 min, with $NaBH_4$ (300 mg, 7.93 mmol). The temperature was allowed to rise to 0 °C during 2 h. The mixture was quenched with saturated aqueous NH_4Cl. After evaporation of most of the MeOH, extraction with EtOAc, concentration and chromatography (PE/EtOAc, 30:70 to 20:80) gave pure **11** as an oil (432 mg, 77%). R_f = 0.39 (PE/EtOAc, 30:70). $C_{13}H_{27}NO_4Si$ (289.44): calcd. C 53.94, H 9.40, N 4.84; found C 54.3, H 9.2, N 4.7. GC-MS: R_t = 7.42; *m*/*z* = 274 [M$^{+\cdot}$ − 15] (2.9), 232 (75.4) [M$^+$ − 57], 204 (10.6), 202 (6.4), 174 (11.8), 144 (36.7), 130 (6.8), 100 (78.6), 88 (100.0), 75 (49.8), 73 (46.1), 71 (64.8), 61 (8.0), 60 (29.2), 59 (26.2), 58 (25.3), 57 (29.2), 56 (26.2), 45 (23.9), 41 (12.7). ^{1}H NMR: δ = 0.09 (s, 6 H, CH_3Si), 0.90 [s, 9 H, (CH_3)$_3$C], 3.08 (t, *J* = 6.6 Hz, 1 H, O*H*), 3.40 (t, *J* = 5.0 Hz, CH_2N), 3.58 (s, 3 H, OCH_3), 3.65−3.95 (m, 5 H, CH_2O, C*H*N), 4.54 (d, *J* = 4.4 Hz, 1 H, C*H*OMe) ppm. ^{13}C NMR (20 MHz): δ = −5.4 (*C*H$_3$Si), 18.34 [*C*(CH$_3$)$_3$], 25.91 [C(*C*H$_3$)$_3$], 43.30 (*C*H_2N), 59.37, 59.73, 60.47, 62.05 (*C*H_3O + *C*HN + CH_2O), 167.49 (*C*=O) ppm.

(3*R,4*S**)-4-[(Benzyloxymethoxy)methyl]-1-[2-(*tert*-butyldimethylsilyloxy)ethyl]-3-methoxyazetidin-2-one (12):** Alcohol **11** (216 mg, 0.746 mmol) was dissolved in dry DMF (3 mL), and treated in sequence with *n*Bu$_4$NI (27 mg, 74 μmol), EtN*i*Pr$_2$ (188 μL, 1.11 mmol) and freshly distilled benzyloxymethyl chloromethyl ether (134 μL, 0.96 mmol). The solution was stirred for 6 h at 60 °C. After cooling, Et_2NH (115 μL, 1.11 mmol) was added. The solution stirred for 1 h at room temp. and then poured into saturated aqueous NH_4Cl. Extraction with Et_2O followed by concentration and chromatography (PE/Et_2O, 30:70 + 1% Et_3N) gave pure **12** as a yellowish oil (223 mg, 73%). R_f = 0.47 (PE/Et_2O, 30:70). $C_{21}H_{35}NO_5Si$ (409.59): calcd. C 61.58, H 8.61, N 3.42; found C 61.75, H 8.7, N 3.35. ^{1}H NMR: δ = 0.06 (s, 6 H, CH_3Si), 0.89 [s, 9 H, (CH_3)$_3$C], 3.19 (dt, *J* = 14.1, 5.7 Hz, 1 H, C*H*HN), 3.52 (dt, *J* = 14.1, 5.5 Hz, 1 H, C*H*HN), 3.53 (s, 3 H, OCH_3), 3.69−3.86 (m, 4 H, CH_2O), 3.87−4.02 (m, 1 H, C*H*N), 4.52 (d, *J* = 4.6 Hz, 1 H, C*H*OMe), 4.61 (s, 2 H, CH_2Ph), 4.78 (s, 2 H, OCH_2O), 7.35 (s, 5 H, aromatics) ppm. IR: $\tilde{\nu}_{max}$ = 2995, 2933, 2884, 2859, 1754 (s), 1602, 1453, 1405, 1358, 1191, 1113, 1046, 958 cm^{-1}.

(3*R,4*S**)-4-[(Benzyloxymethoxy)methyl]-1-(2-hydroxyethyl)-3-methoxyazetidin-2-one (9c):** This compound was prepared in 92% yield from **12** according to the same procedure employed for **9b**. Chromatography (EtOAc) gave pure **9c** as a white solid. R_f = 0.26 (PE/EtOAc, 10:90). $C_{15}H_{21}NO_5$ (295.33): calcd. C 61.00, H 7.17, N 4.74; found C 61.4, H 7.3, N 4.6. GC-MS: R_t = 9.54; *m*/*z* = 295 [M$^{+\cdot}$] (0.2), 173 (0.9), 130 (2.0), 120 (1.5), 119 (1.8), 107 (8.1), 102 (11.4), 101 (20.8), 100 (7.0), 91 (100.0), 87 (76.9), 72 (58.2), 71 (56.9), 70 (77.3), 69 (21.5), 65 (10.0), 59 (39.0), 45 (10.7), 41 (14.8). ^{1}H NMR: δ = 3.26−3.48 (m, 2 H, CH_2N), 3.53 (s, 3 H, OCH_3), 3.58−3.96 (m, 5 H, CH_2O and C*H*N), 4.53 (d, *J* = 4.3 Hz, 1 H, C*H*OMe), 4.62 (s, 2 H, CH_2Ph), 4.79 (s, 2 H, OCH_2O), 7.35 (s, 5 H, aromatics) ppm. IR: $\tilde{\nu}_{max}$ = 3417, 3006, 2937, 2892, 2778, 1738 (s), 1604, 1513, 1404, 1351, 1189, 1107, 1046, 920 cm^{-1}.

(3*R,4*S**)-1-[2-(*tert*-Butyldimethylsilyloxy)ethyl]-3-phenoxy-4-(2-phenylethenyl)azetidin-2-one (13):** A solution of phenoxyacetyl chloride (730 μL, 3.52 mmol) in dry CH_2Cl_2 (40 mL) was cooled to −78 °C and treated dropwise with Et_3N (1.47 mL, 10.4 mmol). The temperature was allowed to rise to −40 °C during 30 min and the solution was treated with a solution of [2-(*tert*-butyldimethylsilyloxy)ethyl][(*E*)-3-phenylpropenylidene]amine[15] (1.020 g, 3.52 mmol) in dry CH_2Cl_2 (18 mL). The mixture was stirred at −20 °C for 48 h and at room temp. for 1 h. After treating with MeOH (6 mL) and stirring for 30 min, the mixture was poured into saturated aqueous NaCl and extracted with CH_2Cl_2. Concentration and chromatography (PE/EtOAc, 8:2 to 7:3) afforded pure **13** as a yellow oil (1.02 g, 68%). R_f = 0.29 (PE/Et_2O, 60:40). $C_{25}H_{33}NO_3Si$ (423.62): calcd. C 70.88, H 7.85, N 3.31; found C 70.55, H 7.9, N 3.2. ^{1}H NMR: δ = 0.08 [s, 6 H, Si(CH_3)$_2$], 0.92 [s, 9 H, C(CH_3)$_3$], 3.14 (ddd, *J* = 4.8, 7.4, 14.0 Hz, 1 H, C*H*HN), 3.52−3.87 (m, 3 H, CH_2OSi, C*H*HN), 4.64 (dd, *J* = 4.4, 8.9 Hz, 1 H, C*H*N), 5.36 (d, *J* = 4.4 Hz, 1 H, C*H*OPh), 6.21 (dd, *J* = 8.9 Hz, 1 H, C*H*=CHPh), 6.71 (d, *J* = 15.9 Hz, 1 H, CH=C*H*Ph), 6.98 (d, *J* = 8.0 Hz, 2 H, aromatics *ortho* to O), 7.18−7.40 (m, 3 H, other aromatics) ppm. ^{13}C NMR (20 MHz): δ = −5.38 [Si(*C*H$_3$)$_2$], 18.19 [*C*(CH$_3$)$_3$], 25.82 [C(*C*H$_3$)$_3$], 42.60 (*C*H_2N), 60.92 (*C*H_2O), 62.02 (*C*HN), 82.22 (*C*HOPh), 115.61, 122.75, 126.59, 128.13, 128.49, 129.34 (aromatic *C*H), 122.01 (*C*H=CHPh), 135.94 (aromatic quat.), 136.73 (CH=*C*HPh), 157.37 (aromatic quat.), 165.49 (*C*=O) ppm. IR: $\tilde{\nu}_{max}$ = 3009, 2954, 2930, 1756 (s), 1598, 1490, 1407, 1362, 1193, 1108, 967 cm^{-1}.

(3*R,4*S**)-1-[2-(*tert*-Butyldimethylsilyloxy)ethyl]-4-(hydroxymethyl)-3-phenoxyazetidin-2-one (14):** This compound was prepared from **13** in 78% yield using the same procedure employed for

11. M.p. 53.9−54.5 °C. R_f = 0.47 (PE/EtOAc, 60:40). $C_{18}H_{29}NO_4Si$ (351.51): calcd. C 61.50, H 8.32, N 3.98; found C 61.6, H 8.4, N 3.85. ^{1}H NMR: δ = 0.12 [s, 6 H, Si(CH_3)$_2$], 0.93 [s, 9 H, C(CH_3)$_3$], 3.26 (dd, *J* = 6.3, 7.6 Hz, 1 H, O*H*), 3.41 (ddd, *J* = 3.6, 7.7, 14.5 Hz, 1 H, C*H*HN), 3.58 (ddd, *J* = 3.3, 5.0, 14.5 Hz, 1 H, C*H*HN), 3.72−4.15 (m, 5 H, CH_2OSi, CH_2OH, C*H*N), 5.27 (d, *J* = 4.4 Hz, 1 H, C*H*OPh), 6.98−7.12 (m, 3 H, aromatics), 7.25−7.42 (m, 2 H, aromatics) ppm. ^{13}C NMR (20 MHz): δ = −5.41 [Si(*C*H$_3$)$_2$], 18.46 [*C*(CH$_3$)$_3$], 25.96 [C(*C*H$_3$)$_3$], 44.0 (*C*H$_2$N), 60.53 (*C*HN), 60.96 (*C*H$_2$O), 62.23 (*C*H$_2$O), 80.72 (*C*HOPh), 115.63, 122.47, 129.67 (aromatic *C*H), 157.44 (aromatic quat.), 166.05 (*C*=O) ppm. IR: $\tilde{\nu}_{max}$ = 3408, 3005, 2952, 2929, 2859, 1759 (s), 1600, 1492, 1407, 1358, 1193, 1097, 1027 cm^{-1}.

(3*R,4*S**)-4-[(Benzyloxymethoxy)methyl]-1-[2-(*tert*-butyldimethylsilyloxy)ethyl]-3-phenoxyazetidin-2-one (15):** A solution of alcohol **14** (260 mg, 0.74 mmol) in dry DMF (3 mL) was treated with *n*Bu$_4$NI (27.4 mg, 0.074 mmol), EtN*i*Pr$_2$ (188 μL, 1.11 mmol) and freshly distilled benzyloxymethyl chloride (134 μL, 0.96 mmol). After 30 min, the solution was heated at 60 °C overnight. After cooling to room temp., the reaction was quenched with diethylamine (115 μL, 1.11 mmol). After stirring for 1 h, the mixture was poured into saturated aqueous NH_4Cl and extracted with Et_2O. Chromatography (PE/Et_2O, 55:45 to 60:40) gave pure **15** as a yellowish oil (258 mg, 74%). R_f = 0.53 (PE/Et_2O, 60:40). $C_{26}H_{37}NO_5Si$ (471.66): calcd. C 66.21, H 7.91, N 2.97; found C 66.5, H 8.1, N 2.75. GC-MS: R_t = 13.92; *m*/*z* = 456 [M$^{+\cdot}$ − 15] (1.0), 414 (30.7) [M$^+$ − 57], 200 (2.5), 184 (8.7), 164 (31.8), 149 (20.0), 144 (5.2), 133 (15.6), 121 (8.4), 105 (7.9), 100 (13.4), 94 (22.0), 91 (100.0), 77 (11.3), 75 (8.3), 73 (18.3), 71 (37.1), 70 (20.6). ^{1}H NMR: δ = 0.08 [s, 6 H, Si(CH_3)$_2$], 0.91 [s, 9 H, C(CH_3)$_3$], 3.26 (dt, *J* = 14.0, 5.7 Hz, 1 H, C*H*HN), 3.61 (dt, *J* = 14.0, 5.4 Hz, 1 H, C*H*HN), 3.74−3.98 (m, 4 H, CH_2OSi, CH_2OBOM), 4.17 (dt, *J* = 6.6, 4.8 Hz, 1 H, C*H*N), 4.51 (s, 2 H, CH_2Ph), 4.71 (s, 2 H, OCH_2O), 5.26 (d, *J* = 4.8 Hz, 1 H, C*H*OPh), 6.98−7.12 (m, 3 H, aromatics), 7.20−7.40 (m, 6 H, aromatics) ppm. ^{13}C NMR (20 MHz): δ = −5.32 [Si(*C*H$_3$)$_2$], 18.25 [*C*(CH$_3$)$_3$], 25.94 [C(*C*H$_3$)$_3$], 43.71 (*C*H$_2$N), 58.24, 60.62, 66.72, 69.59 (*C*HN and *C*H$_2$O), 80.28 (*C*HOPh), 95.05 (O*C*H$_2$O), 115.63, 122.22, 127.84, 128.45, 129.54 (aromatic *C*H), 137.66, 157.69 (aromatic quat.), 166.05 (*C*=O) ppm. IR: $\tilde{\nu}_{max}$ = 3005, 2953, 2931, 2885, 2858, 1757 (s), 1598, 1491, 1405, 1358, 1236, 1111, 1049, 920 cm^{-1}.

(3*R,4*S**)-4-[(Benzyloxymethoxy)methyl]-1-(2-hydroxyethyl)-3-phenoxyazetidin-2-one (9d):** This compound was prepared in 96% yield from **15** according to the same procedure employed for **9b**. Chromatography (PE/EtOAc, 3:7 to 2:8) gave pure **9d** as a white solid. R_f = 0.32 (PE/EtOAc, 3:7). $C_{20}H_{23}NO_5$ (357.40): calcd. C 67.21, H 6.49, N 3.92; found C 67.4, H 6.6, N 3.8. GC-MS: R_t = 11.92 (during GC analysis, partial transformation into the rearranged lactone, R_t = 11.49, took place); *m*/*z* = 357 [M$^{+\cdot}$] (0.7), 177 (1.3), 176 (1.2), 164 (34.5), 149 (22.1), 134 (8.2), 133 (17.8), 131 (8.0), 121 (14.9), 119 (5.8), 105 (14.1), 95 (13.0), 94 (28.3), 92 (21.0), 91 (100.0), 77 (21.6), 71 (37.0), 70 (20.0), 69 (10.4), 65 (9.5), 39 (7.7). ^{1}H NMR: δ = 3.43 and 3.50 (AB part of ABX$_2$ system, J_{AB} = 14.6 Hz, J_{AX} = J_{BX} = 4.8 Hz, 2 H, CH_2N), 3.80−4.00 (m, 4 H, CH_2O), 4.12 (dt, *J* = 7.6, 4.4 Hz, 1 H, C*H*N), 4.56 (s, 2 H, CH_2Ph), 4.76 (s, 2 H, OCH_2O), 5.29 (d, *J* = 4.7 Hz, 1 H, C*H*OPh), 6.95−7.08 (m, 3 H, aromatics), 7.20−7.40 (m, 7 H, aromatics) ppm. ^{13}C NMR (20 MHz): δ = 46.86 (*C*H$_2$N), 58.40, 60.35, 67.24, 69.99 (*C*HN and *C*H$_2$O), 79.51 (*C*HOPh), 95.19 (O*C*H$_2$O), 115.51, 122.40, 127.77, 128.44, 129.60 (aromatic *C*H), 137.48, 157.43 (aromatic quat.), 166.70 (*C*=O) ppm. IR: $\tilde{\nu}_{max}$ = 3442, 3002, 2945, 2890, 1747 (s), 1599, 1492, 1408, 1348, 1194, 1115, 1041 cm^{-1}.

***rac*-1-(2-Azidoethyl)-4-[(benzyloxymethoxy)methyl]azetidin-2-one (16a):** A solution of alcohol **9a** (191.9 mg, 0.72 mmol) in dry CH_2Cl_2 (10 mL) was cooled to −30 °C, and treated with triethylamine (300 μL, 2.17 mmol) and methanesulfonyl chloride (84.0 μL, 1.08 mmol). After 1 h at the same temperature, the reaction was quenched by addition of saturated aqueous NH_4Cl (10 mL). Extraction with EtOAc, and concentration to dryness, gave crude mesylate (R_f = 0.49, EtOAc/MeOH, 90:10), which was taken up in dry DMF (2 mL), treated with NaN_3 (181 mg, 2.80 mmol) and heated at 50 °C for 5 h. After cooling to room temp., the mixture was diluted with saturated aqueous NH_4Cl, and extracted with EtOAc. The organic extracts were washed with H_2O, saturated NaCl, concentrated and chromatographed (PE/EtOAc, 30:70 to 10:90) to give pure azide **16a** as an oil (162.3 mg, 78%). R_f = 0.74 (EtOAc/MeOH, 90:10). $C_{14}H_{18}N_4O_3$ (290.32): calcd. C 57.92, H 6.25, N 19.30; found C 58.25, H 6.5, N 18.8. GC-MS: R_t = 9.55; *m*/*z* = 262 [M$^{+\cdot}$ − 28] (1.2), 234 (0.9), 204 (5.3), 141 (6.5), 120 (3.3), 91 (100.0), 84 (2.9), 69 (5.4), 65 (5.2), 56 (4.3), 55 (4.0), 42 (7.7), 41 (6.5). ^{1}H NMR: δ = 2.68 and 3.01 (AB part of ABX system, J_{AB} = 14.6 Hz, J_{AX} = 5.0 Hz, J_{BX} = 2.3 Hz, 2 H, CH_2C=O), 3.26 (ddd, *J* = 2.6, 9.5, 15.4 Hz, 1 H, C*H*HN), 3.42−3.74 (m, 4 H), 3.78−3.90 (m, 2 H), 4.61 (s, 2 H, CH_2Ph), 4.80 (s, 2 H, OCH_2O), 7.35 (s, 5 H, aromatics) ppm. IR: $\tilde{\nu}_{max}$ = 3001, 2937, 2889, 2107 (s), 1745 (s), 1603, 1453, 1400, 1348, 1331, 1286, 1148, 1110, 1043 cm^{-1}.

(3*R,4*S**)-1-(2-Azidoethyl)-3-methoxy-4-(2-phenylethenyl)azetidin-2-one (16b):** This compound was prepared (oil) in 86% yield from **9b** according to the same procedure used for **16a**. Reaction time of azide substitution: 5 h at 50 °C. R_f = 0.46 (PE/EtOAc, 40:60). $C_{14}H_{16}N_4O_2$ (272.30): calcd. C 61.75, H 5.92, N 20.58, found C 61.7, H 5.9, N 20.5. GC-MS: decomposition during analysis giving two peaks at 8.10 and 8.82 min. ^{1}H NMR: δ = 3.10−3.34 (m, 2 H), 3.40−3.62 (m, 2 H), 3.47 (s, 3 H, OCH_3), 4.40 (dd, *J* = 4.4, 9.0 Hz, 1 H, C*H*N), 4.66 (d, *J* = 4.4 Hz, C*H*OMe), 6.25 (dd, *J* = 9.2, 15.9 Hz, 1 H, C*H*=CHPh), 6.76 (d, *J* = 16.2 Hz, 1 H, C*H*Ph), 7.25−7.50 (m, 5 H, aromatics) ppm. ^{13}C NMR: δ = 39.46 and 49.30 (*C*H$_2$N), 58.70 (*C*H$_3$), 61.73 (*C*HN), 85.62 (*C*HOMe), 122.71 (*C*H=CHPh), 126.74, 128.47, 128.70 (aromatic *C*H), 135.79 (aromatic quat.), 137.03 (CH=*C*HPh), 167.02 (*C*=O) ppm. IR: $\tilde{\nu}_{max}$ = 3037, 2996, 2926, 2833, 2106 (s), 1750 (s), 1399, 1347, 1132, 1058, 999, 968 cm^{-1}.

(3*R,4*S**)-1-(2-Azidoethyl)-4-[(benzyloxymethoxy)methyl]-3-methoxyazetidin-2-one (16c):** This compound was prepared (oil) in 85% yield from **9c** according to the same procedure employed for **16a**. Reaction time of azide substitution: overnight at 40 °C. R_f = 0.73 (PE/EtOAc, 30:70). $C_{15}H_{20}N_4O_4$ (320.34): calcd. C 56.24, H 6.29, N 17.49; found C 56.3, H 6.35, N 17.4. GC-MS: R_t = 9.79; *m*/*z* = 292 [M$^{+\cdot}$ − 28] (2.8), 171 (16.0), 160 (11.7), 113 (8.5), 107 (6.5), 102 (7.3), 101 (13.5), 91 (100.0), 87 (48.9), 84 (8.2), 81 (6.8), 72 (35.0), 71 (38.6), 70 (52.3), 69 (21.5), 65 (9.3), 59 (25.2), 42 (9.1), 41 (13.2). ^{1}H NMR: δ = 3.26−3.40 (m, 1 H), 3.42−3.64 (m, 3 H), 3.53 (s, 3 H, OCH_3), 3.70−4.0 (m, 3 H), 4.54 (d, *J* = 4.7 Hz, C*H*OMe), 4.62 (s, 2 H, CH_2Ph), 4.80 (s, 2 H, OCH_2O), 7.36 (s, 5 H, aromatics) ppm. ^{13}C NMR (50 MHz): δ = 40.54 (*C*H$_2$N), 49.00 (*C*H$_2$N), 57.81 (*C*HN), 59.23 (O*C*H$_3$), 67.23, 69.89 (*C*H$_2$O), 83.51 (*C*OMe), 95.19 (O*C*H$_2$O), 127.70, 127.77, 128.43 (aromatic *C*H), 137.67 (aromatic quat.), 167.64 (*C*=O) ppm.

(3*R,4*S**)-1-(2-Azidoethyl)-4-[(benzyloxymethoxy)methyl]-3-phenoxyazetidin-2-one (16d):** This compound was prepared (oil) in 91% yield from **9d** according to the same procedure employed for **16a**. Reaction time of azide substitution: overnight at 40 °C. R_f = 0.43 (PE/EtOAc, 60:40). $C_{20}H_{22}N_4O_4$ (382.41): calcd. C 62.82, H

5.80, N 14.65; found C 62.55, H 6.55, N 14.5. ^{1}H NMR: δ = 3.32−3.72 (m, 4 H, CH_2CH_2N$_3$), 3.85 and 3.93 (AB part of ABX system, J_{AB} = 10.7 Hz, J_{AX} = 3.5 Hz, J_{BX} = 8.3 Hz, 2 H, CH_2O), 4.14 (dt, J = 8.4, 4.2 Hz, 1 H, C*H*N), 4.56 (s, 2 H, CH_2Ph), 4.76 (s, 2 H, OCH_2O), 5.29 (d, J = 4.8 Hz, C*H*OPh), 6.95−7.10 (m, 3 H, aromatics), 7.20−7.40 (m, 7 H, other aromatics) ppm. ^{13}C NMR (50 MHz): δ = 41.03 (*C*H$_2$N), 49.19 (*C*H$_2$N), 58.27 (*C*HN), 67.48, 70.12 (*C*H$_2$O), 80.32 (*C*OMe), 95.42 (O*C*H$_2$O), 115.71, 122.54, 127.89, 127.98, 128.62, 129.75 (aromatic *C*H), 137.80, 157.69 (aromatic quat.), 166.26 (*C*=O) ppm. IR: $\tilde{\nu}_{max}$ = 3008, 2932, 2106 (s), 1761 (s), 1599, 1492, 1405, 1349, 1241, 1109, 1044 cm^{-1}. $C_{14}H_{18}N_4O_3$ (290.32): calcd. C 57.92, H 6.25, N 19.30; found C 58.25, H 6.5, N 18.8.

(3*R,4*R**,4′*S**)-4-(2,2-Dimethyl-1,3-dioxolan-4-yl)-3-(2-hydroxyethoxy)-1-(4-methoxyphenyl)azetidin-2-one (19):** Racemic β-lactam **18** was obtained in 51% yield from racemic isopropylideneglyceraldehyde according to the procedure already described for the optically active compound.[18] M.p. 94.0−94.2 °C. A solution of **18** (400 mg, 1.2 mmol) in dry CH_2Cl_2 (30 mL) and dry MeOH (20 mL) was cooled to −78 °C and ozonized until the grey-blue color persisted. Me_2S (2 mL) was added. The temperature was allowed to rise to room temp. and the solution stirred for 3 h at this temperature. The solvent was evaporated to dryness and the residue taken up in dry THF (10 mL) and cooled to 0 °C. A solution of BH_3·THF in THF (1 M, 2.4 mL, 2.4 mmol) was added. After 30 min at 0 °C, the reaction was complete and was quenched with saturated aqueous NH_4Cl. Extraction with EtOAc, concentration and chromatography (PE/EtOAc, 40:60 to 30:70) gave pure alcohol **19** as a white solid (360 mg, 90%). R_f = 0.35 (PE/EtOAc, 30:70). $C_{17}H_{23}NO_6$ (337.37): calcd. C 60.52, H 6.87, N 4.15; found C 60.8, H 7.0, N 4.05. GC-MS: R_t = 10.36; *m*/*z* = 337 [M$^{+\cdot}$] (15.8), 322 (4.4), 279 (16.7), 234 (6.0), 209 (5.4), 164 (10.2), 160 (6.8), 150 (10.6), 149 (100.0), 136 (7.5), 135 (10.7), 134 (23.1), 117 (5.2), 101 (9.4), 77 (7.3), 73 (25.2), 72 (15.7), 69 (9.8), 45 (12.9), 43 (35.0). ^{1}H NMR: δ = 1.34 and 1.53 [2 s, 2 × 3 H, (CH_3)$_2$C], 3.70−4.00 (m, 5 H), 3.80 (s, 3 H, OCH_3), 4.22−4.32 (m, 2 H), 4.39 (dt, J = 8.7, 6.4 Hz, 1 H, C*H*O), 4.75 (d, J = 5.4 Hz, C*H*OCH$_2$), 6.87 (d, J = 9.1 Hz, 2 H, aromatics), 7.65 (d, J = 9.1 Hz, 2 H, aromatics) ppm. IR: $\tilde{\nu}_{max}$ = 3402, 2990, 2936, 2838, 1731 (s), 1601, 1505, 1441, 1383, 1298, 1192, 1136, 1069, 1031 cm^{-1}.

(3*R,4*R**,4′*S**)-3-(2-Azidoethoxy)-4-(2,2-dimethyl-1,3-dioxolan-4-yl)-1-(4-methoxyphenyl)azetidin-2-one (20):** This compound was prepared (solid) in 76% yield from **19** according to the same procedure employed for **16a**. Reaction time of azide substitution: 3 h at 50 °C. R_f = 0.60 (PE/EtOAc, 50:50). $C_{17}H_{22}N_4O_5$ (362.38): calcd. C 56.34, H 6.12, N 15.46; found C 56.6, H 6.1, N 15.0. GC-MS: R_t = 10.73; *m*/*z* = 362 [M$^{+\cdot}$] (6.1), 334 [M$^{+\cdot}$ − 28] (13.6), 306 (7.0), 304 (6.1), 236 (11.0), 233 (10.5), 205 (46.3), 190 (8.8), 185 (8.3), 178 (15.5), 176 (17.7), 175 (8.3), 160 (19.5), 149 (100.0), 136 (17.4), 135 (20.6), 134 (59.8), 123 (17.7), 114 (27.5), 107 (9.1), 107 (8.9), 101 (19.3), 92 (9.0), 77 (16.9), 72 (32.6), 59 (11.9), 44 (16.9), 43 (81.3), 42 (16.2), 41 (15.1). ^{1}H NMR: δ = 1.34 and 1.54 [2 s, 2 × 3 H, (CH_3)$_2$C], 3.41 and 3.52 (AB part of ABXY system, J_{AB} = 13.5 Hz, J_{AX} = 3.4 Hz, J_{AY} = 7.2 Hz, J_{BX} = 3.6 Hz, J_{BY} = 5.2 Hz, 2 H, CH_2N$_3$), 3.70−3.90 (m, 2 H), 3.80 (s, 3 H, OCH_3), 4.15 (ddd, J = 3.3, 5.3, 10.5 Hz, C*H*HO), 4.22 (dd, J = 5.6, 8.7 Hz, 1 H, C*H*N), 4.29 (dd, J = 6.8, 8.8 Hz, 1 H, C*H*HO), 4.39 (dt, J = 8.7, 6.4 Hz, 1 H, C*H*O), 4.69 (d, J = 5.6 Hz, 1 H, C*H*OCH$_2$), 6.87 (d, J = 9.0 Hz, 2 H, aromatics), 7.65 (d, J = 9.1 Hz, 2 H, aromatics) ppm. IR: $\tilde{\nu}_{max}$ = 2988, 2934, 2835, 2108 (s), 1742 (s), 1602, 1506, 1463, 1440, 1382, 1338, 1298, 1134, 1061, cm^{-1}.

(3*R,4*R**,4′*S**)-4-(2,2-Dimethyl-1,3-dioxolan-4-yl)-3-(2-propenyloxy)azetidin-2-one (21):** A solution of compound **18** (304 mg, 912 μmol) in CH_3CN (10 mL) was cooled to −20 °C and treated with a solution of Ce(NH$_4$)$_2$(NO$_3$)$_6$ (CAN) (1.513 g, 2.76 mmol) in H_2O (6 mL). After 30 min, the mixture was diluted with 60 mL of ice-cold water, and rapidly extracted with EtOAc. The organic extracts were washed with a mixture of saturated aqueous $NaHCO_3$ (30 mL) and aqueous Na_2SO_3 (10%, 15 mL). After a final washing with saturated NaCl, the organic phase was concentrated and chromatographed (PE/EtOAc, 70:30 to 50:50) to give pure **21** as a white solid (173 mg, 84%). R_f = 0.12 (PE/EtOAc, 70:30). $C_{11}H_{17}NO_4$ (227.26): calcd. C 58.14, H 7.54, N 6.16; found C 58.1, H 7.45, N 6.05. GC-MS: R_t = 6.09; *m*/*z* = 212 [M$^{+\cdot}$ − 15] (10.5), 169 (4.0), 154 (5.1), 143 (11.7), 126 (38.8), 113 (21.5), 101 (13.1), 85 (39.6), 84 (9.3), 83 (6.0), 82 (5.5), 72 (96.5), 71 (11.8), 70 (9.1), 69 (36.0), 68 (7.1), 59 (15.2), 57 (9.7), 56 (10.3), 55 (8.5), 43 (88.0), 42 (32.7), 41 (100.0), 39 (24.4). ^{1}H NMR: δ = 1.36 and 1.43 [2 s, 2 × 3 H, (CH_3)$_2$C], 3.66 [dd, J = 5.7, 8.6 Hz, 1 H, C*H*HOC(CH$_3$)$_2$], 3.71 (dd, J = 5.1, 8.9 Hz, 1 H, C*H*N), 4.05−4.40 [m, 4 H, C*H*O, CH$_2$=CHCH_2O, C*H*HOC(CH$_3$)$_2$], 4.65 (dd, J = 5.1, 2.2 Hz, 1 H, C*H*Oallyl), 5.23 (dq, J = 10.2, 1.4 Hz, 1 H, C*H*H=CH), 5.30 (dq, J = 17.2, 1.6 Hz, 1 H, C*H*H=CH), 5.88 (dddd, J = 5.1, 5.9, 10.3, 17.3 Hz, 1 H, C*H*=CH$_2$), 6.44 (br. s, 1 H, N*H*) ppm.

(3*R,4*R**,4′*S**)-1-(*tert*-Butoxycarbonylmethyl)-4-(2,2-dimethyl-1,3-dioxolan-4-yl)-3-(2-propenyloxy)azetidin-2-one (22):** A solution of azetidinone **21** (130.5 mg, 0.574 mmol) in dry THF (10 mL) was treated with freshly activated powdered molecular sieves (4 Å, 100 mg) and with *n*Bu$_4$NI (84.3 mg, 0.228 mmol). The mixture was cooled to −20 °C, and treated in rapid sequence with *t*BuOK (77 mg, 0.69 mmol) and *tert*-butyl bromoacetate (102 μL, 0.69 mmol). After 30 min, the reaction was quenched with saturated aqueous NH_4Cl, and extracted with EtOAc. Concentration and chromatography afforded pure **22** as an oil (125 mg, 64%). R_f = 0.27 (PE/EtOAc, 70:30). $C_{17}H_{27}NO_6$ (341.40): calcd. C 59.81, H 7.97, N 4.10; found C 60.0, H 8.05, N 4.0. GC-MS: R_t = 8.09; *m*/*z* = 326 [M$^{+\cdot}$ − 15] (3.1), 268 (4.4), 184 (7.0), 182 (22.1), 169 (6.4), 154 (9.3), 143 (24.6), 126 (63.3), 113 (33.1), 112 (8.5), 101 (16.5), 85 (65.7), 84 (9.0), 83 (7.6), 82 (7.1), 72 (100.0), 71 (10.8), 70 (12.3), 69 (39.9), 68 (11.7), 59 (9.6), 57 (48.9), 56 (11.1), 55 (10.9), 43 (68.1), 42 (27.0), 41 (93.9), 39 (16.1). ^{1}H NMR: δ = 1.33 and 1.40 [2 s, 2 × 3 H, (CH_3)$_2$C], 1.46 [s, 9 H, (CH_3)$_3$C], 3.68 [dd, J = 5.4, 8.8 Hz, 1 H, C*H*HOC(CH$_3$)$_2$], 3.87 (d, J = 17.7 Hz, 1 H, C*H*CO$_2$*t*Bu), 3.89 (dd, J = 5.1, 9.3 Hz, 1 H, C*H*N), 4.04−4.18 (m, 2 H), 4.18 (d, J = 17.7 Hz, 1 H, C*H*HCO$_2$*t*Bu), 4.26−4.44 (m, 2 H), 4.67 (d, J = 5.1 Hz, 1 H, C*H*Oallyl), 5.18−5.36 (m, 2 H, CH_2=CH), 5.87 (ddt, J = 10.6, 16.6, 5.3 Hz, 1 H, C*H*=CH$_2$) ppm. ^{13}C NMR (50 MHz): δ = 25.24 and 26.93 [(*C*H$_3$)$_2$C], 28.06 [(*C*H$_3$)$_3$C], 43.03 (*C*H$_2$N), 60.50 (*C*HN), 66.70 and 72.018 (*C*H$_2$O), 76.79 (*C*H−O), 81.14 (*C*H−O), 82.18 [*C*(CH$_3$)$_3$], 109.50 (O*C*O), 117.75 (CH=*C*H$_2$), 133.38 (*C*H=CH$_2$), 167.03 and 167.62 (*C*=O) ppm. IR: $\tilde{\nu}_{max}$ = 2984, 2935, 1759 (s), 1597, 1453, 1410, 1394, 1383, 1371, 1334, 1194, 1152, 1067, 1045 990, 930 cm^{-1}.

(3*R,4*R**,4′*S**)-1-(*tert*-Butoxycarbonylmethyl)-4-(2,2-dimethyl-1,3-dioxolan-4-yl)-3-(2-hydroxyethyloxy)azetidin-2-one (23):** This compound was prepared from ester **22** (96 mg, 0.280 mmol) according to the same procedure described for conversion of **18** into **19**. Yield: 70 mg (72%) (also 11 mg of the corresponding aldehyde were recovered). R_f = 0.20 (PE/EtOAc, 30:70). $C_{16}H_{27}NO_7$ (345.39): calcd. C 55.64, H 7.88, N 4.06; found C 55.9, H 8.05, N 3.95. GC-MS: R_t = 8.78; *m*/*z* = 330 [M$^{+\cdot}$−15] (3.9), 272 (3.7), 244 (7.0), 214 (7.2), 188 (10.4), 186 (19.8), 158 (10.5), 130 (62.4), 117 (34.5), 113 (7.4), 101 (14.2), 99 (7.6), 87 (19.7), 85 (6.5), 82 (5.6), 73 (100.0), 72

(99.2), 71 (18.2), 70 (13.1), 69 (59.0), 68 (9.9), 59 (10.0), 57 (45.5), 45 (26.4), 43 (66.6), 42 (19.4), 41 (32.2) ^{1}H NMR: δ = 1.33 and 1.41 [2 s, 2 × 3 H, (CH_3)$_2$C], 1.47 [s, 9 H, (CH_3)$_3$C], 3.69 [dd, *J* = 5.2, 8.9 Hz, 1 H, C*H*HOC(CH$_3$)$_2$], 3.62−3.94 (m, 3 H), 3.90 (d, *J* = 17.8 Hz, 1 H, C*H*CO$_2$*t*Bu), 3.96 (dd, *J* = 5.2, 9.4 Hz, 1 H, C*H*N), 4.05−4.20 (m, 2 H), 4.17 (d, *J* = 17.7 Hz, 1 H, C*H*HCO$_2$*t*Bu), 4.37 (ddd, *J* = 5.2, 6.5, 9.2 Hz, 1 H, C*H*OC(CH$_3$)$_2$], 4.71 (d, *J* = 5.2 Hz, 1 H, C*H*OCH$_2$) ppm.

(3*R,4*R**,4′*S**)-3-(2-Azidoethyloxy)-1-(*tert*-butoxycarbonylmethyl)-4-(2,2-dimethyl-1,3-dioxolan-4-yl)azetidin-2-one (24):** This compound was prepared in 67% yield from alcohol **23** following the same procedure employed for **16a**. Reaction time of azide substitution: 4 h at 50 °C and overnight at room temp. R_f = 0.58 (PE/EtOAc, 30:70). $C_{16}H_{26}N_4O_6$ (370.40): calcd. C 51.88, H 7.08, N 15.13; found C 52.1, H 7.2, N 14.75. ^{1}H NMR: δ = 1.32 and 1.41 [2 s, 2 × 3 H, (CH_3)$_2$C], 1.47 [s, 9 H, (CH_3)$_3$C], 3.32 (ddd, *J* = 3.3, 5.2, 13.5 Hz, 1 H, C*H*HN$_3$), 3.48 (ddd, *J* = 3.2, 7.6, 13.5 Hz, 1 H, C*H*HN$_3$), 3.71 [dd, *J* = 4.9, 9.0 Hz, 1 H, C*H*HOC(CH$_3$)$_2$], 3.77 (ddd, *J* = 3.2, 7.6, 10.5 Hz, 1 H, N$_3$CH$_2$C*H*H), 3.89 (d, *J* = 17.8 Hz, 1 H, C*H*CO$_2$*t*Bu), 3.92 (dd, *J* = 5.2, 9.4 Hz, 1 H, C*H*N), 4.08 (ddd, *J* = 3.2, 5.2, 10.5 Hz, 1 H, N$_3$CH$_2$C*H*H), 4.13 [dd, *J* = 6.6, 9.0 Hz, 1 H, C*H*HOC(CH$_3$)$_2$], 4.18 (d, *J* = 17.8 Hz, 1 H, C*H*CO$_2$*t*Bu) 4.38 [ddd, *J* = 4.9, 6.6, 9.4 Hz, 1 H, C*H*OC(CH$_3$)$_2$], 4.66 (d, *J* = 5.2 Hz, 1 H, C*H*OCH$_2$) ppm. ^{13}C NMR (50 MHz): δ = 25.11 and 26.94 [(*C*H$_3$)$_2$C], 28.04 [(*C*H$_3$)$_3$C], 43.11 (*C*H$_2$N), 50.73 (*C*H$_2$N), 60.17 (*C*HN), 66.66 and 70.29 (*C*H$_2$O), 76.57 (*C*HO), 82.08 [*C*(CH$_3$)$_3$], 82.28 (*C*HO), 109.59 (O*C*O), 166.99 and 167.04 (*C*=O) ppm. IR: $\tilde{\nu}_{max}$ = 2983, 2934, 2109 (s), 1757 (s), 1601, 1408, 1394, 1383, 1371, 1337, 1286, 1246, 1151, 1113, 1062, 951 cm^{-1}.

Allyloxymethyl Benzyl Ether (26): A solution of Et$_3$N (8.02 mL, 57.52 mmol) in dry CH$_3$CN (50 mL) was cooled to 0 °C and treated, by addition through a dropping funnel, with freshly distilled benzyl chloromethyl ether (8.0 mL, 57.52 mmol). Then the mixture was stirred for 2 h at room temp. Allyl alcohol (4.89 mL, 71.9 mmol) was added and the mixture heated under reflux for 5 h. On cooling an abundant white precipitate was formed. The suspension was filtered and the precipitate washed with Et$_2$O/PE (1:1, 120 mL). The filtrate was diluted with aqueous (NH$_4$)H$_2$PO$_4$ (5%, 65 mL). The phases were separated and the organic one washed with (NH$_4$)H$_2$PO$_4$ (5%), and the solvents evaporated to dryness. The crude oil was distilled at 6 × 10^{-2} mbar to give pure **26** (6.73 g, 67%). B.p. 65−70 °C. $C_{11}H_{14}O_2$ (178.23): calcd. C 74.13, H 7.92; found C 74.2, H 7.9. GC-MS: R_t = 4.07; *m*/*z* = 177 [M$^+$] (0.02), 148 (4.1), 120 (5.7), 119 (6.7), 107 (14.3), 92 (53.3), 91 (100), 79 (9.1), 77 (8.4), 65 (14.5), 51 (6.7), 41 (31.6), 39 (15.8). ^{1}H NMR: δ = 4.13 (dt, *J* = 5.6, 1.4 Hz), 4.63 (CH_2Ph), 4.79 (OCH_2O), 5.20 (dq, *J* = 10.4, 1.4 Hz, 1 H, C*H*H=CH), 5.31 (dq, *J* = 17.2, 1.6 Hz, 1 H, C*H*H=CH), 5.94 (ddt, *J* = 10.4, 17.2, 5.7 Hz, 1 H, C*H*=CH$_2$), 7.25−7.40 (m, 5 H, aromatics) ppm. ^{13}C NMR (20 MHz): δ = 68.51 and 69.48 (*C*H$_2$O), 93.89 (O−*C*−O), 117.14 (*C*H$_2$=CH), 127.69, 127.87, 128.42 (aromatic *C*H), 134.35 (*C*H=CH$_2$), 137.89 (aromatic quat.) ppm.

(3*R,4*S**)-4-[(Benzyloxymethoxy)methyl]-1-(4-methoxyphenyl)-3-(2-propenyloxy)azetidin-2-one (27):** A solution of ether **26** (1.17 g, 6.56 mmol) in dry CH$_2$Cl$_2$ (14 mL) and dry MeOH (21 mL) was cooled to −78 °C and ozonized until the grey-blue color persisted. At this point, Me$_2$S (1.5 mL) was added. The solution was stirred at room temp. for 5 h and then concentrated to dryness and chromatographed (PE/Et$_2$O, 20:80 to 0:100) to give the aldehyde (1.268 g) as an oil. The weight higher than expected is due to the presence of mixed hemiacetal adducts with formaldehyde. In any case, this aldehyde was taken up in CH$_2$Cl$_2$ (20 mL) and treated with freshly activated powdered molecular sieves (4 Å, 1.8 g) and *p*-anisidine (807 mg, 6.56 mmol). After stirring at room temp. for 2.5 h, the suspension was filtered and the filtrate concentrated to give crude imine (1.94 g) as an oil. This imine was taken up in dry CH$_2$Cl$_2$ (35 mL), cooled to 0 °C, and treated with Et$_3$N (3.93 mL, 28.21 mmol) and then (through a dropping funnel during 1 h) with a solution of allyloxyacetyl chloride (1.84 g, 13.70 mmol) in dry CH$_2$Cl$_2$ (25 mL). After stirring at room temp. overnight, the mixture was poured into aqueous (NH$_4$)H$_2$PO$_4$ (5%, 70 mL) and extracted with CH$_2$Cl$_2$. The organic extracts were washed with saturated aqueous NaCl, concentrated and chromatographed twice (PE/EtOAc, 50:50) to give **27** (1.578 g, 63%), about 80% pure by NMR (real yield 51%). R_f = 0.56 (PE/EtOAc, 50:50). GC-MS: R_t = 12.23; *m*/*z* = 383 [M$^+$] (6.0), 312 (14.9), 149 (93.2), 148 (8.2), 134 (22.8), 91 (100.0), 77 (6.0), 71 (8.5), 65 (5.7), 41 (21.9). ^{1}H NMR: δ = 3.78 (OCH_3), 3.93 and 3.99 (AB part of ABX system, J_{AB} = 10.9 Hz, J_{AX} = 4.7 Hz, J_{BX} = 6.0 Hz, 2 H, CH_2O), 4.15−4.50 (m, 3 H), 4.53 (s, 2 H, CH_2Ph), 4.78 (s, 2 H, OCH_2O), 4.79 (d, *J* = not determined, 1 H, C*H*Oallyl), 6.86 (d, *J* = 9.1 Hz, 2 H, aromatics), 7.20−7.40 (m, 5 H, aromatics), 7.48 (d, *J* = 9.1 Hz, 2 H, aromatics) ppm.

(3*R,4*S**)-4-[(Benzyloxymethoxy)methyl]-3-(2-hydroxyethyloxy)-1-(4-methoxyphenyl)azetidin-2-one (28):** This compound was prepared from 80% pure **27** in 62% yield (77% taking into account the purity of starting material) using the same procedure already described for the synthesis of **19**. R_f = 0.40 (EtOAc). $C_{21}H_{25}NO_6$ (387.43): calcd. C 65.10, H 6.50, N 3.62; found C 64.65, H 6.8, N 3.3. GC-MS: R_t = 13.23; *m*/*z* = 387 [M$^+$] (8.3), 357 (6.5), 286 (6.3), 178 (6.1), 149 (100.0), 148 (11.9), 134 (21.0), 91 (97.1), 77 (8.3), 73 (39.4), 70 (8.5), 65 (6.5), 57 (9.3), 45 (17.9). ^{1}H NMR: δ = 3.62 (broad s, 1 H, O*H*), 3.78 (s, 3 H, OCH_3), 3.70−3.90 (m, 4 H, HOCH_2CH_2O), 3.95 and 4.02 (AB part of ABX system, J_{AB} = 11.0 Hz, J_{AX} = 5.0 Hz, J_{BX} = 5.5 Hz, 2 H, CH_2OBOM), 4.40 (q, *J* = 5.3 Hz, 1 H, C*H*−N), 4.54 (s, 2 H, CH_2Ph), 4.78 (s, 2 H, OCH_2O), 4.81 (d, *J* = 5.2 Hz, 1 H, C*H*O), 6.87 (d, *J* = 9.0 Hz, 2 H, aromatics), 7.25−7.36 (m, 5 H, aromatics), 7.46 (d, *J* = 9.0 Hz, 2 H, aromatics) ppm. ^{13}C NMR (50 MHz): δ = 55.48 (O*C*H$_3$), 58.13 (*C*H−N), 62.22 (*C*H$_2$O), 65.40 (*C*H$_2$O), 69.73 (*C*H$_2$O), 74.80 (*C*H$_2$O), 82.12 (*C*HO), 94.89 (O*C*H$_2$O), 114.35, 119.05, 127.85, 128.46 (aromatic *C*H), 130.40, 137.44, 156.62 (aromatic quat.), 165.59 (*C*=O) ppm. IR: $\tilde{\nu}_{max}$ = 3433 (broad), 2998, 2938, 1742 (s), 1613, 1504, 1454, 1395, 1299, 1196, 1138, 1113, 1040 cm^{-1}.

(3*R,4*S**)-3-(2-Azidoethyloxy)-4-[(benzyloxymethoxy)methyl]-1-(4-methoxyphenyl)azetidin-2-one (29):** This compound was prepared in 58% yield from alcohol **28** according to the same procedure employed for **16a**. Reaction time of azide substitution: 4 h at 50 °C and overnight at room temp. R_f = 0.37 (PE/EtOAc, 60:40). $C_{21}H_{24}N_4O_5$ (412.44): calcd. C 61.15, H 5.87, N 13.58; found C 61.5, H 6.0, N 13.05. ^{1}H NMR: δ = 3.37 (ddd, *J* = 3.5, 5.1, 13.3 Hz, 1 H, C*H*HN$_3$), 3.54 (ddd, *J* = 3.5, 7.4, 13.3 Hz, 1 H, C*H*HN$_3$), 3.78 (s, 3 H, OCH_3), 3.80−4.10 (m, 4 H, CH_2O), 4.38 (q, *J* = 5.3 Hz, 1 H, C*H*N), 4.53 (s, 2 H, CH_2Ph), 4.77 (d, *J* not determined, 1 H, C*H*O), 4.78 (s, 2 H, OCH_2O), 6.86 (d, *J* = 9.1 Hz, 2 H, aromatics), 7.25−7.40 (m, 5 H, aromatics), 7.48 (d, *J* = 9.0 Hz, 2 H, aromatics) ppm. ^{13}C NMR (50 MHz): δ = 50.71 (*C*H$_2$N$_3$), 55.48 (O*C*H$_3$), 57.46 (*C*HN), 65.81 (*C*H$_2$O), 69.64 (*C*H$_2$O), 70.60 (*C*H$_2$O), 81.50 (*C*HO), 94.94 (O*C*H$_2$O), 114.28, 119.04, 127.76, 127.82, 128.43 (aromatic *C*H), 130.65, 137.60, 156.52 (aromatic quat.), 163.99 (*C*=O) ppm. IR: $\tilde{\nu}_{max}$ = 2999, 2935, 2887, 2837, 2107 (s), 1745 (s), 1609, 1503, 1463, 1441, 1386, 1341, 1298, 1191, 1135, 1113, 1042 cm^{-1}.

(3*R,4*R**)-4-(Hydroxymethyl)-1-(4-methoxyphenyl)-3-vinylazetidin-2-one (32):** A suspension of finely ground anhydrous $CaCl_2$ (536 mg, 4.83 mmol) in dry THF (15 mL) and absolute EtOH (7.5 mL) was cooled to −20 °C, and treated with $NaBH_4$ (308 mg, 8.14 mmol). After stirring for 15 min, a solution of racemic β-lactam **31**[19] (397 mg, 1.52 mmol) in dry THF (15 mL) was slowly added during 5 min. The suspension was stirred at −20 °C for 15 min, and at 0 °C for 6 h. The reaction was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The organic phase was washed with saturated NaCl, concentrated and chromatographed (PE/EtOAc, 50:50) to give pure **32** as an oil (276 mg, 76%). R_f = 0.32 (PE/EtOAc, 50:50). $C_{13}H_{15}NO_3$ (233.26): calcd. C 66.94, H 6.48, N 6.00; found C 66.7, H 6.5, N 5.8. GC-MS: R_t = 8.62; *m*/*z* = 233 [M^+] (6.1), 174 (1.5), 165 (1.7), 149 (100.0), 136 (10.5), 134 (38.7), 106 (5.1), 92 (6.2), 78 (4.8), 77 (10.2), 64 (5.4), 55 (4.5), 41 (4.6), 39 (7.6). ^{1}H NMR: δ = 3.78 (s, 3 H, OC*H*$_3$), 3.97 (d, *J* = 4.8 Hz, 2 H, C*H*$_2$OH), 4.06 (m_c) (m, 1 H, C*H*CH=CH$_2$, on decoupling at 6.02 ppm, it becomes a d, *J* = 5.5 Hz), 4.28 (q, *J* = 5.2 Hz, 1 H, C*H*N), 5.38 (dt, *J* = 10.3, 1.0 Hz, 1 H, C*H*H=CH), 5.48 (dt, *J* = 17.2, 1.0 Hz, 1 H, C*H*H=CH), 6.02 (ddd, *J* = 8.0, 10.3, 17.2 Hz, 1 H, C*H*=CH$_2$), 6.86 (d, *J* = 9.0 Hz, 2 H, aromatics), 7.42 (d, *J* = 9.0 Hz, 2 H, aromatics) ppm.

(3*R,4*R**)-4-{[(Benzyloxy)methoxy]methyl}-1-(4-methoxyphenyl)-3-vinylazetidin-2-one (33):** This compound was prepared in 85% yield from **32** according to the same procedure reported for **15**. R_f = 0.55 (PE/EtOAc, 50:50). $C_{21}H_{23}NO_4$ (353.41): calcd. C 71.37, H 6.56, N 3.96; found C 71.0, H 6.7, N 3.75. ^{1}H NMR: δ = 3.77 (s, 3 H, OC*H*$_3$), 3.84 and 3.88 (AB part of ABX system, J_{AB} = 11.0 Hz, J_{AX} = 4.6 Hz, J_{BX} = 5.7 Hz, 2 H, C*H*$_2$OBOM), 4.07 (m_c) (m, 1 H, C*H*CH=CH$_2$), 4.32 (q, *J* = 5.4 Hz, 1 H, C*H*N), 5.35 (dt, *J* = 10.3, 1.3 Hz, 1 H, C*H*H=CH), 5.48 (dt, *J* = 17.2, 1.4 Hz, 1 H, C*H*H=CH), 5.94 (ddd, *J* = 8.0, 10.3, 17.2 Hz, 1 H, C*H*=CH$_2$), 6.86 (d, *J* = 9.1 Hz, 2 H, aromatics), 7.18−7.40 (m, 5 H, aromatics), 7.45 (d, *J* = 9.1 Hz, 2 H, aromatics) ppm. IR: $\tilde{\nu}_{max}$ = 3085, 2999, 2937, 2890, 2837, 1738 (s), 1500, 1454, 1441, 1382, 1297, 1193, 1169, 1112, 1043, 989, 928 cm^{-1}.

(3*R,4*R**)-4-[(Benzyloxymethoxy)methyl]-3-(2-hydroxyethyl)-1-(4-methoxyphenyl)azetidin-2-one (34):** A solution of compound **33** (176 mg, 0.497 mmol) in dry THF (8 mL) was cooled to 0 °C and treated with solid 9-borabicyclononane (186 mg, 1.52 mmol). The resulting solution was stirred at room temp. for 5 h and then cooled again to 0 °C and treated with a solution of $KHCO_3$ (1.5 g) and 35% H_2O_2 (2.1 mL) in H_2O (2.1 mL). After stirring for 1 h at room temp., the mixture was diluted with H_2O and extracted with EtOAc. The organic phase was washed with saturated NaCl, concentrated and chromatographed (PE/EtOAc, 30:70 to 10:90) to give pure **34** (134 mg, 72%). R_f = 0.41 (EtOAc). $C_{21}H_{25}NO_5$ (371.43): calcd. C 67.91, H 6.78, N 3.77; found C 68.2, H 6.7, N 3.5. GC-MS: R_t = 13.38 (during GC, **34** in part isomerizes to the corresponding lactone, R_t = 12.74); *m*/*z* = 371 [M^+] (16.8), 341 (17.2), 310 (12.5), 232 (5.8), 220 (45.6), 186 (5.7), 164 (5.3), 149 (28.9), 148 (7.0), 134 (32.2), 107 (6.1), 91 (100.0), 77 (9.7), 65 (7.1). ^{1}H NMR: δ = 1.84−2.20 (m, 2 H, C*H*$_2$CH$_2$OH), 3.46 (dt, *J* = 10.4, 5.8 Hz, 1 H, C*H*C=O), 3.78 (s, 3 H, OC*H*$_3$), 3.75−3.90 (m, 2 H, C*H*$_2$OH), 3.91 (d, *J* = 5.4 Hz, 2 H, C*H*$_2$OBOM), 4.31 (q, *J* = 5.4 Hz, 1 H, C*H*N), 4.46 (s, 2 H, C*H*$_2$Ph), 4.72 and 4.75 (AB system, *J* = 6.9 Hz, 2 H, OC*H*$_2$O), 6.86 (d, *J* = 9.1 Hz, 2 H, aromatics), 7.20−7.38 (m, 5 H, aromatics), 7.41 (d, *J* = 9.1 Hz, 2 H, aromatics) ppm. ^{13}C NMR (50 MHz): δ = 27.85 (*C*H$_2$CH$_2$OH), 50.06 (*C*HC=O), 53.95 (*C*H−N), 55.49 (OC*H*$_3$), 61.47, 65.75, 69.85 (*C*H$_2$O), 94.93 (O*C*H$_2$O), 114.38, 118.96, 127.80, 127.84, 128.45 (aromatic *C*H), 130.94, 137.48, 156.41 (aromatic quat.), 167.91 (*C*=O) ppm. IR: $\tilde{\nu}_{max}$ = 3442 (broad), 3046, 2997, 2936, 1726 (s), 1603, 1504, 1454, 1440, 1396, 1298, 1193, 1111, 1046, 961 cm^{-1}.

(3*R,4*R**)-3-(2-Azidoethyl)-4-[(benzyloxymethoxy)methyl]-1-(4-methoxyphenyl)azetidin-2-one (35):** This compound was prepared in 94% yield from alcohol **34** according to the same procedure employed for **16a**. Reaction time of azide substitution: 3 h at 50 °C and overnight at room temp. R_f = 0.71 (PE/EtOAc, 30:70). $C_{21}H_{24}N_4O_4$ (396.44): calcd. C 63.62, H 6.10, N 14.13; found C 63.95, H 6.3, N 13.8. GC-MS: R_t = 13.50 (it decomposes in part); *m*/*z* = 368 [$M^{+\cdot}$ − 28] (3.2), 286 (8.5), 256 (4.7), 245 (5.3), 164 (7.3), 149 (28.3), 148 (7.9), 134 (24.4), 113 (14.4), 108 (7.4), 107 (6.9), 98 (17.0), 96 (9.6), 91 (100.0), 83 (9.9), 82 (17.1), 77 (11.3), 65 (7.4) ^{1}H NMR: δ = 1.87−2.24 (m, 2 H, C*H*$_2$CH$_2$N$_3$), 3.40−3.70 (m, 3 H, C*H*$_2$N$_3$ and C*H*C=O), 3.77 (s, 3 H, OC*H*$_3$), 3.91 (d, *J* = 5.0 Hz, 2 H, C*H*$_2$OBOM), 4.28 (q, *J* = 5.2 Hz, 1 H, C*H*N), 4.45 (s, 2 H, C*H*$_2$Ph), 4.71 and 4.75 (AB system, *J* =6.9 Hz, 2 H, OC*H*$_2$O), 6.85 (d, *J* = 9.1 Hz, 2 H, aromatics), 7.20−7.38 (m, 5 H, aromatics), 7.39 (d, *J* = 9.1 Hz, 2 H, aromatics) ppm. ^{13}C NMR (20 MHz): δ = 24.65 (*C*H$_2$CH$_2$N$_3$), 48.64, 49.79 and 53.95 (*C*H$_2$N, *C*HC=O, and *C*HN), 55.47 (O*C*H$_3$), 65.36, 69.88 (*C*H$_2$O), 94.90 (O*C*H$_2$O), 114.31, 118.70, 127.74, 128.35 (aromatic *C*H), 130.91, 137.38, 156.12 (aromatic quat.), 166.25 (*C*=O) ppm. IR: $\tilde{\nu}_{max}$ = 3005, 2938, 2100 (s), 1739 (s), 1506, 1454, 1394, 1297, 1192, 1111, 1045, 907 cm^{-1}.

General Procedure for Reduction of Azides 16a−d, 20, 24, 29 and 35 to Amines 2a−d, 3a−c and 4: A solution of azide (0.2 mmol) in THF (5 mL) was treated at room temp. with Ph_3P (0.4 mmol) and, after 10 min, with H_2O (250 μL). After stirring for 15 h, the solution was diluted with CH_2Cl_2, dried (Na_2SO_4), concentrated to dryness, and chromatographed [$CHCl_3$ to $CHCl_3$/MeOH, 9:1 + 2% *i*Pr_2NH]. The amines always contained small percentages of the corresponding transamidated products. Therefore elemental analyses were not performed on these products. They were used at once for the following reactions or else kept in a freezer for a minimum amount of time. They were characterized by transformation into acetamides or phenylacetamides.

General Procedure for Rearrangement of Amines 2a−d, 3a−c and 4: The amines were dissolved in the solvent indicated in Table 1, and stirred at the appropriate temperature. Small aliquots of the crude reaction mixtures were taken from time to time, rapidly concentrated, taken up in $CDCl_3$ and examined by ^{1}H NMR spectroscopy. Integration of the developing amide NH unit allowed the conversion to be estimated in all cases . In most cases other signals could also be used for integration. For a control, a spectrum was taken also of the starting amine at the beginning of the reaction, in order to evaluate the amount of transamidated product already present. At the end of reaction, the solvent was evaporated and the transamidated product purified by chromatography ($CHCl_3$/MeOH).

***rac*-1-(2-Aminoethyl)-4-[(benzyloxymethoxy)methyl]azetidin-2-one (2a):** R_f = 0.22 and 0.29 ($CHCl_3$/MeOH, 95:5). ^{1}H NMR: δ = 2.70 (dd, *J* = 1.8, 14.4 Hz, 1 H, C*H*HC=O), 2.90 (t, *J* = 6.0 Hz, 2 H, C*H*$_2$NH$_2$), 2.99 (dd, *J* = 4.7, 14.4 Hz, 1 H, C*H*HC=O), 3.15−3.50 (m, 2 H), 3.56−3.86 (m, 3 H), 4.61 (s, 2 H, C*H*$_2$Ph), 4.79 (s, 2 H, OC*H*$_2$O), 7.34 (s, 5 H, aromatics) ppm. This amine was better characterized as the corresponding acetamide, which was obtained in 90% yield by reaction with Et_3N (3.3 equiv.) and Ac_2O (2 equiv.) in dry CH_2Cl_2 at 0 °C. The reaction was complete in 4 h. Workup with saturated aqueous NH_4Cl followed by extraction with EtOAc, concentration and chromatography (EtOAc/MeOH, 80:20), gave the acetamide of **2a**. R_f = 0.55 (EtOAc/MeOH, 80:20).

$C_{16}H_{22}N_2O_4$ (306.36): calcd. C 62.73, H 7.24, N 9.14; found C 63.0, H 7.4, N 8.95. GC-MS: R_t = 10.49; *m*/*z* = 278 [$M^{+\cdot}$ − 28] (0.1), 247 (0.1), 235 (0.2), 217 (1.3), 155 (1.8), 141 (8.7), 132 (3.6), 114 (5.1), 113 (4.1), 91 (100.0), 86 (7.9), 72 (6.4), 65 (5.2), 44 (8.9), 43 (14.0), 41 (6.8). ^{1}H NMR: δ = 1.97 (s, 3 H, CH_3C=O), 2.67 (dd, *J* = 2.2, 14.5 Hz, 1 H, C*H*HC=O), 2.96 (dd, *J* = 4.8, 14.5 Hz, 1 H, C*H*HC=O), 3.18−3.46 (m, 3 H), 3.46−3.72 (m, 2 H), 3.76−3.88 (m, 2 H), 4.61 (s, 2 H, CH_2Ph), 4.79 (s, 2 H, OCH_2O), 6.54 (br. s, 1 H, N*H*), 7.34 (s, 5 H, aromatics) ppm. IR: $\tilde{\nu}_{max}$ = 3442, 3357, 2997, 2932, 1737 (s), 1665 (s), 1513, 1402, 1376, 1331, 1240, 1168, 1111, 1040 cm^{-1}.

***rac*-7-[(Benzyloxymethoxy)methyl]-1,4-diazepan-5-one (17a):** R_f = 0.63 ($CHCl_3$/MeOH, 95:5). $C_{14}H_{20}N_2O_3$ (264.32): calcd. C 63.62, H 7.63, N 10.60; found C 63.95, H 7.9, N 10.35. ^{1}H NMR: δ = 2.40 (dt, *J* = 14.2, 1.6 Hz, 1 H, C*H*HC=O), 2.59 (dd, *J* = 9.8, 14.2 Hz, 1 H, C*H*HC=O), 2.84 (dd, *J* = 9.9, 11.8 Hz, 1 H, C*H*HN), 2.98−3.28 (m, 3 H), 3.34−3.52 (m, 1 H), 3.44 (dd, *J* = 8.6, 9.6 Hz, 1 H, C*H*HOBOM), 3.61 (dd, *J* = 3.9, 9.6 Hz, C*H*HOBOM), 4.60 (s, 2 H, CH_2Ph), 4.76 and 4.79 (AB system, *J* = 6.7 Hz, 2 H, OCH_2O), 6.01 (br. s, 1 H, N*H*), 7.35 (s, 5 H, aromatics) ppm. ^{13}C NMR (50 MHz): δ = 42.43, 44.68, 49.60 (*C*H_2), 53.37 (*C*HN), 69.69 and 71.80 (*C*H_2O), 94.89 (O*C*H_2O), 127.80, 127.84, 128.45 (aromatic *C*H), 137.48 (aromatic quat.), 176.34 (*C*=O) ppm. IR: $\tilde{\nu}_{max}$ = 3416, 2998, 2926, 2891, 2824, 1660 (s), 1601, 1466, 1438, 1375, 1351, 1326, 1240, 1167, 1116, 1040, 963, 907 cm^{-1}.

(3*R,4*S**)-1-(2-Aminoethyl)-3-methoxy-4-(2-phenylethenyl)azetidin-2-one (2b):** R_f = 0.10 ($CHCl_3$/MeOH, 95:5). ^{1}H NMR: δ = 2.70−3.30 (m, 4 H, CH_2CH_2), 3.45 (s, 3 H, OCH_3), 4.37 (dd, *J* = 4.3, 9.2 Hz, 1 H, C*H*CH=CH), 4.67 (d, *J* = 4.3 Hz, 1 H, C*H*OMe), 6.24 (dd, *J* = 9.2, 16.0 Hz, 1 H, C*H*=CHPh), 6.75 (d, *J* = 16.0 Hz, 1 H, CH=C*H*Ph), 7.22−7.50 (m, 5 H, aromatics) ppm. This amine was better characterized as the corresponding phenylacetamide **37** (see below), which was prepared in 92% yield by treating **2b**, isolated soon after chromatography, with phenylacetyl chloride and Et_3N in CH_2Cl_2.

(6*R,7*S**)-Methoxy-7-(2-phenylethenyl)-1,4-diazepan-5-one (17b):** R_f = 0.39 ($CHCl_3$/MeOH, 95:5). $C_{14}H_{18}N_2O_2$ (246.30): calcd. C 68.27, H 7.37, N 11.37; found C 68.0, H 7.4, N 11.1. GC-MS: R_t = 8.88; *m*/*z* = 246 [$M^{+\cdot}$] (3.8), 231 (43.0), 217 (18.6), 204 (26.2), 203 (8.4), 185 (24.3), 172 (18.6), 160 (94.7), 159 (67.7), 157 (32.9), 156 (51.7), 145 (25.3), 144 (31.2), 132 (31.3), 129 (63.2), 128 (39.7), 127 (25.4), 117 (58.3), 115 (100.0), 91 (45.4), 44 (33.2). ^{1}H NMR: δ = 2.84−3.10 (m, 3 H), 3.24 (dd, *J* = 4.8, 14.2 Hz, 1 H), 3.51 (s, 3 H, OCH_3), 3.62−3.84 (m, 1 H), 3.71 (d, *J* = 6.5 Hz, 1 H, C*H*N), 3.90 (s, 1 H, C*H*OMe), 6.10 (br. s, 1 H, CON*H*), 6.27 (dd, *J* = 6.4, 16.0 Hz, 1 H, C*H*=CHPh), 6.63 (d, *J* = 16.0 Hz, 1 H, CH=C*H*Ph), 7.22−7.50 (m, 5 H, aromatics) ppm. ^{13}C NMR (50 MHz): δ = 43.74 (*C*H_2N), 49.39 (*C*H_2N), 58.16 (O*C*H_3), 58.60 (*C*HN), 87.75 (*C*HOMe), 126.48, 127.68, 128.54 (aromatic *C*H), 129.28, 131.46 (*C*H=*C*H), 136.69 (aromatic quat.), 174.70 (*C*=O) ppm. IR: $\tilde{\nu}_{max}$ = 3410, 2927, 2852, 1665 (s), 1600, 1464, 1376, 1351, 1260, 1167, 1110, 967, 905 cm^{-1}.

(3*R,4*S**)-1-(2-Aminoethyl)-4-[(benzyloxymethoxy)methyl]-3-methoxyazetidin-2-one (2c):** R_f = 0.30 ($CHCl_3$/MeOH, 80:20). ^{1}H NMR: δ = 2.90 (t, *J* = 6.2 Hz, 2 H, CH_2N), 3.12−3.45 (m, 2 H, CH_2N), 3.53 (s, 3 H, OCH_3), 3.70−3.95 (m, 3 H, CH_2O, C*H*N), 4.53 (d, *J* = 4.4 Hz, 1 H, C*H*OMe), 4.62 (s, 2 H, CH_2Ph), 4.79 (s, 2 H, OCH_2O), 7.35 (s, 5 H, aromatics) ppm.

(6*R,7*S**)-7-[(Benzyloxymethoxy)methyl]-6-methoxy-1,4-diazepan-5-one (17c):** R_f = 0.72 ($CHCl_3$/MeOH, 80:20). $C_{15}H_{22}N_2O_4$ (294.35): calcd. C 61.21, H 7.53, N 9.52; found C 61.4, H 7.6, N 9.3. GC-MS: R_t = 9.98; *m*/*z* = 294 [$M^{+\cdot}$] (11.2), 279 (5.0), 249 (4.7), 173 (7.0), 171 (5.9), 157 (5.4), 143 (14.7), 100 (11.4), 91 (100.0), 86 (7.6), 85 (6.4), 72 (7.8), 71 (7.9), 65 (6.1), 56 (6.8), 44 (8.8), 42 (5.3), 41 (5.1). ^{1}H NMR: δ = 2.75−2.90 (m, 1 H), 2.90−3.07 (m, 1 H), 3.09−3.23(m, 2 H), 3.47 (s, 3 H, OCH_3), 3.60 (d, *J* = 7.0 Hz, 2 H, CH_2OBOM), 3.54−3.80 (m, 1 H), 3.85 (d, *J* = 1.5 Hz, 1 H, C*H*OMe), 4.60 (s, 2 H, CH_2Ph), 4.78 (s, 2 H, OCH_2O), 6.55 (br. s, 1 H, CON*H*), 7.34 (s, 5 H, aromatics) ppm. ^{13}C NMR (50 MHz): δ = 43.77 (*C*H_2N), 49.48 (*C*H_2N), 56.42 (*C*HN), 57.90 (O*C*H_3), 68.83, 69.60 (*C*H_2O), 84.46 (*C*HOMe), 94.94 (O*C*H_2O), 127.71, 127.83, 128.42 (aromatic *C*H), 137.76 (aromatic quat.), 174.81 (*C*=O) ppm. IR: $\tilde{\nu}_{max}$ = 3409, 2998, 2941, 1663 (s), 1467, 1424, 1350, 1249, 1192, 1102, 1042 cm^{-1}.

(3*R,4*S**)-1-(2-Aminoethyl)-4-[(benzyloxymethoxy)methyl]-3-phenoxyazetidin-2-one (2d):** R_f = 0.36 and 0.40 ($CHCl_3$/MeOH, 95:5 + 1% Et_3N). ^{1}H NMR: δ = 2.80−3.14 (m, 2 H), 3.20−3.55 (m, 2 H), 3.85, 3.93 (AB part of ABX system, J_{AB} = 10.8 Hz, J_{AX} = 3.8 Hz, J_{BX} = 7.7 Hz, 2 H, CH_2OBOM), 4.11 (dt, *J* = 7.4, 4.4 Hz, 1 H, C*H*N), 4.55 (s, 2 H, CH_2Ph), 4.74 (s, 2 H, OCH_2O), 5.31 (d, *J* = 4.8 Hz, 1 H, C*H*OPh), 6.90−7.05 (m, 3 H), 7.20−7.35 (m, 7 H).

(6*R,7*S**)-7-[(Benzyloxymethoxy)methyl]-6-phenoxy-1,4-diazepan-5-one (17d):** R_f = 0.50 ($CHCl_3$/MeOH, 90:10). $C_{20}H_{24}N_2O_4$ (356.42): calcd. C 67.40, H 6.79, N 7.86; found C 67.7, H 6.6, N 7.8. GC-MS: R_t = 12.35; *m*/*z* = 356 [$M^{+\cdot}$] (9.3), 235 (5.4), 188 (5.3), 141 (4.0), 129 (6.1), 119 (5.5), 112 (27.3), 107 (4.4), 105 (6.1), 99 (60.0), 91 (100.0), 85 (7.7), 84 (8.0), 83 (5.5), 77 (11.2), 71 (18.0), 65 (9.2), 56 (9.4), 55 (8.4), 44 (10.5), 43 (4.7), 42 (5.1), 39 (5.1). ^{1}H NMR: δ = 2.83−3.06 (m, 2 H), 3.18−3.50 (m, 2 H), 3.54−3.88 (m, 3 H), 4.49 (s, 2 H, CH_2Ph), 4.74 (s, 2 H, OCH_2O), 4.79 (d, *J* = 1.5 Hz, 1 H, C*H*OPh), 6.20 (br. s, 1 H, N*H*), 6.95−7.15 (m, 3 H), 7.18−7.36 (m, 7 H) ppm. ^{13}C NMR (50 MHz): δ = 44.09 (*C*H_2N), 49.50 (*C*H_2N), 56.42 (*C*HN), 68.39, 69.64 (*C*H_2O), 80.23 (*C*HOMe), 94.89 (O*C*H_2O), 115.75, 122.14, 127.67, 127.84, 128.39, 129.76 (aromatic *C*H), 137.75, 157.58 (aromatic quat.), 173.97 (*C*=O) ppm. IR: $\tilde{\nu}_{max}$ = 3410, 2998, 2940, 1666 (s), 1597, 1468, 1349, 1240, 1169, 1115, 1042 cm^{-1}.

(3*R,4*R**,4′*S**)-3-(2-Aminoethoxy)-4-(2,2-dimethyl-1,3-dioxolan-4-yl)-1-(4-methoxyphenyl)azetidin-2-one (3a):** R_f = 0.21 and 0.33 ($CHCl_3$/MeOH, 75:25). ^{1}H NMR: δ = 1.34, 1.53 [2 s, 2 × 3 H, (CH_3)$_2$CO], 2.80−3.07 (m, 2 H, CH_2NH$_2$), 3.64−3.80 (m, 1 H, CH$_2$C*H*HO), 3.76 (dd, *J* = 6.2, 8.6 Hz, 1 H, CHC*H*HO), 3.79 (s, 3 H, OCH_3), 3.84−3.96 (m, 1 H, CH$_2$C*H*HO), 4.21 (dd, *J* = 5.5, 8.7 Hz, 1 H, C*H*N), 4.26 (dd, *J* = 6.7, 8.6 Hz, 1 H, CHC*H*HO), 4.40 (dt, *J* = 8.6, 6.5 Hz, 1 H, C*H*O), 4.68 (d, *J* = 5.5 Hz, 1 H, C*H*OCH$_2$), 6.86 (d, *J* = 9.1 Hz, 2 H, aromatics *ortho* to OCH$_3$), 7.65 (d, *J* = 9.1 Hz, 2 H, aromatics *meta* to OCH$_3$). This compound was best characterized as the acetamide, which was obtained in quantitative yield by reaction with Et_3N (3.3 equiv.) and Ac_2O (2 equiv.) in dry CH_2Cl_2 at 0 °C. $C_{19}H_{26}N_2O_6$ (378.42): calcd. C 60.30, H 6.93, N 7.40; found C 60.55, H 7.05, N 7.2. GC-MS: R_t = 11.80; *m*/*z* = 378 [$M^{+\cdot}$] (21.7), 320 (7.7), 165 (11.8), 160 (5.7), 149 (74.6), 136 (7.1), 135 (7.1), 134 (12.7), 101 (6.5), 86 (100.0), 72 (14.4), 44 (31.6), 43 (35.6). ^{1}H NMR: δ = 1.34, 1.53 [2 s, 2 × 3 H, (CH_3)$_2$CO], 2.02 (s, 3 H, CH_3CO), 3.30−3.50 (m, 1 H, C*H*HNH$_2$), 3.50−3.80 (m, 3 H, CH$_2$C*H*HO, C*H*HNH$_2$, CHC*H*HO), 3.80 (s, 3 H, OCH_3), 3.95 (ddd, *J* = 3.0, 6.0, 11.2 Hz, 1 H, CH$_2$C*H*HO), 4.22 (dd, *J* = 6.8, 8.8 Hz, 1 H, CHC*H*HO), 4.26 (dd, *J* = 5.5, 8.5 Hz, 1 H, C*H*N), 4.37 (dt, *J* = 9.0, 6.4 Hz, 1 H, C*H*O), 4.65 (d, *J* = 5.5 Hz, 1 H, C*H*OCH$_2$), 6.87 (d, *J* = 9.1 Hz, 2 H, aromatics *ortho* to OCH$_3$), 7.64 (d, *J* = 9.1 Hz, 2 H, aromatics *meta* to OCH$_3$) ppm. ^{13}C NMR (50 MHz): δ = 23.21, 24.88, 26.67 (*C*H$_3$), 40.04 (*C*H$_2$N), 55.49 (O*C*H$_3$), 62.55 (*C*HN), 66.89 (*C*H$_2$O), 72.21

(CH_2O), 76.92, 81.96 (*C*HO), 109.92 (O*C*O), 114.10, 119.76 (aromatic *C*H), 130.82, 156.81 (aromatic quat.), 165.77 (*C*=O lactam), 170.48 ($H_3C-C=O$) ppm. IR: $\tilde{\nu}_{max}$ = 3449, 3333, 2991, 2934, 2837, 1734 (s), 1662 (s), 1504, 1455, 1440, 1382, 1297, 1222, 1134, 1066, 905 cm^{-1}.

(3*R,1′*R**)-2-{[(4*S**)-2,2-Dimethyl-1,3-dioxolan-4-yl][4-(methoxyphenyl)amino]methyl}morpholin-3-one (25a):** R_f = 0.44 (EtOAc/MeOH, 95:5). $C_{17}H_{24}N_2O_5$ (336.38): calcd. C 60.70, H 7.19, N 8.33; found C 60.9, H 6.95, N 8.0. GC-MS: R_t = 11.05; *m*/*z* = 336 [$M^{+\cdot}$] (28.1), 321 (8.6), 236 (100.0), 235 (68.6), 178 (87.9), 174 (12.0), 164 (5.1), 162 (5.4), 161 (8.7), 160 (41.5), 150 (14.4), 149 (10.6), 148 (28.1), 136 (23.4), 134 (26.3), 133 (11.9), 123 (8.5), 122 (17.5), 121 (15.8), 108 (9.4), 107 (6.4), 102 (6.1), 101 (9.9), 77 (11.1), 72 (12.4), 44 (16.1), 43 (33.5). ^1H NMR: δ = 1.37, 1.41 (2 s, 2 × 3 H, CH_3), 3.15 (br. dt, *J* = 11.9, 2.9 Hz, 1 H, C*H*HN), 3.50 (dt, *J* = 4.0, 11.7 Hz, 1 H, C*H*HN), 3.72 (s, 3 H, CH_3O), 3.73 (dt, *J* = 2.9, 11.3 Hz, CH_2-CHHO), 3.86 (t, *J* = 7.9 Hz, 1 H, CHC*H*HO), 4.00 (dd, *J* = 6.4, 8.2 Hz, 1 H, CHC*H*HO), 4.04−4.20 (m, 2 H, CH_2C*H*HO, C*H*N), 4.27 (s, 1 H, C*H*OCH_2), 4.36 (dt, *J* = 3.2, 7.3 Hz, CH_2C*H*O), 6.55 (br. d, *J* = 4.0 Hz, 1 H, N*H*), 6.71 (s, 4 H, aromatics) ppm. ^{13}C NMR (50 MHz): δ = 25.62, 26.48 (*C*H_3), 41.72 (*C*H_2N), 55.76 (O*C*H_3), 56.83 (*C*HN), 63.27, 66.70 (*C*H_2O), 76.93, 78.06 (*C*HO), 109.50 (O*C*O), 114.80, 115.75 (aromatic *C*H), 141.54, 152.57 (aromatic quat.), 169.49 (*C*=O) ppm. IR: $\tilde{\nu}_{max}$ = 3405, 2998, 2834, 1673 (s), 1504, 1477, 1383, 1373, 1345, 1190, 1155, 1123, 1071, 1035, 962 cm^{-1}.

(3*R,4*R**,4′*S**)-3-(2-Aminoethoxy)-1-(*tert*-butoxycarbonylmethyl)-4-(2,2-dimethyl-1,3-dioxolan-4-yl)azetidin-2-one (3b):** R_f = 0.40 ($CHCl_3$/MeOH, 80:20). ^1H NMR: δ = 1.33, 1.40 (2 s, 2 × 3 H, CH_3), 1.46 [s, 9 H, (CH_3)$_3$C], 2.84 (ddd, *J* = 4.2, 5.6, 13.6 Hz, 1 H, C*H*HNH_2), 2.94 (ddd, *J* = 4.1, 6.8, 13.6 Hz, 1 H, C*H*HNH_2), 3.63 (ddd, *J* = 4.2, 6.8, 9.9 Hz, 1 H, CH_2C*H*HO), 3.68 (dd, *J* = 5.2, 8.7 Hz, 1 H, CHC*H*HO), 3.83 (ddd, *J* = 4.1, 5.6, 9.9 Hz, 1 H, CH_2C*H*HO), 3.88 (d, *J* = 17.7 Hz, 1 H, C*H*HCO_2tBu), 3.90 (dd, *J* = 5.1, 9.3 Hz, 1 H, C*H*N), 4.11 (dd, *J* = 6.5, 8.7 Hz, 1 H, CHC*H*HO), 4.17 (d, *J* = 17.7 Hz, 1 H, C*H*HCO_2tBu), 4.37 (ddd, *J* = 5.2, 6.5, 9.3 Hz, 1 H, CH_2C*H*O), 4.65 (d, *J* = 5.1 Hz, 1 H, C*H*OCH_2) ppm. ^{13}C NMR (50 MHz): δ = 25.21, 26.90 (*C*H_3), 28.06 [C(*C*H_3)$_3$], 41.83, 43.09 (*C*H_2), 60.67 (*C*HN), 66.72, 74.03 (*C*H_2O), 76.72, 82.24 (*C*HO), 109.61 (O*C*O), 167.05, 167.67 (*C*=O) ppm.

***tert*-Butyl (3*R**,1′*R**)-{[(4*S**)-(2,2-Dimethyl-1,3-dioxolan-4-yl)-(3-oxomorpholin-2-yl)methyl]amino}acetate (25b):** R_f = 0.53 ($CHCl_3$/MeOH, 90:10). $C_{16}H_{28}N_2O_6$ (344.40): calcd. C 55.80, H 8.19, N 8.13; found C 55.85, H 8.3, N 8.05. GC-MS: R_t = 9.64; *m*/*z* = 329 [$M^{+\cdot}$ − 15] (1.0), 273 (2.3), 244 (15.9), 243 (26.5), 187 (100.0), 185 (10.5), 141 (21.0), 130 (24.8), 113 (20.6), 101 (9.0), 84 (5.8), 72 (14.8), 70 (11.0), 68 (5.0), 57 (18.9), 56 (7.4), 44 (15.5), 43 (23.3), 42 (12.6), 41 (18.3). ^1H NMR: δ = 1.35, 1.42 (2 s, 2 × 3 H, CH_3), 1.45 [s, 9 H, C(CH_3)$_3$], 3.17−3.30 (m, 1 H, C*H*HNC=O), 3.35 (dd, *J* = 1.8, 7.4 Hz, 1 H, C*H*N), 3.42, 3.51 (AB system, *J* = 17.5 Hz, 2 H, CH_2CO_2tBu), 3.60−3.82 (m, 2 H, CH_2C*H*HO, C*H*HNC=O), 3.81 (t, *J* = 7.8 Hz, 1 H, CHC*H*HO), 3.98−4.15 (m, 3 H, CHC*H*HO, C*H*OCH_2, CH_2C*H*HO), 4.28 (q, *J* = 7.1 Hz, 1 H, CHC*H*O), 6.42 (br. s, 1 H, N*H*) ppm. ^{13}C NMR (50 MHz): δ = 25.63, 26.71 (*C*H_3), 28.18 [C(*C*H_3)$_3$], 41.90, 50.88 (*C*H_2), 60.67 (*C*HN), 63.25, 66.93 (*C*H_2O), 77.77, 80.75 (*C*HO), 109.29 (O*C*O), 169.55, 171.89 (*C*=O) ppm. IR: $\tilde{\nu}_{max}$ = 3406, 2981, 2932, 2871, 1726 (s), 1674 (s), 1477, 1451, 1380, 1370, 1343, 1235, 1152, 1120, 1069, 968, 907, 844 cm^{-1}.

(3*R,4*S**)-3-(2-Aminoethoxy)-4-[(benzyloxymethoxy)methyl]-1-(4-methoxyphenyl)azetidin-2-one (3c):** R_f = 0.10 and 0.15 ($CHCl_3$/MeOH, 75:25). ^1H NMR: δ = 2.88 (ddd, *J* = 4.3, 5.5, 13.8 Hz, 1 H, C*H*HNH_2), 2.96 (ddd, *J* = 4.2, 6.7, 13.8 Hz, 1 H, C*H*HNH_2), 3.63−3.86 (m, 2 H, OCH_2CH_2N), 3.78 (s, 3 H, OCH_3), 3.93, 3.99 (AB part of ABX system, J_{AB} = 11.4 Hz, J_{AX} = 5.3, J_{BX} = 6.1, 2 H, CH_2OBOM), 4.36 (q, *J* = 5.4 Hz, 1 H, C*H*N), 4.53 (s, 2 H, CH_2Ph), 4.75 (d, *J* = 5.2 Hz, 1 H, C*H*O), 4.77 (s, 2 H, OCH_2O), 6.86 (d, *J* = 9.1 Hz, 2 H, *H ortho* to OCH_3), 7.23−7.40 (m, 5 H, aromatics), 7.48 (d, *J* = 9.1 Hz, 2 H, *H meta* to OCH_3) ppm.

(2*R,1′*S**)-2-{2-(Benzyloxymethoxy)-1-[(4-methoxyphenyl)amino]-ethyl}morpholin-3-one (25c):** R_f = 0.75 ($CHCl_3$/MeOH, 75:25). $C_{21}H_{26}N_2O_5$ (386.44): calcd. C 65.27, H 6.78, N 7.25; found C 65.55, H 6.6, N 7.2. GC-MS: R_t = 15.09; *m*/*z* = 386 [$M^{+\cdot}$] (7.5), 286 (35.2), 235 (13.9), 180 (4.4), 178 (9.4), 165 (9.0), 148 (20.6), 136 (6.7), 134 (9.3), 133 (7.1), 122 (5.9), 91 (100.0), 44 (6.1). ^1H NMR: δ = 3.12−3.24 (m, 1 H, C*H*HN), 3.50−3.85 (m, 4 H, C*H*HN, C*H*HOBOM, NCH_2CH_2O), 3.72 (s, 3 H, CH_3O), 4.05 (dd, *J* = 3.7, 11.1 Hz, 1 H, C*H*HOBOM), 4.28 (m_c, 1 H, C*H*N), 4.43 (d, *J* = 1.7 Hz, 1 H, C*H*O), 4.58 (s, 2 H, CH_2Ph), 4.76 (s, 2 H, OCH_2O), 6.51 (br. d, *J* = 4.0 Hz, 1 H, N*H*), 6.68, 6.73 (AB system, *J* = 9.3 Hz, 4 H, anisyl aromatic), 7.32 (s, 5 H, other aromatics) ppm. ^{13}C NMR (50 MHz): δ = 41.91 (*C*H_2N), 55.41 (*C*HN), 55.79 (O*C*H_3), 63.24, 66.16, 69.46 (*C*H_2O), 76.82 (*C*HO), 94.75 (O*C*H_2O), 114.92, 115.77, 127.69, 127.96, 128.41 (aromatic *C*H), 137.85, 140.91, 152.69 (aromatic quat.), 169.75 (*C*=O) ppm. IR: $\tilde{\nu}_{max}$ = 3406, 2996, 2946, 2877, 1675 (s), 1506, 1478, 1454, 1390, 1345, 1332, 1238, 1112, 1039 cm^{-1}.

(3*R,4*R**)-3-(2-Aminoethyl)-4-[(benzyloxymethoxy)methyl]-1-(4-methoxyphenyl)azetidin-2-one (4):** R_f = 0.19 ($CHCl_3$/MeOH, 75:25). ^1H NMR: δ = 1.75−2.05 (m, 2 H, $CH_2CH_2NH_2$), 2.80−3.05 (m, 2 H, CH_2NH_2), 3.45 (dt, *J* = 9.2, 6.1 Hz, 1 H, C*H*C=O), 3.77 (s, 3 H, OCH_3), 3.90 (d, *J* = 5.3 Hz, 2 H, CH_2O-BOM), 4.27 (q, *J* = 5.5 Hz, 1 H, C*H*N), 4.46 (s, 2 H, CH_2Ph), 4.72, 4.75 (AB system, *J* = 6.9 Hz, 2 H, OCH_2O), 6.85 (d, *J* = 9.0 Hz, 2 H, *H ortho* to OCH_3), 7.18−7.40 (m, 5 H, aromatics), 7.42 (d, *J* = 9.0 Hz, *H meta* to OCH_3) ppm. ^{13}C NMR (50 MHz): δ = 28.86 ($CH_2CH_2NH_2$), 40.77 (*C*H_2N), 49.69, 54.05 (*C*HC=O and *C*HN), 55.48 (*C*H_3O), 65.95, 69.75 (*C*H_2O), 94.89 (O*C*H_2O), 114.31, 118.84, 127.80, 128.44 (aromatic *C*H), 131.27, 137.51, 156.15 (aromatic quat.), 167.42 (*C*=O) ppm.

(3*R,1′*R**)-3-{2-(Benzyloxymethoxy)-1-[(4-methoxyphenyl)amino]-ethyl}pyrrolidin-2-one (36):** R_f = 0.71 ($CHCl_3$/MeOH, 75:25). $C_{21}H_{26}N_2O_4$ (370.44): calcd. C 68.09, H 7.07, N 7.56; found C 67.65, H 7.3, N 7.25. ^1H NMR: δ = 2.12−2.32 (m, 2 H, CH_2CH_2N), 2.73 (dt, *J* = 4.0, 9.2 Hz, 1 H, C*H*HN), 3.25−3.40 (m, 2 H, C*H*HN, C*H*C=O), 3.67−3.84 (m, 2 H, CH_2OBOM), 3.74 (s, 3 H, OCH_3), 3.87−3.98 (m, 1 H, C*H*N), 4.58 (s, 3 H, CH_2Ph), 4.75, 4.77 (AB system, *J* = 6.5 Hz, OCH_2O), 6.72, 6.75 (AB system, *J* = 9.6 Hz, 4 H, aromatics), 7.20−7.40 (m, 5 H, aromatics) ppm. ^{13}C NMR (50 MHz): δ = 23.77 (CH_2CH_2N), 40.41 (*C*H_2N), 42.80 (*C*HC=O), 54.86 (*C*HN), 55.80 (O*C*H_3), 69.02, 69.75 (*C*H_2O), 95.14 (O*C*H_2O), 115.08, 116.14, 127.75, 127.87, 128.45 (aromatic *C*H), 137.81, 141.42, 152.77 (aromatic quat.), 178.57 (*C*=O) ppm. IR: $\tilde{\nu}_{max}$ = 3437, 3003, 2949, 2887, 1692 (s), 1505, 1452, 1193, 1113, 1042, 907 cm^{-1}.

(3*R,4*S**,*E*)-3-Methoxy-1-[2-(phenylacetylamino)ethyl]-4-(2-phenylethenyl)azetidin-2-one (37):** A solution of azide **16b** (141 mg, 0.518 mmol) in THF (5 mL) was treated at room temp. with PPh_3 (204 mg, 0.777 mmol) and H_2O (250 μL). After stirring at room temp. for 6 h, Et_3N (289 μL, 2.07 mmol) and phenylacetyl chloride (137 μL, 1.04 mmol) were added in sequence. After 2 h, the mixture was quenched with saturated aqueous NH_4Cl (15 mL) and NaOH

(1 N, 4 mL). After further stirring for 15 min, the mixture was extracted with Et_2O (1 ×) and EtOAc (2 ×). The combined organic extracts were washed with saturated aqueous $NaHCO_3$, concentrated, and immediately chromatographed (CH_2Cl_2/EtOAc, 50:50 to 30:70), to give **37** containing a slight impurity of triphenylphosphane oxide. A second chromatography afforded pure **37** as a foam (161 mg, 85%). R_f = 0.21 (CH_2Cl_2/EtOAc, 50:50). $C_{22}H_{24}N_2O_3$ (364.44): calcd. C 72.50, H 6.64, N 7.69; found C 72.55, H 6.6, N 7.4. GC-MS: R_t = 12.47; *m/z* = 332 [$M^{+\cdot}$ − 32] (4.7), 241 (9.8), 198 (9.4), 197 (12.9), 172 (88.0), 171 (8.8), 162 (37.0), 161 (10.7), 160 (57.5), 159 (29.5), 156 (19.7), 145 (13.1), 144 (24.6), 142 (12.2), 130 (9.6), 129 (28.4), 127 (24.3), 126 (10.5), 117 (31.1), 116 (13.9), 115 (59.4), 91 (100.0), 70 (9.2), 65 (16.3), 44 (10.1), 42 (9.8). ^{1}H NMR: δ = 3.00−3.45 (m, 3 H), 3.42 (s, 3 H, OC*H*$_3$), 3.54 (s, 2 H, C*H*$_2$Ph), 3.50−3.70 (m, 1 H), 4.29 (dd, *J* = 4.4, 9.0 Hz, 1 H, C*H*−N), 4.45 (d, *J* = 4.4 Hz, 1 H, C*H*−OMe), 6.15 (dd, *J* = 9.0, 15.7 Hz, 1 H, C*H*=CHPh), 6.70 (d, *J* = 16.2 Hz, 1 H, CH=C*H*Ph), 7.25−7.45 (m, 10 H, aromatics) ppm. ^{13}C NMR (50 MHz): δ = 37.42, 41.02, 43.84 (*C*H$_2$), 58.63 (O*C*H$_3$), 61.09 (*C*H−N), 85.15 (*C*H−OMe), 122.70 (*C*H=CHPh), 126.75, 127.27, 128.46, 128.70, 128.94, 129.45 (aromatic *C*H), 134.83, 135.82 (aromatic quat.), 137.00 (CH=*C*HPh), 167.60 and 171.48 (*C*=O) ppm. IR: $\tilde{\nu}_{max}$ = 3421, 3039, 2990, 2931, 2833, 1746 (s), 1664 (s), 1600, 1524, 1400, 1349, 1143, 1063, 998, 969 cm^{-1}.

Hydrolysis of Phenylacetamide 37 with Penicillin G Acylase: Penicillin G acylase [activity: 450 U/g dry basis; supported on polyacrylic resin and suspended in glycerol (80%) and 0.02 M phosphate buffer pH = 7.8 (20%); a gift of Unità Biochimici De. Bi. Recordati] was washed with distilled water and dried by suction just before use. A buffer solution (pH = 7.5) was prepared by dissolving 10 mmol of aminotris(hydroxymethyl)methane in distilled water (10 mL), adjusting the pH to 7.5 with 1 N HCl, and then diluting to 50 mL. The washed and dried enzyme (70 mg) was dissolved in the buffer solution (5 mL). A solution of **37** (18.8 mg, 51.6 μmol) in MeOH (500 μL) was added. The solution became cloudy and was stirred at room temp. for 6 h. At this point TLC ($CHCl_3$/MeOH, 95:5) showed the complete conversion of **37** into **2b** and **17b**. The mixture was stirred at 37 °C overnight. The pH was raised to 12 by addition of 1 N NaOH. The mixture was extracted with EtOAc and the organic phase washed with saturated aqueous NaCl. Concentration and preparative TLC ($CHCl_3$/MeOH, 90:10) furnished azalactam **17b** (9.5 mg, 75%).

(3*R*,4*S*,*E*)- and (3*S*,4*R*,*E*)-1-(2-{[(*N*-*tert*-Butoxycarbonyl-D-valyl)-L-leucyl-(*N*-ε-*tert*-butoxycarbonyl)-L-lysyl]amino}ethyl)-3-methoxy-4-(2-phenylethenyl)azetidin-2-ones (39): A solution of freshly prepared amine **2b** (51.6 mg, 210 μmol) in dry CH_2Cl_2 (1 mL) was cooled to 0 °C and treated in sequence with [(*N*-*tert*-butoxycarbonyl-D-valyl)-L-leucyl]-*N*-ε-*tert*-butoxycarbonyl-L-lysine (**38**)[5] (117.2 mg, 210 μmol), PyBOP (163.4 mg, 314 μmol), and a solution of Et_3N in CH_2Cl_2 (0.5 N, 628 μL, 314 μmol). After stirring at 0 °C for 1 h and at room temp. for 1 h, the solution was diluted with EtOAc (20 mL), MeOH (2 mL) and aqueous $(NH_4)H_2PO_4$ (5%, 30 mL); the phases were separated and the aqueous one was extracted twice again with EtOAc. Concentration and chromatography (CH_2Cl_2/MeOH, 98:2) gave a slightly impure product that was further purified by preparative TLC (EtOAc/MeOH, 8:2) to give pure **39** (107 mg, 65%) as a diastereoisomeric mixture. $C_{41}H_{66}N_6O_9$ (787.00): calcd. C 62.57, H 8.45, N 10.68; found C 62.2, H 8.2, N 10.8. ^{1}H NMR ([D$_6$]DMSO): δ = 0.75−0.95 [m, 12 H, (C*H*$_3$)$_2$CH], 1.10−1.80 [m, 9 H, C*H*$_2$C*H*$_2$C*H*$_2$CH$_2$N, C*H*$_2$C*H*(CH$_3$)$_2$], 1.37 [s, 18 H, (C*H*$_3$)$_3$C], 1.93 (sept, *J* = 6.5 Hz), 2.80−3.05 (m, 2 H, C*H*$_2$N), 3.07−3.42 (m, 2 H, C*H*$_2$N), 3.32 (s, 3 H, OC*H*$_3$), (3.78 (t, *J* = 7.0 Hz, 1 H, C*H*NH), 4.02−4.20 (m, 1 H, C*H*NH), 4.20−4.38 (m, 1 H, C*H*NH), 4.39−4.53 (m, 1 H, CH=CHC*H*N), 4.58 and 4.63 (2 d, *J* = 4.1 and 4.4 Hz, 1 H, C*H*OMe), 6.22 (dd, *J* = 8.1, 16.1 Hz, 1 H, C*H*=CHPh), 6.71 (br. s, 2 H, N*H*), 6.79 (d, *J* = 16.1 Hz, 1 H, CH=C*H*Ph), 7.22−7.44 (m, 3 H, aromatics), 7.50 (d, *J* = 7.7 Hz, 2 H, aromatics), 7.70−8.20 (m, 3 H, N*H*) ppm. ^{13}C NMR ([D$_6$]DMSO, 50 MHz): δ = 18.32, 19.02, 20.96 (*C*H$_3$), 22.85 (*C*H$_2$), 23.17 (*C*H$_3$), 23.99 (*C*H), 28.04 and 28.19 [C(*C*H$_3$)$_2$], 29.18 (*C*H$_2$), 30.08 (*C*H), 31.25, 36.23, 36.65, 39.69, 40.06 (*C*H$_2$), 50.92, 50.97, 52.72 (*C*HN), 57.65 (O*C*H$_3$), 59.67, 59.90, 59.99 (*C*HN), 77.25, 78.10 [*C*(CH$_3$)$_3$], 85.03, 85.12 (*C*HOCH$_3$), 124.06, 124.17 (*C*H=CHPh), 126.51, 127.99, 128.60 (aromatic *C*H), 135.12, 135.24 (CH=*C*HPh), 135.96, 135.99 (aromatic quat.), 155.44, 155.55 (urethane carbonyls), 165.95, 166.07 (β-lactam carbonyls), 171.48, 171.53, 171.84, 171.89 (amidic carbonyls) ppm.

Transformation of Compound 39 into (3*R*,4*S*,*E*)- and (3*S*,4*R*,*E*)-1-{2-[(D-Valyl-L-leucyl-L-lysyl)amino]ethyl}-3-methoxy-4-(2-phenylethenyl)azetidin-2-ones (40) and Their Hydrolysis with Plasmin: Plasmin (from porcine blood, Sigma cat. P-8644, 3.2 units/mg; 2.6 mg) was dissolved in buffer [pH = 7.5, 12.8 mL; prepared by dissolving aminotris(hydroxymethyl)methane (10 mmol) in distilled water (10 mL), adjusting the pH to 7.5 with 1 N HCl, and diluting to 50 mL]. The resulting solution contains 0.65 U/mL of active enzyme. A solution of compound **39** (42.3 mg) in dry CH_2Cl_2 (750 μL) was cooled to 0 °C and treated with CF_3CO_2H (250 μL). After stirring at 0 °C for 40 min and at room temp. for 2 h, the solvents were evaporated to dryness. The residue was taken up twice with *n*-heptane and the solvents were evaporated again to give a white foam (42.1 mg). This material was taken up in MeOH (0.9 mL). One third of this solution (300 μL) was added to the above-prepared Plasmin solution. The mixture was stirred at room temp. for 30 h. At this point TLC ($CHCl_3$/MeOH, 75:25) showed complete conversion of **40** into **2b** and (mostly) **17b**. After a further 18 h, the pH was raised to 12 by addition of 1 N NaOH. The mixture was extracted with EtOAc and the organic phase washed with saturated aqueous NaCl. Concentration and preparative TLC ($CHCl_3$/MeOH, 90:10) afforded pure **17b** (2.9 mg, 68% from **39**).

(3*R,4*S**,*E*)-1-{2-{[(4,5-Dimethoxy-2-nitrophenyl)methoxy]-carbonylamino}ethyl}-3-methoxy-4-(2-phenylethenyl)-azetidin-2-one (41):** A solution of freshly prepared amine **2b** (53.3 mg, 202 μmol) in dry CH_2Cl_2 (1 mL) was kept in the dark, cooled to 0 °C, and treated with Et_3N (181 μL, 1.30 mmol) and 6-nitroveratryl chloroformate (179 mg, 650 μmol). After stirring at 0 °C for 3 h, the reaction was quenched with saturated aqueous NH_4Cl (3 mL) and stirred at room temp. for 15 min. The mixture was diluted with $NaHCO_3$ (5%, 20 mL) and extracted with EtOAc. The organic phase was washed with aqueous $(NH_4)H_2PO_4$ (5%) and saturated aqueous NaCl. Concentration and chromatography (Et_2O/CH_2Cl_2/EtOH, 49:49:2) gave pure **41** as a yellow foam (80.3 mg, 82%). R_f = 0.26 (Et_2O/CH_2Cl_2/EtOH, 49:49:2). $C_{24}H_{27}N_3O_8$ (485.49): calcd. C 59.37, H 5.61, N 8.66; found C 59.4, H 5.75, N 8.7. ^{1}H NMR: δ = 3.10−3.65 (m, 4 H, C*H*$_2$C*H*$_2$N), 3.43 (s, 3 H, OC*H*$_3$), 3.95, 4.00 (2 s, 2 × 3 H, OC*H*$_3$), 4.37 (dd, *J* = 4.4, 9.2 Hz, 1 H, C*H*N), 4.56 (d, *J* = 4.4 Hz, 1 H, C*H*OMe), 5.45, 5.53 (AB system, *J* = 15.3 Hz, 2 H, C*H*$_2$Ar), 5.73 (br. s, 1 H, N*H*), 6.22 (dd, *J* = 9.2, 15.9 Hz, 1 H, C*H*=CHPh), 6.74 (d, *J* = 15.9 Hz, 1 H, CH=C*H*Ph), 7.05 (s, 1 H, veratryl aromatic), 7.20−7.46 (m, 5 H, aromatics), 7.71 (s, 1 H, veratryl aromatic) ppm.

Photochemical Cleavage of Compound 41 To Give Amine 2b: In a quartz test tube, a solution of **41** (20.3 mg, 41.8 μmol) in ethanol (96%, 1 mL) was treated with H_2SO_4 (11 μL, 200 μmol). The solution was placed in a Rayonet "merry-go-round" apparatus and ir-

radiated with 12 lamps (4.5 W, 350 nm) for 24 h. After this time, TLC showed complete disappearance of the starting material. The solution was diluted with CH_2Cl_2 (10 mL) and water (10 mL). The phases were separated and the aqueous one was extracted again with CH_2Cl_2. The combined organic phases were extracted with $(NH_4)H_2PO_4$ (5%). The combined aqueous phases were brought to pH = 13 by addition of aqueous NaOH (1 N) and extracted with CH_2Cl_2. The solvent was evaporated, and the residue taken up again in THF (500 μL) and treated with Et_3N (35 μL, 251 μmol) and phenylacetyl chloride (17 μL, 125 μmol). After 2 h, the reaction was complete. It was worked up as described for the preparation of **37**. Chromatography gave pure phenylacetamide **37** (10 mg, 65%).

Ethyl (1*R,9*R**,10*S**,*Z*)-{9-(*tert*-Butyldimethylsilyloxy)-12-oxo-11-azabicyclo[8.2.0]dodec-5-ene-3,7-diyn-11-yl}acetate (43):** A solution of alcohol **42**[2] (150.2 mg. 0.498 mmol) in dry THF (3 mL) was cooled to 0 °C and treated with a solution of $KN(SiMe_3)_2$ in toluene (0.39 M, 1.40 mL, 0.548 mmol). After 15 min, ethyl bromoacetate (66 μL, 0.598 mmol) was added. After 75 min, the solution was poured into saturated aqueous NH_4Cl. Extraction with Et_2O gave, after concentration and chromatography (PE/Et_2O, 60:40 + 1% Et_3N, to PE/Et_2O, 50:50), pure **43** as a solid (156.3 mg, 81%). R_f = 0.48 (PE/Et_2O, 50:50). M.p. 147.8−148.5 °C. $C_{21}H_{29}NO_4Si$ (387.54): calcd. C 65.08, H 7.54, N 3.61; found C 64.95, H 7.65, N 3.55. GC-MS: R_t = 10.19; *m*/*z* = 330 [$M^{+\cdot}$ − 57] (100), 284 (6.7), 256 (7.8), 228 (7.8), 217 (6.3), 201 (8.4), 182 (5.1), 177 (28.6), 156 (6.5), 155 (6.5), 154 (18.6), 128 (6.8), 127 (11.6), 126 (7.6), 125 (5.3), 115 (9.9), 105 (6.8), 104 (7.2), 103 (10.8), 77 (8.1), 75 (57.9), 73 (72.4), 59 (13.1), 45 (8.9), 41 (7.6). ^{1}H NMR: δ = 0.17 and 0.12 [2 s, 2 × 3 H, $(CH_3)_2Si$], 0.89 [s, 9 H, $(CH_3)_3C$], 2.73 (dd, *J* = 12.5, 17.9 Hz, 1 H, C*H*HC≡C), 1.30 (t, *J* = 7.1 Hz, 3 h, CH_3CH_2), 2.90 (ddd, *J* = 1.5, 4.4, 17.9 Hz, 1 H, C*H*HC≡C), 3.44 (d, *J* =18.0, 1 H, C*H*HCO_2Et), 3.75 (ddd, *J* = 2.2, 4.3, 12.3 Hz, 1 H, C*H*C=O), 4.05 (t, *J* = 2.1 Hz, 1 H, C*H*N), 4.21 (m_c)(m, 2 H, CH_2CH_3), 4.41 (d, *J* = 18.0 Hz, 1 H, C*H*HCO_2Et), 4.72 (t, *J* = 1.8 Hz, 1 H, C*H*OSi), 5.94 and 5.88 (AB part of an ABX_2 system, J_{AB} = 10.0 Hz, J_{AX} = J_{BX} = 0.7 Hz, 2 H, C*H*=C*H*) ppm. ^{13}C NMR (50 MHz): δ = 14.19 (CH_2CH_3), 18.05 [$C(CH_3)_3$], 19.29 (CH_2C≡C), 25.64 [$(CH_3)_3C$], 41.28 (CH_2CO_2Et), 51.83 (CHC=O), 59.49 (CHN), 61.73 (CH_2O), 63.57 (CHOSi), 83.68, 86.52, 97.52, 100.60 (C≡C), 122.16, 125.82 (CH=CH), 167.94, 168.33 (C=O) ppm. IR: $\tilde{\nu}_{max}$ = 2954, 2930, 2857, 1756, 1740, 1462, 1410, 1375, 1363, 1350, 1316, 1191, 1132, 1115, 1094, 1014, 979, 936, 863, 836 cm^{-1}.

(1*R,9*R**,10*S**,*Z*)-9-(*tert*-Butyldimethylsilyloxy)-11-(2-hydroxyethyl)-11-azabicyclo[8.2.0]dodec-5-ene-3,7-diyn-12-one (44):** Powdered anhydrous $CaCl_2$ (140 mg, 1.26 mmol) was suspended in THF (7 mL) and absolute EtOH (4 mL). The mixture was cooled to −20 °C and treated with $NaBH_4$ (75 mg, 1.99 mmol). After 30 min, a solution of lactenediyne **43** (153 mg, 0.394 mmol) in THF (4 mL) was added. The temperature was allowed to rise to 0 °C during 2 h and 30 min. At this point TLC showed complete conversion of the starting material. The mixture was poured into a cooled (ice) saturated aqueous NH_4Cl solution and extracted with Et_2O. Immediate chromatography (CH_2Cl_2/EtOAc, 50:50) gave pure **44** as a solid (120.1 mg, 88%). R_f = 0.47 (CH_2Cl_2/EtOAc, 1:1), R_f = 0.68 (EtOAc). M.p. 122.6−123.8 °C. $C_{19}H_{27}NO_3Si$ (345.51): calcd. C 66.05, H 7.88, N 4.05; found C 66.15, H 7.9, N 3.95. GC-MS: R_t = 10.04; *m*/*z* = 345 [$M^{+\cdot}$] (0.11), 288 [$M^{+\cdot}$ − 57] (19.3), 287 (10.9), 272 (5.1), 271 (15.8), 270 (69.2), 216 (11.4), 186 (7.7), 168 (15.0), 156 (6.7), 143 (7.0), 142 (9.5), 135 (13.1), 127 (12.3), 126 (6.6), 119 (8.1), 115 (11.2), 77 (10.9), 76 (8.9), 75 (100), 73 (76.7), 59 (12.4), 57 (8.1), 47 (7.2), 45 (30.5), 43 (7.0), 41 (9.6). ^{1}H NMR: δ = 0.14, 0.20 [2 s, 2 × 3 H, $(CH_3)_2Si$], 0.90 [s, 9 H, $(CH_3)_3C$], 2.63 (dd, *J* = 12.6, 17.9 Hz, 1 H, C*H*HC≡), 2.90 (ddd, *J* = 1.5, 4.0, 17.9 Hz, 1 H, C*H*HC≡), 3.18, 3.30 (AB part of ABX system, J_{AB} = 14.4 Hz, J_{AX} = 4.5 Hz, J_{BX} = 5.0 Hz, 2 H, CH_2N), 3.62−3.90 (m, 5 H, CH_2OH, O*H*, C*H*N, C*H*C=O), 4.79 (t, *J* = 1.8 Hz, 1 H, C*H*OSi), 5.89, 5.95 (AB part of ABX_2 system, J_{AB} = 9.5 Hz, J_{AX} = J_{BX} = 0.7 Hz, 2 H, C*H*=C*H*) ppm. IR: $\tilde{\nu}_{max}$ = 3371, 2998, 2954, 2929, 2884, 2856, 1729, 1462, 1406, 1360, 1350, 1314, 1194, 1160, 1138, 1114, 1062, 1028, 1001, 977 cm^{-1}.

(1*R,9*R**,10*S**,*Z*)-11-(2-Azidoethyl)-9-(*tert*-butyldimethylsilyloxy)-11-azabicyclo[8.2.0]dodec-5-ene-3,7-diyn-12-one (45):** A solution of alcohol **44** (116.9 mg, 0.338 mmol) in dry CH_2Cl_2 (2 mL) was cooled to −30 °C and treated sequentially with Et_3N (188 μL, 1.352 mmol) and methanesulfonyl chloride (52 μL, 0.676 mmol). After 50 min, the mixture was poured into saturated aqueous NH_4Cl and extracted with Et_2O. After concentration to dryness, the crude mesylate was taken up in dry DMF (1.0 mL), treated with NaN_3 (66 mg, 1.1014 mmol) and heated at 50 °C for 2 h and 15 min. After cooling, the solution was poured into a mixture of saturated aqueous NH_4Cl and H_2O (2:1), and extracted with Et_2O. Chromatography (PE/EtOAc, 70:30) gave pure **45** as a white solid (105.3 mg, 84%). R_f = 0.74 (PE/EtOAc, 50:50). M.p. 87.5−88.4 °C. $C_{19}H_{26}N_4O_2Si$ (370.52): calcd. C 61.59, H 7.07, N 15.12; found C 61.8, H 7.25, N 14.95. GC-MS: R_t = 10.21; *m*/*z* = 342 [$M^{+\cdot}$ − 28] (30.3), 313 [$M^{+\cdot}$ − 57] (8.8), 285 (13.8), 257 (6.3), 211 (7.6), 185 (5.4), 184 (6.0), 183 (14.9), 182 (6.7), 181 (6.8), 169 (5.4), 156 (7.6), 154 (8.6), 143 (6.1), 128 (7.6), 127 (13.5), 126 (6.3), 115 (11.5), 101 (6.0), 84 (9.3), 77 (14.0), 76 (9.1), 75 (100), 74 (13.8), 73 (83.5), 69 (13.7), 59 (15.0), 57 (9.0), 47 (9.6), 45 (14.4), 42 (13.5), 41 (12.1). ^{1}H NMR: δ = 0.14, 0.19 [2 s, 2 × 3 H, $(CH_3)_2Si$], 0.89 [s, 9 H, $(CH_3)_3C$], 2.65 (dd, *J* = 12.6, 17.9 Hz, 1 H, C*H*HC≡C), 2.90 (ddd, *J* = 1.5, 4.0, 17.9 Hz, 1 H, C*H*C≡C), 2.97 (ddd, *J* = 4.4, 8.1, 13.6 Hz, 1 H, C*H*HNC=O), 3.40−3.77 (m, 4 H, C*H*C=O, CH_2N_3, C*H*C=O), 3.87 (t, *J* = 2.1 Hz, 1 H, C*H*N), 4.81 (t, *J* = 1.8 Hz, 1 H, C*H*OSi), 5.89, 5.94 (AB part of ABX_2 system, J_{AB} = 9.5 Hz, J_{AX} = J_{BX} = 0.7 Hz) ppm. ^{13}C NMR (50 MHz): δ = −4.16, −5.04 [$(CH_3)_2Si$], 18.02 [$C(CH_3)_3$], 19.25 (CH_2C≡C), 25.64 [$C(CH_3)_3$], 39.65, 50.05 (CH_2N), 51.67 (CHC=O), 64.16 and 59.49 (CHOSi and CHN), 83.78, 86.68, 97.58, 100.54 (C≡C), 122.20, 125.85 (CH=CH), 168.06 (C=O) ppm. IR: $\tilde{\nu}_{max}$ = 3014, 2955, 2929, 2857, 2105, 1745, 1462, 1400, 1361, 1344, 1315, 1294, 1255, 1160, 116, 1037, 907 cm^{-1}.

(1*R,9*R**,10*S**,*Z*)-11-(2-Aminoethyl)-9-(*tert*-butyldimethylsilyloxy)-11-azabicyclo[8.2.0]dodec-5-ene-3,7-diyn-12-one Hydrochloride (46):** A solution of azide **45** (30.0 mg, 81.0 μmol) in THF (1.5 mL) was treated with H_2O (250 μL) and with Ph_3P (62.0 mg, 236.4 μmol). The mixture was stirred at room temp. for 14 h. The solvent was evaporated and the residue chromatographed ($CHCl_3$ to $CHCl_3$/MeOH, 85:15, to $CHCl_3$/MeOH/*i*$PrNH_2$, 82.5:15:2.5) to give pure amine **46**. This amine was taken up in CH_2Cl_2 (1 mL) and treated with a solution of HCl in Et_2O (1 M, 75 μL). After concentration, the pure hydrochloride (26.1 mg, 85%) was obtained as a white solid, which was stable in a freezer for several weeks. R_f (of free amine) = 0.59 ($CHCl_3$/MeOH, 85:15). GC-MS: R_t = 10.08; *m*/*z* = 344 [$M^{+\cdot}$] (1.2), 343 [$M^{+\cdot}$ − 1] (5.1), 287 [$M^{+\cdot}$ − 57], (85.9), 269 (6.6), 259 (7.9), 233 (14.8), 228 (5.0), 216 (7.8), 215 (5.2), 214 (18.9), 213 (11.5), 212 (5.2), 202 (5.1), 201 (6.4), 186 (10.5), 185 (17.8), 184 (9.2), 183 (12.0), 160 (10.6), 156 (9.0), 154 (12.7), 143 (10.4), 142 (10.6), 141 (7.0), 128 (11.1), 127 (15.1), 126 (8.1), 115 (10.2), 77 (7.6), 75 (51.3), 73 (100), 59 (11.3), 45 (8.8), 44 (19.5). ^{1}H NMR: δ = 0.14, 0.19 [2 s, 2 × 3 H, $(CH_3)_2Si$], 0.90 [s, 9 H, $C(CH_3)_3$], 2.64 (dd, *J* = 12.6, 17.8 Hz, 1 H,

C*H*HC≡C), 2.80−3.10 (m, 3 H, C*H*HNC=O and C*H*HC≡C), 3.43 (dt, J = 10.4, 6.0 Hz, 1 H C*H*HNC=O), 3.70 (ddd, J = 2.0, 4.0, 12.7 Hz, 1 H, C*H*C=O), 3.80 (t, J = 3.9 Hz, 1 H, C*H*N), 4.79 (t, J = 1.8 Hz, 1 H, C*H*OSi), 5.89, 5.94 (AB system, J = 10.2 Hz, 2 H, C*H*=C*H*) ppm.

(5a*R,11*R**,11a*S**)-11-(*tert*-Butyldimethylsilyloxy)-1,2,3,4,5a,6,11,11a-octahydronaphtho[2,3-*e*]-1,4-diazepin-5-one (48):** The hydrochloride salt of amine **46** (23.8 mg, 62.5 μmol) was taken up in THF (2 mL) and treated with Et_3N (100 μL) and 1,4-cyclohexadiene (100 μL). The solution was heated under reflux for 4 d. The solvent was evaporated. A preparative TLC ($CHCl_3$/MeOH, 95:5) gave pure **48** (9.7 mg, 45%). R_f = 0.35 ($CHCl_3$/MeOH, 95:5). GC-MS: R_t = 10.50; m/z = 289 [$M^{+\cdot}$ − 57] (66.3), 234 (71.5), 227 (80.2), 214 (57.0), 163 (100), 129 (77.6), 115 (23.9), 91 (6.9), 75 (99.4), 44 (45.8). ^{1}H NMR: δ = 0.04, 0.17 [2 s, 2 × 3 H, $(CH_3)_2$Si], 0.98 [s, 9 H, C(CH_3)$_3$], 2.80−2.95 (m, 2 H), 2.97−3.10 (m, 3 H), 3.10−3.35 (m, 2 H), 3.50−3.65 (m, 1 H), 4.81 (d, J = 5.1 Hz, 1 H, C*H*OSi), 5.96 (br. s, N*H*), 7.31 (s, 5 H, aromatics) ppm. ^{13}C NMR (50 MHz): δ = −4.80 [(CH_3)$_2$Si], 18.25 [C(CH$_3$)$_3$], 25.86 [C(CH$_3$)$_3$], 27.45 (benzylic CH_2), 45.00, 46.64, 49.95 (CH_2N and CHC=O), 60.0 (*C*HN), 72.27 (*C*HOSi), 124.79, 126.28, 127.36, 127.73 (aromatic *C*H), 136.62, 138.18 (aromatic quat.), 179.04 (C=O) ppm. IR: $\tilde{\nu}_{max}$ = 3416, 3062, 3020, 2997, 2927, 2856, 1663, 1461, 1237, 1105 cm^{-1}.

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