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SYNTHESIS OF 4-VINYL SUBSTITUTED β-LACTAMS OF THE OXAMAZIN FAMILY

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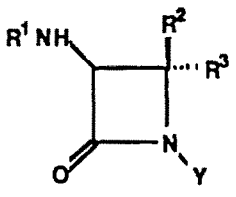
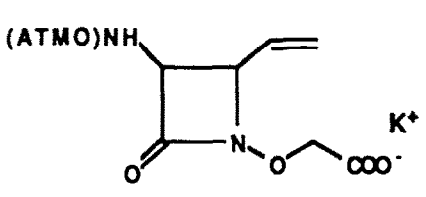
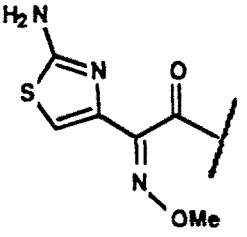
Summary: 4-Vinyl-substituted oxamazins **15**, **16**, and **3** have been prepared. Key steps of the synthesis are: the preparation of protected α-amino-β-hydroxyacid **6** through ester enolate condensation of ethyl glycinate *STABASE* adduct **8** with CH-protected propionaldehyde **9**, the coupling of this acid with an appropriate protected hydroxylamine, the cyclization of resulting hydroxamate, and finally the acylation of the amino-group in 3 with *ATMO* side chain.

The discovery of the monobactams **1**[1] (Scheme 1), a new class of antibiotics particularly active against gram negative bacteria, has stimulated a lively interest in the synthesis of novel monocyclic β-lactams. More recently it was found that good to potent antibiotic activities could be still achieved by substituting the SO_3^- moiety with other electron-withdrawing groups,[2] like for example in oxamazins of general formula **2**.[3,4]

SCHEME 1







1 Y=$SO_3^-M^+$

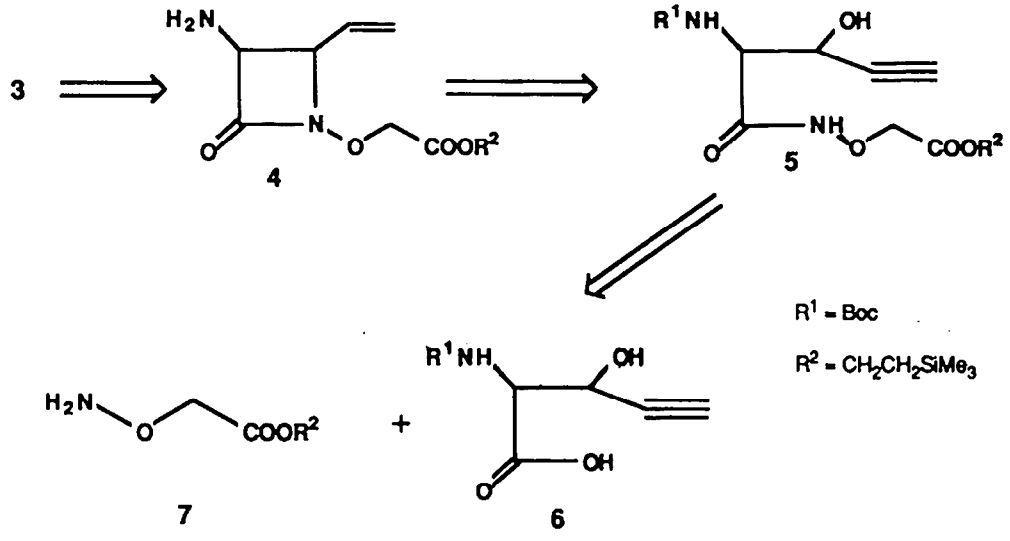
2 Y=OC(R^{4}R^5)COO$^-M^+$

3

(ATMO)

In the course of our project directed towards the synthesis and biological evaluation of new monocyclic β-lactam antibiotics,[5] our attention was drawn by oxamazin **3**, containing a 4-vinyl group. In analogy with some vinyl containing cephalosporins,[6] we envisaged that **3** could be an interesting target not only for its possible antibiotic activity, but also as a useful starting material for other oxamazin derivatives *via* reaction at the double bond and/or at the carboxyl group. As for R^1 we chose the 2-(2-amino-4-thiazolyl)-2-(Z)-(methoxyimino)-acetyl group (ATMO), since this particular side chain is known to dramatically improve the biological activity toward gram-negative bacteria of both cephalosporins and monobactams.[7]

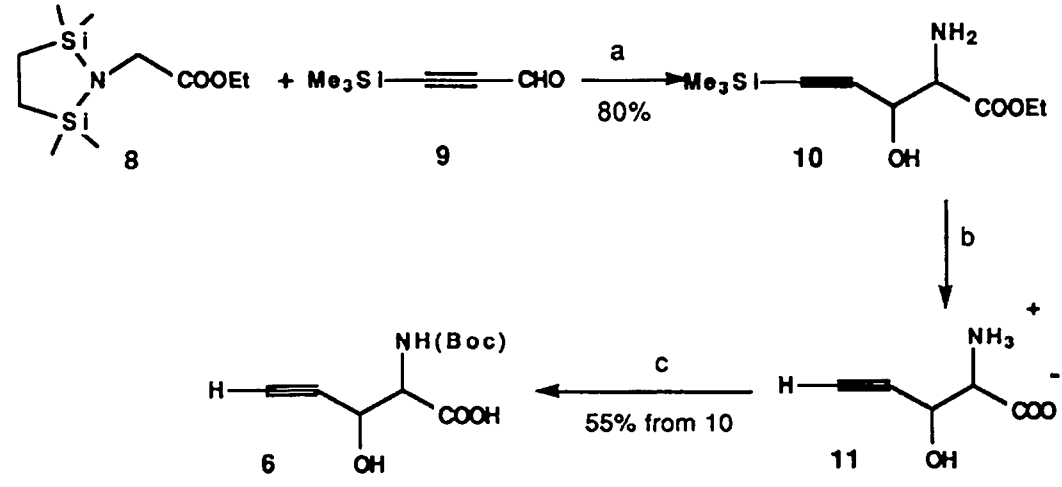
SCHEME 2



Our retrosynthetic strategy is depicted in Scheme 2 and was based on the biomimetic approach developed by Miller[8] involving the intramolecular cyclization of a protected α-amino-β-hydroxy-hydroxamate. The presence in 3 of a vinyl group at C-4 introduces a series of synthetic problems, that is: a) the preparation of the required α-amino-β-hydroxy-acid; b) the judicious choice of protecting groups at the 3-amino moiety and at the carboxyl, since the usually employed protections removable under hydrogenolytic conditions, such as the benzylurethane, are not compatible with the presence of a double bond; c) the possibility of an allylic rearrangement during the cyclization of the 3-hydroxy-hydroxamate. In order to avoid the latter problem, we decided to carry out the cyclization step on the alkinyl derivative 5, instead of on the corresponding vinyl analogue.

As for the two protecting groups on the amino and carboxylic functions, we selected the *t*-butoxycarbonyl (BOC) as R^1 and the 2-trimethylsilylethyl[9] as R^2, which can be removed respectively by acidic and mild basic

SCHEME 3



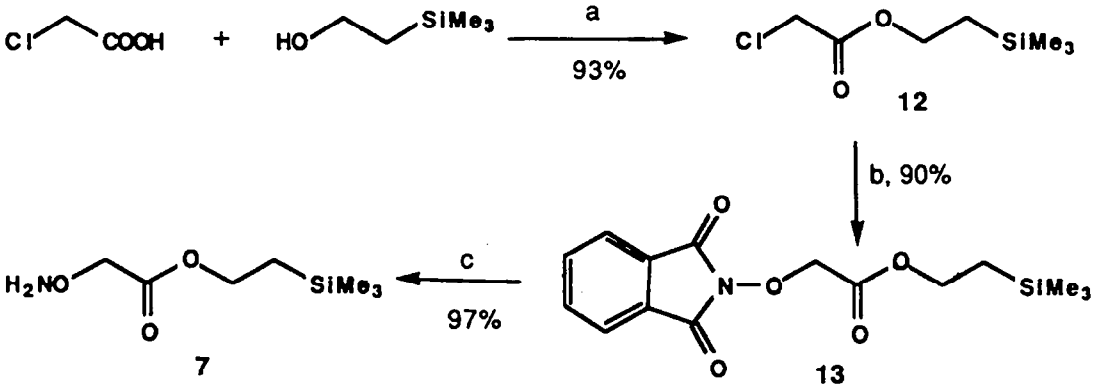
a) 8 + LDA, -78°C; then 9; then HCl, H_2O-THF; b) Et_3N, H_2O-EtOH 2:1, R.T.; c) Boc_2O, Et_3N, H_2O-DMF 1:6

(fluoride ion) treatment, hoping that these conditions would not affect the β-lactam ring. Finally, for the synthesis of α-amino-β-hydroxyacid **6**, we envisaged an aldol type condensation between the lithium enolate derived from ethyl glycinate *STABASE* adduct 8[10,2d] and trimethylsilylpropiolaldehyde **9**.[11]

As shown in Scheme 3, this condensation between **8** and **9** proceeded in good yield giving, after acidic hydrolysis of the STABASE group, the α-amino-β-hydroxyester **10** as a 1:1 mixture of diastereoisomers. Saponification with Et_3N in H_2O-EtOH effected also cleavage of carbon-silicon bond to give the aminoacid **11**, which was directly protected, without purification to the *t*-butylurethane **6**. Preliminary attempts to obtain **6** directly by condensation of *N*-Boc protected glycinates with **9** were discouraging. They were anyway abandoned when we observed that when the amino function in **10** (obtained starting from *STABASE* adduct **8**) was first protected as *t*-butyl urethane, ester hydrolysis was inefficient. Although **6** has been purified by chromatography or by crystallization of the dicyclohexylammonium salt, we found more convenient, from a synthetic point of view, to use the crude acid for further condensation with the hydroxylamine **9**.

The synthesis of **7** is described in Scheme 4. Condensation of chloroacetic acid with 2-trimethylsilylethanol mediated by DCC and dimethylaminopyridine (DMAP)[12] afforded the chloroester **12**. Introduction of the hydroxylamino function was then carried out through nucleophilic substitution by N-hydroxy-phthalimide, to give **13**. Subsequent hydrazine cleavage gave free hydroxylamine **7** in 81% overall yield from 2-trimethylsilylethanol.

SCHEME 4



a) DCC, DMAP, CH_2Cl_2, 0°C; b) N-hydroxyphtalimide, DMF, K_2CO_3; c) H_2N-NH_2, CH_2Cl_2

Attempts to couple hydroxylamine **7** with protected aminoacid **6** under the classic conditions employing a water soluble carbodiimide (WSC) in DMF / H_2O[2c,8b] gave disappointingly low yields (26%) (Scheme 5). On the contrary, the use of the N-hydroxy-benzotriazole / DCC[13] method gave **5**, as a 1:1 mixture of diastereoisomers, in excellent yield (90%). As already pointed out, best overall yields were obtained when crude **6** was employed.

In this case the yield from **10** (three steps) was 69%. Cyclization of **5**, employing diethylazodicarboxylate (DEAD)/triphenylphosphine[8b] proceeded smoothly to give β-lactam **14**, as a 1:1 mixture of 3,4 *cis* and *trans* isomers, in good yield. On the contrary, the use of the system triphenylphosphine/ CCl_4/triethylamine[8b] failed to give the desired products. The overall yield of **14** from trimethylsilylpropiolaldehyde was an appreciable 44%.

The acidic removal of (Boc) group proved to be troublesome. Hydrolysis of **14** with trifluoroacetic acid or formic acid followed by treatment with phenoxyacetyl chloride, as well as with the (ATMO)-OH / N-hydroxybenzotriazole adduct [(ATMO)-OBHT], gave no expected product. Also the attempt to convert **14** into the *t*-butyldimethylsilyloxycarbonyl derivative by reaction with *t*-butyldimethylsilyl triflate, according to a recent report,[14] was unsuccessful.

However, when the triple bond was first reduced to the double one, through hydrogenation on Pd Lindlar in the presence of 2,6-lutidine, the (Boc) protecting group could be efficiently removed with trifluoroacetic to give, after acylation with (ATMO)-OBHT the desired adduct **16**, although in low yields (25%). Finally, deprotection of the trimethylsilylethyl ester and cation exchange[4b] furnished our target **3** as a 1:1 diastereomeric mixture.

With the purpose to test the feasibility of a synthesis of diastereomerically pure *cis* **3a** and *trans* **3b**, we tried to separate one of the couples **15a,b** or **16a,b**. This was possible, by chromatography, at the stage of **15a,b**. The configuration of the two epimers was assessed by ^1H n.m.r. on the basis of the H-3/H-4 vicinal coupling constant. However, since *cis* and *trans* monocyclic β-lactam antibiotics usually do not appear to show strong differences in anti-bacterial behaviour and in β-lactamase resistance, we carried out the preliminary biological tests only on the 1:1 diastereomeric mixture of **3**. Unfortunately they have shown that **3a,b** possess only slight antibiotic activity.

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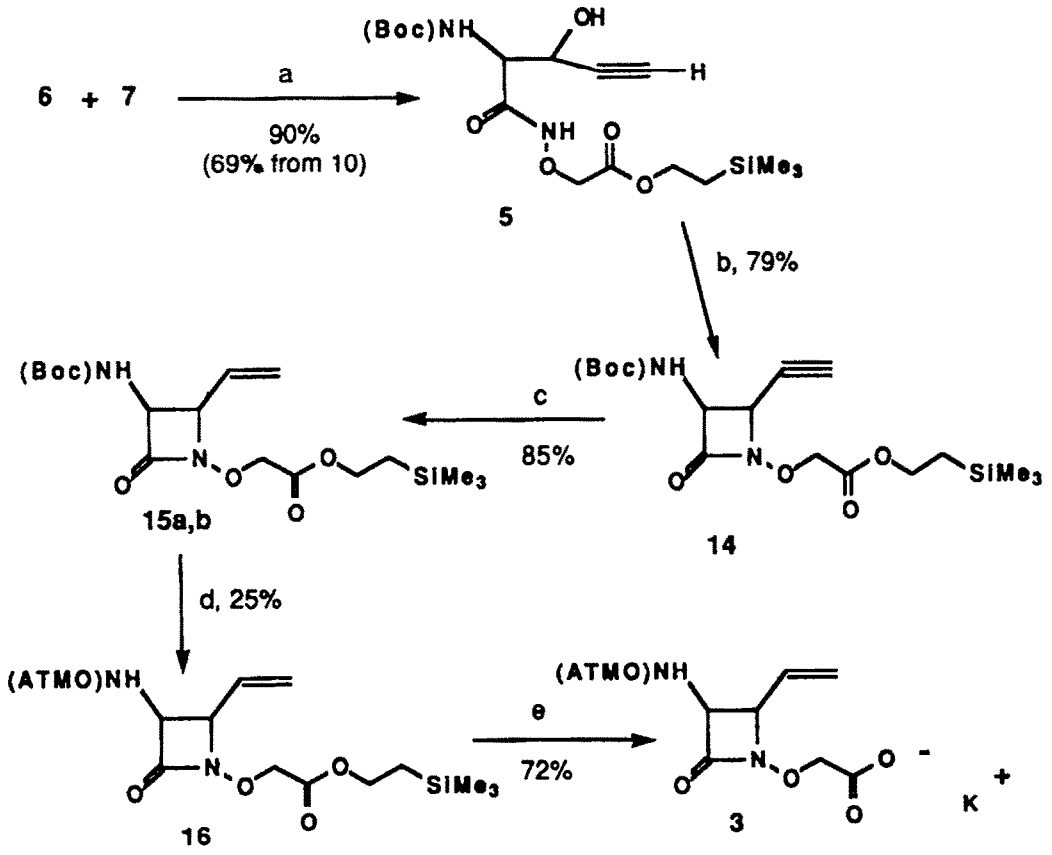
SCHEME 5



a : *cis* **b**: *trans*

a) DCC, N-hydroxybenzotriazole, DMF; b) DEAD, Ph_3P, THF; c) Pd Lindlar, 2,6-lutidine, H_2; d) CF_3COOH, 0°C; then (ATMO)-OBHT, Et_3N, CH_3CN, R.T.; e) *n* Bu_4NF; then Dowex 50 WX8 (K^+ form)

EXPERIMENTAL

N.m.r. spectra were recorded on a Varian FT 80 or a Varian XL-60 spectrometer using tetramethylsylane as internal standard. I.r. spectra were measured with a Perkin-Elmer 257. Elemental analyses were performed with a Perkin-Elmer 240 instrument. 270-400 mesh silica gel (Merck) was used for chromatography. Organic extracts were dried over Na_2SO_4 and filtered before removal of the solvent under reduced pressure. All reactions employing dry solvents were run under a nitrogen atmosphere.

***Anti* and *syn* Ethyl 2-amino-3-hydroxy-5-(trimethylsilyl)-pent-4-ynoates (10).**- A solution of lithium diisopropylamide [prepared from 1.89 ml (13.47 mmol) of diisopropylamine and 8.42 ml of a 1.6 M solution of *n*-BuLi in *n*-hexane (13.47 mmol) in 27 ml of THF] was cooled to -78°C and treated with **8** (3.35 ml, 12.63 mmol). After stirring for 15 min., trimethylsilylpropiolaldehyde **9** (1.27 ml, 8.42 mmol) was added. After 15 min. the solution was poured into 0.5N HCl (50 ml, 25 mmol) and stirred overnight at room temperature. The mixture was diluted with Et_2O and the phases separated. The aqueous layer was treated with NH_4OH to pH 9 and extracted thrice with CH_2Cl_2 to give, after evaporation, a crude product, which was purified by silica gel chromatography (*n*-hexane : AcOEt 1:1) to give pure **10** as an oil (1.55 g, 80%). Elemental analysis: found C, 52.55; H, 8.45; N, 5.95%; calc. for $C_{10}H_{19}NOSi$: C, 52.37; H, 8.35; N, 6.11%. I.r. ($CHCl_3$): ν_{max} 2950, 1730, 1370, 1180, 1020 cm^{-1}. ^1H n.m.r. ($CDCl_3$, 80 MHz.): δ 4.55-4.75 (1 H, m, C<u>H</u>-OH); 4.21 (2 H, q, C<u>H</u>$_2$-CH_3, J 6.8 Hz.); 3.55-3.75 (1 H, m, C<u>H</u>-N); 3.11 (2 H, s, N<u>H</u>$_2$); 1.24 (3 H, t, CH_3-CH_2, J 6.8 Hz.); 0.09 (9 H, s, CH_3-Si).

***Anti* and *syn* 2-(*t*-butyloxyformamido)-3-hydroxy-pent-4-ynoic acids (6).**- A solution of **10** (1.30 g, 5.67 mmol) in H_2O : EtOH 2:1 (11 ml) was treated with triethylamine (4.74 ml, 34 mmol) and stirred overnight at room temperature. After evaporation of the solvent at reduced pressure, the residue was taken up with some water, acidified to pH 4.5 with 1N HCl, and evaporated again. The crude product was taken up with H_2O : DMF 1:6 (10 ml), treated with triethylamine (0.790 ml, 5.67 mmol) and di-*t*-butyldicarbonate (1.56 ml, 6.80 mmol), and stirred overnight at room temperature. The solution was acidified with 1N HCl to pH 1 and extracted thrice with AcOEt. The combined organic extracts were washed with saturated brine and evaporated to dryness to give crude **6** (1.08 g, 83%) which can be utilised as such for the next step. Alternatively it was purified in this way: it was taken up in dry Et_2O (5 ml) and treated with dicyclohexylamine (1.13 ml, 5.67 mmol) to give at once a white precipitate, which was collected by filtration to give pure **6** as dicyclohexylammonium salt, m.p. 180-182°C; elemental analysis: found C, 64.55; H, 9.40; N, 6.80%; calc. for $C_{22}H_{38}N_2O_5$: C, 64.36; H, 9.33; N, 6.82%.

Treatment of this salt with 0.3M aqueous citric acid and Et_2O, separation of the phases, and evaporation of the organic layer gave pure **6** as a 1:1 mixture of diastereoisomers (689 mg, 53%). I.r. ($CHCl_3$): ν_{max} 3420, 3300, 2970, 2120 (weak), 1715, 1490, 1370, 1160, 1040 cm^{-1}; ^1H n.m.r. ($CDCl_3$-D_2O, 80 MHz.): δ 5.88 (1 H, broad s, N<u>H</u>); 4.75-4.95 (1 H, m, C<u>H</u>-OH); 4.47-4.62 (1 H, m, C<u>H</u>-NH); 2.64 (1/2 H, d, <u>H</u>-C≡C, J 2.1Hz.); 1.44 (9 H, s, CH_3).

2-(Trimethylsilyl)-ethyl chloroacetate (12).- A solution of chloroacetic acid (10g, 105.8 mmol) in dry CH_2Cl_2 (120 ml) was treated with dimethylaminopyridine (517 mg, 4.23 mmol) and with trimethylsilylethanol (7.36 ml, 51.6 mmol). After cooling to 0°C, a solution of dicyclohexylcarbodiimide (22.4 g, 108.4 mmol) in dry CH_2Cl_2 (25 ml) was added dropwise. An abundant precipitation of dicyclohexylurea took place. After stirring for 1h, the suspension was filtered through a celite cake, and the solid was washed with pentane : Et_2O 4:1. The filtrate was concentrated at 20 mmHg and finally distilled at 0.4 mmHg (68-70°C) to give pure **12** as a colourless liquid (9.35 g, 93%). Elemental analysis: found C, 43.20; H, 7.80%; calc. for $C_7H_{15}ClO_2Si$: C, 43.17; H, 7.76%. ^1H n.m.r. ($CDCl_3$, 60 MHz.): δ 4.36 (2 H, AA' part of an AA'XX' system, C<u>H</u>$_2$-O); 4.06 (2 H, s, C<u>H</u>$_2$-Cl); 1.04 (2 H, XX' part of an AA'XX' system, C<u>H</u>$_2$-Si); 0.01 (9 H, s, CH_3-Si).

2-(Trimethylsilyl)-ethyl N-phtaloyl-2-aminooxy-acetate (13).- A solution of **12** (2.57 g, 13.2 mmol) and N-hydroxy-phtalimide (3.23 g, 19.8 mmol) in dry DMF (70 ml) was treated with solid anhydrous K_2CO_3 (2.74 g, 19.8 mmol) and heated at 60-65°C for 3h. Then the solvent was evaporated at 0.5 mmHg (bath temperature below 60°C), the residue suspended in H_2O and filtered. The solid was dissolved in AcOEt, washed with water and

saturated brine and evaporated to dryness to give a slightly yellow solid. Crystallization from Et_2O : *n*-hexane gave pure **13** as a white solid (3.82 g, 90%). M.p. 95-96°C. Elemental analysis: found C, 56.15; H, 6.00; N, 4.30%; calc. for $C_{15}H_{19}NO_5Si$: C, 56.06; H, 5.96; N, 4.36%. I.r. ($CHCl_3$): ν_{max} 2950, 1795, 1735, 1605, 1465, 1370, 1350, 1280, 1180, 1125, 1030 cm^{-1}. ^1H n.m.r. ($CDCl_3$, 80 MHz.): δ 7.60-8.00 (4 H, m, aromatics); 4.80 (2 H, s, $C\underline{H}_2$-C=O); 4.28 (2 H, AA' part of an AA'XX' system, O-$C\underline{H}_2$-CH_2); 1.02 (2 H, XX' part of an AA'XX' system, $C\underline{H}_2$-Si); 0.03 (9 H, s, $C\underline{H}_3Si$).

2-(Trimethylsilyl)-ethyl 2-aminoxyacetate (7).- A solution of **13** (2.76 g, 8.59 mmol) in dry CH_2Cl_2 (30 ml) was cooled to 0°C and treated with hydrazine hydrate (0.835 ml, 17.17 mmol). The temperature was allowed to rise to R.T. and the suspension (a white precipitate formed) stirred for 30 min. The mixture was filtered, washing the precipitate with CH_2Cl_2, and the filtrate was washed with diluted NH_4OH and saturated brine (twice), and finally evaporated to dryness to give **7** as a colourless liquid, pure at t.l.c. and ^1H n.m.r. (1.59 g, 97%). ^1H n.m.r. ($CDCl_3$, 80 MHz.): δ 5.84 (2 H, broad s, $N\underline{H}_2$); 4.23 (2 H, AA' part of an AA'XX' system, O-$C\underline{H}_2$-CH_2); 4.18 (2 H, s, $C\underline{H}_2$-C=O); 0.98 (2 H, XX' part of an AA'XX' system, $C\underline{H}_2$-Si); 0.01 (9 H, s, $C\underline{H}_3$-Si).

***Anti* and *syn* 2-(trimethylsilyl)-ethyl 2-[2-(*t*-butyloxyformamido)-3-hydroxy-pent-4-ynamidoxy]-acetates (5).**- A solution of crude **6** (1.08 g, obtained starting from 1.30 g of **10**, 4.72 mmol) and N-hydroxy-benzotriazole (638 mg, 4.72 mmol) in dry dimethylformamide (13 ml) was treated with dicyclohexylcarbodiimide (1.07 g, 5.19 mmol), and stirred for 1h at room temperature. Abundant precipitation of dicyclohexylurea took place. Then hydroxylamine **7** (900 mg, 4.72 mmol) was added, and the mixture stirred overnight at R.T. The mixture was diluted with AcOEt and dicyclohexylurea filtered off. The filtrate was washed with 5% $NaHCO_3$ and water (thrice), and finally evaporated to dryness. The residue was taken up with little ether and filtered again. The filtrate, after evaporation at reduced pressure, was chromatographed on silica gel (*n*-hexane : AcOEt 1:1) to give pure **5** (1.57 g, 83% from crude **6**, 69% from **10**) as a mixture of diastereoisomers in the ratio 1:1 (determined at ^1H n.m.r. by integration of the acetylenic proton signals). When this reaction was carried out starting from purified **6**, the yield was 90%. Elemental analysis: found C, 50.30; H, 7.80; N, 6.70; calc. for $C_{17}H_{30}N_2O_7Si$: C, 50.73; H, 7.51; N, 6.96%. I.r. ($CHCl_3$): ν_{max} 3300, 3000, 2950, 2930, 1735, 1700, 1490, 1370, 1160, 1095 cm^{-1}. ^1H n.m.r. ($CDCl_3$-D_2O, 80 MHz.): δ 5.57 (1 H, broad d, N$\underline{H}$-Boc, J 8.0 Hz.); 4.70-4.90 (1 H, m, C$\underline{H}$-OH); 4.40-4.70 (1 H, m, C$\underline{H}$-NH-Boc); 4.46 (2 H, s, $C\underline{H}_2$-C=O); 4.28 (2 H, AA' part of an AA'XX' system, O-$C\underline{H}_2$-CH_2); 2.53 (1/2 H, d, $\underline{H}$-C$\equiv$C, J 2.0 Hz.); 2.45 (1/2 H, d, $\underline{H}$-C$\equiv$C, J 2.1 Hz.); 1.44 (9 H, s, $C\underline{H}_3$-C); 1.02 (2 H, XX' part of an AA'XX' system, $C\underline{H}_2$-Si); 0.04 (9 H, s, $C\underline{H}_3$-Si).

***Cis* and *trans* 2-(trimethylsilyl)-ethyl {[3-(*t*-butyloxyformamido)-4-ethynyl-2-oxo-1-azetidinyl]-oxy}-acetates (14).**- To a solution of **5** (1.38 g, 3.428 mmol) and triphenylphosphine (899 mg, 3.428 mmol) in dry THF (35 ml), diethylazodicarboxylate (90% purity) (0.597 ml, 3.428 mmol) was added. The mixture was stirred overnight at room temperature and then the solvent was evaporated to dryness. The crude product was purified by silica gel chromatography (CH_2Cl_2 : Et_2O 95:5) to give pure **14** (1.04 g, 79%) as a slightly yellow oil. Elemental analysis: found C, 52.55; H, 7.40; N, 7.15%; calc. for $C_{17}H_{28}N_2O_6Si$: C, 53.10; H, 7.34; N, 7.28%. I.r. ($CHCl_3$): ν_{max} 3430, 3300, 2960, 2930, 2870, 2250 (weak), 1790, 1720, 1490, 1445, 1380, 1370, 1350, 1150, 1105, 905 cm^{-1}. ^1H n.m.r. ($CDCl_3$, 80 MHz.): δ 5.54 (1/2 H, d, N$\underline{H}$, J 7.0 Hz.); 5.35 (1/2 H, d, N$\underline{H}$, J 9.1 Hz.); 4.50-4.70 (1/2 H, m, C$\underline{H}$); 4.43-4.53 (2H, m, $C\underline{H}_2$C=O); 4.10-4.50 (3/2 H, m, C$\underline{H}$); 4.26 (2H, AA' part of an AA'XX' system, O$C\underline{H}_2$-CH_2); 2.62 (1/2 H, d, $\underline{H}$-C$\equiv$C, J 1.8 Hz.); 2.60 (1/2 H, d, $\underline{H}$-C$\equiv$C, J 1.8 Hz.); 1.43 (9 H, s, $(C\underline{H}_3)_3C$); 1.02 (2 H, XX' part of an AA'XX' system, $C\underline{H}_2$-Si); 0.04 (9 H, s, $C\underline{H}_3$-Si).

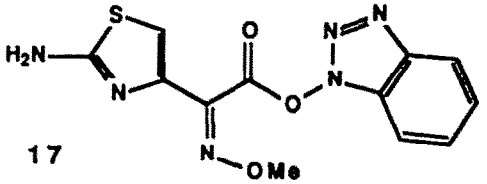
***Cis* and *trans* 2-(trimethylsilyl)-ethyl {[3-(*t*-butyloxyformamido)-4-vinyl-2-oxo-1-azetidinyl]-oxy}-acetates (15a,b).**- A solution of **14** (1.83 g, 4.76 mmol) in EtOH (65 ml) was treated with Pd Lindlar (Janssen) (64 mg) and 2,6-lutidine (0.315 ml, 2.71 mmol) and hydrogenated at room temperature for 5h. After removal of the catalyst, the solvent was evaporated at reduced pressure. The residue was taken up with Et_2O and washed with a pH 4 buffer solution. After evaporation, the residue was chromatographed on silica gel (CH_2Cl_2 :

Et_2O 95:5) to give pure **15a,b** as a 1:1 diastereomeric mixture (1.56 g, 85%). **15a** (R_f 0.28) and **15b** (R_f 0.41) were separated by a preparative t.l.c. eluted with di-*iso*-propylether.

15a : elemental analysis: found C, 53.15; H, 7.95; N, 7.05%; calc. for $C_{17}H_{30}N_2O_6Si$: C, 52.83; H, 7.82; N, 7.25%. I.r. ($CHCl_3$): ν_{max} 3440, 2980, 2960, 1775, 1720, 1600, 1500, 1370, 1250, 1220, 1160, 1050 cm^{-1}. ^1H n.m.r. ($CDCl_3$, 80 MHz.)[15] δ 5.80 (1 H, ddd, C<u>H</u>=CH_2, J 7.9, 13.1 & 17.8 Hz.); 5.47 (1 H, d, CH=C<u>H</u>-H, J 17.8 Hz.); 5.48 (1 H, d, CH=C<u>H</u>-H, J 7.9 Hz.); 4.91 (1 H, d, N<u>H</u>, J 3.1 Hz.); 4.69 (1 H, dd, C<u>H</u>-NH, J 3.1 & 5.4 Hz.); 4.53 & 4.45 (2 H, AB system, CH_2-C=O, J 13.4 Hz.); 4.35-4.50 (1 H, m, C<u>H</u>-N-O); 4.27 (2 H, AA' part of an AA'XX' system, OCH_2-CH_2); 1.42 (9 H, s, $(CH_3)_3$-C); 1.02 (2 H, XX' part of an AA'XX' system, CH_2-Si); 0.04 (9 H, s, $(CH_3)_3$-Si).

15b: elemental analysis: found C, 53.20; H, 7.90; N, 7.10%; calc. for $C_{17}H_{30}N_2O_6Si$: C, 52.83; H, 7.82; N, 7.25%. I.r. ($CHCl_3$): ν_{max} 3440, 2980, 2960, 1775, 1720, 1600, 1500, 1370, 1250, 1220, 1160, 1050 cm^{-1}. ^1H n.m.r. ($CDCl_3$, 80 MHz.)[15] δ 5.98 (1 H, ddd, C<u>H</u>=CH_2, J 6.8, 9.7 & 16.7 Hz.); 5.54 (1 H, dd, CH=C<u>H</u>-H, J 1.6 & 16.7 Hz.); 5.38 (1 H, dd, CH=C<u>H</u>-H, J 1.6 & 9.7 Hz.); 5.20 (1 H, d, N<u>H</u>, J 7.0 Hz.); 4.51 (2 H, s, CH_2-C=O); 4.30-4.45 (1 H, m, C<u>H</u>-N); 4.15-4.30 (1 H, m, C<u>H</u>-N); 4.26 (2 H, AA' part of an AA'XX' system, OCH_2-CH_2); 1.43 (9 H, s, $(CH_3)_3$-C); 1.02 (2 H, XX' part of an AA'XX' system, CH_2-Si); 0.04 (9 H, s, $(CH_3)_3$-Si).

***Cis* and *trans* 2-(trimethylsilyl)-ethyl {[3-(2-(2-amino-4-thiazolyl)-2 (*Z*)-(methoxyimino)-acetamido)-2-oxo-4-vinyl-1-azetidinyl]-oxy}-acetates (16).-** A 1:1 diastereomeric mixture of**15a,b** (400 mg, 1.035 mmol) was dissolved at 0°C in trifluoroacetic acid (4 ml). The temperature was allowed to rise to R.T. in 5 min. and then the solvent was evaporated under reduced pressure (bath temp. 25°C). After stripping at 0.1 mmHg, the residue was taken up in dry acetonitrile (45 ml), cooled to 0°C, and treated with Et_3N (0.290 ml, 2.07 mmol). To this solution 325 mg of benzotriazol-1-yl 2-(2-amino-4-thiazolyl)-2-[(*Z*)-(methoxyimino)]-acetate [(ATMO)-OBHT] 17 (1.056 mmol) were added. The mixture was diluted with 45 ml of dry acetonitrile and stirred at R.T. for 20h. The solvent was evaporated and the residue taken up with chloroform and water. After separation of the phases and evaporation of the organic layer, the resulting residue was purified by preparative t.l.c. (silica gel, AcOEt : *n*-hexane 8:2) to give pure **16** as a 1:1 mixture of diastereoisomers (122 mg, 25%). I.r. ($CHCl_3$): ν_{max} 2960, 2930, 2860, 2230, 1780, 1750, 1675, 1630, 1610, 1520, 1425, 1250, 1215, 1180, 1045 cm^{-1}. ^1H n.m.r. ($CDCl_3$, 80 MHz.): δ 8.12 (1/2 H, d, N<u>H</u>, J 6.4 Hz.); 7.77 (1/2 H, d, N<u>H</u>, J 8.2 Hz.); 6.76 (1/2 H, s, C<u>H</u>-S); 6.74 (1/2 H, s, C<u>H</u>-S); 5.50-6.20 (3 H, m, C<u>H</u>=CH_2); 4.20-4.90 (2 H, m, C<u>H</u>-N); 4.56 & 4.40 (1 H, AB system, CH_2-C=O, J 12.5 Hz.); 4.50 (1 H, s, CH_2-C=O); 4.27 (2 H, AA' part of an AA'XX' system, O-CH_2-CH_2); 3.92 (3/2 H, s, OCH_3); 3.91 (3/2 H, s, OCH_3); 1.07 (2 H, XX' part of an AA'XX' system, CH_2-Si); 0.02 (9 H, s, CH_3-Si).



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***Cis* and *trans* potassium {[3-(2-(2-amino-4-thiazolyl)-2-(*Z*)-(methoxyimino)-acetamido)-2-oxo-4-vinyl-1-azetidinyl]-oxy}-acetates (3).-** To a solution of *n*-Bu_4NF (44 mg, 0.140 mmol) in dry THF (2 ml), a solution of **16** (60 mg, 0.127 mmol) in dry THF (3 ml) was added. After stirring for 2 h at R.T., the solvent was evaporated, the residue taken up with water (15 ml) and treated with 12 g of wet Dowex 50 W-X8 (K^+ form). After stirring for 2h, the resin was removed by filtration, and the aqueous solution freeze-dried to give **3** as a yellow solid (50 mg, 72%).

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15. Interpreted also with the aid of double resonance experiments.