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Rational Design, Synthesis, and Reactivity of Lactendiynes, a New Class of Cyclic Enediynes Ortho-Fused with the β-Lactam Ring

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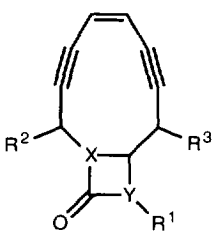
Abstract: A series of 10-membered cyclic enediynes *trans*-fused with N-protected and N-unprotected β-lactams have been stereoselectively prepared. These compounds were found to be stable toward Bergman cycloaromatization, which, on the other hand, takes place readily when the azetidinone ring is opened. © 1997 Elsevier Science Ltd. All rights reserved.

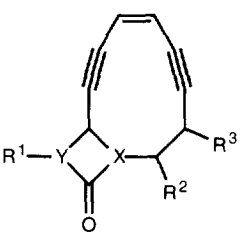
Natural enediyne antibiotics (e.g. calicheamicin, dynemicin) are among the most powerful antitumoral compounds known to date.[2] The most interesting feature of these compounds is that they are natural prodrugs: their biological activity is indeed "triggered" by a particular transformation, which unleashes the reactivity of the enediyne moiety leading, upon Bergman cycloaromatization, to highly reactive aromatic diradicals. However, the difficulty in obtaining the natural enediynes by fermentation, their structural complexity, which makes total synthesis of no practical value, as well as the toxicity of some members of this class, makes desirable the development of new synthetic analogues.[3] The ideal candidates should fulfil these requirements: **a**) They should be as simple as possible in order to facilitate total synthesis. **b**) In order to act as prodrugs, they must be equipped, like the natural compounds, with a triggering device. **c**) The triggering event should possibly take place where and when desired, in order to increase the drug selectivity. **d**) They should possess a handle for appending substructures designed for increasing cell selectivity or DNA-binding properties.

Toward this goal we have now decided to explore a new family of synthetic enediynes which we hope can eventually satisfy all the above quoted requirements. These compounds, called by us "Lactendiynes", are characterised by a 10 membered enediyne ring *ortho*-fused with a β-lactam. As shown in Scheme 1, there are 9 general types of such compounds, depending on the type of fusion, as well as on the relative stereochemistry

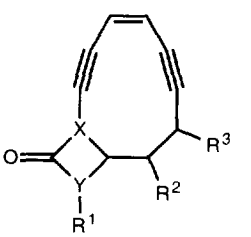
Scheme 1



1 : X = C, Y = N
2 : X = N, Y = C



3 : X = C, Y = N
4 : X = N, Y = C



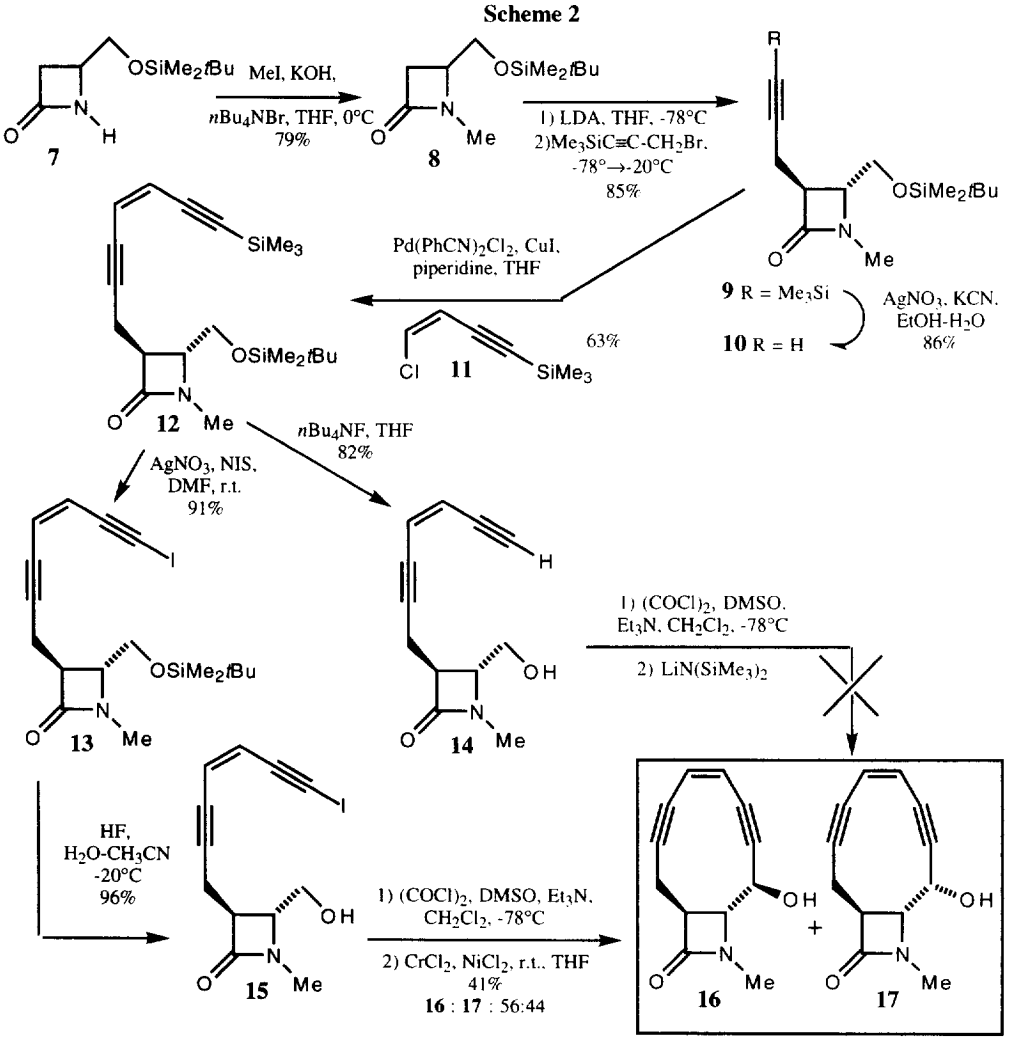
5 : X = C, Y = N
6 : X = N, Y = C

at bridgehead atoms (only in the case of **1**, **3**, **5**).

The rationale behind this project lies in the hypothesis that the β-lactam, at least in some of these classes of compounds, could prevent, for reasons of steric strain, the cycloaromatization of the enediyne, which is known to take place at physiological temperatures in the case of the simple monocyclic enediynic 10-membered rings.[4] On the other hand opening of the β-lactam would play the role of triggering event, removing the steric constraints against Bergman cycloaromatization. The *in vivo* enzymatic opening of activated β-lactams is a well known process and, upon suitable modulation of azetidinone activation, it could be in principle possible to develop selective prodrugs. Moreover R^1, R^2 and R^3 groups can be viewed as handles for appending useful substructures.

We now report the synthesis and properties of the first "Lactendiynes", belonging to the general formula **1**, and characterised by a *trans* ring fusion.[5,6] The *trans* fusion was expected to highly disfavour the

Scheme 2



cycloaromatization process by posing severe steric constraints in the transition state. This expectation was corroborated either by molecular mechanics calculations, performed using the simplified approach proposed by Maier,[3c,9] and by analogy with the work of Nicolaou, who has previously demonstrated the stability of a 10-membered enediyne ring *trans*-fused with a dioxolanone.[4f]

In order to have a suitable handle for appending appropriate carriers, we focused on compounds where R^3= OH. Moreover, for simplicity we initially programmed the preparation of N-methylated targets (R^1= Me). Finally, since we had no idea of the influence of absolute configuration on the biological activity, we chose to synthesise racemic products, though utilising synthetic pathways easily adaptable to enantioselective preparations.

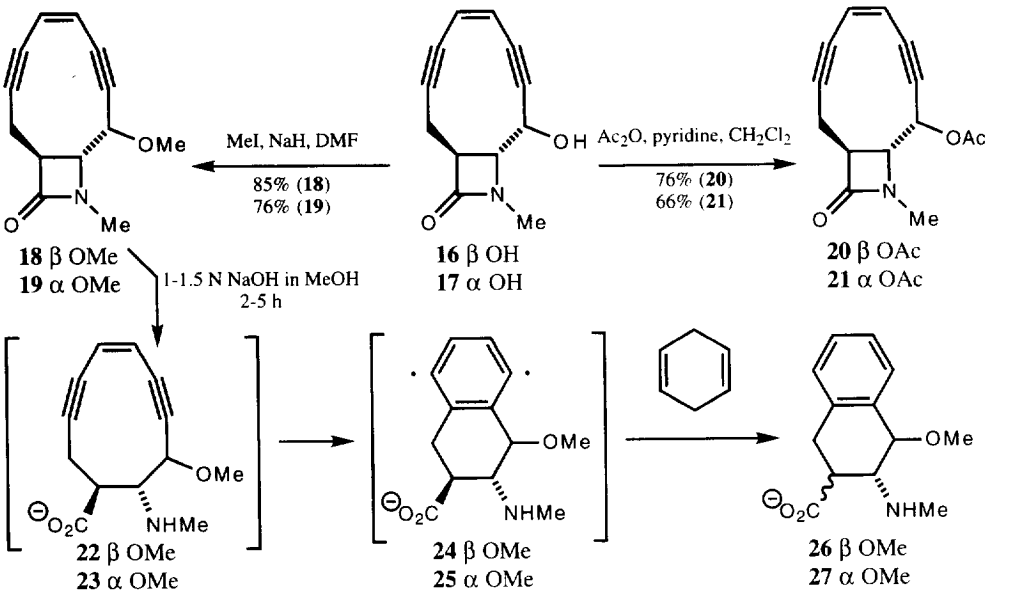
Our synthetic approach involved the generation of the 10-membered enediynic ring by cyclization of an alkynyl aldehyde, which is the most widely used approach to these systems. In order to obtain the required *trans* configuration of the target, we planned to introduce the side-chain a C-3 by alkylation of a 4-substituted azetidinone enolate. These reactions are known to afford usually *trans* adducts with good to excellent diastereoselection.[10] As starting material we employed known azetidinone **7** (Scheme 2), which can be prepared in seven high yielding steps from aspartic acid.[11] Although **7** was employed in this work as the racemate, the availability of both enantiomers of aspartic acid makes this strategy suitable for the obtainment of optically active lactendiynes.

Compound **7** was first protected by a modification of the phase-transfer method first described by Reuschling.[12] While the use of powdered KOH led to variable yields, probably due to competitive β-lactam hydrolysis, good yields were finally obtained by employing partially triturated pellets. Treatment of the resulting derivative **8** with lithium di(*iso*-propyl)amide followed by 3-(trimethylsilyl)-1-bromopropyne furnished the alkyne **9** as a single diastereoisomer. It is worth noting that the analogous reaction with propargyl bromide failed to afford the desired adduct **10**. The latter was instead smoothly obtained from **9** by selective deblocking of the trimethylsilyl group with $AgNO_3$-KCN.[13]

The acyclic enediyne was then synthesised through a palladium catalysed Stephens-Castro[14] coupling with chloroenyne **11**.[15] For this transformation, the conditions usually employed ($Pd(PPh_3)_4$ as catalyst, n-$BuNH_2$ as base) afforded **12** in only moderate yields. The reaction was indeed sluggish and substantial amounts of the dimer of **10** (most likely due to traces of oxygen entering the reaction vessel) formed. On the other hand, the rate of reaction, and the yield, have been greatly improved by employing $Pd(PhCN)_2Cl_2$ as catalyst and excess piperidine as base.[16]

$LiN(SiMe_3)_2$ mediated[17] cyclization of the alkynyl aldehyde derived from Swern oxidation of alcohol **14**,[18] in turn obtained by fluoride induced deblocking of **12**, was unsuccessful. Thus we turned to the Nozaki[19] coupling of the iodoalkynyl aldehyde derived from **15**. The latter was prepared by one pot substitution of the trimethylsilyl group of **12** with iodine, by the action of $AgNO_3$ and N-iodosuccinimide,[20,21] followed by HF-H_2O-CH_3CN mediated deblocking of the hydroxyl. Swern oxidation followed by treatment with $CrCl_2$ in the presence of catalytic $NiCl_2$[19] furnished in satisfactory yield the lactendiynes **16** and **17** in 56:44 diastereomeric ratio. The relative configuration was easily established by the values of coupling constants between the C*H*-OH and the C*H*-N hydrogens (9.2 Hz. for **16** and about 2 Hz. for **17**), which are consistent with the calculated (MM) dihedral angles of respectively 178° and 55°. For the success of this reaction it is important to use an aldehyde freshly chromatographed through silica gel and

Scheme 3



azeotropically dried in order to avoid the presence of the hydrated form. To our satisfaction, these bicyclic compounds turned out to be quite stable either in solution or in the dry state. They could even be examined at GC-MS at temperatures higher than 200 °C!

16 and **17** can be easily separated by silica gel chromatography and have been converted into the O-methyl and O-acetyl derivatives **18-21** (Scheme 3). Treatment of **18** or **19** with 1,4-dicyclohexadiene at 100°C for several hours resulted in complete recovery of starting material indicating that. as expected, these compounds are completely locked against Bergman cycloaromatization

Once established the stability of **16-21**, it remained to be assessed whether opening of the β-lactam could lead to cycloaromatization and, in this case, at which rate. Although it was previously known that cyclodec-3-en-1,5-diyne undergoes cycloaromatization at 37°C with a $t_{1/2}$ of 18h,[4b] the effect of the substituents in compounds like **22-23** was not obvious. Molecular mechanics calculations, performed using the simplified approach proposed by Maier,[3c,9,22] predicted a remarkable increase of reactivity toward cycloaromatizationof **22** and **23** with respect to the parent compound. This prediction is in line with the calculations by Snyder, that shown a decrease by about 1.1 Kcal/mol of activation energy for cyloaromatization by placing two *trans* methyl groups at position 8 and 9 of cyclodec-3-en-1,5-diyne.[23]

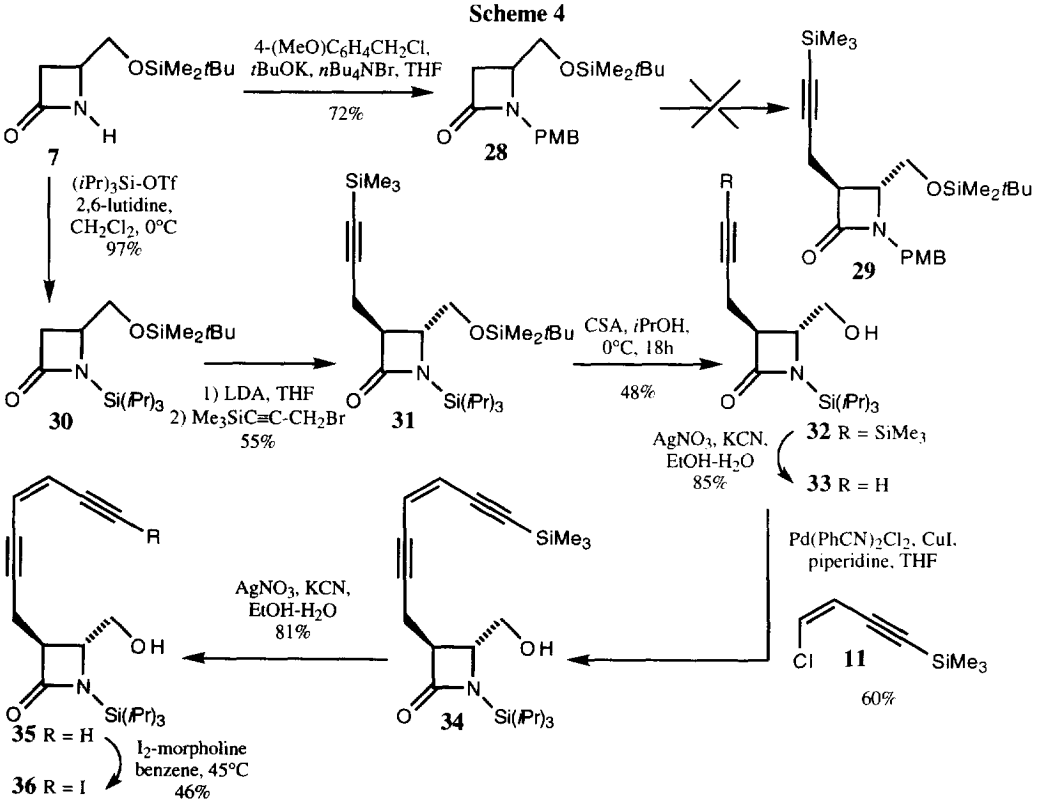
In order to demonstrate this assumption, **18** and **19** were separately treated with 1-1.5 N NaOH in methanol at 50°C in the presence of 1,4-cyclohexadiene as hydrogen radical donor. The reactions were followed by ^{1}H n.m.r. The azetidinone opening was complete in 2h with 1N NaOH for the *pseudo*-equatorial isomer **18**; the hydrolysis was slower for the *pseudo*-axial epimer **19** and it took 5h with 1.5N NaOH. In both cases the ^{1}H n.m.r. showed the gradual disappearance of the signals of substrates, with the appearance of signals attributed to **26** and **27**. No signals of the monocyclic enediynes **22-23** was observed, indicating that cycloaromatization took place readily after azetidinone opening. Both **26-27**, which have been isolated by reverse-phase chromatography, formed as a mixture of two diastereoisomers (different for the two cases).

most likely because of epimerization at the carbon α to the carboxylate group. This epimerization takes place only after β-lactam opening, since no *cis* β-lactam was seen at n.m.r. Moreover, the relative amount of the two epimers varies with time, reaching a final value of 1:1 in the case of **26** and 3:1 in the case of **27** (starting from an initial 1:3).

Now, although these results clearly demonstrate the potentiality of this class of lactendiynes as enediynic prodrugs, there was still a problem to be overcome before attempting to verify the achievement of the triggering event under biological conditions. This is related with the reaction conditions required for the hydrolysis of compounds **18-19**, which are too harsh for *in vivo* applications. A possible solution to this problem would be to increase the reactivity of the β-lactam by replacing the methyl group at the nitrogen atom with activating substituents. However, since the removal of the methyl from **18** and **19** is very difficult, we decided to modify the synthesis, using a protection for the nitrogen of the β-lactam, that could be removed at the final stage, and replaced with suitable substituents. It is worth noting that the nitrogen atom needs to be protected anyway in the course of the synthesis, because the free NH is incompatible with both the enolate propargylation and the final Nozaki cyclization.

The ideal protecting group should be easily introduced, it should not activate the β-lactam toward opening, should be stable during the synthesis, be removable in the final step under conditions that do not affect the enediyne and the β-lactam, and be replaceable with other substituents. Only few groups responded in principles to these requirements. At first we chose the *p*-methoxybenzyl (PMB), a protection orthogonal to

Scheme 4



the dimethyl-*t*-butylsilyl, which can be deblocked under neutral oxidative conditions. However, while introduction of the PMB group on the azetidinone nitrogen of **7** took place in good yield (Scheme 4), we did not succeed in performing the subsequent enolate propargylation: with both LDA or $LiN(SiMe_3)_2$ as bases, no reaction occurred, presumably because of preferential deprotonation at the benzyl group.[24]

Thus we turned our attention to silicon-based protecting groups. In order to differentiate between the nitrogen and alcoholic protections, we prepared the N-(tri-*iso*-propylsilyl) derivative **30**, which was then propargylated to give **31**, again as a single diastereoisomer. Unfortunately we never succeeded in bringing this reaction to completion. Moreover the overall recovery of product and substrate was never quantitative, because of decomposition side-reactions which were favoured by higher temperature. Under the best conditions the yield from unrecovered starting material was 55%. Selective deblocking of the dimethyl-*t*-butylsilyl group was best carried out at this stage, using a methodology previously developed by us.[25] Also in this case the yield was not completely satisfactory. Castro-Stephens coupling of terminal alkyne with chloroenyne **11** was slower than in the N-methylated series. Increasing the amount of palladium catalyst improved the rate, but at the expense of considerable quantities of substrate which were consumed for the reduction of the palladium (II) to palladium(0). We finally circumvented this problem by using a "sacrificial" less precious alkyne for the preliminary palladium reduction (see experimental), raising the yield to a good 60%. After two-step[21] conversion into the iodide **36**, the stage was set for the final Nozaki coupling. To our surprise, however, the aldehyde obtained by Swern oxidation of **36** failed to cyclise to the expected lactendiyne.

Because of this unexpected result, and of the somewhat unsatisfactory yields of some of the synthetic steps, we decided to abandon this route and shift to a different strategy. This time we decided to employ, as protecting group for nitrogen, the dimethyl-*t*-butylsilyl. To this aim the use of **7** as starting material was no longer appropriate, and so we utilised the known 4-benzyloxycarbonyl-2-azetidinone **37**,[26] which was obtained in three steps from racemic aspartic acid. Other advantages of using this starting material are the lower number of steps for its preparation, as well as the absence of expensive reagents and chromatographic separation in the synthetic route.[27]

As shown in Scheme 5, two alternative ways for preparing the key intermediate **43** were followed. In the first one, the ester group was first reduced to the alcohol **40**, which was protected as the ethoxyethyl ether, and propargylated via the lithium enolate with complete diastereoselection. The main by-product of this propargylation reaction was the *bis*(propargyl) derivative, which was obtained, along with unreacted starting material, even using a stoichiometric amount of base. Thus it seems that an acid-base reaction between **42** and the enolate of **41** takes place in competition with propargylation of the latter. Deblocking of the temporary protection led smoothly to the alcohol **43**.

On the other hand, the previous works by Baldwin[26] and Hanessian[28] indicated the possibility to avoid the temporary protection of the alcoholic function, by performing directly the propargylation at the level of carboxylic acid **38**. This reaction gave a mixture of the desired *trans* propargylated acid, its desilylated derivative, and starting material. We never succeeded in bringing the reaction to completion. The formation of desilylated products was already observed by Hanessian,[28] and tentatively attributed to the attack by enolate or by bromide ion on silicon. Another possibility is however represented by intramolecular attack of

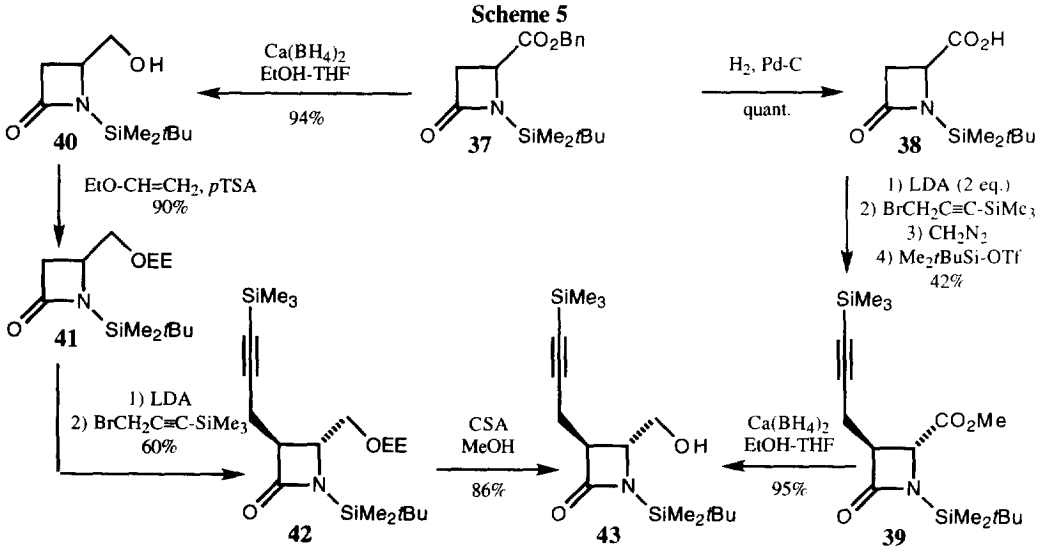
carboxylate anion which would form a labile silyl ester. Anyway the mixture of these acids was directly converted into the corresponding methyl esters, followed by resilylation to give **39** in moderate yield.

Finally, reduction gave in good yields the alcohol **43**. The reduction of **37** to **40** and of **39** to **43** merits further comment. In the case of **39**, the use of $NaBH_4$ in methanol[29] gave only moderate yield of **43** (54%). Using EtOH-THF[30] as solvent the outcome was even worse, leading to considerable amount of a by-product arising from shift of silyl group from nitrogen to the hydroxyl oxygen. After various attempts we found that excellent yields could be obtained with $Ca(BH_4)_2$ in EtOH-THF. This reagent, because of its non-basic nature, did not effect any N→O shift, nor seemed to attack the β-lactam. Thus we use it also for the transformation of **37** to **40**, and recommend it as the reagent of choice for reduction of other β-lactam esters. In conclusion the two routes to **43** turned out to be both efficient, although we prefer for large scale preparations the one depicted on the left, for the better overall yields.

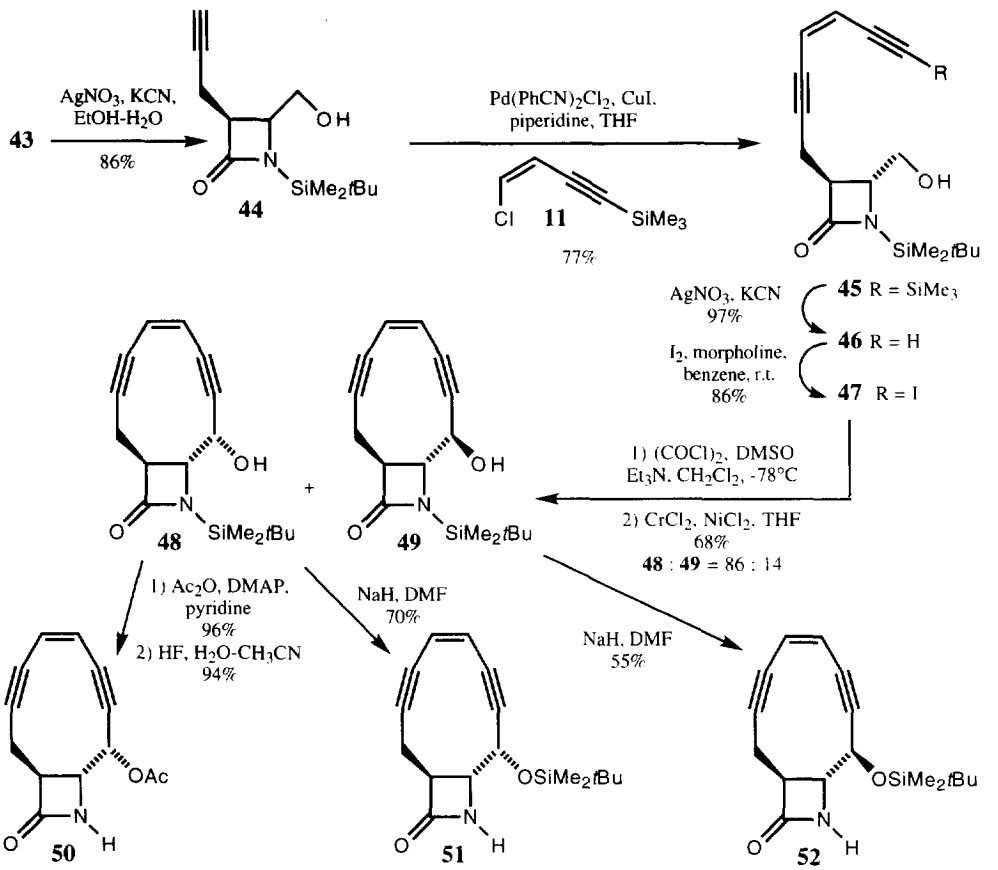
After removal of the trimethylsilyl group (Scheme 6), **43** was then transformed into the acyclic enediyne **45** in good yield under the modified Castro-Stephens conditions above described. Conversion of trimethylsilyl into iodide was best achieved by a two-step sequence.[31] It is worth noting that in the second step it is important to add the substrate to the preformed iodine-morpholine complex, since sequential addition of morpholine and iodine to the substrate led also, in some instances to products deriving from addition of iodine to the triple bond. Swern oxidation followed by Nozaki coupling proceeded with an excellent yield for this type of macrocyclization. The reaction turned out also to be remarkably stereoselective, affording preferentially the *pseudo*-axial isomer with a diastereomeric ratio of 86 : 14. Interestingly, when the reaction was carried out on the N-methylated derivative (see Scheme 2), the *pseudo*-equatorial epimer was prevailing.

The overall yield of lactendiynes **48** and **49** from 37 was a remarkable 16.4%, and this sequence has been easily scaled up to multigram quantities. These compounds turned out to be completely stable, as their N-methylated counterparts. At this point we had still to demonstrate the possibility to remove the TBDMS protecting group. We then converted major product **48** into **50** and **51**, both characterised by an unprotected azetidinone nitrogen. The first one was obtained by acetylation followed by desilylation with HF. On the

Scheme 5



Scheme 6



contrary, the use of nBu$_4$NF for the protecting group removal gave only decomposition products. Compound **51** was prepared by an interesting silicon shift promoted by NaH. Remarkably, though this reaction was expected to be reversible, the conversion of **48** to **51** was complete, indicating an equilibrium highly favouring the silyl ether. The same reaction was also carried out, with identical outcome, on the *pseudo*-equatorial isomer. Studies on suitable activation toward ring opening of these N-unsubstituted β-lactams are in progress.

In conclusion, we have demonstrated that the "lactendiynes" of type **1**, characterised by a *trans* ring fusion at position 3,4 of the azetidinone, are promising candidates for the development of enediynic prodrug. They are indeed chemically stable, can be prepared in an acceptable number of steps, and give rise to highly reactive intermediates upon β-lactam opening. Implementation of these properties on biological targets is in progress.

We wish to thank C.N.R., and M.U.R.S.T. for financial assistance, and Miss Roberta La Rocca for her precious collaboration to this project.

EXPERIMENTAL

N.m.r. spectra were taken, unless otherwise indicated, in $CDCl_3$, at 200 MHz (^1H), and at 50 or 20 MHz (^{13}C). Chemical shifts are reported in ppm (δ scale), coupling constants are reported in Hertz. Peak assignment in ^1H n.m.r. spectra, was also made with the aid of double resonance experiments. In ABX systems, the proton A is considered downfield and B upfield. Peak assignment in ^{13}C spectra was made with the aid of DEPT or off-resonance experiments. GC-MS were carried out on a HP-5971A instrument, using an HP-1 column (12 m long, 0.2 mm wide), electron impact at 70 eV, and a mass temperature of about 167°C. Unless otherwise indicated analyses were performed with a constant He flow of 0.9 ml/min, starting at 100°C for 2 min. and then raising the temperature by 20°C/min. I.R. spectra were measured with a Perkin-Elmer 881 instrument as $CHCl_3$ solutions, unless otherwise stated. TLC analyses were carried out on silica gel plates, which were developed by these detection methods: **A**) U.V.; **B**) dipping into a solution of $(NH_4)_4MoO_4$•4 H_2O (21g) and $Ce(SO_4)_2$•4 H_2O (1g) in H_2SO_4 (31 cc) and H_2O (469 cc) and warming; **C**) dipping into 2% aqueous $KMnO_4$ and warming; **D**) spraying with 48% HBr, warming, then dipping into a ninhydrin solution (900 mg in 300 ml *n*BuOH + 9 ml AcOH), warming. R_f were measured after an elution of 7-9 cm. Chromatographies were carried out on 220-400 mesh silica gel using the "flash" methodology. Petroleum ether (40-60°C) is abbreviated as PE. In extractive work-up, aqueous solutions were always reextracted thrice with the appropriate organic solvent. Organic extracts were dried over Na_2SO_4 and filtered, before evaporation of the solvent under reduced pressure. All reactions employing dry solvents were carried out under a nitrogen (or argon, where indicated) atmosphere. Racemic **7** was prepared as described for the optically active compound.[11] The purity of all compounds was established by TLC, ^1H n.m.r., GC-MS and, in some cases, elemental analysis.

***(R,S)* 4-[((*tert*-Butyldimethylsilyl)oxy)methyl]-1-methyl-2-azetidinone 8.** A solution of **7** (2.957 g, 13.73 mmol) in dry THF (45 ml) was cooled to -20°C, and treated with *n*Bu_4NBr (443 mg, 1.374 mmol), MeI (1.28 ml, 20.56 mmol), and KOH (pellets, 85% pure) (freshly grounded in a mortar) (1.45 mg, 22.0 mmol). After 2h the temperature was allowed to rise to -10°C and the mixture stirred overnight. The temperature was raised to 0°C and the reaction, when nearly complete by TLC (1-4 h), was quenched with saturated NH_4Cl (50 ml), and extracted with AcOEt to give, after chromatography (AcOEt / PE 7:3) pure **8** as an oil (2.360 g, 75%), and recovered **7** (148 mg, 5.0 %). Yield from non recovered s.m. = 79%. R_f 0.31 (PE / AcOEt 1:1, det. C). Anal.: found C, 57.3; H, 10.0; N, 6.15. $C_{11}H_{23}NO_2Si$ requires C, 57.60; H, 10.11; N, 6.11%. GC-MS: R_t 5.68 min. M/z 172 (M- 57, 6.8), 131 (10.8), 130 (100, Me-N=CH-CH_2O=$SiMe_2^+$), 115 (5.7), 73 (6.8), 59 (5.9). I.r.: ν_{max} 2950, 2930, 2860, 1740, 1465, 1390, 1190, 1135, 1100, 830 cm^{-1}. ^1H n.m.r.: δ 3.84 [1 H, dd, C*H*-OSi, J 3.0 & 10.5]; 3.73-3.54 [2 H, m, C*H*OSi & C*H*-N]; 2.90 [1 H, dd, C*H*H-C=O, J 4.7 & 14.6]; 2.84 [3 H, s, CH_3N]; 2.62 [1 H, dd, C*H*H-C=O, J 1.4 & 14.6]; 0.90 [9 H, s, $(CH_3)_3C$]; 0.07 [6 H, s, $(CH_3)_2Si$].

***(3R*,4S*)* 4-[((*tert*-Butyldimethylsilyl)oxy)methyl]-1-methyl-3-[(3-trimethylsilyl)prop-2-yn-1-yl]-2-azetidinone 9.** A solution of **8** (2.166 g, 9.44 mmol) in dry THF (8 ml) was added, at -78°C, to a 0.4 M solution of lithium diisopropylamide in THF/hexane (28.3 ml, 11.33 mmol). After 10 min, 3-bromo-1-trimethylsilyl-1-propyne (2.67 ml, 18.9 mmol) was added, and the temperature allowed to rise to 0°C during 4 h. Quenching with saturated NH_4Cl, followed by extraction with Et_2O, and chromatography (PE / AcOEt 7:3 → 3:7) gave pure **9** as an oil (2.08 g, 65%) and recovered **8** (513 mg, 24%). Yield from non recovered s.m. = 85%. R_f 0.61 (PE / AcOEt 7:3, det. C). Anal.: found C, 60.35; H, 9.9; N, 4.0. $C_{17}H_{33}NO_2Si_2$ requires C, 60.12; H, 9.79; N, 4.12%. GC-MS: R_t 8.06 min. M/z 339 (M^+, 0.14), 324 (9.7), 282 (11.5), 172 (6.1), 147 (5.6), 131 (10.4), 130 (100, Me-N=CH-CH_2O=$SiMe_2^+$), 73 (6.3). I.r.: ν_{max} 2950, 2930, 2860, 2180, 1740, 1465, 1420, 1390, 1330, 1190, 1110, 830 cm^{-1}. ^1H n.m.r.: δ 3.91 & 3.71 [2 H, AB part of an ABX syst., CH_2O, J_{AB} 11.0, J_{AX} 2.8, J_{BX} 6.0]; 3.52 [1 H, dt, C*H*N, J_d 6.0, J_t 2.7]; 3.05-2.94 [1 H, m, C*H*-C=O]; 2.85 [3 H, s, CH_3N]; 2.64 & 2.53 [2 H, AB part of an ABX syst., CH_2-C≡C, J_{AB} 17.3; J_{AX} 4.4; J_{BX} 9.2]; 0.90 [9 H, s, $(CH_3)_3C$]; 0.14 [9 H, s, $(CH_3)_3Si$]; 0.08 [6 H, s, $(CH_3)_2Si$].

(*3R*,4S) 4-[((*tert*-Butyldimethylsilyl)oxy)methyl]-1-methyl-3-[prop-2-yn-1-yl]-2-azetidinone 10.** A solution of **9** (1.92 g, 5.65 mmol) in 96% EtOH (55 ml) was cooled to 0°C, and treated with a 2M aqueous solution of $AgNO_3$ (5.7 ml, 11.4 mmol). When the reaction was judged complete by TLC (usually 5h), it was quenched with a solution of KCN (2.5 g, 38 mmol) in H_2O (13 ml). The mixture was stirred for 15 min. at 0°C and then poured into H_2O and extracted with Et_2O. The organic phase was washed with 50 ml of sat. NaCl and 1M KH_2PO_4 1:1, and evaporated to give, after chromatography (PE / AcOEt 1:1), pure **10** as an oil (1.32 g, 87%). R_f 0.49 (PE / AcOEt 7:3, det. C). GC-MS: R_t 6.64 min. M/z 266 (M-1, 0.04), 210 (4.5), 172 (3.9), 158 (1.6), 131 (10.0), 130 (100, Me-N=CH-CH_2O=$SiMe_2^+$), 75 (15.3), 73 (7.5). I.r.: ν_{max} 3310, 2950, 2930, 2860, 1742, 1463, 1425, 1390, 1328, 1250, 115, 830 cm^{-1}. ^1H n.m.r.: δ 3.89 & 3.73 [2 H, AB part of an ABX syst., CH_2O, J_{AB} 11.0; J_{AX} 3.1; J_{BX} 5.7]; 3.51 [1 H, ddd, C*H*-N, J 2.1, 3.2, 5.6]; 3.09-2.95 [1 H, m, C*H*-C=O]; 2.85 [3H, s, CH_3N]; 2.61 & 2.53 [2 H, AB part of an ABXY syst., CH_2-C≡C, J_{AB} 17.1; J_{AX} 4.3, J_{BX} 8.8, J_{AY}=J_{BY} 2.6]; 2.01 [1 H, t, C≡C*H*, J 2.7]; 0.90 [9 H, s, (CH_3)$_3$C]; 0.08 [6 H, s, (CH_3)$_2$Si]. ^{13}C n.m.r. (50 MHz.): δ 167.86 [*C*=O]; 80.23 [*C*≡CH]; 69.96 [C≡*C*H]; 62.65 [CH_2O]; 59.49 & 49.62 [*C*H]; 27.37 [N-*C*H_3]; 25.75 [C(*C*H_3)$_3$]; 18.13 [*C*(CH_3)$_3$]; 17.18 [*C*H_2-C≡]; -5.50 [(*C*H_3)$_2$Si].

(*3R*,4S)(*Z*) 4-[((*tert*-Butyldimethylsilyl)oxy)methyl]-1-methyl-3-[7-(trimethylsilyl)hept-4-en-2,6-diyn-1-yl]-2-azetidinone 12.** CuI (85 mg, 0.45 mmol) and $Pd(PhCN)_2Cl_2$ (172 mg, 0.45 mmol) were suspended, under an argon atmosphere, in dry THF (10 ml). Piperidine (8.9 ml, 89.7 mmol) was added, followed by a solution of **10** (1.20 g, 4.49 mmol) and 1-chloro-4-(trimethylsilyl)but-1-en-3-yne[15] (1.42 g, 1.525 ml, 8.95 mmol) in THF (7 ml). The initial brown mixture became yellow-green after piperidine addition, and back to yellow after few minutes from substrates addition. The solution was stirred for 2h at r.t., poured into saturated NH_4Cl / H_2O 1:1, and extracted with Et_2O. The crude product was purified by two chromatographies (Et_2O / PE 1:1 → 4:6) to give pure **12** as a yellow oil (1.10 g, 63%). The main by-product was the dimer of **10** [R_f 0.60 (Et_2O, det. C)]. R_f 0.55 (PE / Et_2O 4:6, det. A). Anal.: found C, 64.3; H, 8.8; N, 3.4. $C_{21}H_{35}NO_2Si_2$ requires: C, 64.73; H, 9.05; N, 3.59%. GC-MS: R_t 9.83 min. M/z: 389 (M^+, 6.8), 374 (3.5), 332 (3.0), 230 (4.6), 172 (3.6); 147 (4.5); 131 (12.2), 130 (100, Me-N=CH-CH_2O=$SiMe_2^+$), 75 (5.3), 73 (22.3), 59 (5.5). I.r.: ν_{max} 2950, 2930, 2860, 2220, 2140, 1740, 1600, 1463, 1420, 1390, 1328, 1190, 1115, 1010, 835 cm^{-1}. ^1H n.m.r.: δ 5.80 [2 H, s, C*H*=C*H*]; 3.90 & 3.73 [2 H, AB part of an ABX syst., CH_2O, J_{AB} 11.0, J_{AX} 3.1, J_{BX} 5.6]; 3.54 [1 H, ddd, C*H*N, J 2.3, 3.1, 5.6]; 3.11-3.00 [1 H, m, C*H*-C=O]; 2.85 [3 H, s, CH_3N]; 2.94-2.54 [2 H, m, CH_2C≡C]; 0.90 [9 H, s, (CH_3)$_3$C]; 0.22 [9 H, s, (CH_3)$_3$Si]; 0.07 [6 H, s, (CH_3)$_2$Si].

(*3R*,4S)(*Z*) 4-[((*tert*-Butyldimethylsilyl)oxy)methyl]-3-[7-iodohept-4-en-2,6-diyn-1-yl]-1-methyl-2-azetidinone 13.** A solution of **12** (585 mg, 1.50 mmol) in dry DMF (20 ml) was treated, at r.t., in the dark, with N-iodosuccinimide (507 mg, 2.25 mmol) and silver nitrate (25 mg, 0.15 mmol). The reaction was followed by TLC and when complete poured into a saturated NH_4Cl solution containing few drops of conc. NH_4OH. Extraction with AcOEt followed by chromatography gave pure **13** as an oil (605 mg, 91%). R_f 0.41 (Et_2O / PE 4:6, det. A). I.r.: ν_{max} 3005, 2950, 2930, 2860, 1740, 1600, 1465, 1420, 1390, 1325, 1190, 1115, 830 cm^{-1}. ^1H n.m.r.: δ 5.90 [1 H, d, I-C≡C-C*H*, J 10.9]; 5.77 [1 H, dt, CH_2C≡C-C*H*, J_t 2.1, J_d 10.9]; 3.94 & 3.77 [2 H, AB part of an ABX syst., CH_2O, J_{AB} 11.1; J_{AX} 3.0, J_{BX} 5.3]; 3.59 [1 H, dt, C*H*N, J_t 2.6, J_d 4.4]; 3.16-3.00 [1 H, m, C*H*-C=O]; 2.86 [3 H, s, CH_3N]; 2.95-2.64 [2 H, m, CH_2-C≡C]; 0.90 [9 H, s, (CH_3)$_3$C]; 0.08 [6 H, s, (CH_3)$_2$Si]. ^{13}C (50 MHz.): δ 168.05 [*C*=O]; 122.11 & 119.01 [*C*H=*C*H]; 94.72, 91.83, 79.23 [*C*≡*C*]; 62.44 [CH_2O]; 59.49 & 49.56 [*C*H]; 27.36 [*C*H_3N]; 25.80 [(*C*H_3)$_3$C]; 18.50 [*C*H_2C≡C]; 18.16 [*C*(CH_3)$_3$]; 13.59 [C≡*C*-I]; -5.44 [(*C*H_3)$_2$Si].

(*3R*,4S)(*Z*) 4-[Hydroxymethyl]-3-[7-iodohept-4-en-2,6-diyn-1-yl]-1-methyl-2-azetidinone 15.** A solution of **13** (579 mg, 1.31 mmol) in CH_3CN (20 ml) was treated at -20°C with 40% aqueous HF (1 ml) and stirred overnight. After 3 hours at 0°C the reaction was quenched with 50% of 2.5% $NaHCO_3$, extracted with AcOEt and chromatographed (AcOEt → AcOEt / MeOH 95:5) to give pure **15** as an oil (412 mg, 96%). R_f 0.40 (AcOEt / MeOH 95:5, det. A). GC-MS: R_t 5.22. M/z: 202 (M-127, 8.9); 176 (11.5), 172 (7.5); 164 (11.2), 158 (9.2), 146 (8.8), 144 (17.2), 131 (8.0), 128 (18.2), 127 (14.5), 119 (6.8), 118 (15.2), 117 (21.4),

116 (18.9), 115 (100), 103 (16.2), 102 (25.8), 91 (20.0), 89 (22.6), 77 (17.1), 76 (14.8), 63 (23.6), 42 (53.8), 39 (10.7). I.r.: ν_{max} 3420 (broad), 3040, 2990, 2960, 2870, 1745, 1605, 1420, 1390, 1250, 1190, 1115 cm^{-1}. ^1H n.m.r.: δ 5.91 [1 H, d, I-C≡C-C*H*, J 11.0]; 5.77 [1 H, dt, CH_2-C≡C-C*H*, J_t 2.1, J_d 10.9]; 4.08-3.94 [1 H, m, C*H*HOH]; 3.92-3.75 [1 H, m, C*H*HOH]; 3.65 [1 H, ddd, C*H*N, J 2.1, 3.3, 4.5]; 3.21 [1 H, broad t, C*H*-C=O, J 6.5]; 2.90 [3 H, s, CH_3N]; 2.87 & 2.77 [2 H, AB part of an ABXY syst., CH_2C≡C, J_{AB} 17.6, J_{AX} 4.8, J_{BX} 8.8, J_{AY}=J_{BY} 2.1]; ^{13}C n.m.r. (50 MHz.): δ 168.20 [*C*=O]; 122.02 & 119.09 [*C*H=*C*H]; 94.52, 91.94, 79.42 [*C*≡*C*]; 61.84 [CH_2O]; 59.57 & 49.82 [CH]; 27.44 [CH_3N]; 25.80 [$(CH_3)_3$C]; 18.50 [CH_2C≡C]; 18.16 [$C(CH_3)_3$]; 13.59 [C≡*C*-I]; -5.44 [$(CH_3)_2$Si].

***(1R*,9S*,10S*)* and *(1R*,9R*,10S*)* (*Z*) 9-Hydroxy-11-methyl-11-azabicyclo[8.2.0]dodec-5-en-3,7-diyn-12-ones 16 and 17.** A solution of $(COCl)_2$ (2.0 ml of a 2.4 M CH_2Cl_2 solution, 4.70 mmol) in dry CH_2Cl_2 (3 ml) was cooled to -78°C, and treated with a 1.8 M solution of dimethyl sulfoxide in CH_2Cl_2 (3.9 ml, 7.05 mmol). After 10 min, a solution of **15** (387 mg, 1.18 mmol) in CH_2Cl_2 (20 ml) was slowly added. After 10 min. the mixture was treated with Et_3N (1.5 ml, 10.58 mmol). After 3h and 30 min the reaction was complete. It was quenched with 50 ml of 5% aqueous $(NH_4)H_2PO_4$, and extracted with Et_2O. The crude aldehyde (R_f 0.51 (AcOEt / MeOH 95:5, det. A) was chromatographed (AcOEt) to give the pure product, which was further essicated by three times azeotroping with dry toluene. It was then taken up with dry THF (10 ml), treated with freshly activated 4Å powdered mol. sieves, and stirred under argon for 30 min. Meanwhile, $CrCl_2$ (1.01 g, 8.1 mmol), $NiCl_2$ (24 mg, 0.18 mmol) and powdered 4Å mol. sieves were suspended under argon in THF (20 ml). The aldehyde solution was slowly added to this suspension during 40 min at r.t. After stirring for 3 h, the reaction was quenched with H_2O, and extracted with Et_2O to give, after chromatography (AcOEt / PE 8:2), pure **16** (54 mg, 23%) and **17** (43 mg, 18%) as white solids.

16: R_f 0.63 (AcOEt, det. A). GC-MS: R_t 7.70 min. M/z 201 (M^+, 23.5), 200 (22.4), 172 (43.8), 156 (17.3), 144 (64.4), 134 (21.7), 115 (88.7), 89 (61.3), 84 (36.9), 77 (26.7), 70 (29.1), 63 (35.1), 62 (21.3), 51 (20.3), 50 (19.7), 42 (100), 39 (24.1). ^1H n.m.r. (CD_3COCD_3 / D_2O): δ 6.03 & 5.98 [2 H, AB syst., C*H*=C*H*, J 9.9]; 4.67 [1 H, d, C*H*OH, J 9.2]; 3.73 [1 H, dd, C*H*-N, J 2.3 & 9.2]; 3.26 [1 H, bt, C*H*-C=O, J 7.4]; 2.91 [3 H, s, CH_3N]; 2.76 & 2.73 [2 H, AB part of an ABX syst., CH_2-C≡C, J_{AB} 17.2, other J not det.]. ^{13}C n.m.r. (50 MHz.)(CD_3COCD_3): δ 167.64 [*C*=O]; 124.92 & 123.41 [*C*H=*C*H]; 101.43, 99.98, 86.70, 84.51 [*C*≡*C*]; 67.50, 66.36, 55.62 [CH]; 28.98 [CH_3N]; 19.58 [CH_2-C≡].

17: R_f 0.53 (AcOEt, det. A). GC-MS: R_t 7.93 min. M/z 201 (M^+, 35.8), 200 (44.6), 172 (62.2), 156 (19.8), 144 (93.7), 134 (22.5), 116 (25.3), 115 (100), 103 (19.6), 89 (64.4), 84 (38.5), 77 (25.3), 70 (31.8), 63 (37.1), 62 (15.4), 51 (30.1), 50 (19.7), 42 (99.5), 39 (24.1). ^1H n.m.r. ($CDCl_3$): δ 5.97 & 5.90 [2 H, AB syst., C*H*=C*H*, J 9.7]; 4.82 [1 H, broad s, C*H*OH]; 3.75-3.73 [2 H, m, C*H*-N and C*H*-C=O]; 2.85 [3 H, s, CH_3N]; 2.98-2.85 [1 H, m, C*H*H-C≡], 2.62 [1 H, dd, C*H*H-C≡, J 12.4 & 17.9]. ^{13}C n.m.r. (50 MHz.)(CD_3COCD_3): δ 168.19 [*C*=O]; 126.37 & 122.03 [*C*H=*C*H]; 100.64, 96.71, 86.98, 83.76 [*C*≡*C*]; 64.31, 58.96, 51.47 [CH]; 26.95 [CH_3N]; 19.25 [CH_2-C≡].

***(1R*,9S*,10S*)*(*Z*) 9-Methoxy-11-methyl-11-azabicyclo[8.2.0]dodec-5-en-3,7-diyn-12-one 18.** A solution of **16** (37 mg, 0.184 mmol) in dry dimethylformamide (1 ml) was treated with CH_3I (36 µl, 0.54 mmol) and 60% NaH in mineral oil (12 mg, 0.27 mmol). After 1 h the reacton was quenched with saurated NH_4Cl, extracted with Et_2O, and purified by preparative TLC to give pure **18** as an oil (33 mg, 85%). R_f 0.54 (AcOEt / PE 6:4, det. A). GC-MS: R_t 7.38 min. M/z: 215 (M^+, 29), 200 (76), 184 (14.6), 172 (21.9), 156 (43), 144 (25.5), 143 (32.5), 129 (21.2), 115 (66), 105 (100), 89 (22.9), 77 (25.6), 63 (39), 51 (26.3), 42 (82). I.r.: ν_{max} 3000, 2925, 2830, 1745, 1425, 1390, 1320, 1192, 1105. ^1H n.m.r.: δ 5.91 [2H, s, C*H*=C*H*]; 4.25 [1 H, d, C*H*-OMe, J 9.1]; 3.73 [1H, dd, C*H*-N, J 2.3 & 9.1]; 3.46 [3 H, s, CH_3O]; 3.24-3.38 [1 H, m, C*H*-C=O]; 2.92 [3H, s, CH_3N]; 2.88 [1H, dd, C*H*H-C≡, J 17.9 & 3.9]; 2.66 [1 H, dd, C*H*H-C≡, J 17.9 & 12.2]. ^{13}C n.m.r. (50 MHz.): δ 167.45 [*C*=O]; 124.57 & 122.20 [*C*H=*C*H]; 100.00, 95.18, 88.30, 83.93 [*C*≡*C*]; 64.19, 63.76, 56.87, 54.93 [*C*H and CH_3O]; 28.90 [CH_3N]; 19.50 [CH_2-C≡].

***(1R*,9R*,10S*)*(*Z*) 9-Methoxy-11-methyl-11-azabicyclo[8.2.0]dodec-5-en-3,7-diyn-12-one 19.** It was prepared in 76% yield from **17** as above described for **18**. R_f 0.40 (AcOEt / PE 6:4, det. A). GC-MS: R_t

7.65 min. M/z: 215 (M^+, 42), 200 (100), 184 (15.7), 172 (24), 156 (45), 144 (31), 143 (32), 129 (22.5), 128 (19.4), 115 (67), 105 (94), 89 (24.6), 77 (28.1), 63 (40), 51 (24.1), 42 (83). I.r.: ν_{max} 3000, 2930, 2830, 2320, 2300, 1745, 1425, 1390, 1360, 1320, 1300, 1255, 1195, 1120, 1068, 1010. ^{1}H n.m.r.: δ 5.96 & 5.89 [2H, AB syst., C*H*=C*H*, J_{AB} 9.7]; 4.37 [1 H, t, C*H*-OMe, J 1.8]; 3.64-3.80 [2 H, m, C*H*-N and C*H*-C=O]; 3.46 [3 H, s, CH_3O]; 2.89 [1H, ddd, C*H*H-C≡, J 17.9, 3.8, 1.7]; 2.81 [3H, s, CH_3N]; 2.59 [1 H, dd, C*H*H-C≡, J 17.9 & 13.1]. ^{13}C n.m.r. (50 MHz.): δ 167.82 [*C*=O]; 126.26 & 122.02 [*C*H=*C*H]; 100.79, 95.66, 87.28, 83.58 [*C*≡*C*]; 67.72, 63.25, 57.20, 52.19 [*C*H and CH_3O]; 26.60 [CH_3N]; 19.36 [CH_2-C≡].

***(1R*,9S*,10S*)(Z)* 9-Acetoxy-11-methyl-11-azabicyclo[8.2.0]dodec-5-en-3,7-diyn-12-one 20.** A solution of **16** (22 mg, 0.109 mmol) in dry CH_2Cl_2 (1.5 ml) was treated with 0.25 ml of pyridine and 100 µl of Ac_2O (1.06 mmol). After stirring for 4h, the solution was poured into 15 ml of $(NH_4)H_2PO_4$ containing few drops of 1N HCl (so that the resulting pH was 4), extracted with Et_2O and chromatographed (AcOEt / PE 1:1) to give pure **20** as an oil (20.2 mg, 76%). R_f 0.59 (AcOEt / PE 7:3, det. A). GC-MS: R_t 8.25 min. M/z: 243 (M^+, 29.1), 201 (31.3), 200 (24.5), 183 (16.8), 173 (14.8), 172 (32.0), 156 (13.0); 144 (55.0), 126 (100), 118 (24.9), 115 (54.1), 98 (34.7), 89 (13.9), 63 (16.1), 43 (88.8), 42 (52.5). ^{1}H n.m.r.: δ 5.91 [2 H, s, C*H*=C*H*]; 5.48 [1 H, d, C*H*-OAc, J 9.5]; 3.90 [1 H, dd, C*H*-N, J 2.4 & 9.5]; 3.43 [1 H, broad d, C*H*-C=O, J 12.1]; 2.92 [1 H, dd, C*H*H-C≡, J 3.8 and 18.0]; 2.87 [3 H, s, CH_3N]; 2.69 [1 H, dd, C*H*H-C≡, J 12.1 & 18.0]; 2.15 [3H, s, CH_3-C=O]. ^{13}C (50 MHz.): δ 169.37 & 167.07 [*C*=O]; 125.22, 122.00 [*C*H=*C*H]; 99.80, 93.47, 88.21, 84.02 [*C*≡*C*]; 68.15, 62.80, 55.48 [*C*H]; 28.64 [CH_3N]; 20.81 [CH_3C=O]; 19.50 [CH_2-C≡].

***(1R*,9R*,10S*)(Z)* 9-Acetoxy-11-methyl-11-azabicyclo[8.2.0]dodec-5-en-3,7-diyn-12-one 21.** It was prepared from **17** in 66% yield by the same procedure employed for the synthesis of **20**. R_f 0.71 (AcOEt / PE 7:3, det. A). GC-MS: R_t 7.93 min. M/z: 243 (M^+, 28.7), 201 (25.7), 200 (20.8), 183 (13.2), 173 (12.0), 172 (26.4), 156 (11.1); 144 (22.0), 126 (73.6), 118 (20.4), 116 (15.1), 115 (52.6), 98 (30.5), 89 (12.1), 63 (16.4), 43 (100), 42 (62.9). ^{1}H n.m.r.: δ 6.01 & 5.90 [2 H, broad AB syst., C*H*=C*H*, J 10.0]; 5.49 [1 H, t, C*H*-OAc, J 1.8]; 3.81 [1 H, t, C*H*-N, J 2.2]; 3.77-3.64 [1 H, m, C*H*-C=O]; 2.91 [1 H, ddd, C*H*H-C≡, J 1.8, 3.9, 18.0]; 2.78 [3 H, s, CH_3N]; 2.64 [1 H, dd, C*H*H-C≡, J 12.6 & 18.0]; 2.14 [3H, s, CH_3-C=O].

Opening and Cycloaromatization of Compounds 18,19. A solution of **18** (9 mg, 0.042 mmol) in CD_3OD (0.56 ml) was placed in an n.m.r. tube, treated with 1,4-cyclohexadiene (100 µl) and 40% NaOD in D_2O (100 µl, 0.76 mmol). This solution was suddenly warmed to 50°C and the reaction followed by ^{1}H n.m.r. at intervals of 10 min. After 2h the reaction was complete. The solution, after cooling, was treated with solid NH_4Cl (21 mg, 0.4 mmol) and 1N aqueous HCl (0.7 ml), and evaporated to dryness. The residue was examined at ^{1}H n.m.r. and further purified by chromatography on RP-18 ($H_2O \rightarrow H_2O$ / MeOH → MeOH) to give the 1:1 epimeric mixture of **26** (5.1 mg). ^{1}H n.m.r. (CD_3OD / NaOD)[32]: δ 7.25-7.35 [1 H, m, aromatics]; 7.10-7.25 [3 H, m, aromatics]; 4.41 [1/2 H, d, C*H*-OMe, J 5.8]; 4.23 [1/2 H, d, C*H*-OMe, J 2.6]; 3.49 & 3.23 [3 H, 2s, CH_3O]; 2.80-3.40 [4 H, m, CH_2Ar, C*H*COO, C*H*N]; 2.49 & 2.42 [3 H, 2s, CH_3N]. **27** was obtained in a similar way as a 3:1 epimeric ratio, but using 150 µl of NaOD and with a reaction time of 5h. ^{1}H n.m.r. (CD_3OD / NaOD)[32]: δ 7.05-7.30 [4 H, m, aromatics]; 4.43 [1/4 H, d, C*H*-OMe, J 4.0]; 4.36 [3/4 H, broad s, C*H*-OMe]; 3.38 & 3.33 [3H, 2s, CH_3O]; 2.70-3.60 [4 H, m, CH_2Ar, C*H*COO, C*H*N]; 2.49 & 2.44 [3 H, 2s, CH_3N].

***(R,S)* 4-[((*t*-Butyldimethylsilyl)oxy)methyl]-1-(4-methoxybenzyl)-2-azetidinone 28.** A solution of **7** (100 mg, 0.464 mmol) in dry THF (2 ml) was cooled to -10°C and treated with nBu_4NI (17 mg, 0.046 mmol), *p*-methoxybenzyl chloride (95 µl, 0.701 mmol), and KO*t*Bu (70 mg, 0.624 mmol). The mixture was stirred for 16h at -10°C, 5h at 0°C, and 2h at r.t., quenched with saturated NH_4Cl, and extracted with Et_2O. The organic phase was washed with saturated NaCl, evaporated and chromatographed (PE / AcOEt 6:4) to give pure **28** as an oil (113 mg, 72.5%). R_f 0.57 (PE / AcOEt 1:1, det. A, B, C). GC-MS: R_t 9.83 min. M/z: 335 (M^+, 0.1), 307 (1.4), 278 (2.1), 236 (11.9), 162 (6.0), 121 (100), 73 (6.7), 59 (4.1), 41 (4.8). ^{1}H n.m.r.: δ 7.20 [2 H, d, aromatics, J 8.7]; 6.86 [2 H, d, aromatics, J 8.7]; 4.62 [1 H, d, C*H*H-Ar, J 14.9]; 4.07 [1 H, d, C*H*H-Ar, J

14.9]; 3.80 [3 H, s, C*H*$_3$O]; 3.83-3.50 [3 H, m, C*H*$_2$O and C*H*N]; 2.88 & 2.68 [2 H, AB part of an ABX syst., C*H*$_2$-C=O, J_{AB} 14.2, J_{AX} 4.9, J_{BX} 2.1]; 0.89 [9 H, s, (C*H*$_3$)$_3$C]; 0.04 [6 H, s, (C*H*$_3$)$_2$Si].

(*R,S*) 4-[((*t*-Butyldimethylsilyl)oxy)methyl]-1-(tri-*iso*-propylsilyl)-2-azetidinone 30. A solution of **7** (2.365 g, 10.98 mmol) in dry CH_2Cl_2 (50 ml), was cooled to 0°C, and treated with 2,6-lutidine (3.20 ml, 27.5 mmol) and tri-*iso*-propylsilyl triflate (3.8 ml, 14.1 mmol). The solution was stirred at 0°C for 1h and 30 min, poured into saturated NH_4Cl, extracted with Et_2O, and chromatographed (PE / Et_2O 9:1 → 7:3) to give pure **30** as an oil (3.957 g, 97%). R_f 0.35 (PE / Et_2O 75:25, det. C). Anal.: found: C, 61.8; H, 11.35, N, 3.6; $C_{19}H_{41}NO_2Si_2$ requires: C, 61.39; H, 11.12; N, 3.77%. GC-MS: R_t 8.93 min. M/z: 356 (M-15, 2.3), 328 (M-43, 69.7), 314 (M-57, 7.4), 286 (27.5), 272 (16.7), 203 (59.5), 175 (41.5), 161 (40.7), 133(44.3), 115(46.2), 100(30.8), 73(100), 59(59.8), 41(23.7). ^{1}H n.m.r.: δ 3.86-3.58 [3 H, m, C*H*$_2$O, C*H*N]; 3.09 [1 H, dd, C*H*-C=O, J 15.2, 5.2]; 2.78 [1 H, dd, C*H*-C=O, J 2.3, 15.2]; 1.37 [3H, heptuplet, C*H*(CH$_3$)$_2$, J 7.3]; 1.12 [9 H, d, (C*H*)$_3$-C(CH$_3$), J 7.3]; 1.10 [9 H, d, (C*H*$_3$)-C(CH$_3$)]; 0.90 [9 H, s, (C*H*$_3$)$_3$C]; 0.06 [6 H, s, (C*H*$_3$)$_2$Si].

(*3R*,4S) 4-[((*t*-Butyldimethylsilyl)oxy)methyl]-3-[3-(trimethylsilyl)prop-2-yn-1yl]-1-(tri-*iso*-propylsilyl)-2-azetidinone 31**. A solution of **30** (431 mg, 1.16 mmol) in dry THF (4 ml) was added, at -50°C, to a 0.4 M solution of lithium diisopropylamide in THF/hexane (5.8 ml, 2.32 mmol). The temperature was allowed to rise to -20°C during 30 min. Then the solution was cooled again to -50°C, and treated with 3-bromo-1-trimethylsilyl-1-propyne (0.330 ml, 2.33 mmol). The temperature allowed to rise to 0°C during 3h and 20 min. Quenching with saturated NH_4Cl, followed by extraction with Et_2O, and chromatography (PE / Et_2O 9:1 containing 1% of Et_3N) gave pure **31** as an oil (258 mg, 46%) and recovered **30** (69 mg, 16%). Yield from non recovered s.m. = 55%. R_f 0.44 (PE / Et_2O 85:15, det. C). GC-MS: R_t 10.54 min.. M/z: 438 (M-43, 30.1), 424 (M-57, 13.0), 308 (2.9), 286 (3.1), 272 (7.4), 225 (6.7), 203 (27.7), 175 (16.9), 161 (16.0), 147 (30.6), 133 (44.3), 100 (13.7), 73 (100), 59 (40.6). I.r.: ν_{max} 2955, 2900, 2875, 2180, 1740, 1468, 1345, 1245, 1075, 1020, 840 cm^{-1}. ^{1}H n.m.r.: 3.78 [2 H, d, C*H*$_2$OSi, J 4.5]; 3.64 [1 H, dt, C*H*-N, J_d 2.6, J_t 4.5]; 3.09 [1 H, ddd, C*H*-C=O, J 2.6, 5.4, 7.7]; 2.67 & 2.60 [2 H, AB part of an ABX syst., C*H*$_2$C≡, J_{AB} 17.3, J_{AX} 8.2, J_{BX} 4.6]; 1.47-1.26 [3 H, m, C*H*(CH$_3$)$_2$]; 1.14 [9 H, d, (C*H*$_3$)-C(CH$_3$), J 7.3]; 1.11 [9 H, d, (C*H*$_3$)-C(CH$_3$), J 7.3]; 0.91 [9 H, s, (C*H*$_3$)$_3$C]; 0.13 [9 H, s, (C*H*$_3$)$_3$Si]; 0.07 [6 H, s, (C*H*$_3$)$_2$Si].

(*3R*,4S) 4-Hydroxymethyl-3-[3-(trimethylsilyl)prop-2-yn-1yl]-1-(tri-*iso*-propylsilyl)-2-azetidinone 32**. A solution of **31** (1.825 g, 3.79 mmol) in dry *iso*-propyl alcohol (50 ml) was treated, under nitrogen, with 4Å powdered molecular sieves (140 mg). After stirring for 15 min., the mixture was cooled to 0°C, treated with 5.80 g of camphorsulfonic acid (25 mmol), and stirred at 0°C for 18h. Quenching with saturated aqueous $NaHCO_3$ (100 ml), extraction with Et_2O (2 times) and AcOEt (1 time) gave, after chromatography (PE / Et_2O 7:3 → 3:7) pure **32** as a solid (592 mg, 42.5%), and recovered **31** (212 mg, 11.6%). Yield from non recovered s.m. = 48%. P.f. 108.6-108.9°C. R_f 0.53 (PE / Et_2O 3:7, det. C). Anal.: found C, 62.2; H, 10.3; N, 3.7. $C_{19}H_{37}NO_2Si_2$ requires C, 62.07; H, 10.14, N, 3.81%. GC-MS: R_t 9.60 min. M/z 352 (M-15, 5.9), 324 (M-43, 66.0), 308 (7.3), 306 (7.2), 282 (3.4), 280 (3.6), 269 (2.5), 242 (3.6), 241 (7.1), 234 (14.1), 199 (16.7), 156 (73.4), 133 (18.5), 131 (24.4), 128 (26.6), 103 (62.1), 100 (38.7), 75 (100), 73 (82.5), 61 (37.7), 59 (36.3). I.r.: ν_{max} 3630, 3005, 2950, 2900, 2870, 2180, 1740, 1465, 1390, 1365, 1300, 1250, 1177, 1157, 1107, 1075, 1020, 930, 885, 840 cm^{-1}. ^{1}H n.m.r.: δ 3.95-3.63 [3 H, m, C*H*$_2$OH and C*H*N]; 3.18 [1 H, ddd, C*H*-C=O, J 2.4, 5.1, 7.4]; 2.72 & 2.60 [2 H, AB part of an ABX syst., C*H*$_2$-C≡, J_{AB} 17.3, J_{AX} 4.7, J_{BX} 8.6]; 1.71 [1 H, broad t, O*H* J 4.0]; 1.46-1.24 [3 H, m, C*H*(CH$_3$)$_2$]; 1.15 [9 H, d, (C*H*$_3$)C(CH$_3$), J 7.3]; 1.11 [9 H, d, (C*H*$_3$)C(CH$_3$), J 7.3]; 0.14 [9 H, s, (C*H*$_3$)$_3$Si]. ^{13}C n.m.r. (50 MHz.): δ 173.87 [*C*=O], 103.16, 86.91 [*C*≡*C*]; 64.58 [*C*H$_2$OH]; 56.30, 52.61 [*C*H]; 19.17 [*C*H$_2$C≡]; 18.23 & 18.13 [(*C*H$_3$)$_2$Si]; 11.77 [*C*H(CH$_3$)$_2$]; -0.01 [(*C*H$_3$)$_3$Si].

(*3R*,4S) 4-Hydroxymethyl-3-[prop-2-yn-1yl]-1-(tri-*iso*-propylsilyl)-2-azetidinone 33**. It was prepared from **32** in 85% yield by the same procedure employed for **10**. R_f 0.42 (PE / Et_2O 3:7, det. C). GC-MS: R_t 8.44 min. M/z: 252 (M-43, 100), 234 (4.4), 210 (36.9), 199 (9.7), 170 (6.3), 156 (91.4), 131 (55.0), 128 (35.9), 103 (87.6), 100(45.5), 86 (18.1), 77 (34.0), 75 (53.5), 61 (19.9). ^{1}H n.m.r.: δ 3.96-3.64 [3 H, m, C*H*$_2$O & C*H*N]; 3.22 [1 H, ddd, C*H*-C=O, J 2.3, 5.4, 7.5]; 2.66 & 2.59 [2 H, AB part of an ABXY syst.,

$CH_2C\equiv$, J_{AB} 17.3, J_{AX} 4.5, J_{BX} 8.1, $J_{AY}=J_{BY}$ 2.7]; 2.03 [1 H, t, C≡C*H*, J 2.7]. 1.45-1.20 [3 H, m, $CH(CH_3)_2$]; 1.14 [9 H, d, $(CH)_3C(CH_3)$, J 7.1]; 1.11 [9 H, d, $(CH_3)C(CH_3)$ J 7.1].

(*3R*,4S)(*Z*) 4-Hydroxymethyl-3-[7-(trimethylsilyl)hept-4-en-2,6-diyn-1-yl]-1-(tri-*iso*-propylsilyl)-2-azetidinone 34**. $(PhCN)_2PdCl_2$ (64 mg, 0.168 mmol) and CuI (16 mg, 0.084 mmol) were suspended, under an argon atmosphere, in dry piperidine (1.66 ml, 16.8 mmol) and treated with trimethylsilylacetylene (95 µl, 0.67 mmol). After 10 min, chloroenyne **11**[15] (71 µl, 66 mg, 0.42 mmol) was added, and the resulting solution stirred at room temp. for 30 min. A solution of **33** (250 mg, 0.84 mmol) and chloroenyne **11** (408 µl, 380 mg, 2.39 mmol) in dry THF (5 ml) was then added. The mixture was stirred under Ar for 4h, and then poured into saturated NH_4Cl (20 ml), diluted with H_2O (20 ml), and extracted with Et_2O to give, after chromatography, pure **34** as a reddish oil (212 mg, 60%). R_f 0.39 (PE / Et_2O 6:4, det. A,C). GC-MS: not feasible.[33] I.r.: ν_{max} 3630, 2950, 2900, 2870, 2250, 2220, 2150, 1740, 1460, 1430, 1390, 1365, 1328, 1300, 1255, 1200, 1180, 1155, 1090, 1072, 1020, 840 cm^{-1}. ^1H n.m.r.: δ 5.79 [2 H, s, C*H*=C*H*]; 3.96-3.64 [3 H, m, CH_2O and C*H*N]; 3.25 [1 H, ddd, C*H*-C=O, J 2.2, 5.0, 8.1]; 2.91 & 2.78 [2 H, AB part of an ABXY syst., CH_2-C≡C, J_{AB} 17.7, J_{AX} 4.5, J_{BX} 8.8, $J_{AY} \approx J_{BY}$ 1.4]; 1.42-1.24 [3 H, m, $CH(CH_3)_2$]; 1.13 [9 H, d, $(CH_3)C(CH_3)$, J 7.1]; 1.11 [9 H, d, $(CH_3)C(CH_3)$, J 7.1]; 0.22 [9 H, s, $(CH_3)_3Si$]. ^{13}C (50 MHz.): δ 173.91 [*C*=O]; 120.52 & 119.33 [*C*H=*C*H]; 102.56, 102.18, 94.73, 79.76 [*C*≡*C*]; 64.42 [CH_2OH]; 56.49, 52.41 [*C*H]; 19.25 [CH_2-C≡]; 18.18 & 18.04 [$(CH_3)_2C$]; 11.81 [*C*H$(CH_3)_2$]; -0.10 [$(CH_3)_3$].

(*3R*,4S)(*Z*) 4-Hydroxymethyl-3-(hept-4-en-2,6-diyn-1-yl)-1-(tri-*iso*-propylsilyl)-2-azetidinone 35**. It was prepared in 81% yield from **34**, following the same procedure employed for **10**. This time, however, the reaction with $AgNO_3$ was carried out for 3h at -15°C. R_f 0.43 (Et_2O / PE 7:3, det. A), 0.51 (CH_2Cl_2 / toluene / Et_2O 1:1:1). GC-MS: not feasible.[33] I.r.: ν_{max} 3630, 3305, 2950, 2880, 2240, 2220, 1750, 1725, 1455, 1428, 1325, 1300, 1265, 1200, 1180, 1160, 1075, 1025 cm^{-1}. ^1H n.m.r.: δ 5.85 [1 H, dt, C*H*=CH, J 11.3, 2.0]; 5.76 [1 H, dd, C*H*=CH, J 11.3, 2.1]; 3.96-3.64 [3 H, m, CH_2OH and C*H*N]; 3.32 [1 H, d, C≡C*H*, J 2.1]; 3.24 [1 H, ddd, C*H*-C=O, J 2.1, 5.1, 7.8]; 2.89 & 2.79 [2 H, AB part of an ABXY syst., CH_2-C≡, J_{AB} 17.6, J_{AX} 4.5, J_{BX} 8.4, $J_{AY}=J_{BY}$ 2.0]; 1.46-1.20 [3 H, m, $CH(CH_3)_2$]; 1.12 [9 H, d, $(CH_3)C(CH_3)$, J 7.0]; 1.10 [9 H, d, $(CH_3)C(CH_3)$, J 7.0]. ^{13}C n.m.r. (50 MHz.): δ 174.06 [*C*=O]; 121.67& 118.12 [*C*H=*C*H]; 94.84, 80.90 & 79.40 [*C*≡*C*]; 84.26 [C≡*C*H]; 64.35 [CH_2O]; 56.41& 52.10 [*C*H]; 19.17 [$CH_2C\equiv C$]; 18.15 & 18.02 [$(CH_3)_2C$]; 11.77 [*C*H$(CH_3)_2$].

(*3R*,4S)(*Z*) 4-Hydroxymethyl-3-(7-iodohept-4-en-2,6-diyn-1-yl)-1-(tri-*iso*-propylsilyl)-2-azetidinone 36**. A solution of **35** (94 mg, 0.272 mmol) in dry benzene (5 ml) was warmed to 45°C, and treated sequentially with morpholine (213 µl, 2.448 mmol) and iodine (207 mg, 0.816 mmol). The dark brown mixture was stirred for 3h at 45°C, and quenched with 5% $(NH_4)H_2PO_4$ (20 ml). The pH was adjusted to 3 with 1N HCl, and the mixture extracted with Et_2O. The organic layer was washed with aqueous $NaHSO_3$, evaporated, and chromatographed with PE / Et_2O 3:7 to give pure **36** as an oil (59.5 mg, 46.5%). R_f 0.43 (Et_2O / PE 7:3, det. A), 0.55 (CH_2Cl_2 / toluene / Et_2O 1:1:1). ^1H n.m.r.: δ 5.90 [1 H, d, C*H*=CH, J 10.8]; 5.75 [1 H, dt, C*H*=CH, J_t 2.1, J_d 10.8]; 4.00-3.64 [3 H, m, CH_2OH, C*H*N]; 3.27 [1 H, ddd, C*H*-C=O, J 2.4, 4.9, 8.3]; 2.92 & 2.79 [2 H, AB part of an ABXY syst., CH_2-C≡, J_{AB} 17.5, J_{AX} 4.5, J_{BX} 8.6, $J_{AY}=J_{BY}$ 2.1]; 1.47-1.22 [3 H, m, $CH(CH_3)_2$]; 1.14 & 1.11 [2 x 9 H, 2s, $(CH_3)_2CH$, J not determinable].

(*2R*,3S) Methyl 1-(*t*-Butyldimethylsilyl)-4-oxo-3-[3-(trimethylsilyl)prop-2-yn-1-yl]azetidin-2-carboxylate 39.** A solution of acid **38**[26] (3.299 g, 14.38 mmol) in dry THF (15 ml) was cooled to -20°C and treated, by slow dropping, with a 0.5 M solution of lithium di-*iso*-propylamide in THF-*n*-hexane (63.26 ml, 31.63 mmol). The temperature was allowed to rise to 0°C during 15 min. The solution was then treated with 3-bromo-1-(trimethylsilyl)propyne (3.05 ml, 21.57 mmol) and stirred at 0°C for 3h and 30 min. After quenching with 60 ml of saturated NH_4Cl, most THF was evaporated under reduced pressure. The aqueous phase was adjusted to pH 2 with 1N HCl, and extracted with Et_2O (2 x 70 ml) and AcOEt (2 x 50 ml). Evaporation afforded a crude mixture (5.46 g), which was taken up in CH_2Cl_2(50 ml), cooled to 0°C, and slowly treated with an approximately 0.45 M solution of CH_2N_2 in Et_2O. When effeverscence ceased (after

30 ml of solution), 10 ml more were added. After 15 min. the reaction was quenched with glacial AcOH (1.2 ml), poured into 5% $NaHCO_3$, and extracted with AcOEt. The organic phase was washed with saturated NaCl, and evaporated to dryness. The crude product was taken up in dry CH_2Cl_2 (16 ml), cooled to 0°C, and treated with 2,6-lutidine (990 µl, 8.5 mmol) and *t*-butyldimethylsilyl triflate (990 µl, 4.3 mmol). After stirring for 4 h at 0°C, the reaction was quenched with saturated NH_4Cl, and extracted with AcOEt. The organic phase was washed with saturated NaCl to give, after evaporation and chromatography (PE / Et_2O 2:1 → 4:6), pure **39** (2.258 g, 44%) as well as the methyl ester of acid **38** [R_f 0.2 (PE / Et_2O 2:1, det. D)], (299 mg, 8.5%). R_f 0.34 (PE / Et_2O 2:1, det. D), 0.79 (PE / Et_2O 1:2). Anal.: found: C, 57.4; H, 8.7; N, 3.9. $C_{17}H_{31}NO_3Si_2$ requires C, 57.74; H, 8.84; N, 3.96%. GC-MS: R_t 8.10 min. M/z: 338 (M-15, 5.8); 296 (M-57, 53.9), 196 (2.5), 181 (11.8), 116 (100), 100(43), 89 (79), 73 (43.7), 59 (25.8). I.r.: ν_{max} 2962, 2940, 2870, 2190, 1760, 1745, 1440, 1368, 1345, 1295, 1260, 1210, 1180, 1160, 1080, 1025 cm^{-1}. ^1H n.m.r.: δ 4.05 [1H, d, C*H*-CO_2Me, J 2.9]; 3.77 [3 H, s, CH_3O]; 3.38 [1 H, dt, C*H*-C≡O, J_d 2.8, J_t 5.7]; 2.70 [2 H, d, CH_2-C≡, J 5.7]; 0.98 [9 H, s, $C(CH_3)_3$]; 0.28 [3H, s, CH_3-$SiCH_3$]; 0.14 [12 H, s, $(CH_3)_3Si$ and CH_3-$SiCH_3$]. ^{13}C n.m.r. (20 Mhz.): δ 172.26 & 171.85 [*C*=O]; 101.07 & 87.54 [*C*≡*C*]; 54.98, 53.76, 52.35 [*C*H_3O, *C*H-N, *C*H-C=O]; 26.22 [$C(CH_3)_3$]; 18.78 [CH_2-C≡]; 18.41 [$C(CH_3)_3$]; -5.89 & -6.01 [Si-$C(CH_3)_2$].

(*R,S*) 1-(*t*-Butyldimethylsilyl)-4-(hydroxymethyl)-2-azetidinone 40. A suspension of powdered anhydrous $CaCl_2$ (6.59 g, 59.4 mmol) in a mixture of dry EtOH (25 ml) and dry THF (50 ml) was cooled to -20°C and treated, portionwise, with solid $NaBH_4$ (3.74 g, 98.9 mmol). After stirring for 10 min, a solution of benzyl ester **37**[26] (6.33 g, 19.8 mmol) in dry THF (50 ml) was added to the resulting suspension. After 30 min. the temperature was raised to 0°C and the mixture stirred for 3h at 0°C and 2h at r.t. After cooling to 0°C the reaction was quenched by slow addition (during 1h) of a mixture of 40 ml of saturated NH_4Cl and 40 ml of H_2O. Extraction with AcOEt gave a crude product which was chromatographed with PE / AcOEt 6:4 → 1:1 to give pure **40** as an oil (4.16 g, 94%). R_f 0.33 (PE / AcOEt 1:1, det. C, D). GC-MS: R_t 7.24 min. (2 min. at 70°C, then 20°C/min to 250°C). M/z: 158 (M-57, 19.8); 140 (8.5); 100 (36.8); 75 (100); 41 (48.6). I.r.(liquid film): ν_{max} 3420, 2950, 2930, 2860, 1722, 1465, 1340, 1255, 1190, 1050, 1005, 840, 822, 810, 775, 670 cm^{-1}. ^1H n.m.r.: δ 3.84-3.58 [3 H, m, CH_2OH & C*H*-N]; 3.07 & 2.83 [2 H, AB part of an ABX syst., CH_2-C=O, J_{AB} 15.3, J_{AX} 5.1, J_{BX} 2.3]; 2.60 [1 H, broad s, O*H*]; 0.94 [9 H, s, $(CH_3)_3C$]; 0.23 & 0.21 [2 x 3H, 2s, $(CH_3)_2Si$]. ^{13}C n.m.r. (20 MHz.): δ 172.84 [*C*=O]; 64.72 [*C*H_2OH]; 50.07 [*C*H-N]; 41.22 [CH_2-C=O]; 26.26 [$(CH_3)_3C$]; 18.51 [Si-$C(CH_3)_3$]; -5.30 & -5.61 [$(CH_3)_2Si$].

(*4R) 1-(*t*-Butyldimethylsilyl)-4-[((*1R*,S**)-1-ethoxyeth-1-yl)oxymethyl]-2-azetidinone 41.** A solution of alcohol **40** (9.91 g, 46.02 mmol) in dry CH_2Cl_2 (140 ml) was cooled to 0°C, and treated with 0.1N *p*-toluensulfonic acid in dry THF (12 ml, 1.2 mmol)(the quantity of acid catalyst to be added can vary upon the quantity of basic stabilizer contained in commercial ethyl vinyl ether). The resulting solution was stirred at 0°C for 1 h and then at room temperature until judged complete by tlc (usually 1-3h). Quenching with saturated $NaHCO_3$, followed by extraction with Et_2O gave a crude product which, upon chromatography (PE / Et_2O 31:1 → 3:7) gave pure **41** as a 1:1 diastereomeric mixture (11.86 g, 90%). R_f 0.34 (PE / Et_2O 1:1, det. C). Anal.: found: C, 58.1; H, 10.0; N, 4.7. $C_{14}H_{29}NO_2Si$ requires C, 58.49; H, 10.17; 4.87%. GC-MS: R_t 6.90 min. M/z: 230 (M-57, 2.3); 200 (6.6); 188 (4.6); 158 (M-129, 29.4); 103 (5.4); 100 (15.6); 73 (100); 45 (54.5). I.r.: ν_{max} 2930, 2895, 2880, 2860, 1728, 1450, 1375, 1330, 1295, 1255, 1190, 1135, 1080, 1050, 1005 cm^{-1}. ^1H n.m.r.: δ 4.72 & 4.70 [1H, 2 q, C*H*-CH_3, J 5.4]; 3.80-3.38 [5 H, m, CH_2O and C*H*-N]; 3.14 & 3.13 [1 H, 2dd, J 5.2 & 15.3]; 2.78 & 2.74 [1 H, 2 dd, J 2.6 & 15.3]; 1.31 [3 H, d, C*H*$_3$CH, J 5.4]; 1.21 [3 H, t, C*H*$_3$CH$_2$, J 7.1]; 0.96 [9 H, s, $(CH_3)_3$]; 0.25 & 0.23 [2 x 3H, 2s, $(CH_3)_2Si$]. ^{13}C (20 MHz.): δ 172.48 [*C*=O]; 99.71 [*C*H-CH_3]; 67.76 & 67.46 [CH_2OEE or OCH_2CH_3]; 60.87 [CH_2OEE or OCH_2CH_3]; 48.42 [*C*H-N]; 42.14 [CH_2-C=O]; 26.27 [$(CH_3)_3C$]; 19.62 & 15.29 [CH_3CH_2 & CH_3CH]; 18.40 [$C(CH_3)_3$]; -5.28 & -5.58 [$(CH_3)_2Si$].

(*3R*,4S) 1-(*t*-Butyldimethylsilyl)-4-[((*1R*,S**)-1-ethoxyeth-1-yl)oxymethyl]-3-[(3-(trimethylsilyl)prop-2-yn-1-yl]-2-azetidinone 42.** A solution of **41** (11.74 g, 40.83 mmol) in dry THF (60 ml) was slowly added, at -78°C, to a ≈0.4 M solution of lithium di-*iso*-propylamide in THF-*n*-hexane (prepared from 26.8 ml, 42.87 mmol of 1.6 M *n*BuLi). The temperature was allowed to rise to -50°C during 20 min. At this

point 3-bromo-1-(trimethylsilyl)propyne (7.36 ml, 52.0 mmol) was added. The temperature was allowed to rise to 0°C during 2h, and then the reaction was quenched and worked out as usual (see the preparation of **9**) to give, after chromatography, pure **42** as a 1:1 diastereomeric mixture (relative to the ethoxyethyl chiral centre)(8.049 g, 50%), plus recovered **41** (1.9206 g, 16.4%) and the *bis*-propargylated adduct (1.106 g, 5.3%). Yield from non-recovered starting material = 60%. R_f 0.58 (PE / Et_2O 1:1 det. C). GC-MS: R_t 8.97 min. M/z: 382 (M-15, 1.7); 340 (M-57, 2.8); 268 (M-129, 26.3); 200 (6.6), 188 (5.9), 100 (10.3), 73 (100), 59 (9.0), 45 (55.7). I.r.(liquid film): ν_{max}: 2955, 2930, 2900, 2855, 2175, 1750, 1470, 1340, 1250, 1175, 1135, 1100, 1055, 840 cm^{-1}. ^1H n.m.r.: δ 4.71 & 4.70 [1H, 2q, J 5.3]; 3.84-3.40 [5h, m, CH_2OEE, CH_3CH_2O, CHN]; 3.11 & 3.04 [1 H, 2 dt, J_d 2.5, J_t 6.1]; 2.64 & 2.62 [2 H, AB part of an ABX syst., J_{AB}17.3, J_{AX} 9.8, J_{BX} 1.7]; 1.31 & 1.30 [3 H, 2d, CH_3-CH, J 5.3]; 1.21 [3 H, t, CH_3CH_2, J 7.1]; 0.97 [9 H, s, $(CH_3)_3C$]; 0.25 [6 H, s, $(CH_3)_2Si$]; 0.14 [9 H, s, $(CH_3)_3Si$]. ^{13}C n.m.r. (20 MHz.): 173.5 [*C*=O]; 102.62 & 86.57 [*C*≡*C*]; 99.82 [O-*C*H-O]; 66.91, 66.55, 61.05, 60.87 [CH_2O]; 54.46, 52.2 [*C*H-N & *C*H-C=O]; 26.36 [$C(CH_3)_3$]; 19.7 [CH_3]; 18.97 [CH_2-C≡C]; 18.36 [$C(CH_3)_3$]; 15.43 [CH_3]; 0.22 [$Si(CH_3)_3$]; -5.09 & -5.59 [$(CH_3)_2Si$].

(*3R*,4S) 1-(*t*-Butyldimethylsilyl)-4-[hydroxymethyl]-3-[(3-(trimethylsilyl)prop-2-yn-1-yl]-2-azetidinone 43.** *Method A*: It was prepared in 95% yield from ester **39** by reduction with $Ca(BH_4)_2$, following the same procedure employed for the synthesis of **40** from **37**. *Method B*: A solution of **42** (1.072 g, 2.70 mmol) in dry MeOH (20 ml), was cooled to 0°C, and treated with 1N camphorsulfonic acid in dry MeOH (0.400 ml, 0.4 mmol). After stirring for 3h at the same temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ (20 ml), extracted with Et_2O, evaporated to dryness and chromatographed (PE / Et_2O 3:7) to give pure **43** as an oil (753 mg, 86%). R_f 0.44 (PE / Et_2O 3:7, det. D). Anal.: found (from method A): C, 59.45; H, 9.6; N, 4.25. $C_{16}H_{31}NO_2Si_2$ requires C, 59.02; H, 9.60; N, 4.30%. GC-MS: R_t 8.19 min. M/z: 310 (M-15, 2.6); 268 (M-57, 22.2); 213 (26.0); 178 (11.8); 157 (6.1); 153 (10.4); 147 (21.9); 135 (9.9); 116 (8.0); 100 (48.8); 99 (5.6); 83 (5.7); 78 (10.3); 75 (87.2); 73 (100); 61 (15.3); 59 (18.0). I.r.: ν_{max}: 3690, 3630, 3000, 2960, 2940, 2905, 2890, 2865, 2190, 1735, 1605, 1467, 1395, 1365, 1300, 1250, 1110, 1030, 840 cm^{-1}. ^1H n.m.r.: δ 3.90-3.66 [2 H, m, CH_2OH]; 3.61 [1 H, ddd, *C*H-N, J 2.6, 4.1, 5.2]; 3.17 [1 H, ddd, *C*H-C=O, J 2.6, 5.1, 8.0]; 2.68 & 2.59 [2 H, AB part of an ABX syst., J_{AB} 17.3, J_{AX} 4.7, J_{BX} 8.5]; 0.97 [9 H, s, $(CH_3)_3C$]; 0.26 & 0.25 [2 x 3H, 2s, $(CH_3)_2Si$]; 0.15 [9 H, s, $(CH_3)_3Si$]. ^{13}C n.m.r. (20 MHz.): 173.37 [*C*=O]; 102.82 & 86.77 [*C*≡*C*]; 64.12 [CH_2O]; 56.01, 52.10 [*C*H-N & *C*H-C=O]; 26.22 [$C(CH_3)_3$]; 18.96 [CH_2-C≡C]; 18.35 [$C(CH_3)_3$]; 0.10 [$Si(CH_3)_3$]; -5.21 & -5.63 [$(CH_3)_2Si$].

(*3R*,4S) 1-(*t*-Butyldimethylsilyl)-4-[hydroxymethyl]-3-(prop-2-yn-1-yl)-2-azetidinone 44.** It was prepared in 86% yield from **43**, by the same procedure already described for **10**. However, in this case the reaction with $AgNO_3$ was carried out at -10°C for 1.5h. R_f 0.35 (PE / Et_2O 3:7, det. C). GC-MS: R_t 6.83 min. M/z: 196 (M-57, 30.6); 178 (13.6); 157 (15.0); 156 (19.4); 115 (5.4); 100 (86.2); 79 (14.0); 77 (45.1); 75 (100); 73 (23.1); 57 (20.2); 56 (7.65); 41 (5.8). I.r.: ν_{max} 3315, 2960, 2940, 2890, 2860, 2250, 1743, 1470, 1260, 1205, 1090, 1030, 875 cm^{-1}. ^1H n.m.r.: δ 3.90-3.56 [3 H, m, CH_2OH & *C*H-N]; 3.19 [1 H, dt, *C*H-C=O, J_t 6.4, J_d 2.5]; 2.59 [2 H, dd, J 2.6 & 6.4]; 2.26 [1 H, broad s, O*H*]; 2.02 [1 H, t, C≡C*H*, J 5.3]; 0.96 [9 H, s, $(CH_3)_3C$]; 0.26 & 0.23 [2 x 3H, 2s, $(CH_3)_2Si$]. ^{13}C n.m.r. (50 MHz.]: δ 173.65 [*C*=O]; 80.35 [*C*≡CH]; 70.32 [C≡*C*H]; 63.82 [*C*H_2OH]; 55.88 & 51.63 [CH-N & *C*H-C=O]; 26.12 [$C(CH_3)_3$]; 18.29 [$C(CH_3)_3$]; 17.50 [CH_2-C≡C]; -5.34 & -5.69 [$(CH_3)_2Si$].

(*3R*,4S) 1-(*t*-Butyldimethylsilyl)-4-[hydroxymethyl]-3-[7-(trimethylsilyl)hept-4-en-2,6-diyn-1-yl]-2-azetidinone 45.** A suspension of $Pd(PhCN)_2Cl_2$ (313 mg, 0.816 mmol) and CuI (169 mg, 0.889 mmol) in dry THF (25 ml), under argon, was treated at r.t. with piperidine (11.6 ml, 117 mmol) and with trimethylsilylacetylene (330 µl, 2.36 mmol). After 15 min., (*Z*) 1-chloro-4-(trimethylsilyl)but-1-en-3-yne (2.165 ml, 2.015 g, 12.70 mmol) was added, and the dark solution stirred for 1 h at r.t., followed by addition of a solution of **44** (1.991 g, 7.86 mmol) in dry THF (25 ml). After stirring for 4 h, the reaction was quenched with saturated aqueous NH_4Cl (100 ml). The mixture was adjusted to pH 8 with 1N HCl and extracted with Et_2O to give, after chromatography (PE / Et_2O 6:4 → 3:7), pure **45** as a brown solid (2.274 g, 77%). An analytical sample (white solid) was obtained by crystallization from AcOEt / PE. M.p.: 110.1-110.2°C. R_f

0.47 (PE / Et_2O 3:7, det. A,C). GC-MS: R_t 10.14 min. M/z: 360 (M-15, 2.0); 318 (M-57, 32.3); 185 (7.0); 183 (5.2); 147 (13.9); 128 (8.7); 116 (100); 100 (12.3); 75 (69.8); 73 (78.8); 59 (12.2); 45 (9.1); 43 (7.0). I.r.: ν_{max} 3700, 3620, 3030, 2965, 2940, 2870, 2405, 2250, 2220, 2150, 1740, 1610, 1260, 1220, 1020, 840 cm^{-1}. ^1H n.m.r.: δ 5.81 [2 H, s, C*H*=C*H*]; 3.92-3.58 [3 H, m, CH_2OH & C*H*-N]; 3.24 [1 H, ddd, C*H*-C=O, J 2.5, 5.0, 7.9]; 2.77 & 2.87 [2 H, AB part of an ABXY syst., J_{AB} 17.7, J_{AX} 5.2, J_{BX} 7.9, $J_{AY}\approx J_{BX}$ 1.5]; 0.97 [9 H, s, $(CH_3)_3C$]; 0.28 [3 H, s, CH_3Si]; 0.23 [12 H, s, $(CH_3)_3Si$ & CH_3Si]. ^{13}C n.m.r.(20 MHz.): δ 173.36 [*C*=O]; 120.49 & 119.33 [*C*H=*C*H]; 102.18, 94.49, 79.66 [*C*≡*C*]; 63.96 [CH_2OH]; 56.21 & 51.99 [CH]; 26.17 [$(CH_3)_3C$]; 18.97 [$CH_2C{\equiv}C$]; 18.35 [$C(CH_3)_3$], -0.08 [$(CH_3)_3Si$]; -5.39 & -5.58 [$(CH_3)_2Si$].

***(3R*,4S*)* 1-(*t*-Butyldimethylsilyl)-4-[hydroxymethyl]-3-[hept-4-en-2,6-diyn-1-yl]-2-azetidinone 46.** It was prepared from **45** in 97% yield by following the same procedure already described for **10**. However, the reaction with $AgNO_3$ was carried out for 1h at -15°C, and treatment with KCN at 0°C lasted 30 min. R_f 0.34 (PE / Et_2O 3:7, det. A), 0.44 (Et_2O / toluene / CH_2Cl_2 2:1:1). GC-MS: not feasible.[33] ^1H n.m.r.: δ 5.88 [1 H, dt, C*H*-C≡C-CH_2, J_t 2.0, J_d 11.0]; 5.78 [1 H, dd, C*H*-C≡C, J 2.1 & 11.0]; 3.93-3.62 [3 H, m, CH_2OH & C*H*-N]; 3.34 [1 H, d, C≡C*H*, J 2.2]; 3.25 [1 H, ddd, C*H*-C=O, J 2.6, 5.1, 7.8]; 2.87 & 2.79 [2 H, AB part of an ABXY syst., $CH_2C{\equiv}C$, J_{AB} 17.8, J_{AX} 5.2, J_{BX} 8.2, $J_{AY}\approx J_{BY}$ 2.0]; 0.97 [9 H, s, $(CH_3)_3C$]; 0.27 & 0.23 [2 x 3 H, 2s, $(CH_3)_2Si$].

***(3R*,4S*)* 1 - (*t*-Butyldimethylsilyl)-4-[hydroxymethyl]-3-[7-iodohept-4-en-2,6-diyn-1-yl]-2-azetidinone 47.** A suspension of iodine (1.345 g, 5.3 mmol) in dry benzene (10 ml) was treated, in the dark, with morpholine (1.40 ml, 16.05 mmol). After stirring for 30 min. at room temp., a solution of alkyne **46** (322 mg, 1.06 mmol) in dry benzene (10 ml) was added. After 2.5 h at r.t., the reaction was quenched with 5% aqueous $(NH_4)H_2PO_4$ (45 ml), and 0.4M $Na_2S_2O_3$ (30 ml). Extraction with Et_2O (twice) and AcOEt (once) gave a crude product which, upon chromatography (PE / Et_2O 3:7) furnished pure **47** as an oil (392 mg, 86%). R_f 0.46 (Et_2O / toluene / CH_2Cl_2 2:1:1, det. A). GC-MS: not feasible.[33] ^1H n.m.r.: δ 5.91 [1 H, d, C*H*-C≡C-I, J 10.9]; 5.77 [1 H, dt, C*H*-C≡C-CH_2, J_d 10.9, J_t 2.2]; 3.94-3.70 [2 H, m, CH_2OH]; 3.67 [1 H, dt, C*H*-N, J_d 2.6, J_t 4.6]; 3.27 [1 H, ddd, C*H*-C=O, J 2.6, 4.8, 7.9]; 2.88 & 2.79 [2 H, AB part of an ABXY syst. CH_2-C≡C, J_{AB} 17.5, J_{AX} 4.6, J_{BX} 8.4, $J_{AY}=J_{BY}$ 2.0]; 1.70 [1 H, broad s, O*H*]; 0.98 [9 H, s, $(CH_3)_3C$]; 0.29 & 0.24 [2 x 3 H, 2s, $(CH_3)_2Si$]. ^{13}C n.m.r. (50 MHz.): δ 173.56 [*C*=O]; 122.08 & 119.23 [*C*=*C*]; 94.77, 91.91, 79.43 [*C*≡*C*]; 63.93 [CH_2OH]; 56.26 & 51.57 [CH-N & CH-C=O]; 26.17 [$(CH_3)_3C$]; 18.95 [CH_2-C≡C]; 18.33 [$C(CH_3)_3$]; 14.01 [C≡*C*-I]; -5.38 & -5.59 [$(CH_3)_2Si$].

***(1R*,9R*,10S*)* and *(1R*, 9S*, 10S*) (Z)* 11-(*tert*-Butyldimethylsilyl)-9-hydroxy-11-azabicyclo[8.2.0]dodec-5-en-3,7-diyn-12-ones 48 and 49.** They were prepared in two steps from **47** (237 mg, 552 μmol), by following the same procedure employed for **16** and **17**. Chromatography (PE / Et_2O 1:1 → 2:8) gave pure **48** (94 mg, 56.5%) and **49** (12 mg, 7.2%) as white solids, plus 12 mg of recovered aldehyde. Overall yield from non recovered starting material= 68%.

48: R_f 0.46 (PE / Et_2O 1:1, det. A,B), 0.72 (PE / Et_2O 3:7). GC-MS: R_t 9.59 min. M/z: 286 (M-15, 0.2); 244 (M-57, 49.7); 226 (10.1); 202 (4.3); 184 (3.4); 172 (3.7); 142 (19.9); 127 (17.0); 115 (100) 75 (91.7) 73 (66.8); 57 (22.6) 55 (11.2). I.r. : ν_{max} 3690, 3620, 3040, 2965, 2940, 2870, 1742, 1605 (w), 1340, 1260, 1195, 1110, 1080, 1055, 1010, 820 cm^{-1}. ^1H n.m.r.: δ 5.96 & 5.91 [2 H, AB syst. C*H*=C*H*, J 10.2]; 4.71 [1 H, broad s, C*H*OH]; 3.82-3.66 [2 H, m, C*H*-N & C*H*-C=O]; 2.93 [1 H, ddd, C*H*H-C≡C, J 1.5, 3.8, 17.8]. 2.59 [1 H, dd, C*H*H-C≡C, J 12.2 & 17.8]; 2.48 [1 H, broad s, O*H*]; 0.98 [9 H, s, $(CH_3)_3C$]; 0.31 & 0.24 [2 x 3H, 2s, $(CH_3)_2Si$]. ^{13}C n.m.r. (50 MHz): δ 173.33 [*C*=O]; 126.18 & 122.12 [*C*=*C*]; 100.95, 97.27, 86.80, 83.79 [*C*≡*C*]; 61.60, 61.09, 52.44 [CH-OH, CH-N, CH-C=O]; 26.22 [$(CH_3)_3$]; 19.99 [CH_2-C≡C]; 18.63 [$C(CH_3)_3$]; -5.44 & -5.64 [$(CH_3)_2Si$].

49: R_f 0.61 (PE / Et_2O 1:1, det. A,B). GC-MS: R_t 9.53 min. M/z: 286 (M-15, 0.24); 244 (M-57, 38.3); 226 (11.1); 212 (3.1); 202 (4.7); 184 (4.2); 172 (3.9); 142 (14.0); 127 (19.0); 115 (66.4) 100 (11.5); 75 (100); 73 (47.9); 57 (23.0); 55 (10.0). ^1H n.m.r.: δ 5.90 [2 H, s, C*H*=C*H*]; 4.49 [1 H, dd, C*H*-OH, J 5.5, 8.8]; 3.75 [1 H, dd, C*H*-N, J 2.7, 8.8]; 3.34 [1 H, dt, C*H*-C=O, J_t 3.2, J_d 12.2]; 2.91 [1 H, dd, C*H*H-C≡C, J 3.6, 17.8]; 2.64 [1 H, dd, C*H*H-C≡C, J 12.2, 17.8]; 2.06 [1 H, d, O*H*, J 5.5]; 0.98 [9 H, s, $(CH_3)_3C$]; 0.29 [6 H, s, $(CH_3)_2Si$].

^{13}C (50 MHz.): δ 172.83 [*C*=O]; 124.76 & 122.24 [*C*H=*C*H]; 100.74, 97.24, 87.02, 84.08 [*C*≡*C*]; 67.57, 63.19, 56.14 [*C*H-OH, *C*H-N, *C*H-C=O]; 26.43 [(*C*H$_3$)$_3$C]; 20.17 [*C*H$_2$-C≡C]; 18.51 [*C*(CH$_3$)$_3$]; -4.82 & -5.00 [(*C*H$_3$)$_2$Si].

***(1R*,9R*,10S*)* (Z) 9-(Acetoxy)-11-azabicyclo[8.2.0]dodec-5-en-3,7-diyn-12-one 50.** A solution of alcohol **48** (23 mg, 76.3 μmol) in dry CH_2Cl_2 (0.5 ml), was treated at r.t. with dry pyridine (0.5 ml), 4-(dimethylamino)pyridine (5 mg, 41 μmol), and acetic anhydride (36 μl, 381 μmol). After stirring for 75 min, the reaction was quenched with H_2O, and extracted with AcOEt. Evaporation to dryness, followed by azeotropically evaporation of pyridine with *n*-heptane, and preparative thin layer chromatography (PE / Et_2O 1:1) furnished the acetate of **48** as an oil (25 mg, 96%). R_f 0.48 (PE / Et_2O 1:1); GC-MS: R_t 9.57 min. M/z: 286 (M- 57, 7.4); 144 (10.2); 126 (4.7); 117 (100); 115 (17.0); 100 (5.5); 75 (29.3); 73 (17.6); 57 (6.9); 43 (21.7). I.r.: ν_{max} 3060, 2995, 2970, 2940, 2870, 2305, 1745, 1605 (w), 1425, 1370, 1325, 1265, 1230, 1200, 1155, 1090, 1010, 920 cm^{-1}. ^1H n.m.r.: δ 6.00 & 5.90 [2 H, AB syst. C*H*=C*H*, J 9.7]; 5.61 [1 H, t, C*H*-OAc, J 1.9]; 3.90-3.73 [2 H, m, C*H*-N & C*H*-C=O]; 2.93 [1 H, ddd, C*H*H-C≡C, J 1.8, 3.9, 17.9]; 2.61 [1 H, dd, C*H*H-C≡C, J 12.5, 17.9]; 2.12 [3 H, s, C*H*$_3$C=O]; 0.95 [9 H, s, (C*H*$_3$)$_3$C]; 0.25 & 0.20 [2 x 3H, 2s, (C*H*$_3$)$_2$Si]. This product was taken up in CH_3CN (2.85 ml), cooled to -20°C, and treated with 40% aqueous HF (150 μl). After 1 h the temperature was raised to 0°C. After 2 h the reaction was complete by tlc and quenched with saturated aqueous $NaHCO_3$, extracted with AcOEt, and evaporated to dryness. Preparative t.l.c. (PE / AcOEt 1:1) afforded pure **50** as a white solid (15.8 mg, 90% from **48**). R_f 0.35 (PE / AcOEt 1:1, det. A,B). GC-MS: R_t 8.23 min. M/z: 229 (M$^+$, 30.9); 187 (23.9); 186 (38.1); 170 (7.5); 159 (14.5); 158 (33.9); 144 (16.1) 142 (12.4); 141 (14.2); 140 (9.4); 130 (71.1); 115 (57.9); 114 (18.7); 112 (55.1); 103 (14.6) 91 (11.8); 89 (15.5); 84 (15.8); 77 (17.1); 63 (23.9); 51 (14.1); 43 (100). ^1H n.m.r.: δ 6.05-5.80 [4 H, m, C*H*=C*H*, C*H*-OAc, N*H*]; 3.98 [1 H, t, C*H*-N, J 2.4]; 3.76 [1 H, ddd, C*H*-C=O, J 2.6, 3.9, 12.5]; 2.93 [1 H, ddd, C*H*H-C≡C, J 1.8, 4.0, 18.0]; 2.67 [1 H, dd, C*H*H-C≡C, J 12.7, 18.0]. 2.15 [3 H, s, C*H*$_3$C=O]. ^{13}C n.m.r. (50 MHz): δ 170.28 & 167.41 [*C*=O]; 127.01 & 121.87 [*C*H=*C*H]; 100.40, 93.25, 88.20, 83.98 [*C*≡*C*]; 61.58, 58.14; 53.55 [*C*H-OAc, *C*H-N, *C*H-C=O]; 20.71 [*C*H$_3$C=O]; 19.32 [*C*H$_2$-C≡C].

***(1R*,9R*,10S*)* (Z) 9-[(*tert*-Butyldimethylsilyl)oxy]-11-azabicyclo[8.2.0]dodec-5-en-3,7-diyn-12-one 51.** A solution of **48** (22 mg, 73 μmol) in dry dimethylformamide (1 ml) was cooled to 0°C, and treated with a 50% suspension of NaH in mineral oil (6 mg, 125 μmol). After 30 min the reaction was quenched with saturated NH_4Cl. Extraction with AcOEt, followed by evaporation and preparative t.l.c. (PE / Et_2O 1:1) gave pure **51** (15.3 mg, 70%). R_f 0.43 (PE / Et_2O 3:7, det. A,B). GC-MS: R_t 9.30 min. M/z: 286 (M-15, 0.90); 244 (M-57, 100); 216 (9.9); 202 (16.6); 185 (8.4); 170 (7.4); 142 (38.1); 127 (20.3); 115 (11.2); 100 (17.8); 75 (60.9); 73 (57.4); 59 (10.4); 45 (12.9). ^1H n.m.r.: δ 5.94 & 5.90 [2 H, AB syst., C*H*=C*H*, J 10.8]; 5.81 [1 H, broad s, N*H*]; 4.65 [1 H, t, C*H*-OSi, J 3.3]; 3.86-3.70 [2 H, m, C*H*-N & C*H*-C=O]; 2.91 [1 H, ddd, C*H*H-C≡C, J 1.5, 4.0, 17.8]; 2.64 [1 H, dd, C*H*H-C≡C, J 12.6, 17.8]; 0.91 [9 H, s, (C*H*$_3$)$_3$C]; 0.15 & 0.12 [2 x 3H, 2s, (C*H*$_3$)$_2$Si]. ^{13}C n.m.r. (50 MHz): δ 168.48 [*C*=O]; 125.64 & 122.36 [*C*=CH]; 100.36, 98.14, 86.28, 83.82 [*C*≡*C*]; 61.56, 59.97, 52.01 [*C*H-OSi, *C*H-N, *C*H-C=O]; 25.70 [(*C*H$_3$)$_3$C]; 19.32 [*C*H$_2$-C≡C]; 18.23 [*C*(CH$_3$)$_3$]; -4.62 & -5.15 [(*C*H$_3$)$_2$Si].

***(1R*,9S*,10S*)* (Z) 9-[(*tert*-Butyldimethylsilyl)oxy]-11-azabicyclo[8.2.0]dodec-5-en-3,7-diyn-12-one 52.** It was obtained in 55% yield starting from **49**, by following the procedure already described for **51**. R_f 0.38 (PE / Et_2O 1:1, det. A,B). GC-MS: R_t 9.23 min. M/z: 286 (M-15, 0.66); 244 (M-57, 100); 216 (8.8); 202 (12.5); 201 (5.7); 185 (11.2); 170 (7.4); 145 (5.0); 142 (38.5); 141 (7.7); 127 (5.3); 125 (6.2); 115 (8.0); 100 (5.1); 91 (7.0); 75 (38.7); 73 (40.4); 59 (6.8); 45 (7.3). I.r.: ν_{max} 3700, 3430, 2970, 2940, 2905, 2860, 1770, 1610, 1265, 1090, 1010, 795 cm^{-1}. ^1H n.m.r.: δ 6.10 [1 H, broad s, N*H*]; 5.93 [2 H, s, C*H*=C*H*]; 4.53 [1 H, d, C*H*-OSi, J 8.8]; 3.90 [1 H, dd, C*H*-N, J 2.5, 8.8]; 3.40 [1 ddd, C*H*-C=O, J 2.5, 4.1, 12.1]; 2.92 [1 H, ddd, C*H*H-C≡C, J 1.1, 4.1, 17.7, 4.0]; 2.74 [1 H, dd, C*H*H-C≡C, J 12.1, 17.7]; 0.95 [9 H, s, (C*H*$_3$)$_3$C]; 0.22 & 0.19 [2 x 3H, 2s, (C*H*$_3$)$_2$Si]. ^{13}C n.m.r. (50 MHz): δ 167.41 [*C*=O]; 124.17 & 122.38 [*C*=*C*H]; 99.35, 97.47 86.85, 84.02[*C*≡*C*]; 67.63, 61.31, 55.52 [*C*H-OSi, *C*H-N, *C*H-C=O]; 25.77 [(*C*H$_3$)$_3$C]; 19.48 [*C*H$_2$-C≡C]; 18.20 [*C*(CH$_3$)$_3$]; -4.40 & -54.89[(*C*H$_3$)$_2$Si].

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22. Calculations were performed for the cycloaromatization of the aminoacids derived from hydrolysis of **16** and **17** and indicated a ΔSE respectively 3.5 and 2.15 Kcal/mole lower than the ΔSE for the model reaction (cycloaromatization of cyclodec-3-en-1,5-diyne). Thus these compounds were expected to be more reactive than the unsubstituted cyclic enediyne. In particular, a $t_{1/2}$ of few minutes at 50°C was predicted.
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32. In CD_3OD alone, the peaks were badly resolved.
33. These compounds failed to elute in GC at temperatures up to 280°C, because of their too low volatility, or of their low thermal stability.

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