Synthesis of *N*-Fused "Lactendiynes"

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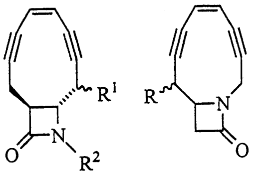
New "lactendiynes", characterized by the fusion at C-4 and N-1 of a β-lactam with a hydroxylated 10-membered cyclic enediyne, were synthesized. Studies on their reactivity have shown that this type of fusion with the azetidinone represents a sufficient "safety-catch" against cycloaromatization. These compounds are relatively reactive toward basic hydrolysis, affording monocyclic enediynes which undergo fast cycloaromatization at room temperature.

The natural enediyne antibiotics[1] represent a small family of compounds endowed with a powerful antitumoral activity due to an unprecedented mode of action. They are usually provided with a "safety-catch", that is a structural feature which prevents the cycloaromatization of the enediyne moiety (Bergman reaction) leading to a reactive arene diradical. The "safety-catch" is removed in vivo by a suitable "trigger", that is an activating event which eliminates the structural constraint, allowing the cyclization of the unsaturated moiety to take place.

The difficult availability of the natural members of this family, as well as the problems connected with their high toxicity, have prompted several research groups to design, prepare, and test new simplified, fully synthetic, analogues, characterized by a similar mode of action.[2] The final goal is to develop new families of stable enediynes that can be activated under selective conditions, in order to direct the cytotoxicity toward a specific cell line. They must be of course also as simple as possible, in order to facilitate their total synthesis.

Toward this goal, we have recently introduced a new family of synthetic enediynes, characterized by the fusion[3] of a 10-membered ring containing the unsaturated pattern, with a β-lactam, naming them "Lactendiynes".[4] In particular, we have previously synthesized[4] various compounds of general formula **1**, where the enediyne ring is *trans*-fused with the C-3 and C-4 of the β-lactam (Scheme 1). As anticipated by force field calculations,[*] these compounds proved to be exceptionally stable toward cycloaromatization, while opening of the azetidinone led to highly reactive derivatives. Thus the β-lactam was demonstrated to be an efficient "safety-catch" in this strategy.

Scheme 1



1 **2**

In continuation of our studies we have later decided to explore the synthesis and reactivity of a different class of "lactendiynes", corresponding to the general formula **2**, where the enediyne ring is fused with C-4 and N-1 of the β-lactam.

Although the higher conformational flexibility of these systems was expected to induce a less marked steric constraint against cycloaromatization, preliminary force field calculations[*] based on the simplified Maier's approach,[1b] indicated that the inhibiting effect of this type of fusion could be sufficient to supply lactendiynes like **2** with an adequate stability under physiological conditions. Another interesting feature of **2** is given by the presence of a nitrogen in the ring containing the enediyne. In the literature there are very few examples of heterocyclic enediynes,[5][6] and in particular, at the outset of this work, there were no examples of cyclic azaenediynes, although more recently three papers dealing with such compounds have appeared.[6]

We chose, as our target compound, **2** (R = OH), since the presence of an oxygenated functionality on the bicyclic system was anticipated to be precious in view of the possible attachment of a triggering device or of a DNA-complexing substructure. When our work was still in progress, Basak and coworkers published[6b] the synthesis of the unfunctionalized analogue **2** (R = H), reporting that it was stable toward cycloaromatization at room temperature. They however did not give detailed informations on the effect of the fusion on the reactivity of the β-lactam toward

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[*] Force field calculations have been carried out with the program Chem3D Plus 3.0 from CSC.

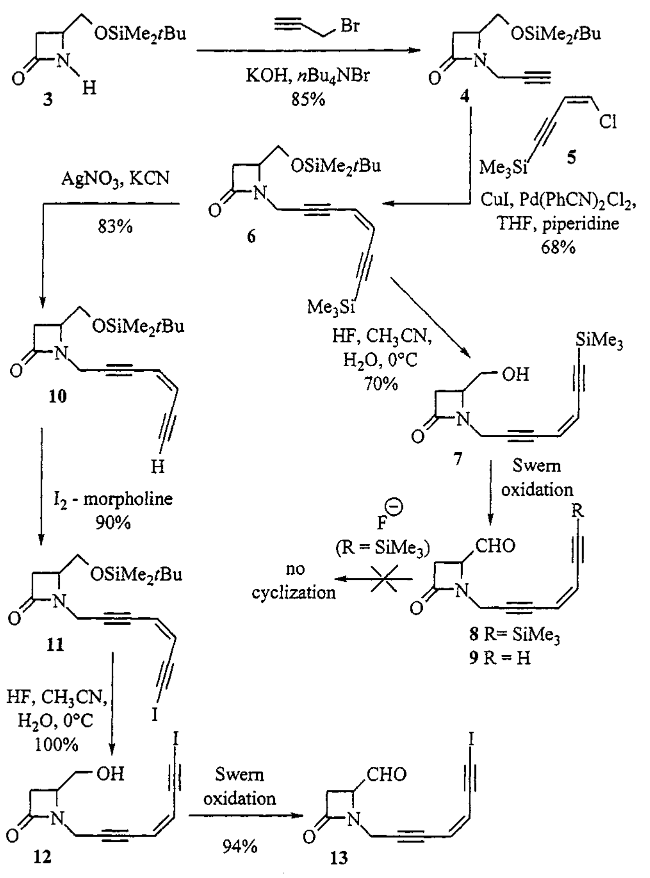
1434−193X/98/0808−1543 $ 17.50+.50/0

nucleophilic opening, nor on the prospective cycloaromatization of opened derivatives.

Moreover, both the chosen target and the synthetic scheme followed by us were different from those pursued by Basak. Thus we decided to bring our project to completion and we report now the successful preparation of these hydroxylated derivatives and the findings collected on their reactivity.

Our synthetic approach involved the intramolecular condensation of an alkynylic aldehyde like **8**, **9**, or **13** to afford the desired byclic secondary alcohols **14a**, **b** (Scheme 2).

Scheme 2



As starting material for these aldehydes we employed 4-(silyloxymethyl)-2-azetidinone **3**, prepared in racemic form from *d,l* aspartic acid following a literature procedure.[7] Reaction with propargyl bromide, under Reuschling's liquid-solid phase transfer conditions,[8] gave **4** in high yield. This terminal alkyne was then subjected to cross-coupling with chloroenyne **5** under Castro-Stephens conditions to furnish the acyclic enediyne **6**. As already found in other instances,[4][9] this reaction proceeded faster and with better yield when a Pd^{II} catalyst bearing weaker ligands, like benzonitrile, was employed. The use of Pd^{II} catalyst, though, brings about an unavoidable decrease of yield provoked by the dimerization of starting alkyne, which is necessary to reduce the metal to Pd^0. In order to overcome this problem we used trimethylsilylacetylene as "sacrificial" alkyne for the reduction of the catalyst, prior to addition of **4** to the reaction mixture (see the Experimental Section for details).[4]

The enediyne **6** was selectively desilylated with HF to give the alcohol **7**, which was in turn oxidized by the Swern methodology to the aldehyde **8**. Attempts to cyclize it with CsF[10] either in the presence of 18-crown-6[10a][10b] or Ac_2O and $NaHCO_3$[10c] failed, affording in low yield, together with unidentified by-products, the unstable desilylated aldehyde **9**. The extreme instability of **9** discouraged any possible efforts for its direct cyclization under strong basic conditions.

Thus we turned our attention to Nozaki's cyclization,[11] which was previously perceived by us[4] and others[11b] to be probably the most efficient methodology for the macrocyclization of alkynylic aldehydes.

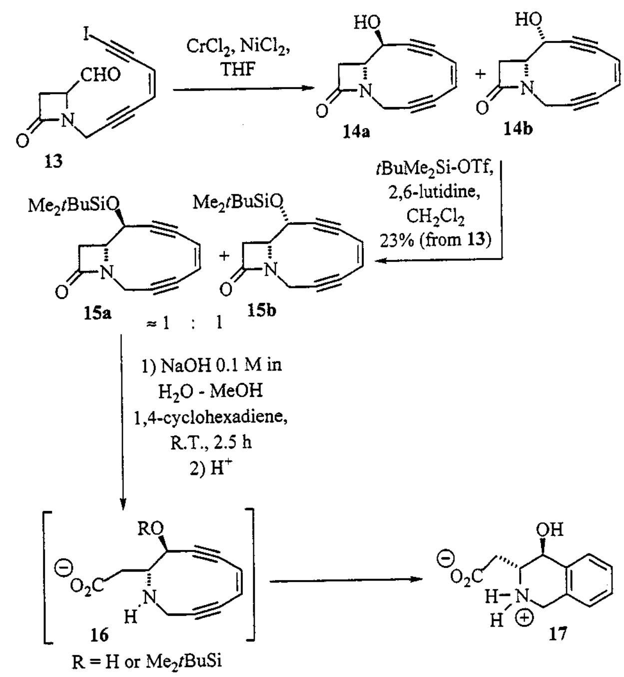
Enediyne **6** was converted into the iodoalkyne **12** by a two-step methodology, since the direct reaction with $AgNO_3$ and *N*-iodosuccinimide[11b] was found to be problematic. The overall yield was however very good, provided that, in the iodination step, complete formation of iodine-morpholine complex was ensured before addition of the unsubstituted alkyne **10**. Removal of the silyl protecting group gave alcohol **12** in excellent overall yield from **3** (43%). Finally, Swern oxidation produced aldehyde **13** in 94% yield.

All the above mentioned acyclic enediynes were found to be less stable than the corresponding intermediates employed in the synthesis of *C*-fused lactendiynes **1**.[4] While **6**, **7**, and **8**, that still bear the trimethylsilyl group, can be stored without problems in the dry state, being also fairly thermally stable (for example they can be analyzed at GC-MS without problems), compounds **9**–**13** have a certain tendency to decompose in the dry state or by warming and were thus routinely stored by us in solution in the presence of (5-*tert*-butyl-4-hydroxy-2-methylphenyl)sulfide (BHMS) as radical inhibitor.[12] Among them the most unstable was aldehyde **9**, followed by alkyne **10**, whose solutions became rapidly intensely coloured upon concentration. Iodoalkynes **11**–**13** were in comparison more stable and easier to manipulate. Thus **10** was always converted into **11** as soon as possible.

Aldehyde **13** was treated with $CrCl_2$ and catalytic $NiCl_2$ in order to promote cyclization to the diastereomeric alcohols **14** (Scheme 3). This reaction turned out to be more difficult than the analogous one employed for the synthesis of *C*-fused lactendiynes **1**. We have never succeeded to drive the reaction to completion: in all instances, after work-up, we detected variable amounts of the unstable deiodinated aldehyde **9**. Moreover, TLC and ^{1}H-NMR analysis of the crude product showed the presence, beside the expected diastereomeric alcohols **14a**, **b**, of other by-products, most likely derived from intermolecular reactions.

The difficult cyclization is an indication of a higher steric strain of the bicyclic systems of general formula **2** as compared with the previously reported compounds **1**. This strain was anticipated by force field calculations and it was furtherly confirmed by the easier hydrolysis of this class of lactendiynes (vide infra).

Scheme 3



The isolation of alcohols **14a** and **14b** from this complex reaction mixture was troublesome, also because of a certain instability of these adducts, which tend to form unsoluble solids on standing even in solution. This behaviour is not completely surprising, at the light of the similar obervations made by Crevisy and Beau[13] on the monocyclic compound cyclodeca-4-en-2,6-diyn-1-ol. Direct protection of the crude reaction mixture furnished the corresponding silyl ethers **15**, which, on the contrary, could be purified and separated by silica gel chromatography. Of them, the *anti* diastereoisomer **15a** was found to be quite stable on silica gel and in solution. On the other hand, **15b** was never obtained completely pure even by repeated chromatographies, and every treatment on silica gel led to a decrease in isolated yield, suggesting some sort of silica promoted decomposition process. The impurities present in variable amounts in samples of chromatographed **15b** gave at ^{1}H-NMR broad peaks in the aromatic region. It is not clear if this is due to slow cycloaromatization at room temperature or, as the broadness of the signal suggests, to intermolecular radical processes facilitated during chromatographic purification.

Although the diastereomeric ratio of isolated **15a**, **b** was very close to 1:1, from tlc and ^{1}H-NMR analysis we deduced a certain kinetic preference, in the condensation itself, for the *syn* isomer **14b**. We believe that the subsequent treatments (work-up, protection, chromatography, and so on) enriched the mixture in the more stable *anti* epimer **15a**.

The relative configuration was determined at ^{1}H NMR, by examination of the vicinal coupling costant between C*H*–N and C*H*–OSi which were 7.9 Hz for **15a** and 1.4 Hz for **15b**. The *J* of 7.9 Hz is consistent with a *trans* arrangement (relative to the enediynic ring) of these two hydrogens.[*]

Compound **15a** did not give any cycloaromatized product on standing in solution for several days in the presence of 1,4-cyclohexadiene as a hydrogen atom donor and it could be recovered without loss. It was then subjected to basic hydrolysis in the presence of 1,4-cyclohexadiene. The opening of β-lactam was found to be in this case much easier than that of lactendiynes **1**. While compounds **1** (R^1 = OMe, R^2= Me) required 1–1.5 M NaOH and a temperature of 50°C for 2–3 h, **15a** was completely hydrolysed by 0.1 N NaOH at 20°C for 2.5 h, and was thus extimated to be about 50 times more reactive, probably because of the steric strain induced by the fusion with the enediynic ring. During hydrolysis, concomitant removal of the silyl protecting group took place.

After disappearing of starting material, quenching with NH_4Cl followed by rapid lyophilization, furnished a crude product which, at ^{1}H NMR, showed no trace of the typical signals of the double bond, which would have been present in the transient opened enediyne **16**. On the contrary there was clear presence of the aromatic signals of **17**. Thus cycloaromatization of **16** seems a relatively fast process, occurring soon after azetidinone hydrolysis. Purification on ion exchange resin afforded the pure desilylated β-aminoacid **17**, which was characterized by ^{1}H NMR.

In conclusion these results demonstrated that, at least for the *anti* isomer **15a**, the fusion with the β-lactam through C-4 and N-1 succeeded in avoiding room temperature cycloaromatization of a 10-membered cyclic enediyne. Opening of the β-lactam led on the contrary to very reactive species which underwent easy cycloaromatization at room temperature. The easy basic hydrolysis of **15a** indicates that the fusion with the enediyne activates in this case the β-lactam toward ring opening (contrary to what happened for lactendiynes **1**, where the reactivity was not increased by the ring fusion), suggesting the presence of a certain degree of steric strain in this family of compounds (as anticipated by force field calculations). As regards with the synthesis of **15a**, **b** it should be remarked that, although the yield of the crucial cyclization step turned out to be low, the preparation of the iodoaldehyde **13** from **3** was very efficient.

Although the not exceptional stability of these *N*-fused lactendiynes represents a possible problem for future applications, we hope that structural modifications on the azetidinonic or enediynic rings could increase the chemical sta-

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[*] Force field calculations indicated that byclic system **2** (R = H) exist in two conformations of similar stability. In one of them the β-lactam assumes a *pseudo*-equatorial position relative to the enediynic ring, while in the alternative one the β-lactam is *pseudo*-axial. However, in none of the two conformations the *cis* isomer **15b** has a dihedral angle justifying the coupling constant of 7.9 Hz. The dihedral angles should indeed be equal to A 75° and 48° respectively. The measured *J* for **15a** and **15b** are anyway more in agreement with a *pseudo*-equatorial arrangement of the β-lactam. The ^{1}H-NMR spectra of **2** (R = H), reported by Basak,[6b] does not allow the determination of these *J*, so we do not know if the preference for the *pseudo*-equatorial conformation is typical of **15a,b** or general for this bicyclic system.

bility leading to more easily manipulated compounds. Studies toward this goal are in progress.

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Experimental Section

NMR 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) from TMS, coupling constants are reported in Hertz. Peak assignment in ^1H-NMR spectra was also made with the aid of double resonance or COSY 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. Retention time are measured in minutes from injection. IR spectra were measured with a Perkin-Elmer 881 instrument as $CHCl_3$ solutions. 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 $(NH_4)_4MoO_4 \cdot 4\ H_2O$ (21 g) and $Ce(SO_4)_2 \cdot 4\ H_2O$ (1 g) in H_2SO_4 (31 ml) and H_2O (469 ml) and warming; **C**) dipping into 2% aqueous $KMnO_4$ and warming; **D**) dipping into a ninhydrin solution (900 mg in 300 ml *n*BuOH + 9 ml AcOH) and 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 **3** was prepared as described for the optically active compound.[7] The purity of all compounds was established by TLC, ^1H-NMR, and (when possible) GC-MS.

(+/−)-4-{[(tert-Butyldimethylsilyl)oxy]methyl}-1-(prop-2-yn-1-yl)-2-azetidinone (**4**): A solution of azetidinone **3**[7] (2.00 g, 9.29 mmol) in dry THF (30 ml) was cooled to −12°C and treated sequentially with solid tetra-*n*-butylammonium bromide (298 mg, 0.93 mmol), propargyl bromide (80% w/w in toluene, 1.55 ml, 13.9 mmol), and roughly powdered KOH (85% purity, 980 mg, 14.85 mmol). After stirring at −12°C for 5 h and 20 min, the reaction was quenched with saturated NH_4Cl and extracted with AcOEt to give, after chromatography (PE/Et_2O, 1:1), pure **4** as a pale yellow oil (2.01 g, 85%). R_f 0.35 (PE/Et_2O, 1:1, det. C). − GC-MS: R_t 6.41; *m/z* (%): 238 [M^+ − 15] (0.1); 196 [M^+ − 57] (5.2); 167 (0.54); 115 (4.4); 73 (5.0); 59 (2.8). − ^1H NMR: δ 4.29 [1 H, dd, C*H*H−C≡, *J* = 2.6, 17.7]; 3.93−3.66 [4 H, m, C*H*−N, CH_2O, CH*H*−C≡]; 2.93 [1 H, dd, C*H*H−C=O, *J* = 4.6, 14.4]; 2.68 [1 H, dd, CH*H*−C=O, *J* = 2.1, 14.4]; 2.23 [1 H, t, C≡C−*H*, *J* = 3.1]; 0.90 [9 H, s, $(CH_3)_3C$]; 0.08 [6 H, s, $(CH_3)_2Si$]. − ^{13}C NMR (20 MHz): δ 166.6 [*C*=O]; 77.3 [*C*≡CH]; 72.13 [C≡*C*H]; 63.5 [CH_2O]; 52.1 [*C*H−N]; 39.0 [CH_2−C=O]; 30.6 [CH_2N]; 25.85 [$C(CH_3)_3$]; 18.28 [$C(CH_3)_3$]; −5.41 [$Si(CH_3)_2$]. − IR: ν 3307, 3005, 2954, 2931, 2893, 2858, 1749, 1462, 1392, 1349, 1330, 1250, 1194, 1137, 1098, 1004, 980 cm^{-1}.

(+/−)-4-{[(tert-Butyldimethylsilyl)oxy]methyl}-1-[7-(trimethylsilyl)hept-4-ene-2,6-diyn-1-yl]-2-azetidinone (**6**): A suspension of CuI (105 mg, 0.55 mmol) and $Pd(PhCN)_2Cl_2$ (318 mg, 0.83 mmol) in dry THF in a two-stoppered flask equipped with a dropping funnel, was treated, under argon, with dry piperidine (8.2 ml, 83 mmol) and trimethylsilylacetylene (0.390 ml, 2.76 mmol). The suspension became first yellow, then green, and finally brown. After 10 min (*Z*)-1-chloro-4-(trimethylsilyl)but-1-en-3-yne **5**[14] (1.88 ml, 11.05 mmol) was added. A solution of **4** (1.400 g, 5.52 mmol) in dry THF (10 ml) was transferred in the dropping funnel and the whole apparatus was placed in a glove-box under nitrogen. After 1 h from the addition of **5**, the solution of **4** was added to the reaction mixture, which was then stirred for 5 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl and extracted three times with Et_2O. The organic extracts were washed with saturated NaCl, and evaporated to dryness to give, after chromatography (PE/Et_2O, 7:3 → 1:1), pure **6** (1.407 g, 68%) as a brown oil. R_f 0.49 (PE/Et_2O, 1:1, det. A,C). − GC-MS: R_t: 9.71; *m/z* (%): 375 [M^+] (1.2); 360 (2.95); 318 (7.3); 276 (100); 205 (3.7); 202 (4.4); 161 (8.9); 145 (6.6); 131 (21.7); 75 (11.5); 73 (56.3); 59 (16.8); 45 (7.1); 43 (8.9); 41 (7.3). − ^1H NMR: δ 5.90−5.76 [2 H, m, C*H*=C*H*]; 4.52 [1 H, dd, C*H*H−N, *J* = 1.4, 18.0]; 4.05−3.64 [4 H, m, CH*H*−N, C*H*−N, CH_2OSi]; 2.91 [1 H, dd, C*H*H−C=O, *J* = 4.7, 14.4]; 2.73 [1 H, dd, CH*H*−C=O, *J* = 2.3, 14.4]; 0.90 [9 H, s, $(CH_3)_3C$]; 0.22 [9 H, s, $(CH_3)_3Si$]; 0.07 [6 H, s, $(CH_3)_2Si$]. − ^{13}C NMR (20 MHz): δ 166.45 [*C*=O]; 120.11 and 119.62 [*C*H=*C*H]; 103.09, 101.80, 90.68, 81.16 [*C*≡*C*]; 63.09 [CH_2O]; 51.92 [*C*H−N]; 38.98 [CH_2−C=O]; 31.41 [CH_2−N]; 25.85 [$C(CH_3)_3$]; 18.22 [$C(CH_3)_3$]; −0.04 [$Si(CH_3)_3$]; −5.41 [$Si(CH_3)_2$]. − IR: ν 3043, 3023, 2958, 2930, 2855, 1745, 1600, 1245 cm^{-1}.

(+/−)-4-(Hydroxymethyl)-1-[7-(trimethylsilyl)hept-4-ene-2,6-diyn-1-yl]-2-azetidinone (**7**): A solution of **6** (201.8 mg, 537 μmol) in CH_3CN (3.9 ml) was cooled to −30°C and treated with 40% aqueous HF (100 μl). The solution was stirred for 20 h at −30°C and for 5 h at −10°C. The reaction was quenched with saturated aqueous $NaHCO_3$, extracted with AcOEt, and chromatographed (AcOEt/Et_2O, 2:1) to give pure **7** as an oil (98.5 mg, 70%). R_f 0.55 (AcOEt/Et_2O, 2:1, det. A). − GC-MS: R_t 8.34; *m/z*: 261 [M^+] (12.7); 246 (100); 230 (40.6); 202 (6.7); 188 (17.4); 175 (5.9); 162 (11.0); 161 (12.1); 160 (8.4); 159 (8.5); 147 (8.9); 145 (23.8); 135 (11.5); 133 (10.9); 131 (15.6); 130 (16.1); 128 (7.6); 119 (7.6); 117 (8.8); 116 (7.6); 115 (8.1); 105 (11.4); 103 (8.9); 100 (11.2); 89 (10.7); 83 (12.3); 75 (33.6); 73 (65.9); 70 (9.2); 59 (10.5); 53 (11.0); 45 (9.3); 43 (18.8). − ^1H NMR: δ 5.90 [1 H, d, C*H*=CH, *J* = 11.0]; 5.82 [1 H, dt, CH=C*H*, *J* = 1.8 (t), 11.0 (d)]; 4.42 [1 H, dd, C*H*H−N, *J* = 1.8, 18.2]; 4.15 [1 H, dd, CH*H*−N, *J* = 1.8, 18.2]; 4.06 [1 H, dd, C*H*H−OH, *J* = 2.3, 11.4]; 3.87 [1 H, apparent heptuplet, tt, C*H*−N, *J* = 2.5 and 5.0]; 3.75 [1 H, broad dd, CH*H*−OH, *J* not det.]; 2.97 & 2.87 [2 H, AB part of an ABX syst., $J_{AB = 1}$4.4; J_{AX} = 5.2, J_{BX} = 2.4]; 0.23 [9 H, s, $(CH_3)_3Si$].

(+/−)-4-{[(tert-Butyldimethylsilyl)oxy]methyl}-1-(hept-4-ene-2,6-diyn-1-yl)-2-azetidinone (**10**): A solution of **6** (1.504 g, 4.00 mmol) in EtOH (15 ml) was cooled to −20°C and treated with a 2 M solution of $AgNO_3$ in H_2O (3.0 ml, 6.0 mmol). After 1.5 h, the resulting suspension was treated with a solution of KCN (1.76 g, 27.0 mmol) in H_2O (15 ml) and warmed to 0°C. After stirring for 30 min at this temperature, the reaction was quenched with a 0.3 N pH 7 phosphate buffer solution (27 ml, 8.1 mmol). The mixture was extracted with AcOEt and the organic phases washed with saturated NaCl, dried, evaporated to dryness, and immediately chromatographed (Et_2O/PE, 7:3) to give pure **10** (1.01 g, 83%) as an oil, which tends to become rapidly coloured (blue-green) and thus was stored as benzene solutions in freezer at −20°C in the presence of (5-*tert*-butyl-4-hydroxy-2-methylphenyl) sulfide

(BHMS) as radical inhibitor,[12] or better used as soon as possible for the next reaction. R_f 0.46 (PE/Et_2O, 3:7, det. A, C). − GC-MS: not feasible (unstable). − ^1H NMR: δ 5.90 [1 H, dt, C*H*=CH, *J* = 1.6 (t) and 11.1]; 5.83 [1 H, dd, C*H*=CH, *J* = 2.0, 11.1]. 4.51 [1 H, dd, C*H*H−N, *J* = 1.8, 18.0]; 4.05−3.82 [3 H, m, C*H*H−N, C*H*−N, C*H*H−O]; 3.75 [1 H, dd, CH*H*−O, *J* = 6.2, 11.7]; 3.33 [1 H, d, C≡C*H*, *J* = 2.0]; 2.92 & 2.71 [2 H, AB part of an ABX syst., CH_2−C=O, J_{AB} = 14.4; J_{AX} = 4.8, J_{BX} = 2.0]; 0.90 [9 H, s, $(CH_3)_3C$]; 0.07 [6 H, s, $(CH_3)_2Si$]. − IR: ν 3302, 2998, 2956, 2929, 2900, 2858, 1743, 1463, 1390, 1348, 1247, 1191, 1135, 1100, 1063, 1033, 1003, 979 cm^{-1}.

(+/−)-4-{[(tert-Butyldimethylsilyl)oxy]methyl}-1-(7-iodohept-4-ene-2,6-diyn-1-yl)-2-azetidinone (**11**): A suspension of iodine (3.45 g, 13.6 mmol) in dry benzene (30 ml) was treated, in the dark, with morpholine (3.56 ml, 40.8 mmol). The mixture was stirred for 1 h to give a red suspension. A solution of **10** (826 mg, 2.72 mmol) in dry benzene (15 ml) was then added. The suspension was stirred for 4 h at r.t. and then filtered washing the filter with CH_2Cl_2. The filtrate was washed with a 1:1 mixture of 0.4 M aqueous $Na_2S_2O_3$ and 5% aqueous $(NH_4)H_2PO_4$, reextracting the aqueous phase with CH_2Cl_2. Evaporation to dryness was followed immediately by chromatography (Et_2O/PE, 7:3) to give pure **11** as an oil (1.053 g, 90%), which was stored in freezer as benzene solutions the presence of BHMS. R_f 0.46 (PE/Et_2O, 3:7, det. A, C). − GC-MS: not feasible (unstable). − ^1H NMR: δ 5.96 [1 H, d, C*H*=CH, *J* = 10.9]; 5.78 [1 H, dt, C*H*=CH, *J* = 1.9 (t) and 10.9 (d)]; 4.53 [1 H, dd, C*H*H−N, *J* = 2.0, 18.1]; 4.04−3.86 [3 H, m, C*H*H−N, C*H*−N, C*H*H−O]; 3.76 [1 H, dd, CH*H*−O, *J* = 6.1, 11.8]; 2.95 [1 H, dd, C*H*H−C=O, *J* = 4.8, 14.3]; 2.73 [1 H, ddd, CH*H*−C=O, *J* = 0.9, 2.3, 14.3]; 0.90 [9 H, s, $(CH_3)_3C$]; 0.08 [6 H, s, $(CH_3)_2Si$]. − ^{13}C NMR (50 MHz): δ 166.63 [*C*=O]; 121.17, 120.08 [*C*H=*C*H]; 91.52, 90.72 [H_2C−*C*≡*C*]; 81.05 [*C*≡C−I]; 63.09 [*C*H_2−O]; 51.83 [*C*H−N]; 38.76 [*C*H_2−C=O]; 31.45 [*C*H_2−N]; 25.74 [$C(CH_3)_3$]; 18.11 [$C(CH_3)_3$]; 14.79 [C≡*C*−I]; −5.45, −5.52 [$Si(CH_3)_2$]. − IR: ν 3043, 2995, 2953, 2928, 2895, 2857, 1746, 1600, 1462, 1392, 1347, 1241, 1193, 1137, 1099, 1004, 834 cm^{-1}.

(+/−)-4-(Hydroxymethyl)-1-(7-iodohept-4-ene-2,6-diyn-1-yl)-2-azetidinone (**12**): A solution of **11** (1.013 g, 2.36 mmol) in CH_3CN (50 ml) was cooled to −12°C and treated with 40% aqueous HF (2.5 ml). The mixture was stirred for 6.5 h, and then quenched with saturated aqueous $NaHCO_3$, and extracted with AcOEt. Evaporation and immediate chromatography (AcOEt/Et_2O, 6:4 → 10:0) gave pure **12** (742 mg, 100%) as an oil which was stored in freezer as benzene solutions the presence of BHMS. R_f 0.46 (PE/Et_2O, 3:7, det. A, C). − GC-MS: not feasible (unstable). − ^1H NMR: δ 5.99 [1 H, d, C*H*=CH, *J* = 10.9]; 5.79 [1 H, dt, C*H*=CH, *J* = 2.0 (t) and 10.9 (d)]; 4.27 and 4.31 [2 H, AB part of an ABX_2 syst., CH_2−N, *J* not measurable]; 4.05 [1 H, dd, C*H*H−OH, *J* = 2.8, 12.0]; 3.91 [1 H, apparent heptuplet, tt, C*H*−N, *J* = 2.5, 5.0] 3.79 [1 H, dd, CH*H*−O, *J* = 4.5, 12.0]; 2.99 & 2.88 [2 H, AB part of an ABX syst., J_{AB} = 14.5, J_{AX} = 5.1, J_{BX} = 2.4].

(9R,10S*)- and (9R*,10R*)-9-[(tert-Butyldimethylsilyl)oxy]-1-aza[8,2,0]cyclododec-5-ene-3,7-diyn-12-ones* (**15a**) *and* (**15b**): A solution of DMSO (950 μl, 13.4 mmol) in dry CH_2Cl_2 (35 ml) was cooled to −78°C and treated with a 2.4 M solution of $(COCl)_2$ in CH_2Cl_2 (3.70 ml, 8.88 mmol). After 10 min, a solution of **12** (706 mg, 2.24 mmol) in dry CH_2Cl_2 (15 ml) was added. After 10 min, triethylamine (2.80 ml, 20.1 mmol) was added. After stirring at −78°C for 2h, the reaction was quenched with water (50 ml), diluted with AcOEt (50 ml), and warmed to r.t. The phases were separated and the aqueous phase reextracted with AcOEt. Evaporation was immediately followed by chromatography (AcOEt/Et_2O, 3:1 → 10:0) to give aldehyde **13** (662 mg, 94%), which was stored overnight in freezer as toluene solution in the presence of BHMS. The next day it was evaporated to dryness, and taken up again twice with dry toluene (5 ml) and evaporated to dryness in order to dehydrate it as much as possible. It was finally stripped at 0.1 mmbar for 1 h, and then taken up in dry THF (27 ml), and treated, under argon, with freshly activated 4A powdered molecular sieves. The suspension was stirred at r.t. for 30 min and then added slowly through a dropping funnel (during 40 min) to a stirring mixture of $CrCl_2$ (1.097 g, 8.93 mmol), $NiCl_2$ (25.7 mg, 198 μmol), and 4-A powdered molecular sieves (85 mg) in dry THF (27 ml). The resulting dark mixture was furtherly stirred for 4 h at r.t., cooled to 0°C, and quenched with H_2O. Extraction with AcOEt, followed by washing with saturated aqueous NaCl, evaporation to dryness and filtration through 10 g of silica gel packed and eluted with AcOEt, gave a crude product, containing **14a**, **b** as well as several by-products. It was suddenly taken up with dry CH_2Cl_2, cooled to 0°C, and treated sequentially with 2,6-lutidine (700 μl, 6.01 mmol) and *tert*-butyldimethylsilyl triflate (680 μl, 2.96 mmol). After stirring for 1.5 h at 0°C, the reaction was quenched with 1 M pH 7 phosphate buffer solution, and extracted with AcOEt. The organic extracts were washed with a pH 3 buffer solution [$(NH_4)H_2PO_4$ + HCl], and saturated NaCl. Evaporation was followed by chromatography (PE/Et_2O, 1:1), which gave pure **15a** (69 mg, 11% from **13**) and slightly impure **15b** (94 mg, estimated yield from **13** (NMR) = 12%). Attempts to purify **15b** by repeated preparative TLC with various solvent systems resulted only in decrease of isolated yield without noticeable increase of purity.

15a: R_f 0.50 (Et_2O/PE, 1:1, det. A, B). − GC-MS: not feasible (unstable). − ^1H NMR: δ 5.97 [2 H, s, C*H*−C*H*]; 4.57 [1 H, d, C*H*−O, *J* = 7.9 Hz] 4.55 [1 H, d, C*H*H−N, *J* = 19.0]; 4.10 [1 H, d, CH*H*−N, *J* = 19.0]; 3.93 [1 H, ddd, C*H*−N, *J* = 2.5, 5.5, 7.9]; 3.18 [1 H, dd, C*H*H−C=O, *J* = 5.5, 15.4]; 2.72 [1 H, broad d, CH*H*−N, *J* = 15.4]; 0.90 [9 H, s, $C(CH_3)_3$]; 0.20 and 0.16 [2× 3 H, 2s, $(CH_3)_3Si$]. − ^{13}C NMR (50 MHz): δ 169.22 [*C*=O]; 123.70, 123.34 [*C*H=*C*H]; 101.48, 96.44, 87.20 (× 2) [*C*≡*C*]; 67.10 [*C*H−O]; 59.23 [*C*H−N]; 42.46 [*C*H_2−C=O]; 34.28 [*C*H_2−N]; 25.64 [$C(CH_3)_3$]; 18.06 [$C(CH_3)_3$]; −3.56, −4.25 [$(CH_3)_2Si$].

15b: R_f 0.29 (Et_2O/PE, 1:1, det. A, B). GC-MS: not feasible (unstable). − ^1H NMR: δ 6.04 [1 H, dt, C*H*=CH, *J* = 1.3 (t) and 9.6]; 5.95 [1 H, dd, C*H*=CH, *J* = 2.2, 9.6]; 4.64 [1 H, t, C*H*−O, *J* = 1.7 Hz] 4.55 [1 H, d, C*H*H−N, *J* = 18.8]; 4.21 [1 H, d, CH*H*−N, *J* = 198.8]; 4.12 [1 H, ddd, C*H*−N, *J* = 1.4, 3.2, 4.6]; 3.02−2.85 [2 H, m, CH_2−C=O]; 0.90 [9 H, s, $C(CH_3)_3$]; 0.15 and 0.14 [2× 3 H, 2s, $(CH_3)_3Si$].

(3R,4S*)-3-(Carboxymethyl)-4-hydroxy-1,2,3,4-tetrahydroisoquinoline* (**17**): A solution of **15a** (9.2 mg, 30.5 μmol) in MeOH (0.5 ml) was treated with H_2O (110 μl), 1,4-cyclohexadiene (200 μl) and 1 N aqueous NaOH (90 μl). The disappearing of substrate (and of the corresponding desilylated alcohol **14a**) was followed by TLC. After 2.5 h the reaction was complete. The solution was treated with solid NH_4Cl (53 mg, 99 μmol) and evaporated to dryness in a lyophilizator. ^1H-NMR analysis of this crude product showed no trace of typical enediynic signals. The crude product was taken up in H_2O and little MeOH and purified through 5 g of Dowex 50W8 (H^+ form). After elution with 30 ml of H_2O, **17** was collected by eluting with 30 ml of 10% NH_4OH to give 6.3 mg of a white solid (76%). R_f 0.40 (*n*BuOH/H_2O/AcOH, 7:2:1, det. D). − ^1H NMR (CD_3OD): δ 7.60−7.18 [4 H, m, aromatics]; 4.68 [1 H, d, C*H*−OH, *J* = 7.0]; 4.39 & 4.32 [2 H, AB syst., CH_2−N, *J* = 17.1]; 3.55 [1 H, ddd, C*H*−N, *J* = 4.0, 7.0, 9.8]; 2.78 [1 H, dd, C*H*H−C=O, *J* = 4.0, 17.2]; 2.41 [1 H, dd, CH*H*−C=O, *J* = 9.8, 17.1].

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