New Approach to β-Lactam-Fused Enediynes ("Lactenediynes") by Stereoselective Pinacol Coupling

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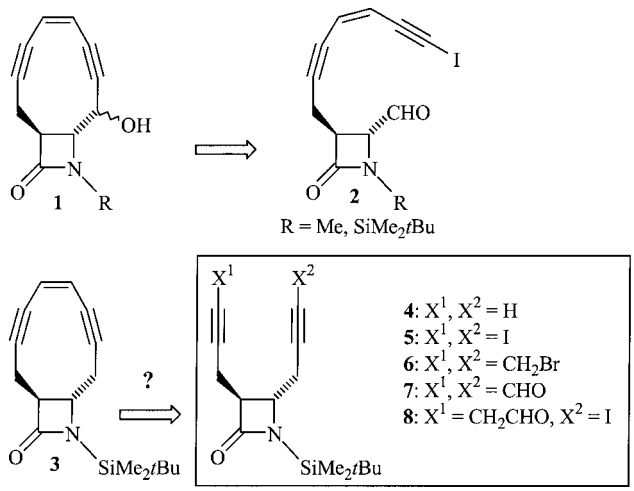
A short synthesis of unfunctionalized lactenediyne **3** by closure of the ten-membered ring at the double bond site is reported. After failure of the known methodologies, this closure was eventually successfully achieved thanks to a highly stereoselective, vanadium(II)-mediated pinacol coupling of bis-(alk-2-ynal) **7**.

Introduction

We recently introduced[1] a new class of rationally designed enediyne analogues,[2] called "lactenediynes," which are characterized by the fusion of a β-lactam with a ten-membered enediyne ring. Of these, the derivatives with a *trans* fusion involving carbon atoms 3 and 4 of the azetidinone, of general formula **1** (Scheme 1), were demonstrated to be particularly promising, because of their high stability and the easy cycloaromatization of the adducts that derive from β-lactam opening.



Scheme 1

Our previously reported syntheses of compounds **1**[1a][1b] involved the construction of the conjugated enediyne prior to closure of the ten-membered ring, which was carried out by the Nozaki intramolecular condensation of an iodoaldehyde of general formula **2**. Therefore, all these lactenediynes were characterized by the presence of a hydroxy group at C-9.

Although this hydroxy group can be useful for attaching DNA-complexing substructures, it obviously decreases the simplicity of these derivatives, adding to the basic bicyclic structure an additional functional group as well as an additional stereogenic centre.

On the other hand, we reasoned that a completely different approach, based on the macrocyclization of an appropriate dialkyne **4**–**8**, with generation of the double bond at the end of the synthesis, would have opened a new way toward "unfunctionalized" lactenediyne **3**, at the same time allowing more concise and convergent synthetic strategies.

In this paper we document the successful achievement of this goal and the shortest synthesis so far of a lactendiyne (only ten steps from a commercially available starting material).

Results and Discussion

At the outset of this work, only three methods for the synthesis of simple cyclic 3-ene-1,5-diynes by ring closure at the double bond site were known: (a) Nicolaou's method, which starts from a bis(propargyl bromide), proceeds through a cyclic sulfide and eventually involves Ramberg–Bäcklund rearrangement of a α-chlorosulfone;[3] (b) Jones' method, which also starts from a bis(propargyl bromide), but is considerably shorter, needing just one step for the base-promoted ring closure through carbenoid intermediates;[4] (c) Danishefsky's method,[5] which employs the unusual Stille double condensation of (*Z*)-bis(trimethylstannyl)-ethylene with a bis(iodoalkyne).

The first of these methods seemed less promising because of the high number of required steps when starting from the dibromide and because we felt that the reaction conditions are not compatible with the azetidinone. We therefore decided to test the other two routes, and prepared the requisite intermediates **5** and **6**. All the chiral compounds quoted in this paper were prepared in racemic form, al-

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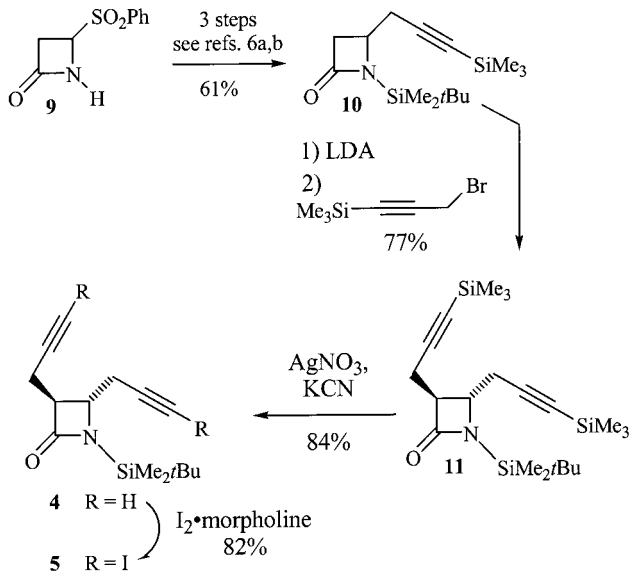
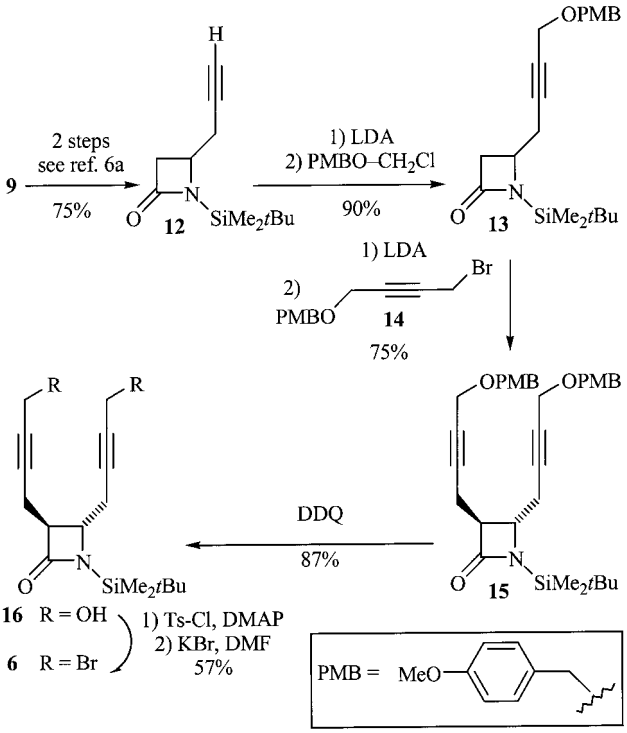
though, for the sake of clarity, one enantiomer is arbitrarily shown.

As starting material for the synthesis of **5** (Scheme 2) we employed the known[6] 4-propargyl azetidinone **10**, which can be prepared in three steps from 4-(sulfonyloxy)azetidinone **9**, in turn easily synthesized from commercially available 4-acetoxyazetidinone.[7] Highly stereoselective propargylation of the lithium enolate derived from **10** afforded *trans* compound **11** (no *cis* isomer was detected). Substitution of the trimethylsilyl groups with iodine atoms was best carried out in two steps, by selective alkyne desilylation, through the good method developed by Schmidt and Arens,[8] followed by iodination by the complex iodine–morpholine.



Scheme 2

For the preparation of **6** (Scheme 3), we first attempted to add two protected hydroxymethyl groups to **4**, by reaction of the corresponding lithium diacetylide with *p*-methoxybenzyloxymethyl chloride as synthetic equivalent of an electrophilic hydroxymethyl group.[9] The yields were, however, unsatisfactory. The use of HMPA as cosolvent led to even worse yields, because of extensive decomposition of the dianion. Thus we turned to a different route, which was also shorter, and involved introduction of the first protected hydroxymethyl group at the stage of **12**, to give **13**; this was followed by alkylation of the enolate derived from **13** with the propargylic bromide **14**, in turn prepared from 4-methoxybenzyl alcohol, as described in the Experimental Section. It is noteworthy that, contrary to what happened when the dialkyne **4** was employed, the alkylation of **12** with PMBOM–Cl proceeded in good yield. We think that the problems encountered in the double alkylation of **4** may be a consequence of the easier deprotonation at position 3 of the β-lactam, leading to unwanted side reactions. Oxidative removal of the protecting groups in **15** gave the diol **16**, which was in turn transformed into dibromide **6** by a two-step, not optimized sequence.

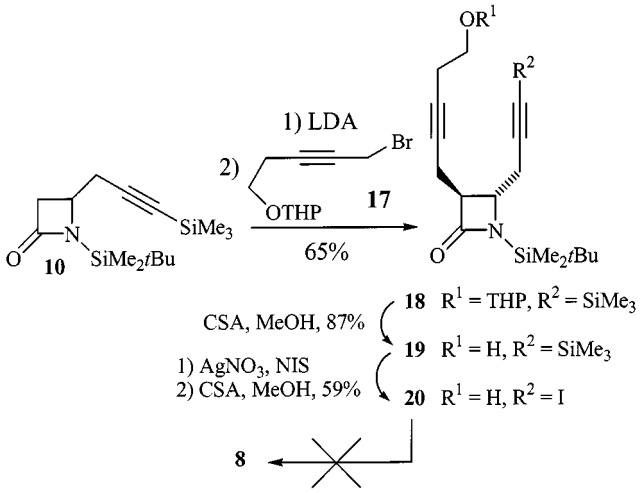


Scheme 3

Unfortunately, attempts to convert **5** and **6** into lactendiyne **3** by the methods of Danishefsky and Jones, respectively, failed. In the first case, the conformational freedom of our substrate **5** is perhaps the source of the problem. In all the successful reported examples of this modified Stille reaction,[5] the starting diiododiyne was conformationally quite rigid, with the two acetylenic groups nearby. For the second case, we think that Jones' methodology is not compatible with the presence of an enolizable carbon (C-3 of the β-lactam). As already mentioned, we previously observed that treatment of **4** (or other similar derivatives possessing a propargyl substituent at C-3) with strong bases in the presence of HMPA led to decomposition products. We also tried to transform dialkyne **4** into **3** by a double Castro–Stephens reaction with (*Z*)-dichloroethylene. Also in this case, as anticipated by previous reports,[5b,10] no desired product was formed.

We then turned to another possible approach, which involved iodoaldehyde **8** (Scheme 1). Since Nozaki intramolecular condensation of an iodoalkyne with an aldehyde is one of the most efficient methodologies for the construction of cyclic enediynes, as demostrated also by our previous syntheses of lactenediynes,[1a–1c] we reasoned that application of this reaction to **8** could lead to a secondary alcohol, which, upon elimination, would give **3**. This elimination was anticipated to be feasible, in the light of previous reports.[11] Preparation of iodoalcohol **20** (Scheme 4) was realized straightforwardly and convergently, through alkylation of the enolate derived from **10** with propargylic bromide **17**. However, all our attempts, under various con-

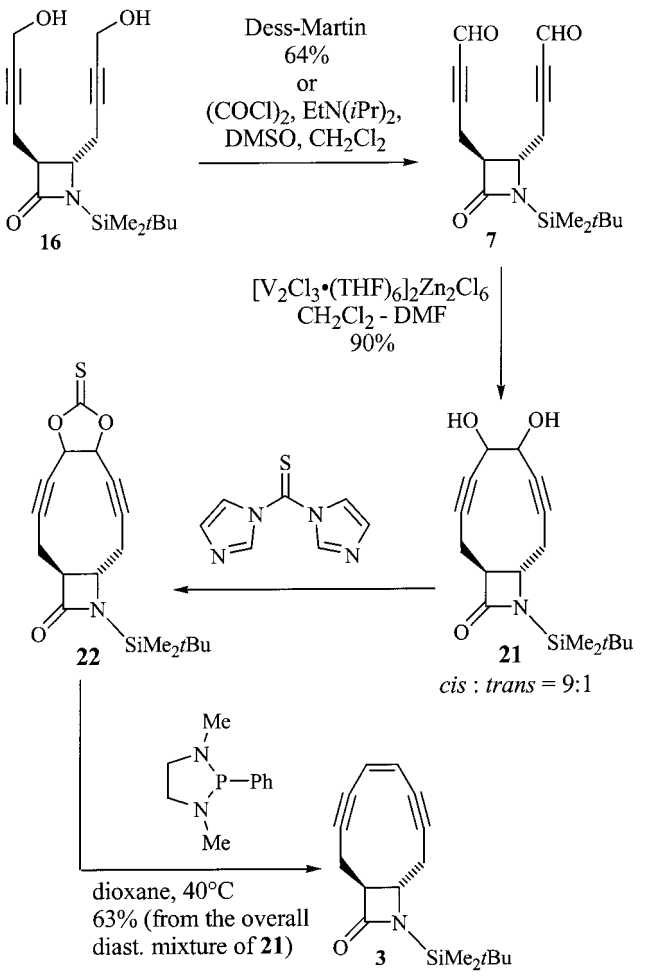
ditions, to oxidize this alcohol to the aldehyde **8** failed and unidentified decomposition products were obtained. A similar failure was also very recently reported by Caddick.[12] Thus it seems that alk-3-ynals are elusive compounds with low stability.[13]



Scheme 4

We finally decided to examine the reductive coupling of bis(alk-2-ynal) **7** (Scheme 5). Its synthesis from diol **16** was not trivial. Of the various reagents and conditions tested, only the Dess–Martin reagent or modified Swern oxidation furnished the desired compound in acceptable yields. Although relatively stable when pure, this dialdehyde seems to be very prone to forming insoluble polymerization adducts in the presence of various impurities. Thus it is essential to extractively remove all byproducts (especially the employed amine in case of Swern oxidation) before evaporation to dryness. While with the Dess–Martin method it is necessary to purify the aldehyde by chromatography, the crude aldehyde could be used as such without further purification in the case of Swern oxidation.

In principle, depending on the reaction conditions, reductive coupling of a dialdehyde can lead either to the alkene or to the diol. The yield of the only example of a McMurry direct coupling to an enediyne found in the literature[14] was low, however, and we thus preferred to examine the milder conversion into diol **21**. The stereochemical fate of this reaction is of paramount importance, since only the *cis* diol is anticipated to be convertible into the desired enediyne **3**. From this point of view, the use of the Pedersen vanadium (II) reagent[15] seemed particularly promising because: (a) it was already employed by Myers[16] on a similar dialdehyde with moderate yield (40%) and stereoselectivity (*cis*:*trans* = 4:1); and (b) the pinacol coupling is thought to proceed through a cyclic chelated transition state,[15b] and our force-field calculations on the corresponding cyclic carbonates showed that, in our case, the formation of *trans* cyclic transition states should be rather disfavoured. Molecular mechanics calculations (CSC Chem3D Pro, v4.5), carried out on the four diastereoisomers of the cyclic carbonate of desilylated **21**, showed that the *cis* isomers are approximately 8 kcal/mol more stable than the corresponding *trans* compounds. Results of these calculations as well as all parameters used are available as supplementary material.



Scheme 5

We were pleased that our hopes were well founded. The reaction was indeed very efficient both in terms of chemical yield and stereoselection. The overall yield was 90% when chromatographed dialdehyde was used as starting material, and was 58% when the crude aldehyde obtained from Swern oxidation (2 steps) was used. The yield of the combined steps was equal for the two cases. We could detect (GC, TLC) only three diastereoisomers in a 33:10:57 ratio. The two major isomers were later recognized to be *cis* (vide infra). Thus the overall *cis:trans* ratio was 9:1. The reaction was very fast (the dialdehyde disappeared in less than 2–3 min) and thus slow addition to the reducing agent solution ensured high dilution throughout the reaction. This explains the high yield and the absence of intermolecular adducts.

Conversion of *cis* diols **21** into the desired cyclic enediyne **3** was then carried out by the Corey–Hopkins modification of the Corey–Winter reaction.[17] This protocol had been used previously in the enediyne field, although not on diols derived from pinacol condensations.[18] The diastereoisomeric mixture of diols **21** was converted, by reaction with thiocarbonyl diimidazole, into the two *cis* isomers of the

thionocarbonates **22**. The same compounds were obtained independently by reaction of the two isolated major diols. In contrast, the minor (presumably *trans*) isomer reacted with thiocarbonyl diimidazole only sluggishly, to furnish only traces of the presumed *trans* thionocarbonate. Both isolated thionocarbonates independently gave, by reduction with *P*-phenyl-*N*,*N*-dimethyl-1,3-diaza-2-phospholidine at 40 °C, the same lactendiyne **3**, thus proving their relative *cis* configuration. The overall conversion of **21** into **3** can obviously be carried out more conveniently without isolation of the single isomers, in a 63% overall yield. While Semmelhack used *P*-methyl diazaphospholidine for the final reduction, we could, thanks to the thermal stability of lactenediyne **3**, employ the less reactive, but more convenient and commercially available *P*-phenyl diazaphospholidine.

Hudlicky[19] recently reported the failure of a similar diynediol to eliminate by the Corey–Winter reaction. However, in that case the pinacol reaction was carried out with SmI_2 and, although no hint was given on the stereoselection of the coupling reaction, we guess that in their case the *trans* diol could have been formed. Actually, usually SmI_2-mediated cyclizations afford *trans* stereoselectivity.[20] Therefore, a possible reason for the unsuccessful elimination could be the *trans* configuration of the starting diol, which, due to the well-known *syn* mechanism of the Corey–Winter reaction, prevents the elimination. This fact once again underlines the importance of *cis* stereoselection in the Pedersen reaction in our case.

Conclusion

We demonstrated the first possibility of closing a ten-membered enediyne ring by a three-step protocol which involves stereoselective Pedersen pinacol coupling followed by Corey–Winter reduction. This methodology is, in our opinion, a new, very useful addition to the few known methods for synthesizing this class of compounds by ring closure at the double-bond site. Our experience shows that this protocol is less sensitive to functional groups than Jones' methodology is, and it is less dependent on conformational biases (and on experimental conditions) than Danishefsky's modification of the Stille cross-coupling is.

Thanks to this successful approach we were able to complete the shortest synthesis so far of lactenediynes (ten steps) in good overall yield (13%) from commercially available 4-acetoxy-2-azetidinone.

Extension of this methodology to the convergent synthesis of other classes of lactenediynes is in progress.

Experimental Section

General Remarks: NMR spectra were measured in $CDCl_3$, at 200 MHz (^1H), and at 50 or 20 MHz (^{13}C). Chemical shifts, δ, are reported relative to TMS; coupling constants are reported in Hz. Peak assignment of ^1H NMR spectra was also made with the aid of double resonance experiments. In ABX systems, the proton A is considered to be downfield and B upfield. Peak assignment in ^{13}C spectra was made with the aid of DEPT or off-resonance experiments. – GC-MS was carried out on a HP-5971A instrument, with an HP-1 column (12 m long, 0.2 mm wide), electron impact was done at 70 eV, and at a mass temperature of approximately 167 °C. Analyses were performed with a constant He flow of 0.9 mL/min, starting at 100 °C for 2 min. and then the temperature was raised by 20 °C/min to 280 °C. Retention times are measured in minutes from injection. Masses below 33 *m*/*z* were excluded. – IR spectra were measured with a Perkin–Elmer 881 instrument, and as $CHCl_3$ solutions. – TLC analyses were carried out on silica gel plates, which were developed by being dipped into a solution of $(NH_4)_4MoO_4$•4 H_2O (21 g) and $Ce(SO_4)_2$•4 H_2O (1 g) in H_2SO_4 (31 mL) and H_2O (469 mL), and warming. R_f values were measured after an elution of 7–9 cm. – Chromatographies were carried out on 220–400-mesh silica gel, by the "flash" methodology. Petroleum ether (40–60 °C) is abbreviated as PE. – In extractive workup, aqueous solutions were always reextracted three times with the appropriate organic solvent. Organic extracts were dried over Na_2SO_4 and then filtered, before the solvent was removed by evaporation under reduced pressure. – All reactions employing dry solvents were carried out under a nitrogen or argon (where indicated) atmosphere. The purity of all new compounds was established by TLC, ^1H NMR, and (when possible) GC MS.

4-(Phenylsulfonyl)-2-azetidinone (9): In our hands, the described procedure[7] did not work well. We thus employed a slightly different method: A solution of 4-acetoxy-2-azetidinone (2.42 g, 18.74 mmol) in H_2O (10 mL) was treated with sodium benzenesulfinate (3.23 g, 19.68 mmol). The slightly yellow solution was stirred at 60 °C for 5 h. After standing overnight at room temperature, the white solid was filtered and washed with the minimal amount of water to give, after drying over P_4O_{10}, pure **9** (3.294 g, 83%). If, when working on smaller scale, it is impossible to avoid dissolution of product during washing, more product can be recovered by thoroughly extracting mother liquors, after saturation with NaCl, with AcOEt. M.p. 151–154 °C (Ref.[7] 156–157 °C).

(3*R,4*R**)-1-(*tert*-Butyldimethylsilyl)-3,4-bis[3-(trimethylsilylprop-2-yn-1-yl)]-2-azetidinone (11):** A solution of lithium diisopropylamide (LDA) in THF/hexanes (0.4 M; prepared under N_2 at –18 °C from 1.6 M *n*BuLi in hexanes) (23.3 mL, 9.32 mmol) was cooled to –78 °C and was treated with a solution of **10** (prepared from **9** as described in ref.[6a][6b]) (1.967 g, 6.65 mmol) in dry THF (4 + 2 + 2 mL). The temperature was allowed to rise to –50 °C over 30 min. Then the solution was cooled again to –78 °C and was treated with 1-trimethylsilyl-3-bromopropyne (1.40 mL, 9.9 mmol). The temperature was maintained at –78 °C for 30 min and was then allowed to rise to 0 °C over 2 h. Quenching with saturated NH_4Cl (50 mL), extraction with Et_2O, and chromatography (PE/Et_2O 85:15 + 1% Et_3N) gave pure **11** as a white solid (2.19 g, 81%). M.p. 95.6–96.2 °C. R_f 0.62 (PE/Et_2O 75:25). GC-MS: R_t: 8.88. *M*/*z* (%): 390 (M^+–15, 0.9); 348 (M^+ –57, 14.1); 233 (11.0); 169 (30.5); 160 (9.7); 159 (12.5); 155 (12.6); 145 (8.5); 135 (7.9); 109 (5.0); 100 (28.6); 97 (6.4); 83 (5.4); 73 (100); 59 (9.5); 45 (6.0). ^1H NMR: δ 3.67 [1 H, ddd, C*H*N, *J* 2.6, 4.0, 5.6]; 3.20 [1 H, dt, C*H*–C=O, J 2.6 (d), 5.8 (t)]; 2.76–2.49 [4 H, m, CH_2]; 0.98 [9 H, s, $C(CH_3)_3$]; 0.26 and 0.25 [2 × 3 H, 2 s, $(CH_3)_2Si$]; 0.15 and 0.14 [2 × 9 H, 2s, $(CH_3)_3Si$]. ^{13}C NMR (50 MHz.): δ 172.8 [*C*=O]; 102.4, 101.4, 88.3, 86.7 [*C*≡*C*]; 53.5, 52.5 [*C*H]; 26.2 [$C(CH_3)_3$]; 25.8, 18.6 [CH_2], 18.3 [$C(CH_3)_3$]; 0.1, 0.0 [$Si(CH_3)_3$]; –5.5, –5.8 [$Si(CH_3)_2$]. IR: ν 2960, 2928, 2897, 2857, 2175, 1738, 1421, 1343, 1317, 1252, 1211, 1175, 1153, 1086, 1045, 1014, 837 cm^{-1}.

(3*R,4*R**)-1-(*tert*-Butyldimethylsilyl)-3,4-bis(prop-2-yn-1-yl)-2-azetidinone (4):** A solution of diyne **11** (850 mg, 2.09 mmol) in 96% ethanol (20 mL) was cooled to 0 °C and was treated with a 2 M solution of $AgNO_3$ in H_2O (4.2 mL, 8.4 mmol). The resulting thick white suspension was stirred for 280 min at 0 °C. Then KCN (1.84 g, 28.22 mmol) in H_2O (10 mL) was added. After 15 min, the reaction mixture was poured into water (50 mL) and Et_2O (100 mL). The phases were rapidly separated and the aqueous phase was reextracted twice with Et_2O. The organic extracts were washed with sat. NaCl, evaporated to dryness, and chromatographed (PE/Et_2O 6:4) to give pure **4** (462 mg, 84%). R_f 0.41 (PE/Et_2O 6:4). GC-MS: R_t: 6.44. *M*/*z* (%): 246 (M^+–15, 0.3); 204 (M^+ – 57, 39.2); 157 (22.7); 124 (57.7); 104 (8.8); 103 (16.2); 100 (100); 97 (48.1); 78 (11.3); 73 (12.4); 57 (5.5); 56 (6.2). ^{1}H NMR: δ 3.67 [1 H, ddd, C*H*N, *J* 2.5, 3.1, 6.7]; 3.22 [1 H, dt, C*H*–C=O, J 2.5 (d), 5.7 (t)]; 2.75–2.41 [4 H, m, CH_2]; 2.04 [1 H, t, C≡C*H*, J 2.6]; 2.01 [1 H, t, C≡C*H*, J 2.6]; 0.98 [9 H, s, $C(CH_3)_3$]; 0.28 and 0.23 [2 × 3 H, 2 s, $(CH_3)_2$Si]. ^{13}C NMR (50 MHz.): δ 172.7 [*C*=O]; 80.1, 78.9, 71.4, 70.4 [*C*≡*C*]; 54.0, 52.7 [*C*H]; 26.1 [$C(CH_3)_3$]; 24.6, 17.5 [CH_2], 18.3 [$C(CH_3)_3$]; –5.5, –5.7 [$Si(CH_3)_2$]. IR: ν 3305, 2955, 2930, 2883, 2858, 2123, 1742, 1460, 1425, 1360, 1343, 1319, 1255, 1212, 1174, 1154, 1078, 1042, 1013, 836, 821, 808 cm^{-1}.

(3*R,4*R**)-1-(*tert*-Butyldimethylsilyl)-3,4-bis(3-iodoprop-2-yn-1-yl)-2-azetidinone (5):** A solution of dialkyne **4** (192 mg, 0.734 mmol) in dry benzene (20 mL) was treated with morpholine (1.92 mL, 22.0 mmol) and iodine (1.86 g, 7.3 mmol). The suspension was stirred in the dark for 4 h at 45 °C. The reaction was quenched with 0.5 M $(NH_4)H_2PO_4$ (50 mL) + 1 N HCl (15 mL) and the reaction mixture was extracted with Et_2O. The organic layers were washed with 10% $Na_2S_2O_3$, and were evaporated to dryness to give, after chromatography (PE/Et_2O 7:3 to 6:4) , pure **5** (310 mg, 82%). R_f 0.34 (PE/Et_2O 7:3). GC-MS: R_t: 10.35. *M*/*z* (%): 456 (M^+–57, 17.5); 356 (11.8); 330 (13.1); 251 (11.8); 250 (100); 229 (5.4); 223 (91.9); 195 (10.0); 191 (12.8); 185 (6.0); 165 (6.2); 157 (37.5); 102 (20.3); 100 (48.5); 73 (7.3). ^{1}H NMR: δ 3.64 [1 H, ddd, C*H*N, *J* 2.6, 3.7, 6.8]; 3.15 [1 H, dt, C*H*–C=O, J 2.5 (d), 5.5 (t)]; 2.90–2.56 [4 H, m, CH_2]; 0.98 [9 H, s, $C(CH_3)_3$]; 0.28 and 0.24 [2 × 3 H, 2 s, $(CH_3)_2$Si]. IR: ν 2954, 2929, 2857, 2242, 1744, 1457, 1422, 1358, 1343, 1317, 1273, 1255, 1208, 1173, 1152, 1077, 1042, 1013, 821 cm^{-1}.

(*rac*)-1-(*tert*-Butyldimethylsilyl)-4-{4-[(4-methoxyphenyl)-methoxy]but-2-yn-1-yl}-2-azetidinone (13): A solution of alkyne **12** (2.224 g, 10.0 mmol), prepared from **9** as described in Ref.,[6a] in dry THF (40 mL) was cooled to –78 °C, and treated with asolution of lithium diisopropylamide (LDA) in THF-hexanes (0.4 M; prepared under N_2 at –18 °C from 1.6 M *n*BuLi in hexanes) (32.5 mL, 13.0 mmol). After 30 min, the solution was treated with *p*-methoxybenzyloxymethyl chloride[9b] (2.80 g, 15.0 mmol). The mixture was allowed to warm to room temp over 4 h. Then it was quenched with saturated NH_4Cl, extracted with Et_2O, evaporated to dryness, and immediately chromatographed (PE/Et_2O 60:40 + 1% Et_3N to PE/Et_2O 20:80), to give pure **13** as an oil (2.65 g, 71%) and to recover unchanged **12** (462 mg, 20.8%). Yield from nonrecovered **12** = 90%. R_f 0.66 (PE/AcOEt 1:1; R_f of **12**: 0.76) R_f 0.39 (PE/AcOEt 7:3). GC-MS: R_t: 10.98. *M*/*z* (%): 328 (M^+–30–15, 0.05); 286 (M^+–30–57, 0.86); 237 (M^+–136, 20.2); 180 (2.05); 175 (2.5); 142 (1.6); 138 (2.2); 135 (3.5); 121 (100); 100 (8.8); 97 (5.0); 77 (6.3); 75 (6.2); 73 (12.1). ^{1}H NMR: δ 7.35–7.20 [2 H, m, *H meta* to OMe]; 6.95–6.82 [2 H, m, *H ortho* to OMe]; 4.50 [2 H, s, O–C*H*–O]; 4.12 [2 H, t, C≡C–CH_2O, *J* 2.1]; 3.81 [3 H, s, OCH_3]; 3.77–3.62 [1 H, m, C*H*–N]; 3.20 [1 H, dd, C*H*H–C=O, *J* 5.4, 15.4]; 2.89 [1 H, dd, C*H*H–C=O, *J* 2.7, 15.4]; 2.70 [1 H, ddt, N–CH–C*H*H, *J* 2.1 (t), 3.4, 16.8]; 2.51 [1 H, ddt, N–CH–C*H*H, *J* 2.1 (t), 7.4, 16.8]; 0.97 [9 H, s, $C(CH_3)_3$]; 0.26 and 0.23 [2 × 3 H, 2 s, $Si(CH_3)_2$]. ^{13}C NMR (50 MHz.): δ 172.1 [*C*=O]; 159.4 [*C*–OMe]; 129.7 [aromatics *meta* to OMe]; 129.5 [*C*–CH_2]; 113.8 [aromatics *ortho* to OMe]; 81.2, 79.1 [*C*≡*C*]; 71.2 [*C*H_2O]; 57.1 [*C*H_2O]; 55.3 [*C*H_3O]; 47.4 [*C*H–N]; 43.7 [*C*H_2–C=O]; 26.2 [$C(CH_3)_3$]; 25.9 [C≡C–*C*H_2]; 18.4 [$C(CH_3)_3$]; –5.5, –5.8 [$Si(CH_3)_2$].

[(4-Methoxyphenyl)methyl Propargyl Ether: A suspension of NaH (60% dispersion in mineral oil, 3.53 g, 88.2 mmol) in dry DMF (100 mL) was cooled to 0 °C and was slowly treated, dropwise from a dropping funnel, with 4-methoxybenzyl alcohol (10 mL, 80.2 mL). After 25 min, propargyl bromide (80% in toluene) (9.83 mL, 88.22 mmol) was added dropwise. After 150 min at 0 °C and 40 min at room temp, the mixture was cooled again to 0 °C, and treated with a solution of K_2CO_3 (4.5 g) in H_2O (50 mL). After it was stirred for 15 min, the mixture was diluted with H_2O (50 mL) and was extracted three times with PE/Et_2O 1:1. After a last extraction with Et_2O, the reunited organic extracts were washed with H_2O, evaporated, and chromatographed (PE/Et_2O 8:2) to give pure (4-methoxyphenyl)methyl propargyl ether as a pale yellow liquid (10.75 g, 76%). R_f 0.73 (PE/Et_2O 6: 4). ^{1}H NMR: δ 7.28 [2 H, d, C*H meta* to OCH_3, *J* 8.7]; 6.88 [2 H, d, C*H ortho* to OCH_3, *J* 8.7]; 4.54 [2 H, s, ArCH_2O]; 4.14 [2 H, d, C≡C–CH_2O, *J* 2.3]; 3.80 [3 H, s, OCH_3]; 2.46 [1 H, t, C≡C*H*, *J* 2.3].

4-[(4-Methoxyphenyl)methoxy]but-2-yn-1-ol: A solution of (4-methoxyphenyl)methyl propargyl ether (5.0 g, 28.4 mmol) in dry THF (100 mL), was cooled to 0 °C and treated dropwise with a 3 M solution of EtMgBr in Et_2O (11.35 mL, 34.05 mmol). After 30 min, paraformaldehyde (5.12 g, 170.4 mmol) was added by rapidly opening the reaction flask. The resulting suspension was stirred for 2 h at 0 °C and overnight at room temp. Quenching was carried out at 0 °C with saturated NH_4Cl (50 mL) + 20 mL of H_2O. After dilution with Et_2O (100 mL), the mixture was filtered through a celite cake. The phases were separated and the aqueous one was reextracted twice with Et_2O. Evaporation followed by chromatography (PE/Et_2O 3:7 to 0:10) gave 4.38 g of nearly pure product, which by ^{1}H NMR was shown to be contaminated by 5–6% of the corresponding hemiacetal with formaldehyde. This product was dissolved in MeOH (30 mL), treated with anhydrous K_2CO_3 (1.5 g) and stirred at room temp for 4 h. The mixture was carefully neutralized with AcOH (1.27 mL) and the solvent was removed by evaporation. The residue was dissolved in Et_2O and washed with saturated NaCl. After evaporation, pure (by t.l.c. and ^{1}H NMR) 4-[(4-methoxyphenyl)methoxy]but-2-yn-1-ol was obtained as an oil (4.099 g, 70%). R_f 0.26 (PE/Et_2O 6: 4). ^{1}H NMR: δ 7.28 [2 H, d, C*H meta* to OCH_3, *J* 8.7]; 6.88 [2 H, d, C*H ortho* to OCH_3, *J* 8.7]; 4.52 [2 H, s, ArCH_2O]; 4.31 [2 H, broad s, CH_2OH]; 4.17 [2 H, d, C≡C–CH_2O, *J* 1.8]; 3.80 [3 H, s, OCH_3]; 2.05 [1 H, broad s, OH]. GC-MS: R_t: 7.28. *M*/*z* (%): 206 (M^+, 21.2); 175 (21.7); 160 (7.3); 147 (8.0); 145 (12.1); 137 (17.6); 136 (37.9); 135 (64.5); 122 (15.6); 121 (100); 109 (18.6); 107 (7.7); 94 (14.6); 91 (11.2); 78 (18.6); 77 (34.2); 69 (7.2); 65 (7.9); 63 (6.1); 52 (8.3); 51 (12.2); 50 (5.1); 41 (13.9); 39 (21.9).

1-Bromo-4-[(4-methoxyphenyl)methoxy]but-2-yne (14): 4-[(4-Methoxyphenyl)methoxy]but-2-yn-1-ol (2.188 g, 10.61 mmol) was dissolved in dry Et_2O (50 mL), treated with CBr_4 (7.04 g, 21.22 mmol), and cooled to 0 °C. The resulting solution was treated, over 5 min, with a solution of nBu_3P (5.29 mL, 21.22 mmol) in dry Et_2O (10 mL). A thick precipitate formed. The suspension was stirred for 30 min at 0 °C and for 1 h at room temp. Then the suspension was transferred to the top of a silica gel column (50 g) packed with Et_2O. For quantitative transfer of the crude

product, the flask was washed with CH_2Cl_2. Elution with Et_2O gave a crude product (6.83 g) that was chromatographed (PE/Et_2O to pure Et_2O) to give pure **14** as a colourless oil (with a tendency to become darker on standing) (2.237 g, 78%) plus 194 mg of recovered 4-[(4-methoxyphenyl)methoxy]but-2-yn-1-ol (9%). Yield from unrecovered starting material = 86%. R_f 0.73 (PE/Et_2O 1: 1). ^{1}H NMR: δ 7.28 [2 H, d, C*H meta* to OCH_3, *J* 8.7]; 6.88 [2 H, d, C*H ortho* to OCH_3, *J* 8.7]; 4.53 [2 H, s, ArCH_2O]; 4.19 [2 H, d, C≡C–CH_2O, *J* 2.0]; 3.97 [2 H, t, CH_2Br, *J* 2.0]; 3.81 [3 H, s, OCH_3]. ^{13}C NMR (50 MHz): δ 159.4 [MeO–*C*]; 129.8 [*C*H *meta* to OCH_3]; 129.2 [*C*–CH_2O]; 113.9 [*C*H *ortho* to OCH_3]; 83.0, 81.4 [*C*≡*C*]; 71.4 [CH_2O]; 56.9 [C≡C–CH_2O]; 55.3 [O*C*H$_3$]; 14.3 [CH_2Br].

(3*R,4*R**)-1-(*tert*-Butyldimethylsilyl)-3,4-bis{4-[(4-methoxyphenyl)-methoxy]but-2-yn-1-yl}-2-azetidinone (15):** A solution of alkyne **13** (2.331 g, 6.24 mmol) in dry THF (5 + 2 mL) was added, at –78 °C, to a solution of lithium diisopropylamide (LDA) in THF/hexanes (0.4 M; prepared under N_2 at –18 °C from 1.6 M *n*BuLi in hexanes) (19.5 mL, 7.80 mmol). After 20 min, the solution was treated with bromide **14** (2.100 g, 7.80 mmol), dissolved in 5 + 2 mL of THF. The temperature was allowed to rise to 0 °C over 140 min. Then the reaction was quenched with saturated NH_4Cl (10 mL). After it was stirred for 1 h at 0 °C, the mixture was diluted with saturated NH_4Cl (50 mL) and extracted with Et_2O. Evaporation and careful chromatography (PE/AcOEt 7:3 + 1% Et_3N) gave pure **15** as an oil (2.627 g, 75%). R_f 0.29 (PE/AcOEt 7:3). ^{1}H NMR: δ 7.35–7.22 [4 H, m, *H meta* to OMe]; 6.95–6.82 [4 H, m, *H ortho* to OMe]; 4.49 [4 H, s, O–C*H*–O]; 4.12 [2 H, t, C≡C–CH_2O, *J* 2.1]; 4.10 [2 H, t, C≡C–CH_2O, *J* 2.1]; 3.80 [6 H, s, OCH_3]; 3.75–3.62 [1 H, m, C*H*–N]; 3.22 [1 H, dt, C*H*–C=O, *J* 2.5 (d), 5.8 (t)]; 2.80–2.48 [4 H, m, C≡C–CH_2]; 0.97 [9 H, s, C(CH_3)$_3$]; 0.27 and 0.22 [2 × 3 H, 2 s, Si(CH_3)$_2$]. ^{13}C NMR (20 MHz.): δ 172.8 [*C*=O]; 159.3 [*C*–OMe]; 129.5 [*C meta* to OMe + *C*–CH_2O]; 113.8 [*C ortho* to OMe]; 82.4, 81.2, 79.2, 78.1 [*C*≡*C*]; 71.2 [*C*H$_2$–Ar]; 57.3, 57.2 [C≡C–*C*H$_2$O]; 55.3 [O*C*H$_3$]; 54.2, 52.9 [*C*H]; 26.1 [C(*C*H$_3$)$_3$]; 25.0, 17.9 [C≡C–*C*H$_2$–C]; 18.4 [*C*(CH$_3$)$_3$]; –5.5, –5.7 [Si(*C*H$_3$)$_2$]. IR: ν 3000, 2931, 2857, 1739, 1612, 1505, 1465, 1355, 1302, 1194, 1070, 1033 cm^{-1}.

(3*R,4*R**)-1-(*tert*-Butyldimethylsilyl)-3,4-bis(4-hydroxybut-2-yn-1-yl)-2-azetidinone (16):** A solution of dialkyne **15** (534 mg, 0.95 mmol) in CH_2Cl_2 (30 mL) was treated with a phosphate buffer (pH 7; 0.2 M; 4.75 mL), *tert*-butyl alcohol (4.75 mL) and dichlorodicyano-*p*-benzoquinone (DDQ) (689 mg, 3.03 mmol). The mixture was stirred at room temp for 13 h, and then treated with sat $NaHCO_3$ (40 mL) and filtered through a celite cake. After addition of 10% $NaHSO_3$ (8 mL) and neutralization with 1 M NaOH, the phases were separated and the aqueous one was extracted twice with CH_2Cl_2. The organic layers were washed with saturated NaCl, evaporated, and chromatographed (AcOEt/PE 7:3 to 8:2) to give pure **16** as a colourless oil (267 mg, 87%). R_f 0.43 (PE/AcOEt 2:8). ^{1}H NMR: δ 4.23 [4 H, broad, CH_2OH]; 3.61 [1 H, ddd, C*H*N, *J* 2.3, 3.4, 5.8]; 3.19 [1 H, ddd, C*H*–C=O, *J* 2.3, 5.2, 7.5]; 3.05 [2 H, broad s, O*H*]; 2.82–2.38 [4 H, m, C≡C–CH_2–C]; 0.97 [9 H, s, C(CH_3)$_3$]; 0.28 and 0.22 [2 × 3 H, 2 s, Si(CH_3)$_2$]. GC-MS: R_t: 9.95. *M*/*z* (%): 278 (M^+– 43, 0.63); 264 (M^+– 57, 23.1); 154 (11.1); 146 (6.3); 145 (8.1); 142 (5.6); 131 (7.0); 129 (7.1); 128 (21.2); 127 (10.1); 117 (28.7); 116 (9.1); 115 (31.9); 104 (7.1); 103 (16.4); 102 (50.2); 101 (9.6); 100 (88.8); 93 (23.9); 91 (28.0); 79 (18.9); 78 (9.8); 77 (21.5); 76 (8.2); 75 (100); 74 (6.2); 73 (42.1); 72 (8.9); 67 (8.4); 65 (15.4); 59 (8.2); 57 (16.6); 56 (10.8); 55 (11.9); 53 (7.6); 45 (9.7); 43 (9.3); 41 (29.4); 39 (16.4).

(3*R,4*R**)-3,4-Bis(4-bromobut-2-yn-1-yl)-1-(*tert*-butyldimethylsilyl)-2-azetidinone (6):** A solution of diol **16** (155 mg, 0.482 mmol) in dry CH_2Cl_2 (4 mL) was cooled to –20 °C, and treated with 4-dimethylaminopyridine (DMAP) (290 mg, 2.37 mmol) and *p*-toluenesulfonyl chloride (240 mg, 1.26 mmol). After 30 min, the mixture was warmed to 0 °C and stirred at that temperature for 1 h. After addition of saturated NH_4Cl, extraction with Et_2O, and evaporation to dryness, the crude tosylate was taken up in dry DMF (4 mL) and treated with KBr (340 mg, 2.86 mmol). After 2 h at room temp, the mixture was diluted with saturated NaCl/H_2O 1:1 and extracted with Et_2O. Evaporation to dryness and chromatography (PE/AcOEt 85:15 to 60:40) gave pure **6** (122 mg, 57%). R_f 0.61 (PE/Et_2O 1:1).

(3*R,4*R**)-1-(*tert*-Butyldimethylsilyl)-3,4-bis(4-oxobut-2-yn-1-yl)-2-azetidinone (7). – Method A:** A solution of diol **16** (111.4 mg, 347 μmol) in dry CH_2Cl_2 (4 mL) was treated with Dess–Martin periodinane[21] (440 mg, 1.037 mmol). The suspension was stirred at room temp for 17 h. After removal of the unsoluble matter by filtration, the filtrate was washed with 0.4 M $Na_2S_2O_5$ (20 mL), dried, and evaporated to give a crude product (93.7 mg), which contained small amounts of monoaldehydes and other impurities. Further purification by chromatography (PE/AcOEt 6:4 to 1:1) afforded pure **7** as colourless oil (69.0 mg, 63%).

Method B: A solution of dimethyl sulfoxide (DMSO) (128 μL, 1.80 mmol) in dry CH_2Cl_2 (15 mL) was cooled to –78 °C, and was treated with a 2.6 M solution of $(COCl)_2$ in CH_2Cl_2 (550 μL, 1.43 mmol). After 10 min, a solution of diol **16** (116.0 mg, 361 μmol) in dry CH_2Cl_2 (3 × 1 mL) was added. After 10 min, Et-N(*i*Pr)$_2$ (630 μL, 3.62 mmol) was added. After being stirred overnight at –78 °C, the mixture was allowed to warm to –40 °C over 30 min and was stirred at this temperature for 2 h. Then it was poured into 50 mL of 5% $(NH_4)H_2PO_4$. Extraction with Et_2O, followed by washing of the organic layers with 5% $(NH_4)H_2PO_4$, H_2O, and saturated NaCl gave, after evaporation to dryness, a crude product as colourless oil. It was taken up with CH_2Cl_2 and toluene and was evaporated to dryness in order to remove traces of water. This procedure was repeated twice (the oil tended to become red upon evaporation) to give, after drying at 5•10^{-2} mbar, 102.0 mg of crude product, which contained no monoaldehydes, and was used without further purification for the next reaction. R_f 0.80 (PE/AcOEt 2:8), 0.57 (PE/AcOEt 1:1). ^{1}H NMR: δ 9.18, 9.16 [2 × 1 H, 2 s, C*H*=O]; 3.70 [1 H, ddd, C*H*N, *J* 2.5, 3.5, 6.1]; 3.27 [1 H, ddd, C*H*–C=O, *J* 2.5, 5.5, 6.6]; 2.93 and 2.74 [2 H, AB part of an ABX syst., C≡C–CH_2–C, J_{AB} 17.6, J_{AX} 3.5, J_{BX} 7.5]; 2.88 and 2.85[2 H, AB part of an ABX syst., C≡C–CH_2–C, *J* could not be determined accurately]; 0.98 [9 H, s, C(CH_3)$_3$]; 0.30 and 0.25 [2 × 3 H, 2 s, Si(CH_3)$_2$]. GC-MS: R_t: 9.32. *M*/*z* (%): 260 (M^+– 57, 34.7); 152 (20.0); 125 (91.7); 115 (8.18); 102 (5.9); 100 (100); 97 (6.5); 77 (7.7); 75 (14.9); 73 (27.6); 72 (8.6); 59 (8.4); 57 (16.1); 56 (10.5); 51 (6.0); 45 (6.8); 43 (6.7); 41 (8.4); 39 (8.9). ^{13}C NMR (50 MHz.): δ 176.3, 176.1 [*C*HO]; 171.2 [*C*=O]; 92.9, 91.4, 83.6, 82.8 [*C*≡*C*]; 53.9, 52.5 [*C*H]; 26.1 [C(*C*H$_3$)$_3$]; 25.5 [C≡C–*C*H$_2$]; 18.4, 18.3 [C≡C–*C*H$_2$ + *C*(CH$_3$)$_3$].

11-(*tert*-Butyldimethylsilyl)-5,6-dihydroxy-11-azabicyclo-[8.2.0]dodeca-3,7-diyn-12-ones (21): *Note*: for this reaction freshly prepared[22] VCl_3•3 THF is recommended (the commercially available samples were not suitable). This complex is very sensitive to air. It can be stored only for a few months under nitrogen or argon and should be manipulated in a dry-box or in a glove-bag. When it becomes doughy or the colour changes from pale pink to grey or green, it should be discarded. A solution of VCl_3•3THF (1.236 g, 3.30 mmol) in dry CH_2Cl_2 (12 mL), kept under argon, was treated (by rapidly opening the flask) with powdered zinc (136 mg, 2.092 mmol). After being stirred for 30 min at room temp, the mixture was diluted with CH_2Cl_2 (12 mL), and was treated with dry

DMF (1.4 mL). To this mixture, a solution of dialdehyde **7** (chromatographed, from method A) (114 mg, 0.359 mmol) in 14 mL of CH_2Cl_2 was slowly added through a dropping funnel, over 100 min. At the end of the addition, the reaction was stirred for a further 30 min and then poured into 30 mL of H_2O. The phases were separated and the organic phase was washed with 40% Na,K tartrate (30 mL) and saturated NaCl. After evaporation and chromatography (AcOEt/PE 6:4 to 7:3), the diastereomeric mixture of diols **21** could be obtained (103 mg, 90%). With the crude product from the Swern oxidation (obtained as described in method B) as starting material, 67 mg of the diastereomeric mixture was obtained (58% from **16**).

The diastereomeric mixture described above gave three well-separated TLC spots (CH_2Cl_2/Et_2O 1:1): **21a** (R_f 0.47); **21b** (R_f 0.33); **21c** (R_f 0.26). GC analysis (SE-54 capillary column, length 18 m, i.d. 0.25 mm, P = 150 KPa, T = 150 °C for 2 min, then increased by 10 °C/min to 200 °C; det.: FID) indicated a **21a** (R_t 26.53): **21b** (R_t 29.13): **21c** (R_t 26.99) ratio = 33:10:57. Chromatography (CH_2Cl_2/Et_2O) furnished pure samples of **21a** and **21c**, whereas only enriched samples of **21b** could be obtained. The relative configurations of these compounds were not completely determined, although stereogenic centres 5 and 6 of **21a** and **21c** have been demonstrated to be *cis* in relation to each other.

21a: ^{1}H NMR: δ 4.53, 4.39 [2 × 1 H, 2 broad s, C*H*OH]; 3.59 [1 H, ddd, C*H*N, *J* 2.6, 3.9, 11.1]; 3.17 [1 H, ddd, C*H*–C=O, *J* 2.6, 4.1, 12.8]; 2.90–2.50 [2 H, broad peak, O*H*]; 2.77 [2 H, ddd, C*H*H–C≡C (*pseudo*-eq), *J* 2.0, 4.1, 16.2]; 2.39 [1 H, ddd, C*H*H–C≡C *pseudo*-ax, *J* 1.0, 11.1, 16.2]; 2.25 [1 H, ddd, C*H*H–C≡C *pseudo*-ax, *J* 2.9, 4.1, 16.1]; 0.95 [9 H, s, C(CH_3)$_3$]; 0.25 and 0.21 [2 × 3 H, 2 s, Si(CH_3)$_2$]. GC-MS: R_t: 9.90. *M*/*z* (%): 262 (M^+– 57, 10.3); 154 (5.3); 142 (5.3); 128 (36.7); 127 (8.8); 125 (8.3); 116 (5.7); 115 (28.9); 105 (6.9); 102 (9.0); 100 (26.7); 95 (100); 94 (6.8); 91 (6.7); 79 (7.0); 77 (13.4); 75 (66.7); 73 (68.7); 68 (21.9); 67 (27.1); 65 (6.1); 59 (9.5); 57 (8.7); 55 (7.7); 45 (7.7); 43 (7.9); 41 (7.9); 39 (9.7). ^{13}C NMR (50 MHz.): δ 172.8 [*C*=O]; 88.5, 84.1, 83.7, 83.6 [*C*≡*C*]; 66.9, 66.3 [*C*H–OH]; 58.5, 56.9 [*C*H–N, *C*H–C=O]; 26.6 [C(*C*H_3)$_3$]; 26.5, 19.5 [C≡C–*C*H_2]; 18.7 [*C*(CH_3)$_3$]; –4.9, –5.3 [(*C*H_3)$_2$Si].

21b: GC-MS: R_t: 10.02. *M*/*z* (%): 262 (M^+– 57, 20.0); 154 (7.4); 142 (6.9); 128 (13.5); 125 (14.4); 115 (36.5); 105 (7.9); 102 (6.7); 100 (37.7); 99 (7.9); 95 (100); 94 (7.0); 91 (7.9); 79 (7.0); 77 (12.1); 75 (58.1); 73 (67.9); 68 (23.2); 67 (22.3); 66 (6.3); 65 (6.3); 59 (8.4); 57 (7.2); 55 (9.3); 45 (7.9); 41 (10.6); 39 (7.5).

21c: ^{1}H NMR: δ 4.51, 4.38 [2 × 1 H, 2 broad s, C*H*OH]; 3.53 [1 H, ddd, C*H*N, *J* 2.6, 3.9, 11.2]; 3.27 [1 H, ddd, C*H*–C=O, *J* 2.6, 4.1, 12.7]; 3.30–2.80 [2 H, broad peak, O*H*]; 2.78 [1 H, ddd, C*H*H–C≡C (*pseudo*-eq), *J* 1.8, 4.1, 17.1]; 2.71 [1 H, ddd, C*H*H–C≡C (*pseudo*-eq), *J* 2.5, 3.9, 16.2]; 2.29 [2 H, ddd, C*H*H–C≡C *pseudo*-ax, *J* 1.0, 12.1, 16.4]; 0.93 [9 H, s, C(CH_3)$_3$]; 0.24 and 0.20 [2 × 3 H, 2 s, Si(CH_3)$_2$]. GC-MS: R_t: 9.95. *M*/*z* (%): 319 (M^+, 0.72); 262 (M^+– 57, 15.7); 154 (5.5); 128 (7.1); 125 (8.3); 116 (5.4); 115 (31.3); 105 (6.6); 100 (21.9); 95 (100); 91 (5.9); 79 (6.3); 77 (11.2); 75 (63.1); 73 (65.7); 68 (25.2); 67 (27.1); 65 (6.0); 59 (9.0); 57 (6.2); 55 (7.0); 45 (7.8); 41 (7.2); 39 (8.8). ^{13}C NMR (50 MHz.): δ 173.0 [*C*=O]; 86.5, 86.2, 84.3, 83.3 [*C*≡*C*]; 66.8, 66.5 [*C*H–OH]; 58.7, 56.9 [*C*H–N, *C*H–C=O]; 26.6 [C(*C*H_3)$_3$ + C≡C–*C*H_2]; 19.4 [C≡C–*C*H_2]; 18.7 [*C*(CH_3)$_3$]; –4.9, –5.3 [(*C*H_3)$_2$Si].

(1*R,5*R**,6*S**,10*R**)- and (1*R**,5*S**,6*R**,10*R**)-11-(*tert*-Butyldimethylsilyl)-5,6-(thiocarbonyldioxy)-11-azabicyclo[8,2,0]dodeca-3,7-diyn-12-ones (22):** A diastereomeric mixture of diols **21** (53.4 mg, 167.2 μmol), obtained as described above, was dissolved in dry THF, treated with thiocarbonyl diimidazole (88 mg, 494 μmol), and refluxed under N_2 for 6 h. The solvent was concentrated and the residue was chromatographed (PE/AcOEt 75: 25 to 6:4) to give a mixture of **22a** and **22b** (50.4 mg, 83%). These two *cis* diastereoisomers could also be separated by chromatography, or obtained under the same conditions from isolated **21a** and **21c**. More precisely, **21a** affords **22b** and **21c** gives **22a**. The relative configurations of these isomers were not determined. R_f (PE/AcOEt 1:1): **22a**: 0.76; **22b**: 0.64. ^{1}H NMR: **22a**: δ 5.52 [2 H, s, C*H*–O]; 3.51 [1 H, ddd, C*H*–N, *J* 2.6, 3.4, 11.2]; 3.30 [1 H, ddd, C*H*–C=O, *J* 2.6, 3.9, 12.8]; 2.86 [1 H, dd, C≡C–C*H*H, *J* 3.9, 17.6]; 2.81 [1 H, broad dt, C≡C–C*H*H, *J*(d) 16.4, *J*(t) 2.9]; 2.53–2.31 [2 H, m, C≡C–C*H*H]; 0.95 [9 H, s, C(CH_3)$_3$]; 0.26, 0.23 [2 × 3 H, 2 s, Si(CH_3)$_2$]. **22b**: δ 5.54 [2 H, s, C*H*–O]; 3.66 [1 H, ddd, C*H*–N, *J* 2.7, 3.7, 11.2]; 3.14 [1 H, ddd, C*H*–C=O, *J* 2.7, 3.8, 12.9]; 2.86 [1 H, dd, C≡C–C*H*H, *J* 3.8, 16.6]; 2.83 [1 H, ddd, C≡C–C*H*H, *J* 2.0, 3.8, 17.3]; 2.50 [1 H, dd, C≡C–C*H*H, *J* 12.9, 17.3]; 2.33 [1 H, ddt, C≡C–C*H*H, *J* 1.1 (t), 11.1, 16.6]; 0.96 [9 H, s, C(CH_3)$_3$]; 0.27, 0.24 [2 × 3 H, 2 s, Si(CH_3)$_2$]. GC-MS (*Note*: these thionocarbonates are not completely stable under the conditions of analysis; they give several byproducts, including enediyne **3**): **22a**: R_t: 12.57. *M*/*z* (%): 304 (M^+– 57, 29.0); 288 (16.3); 228 (13.6); 204 (46.3); 147 (8.2); 128 (100); 127 (24.1); 126 (12.7); 115 (65.3); 109 (13.6); 102 (14.0); 100 (47.7); 75 (30.1); 73 (48.0); 59 (11.4); 44 (25.6). **22b**: R_t: 12.20. *M*/*z* (%): 304 (M^+– 57, 32.3); 288 (12.6); 228 (13.1); 204 (44.8); 147 (10.5); 128 (100); 127 (25.4); 126 (9.6); 115 (69.0); 109 (9.5); 102 (16.4); 100 (47.9); 75 (33.9); 73 (46.5); 59 (13.1); 44 (24.4).

(1*R,10*R**)-11-(*tert*-Butyl-dimethylsilyl)-11-azabicyclo-[8,2,0]dodeca-5-ene-3,7-diyn-12-one (3):** A diastereomeric mixture of thionocarbonates **22** (19.6 mg, 54.2 μmol) was dissolved, under Ar, in dry dioxane (2 mL), and was treated with 2-phenyl-1,3-dimethyl-1,3,2-diazaphospholidine (70 μL, 380 μmol). The solution was stirred at 40 °C for 4 h. Then, after concentration of the solvent, the solution was directly chromatographed (PE/AcOEt 9:1), to give pure **3** as a white solid (11.7 mg, 75.5%). This compound could be obtained in the same way and in similar yield from either isolated **22a** or **22b** as starting material. R_f 0.66 (PE/AcOEt 8:2). ^{1}H NMR: δ 5.86 [2 H, s, C*H*=C*H*]; 3.71 [1 H, ddd, C*H*–N, *J* 2.7, 3.5, 10.9]; 3.37 [1 H, ddd, C*H*–C=O, *J* 2.7, 4.0, 12.5]; 2.97 [1 H, dd, C≡C–C*H*H, *J* 3.7, 17.6]; 2.97 [1 H, dd, C≡C–C*H*H, *J* 3.7, 16.9]; 2.62 [1 H, dd, C≡C–C*H*H, *J* 12.5, 17.6]; 2.49 [1 H, dd, C≡C–C*H*H, *J* 10.9, 16.9]; 0.96 [9 H, s, C(CH_3)$_3$]; 0.27, 0.23 [2 × 3H, 2 s, Si(CH_3)$_2$]. GC-MS: R_t: 8.73. *M*/*z* (%): 228 (M^+– 57, 4.7); 128 (100); 127 (18.0); 102 (11.7); 100 (11.1); 75 (9.5); 73 (20.9); 59 (5.4). ^{13}C NMR (50 MHz.): δ 172.9 [*C*=O]; 123.6, 123.1 [*C*H=*C*H]; 99.7, 97.0, 84.7, 84.1 [*C*≡*C*]; 59.1, 57.2 [*C*H]; 27.2, 20.1 [C≡C–*C*H_2]; 26.2 [C(*C*H_3)$_3$]; 18.3 [*C*(CH_3)$_3$]; –5.3, –5.7 [Si(*C*H_3)$_2$]. IR: ν 3004, 2955, 2928, 2858, 1737, 1599, 1463, 1354, 1331, 1318, 1282, 1189, 1138, 1103, 1068, 1011, 965 cm^{-1}.

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