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Toward the synthesis of the esperamicin-A_1/calicheamicin γ_1^I aglycone: the study of an 'azoxy' version of the [2,3]-Wittig rearrangement

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Summary — A strategy based upon an 'azoxy' version of the [2,3]-Wittig rearrangement was investigated as a means to access the aglycone component of the enediyne antitumor antibiotics esperamicin-A_1 and calicheamicin γ_1^I. Although the *N*-methoxycarbonylated enamine **8** could not be prepared, the corresponding enamides **22** and **23** were obtained in high yield through reaction of the bicyclic oxime ether **12** with acetyl bromide and trifluoroacetic anhydride, respectively, in the absence of base. Reaction of enamide **22** with lithium amide base led to formation of either dimer **37** or the acyclic 1,5-diyne product **40**. Aldehyde **36**, generated by competing cleavage of the N-O bond in **34**, was an intermediate in both reactions. Similarly, treatment of enamide **23** with LiTMP led to formation of the ring-opened aldehyde **41** rather than to the [2,3]-Wittig rearrangement product. Attempts to ring close this intermediate to **43** resulted in formation of the decarbonylated alkyne **46**.

enediyne / [2,3]-Wittig rearrangement / oxime ether / *N*-acylation

Résumé — Une approche de la synthèse de la partie aglycone de l'espéramicine-A_1/calichéamicine γ_1^I: étude d'une version «azoxy» du réarrangement de Wittig-[2,3]. *Une stratégie basée sur une version «azoxy» du réarrangement de Wittig-[2,3] a été étudiée dans le but d'accéder à la partie aglycone des énediynes espéramicine-A_1 et calichéamicine γ_1^I, antibiotiques antitumoraux. Bien que l'énamine N-méthoxycarbonylée* ***8*** *ne puisse pas être préparée, les énamides correspondantes* ***22*** *et* ***23*** *ont été obtenues très efficacement grâce à la réaction de l'éther d'oxime bicyclique* ***12*** *respectivement avec le bromure d'acétyl et l'anhydride trifluoroacétique en l'absence de base. La réaction du composé* ***22*** *avec des amidures de lithium a conduit soit à la formation du dimère* ***37****, soit au produit 1,5-diyne acyclique* ***40****. L'aldéhyde* ***36****, généré par coupure de la liaison N-O du composé* ***34****, était un intermédiaire dans ces deux réactions. De façon similaire, le traitement de l'énamide* ***23*** *avec LiTMP a entraîné la formation de l'aldéhyde 1,5-diyne acyclique* ***41*** *au lieu du produit issu du réarrangement de Wittig-[2,3]. Des essais de fermeture de cycle de cet intermédiaire en vue de l'obtention de* ***43*** *ont résulté de la formation de l'alcyne décarbonylé* ***46****.*

énediyne / réarrangement de Wittig-[2,3] / éther d'oxime / *N*-acylation

Introduction

The discovery of the antitumor antibiotics calicheamicin γ_1^I **1** and esperamicin-A_1 **2** (fig 1) has opened new horizons for the development of chemotherapeutic agents for the treatment of cancer [1, 2]. It has also posed a formidable challenge to organic chemists to devise means to construct the fragile, highly strained bicyclo-[7.3.1]tridecenediyne unit, which is common to these molecules, and to couple it to the equally structurally unique sugar component(s) [3].

Recently, we developed a strategy for the construction of the bicyclic ten-membered enediyne skeleton of **1** and **2** based upon the [2,3]-Wittig rearrangement of an unstrained 13-membered macrocyclic precursor [4, 5] (fig 2). These studies showed that whereas the ring contraction of enediyne **3** was complicated by competing electron-transfer processes, the rearrangement of the 'dihydro' compound **4** was highly efficient. Subsequent base-induced elimination of HOX from **5** provided a facile means to introduce the missing double bond, producing the target molecule **6**. As predicted from molecular mechanics calculations, this simple calicheamicin/esperamicin analog underwent spontaneous Bergman cycloaromatization producing a series of products derived from the diradical intermediate **7**.

Having demonstrated the effectiveness of the [2,3]-Wittig strategy, our attention has turned to a study of a new 'azoxy' version of this rearrangement for the construction of more highly functionalized bicyclic 1,5-diyne or dihydroenediyne systems, which could serve as advanced intermediates in the synthesis of the aglycone components in the antibiotics **1** and **2**. As illustrated in figure 3, we envisaged that [2,3]-Wittig ring contraction of the bicyclic *N*-methoxycarbonylated hydroxylamine derivative **8** would ultimately lead to the enamine **9**, and that in situ treatment of this interme-

* Correspondence and reprints

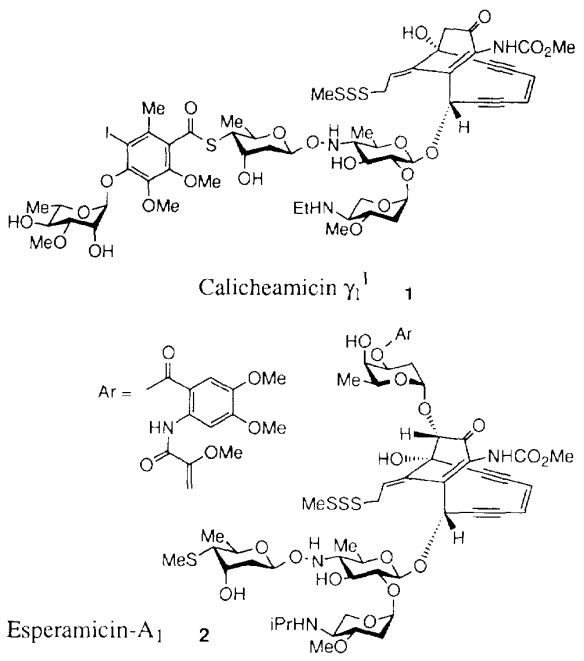

Fig 1. Structures of calicheamicin γ_1^I **1** and esperamicin-A_1.

diate with two equivalents of MeSCl [6], would provide access to the $\Delta^{9,10}$ double-bond-isomerized product **10**. Thus, the C-10 urethane unit, the bridgehead double bond, and the C-11 keto functionality (in its protected dithioketal form) present in calicheamicinone **11** could, in principle, be correctly positioned in compound **10** in essentially one operation. In this paper we describe the results of preliminary efforts to implement this azoxy variant of the [2,3]-Wittig rearrangement to the synthesis of calicheamicinone.

Results

A key step in the route envisaged to the precursor **8** (R = H) for the [2,3]-Wittig rearrangement step involves *N*-methoxycarbonylation of the oxime ether

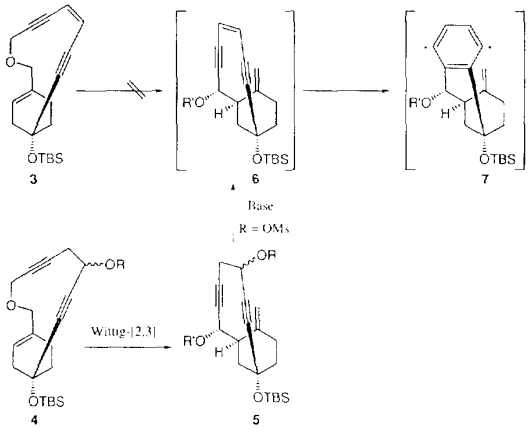

Fig 2

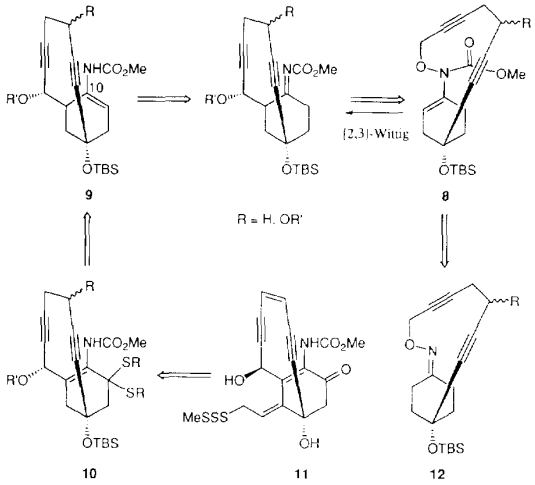

Fig 3

12 (R = H). The preparation of **12** was initiated by the condensation of the dilithio dianion of commercially available hexa-1,5-diyne with the monoketal **13** of cyclohexane-1,4-dione to give **14** (fig 4). Reaction of the monoanion of the *O*-*t*-butyldimethylsilyl (*O*-TBS) derivative **15** with paraformaldehyde then gave the propargyl alcohol **16**, which was converted to the corresponding chloride **17** on treatment with MsCl/LiCl. Finally, ketal hydrolysis, followed by reaction of the derived ketone with *O*-TBS hydroxylamine [7], deprotection of **18** (TBAF), and Cl → Br exchange gave the bromooxime **19**.

The synthesis of **19** was subsequently improved upon by converting alcohol **16** to the bromo compound **20** (Mitsunobu conditions [8]) prior to ketal hydrolysis and oxime formation [9]. In this way intermediate **19** was obtained in 67% overall yield from cyclohexane-1,4-dione monoketal **13**.

Macrocyclization of this bromo oxime to compound **12** was found to be highly efficient (79%) when the reaction was carried out using NaH in THF containing a small quantity of water. Previous experience with related ring closures demonstrated that without the addition of H_2O to the medium, ether formation does not proceed at an appreciable rate [10]. The precise reason why added water 'catalyzes' this process remains to be clarified, since the use of an equivalent quantity of aqueous NaOH promotes a number of side reactions which lowers the conversion to **12**, and also makes its isolation difficult.

The greater complexity of the ^{1}H NMR spectrum of **12** compared to that for **19** is consistent with the formation of a cyclic product. For instance, the C-8 propargylic methylene protons were no longer equivalent, appearing as a pair of doublets at δ 4.64 and 4.48. Similarly, only one hydrogen of the CH_2 on the cyclohexane ring α to the C=N bond gave a double double doublet at 3.19 ppm. We can explain this downfield shift by an anisotropic effect owing to the C=NO bond. In further agreement with the formation of the cyclic ether was the absence of a peak at δ 8.08 characteristic of the oxime OH, and the presence of a molecular

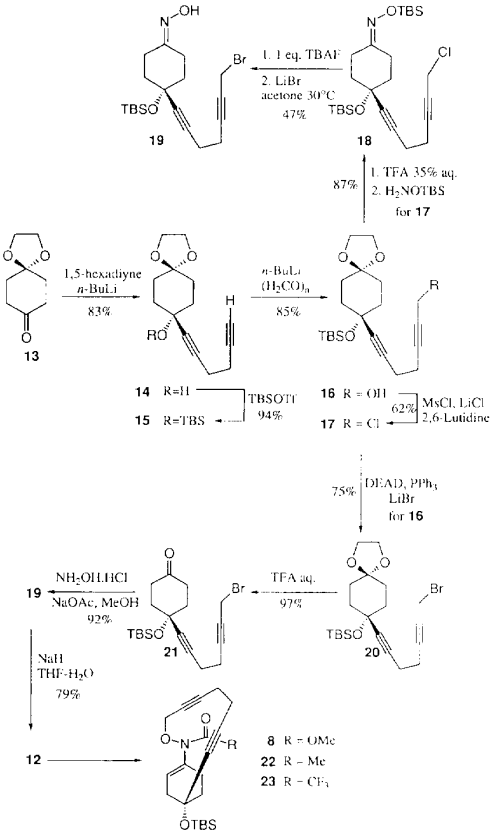

Fig 4

ion peak at m/z = 332 (MH^+) in the CI mass spectrum. However, as oxime alkylation can also result in nitrone formation [11], the structure of the *O*-desilylated derivative of **12** was confirmed by X-ray diffraction (fig 5). As determined from bond angle (2-3-4 = 176.5°, 5-6-7 = 176.7°), dihedral angle (3-4-5-6 = 50.2°), and interatomic distance measurements, the diyne bridge in this bicyclic oxime ether is relatively strain free with $r_{2,7}$ = 4.106 Å, whereas the six-membered ring adopts a twist-boat conformation.

With oxime ether **12** in hand, its conversion to *N*-vinylurethane **8** by reaction with methyl chloroformate was studied under a wide variety of base conditions. These include the use of different solvents (DMF, THF, Et_2O) in combination with diisopropylethylamine (DIPEA), 4-(dimethylamino)pyridine (DMAP), triethylamine (TEA) or pyridine over a range of temperatures. However, in all cases the starting material was recovered intact, even when $AgBF_4$ was employed as an additive.

Although compound **12** was also unreactive toward acetyl chloride/base, it was successfully *N*-acetylated (24–46%) to give **22** when treated with acetyl chloride in Et_2O, DMF or CH_3CN in the absence of base [12]. Furthermore, the yield of **22** was increased to 78% when acetyl bromide was employed as the acylating agent. In the ^1H NMR spectrum of compound **22** the doublet signal at δ 5.67 was attributed to the enamine CH, and the singlet at δ 2.13 ppm to the acetyl methyl group. An amide carbonyl absorption was also observed

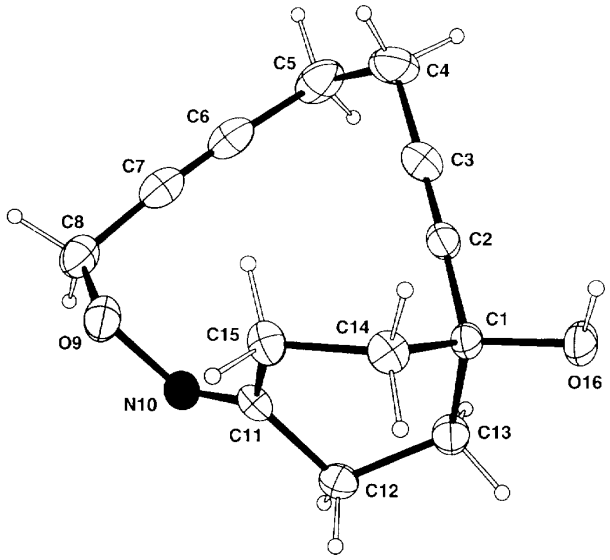

Fig 5. Structure of the *O*-desilylated derivative of **12**.

at 1 681 cm^{-1} in the IR spectrum for this product. In a similar manner, the *N*-trifluoroacetylated compound **23** was prepared in 89% yield by reaction of **12** with $(CF_3CO)_2O$, but all attempts to obtain **8** by reaction of **12** with methyl chloroformate or methyl cyanoformate without added base failed.

To overcome the difficulties encountered in obtaining **8**, we investigated its preparation by *N*-methoxycarbonylation of the acyclic *O*-TBS-protected oxime **24** and by dehydrative condensation of the ketone and amide functions in compound **30** (figs 6 and 7). In the first of these alternative approaches, trial experiments using acetyl and benzoyl bromide revealed that, rather than producing the desired product, acylation of **24** occurs exclusively at oxygen to give compounds **26**. This presumably involves direct reaction of the acylating agent with the oxime oxygen and elimination of TBS-Br from intermediate **25**.

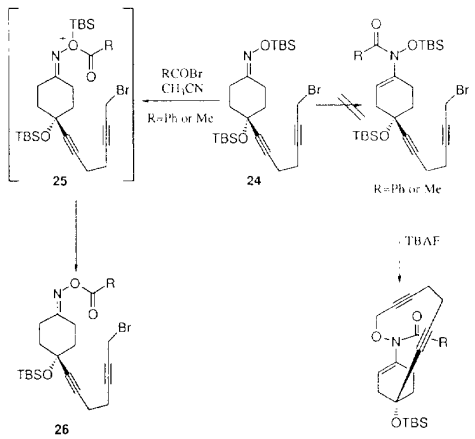

Fig 6

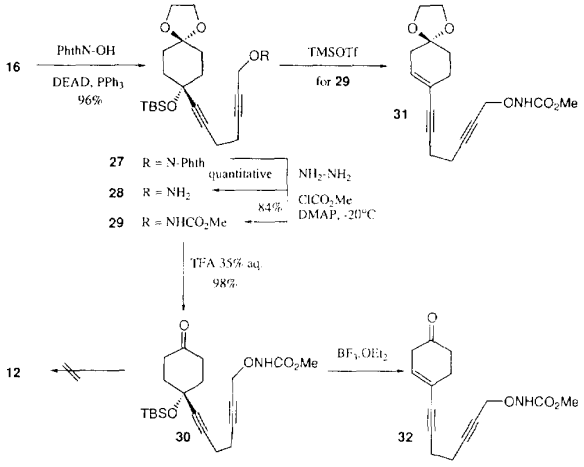

Fig 7

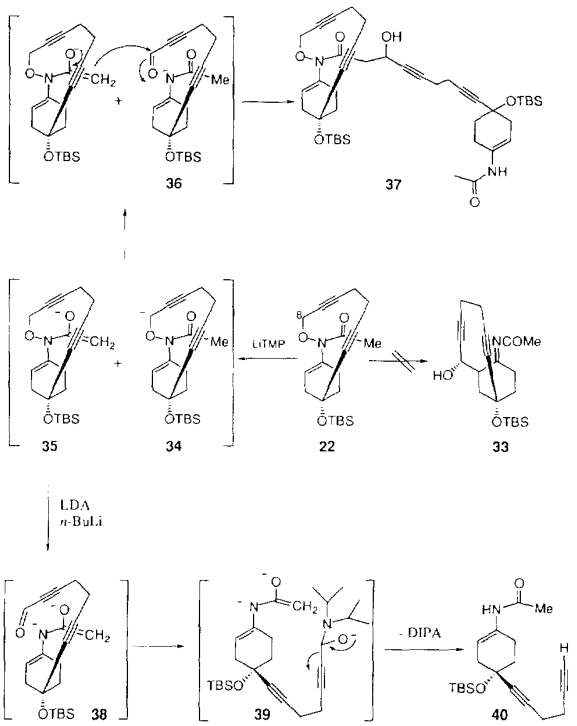

Fig 8

Following the second strategy, intermediate **30** was prepared by reaction of alcohol **16** with *N*-hydroxyphthalimide under Mitsunobu conditions, hydrazinolysis of **27**, reaction of the resulting hydroxylamine **28** with methyl chloroformate and treatment of **29** with aqueous acid. However, despite literature precedent [13], Lewis-acid-mediated ring closure of compound **30**, or its ketal precursor **29**, to bicycle **12** could not be effected. Indeed, competing reaction of the tertiary alcohol function in these molecules led to preferential formation of the enyne derivatives **31** and **32**.

In view of the difficulties in obtaining enamine **8**, the decision was taken to proceed with the investigation of the [2,3]-Wittig rearrangement using the *N*-acetyl, and *N*-trifluoroacetylated enamines **22** and **23** (figs 8 and 9). In contrast to the dihydro compound **4**, vinyl enamide **22** reacted only slowly when treated with lithium tetramethylpiperidide (LiTMP) in THF at −25 °C [4]. As a consequence the reaction did not go to completion, and extensive degradation was observed. However, the major non-polar reaction component **37** could be isolated (13%) by silica-gel flash column chromatography. From the occurrence of a peak at m/z 769 for (M + Na) in the mass spectrum of this product, it was clear that it corresponded to a dimer, and not to the desired [2,3]-rearrangement product **33**. Distinctive features in the ^{1}H NMR spectrum which permitted its complete structure assignment were two sets of signals for the *O*-TBS group (δ 0.87, 0.85 (s, 9H, *t*-BuSi), and δ 0.16, 0.18 (s, 6H, $SiMe_2$)), two broad singlets for the olefinic hydrogens (δ 5.93 ppm and 5.72), and a broad singlet at δ 6.81 corresponding to an NH.

Concerning the origin of dimer **37**, from earlier studies on the reactivity of macrocycle **4** [4] it was demonstrated that the removal of the pro-*R* propargyl hydrogen by the amide base is involved in the ring contraction reaction. As this hydrogen is also antiperiplanar to the N-O bond in vinyl ether **22** (as well in **8** and **23**), it was recognized that the anion species **34** which is formally generated could react either in the [2,3]-Wittig rearrangement mode or in a β-elimination reaction leading to aldehyde **36**. This aldehyde could then condense with the amide enolate **35** to give dimer **37** (fig 8). As the formation of these two species in the reaction medium took precedent over the desired [2,3]-Wittig rearrangement reaction, indications were that the E_2-elimination reaction mode of anion **34** is lower in energy, and thus favored.

In an attempt to suppress the formation of the aldehyde **36**, compound **22** was initially treated with only one equivalent of amide base at −78 °C (LiTMP or lithium diisopropylamide (LDA)). The idea behind this manoeuver was to selectively form the amide enolate intermediate **35**, and thereby transform the amide nitrogen into a poor leaving group during the subsequent deprotonation at C-8 when further LiTMP is added. Unfortunately, the only products isolated in this instance were the dimer **37** (10%) and the starting material (44%).

Interestingly however, when an LDA/BuLi combination [14] was used to generate the propargyl anion from the preformed enolate **35** at −78 °C, the reaction took yet a different course producing alkyne **40** (fig 8). This result can best be rationalized by evoking reaction of the intermediate aldehyde **38** formed by ring opening with the amide base to give the 1,2-addition adduct **39**, which undergoes a known retro-condensation reaction [15] producing **40** and *N*,*N*-diisopropylformamide (not isolated).

Attempting to effect the [2,3]-Wittig rearrangement of the *N*-trifluoroacetyl enamide **23** next, it was again found that the reaction with LiTMP at −30 °C was unexpectedly slow, producing several new products (and polar material), two of which were isolated by chromatography and shown to correspond to the oxime ether **12** (29%), and the propargyl aldehyde **41** (14%

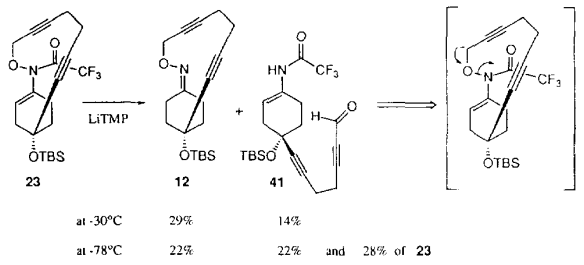

Fig 9

at −30 °C, and 22% at −78 °C) (fig 9). The formation of aldehyde **41** demonstrates that deprotonation at the C-8 center does occur, but that in this process the β-elimination pathway is preferred. This may simply be a consequence of the facility with which the weak N-O bond is broken. However, the slowness with which compound **23** (and **22**) reacts with the amide base compared to **4** suggests that the molecule may experience difficulty in attaining the geometry required for the transition state of the [2,3]-Wittig rearrangement.

Although the planned ring contraction of macrocycle **23** was thwarted by a competing eliminative ring-opening reaction, the possibility of converting the derived aldehyde product **41** to the target bicycle **43** via intramolecular condensation of its metalloenamide derivative **42** remained (fig 10, pathway a). In order to favor this transformation, NaH was employed as the base for this operation as an attempt to suppress the above-mentioned decarbonylation process. However, even under these conditions the formation of alkyne **46** was observed. Several pathways are envisagable [16] for the formation of this product but the route involving reaction of the nitrogen atom of the metalloenamide species **42** with the carbonyl oxygen to give **44**, followed by retrocondensation to the *N,N*-diacyl intermediate **45** and loss of the formyl group during work-up appears to be the most consistent with our observations (pathway **b**).

It is hoped that this process, which results in ring closure to the larger and less strained of the two possible macrocycles (ie, **44**), can be suppressed by a change in the metal counterion of the base and/or a change in solvent. Further work in this direction is in progress.

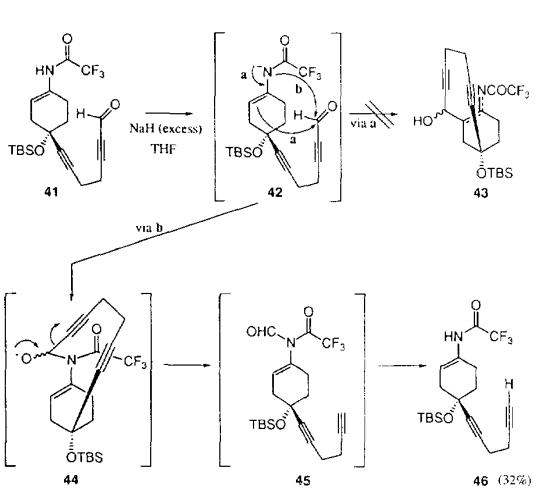

Fig 10

Experimental section

General

Mass spectra were obtained on an MS-50 AEI (EI, 70 eV) or an MS-9 AEI (CI, isobutane) spectrometer. ^{1}H NMR spectra were recorded in $CDCl_3$ (except where noted) on a Bruker spectrometer (200 or 250 MHz), using tetramethylsilane as an internal standard. Chemical shift data are reported in parts per million (δ) where s, d, dd, t, q and m designate singlet, doublet, doublet of doublets, triplet, quartet and multiplet, respectively. ^{13}C NMR spectra were recorded in $CDCl_3$ on the same instruments. Flash column chromatography was performed using Merck silica gel 60 (Art 9385). In all cases the solvent system used for the chromatographic separations was chosen such that on TLC an R_f of 0.25–0.30 was observed for the compound to be isolated. All microanalytical results for C, H and N are within ±0.4% of the theoretical values.

4-(Hexa-1,5-diynyl)-4-hydroxycyclohexanone-ethyleneacetal **14**

Butyllithium 1.5 M in hexane (5.76 mL, 9.22 mmol) was added dropwise to a solution of hexa-1,5-diyne (300 mg, 3.84 mmol) in dry THF (10 mL) under argon at −78 °C, and the resultant mixture was stirred for 20 min before addition of cyclohexane-1,4-dione-monoethyleneacetal (200 mg, 1.28 mmol) in THF (2 mL). After a further 30 min, the reaction was stopped by the addition NH_4Cl aq (sat) and extracted with ether. The combined organic phases were washed with H_2O and NaCl aq (sat), then dried over Na_2SO_4 and evaporated to dryness. The resulting yellow oil was purified by silica-gel flash column chromatography (heptane/EtOAc, 2:1). Compound **14** was obtained as an oil (248 mg; 83%).

IR (neat) 3 443, 3 293, 2 950, 2 931, 2 887, 1 437, 1 368, 1 337, 1 281, 1 250, 1 181, 1 106, 1 031, 981, 950, 931 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) δ 3.92 (s, 4H, -OCH_2CH_2O-), 2.41 (m, 4H, $CCCH_2CH_2CC$), 2.14 (broad s, 1H, OH), 2.01 (t, J = 2.5 Hz, 1H, CCH), 1.99–1.65 (m, 8H, cyclohexane).

^{13}C NMR (62.89 MHz, $CDCl_3$) δ 108.14, 84.50, 82.68, 69.51, 67.58, 64.40, 64.34, 37.50, 31.65, 18.87, 18.83.

MS (CI, isobutane) m/z 235 (M + 1), 217 (M + 1 − H_2O).

Anal calc for $C_{14}H_{18}O_3$: C, 71.76; O, 20.50; H, 7.75. Found: C, 71.51; O, 20.26; H, 8.02.

4-[(t-Butyldimethylsilyl)oxy]-4-(hexa-1,5-diynyl)cyclohexanone-ethyleneacetal **15**

Triethylamine (5.5 mL, 39.3 mmol) and TBSOTf (5.9 mL, 25.6 mmol) were added to a stirred solution of alcohol **14** (4.60 g, 19.7 mmol) in CH_2Cl_2 (160 mL) at 0 °C. The resulting solution was stirred for 1 h at 0 °C, then washed with NaCl aq (sat) (twice), dried over Na_2SO_4 and concentrated under vacuum. The resulting oil was purified by silica-gel flash chromatography (heptane/EtOAc, 30:1). Compound **15** was obtained as a colorless liquid (6.48 g; 94%).

IR (neat) 3 309, 2 957, 2 930, 2 884, 2 857, 1 370, 1 250, 1 104, 1 051, 938, 839, 779 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) δ 3.91 (s, 4H, -OCH_2CH_2O-), 2.42 (m, 4H, $CCCH_2CH_2CC$), 2.00 (t, J = 2.5 Hz, 1H, CCH), 1.93–1.58 (m, 8H, cyclohexane), 0.86 (s, 9H, t-BuSi), 0.13 (s, 6H, Me_2Si).

^{13}C NMR (62.89 MHz, $CDCl_3$) δ 108.40, 85.17, 82.93, 82.74, 69.51, 67.99, 64.31, 38.63, 31.20, 25.95, 18.94, 18.80, 18.24, −2.83.

MS (CI, isobutane) m/z 349 (M + 1), 217 (M + 1 − TBSOH), 133 ($TBSOH_2^+$).

Anal calc for $C_{20}H_{32}O_3Si$: C, 68.92; H, 9.26. Found: C, 68.85; H, 9.19.

4-[(t-Butyldimethylsilyl)oxy]-4-(7-hydroxyhepta-1,5-diynyl)cyclohexanone-ethyleneacetal **16**

Butyllithium 1.3 M in hexane (8.0 mL, 10.3 mmol) was added to a solution of alkyne **15** (3.00 g, 8.6 mmol) in THF (60 mL) at −78 °C under argon. After stirring for 15 min paraformaldehyde (780 mg, 26.0 mmol) was added. The dry ice-bath was then removed and stirring was continued at ambient temperature for 3 h. The reaction was stopped by adding NH_4Cl aq (sat) and extracted with ether. The organic phase was washed with water (twice), then NaCl aq (sat), dried over Na_2SO_4 and concentrated under vacuum. The resulting oil was purified by silica-gel flash chromatography (heptane/EtOAc, 3:1). Compound **16** was obtained as a colorless liquid (2.78 g, 85%).

IR (neat) 3 452, 2 954, 2 929, 2 886, 2 855, 1 372, 1 249, 1 108, 1 053, 1 034, 1 022, 936, 874 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$) δ 4.23 (d, 2H, CH_2OH), 3.95 (s, 4H, -OCH_2CH_2O-), 2.87 (broad s, 1H, OH), 2.42 (s, 4H, $CCCH_2CH_2CC$), 2.02–1.68 (m, 8H, cyclohexane), 0.87 (s, 9H, t-BuSi), 0.17 (s, 6H, Me_2Si).

^{13}C NMR (62.89 MHz, $CDCl_3$) δ 108.69, 85.17, 84.25, 83.87, 80.08, 68.75, 64.34, 51.11, 38.81, 31.81, 25.91, 19.22, 18.90, 18.16, −2.79.

MS (CI, isobutane) m/z 379 (M + 1), 361 (M + 1 − H_2O), 317 (M + 1 − CH_3CHO − H_2O), 303 (M + 57 − TBSOH), 247 (M + 1 − TBSOH), 229 (M + 1 − TBSOH − H_2O), 203 (M + 1 − TBSOH − CH_3CHO), 133 ($TBSOH_2^+$).

Anal calc for $C_{21}H_{34}O_4Si$: C, 66.62; H, 9.05. Found: C, 66.88; H, 9.31.

4-[(t-Butyldimethylsilyl)oxy]-4-(7-chlorohepta-1,5-diynyl)cyclohexanone-ethyleneacetal **17**

Propargylic alcohol **16** (184 mg, 0.48 mmol) in DMF (0.5 mL) containing 2,6-lutidine (150 μL) was added to a stirred precooled (0 °C) solution of LiCl (55 mg, 1.23 mmol) in DMF (2 mL). After 45 min, mesyl chloride (62 μL, 0.80 mmol) was added and the mixture was stirred for an additional 2.5 h. Pentane and water were then added and the organic phase was washed several times with water, dried over Na_2SO_4 and evaporated to dryness in vacuo. Silica-gel flash chromatography (heptane/EtOAc, 15:1) afforded chloride **17** as a colorless oil (120 mg, 63% (non-optimized).

IR (neat) 2 956, 2 931, 2 887, 2 856, 1 369, 1 250, 1 106, 1 056, 1 044, 1 019, 837 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) δ 4.15 (s, 2H, CH_2Cl), 3.96 (s, 4H, -OCH_2CH_2O-), 2.47 (s, 4H, $CCCH_2CH_2CC$), 1.97–1.61 (m, 8H, cyclohexane), 0.88 (s, 9H, t-BuSi), 0.18 (s, 6H, Me_2Si).

^{13}C NMR (62.89 MHz, $CDCl_3$) δ 108.35, 85.70, 85.21, 82.92, 76.20, 68.07, 64.29, 38.62, 31.24, 30.98, 25.91, 19.16, 18.76, 18.19, −2.89.

4-[(t-Butyldimethylsilyl)oxy]-4-(7-chlorohepta-1,5-diynyl)cyclohexanone(t-butyldimethylsilyl)-oxime **18**

To dioxolane **17** (395 mg, 0.99 mmol) in $CHCl_3$ (10 mL) was added a 35% aqueous solution of trifluoroacetic acid (6.6 mL), and the resulting mixture was stirred for 1.5 days at room temperature. Dichloromethane was then added, and the organic phase was washed with $NaHCO_3$ aq (sat), with NaCl aq (sat), dried over Na_2SO_4 and concentrated under vacuum. The colorless liquid obtained was taken on to the next step without further purification.

To the derived ketone (0.99 mmol) in dry CH_2Cl_2 (3 mL) containing 4 Å molecular sieves was added hydroxylamine-*O*-TBS ether (150 mg, 1.02 mmol). The reaction was left under stirring at room temperature overnight. The mixture was then filtered, and the solvent was evaporated, giving an oil which was silica-gel flash chromatographed (heptane/EtOAc, 30:1). Compound **18** was obtained as a colorless liquid (447 mg, 93% from the ketal).

IR (neat) 2 956, 2 931, 2 887, 2 856, 1 462, 1 250, 1 100, 1 044, 925, 862, 837 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) δ 4.12 (s, 2H, CH_2Cl), 2.67 (m, 2H, cyclohexane), 2.51–2.24 (m, 6H, $CCCH_2CH_2CC$ and 2H cyclohexane), 1.93–1.76 (m, 4H, cyclohexane), 0.92 (s, 9H, t-BuSi), 0.89 (s, 9H, t-BuSi), 0.19 (s, 6H, Me_2Si), 0.14 (s, 6H, Me_2Si).

4-(7-Bromohepta-1,5-diynyl)-4-[(t-butyldimethylsilyl)-oxy]cyclohexanone-oxime **19** *from oxime ether* **18**

To the oxime *O*-TBS ether **18** (224 mg, 0.46 mmol) in THF (50 mL), was added TBAF.$3H_2O$ (161 mg, 0.51 mmol). After stirring for 20 min at 20 °C, ether and water were added, and the organic phase was washed with water and brine, dried over Na_2SO_4 and concentrated under vacuum. The resulting residue was flash column chromatographed (heptane/EtOAc, 3:1) and was directly used in the next step.

A solution of chlorooxime (115 mg, 0.31 mmol) and dried LiBr (541 mg, 6.24 mmol) in acetone (15 mL) was allowed to stir for 48 h at 30 °C. Pentane and water were added, and the organic phase was washed several times with water, dried over Na_2SO_4 and evaporated to dryness under vacuum, affording **19** as a colorless syrup (124 mg, 96%).

IR (neat) 3 231, 3 118, 2 956, 2 937, 2 856, 1 669, 1 462, 1 437, 1 337, 1 250, 1 212, 1 106, 1 044, 1 006, 987, 937, 868, 837 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (broad s, 1H, NOH), 3.91 (s, 2H, CH_2Br), 2.66 (m, 2H, CH_2 cyclohexane), 2.52–2.38 (m, 5H, 2 CH_2 hexadiyne and *H*CH cyclohexane), 2.37–2.26 (m, 1H, HC*H* cyclohexane), 1.88 (m, 4H, 2 CH_2 cyclohexane), 0.89 (s, 9H, t-BuSi), 0.19 (s, 6H, Me_2Si).

^{13}C NMR (75.47 MHz, $CDCl_3$) δ 158.77, 85.65, 84.12, 83.38, 76.19, 67.81, 40.17, 39.03, 27.54, 25.54, 19.99, 18.84, 18.33, 17.85, 14.74, −3.24.

MS (CI, isobutane) m/z 414–412 (M + 1), 396–394 (M + 1 − H_2O), 133 ($TBSOH_2^+$).

Anal calc for $C_{19}H_{30}BrNO_2Si$: C, 55.33; H, 7.33; N, 3.39. Found: C, 55.30; H, 7.12; N, 3.34.

4-(7-Bromohepta-1,5-diynyl)-4-[(t-butyldimethylsilyl)-oxy]cyclohexanone-ethyleneacetal **20**

Diethyl azodicarboxylate (DEAD) (1.55 mL, 9.85 mmol) was added dropwise to a solution of PPh_3 (2.64 g, 10 mmol)

in dry THF (60 mL) at 0 °C under argon. After stirring for 20 min LiBr (2.8 g, 32 mmol) was added, followed by alcohol **16** (1.52 g, 4.02 mmol) in dry THF (8 mL). The mixture was stirred at 0 °C until no more starting material was detected by TLC (approximately 2.5 h). Ether was then added and the organic phase was washed twice with water and NaCl aq (sat), dried over Na_2SO_4 and concentrated under vacuum. The resulting residue was silica-gel flash column chromatographed (heptane/EtOAc, 15:1). Compound **20** was obtained as a colorless liquid (1.33 g, 75%).

IR (neat) 2 956, 2 931, 2 887, 2 856, 1 369, 1 250, 1 106, 1 057, 1 036, 1 020, 839, 776 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) δ 3.92 (s, 6H, CH_2Br and 2 CH_2 dioxolane), 2.43 (s, 4H, 2 CH_2 hexadiyne), 1.94–1.61 (m, 8H, 4 CH_2 cyclohexane), 0.88 (s, 9H, *t*-BuSi), 0.17 (s, 6H, Me_2Si).

^{13}C NMR (75.47 MHz, $CDCl_3$) δ 107.52, 85.32, 84.32, 82.06, 75.65, 67.15, 63.45, 37.75, 30.37, 25.06, 18.42, 17.90, 17.35, 14.47, −3.71.

MS (CI, isobutane) *m/z* 443–441 (M + 1), 311–309 (M + 1 − TBSOH), 133 ($TBSOH_2^+$).

Anal calc for $C_{21}H_{33}BrO_3Si$: C, 57.13; H, 7.53; Br, 18.10. Found: C, 57.15; H, 7.47; Br, 18.25.

4-(7-Bromohepta-1,5-diynyl)-4-[(t-butyldimethylsilyl)-oxy]cyclohexanone **21**

To dioxolane **20** (1.28 g, 2.90 mmol) in $CHCl_3$ (50 mL) was added a 35% aqueous solution of trifluoroacetic acid (37 mL), and the resulting mixture was stirred for 1.5 days at room temperature. Dichloromethane was then added, and the organic phase was washed with $NaHCO_3$ aq (sat), with NaCl aq (sat), dried over Na_2SO_4 and concentrated under vacuum. The colorless liquid obtained **21** was taken on to the next step without further purification (99%).

IR (neat) 2 956, 2 930, 2 859, 1 718, 1 473, 1 428, 1 254, 1 222, 1 106, 1 048, 1 003, 867, 835, 777 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) δ 3.91 (s, 2H, CH_2Br), 2.68–2.32 (m, 8H, 2 CH_2 hexadiyne and 2 CH_2 cyclohexane), 2.20–2.02 (m, 4H, 2 CH_2 cyclohexane), 0.90 (s, 9H, *t*-BuSi), 0.22 (s, 6H, Me_2Si).

^{13}C NMR (75.47 MHz, $CDCl_3$) δ 210.82, 85.93, 84.02, 76.63, 67.21, 40.51, 37.53, 25.92, 19.15, 18.71, 18.25, 15.07, −2.90.

MS (CI, isobutane) *m/z* 399–397 (M + 1), 267–265 (M + 1 − TBSOH), 133 ($TBSOH_2^+$).

4-(7-Bromohepta-1,5-diynyl)-4-[(t-butyldimethylsilyl)-oxy]cyclohexanone-oxime **19** *from ketone* **21**

Ketone **21** (1.15 g, 2.90 mmol) in MeOH (20 mL) was added to a solution of hydroxylamine hydrochloride (242 mg, 3.48 mmol) and sodium acetate (571 mg, 6.96 mmol) in MeOH (35 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h, stopped by the addition of H_2O and extraction with ether. The combined organic phases were washed with NaCl aq (sat), dried over Na_2SO_4 and concentrated under vacuum. The resulting yellow oil was purified by silica-gel flash column chromatography (heptane/EtOAc, 3:1). Compound **19** was obtained as a colorless liquid (1.12 g, 94%).

1-[(t-Butyldimethylsilyl)oxy]-9-oxa-10-aza-bicyclo[9.2.2]pentadec-10-ene-2,6-diyne **12**

To the oxime **19** (335 mg, 0.81 mmol) in THF (900 mL) was successively added sodium hydride (50% in paraffin; 234 mg, 4.90 mmol) and several drops of water. After 1.5 days stirring at room temperature in the dark, the reaction was stopped by the addition of H_2O. Most of the THF was then removed under vacuum, and the resulting liquid was extracted with ether. The organic phase was washed with water and NaCl aq (sat), dried over Na_2SO_4 and concentrated under vacuum. The resulting oil was purified by silica-gel flash column chromatography (heptane/EtOAc, 10:1). Compound **12** was obtained as a colorless liquid (211 mg, 79%).

IR (neat) 2 956, 2 931, 2 856, 1 250, 1 094, 1 031, 1 000, 856, 837 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) δ 4.64 (d, J = 15.8 Hz, 1H, *H*CHON), 4.48 (d, J = 15.8 Hz, 1H, HC*H*ON), 3.19 (ddd, J = 19.1, 11.9, 7.8 Hz, 1H, *H*CHC=N), 2.58–2.46 (m, 2H), 2.45–2.21 (m, 6H, 2 CH_2 hexadiyne and CH_2 cyclohexane), 2.11–1.82 (m, 3H), 0.86 (s, 9H, *t*-BuSi), 0.14 (s, 6H, Me_2Si).

^{13}C NMR (75.47 MHz, $CDCl_3$) δ 166.13, 84.93, 84.86, 84.71, 79.26, 68.84, 60.86, 39.53, 35.79, 26.18, 25.87, 24.31, 18.91, 18.81, 18.03, −2.65, −2.75.

MS (CI, isobutane) *m/z* 388 (M + 57), 332 (M + 1), 200 (M + 1 − TBSOH), 133 ($TBSOH_2^+$).

HRMS (CI) calc for $C_{19}H_{29}NO_2Si + H^+$: 332.2047. Found: 332.2033.

10-Acetoxy-1-[(t-butyldimethylsilyl)oxy]-9-oxa-10-aza-bicyclo[9.2.2]pentadec-11-ene-2,6-diyne **22**

Acetyl bromide (20 μL, 0.24 mmol) was added to the oxime ether **12** (40 mg, 0.12 mmol) in dry acetonitrile (2 mL) containing 4 Å molecular sieves. After stirring overnight at room temperature, the reaction mixture was filtered, and the residue was washed with ether. The combined organic phase was washed with water and brine, dried over Na_2SO_4 and concentrated under vacuum. The resulting oil was purified by silica-gel flash column chromatography (heptane/EtOAc, 3:1). Compound **22** was obtained as a colorless liquid (35 mg, 78%).

IR (neat) 2 956, 2 931, 2 856, 1 681, 1 375, 1 331, 1 300, 1 250, 1 100, 912, 837 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) δ 5.67 (m, 1H, C=CH), 4.62 (d, J = 16.5 Hz, 1H, *H*CHON), 4.36 (d, J = 16.5 Hz, 1H, HC*H*ON), 2.88 (m, 1H), 2.63–2.31 (m, 6H, 2 CH_2 hexadiyne and CH_2 cyclohexene), 2.29–2.16 (m, 1H), 2.13 (s, 3H, $COCH_3$), 2.04–1.81 (m, 2H), 0.88 (s, 9H, *t*-BuSi), 0.19 (s, 6H, Me_2Si).

^{13}C NMR (75.47 MHz, $CDCl_3$) δ 159.03, 136.27, 119.74, 86.38, 83.94, 82.37, 75.50, 66.63, 63.80, 40.48, 36.48, 25.81, 24.99, 20.73, 18.53, 17.55, 17.18, −3.51.

MS (EI) *m/z* 373 (M), 330 (M − $COCH_3$), 316 (M − *t*-Bu).

HRMS (EI) calc for $C_{21}H_{31}O_3NSi$ − $COCH_3$: 330.1890. Found: 330.1889.

1-[(t-Butyldimethylsilyl)oxy]-10-(trifluoroacetoxy)-9-oxa-10-azabicyclo[9.2.2]pentadec-11-ene-2,6-diyne **23**

Trifluoroacetic anhydride (50 μL, 0.36 mmol) was added to a solution of oxime ether **12** (60 mg, 0.18 mmol) in dry CH_2Cl_2 (5 mL) under argon. After 2.5 h at room temperature, the reaction was stopped by the addition of H_2O. The organic phase was washed with water and with NaCl aq (sat), dried over Na_2SO_4 and concentrated under vacuum. The resulting yellow oil was purified by silica-gel flash column chromatography (heptane/EtOAc, 15:1). Compound **23** was obtained as a colorless oil (69 mg, 89%).

IR (neat) 2 956, 2 931, 2 856, 1 719, 1 431, 1 406, 1 250, 1 225, 1 206, 1 162, 1 106, 1 006, 937, 875, 837 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) δ 5.83 (m, 1H, C=CH), 4.69 (d, J = 16.6 Hz, 1H, $HCHON$), 4.41 (d, J = 16.5 Hz, 1H, $HCHON$), 2.93 (m, 1H), 2.68–2.33 (m, 6H, 2 CH_2 hexadiyne and CH_2 cyclohexene), 2.25–2.11 (m, 1H), 2.08–1.84 (m, 2H), 0.88 (s, 9H, t-BuSi), 0.19 (s, 6H, Me_2Si).

^{13}C NMR (62.89 MHz, $CDCl_3$) δ 134.80, 123.96, 118.27, 114.47, 88.46, 84.60, 83.50, 75.76, 67.13, 66.35, 41.37, 37.12, 26.07, 25.82, 19.34, 18.31, 18.02, −2.69.

MS (CI, isobutane) m/z 428 (M + 1), 296 (M + 1 - TBSOH), 133 ($TBSOH_2^+$).

HRMS (CI) calc for $C_{21}H_{28}F_3O_3NSi$ + H^+: 428.1869. Found: 428.1841.

4-(7-Bromohepta-1,5-diynyl)-4-[(t-butyldimethylsilyl)-oxy]cyclohexanone-(t-butyldimethylsilyl)oxime **24**

TBSCl (32 mg, 0.21 mmol) and imidazole (36 mg, 0.54 mmol) were added to a stirred solution of oxime **19** (74 mg, 0.18 mmol) in THF (4 mL). After stirring overnight at room temperature, ether was added and the organic phase was washed successively with water and brine, dried over Na_2SO_4 and evaporated to dryness under vacuum. Compound **24**, obtained as a colorless oil (94.5 mg, quantitative yield), was taken directly through to the next step without purification.

^1H NMR (300 MHz, $CDCl_3$) δ 3.90 (s, 2H, CH_2Br), 2.68 (m, 2H, CH_2 cyclohexane), 2.50–2.22 (m, 6H, 2 CH_2 hexadiyne and CH_2 cyclohexane), 1.92–1.72 (m, 4H, 2 CH_2 cyclohexane), 0.91 (s, 9H, t-BuSi), 0.89 (s, 9H, t-BuSi), 0.19 (s, 6H, Me_2Si), 0.17 (s, 6H, Me_2Si).

Formation of compound **26** *from* **24**

Acetyl bromide (9 μL, 0.11 mmol) was added to the O-TBS protected oxime **24** (20 mg, 0.04 mmol) in dry acetonitrile (1.5 mL) at room temperature. After stirring for 1 h the reaction ether was added, and the organic phase was washed with water and NaCl aq (sat), then dried over Na_2SO_4 and concentrated under vacuum. The resulting oil was purified by silica-gel flash chromatography (heptane/EtOAc, 3:1) permitting isolation of compound **26** (8.1 mg, 47%).

^1H NMR (200 MHz, $CDCl_3$) δ 3.90 (s, 2H, CH_2Br), 2.85–2.29 (m, 8H, 2 CH_2 hexadiyne and 2 CH_2 cyclohexane), 2.16 (s, 3H, CH_3CO), 2.03–1.79 (m, 4H, 2 CH_2 cyclohexane), 0.88 (s, 9H, t-BuSi), 0.20 (s, 6H, Me_2Si).

MS (CI, isobutane) m/z 456–454 (M + 1), 396–394 (M + 1 - MeCOOH).

4-[(t-Butyldimethylsilyl)oxy]-4-[7-(phthalimidooxy)-hepta-1,5-diynyl]cyclohexanone-ethyleneacetal **27**

N-Hydroxyphthalimide (520 mg, 3.17 mmol), PPh_3 (762 mg, 2.90 mmol) and DEAD (0.50 mL, 3.17 mmol) were added to alcohol **16** (1.00 g, 2.64 mmol) in dry THF (15 mL) under argon. The mixture turned yellow and got slightly warm. After 24 h stirring at room temperature the solvent was evaporated, and the resulting oil was purified by silica-gel flash column chromatography (heptane/EtOAc, 3:1). Compound **27** was obtained as a colorless oil (1.33 g, 96%).

IR (neat) 2 956, 2 931, 2 887, 2 856, 1 737, 1 369, 1 250, 1 187, 1 106, 837 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) δ 7.90–7.69 (m, 4H, H aromatics), 4.82 (s, 2H, CH_2ON), 3.90 (s, 4H, OCH_2CH_2O), 2.38 (broad s, 4H, $CCCH_2CH_2CC$), 1.87–1.53 (m, 8H, 4 CH_2 cyclohexane), 0.83 (s, 9H, t-BuSi), 0.10 (s, 6H, Me_2Si).

^{13}C NMR (75.47 MHz, $CDCl_3$) δ 163.15, 134.41, 128.81, 123.40, 108.05, 89.01, 84.94, 82.76, 74.10, 67.85, 65.58, 64.07, 38.39, 31.01, 25.71, 18.98, 18.38, 17.97, −3.08.

MS (CI, isobutane) m/z 392 (M + 1 - TBSOH), 245 (M + 1 - TBSOH - PhtNH), 229 (M + 1 - TBSOH - PhtNOH), 164 ($PhtNOH_2^+$), 148 ($PhtNH_2^+$), 133 ($TBSOH_2^+$).

Anal calc for $C_{29}H_{37}O_6NSi$: C, 66.51; H, 7.12. Found: C, 66.12; H, 6.77.

4-[7-(Aminooxy)hepta-1,5-diynyl]-4-[(t-butyldimethylsilyl)oxy]cyclohexanone-ethyleneacetal **28**

Hydrazine (27 μL, 0.62 mmol) was added to a solution of phthalimide **27** (327 mg, 0.62 mmol) in MeOH (10 mL). After 30 min stirring at room temperature, the MeOH was evaporated, and the residue was taken up in pentane to precipitate the phthalazine-1,4-dione. Filtration and concentration of the filtrate provided hydroxylamine **28**. This operation was repeated until no further precipitation occurred. Compound **28** (colorless oil; quantitative) was directly employed in to the next step without further purification.

IR (neat) 2 956, 2 931, 2 887, 2 856, 1 737, 1 369, 1 250, 1 187, 1 106, 837 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) δ 5.54 (broad s, 2H, ONH_2), 4.30 (s, 2H, CH_2ON), 3.93 (s, 4H, OCH_2CH_2O), 2.47 (s, 4H, $CCCH_2CH_2CC$), 1.94–1.63 (m, 8H, CH_2 cyclohexane), 0.89 (s, 9H, t-BuSi), 0.18 (s, 6H, Me_2Si).

^{13}C NMR (75.47 MHz, $CDCl_3$) δ 108.26, 85.38, 84.98, 83.01, 76.77, 67.88, 64.19, 63.84, 38.50, 31.10, 25.82, 19.03, 18.88, 18.10, −2.98.

MS (CI, isobutane) m/z 450 (M + 57), 394 (M + 1), 262 (M + 1 - TBSOH), 133 ($TBSOH_2^+$).

4-[(t-Butyldimethylsilyl)oxy]-4-{[(methoxycarbonyl)-amino]oxy}hepta-1,5-diynylcyclohexanone-ethylene-acetal **29**

DMAP (31 mg, 0.25 mmol) and methyl chloroformate (20 μL, 0.25 mmol) were added to a solution of hydroxylamine **28** (90 mg, 0.23 mmol) in dry CH_2Cl_2 (8 mL) under argon at −20 °C. After 3 h at −20 °C the organic phase was washed successively with 1 N HOAc, $NaHCO_3$ aq (sat), and NaCl aq (sat), dried over Na_2SO_4, and concentrated under vacuum. Silica gel flash chromatography of the resulting oil (heptane/EtOAc, 3:1) provided compound **29** as a colorless oil (87 mg, 84%).

IR (neat) 3 287, 2 956, 2 931, 2 887, 2 856, 1 737, 1 369, 1 269, 1 250, 1 106, 1 056, 837 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) δ 7.90 (broad s, 1H, NH), 4.49 (s, 2H, CH_2ON), 3.94 (s, 4H, OCH_2CH_2O), 3.78 (s, 3H, OCH_3), 2.44 (broad s, 4H, $CCCH_2CH_2CC$), 1.94–1.63 (m, 8H, 4CH_2 cyclohexane), 0.88 (s, 9H, t-BuSi), 0.16 (s, 6H, Me_2Si).

MS (CI, isobutane) m/z 452 (M + 1), 320 (M + 1 - TBSOH), 229 (M + 1 - TBSOH - $HONHCO_2Me$), 133 ($TBSOH_2^+$), 92 ($MeO_2CNHOH_2^+$).

4-[(t-Butyldimethylsilyl)oxy]-4-7-{[(methoxycarbonyl)-amino]oxy}hepta-1,5-diynylcyclohexanone **30**

To a solution of dioxolane **29** (156 mg, 0.35 mmol) in $CHCl_3$ (40 mL) was added a 35% aqueous solution of trifluoroacetic acid (27 mL), and the resulting mixture was stirred for 1.5 days at room temperature. CH_2Cl_2 was then added, and the organic phase was washed with $NaHCO_3$ aq (sat), with NaCl aq (sat), dried over Na_2SO_4 and concentrated under vacuum. A yellowish liquid corresponding to compound

30 was isolated and taken on to the next step without purification (135 mg, 95%).

IR (neat) 3 275, 2 956, 2 931, 2 856, 1 718, 1 462, 1 250, 1 106, 1 044, 837 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) δ 7.60 (broad s, 1H, NH), 4.48 (s, 2H, CH_2ON), 3.79 (s, 3H, OCH_3), 2.62–2.35 (m, 8H, $2CH_2$ cyclohexane + $CCCH_2CH_2CC$), 2.18–2.00 (m, 4H, $2CH_2$ cyclohexane), 0.89 (s, 9H, *t*-BuSi), 0.21 (s, 6H, $SiMe_2$).

^{13}C NMR (62.89 MHz, $CDCl_3$) δ 210.90, 86.79, 84.14, 84.02, 75.50, 67.28, 64.55, 53.00, 40.48, 37.51, 25.90, 19.01, 18.81, 18.24, −2.92.

MS (CI, isobutane) *m/z* 408 (M + 1), 276 (M + 1 − TBSOH), 185 (M + 1 − TBSOH − $HONHCO_2Me$), 133 ($TBSOH_2^+$).

Formation of compound **31** *from carbamate* **29**

TMSOTf (2 μL, 0.008 mmol) was added to a dilute solution of **29** (18.7 mg, 0.041 mmol) in dry acetonitrile (15 mL) at 0 °C. The mixture rapidly turned yellow and then orange. After 3 h the starting material was totally consumed. The reaction was then stopped by the addition of H_2O, and mixture was extracted with ether. The organic phases were washed with water, and brine, dried over Na_2SO_4, and concentrated under vacuum. The resulting oil was purified by silica-gel flash column chromatography (heptane/EtOAc, 2:1). Among the numerous products, compound **31** was isolated (1.3 mg, 10%).

^1H NMR (300 MHz, $CDCl_3$) δ 7.51 (broad s, 1H, NH), 5.92 (broad s, 1H, C=CH), 4.48 (t, J = 2.0 Hz, 2H, CH_2ON), 3.97 (s, 4H, OCH_2CH_2O), 3.79 (s, 3H, OCH_3), 2.61–2.28 (m, 8H, $2CH_2$ cyclohexane and $2CH_2$ hexadiyne), 1.77 (m, 2H, CH_2 cyclohexane).

MS (CI, isobutane) *m/z* 320 (M + 1), 229 (M + 1 − $HONHCO_2Me$).

Formation of compound **32** *from carbamate* **30**

BF_3/OEt_2 (10 μL) was added to a dilute solution of **30** (29 mg, 0.071 mmol) in dry CH_2Cl_2 (40 mL), and the mixture was stirred at −5 °C for 30 min and at room temperature for 2 h 30 min. The reaction was quenched by adding water, and the organic phase was washed with water and brine, dried over Na_2SO_4 and concentrated under vacuum. The resulting oil was purified by silica-gel flash chromatography (heptane/EtOAc, 2:1). Two products were isolated. The less polar component corresponded to the starting material, and the more polar material to compound **32** (5 mg, 27%).

IR (neat) 3 275, 2 962, 2 925, 2 850, 1 711, 1 444, 1 338, 1 257, 1 113 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) δ 7.50 (broad s, 1H, NH), 6.08 (broad s, 1H, C=CH), 4.49 (t, J = 2.0 Hz, 2H, CH_2ON), 3.78 (s, 3H, OCH_3), 2.96 (m, 2H, CH_2 cyclohexane), 2.68–2.40 (m, 8H, $2CH_2$ cyclohexane and $2CH_2$ hexadiyne).

Attempted [2,3]-Wittig rearrangement on the N*-acetyl enamine* **22** *using LiTMP. Formation of dimer* **37**

To a stirred solution of **22** (26.3 mg, 0.07 mmol) in dry THF (8 mL) at −25 °C was added a preformed 0.5 M solution of LiTMP (0.42 mL, 0.21 mmol) in THF/hexanes. Stirring was continued for 30 min, and then the reaction was quenched with NH_4Cl aq (sat) and extracted with ether. The organic phase was washed with water and brine, dried over Na_2SO_4 and evaporated to dryness in vacuo. The resulting yellowish oil was silica-gel flash column chromatographed (heptane/EtOAc, 1:1). Compound **37** (6.8 mg, 13%) corresponded to a major product component.

IR (neat) 3 319, 2 956, 2 931, 2 856, 1 719, 1 669, 1 281, 1 250, 1 100, 837 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) δ 6.81 (broad s, 1H, NH), 5.92 (m, 1H, C=CH), 5.71 (m, 1H, C=CH), 4.79 (m, 1H, C*H*OH), 4.64 (d, J = 16.5 Hz, 1H, *H*CHON), 4.39 (d, J = 16.5 Hz, 1H, HC*H*ON), 2.87 (m, 2H), 2.68–2.11 (m, 19H), 2.02 (s, 3H, $COCH_3$), 2.03–1.76 (m, 2H), 0.87 (s, 9H, *t*-BuSi), 0.85 (s, 9H, *t*-BuSi), 0.18 (s, 6H, Me_2Si), 0.16 (s, 6H, Me_2Si).

MS (FAB, LiCl) *m/z* 753 (M + Li).

Attempted [2,3]-Wittig rearrangement on the N*-acetyl enamine* **22** *using LDA/*n*-BuLi. Formation of compound* **40**

To a stirred solution of **22** (35.5 mg, 0.095 mmol) in dry THF (10 mL) at −78 °C was added a preformed 0.36 M solution of LDA (2.63 mL, 0.95 mmol) in THF/hexanes. Stirring was continued for 1 h at −78 °C (no change observed by TLC), then, 3 equiv of *n*-BuLi in hexanes (1.5 M) were added (190 μL, 0.28 mmol). After 5 min the reaction was quenched with NH_4Cl aq (sat) and extracted with ether. The combined organic phases were washed with water and brine, dried over Na_2SO_4 and evaporated to dryness in vacuo. Compound **40** was isolated from the mixture as a colorless oil (6 mg, 18%) by silica-gel flash column chromatography (heptane/EtOAc, 15:1), and characterized by ^1H NMR, and by comparison with compound **46**.

^1H NMR (300 MHz, $CDCl_3$) δ 6.30 (broad s, 1H, NH), 5.92 (broad s, 1H, C=CH), 2.57–2.22 (m, 8H, $2CH_2$ cyclohexene and $2CH_2$ hexadiyne), 2.02 (s, 3H, $COCH_3$), 1.98 (t, J = 2.5 Hz, 1H, CC-H), 1.87 (m, 2H), 0.86 (s, 9H, *t*-BuSi), 0.18 (s, 6H, Me_2Si).

Reaction of N*-(trifluoroacetyl)enamine* **23** *under [2,3]-Wittig rearrangement conditions. Formation of compound* **41** *using LiTMP*

To a stirred solution of **23** (18 mg, 0.042 mmol) in dry THF (2 mL) at −30 °C was added a preformed 0.5 M solution of LiTMP (0.26 mL, 0.12 mmol) in THF/hexanes. Stirring was continued for 1 h, and then the reaction was quenched with aqueous NH_4Cl (sat) and extracted with ether. The combined organic phases were washed with water and brine, dried over Na_2SO_4 and evaporated to dryness in vacuo. The residue was purified by silica-gel flash column chromatography (heptane/EtOAc, 15:1 then 5:1). The less polar product component corresponded to oxime **12** (4 mg, 29%), and the more polar fraction corresponded to propargylic aldehyde **41** (2.5 mg, 14%).

^1H NMR (300 MHz, $CDCl_3$) δ 9.18 (s, 1H, CHO), 7.43 (broad s, 1H, NH), 6.09 (m, 1H, C=CH), 2.80–2.31 (m, 8H, $2CH_2$ hexadiyne and $2CH_2$ cyclohexene), 1.92 (m, 2H), 0.88 (s, 9H, *t*-BuSi), 0.18 (s, 6H, Me_2Si).

MS (CI, isobutane) *m/z* 428 (M + 1), 296 (M + 1 − TBSOH).

Attempted cyclization of enamide **41**. *Formation of compound* **46**

To a solution of **41** (10 mg, 0.023 mmol) in dry THF (20 mL) at 0 °C was added NaH (50% in paraffin) (6 mg,

0.094 mmol). Stirring was continued for 3 h, and then the reaction was quenched by the addition of water and extracted with ether. The combined organic phases were washed with water and brine, dried over Na_2SO_4 and evaporated to dryness in vacuo. The resulting yellow oil was purified by silica-gel flash column chromatography (heptane/EtOAc, 9:1). One major compound was isolated, corresponding to **46** (3 mg, 32%).

IR (neat) 3 313, 2 957, 2 930, 2 899, 2 857, 1 720, 1 560, 1 252, 1 221, 1 190, 1 163, 1 097, 838 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) δ 6.99 (broad s, 1H, NH), 6.08 (broad s, 1H, C=CH), 2.59-2.28 (m, 8H, $2CH_2$ cyclohexene and $2CH_2$ hexadiyne), 2.01 (t, J = 2.5 Hz, 1H, CCH), 1.92 (m, 2H), 0.84 (s, 9H, t-BuSi), 0.19 (s, 6H, Me_2Si).

MS (CI, isobutane) m/z 400 (M + 1), 268 (M + 1 - TBSOH), 133 ($TBSOH_2^+$).

X-ray crystal structure of the O*-desilylated derivative of* **12**

Crystal data: $C_{13}H_{15}NO_2$, M_w = 217.27, monoclinic, space group $P2_1$, Z = 2, a = 7.224 (5), b = 6.968 (4), c = 11.372 (8) Å, β = 95.30 (3)°, V = 570 Å^3, d_c = 1.27 g cm^{-3}, $F(000)$ = 232, λ (Cu$K\alpha$) = 1.5418 Å, μ = 0.65 mm^{-1}; 2 143 Nonius CAD-4 diffractometric intensities measured of which 1 113 unique (R_{int} = 0.024); 1 077 reflections considered as observed with $I > 3.0\sigma(I)$ kept in refinement calculations.

The structure was solved by direct methods using SHELXS86 [17] and refined by full-matrix least-squares with SHELX76 [18] minimizing the function $\Sigma w(Fo - |Fc|)^2$. All the hydrogen atoms located in difference Fourier maps were fitted at theoretical positions ($d_{C\text{-}H}$ = 1.00 Å) and assigned an isotropic thermal factor equivalent to that of the bonded atom, plus 10%. Convergence was reached at R = 0.040 and R_w = 0.060 (with $R_w = [\Sigma w(Fo - |Fc|)^2/\Sigma wFo^2]^{1/2}$ and $w = 1/[\sigma^2(Fo) + 0.00335\ Fo^2]$. No residue was higher than 0.29 eÅ^{-3} in the final difference map. In the crystal, the molecules are linked in chains through the hydroxyl groups OH16 and the nitrogen atoms N10 of the nearest molecules by means of hydrogen bonds of type : O16-H...$N10_{(x-1,y,z)}$ = 2.897 (4), $H_{O16...}N$ = 1.90 Å, angle O-H...N = 172°. Lists of fractional atomic coordinates, thermal parameters, bond distances and selected bond and torsion angles have been deposited with the British Library, Document Supply Center at Boston Spa, West Yorkshire, LS23 7BQ UK, as supplementary publication n° SUP 90437 and is available on request from the Document Supply Center.

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