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INTRAMOLECULAR REACTIONS OF 2-PROPYNYLSILANES WITH *N*-ACYLIMINIUM IONS; CUPRATE S_N2' REACTIONS OF THE ALLENIC PRODUCTS AS A ROUTE TO *TRANS*-FUSED CARBOBICYCLES

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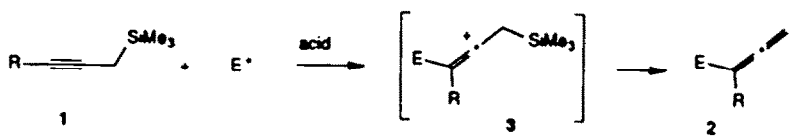
Summary: Intramolecular acid-assisted reactions of 2-propynylsilanes with cyclic *N*-acyliminium ion precursors lead to bridged azabicyclic systems **34-45** (Table I), containing the uncommon α-allenic amide functionality. After introduction of a *tert*-butoxycarbonyl or a tosyl group onto the lactam nitrogen atom, these molecules react with cuprates in an S_N2' fashion. The products **52-58** (Table II) are angularly functionalized *trans*-fused carbobicycles containing a 1,3-diene moiety.

INTRODUCTION

The 2-propynyltrimethylsilane functionality (**1**) constitutes a reactive π-nucleophile, which is very useful for the synthesis of allenes **2** of diverse structural types (Scheme 1).[1-5] In the presence of acid, **1** reacts with various electrophiles E^+, such as acid chlorides, acetals, aldehydes, ketones, and Michael acceptors. These reactions are characterized by a propynyl-allenyl rearrangement, which proceeds through the intermediacy of a vinylic carbocation **3**, stabilized by a β-silicon atom.

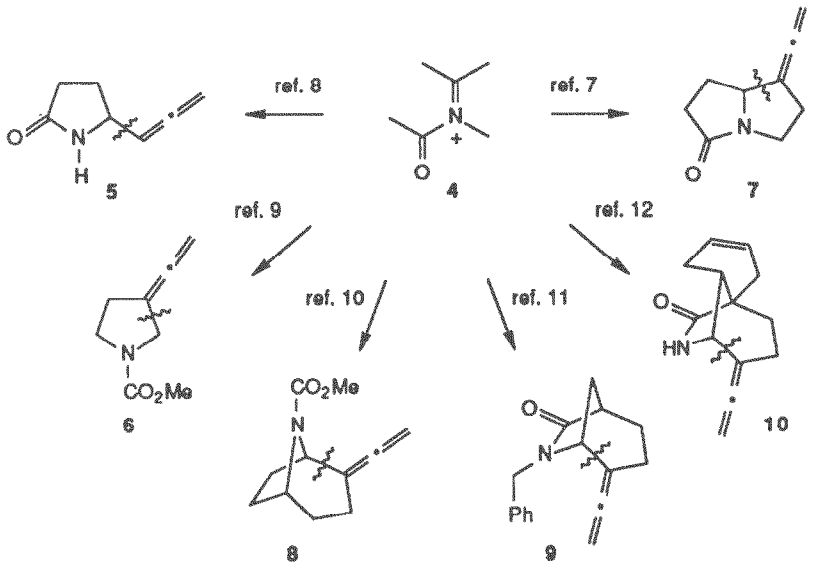


1 3 2

Scheme 1

Since 1982, we have been studying the reactions of 2-propynylsilanes **1** with *N*-acyliminium intermediates **4**.[6] We showed that such processes give high yields of allenic nitrogen compounds in many cases.[7-14] Scheme 2 gives a survey of the structural types of allenes which were prepared in this manner, with ⌇ indicating the carbon-carbon bonds formed. Reactions were successful both in the inter- (**4** → **5**) and the intramolecular fashion (**4** → **6**–**10**), and endocyclic (**5**, **7-10**) as well as acyclic iminium ions (**6**) could be used. The preparative value of these reactions was illustrated by means of syntheses of the GABA-analogues gabaculine[13] and γ-allenyl-GABA.[8]

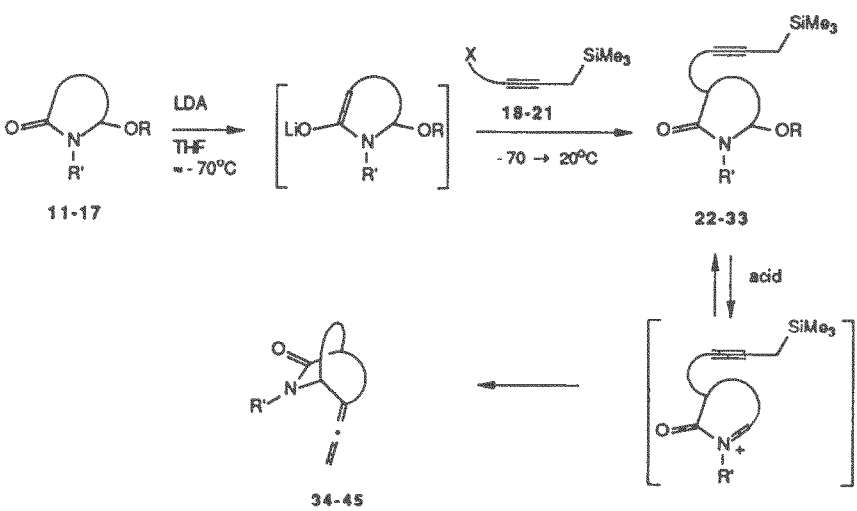
In this report, we present the full details of our research concerning the synthesis of bridged allenes of type **9** and **10**.[11,12] In addition, we describe a remarkable synthetic application of the allenes of type **10**, which involves S_N2' substitution of the α-allenic nitrogen substituent by cuprate reagents. The products are *trans*-fused carbobicyclic systems with a unique substitution pattern.



Scheme 2

RESULTS

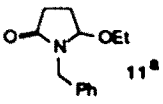
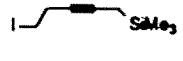
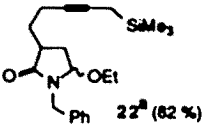
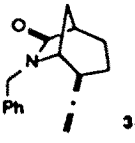
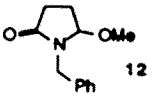
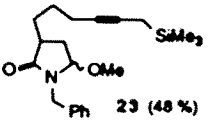
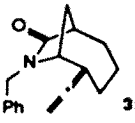
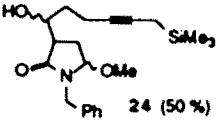
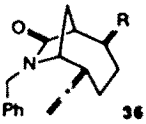
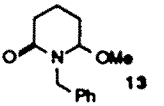
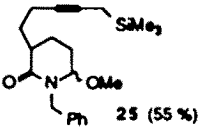
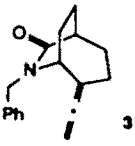
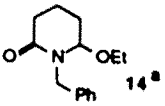
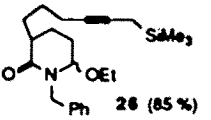
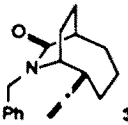
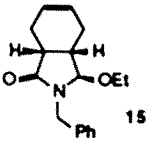
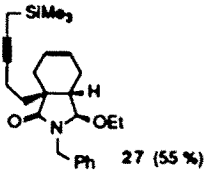
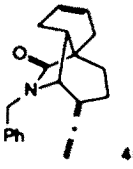
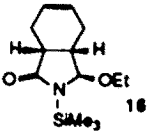
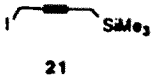
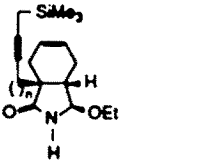
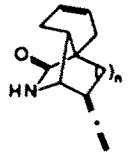
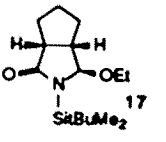
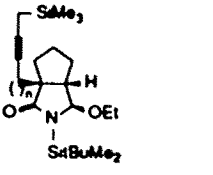
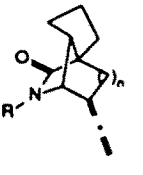
The general principle for the synthesis of the bridged skeletons of type **9** and **10** is based on the use of alkoxylactams **11-17** as dipolar synthons (Scheme 3).[11] This designation refers to the fact that deprotonation using lithium diisopropylamide (LDA) leads to a *nucleophilic* enolate anion, whereas acidic treatment generates an *electrophilic* acyliminium ion. Both of these reactive intermediates are utilized in two consecutive steps for the formation of two C-C bonds. The 2-propynylsilanes **18-21**, which can also be viewed as dipolar synthons, serve as reaction partners. In our procedure, the enolate alkylation is carried out intermolecularly, after which the *N*-acyliminium ion is employed in an intramolecular reaction. The results are collected in Table I.



Scheme 3

The *N*-silyllactams **16** and **17** were obtained by base-assisted silylation of the corresponding *N*-unsubstituted lactams. The latter lactams as well as *N*-benzyllactams **11-15** were readily prepared by acid-assisted $NaBH_4$--reduction of the corresponding cyclic imides, followed by alcoholysis.[13,15] In this way the ethoxylactams **15-17**

Table I

entry	alkoxylactam	alkylating reagent	alkylation product (yield)	acid for cyclization	cyclization product (yield)
1 a b	 11[a]	 18[a]	 22[a] (82 %)	CF_3COOH HCOOH	 (88 %) (97 %) 34[a]
2	 12	 19	 23 (48 %)	HCOOH	 35 (89 %)
3	12	 20	 24 (50 %)	CF_3COOH	 36 R = H, OH (65 %) 37 R = O
4	 13	18	 25 (55 %)	HCOOH	 38 (93 %)
5 a b	 14[a]	19	 26 (85 %)	HCOOH $SnCl_4$	 (< 10 %) (81 %) 39
6	 15	18	 27 (55 %)	HCOOH	 40 (97 %)
	 16	 21			
7	16	21	28 n = 1 (42 %)	HCOOH	41 n = 1 (95 %)
8	16	18	29 n = 2 (79 %)	HCOOH	42 n = 2 (91 %)
9	16	19	30 n = 3 (81 %)	HCOOH	43 n = 3 (100 %)
	 17				
10	17	21	31 n = 1 (64 %)	HCOOH	—
11	17	18	32 n = 2 (54 %)	HCOOH	44 n = 2 R = H (53 %)
12	17	19	33 n = 3 (87 %)	HCOOH	45 n = 3 R = $SiBuMe_2$ (98 %) 46 n = 3 R = H

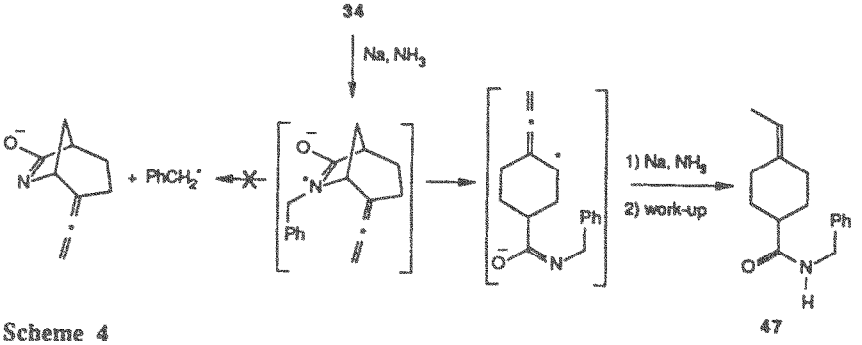
[a] See ref 13.

were obtained as their thermodynamically most stable isomers in >95% isomeric purity (*cis*-relationship between the ethoxy function and the angular hydrogens). The cyclic imides used as starting materials were readily available except for the imide leading to **17**, which was prepared from 2-carbethoxycyclohexanone by way of a Favorskii ring contraction.[16] The iodides and aldehyde **18-21** were prepared from the corresponding alcohols.[7,11,13,17]

The lithium enolates of the lactams **11-17** were readily formed between -80 and -70°C by using LDA as base in THF. Reaction with the alkylating reagents **18-21** gave reasonable to good yields of alkylation products **22-33** (Table I). The products from **16** lost the *N*-trimethylsilyl group after hydroxide treatment during work-up. From lactams **11-14** mixtures of stereoisomers were obtained (about 60:40 ratio's, excepting **24** which was a more complex mixture because of the extra asymmetric centre). From the bicyclic lactams **15-17**, isomerically pure alkylation products were obtained. We assume that the *cis* ring junction is retained on the basis of kinetic (alkylation takes place at the least hindered side of the molecules) and thermodynamic factors (the greater stability of products with a *cis* ring junction is reflected in the transition state of alkylation). Literature precedent[18] and ^{1}H NMR data provide convincing evidence. The magnitude of the vicinal coupling constant of the acetal hydrogen atom with the adjacent angular hydrogen is indicative of the stereochemistry of ring junction.[19] We found this ^3J to be <1 Hz in **31-33** and 2-3 Hz in **27-30**.

The *N*-acyliminium ion cyclizations were best performed by simply stirring the precursors in neat formic acid for 30 min at room temperature. Treatment with 5 equiv of trifluoroacetic acid in dichloromethane was also satisfactory (entries 1a and 3). At two occasions (entries 5a and 10) no cyclization products could be isolated under these conditions, probably due to prevailing side reactions, induced by Brønsted acid, such as protodesilylation and ethanol elimination. These side reactions can occur, if cyclization is slow. Slow ring closure can be expected for **26**, which should give an eight-membered ring, and for **31**, which should lead to a strained bridged trans-fused bicyclo[3.3.0]octane skeleton. Interestingly, **26** could be cyclized in good yield by using the Lewis acid tin tetrachloride (entry 5b). Cyclization of **33** in formic acid appeared to be a very fast reaction (entry 12) and was complete as soon as all starting material had dissolved. Immediate work-up gave allene **45** in virtually quantitative yield with the *N*-silyl group still present. Longer reaction times led, in addition to *N*-desilylation product **46**, to byproducts of yet unknown structures (lactam **46** was obtained in quantitative yield through treatment of **45** with tetrabutylammonium fluoride in THF). Cyclization of **32** (entry 11) was considerably slower, and could best be stopped after 15 min to furnish the unprotected lactam **44** in 53% yield.

All cyclization products showed the typical allene frequency in their IR spectra at 1955-1975 cm^{-1}. The allene hydrogens gave a narrow multiplet at about 4.75 ppm in the ^{1}H NMR spectra. All products were single isomers except for **36**. Oxidation of this alcohol mixture with the CrO_3-pyridine complex furnished a single ketone **37** in 92% yield.



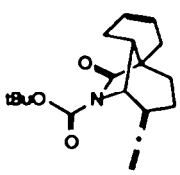
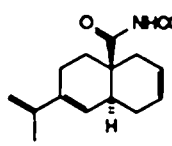
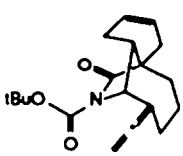
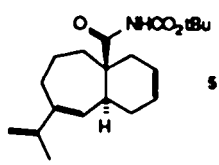
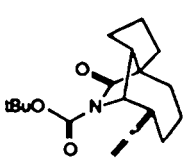
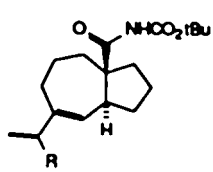
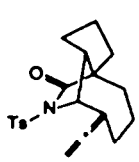
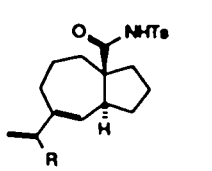
Scheme 4

The above results show that a general method has been developed for the synthesis of a great variety of bridged bicyclic nitrogen compounds. Most of these ring structures are not readily available via other routes.[20] Moreover, the products contain the rare α-allenic amide functionality[21] which is useful for further synthetic applications *(vide infra)*. Finally, the 2-propynylsilane moiety has proven its reliability as π-nucleophile in *N*-acyliminium cyclizations.

Turning our attention to the chemical properties of the allenic amides, we first attempted to remove the *N*-benzyl function by way of treatment of **34** with sodium in liquid ammonia.[22] However, the radical anion of **34** did not lead to formation of a benzyl radical but gave an allylic radical, because cyclohexane derivative **47** was isolated in 95% yield (Scheme 4). Thus, for the synthesis of *N*-unprotected allenic amides a different protecting group was required. The silyl function appeared to be very convenient in this respect as was shown in the total synthesis of gabaculine[13], and follows from entries 7-12 in Table I.

The allenic amides **40-46** are in essence bridged derivatives of *trans*-fused carbobicyclic systems. Because the latter molecules are interesting synthetic targets we investigated the S_N2' substitution of nitrogen as a potential way to open the lactam bridge. To this end the leaving group ability of nitrogen[23] was enhanced by introduction of the *tert*-butoxycarbonyl[24] or the tosyl function.[25] The preparations of lactams **48-51** (Table II) proceeded in high yield (80 - 94%, see experimental).

Table II

entry	allene		cuprate	product (yield)
1		**48**	Me_2CuLi	 **52** (75 %)
2		**49**	Me_2CuLi	 **53** (91 %)
				
3	**50**		Me_2CuLi	**54** R = Me (84 %)
4	**50**		Ph_2CuLi	**55** R = Ph (27 %)
				
5	**51**		Me_2CuLi	**56** R = Me (93 %)
6	**51**		Ph_2CuLi	**57** R = Ph (67 %)
7	**51**		$(Me_3SiCH_2)_2CuLi$	**58** R = Me_3SiCH_2 (100 %)

When allene **48** was added at -78°C to a solution of 1.5 equiv of lithium dimethyl cuprate in ether, a fast reaction ensued (90 min, -78°C; 30 min, -78 to -40°C) to give bicyclic **52** in 75% yield as a crystalline solid (Table II). In a similar fashion the homologue **53** was obtained. Reaction of **50** with lithium dimethyl cuprate required 3 h at 0°C to give *trans*-fused octahydroazulene **54** in good yield. The corresponding reaction with diphenyl cuprate produced only a low yield of **55**. To our surprise the main product from this reaction was lactam **46** (65%). This problem was remedied by using the tosyl function as *N*-substituent. Tosylamide **51** reacted cleanly in 3 h at 0° with three different cuprates (Table II) to produce compounds **56-58** in good to excellent yields.

It was thus established that an allylic imide nitrogen atom is an excellent leaving group[23,26] with respect to S_N2' substitution with cuprate reagents. Complete γ-regioselectivity is observed, which has been found also in similar reaction of derivatives of α-allenic alcohols.[29] More research is necessary to assess the scope of this cuprate reaction, as well as to test other nucleophiles.

The products (**52-58**) are trans-fused carbobicycles with an unusual substitution pattern, characterized by a functionalized angular carbon atom and a 1,3-diene moiety. To the best of our knowledge the hexahydro-*H*--benzocycloheptene skeleton of **53** is unknown in the literature, and the octahydroazulene skeleton (**54-58**) is rare.[30] Hexahydronaphthalene **52** resembles the skeleton of the eudesmane sesquiterpenes.[31] Our current research in this area is directed at synthetic applications of the cuprate substitution products, as well as at the further development of the chemistry of α-allenic amides.

EXPERIMENTAL

General information. Infrared (IR) spectra were obtained from $CHCl_3$ solutions using a Perkin Elmer 298 spectrophotometer and are reported in cm^{-1}. Proton nuclear magnetic resonance (^1H NMR) spectra were determined in $CDCl_3$ as solvent using a Varian XL-100 (100 MHz) or a Bruker WM 250 (250 MHz) instrument. The latter apparatus was also used for the ^{13}C NMR spectra (62.9 MHz) in $CDCl_3$ solution. Chemical shifts are given in ppm downfield from tetramethylsilane. Exact mass measurements were carried out using a Varian MAT 711 or a VG Micromass ZAB-2HF instrument. R_f values were obtained by using thin-layer chromatography (TLC) on silica--gel-coated plastic sheets (Merck silica gel 60 F_{254}) with the indicated solvent (mixture). Chromatographic purification refers to flash chromatography using the same solvent as for TLC and Merck silica gel 60 (230-400 mesh). Melting and boiling points are uncorrected.

General procedure for the reduction of imides. An excess of sodium borohydride was added at 0-5°C to a stirred 0.1 M solution of the imide in EtOH. The reaction mixture was stirred at 0-5°C while a 2 M solution of HCl in EtOH was added dropwise (ca. 1 equiv in 3 h). After completion of the reduction (3-4 h, checked with TLC), the solution was cooled to -30°C, acidified with the same ethanolic HCl solution, and stirred for 1 h at room temperature. The reaction mixture was then poured into saturated aq $NaHCO_3$ and extracted with $CHCl_3$ (4 x). The combined organic extracts were dried (K_2CO_3) and concentrated *in vacuo*. The residue was chromatographed.

1-Benzyl-5-methoxy-2-pyrrolidinone (12). *N*-Benzylsuccinimide (2.00 g, 10.6 mmol) was reduced with 3.22 g (84.7 mmol) of $NaBH_4$, by using MeOH instead of EtOH, to give 1.21 g (5.92 mmol, 56%) of **12** as a colourless oil. R_f 0.31 (EtOAc). IR 1685 (CO). ^1H NMR (100 MHz) 1.90-2.78 (m, 4 H), 3.23 (s, 3 H, OCH_3), 4.03 (d, *J* 15 Hz, 1 H, CHPh), 4.75 (m, 1 H, CHOMe), 4.96 (d, *J* 15 Hz, 1 H, CHPh), 7.33 (m, 5 H, Ph).

1-Benzyl-6-methoxy-2-piperidinone (13). *N*-Benzylglutarimide (501 mg, 2.47 mmol) was reduced at ca. -15°C with 560 mg (14.7 mmol) of $NaBH_4$, by using MeOH instead of EtOH, to give 264 mg (1.20 mmol, 49%) of **13** as a colourless oil. R_f 0.39 (EtOAc). IR 1645 (CO). ^1H NMR (100 MHz) 1.42-2.78 (m, 6 H), 3.31 (s, 3 H, OCH_3), 4.03 (d, *J* 15 Hz, 1 H, CHPh), 4.42 (m, 1 H, CHOMe), 5.39 (d, *J* 15 Hz, 1 H, CHPh), 7.33 (m, 5 H, Ph).

***rel*-(3*R*,3a*S*,7a*R*)-2-Benzyl-3-ethoxy-2,3,3a,4,7,7a-hexahydro-1-isoindolone (15).** *N*-Benzyl-4--cyclohexene-1,2-dicarboximide (1.00 g, 4.15 mmol) was reduced with 1.58 g (41.5 mmol) of $NaBH_4$ to give 1.00 g (3.68 mmol, 89 %) of **15** as a colourless oil. R_f 0.42 (EtOAc:hexane 1:1). IR 1685 (CO). ^1H NMR (100 MHz) 1.20 (t, *J* 7 Hz, 3 H, $OCH_2\underline{CH_3}$), 1.38-1.78 (m, 1 H), 1.92-2.74 (m, 4 H), 2.99 (dt, *J*d 3 Hz, *J*t 8 Hz, 1 H, COCH), 3.47 (m, 2 H, $O\underline{CH_2}CH_3$), 4.03 (d, *J* 15 Hz, 1 H, CHPh), 4.22 (s, 1 H, CHOEt), 5.01 (d, *J* 15 Hz, 1 H, CHPh), 5.58-5.96 (m, 2 H, HC=CH), 7.32 (m, 5 H, Ph).

***rel*-(3*R*,3a*S*,7a*R*)-3-ethoxy-2,3,3a,4,7,7a-hexahydro-2-(trimethylsilyl)-1-isoindolone (16).** 4-Cyclohexene-1,2-dicarboximide (4.90 g, 32.5 mmol) was reduced at -25°C with 4.00 g (105 mmol) of $NaBH_4$. A modified work-up procedure was used: After stirring with acid, the reaction mixture was neutralized with a 2% ethanolic KOH solution, and then concentrated *in vacuo*. The residue was diluted with $CHCl_3$, filtered over celite, concentrated *in vacuo*, and chromatographed (CH_2Cl_2 : acetone 4:1), to give 5.19 g (28.6 mmol, 88%) of ethoxylactam as a white solid (98:2 mixture of epimers), along with 0.245 g (1.62 mmol) of starting material (5%). **Major isomer:** R_f 0.38, mp 65-67°C (Et_2O). IR 3440 and 3230 (br, NH), 1705 (CO). ^{1}H NMR (100 MHz) 1.20 (t, *J* 7 Hz, 3 H, $OCH_2\underline{CH_3}$), 1.6-3.1 (m, 6 H), 3.50 (m, 2 H, $OC\underline{H_2}CH_3$), 4.51 (br s, 1 H, CHOEt), 5.74 (m, 2 H, HC=CH), 8.05 (br s, 1 H, NH). Exact mass 181.1112 (calcd for $C_{10}H_{15}NO_2$ 181.1103). **Minor isomer:** R_f 0.30, IR 3430 and 3220 (br, NH), 1700 (CO). ^{1}H NMR (100 MHz) 1.20 (t, *J* 7 Hz, 3 H, $OCH_2\underline{CH_3}$), 2.1-2.8 (m, 6 H), 3.55 (m, 2 H, $OC\underline{H_2}CH_3$), 4.90 (d, *J* 5.5 Hz, 1 H, CHOEt), 5.78 (m, 2 H, HC=CH), 7.80 (br s, 1 H, NH). A mixture of 3.04 g (16.8 mmol) of ethoxylactam (pure major isomer) and 4.32 mL (20.5 mmol) of 1,1,1,3,3,3-hexamethyldisilazane was refluxed under nitrogen for 1.5 h. The reaction mixture was concentrated *in vacuo* and the product destilled under reduced pressure (bulb to bulb, bp ca. 190°C, 0.5 mmHg) yielding 3.56 g (14.1 mmol, 84%) of **16** as a colourless oil. IR 1690 (CO), 1250 and 850 (Si-C). ^{1}H NMR (100 MHz) 0.28 (s, 9 H, $Si(CH_3)_3$), 1.21 (t, *J* 7 Hz, 3 H, $OCH_2\underline{CH_3}$), 1.38-2.70 (m, 5 H), 2.94 (mt, *J*t 8 Hz, 1 H, COCH), 3.46 (m, 2 H, $OC\underline{H_2}CH_3$), 4.40 (s, 1 H, CHOEt), 5.54-5.90 (m, 2 H, HC=CH). Exact mass 253.1486 (calcd for $C_{13}H_{23}NO_2Si$ 253.1498).

***rel*-(2a*R*,5a*S*,6*R*)-1-(*tert*-Butyldimethylsilyl)-6-ethoxy-2a,3,4,5,5a,6-hexahydro-2*H*-cyclopenta-[c]pyrrol-2-one (17).** Cyclopentane-1,2-dicarboximide[16] (4.40 g, 31.7 mmol) was reduced at -5°C with 4.40 g (116 mmol) of $NaBH_4$. The modified work-up procedure was used as described for the preparation of **16** to yield 3.58 g (21.2 mmol) of ethoxylactam (67%, 96:4 mixture of epimers), along with 1.14 g (8.21 mmol, 26%) of starting material. **Major isomer:** R_f 0.38 (CH_2Cl_2:acetone 4:1). IR 3440 and 3230(br, NH), 1705 (CO). ^{1}H NMR (250 MHz) 1.22 (t, *J* 7 Hz, 3 H, $OCH_2\underline{CH_3}$), 1.3-2.2 (m, 6 H), 2.65 (m, 1 H), 2.98 (m, 1 H, COCH), 3.55 (m, 2 H, $OC\underline{H_2}CH_3$), 4.62 (s, 1 H, CHOEt), 7.75 (br s, 1 H, NH). Exact mass 169.1104 (calcd for $C_9H_{15}NO_2$ 169.1103). **Minor isomer:** R_f 0.25 (CH_2Cl_2:acetone 4:1), IR 3420 and 3210 (br, NH), 1695 (CO). ^{1}H NMR (100 MHz) 1.22 (t, *J* 7 Hz, 3 H, $OCH_2\underline{CH_3}$), 1.3-2.2 (m, 6 H), 2.65 (m, 1 H), 2.95 (m, 1 H, COCH), 3.55 (m, 2 H, $OC\underline{H_2}CH_3$), 4.96 (d, *J* 6.5 Hz, 1 H, CHOEt), 7.50 (br s, 1 H, NH). To a solution of 2.93 g (17.3 mmol) of the ethoxylactam (pure major isomer) in 50 mL of CH_2Cl_2 was added under nitrogen at 0°C 3.92 g (26.0 mmol) of *tert*-butyldimethylsilyl chloride , 4.87 mL (35 mmol) of Et_3N, and catalytic amounts of 4-dimethylaminopyridine and imidazole. After stirring the solution for 24 h at room temperature, 50 mL of CH_2Cl_2 was added. The organic layer was washed with water (3 x 25 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was chromatographed to yield 3.87 g (13.7 mmol, 79%) of **17**. R_f 0.44 (EtOAc:hexane 1:4). IR 1685 (CO), 1260 and 840 (Si-C). ^{1}H NMR (250 MHz) 0.21 (s, 3 H, $SiCH_3$), 0.26 (s, 3 H, $SiCH_3$), 0.92 (s, 9 H, $SiC(CH_3)_3$), 1.17 (t, *J* 7 Hz, 3 H, $OCH_2\underline{CH_3}$), 1.25-2.10 (m, 6 H), 2.55 (m, 1 H), 2.92 (m, 1 H, COCH), 3.40 (m, 2 H, $O\underline{CH_2}CH_3$), 4.75 (s, 1 H, CHOEt). Exact mass 283.2045 (calcd for $C_{15}H_{29}NO_2Si$ 283.1968).

6-Iodo-1-(trimethylsilyl)-2-hexyne (19). To a solution of 2.00 g (11.7 mmol) of 6-(trimethylsilyl)-4-hexyn-1-ol in 12 mL of CH_2Cl_2 was added at 0°C 1.96 mL (14.1 mmol) of triethylamine. Subsequently, 0.95 mL (12.3 mmol) of methanesulfonyl chloride was added dropwise with stirring and cooling at 0°C. The mixture was allowed to warm to room temperature, and after 15 min treated with water. The mixture was extracted with CH_2Cl_2 (4 x) and the combined extracts dried ($MgSO_4$) and concentrated *in vacuo* to give the almost pure methanesulfonate as a light yellow oil. IR 2220 (w, C≡C), 1360 and 1170 (OSO_2), 1245 and 850 (Si-C). ^{1}H NMR (100 MHz) 0.08 (s, 9 H, $Si(CH_3)_3$), 1.45 (t, *J* 2.5 Hz, 2 H, CH_2Si), 1.68-2.55 (m, 4 H, $C{\equiv}CCH_2CH_2$), 3.03 (s, 3 H, CH_3), 4.41 (t, *J* 6 Hz, 2 H, $C\underline{H_2}O$). Exact mass 248.0908 (calcd for $C_{10}H_{20}O_3SSi$ 248.0902). The crude methanesulfonate was dissolved in 20 mL of DMF and heated with 5.83 g (35.1 mmol) of potassium iodide at 80°C for 17 h. The reaction mixture was cooled and poured into 75 mL of water. The aq layer was extracted with hexane (4 x 25 mL). The combined hexane extracts were washed with 1 M aq sodium metabisulfite (25 mL) and water (25 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed to give 2.62 g (9.35 mmol, 80%) of **19** as a colourless oil. R_f 0.42 (hexane). IR 2210 (w, C≡C), 1245 and 850 (Si-C). ^{1}H NMR (100 MHz) 0.08 (s, 9 H, $Si(CH_3)_3$), 1.40 (t, *J* 2.5 Hz, 2 H, CH_2Si), 1.68-2.53 (m, 4 H, $C{\equiv}CCH_2CH_2$), 3.32 (t, *J* 6 Hz, 2 H, CH_2I). Exact mass 280.0107 (calcd for $C_9H_{17}ISi$ 280.0143).

6-(Trimethylsilyl)-4-hexynal (20). 6-(Trimethylsilyl)-4-hexyn-1-ol (300 mg, 1.76 mmol) was oxidized[32] by using 1.70 mL (21.1 mmol) of pyridine and 1.06 g (10.6 mmol) of CrO_3, to give after chromatography 240 mg (1.43 mmol, 81%) of **20** as a light yellow oil. R_f 0.64 (EtOAc). IR 2210 (w, C≡C), 1725 (CO), 1245 and 840 (Si-C). ^{1}H NMR (100 MHz) 0.09 (s, 9 H, $Si(CH_3)_3$), 1.42 (t, *J* 2 Hz, 2H, CH_2Si), 2.56 (m, 4 H, $C\underline{H_2}C\underline{H_2}CHO$), 9.83 (t, *J* 1 Hz, 1 H, CHO).

4-Iodo-1-(trimethylsilyl)-2-butyne (21). To a solution of 1.37 g (9.62 mmol) of 4-(trimethylsilyl)-2-butyn-1-ol in 10 mL of CH_2Cl_2 was added at 0°C 1.61 mL (11.6 mmol) of triethylamine. Subsequently, 0.78 mL (10.1 mmol) of methanesulfonyl chloride was added dropwise with stirring and cooling at 0°C. The mixture was allowed to warm to room temperature, and after 30 min treated with water. The mixture was extracted with CH_2Cl_2 (4 x), and the combined extracts dried (K_2CO_3) and concentrated *in vacuo* to give 2.06 g (9.35 mmol, 97%) of almost pure

methanesulfonate as a light yellow oil. IR 2210 (w, C≡C), 1365 and 1170 (OSO_2), 1250 and 850 (Si-C). ^{1}H NMR (100 MHz) 0.07 (s, 9 H, $Si(CH_3)_3$), 1.56 (t, *J* 2.5 Hz, 2 H, CH_2Si), 3.10 (s, 3 H, CH_3), 4.86 (t, *J* 2.5 Hz, 2 H, CH_2O). The crude methanesulfonate (2.03 g, 9.19 mmol) was dissolved in 20 mL of DMF. At 0°C, 4.58 g (27.6 mmol) of potassium iodide was added in small portions over a 30 min period. The reaction mixture was stirred at room temperature for 18 h and poured into 100 mL of Et_2O:pentane 1:1. The organic layer was washed with 1 M aq sodium metabisulfite (20 mL) and water (2 x 20 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed to give 1.87 g (7.41 mmol, 81%) of **21** as a light yellow oil. R_f 0.53 (hexane). IR 2210 (w, C≡C), 1250 and 850 (Si-C). ^{1}H NMR (100 MHz) 0.12 (s, 9 H, $Si(CH_3)_3$), 1.48 (t, *J* 2.5 Hz, 2 H, CH_2Si), 3.74 (t, *J* 2.5 Hz, 2 H, CH_2I).

General procedure for the alkylation of alkoxylactams. To a stirred 0.5 M solution of 1.2 equiv of diisopropylamine in THF was added under nitrogen at -78°C, 1.2 equiv of *n*-butyllithium (1.6 M in hexane). After stirring for 15 min, a solution of the alkoxylactam in THF was added dropwise. After stirring the solution for 30 min at -78°C, a solution of 1.3 equiv of iodide (or aldehyde) in THF was added. The reaction mixture was stirred for 1 h at -78°C, then warmed up to room temperature in 1 h, and diluted with ether and saturated aq NH_4Cl. After extraction with ether (4 x), the combined organic extracts were dried (K_2CO_3) and concentrated *in vacuo*. The residue was chromatographed.

1-Benzyl-5-methoxy-3-[6-(trimethylsilyl)-4-hexynyl]-2-pyrrolidinone (23). Alkoxylactam **12** (1.30 g, 6.34 mmol) was alkylated by using 7.61 mmol of LDA and 2.31 g (8.25 mmol) of iodide **19** to give 1.08 g (3.03 mmol, 48%) of **23** as a light yellow oil. R_f 0.34 (EtOAc:hexane 1:2). IR 2215 (w, C≡C), 1685 (CO), 1245 and 850 (Si-C). ^{1}H NMR (100 MHz) 0.10 (s, 9 H, $Si(CH_3)_3$), 1.18-2.78 (m, 9 H), 1.42 (t, *J* 2.5 Hz, 2 H, CH_2Si), 3.22 and 3.24 (s, 3 H, OCH_3), 4.02 and 4.03 (d, *J* 15 Hz, 1 H, CHPh), 4.63 (m, 1 H, CHOMe), 4.97 (d, *J* 15 Hz, 1 H, CHPh), 7.32 (m, 5 H, Ph). Exact mass 357.2121 (calcd for $C_{21}H_{31}NO_2Si$ 357.2124).

1-Benzyl-5-methoxy-3-[1-hydroxy-6-(trimethylsilyl)-4-hexynyl]-2-pyrrolidinone (24). Alkoxylactam **12** (0.170 g, 0.83 mmol) was alkylated by using 1.00 mmol of LDA and 0.181 g (1.08 mmol) of aldehyde **20** to give 0.154 g (0.41 mmol, 50%) of **24** as a light yellow oil. R_f 0.37 (EtOAc:hexane 1:1). IR 3450 (br, OH), 2210 (w, C≡C), 1675 (CO), 1245 and 850 (Si-C). ^{1}H NMR (100 MHz) 0.10 (s, 9 H, $Si(CH_3)_3$), 1.10-2.94 (m, 7 H), 1.43 (t, *J* 2.5 Hz, 2 H, CH_2Si), 3.21, 3.23, 3.24 and 3.28 (s, 3 H, OCH_3), 3.66-4.04 (m, 1 H, CHOH), 4.07 (d, *J* 15 Hz, 1 H, CHPh), 4.22-4.48 (m, 1 H, OH), 4.54-4.76 (m, 1 H, CHOMe), 4.96 and 4.99 (d, *J* 15 Hz, 1 H, CHPh), 7.33 (m, 5 H, Ph).

1-Benzyl-6-ethoxy-3-[5-(trimethylsilyl)-3-pentynyl]-2-piperidinone (25). Alkoxylactam **13** (80 mg, 0.37 mmol) was alkylated by using 0.44 mmol of LDA and 0.125 g (0.47 mmol) of iodide **18** to give 71 mg (0.20 mmol, 55%) of **25** as a colourless oil. R_f 0.42 (EtOAc:hexane 1:2). IR 2210 (w, C≡C), 1640 (CO), 1245 and 850 (Si-C). ^{1}H NMR (100 MHz) 0.09 (s, 9 H, $Si(CH_3)_3$), 1.20-2.78 (m, 9 H), 1.41 (t, *J* 2.5 Hz, 2 H, CH_2Si), 3.26 and 3.29 (s, 3 H, OCH_3), 3.99 and 4.03 (d, *J* 15 Hz, 1 H, CHPh), 4.41 (m, 1 H, CHOMe), 5.35 (d, *J* 15 Hz, 1 H, CHPh), 7.30 (m, 5 H, Ph).

1-Benzyl-6-ethoxy-3-[6-(trimethylsilyl)-4-hexynyl]-2-piperidinone (26). Alkoxylactam **14** (0.200 g, 0.86 mmol) was alkylated by using 1.03 mmol of LDA and 0.312 g (1.11 mmol) of iodide **19** to give 0.279 g (0.73 mmol, 85%) of **26** as a colourless oil. R_f 0.35 (EtOAc:hexane 1:3). IR 2220 (w, C≡C), 1640 (CO), 1245 and 850 (Si-C). ^{1}H NMR (100 MHz) 0.09 (s, 9 H, $Si(CH_3)_3$), 1.10-2.61 (m, 11 H), 1.20 (t, *J* 7 Hz, 3 H, OCH_2CH_3), 1.42 (t, *J* 2.5 Hz, 2 H, CH_2Si), 3.43 (m, 2 H, OCH_2CH_3), 4.00 (d, *J* 15 Hz, 1 H, CHPh), 4.46 (m,1 H, CHOEt), 5.34 and 5.36 (d, *J* 15 Hz, 1 H, CHPh), 7.30 (m, 5 H, Ph).

***rel*-(3*R*,3a*S*,7a*R*)-2-Benzyl-3-ethoxy-2,3,3a,4,7,7a-hexahydro-7a-[5-(trimethylsilyl)-3-pentynyl]-1-isoindolone (27).** Alkoxylactam **15** (0.250 g, 0.92 mmol) was alkylated by using 1.11 mmol of LDA and 0.319 g (1.20 mmol) of iodide **18** to give 0.207 g (0.51 mmol, 55%) of **27** as a colourless oil. R_f 0.42 (EtOAc:hexane 1:4). IR 2210 (w, C≡C), 1685 (CO), 1245 and 850 (Si-C). ^{1}H NMR (100 MHz) 0.10 (s, 9 H, $Si(CH_3)_3$), 1.20 (t, *J* 7 Hz, 3 H, OCH_2CH_3), 1.42 (t, *J* 2.5 Hz, 2 H, CH_2Si), 1.68-2.53 (m, 9 H), 3.46 (m, 2 H, OCH_2CH_3), 3.99 (d, *J* 15 Hz, 1 H, CHPh), 4.16 (d, *J* 3 Hz, 1 H, CHOEt), 4.99 (d, *J* 15 Hz, 1 H, CHPh), 5.62-6.04 (m, 2 H, HC=CH), 7.30 (m, 5 H, Ph). FD MS: 409 (M^+, $C_{25}H_{35}NO_2Si$).

***rel*-(3*R*,3a*S*,7a*S*)-3-Ethoxy-2,3,3a,4,7,7a-hexahydro-7a-[4-(trimethylsilyl)-2-butynyl]-1-isoindolone (28).** Alkoxylactam **16** (1.01 g, 4.00 mmol) was alkylated by using 4.1 mmol of LDA and 1.01 g (4.00 mmol) of iodide **21**. A modified work-up procedure was used: The reaction mixture was quenched with 20 mL of a 5% aq NaOH solution and stirred for 30 min at room temperature before extraction with ether, to give 512 mg (1.68 mmol, 42%) of **28**. R_f 0.45 (EtOAc:hexane 1:3). IR 3420 and 3200 (br, NH), 2215 (w, C≡C), 1700 (CO), 1245 and 850 (Si-C). ^{1}H NMR (100 MHz) 0.04 (s, 9 H, $Si(CH_3)_3$), 1.18 (t, *J* 7 Hz, 3 H, OCH_2CH_3), 1.39 (t, *J* 2.5 Hz, 2 H, CH_2Si), 1.7-2.7 (m, 7 H), 3.53 (m, 2 H, OCH_2CH_3), 4.45 (d, *J* 2.5 Hz, 1 H, CHOEt), 5.78 (m, 2 H, HC=CH), 6.9 (br s, 1 H, NH). Exact mass 305.1809 (calcd for $C_{17}H_{27}NO_2Si$ 305.1811).

***rel*-(3*R*,3a*S*,7a*R*)-3-Ethoxy-2,3,3a,4,7,7a-hexahydro-7a-[5-(trimethylsilyl)-3-pentynyl]-1-isoin-**

dolone (29). Alkoxylactam 16 (2.25 g, 8.89 mmol) was alkylated by using 10.7 mmol of LDA and 3.07 g (11.5 mmol) of iodide 18. Work-up as mentioned for 28 gave 2.25 g (7.05 mmol, 79%) of 29 as a light yellow solid, mp 65-90°C. R_f 0.31 (EtOAc:hexane 1:1). IR 3430 and 3210 (br, NH), 2220 (w, C≡C), 1700 (CO), 1245 and 855 (Si-C). ^{1}H NMR (100 MHz) 0.08 (s, 9 H, $Si(CH_3)_3$), 1.23 (t, *J* 7 Hz, 3 H, OCH_2CH_3), 1.39 (t, *J* 2 Hz, 2 H, CH_2Si), 1.61-2.55 (m, 9 H), 3.52 (m, 2 H, OCH_2CH_3), 4.47 (d, *J* 2 Hz, 1 H, CHOEt), 5.67-6.03 (m, 2 H, HC=CH), 8.17 (br s, 1 H, NH).

***rel*-(3*R*,3a*S*,7a*R*)-3-Ethoxy-2,3,3a,4,7,7a-hexahydro-7a-[6-(trimethylsilyl)-4-hexynyl]-1-isoindolone (30).** Alkoxylactam 16 (759 mg, 3.00 mmol) was alkylated by using 3.9 mmol of LDA and 1.26 g (4.50 mmol) of iodide 19. Work-up as mentioned for 28 gave 808 mg (2.42 mmol, 81%) of 30. R_f 0.32 (EtOAc:hexane 1:1). IR 3450 (NH), 2210 (w, C≡C), 1700 (CO), 1250 and 850 (Si-C). ^{1}H NMR (100 MHz) 0.08 (s, 9 H, $Si(CH_3)_3$), 1.23 (t, *J* 7 Hz, 3 H, OCH_2CH_3), 1.40 (t, *J* 2 Hz, 2 H, CH_2Si), 1.5-2.5 (m, 11 H), 3.50 (m, 2 H, OCH_2CH_3), 4.48 (d, *J* 3 Hz, 1 H, CHOEt), 5.9 (m, 2 H, HC=CH), 7.3 (br s, 1 H, NH). Exact mass 333.2120 (calcd for $C_{19}H_{31}NO_2Si$ 333.2124).

***rel*-(2a*R*,5a*R*,6*S*)-1-(*tert*-Butyldimethylsilyl)-6-ethoxy-2a,3,4,5,5a,6-hexahydro-2a-[4-(trimethylsilyl)-2-butynyl]-2*H*- cyclopenta[c]pyrrol-2-one (31).** Alkoxylactam 17 (774 mg, 2.73 mmol) was alkylated by using 3 mmol of LDA and 642 mg (2.54 mmol) of iodide 21 to give 711 mg (1.74 mmol, 64%) of 31. R_f 0.38 (EtOAc:hexane 1:19). IR 2210 (w, C≡C), 1680 (CO), 1245 and 840 (Si-C). ^{1}H NMR (100 MHz) 0.05 (s, 9 H, $Si(CH_3)_3$), 0.20 (s, 6 H, $Si(CH_3)_2$), 0.91 (s, 9 H, $SiC(CH_3)_3$), 1.16 (t, *J* 7 Hz, 3 H, OCH_2CH_3), 1.3-2.1 (m, 7 H), 1.40 (t, *J* 2 Hz, 2 H, CH_2Si), 2.5 (m, 2 H), 3.40 (m, 2 H, OCH_2CH_3), 4.32 (s, 1 H, CHOEt). Exact mass 407.2660 (calcd for $C_{22}H_{41}NO_2Si_2$ 407.2676).

***rel*-(2a*R*,5a*R*,6*S*)-1-(*tert*-Butyldimethylsilyl)-6-ethoxy-2a,3,4,5,5a,6-hexahydro-6a-[5-(trimethylsilyl)-3-pentynyl]-2*H*-cyclopenta[c]pyrrol-2-one (32).** Alkoxylactam 17 (283 mg, 1.00 mmol) was alkylated by using 1.3 mmol of LDA and 400 mg (1.50 mmol) of iodide 18 to give 229 mg (0.543 mmol, 54%) of 32. R_f 0.46 (EtOAc:hexane 1:19). IR 2215 (w, C≡C), 1680 (CO), 1250 and 840 (Si-C). ^{1}H NMR (100 MHz) 0.01 (s, 9 H, $Si(CH_3)_3$), 0.16 (s, 6 H, $Si(CH_3)_2$), 0.88 (s, 9 H, $SiC(CH_3)_3$), 1.22 (t, *J* 7 Hz, 3 H, OCH_2CH_3), 1.3-2.4 (m, 11 H), 1.32 (t, *J* 2 Hz, 2 H, CH_2Si), 3.33 (m, 2 H, OCH_2CH_3), 4.21 (s, 1 H, CHOEt). Exact mass 421.2844 (calcd for $C_{23}H_{43}NO_2Si_2$ 421.2832).

***rel*-(2a*R*,5a*R*,6*S*)-1-(*tert*-Butyldimethylsilyl)-6-ethoxy-2a,3,4,5,5a,6-hexahydro-6a-[6-(trimethylsilyl)-4-hexynyl]-2*H*-cyclopenta[c]pyrrol-2-one (33).** Alkoxylactam 17 (283 mg, 1.00 mmol) was alkylated by using 1.3 mmol of LDA and 420 mg (1.50 mmol) of iodide 19 to give 378 mg (0.867 mmol, 87%) of 33 as a white solid, mp 45-47°C. R_f 0.20 (EtOAc:hexane 1:19). IR 2210 (w, C≡C), 1675 (CO), 1250 and 840 (Si-C). ^{1}H NMR (100 MHz) 0.01 (s, 9 H, $Si(CH_3)_3$), 0.17 (s, 6 H, $Si(CH_3)_2$), 0.88 (s, 9 H, $SiC(CH_3)_3$), 1.13 (t, *J* 7 Hz, 3 H, OCH_2CH_3), 1.2-2.3 (m, 13 H), 1.34 (t, *J* 2.5 Hz, 2 H, CH_2Si), 3.35 (m, 2 H, OCH_2CH_3), 4.22 (s, 1 H, CHOEt). Exact mass 435.3003 (calcd for $C_{24}H_{45}NO_2Si_2$ 435.2989).

General procedure for cyclizations in formic acid. A 0.1 M solution of the alkoxylactam in formic acid was stirred for 30 min at room temperature and then concentrated *in vacuo*. The residue was diluted with CH_2Cl_2 and washed with 25 mL of saturated aq $NaHCO_3$. After extraction of the aq layer with CH_2Cl_2 (3 x), the combined organic extracts were dried (K_2CO_3) and concentrated *in vacuo*. The residue was chromatographed.

General procedure for cyclizations using trifluoroacetic acid. Under a dry nitrogen atmosphere, a solution of the alkoxylactam in CH_2Cl_2 was added at 0°C to a 0.04 M solution of 10 equiv of trifluoroacetic acid in CH_2Cl_2. After warming up to room temperature and stirring for 1 h, the reaction mixture was poured out into 100 mL of saturated aq $NaHCO_3$. The aq layer was extracted with CH_2Cl_2 (4 x), and the organic extracts were dried (K_2CO_3) and concentrated *in vacuo*. The residue was chromatographed.

6-Benzyl-4-vinylidene-6-azabicyclo[3.2.1]octan-7-one (34). Alkoxylactam 22 (53.5 mg, 0.156 mmol) was cyclized by using 0.12 mL (1.56 mmol) of trifluoroacetic acid, to give 32.7 mg (0.137 mmol, 88%) of 34 as a white crystalline solid, mp 44-46°C (hexane). R_f 0.42 (EtOAc). For spectral data see reference 13.

7-Benzyl-5-vinylidene-7-azabicyclo[4.2.1]nonan-8-one (35). Alkoxylactam 23 (0.283 g, 0.79 mmol) was cyclized in formic acid to give 0.177 g (0.70 mmol, 89%) of 35 as a white crystalline solid, mp 70.5-73.5°C (hexane). R_f 0.51 (EtOAc). IR 1955 (C=C=C), 1670 (CO). ^{1}H NMR (100 MHz) 1.36-2.44 (m, 8 H), 2.72 (m, 1 H, COCH), 3.81 (d, *J* 15 Hz, 1 H, CHPh), 4.06 (d, *J* 7 Hz, 1 H, NCH), 4.70 (m, 2 H, C=CH_2), 5.03 (d, *J* 15 Hz, 1 H, CHPh), 7.32 (m, 5 H, Ph). ^{13}C NMR (63 MHz) 24.3 (t), 29.7 (t), 30.0 (t), 31.7 (t), 41.2 (d, COCH), 43.3 (t, CH_2Ph), 59.8 (d, NCH), 73.6 (t, C=CH_2), 100.6 (s, C=C=CH_2), 127.1 (d, Ph), 128.1 (d, Ph), 128.2 (d, Ph), 136.6 (s, Ph), 176.5 (s, CO), 206.7 (s, C=CH_2). Exact mass 253.1449 (calcd for $C_{17}H_{19}NO$ 253.1467).

7-Benzyl-2-hydroxy-5-vinylidene-7-azabicyclo[4.2.1]nonan-8-one (36). Alkoxylactam 24 (61 mg, 0.16 mmol) was cyclized by using 0.125 mL (1.62 mmol) of trifluoroacetic acid, to give 28.5 mg (0.106 mmol, 65%) of 36 as a white solid. R_f 0.23 (EtOAc). IR 3370 (br, OH), 1955 (C=C=C), 1670 (CO). ^{1}H NMR (100

MHz) 1.18-3.40 (m, 8 H), 3.81 and 3.87 (d, *J* 15 Hz, 1 H, CHPh), 4.04-4.18 (m, 1 H, NCH), 4.39 (br s, OH), 4.77 (m, 2 H, C=CH_2), 4.99 and 5.07 (d, *J* 15 Hz, 1 H, CHPh), 7.34 (m, 5 H, Ph).

7-Benzyl-5-vinylidene-7-azabicyclo[4.2.1]nonan-2,8-dione (37). Alcohol **36** (24.5 mg, 0.092 mmol) was oxidized[32] by using 89 μL (1.10 mmol) of pyridine and 55 mg (0.55 mmol) of CrO_3 to give 22.8 mg (0.085 mmol, 92%) of **37** as a colourless oil. IR 1955 (C=C=C), 1710 and 1675 (CO). ^{1}H NMR (100 MHz) 1.95-2.85 (m, 6 H), 3.46 (d, *J* 7 Hz, 1 H, COCH), 3.87 (d, *J* 15 Hz, 1 H, CHPh), 4.29 (d, *J* 7 Hz, 1 H, NCH), 4.84 (m, 2 H, C=CH_2), 5.01 (d, *J* 15 Hz, 1 H, CHPh), 7.35 (m, 5 H, Ph). EI MS (70 eV) 267 (M^+, $C_{17}H_{17}NO_2$, 8), 173 (4), 94 (4), 91 (12, Bn^+), 73 (4), 32 (24), 28 (100). Exact mass 267.1230 (calcd for $C_{17}H_{17}NO_2$ 267.1259).

6-Benzyl-4-vinylidene-6-azabicyclo[3.2.2]nonan-7-one (38). Alkoxylactam **25** (59.0 mg, 0.165 mmol) was cyclized in formic acid to give 38.7 mg (0.153 mmol, 93%) of **38** as a colourless oil. R_f 0.38 (EtOAc:hexane 1:1). IR 1955 (C=C=C), 1640 (CO). ^{1}H NMR (100 MHz) 1.56-2.70 (m, 8 H), 2.88 (m, 1 H, COCH), 3.98 (m, 1 H, NCH), 4.11 (d, *J* 15 Hz, 1 H, CHPh), 4.62 (m, 2 H, C=CH_2), 5.15 (d, *J* 15 Hz, 1 H, CHPh), 7.33 (m, 5 H, Ph). EI MS (70 eV) 253 (M^+, $C_{17}H_{19}NO$, 13), 162 (4), 132 (3), 122 (8), 105 (19), 91 (52, Bn^+), 86 (42), 84 (73), 65 (4), 58 (25), 49 (81), 43 (100), 32 (85). Exact mass 253.1449 (calcd for $C_{17}H_{19}NO$ 253.1467).

7-Benzyl-5-vinylidene-7-azabicyclo[4.2.2]decan-8-one (39). To a solution of 28.5 mg (0.074 mmol) of ethoxylactam **26** in 3 mL of CH_2Cl_2 was added under nitrogen at room temperature 0.11 mL of a 1 M solution of $SnCl_4$ in CH_2Cl_2. The yellow reaction mixture was stirred for 17 h and then poured out into 50 mL of saturated brine. The aq layer was extracted with CH_2Cl_2 (4 x 25 mL). The organic extracts were dried (K_2CO_3) and concentrated *in vacuo*. The residue was chromatographed to give 16.1 mg (0.060 mmol, 81%) of **39** as a colourless oil. R_f 0.25 (EtOAc:hexane 1:1). IR 1955 (C=C=C), 1630 (CO). ^{1}H NMR (100 MHz) 1.10-2.50 (m, 10 H), 2.92 (m, 1 H, COCH), 3.78 (d, *J* 15 Hz, 1 H, CHPh), 4.08 (m, 1 H, NCH), 4.62 (m, 2 H, C=CH_2), 5.40 (d, *J* 15 Hz, 1 H, CHPh), 7.32 (m, 5 H, Ph). Exact mass 267.1612 (calcd for $C_{18}H_{21}NO$ 267.1623).

***rel*-(1*R*,2*R*)-11-Benzyl-10-vinylidene-11-azatricyclo[5.3.2.0^{2,7}]-4-dodecen-12-one (40).** Alkoxylactam **27** (38.4 mg, 0.094 mmol) was cyclized in formic acid to give 26.5 mg (0.091 mmol, 97%) of **40** as a colourless oil. R_f 0.50 (EtOAc:hexane 1:1). IR 1960 (C=C=C), 1680 (CO). ^{1}H NMR (100 MHz) 1.14-2.42 (m, 8 H), 2.68 (md, *J*d 18 Hz, 1 H), 3.52 (s, 1 H, NCH), 3.86 (d, *J* 15 Hz, 1 H, CHPh), 4.75 (m, 2 H, C=CH_2), 4.97 (d, *J* 15 Hz, 1 H, CHPh), 5.48-5.84 (m, 2 H, HC=CH), 7.32 (m, 5 H, Ph). Exact mass 291.1624 (calcd for $C_{20}H_{21}NO$ 291.1623).

***rel*-(1*R*,6*R*)-11-Vinylidene-8-azatricyclo[5.2.2.0^{1,6}]-3-undecen-9-one (41).** A solution of alkoxylactam **28** (50 mg, 0.164 mmol) in 5 mL of formic acid was stirred for 3 h at room temperature and then diluted with 50 mL of CH_2Cl_2. The organic layer was washed with water (2 x), saturated aq $NaHCO_3$, and brine, then dried (Na_2SO_4) and concentrated *in vacuo* to give 29 mg (0.155 mmol, 95%) of **41**. IR 3430 (NH), 1970 (C=C=C), 1705 (CO). ^{1}H NMR (100 MHz) 2.0-2.4 (m, 4 H, CH_2CH=CHCH_2), 2.47 (t, *J* 4 Hz, 2 H, CH_2C=C), 2.68 (m, 1 H, CH), 4.03 (br s, 1 H, NCH), 4.87 (t, *J* 4 Hz, 2 H, C=CH_2), 5.71 (m, 2 H, HC=CH), 6.45 (br s, NH). Exact mass 187.0997 (calcd for $C_{12}H_{13}NO$ 187.0997).

***rel*-(1*R*,2*R*)-10-Vinylidene-11-azatricyclo[5.3.2.0^{2,7}]-4-dodecen-12-one (42).** Alkoxylactam **29** (0.271 g, 0.85 mmol) was cyclized in formic acid to give 0.155 g (0.77 mmol, 91%) of **42** as a white crystalline solid, mp 150-152°C (EtOAc). R_f 0.52 (EtOAc). IR 3430 and 3220 (br, NH), 1970 (C=C=C), 1710 (CO). ^{1}H NMR (100 MHz) 1.16-2.80 (m, 9 H), 3.78 (br s, 1 H, NCH), 4.73 (m, 2 H, C=CH_2), 5.50-5.82 (m, 2 H, HC=CH), 6.96 (br s, 1 H, NH). ^{13}C NMR (63 MHz) 24.4 (t), 25.7 (t), 28.2 (t), 34.1 (t), 44.1 (s, CO$\underline{C}$), 46.0 (d, NCH$\underline{C}$H), 59.5 (d, NCH), 76.0 (t, C=$\underline{C}H_2$), 99.2 (s, $\underline{C}$=C=CH_2), 124.9 (d, H$\underline{C}$=CH), 125.1 (d, HC=$\underline{C}$H), 179.4 (s, CO), 201.9 (s, $\underline{C}$=CH_2). Exact mass 201.1154 (calcd for $C_{13}H_{15}NO$ 201.1154).

***rel*-(1*R*,2*R*)-11-Vinylidene-12-azatricyclo[5.4.2.0^{2,7}]-4-tridecen-13-one (43).** Alkoxylactam **30** (200 mg, 0.600 mmol) was treated with 2 mL of formic acid according to the procedure used for **41** to give 129 mg (0.599 mmol, 100%) of **43**. IR 3450 and 3210 (br, NH), 1975 (C=C=C), 1710 (CO). ^{1}H NMR (100 MHz) 1.2-2.8 (m, 11 H), 3.86 (br s, 1 H, NCH), 4.70 (m, 2 H, C=CH_2), 5.75 (m, 2 H, HC=CH), 6.1 (br s, NH). Exact mass 215.1324 (calcd for $C_{14}H_{17}NO$ 215.1310).

***rel*-(1*R*,2*R*)-9-Vinylidene-10-azatricyclo[4.3.2.0^{2,6}]undecan-11-one (44).** Alkoxylactam **32** (200 mg, 0.475 mmol) was treated with 4 mL of formic acid according to the procedure used for **41** to give after flash chromatography 48 mg (0.254 mmol, 53%) of **44** as a white solid, mp 131-133°C. R_f 0.46 (EtOAc:hexane 1:1). IR 3420 and 3210 (br, NH), 1950 (C=C=C), 1680 (CO). ^{1}H NMR (250 MHz) 1.2-2.55 (m, 11 H), 4.01 (s, 1 H, NCH), 4.67 (d, *J* 2 Hz, 2 H, C=CH_2), 5.64 (br s, 1 H, NH). Exact mass 189.1162 (calcd for $C_{12}H_{15}NO$ 189.1154).

***rel*-(1*R*,2*R*)-11-(*tert*-Butyldimethylsilyl)-10-vinylidene-11-azatricyclo[4.4.2.0^{2,6}]dodecan-12-one (45).** Alkoxylactam **33** (640 mg, 1.47 mmol) was dissolved in 10 mL of formic acid. After stirring for 6 min at room temperature, the work up procedure used for **41** was followed to yield 457 mg (1.44 mmol, 98%) of **45**. IR 1955 (C=C=C), 1670 (CO), 1240 and 840 (Si-C). ^{1}H NMR (100 MHz) 0.19 (s, 3 H, $SiCH_3$), 0.23 (s, 3 H,

$SiCH_3$), 0.94 (s, 9 H, $SiC(CH_3)_3$), 1.2-2.5 (m, 13 H), 4.03 (s, 1 H, NCH), 4.64 (t, *J* 2.5 Hz, 2 H, $C{=}CH_2$). Exact mass 317.2153 (calcd for $C_{19}H_{31}NOSi$ 317.2175).

***rel*-(1*R*,2*R*)-10-Vinylidene-11-azatricyclo[4.4.2.0^{2,6}]dodecan-12-one (46).** To a solution of 317 mg (1.00 mmol) of **45** in 3.5 mL of THF was added at 0 °C 2 mL of a 2 M solution of tetrabutylammonium fluoride in THF. After stirring for 10 min at 0°C, and for 30 min at room temperature, the solution was poured out into saturated aq NaCl. Extraction with CH_2Cl_2 was followed by drying (Na_2SO_4) and concentration of the organic layer *in vacuo*. Purification of the residue using flashchromatography gave 203 mg (1.00 mmol, 100%) of **46** as a white solid, mp 119-123°C. R_f 0.35 (EtOAc:hexane 1:1). IR 3420 and 3220 (br, NH), 1955 (C=C=C), 1685 (CO). ^{1}H NMR (250 MHz) 1.4-2.5 (m, 13 H), 3.98 (s, 1 H, NCH), 4.63 (t, *J* 2 Hz, 2 H, $C{=}CH_2$), 6.1 (br s, 1 H, NH). Exact mass 203.1315 (calcd for $C_{13}H_{17}NO$ 203.1310).

***N*-Benzyl-4-ethylidenecyclohexanecarboxamide (47).** To a blue solution of 55 mg (2.39 mmol) of sodium in 30 mL of destilled ammonia was added under nitrogen 50 mg (0.21 mmol) of lactam **34**. After stirring the solution at -78°C for 1 h, 3 mL of saturated aq NH_4Cl was added. The ammonia was allowed to evaporate at atmospheric pressure. To the residue was added 20 mL of water. The aq layer was extracted with CH_2Cl_2 (4 x 25 mL). The organic extracts were dried (K_2CO_3) and concentrated *in vacuo*. The residue was chromatographed to yield 49.5 mg (0.20 mmol, 95%) of **47** as a white solid, mp 134-136°C (EtOAc/hexane). R_f 0.67 (EtOAc). IR 3440 (NH), 1660 (CO). ^{1}H NMR (100 MHz) 1.29-2.85 (m, 9 H), 1.57 (md, *J*d 7 Hz, 3 H, CH_3), 4.44 (d, *J* 6 Hz, 2 H, CH_2Ph), 5.20 (mq, *J*q 7 Hz, 1 H, $CHCH_3$), 5.83 (m, 1 H, NH), 7.32 (m, 5 H, Ph). Exact mass 243.1606 (calcd for $C_{16}H_{21}NO$ 243.1623).

***N*-*tert*-Butoxycarbonyl derivative 48.** To a solution of 93.9 mg (0.467 mmol) of **42** in 1 mL of CH_2Cl_2 was added under nitrogen 69 µL (0.50 mmol) of Et_3N, 0.299 mL (1.00 mmol) of di-*tert*-butyl dicarbonate and 60.8 mg (0.50 mmol) of 4-dimethylaminopyridine. After stirring the solution for 24 h at room temperature, it was concentrated *in vacuo*, and the residue was chromatographed to yield 125.0 mg (0.415 mmol, 89%) of **48** as a viscous colourless oil. R_f 0.44 (EtOAc:hexane 1:2). IR 1970 (C=C=C), 1780 and 1715 (CO). ^{1}H NMR (100 MHz) 1.16-2.80 (m, 9 H), 1.54 (s, 9 H, $OC(CH_3)_3$), 4.36 (s, 1 H, NCH), 4.82 (m, 2 H, $C{=}CH_2$), 5.48-5.80 (m, 2 H, HC=CH).

***N*-*tert*-Butoxycarbonyl derivative 49.** According to the procedure used for the preparation of **48**, 107 mg (0.500 mmol) of **43** was treated with 74 µL (0.53 mmol) of Et_3N, 0.230 mL (1.00 mmol) of di-*tert*-butyl dicarbonate and 65 mg (0.53 mmol) of 4-dimethylaminopyridine to yield after purification 148 mg (0.469 mmol, 94%) of **49**. R_f 0.36 (EtOAc:hexane 1:3). IR 1970 (C=C=C), 1770 and 1710 (CO). ^{1}H NMR (100 MHz) 1.3-2.9 (m, 11 H), 1.55 (s, 9 H, $OC(CH_3)_3$), 4.46 (s, 1 H, NCH), 4.73 (d, *J* 4 Hz, H, $C{=}C\underline{H}H$), 4.76 (d, *J* 2 Hz, H, $C{=}CH\underline{H}$), 5.72 (m, 2 H, HC=CH). Exact mass 315.1812 (calcd for $C_{19}H_{25}NO_3$ 315.1834).

***N*-*tert*-Butoxycarbonyl derivative 50.** According to the procedure used for the preparation of **48**, 31 mg (0.153 mmol) of **46** was treated with 25 µL (0.16 mmol) of Et_3N, 80 µL (0.35 mmol) of di-*tert*-butyl dicarbonate and 20 mg (0.16 mmol) of 4-dimethylaminopyridine to yield after purification 37.1 mg (0.122 mmol, 80%) of **50** as white crystals, mp. 92-94°C. R_f 0.36 (EtOAc:hexane 1:4). IR 1955 (C=C=C), 1770 and 1715 (CO). ^{1}H NMR (250 MHz) 1.4-2.5 (m, 13 H), 1.45 (s, 9 H, $OC(CH_3)_3$), 4.60 (s, 1 H, NCH), 4.66 (t, *J* 1 Hz, 2 H, $C{=}CH_2$). Exact mass 303.1834 (calcd for $C_{18}H_{25}NO_3$ 303.1834).

***N*-Tosyl derivative 51.** A solution of 203 mg (1.00 mmol) of **46** in 2 mL of Et_2O was added dropwise to a suspension of 1.38 mmol of NaH in 2 mL of Et_2O at 0°C. After refluxing the resulting mixture for 1 h, it was cooled to -10°C. A solution of 267 mg (1.40 mmol) of TsCl in 5 mL of Et_2O was then added dropwise. After stirring the reaction mixture for 5 h at room temperature it was poured out into saturated aq NH_4Cl. After extraction of the aq layer with Et_2O (5 x), the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed to yield 328 mg (0.918 mmol, 92%) of **51** as a white solid, mp 160-162°C. R_f 0.40 (EtOAc:hexane 1:3). IR 1955 (C=C=C), 1723 (CO), 1595, 1495, 1360, 1170, 1088, 1070, 850 . ^{1}H NMR (100 MHz) 1.0-2.4 (m, 13 H), 2.40 (s, 3 H, CH_3), 4.8 (m, 2 H, $C{=}CH_2$),4.86 (s, 1H, NCH) 7.29 (d, *J* 8 Hz, 2 H, Ts), 7.90 (d, *J* 8 Hz, 2 H, Ts). Exact mass 357.1396 (calcd for $C_{20}H_{23}NO_3S$ 357.1399).

General procedure for the reaction of the allenes with cuprates. To a suspension of 1.5 equiv of dry CuI in Et_2O (5 mL per mmol of CuI) was added under nitrogen at 0°C 3 equiv of a solution of RLi in Et_2O. After stirring the reaction mixture for 15 min at 0°C, it was cooled to -78°C. Then, a solution of the allene in Et_2O was added dropwise. After stirring the mixture for 1.5 h at -78°C, it was warmed up to 0°C and stirred for 3 h. Saturated aq NH_4Cl was added. The resulting mixture was stirred for 1 h at room temperature and then extracted with of Et_2O (4 x). The combined etheral extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was chromatographed.

***tert*-Butyl *N*-[[1,4,4a,5,6,8a-hexahydro-7-(1-methylethenyl)-4a-*trans*-naphthalenyl]carbonyl]-carbamate (52).** Carbamate **48** (72.2 mg, 0.24 mmol) was treated with the cuprate prepared from 69.2 mg (0.36 mmol) of CuI and 0.45 mL (0.73 mmol) of a 1.6 M solution of MeLi in Et_2O. The reaction was quenched after

warming the solution to -40°C and yielded 57.0 mg (0.180 mmol, 75%) of **52** as a white solid, mp 134-137°C (EtOAc/hexane). R_f 0.30 (EtOAc:hexane 1:3). IR 3350 (NH), 1780 and 1710 (CO), 1610 (C=C). ^{1}H NMR (100 MHz) 1.14-3.02 (m, 9 H), 1.45 (s, 9 H, $OC(CH_3)_3$), 1.95 (s, 3 H, CH_3), 4.97 (s, 1 H, C=CHH), 5.05 (s, 1 H, C=CHH), 5.72 (m, 2 H, HC=CH), 5.84 (m, 1 H, C=CH), 8.12 (br s, 1 H, NH). Exact mass 317.1980 (calcd for $C_{19}H_{27}NO_3$ 317.1991).

***tert*-Butyl *N*-[[1,4a,5,6,7,9a-hexahydro-8-(1-methylethenyl)-4a-*trans*-4*H*-benzocycloheptenyl]carbonyl]carbamate (53).** Carbamate **49** (128 mg, 0.406 mmol) was treated with the cuprate prepared from 117 mg (0.61 mmol) of CuI and 0.77 mL (1.25 mmol) of a 1.6 M solution of MeLi in Et_2O to give 122 mg (0.368 mmol, 91%) of **53**. R_f 0.29 (EtOAc:hexane 1:3). IR 3340 (NH), 1785 and 1710 (CO). ^{1}H NMR (100 MHz) 1.1-3.2 (m, 11 H), 1.45 (s, 9 H, $OC(CH_3)_3$), 1.90 (s, 3 H, CH_3), 4.92 (s, 1 H, C=CHH), 5.02 (s, 1 H, C=CHH), 5.6 (m, 3 H, HC=CH and C=CH), 8.0 (br s, 1 H, NH). ^{13}C NMR (63 MHz) 20.4 (t), 21.3 (q, CH_3), 28.0 (q, $C(CH_3)_3$), 31.4 (t), 31.4 (t), 35.5 (t), 36.9 (d, C-CH), 38.9 (t), 50.4 (s, NCOC), 81.9 (s, NCO_2C), 112.3 (t, C=CH_2), 125.8 (d, C=CH), 126.2 (d, HC=CH), 128.6 (d, HC=CH), 143.8 (s, C=CH_2), 144.6 (s, C=CH), 149.3 (s, NCO_2), 173.1 (s, NCO). Exact mass 331.2144 (calcd for $C_{20}H_{29}NO_3$ 331.2147).

***tert*-Butyl *N*-[[1,2,3,3a,4,5,6,8a-octahydro-7-(1-methylethenyl)-3a-*trans*-azulenyl]carbonyl]carbamate (54).** Carbamate **50** (24 mg, 0.079 mmol) was treated with the cuprate prepared from 30 mg (0.16 mmol) of CuI and 0.20 mL (0.32 mmol) of a 1.6 M solution of MeLi in Et_2O to give 21 mg (0.066 mmol, 84%) of **54** as a white solid, mp 137-137.5°C (Et_2O/pentane). R_f 0.42 (EtOAc:hexane 1:3). IR 3340 (NH), 1775 and 1710 (CO). ^{1}H NMR (250 MHz) 1.2-2.8 (m, 13 H), 1.45 (s, 9 H, $OC(CH_3)_3$), 1.94 (s, 3 H, CH_3), 4.95 (s, 1 H, C=CHH), 5.05 (s, 1 H, C=CHH), 6.0 (br s, 1 H, C=CH), 7.95 (br s, 1 H, NH). Exact mass 319.2137 (calcd for $C_{19}H_{29}NO_3$ 319.2137).

***tert*-Butyl *N*-[[1,2,3,3a,4,5,6,8a-octahydro-7-(1-phenylethenyl)-3a-*trans*-azulenyl]carbonyl]carbamate (55).** Carbamate **50** (80 mg, 0.264 mmol) in THF was treated with the cuprate prepared in THF from 89.5 mg (0.47 mmol) of CuI and 0.42 mL (0.95 mmol) of a 2.25 M solution of PhLi in cyclohexane:Et_2O 2:1 to give 27 mg (0.071 mmol, 27%) of **55**. R_f 0.46 (EtOAc:hexane 1:3). IR 3440 and 3340 (NH), 1770 and 1710 (CO). ^{1}H NMR (250 MHz) 1.3-2.8 (m, 13 H), 1.50 (s, 9 H, $OC(CH_3)_3$), 5.11 (s, 1 H, C=CHH), 5.30 (s, 1 H, C=CHH), 6.01 (d, *J* 2.5 Hz, 1 H, C=CH), 7.1-7.4 (m, 5 H, Ph), 7.9 (br s, 1 H, NH). Exact mass 381.2288 (calcd for $C_{24}H_{31}NO_3$ 381.2304).

***N*-[[1,2,3,3a,4,5,6,8a-Octahydro-7-(1-methylethenyl)-3a-*trans*-azulenyl]carbonyl]-*p*-toluenesulfonamide (56).** Sulfonamide **51** (72 mg, 0.20 mmol) was treated with the cuprate prepared from 58 mg (0.30 mmol) of CuI and 0.375 mL (0.60 mmol) of a 1.6 M solution of MeLi in Et_2O to give 69 mg (0.185 mmol, 93%) of **56** as a white solid, mp 143-145°C (iPr_2O). R_f 0.40 (EtOAc:hexane 1:3). IR 3390 and 3250 (NH), 1700 (CO). ^{1}H NMR (250 MHz) 1.1-2.9 (m, 13 H), 1.94 (s, 3 H, $C=CCH_3$), 2.46 (s, 3 H, $ArCH_3$), 5.0 (s, 1 H, C=CHH), 5.07 (s, 1 H, C=CHH),5.98 (m, 1 H, C=CH), 7.35 (d, *J* 8 Hz, 2 H, Ts), 7.93 (d, *J* 8 Hz, 2 H, Ts), 8.6 (br s, 1 H, NH). Exact mass 373.1702 (calcd for $C_{21}H_{27}NO_3S$ 373.1712).

***N*-[[1,2,3,3a,4,5,6,8a-Octahydro-7-(1-phenylethenyl)-3a-*trans*-azulenyl]carbonyl]-*p*-toluenesulfonamide (57).** Sulfonamide **51** (72 mg, 0.20 mmol) was treated with the cuprate prepared from 58 mg (0.30 mmol) of CuI and 0.267 mL (0.601 mmol) of a 2.25 M solution of PhLi in cyclohexane:Et_2O 2:1 to give 58 mg (0.133 mmol, 67%) of **57**. R_f 0.34 (EtOAc:hexane 1:3). IR 3380 and 3250 (NH), 1700 (CO). ^{1}H NMR (250 MHz) 1.0-2.8 (m, 13 H), 2.47 (s, 3 H, CH_3), 5.16 (m, 2 H, C=CH_2), 5.97 (d, *J* 6 Hz, 1 H, C=CH), 7.1-8.2 (m, 9 H, Ph and Ts), 8.5 (br s, 1 H, NH). Exact mass 435.1871 (calcd for $C_{26}H_{29}NO_3S$ 435.1868).

***N*-[[1,2,3,3a,4,5,6,8a-Octahydro-7-{1-(trimethylsilylmethyl)-ethenyl}-3a-*trans*-azulenyl]carbonyl]-*p*-toluenesulfonamide (58).** Sulfonamide **51** (72 mg, 0.20 mmol) was treated with the cuprate prepared from 58 mg (0.30 mmol) of CuI and 0.87 mL (0.60 mmol) of a 0.69 M solution of trimethylsilylmethyllithium[33,34] in hexane to give 89 mg (0.20 mmol, 100%) of **58** after work-up, mp 113-114°C (iPr_2O). IR 3380 and 3240 (NH), 1695 (CO). ^{1}H NMR (250 MHz) 0.02 (s, 9 H, $Si(CH_3)_3$), 0.9-2.8 (m, 15 H), 2.46 (s, 3 H, CH_3), 4.73 (s, 1 H, C=CHH), 4.92 (s, 1 H, C=CHH), 5.9 (m, 1 H, C=CH), 7.36 (d, *J* 8 Hz, 2 H, Ts), 7.94 (d, *J* 8 Hz, 2 H, Ts), 8.6 (br s, 1 H, NH). Exact mass 445.2103 (calcd for $C_{24}H_{35}NO_3SSi$ 445.2107).

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