Intramolecular *N*-(Acyloxy)iminium Ion–Alkyne Cycloadditions. A New Route to Bicyclic α-Amino Ketones

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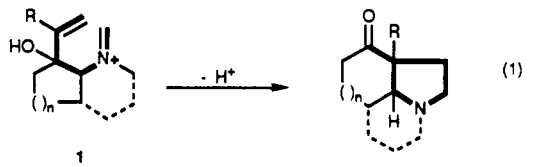
The intramolecular cyclocondensation of 15 cyclic *N*-(acyloxy)iminium cations containing tethered alkyne and alkene nucleophiles is reported (eqs 5 and 6). This route to heterotricyclic systems was specifically demonstrated with substrates in which the heterodiene moiety was contained in five-, six-, and seven-membered azacyclic rings. The stereochemistry of the cycloadducts (Table IV) was controlled primarily by the size and substitution of the starting azacyclic ring. When the azacyclic ring is monosubstituted, the amount of the trans cycloadduct increases as the size of this spectator ring increases from five to seven. In one case the 2-oxazinone ring of an alkyne cycloadduct was subsequently cleaved by ozone to provide a bicyclic α-amino ketone product (eq 21). This result demonstrates that a simple alkyne can function as the equivalent of an acyl anion nucleophile in intramolecular cyclizations with *N*-acyliminium ion electrophiles. The 15 cyclocondensation substrates were prepared in three stages from *N*-(trimethylsilyl) lactams. First a side chain nucleophile was incorporated by alkylation of lithium *N*-(trimethylsilyl) lactam enolates (Table I). These lactams were N-acylated (Table II), and the resulting mixed imides were selectively reduced (Table III) to provide the α-alkoxy-*N*-(acyloxy)pyrrolidine, -piperidine, and -azepine cyclization substrates. The new methods developed during this investigation for preparing α-alkoxy *N*-carbamates are likely to be of general utility for accessing these *N*-(acyloxy)iminium ion precursors.

Recent publications from our laboratories have introduced a new general strategy for alkaloid synthesis in which derivatives of 3-acylpyrrolidines are the central element.[2-5] A wide variety of azacycles containing the 3-acylpyrrolidine core can be accessed with high efficiency by sequential aza-Cope rearrangement–Mannich cyclization reactions (eq 1).[6] For ongoing studies to further



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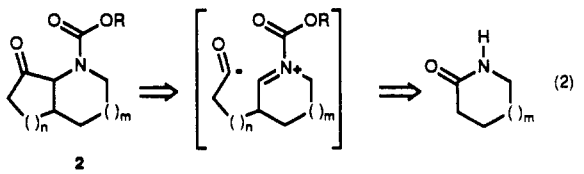
implement and develop this strategy, we required a route to azacyclic ketones **2**, intermediates that can serve[3,4] as precursors of the key rearrangement substrates **1**. A potential general approach to **2**, which, in principle, could allow the size of both the azacyclic and carbocyclic rings to be varied, is outlined in retrosynthetic form in eq 2. We were particularly interested in bicyclic products that contain an azepine ring ($m = 2$), as a result of the occurrence of this ring system in bioactive alkaloids of the *Stemona* family.[7]



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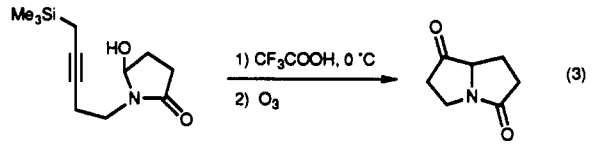
Reducing the scheme outlined in eq 2 to practice would require a general route to cyclic *N*-(acyloxy)iminium cations as well as the development of an acyl anion equivalent that would be compatible with such intramolecular electrophiles. The literature provides scant guidance with regard to the preparation and cyclization of azacyclic iminium cations containing *N*-acyloxy substitution.[8,9] In marked contrast, the chemistry of cyclic iminium cations with an acyl carbon as a constituent of the ring has been extensively developed.[9] In fact for cations of this latter type, Speckamp and co-workers have reported that a propargylsilane can function as an equivalent of an intramolecular acyl anion (eq 3).[9c]



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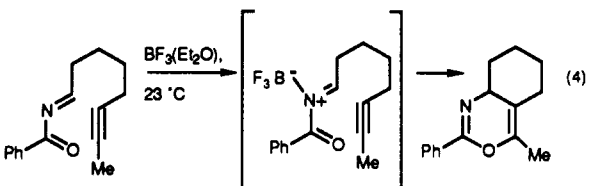
The approach we have pursued in our development of the strategy adumbrated in eq 2 was stimulated by the early studies of Schmidt and co-workers concerning the cyclocondensation of acylic *N*-acyliminium species with alkynes and alkenes.[10] An example of this approach to 1,3-oxazines, taken from Weinreb's[11] recent studies of intramolecular cyclocondensations of this type, is provided in eq 4. Armed with these precedents, we envisioned that



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(1) University of California, Reagents Dissertation Fellow, 1988.
(2) *Amaryllidaceae* alkaloids: Overman, L. E.; Mendelson, L. T.; Jacobsen, E. J. *J. Am. Chem. Soc.* **1983**, *105*, 6629. Overman, L. E.; Sugai, S. *Helv. Chim. Acta* **1985**, *68*, 745. Overman, L. E.; Wild, H. *Tetrahedron Lett.* **1989**, *30*, 647.
(3) *Aspidosperma* alkaloids: Overman, L. E.; Sworin, M.; Burk, R. M. *J. Org. Chem.* **1983**, *48*, 2685.
(4) *Melodinus* alkaloids: Overman, L. E.; Robertson, G.; Robichaud, A. J. *J. Org. Chem.* **1989**, 1236.
(5) *Gelseminium* alkaloids: Earley, W. G.; Jacobsen, E. J.; Meier, G. P.; Overman, L. E. *Tetrahedron Lett.* **1988**, *29*, 3781. Earley, W. G.; Oh, T.; Overman, L. E. *Tetrahedron Lett.* **1988**, *29*, 3785.
(6) For a brief review, see Overman, L. E.; Ricca, D. J. Intramolecular Mannich and Related Reactions. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: London, 1990.
(7) For the first total synthesis accomplishment in this area and leading references, see: Williams, D. R.; Brown, D. L.; Benbow, J. W. *J. Am. Chem. Soc.* **1989**, *111*, 1923.
(8) (a) Melching, K. H.; Hiemstra, H.; Klaver, W. J.; Speckamp, W. N. *Tetrahedron Lett.* **1986**, *27*, 4799. (b) Shono, T.; Hamaguchi, H.; Matsumura, Y. *J. Am. Chem. Soc.* **1975**, *97*, 4264. Shono, T.; Matsumura, Y.; Uchida, K.; Tsubata, K.; Makino, A. *J. Org. Chem.* **1984**, *49*, 300.
(9) (a) For a review of intramolecular reactions, see: Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367. (b) For a more general review of *N*-acyliminium ion chemistry, see: Zaugg, H. E. *Synthesis* **1984**, *85*, 181. (c) Heimstra, H.; Speckamp, W. N. *Tetrahedron Lett.* **1983**, *24*, 1407.
(10) Schmidt, R. R.; Hoffman, A. R. *Chem. Ber.* **1974**, *107*, 78, and references therein.
(11) Weinreb, S. M.; Scola, P. M. *J. Org. Chem.* **1986**, *51*, 3248.

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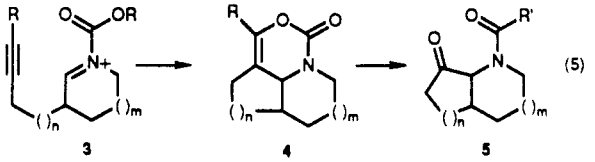
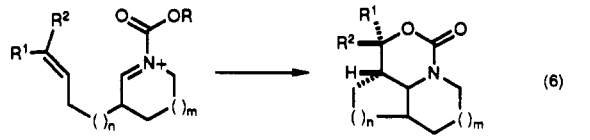
Table I. Preparation of Substituted Lactams as Outlined in Eq 8

compd	m	R	yield, %
16	1	$CH_2C{\equiv}CPh$	45
17	2	$CH_2C{\equiv}CPh$	94
18	2	$C{\equiv}CMe$	69
19	3	$CH_2C{\equiv}CPh$	81
20	3	$C{\equiv}CMe$	79
21	3	$C{\equiv}CSiMe_3$	37
22	3	$C{\equiv}CCH_2SiMe_3$	77
23	3	$C{\equiv}CPh$	41
24	3	(*E*)-CH=CHPh	69
25	3	(*E*)-CH=CHMe	71

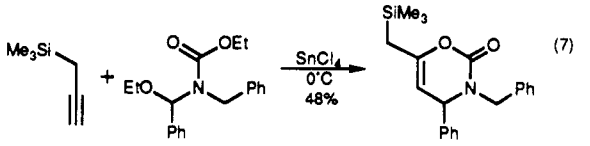
cyclocondensation of a cyclic *N*-(acyloxy)iminium cation **3** with a tethered alkyne would provide, after O-dealkylation, the tricyclic oxazinone **4** (eq 5). Oxidative cleavage



of the oxazinone ring was then envisaged to provide access to the targeted bicyclic α-amino ketones **5**. A related sequence with an alkene two-electron component, although not leading to a cycloadduct easily permuted to an α-amino ketone, is of intrinsic interest since four contiguous stereogenic centers (one exocyclic to the newly formed carbocyclic ring) would be established in the cyclization event (eq 6).



During the course of our investigations, the Amsterdam group disclosed several examples of the formation of 2-oxazinones from the bimolecular reaction of alkynes with acyclic *N*-(acyloxy)iminium cations (e.g. eq 7).[12]

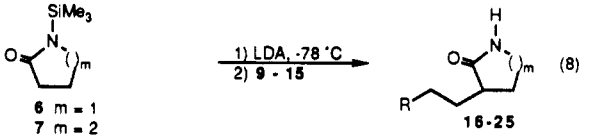


In this paper, we detail useful methods for preparing cyclic *N*-(acyloxy)iminium cations containing azacyclic rings of five to seven members. Most significantly, we report that these cations participate in intramolecular cyclocondensations with both alkynes and alkenes to proffer the versatile tricyclic oxazinones pictured in eqs 5 and 6. We also report that the stereochemistry of the newly formed carbocyclic ring is determined primarily by the nature of the azacyclic ring in which the *N*-(acyloxy)iminium functionality is imbedded.

Results

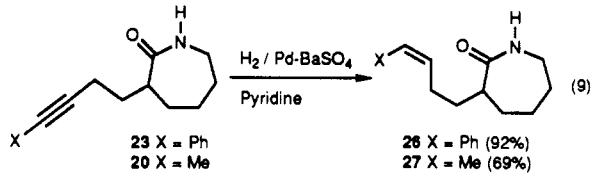
Preparation of Cyclocondensation Precursors. As precursors of the *N*-(acyloxy)iminium cations, we have employed α-alkoxy-*N*-(acyloxy)pyrrolidines, -piperidines, or -azepines. These intermediates can be accessed in three steps from the known *N*-(trimethylsilyl) lactams **6**–**8**.[13]

Deprotonation of the five-, six-, or seven-membered silyl lactams **6**–**8** with 1.1 equiv of lithium diisopropylamide (LDA) was complete within 15 min at −78 °C. Addition of the resulting enolates to 1 equiv of the unsaturated iodides **9**–**15** at −78 °C provided moderate to good yields of the monoalkylated lactams **16**–**25** after aqueous desilylation (eq 8 and Table I).[14] Inverse addition was employed to minimize formation of products resulting from bis-alkylation. Homopropargylic iodides **11** and **13** in which the alkyne substituent was Me_3Si or Ph afforded considerably lower yields as elimination to form a conjugated enyne became an important competing process.

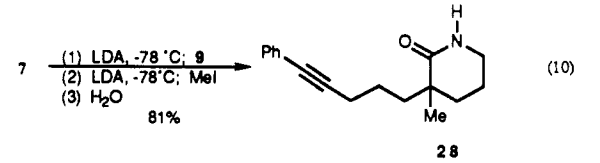


9 $PhC{\equiv}C(CH_2)_3I$
10 $MeC{\equiv}C(CH_2)_2I$
11 $Me_3SiC{\equiv}C(CH_2)_2I$
12 $Me_3SiCH_2{\equiv}C(CH_2)_2I$
13 $PhC{\equiv}C(CH_2)_2I$
14 (*E*) $PhCH{=}CH(CH_2)_2I$
15 (*E*) $MeCH{=}CH(CH_2)_2I$

Lactams containing *Z*-alkenyl side chains were readily prepared by semihydrogenation of the parent alkynyl lactams (eq 9). Analysis of **27** by capillary GLC indicated that the isomeric purity was >98%, while the stereochemical purity of **26**, determined in the same fashion, was 96%.



Disubstituted lactams containing a quaternary α-carbon were prepared in two ways. In the most direct approach, silyl lactam **7** was deprotonated with 1.0 equiv of LDA at −78 °C followed by addition of the resulting enolate to a solution of iodide **9** at −78 °C. The resulting monoalkylated lactam was then treated directly at −78 °C with additional LDA and subsequently quenched with CH_3I to provide the bis-alkylated lactam **28** in 81% yield (eq 10).



In general, this method was practical only when the initial alkylation occurred cleanly. The second method employed a more conservative two-step sequence, which allowed isolation and purification of the monoalkylated lactam. Thus, lactams **18** and **20** were reprotected with Me_3SiCl in the presence of excess Et_3N to afford the corresponding *N*-silyl lactams **29** and **30** (83% and 84% yields, respectively). Enolization of these monoalkylated lactams with LDA necessitated higher temperatures (−23 °C) than required for the parent *N*-silyl lactams. Subsequent al-

(12) Esch, P. M.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron Lett.* **1988**, *29*, 367.

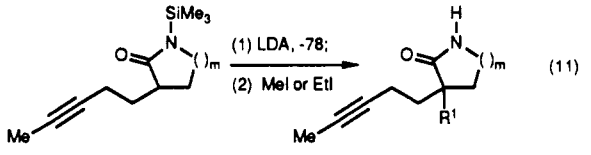
(13) Ruhlmann, K.; Rupprich, B. *Chem. Ber.* **1965**, 226. Lane, T. H.; Frye, C. L. *J. Org. Chem.* **1978**, *43*, 4890.

(14) Hiemstra, H.; Klaver, W. J.; Speckamp, W. N. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 299. Klaver, W. J.; Moolenaar, M. J.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1988**, *44*, 3805.

Table II. Preparation of Imides 33–47 as Outlined in Eq 12

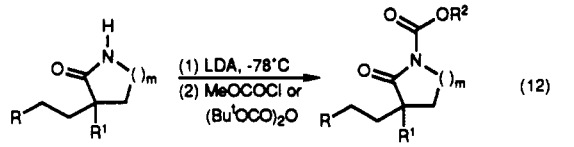
compd	m	R	R^2	R^1	yield, %
33	1	$CH_2C{\equiv}CPh$	Bu^t	H	73
34	2	$CH_2C{\equiv}CPh$	Bu^t	H	69
35	2	$CH_2C{\equiv}CPh$	Bu^t	Me	97
36	2	$C{\equiv}CMe$	Bu^t	Et	76
37	2	$CH_2C{\equiv}CPh$	Bu^t	H	58
38	3	$C{\equiv}CMe$	Bu^t	H	98
39	3	$C{\equiv}CSiMe_3$	Bu^t	H	94
40	3	$C{\equiv}CCH_2SiMe_3$	Bu^t	H	95
41	3	$C{\equiv}CPh$	Bu^t	H	57
42	3	(*E*)-C=CHPh	Bu^t	H	96
43	3	(*E*)-C=CHMe	Bu^t	H	75
44	3	(*Z*)-C=CHPh	Bu^t	H	77
45	3	(*Z*)-C=CHMe	Bu^t	H	66
46	3	$C{\equiv}CMe$	Bu^t	Me	95
47	3	$CH_2C{\equiv}CPh$	Me	H	73

kylation of these enolates proceeded smoothly to provide lactams **31** and **32** in good yields (eq 11).



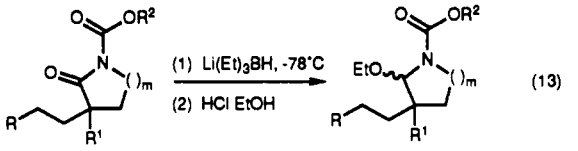
29 m = 2 (83%)
30 m = 3 (84%)
31 m = 2, R^1 = Et (95%)
32 m = 3, R^1 = Me (66%)

N-Acylation was best accomplished by treating the α-alkylated lactams with 1.2 equiv of LDA at −78 °C, followed by quenching the resulting lactam anion with methyl chloroformate or di-*tert*-butyl dicarbonate to provide the corresponding mixed imides **33–47** in good yields (eq 12 and Table II).[7a] It is worthy of note that NaH, KH, or KH in the presence of catalytic ethanol were less effective bases for this N-acylation.



33 - 47

Selective reduction of *N*-(acyloxy)pyrrolidone **33**, *N*-(acyloxy)azepinones **37–47**, and the α,α-dialkylated *N*-(acyloxy)piperidinones **35** and **36** could be achieved with an excess of lithium triethylborohydride at −78 °C in THF (eq 13).[15] Quenching this reaction mixture at −78 °C with



48 - 61

absolute EtOH and excess HCl provided the α-ethoxy carbamates **48–61**, as mixtures of ethoxy epimers, in excellent yields (Table III). The efficiency of this two-step sequence is noteworthy, as is the fact that no products of overreduction or lactam cleavage were detected. Also deserving of comment is the fact that diisobutylaluminum hydride is a significantly less selective reductant for this application.

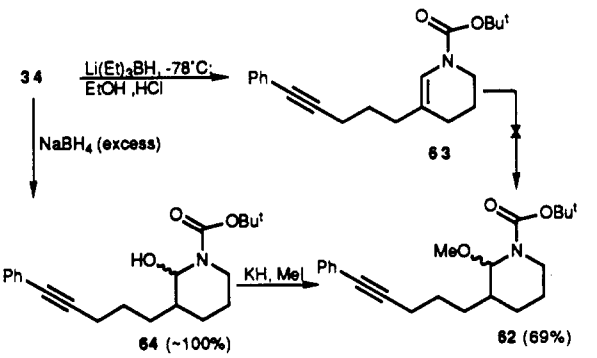
Preparation of *N*-(*tert*-butoxycarbonyl)piperidine **62** proved to be more difficult. Reduction of **34** by the above protocol afforded the encarbamate **63** as the sole product

(15) Brown, H. C.; Krishnam, S. *J. Am. Chem. Soc.* **1973**, *95*, 1669.

Table III. Preparation of α-Ethoxy Carbamates 48–61 as Outlined in Eq 13

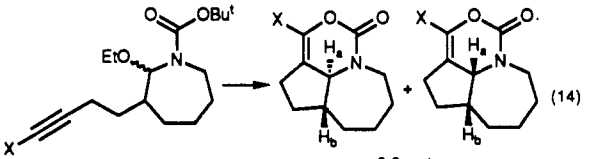
compd	m	R	R^2	R^1	yield, %
48	1	$CH_2C{\equiv}CPh$	Bu^t	H	82
49	2	$CH_2C{\equiv}CPh$	Bu^t	Me	60
50	2	$C{\equiv}CMe$	Bu^t	Et	88
51	3	$CH_2C{\equiv}CPh$	Bu^t	H	82
52	3	$C{\equiv}CMe$	Bu^t	H	98
53	3	$C{\equiv}CSiMe_3$	Bu^t	H	74
54	3	$C{\equiv}CCH_2SiMe_3$	Bu^t	H	83
55	3	$C{\equiv}CPh$	Bu^t	H	94
56	3	(*E*)-CH=CHPh	Bu^t	H	85
57	3	(*E*)-CH=CHMe	Bu^t	H	85
58	3	(*Z*)-CH=CHPh	Bu^t	H	88
59	3	(*Z*)-CH=CHMe	Bu^t	H	99
60	3	C=CMe	Bu^t	Me	93
61	3	$CH_2C{\equiv}CPh$	Me	H	78

Scheme I



(Scheme I). This intermediate was not converted to the desired α-ethoxy carbamate when treated with anhydrous HCl in absolute EtOH. The apparent propensity of the six-membered ring substrate to eliminate EtOH to form the encarbamate was finally circumvented using the two-step sequence outlined in Scheme I. Reduction of **34** with excess $NaBH_4$ in MeOH at room temperature[16] provided the labile α-hydroxy carbamate **64** in essentially quantitative yield. O-Methylation could then be accomplished[17] by addition of a solution of **64** and neat MeI to a suspension of KH in THF at room temperature to give the desired α-methoxy carbamate **62** in an overall yield of 69%.

Cyclocondensations of Azepine Substrates. We will first consider cyclizations of substrates with homopropargyl side chains. Treatment of α-ethoxy carbamate **53** with 1.2 equiv of $SnCl_4$ at −23 °C in CH_2Cl_2 for 1 h effected complete conversion to a 1.75:1 mixture (by capillary GLC analysis) of tricyclic enol carbamates **67** and **68**, respectively, in a combined crude yield of 86% (eq 14). That



52 X = Me
53 X = Me_3Si
54 X = Me_3SiCH_2
55 X = Ph

65 2.2 : 1 **66**
67 1.75 : 1 **68**
69 30 : 1 **70**
71 (80%)

67 and 68 were products of intramolecular cyclocondensation was readily apparent from the lack of signals in the ^1H NMR spectrum characteristic of the ethoxy and *tert*-butyl groups. In addition, a strong carbonyl absorp-

(16) Speckamp, W. N. *Recl. Trav. Chim. Pays-Bas* **1981**, *100*, 345. Chamberlin, A. R.; Chung, J. Y. L. *J. Am. Chem. Soc.* **1983**, *105*, 3653.
(17) Vijn, R. J.; Hiemstra, H.; Kok, J. J.; Knotter, M.; Speckamp, W. N. *Tetrahedron* **1987**, *43*, 5019.

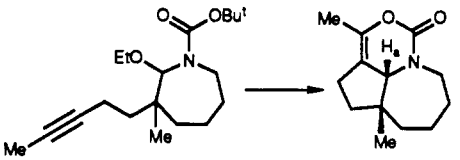
tion at 1708 cm^{-1} indicated retention of the carbamate moiety. The mixture could be separated by careful chromatography on silica gel providing pure samples of both isomers. The major isomer **67** exhibited characteristic signals in the ^1H NMR spectrum at δ 4.50 and 3.75 for the diastereotopic methylene hydrogens adjacent to nitrogen, while the bridgehead methine hydrogen H_a appeared as a broad doublet (J = 10.0 Hz) at δ 3.28. The ^1H NMR spectrum of the minor isomer **68** was similar displaying characteristic signals at δ 4.45 and 2.30 for the diastereotopic CH_2N hydrogens, and a doublet of triplets (J_{ab} = 6.3 Hz) at δ 3.81 for the bridgehead hydrogen H_a. The 10-Hz coupling constant observed for H_a of **67** suggests that the stereochemistry of the ring fusion in trans. The strong ^1H NOE ($H_a \rightarrow H_b$ = 9.5%) observed between the bridgehead hydrogens of the minor isomer **68** together with the weak ($H_a \rightarrow H_b$ = 0–1.3%) ^1H NOE observed for these hydrogens of the major isomer **67** unambiguously define the stereochemistry of these products.

Exposure of α-ethoxy carbamate **52** to $SnCl_4$ at −23 °C produced after 2 h a 2.2:1 mixture (by capillary GLC analysis) of cycloadducts **65** and **66** as a crystalline solid in 90% combined yield. Analysis of the crude isolate by capillary GLC indicated that these isomers comprised >96% of the volatile product. These compounds were more delicate than their silyl-substituted analogues as chromatography on silica gel effected extensive decomposition, and storage at room temperature resulted in significant loss of material. In addition, use of chlorinated solvents during handling accelerated decomposition. Traces of acid are most likely responsible for this observed instability. The major isomer **65** (mp 99–103 °C) could be isolated in pure form from the crude product by recrystallization from Et_2O/hexane, while the minor isomer **66** could be obtained only in enriched form (ca. 70% pure) from the mother liquors. Enol carbamate **65** displayed a doublet of quartets (J = 2.0, 9.7 Hz) at δ 3.28 in the ^1H NMR spectrum for the bridgehead methine hydrogen H_a, while the bridgehead methine hydrogen H_a of the minor isomer **66** appeared as a doublet of quartets (J = 2.0, 6.5 Hz) at δ 3.62. Difference ^1H NOE experiments similar to those described for enol carbamates **67** and **68** unambiguously defined the stereochemistry of these adducts.

In similar fashion, ethoxy carbamate **54** could be cyclized ($SnCl_4$, −23 °C, 1 h) to afford an 83% crude yield of two isomeric enol carbamates **69** and **70** in a 30:1 ratio, respectively. Analysis of the crude mixture by capillary GLC indicated that the two cycloadducts were contaminated with <5% of other volatile materials. This crude product mixture also underwent extensive decomposition upon chromatography, necessitating analysis of the crude isolate. The bridgehead methine hydrogen H_a of the major isomer **69** appeared as a doublet (J = 9.6 Hz) at δ 3.36, while the minor isomer **70** exhibited a broad doublet (J = 5.7 Hz) at δ 3.7 in the ^1H NMR spectrum characteristic of this hydrogen. This data allows assignment of a trans stereorelationship at the ring fusion for the major isomer **69**. Worthy of note is the complete lack of allene-containing side products, which could have arisen from conventional reaction of the propargyl silane with an acyliminium ion electrophile.[9]

In contrast to ethoxy carbamates **52–54**, the reaction of **55** with $SnCl_4$ (−23 °C, 1 h) gave a single crystalline cycloadduct **71**, in 80% yield. Examination of the crude product by 500-MHz ^1H NMR and 125-MHz ^{13}C NMR spectroscopy failed to reveal other products of cyclization. The ^1H NMR spectrum of enol carbamate **71** exhibited a doublet (J = 10.0 Hz) at δ 4.12 for bridgehead methine hydrogen H_a, thus allowing assignment of trans stereochemistry to this material.

Carbamate **60**, which contains a quaternary center adjacent to the ethoxy substituent, also cyclized upon exposure to $SnCl_4$ at −23 °C to give, in 69% crude yield, a single enol carbamate **72** (eq 15). As with analogous

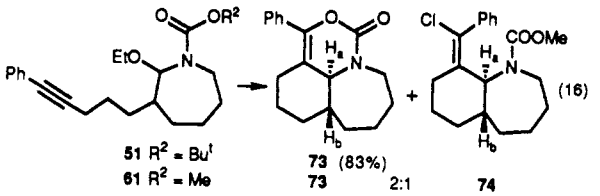


(15)

60 **72**(69%)

compounds **65** and **66**, hydroazabenzazulene **72** was unstable toward chromatography. Analysis of the ^1H NMR spectrum of **72** revealed a quartet (J = 1.9 Hz) at δ 3.12, characteristic for the bridgehead methine proton H_a and a singlet at δ 1.48 for the angular methyl group. The strong ^1H NOE ($H_a \rightarrow CH_3$ = 8%) observed between the bridgehead methine hydrogen and the hydrogens of the bridgehead methyl is consistent with a cis relationship of these groups.

The results obtained from cyclizations of azepine substrates containing 4-alkynyl side chains are presented in eq 16. The α-ethoxy *N*-(*tert*-butoxycarbonyl)azepine **51**

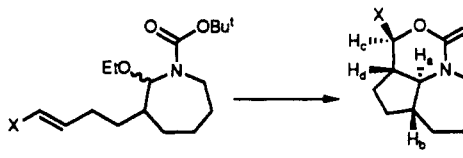


(16)

51 R^2 = Bu^t **61** R^2 = Me **73** (83%) **73** 2:1 **74**

provided tricycle **73** in 83% yield when treated with $SnCl_4$ at −23 °C. The ^1H NMR spectrum of **73** shows the bridgehead methine hydrogen H_a as a doublet (J = 10.5 Hz) at δ 3.40. The observed 10.5-Hz coupling is only consistent with methine hydrogen H_a having a trans diaxial relationship with H_b. In a similar experiment, reaction of *N*-(methoxycarbonyl)azepine **61** with $SnCl_4$ at −23 °C for 2 h provided a 2:1 mixture of tricycle **73** and the bicyclic vinyl chloride **74**. Separation of this mixture on silica gel gave pure samples of **73** and **74** in 65% and 25% yields (based on consumed **61**), respectively. The structure of **74** followed directly from spectral data (see the Experimental Section). The 11.0-Hz coupling constant observed between the bridgehead methine hydrogens establishes a trans ring fusion for **74**. The stereochemistry of the alkylidene moiety is assigned as *E* on the expectation that addition to the alkyne would occur in an antiperiplanar fashion.

Azepine substrates containing tethered 3-alkenyl side chains underwent intramolecular cyclocondensations under identical conditions (eq 17). For example, treatment of



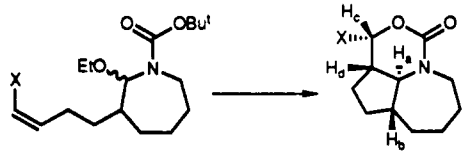
(17)

56 X = Ph **57** X = Me **75** X = Ph (80%) **76** X = Me (78%)

56 containing an (*E*)-styrenyl side chain with $SnCl_4$ (−23 °C, 1.5 h) gave a single crystalline, mp 151.5–153.5 °C, cycloadduct **75** in 80% yield after chromatographic purification (eq 17). The stereostructure of **75** followed directly from ^1H NMR data. The bridgehead methine hy-

drogen H_a appeared as an apparent triplet ($J_{ab} = J_{ad} = 10.4$ Hz) at δ 3.23, while methine hydrogen H_c appeared as a doublet ($J_{cd} = 10.6$ Hz) at δ 5.06. The large vicinal coupling constants observed for H_a and H_c require that they both have a trans diaxial relationship with H_d. The 10-Hz coupling constant observed between H_a and H_b is also consistent with a trans orientation for these hydrogens. The strong ^1H NOE ($H_d \rightarrow$ *o*-Ph) between methine hydrogen H_d and the ortho hydrogens of the phenyl group further support the structural assignment for **75**. Similarly, **57** containing an (*E*)-3-pentenyl side chain cyclized in the presence of $SnCl_4$ (−23 °C for 8 h) to provide a single crystalline, mp 102.5–104.5 °C, cycloadduct **76** in 78% yield. The stereostructure for **76** was secured from spectral data in a fashion analogous to **75**.

Substrates containing (*Z*)-alkenyl side chains also underwent cyclocondensation with complete stereoselectivity (eq 18). Thus, a 24:1 mixture of the geometric isomers



(18)

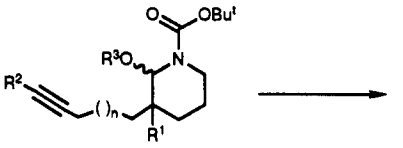
58 X = Ph
59 X = Me

77 X = Ph (76%)
78 X = Me (80%)

58 and **56** reacted ($SnCl_4$, −23 °C, 1 h) to provide an 80% crude yield of a mixture of cycloadducts **77** and **75** (in a 24:1 ratio by capillary GLC analysis). The major isomer **77** could be easily separated by chromatography on silica gel, and the stereochemistry for **77** followed directly from ^1H NMR data. Bridgehead methine hydrogen H_a appeared as an apparent triplet ($J_{ab} = J_{ad} = 10.9$ Hz) at δ 2.91, while methine hydrogen H_c appeared as a doublet ($J_{cd} = 5.7$ Hz) at δ 5.51. The large coupling between H_a and H_d requires that these hydrogens are trans diaxial, while the small coupling between H_c and H_d requires an axial–equatorial relationship for these two hydrogens. The 11-Hz coupling constant observed between H_a and H_b is also consistent with a trans ring fusion. The strong ^1H NOE ($H_d \rightarrow H_c$ = 13%, $H_c \rightarrow H_d$ = 12%) observed between the methine hydrogen H_c and methine hydrogen H_d along with the lack of ^1H NOE between the bridgehead methine hydrogen H_a and methine hydrogens H_d, H_c, and H_b further support the structural assignment for **77**. In an identical fashion, **59** gave ($SnCl_4$, −23 °C, 8 h) a single cycloadduct **78** as a waxy solid in 80% yield. No trace of the isomeric adduct **76** was seen in the 500-MHz ^1H NMR spectrum of the crude product. The structural assignment for **78** followed from ^1H NMR data in a manner analogous to that of cycloadduct **77**.

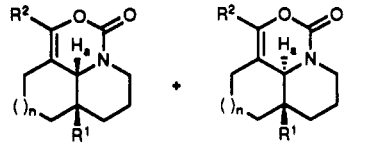
Cyclocondensations of Piperidine Substrates. Piperidine substrates containing tethered 4-alkynyl side chains underwent Lewis acid promoted cyclizations under identical conditions; however, in this case the new carbocyclic ring was formed preferentially with a cis ring fusion (eq 19). For example, treatment of **62** with $SnCl_4$ at −23 °C afforded a 3:1 mixture of adducts **79** and **80** in 91% yield after purification on silica gel. Preparative HPLC allowed isolation of pure samples of each isomer. The smaller vicinal coupling observed between H_a and H_b of the major adduct **79** (J = 5.0 vs 10.1 Hz) established that this material was the cis stereoisomer.

The preference for forming the cis-bicyclic subnucleus was more pronounced in cyclocondensations of α-ethoxy carbamates **63** and **64**, which have the alkyne side chain tethered from a quaternary carbon center. Thus, cyclization of **63** ($SnCl_4$, −78 °C) and **64** ($SnCl_4$) gave a single



62 $R^1 = H_a$ R^2 = Ph R^3 = Me n = 1
63 R^1 = Me R^2 = Ph R^3 = Et n = 1
64 R^1 = Et R^2 = Me R^3 = Et n = 0

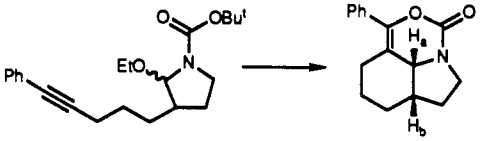
(19)



79 $R^1 = H_b$ n = 1 3:1 **80** $R^1 = H_b$ n = 1
81 R^1 = Me n = 1 (87%)
82 R^1 = Et n = 0 (90%)

product in each case. The azahydrophenalene **81** was isolated in pure form in 87% yield after chromatography, while the more labile **82** was produced in a crude yield of 90%. The stereochemistry of **81** followed from the large ^1H NOE ($H_a \rightarrow CH_3$ = 10%) observed between the angular substituents. Similarly **82** showed an 11% ^1H NOE between H_a and the methylene hydrogens of the angular ethyl group.

Cyclocondensation of a Pyrrolidine Substrate. Only one substrate of this type was examined. Cyclization of **48** with $SnCl_4$ (−23 °C, 1 h) provided a single tricycle **83**, which was isolated as a colorless oil in 98% crude yield (eq 20). Analysis of the crude product by capillary GLC



(20)

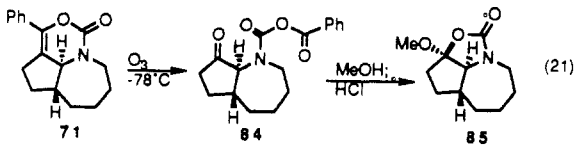
48 **83** (98%)

indicated that **83** composed >99% of the volatile product. The tricyclic oxazinone **83** was not stable at room temperature, and thus required storage in a benzene matrix at −20 °C. The bridgehead methine hydrogen H_a appeared as a doublet (J = 8.2 Hz) at δ 4.29 in the ^1H NMR spectrum. The observed coupling constant for H_a is somewhat smaller (Δ 1.8 Hz) than that of related trans-fused cycloadducts **79** and **81**, suggesting that the ring fusion stereochemistry of **83** is cis. A molecular mechanics (MMX) model[18] of the hypothetical trans stereoisomer of **83** indicates, according to the Karplus relationship,[19] that J_{ab} would be considerably larger than 8.2 Hz for this stereoisomer (11.2 Hz, H_a–H_b dihedral angle ~179°). It should be added that the angular coupling constants (J_{ab}) observed for adducts **65**, **66**, **73**, **79**, and **80** agree within ±0.61 Hz (1σ) of those calculated from MMX minimized conformations.

Oxidative Degradation of Tricyclic Oxazinone 71. For one oxazinone cycloadduct we have examined, in a preliminary way, its oxidative modification to reveal the latent α-amino ketone functionality (eq 21). The bicyclic mixed anhydride **84** was produced cleanly upon ozonolysis

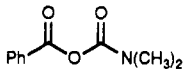
(18) PCMODEL Molecular Modeling Software for the Macintosh II, obtained from Serena Software, Bloomington, IN, was used for these calculations. For a discussion of the MMX enhanced version of MM2, see: Gajewski, J. J.; Gilbert, K. E.; McKelvey, J. In *Advances in Molecular Modeling*; JAI Press, Vol. 2, in press. The Chem 3D modeling system, obtained from Cambridge Scientific Computing, was used to generate ball and stick models.

(19) Karplus, M. *J. Chem. Phys.* **1959**, *30*, 11.



71 84 85

of enol carbamate **71** at −78 °C in a 10:1 mixture of CH_2Cl_2 and MeOH. Analysis of the crude product by IR revealed strong absorptions at 1755 and 1725 cm^{-1}, suggesting the presence of the mixed carbamic carboxylic anhydride. Analysis of the ^{13}C NMR spectrum of **84** revealed signals at 160 and 154 ppm assignable to the carbonyl carbons of this functional group. Rigorous identification of this moiety was made by comparison to benzoic dimethylcarbamic anhydride (**86**), which was prepared according



86

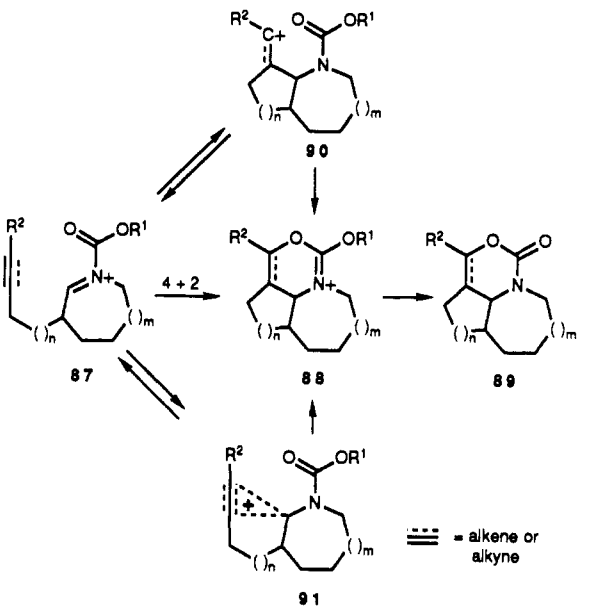
to the procedure of Rawlingson and Humke.[20] This model compound exhibited resonances in the ^{13}C NMR at 162 and 149 ppm for the carbonyl carbons of the mixed anhydride as well as strong absorptions in the infrared spectrum at 1768 and 1725 cm^{-1}. The crude product was marginally stable toward chromatography on silica gel, allowing recovery of 60% of the expected mass. Nonetheless, the stability of **84** was poor and decomposition was apparent within hours at room temperature.

In a similar experiment, the ozonolysis product (after quenching with Me_2S) was treated with 10 equiv of HCl in absolute MeOH to provide the mixed acetal **85** in 69% yield after chromatographic purification. The structure of **85** followed unambiguously from spectral data. Particularly diagnostic were (a) signals in the ^{13}C NMR spectrum at 156 and 112 ppm, which are characteristic of the carbamate carbonyl and acetal carbons, respectively, (b) the observation of a *single* carbonyl absorption at 1775 cm^{-1} in the infrared spectrum characteristic of a five-membered ring carbamate, and (c) the appearance of a three hydrogen singlet at δ 3.35 in the ^1H NMR spectrum for the MeO group. The configuration at the acetal carbon is assigned on the reasonable assumption that the bicyclo[3.3.0]octane subnucleus would have a cis ring fusion.

Discussion

Mechanism. Three possible mechanistic scenarios for the cyclocondensations reported here are outlined in Scheme II. These mechanisms envisage formation of the tricyclic cation **88** from the monocyclic *N*-(acyloxy)iminium ion precursor **87** by either (a) a stepwise sequence proceeding via a bicyclic carbenium ion intermediate **90**, (b) a direct [4 + 2] cycloaddition, or (c) initial formation of π-complex **91**, which is subsequently trapped intramolecularly by the acyloxy group. A stepwise sequence proceeding via a discrete, freely rotating, carbocation intermediate **90** would not be consistent with the complete retention of stereochemistry observed in cyclocondensations of the *E* and *Z* alkene substrates **56–59**. Although this stereochemical test can be applied only to alkene participants, there is no reason to believe that a stepwise process of this type would be more favorable with an alkyne nucleophile, particularly in light of the relative instability of vinyl cations.[21] Since the four-electron *N*-(acyloxy)iminium ion function is highly polarized, a cycloaddition involving this unit with an alkyne or alkene

Scheme II

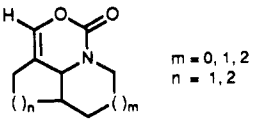


90 87 88 89 91

would be expected to be highly asynchronous, with C–C bond formation far advanced relative to C–O bond formation.[22] Thus, the distinction between an asynchronous [4 + 2] cycloaddition and a two-step sequence proceeding via π-complex **91** is subtle and of little consequence in analyzing the stereochemical outcome of the cyclocondensations discovered in this study.

Two additional observations merit brief discussion. As reported in detail in the preceding section, cyclizations of substrates in which the nitrogen substituent was a *tert*-butoxycarbonyl group were cleaner than a comparble reaction in which this group was methoxycarbonyl. This result is consistent with the more rapid loss of the *tert*-butyl group by simple ionization than the methyl group by S_N2 dealkylation. Thus, the formation of the bicyclic vinyl chloride **74**, in addition to tricyclic product **73**, from treatment of the methoxycarbonyl-containing substrate **61** with $SnCl_4$ (see eq 16) could be rationalized in the following way. When $R^1 = CH_3$, dealkylation of **88** (Scheme II) is sufficiently slow that fragmentation to the bicyclic cation **90** (which is then trapped by chloride to yield vinyl chloride **74**) is competitive with demethylation.[23] There is some precedent from earlier investigations of Schmidt for reversible fragmentation (ionization) of cationic cycloadducts of this general type.[10]

Stereochemistry. Table IV summarizes the stereochemistry observed in the cyclization reactions targeted in this study. The steric energies of the stereoisomeric tricyclic ring systems **92**, obtained by molecular mechanics



92

calculations using the MMX[18] force field, are also included in this table. Apparent is the lack of correlation between cyclization stereoselectivity and the steric energy of the products, a result which provides strong evidence that the

(20) Rawlinson, D. J.; Humke, B. M. *Tetrahedron Lett.* **1972**, *43*, 4395.
(21) Stang, P. J.; Rappoport, Z.; Hannach, M.; Subramanian, L. R. *Vinyl Cations*; Academic: New York, 1979.
(22) See, e.g.: Ciganek, E. *Org. React.* **1984**, 11.
(23) An alternate rationale would involve competitive capture of **91** by external chloride to afford **74** and by the internal oxygen to afford ultimately **89**.

Table IV. Summary of Cyclization Stereoselectivity

		spectator ring		tethered nucleophile		stereochemistry		steric energy of tricyclic product[a]	
	compd	size	α-substituent	nascent ring size	2π component	% cis	% trans	cis	trans
1	**55**	7	H	5	PhC≡C	0	100	25.5	25.5
2	**54**	7	H	5	Me_3SiCH_2C≡C	4	96		
3	**52**	7	H	5	MeC≡C	25	75		
4	**53**	7	H	5	Me_3SiC≡C	36	64		
5	**60**	7	Me	5	MeC≡C	100	0	29.8	27.4
6	**56**	7	H	5	(*E*)-PhCH=CH	0	100		
7	**58**	7	H	5	(*Z*)-PhCH=CH	0	100		
8	**57**	7	H	5	(*E*)-MeCH=CH	0	100		
9	**59**	7	H	5	(*Z*)-MeCH=CH	0	100		
10	**51**	7	H	6	PhC≡CCH_2	0	100		
11	**64**	6	Et	5	MeC≡C	100	0		
12	**62**	6	H	6	PhC≡CCH_2	75	25	16.9	8.4
13	**63**	6	Me	6	PhC≡CCH_2	100	0	27.1	17.4
14	**48**	5	H	6	PhC≡CCH_2	100	0	19.3	18.2

[a] By molecular mechanics (MMX)[18] calculations of the parent ring system **92** (kcal/mol).

cyclocondensation reactions are under kinetic control. Since the geometry of tricycles **88** and **89** (see Scheme II) should be similar, the lack of correlation of ring-fusion stereochemistry with the steric energy of **92** also implies that the relative energies of stereoisomeric cations **88** are not accurately mirrored in the product-determining transition states. A reactant-like transition state is indicated.

The α-alkoxy carbamates examined in this study contain several elements that are capable of governing the stereochemical outcome of the cycloadditions: the size and substitution of the original azacyclic ring (spectator ring), the length of the tether, and the type (alkene vs alkyne) and substitution of the two-electron component.

That the nature of the two-electron component is not of major significance is apparent in the similar stereochemical outcome of the cyclizations of the phenylethynyl and (*E*)- and (*Z*)-styrenyl substrates (entries 1, 6, and 7). Nonetheless, small effects attributable to the substituents on the distal alkyne carbon are apparent in the decrease in trans stereoselectivity observed in proceeding from entry 1 to 4 in Table IV. An analogous small influence is apparent in the greater trans stereoselectivity of the cyclization reaction of 2-propynyl (entry 3) than 2-propenyl (entries 8 and 9) nucleophiles.

The effect of tether length, and thus the size of the forming ring, was not examined in any detail in our studies. In the one pertinent comparison (entries 1 and 10) complete trans selectivity was seen in forming both five- and six-membered carbocyclic rings when the four-electron component was contained in an azepine ring.

In contrast to the small effect on stereoselectivity attributable to the side chain, the size of the azacyclic ring and the extent of substitution at the ring carbon bearing the side chain dramatically affect the stereochemical outcome of the cyclocondensation reaction. For example, in forming a six-membered carbocyclic ring with a phenylethynyl two-electron component, the ring-fusion stereochemistry varies with the size of the starting azacyclic ring from 100% cis (five-membered azacycle, entry 14) to 75% cis (six-membered azacycle, entry 12) to 100% trans (seven-membered azacycle, entry 10).[24] In the six- and seven-membered ring azacyclic series tethering the side chain from a quaternary carbon (entries 5, 11, and 13) leads to forming only the cis-fused cycloadduct; in the seven-membered ring series this outcome corresponds to a complete reversal of stereoselectivity.

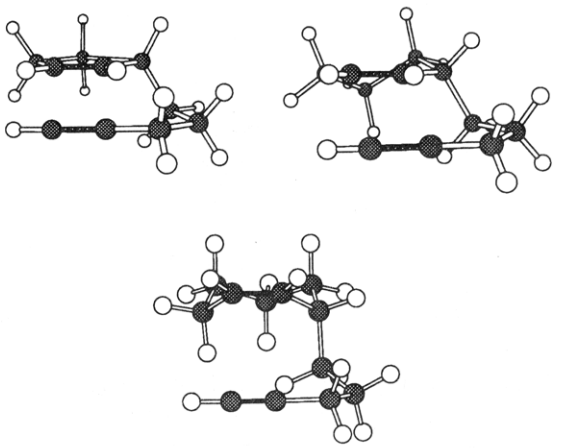


Figure 1. Generalized reacting conformations of 3-(4-pentynyl)cycloalkenes in which the side chain is axially disposed. These models, and those in Figures 2–4, were generated by substituting a side chain moiety for an allylic hydrogen in the calculated (MMX)[18] minimum energy structures of the appropriate cycloalkenes.

How can we rationalize the stereochemical outcome of these cyclocondensation reactions? Let us first address substrates that exclusively form cis tricyclic products. These contain either a five-membered spectator ring or are piperidine or azepine substrates in which the tether eminates from a quaternary ring site. A common feature of these substrates is that conformations in which the tethered side chain is disposed in an axial fashion would not be appreciably higher in energy than ones in which the tethered nucleophile resides equatorially.[25,26] It is thus reasonable to conclude that cis adducts result in these cases from preferential cyclocondensation via axial transition-state conformers. The excellent overlap of an axially tethered alkyne nucleophile with the π-bond of a five-, six-, or seven-membered unsaturated azacycle is apparent from the models depicted in Figure 1.

Remaining for discussion are the cyclizations of azepine substrates which were highly trans stereoselective. All recent calculations find the chair conformation of cyclo-

(24) Similar trends are seen in the intramolecular cycloaddition of vinylnitrosonium cations with 1-substituted 2-cycloalkenes. Denmark, S. E., personal communication.

(25) The trans isomer of 1,3-dimethylcyclopentane (in which one of the methyl groups adopts an axial orientation) is only 0.5 kcal/mol less stable than the cis stereoisomer.[26]

(26) Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. *Conformational Analysis*; American Chemical Society: Washington, D.C., 1981; pp 200–206.

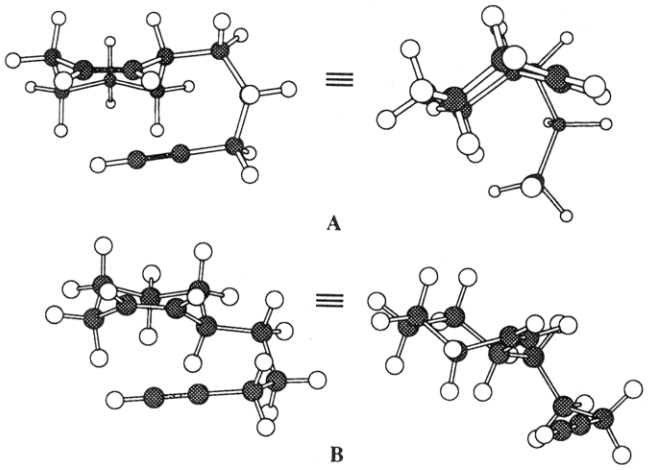


Figure 2. Generalized reacting conformations for 3-(4-pentynyl)cycloheptenes in which the side chain resides equatorially. A illustrates a conformation favoring the formation of the cis product while the conformation in B favors formation of the trans product.

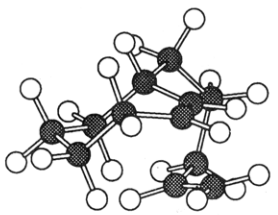


Figure 3. Cis reacting conformer for a 3-(4-pentenyl)cycloheptene in which the side chain resides equatorially.

heptene as the energy minimum.[27] In this conformation an equatorial allylic substituent is oriented in the nodal plane of the alkene, and, as a result, one would expect that an equatorially tethered nucleophile could reach either side of the alkene π-bond with similar facility.[28] Figure 2 illustrates plausible reactive conformations for this case which would lead to either the cis- or trans-fused cycloadduct. Apparent from these models is the severe steric interaction that exists between the alkyne nucleophile and the axial hydrogens of the ring in cyclization conformations that lead to the cis-fused product (Figure 2A). Alternatively, the conformation leading to the trans isomer is quite attractive since the tethered nucleophile approaches the cycloalkene from the outside (unhindered) face of the molecule (see Figure 2B). Thus, the preference for forming the trans cycloadduct with azepine substrates is reasonable.

One can also readily rationalize the higher trans stereoselectivity observed in the azepine series with alkene than with alkyne nucleophiles. When the two-electron component is an alkene, formation of the cis isomer is strongly disfavored as a result of the increased size of the alkene moiety. Figure 3 illustrates the fact that in a cyclization to form a cis-fused product, the vinyl hydrogens on the proximal carbon of the alkene develop a severe destabilizing steric interaction with the axial hydrogens of the seven-membered ring.

The other case in which a trans product was observed (although as the minor product) was when the azacyclic

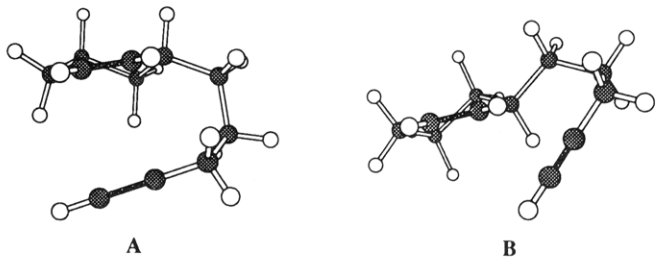


Figure 4. Generalized reacting conformations for 3-(4-pentynyl)cyclohexenes that contain an equatorial side chain. The conformation depicted in A gives rise to the cis product while that of B affords the trans product.

spectator ring was six-membered. Two possible reacting conformers available in the six-membered ring series for an equatorially oriented 4-pentynyl side chain are depicted in Figure 4. These conformations show no particularly objectionable steric interactions for addition to either alkene face. However, unlike seven-membered substrates, the allylic equatorial substituent is ~45° out of the alkene plane and, as a result, overlap between the nonterminal alkyne and iminium carbons is considerably better when the tether reaches to the proximal alkene face. That the trans stereoisomer is formed to even a minor extent (25%) is perhaps surprising. This result may reflect that the energy difference between cis and trans cycloadducts (see Table IV, entries 12 and 13) is sufficiently large that this difference is felt even in an early transition state.

Conclusion

The intramolecular condensation of cyclic *N*-(acyloxy)iminium cations with alkynes and alkenes occurs in high yield to form tricyclic adducts of the types illustrated in eqs 5 and 6. These reactions were specifically demonstrated when the heterodiene moiety was contained in five-, six-, and seven-membered rings and when the two-electron component was either a 1,2-disubstituted alkene or alkyne. Cyclization to form both five- and six-membered carbocyclic rings occurred with equal facility.

The stereochemistry of the resulting cycloadducts was found to be controlled primarily by the spectator ring in which the iminium ion was imbedded. When the azacyclic ring is monosubstituted, the amount of trans product increases as the size of the spectator ring increases from five to seven. Additionally, when the spectator ring contains no large conformational bias, cyclization of the tethered nucleophile via an axial manifold to form the cis product is highly preferred. The conformational rationales advanced to explain these trends should be useful in the design of other cyclization reactions. In particular, a large preference for forming a trans-fused product should be observed in cyclization reactions of cyclic seven-membered alkenes (or related heterocycles) in which a reactive side chain eminates from the allylic site.

We have also shown in one case that the oxazinone ring of the alkyne cycloadducts can be cleaved to liberate a protected α-amino ketone. This cycloaddition–oxidative cleavage sequence demonstrates that a simple alkyne can function as a surrogate for an acyl anion in the straightforward route to bicyclic α-amino ketones outlined in eq 2.

Experimental Procedures[29]

1-Iodo-4-phenyl-3-butyne (13). A solution of 4-phenyl-3-butyn-1-ol (15.0 g, 0.103 mol) in $CHCl_3$ (50 mL) was treated

(27) Burkert, U.; Allinger, N. L. *Molecular Mechanics*, ACS Monograph 177; American Chemical Society: Washington, D.C., 1982; p 129.

(28) The MMX force field[18] finds chair cycloheptene to be 0.8 kcal/mol more stable than the twist conformer and the dihedral angle between the equatorial allylic hydrogen and the adjacent vinylic hydrogen to be 3°. The equatorial conformer of 3-methylcycloheptene is also found to be 1.0 kcal/mol more stable than the axial stereoisomer. (Compare with 0.8 kcal/mol for the respective conformers of 3-methylcyclohexene.)

(29) General experimental details were recently described: Fisher, M. J.; Overman, L. E. *J. Org. Chem.* **1988**, *53*, 2630.

sequentially with pyridine (20.0 mL, 0.24 mol) and *p*-toluenesulfonyl chloride (27.3 g, 0.143 mol) at room temperature. The resulting solution was maintained at room temperature for 12 h. The reaction mixture was then diluted with Et_2O (400 mL) and washed successively with 1 N HCl, saturated aqueous Na_2CO_3, and brine. The organic portion was dried ($MgSO_4$) and concentrated. The crude tosylate was taken up in acetone (75 mL), NaI (30.8 g, 0.21 mmol) was added, and the resulting mixture was maintained at reflux for 2 h and then allowed to cool to room temperature. This mixture was diluted with pentane (400 mL) and washed successively with water, 15% aqueous $Na_2S_2O_3$, and brine. The organic material was dried ($MgSO_4$) and concentrated. The crude product was distilled (bp 75–76 °C, 0.2 mmHg), giving 18.9 g (72%) of **13** as a clear liquid: ^{1}H NMR (250 MHz, $CDCl_3$) 7.40–7.20 (m, ArH), 3.32 (t, J = 7.5 Hz, CH_2I), 3.01 (t, J = 7.5 Hz, $\equiv CH_2$); IR (film) 3055, 1597, 1488, 756, 691 cm^{-1}; MS (EI) m/e 255.9749 (255.9749 calcd for $C_{10}H_9I$, 21), 129 (100).

(*E*)-1-Iodo-4-phenyl-3-butene (14). To a solution of 4-phenyl-3-butyn-1-ol (2.00 g, 13.7 mmol) in THF (30 mL) was added lithium aluminum hydride (0.78 g, 20.5 mmol). The resulting mixture was maintained at reflux for 24 h and then allowed to cool to room temperature. The reaction was quenched by the careful addition of 1 N HCl (50 mL), and the resulting mixture was extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated to give 2.00 g of the desired trans homoallylic alcohol as an essentially pure clear oil: ^{1}H NMR (250 MHz, $CDCl_3$) 7.40–7.10 (m, ArH), 6.44 (d, J = 15.9 Hz, =CH), 5.15 (dt, J = 15.8, 7.0 Hz, =CH), 3.70 (t, J = 6.3 Hz, CH_2OH), 2.42 (m, =CHCH_2), 1.50 (br s, OH); IR (film) 3403, 2932, 1493, 743 cm^{-1}.

The crude trans homoallylic alcohol was taken up in $CHCl_3$ (10 mL) and treated sequentially with pyridine (2.6 mL, 32.7 mmol) and *p*-toluenesulfonyl chloride (3.11 g, 16.3 mmol). After 8 h at room temperature, the reaction mixture was diluted with Et_2O (100 mL) and washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic extracts were dried ($MgSO_4$) and concentrated. The crude tosylate was taken up in acetone (10 mL) and treated with NaI (4.90 g, 32.7 mmol). The resulting mixture was maintained at reflux for 2 h and then allowed to cool to room temperature. The reaction mixture was diluted with pentane (100 mL) and washed successively with water, 15% aqueous $Na_2S_2O_3$, and brine. The organic material was dried ($MgSO_4$) and concentrated. The crude product was purified by distillation (bp 79–85 °C, 0.1 mmHg), giving 2.24 g (66% overall) of **14** as a pure clear liquid: ^{1}H NMR (250 MHz, $CDCl_3$) 7.40–7.10 (m, ArH), 6.44 (d, J = 15.9 Hz, =CH), 6.15 (dt, J = 15.8, 7.0 Hz, =CH), 3.19 (t, J = 7.2 Hz, CH_2I), 2.74 (ap q, J = 7.1 Hz, =CHCH_2); IR (film) 3026, 1494, 964, 692, 603 cm^{-1}; MS (CI) m/e 259 (MH^+, 13) 131 (100); MS (EI) m/e 257.9904 (257.9899 calcd for $C_{10}H_{11}I$, 10), 131 (100).

(*E*)-1-Iodo-3-pentene (15). To a solution of (*E*)-3-penten-1-ol (3.91 g, 45.5 mmol), pyridine (8.7 mL, 109.0 mmol), and $CHCl_3$ (22 mL) was added *p*-toluenesulfonyl chloride (10.4 g, 54.6 mmol) at room temperature. After 12 h at room temperature, the reaction mixture was diluted with Et_2O (200 mL) and washed sequentially with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic portion was dried ($MgSO_4$) and concentrated. The crude tosylate was taken up in acetone (50 mL) and treated with NaI (13.6 g, 90.9 mmol). The resulting mixture was refluxed for 2 h and then allowed to cool to room temperature. The reaction mixture was diluted with pentane (200 mL) and washed with water, 10% aqueous $Na_2S_2O_3$, and brine. The organic portion was dried ($MgSO_4$), and the pentane was removed by distillation. The crude product was purified by distillation (bp 65–67 °C, 30 mmHg), giving 5.31 g (60%) of **15** as a clear liquid: ^{1}H NMR (250 MHz, $CDCl_3$) 5.50 (m, =CH), 5.30 (m, =CH), 3.02 (t, J = 7.3 Hz, CH_2I), 2.49 (br q, J = 7.3 Hz, =CCH_2), 1.59 (dd, J = 6.2, 1.1 Hz, CH_3); IR (film) 2961, 1448, 1241, 1169, 964 cm^{-1}; MS (CI) m/e 197 (MH^+, 30), 70 (100); MS (EI) m/e 195.9741 (195.9748 calcd for C_5H_9I, 4), 127 (54), 69 (100).

3-(3-Pentynyl)-hexahydro-2*H*-azepin-2-one (20). Representative Procedure for the Preparation of Lactams 16–25. To a solution of diisopropylamine (5.7 mL, 40.8 mmol) and THF (20 mL) was added *n*-BuLi (17.6 mL of a 2.3 M solution in hexanes, 40.8 mmol) at −78 °C. After 15 min, a solution of 1-(trimethylsilyl)hexahydro-2*H*-azepin-2-one (**8**) (7.55 g, 40.8 mmol) and THF (20 mL) was added. This solution was maintained at −78 °C for 15 min and then transferred to a solution of 1-iodo-3-pentyne (**10**)[30] (7.19 g, 37.1 mmol) and THF (40 mL) at −78 °C. This solution was allowed to warm to room temperature where it was diluted with Et_2O (250 mL) and washed with water and brine. The organic material was dried ($MgSO_4$) and concentrated to give the crude product as a pale yellow solid. This material was recrystallized from hexane to give 5.23 g (79%) of **20** as white needles: mp 78–79 °C; ^{1}H NMR (250, MHz $CDCl_3$) 6.05 (br s, NH), 3.40–3.10 (m, NCH_2), 3.60 (m, 1 H), 2.25 (m, 2 H), 2.10–1.90 (m, 2 H), 1.90–1.30 (m, 6 H), 1.79 (t, J = 2.5 Hz, CH_3); IR (film) 3298, 2924, 2665, 2475, 1300 cm^{-1}; MS (CI) m/e 180 (MH^+, 100); MS (EI) m/e 179.1310 (179.1310 calcd for $C_{11}H_{17}NO$, 3) 157 (100). Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.69; H, 9.55; N, 7.86.

((*Z*)-4-Phenyl-3-butynyl)hexahydro-2*H*-azepin-2-one (26). Representative Procedure for the Preparation of Lactams 26–27. To a solution of **23** (0.259 g, 1.07 mmol) and pyridine (5 mL) was added 5% Pd on $BaSO_4$ (0.018 g). This mixture was degassed and stirred under an atmosphere of H_2 (balloon) for 12 h. At this time, the reaction mixture was degassed with Ar, diluted with EtOAc (25 mL), and filtered. The filtrate was washed with water and brine, dried ($MgSO_4$), and concentrated. The crude product was purified on silica gel (1:1 hexane–EtOAc), giving 0.239 g (92%) of **26** as a clear oil. Analysis of the product by capillary GLC indicated that it contained 4% of the trans isomer **24**. Data for **26**: ^{1}H NMR (300 MHz, $CDCl_3$) 7.30–7.10 (m, ArH), 6.43 (d, J = 11.62 Hz, =CH), 5.90 (br s, NH), 5.62 (dt, J = 11.6, 7.3 Hz, =CH), 3.15 (m, NCH_2), 2.50–2.20 (m, 3 H), 2.10–1.80 (m, 2 H), 1.80–1.30 (m, 6 H); IR (film) 3240, 2926, 1663, 1655, 1434, 770 cm^{-1}; MS (CI) m/e 244 (MH^+, 100); MS (EI) m/e 243.1624 (243.1623 calcd for $C_{16}H_{21}NO$, 7), 149 (68), 113 (100).

3-Methyl-3-(5-phenyl-4-pentynyl)-2-piperidinone (28). To a solution of diisopropylamine (0.304 g, 3.01 mmol) in THF (2.5 mL) was added *n*-BuLi (1.3 mL of a 2.3 M solution in hexanes, 3.0 mmol) at −78 °C. After 15 min, a solution of 1-(trimethylsilyl)-2-piperidinone (**7**) (0.515 g, 3.01 mmol) in THF (2.5 mL) was added dropwise at −78 °C. After 30 min, this solution was transferred (cannula) to a −78 °C solution of **9**[31] (0.736 g, 2.74 mmol) in THF (2.5 mL). After 30 min, a solution of LDA [prepared in a separate flask from *n*-BuLi (2.4 mL of a 2.3 M solution in hexanes, 5.5 mmol) and diisopropylamine (0.554 g, 5.47 mmol)] in THF (5 mL) was added. The resulting solution was maintained at −78 °C for 30 min, and then MeI (1.94 g, 13.7 mmol) was added. The resulting solution was allowed to warm to room temperature, whereupon it was diluted with Et_2O (40 mL) and washed with water and brine. The organic portion was dried ($MgSO_4$) and concentrated. The crude material was purified on silica gel (1:1 hexane–EtOAc), giving 0.567 g (81%) of **28** as a white solid, which was homogeneous by TLC. An analytical sample was prepared by recrystallization from hexane: mp 103–105 °C; ^{1}H NMR (250 MHz, $CDCl_3$) 7.40–7.20 (m, ArH), 6.55 (br s, NH), 3.25 (m, NCH_2), 2.37 (dt, J = 5.7, 1.6 Hz, $\equiv CH_2$), 1.80–1.50 (m, 8 H), 1.20 (s, CH_3); IR (KBr) 3187, 2931, 1656, 1487, 862, 762, 693 cm^{-1}; MS (CI) m/e 256 (MH^+, 100); MS (EI) m/e 255.1628 (255.1623 calcd for $C_{17}H_{21}NO$, 100), 143 (80), 113 (100), 98 (52). Anal. Calcd for $C_{17}H_{21}NO$: C, 79.79; H, 8.33; N, 5.43. Found: C, 79.96; H, 8.29; N, 5.49.

3-(3-Pentynyl)-1-(trimethylsilyl)-2-piperidinone (29). To a suspension of **18** (0.67 g, 4.03 mmol) in a solution of pentane (10 mL) and Et_3N (5 mL) was added TMSCl (1.00 mL, 8.05 mmol). The resulting mixture was stirred at room temperature for 4 h, at which time it was diluted with pentane (100 mL) and filtered through a pad of Celite. The filtrate was concentrated, and the residue was distilled (bulb-to-bulb, oven temperature 130 °C/0.1 mm) to give 0.79 g (83%) of **29** as a clear liquid: ^{1}H NMR (250 MHz, $CDCl_3$) 3.30–3.05 (m, NCH_2), 2.43–1.91 (m, 5 H), 1.81–1.35 (m, 4 H), 1.75 (t, J = 2.3 Hz, CH_3), 0.24 (s, TMS); IR (film) 2947, 1683, 1663, 1625, 1418, 1302, 845 cm^{-1}; MS (CI) m/e 238.1615 (238.1623 calcd for $C_{13}H_{24}NOSi$, 3, MH − $(CH_3)_2SiCH_2$), 100 (100); MS (EI) m/e 165 (10), 99 (100).

3-(3-Pentynyl)-1-(trimethylsilyl)hexahydro-2*H*-azepin-

(30) Answll, M. F.; Emmett, J. C.; Coombs, R. V. *J. Chem. Soc. C* **1968**, *3*, 217.

(31) McCann, S. F.; Ph.D. Dissertation, University of California, Irvine, 1987.

2-one (30). To a suspension of **20** (1.0 g, 5.6 mmol) in a solution of pentane (5 mL) and Et_3N (5.5 mL) was added TMSCl (1.40 mL, 11.1 mmol). The resulting mixture was stirred at room temperature for 12 h. At this time, the mixture was diluted with pentane (30 mL) and filtered through a pad of Celite. The filtrate was concentrated, yielding an oil, which was distilled (bulb-to-bulb, oven temperature 160 °C, 0.1 mmHg) to give 1.2 g (84%) of **30** as a clear liquid: ^{1}H NMR (300 MHz, $CDCl_3$) 3.40–3.15 (m, NCH_2), 2.75 (m, CHCO), 2.20 (m, 2 H), 2.10–1.50 (m, 5 H), 1.77 (t, J = 2.5 Hz, CH_3), 1.50–1.20 (m, 3 H), 0.24 (s, TMS); IR (film) 2978, 1717, 1456, 1368, 1152 cm^{-1}; MS (CI) m/e 180 (MH – $(CH_3)_2SiCH_2$), MS (EI) m/e 179.1304 (179.1310 calcd for $C_{11}H_{17}NO$, 5.3), 113 (100).

3-Ethyl-3-(3-pentynyl)-2-piperidinone (31). To a solution of diisopropylamine (0.70 mL, 5.0 mmol) in THF (5 mL) was added *n*-BuLi (2.4 mL of a 2.1 M solution in hexanes, 5.0 mmol) at –78 °C. After 15 min, a solution of **29** (0.79 g, 3.33 mmol) in THF (5 mL) was added, and the resulting solution was allowed to warm to –23 °C. After 15 min, the solution was recooled to –78 °C, and EtI (0.53 mL, 6.60 mmol) was added in one portion. The resulting mixture was allowed to warm to room temperature, whereupon it was diluted with Et_2O (40 mL) and washed with water and brine. The organic portion was dried ($MgSO_4$) and concentrated. The crude product was purified on silica gel (1:1 hexane–EtOAc), giving 0.622 g (97%) of **31** as a pure clear oil: ^{1}H NMR (250 MHz, $CDCl_3$) 6.02 (br s, NH), 3.25 (m, NCH_2), 2.18 (m, $\equiv CH_2$), 1.94–1.45 (m, 8 H), 1.74 (t, J = 2.5 Hz, CH_3), 0.87 (t, J = 7.4 Hz, CH_2CH_3); IR (film) 3289, 2945, 1655, 1489, 1447, 841 cm^{-1}; MS (CI) m/e 194.1542 (194.1545 calcd for $C_{12}H_{20}NO$, 100).

3-Methyl-3-(3-pentynyl)hexahydro-2*H*-azepin-2-one (32). To a solution of diisopropylamine (0.11 mL, 0.79 mmol) in THF (3 mL) was added *n*-BuLi (0.38 mL of a 2.1 M solution in hexanes, 0.79 mmol) at –78 °C. After 15 min, a solution of **30** (0.10 g, 0.04 mmol) in THF (3 mL) was added dropwise. This solution was allowed to warm to –23 °C and maintained at this temperature for 0.5 h. At this time MeI (0.10 mL, 1.60 mmol) was added in one portion. The resulting solution was allowed to warm to room temperature, where it was diluted with Et_2O (30 mL) and washed with water and brine. The organic phase was dried (K_2CO_3) and concentrated. The crude material was purified on silica gel (1:1 hexane–EtOAc) to give 0.047 g (66%) of **32** as a white solid. An analytical sample was prepared by recrystallization from hexane: mp 88.5–90.5 °C; ^{1}H NMR (250 MHz, $CDCl_3$) 6.04 (br s, NH), 3.30–3.10 (m, NCH_2), 2.30–1.40 (m, 10 H), 1.76 (t, J = 2.4 Hz, $\equiv CCH_3$), 1.16 (s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) 180.12, 79.27, 75.51, 44.91, 42.52, 36.85, 35.52, 29.31, 24.68, 24.31, 14.12, 3.52 ppm; IR (film) 3282, 2920, 1648, 1460, 1360, 703 cm^{-1}; MS (CI) m/e 194.1538 (194.1545 calcd for $C_{12}H_{20}NO$, 100).

1-(*tert*-Butoxycarbonyl)-3-(3-pentynyl)hexahydro-2*H*-azepin-2-one (38). Representative Procedure for the Preparation of Imides 33–47. To a solution of diisopropylamine (0.19 mL, 1.33 mmol) and THF (3 mL) was added *n*-BuLi (0.58 mL of a 2.3 M solution in hexanes, 1.33 mmol) at –78 °C. After 15 min, a solution of **20** (0.20 g, 1.11 mmol) and THF (3 mL) was added. The resulting solution was maintained at –78 °C for 15 min, at which time di-*tert*-butyl dicarbonate (0.30 mL, 1.33 mmol) was added in one portion. The resulting mixture was allowed to warm to room temperature, where it was diluted with Et_2O (25 mL) and washed with water and brine. The organic portion was dried (K_2CO_3) and concentrated. The crude product was purified on silica gel (5:1 hexane–EtOAc) to give 0.31 g (89%) of **38** as a white solid. An analytical sample was obtained by recrystallization from hexane: mp 64–65 °C; ^{1}H NMR (250 MHz, $CDCl_3$) 4.19 (m, NC*H*H), 3.40 (dd, J = 15.1, 10.6 Hz, NCH*H*), 2.85 (m, 1 H), 2.30–2.00 (m, 3 H), 2.00–1.40 (m, 7 H), 1.77 (t, J = 2.4 Hz, CH_3), 1.52 (s, Bu^t); IR (film) 2980, 1769, 1718, 1456, 1389 cm^{-1}; MS (CI) m/e 280.1891 (280.1913 calcd for $C_{16}H_{26}NO_3$, 3), 224 (100). Anal. Calcd for $C_{16}H_{26}NO_3$: C, 68.79; H, 8.95; N, 5.00. Found: C, 68.79; H, 9.01; N, 5.04.

1-(*tert*-Butoxycarbonyl)-2-ethoxy-3-(3-pentynyl)hexahydro-1*H*-azepine (52). Representative Procedures for the Preparation of α-Ethoxy Carbamates 48–61. To a solution of **38** (0.31 g, 1.10 mmol) and THF (5 mL) was added lithium triethylborohydride (4.4 mL of a 1.0 M solution in THF, 4.4 mmol) in one portion at –78 °C. This solution was maintained at –78 °C for 15 min and then quenched with HCl (10.0 mL of a 1.82 M solution in absolute EtOH, 18.2 mmol) and allowed to warm to room temperature. The reaction mixture was diluted with Et_2O (100 mL) and washed with water and brine. The organic material was dried (K_2CO_3) and concentrated. The crude material was purified on silica gel (7:1:0.1 hexane–EtOAc–Et_3N), giving 0.33 g (98%) of **52** as a pure clear oil. Analysis of the product by ^{1}H NMR revealed that it was composed of a 2:1 mixture of ethoxy epimers. Characteristic data for the product mixture: ^{1}H NMR (250 MHz, $CDCl_3$) 5.06 (d, J = 8.1 Hz, CHOEt major), 4.90 (d, J = 7.6 Hz, CHOEt minor), 3.71–3.30 (m, 3 H), 2.91 (m, 1 H), 2.30–2.10 (m, 2 H), 1.90–1.70 (m, 4 H), 1.65–1.20 (m, 6 H), 1.48 (s, Bu^t minor), 1.47 (s, Bu^t major), 1.67 (t, J = 7.0 Hz, CH_2CH_3); IR (film) 2974, 1697, 1454, 1387, 1156, 1079 cm^{-1}; MS (CI) m/e 310.2379 (310.2382 calcd for $C_{18}H_{32}NO_3$, 0.5), 248 (75), 208 (100); MS (EI) m/e 309 (1), 208 (25), 57 (100).

1-(*tert*-Butoxycarbonyl)-2-methoxy-3-(5-phenyl-4-pentynyl)piperidine (62). Sodium borohydride (0.09 g, 2.5 mmol) was added to a solution of **34** (0.210 g, 0.620 mmol) and MeOH (5 mL) at room temperature. After 15 min, H_2O (50 mL) was added, and the resulting mixture was extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and concentrated. The crude material was taken up in MeI (5 mL), and the resulting solution was added dropwise to a suspension of KH (0.1 g of a 50% dispersion in mineral oil, ~1.2 mmol) in THF (5 mL). After the reaction was judged complete (TLC), absolute MeOH (3 mL) was carefully added. This mixture was diluted with Et_2O (50 mL) and washed with water and brine. The organic portion was dried (K_2CO_3) and concentrated. The crude material was purified on silica gel (5:1 hexane–EtOAc) to give 0.153 g (69%) of **62** as a clear oil. Analysis of the product by ^{1}H NMR revealed that it was composed of a 2.3:1 mixture of ethoxy epimers. Characteristic data for the product mixture: ^{1}H NMR (250 MHz, $CDCl_3$) 7.40–7.20 (m, ArH), 5.28 (s, CHOMe major), 5.10 (s, CHOMe minor), 4.01–3.80 (m, NCH_2), 2.45 (m, 2 H), 2.00–1.30 (m, 9 H), 1.48 (s, Bu^t major), 1.46 (s, Bu^t minor); IR (film) 2938, 1696, 1411, 1319, 1152, 756 cm^{-1}; MS (CI) m/e 270 (MH – MeOH – isobutylene, 100); MS (EI) m/e 301.1671 (301.1678 calcd for $C_{18}H_{23}NO_2$, 3), 269 (100).

(9a*R,9b*S**)-5a-Aza-2,5,6,7,8,9,9a,9b-octahydro-5-oxo-4-oxa-3-(trimethylsilyl)-1*H*-benz[*cd*]azulene (67) and (9a*R**,9b*R**)-5a-Aza-2,5,6,7,8,9,9a,9b-octahydro-5-oxo-4-oxa-3-(trimethylsilyl)-1*H*-benz[*cd*]azulene (68). Representative Procedure for the Preparation of Cycloadducts 65–83.** Tin tetrachloride (0.16 mL of a 1.03 M solution in CH_2Cl_2, 0.16 mmol) was added to a solution of **53** (0.050 g, 0.136 mmol) in CH_2Cl_2 (2 mL) at –23 °C. This solution was maintained at –23 °C for 1.5 h, and then Et_3N (0.12 mL, 0.82 mmol) was added. The resulting solution was diluted with Et_2O (25 mL) and washed with 15% aqueous NaOH, water, and brine. The organic phase was dried (K_2CO_3) and concentrated, giving (0.032 g of a clear oil. Analysis of the crude material by capillary GLC revealed a 1.75:1 (**67**:**68**) mixture of products whose combined purity was >90%. The two isomers could be separated on silica gel (8:1:01 hexane–EtOAc–Et_3N), giving pure samples of each isomer. **67**: ^{1}H NMR (500 MHz, C_6D_6) 4.51 (dd, J = 14.2, 6.7 Hz, NCH*H*), 3.25 (d, J = 10.2 Hz, CHN), 2.77 (dd, J = 14.1, 11.2 Hz, NC*H*H), 2.00 (m, 2 H), 1.45–1.25 (m, 5 H), 1.00 (m, 1 H), 0.90–0.70 (m, 2 H), 0.55 (m, 1 H), 0.12 (s, TMS); ^{13}C NMR (125 MHz, C_6D_6) 152.1, 148.9, 132.3, 63.8, 47.3, 44.0, 34.0, 31.4, 29.0, 25.5, 24.4, –2.5 ppm. **68**: ^{1}H NMR (500 MHz, C_6D_6) 4.41 (m, NCH*H*), 3.81 (dt, J = 6.8, 2.1 Hz, CHN), 2.20 (m, 2 H), 2.10 (ddt, J = 16.9, 9.9, 2.1 Hz, NC*H*H), 1.65–1.30 (m, 6 H), 1.15 (m, 1 H), 0.95 (m, 2 H), 0.21 (s, TMS); ^{13}C NMR (125 MHz, C_6D_6) 151.7, 150.5, 129.2, 62.9, 46.5, 44.9, 31.5, 30.13, 29.5, 29.4, 24.2, –2.4 ppm. Characteristic data for the product mixture: IR (film) 2928, 1708, 1646, 1249, 1079, 844 cm^{-1}; MS (CI) m/e 266.1549 (266.1576 calcd for $C_{14}H_{24}NO_2Si$, 100); MS (EI) m/e 265.1457 (265.1498 calcd for $C_{14}H_{23}NO_2Si$, 80), 263 (100).

^{1}H NOE Experiment for 67. Irradiation of the bridgehead methine hydrogen at δ 3.25 gave a 1.3% enhancement of the bridgehead methine hydrogen at δ 1.32.

^{1}H NOE Experiment for 68. Irradiation of the bridgehead methine hydrogen at δ 3.81 gave a 9.5% enhancement of the bridgehead methine hydrogen at δ 1.60.

(9a*R,9b*S**)-5a-Aza-2,5,6,7,8,9,9a,9b-octahydro-3-methyl-5-oxo-4-oxa-1*H*-benz[*cd*]azulene (65) and (9a*R**,9b*R**)-5a-**

Aza-2,5,6,7,8,9,9a,9b-octahydro-3-methyl-5-oxo-4-oxa-1*H*-benz[*cd*]azulene (66). Via the procedure employed for the cycloaddition of **53**, **52** (0.148 g, 0.479 mmol) was allowed to react with $SnCl_4$ (0.56 mL of a 1.03 M solution in CH_2Cl_2, 0.57 mmol) for 2 h, to give after quenching with Et_3N (0.40 mL, 2.87 mmol) and basic workup, 0.090 g (90%) of a white solid. Analysis of the crude material by capillary GLC revealed a 2.2:1 (**65**:**66**) mixture of products whose combined purity was >96%. The major isomer **65** could be isolated by fractional recrystallization from hexane/Et_2O at −30 °C (mp 99–103 °C), while the minor isomer **66** could only be obtained in enriched form (ca. 70%). Once pure, the major isomer **65** was stable at room temperature while the minor isomer **66** decomposed even at −20 °C. **65**: ^1H NMR (500 MHz, C_6D_6) 4.73 (dd, J = 13.9, 6.5 Hz, NCH*H*), 3.28 (dq, J = 9.7, 2.0 Hz, CHN), 2.97 (app t, J = 13.6 Hz, NC*H*H), 1.90–1.75 (m, 2 H), 1.51 (dd, J = 3.4, 1.6 Hz, CH_3), 1.50–1.25 (m, 5 H), 1.10 (m, 1 H), 0.86 (m, 2 H), 0.60 (m, 1 H); ^{13}C NMR (125 MHz, C_6D_6) 152.5, 140.8, 114.9, 64.05, 49.2, 46.5, 35.1, 31.6, 30.0, 26.4, 24.2, 16.2 ppm. Characteristic data for **66**: ^1H NMR (500 MHz C_6D_6) 4.25–4.19 (m, NCH*H*), 3.62 (dq, J = 6.5, 2.0 Hz, CHN), 2.11 (tq, J = 11.7, 1.7 Hz, NC*H*H). Characteristic data for the product mixture: IR (film) 2934, 1704, 1702, 1458, 1403, 1206 cm^{-1}; MS (CI) m/e 208 (MH^+, 100); MS (EI) m/e 207.1260 (207.1259 calcd for $C_{12}H_{17}NO_2$, 31), 137 (100).

^1H NOE Experiments for 65. Irradiation of the bridgehead methine hydrogen at δ 3.28 gave a 1.8% enhancement of the bridgehead methine hydrogen at δ 1.30. Irradiation of the bridgehead methine hydrogen at δ 1.30 gave a 0.6% enhancement at δ 3.28.

^1H NOE Experiments for 66. Irradiation of the bridgehead methine hydrogen at δ 3.62 gave a 13% enhancement of the bridgehead methine hydrogen at δ 1.50. Irradiation of the bridgehead methine hydrogen at δ 1.50 gave a 7% enhancement of the bridgehead methine hydrogen at δ 3.62.

(9a*R,9b*S**)-5a-Aza-2,5,6,7,8,9,9a,9b-octahydro-5-oxo-4-oxa-3-((trimethylsilyl)methyl)-1*H*-benz[*cd*]azulene (69) and (9a*R**,9b*R**)-5a-Aza-2,5,6,7,8,9,9a,9b-octahydro-5-oxo-4-oxa-3-((trimethylsilyl)methyl)-1*H*-benz[*cd*]azulene (70).** Via the procedure employed for the cycloaddition of **53**, **54** (0.041 g, 0.108 mmol) was allowed to react with $SnCl_4$ (0.13 mL of a 1.03 M solution in CH_2Cl_2, 0.19 mmol) for 1 h to give after quenching with Et_3N (0.09 mL, 0.07 mmol) and basic workup, 0.025 g of a clear oil. Analysis of the crude material by capillary GLC revealed a 30:1 (**69**:**70**) mixture of products whose combined purity was >95%. Characteristic data for the product mixture: ^1H NMR (500 MHz, C_6D_6) 4.35 (app dd, J = 14.0, 6.7 Hz, NCH*H* major), 4.24 (m, NCH*H* minor), 3.71 (br d, J = 6.9 Hz, CHN minor), 3.32 (dt, J = 9.55, 1.5 Hz, CHN major), 2.93 (ddd, J = 14.0, 11.6, 1.1 Hz, NC*H*H), 1.90 (m, 2 H), 1.50–1.20 (m, 9 H), 1.05 (m, 1 H), 0.95–0.75 (m, 2 H), 0.60 (m, 1 H); ^{13}C NMR (125 MHz, C_6D_6) 151.6, 142.8, 111.1, 63.1, 48.2, 45.8, 34.2, 30.8, 29.0, 25.5, 23.8, 20.3, −1.4 ppm; IR (film) 2950, 1717, 1398, 1205, 1179, 950 cm^{-1}; MS (CI) m/e 280 (MH^+, 100); MS (EI) m/e 279.1650 (279.1654 calcd for $C_{15}H_{25}NO_2$, 17), 151 (100).

(9a*R,9b*S**)-5a-Aza-2,5,6,7,8,9,9a,9b-octahydro-5-oxo-4-oxa-3-phenyl-1*H*-benz[*cd*]azulene (71).** Via the procedure employed for the cycloaddition of **53**, **55** (0.050 g, 0.135 mmol) was allowed to react with $SnCl_4$ (0.16 mL of a 1.0 M solution in CH_2Cl_2, 0.16 mmol) for 5 min, to give after quenching with Et_3N (0.12 mL, 0.81 mmol) and basic workup, 0.029 g (80%) of **71** as an essentially pure white solid: mp 180–181 °C dec; ^1H NMR (500 MHz, $CDCl_3$) 7.60–7.30 (m, ArH), 4.44 (ddt, J = 1.4, 6.6, 14.2 Hz, NCH*H*), 4.12 (br d, J = 10 Hz, NCH), 3.25 (dd, J = 11.0, 14.0 Hz, NC*H*H), 2.80 (m, =C*H*H), 2.65 (m, =CH*H*), 2.00 (m, 5 H) 1.80–1.20 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) 152.5, 141.0, 132.6, 128.3, 128.2, 126.5, 117.7, 65.0, 48.2, 45.0, 34.5, 31.5, 29.2, 26.2, 26.0 ppm; IR (KBr) 1698, 1445, 1231, 1102, 1075, 697 cm^{-1}; MS (CI) m/e 270 (100, MH^+); MS (EI) m/e 269.1387 (269.1416 calcd for $C_{17}H_{19}NO_2$, 7) 224 (76), 213 (65), 105 (100).

(9a*R,9b*R**)-5a-Aza-2,4,5,6,7,8,9,9b-octahydro-3,9a-dimethyl-5-oxo-4-oxa-1*H*-benz[*cd*]azulene (72).** Via the procedure employed for the cycloaddition of **53**, **60** (0.050 g, 0.155 mmol) was allowed to react with $SnCl_4$ (0.18 mL of a 1.03 M solution in CH_2Cl_2, 0.19 mmol) for 1 h, to give after quenching with Et_3N (0.22 mL, 1.55 mmol) and basic workup, 0.023 g (69%) of **72** as a clear oil. Analysis of the crude product by capillary GLC indicated that its purity was >99%: ^1H NMR (500 MHz, C_6D_6) 4.33 (dddd, J = 14.1, 4.15, 2.5, 1.4 Hz, NCH*H*), 3.12 (q, J = 1.9 Hz, CHN), 2.16 (ddd, J = 14.0, 11.9, 1.9 Hz, NC*H*H), 1.8 (m, 1 H), 1.65 (m, 1 H), 1.48 (br s, =CMe), 1.40–1.30 (m, 3 H), 1.20–1.10 (m, 3 H), 1.00 (m, 1 H), 0.85 (m, 1 H), 0.68 (s, Me); ^{13}C NMR (125, MHz C_6D_6) 151.1, 139.9, 113.2, 67.3, 46.2, 45.1, 42.4, 36.1, 29.6, 26.5, 23.1, 23.0, 15.2 ppm; IR (film) 2973, 1714, 1441, 1386, 1198, 1161 cm^{-1}; MS (CI) m/e 222 (MH^+, 100); MS (EI) m/e 221.1410 (221.1416 calcd for $C_{13}H_{19}NO_2$, 81), 193 (100).

^1H NOE Experiments for 72. Irradiation of the bridgehead methine hydrogen at δ 3.12 gave an 8% enhancement of the hydrogens assigned to the methyl group (δ 0.68). Irradiation of the hydrogens of the bridgehead methyl group at δ 0.68 gave a 5% enhancement of the bridgehead methine hydrogen at δ 3.12.

(10a*R,10b*S**)-6a-Aza-1,2,3,6,7,8,9,10,10a,10b-decahydro-6-oxo-5-oxa-4-phenylcyclohepta[*de*]naphthalene (73).** Via the procedure employed for the cycloaddition of **53**, **51** (0.028 g, 0.073 mmol) was allowed to react with $SnCl_4$ (0.087 mL of a 1 M solution in CH_2Cl_2, 0.087 mmol) for 5 min to give after quenching with Et_3N (0.07 mL, 0.44 mmol) and basic workup, 0.018 g (85%) of **73** as an essentially pure clear oil: ^1H NMR (500 MHz, $CDCl_3$) 7.50–7.20 (m, ArH), 4.30 (dd, J = 7.1, 14.2 Hz, NCH*H*), 3.36 (d, J = 10.3 Hz, NCH), 2.88 (ddd, J = 5.4, 12.6, 14.1 Hz, NC*H*H), 2.63 (m, =C*H*H), 2.20 (m, =CH*H*), 2.00–1.80 (m, 4 H), 1.70–1.50 (m, 4 H), 1.5–1.2 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) 150.0, 140.7, 132.5, 128.6, 128.5, 128.0, 112.6, 67.8, 51.4, 47.9, 33.3, 32.0, 28.0, 27.3, 24.4, 24.0 ppm; IR (film) 2927, 1718, 1686, 1459, 1250, 1117, 1074 cm^{-1}; MS (CI) m/e 284 (100, MH^+); MS (EI) m/e 283.1570 (283.1582 calcd for $C_{18}H_{21}NO_2$, 84), 199 (100).

(10a*R,10b*S**)-6a-Aza-1,2,3,6,7,8,9,10,10a,10b-decahydro-6-oxo-5-oxa-4-phenylcyclohepta[*de*]naphthalene (73) and (5a*R**,9a*S**)-9-((*Z*)-Chlorophenylmethylidene)-2,3,4,5,5a,6,7,8,9,9a-decahydro-1-(methoxycarbonyl)-1*H*-1-benzazepine (74).** Via the procedure employed for the cycloaddition of **53**, **61** (0.142 g, 0.413 mmol) was allowed to react with $SnCl_4$ (0.48 mL of a 1.03 M solution in CH_2Cl_2, 0.48 mmol) for 1 h, to give after quenching with Et_3N (0.35 mL, 2.48 mmol) and basic workup, 0.118 g of a clear oil. Analysis of the crude material by capillary GLC revealed that it was composed of **61**, **73**, and **74** in a 1.5:2:1 ratio, respectively. The product mixture was separated on silica gel (7:1:01 hexane–EtOAc–Et_3N), giving 0.034 g of recovered **61**, 0.024 g of **74** (23% based on consumed **61**), and 0.058 g of **73** (65% based on consumed **105**). **74**: ^1H NMR (500 MHz, $CDCl_3$) 4.25 (d, J = 11.0 Hz, 0.67 H, CHN), 4.07 (d, J = 11.0 Hz, 0.33 H, CNH), 3.70 (s, 1 H, OMe), 3.54 (s, 2 H, OMe), 3.30 (br d, J = 14.1 Hz, NCH*H*), 2.20–1.80 (m, 5 H), 1.70–1.10 (m, 9 H); IR (film) 2926, 1698, 1470, 1437, 1198, 757 cm^{-1}; MS (CI) m/e 334.1573 (334,1597 calcd for $C_{19}H_{25}NO_2Cl$, 50), 298 (100).

(9a*R,3*S**,2a*S**,9b*S**)-5a-Aza-2,2a,3,5,6,7,8,9,9a,9b-decahydro-5-oxo-4-oxa-3-phenyl-1*H*-benz[*cd*]azulene (75).** Via the procedure employed for the cycloaddition of **53**, **56** (0.072 g, 0.193 mmol) was allowed to react with $SnCl_4$ (0.23 mL of a 1.03 M solution in CH_2Cl_2, 0.23 mmol) for 1 h, to give after quenching with Et_3N (0.16 mL, 1.16 mmol), basic workup, and purification on silica gel (1:1 hexane–EtOAc), 0.042 g (80%) of **75** as a white powder: mp 151.5–153.5 °C; ^1H NMR (500 MHz, $CDCl_3$) 7.40–7.20 (m, ArH), 5.06 (d, J = 10.6 Hz, CHO), 4.46 (dd, J = 13.7, 6.5 Hz, NCH*H*), 3.23 (t, J = 10.4 Hz, CHN), 3.12 (dd, J = 13.7, 11.6 Hz, NC*H*H), 2.50 (m, C*H*CHO), 2.05 (m, 1 H), 2.00–1.90 (m, 4 H), 1.60–1.40 (m, 4 H), 1.40–1.20 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) 154.0, 138.8, 128.5, 128.4, 126.0, 84.8, 66.6, 49.5, 48.6, 42.6, 36.7, 30.1, 29.9, 27.3, 23.7 ppm; IR (KBr) 2928, 1686, 1411, 1282, 1256, 1151, 766 cm^{-1}; MS (CI) m/e 272 (MH^+, 100); MS (EI) m/e 271.1592 (271.1572 calcd for $C_{17}H_{21}NO_2$, 10), 227 (100).

^1H NOE Experiments for 75. Irradiation of the bridgehead methine hydrogen at δ 3.23 gave 12% enhancement of the methine hydrogen α to the phenyl group (δ 5.06). Irradiation of the methine hydrogen α to the phenyl group at δ 5.06 gave an 11% enhancement of the bridgehead methine hydrogen at δ 3.22 and a 21% enhancement of the hydrogens of the phenyl group (δ ~7.3). Irradiation of the bridgehead methine hydrogen at δ 2.15 gave an 8.8% enhancement of the hydrogens on the phenyl group (δ ~7.3).

(3*R,2a*S**,9b*S**,9a*S**)-5a-Aza-2,2a,3,5,6,7,8,9,9a,9b-decahydro-3-methyl-5-oxo-4-oxa-1*H*-benz[*cd*]azulene (76).** Via the procedure employed for the cycloaddition of **53**, **57** (0.126 g,

0.404 mmol) was allowed to react with $SnCl_4$ (0.47 mL of a 1.03 M solution in CH_2Cl_2, 0.48 mmol) for 8 h to give after quenching with Et_3N (0.34 mL, 2.43 mmol), basic workup, and purification on silica gel (1:1 hexane–EtOAc) 0.065 g (78%) of **76** as a white powder: mp 102.5–104.5 °C; ^1H NMR (500 MHz, $CDCl_3$) 4.39 (ap dd, J = 12.6, 6.9 Hz, NCH*H*), 4.21 (dq, J = 6.6, 10.4 Hz, CHO), 3.05 (dd, J = 11.0, 4.7 Hz, NC*H*H), 3.02 (t, J = 10.4 Hz, CHN), 2.15 (m, 1 H), 2.00–1.70 (m, 6 H), 1.60–1.10 (m, 5 H), 1.28 (d, J = 6.2 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) 154.1, 79.5, 66.4, 49.0, 48.5, 42.5, 36.6, 30.3, 29.9, 27.2, 23.3, 20.5 ppm; IR (film) 2968, 1684, 1472, 1397, 1258, 1073 cm^{-1}; MS (CI) m/e 210 (MH^+, 100); MS (EI) m/e 209.1399 (209.1416 calcd for $C_{12}H_{19}NO_2$, 100).

(3*R,2a*S**,9a*S**,9b*S**)-5a-Aza-2,2a,3,5,6,7,8,9,9a,9b-decahydro-5-oxo-4-oxa-3-phenyl-1*H*-benz[*cd*]azulene (77).** Via the procedure employed for the cycloaddition of **53**, a 24:1 mixture of **58** and **56** (0.020 g, 0.054 mmol) was allowed to react with $SnCl_4$ (0.063 mL of a 1.03 M solution in CH_2Cl_2, 0.054 mmol) for 1 h to give after quenching with Et_3N (0.05 mL, 0.32 mmol) and basic workup a 24:1 (by capillary GLC) mixture of **77** and **75**. The crude product was separated on silica gel (1:1 hexane–EtOAc), giving 0.011 g (76%) of **77** as a clear oil, which was homogeneous by TLC: ^1H NMR (500 MHz, $CDCl_3$) 7.40–7.20 (m, ArH), 5.51 (d, J = 5.67 Hz, CHO), 4.48 (dd, J = 14.0, 7.3 Hz, NCH*H*), 3.16 (dd, J = 13.1, 11.42 Hz, NC*H*H), 2.91 (t, J = 10.9 Hz, CHN), 2.53 (m, C*H*CHO), 2.10 (m, 1 H), 2.00–1.80 (m, 4 H), 1.80–1.70 (m, 1 H), 1.55–1.45 (m, 1 H), 1.35–1.25 (m, 1 H), 1.20–1.15 (m, 1 H), 1.10–1.00 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) 153.8, 137.0, 128.2, 128.0, 126.4, 80.8, 60.2, 49.1, 45.8, 42.2, 36.3, 30.0, 29.8, 27.0, 22.8 ppm; IR (film) 2921, 1690, 1409, 1373, 1150, 702 cm^{-1}; MS (CI) m/e 272 (MH^+, 100); MS (EI) m/e 271.1568 (271.1572 calcd for $C_{17}H_{21}NO_2$, 4), 227 (100).

^1H NOE Experiments for 77. Irradiation of the methine hydrogen α to the O, at δ 2.91 gave an 11% enhancement of the hydrogens on the phenyl group (δ ~7.3). Irradiation of the methine hydrogen at δ 2.53 gave a 13% enhancement of the methine hydrogen α to the phenyl group at δ 5.51. Irradiation of the bridgehead methine hydrogen at δ 5.51 gave a 12% enhancement of the bridgehead methine hydrogen at δ 2.53 as well as a 15% enhancement of the hydrogens on the phenyl group (δ ~7.3).

(3*S,2a*S**,9b*S**,9a*S**)-5a-Aza-2,2a,3,5,6,7,8,9,9a,9b-decahydro-3-methyl-5-oxo-4-oxa-1*H*-benz[*cd*]azulene (78).** Via the procedure employed for the cycloaddition of **53**, **59** (0.108 g, 0.347 mmol) was allowed to react with $SnCl_4$ (0.41 mL of a 1.03 M solution in CH_2Cl_2, 0.41 mmol) for 8 h to give after quenching with Et_3N (0.30 mL, 2.0 mmol), basic workup, and purification on silica gel (1:1 hexane–EtOAc) 0.055 g (80%) of **78** as a waxy semisolid, which was homogeneous by TLC: ^1H NMR (500 MHz, $CDCl_3$) 4.62 (dq, J = 7.5, 6.6 Hz, CHO), 4.37 (ddt, J = 14.0, 7.1, 1.3 Hz, NCH*H*), 3.17 (t, J = 10.6 Hz, CHN), 3.08 (dd, J = 14.0, 11.1 Hz, NC*H*H), 2.32 (m, C*H*CHO), 2.15 (m, 1 H), 2.00–1.75 (m, 4 H), 1.75 (m, 1 H), 1.55–1.20 (m, 9 H), 1.29 (d, J = 6.6 Hz, CH_3); ^{13}C NMR (125, MHz $CDCl_3$) 153.9, 75.3, 60.9, 48.8, 45.6, 42.7, 36.5, 30.4, 29.9, 27.0, 22.6, 16.0 ppm; IR (film) 2957, 1733, 1690, 1411, 1122, cm^{-1}; MS (CI) m/e 210 (MH^+, 100); MS (EI) m/e 209.1407 (209.1416 calcd for $C_{12}H_{19}NO_2$, 59), 129 (100).

^1H NOE Experiments for 78. Irradiation of the methine hydrogen α to the methyl group at δ 4.62 gave a 5.5% enhancement of the bridgehead methine hydrogen at δ 2.32. Irradiation of the bridgehead methine hydrogen at δ 2.32 gave a 6.4% enhancement of the methine hydrogen α to the methyl group at δ 4.62. Irradiation of the bridgehead methine hydrogen at δ 3.17 gave a 7% enhancement of the hydrogens of the methyl group.

(9a*R,9b*R**)-6a-Aza-2,3,6,7,8,9,9a,9b-octahydro-5-oxa-6-oxo-4-phenyl-1*H*-phenalene (79) and (9b*R**,9a*S**)-6a-Aza-2,3,6,7,8,9,9a,9b-octahydro-5-oxa-6-oxo-4-phenyl-1*H*-phenalene (80).** Via the procedure employed for the cycloaddition of **53**, **62** (0.047 g, 0.131 mmol) was allowed to react with $SnCl_4$ (0.15 mL of a 1.0 M solution in CH_2Cl_2, 0.15 mmol) for 15 min to give, after quenching with Et_3N (0.11 mL, 0.79 mmol) and basic workup, a 2:1 mixture (^1H NMR) of two isomers (**79** and **80**). This mixture was passed through a small plug of silica gel (3:1 hexane–EtOAc), giving 0.030 g (91%) of material composed of the same ratio of isomers. Preparative HPLC (silica gel, 10:1 hexane–EtOAc) allowed isolation of pure samples of each isomer. **79**: ^1H NMR (500 MHz, $CDCl_3$) 7.48 (d, J = 6.9 Hz, 2 H, ArH), 7.30, 7.00 (m, 3 H, ArH), 4.40–4.35 (m, NCH*H*), 3.53 (d, J = 5.0 Hz, CHN), 2.47 (dt, J = 12.4, 3.8 Hz, NC*H*H), 2.40 (ddd, J = 14.2, 5.9, 5.5 Hz, =CH*H*), 1.63 (m, =C*H*H), 1.41–1.25 (m, 4 H), 1.23–1.15 (m, 2 H), 1.10–1.00 (m, 2 H), 0.90–0.80 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) 153.3, 144.6, 132.4, 128.7, 128.0, 128.0, 110.9, 54.4, 42.6, 32.0, 26.5, 23.8, 21.6, 20.8, 19.7 ppm **80**: ^1H NMR (500 MHz, $CDCl_3$) 7.50–7.30 (m, ArH), 4.54 (app dq, J = 13.3, 2.0 Hz, NCH*H*), 3.55 (d, J = 10.1 Hz, CHN), 2.77 (dt, J = 12.9 3.2 Hz, NC*H*H), 2.69 (app dq, J = 14.1, 2.0 Hz, =CH*H*), 2.00–1.50 (m, 7 H), 1.45–1.35 (m, 1 H), 1.30–1.17 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) 149.0, 140.9, 132.3, 128.7, 128.6, 128.0, 109.4, 62.4, 44.7, 43.3, 31.4, 31.4, 27.4, 25.9, 24.6 ppm. Characteristic data for the product mixture: IR (film) 2934, 1719, 1445, 1262, 1105, cm^{-1}; MS (CI) m/e 2770 (MH^+, 100); MS (EI) m/e 269.1411 (269.1416 calcd for $C_{17}H_{19}NO_2$, 40), 149 (100), 105 (50).

(9a*R,9b*R**)-6a-Aza-2,3,6,7,8,9,9a,9b-octahydro-9a-methyl-5-oxa-6-oxo-4-phenyl-1*H*-phenalene (81).** Via the procedure employed for the cycloaddition of **53**, **63** (0.040 g, 0.103 mmol) was allowed to react with $SnCl_4$ (0.12 mL of a 1.03 M solution in CH_2Cl_2, 0.12 mmol) for 8 h at −78 °C to give, after quenching with Et_3N (0.10 mL, 0.72 mmol), basic workup, and purification on silica gel (3:1:01 hexane–EtOAc–Et_3N), 0.025 g (86%) of **81** as a clear oil: ^1H NMR (500 MHz, $CDCl_3$) 7.50–7.30 (m, ArH), 4.15 (ddd, J = 13.2, 7.8, 5.4 Hz, NCH*H*), 3.80 (s, CHN), 2.99 (ddd, J = 13.3, 7.9, 6.7 Hz, NC*H*H), 2.51 (m, 1 H), 2.19 (m, 1 H), 1.85–1.35 (m, 7 H), 1.17 (m, 1 H), 1.15 (s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) 152.5, 143.8, 132.4, 128.8, 128.7, 127.9, 109.6, 60.2, 42.5, 34.8, 34.6, 26.2, 21.5, 18.2, 17.8 ppm; IR (film) 2936, 1719, 1654, 1415, 1114, 700 cm^{-1}; MS (CI) m/e 284 (MH^+, 100); MS (EI) 283.1571 (283.1572 calcd for $C_{18}H_{21}NO_2$, 30), 105 (100).

^1H NOE Experiments for 81. Irradiation of the bridgehead methine hydrogen at δ 3.80 gave a 10.5% enhancement of the hydrogens assigned to the bridgehead methyl group (δ 1.15). Irradiation of the hydrogens of the bridgehead methyl group at δ 1.15 gave a 6% enhancement of the bridgehead methine hydrogen at δ 3.80.

(8a*R,8b*R**)-5a-Aza-8a-ethyl-1,2,5,6,7,8,8a,8b-octahydro-3-methyl-4-oxa-5-oxoacenaphthylene (82).** Via the procedure employed for the cycloaddition of **53**, **64** (0.056 g, 0.172 mmol) was allowed to react with $SnCl_4$ (0.21 mL of a 1.03 M solution in CH_2Cl_2, 0.21 mmol) for 2 h to give, after quenching with Et_3N (0.15 mL, 1.03 mmol) and basic workup, 0.034 g (90%) of **82** as a clear oil. Analysis of the crude product by capillary GLC indicated that its purity was >96%: ^1H NMR (500 MHz, $CDCl_3$) 3.99 (ddd, J = 13.3, 7.9, 3.7 Hz, NCH*H*), 3.52 (s, NCH), 2.85 (ddd, J = 13.4, 9.0, 6.3 Hz, NC*H*H), 2.31–2.18 (m, 2 H), 1.84 (t, J = 1.6 Hz, =CCH_3), 1.82–1.74 (m, 1 H), 1.71–1.63 (m, 1 H), 1.59–1.51 (m, 2 H), 1.48–1.29 (m, 4 H), 0.87 (t, J = 7.4 Hz, CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) 153.3, 142.3, 116.7, 61.7, 43.4, 39.9, 35.6, 31.2, 28.2, 24.5, 18.7, 15.9, 8.7 ppm; IR (film) 2924, 2847, 1716, 1376, 1279, 1172 cm^{-1}; MS (CI) m/e 222 (MH^+, 100); MS (EI) m/e 221.1412 (221.1416 calcd for $C_{13}H_{19}NO_2$, 17), 192 (65), 137 (100).

^1H NOE Experiments for 82. Irradiation of the bridgehead methine hydrogen at δ 3.52 gave an 11.2% and 4.4% enhancement of the methylene (δ ~1.3) and methyl hydrogens (δ 0.87) of the bridgehead ethyl group, respectively.

(2b*R,2a*S**)-8a-Aza-1,2,2a,2b,3,4,5,8-octahydro-7-oxa-8-oxo-6-phenylacenaphthylene (83).** Via the procedure employed for the cycloaddition of **53**, **48** (0.052 g, 0.144 mmol) was allowed to react with $SnCl_4$ (0.17 mL of a 1.03 M solution in CH_2Cl_2, 0.17 mmol) for 1.5 h to give, after quenching with Et_3N (0.10 mL, 0.72 mmol) and basic workup, 0.036 g (98%) of **83** as a clear oil: ^1H NMR (500 MHz, $CDCl_3$) 7.40–7.20 (m, ArH), 4.29 (d, J = 8.2 Hz, CHN), 3.87 (ddd, J = 11.4, 7.9, 3.8 Hz, NCH*H*), 3.36 (ddd, J = 11.2, 8.5, 7.3 Hz, NC*H*H), 2.66 (ddd, J = 15.0, 6.6, 3.4 Hz, =C*H*H), 2.54 (m, CH), 2.20 (m, =CH*H*), 1.95 (m, 1 H), 1.70–1.40 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) 150.80, 145.9, 132.9, 128.8, 128.5, 128.0, 111.2, 55.3, 45.5, 37.5, 28.6, 25.0, 23.2, 19.5 ppm; IR (film) 2934, 1727, 1652, 1612, 1259, 700 cm^{-1}; MS (CI) m/e 256.1321 (256.1337 calcd for $C_{16}H_{17}NO_2$, 100); MS (EI) m/e 255 (19), 226 (33), 105 (100).

^1H NOE Experiments for 83. Irradiation of the bridgehead methine hydrogen at δ 4.29 gave a 13% enhancement of the bridgehead methine hydrogen at δ 2.54. Irradiation of the bridgehead methine hydrogen at δ 2.54 gave a 19% enhancement of the bridgehead methine hydrogen at δ 4.29.

Ozonolysis of 71 (85). A stream of O_3 was bubbled through a solution of **71** (0.050 g, 0.896 mmol) in MeOH (1 mL) and CH_2Cl_2 (4 mL) at −78 °C until a blue color persisted. The excess O_3 was then removed with a stream of Ar, and Me_2S (2 mL) was added. This solution was allowed to warm to room temperature and maintained for 0.5 h. At this time, HCl (1.4 mL of a 1.4 M solution in absolute MeOH, 1.4 mmol) was added, and the resulting solution was maintained at room temperature for 0.5 h. Saturated aqueous $NaHCO_3$ (10 mL) was added, and the mixture was extracted with Et_2O. The combined organic extracts were dried (K_2CO_3) and concentrated. The crude material was purified on silica gel (3:1:.01 hexane–EtOAc–Et_3N) to give 0.027 g (57%) of **85** as a slightly yellow oil: ^1H NMR (500 MHz, $CDCl_3$) 3.48 (m, 1 H), 3.40–3.30 (m, 2 H), 3.35 (s, OMe), 2.28 (dd, J = 14.0, 7.3 Hz, 1 H), 2.05 (m, 1 H), 2.00–1.85 (m, 3 H), 1.81 (ddd, J = 12.5, 7.2, 5.5 Hz, 1 H), 1.70–1.60 (m, 2 H), 1.46 (m, 1 H), 1.32 (app dq, J = 12.8, 7.4 Hz, 1 H), 1.18 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) 156.0, 112.4, 69.2, 50.7, 49.9, 45.1, 35.6, 31.3, 29.0, 28.5, 26.1 ppm; IR (film) 2954, 1725, 1272, 1067, 690 cm^{-1}; MS (CI) m/e 212 (MH^+, 100); MS (EI) m/e 211.1203 (211.1208 calcd for $C_{11}H_{17}NO_3$, 5), 137 (100).

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Supplementary Material Available: Preparations of **16–19**, **21–25**, **27**, **33–37**, **39–51**, **53–61** and related spectra (58 pages). Ordering information is given on any current masthead page.

Polyazapolycyclics by Condensation of Aldehydes with Amines. 2. Formation of 2,4,6,8,10,12-Hexabenzyl-2,4,6,8,10,12-hexaazatetracyclo[5.5.0.0^{5,9}.0^{3,11}]dodecanes from Glyoxal and Benzylamines[1,2]

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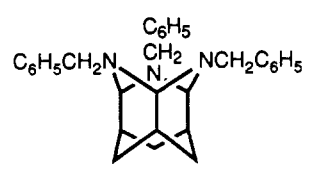
The condensation of glyoxal with benzylamine leads to 2,4,6,8,10,12-hexabenzyl-2,4,6,8,10,12-tetraazatetracyclo[5.5.0.0^{5,9}.0^{3,11}]dodecane (**2a**) in solvents such as acetonitrile or methanol with formic acid catalyst. Six phenyl-substituted derivatives of **2a** have been prepared and the scope of the reaction has been examined. Intermediates 1,2,-bis(benzylamino)-1,2-ethanediol (**6**) and *N,N'*-dibenzyl-1,2-ethanediimine (**7**) have been prepared and the mechanism of their conversion to **2a** is discussed. In the absence of acid catalysts, the glyoxal hemiacetal derivative 2,3-dihydroxy-1,4-dioxane reacts with benzylamine or 4-pyridylmethylamine in acetonitrile solvent to produce 9,10-bis(arylmethyl)-9,10-diaza-1,4,5,8-tetraoxaperhydroanthracenes **13a,b**.

The condensation of aldehydes with amines or ammonia is a valuable synthetic method leading to polyazapolycyclics, including cage compounds. The reaction of formaldehyde with ammonia to produce hexamethylenetetraamine is an important example.[3] Recently, as part of a program to synthesize polyazapolycyclics by condensation of aldehydes with amines, we reported the synthesis of 3,5,12-triazawurtzitanes (3,5,12-triazatetracyclo[5.3.1.1^{2,6}.0^{4,9}]dodecanes), including the 3,5,12-tribenzyl derivative **1**, by condensation of 1,3,5-triformylcyclohexane with selected primary amines.[1]



1

In this report we describe a facile condensation of glyoxal with benzylamine to produce a new polyazapolycyclic ring system, 2,4,6,8,10,12-hexabenzyl-2,4,6,8,10,12-hexaazatetracyclo[5.5.0.0^{5,9}.0^{3,11}]dodecane (hexabenzylhexaazaisowurtzitane, **2a**). The reaction is also successful with phenyl-substituted benzylamines leading to derivatives **2b–g**. The caged product is unusual in that all of the endocyclic nitrogens are at bridges, with none at bridgeheads as in hexamethylenetetraamine. We ascribe the name isowurtzitane to the new cage system **2** owing to its close relationship to wurtzitane, tetracyclo[5.3.1.1^{2,6}.0^{4,9}]-dodecane (see **1**).[4,5] These isomeric cages have the same adjacent groupings of atoms (six methylene bridges, six methines at bridgeheads, and three CHCH groups bonded through the methylenes). The hydrocarbon wurtzitane is known (**1**, $NCH_2C_6H_5 = CH_2$),[4] but the parent hydrocarbon isowurtzitane (tetracyclo[5.5.0.0^{5,9}.0^{3,11}]dodecane (**2**, $NCH_2Ar = CH_2$) apparently is not.

The new condensation reactions of amines with glyoxal to yield hexaazaisowurtzitane derivatives **2** appears to be limited to benzylamine and certain phenyl-substituted

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