Awardee. H.N. wishes to thank the Humboldt Foundation for a postdoctoral fellowship and the Fulbright-Kommission for a travel grant. Use of the high-field NMR spectrometer used in these studies was made possible through a NSF equipment grant.

Registry No. **3**, 87813-07-8; **5**, 78394-12-4; **6**, 18159-18-7; **7**, 97998-39-5; **9**, 97998-53-3; **10**, 93102-03-5; **11**, 87813-01-2; **12**, 87813-03-4; **15**, 97998-43-1; **16**, 97998-44-2; **17**, 87281-49-0; **18**, 87281-50-3; **20**, 7662-79-5; **21**, 97998-45-3; **29**, 97998-47-5; **30**, 97998-48-6; **32**, 17190-29-3; **35a**, 96611-44-8; **35b**, 95832-83-0; **36a**, 95832-84-1; **36b**, 95832-85-2; **40**, 79664-59-8; **41**, 95832-82-9; **42**, 97998-49-7; *cis*-**44**, 97998-50-0; *trans*-**44**, 97998-51-1; $TMSCH_2N^+(CH_2Ph)$=CHSMe·I^-, 97998-42-0; pyrrolidine, 123-75-1; (chloromethyl)trimethylsilane, 2344-80-1; benzylamine, 100-46-9; *N*-benzyl-*N*-[(trimethylsilyl)methyl]amine, 53215-95-5; formaldehyde, 50-00-0; dimethyl acetylenedicarboxylate, 762-42-5; methyl propiolate, 922-67-8; butyl formate, 592-84-7; benzyl(trimethylsilylmethyl)formamide, 97998-40-8; benzyl(trimethylsilylmethyl)thioformamide, 97998-41-9; *N*-phenylmaleimide, 941-69-5; 4-phenyl-3-buten-2-one, 1896-62-4; methyl cinnamate, 103-26-4; 1-bromo-4-pentene, 1119-51-3; 5-benzyl-1,3-dioxo-4-(1-penten-5-yl)-2-phenylpyrrolo[3,4-*c*]pyrrole, 97998-52-2; acetaldehyde, 75-07-0; (α-chloroethyl)trimethylsilane, 7787-87-3; *N*-benzyl-*N*-[α(trimethylsilyl)ethyl]amine, 97998-46-4; *tert*-butyl bromoacetate, 5292-43-3; *N*-benzylglycine *tert*-butyl ester, 7662-76-2; *N*-acetyl-*N*-benzylglycine *tert*-butyl ester, 7662-78-4; *N*-methylbenzylamine, 103-67-3; tris(dimethylamino)sulfonium difluorotrimethylsilicate, 59218-87-0; benzaldehyde, 100-52-7; acetonitrile, 75-05-8; *N*-methyl-*N*-[(trimethylsilyl)methyl]amine, 18135-05-2; benzoquinone, 106-51-4; 2,3-dimethylbenzoquinone, 526-86-3; 2-methyl-3-methoxybenzoquinone, 2207-57-0; nicotinaldehyde, 500-22-1; phenyl vinyl sulfone, 5535-48-8; nicotine, 54-11-5.

Silicon Directed *N*-Acyliminium Ion Cyclizations. Highly Selective Syntheses of (±)-Isoretronecanol and (±)-Epilupinine

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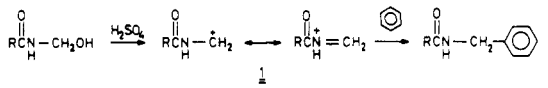
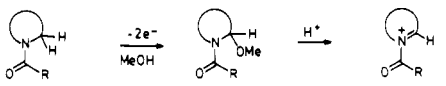
Intramolecular reactions of *N*-acyliminium ions with allyl- and propargylsilanes are described. The cyclization precursors are hydroxy lactams **4b–10b**, derived from succinimide and glutarimide, with the π-nucleophile connected to the nitrogen via an ethylene or propylene chain. Cyclizations are induced by treatment with trifluoroacetic or formic acid and lead to products containing the pyrrolizidine (**4c**, **7c**), indolizidine (**5c**, **8c**), or quinolizidine (**6c**, **9c**) ring system with a vinylidene substituent (propargylsilane cyclization) or a vinyl substituent (allylsilane cyclization). Reactions proceed in high yield with complete regiocontrol (governed by the β-effect of silicon) and with complete stereocontrol (chair-like transition-state conformations). Two allylsilane cyclization products **7c** and **9c** are further transformed into racemic isoretronecanol (**7e**) and epilupinine (**9e**), respectively.

N-Acyliminium ions (**1–3**) are highly useful intermediates in organic synthesis.[1] The ease of generation and the high reactivity of simple representatives (**1**) have been known since the beginning of this century, when the Tscherniac–Einhorn reaction (eq 1) was discovered.[2] The

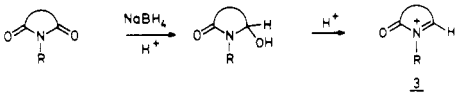


(1)

acid-catalyzed heterolysis of *N*-(α-oxyalkyl)amides, as shown in eq 1, is still the most direct and successful route for the formation of *N*-acyliminium ions. Obviously, the shortest synthesis of such functionalized amides is the reaction of primary or secondary amides with aldehydes or ketones, but this reaction is not always useful. The development of two novel and versatile methods for the preparation of *N*-(α-alkoxyalkyl)amides, some 10 years ago, spurred an upsurge of the interest in the synthetic potential of *N*-acyliminium ions, in particular cyclic ones (**2** or **3**). These new methods are the electrochemical oxidation of amides[1c,3] (eq 2) and the pH controlled $NaBH_4$ reduction of imides[1d,4] (eq 3). Such new entries into the



(2)



(3)

chemistry of *N*-acyliminium ions enabled a more systematic study of their reactivity and a more subtle use in synthesis. Intramolecular reactions with acetylenes and olefins need special attention in this respect. These reactions have shown in several cases to be attended with high regio- and stereocontrol, permitting highly selective total syntheses of alkaloids such as perhydrohistrionicotoxin,[5] vertaline,[6] and gephyrotoxin.[7] Equation 4 illustrates regioselectivity in the intramolecular reaction of *N*-acyliminium ions with electronically unbiased acetylenes.[8] The results are explained on the basis of stability of vinyl cations and ring strain. Linear vinyl cations are

(1) Reviews: (a) Zaugg, H. E. *Synthesis* **1984**, 85, 181 (intermolecular reactions). (b) Speckamp, W. N.; Hiemstra, H. *Tetrahedron*, in press (intramolecular reactions). (c) Shono, T. *Tetrahedron* **1984**, *40*, 824. (d) Speckamp, W. N. *Recl. Trav. Chim. Pays-Bas* **1981**, *100*, 345.

(2) (a) Tscherniac, J. Ger. Pat. 134979, 1984; *Chem. Zentr.* **1902**, *II*, 1084. (b) Einhorn, A. *Liebigs Ann. Chem.* **1905**, *343*, 207.

(3) (a) Ross, S. D.; Finkelstein, M.; Petersen, R. C. *J. Org. Chem.* **1966**, *31*, 128. (b) Nyberg, K.; Servin, R. *Acta Chem. Scand., Ser. B* **1976**, *30*, 640. (c) Mitzlaff, M.; Warning, K.; Jensen, H. *Liebigs Ann. Chem.* **1978**, 1713.

(4) Hubert, J. C.; Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1975**, *31*, 1437.

(5) (a) Schoemaker, H. E.; Speckamp, W. N. *Tetrahedron* **1980**, *36*, 951. (b) Evans, D. A.; Thomas, E. W.; Cherpeck, R. E. *J. Am. Chem. Soc.* **1982**, *104*, 3695.

(6) Hart, D. J.; Kanai, K. *J. Org. Chem.* **1982**, *47*, 1555.

(7) Hart, D. J.; Kanai, K. *J. Am. Chem. Soc.* **1983**, *105*, 1255.

(8) Schoemaker, H. E.; Boer-Terpstra, Tj.; Dijkink, J.; Speckamp, W. N. *Tetrahedron* **1980**, *36*, 143.

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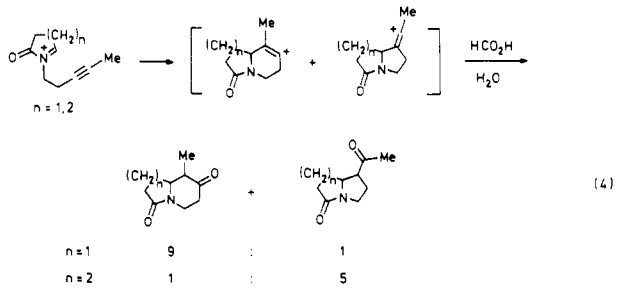
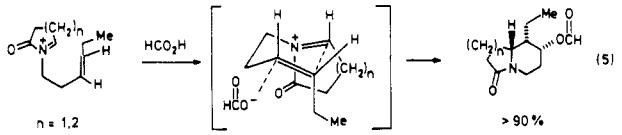
more stable than bent vinyl cations which explains the outcome in the case of $n = 2$. This effect is offset by the higher ring strain of a 5,5-ring system compared to a 5,6-ring system, thus giving a preponderance of the latter ring system in the case of $n = 1$.



(4)

Equation 5 illustrates aspects of regio- and stereocontrol in cyclization reactions with unbiased olefins.[9] In both cases a single isomer is obtained with a newly formed six-membered ring. The structure of the products indicates, that the reaction proceeds through a chair-like transition state, obeying the Stork–Eschenmoser hypothesis on olefin cyclization.[10]

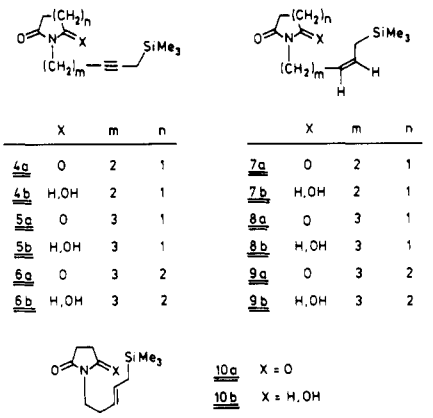


(5)

The regiochemical outcome of an *N*-acyliminium ion cyclization can be influenced by introducing a cation (de)stabilizing group onto the π-nucleophile, i.e., affecting its electronic bias. Nucleophiles like phenylacetylenes,[11] (phenylthio)acetylenes,[11] and ketene dithioacetals[12] have shown to react with complete regioselectivity. We here describe in full detail our study of the utility of allyl- and propargylsilanes as π-nucleophiles in *N*-acyliminium ion cyclizations.[13] These moieties are known to react with electrophiles with high regiocontrol, due to the β-effect of silicon.[14] Allyl- and propargylsilanes have been used successfully as terminating groups in polyene cyclizations yielding the steroid skeleton.[15] Intermolecular reactions of allylsilanes with *N*-acyliminium ions are known.[16] Recently, intramolecular reactions with vinylsilanes were published.[17]

Results

N-Acyliminium ion cyclizations were carried out with propargylsilanes **4b–6b**, (*Z*)-allylsilanes **7b–9b**, and (*E*)-allylsilane **10b**, all containing the hydroxy lactam moiety.

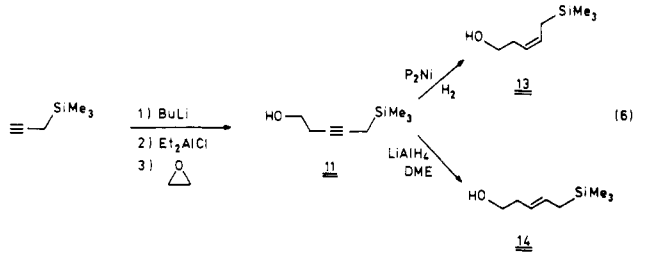


	X	m	n
4a	O	2	1
4b	H,OH	2	1
5a	O	3	1
5b	H,OH	3	1
6a	O	3	2
6b	H,OH	3	2

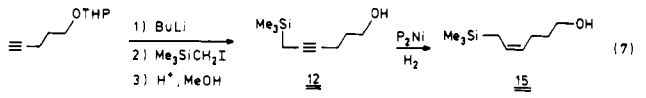
	X	m	n
7a	O	2	1
7b	H,OH	2	1
8a	O	3	1
8b	H,OH	3	1
9a	O	3	2
9b	H,OH	3	2

10a X = O
10b X = H,OH

These compounds were prepared from the corresponding imides **4a–10a** via the well-known $NaBH_4$ reduction.[4] Two methods were used for synthesis of the imides **4a–10a**: (1) reaction of an alkali metal salt of succinimide or glutarimide with the mesylate of the appropriate alcohol; (2) direct reaction of succinimide or glutarimide with the alcohol, mediated by triphenylphosphine and dimethyl azodicarboxylate (Mitsunobu reaction).[13] The mesylate substitution process was more convenient for large scale work, since the Mitsunobu reaction required more or less tedious chromatographic separations. The syntheses of the required alcohols **11–15** are given in eq 6 and 7. A



(6)



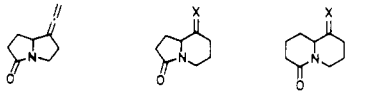
(7)

modification[18] of the procedure of Peterson[19] was used for the syntheses of hexynol **12**. This involved reaction of a lithium acetylide with (iodomethyl)trimethylsilane at 55 °C for 20 h in THF. Protection of the hydroxyl group led to much higher yield than use of 2 equiv of base. In this manner **12** was obtained in an overall yield of 70% from 4-pentyn-1-ol. The same procedure could not be successfully applied to 3-butyn-1-ol in order to arrive at **11**, probably due to competing β-elimination of the oxygen functionality. We therefore, examined propargyltrimethylsilane[18] as starting material. Reaction of its anion with oxirane proceeded unsatisfactorily, when lithium or magnesium served as cations. Better results were obtained by using the method of Fried.[20] The lithium acetylide, prepared in toluene, was treated with a hexane solution of 1 equiv of diethylaluminum chloride, followed by a toluene solution of 1 equiv of oxirane. In this way alcohol **11** was obtained in an acceptable yield of 55%. The ob-

(9) Schoemaker, H. E.; Dijkink, J.; Speckamp, W. N. *Tetrahedron* **1978**, *34*, 163.
(10) (a) Stork, G.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1955**, *77*, 5068. (b) Eschenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta* **1955**, *38*, 1890.
(11) Nossin, P. M. M.; Speckamp, W. N. *Tetrahedron Lett.* **1979**, 4411.
(12) (a) Chamberlin, A. R.; Chung, J. Y. L. *J. Am. Chem. Soc.* **1983**, *105*, 3653. (b) Chamberlin, A. R.; Nguyen, H. D.; Chung, J. Y. L. *J. Org. Chem.* **1984**, *49*, 1682.
(13) Preliminary communication: Hiemstra, H.; Speckamp, W. N. *Tetrahedron Lett.* **1983**, *24*, 1407.
(14) Reviews: (a) Colvin, E. "Silicon in Organic Synthesis"; Butterworths: London, 1981. (b) Sakurai, H. *Pure Appl. Chem.* **1982**, *54*, 1.
(15) (a) Schmid, R.; Huesmann, P. L.; Johnson, W. S. *J. Am. Chem. Soc.* **1980**, *102*, 5122. (b) Johnson, W. S.; Chen, Y-Q.; Kellogg, M. S. *Ibid.* **1983**, *105*, 6653. (c) Johnson, W. S.; Elliott, J. D.; Hanson, G. J. *Ibid.* **1984**, *106*, 1138.
(16) (a) Hart, D. J.; Tsai, Y.N. *Tetrahedron Lett.* **1981**, *22*, 1567. (b) Kraus, G. A.; Neuenschwander, K. *J. Chem. Soc., Chem. Commun.* **1982**, 134. (c) Aratani, M.; Sawada, K.; Hashimoto, M. *Tetrahedron Lett.* **1982**, *23*, 3921.
(17) Overman, L. E.; Malone, T. C.; Meier, G. P. *J. Am. Chem. Soc.* **1983**, *105*, 6993.
(18) Pornet, J.; Kolani, N. B.; Mesnard, D.; Miginiac, L.; Jaworski, K. *J. Organometal. Chem.* **1982**, *236*, 177.
(19) (a) Despo, A. D.; Chiu, S. K.; Flood, T.; Peterson, P. E. *J. Am. Chem. Soc.* **1980**, *102*, 5120. (b) Chiu, S. K.; Peterson, P. E. *Tetrahedron Lett.* **1980**, *21*, 4047.
(20) (a) Fried, J.; Lin, C.-H.; Ford, S. H. *Tetrahedron Lett.* **1969**, 1379. (b) Danishefsky, S.; Kitahara, T.; Tsai, M.; Dynak, J. *J. Org. Chem.* **1976**, *41*, 1669.

vious route to (*Z*)-allylsilanes **13** and **15** involves partial hydrogenation of **11** and **12**. High and reproducible yields were obtained by using the procedure of Brown.[21] (*E*)-Allylsilane **14** was prepared in 52% yield through reduction of **11** with lithium aluminum hydride in boiling DME.[22]

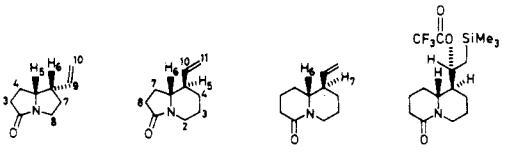
Cyclization of Propargylsilanes. On treatment with 5 equiv of trifluoroacetic acid in CH_2Cl_2 substrates **4b–6b** smoothly cyclized to the allenes **4c–6c**, respectively. Reactions were complete within 1 h at 0 °C and no other cyclization products could be detected in the crude products. The formation of allenes was immediately clear from inspection of the IR and ^1H NMR spectra of the crude products. The allenes showed a very diagnostic signal at 1960–1970 cm^{-1} in the IR. The allenic methylene protons were found in the ^1H NMR as a complex multiplet centered around 4.8–4.9 ppm. The products were unstable in the air, probably due to easy autoxidation at the angular carbon atom. Compounds **5c** and **6c** were further characterized by ozonolysis to ketones **5d** and **6d**. These ketones were also sensitive to air.[23]



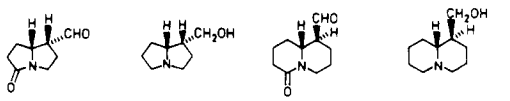
4c **5c** X = C=CH$_2$ **6c** X = C=CH$_2$
5d X = O **6d** X = O

Cyclization of Allylsilanes. Cyclization of **7b–9b** was induced by treatment with 5 equiv of trifluoroacetic acid in CH_2Cl and was complete within 1 h at 0 °C to room temperature. Later,[26] it was found for other cases that formic acid is the preferred medium for this reaction and **10b** was cyclized with this method. In general, cyclizations occurred in high yield to afford air-stable bicyclic amides **7c–9c**, bearing a vinyl substituent. This vinyl group showed characteristic absorptions in the ^1H proton spectrum, namely a broad one proton multiplet at 5.4–5.8 ppm and a two proton multiplet at 4.95–5.25 ppm.

In principle, two stereoisomes can be formed in these allylsilane cyclizations. Substrates **7b** and **10b** furnished only one, i.e., the same product **7c**. The assignment of the endo stereochemistry is based on NOE difference spectra. Irradiation of the angular hydrogen (H_5) showed a positive NOE for H_6 and for one of the two H_4's. Irradiation of the vinyl methine H_9 showed no NOE for H_5, but weak effects for the other H_4 and for one H_7. This assignment was confirmed through conversion of **7c** into (±)-isoretronecanol (vide infra). Cyclization of **8b** afforded a single product **8c** with H_5 and H_6 trans and an equatorial vinyl substituent. This assignment is based on the chemical shift of H_6 in the ^1H NMR spectra of **8c**, i.e., 3.17 ppm. From earlier work[9] it is known that the chemical shift of the angular proton H_6 is very sensitive to the orientation of a substituent at C_5. In the case of an axial C_5 substituent, H_6 absorbs at 3.75 ppm, and in the case of an equatorial C_5 substituent at 3.1 ppm. The value of 3.17 ppm for **8c** points to an equatorial vinyl group. Surprisingly, cyclization of **9b** afforded a 9:1 mixture of **9c** and **9f**. The assignment of the structure of **9c** with an equatorial vinyl group is based on the same reasoning as given for **8c**. For a similar system as **9c** with an axial C_7 substituent H_6 is found at 3.4 ppm, whereas in the case of an equatorial C_7 substituent H_6 absorbs at 3.05 ppm.[9] In our case H_6 is found at 3.05 ppm, clearly attesting to an equatorial vinyl group. This is confirmed through conversion of **9c** to (±)-epilupinine (vide infra) The NMR of **9f** showed a one hydrogen triplet at 5.42 ppm, assigned as the hydrogen adjacent to the trifluoroacetate function (thus, the vicinal coupling constant between this hydrogen and the ring hydrogen must be close to 0 Hz), and a two hydrogen doublet at 1.14 ppm as the methylene bearing the trimethylsilyl group. The easy conversion of **9f** into **9c** on treatment with aqueous hydrochloric acid provides further evidence for the structure of **9f**. The stereochemistry of the carbon atom bearing the trifluoroacetate group was not established but is most reasonable in connection with the reaction mechanism (vide infra).



7c **8c** **9c** **9f**



7d **7e** **9d** **9e**

Synthesis of (±)-Isoretronecanol and (±)-Epilupinine. Via a two-step procedure compounds **7c** and **9c** were converted into (±)-isoretronecanol[27] (**7e**) and (±)-epilupinine[28] (**9e**), respectively. The first step comprised ozonolysis at −78 °C, followed by reduction with dimethyl sulfide to furnish aldehydes **7d** and **9d**. In the case of the pyrrolizidine system **7c** about 10% of epimerization was observed. The second step involved reduction of the carbonyls with lithium aluminum hydride in boiling THF, affording the natural products **7e** and **9e** in excellent overall yields, although **7e** was contaminated with about 10% of its epimer (±)-trachelanthamidine. Structures were proved by comparison of their ^{13}C NMR spectra with literature data (see Experimental Section).

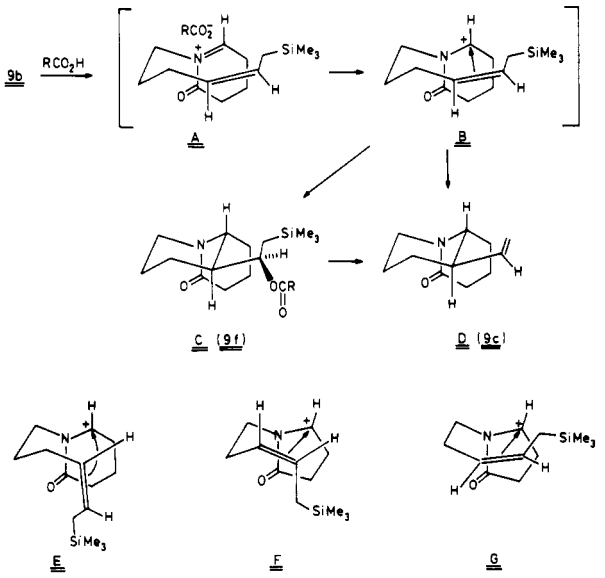
Discussion

The results show that the intramolecular reaction of *N*-acyliminium ions with allyl- and propargylsilanes in the fashion as described here (5- and 6-exo–endo reactions[29]) is a fast and high yielding process. Remarkably, protic acids give excellent results indicating that *N*-acyliminium ion formation and cyclization are much faster than protodesilylation. Recently,[26] we have shown that in the case of more difficult cyclizations like formation of eight-membered rings protodesilylation does compete. In such cases Lewis acids, e.g., $SnCl_4$, should be used to effect cyclization.[26]

It will be obvious that the mechanism of the allylsilane cyclization reaction is similar to the well-known cationic

(21) (a) Brown, C. A.; Ahuja, V. K. *J. Chem. Soc., Chem. Commun.* **1973**, 553. (b) Brown, C. A.; Ahuja, V. K. *J. Org. Chem.* **1973**, *38*, 2226.
(22) Rossi, R.; Carpita, A. *Synthesis* **1977**, 561.
(23) Ketones **5d**[24] and **6d**[25] have been prepared before. The air-sensitivity of **5d** has been investigated.[24]
(24) Yates, P.; MacLachlan, F. N. *J. Indian Chem. Soc.* **1978**, *55*, 1116.
(25) Japan Patent **1964**, 5494; *Chem. Abstr.* **1964**, *61*, 10664g.
(26) Hiemstra, H.; Klaver, W. J.; Speckamp, W. N. *J. Org. Chem.* **1984**, *49*, 1149.
(27) For recent syntheses of isoretronecanol see: (a) Flitsch, W.; Russkamp, P. *Liebigs Ann. Chem.* **1983**, 521. (b) Rüeger, H.; Benn, M. *Heterocycles* **1982**, *19*, 1677 and papers cited therein.
(28) For recent syntheses of epilupine see: Bremmer, M. L.; Khatri, N. A.; Weinreb, S. M. *J. Org. Chem.* **1983**, *48*, 3661 and papers cited therein.
(29) (a) Ben-Ishai, D. *J. Chem. Soc., Chem. Commun.* **1980**, 687. (b) Lochead, A. W.; Proctor, G. R.; Caton, M. P. L. *J. Chem. Soc. Perkin Trans. 1* **1984**, 2477.

Scheme I



olefin cyclization reaction,[10] which was recently rediscussed by Dewar and Reynolds.[30] This mechanism is illustrated for ring closure of **9b** in Scheme I. First, the *N*-acyliminium ion is formed, probably as a tight ion pair with the carboxylate anion (A). This species then cyclizes to a π-complex (B) which is unsymmetrical, due to the influence of silicon, stabilizing positive charge on the β-carbon, relative to silicon. C–C bond formation then occurs at the γ-carbon, and concomitantly the carboxylate anion attacks either the β-carbon atom to form the anti addition product C, or the silicon leading to the allylic substitution product D. Only in the case of cyclization of **9b** was an addition product of type C (**9f**) observed and isolated. In all other cyclizations only the allylic substitution product of type D was obtained. It cannot be excluded that in all cyclizations, compounds of type C are real intermediates, which subsequently give 1,2-elimination under the reaction conditions. This interesting question was not further investigated. The mechanism of cyclization of propargylsilanes will be much like the mechanism of allylsilane cyclization.

Our results show that the β-effect of silicon completely determines the regiochemistry of the reaction and by far overrides the effects of ring strain. This is most convincingly demonstrated by comparison of eq 4 (n = 1) with cyclization of **4b** and of eq 5 (n = 1) with cyclization of **7b**.

The stereochemical course of the allylsilane cyclizations can best be understood by comparison of the stabilities of the π-complex configurations, since these will reflect to a considerable extent, the stabilities of the corresponding transition states leading to the different stereoisomers. The two relevant chair like π-complexes for cyclization of **9b** are B and E. The product **9c** arises from B, which is understandably the more stable situation in view of the quasi-axial position and thus unfavorable steric interactions of the allylsilane functionality in E. Similar considerations explain the stereochemical course of cyclization of **8b**. The two relevant π-complexes for cyclization of **7b** are F and G. The former having a chair like structure is expected to be more stable than the latter (boat like), and F indeed leads to the observed product **7c**. The preference of F over G is independent of the configuration of the double bond, which explains that cyclization of (*E*)-allylsilane **10b** leads to the same product **7c**.[40]

Conclusions

An allylic or propargylic trimethylsilyl group serves exceedingly well in controlling the regio- and stereochemical outcome of intramolecular reactions of cyclic *N*-acyliminium ions with olefin or acetylenes. This reaction, leading to bicyclic amides, containing an olefinic or an allenic moiety, is potentially very useful for the total synthesis of alkaloids as was shown here by short syntheses of racemic isoretronecanol and epilupinine. Further investigations into its scope and applications are under way.

Experimental Section

General Procedures. Infrared spectra (IR) were obtained from $CHCl_3$ solutions on a Perkin Elmer 298 spectrophotometer and are reported in cm^{-1}. Proton nuclear magnetic resonance (^1H NMR) spectra were determined in $CDCl_3$ as solvent on a Varian A-60, Varian XL-100, or Brucker WM-250 instrument. ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Varian XL-100 or Bruker WM-250 instrument. Chemical shifts are given in ppm downfield from tetramethylsilane. Accurate mass measurements were performed on a Varian MAT 711 instrument. R_f values were obtained via thin layer chromatography (TLC) on silica gel coated plastic sheets (Merck silica gel 60 F_{254}) with the indicated solvent (mixture). Chromatographic purification refers to flash chromatography[31] using the same solvent as for TLC (unless otherwise indicated) and Merck silica gel 60 (230–400 mesh).

5-(Trimethylsilyl)-3-pentyn-1-ol (11). To a magnetically stirred solution of 1-(trimethylsilyl)-2-propyne[18] (5.0 g, 44.6 mmol) in 65 mL of dry toluene was added dropwise under nitrogen at −45 °C 27.9 mL (44.6 mmol) of a 1.6 M solution of *n*-butyllithium in hexane. After 25 min of stirring at −45 °C, 28 mL (44.6 mmol) of a 1.6 M solution of diethylaluminum chloride in hexane was added dropwise at the same temperature. The solution became turbid (formation of LiCl). After another 15 min of stirring at −45 °C a solution of 2.23 mL (45 mmol) of oxirane in 20 mL of dry toluene was added dropwise over 15 min. (Gaseous oxirane was condensed at 0 °C until the desired volume had been attained and then dissolved in cold toluene.) The mixture was kept at −45 °C for another 20 min. The cooling bath was then removed and after 45 min 100 mL of ether was added. The reaction mixture was poured into 250 mL of 0.6 N aqueous $NaHSO_4$. The aqueous layer was extracted with 50 mL of ether. The combined organic layers were washed with water (2 × 250 mL) and brine (100 mL), dried (K_2CO_3), and concentrated in vacuo (20 °C (10 mm)). The residue was distilled to afford 3.84 g (24.9 mmol, 55%) of a colorless liquid (bp 64–66 °C (0.9 mmHg)): R_f 0.50 (EtOAc/hexane 1:1); IR 3580, 3440, 2225, 1250, 1045, 850; ^1H NMR δ 3.64 (t, J = 7 Hz, 2 H), 2.40 (m, 2 H), 1.9 (s, 1 H), 1.41 (t, J = 3 Hz, 2 H), 0.07 (s, 9 H); exact mass calcd for $C_8H_{16}OSi$ 156.0970, found 156.0971.

6-(Trimethylsilyl)-4-hexyn-1-ol (12).[18] To a stirred solution of 15.34 g (91.3 mmol) of THF-protected 4-pentyn-1-ol[32] in 90 mL of dry THF was added dropwise at −30 °C under nitrogen 57 mL (91.3 mmol) of a 1.6 M solution of *n*-BuLi in hexane. After stirring for 15 min at −30 °C and for 15 min at 0 °C, 13.54 mL (91.3 mmol) of (iodomethyl)trimethylsilane[33] was added. The reaction flask was then covered with aluminum foil and the mixture heated with stirring (in the dark) for 17 h at 55–60 ° C. After the reaction was cooled to room temperature, 250 mL of pentane was added. The mixture was washed with water (3 × 150 mL), dried ($MgSO_4$), and concentrated in vacuo. The residual yellow oil was dissolved in 150 mL of methanol containing 0.05 mL in H_2SO_4. This methanol solution was stirred overnight at room temperature and then diluted with 300 mL of a 1:1 mixture of ether and pentane. The resultant mixture was washed with saturated aqueous $NaHCO_3$ (250 mL), water (200 mL), and brine (200 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue

(30) Dewar, M. J. S.; Reynolds, C. H. *J. Am. Chem. Soc.* **1984**, *106*, 1744.

(31) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(32) Negishi, E.; Chiu, K.-W. *J. Org. Chem.* **1976**, *41*, 3484.
(33) Ambasht, S.; Chiu, S. K.; Peterson, P. E.; Queen, J. *Synthesis* **1980**, 318.

was distilled to furnish 11.8 g (69.4 mmol, 76%) of a colorless liquid (bp 70 °C (0.2 mmHg)); R_f 0.55 (EtOAc/hexane 1:1); IR 3610, 3680–3200, 2200, 1250, 850; ^{1}H NMR δ 3.75 (t, J = 6 Hz, 2 H), 2.45 (s, 1 H), 2.02–2.50 (m, 2 H), 1.57–2.02 (m, 2 H), 1.41 (t, J = 2.5 Hz, 2 H), 0.08 (s, 9 H); exact mass calcd for $C_9H_{18}OSi$ 170.1127, found 170.1092.

(*Z*)-5-(Trimethylsilyl)-3-penten-1-ol (13).[21] To a stirred solution of 82 mg of $Ni(OAc)_2 \cdot 4H_2O$ (0.33 mmol) in 2.2 mL of 95% EtOH, kept under a hydrogen atmosphere, was added at room-temperature 0.32 mL of a 1 M solution of $NaBH_4$ in 95% EtOH (0.32 mmol). The mixture turned black immediately. After 1 min two drops of 1,2-diaminoethane were introduced, and after 10 min 1.0 g (6.4 mmol) of propargylsilane **11**. The mixture was stirred for 21 h at room temperature and continuously kept under hydrogen (1 atm). Workup began with addition of a small amount of active charcoal and filtration over Celite. The reaction flask and the filter were thoroughly washed with a total amount of 70 mL of CH_2Cl_2, and the resultant CH_2Cl_2 solution combined with the original filtrate. The combined organic solutions were washed with water (2 × 50 mL), dried (K_2CO_3), and concentrated in vacuo. The residue was distilled (Kugelrohr) to furnish 800 mg (5.05 mmol, 79%) of a colorless liquid (bp approximately 50–60 °C (0.5–1.0 mmHg)): R_f 0.48 (EtOAc/hexane 1:1); IR 3620, 3450, 1645, 1250, 850; ^{1}H NMR δ 5.10–5.73 (m, 2 H), 3.63 (t, J = 7.0 Hz, 2 H), 2.27 (dt, J = 7.0, 6.5 Hz, 2 H), 1.60 (s, 1 H), 1.50 (d, J = 8 Hz, 2 H), –0.01 (s, 9 H). Irradiation of the doublet at 1.50 ppm led to simplified olefinic absorptions: δ 5.61 (dd, J = 11, 2 Hz, 1 H) and 5.27 (dt, J = 11, 7 Hz, 1 H). The coupling constant of 11 Hz proves the Z geometry of the double bond. ^{13}C NMR δ 128.7 (d), 122.7 (d), 62.4 (t), 30.7 (t), 18.7 (t), –1.9 (q).

(*E*)-5-(Trimethylsilyl)-3-penten-1-ol (14). To a solution of 5.0 g (32.0 mmol) of propargylsilane **11** in 45 mL of DME, cooled in an ice bath, was added slowly 2.4 g (63 mmol) of $LiAlH_4$. The mixture was refluxed for 48 h. After dilution with 40 mL of ether, 4.5 mL of saturated aqueous NH_4Cl was slowly added while the mixture was cooled in ice. Subsequently, more ether was added (about 150 mL) until a loose precipitate of lithium and aluminum salts was obtained. The organic solution was decanted and the salts washed with ether (4 × 50 mL). The combined organic solutions were dried (K_2CO_3) and concentrated in vacuo (20 °C (10 mmHg)). There was obtained 4.15 g (82%) of a light yellow oil which was distilled to furnish 2.83 g (17.9 mmol, 56%) of a colorless liquid (bp 86–89 °C (12.5 mmHg)): R_f 0.49 (EtOAc/hexane 1:1); IR 3600, 3450, 1655, 1245, 1040, 970, 850; ^{1}H NMR δ 5.02–5.71 (m, 2 H), 3.58 (t, J = 6 Hz, 2 H), 2.22 (m, 2 H), 1.71 (s, 1 H), 1.43 (d, J = 8 Hz, 2 H), –0.04 (s, 9 H). Irradiation of the doublet at 1.43 ppm led to simplified olefinic absorptions: δ 5.53 (dd, J = 15, 1 Hz, 1 H) and 5.19 (dt, J = 15, 7 Hz, 1 H). The coupling constant of 15 Hz proves the E geometry of the double bond. ^{13}C NMR δ 129.7 (d), 124.2 (d), 62.3 (t), 36.2 (t), 22.9 (t), –2.1 (q); exact mass calcd for $C_8H_{18}OSi$ 158.1127, found 158.1136.

(*Z*)-6-(Trimethylsilyl)-4-hexen-1-ol (15). This preparation was carried out analogous to the synthesis of **13**. From 200 mg (1.18 mmol) of propargylsilane **12** was obtained 192 mg (1.12 mmol, 95%) of **15**, purified with chromatography: R_f 0.27 (EtOAc/hexane 1:3); IR 3340, 1640, 1240, 850; ^{1}H NMR δ 5.14–5.68 (m, 2 H), 3.68 (t, J = 6 Hz, 2 H), 1.98–2.23 (m, 2 H), 1.48–1.80 (m, 2 H), 1.63 (s, 1 H), 1.50 (d, J = 7 Hz, 2 H), 0.00 (s, 9 H); exact mass calcd for $C_9H_{20}OSi$ 172.1283, found 172.1253.

Imide 4a (Mitsunobu Reaction). To a stirred mixture of alcohol **11** (840 mg, 5.37 mmol), triphenylphosphine (1.45 g, 5.50 mmol), succinimide (750 mg, 7.5 mmol), and THF (20 mL) was added dropwise (15 min) at 0 °C under nitrogen a solution of dimethyl azodicarboxylate (805 mg, 5.50 mmol) in 10 mL of THF. Stirring was continued for 15 h at room temperature. The mixture was then diluted with 100 mL of CH_2Cl_2 and washed with 5% aqueous KOH (50 mL). This aqueous solution was extracted with 25 mL of CH_2Cl_2. The combined organic solutions were washed with water (50 mL), 1% aqueous H_2SO_4 (50 mL), and saturated aqueous $NaHCO_3$ (50 mL). The resultant organic solution was dried (K_2CO_3) and concentrated in vacuo. The crude product was freed from most of the triphenylphosphine oxide via chromatography using a column of 15 cm length and 2 cm diameter and EtOAc/hexane 1:1 as eluant. The product was further purified with a 4.5 cm diameter column and EtOAc/hexane 1:2 as eluant, to furnish a colorless oil 897 mg, 3.78 mmol, 70%, which solidified on standing: mp 48–51 °C; IR 2220, 1780, 1710, 1400, 1160, 850; ^{1}H NMR δ 3.64 (t, J = 7 Hz, 2 H), 2.72 (s, 4 H), 2.27 (m, 2 H), 1.40 (t, J = 2.5 Hz, 2 H), 0.08 (s, 9 H); exact mass calcd for $C_{12}H_{19}NO_2Si$ 237.1185, found 237.1206.

Imide 7a (Mitsunobu Reaction). This synthesis was performed in the same way as described for **4a**. From 1.27 g (8.0 mmol) of **13** there was obtained 1.21 g (5.05 mmol, 63%) of **7a** as a colorless oil; R_f 0.43 (EtOAc/hexane 1:1); IR 1775, 1705, 1400, 1140, 855; ^{1}H NMR δ 5.0–5.65 (m, 2 H), 3.51 (t, J = 7 Hz, 2 H), 2.65 (s, 4 H), 2.25 (dt, J = 7, 7 Hz, 2 H), 1.41 (d, J = 8 Hz, 2 H), –0.05 (s, 9 H); exact mass calcd for $C_{12}H_{21}NO_2Si$ 239.1341, found 239.1348.

Imide 5a (Mesylate Substitution). To a stirred solution of **12** (3.0 g, 17.7 mmol) in 70 mL of CH_2Cl_2 was added at 0 °C 2.2 g (19.2 mmol) of methanesulfonyl chloride and 2.9 mL (20.8 mmol) of triethylamine. After 5 min TLC showed that the starting alcohol had disappeared. The mixture was diluted with 100 mL of CH_2Cl_2, washed with water (2 × 100 mL), dried (K_2CO_3), and freed from the solvent in vacuo. The residue (4.38 g, 17.7 mmol, 100%) was pure enough for the next step: R_f 0.60 (EtOAc/hexane 1:1); ^{1}H NMR δ 4.40 (t, J = 7 Hz, 2 H), 3.05 (s, 3 H), 2.2–2.6 (m, 2 H), 1.68–2.2 (m, 2 H), 1.46 (t, J = 2 Hz, 2 H), 0.10 (s, 9 H); exact mass calcd for $C_{10}H_{20}O_3SSi$ 248.0902, found 248.0883. The crude mesylate (1.50 g, 6.1 mmol) was heated in 20 mL of DMF at 80 °C under nitrogen for 2 h with 1.24 g (9.1 mmol) of the potassium salt of succinimide[34] and 200 mg of NaI. The mixture was cooled to room temperature, diluted with 100 mL of ether, and washed with water (2 × 150 mL) and brine (100 mL). After drying of the solution (K_2CO_3), the solvent was removed in vacuo. The residue (1.47 g, 5.9 mmol, 97%) was a light yellow oil which was pure enough for the next step: R_f 0.55 (EtOAc); IR 2220, 1775, 1700, 1245, 850; ^{1}H NMR δ 3.63 (t, J = 7 Hz, 2 H), 2.74 (s, 4 H), 2.1–2.3 (m, 2 H), 1.62–1.94 (m, 2 H), 1.44 (t, J = 2.5 Hz, 2 H), 0.10 (s, 9 H); exact mass calcd for $C_{13}H_{21}NO_2Si$ 251.1341, found 251.1305.

Imide 6a (Mesylate Substitution). For the synthesis of the required mesylate see the above procedure. This crude mesylate (1.50 g, 6.1 mmol) was heated in 20 mL of DMF at 90 °C under nitrogen for 30 min with 1.23 g (9.1 mmol) of the sodium salt of glutarimide[35] and 200 mg of NaI. The mixture was worked up as described above to yield 1.35 g (5.1 mmol, 84%) of a light yellow oil, pure enough for the next step: R_f 0.32 (EtOAc/hexane 1:1); IR 2200, 1720, 1670, 1245, 850; ^{1}H NMR δ 3.88 (t, J = 7.5 Hz, 2 H), 2.70 (t, J = 7 Hz, 4 H), 1.4–2.4 (m, 6 H), 1.45 (t, J = 2.5 Hz, 2 H), 0.10 (s, 9 H); exact mass calcd for $C_{14}H_{23}NO_2Si$ 265.1498, found 265.1501.

Imide 8a (Mesylate Substitution). Alcohol **15** (4.09 g, 23.3 mmol) was converted into its mesylate as described for alcohol **12** in the synthesis of imide **5a**. The crude mesylate of **15** was obtained in 95% yield (5.5 g, 22 mmol) as a light yellow oil: R_f 0.47 (EtOAc/hexane 1:1); NMR δ 5.08–5.68 (m, 2 H), 4.25 (t, J = 7 Hz, 2 H), 2.99 (s, 3 H), 1.98–2.33 (m, 2 H), 1.58–1.98 (m, 2 H), 1.48 (d, J = 8 Hz, 2 H), 0.00 (s, 9 H); exact mass calcd for $C_{10}H_{22}O_3SSi$ 250.1059, found 250.1027. A mixture of 1.0 g (4.0 mmol) of this crude mesylate, 0.80 g (5.8 mmol) of the potassium salt of succinimide,[34] 100 mg of NaI, and 20 mL of DMF was heated at 50 °C under nitrogen for 15 h. The mixture was worked up as described for the synthesis of imide **5a** to yield 0.94 g (3.7 mmol, 93%) of a light yellow oil, pure enough for the next step: R_f 0.35 (EtOAc/hexane 1:1); IR 1775, 1700, 1245, 850; ^{1}H NMR δ 5.08–5.75 (m, 2 H), 3.52 (t, J = 7.5 Hz, 2 H), 2.70 (s, 4 H), 1.89–2.17 (m, 2 H), 1.46 (d, J = 8 Hz, 2 H), 1.38–1.82 (m, 2 H), 0.00 (s, 9 H); exact mass calcd for $C_{13}H_{23}NO_2Si$ 253.1498, found 253.1497.

Imide 9a (Mesylate Substitution). For the synthesis of the required mesylate see the above procedure. This crude mesylate (1.50 g, 6.1 mmol) was heated in 20 mL of DMF at 50 °C under nitrogen for 15 h with 1.20 g (8.9 mmol) of the sodium salt of glutarimide.[35] The mixture was worked up as described for the synthesis of imide **5a**, to yield 1.34 g (5.0 mmol, 83%) of an oil,

(34) Bombala, M. U.; Ley, S. V. *J. Chem. Soc. Perkin Trans. 1* **1979**, 3013.

(35) Muchowski, J. M.; Nelson, P. H. *Tetrahedron Lett.* **1980**, *21*, 4585.

which was pure enough for the next step: R_f 0.47 (EtOAc/hexane 1:1); IR 1720, 1665, 1245, 855; ^{1}H NMR δ 5.10–5.60 (m, 2 H), 3.76 (m, 2 H), 2.64 (t, J = 7 Hz, 4 H), 1.80–2.15 (m, 4 H), 1.47 (d, J = 7.5 Hz, 2 H), 1.40–1.75 (m, 2 H), 0.00 (s, 9 H); exact mass calcd for $C_{14}H_{25}NO_2Si$ 267.1655, found 267.1637.

Imide 10a (Mesylate Substitution). Alcohol **14** (2.61 g, 16.4 mmol) was converted into its mesylate as described for alcohol **12** in the synthesis of imide **5a**. There was obtained 3.98 g (16.8 mmol, 100%) of crude mesylate as a light yellow oil: R_f 0.53 (EtOAc/hexane 1:1); ^{1}H NMR δ 5.05–5.80 (m, 2 H), 4.23 (t, J = 7 Hz, 2 H), 3.02 (s, 3 H), 2.25–2.65 (m, 2 H), 1.48 (d, J = 7.5 Hz, 2 H), 0.00 (s, 9 H). A mixture of this crude mesylate (3.98 g, 16.8 mmol), 3.6 g (26.2 mmol) of the potassium salt of succinimide,[34] 0.28 g of KI, and 90 mL of DMF was heated at 90–110 °C under nitrogen for 30 min. The mixture was worked up as described for the synthesis of **5a** to yield 3.60 g of crude yellow oil. This was purified with chromatography affording 2.73 g (11.40 mmol, 70% from **14**) of a light yellow oil: R_f 0.32 (EtOAc/hexane 1:1); IR 1775, 1700, 1245, 850; ^{1}H NMR δ 5.42 (m, 1 H), 5.10 (m, 1 H), 3.47 (t, J = 7 Hz, 2 H), 2.63 (s, 4 H), 2.22 (m, 2 H), 1.34 (d, J = 8 Hz, 2 H), −0.08 (s, 9 H); exact mass calcd for $C_{12}H_{21}NO_2Si$ 239.1341, found 239.1309.

General Procedure for Conversion of Imides into Hydroxy Lactams (4b–10b). This reduction reaction was carried out at −10 to −20 °C for six-membered ring imides and at +5 to 0 °C for five-membered ring imides. To a solution of 2 mmol of imide **4a–10a** in 10 mL of ethanol was added all at once 380 mg (10 mmol) of powdered $NaBH_4$. The mixture was well stirred and every 15 min 6–8 drops of a 1 M solution of sulfuric acid in ethanol was added. The reaction could be easily followed with TLC and was complete in most cases after 4 h. The mixture was then diluted with 50 mL of ether and poured out in 50 mL of cold (0–5 °C) water. The aqueous layer was extracted with 25 mL of ether. The combined organic layers were washed with water (2 × 50 mL) and brine (25 mL) and dried (K_2CO_3). Concentration in vacuo gave an oil which was generally pure enough for the next step but could be easily purified with chromatography.

4b: R_f 0.37 (EtOAc): ^{1}H NMR δ 5.36 (m, 1 H), 4.62 (br d, J = 6 Hz, 1 H), 3.48 (t, J = 7 Hz, 2 H), 1.90–2.70 (m, 6 H), 1.43 (t, J = 2.5 Hz, 2 H), 0.09 (s, 9 H).

5b: R_f 0.23 (EtOAc); IR 3600–3100, 2220, 1675, 1245, 850; ^{1}H NMR δ 5.32 (m, 1 H), 4.31 (br s, 1 H), 3.2–3.6 (m, 2 H), 1.5–2.7 (m, 8 H), 1.42 (t, J = 2.5 Hz, 2 H), 0.09 (s, 9 H).

6b: R_f 0.30 (EtOAc); IR 3600–3050, 1630, 1245, 850; ^{1}H NMR δ 5.00 (m, 1 H), 3.86 (br d, J = 6 Hz, 1 H), 3.20–3.75 (m, 2 H), 1.5–2.5 (m, 10 H), 1.42 (t, J = 2.5 Hz, 2 H), 0.09 (s, 9 H).

7b: R_f 0.20 (EtOAc); IR 3580, 3360, 1680, 1250, 855; ^{1}H NMR δ 5.04–5.65 (m, 3 H), 2.9–3.7 (m, 3 H), 1.8–2.65 (m, 6 H), 1.43 (d, J = 8 Hz, 2 H), −0.03 (s, 9 H); ^{13}C NMR δ 174.7 (s), 128.1 (d), 123.6 (d), 83.4 (d), 39.9 (t), 28.9 (t), 28.4 (t), 25.6 (t), 18.7 (t), −1.9 (q).

8b: R_f 0.57 (CH_2Cl_2/acetone 1:1); IR 3600–3050, 1670, 1245, 855; ^{1}H NMR δ 5.1–5.6 (m, 3 H), 4.36 (d, J = 4 Hz, 1 H), 2.96–3.66 (m, 2 H), 1.3–2.7 (m, 8 H), 1.42 (d, J = 8 Hz, 2 H), −0.04 (s, 9 H).

9b: R_f 0.30 (EtOAc); IR 3360, 1635, 1245, 855; ^{1}H NMR δ 5.10–5.60 (m, 2 H), 4.96 (m, 1 H), 4.32 (d, J = 7 Hz, 1 H), 3.70 (dt, J = 13, 7 Hz, 1 H), 3.16 (dt, J = 13, 7 Hz, 1 H), 1.4–2.5 (m, 10 H), 1.44 (d, J = 8 Hz, 2 H), 0.00 (s, 9 H).

10b: R_f 0.22 (EtOAc); IR 3350, 1680, 1245, 1065, 850; ^{1}H NMR δ 4.95–5.63 (m, 3 H), 3.60 (br s, 1 H), 2.93–3.62 (m, 2 H), 1.76–2.61 (m, 6 H), 1.37 (d, J = 7.5 Hz, 2 H), −0.07 (s, 9 H); ^{13}C NMR δ 174.5 (s), 129.1 (d), 125.1 (d), 83.4 (d), 40.4 (t), 31.2 (t), 28.9 (t), 28.5 (t), 22.9 (t), −2.0 (q).

6-Vinylidene-1-azabicyclo[3.3.0]octan-2-one (4c). A solution of 114 mg (0.48 mmol) of hydroxy lactam **4b** in 2 mL of CH_2Cl_2 was added dropwise at 0 °C to a stirred solution of 250 μL of CF_3COOH (3.25 mmol) in 10 mL of CH_2Cl_2. Stirring was continued for 2 h at 0 °C. The mixture was then diluted with 15 mL of CH_2Cl_2 and extracted with saturated aqueous $NaHCO_3$ (2 × 25 mL). After drying of the organic solution (K_2CO_3), the solvent was removed in vacuo. The residue was a light yellow oil, which showed virtually one spot on TLC: R_f 0.32 (EtOAc); IR 1970, 1680; ^{1}H NMR δ 4.92 (m, 2 H), 4.48 (m, 1 H), 3.93 (dt, J = 11, 5.5 Hz, 1 H), 1.7–3.1 (m, 7 H). This allene was unstable in air.

5-Vinylidene-1-azabicyclo[4.3.0]nonan-9-one (5c). To a stirred solution of 300 mg (1.19 mmol) of crude **5b** in 5 mL of CH_2Cl_2 was added over 10 min at 0 °C under nitrogen a solution of 0.44 mL (5.7 mmol) of CF_3COOH in 20 mL of CH_2Cl_2. After 45 min of stirring the mixture was diluted with 25 mL of CH_2Cl_2 and washed with water (3 × 50 mL). Drying of this solution ($MgSO_4$) and concentration in vacuo afforded 180 mg of a light yellow oil: R_f 0.16 (EtOAc); IR 1965, 1670; ^{1}H NMR δ 4.86 (m, 2 H), 3.85–4.40 (m, 2 H), 1.2–2.9 (m, 9 H).

1-Azabicyclo[4.3.0]nonane-5,9-dione (5d). A solution of 180 mg of the above allene in 4 mL of a 1:1 mixture of CH_2Cl_2 and methanol was treated with ozone at −78 °C until the color turned blue. The mixture was then flushed with nitrogen and treated with 1 mL of dimethyl sulfide. The cooling bath was removed and after the mixture had attained room temperature the volatiles were removed in vacuo. The residue was dissolved in 4 mL of dimethyl sulfide and allowed to stand at about 4 °C for 5 days. Removal of the volatiles in vacuo and chromatography of the residue afforded 153 mg (10 mmol, 80% overall from **12**) of a colorless oil, which crystallized in the freezer (−20 °C). The product is rather stable if kept under nitrogen: R_f 0.25 (CH_2Cl_2/acetone 1:1); IR 1725, 1680; ^{1}H NMR δ 4.0–4.3 (m, 2 H), 3.17 (m, 1 H), 1.7–2.8 (m, 8 H); exact mass calcd for $C_8H_{11}NO_2$ 153.0790, found 153.0787.

7-Vinylidene-1-azabicyclo[4.4.0]decan-2-one (6c). From 300 mg (1.12 mmol) of crude **6b** was obtained in the same manner as described for the synthesis of **5c** 188 mg (1.06 mmol) of a light yellow oil: R_f 0.25 (EtOAc); IR 1960, 1620; ^{1}H NMR δ 4.68–4.96 (m, 3 H), 3.65–4.00 (m, 1 H), 1.30–2.75 (m, 11 H).

1-Azabicyclo[4.4.0]decane-2,7-dione (6d). The above allene was ozonolyzed and the resultant reaction mixture worked up as described for **5d**. From 188 mg of **6c** was obtained 139 mg (0.83 mmol, 63% overall from **12**) of **6d** as a colorless oil which crystallized in the freezer (−20 °C): R_f 0.31 (CH_2Cl_3/acetone 1:1); IR 1725, 1630; ^{1}H NMR δ 4.64 (dt, J = 13.0, 5.0 Hz, 1 H), 3.98 (t, J = 6.0 Hz, 1 H), 3.02 (m, 1 H), 1.5–2.8 (m, 10 Hz); exact mass calcd for $C_9H_{13}NO_2$ 167.0946, found 167.0953.

(±)-(5β)-6α-Vinyl-1-azabicyclo[3.3.0]octan-2-one (7c) (from 7b). To a stirred solution of 200 μL of CF_3CO_2H (2.6 mmol) in 10 mL of CH_2Cl_2 was added dropwise under a nitrogen atmosphere a solution of 140 mg of **7b** (0.60 mmol) in 2 mL of CH_2Cl_2. Stirring was continued for 1 h at 0 °C. The mixture was then diluted with 20 mL of CH_2Cl_2 and extracted with saturated aqueous $NaHCO_3$ (2 × 25 mL). The organic solution was dried (K_2CO_3) and concentrated in vacuo. The residue was purified with chromatography affording 64 mg (0.42 mmol, 72%) of a colorless oil: R_f 0.18 (EtOAc); IR 1675, 995, 925; ^{1}H NMR δ 5.5–5.7 (m, H_9), 5.0–5.15 (m, H_{10}), 4.03 (br q, H_5), 3.61 (dt, $H_{8\alpha}$), 3.07 (m, $H_{8\beta}$), 2.55–2.7 (m, H_6, $H_{3\alpha}$), 2.32 (m, $H_{3\beta}$), 2.18 (m, $H_{7\beta}$), 1.75–2.10 (m, $H_{4\alpha}$, $H_{7\alpha}$, $H_{4\beta}$); ^{13}C NMR δ 173.9 (C_2), 134.5 (C_9), 116.0 (C_{10}), 63.2 (C_5), 42.8 (C_6), 39.1 (C_8), 33.2 (C_3), 31.7 (C_7), 19.9 (C_4); exact mass calcd for $C_9H_{13}NO$ 151.0997, found 151.1004.

(±)-(5β)-6α-Vinyl-1-azabicyclo[3.3.0]octan-2-one (7c) (from 10b). A solution of 1.75 g (7.2 mmol) of **10b** in 75 mL of formic acid was stirred for 60 min at room temperature. Most of the formic acid was then removed in vacuo and the residue treated with 100 mL of CH_2Cl_2 and (carefully) 100 mL of saturated aqueous $NaHCO_3$. The organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were washed with brine (100 mL), dried (K_2CO_3), and concentrated in vacuo to give a light yellow oil which after chromatography (EtOAc/acetone 1:1) furnished 917 mg (6.06 mmol, 84%) of a colorless oil. Spectral data were identical with those of the product obtained from **7b** (vide supra).

(±)-(5β)-6α-Formyl-1-azabicyclo[3.3.0]octan-2-one (7d). A solution of 265 mg (1.75 mmol) of **7c** in a mixture of 2.5 mL of CH_3OH and 4 mL of CH_2Cl_2 was treated with ozone (5% in O_2) at −78 °C until the color turned blue. After removal of the excess ozone with nitrogen, 0.8 mL of dimethyl sulfide was added. The reaction mixture was then allowed to warm up to room temperature. After standing for 1 h at room temperature all volatiles were removed in vacuo. The residue was stirred with 2 mL of dimethyl sulfide for 30 h at room temperature. Removal of the volatiles and chromatography of the residue afforded 232 mg (1.51 mmol, 87%) of a 88:12 mixture of two aldehydes: R_f 0.27 (EtOAc/acetone 1:1); IR 1725, 1680; ^{1}H NMR (major product) δ 9.85 (d, J = 2 Hz, 1 H), 4.29 (br q, 1 H), 3.72 (dt, 1 H), 2.9–3.3 (m, 2 H), 1.7–2.8 (m, 6 H); ^{13}C NMR (major product) δ 201.2 (d), 174.1 (s), 62.0 (d), 49.9 (d), 39.9 (t), 33.3 (t), 26.7 (t), 20.8 (t); exact mass

calcd for $C_8H_{11}NO_2$ 153.0790, found 153.0772.

(±)-(5β)-4α-(Hydroxymethyl)-1-azabicyclo[3.3.0]octane ((±)-Isoretronecanol, 7e). To a suspension of 70 mg of $LiAlH_4$ (1.84 mmol) in 15 mL of THF was added dropwise at 0 °C a solution of 132 mg (0.86 mmol) of the above aldehyde mixture (**7d**) in 10 mL of THF. The resultant mixture was refluxed for 3 h. After cooling below room temperature in an ice bath 0.2 mL of water was added carefully. The mixture was filtered over Celite through a sintered glass funnel. The salts on the filter was washed well with wet ether. The filtrate was dried (K_2CO_3) and concentrated in vacuo to afford 105 mg (0.74 mmol, 86%) of a colorless oil: IR 3650, 3500–3000, 1418, 1010; ^1H NMR δ 4.96 (br s, 1 H), 3.64 (d, J = 7 Hz, 2 H), 3.54 (m, 1 H), 2.8–3.3 (m, 2 H), 2.2–2.7 (m, 3 H), 1.1–2.1 (m, 6 H). The ^{13}C NMR spectrum showed a mixture of two compounds in a ratio of about 9:1; major isomer: δ 66.1, 62.6, 55.4, 53.8, 44.1, 27.1, 26.2, 25.7. These ^{13}C chemical shift data are in excellent agreement with literature data for isoretronecanol.[36] The ^{13}C chemical shift data of the minor isomer show good correspondence with literature data for trachelanthamidine.[37]

(±)-(6β)-5β-Vinyl-1-azabicyclo[4.3.0]nonan-9-one (8c). To a stirred solution of 350 mg (1.37 mmol) of crude **8b** in 5 mL of CH_2Cl_2 was added under nitrogen at 0 °C over 10 min a solution of 0.42 mL (5.45 mmol) of CF_3CO_2H in 20 mL of CH_2Cl_2. Stirring was continued for 1 h at room temperature. The mixture was then diluted with CH_2Cl_2 (50 mL) and extracted with excess saturated aqueous $NaHCO_3$ (2 × 100 mL). The combined aqueous layers were reextracted with 50 mL of CH_2Cl_2 and the combined organic solutions washed with brine (50 mL), dried (K_2CO_3), and concentrated in vacuo. The residue was purified with chromatography to give 195 mg (1.18 mmol, 76% overall from **15**) of a colorless oil: R_f 0.25 (EtOAc); IR 1665, 995, 920; ^1H NMR δ 5.5–5.9 (m, H_{10}), 5.0–5.3 (m, H_{11}), 4.15 (m, $H_{2\alpha}$), 3.17 (m, H_6), 2.60 (m, $H_{2\beta}$), 1.2–2.5 (m, 9 H); ^{13}C NMR δ 172.0 (s), 137.4 (d), 115.0 (t), 59.5 (d), 47.5 (d), 38.6 (t), 29.3 (t), 29.2 (t), 23.1 (t), 22.6 (t); exact mass calcd for $C_{10}H_{15}NO$ 165.1154, found 165.1138.

(±)-(6β)-7β-Vinyl-1-azabicyclo[4.4.0]decan-2-one (9c). To a stirred solution of 162 mg (0.60 mmol) of crude **9b** in 3 mL of CH_2Cl_2 was added under nitrogen at 0 °C over 10 min a solution of 0.23 mL (3.0 mmol) of CF_3CO_2H in 11 mL of CH_2Cl_2. Stirring was continued for 1 h at room temperature. The volatiles were then removed in vacuo and the residue stirred at room temperature for 30 min with 3 mL of a 1:1 mixture of 30% aqueous HCl and methanol. To work up the reaction mixture, it was partitioned between 30 mL of CH_2Cl_2 and 20 mL of water. The organic layer was separated and the aqueous layer extracted with 10 mL of CH_2Cl_2. The combined organic solutions were washed with water (2 × 30 mL) and dried (K_2CO_3). Removal of the solvent in vacuo followed by chromatography of the residue afforded 99 mg (0.55 mmol, 74% overall from **15**) of a colorless oil: R_f 0.25 (EtOAc); IR 1615, 990, 915; ^1H NMR δ 5.42–5.84 (m, H_{11}), 5.00–5.20 (m, H_{12}), 4.86 (m, $H_{10\alpha}$), 3.05 (m, H_6), 1.1–2.6 (m, 12 H); exact mass calcd for $C_{11}H_{17}NO$ 179.1310, found 179.1315. In a separate experiment, starting with 325 mg (1.21 mmol) of crude **9b** the reaction mixture after stirring with CF_3CO_2H was worked up as described for the synthesis of **8c**. After chromatography there was obtained 24 mg (0.066 mmol) of **9f** (R_f 0.43, EtOAc) and 144 mg (0.80 mmol) of **9c** (R_f 0.25, EtOAc). ^1H NMR of **9f**: δ 5.42 (t, J = 7 Hz, 1 H), 4.89 (m, 1 H), 3.15 (m, 1 H), 1.2–2.6 (m, 12 H), 1.15 (d, J = 7 Hz, 2 H), 0.09 (s, 9 H).

(±)-(6β)-7β-Formyl-1-azabicyclo[4.4.0]decan-2-one (9d). A solution of 160 mg (0.89 mmol) of **9c** in 4 mL of a 1:1 mixture of methanol and CH_2Cl_2 was treated with ozone (5% in O_2) at −78 °C until the color turned blue. The reaction was further performed as described for **7d**. After chromatography there was obtained 156 mg (0.86 mmol, 96%) of a colorless oil which crystallized in the freezer (−20 °C): R_f 0.32 (EtOAc/acetone 1:1); IR 1725, 1625, 910; ^1H NMR δ 9.69 (d, J = 3 Hz, 1 H), 4.86 (m, 1 H), 3.54 (m, 1 H), 1.2–2.6 (m, 12 H); exact mass calcd for $C_{10}H_{15}NO_2$ 181.1103, found 181.1101.

(±)-(6β)-5β-(Hydroxymethyl)-1-azabicyclo[4.4.0]decane ((±)-Epilupinine, 9e). This synthesis was performed in the same way as described for **7e**. From 156 mg (0.86 mmol) of **9d** there was obtained 144 mg (0.85 mmol, 99%) of crude product, which was a single compound according to ^{13}C NMR. Spectral data: IR 3000–3700, 1440, 1295, 1110, 1090, 1010; ^1H NMR δ 3.58 (m, 2 H), 2.80 (m, 2 H + OH), 1.0–2.2 (m, 14 H); ^{13}C NMR δ 64.2, 63.3, 56.6, 56.3, 43.5, 29.3, 28.1, 25.2, 24.7, 24.2; exact mass calcd for $C_{10}H_{19}NO$ 169.1467, found 169.1460. The ^{13}C NMR spectral data are in good agreement with literature data.[38,39] Especially the signal at 43.5 ppm is characteristic for the relative stereochemistry of epilupinine.

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Registry No. **4a**, 86486-04-6; (±)-**4b**, 97998-01-1; (±)-**4c**, 97998-08-8; **5a**, 97997-93-8; (±)-**5b**, 97998-02-2; (±)-**5c**, 97998-09-9; (±)-**5d**, 97998-10-2; **6a**, 97997-95-0; (±)-**6b**, 97998-03-3; (±)-**6c**, 97998-11-3; (±)-**6d**, 97998-12-4; **7a**, 97997-92-7; (±)-**7b**, 97998-04-4; (±)-**7c**, 97998-13-5; (±)-**7d**, 97998-14-6; (±)-(5β,6β)-**7d**, 89556-97-8; **7e**, 18929-90-3; (±)-(4β,5β)-**7e**, 18929-91-4; **8a**, 97997-97-2; (±)-**8b**, 97998-05-5; (±)-**8c**, 97998-15-7; **9a**, 97997-98-3; (±)-**9b**, 97998-06-6; (±)-**9c**, 97998-16-8; (±)-**9d**, 97998-18-0; (±)-**9e**, 486-72-6; (±)-**9f**, 97998-17-9; **10a**, 97998-00-0; (±)-**10b**, 97998-07-7; **11**, 86486-02-4; **12**, 76711-41-6; **12** (mesylate), 97997-94-9; **13**, 97997-89-2; **14**, 97997-90-5; **14** (mesylate), 97997-99-4; **15**, 97997-91-6; **15** (mesylate), 97997-96-1; $HC{\equiv}CCH_2SiMe_3$, 13361-64-3; (±)-$HC{\equiv}C(CH_2)_3OTHP$, 69841-55-0; Me_3SiCH_2I, 4206-67-1; oxirane, 75-21-8; succinimide, 123-56-8; succinimide potassium salt, 50433-20-0; glutarimide sodium salt, 54807-39-5.

(36) Pinnick, H. W.; Chang, Y.-H. *J. Org. Chem.* **1978**, *43*, 4662.
(37) Terao, Y.; Imai, N.; Achiwa, K.; Sekiya, M. *Chem. Pharm. Bull.* **1982**, *30*, 3167.
(38) Bohlmann, F.; Zeisberg, R. *Chem. Ber.* **1975**, *108*, 1043.
(39) Podkowinska, H.; Skolik, J. *Org. Magn. Reson.* **1984**, *22*, 379.
(40) In a recent paper[41] Hart et al. report the formic acid induced cyclization of 5-hydroxy-1-(4-methyl-3-penten-1-yl)-2-pyrrolidone, which leads to the pyrrolizidine ring system with low stereoselectivity. Assuming that Hart's reaction is kinetically controlled, its outcome implies, that our explanation of the stereochemical course of cyclization to five-membered rings is not generally valid.
(41) Footnote 26 in Burnett, D. A.; Choi, J.-K.; Hart, D. J.; Tsai, Y.-M. *J. Am. Chem. Soc.* **1984**, *106*, 8201.