t-CH=CHC$_6$H$_5$, 69%, mp 99–102 °C).

To demonstrate the utility of these transformations in natural product construction two formal total syntheses of camptothecin (**7**), a molecule of renewed recent interest,[16,17] were executed[4] as in Scheme II in respectable yield[21] through the intermediacy of the two key intermediates **5** and **6**.

The present work offers a uniquely versatile way to assemble annulated pyridones with extensive control of their substitution pattern,[13] by using a transition metal as a template on which to simultaneously generate three new bonds. This approach should surpass the flexibility attained by conventional Diels–Alder routes.[22]

Finally, we note that another catalyst reported to catalyze the formation of 2-pyridones from alkynes and isocyanates, bis(η^4-cyclooctadiene)nickel,[23] is unsuccessful in our systems and very likely operates through an alternative mechanism.[11]

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(16) Ihara, M.; Noguchi, K.; Ohsawa, T.; Fukumoto, K.; Kametani, T. *Heterocycles* **1982**, *19*, 1835. Miyasaka, T.; Sawada, S.; Nokata, K. *Ibid.* **1981**, *16*, 1713. Eckert, H. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 208.

(17) Wani, M. C.; Rowman, P. E.; Lindley, J. T.; Wall, M. E. *J. Med. Chem.* **1980**, *23*, 554. Shanghai No. 5 Pharm. Plant, *Sci. Sin.* (*Engl. Transl.*) **1978**, *21*, 87.

(18) Tang, C. S. F.; Morrow, C. J.; Rapoport, H. *J. Am. Chem. Soc.* **1975**, *97*, 159.

(19) Volkmann, R.; Danishefsky, S.; Eggler, J.; Solomon, D. M. *J. Am. Chem. Soc.* **1971**, *93*, 5576. Bradley, J. C.; Büchi, G. *J. Org. Chem.* **1976**, *41*, 699. Kende, A. S.; Bentley, T. J.; Draper, R. W.; Jenkins, J. K.; Joyeux, M.; Kubo, I. *Tetrahedron Lett.* **1973**, 1307. Quick, J. *Ibid.* **1977**, 327.

(20) Sosnovsky, G.; Krogh, J. A.; Umhoefer, S. G. *Synthesis* **1979**, 722.

(21) For example, **5** is made by us starting from 3-carbomethoxypropanoyl chloride in 9 steps, 9% yield, superior to the Danishefsky route[19] (11 steps, 1.2%) and Quick's synthesis[19] (10 steps, 9%) both from 3-aminopropanal diethylacetal, and the Kende approach[19] from furfural dimethylacetal (13 steps, 2.7%), but inferior to Büchi's strategy[19] from methyl 2,2-dimethoxyethanoate (6 steps, 18%).

(22) Sainte, F.; Serckx-Poncin, B.; Hesbain-Frisque, A.-M; Ghosez, L. *J. Am. Chem. Soc.* **1982**, *104*, 1428.

(23) Hoberg, H; Oster, B. W. *J. Organomet. Chem.* **1982**, *234*, C35; **1983**, *252*, 359; *Synthesis* **1982**, 324.

Iminium Ion and Acyliminium Ion Initiated Cyclizations of Vinylsilanes. Regiocontrolled Construction of Unsaturated Azacyclics

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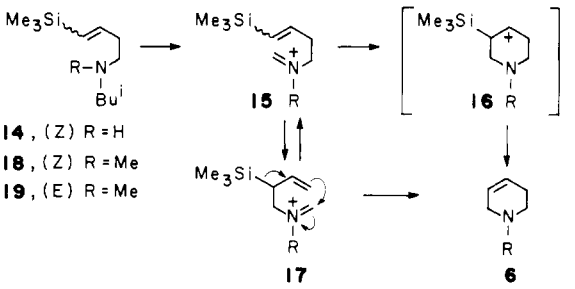
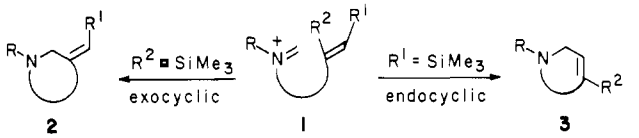
Vinylsilanes are rapidly becoming important terminators for cationic cyclizations.[2] We have described[2a,b] a general stereocontrolled synthesis of alkylidene azacyclics by the intramolecular reaction of vinylsilanes with iminium ions (**1** → **2**). During the course of these studies, we became interested in whether these weakly reactive cyclization components would also participate in

Scheme I

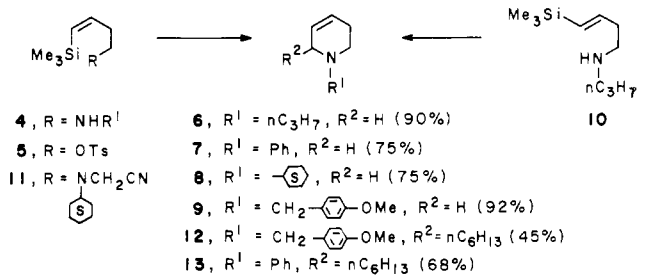


ring closures that are endocyclic[3] with respect to the vinylsilane terminator (**1** → **3**). In this communication, we report that such



cyclizations do occur readily and provide a useful new method for the regiocontrolled assembly of unsaturated azacyclic systems.

We initially explored cyclizations to form tetrahydropyridines. The starting (*Z*)-4-(trimethylsilyl)-3-butenamines (**4**)[4] were prepared by aminolysis (excess amine, 25–80 °C) of readily available tosylate **5**.[4,5] Reactions of **4** with excess paraformaldehyde occured in refluxing acetonitrile in the presence of 0.95 equiv of camphorsulfonic acid to give 1,2,5,6-tetrahydropyridines **6–9**[4] in excellent yields. Alternatively, a (cyanomethyl)amine[6]



could be employed and the cyclization (e.g., **11** → **8**, 56%) accomplished by treatment with silver trifluoroacetate (1 equiv, 100 °C). The stereochemistry of the vinylsilane terminator was not critical, since the (*E*)-vinylsilane **10**[4,7,8] was converted to **6** in 73% yield when treated under similar conditions with paraformaldehyde and acid. Other aldehydes could also be employed. For example, amines **4** (R^1 = Ph and *p*-methoxybenzyl) were cleanly cyclized at 120 °C with heptanal (3 equiv) and camphorsulfonic acid (0.95 equiv) to yield the 2-substituted tetrahydropyridines **12**[4] and **13**.[4]

The 1,2,5,6-tetrahydropyridine ring is found in several natural products and numerous pharmacologically active materials.[9] This

(1) NIH Postdoctoral Fellow, 1981–1983.

(2) (a) Overman, L. E.; Bell, K. L. *J. Am. Chem. Soc.* **1981**, *103*, 1851–1853. (b) Overman, L. E.; Malone, T. C. *J. Org. Chem.* **1982**, *47*, 5297–5300. (c) Burke, S. D.; Murtiashaw, C. W.; Dike, M. S.; Smith-Strickland, S. M.; Saunders, J. O. *Ibid.* **1981**, *46*, 2400–2402. (d) Trost, B. M.; Murayama, E. *J. Am. Chem. Soc.* **1981**, *103*, 6529–6530. (e) Mikami, K.; Kishi, N.; Nakai, T. *Tetrahedron Lett.* **1983**, *24*, 795–798. (f) Nakamura, E.; Fukuzaki, K.; Kuwajima, I. *J. Chem. Soc., Chem. Commun.* **1983**, 499–501.

(3) Cf.: Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734–736.

(4) Yields refer to material purified by chromatography on silica gel. All compounds reported were homogeneous by TLC analysis and showed 250-MHz ^{1}H NMR, IR, and mass spectra consistent with the assigned structures. The molecular composition of key compounds was determined by high-resolution mass spectrometry or combustion analysis.

(5) Available on a large scale from the tetrahydropyranyl ether of 3-butyn-1-ol by silylation (BuMgBr, Me$_3$SiCl), semihydrogenation (*i*-Bu$_2$AlH, H$_2$O), deprotection (MeOH, pyridinium tosylate), and tosylation (TsCl, pyridine) using standard reaction conditions.

(6) Prepared from the reaction of **4** (R = cyclohexyl) with paraformaldehyde, KCN, and acid; cf.: Overman, L. E.; Jacobsen, E. J. *Tetrahedron Lett.* **1982**, *23*, 2741–2744 and references cited therein.

(7) Prepared analogously to **4** from (*E*)-4-(trimethylsilyl)-3-butenol, which was readily prepared from the corresponding *Z* stereoisomer[4] by bromine atom equilibration.

(8) Cf.: Zweifel, G.; On, H. P. *Synthesis* **1980**, 803–805.

(9) (a) For reviews, see: Pinder, A. R. In "The Alkaloids"; Grundon, M. F., Ed.; Chemical Society: London, 1982; Vol. 12, Chapter 2, pp 29–35, and earlier volumes of this series. Coutts, R. T.; Scott, J. R. *Can. J. Pharm. Sci.* **1971**, *6*, 78–84. (b) 1-Methyl-4-phenyl-1,2,5,6-tetrahydropyridine has recently been reported to induce Parkinson's disease in monkeys: *Science* (*Washington, D.C.*) **1983**, 705.

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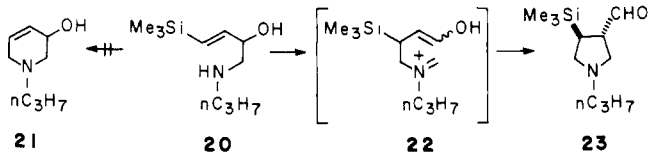
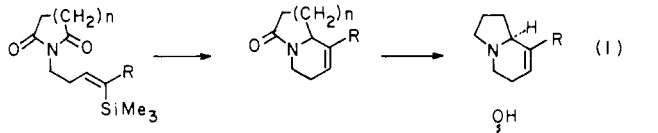
ring system is most commonly constructed by reduction of the corresponding pyridinium salt or from 4-piperidone precursors.[9,10] The cyclization approach reported here has the advantage of complete regiocontrol of the double-bond position and, moreover, should be of particular use for preparing 1-aryl-substituted tetrahydropyridines, which are not generally available from pyridine precursors.

Two mechanisms can be considered for these cyclization reactions (Scheme I). The simplest is direct cyclization of iminium ion **15** to **6**, presumably via a β-silyl cation intermediate **16**.[11] Alternatively, **15** could undergo cationic aza-Cope rearrangement[12] to allylsilane iminium ion isomer **17**, which then cyclizes to **6**.[11-14] Two experiments demonstrate that cationic aza-Cope equilibration occurs more rapidly than cyclization. First, treatment of (*Z*)-vinylsilane amine **14** in refluxing acetonitrile for 1.2 h with formaldehyde containing a trace of formic acid gave a 6:1:3 mixture of 1-isobutyl-1,2,5,6-tetrahydropyridine and the (*Z*)- and (*E*)-methylated amines **18**[4] and **19**,[4] respectively. Since **14** does not undergo $Z \rightarrow E$ isomerization in the absence of formaldehyde,[15] the loss of stereochemistry when formaldehyde is present implies equilibration of **15** and **17** (R = *i*-Bu). Conclusive evidence for the facile formation of a rearranged allylsilane comes from treatment of **20** with paraformaldehyde and camphorsulfonic acid (0.95 equiv in refluxing ethanol). This reaction did not yield tetrahydropyridine **21** but rather pyrrolidine **23**,[4,16] which arises from intramolecular Mannich cyclization[12] of allylsilane iminium ion **22**.



21 **20** **22** **23**

Related cyclizations to form unsaturated azabicyclics, which utilize acyliminium ion initiators,[17] are illustrated in eq 1. Imides



(1)

24 **25**, n = 1, R = H; **26**, n = 2, R = H; **27**, n = 1, R = Br; **28**, R = CH(OH)CH2CH2CH3; **29**, R = C(=O)CH2CH2CH3

24[4] were readily prepared by Mitsunobu[18] coupling of succinimide and glutarimide with the appropriate vinylsilane alcohol.[5] Reduction ($NaBH_4$, MeOH, 0 °C)[17,19] of **24** (R = H, n = 1 or 2) to the hydroxy lactam, followed by cyclization at 25 °C in trifluoroacetic acid afforded indolizidine **25**[4] and quinolizidine **26**[4], in 92% and 91% yields, respectively. The *Elaeocarpus* alkaloids, elaeokanine B (**28**) and A (**29**),[20,21] could be easily assembled using this chemistry. Thus, reduction[19] of **24** (R = Br) and cyclization of the resulting hydroxy lactam in refluxing trifluoroacetic acid provided the bromoindolizidine **27**[4] in 63% yield. This reaction constitutes the first report of the use of a 1-substituted vinylsilane terminator and, importantly, yields directly an alkene product regioselectively functionalized for subsequent transformations. Hydride reduction ($LiAlH_4$) of **27** followed by bromine-lithium exchange (*sec*-BuLi, -78 °C, THF) and reaction of the derived alkenyllithium with butanal gave elaeokanine B (**28**)[20,21] as a 1:1 mixture of alcohol diastereomers in 58% overall yield from **27**. Oxidation of **28** as described by Weinreb[21] provided elaeokanine A (**29**), which showed spectral properties identical with those of natural material.[20,21]

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Supplementary Material Available: Copies of the 250-MHz ^1H NMR spectra for new compounds **6-13**, **23**, and **25-29** (12 pages). Ordering information is given on any current masthead page.

(10) For two recent examples, see: Bac, N. V.; Langlois, Y. *J. Am. Chem. Soc.* **1982**, *104*, 7667-7669. Evans, D. A.; Mitch, C. H. *Tetrahedron Lett.* **1982**, *23*, 285-288.

(11) Electrophilic reactions of vinylsilanes and allylsilanes have been discussed in detail, see: Weber, W. P. "Silicon Reagents for Organic Synthesis"; Springer Verlag: Berlin, 1983. Colvin, E. "Silicon in Organic Synthesis"; Butterworths: London, 1981.

(12) For recent examples and leading references, see: Overman, L. E.; Kakimoto, M.; Okazaki, M.; Meier, G. P. *J. Am. Chem. Soc.*, in press. Overman, L. E.; Sworin, M. *Tetrahedron* **1981**, *37*, 4041-4045.

(13) For a recent example and leading references to intramolecular cyclization reactions of allylsilanes, see: Trost, B. M.; Remuson, R. *Tetrahedron Lett.* **1983**, *24*, 1129-1132.

(14) Cationic cyclizations of iminium ions produced by cationic aza-Cope rearrangements are well-known, see, inter alia: Rischke, H.; Wilcock, J. D.; Winterfeldt, E. *Chem. Ber.* **1973**, *106*, 3106-3118. Overman, L. E.; Kakimoto, M. *J. Am. Chem. Soc.* **1979**, *101*, 1310-1312 and ref 12. Hart, D. J.; Tsai, Y.-M. *Tetrahedron Lett.* **1981**, *22*, 1537-1570. Nossin, P. M. M.; Speckamp, W. N. *Ibid.* **1981**, *22*, 3289-3292.

(15) (*Z*)-Alkene **14** was recovered unchanged (86% yield) when heated for 17 h in refluxing acetonitrile in the presence of 0.95 equiv of camphorsulfonic acid.

(16) Isolated as the corresponding primary alcohol, formed by $NaBH_4$ reduction, in 73% yield.

(17) For a recent brief review, see: Speckamp, W. N. *Recl. Trav. Chim. Pays-Bas* **1981**, *100*, 345-362.

(18) Mitsunobu, O.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* **1972**, *94*, 679-681.

(19) Chamberlin, A. R.; Chung, J. Y. L. *J. Am. Chem. Soc.* **1983**, *105*, 3653-3656.

(20) Johns, S. R.; Lamberton, J. A. In "The Alkaloids"; Manske, R., Ed.; Academic Press: New York, 1973; Vol. 14, p 325.

(21) For a recent synthesis and references to other synthetic work in this area, see: Khatri, N. A.; Schmitthenner, H. F.; Shringarpure, J.; Weinreb, S. W. *J. Am. Chem. Soc.* **1981**, *103*, 6387-6393.

Solvent and Intramolecular Proton Dipolar Relaxation of the Three Phosphates of ATP: A Heteronuclear 2D NOE Study

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The nuclear Overhauser effect (NOE) arises from changes in nuclear spin populations resulting from dipolar relaxation in the presence of double irradiation.[1] Because it is related to $(r_{AB})^{-6}$, where r_{AB} is the distance between two dipolar coupled spins, A and B, nuclear Overhauser effects can provide valuable molecular structure information for solutions of organic and biological molecules. Due to their inverse dependence on the sixth power of r_{AB}, most reports of NOE arise from intramolecular relaxation. However intermolecular effects have been noted.[2-6]

(1) Noggle, J. H.; Schirmer, R. E. "The Nuclear Overhauser Effect"; Academic Press: New York, 1971.

(2) Kaiser, R. *J. Chem. Phy.* **1965**, *42*, 1838.

(3) Chan, S. I.; Kreishman, G. P. *J. Am. Chem. Soc.* **1970**, *92*, 1102.

(4) Levy, G. C.; Cargioli, J. D.; Juliano, P. C.; Mitchel, T. D. *J. Am. Chem. Soc.* **1973**, *95*, 3445.

(5) Yuhasz, S. C.; Kan, L.; Ts'o, P. O. P. In "Conversation in Biomolecular Sterodynamics III" Sarma, R. H., Ed.; Academic Press: New York, 1983; page 50.

(6) Bacon, M.; Maciel, G. E.; Musker, W. K.; Scholl, R. *J. Am. Chem. Soc.* **1971**, *93*, 2537.

0002-7863/83/1505-6994$01.50/0