We submit that the foregoing results demonstrate the viability of the overall design strategy inherent in **4**. Further studies are in progress.[17]

Acknowledgment. Support of this project by Grant CA-17631 from the National Cancer Institute is gratefully apppreciated. We thank Drs. B. Boudet, J. Steele, P. King, and Z.-H. Chen for their contributions to earlier parts of this work, Dr. D. A. Evans and K. Chapman (Harvard University) for a helpful discussion, and Dr. G. R. Weisman (University of New Hampshire) for a valuable suggestion.

(17) Other[5,11] $[\alpha]^{22}_D$'s (in CH_2Cl_2) and mp's of stable solids: **9**, +93.7° (*c* 0.30); **15**, +160.4° (*c* 1.0); **18** [mp 215-217 °C (lit.[14b] mp for (±)-**18**: 212-213 °C)], +344° (*c* 1.0); **19** (mp 132-133 °C), +333° (*c* 1.0). All compounds gave spectra consistent with the structures assigned.

Reactions of Allylsilanes with Simple Iminium Salts in Water: A Facile Route to Piperidines via an Aminomethano Desilylation–Cyclization Process

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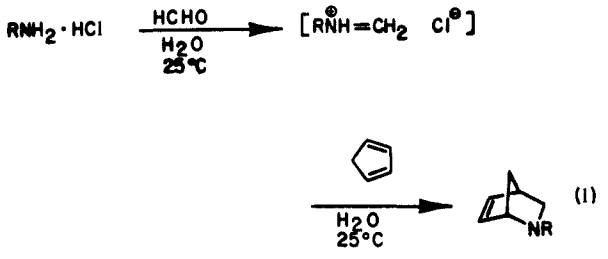
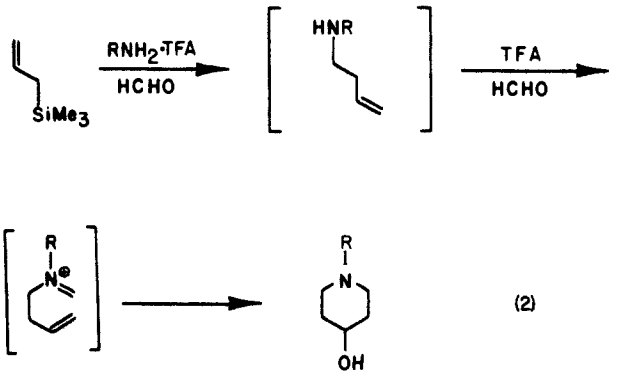
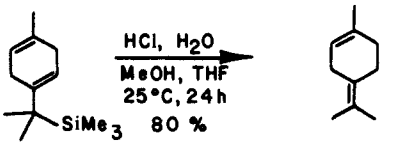
We recently demonstrated that simple iminium salts generated in aqueous medium are sufficiently reactive to undergo [4 + 2] cyclocondensation with unactivated dienes (cf. eq 1).[1] In con-



nection with an ongoing project it was of interest to determine if iminium ion chemistry could be extended to allylsilanes in water.[2] The well-documented reactivity of allylsilanes toward electrophiles[3-5] suggested that treatment of allyltrimethylsilane with an *N*-alkyliminium ion under Mannich-like conditions should provide access to homoallylamines via an aminomethano desilylation process. It was anticipated that subsequent reaction of the homoallylamine with formaldehyde would lead exclusively to 4-substituted *N*-alkylpiperidines via an intramolecular olefin–iminium ion cyclization[6] (eq 2). Of particular concern was the fact

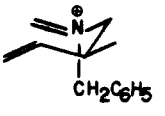


that the acidic conditions (pH 3–4) required to generate iminium ions in aqueous medium would not be compatible with the initial aminomethano desilylation process. It is well established that allylsilanes readily undergo protodesilylation in acidic media.[3] For example exposure of (dihydrobenzyl)silane **1** to hydrochloric acid in aqueous methanol–tetrahydrofuran at ambient temperature for 20 h gives rise to an 80% yield of terpinoline (**2**).[7]



1 2

In order to probe the chemistry depicted in eq 2, a heterogeneous mixture of allyltrimethylsilane, *N*-benzylammonium trifluoroacetate, and 37% aqueous formaldehyde in water was stirred at 35 °C. After 24 h, an 81% yield of *N*-benzyl-4-hydroxypiperidine was isolated (Table I). Use of tetrahydrofuran as a cosolvent resulted in a reduced reaction rate and an increase in the amount of undesired side products. Somewhat surprising was the fact that the corresponding 4-chloropiperidine derivative could be obtained (entry 2) by employing the hydrochloride salt of benzylamine in the presence of lithium chloride. In general, the aminomethano desilylation–cyclization process proceeds smoothly with terminal allylsilanes (entries 4–8). Entries 7 and 8 are of particular interest since they demonstrate the potential for internal participation by a nucleophile during the cyclization process. Crotyltrimethylsilane (entry 3) reacts under the general reaction conditions providing as the sole product a 3,4-trans-disubstituted piperidine which undoubtedly arises from a concerted olefin–iminium ion cyclization of intermediate **3**. Also noteworthy is the fact that substrates



3

possessing free hydroxyl groups exhibited greatly accelerated reaction rates relative to those lacking a polar functional group. Table I also reveals that cyclic allylsilanes could be efficiently converted into bicyclic amines (entries 9–11) giving rise to only cis-fused products in the case of entries 9 and 10.

Our studies suggest that the cyclization step is very rapid relative to homoallylamine formation since only traces of the intermediate homoallylamine were ever observed even when only 1 equiv of formaldehyde was used. However, exclusive homoallylamine

(1) Larsen, S. D.; Grieco, P. A. *J. Am. Chem. Soc.* **1985**, *107*, 1768.

(2) The reaction of iminium ions with olefins (e.g., α-methylstyrene, β-pinene) has been reported to give rise to aminomethylated products in poor yield; see: (a) Hennion, G. F.; Price, C. C.; Wolff, C. V. *J. Am. Chem. Soc.* **1955**, *77*, 4633. (b) Schmidle, C. J.; Mansfield, R. C. *J. Am. Chem. Soc.* **1955**, *77*, 4636, 5698, 5754. (c) Bohme, H.; Fresenius, W. *Arch. Pharm. (Weinheim, Ger.)* **1972**, *305*, 601, 610. (d) Manninen, K.; Haaple, J. *Acta Chem. Scand., Ser. B* **1974**, *B28*, 433.

(3) Fleming, I. *Chem. Soc. Rev.* **1981**, *10*, 83. For some recent examples of allylsilane additions to *N*-acyliminium ions, see: (a) Kozikowski, A. P.; Pyeong-uk, P. *J. Org. Chem.* **1984**, *49*, 1674. (b) Gramain, J.-C.; Remuson, R. *Tetrahedron Lett.* **1985**, 327. (c) Hiemstra, H.; Fortgens, H. P.; Speckamp, W. N. *Ibid.* **1985**, 3155. (d) Shono, T.; Matsumura, Y.; Uchida, K.; Kobayashi, H. *J. Org. Chem.* **1985**, *50*, 3243.

(4) For an example of an iminium ion–vinylsilane cyclization, see: Overman, L. E.; Bell, K. L.; Ito, F. *J. Am. Chem. Soc.* **1984**, *106*, 4192.

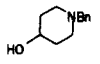
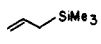
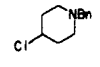
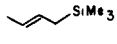
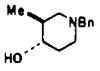
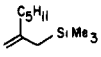
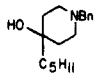
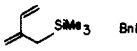
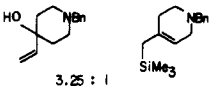
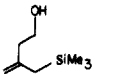
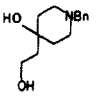
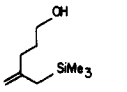
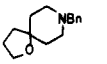
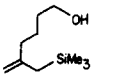
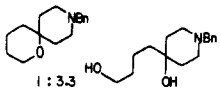
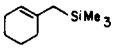
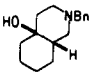
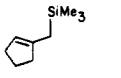
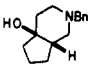
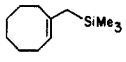
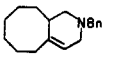
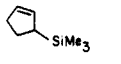
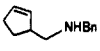
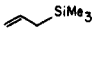
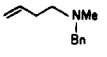
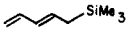
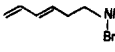
(5) A photochemically initiated reaction of allylsilanes with iminium ions has recently been reported (Ahmed-Schofield, R.; Mariano, P. S. *J. Org. Chem.* **1985**, *50*, 5667).

(6) For examples of intramolecular olefin–iminium ion cyclizations, see: Grewe, V. R.; Hamann, R.; Jacobsen, G.; Nolte, E.; Riecke, K. *Liebigs. Ann. Chem.* **1953**, *581*, 85. Bohlmann, F.; Winterfeldt, E. *Chem. Ber.* **1960**, *93*, 1956. Cope, A. C.; Burrows, W. D. *J. Org. Chem.* **1966**, *31*, 3099. Wilcock, J. D.; Winterfeldt, E. *Chem. Ber.* **1974**, *107*, 975.

(7) Coughlin, D. J.; Salomon, R. G. *J. Org. Chem.* **1979**, *44*, 3784.

0002-7863/86/1508-3512$01.50/0

Table I. Reaction of Allysilanes with *N*-Alkylmethyleneiminium Salts in Water[a]

entry	allylsilane	amine	temp, °C	time, h	prod.	yield, %[b]
1		$BnNH_2$·TFA	35	24		81
2		$BnNH_2$·HCl[c] LiCl	35	45		48
3		$BnNH_2$·TFA	45	48		54
4		$BnNH_2$·TFA	30	48		53
5		$BnNH_2$·TFA	25	24	 3.25 : 1	85
6		$BnNH_2$·TFA	25	4		100
7		$BnNH_2$·TFA	25	6		58
8		$BnNH_2$·TFA	25	6	 1 : 3.3	83
9		$BnNH_2$·TFA	35	48		94
10		$BnNH_2$·TFA	25	84		68
11		$BnNH_2$·TFA	25	82		62
12		$BnNH_2$·TFA	45	42		50
13		BnNHMe·TFA	50	68		76[d]
14		BnNHMe·TFA	45	65		95

[a] All reactions were run in 3.0–3.5 M aqueous solutions of the amine salt (1.0 equiv) using 1.1 equiv of the allylsilane and 2.3 equiv of 37% aqueous formaldehyde. [b] Isolated yields. [c] Reaction run in a 2.9 M solution of the amine salt in THF with 2 equiv of LiCl and 2.1 equiv of 37% aqueous formaldehyde. [d] 15% of BnNHMe recovered.

production occurred with 3-(trimethylsilyl)cyclopentene (entry 12). Even under forcing conditions, the product of aminomethano desilylation would not cyclize to a bicyclo[3.3.0] system. Tertiary homoallylamines could be prepared directly from acyclic allylsilanes by using a secondary amine salt (entries 13 and 14); however, these reactions were much slower relative to those cases employing primary amine salts (compare entries 1 and 13).

In summary, a generally useful synthesis of piperidines from primary amines, formaldehyde, and allylsilanes is now possible via an aminomethano desilylation–cyclization process. Further studies with iminium ions and allylsilanes are in progress.

Acknowledgment. This investigation was supported in part by a Grant from the National Science Foundation. The 300-MHz NMR instrument (Varian XL-300) used in the above studies was purchased with funds provided by the National Institutes of Health (Grant RR-1882).

Synthesis of a Taxane Triene

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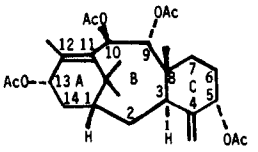
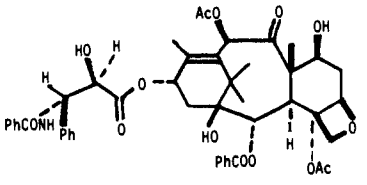
Received November 14, 1985

The highly oxygenated tricyclic structures of the taxane diterpenes[1] (e.g., taxusin, **1**)[2] and the powerful antitumor activities of certain members of this series (e.g., taxol, **2**)[3] have stimulated much recent effort toward their total synthesis. Despite the diversity of such approaches,[4] none have succeeded in constructing the complete carbon framework of the natural taxanes. We now report the first total synthesis of a racemic taxane triene comprising the *full and stereochemically correct carbon framework* of natural taxusin (**1**).



1



2

Directed-aldol $TiCl_4$-mediated coupling[5] of acetal **3**[6] with enol silane **4**[7] gave β-alkoxy ketones which on acid treatment gave 90%

(1) (a) Lythgoe, B. *The Alkaloids*; Manske, R. H. E. Ed.; Academic Press: New York, 1968; Vol. X, p 597. (b) Miller, R. W. *J. Nat. Prod.* **1980**, *43*, 425.

(2) (a) Miyazaki, M.; Shimizu, K.; Mishima, N.; Kurabayashi, M. *Chem. Pharm. Bull.* **1968**, *16*, 546. (b) Chan, W. R.; Halsall, T. G.; Hornby, G. M.; Oxford, A. W.; Sabel, W.; Bjamer, K.; Ferguson, G.; Robertson, J. M. *Chem. Commun.* **1966**, 923.

(3) Wani, M. C.; Taylor, M. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325.

(4) Recent approaches that have yielded tricyclic compounds include: (a) Martin, S. F.; White, J. B.; Wagner, R. *J. Org. Chem.* **1982**, *47*, 3190. (b) Shea, K. J.; David, P. D. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 419. (c) Brown, P. A.; Jenkins, P. R.; Fawcett, J.; Russell, D. R. *J. Chem. Soc., Chem. Commun.* **1984**, 253. (d) Neh, H.; Blechert, S.; Schnick, W.; Jansen, M. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 905. (e) Holton, R. A. *J. Am. Chem. Soc.* **1984**, *106*, 5731. (f) Kojima, T.; Inouye, Y.; Kakisawa, H. *Chem. Lett.* **1985**, 323. A recent synthesis of a possible bicyclic biogenetic taxane precursor, verticillene, has been reported (Jackson, C. B.; Pattenden, G. *Tetrahedron Lett.* **1985**, 3393), but this system fails to cyclize to taxanes with acids (Begley, M. J.; Jackson, C. B.; Pattenden, G. *Ibid.* **1985**, 3397).

(5) Mukaiyama, T. *Org. React.* **1982**, *28*, 203.

(6) Acetal **3** was prepared from 2,6-dimethylcyclohexenone by the following 10 steps in 21% yield. Conjugate addition of CH_2=$CHMgBr$ (1.4 equiv, 0.1 equiv of CuI, Et_2O–THF, −78 °C, 2.5 h) and trapping with CH_3I (4 equiv, 1 equiv of HMPA, −78 to 25 °C, 16 h, 78%), then α-chlorination (1.2 equiv of SO_2Cl_2, CCl_4, catalytic pTSA, 10–25 °C, 12 h), and HCl elimination (3 equiv of LiCl, 3 equiv Li_2CO_3, DMF, 100 °C, 2 h, 75%) gave 2,2,6-trimethyl-3-vinyl-5-cyclohexenone. Reaction with the anion of Me_3SiCH_2Cl (1.5 equiv of Me_3SiCH_2Cl, 1.5 equiv of sec-BuLi, THF/TMEDA, then addition of enone at −55 °C and warming to 25 °C for 2 h) followed by direct hydrolysis (90% HCOOH, 25 °C, 1.5 h) gave 90% of a dienal which was oxidized (1.1 equiv of $NaClO_2$, 2:1 H_2O–dioxane, 1.3 equiv of NH_2SO_3H, 0–25 °C, 1.5 h) and reacted with excess CH_2N_2 in ether (0 °C, 30 m) to give 69% of methyl 2,2,6-trimethyl-3-vinyl-5-cyclohexenecarboxylate. Vinyl cleavage (2.6 equiv of *N*-methyl-morpholine *N*-oxide (NMO), 0.02 equiv of OsO_4, 2:1 Me_2CO–H_2O, 25 °C, 16 h, bisulfite workup, followed by 1.1 equiv of $NaIO_4$ in 1:1 Me_2CO-H_2O, 25 °C, 30 m) gave 63% of noraldehyde which was converted in 95% yield (glycol, pTSA, C_6H_6, reflux) to acetal **3** (C, 65.88; H, 8.65).

(7) Cf.: House, H. O.; Chu, C.-Y.; Wilkins, J. M.; Umen, M. J. *J. Org. Chem.* **1975**, *40*, 1460.

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