Tetrahedron Letters,Vol.25,No.50,pp 5739-5742,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

THE IMPORTANCE OF VINYLSILANE STEREOCHEMISTRY AND σ-π STABILIZATION IN IMINIUM ION-VINYLSILANE CYCLIZATIONS. A SHORT TOTAL SYNTHESIS OF THE AMARYLLIDACEAE ALKALOID (±)-EPIELWESINE.

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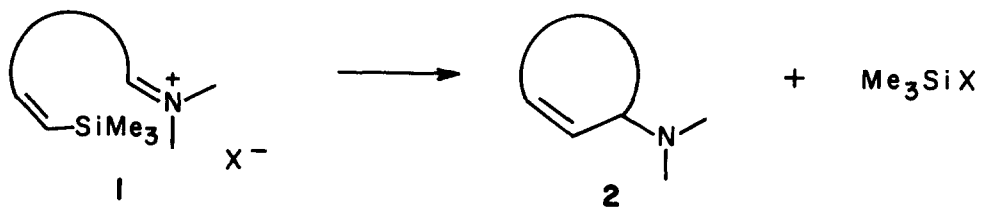
Summary: cis-3a-Aryl-2,3,3a,4,5,7a-hexahydro-1H-indoles 5 and 10 are formed in excellent yield from acid promoted cyclization of (Z)-vinylsilane imines 3 and 9. The failure of the corresponding (E)-vinylsilane isomer 4 to cyclize under similar conditions demonstrates that the β-silylcation intermediates formed in these reactions derive significant stabilization from σ-π delocalization.

We recently reported that a variety of unsaturated azacyclics can be prepared by the intramolecular reaction of iminium ions with vinylsilanes.[1] An important feature of these cyclizations is the ability of the silicon substituent[2] to control the stereochemistry[1a] and regiochemistry[1] of the product double bond. An important class of cyclizations which have not been explored previously are ring closures that are exocyclic with respect to the iminium ion initiator (1→2). In this Letter, we report that iminium ion-vinylsilane



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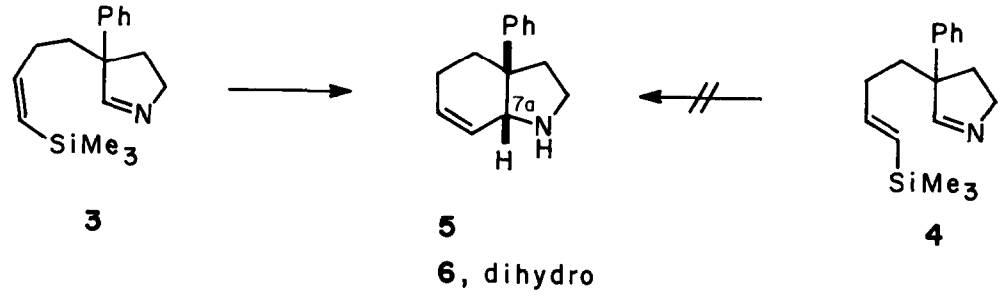
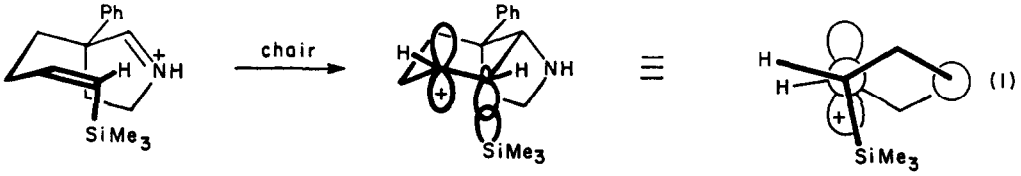
cyclizations of this type that form six-membered rings are facile with (Z)-vinylsilanes.

We initially examined the cyclization of vinylsilane imines 3 and 4. Cyclization of 3[3] in acetonitrile (0.2 M, 82°C, 2h) proceeded cleanly in the presence of 1 equiv of CF_3COOH to give 5[4] in 90% yield. cis-Hexahydroindole 5 showed diagnostic signals in the ^1H NMR spectrum at δ 5.9-6.2 (m, CH=CH) and 3.66 (narrow m, C-7$_a$H), and was converted to known[5] cis-3a-phenyl-2,3,3a,4,5,6,-7,7a-cis-1H-indole 6 (maleate salt mp 152°C) upon catalytic hydrogenation. In marked contrast, attempted cyclization of (E)-vinylsilane imine 4[3] under identical conditions afforded no trace of 5 after 48 h, while treatment of 4 under more forcing conditions resulted in significant protodesilylation.



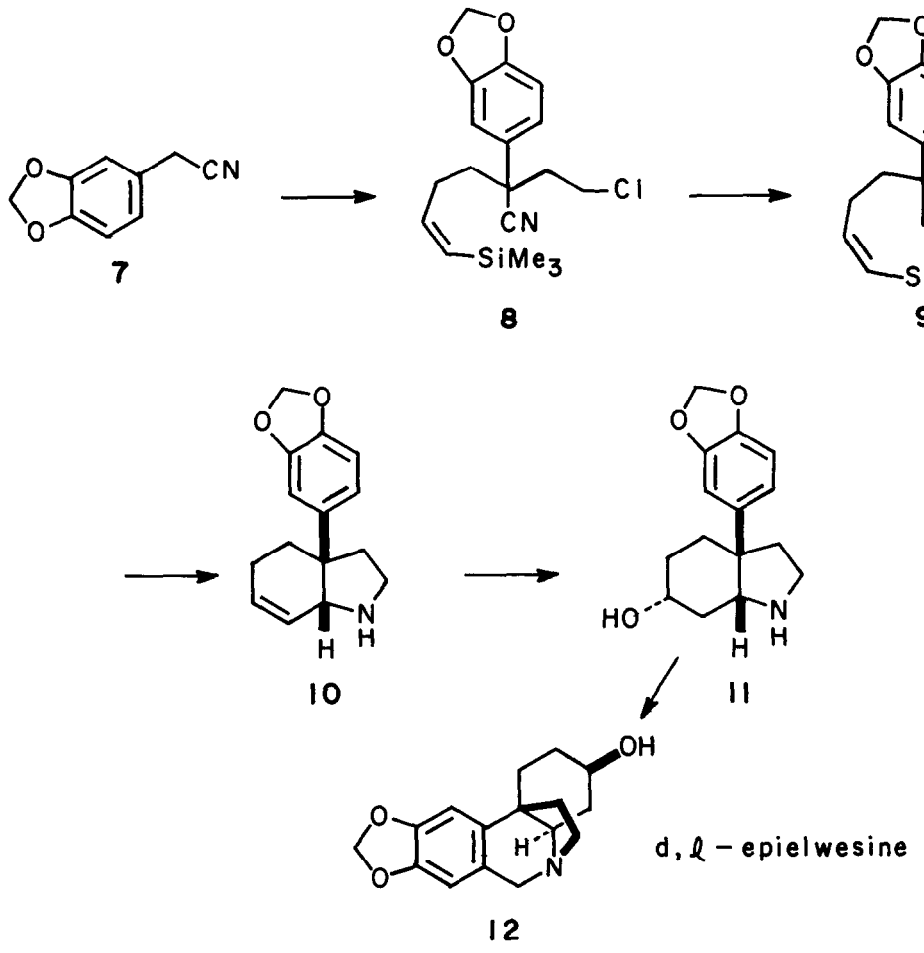
Cyclization of (Z)-vinylsilane 3 at a rate which is at least 7000 times greater[6] than that of the (E)-isomer 4 provides a striking demonstration of the importance of σ-π (hyperconjugative or vertical)[7] stabilization in the cyclization transition state. As illustrated in eq 1, only the Z-alkene substituent can initially participate in σ-π stabilization of the developing β-silyl cation. Although not illustrated in eq 1, this situation is unchanged if the cyclization occurred alternatively in a boat geometry. It could be noted that an iminium ion is a weak cyclization initiator[1] which should magnify the rate difference between the vinylsilane stereoisomers.[8]



The use of this chemistry to achieve a short stereocontrolled entry to simple amaryllidaceae alkaloids is outlined in the Scheme. Sequential alkylation[3] of 3,4-(methylenedioxy)phenylacetonitrile 7 with (Z)-(4-bromo-1-butenyl)-trimethylsilane[1b] and 1-bromo-2-chloroethane provided 8[4] in 62% yield. Reduction of nitrile 8 at -78°C with i-Bu_2AlH[3] afforded Δ^1-pyrroline 9[4] (81% yield; IR 1608 cm^{-1}, ^{13}C NMR 171.1 ppm, C=N), which was cyclized in refluxing acetonitrile in the presence of 1 equiv of CF_3COOH to give cis-hexahydroindole 10[4] (mp 101-103°C) in 73% overall yield from 8. Although hydroboration of 10 was not successful, this intermediate was cleanly hydrated by sequential treatment with 2.0 equiv of $Hg(OAc)_2$ in $THF-H_2O$ and $NaBH_4$[9] to give the known aminoalcohol 11[4] (mp 176-178°C, lit.[10] 179-180°C) as the sole product. This remarkably selective hydration[11] was best accomplished under conditions which left 39% of 10 unchanged, although the yield based on consumed starting material

was excellent (98%). Pictet-Spengler cyclization[12] of 11 provided d,l-epielwesine (12, mp 182-184°C, lit.[10] mp 182-184°C) in 68% yield. This short sequence is efficient and provides 12 in 30% overall yield from commercially available 7.

Scheme



Acknowledgment. We particularly wish to thank Professor R. Pinder of Clemson University for his initial studies of alternate routes for preparing 3, and Professor I.H. Sánchez for a sample of d,l-epielwesine and other comparison spectra. The financial support of the NIH (GM 30859-01-03) and NSF (Departmental instrumentation grants) is gratefully acknowledged.

References and Notes

1. For leading references, see (a) Overman, L.E.; Bell, K.L.; Ito, F. J. Am. Chem. Soc. 1984, 106, 4192. (b) Overman, L.E.; Malone, T.C.; Meier, G.P. Ibid. 1983, 105, 6993.
2. Weber, W.P. "Silicon Reagents for Organic Synthesis"; Springer Verlag: Berlin, 1983.
3. Overman, L.E.; Burk, R.M. preceding Letter in this issue.
4. Yields refer to material purified by chromatography on silica gel. All new compounds were homogeneous by TLC analysis and showed 250 MHz ^{1}H NMR, 63 MHz ^{13}C NMR, IR and mass spectra consistent with their assigned structures. Molecular composition of key intermediates was confirmed by high resolution MS or elemental analysis.
5. Langlois, M.; Guillonneau, C.; Mangan, J.; Maillard, J. Tetrahedron 1971, 27, 5641.
6. This estimate follows from cyclizations of 3 and 4 conducted identically in C_6D_6 (0.13 M, 1.00 equiv of CF_3COOH, 115°C): 3 half-life = 9 min; 4 no reaction after 48 h; a trace of 5 was detectable (^{1}H NMR analysis at δ 3.88 ppm) after 76 h. The calculation assumes that 5% of 5 could have been formed from 4 at 76 h.
7. β-Silyl cations certainly derive stabilization from the silyl substituent by both inductive and hyperconjugative mechanisms.[2] For a recent study of this issue that apparently underestimates the importance of σ-π delocalization, see Lambert, J.B.; Finzel, R.B. J. Am. Chem. Soc. 1982, 104, 2020.
8. Successful cyclizations of (E)-vinylsilanes with powerful initiators are known, see, inter alia Burke, S.D.; Murtiashaw, C.W.; Dike, M.S.; Smith-Strickland, S.M.; Saunders, J.O. J. Org. Chem. 1981, 46, 2400.
9. Brown, H.C.; Geoghegan, P.J., Jr. J. Org. Chem. 1970, 35, 1844.
10. For previous syntheses of d,l-epielwesine, see Stevens, R.V.; Dupree, L.E., Jr. J. Chem. Soc. Chem. Commun. 1970, 1585; Sanchez, I.H.; Lopez, F.J.; Flores, H.J.; Larraza, M.I. Heterocycles 1983, 20, 247. Sanchez, I.H.; Lopez, F.J.; Sorice, J.J.; Larraza, M.I.; Flores, H.J. J. Am. Chem. Soc. 1983, 105, 7640.
11. For a closely related conversion, see Keck, G.E.; Webb, R.R., J. Org. Chem. 1982, 47, 1302.
12. Whitlock, H.W., Jr.; Smith, G.L. J. Am. Chem. Soc. 1967, 89, 3600.

(Received in USA 5 September 1984)