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Preparation of Enantioenriched Tetrahydropyridines by Iminium Ion-Vinylsilane Cyclizations

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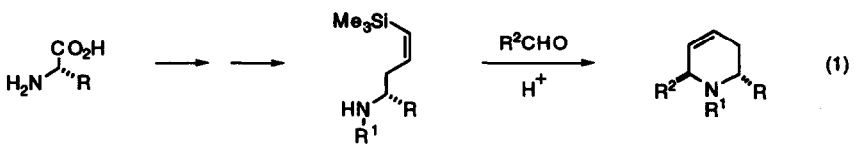
Abstract. Tetrahydropyridines can be prepared from (*S*)-amino acids in high enantiomeric purity as outlined in equation 1.

Electrophilic cyclization reactions of iminium ions (Mannich cyclizations) constitute some of the most important methods for preparing nitrogen heterocycles. A continuing theme in the evolution of this chemistry has been the development of selective methods for initiating and terminating the cyclization event.[1,2] In recent years vinylsilanes have emerged as extremely valuable π-nucleophiles in Mannich-type cyclizations.[2,3] A wide variety of nitrogen heterocycles containing endocyclic or exocyclic unsaturation have been prepared by iminium ion-vinylsilane cyclizations. Among the more important ring systems assembled in this way is the 1,2,5,6-tetrahydropyridine ring, a heterocyclic unit found in a variety of alkaloids and other pharmacologically active agents.[4] In this Letter we report, contrary to the conclusions of an earlier study,[5] that substituted 1,2,5,6-tetrahydropyridines can be prepared in high enantiomeric purity by Mannich cyclizations of amino acid-derived 4-silyl-3-alkenylamines (eq 1). Differing methods of iminium ion generation and their effect on the stereochemical outcome of these iminium ion-vinylsilane cyclizations are also described.

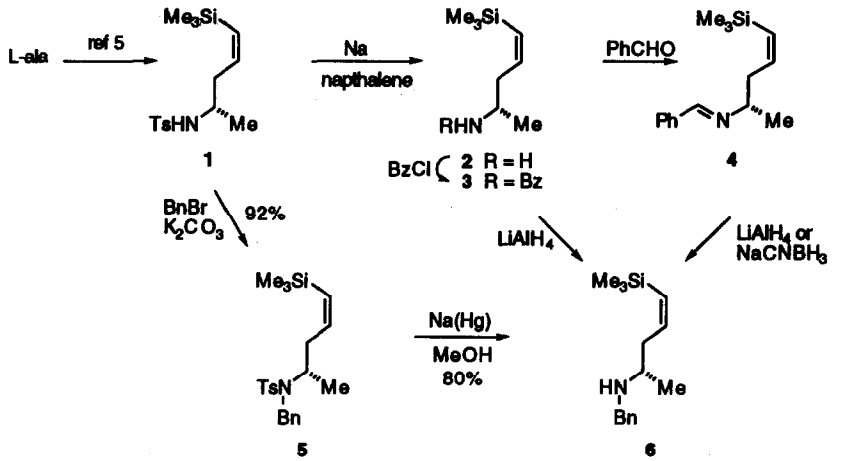


(1)

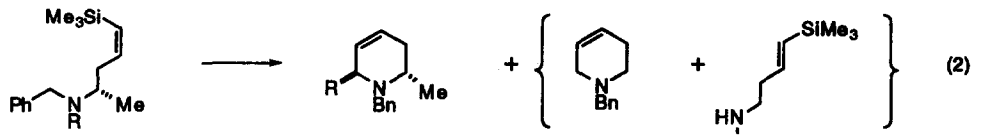
Enantiopure (*S*)-*N*-benzyl-5-(trimethylsilyl)-4*Z*-pentenyl-2-amine (**6**) was prepared from L-alanine along lines outlined earlier.[5] Amine **6** of excellent enantiomeric purity (>96% ee) could be obtained from reduction of benzamide **3** or imine **4**, or more conveniently by *N*-benzylation of **1** to

afford **5** followed by desulfonylation with Na(Hg).[6] The enantiomeric purity of **6** was best assessed by converting it to the *N*-tosyl derivative **5** followed by HPLC analysis using a Chiracel OD column.[7] Pentenylamine **6**, prepared by the preferred **1** → **5** → **6** sequence, was >98% enantiomerically pure.

Scheme I



We initially examined the formation of tetrahydropyridines **10** and **11** (eq 2). Three methods for forming the iminium ion intermediates were examined: direct acid promoted reaction of **6** with paraformaldehyde or formalin, oxidation of α-silylmethylamine **7**,[1] and silver promoted decyanation of cyanoalkylamines **8** and **9**. As summarized in Table 1, all precursors afforded enantioenriched tetrahydropyridine products **10** or **11**.[8] As reported earlier, only the *trans*-2,6-disubstituted stereoisomer **11** is produced from **9**.[5] The reactions summarized in entries 1-5 produced significant amounts of 1-benzyl-1,2,5,6-tetrahydropyridine (**12**), which required careful chromatography to separate it from **10**. Monitoring the reaction summarized in entry 4 by GLC demonstrated that **10** and *N*-benzyl-4-(trimethylsilyl)-3*E*-pentenylamine (**13**) formed within hours, while **12** was produced more slowly, presumably from cyclization of **13**. Tetrahydropyridine **12** was not detected (GLC analysis) in reactions in which water or formaldehyde were not present (e.g., Table 1, entries 6-8).



6 R = H
7 R = CH_2SiMe_3
8 R = CH_2CN
9 R = CHPhCN

10 R = H
11 R = Ph

12

13

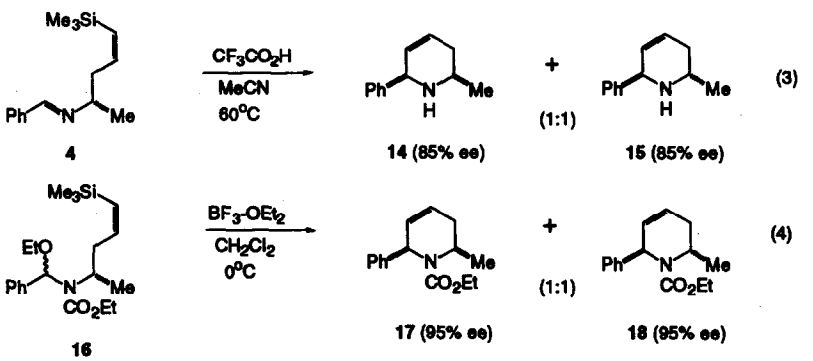
Results of related cyclizations of imine **4** and α-ethoxycarbamate **16**[9] are summarized in eqs 3 and 4. As previously reported, both reactions afford a ~1:1 mixture of stereoisomeric 2,6-disubstituted tetrahydropyridine products in crude yields of 50-70%.[5] After separation by flash chromatography or HPLC, analytically pure **14** and **15** (and **17** and **18**) were isolated in combined yields of 33-37%.

Table 1. Iminium Ion-Vinylsilane Cyclizations of **6** - **9**.

		Amine **10** or **11**				**12**
Entry	**Cyclization Conditions**[a]	**Cpd**	**Yield, %**	$[\alpha]_D$[b]	**ee, %**[c]	**Yield, %**[d]
1	$(CH_2O)_n$, p-TsOH·H_2O, MeCN, 60 °C[e]	**10**	67-69	+33-36	64-67	(4-10)
2	$(CH_2O)_n$, p-TsOH, 4Å MS, MeCN, 60 °C[e]	**10**	38-48	+50-54	97-98	15
3	$(CH_2O)_n$, TFA, MeCN, 70 °C	**10**	40-45	+56	>99	21
4	formalin, TFA, THF-H_2O (1:3), 23 °C[e]	**10**	44-50	+57-62	98-99	(15-27)
5	formalin, TFA, THF-H_2O (1:3), 70 °C	**10**	44	+60	>99	9
6	**7**, $(Bu_4N)_2Ce(NO_3)_6$, MeCN, 23 °C	**10**	61	+56	>90[f]	--
7	**8**, $AgBF_4$, MeCN, 100 °C	**10**	33-34	+50-51	92-94	--
8	**9**, $AgBF_4$, MeCN, 100 °C[e]	**11**	45-55	+136-147	79-83	--

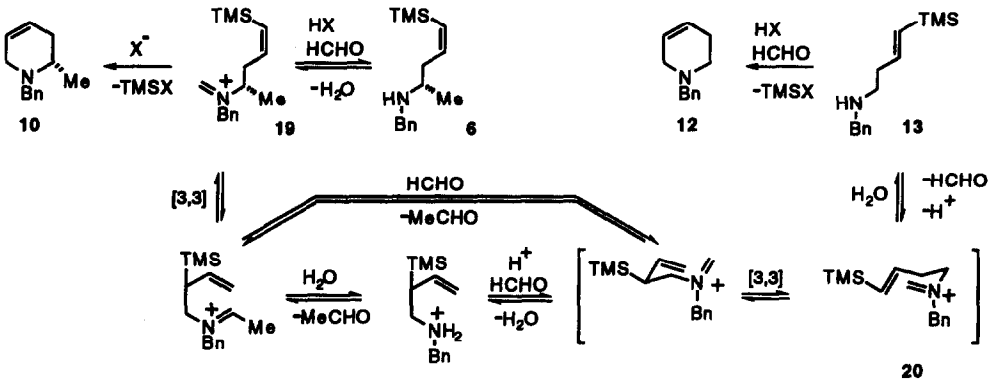
[a]The substrate for entries 1-5 was **6**; 1.1-1.3 equiv of acid was employed. [b]In $CHCl_3$, c = 1.0; except entry 4 (c 0.4) and entries 2 and 7 (c 0.25). [c]By HPLC analysis (Chiracel OD) of **10** or capillary GLC analysis (J&W Cyclodex-B) of **11**. [d]GLC yields are in parentheses. [e]Results of 2-3 identical experiments. [f]^1H NMR analysis of the MPTA derivative of 2-methylpiperidine, prepared from **10**, showed only a single diastereomer.

Enantiomeric purity of **14** and **15** was best determined by HPLC analysis (Chiracel OJ) of the carbamate derivatives **17** and **18**. As shown in eqs 3 and 4, the tetrahydropyridine epimers were formed in identical enantiomeric purities: 85% for cyclization of the iminium ion derivative at 60 °C and 95% for cyclization of the more reactive *N*-ethoxycarbonyl iminium ion derivative at 0 °C.



The origin of the partial racemization seen in some of the cyclizations reported here is undoubtedly complex. As we have discussed, racemization results from a combination of aza-Cope equilibrations and iminium ion stereomutations.[5a] It is not surprising that the formation of **10** in high enantiopurity (entries 2-5) is accompanied by significant formation of the "des-methyl" tetrahydropyridine **12**, since conversion of **19** to **20** and eventually to **13** would prevent **19** from further rearrangements leading to racemization (Scheme II).[5a] However, further mechanistic discussion must be deferred to a future full account of this work.

Scheme II



In summary, enantioenriched 6-substituted and 2,6-disubstituted tetrahydropyridines can be prepared by iminium ion-vinylsilane cyclizations of the L-alanine-derived silylpentenylamine **6**. Cyclization is more rapid than racemization with both iminium ion (*N*-benzyl and *N*-H) and acyl iminium ion (*N*-ethoxycarbonyl) intermediates. Under optimum conditions, tetrahydropyridine products of 85-99% ee can be obtained. The extent of racemization in cyclizations of the *N*-benzyl formaldiminium ion to produce **10** varies somewhat with reaction conditions, although further investigations will be required to fully understand these effects. Lastly, oxidative cyclization of the α-silylmethyl precursor **7** allows **10** to be formed in good yield at room temperature and under neutral conditions.

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References and Notes

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4. Flann, C. J.; Malone, T. C.; Overman, L. E. *Org. Synth.* **1989**, *68*, 188.
5. (a) Daub, G. W.; Heerding, D. A.; Overman, L. E. *Tetrahedron* **1988**, *44*, 3919. (b) Heerding, D. A. *Ph.D. Dissertation*, University of California, Irvine, 1989.
6. Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.*, **1976**, 3477.
7. Amine **6** yellows readily and its optical rotation is somewhat unreliable in gauging enantiomeric purity.
8. Contrary to the earlier report and consistent with the results of entry 7, reexamination of a sample of **11** prepared earlier[5] showed that it was enantioenriched $[\alpha]_D$ +106 (c 0.9, $CHCl_3$).
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