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SYNTHESIS OF ALLOPUMILIOTOXIN A ALKALOIDS *VIA* IMINIUM ION-VINYLSILANE CYCLIZATIONS

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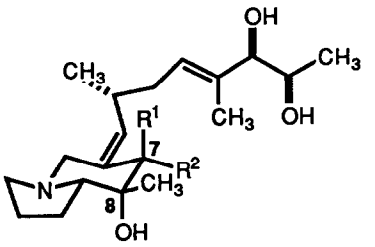
Summary: *The title reaction can be employed to assemble the allopumiliotoxin A alkaloid skeleton with either stereochemistry of the C-7 allylic hydroxyl group.*

The most complex members of the pumiliotoxin A class of amphibian alkaloids, the allopumiliotoxins, contain oxidation at both C-7 and C-8 of the indolizidine ring.[2] Since these alkaloids, e.g. **1** and **2**, are found in much smaller amounts in *Dendrobatid* frogs than alkaloids such as pumiliotoxin B (**3**), chemical synthesis[3] will be required to fully explore cardiotonic activity[4] in the allopumiliotoxin series. In this communication, we report that the stereospecific iminium ion-vinylsilane cyclization approach we developed earlier to prepare (+)-pumiliotoxin B and related alkaloids[5,6] can be used also to assemble the basic skeleton of the allopumiliotoxin A alkaloids. This enantioselective route provides access to both C-7 hydroxyl epimers, and by design is particularly well-suited for preparing the more active[4d] C-7 axial hydroxyl stereoisomers (R^1 = OH).

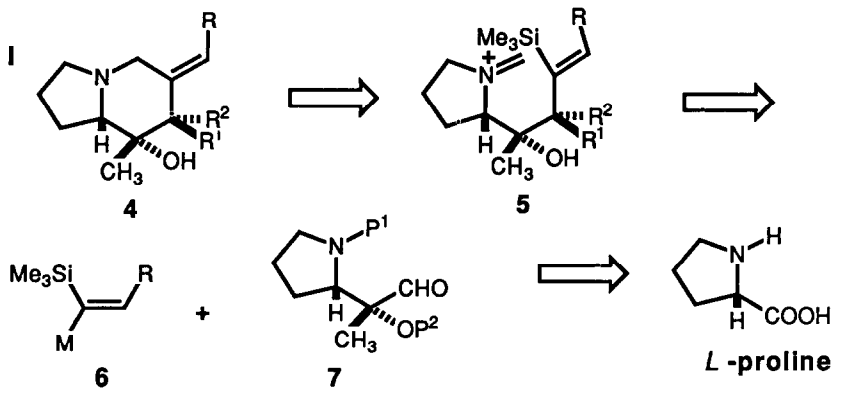
Our basic synthesis strategy is outlined in Scheme I. We envisaged formation of the cyclization substrate **5** by the combination of a side chain nucleophile **6** with a highly functionalized aldehyde component **7** derived from *L*-proline. We anticipated that if the metal M and the protecting groups P^1 and P^2 were chosen properly, facial selectivity in the addition of **6** could be controlled by the C-8 oxygen substituent in the sense of Cram's chelate model[7] to provide stereoisomer **5** (R^1 = OH, R^2 = H) predominantly. The foremost issue to be examined was the viability of the key cyclization step **5** → **4** with a substrate containing a potentially labile and inductively deactivating allylic oxygen substituent.[8] We chose to examine this sequence initially in a model series with a *n*-butyl side chain.

After considering several possible candidates for the aldehyde component **7**, aldehyde **16**[10] was chosen since it held good promise to deliver the desired facial selectivity in the addition of nucleophiles.[9] In particular, the cyanomethyl group is an ideal choice for P^1 since it is a latent iminium ion precursor, it may decrease the propensity of chelation to the nitrogen through inductive electron-withdrawal, and it has proven to be stable to vinyl organometallics at low temperature (<-78°C).[11] This intermediate can be



	R^1	R^2	
1	OH	H	allopumiliotoxin 339 A
2	H	OH	allopumiliotoxin 339 B
3	H	H	pumiliotoxin B

Scheme I

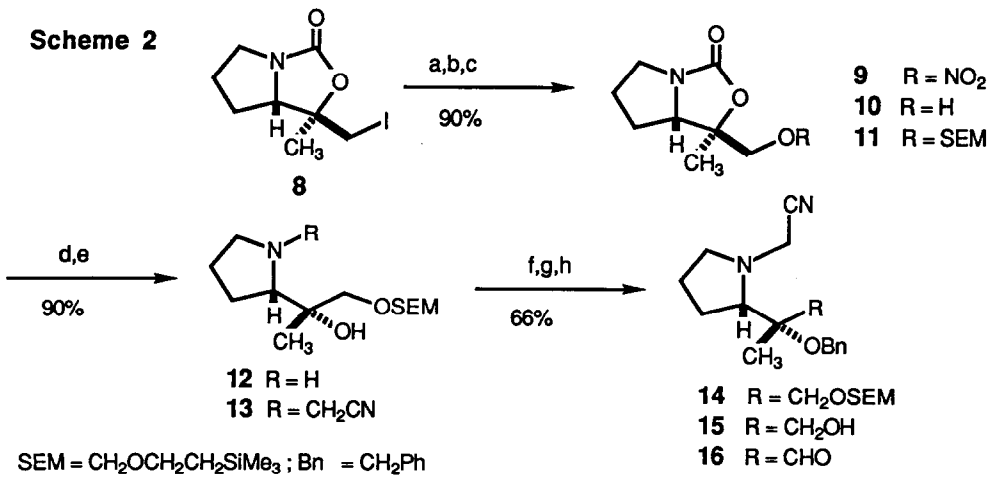


R^1,R^2= OH,H or H,OH; M= metal; P^1,P^2= unspecified protecting group(s)

prepared in a straightforward fashion (see Scheme 2) in 53% overall yield from the known iodide **8**;[12] this latter intermediate is available in 4 steps (45% yield) from commercially available Cbz-*L*-proline. Key steps in this sequence are (a) silver-assisted displacement of the poorly reactive[5b] iodide **8** with nitrate anion to afford, after reduction, alcohol **10**,[10b] (b) protection of the secondary amine with a cyanomethyl group (**12** → **13**), (c) removal of the SEM protecting group under mild conditions[13] to give alcohol **15** ($[\alpha]_D$ -46.7°, c 1.20 $CHCl_3$),[10b] and (d) use of a non-aqueous work-up[14] to isolate aldehyde **16**[10a] from Swern oxidation[15] of **15**.

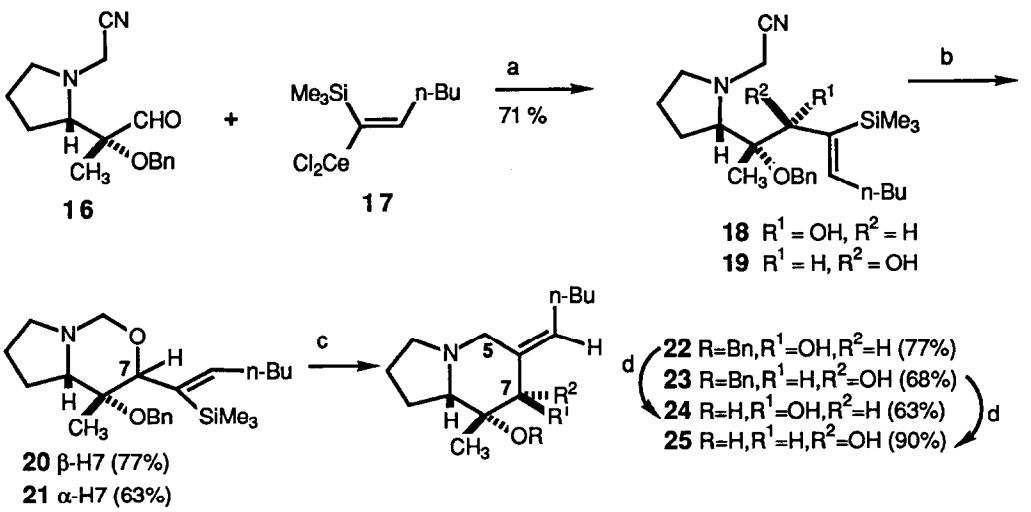
Although α-silyl vinyl lithium and vinyl Grignard reagents added to aldehyde **16** in low yield only, the cerium reagent **17**, prepared from the corresponding lithium intermediate[16] by the general procedure of Imamoto,[17] reacted in good yield at -78°C in THF to give alcohols **18**[10a] and **19**[10b] in 51% and 20% yields, respectively (see Scheme 3). The stereostructures of these allylic alcohols could be specified only

Scheme 2



(a) $AgNO_3$, CH_3CN, 80°C (b) Zn, NH_4OAc, MeOH, 0°C (c) SEM-Cl, i-Pr_2NEt,CH_2Cl_2,23°C (d) KOH, EtOH-H_2O, 80°C
(e) ICH_2CN, Et_3N, THF, 23°C (f) BnBr, KH, THF, 23°C to reflux (g) $LiBF_4$, CH_3CN-H_2O, 70°C (h) Swern conditions-Ref. 15

Scheme 3



(a) **17** added to **16** at -78°C,THF (b) $AgNO_3$, EtOH, 23°C (c) RSO_3H, $(CH_2O)_n$, CH_3CN, 100°C (d) Li, NH_3,THF,-78°C

after their cyclization to form the allopumiliotoxin ring system. For convenience, this conversion was accomplished with each stereoisomer in three steps:[18] (a) Conversion to the cyclopentaoxazines **20**[10a] and **21**[10a] ($AgNO_3$ at room temperature). (b) Cyclization of these intermediates at 100°C in the presence of 0.95 equiv of camphorsulfonic acid and excess paraformaldehyde to afford **22**[10a] and **23**[10a]. (c) Cleavage of the benzyl protecting group with Li in liquid NH_3. This sequence provided **24**[10a] (11,15-*bis*-*nor*-methylallopumiliotoxin *267A*, $[\alpha]_D$ + 16.4°, c 2.2 $CHCl_3$) and **25**[10a] ($[\alpha]_D$ -11.0°, c 1.8 $CHCl_3$) in 37% and 39% overall yields, respectively, from **18** and **19**. To the limits of detection by 300 MHz ^1H NMR the cyclization to form the allopumiliotoxin ring system proceeded **without** loss of stereochemistry at both C-7 and the double bond. Stereochemical assignments for **24** and **25** follow from the diagnostic[3] allylic coupling observed between an axial hydrogen at C-7 and the vinylic hydrogen (**25** $J_{7\beta,10}$ = 2 Hz), and the characteristic[19] chemical shifts of the C-5 methylene hydrogens of both isomers: **24** δ 3.65 (d, J = 12.0 Hz, H-5α), 2.73 (d, J = 12.0 Hz, H-5ß); **25** 3.83 (d, J = 12.0 Hz, H-5α), 2.38 (d, J = 12.0 Hz, H-5ß).

In summary, aldehyde **16**, an intermediate of potential general utility for the synthesis of allopumiliotoxin A alkaloids, can be prepared in a practical fashion from *L*-proline. The successful cyclizations of **20** and **21** moreover demonstrate that allylic alcohol functionality is compatible with iminium ion-vinylsilane cyclizations. Our ongoing efforts to prepare the natural allopumiliotoxins 323B′ and 339A evolve from aldehyde **16** and envisage use of a nucleophile-promoted alkyne cyclization[6] for elaboration of the alkylideneindolizidine ring.

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9. Dr. Christian Caderas contributed to our early studies in this area.
10. (a) All new compounds showed 250, 300, or 500 MHz ^{1}H NMR, ^{13}C NMR, IR, and high resolution mass spec in accord with their assigned structures. All of the quoted yields are after purification on silica gel. (b) A satisfactory elemental analysis was also obtained for this compound.
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