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PREPARATION OF FUNCTIONALIZED HYDROINDOL-3-OLS *VIA* TANDEM AZA-COPE REARRANGEMENT-MANNICH CYCLIZATIONS. FORMAL TOTAL SYNTHESIS OF (±)-6a-EPIPRETAZETTINE AND RELATED ALKALOIDS

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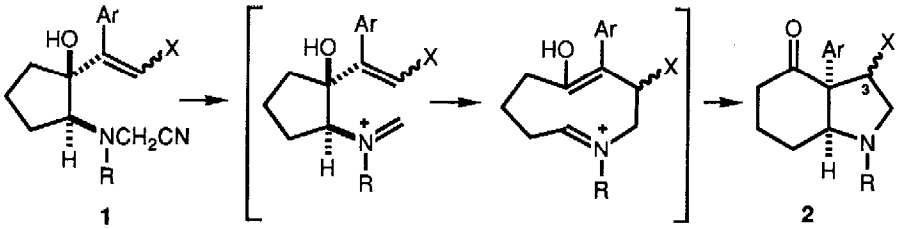
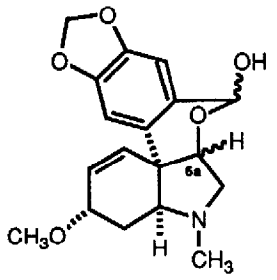
Summary: Key steps in this approach to *amaryllidaceae* alkaloids containing oxidation at the ß-position of the pyrroline ring are (a) copper(II)-promoted rearrangement of aminocyclopentanol **11** to afford the 3-silylhydroindole **12**, and (b) oxidation of **12** by the general procedures of Kumada and Fleming to give the *cis*-3a-aryl-3-hydroxyhexahydroindolone **13** in 71% overall yield from **11**.

We have reported an efficient method for preparing *cis*-3a-arylhydroindoles **2** that involves a tandem aza-Cope rearrangement-Mannich cyclization reaction (eq 1) as its key element.[2] This chemistry

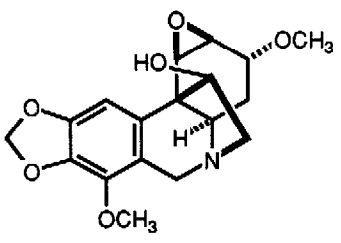


constitutes a general approach for alkaloid synthesis, since the *cis*-3a-arylhydroindole ring system is found in a number of alkaloids, and has been utilized by us to achieve total syntheses of *amaryllidaceae*,[3] *aspidosperma*,[4] and *melodinus*[5] alkaloids. A number of alkaloids, including the most pharmacologically active members of the crinine class of *amaryllidaceae* alkaloids (e.g. **3** and **4**),[6] contain *cis*-3a-aryl-hydroindole rings that are oxidized at the ß-carbon of the pyrrolidine ring.[7] Not surprisingly, oxygen functionality of this type is not compatible with the cationic aza-Cope rearrangement-Mannich cyclization reaction (eq 1, X=OH or OR).[8] We have investigated, therefore, the transformation illustrated in eq 1



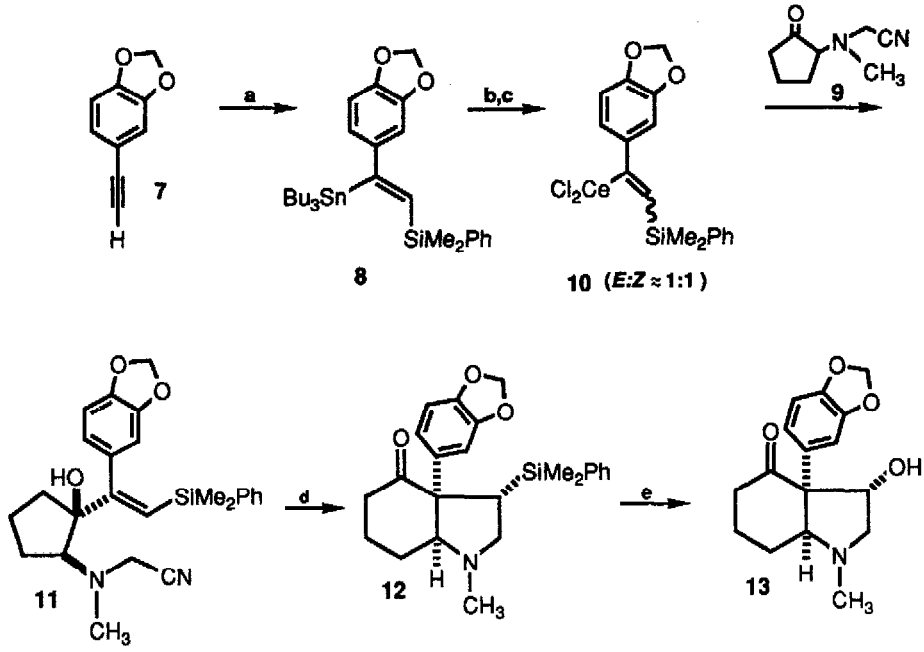
3 α - 6a-H , pretazettine

5 β - 6a-H, 6a-epipretazettine



4, cavinine

SCHEME I

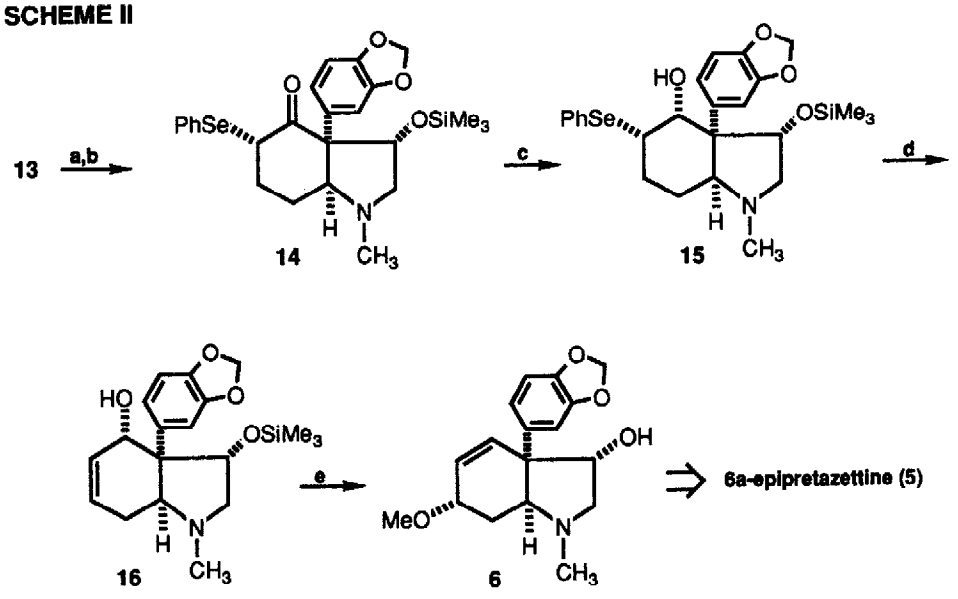


(a) $Bu_3SnSiMe_2Ph$, $Pd(Ph_3P)_4$, THF, 60°, 8h (95%); (b) *n*-BuLi, THF, -78°C, 1h; (c) 0°C, 5 min, $CeCl_3$; **9** , -78°C (25% from 8); (d) $Cu(OTf)_2$, THF, reflux, 2h (94%); (e) HBF_4-OEt_2, CH_2Cl_2, rt, 2h; H_2O_2, KF, DMF, 60°C, 7h (76%).

where X is a silyl substituent, since Kumada[9] and Fleming[10] have developed versatile sequences for the conversion of C-SiR_3 → C-OH. In this communication we report that the "hydroxyl equivalency" of the $PhMe_2Si$ group[10] can be exploited to prepare oxidized *cis*-3a-arylhydroindoles **2** (X=α-OH) by the aza-Cope rearrangement-Mannich cyclization strategem. Specifically, we describe the synthesis of **6** (see Scheme II), a late intermediate in incisive total syntheses of (±)-6a-epipretazettine and (±)-tazettine achieved by the Danishefsky group.[11]

Our investigations began with silylstannane **8**[12a] which was prepared from (3,4-methylenedioxy)phenylacetylene (**7**)[13] and (dimethylphenylsilyl)tributylstannane by the general method of Chenard and Van Zyl.[14] We initially examined the reaction of readily available aminocyclopentanone **9**[3] with the vinyllithium[15] and vinylcerium[16] reagents derived from **8** in the hope of preparing a cyclization substrate with the *trans*-orientation of aryl and silicon functionality. Unfortunately, enolization of **9** predominated under all conditions examined, presumably reflecting the steric bulk of these organometallic intermediates which have the silyl group *cis* to the metal and the well-known susceptibility of cyclopentanones to deprotonation.[17] On the other hand, the (*E*)-cerium reagent, which could be formed from **8** as a 1:1 mixture of stereoisomers by equilibration of the corresponding lithium intermediate at 0°C, reacted with **9** at -78°C in modest yield (41% based on consumed **9**, 25% actual yield) to provide a single adduct **11**[12a] whose stereochemistry was ascertained by ^1H NMR NOE experiments.

SCHEME II



(a) Me_3SiOTf, NEt_3, CH_2Cl_2, 0°C, 1h (95%); (b) PhSeCl, CH_2Cl_2, 0°C, 1h (78%); (c) *i*-Bu_2AlH, toluene, -78°C, 15 min (81%); (d) *m*-$ClC_6H_4CO_3H$, CH_2Cl_2, -78°C, 45 min; xylene, reflux, 15 min (61%); (e) $(CH_3SO_2)_2O$, NEt_3, THF, 0°C, 20 min; MeOH, NEt_3, reflux, 15 min; *n*-Bu_4NF, THF, rt, 15 min (25%).

The key rearrangement of **11** was accomplished by treatment with 2 equiv of copper(II)triflate in refluxing tetrahydrofuran (THF) to give the silyl hydroindolone **12**[12a,b], mp 129°C, in 94% yield. Conversion of **12** to the fluorosilane,[10] followed by oxidation of this intermediate at 60°C with 20 equiv of 30% H_2O_2 in the presence of 5 equiv of KF[9] gave cleanly the desired hydroxylated hydroindolone **13**[12a,c] in 76% yield. Significantly, the basic nitrogen did not require protection during this oxidative transformation.

The conversion of **13** to the Danishefsky intermediate **6**[11] is summarized in Scheme II. Of note in this sequence was the reduction of the selenoketone **14** with *i*-Bu_2AlH which provided exclusively the α alcohol **15**.[12a,18] The steric bulk of the angular aryl and α-phenylseleno groups is apparently sufficient to direct the reducing agent to the concave face of this *cis*-fused bicyclic ketone. The conversion of **16**[12a] to **6** was accomplished by methanolysis of the allylic mesylate intermediate following a general strategy defined earlier by Whitlock[19] and Danishefsky.[11] Hydroindole **6** prepared in this fashion was indistinguishable (^1H NMR, IR, mass spec, and TLC comparisons in three solvents) with an authentic sample.

In summary, the efficient (71% overall yield) two-step conversion of aminocyclopentanol **11** to the *cis*-3a-aryl-3-hydroxyhexahydroindolone **13** demonstrates that a silicon substituent can be employed as an alcohol surrogate in the stereocontrolled synthesis of hydroxylated hydroindoles by the tandem aza-Cope rearrangement-Mannich cyclization method. For this sequence to be a practical route to these intermediates, more efficient methods for assembling the silicon-containing rearrangement precursors will be required.

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12. (a) All new compounds exhibited spectroscopic properties (^{1}H NMR, ^{13}C NMR, IR, high resolution MS) in accord with their assigned structures. (b) The molecular composition of this intermediate was confirmed by combustion analysis. (c) Characterization data for **13**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.79 (dd, J= 6.1, 1.9 Hz, $H_{3ß}$), 3.52 (dd, J = 10.6, 6.2 Hz, $H_{2ß}$), 3.29 (broad s, H_{7a}), 2.28 (s, NCH_3), 2.24 (dd, J = 10.7, 2.0 Hz, $H_{2α}$); ^{13}C NMR (75 MHz, $CDCl_3$) 210.3, 148.8, 147.4, 128.8, 121.8, 109.2, 108.8, 101.9, 72.8, 68.0, 65.8, 62.1, 39.7, 39.4, 22.6, 22.0; IR (CCl_4) 3596, 1708 cm^{-1}; MS (EI) m/z 289.1300 (78%, 289.1314 calcd. for $C_{16}H_{19}NO_4$).
13. Prepared in 78% yield from piperonal by the general method of Corey and Fuchs: Corey, E.J.; Fuchs, P.L. *Tetrahedron Lett.* **1972**, 3769.
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15. In contrast to the 2-silyl-1-phenylvinyl lithium reagents described in ref 14, this vinyllithium intermediate was configurationally stable at -78°C for 2.5 h.
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17. The (*E*)-vinyllithium reagent derived from **8** was successfully added to cyclohexanone to give the corresponding tertiary alcohol in 46% yield. Enolization with **9** was confirmed by quenching reaction mixtures with D_2O.
18. The stereostructure of **15** followed from its 500 MHz ^{1}H NMR spectrum ($CDCl_3$): δ 4.46 (dd, J = 5.4, 2.5 Hz, $H_{3ß}$), 3.93 (dd, J = 11.6, 4.1 Hz, $H_{4ß}$), 3.13 (broad s, $H_{5ß}$), 2.60 (d, J = 11.7 Hz, OH).
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