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SYNTHETIC STUDIES ON PYRROLIZIDINE ALKALOIDS. II. INTRAMOLECULAR ADDITIONS OF RADICALS AND ELECTROPHILES TO ALLYLSTANNANES AS METHODS FOR RING CLOSURE[1]

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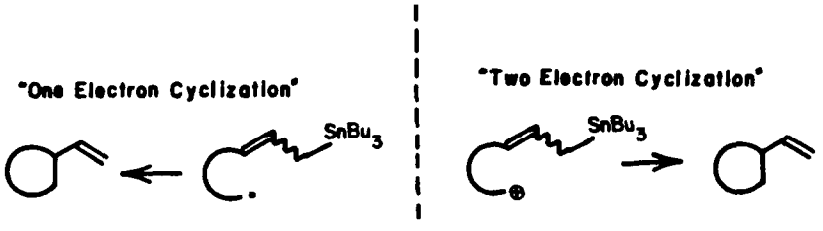
Summary: The simple pyrrolizidine alkaloid (±)-isoretronecanol was efficiently constructed by a route involving the attachment of an allylstannane moiety to succinimide followed by appropriate reduction, activation, and cyclization by either "one-electron" or "two-electron" protocols.

The pyrrolizidine alkaloids have been the subject of intensive investigation with respect to total synthesis over the last several years, particularly as vehicles for the investigation of new methodology for alkaloid synthesis.[2] In this context, we record herein a preliminary account of an investigation on the use of allylstannanes as terminators for both free radical and cationic cyclization processes, as shown schematically in Eq (1) below. Thus, the well known reactivity of allylstannanes with both electrophiles[3] and radicals[4] suggested that such cyclization processes should proceed readily to afford terminal olefins, thus preserving highly useful functionality expected to be unreactive under either "one-electron" or "two-electron" cyclization protocols.



The synthesis of (±)-isoretronecanol began by lithiation of allylphenylsulfide (nBuLi, THF, 0°) followed by introduction of ethylene oxide to give alcohol 1 in 83% isolated yield

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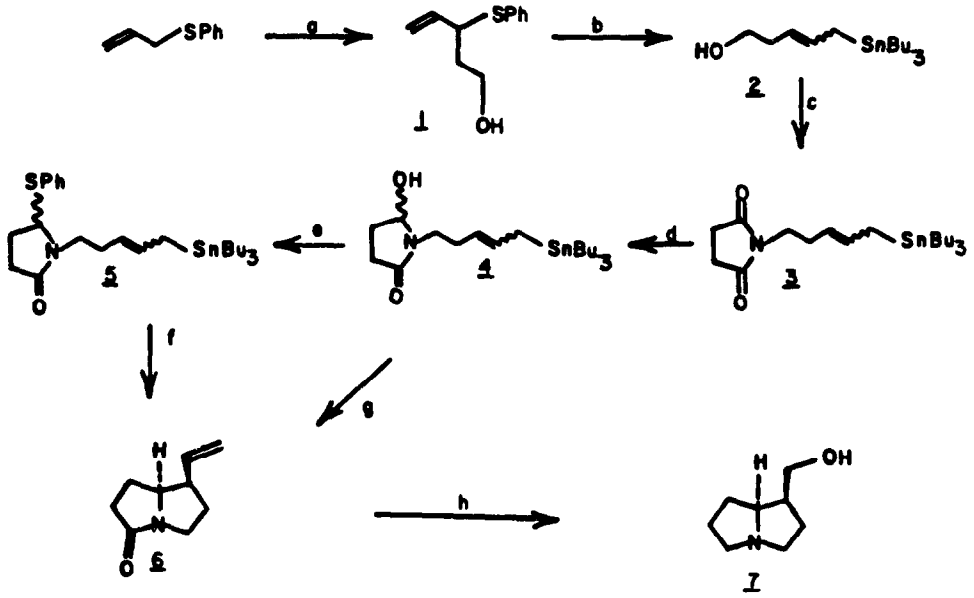
after purification by column chromatography over silica gel.[5] Reaction of this material with tri-n-butyltinhydride according to the general procedure of Ueno[6] gave stannane 2 (as a ca. 3:1 mixture of trans and cis geometric isomers) in 62% yield. Mitsunobu[7] coupling with succinimide (1 eq. each of triphenylphosphine and diethylazodicarboxylate, THF, 23°C) proceeded exceptionally cleanly to give (95% isolated yield) imide 3. Reduction with sodium borohydride in methanol[2k] also proceeded smoothly, despite the somewhat capricious nature of this transformation, to afford hydroxylactam 4 in 72% yield.

This intermediate served as a branch point for the commencement of either "one-electron" or "two-electron" cyclization processes. For the "one-electron" cyclization, 4 was converted (2 eq. each of diphenydisulfide and tri-n-butylphosphine, CH_2Cl_2, 23°C, 56% yield) to sulfide 5. Irradiation of this material (450 W Hanovia with Pyrex filter) led smoothly to the desired 6 with good (11.3:1) stereoselectivity,[8] albeit in modest yield (45%) after isolation by Kugelrohr distillation (105°C, 0.2 mm).

Synthesis of (±)-Isoretronecanol



Reagents: (a) n-BuLi; ethylene oxide (b) $n\text{-}Bu_3SnH$, AIBN, 80°. (c) succinimide, $(Ph)_3P$, DEAD (d) $NaBH_4$, MeOH (e) $(PhS)_2$, $(nBu)_3P$ (f) hν (g) MsCl, NEt_3 (h) OsO_4, $NaIO_4$; then $LiAlH_4$

In this particular case, "two-electron" cyclization proved more expedient, higher yielding, and more highly stereoselective. Thus, treatment of hydroxylactam 4 with methanesulfonyl chloride (1.2 eq.) and triethylamine (2 eq) in methylene chloride at 0°-23°C led directly to 6 in 72% isolated yield, and with surprisingly high (74:1) stereoselectivity for formation of the C_1-endo isomer. Oxidative cleavage of the vinyl unit (catalytic OsO_4, $NaIO_4$, 4:1 THF-H_2O, 0° → 23°C) followed by reduction (LAH, THF, reflux) afforded (±)-isoretronecanol[9] in 94% yield for the final two steps (24% overall for the route using the "two-electron" cyclization protocol). Investigations of such strategies for the synthesis of more complex pyrrolizidines, other alkaloid ring systems, and carbocyclic analogues are in progress.[10]

References and Notes

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5. A ca. 9:1 mixture of α and δ alkylation products was produced in this reaction. In the presence of HMPA, predominant δ alkylation was observed.

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8. (a) Product ratios were determined by capillary VPC analysis. (b) For very similar stereoselectivity in a closely related free radical cyclization process, note reference 2n. (c) The origin of the stereoselectivity of such cyclizations, which result in the predominant formation of the apparently less stable product, is obscure. (Note reference 2n and references therein.) Recently, however, Beckwith and Schliesser have reported that MMZ calculations correctly predict that cyclization of a 1-substituted hexenyl radical should favor the formation of cis product, and have proposed an explanation based upon detailed examination of the strain energy components: A.L.J. Beckwith and C.H. Schliesser, Tetrahedron Lett. 373 (1985).
9. We thank Professors David Hart and Richard Chamberlin for spectra and comparison samples of isoretronecanol and trachelanthamidine.
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