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Communication

Radical-induced Ring Opening of Epoxysilane in the Synthesis of (±)-Supinidine and (±)-Trachelanthamidine

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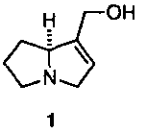
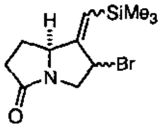
An α-(2-silyloxiranyl)carbinyl radical fused to a pyrrolizidine skeleton was generated from the corresponding bromide **4**. This radical underwent rearrangements followed by hydrogen abstraction to give silyl allyl ether **8** and silyl enol ether **9**. The mixture was converted to (±)-supinidine **1** and (±)-trachelanthamidine **3**. When triethylborane/oxygen was used to initiate the radical reaction, an α,β-unsaturated aldehyde **15** was obtained, thus to accomplish a formal synthesis of (±)-**1**.

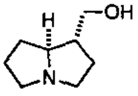
During our investigation of the synthesis of pyrrolizidine alkaloid (±)-supinidine **1**,[1] we developed an efficient synthesis of bromide **2**. The conversion of **2** to **1** under hydrolytic conditions (NaOH, H_2O, heat) was a low yield process.[1] Here, we report the successful conversion of **2** to (±)-supinidine **1** and (±)-trachelanthamidine **3**.[2,3]



1
supinidine

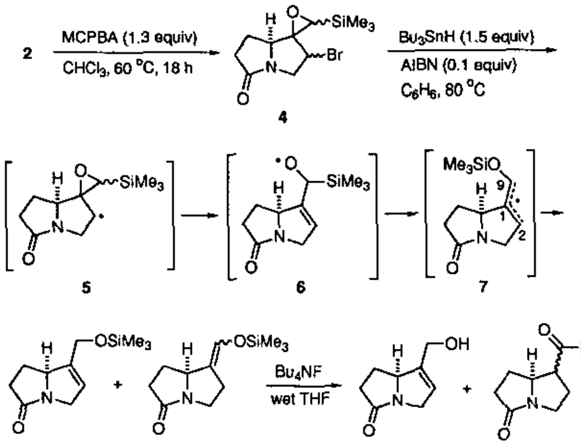


2

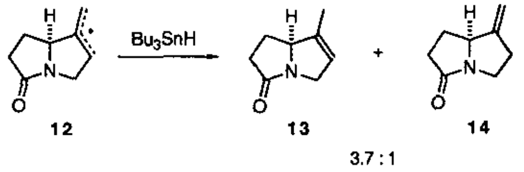


3
trachelanthamidine

Scheme I



As shown in Scheme I, bromide **2** was converted to epoxide **4** by treatment with 3-chloroperbenzoic acid (MCPBA) in refluxing chloroform. As **2** was a mixture of stereoisomers, a mixture of isomeric epoxides was obtained. However, only the major isomer[4] (62%) was used in subsequent work. Epoxide **4** was heated with tributyltin hydride (1.5 equiv, added over 2 h and heated for another 2 h) and a catalytic amount of azobisisobutyronitrile (AIBN) in refluxing benzene (0.2 M relative to **4**). After the removal of benzene, the crude product was stirred with wet tetrabutylammonium fluoride (3 equiv) in tetrahydrofuran to give a mixture of alcohol **10** and aldehyde **11** (**10**/**11** = 1/3)[5] in a total yield 66%. The entire process involved the generation of radical **5** followed by a well known β scission[6] to give oxygen radical **6**. This radical underwent a radical-Brook rearrangement[7] to give allylic radical **7**. Hydrogen abstraction occurred at C-9 and C-2 to yield **8** and **9**, respectively. Subsequent desilylation led to **10** and **11**. Previously,[8] hydrogen abstraction of radical **12** (Eq. 1) from tin hydride was found to give **13** and **14** in a ratio 3.7/1 in favor of endocyclic olefin **13**. The reason for reversal of the selectivity for radical **7** is presumably conjugative stabilization present in the silyl enol ether.



(1)

Aldehyde **11** is a 6:94 mixture of stereoisomers according to ^{1}H NMR integration of the aldehydic proton signals.[9] To determine the stereochemistry of the major isomer, we treated the mixture **10** and **11** with lithium alumi-

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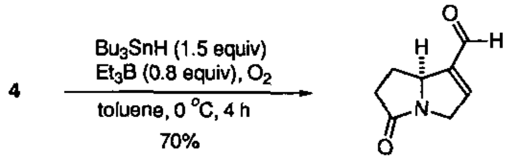
Dedicated to Professor Fa-Ching Chen (陳發清) on the occasion of his eightieth birthday.

num hydride (THF, 60 °C, 15 h) to produce the corresponding pyrrolizidine alcohols. The ^{1}H NMR spectrum of the major isomer is in perfect match with that of trachelanthamidine **3** reported by Mohanraj et al.[10] Thus, the major isomer of **11** must be the thermodynamically more stable *exo* isomer, in accord with our expectation, because the desilylation step is a thermodynamically controlled process.



15

(2)

Hoping that the selectivity would be improved at lower temperature, we used triethylborane/oxygen[11] to initiate the reaction of **4** with tributyltin hydride at 0 °C in toluene (Eq. 2). The product we obtained was an α,β-unsaturated aldehyde **15**.[12,13] As **15** was converted to (±)-supinidine **1** by Chamberlin,[12] this two step process from **2** provides an interesting approach to the synthesis of (±)-**1**. The mechanism of formation of **15** is unknown. A control experiment performed by stirring **4** with triethylborane (0.8 equiv) in toluene under oxygen atmosphere at 25 °C for 5 h led to recovery of **4** without formation of **15**. Further investigations are required to understand this interesting transformation.

ACKNOWLEDGMENT

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Key Words

Radical; Epoxysilane; Supinidine; Trachelanthamidine; β-Scission; Triethylborane; Tributyltin hydride.

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3. For a review about recent synthesis of pyrrolizidines, see Ikeda, M.; Sato, T.; Ishibashi, H. *Heterocycles* **1988**, *27*, 1465.
4. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.19 (*s*, 9 H, $SiMe_3$), 2.13-2.35 (*m*, 2 H, CO-C-CH_2), 2.47 (*ddd*, J = 16, 8, 2 Hz, 1H, $COCH_2$), 2.54 (*s*, 1 H, SiCH), 2.55-2.72 (*m*, 1 H, $COCH_2$), 3.60 (*dd*, J = 14, 3.5 Hz, 1 H, NCH_2), 3.75 (*t*, J = 9 Hz, 1 H, angular NCH), 3.93 (*d*, J = 3.5 Hz, 1 H, BrCH), 4.35 (*d*, J = 14 Hz, 1 H, NCH_2) ppm.
5. This ratio was determined by integration of ^{1}H NMR signals.
6. For leading references about β scission of this type, see Murphy, J. A.; Patterson, C. W. *Tetrahedron Lett.* **1993**, *34*, 867, and references therein.
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13. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.60-2.00 (*m*, 1 H, CO-C-CH_2), 2.15-2.35 (*m*, 1 H, CO-C-CH_2), 2.55-2.75 (*m*, 2 H, $COCH_2$), 3.87 (*dd*, J = 19, 3 Hz, 1 H, NCH_2), 4.63 (*dt*, J = 19, 3 Hz, 1 H, NCH_2), 4.80 (*br s*, 1 H, angular NCH), 6.86 (*br s*, 1 H, vinyl), 9.75 (*br s*, 1 H, COH) ppm.