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LETTERS

Polyfunctionalized Cyclopentanes *via* 5-Exo-trig Tributyltin Hydride Mediated Free Radical Cyclization of δ-Functionalized Tethered Acetylenic Derivatives from Sugars

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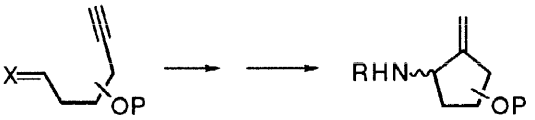
Abstract.- The first examples of the tributyltin hydride mediated free radical cyclizations of alkyne-tethered *N,N*-disubstituted hydrazones and imines, derived from sugars, are described. © 1998 Elsevier Science Ltd. All rights reserved.

Continuing with our work on the development of new methodologies for the synthesis of chiral, densely functionalized carbocycles from carbohydrates, using free radical based methodologies,[1] in this *Letter* we now disclose the first examples of the tributyltin hydride mediated free radical cyclizations of alkyne-tethered multiple carbon-nitrogen containing molecules,[2,3] as *N,N*-disubstituted hydrazones[4] and imines[5] (Scheme 1). We have selected simple, easily available intermediates from D-ribose as radical precursors. As a result, we report a new, simple and efficient strategy for the preparation of useful chiral intermediates for the synthesis of aminocyclitols.[6]



[X: NOR (ref.2); X: N-NRR, NR (this work)]

Scheme 1

Compound 1[2] was submitted to standard conditions for hydrazone formation[7] to give radical precursor **2** as a single (E) isomer (^{1}H NMR: 6.48 ppm, d, J= 7.5 Hz, H-1) in 82% yield. Reaction with tributyltin hydride in the presence of triethylborane[8] in toluene at 60 °C gave the *N,N*-diphenyl hydrazine **3** {$[\alpha]_D^{25}$ -15.9 (*c* 0.86, $CHCl_3$)}, in good yield (62%). This intermediate upon treatment with HCl in EtOH afforded the destannylated compound, that was characterized as the free base **4** {$[\alpha]_D^{25}$ -17.9 (*c* 1.23, $CHCl_3$)} (33% yield from **3**) after standard manipulation (Scheme 2). The success of this process moved us to test this protocol on a more simple precursor as **5** (E isomer; ^{1}H NMR: 6.60 ppm, t, J= 5.4 Hz, H-1).[9] Again, the 5-exo-trig cyclization of the vinyl radical resulting from the tributyltin hydride attack to the terminal acetylenic carbon, proved efficient and provided the carbocycle **6** in 65% yield. Unfortunately, we were unable to reduce the nitrogen-nitrogen bond in hydrazine **4**. This fact prompted us to design an analogous free radical cyclization protocol with imines as radical trap. The selected radical precursor was imine **7** (E isomer; ^{1}H NMR: 7.81 ppm, d, J= 5.6 Hz, H-1).[9] Under similar conditions,[8] we obtained the carbocycle **8**, that after reaction with HCl/EtOH gave hydrochloride **9** {$[\alpha]_D^{25}$ -36.2 (*c* 0.96, EtOH)} in 47% yield from **8** (Scheme 2).

All new compounds showed excellent spectroscopic and analytical data. The stereochemistry at the exo-double bond in compounds **3**, **6** and **8** has been established as *Z*, by detailed spectroscopic analysis, and it is in good agreement with the results known before for similar oxime ether cylizations.[2] In all the cases studied here,

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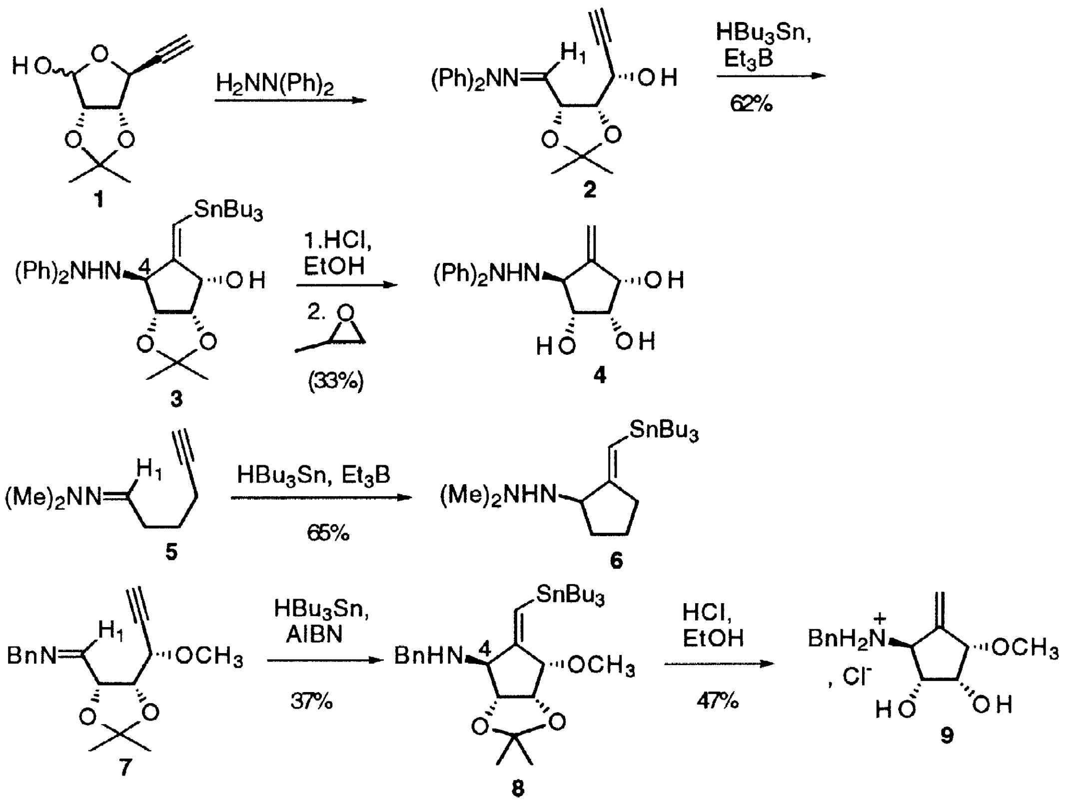
the absolute configuration at the new stereocenter (C-4) formed during the cyclization, has been established as *S* after careful analysis of the COSY and NOESY experiments in the ^{1}H NMR spectra. In addition, it has been observed that the vicinal coupling constant between H-3 and H-4 is 0 Hz, as it was expected for a *trans* arrangement of protons in a very rigid structure. In all the carbocyclizations described here only one diastereomer at C-4 has been detected and finally isolated after protodestannylation.



Scheme 2

In summary, we have shown that the tibutyltin hydride free radical cyclization of alkyne-tethered hydrazones and imines is possible and gives the aminocarbocycles in good yield.

Acknowledgments

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References and Notes

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8. In a typical experiment, compound **2** (1 equiv) dissolved in toluene (0.018 M), under argon, at 60 °C, was treated with $HSnBu_3$ (2 equiv) and Et_3B (1 equiv). After 18 h the solvent was removed and the residue was dissolved in ethyl ether and 15% aqueous solution of KF, and stirred for 2 h. The organic phase was separarted, dried, filtered and evaporated. The crude material was submitted to flash chromatography eluting with hexane/ethyl acetate mixtures to give product **3** (346 mg, 62% yield).
9. Details of the synthetic sequences leading to these radical precursors will be described elsewhere.