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SILICON IN ORGANIC SYNTHESIS. 16. A SHORT SYNTHESIS OF (±)-α-VETISPIRENE[1]

Tu-Hsin Yan and Leo A. Paquette*

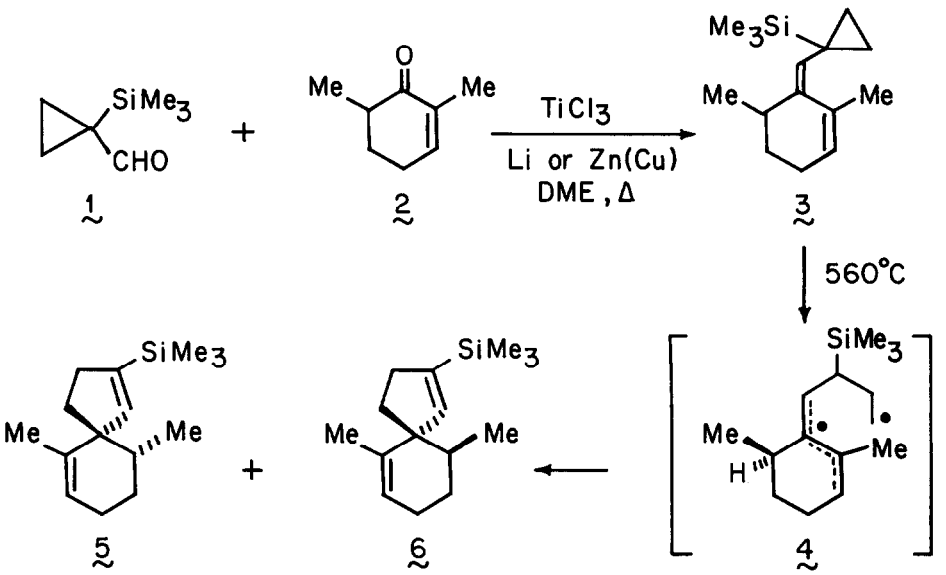
Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210

Summary: α-Vetispirene, a prototypical [4.5]spirobicyclic sesquiterpene, has been prepared in an efficient five-step reaction sequence beginning with α-trimethylsilyl cyclopropanecarboxaldehyde. A new desiliconative alkylation is featured.

Although advantage has previously been taken of cyclopropane rings as building blocks in molecular construction, recognition of the special merits of silylcyclopropanes has gone virtually unrecognized.[2] In the course of studies designed to develop the unique advantages offered by this class of reagents in synthesis,[3] we initiated an investigation aimed at the stereoselective construction of quaternary carbon centers such as those which occur in the many known spirovetivane-type sesquiterpenes.[4] The challenge posed by stereocontrolled spiroannulation has attracted considerable interest.[5] Reported here is a particularly expedient synthesis of (±)-vetispirene (12)[6] which highlights a new desiliconation-alkylation sequence of potentially wide applicability.

Our approach begins with the bifunctional reagent 1[7] which is readily available in 72% overall yield by modified Simmons-Smith cyclopropanation[8] of 2-(trimethylsilyl)-2-propen-1-ol[9] followed by oxidation with activated manganese dioxide.[10] Coupling of 1 with 2,6-dimethylcyclohexenone (2)[11] in the presence of the Ti(0) reagent prepared by reduction of $TiCl_3$[12] provided the silylated diene 3 in 50-60% yield. Although the 300 MHz ^1H NMR spectrum of 3 (in C_6D_6) clearly revealed it to be a single stereoisomer, an unequivocal distinction between the two structural possibilities has not been made. Nor is it ultimately relevant.

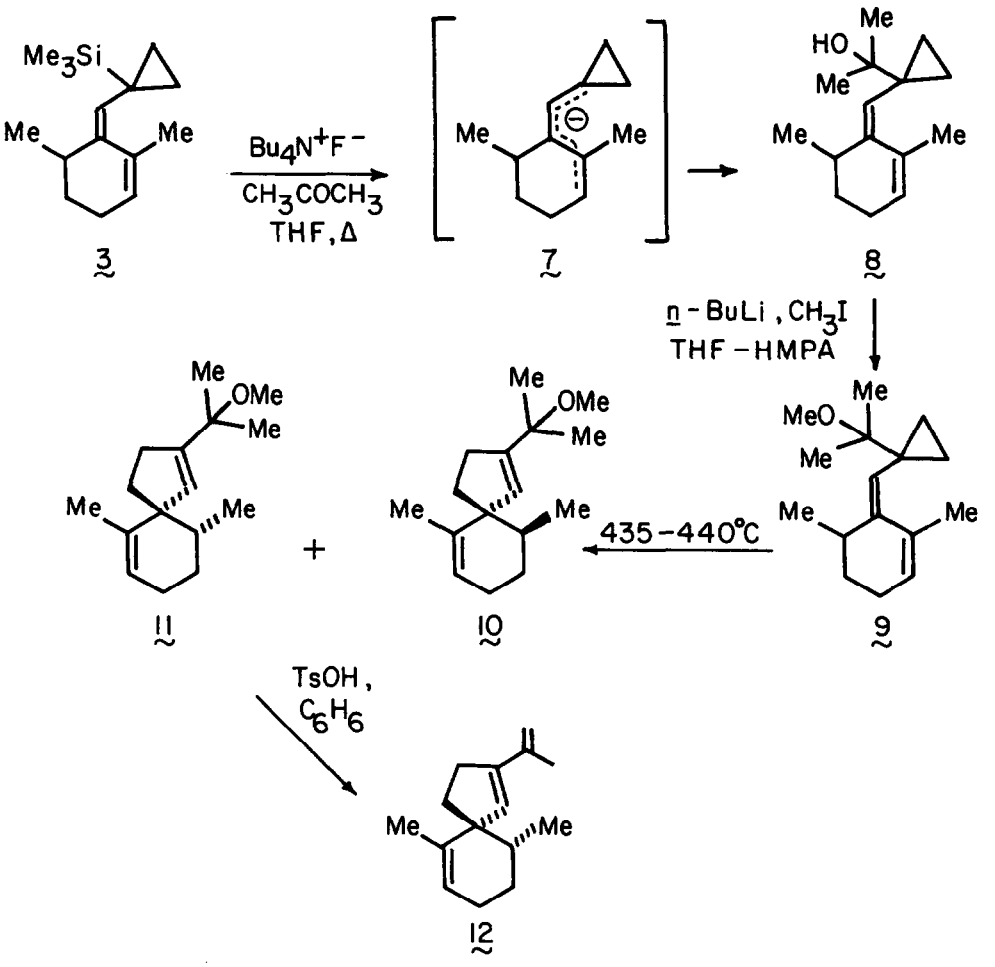
Subjection of 3 to pyrolysis in a quartz chip-packed tube (30 cm long) at 30-40 torr (N_2 as carrier gas) expectedly[3b] required relatively high temperatures to achieve the vinylcyclopropane rearrangement. Under these conditions, smooth efficient bond reorganization occurred to yield



a 4:1 mixture of the spirocyclic vinylsilanes 5 and 6. The dominance of 5 signaled preferential recombination of biradical 4 from that surface of the six-membered ring which is less sterically shielded.[13]

The stage was now set for introduction of the remaining three carbon atoms. To this end, 3 was heated with anhydrous tetra-*n*-butylammonium fluoride and acetone in tetrahydrofuran solution at the reflux temperature for 10 h. These conditions serve to generate pentadienyl anion 7 which presumably experiences entirely regioselective alkylation at the cyclopropyl carbon atom in order to avoid the development of methylenecyclopropane character.[14] Isomerically pure alcohol 8 was isolated in > 90% yield. Following conversion to methyl ether 9, thermal rearrangement was effected at 435-440°C as before to produce in quantitative yield a mixture of 10 and 11 (1:5 ratio). The heightened stereoselectivity of this reaction, coupled with its efficiency and the ease with which 11 affords (±)-α-vetispirene (12, 100%)[15] upon exposure to *p*-toluenesulfonic acid in benzene for 25-30 min at 5-20°C are particularly attractive. The overall yield for the five-step conversion of 1 into 12, which can be executed on milligram and multigram scale as desired, was 38%.

Since difficulties are frequently encountered in the preparation of carbonyl activated cyclopropyl carbanions,[16] the conversion of 3 to 8 represents a useful alternative to those synthetic strategies which might normally require reactive intermediates of this type. The scope and limitations of this C-C bond-forming process are presently under intensive investigation and will be reported in due course.



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