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SYNTHESIS OF THE PHEROMONE OF THE COMSTOCK MEALYBUG VIA A SILA-COPE ELIMINATION

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Summary :

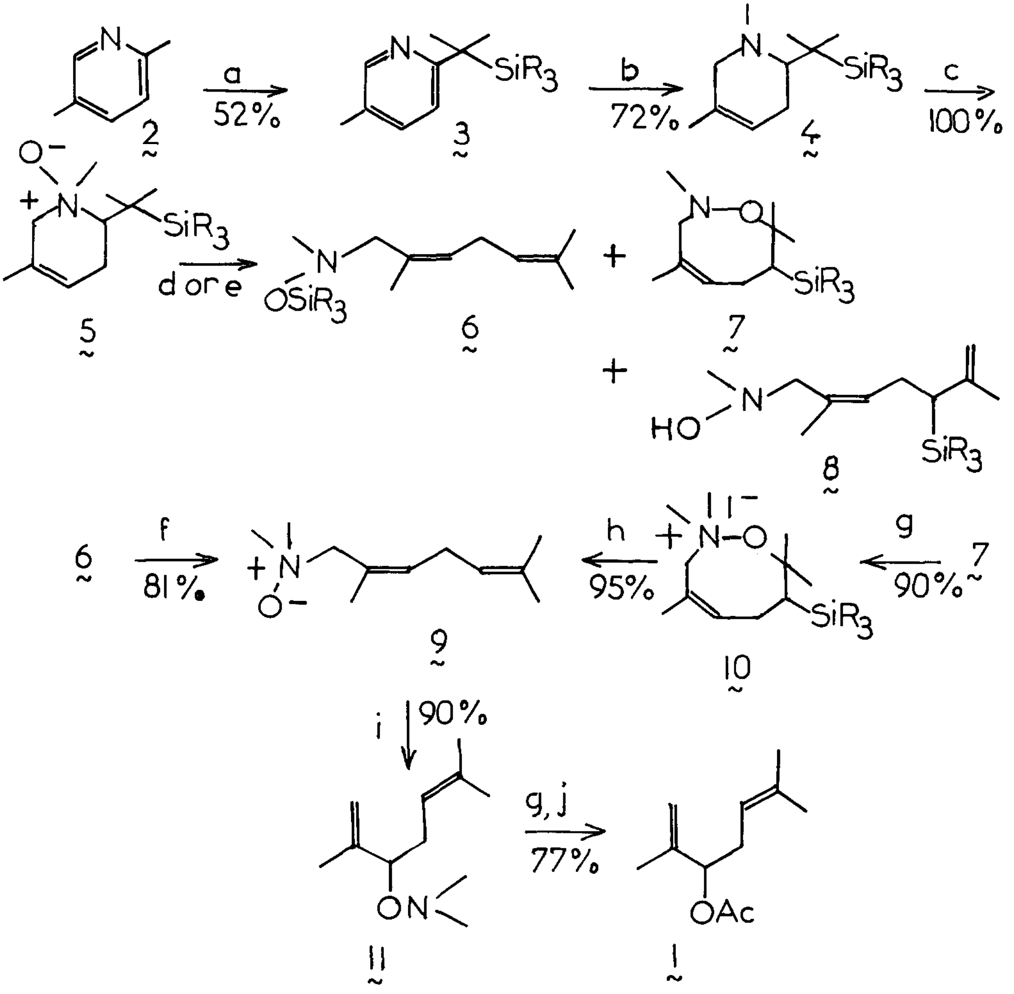
The synthesis of pheromone 1 of the Comstock mealybug has been achieved via a Sila-Cope elimination during which a new type of 1,2 silicon shift was observed.

Our recent approach to the stereoselective synthesis of 1,3 and 1,4 dienes[1], using 2-alkylpyridine as starting material, has provided access to various pheromones. Further scope of this methodology is now illustrated by a synthesis of 2,6-dimethyl-1,5-heptadiene-3-ol acetate 1[2], the pheromone of the Comstock mealybug, Pseudococcus comstocki[3], an insect extremely harmful to many agricultural crops, e.g., apples, pears, etc... Moreover, in the course of this synthesis, a new 1,2 silicon shift was observed beside the expected Sila-Cope elimination. The reaction steps involved in achieving our synthesis of 1 are outlined in scheme 1.

2,5-Dimethylpyridine 2 was silylated with t-butyl-dimethylchlorosilane (1 equiv., LDA, 1 equiv., THF - 60°, 1 h) at the 2-methyl carbon which was then doubly methylated (LDA, 1.3 equiv., THF - 60°, 1 h) by using methyl iodide (1 equiv.) to afford 2,5-disubstituted pyridine 3. The corresponding N-methyl pyridinium salt[4] was subsequently reduced with an excess of sodium borohydride in methanol and the resulting 1,2,3,6-tetrahydropyridine 4 was converted into the N-oxide 5 with m-chloroperbenzoic acid[5] (4 equiv., CH_2Cl_2, 0°C).

Thermolysis of the N-oxide 5 in refluxing dichloromethane afforded three products 6, 7 and 8 in 25%, 50% and 25% yields, respectively. In contrast only the compounds 6 and 7, each in 50% yield, were obtained by heating 5 in acetonitrile at 80°C.

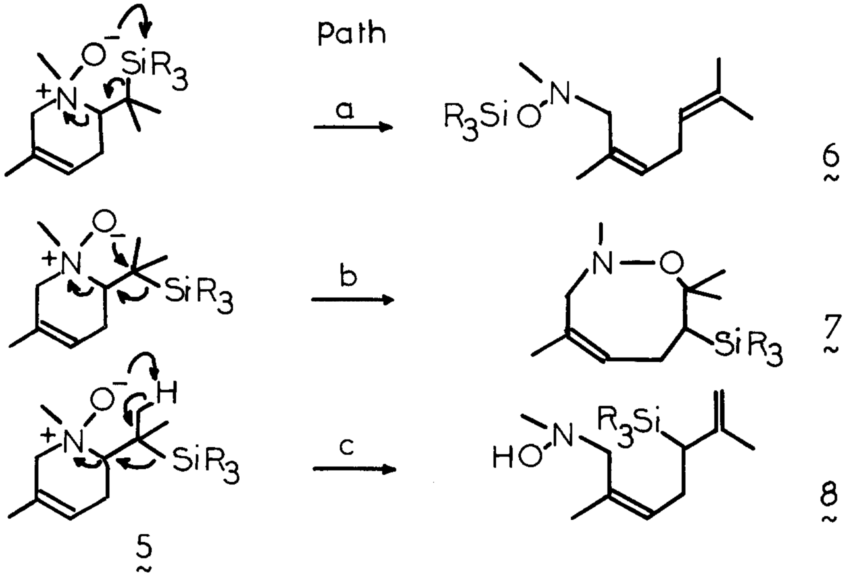
Three different pathways (Scheme 2) could be involved in the formation of the compounds 6, 7 and 8 : path a gave rise to the anticipated dienic compound 6 by a Sila-Cope elimination. On the other hand, compounds 7 and 8 could be the result of 1,2 C-C silicon shifts (paths b and c). To our



R_3 = tBuMe$_2$. a : i) LDA, tBuMe$_2$SiCl, THF. ii) LDA, IMe, THF. iii) id. ; b : i) SO_4Me_2. ii) $NaBH_4$, MeOH ; c : MCPBA, CH_2Cl_2 ; d : 40°C, CH_2Cl_2 ; e : 80°C, CH_3CN ; f : MeI, CsF, MeOH ; g : IMe, MeOH ; h : CsF, CH_3CN ; i : 80°C, CH_3CN ; j : i) $LiAlH_4$, THF. ii) Ac_2O, C_5H_5N.

Scheme 1

knowledge, these are one of the first examples of this kind of silicon shift[6].



Scheme 2

However, both the compounds 6 and 7 gave the anticipated dienamine N-oxide 9 : the silyl protected diene hydroxyl-amine 6 by treatment with methyl iodide (10 equiv.) in the presence of caesium fluoride (6 equiv.) in methanol at room temperature ; while the cyclic compound 7 by treatment with methyl iodide (6 equiv.), in methanol followed by caesium fluoride (3 equiv.) in acetonitrile[7]. The allylic N-oxide 9 was next heated at 80°C in acetonitrile leading to the dienic compound 11 by a [2,3] sigmatropic rearrangement. Conversion of 11 into the required pheromone was accomplished in three steps : quaternarization, (IMe, MeOH), hydrogenolysis of the N-O bond with lithium aluminium hydride in THF and acetylation of the resulting alcohol (overall yield from 2 : 20%).

Acknowledgement :

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References and Notes :

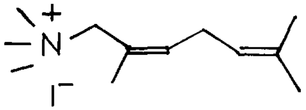
1. a) N.V. Bac and Y. Langlois, *J. Amer. Chem. Soc.*, **104**, 7666 (1982) and references therein. b) N.V. Bac, Y. Fall and Y. Langlois, *Tetrahedron Letters*, **27**, 841 (1986).

2. For an enantioselective synthesis of this pheromone, see K. Mori and H. Ueda, *Tetrahedron*, **37**, 2581 (1981).

3. a) T. Negishi, M. Uchida, Y. Tamaki, K. Mori, S. Ishiwatari, S. Asano and K. Nakagawa, *Appl. Entomol. Zool.*, **15**, 328 (1980). b) B.A. Bierl-Leonhardt, D.S. Moreno, M. Schwarz, H.S. Forster, J.R. Plimmer and E.D. de Vilbiss, *Life Sciences*, **27**, 399 (1980).

4. The pyridinium salt corresponding to pyridine **3** was isolated after treatment with excess of dimethyl sulfate at 100°C for 12 h. Methyl iodide was unreactive in this N-alkylation.

5. In order to compare Sila-Cope and Sila-Hofmann eliminations[1], tetrahydropyridine **4** was treated with an excess of methyl iodide in methanol at room temperature. Under this reaction condition diene ammonium salt **12**, which was the result of a spontaneous Sila-Hofmann elimination followed by a N-alkylation, was isolated :



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6. For other examples of 1,2 silicon shifts see : a) M. Ochiai, K. Sumi, E. Fujita & M. Shiro, *Tetrahedron Letters*, **23**, 5419 (1982) and references therein. b) J.M. Muchowski, R. Naef and M.L. Maddox, *Tetrahedron Letters*, **26**, 5375 (1985).

7. When compound **7** was treated simultaneously with methyl iodide and caesium fluoride in methanol diene ammonium salt **12** was obtained in 75% yield.

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