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# A Novel Approach to Complex Terpenoid Methylenecyclohexanes

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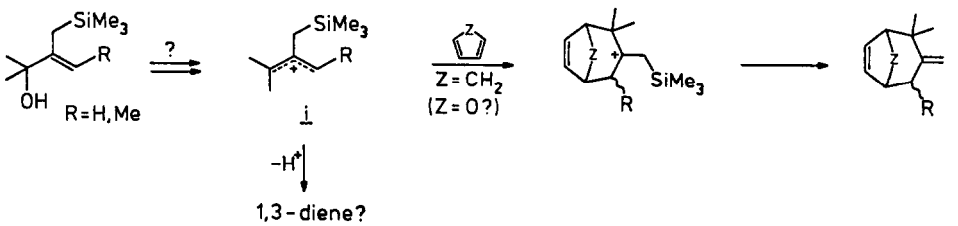
*Summary*: *Allylic alcohols* 3 *and* 4 *have been prepared and activated toward formation of allyl cations, giving 3-methylenebicyclo[3.2.1]oct-6-enes* 7 *and* 9, *respectively, in the presence of cyclopentadiene; with furan, not only the products of conventional electrophilic substitution* 11 *and* 13 *are formed, but also 3-methylene-8-oxabicyclo[3.2.1]oct-6-enes* 12 *and* 14.

The methylenecyclohexane moiety occurs widely in terpenes and terpenoid natural products, e.g. vitamin D and derivatives. Thanks to the Wittig reaction and its variants, the synthesis of methylenecyclohexanes via olefination of cyclohexanone precursors is generally not difficult, except when steric hindrance and enolization of the carbonyl group interfere. Two pertinent examples are the zizaene class of sesquiterpenes, where the methylene group is flanked by a tertiary and a quaternary carbon[2] and isobarbatene, where the methylene group is flanked by two quaternary centres[3].

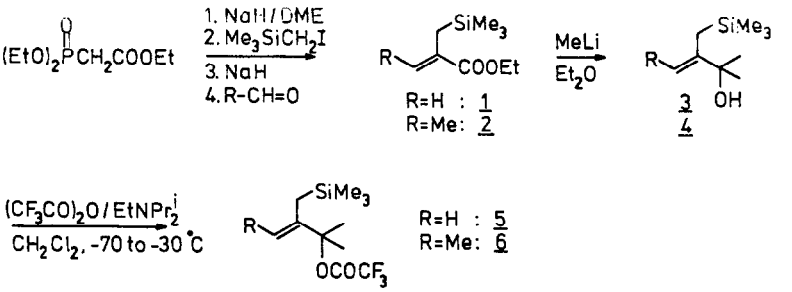
As a more direct approach to these bridged methylenecyclohexanes we considered a cycloaddition of a 2-silylmethylallyl cation to cyclopentadiene. Because of the stabilizing effect of silicon on a ß-sited carbocation[4] it seemed feasible that the two new σ-bonds and exo-methylene group might all be formed in one step (Scheme 1).




Scheme 1. Generation, Capture, and Collapse of Crowded 2-Silylmethylallyl Cation.

However, from previous experience with the biomimetic preparation of monoterpenoids we knew that highly alkylated allyl cation intermediates such as $\underline{i}$ suffered ready loss of a proton at 0 to 25°C, even in acidic media.[5] If the rate of elimination remained fast under all conditions, intermolecular capture of $\underline{i}$ with cyclopentadiene would, of course, be difficult.

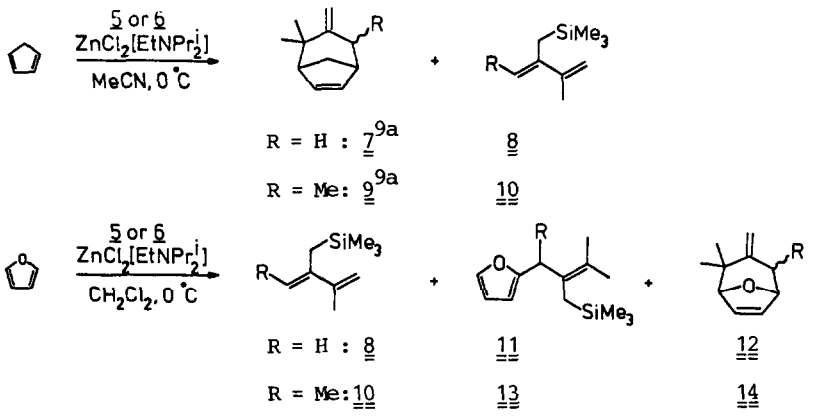
As 2-silylmethylallyl cation precursors we chose $\underline{3}$ and $\underline{4}$, which are not only allyl alcohols, but also functionalized allylsilanes. Using the Horner-Emmons variant[6] of the Wittig reaction we obtained the silylated acrylic ester derivatives $\underline{1}$ and $\underline{2}$ in a single-flask procedure. Methylation with an excess of methyllithium in ether at -20°C furnished $\underline{3}$ and $\underline{4}$ in high yield.[7,8]




Scheme 2. Preparation and Trifluoroacetylation of 2-Silylmethylallyl Alcohols.

Cycloadditions. Previously, allylic alcohols structurally related to $\underline{3}$ and $\underline{4}$, but without silyl group, have been found to react with cyclopentadiene in a two-phase system consisting of aqueous sulfonic acid/pentane.[1] Experiments with $\underline{3}$ and $\underline{4}$ under these conditions led to slow formation of dicyclopentadiene and decomposition of the acid-sensitive alcohols $\underline{3}$ and $\underline{4}$. As a milder and more selective method of activation we tried trifluoroacetylation.[9b] The alcohol was dropped into a mixture of trifluoroacetic anhydride/ethyldiisopropylamine prepared at -70°C, the resulting mixture was stirred and allowed to reach -30°C, becoming homogeneous. The trifluoroacetates $\underline{5}$ and $\underline{6}$ (characteristic IR carbonyl band at 1780 $cm^{-1}$) were separated from the salt of the amine and trifluoroacetic acid by dilution with pre-cooled pentane and filtration through a short column of basic aluminium oxide, cooled to -60 to -40°C. Since $\underline{5}$ and especially $\underline{6}$ were very unstable, decomposing even in dilute solution at 0°C with formation of a deep-violet coloration, they were used without delay or stored at -78°C.

Reaction of $\underline{6}$ and cyclopentadiene in solvent acetonitrile in the presence of ethyldiisopropylamine and zinc chloride at 0°C gave diene $\underline{10}$ as major product (ca. 55%) and only a minor




Scheme 3. Products from the Generation of 2-Silylmethylallyl Cations in the Presence of Cyclopentadiene and Furan

amount of 9 (ratio 10 : 9 = 4 : 1). In the absence of ethyldiisopropylamine, but otherwise identical conditions, the proportion of products changed completely, diene 10 being the minor product and the desired 9 the major (ca. 60%) product (ratio 10 : 9 = 1 : 6). Generally, best results were obtained in solvent acetonitrile at 0°C and below without added base and using ca. 1.3-1.5 equiv. of cyclopentadiene. The products were isolated by extraction with pentane and Kugelrohr distillation. Although trifluoroacetate 5 ionizes less readily than 6, cycloadditions with 5 were easier to perform, 7 (ca. 45%) being accompanied by little diene 8.

A special test of the driving force of the 2-silylmethylallyl cation cycloaddition was the reaction with furan, because hitherto all allylic cations expect oxyallyl species had been found to react with furan to give the product of conventional electrophilic substitution.[10] In the present instance regioselective electrophilic substitution occurred (cf. 11 and 13), but it did not occur exclusively, adducts 12[11] and 14[12] being formed as well. Thus, 2-silylmethylallyl alcohols such as 3, 4 and their trifluoroacetic esters are cycloaddition reagents of both practical and theoretical interest.

Acknowledgments. We thank the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for support of this work.

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7. Preparation of 1 and 2. Phosphonoacetic triethyl ester (15 g, 13.4 ml, 66.9 mmol) in dry DME (15 ml) was stirred slowly into 75% NaH (2.36 g, 73.6 mmol; suspension in mineral oil) in dry DME (40 ml) under nitrogen at 0°C. After 0.5 h at room temperature a solution of iodomethyltrimethylsilane (16.5 g, 77.1 mmol) in DME (20 ml) was added and the resulting mixture was heated to 70°C for 3 h, cooled to 0°C and treated with 75% NaH (2.36 g, 73.6 mmol). The yellow suspension was allowed to reach 25°C whilst being stirred for 1.5 h. After re-cooling to 0°C a suspension of paraformaldehyde (2.4 g, 79.9 mmol) in DME (20 ml) [freshly prepared acetaldehyde (3.4 g, 77.2 mmol) in DME for the preparation of 2] was added dropwise in an exothermic reaction. After being stirred at 25°C for 3 h the yellow-brown mixture was carefully poured into dilute aqueous ammonium chloride (350 ml) and the aqueous phase was extracted with ether (3 x 100 ml). The combined organic phase was washed with dilute aqueous NaCl solution (70 ml) to neutrality, dried ($MgSO_4$) and distilled, yielding 4.9 g (39%) of 1 (bp 80-82°C/19 torr) and 6.6 g (49%) of 2 (bp 40-60°C/2 torr , Kugelrohr apparatus) (E : Z = 1 : 4).
2-Silylmethylallyl alcohols 3 and 4. A 1.6 M solution of methyllithium in ether (40 ml, 64 mmol) was stirred slowly into a cooled (-70°C) solution of 1 (4.77 g, 25.6 mmol) [respectively 2 (5.13 g, 25.6 mmol)] in dry ether (50 ml) under nitrogen. The solution was allowed to reach -20°C whilst being stirred for 2 h, and treated carefully with ice-cold water (150 ml). The organic phase was separated, the aqueous phase was extracted with ether (2 x 50 ml), the combined organic phase was washed with a saturated solution (2 x 25 ml) of aq. NaCl and dried ($MgSO_4$). The ether was removed at 30°C under reduced pressure, leaving 3 (4.15 g, 94%) and, respectively, 4 (4.3 g, 90%) as colorless to slightly yellow liquids which were practically pure by GC and were used without further purification in the next step.
90 MHz $^1$H NMR (solvent $CDCl_3$, internal benzene as standard) of 3: $\delta$ = -0.03 (s, 9H, $SiMe_3$), 1.24 (s, 6H, $CMe_2$), 1.49 (br s, 2H, $CH_2Si$), 4.52 (d, J=1 Hz, 1 vinyl-H), 4.85 (d, J=1 Hz, 1 vinyl-H).
4: $\delta$ = -0.03 (s, 9H, $SiMe_3$), 1.22 (s, 6H, $CMe_2$), 1.45 (d, J=6.5 Hz, 3H, olefinic $CH_3$), 1.54 (br s, 2H, $CH_2Si$), 5.32 (q, J=6.5 Hz, 1 vinyl-H).

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(b) H.M.R.Hoffmann, J.Matthei, ibid., 113 (1980), 3837.

10. See H.M.R.Hoffmann, Angew.Chem.Int.Ed.Engl. 12 (1973), 819.

11. Ratio 8 : 11 : 12 = 1 : 6 : 3. $^1$H NMR of 12: inter al. 0.96 (s, $CH_3$), 1.25 (s, $CH_3$), 4.68, 4.77, 6.20 (complex, olefinic protons).

12. Ratio 10 : 13 : 14 = 1 : 2 : 1. $^1$H NMR of 14: inter al. 0.96 (d, J=7 Hz, $CHCH_3$), 0.99 (s, $CH_3$), 1.32 (s, $CH_3$), 4.81, 4.93, 6.28 (complex, olefinic protons).

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