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REACTION OF CHLOROMETHYLCARBENE WITH TRIMETHYLSILYL ENOL ETHERS. SYNTHESIS OF EUCARVONE, (±)-NUCIFERAL AND (±)-MANICONE.

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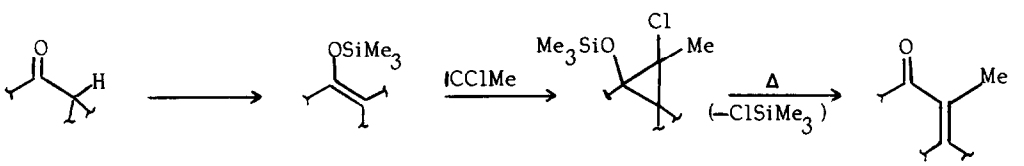
Summary. New synthesis of Eucarvone 7, (±)-Nuciferal 12 and (±)-Manicone 16 are described from trimethylsilyl enol ethers 2, 10 and 14 via their chloromethylenation products by means of a two carbons homologation reaction.

As a part of our synthetic program from silyl enol ethers and carbenes and carbenoids, i.e methylenation by a modified Simmons-Smith reaction (1) and dihalomethylenation (2), we recently reported the addition of chloromethylcarbene to silyl enol ethers which, followed by thermal rearrangement, constitutes a convenient way to α-methyl α-ethylenic compounds (3).



The purpose of the present communication is to show that such a pathway can be conveniently applied to the synthesis of natural products containing the α-methyl α-ethylenic carbonyl pattern ; for instance Eucarvone 7, (±)- nuciferal 12 and (±)-manicone 16.

Synthesis of Eucarvone 7

To our knowledge, there is only one report concerning the total synthesis of Eucarvone 7 carried out by Barnes and Houlihan (4), from 2,2-dimethylcyclohexanone, in low yield. As reported in scheme 1, our synthesis started from the readily available 5,5-dimethylcyclohexene-2-one 1, which was converted, following the standard procedure of House (5), into a 85:15 mixture of trimethylsilyl enol ether 2 and its kinetic isomer 2' (yield : 72%). Diene 2, purified by distillation (yield : 61% from 1 ; b.p. 71°/12 mmHg) (6) was treated with chloromethylcarbene generated in situ by a slow addition (7 hours) of n-butyllithium to 1,1-dichloroethane in ether. A mixture of four products was obtained : the expected chloromethyltrimethylsiloxycyclopropanes 3, 3' (83%), beside the two trimethylsilyl enol ethers 4, 4'. All these

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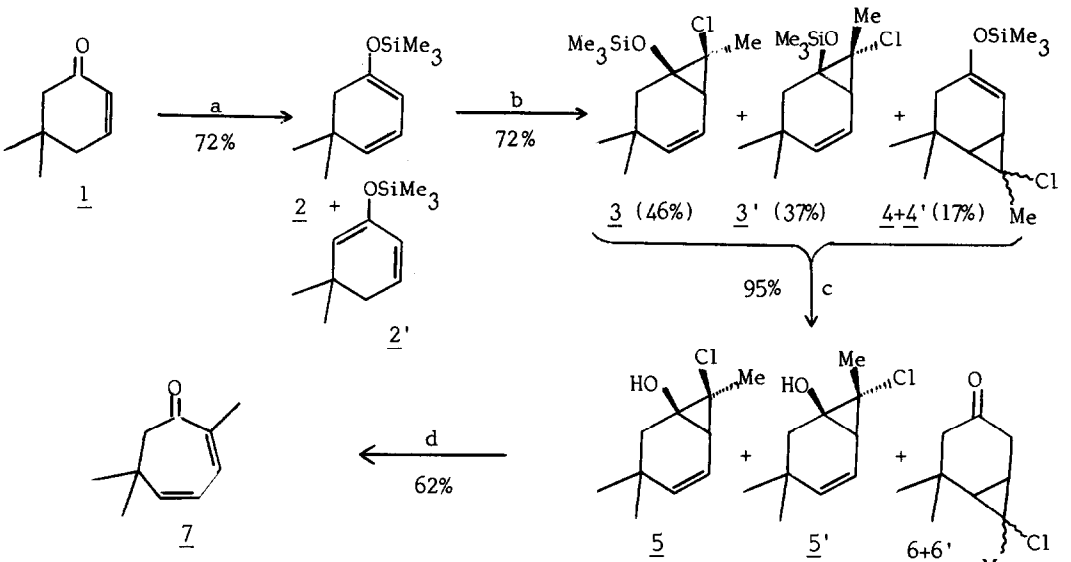


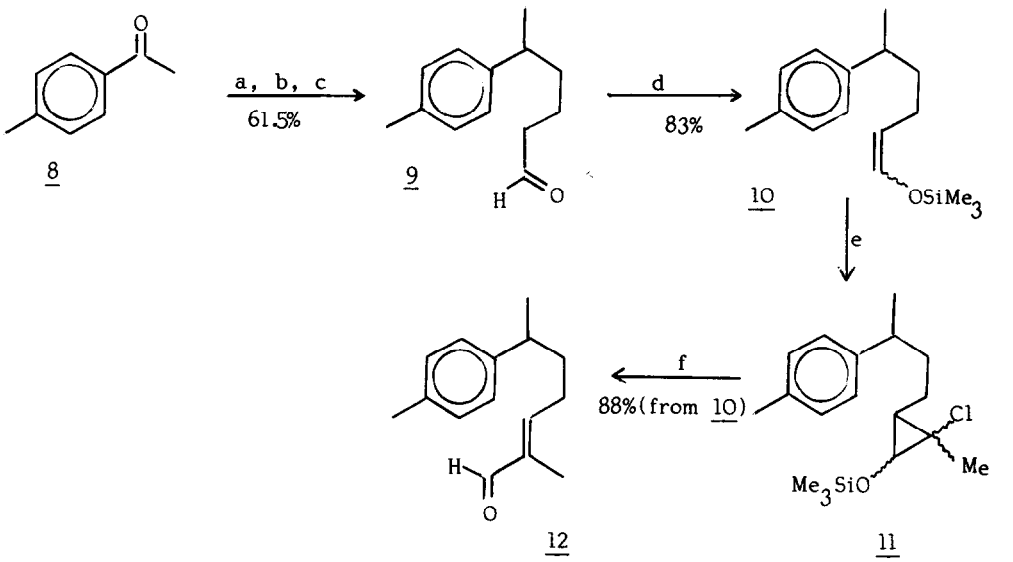
a) 5 days reflux in DMF-NEt_3-$ClSiMe_3$; b) $CHCl_2CH_3$-nBuLi in ether (-30°)
c) MeOH (14h, 25°C) ; d) MeOH-NEt_3 (reflux)

Scheme 1 - Synthesis of Eucarvone 7

products were identified by glc-ms analysis. Upon methanolysis the mixture 3, 3', 4, 4' gave two alcohols 5, 5' (78.5%), readily separated (ratio 55:45) by liquid chromatography (ether-pentane) on silica gel (6), and two ketones 6, 6' (16%). The structure of alcohols 5 and 5' was determined by their IR spectra : 5 (Cl and OH cis) showed a strong intramolecular H bond, which was absent for the isomer 5' (Cl and OH trans). The later, on reflux in the mixture MeOH-NEt_3 (85:15), led after one day to Eucarvone 7 (yield : 86%), while, on reflux in the same conditions for one week, the epimeric alcohol 5 underwent the conversion into 7 in 40% yield only. This difference of behaviour between 5 and 5' gives rise to interesting mechanistic problems, now under investigation. Eucarvone 7 was finally obtained in an overall yield of 30% from ketone 1.

Synthesis of (±)-Nuciferal 12

Sesquiterpene Nuciferal was exceeding studied (7). Our synthesis (scheme 2) was carried out through aldehyde 9, easily obtained in a three steps process from p.methylacetophenone 8 ((10), yield : 61.5%). Then, the standard procedure of House (5) led to the trimethylsilyl enol ethers 10 (10) (Z : E mixture (42:58)) which underwent quantitatively chloromethylcarbene addition to give the chloromethyltrimethylsiloxycyclopropane isomers 11 (identified from the mixture by glc-ms analysis and by solvent effect in NMR). On heating in methanol-triethylamine 11 gave pure (±)-Nuciferal 12 (yield : 88% from 10).



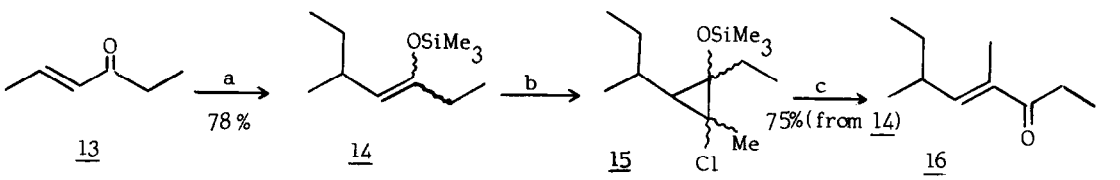
8 9 10 11 12

a) 1°) Cl-(CH2)4-OCH2φ (8) /Mg/Et2O (20°C) ; 2°) H3O+. b) H2-Pd/C (MeOH, HCl conc)
c) (COCl)2-DMSO in CH2Cl2 (9). d) 1 day reflux in DMF-NEt3-ClSiMe3 (under N2)
e) CHCl2-CH3/n-BuLi in ether (-30°C). f) MeOH-NEt3 (1.5 days reflux).

Scheme 2 : Synthesis of (±)-Nuciferal 12

Synthesis of (±)-Manicone 16

Manicone, an alarm pheromone of certain species of Manica ants, has been identified as (E) 4,6-dimethyl-4-octen-3-one 16 (11). Our synthesis (scheme 3) started from the readily available 4-hexen-3-one 13 (12), which by a 1,4-addition of EtMgBr, followed by quenching of the enolate with $ClSiMe_3$, led to the trimethylsilyl enol ethers 14 (Z:E mixture (30:70)) (13). Then, the addition of chloromethylcarbene to 14 led to the isomeric chloromethyltrimethylsiloxycyclopropanes 15 (analysis carried out by glc.ms). On heating in toluene, the mixture of 15 gave pure (±)-Manicone 16 (yield : 75% from 14).



13 14 15 16

a) 1°) EtMgBr, 0.5 CuI (Et2O, -60°C) ; 2°) ClSiMe3 (20°C) (in the presence of HMPA)
b) CHCl2CH3/n-BuLi in ether (-30°C). c) Toluene (10 days reflux).

Scheme 3 : Synthesis of (±)-Manicone 16

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6) 2 ^{1}HNMR (CCl_4) δ (ppm) : 0.20 (s, 9H), 1.11 (s, 6H), 2.05 (d, 2H), 5.02 (m, 2H), 5.62 (dd, 1H) ; IR (CCl_4) (cm^{-1}) : 3040, 1650, 1590. 5 ^{1}HNMR (CCl_4) δ (ppm) : 1.00 (s, 3H), 1.15 (s, 3H), 1.46 (s, 3H), 1.00 to 2.00 (m, 3H), 5.70 (m, 2H) ; IR (CCl_4) (cm^{-1}) : 3580 (Intramol. H bond), 3030, 1670. 5' ^{1}HNMR (CCl_4) δ (ppm) : 1.02 (s, 3H), 1.12 (s, 3H), 1.75 (s, 3H), 1.00 to 2.00 (m, 3H), 5.65 (m, 2H) ; IR (CCl_4) (cm^{-1}) : 3600 (free H bond), 3420 (Intermol. H bond), 3030, 1660. 6 + 6' ^{1}HNMR (CCl_4) δ (ppm) : 1.10 and 1.15 (s, 3H), 1.25 (s, 3H), 1.68 and 1.76 (s, 3H), 1.00 to 2.80 (m, 6H) ; IR (CCl_4) (cm^{-1}) : 1720 (ν C=O). 7 ^{1}HNMR (CCl_4) δ (ppm) : 1.16 (s, 6H), 1.88 (s, 3H), 2.62 (s, 2H), 5.55 to 6.55 (m, 3H) ; IR (CCl_4) (cm^{-1}) : 1655 (ν C=O).

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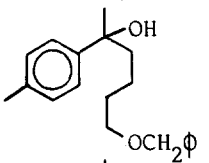
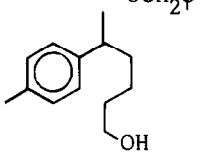
10) 

^{1}HNMR (CCl_4) δ (ppm) : 1.40 (s, 3H), 2.25 (s, 3H), 0.80 to 2.50 (m, 7H), 3.30 (t, J = 6 Hz, 2H), 4.22 (d, 2H), 7.10 (m, 4H) ; IR (CCl_4) (cm^{-1}) : 3597 (free H bond).



^{1}HNMR (CCl_4) δ (ppm) : 1.18 (d, J = 7 Hz, 3H), 0.95 to 1.85 (m, 6H), 2.26 (s, 3H), 2.35 to 2.80 (m, 1H), 3.00 (bs, 1H (OH)), 3.40 (bt, J = 6 Hz, 2H), 6.98 (s, 4H) ; IR (CCl_4) (cm^{-1}) : 3635 (free H bond).

9 ^{1}HNMR (CCl_4) δ (ppm) : 1.20 (d, J = 7 Hz, 3H), 1.35 to 1.70 (m, 4H), 2.26 (s, 3H), 2.05 to 2.90 (m, 3H), 6.98 (s, 4H), 9.58 (t, J = 1.5 Hz, 1H) ; IR (CCl_4) (cm^{-1}) : 2705, 1900, 1725 (ν C=O), 1510, 1450. 10 ^{1}HNMR (CCl_4) δ (ppm): (Z+E) 0.09 (s, 9H), 1.20 (d, J = 7 Hz, 3H), 0.90 to 2.30 (m, 4H), 2.25 (s, 3H), 4.20 to 6.20 (m, 2H), 6.98 (s, 4H).

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12) Obtained by isomerisation of 5-hexen-3-one ; see G. Rousseau and J.M. Conia, following communication.

13) 14 ^{1}HNMR (CCl_4) δ (ppm) : 0.15 (s, 9H), 0.60 to 2.70 (m, 14H), 4.08 (d, J = 10 Hz, 1H) (isomer E), 4.12 (d, J = 10 Hz, 1H) (isomer Z) ; IR (CCl_4) (cm^{-1}) 2960, 1662 (ν C=C), 840.

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