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Titanium-Mediated Formation of 1,2-Disubstituted Cyclopropanols from Esters and Alkenes. A New Approach to the Synthesis of 3,11-Dimethylnonacosan-2-one, a Sex Pheromone of the German Cockroach

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Abstract: A convenient new approach to the synthesis of 3,11-dimethylnonacosan-2-one (**1**), a component of the sex pheromone of the German cockroach *Blattella germanica*, using base-induced ring opening of corresponding easily available 1,2-disubstituted cyclopropanols has been performed.

3,11-Dimethylnonacosan-2-one (**1**) was isolated by Nishida *et al* as a component of the female-produced sex pheromone of the German cockroach *Blattella germanica*[1]. Upon contact with antennae it induces wing-raising and direction-turning response from the adult male species[2].

Mori *et al* synthesised all the four stereoisomers from (R)-citronellol and ethyl (R)-3-hydroxy butanoate, established 3S, 11S configuration of natural pheromone and showed that all the four stereoisomers of **1** were equally bioactive[3]. Some syntheses of the stereoisomeric mixture of **1** have been published[4]. In present work we report a convenient new approach to the synthesis of **1** with the use of available starting materials. The formation of the branched skeleton of **1** was based on regioselective base-induced cleavage of 1,2-disubstituted cyclopropanols in corresponding α-methyl ketones[5].

1,2-Disubstituted cyclopropanol **2** was used in the synthesis of **1** as a key intermediate. The general approach to the preparation of 1,2-disubstituted cyclopropanols by the reaction of esters with alkylmagnesium halides in the presence of $Ti(OPr^i)_4$ has been recently elaborated[6]. It was supposed the key step in this process is disproportionation of dialkyldiisopropyloxytitanium into the corresponding titanacyclopropane intermediate[7], which is further transformed into 1,2-disubstituted cyclopropanols by reaction with ester. The

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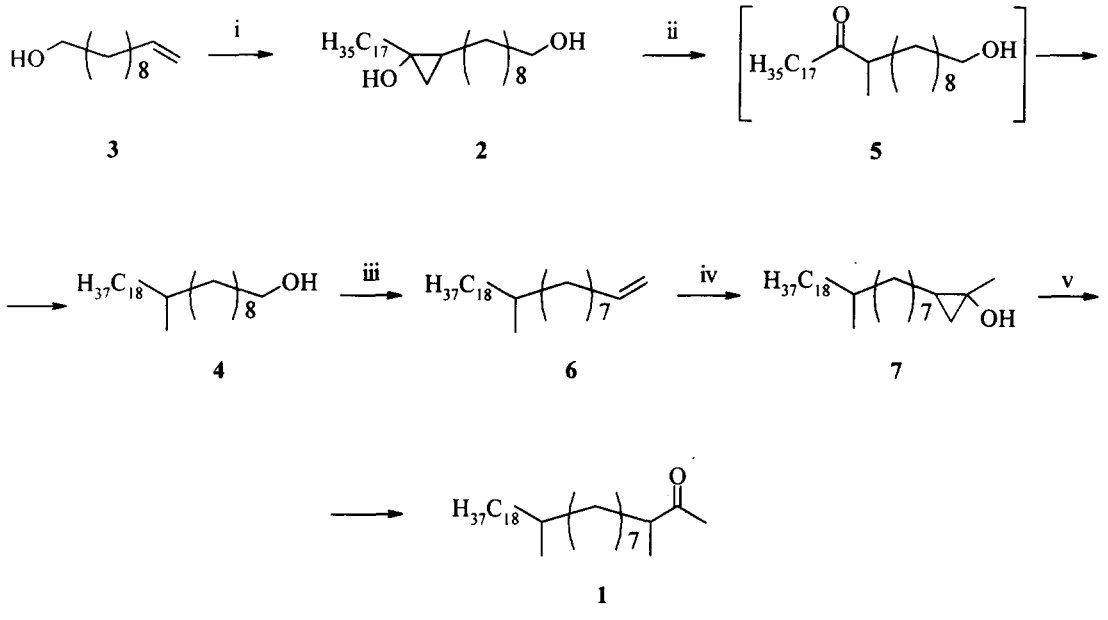
modification of this method, consisting in the use of esters and either linear[8] or branched[9] organomagnesium compounds in the presence of $Ti(OPr^i)_4$ or $TiCl(OPr^i)_3$ for hydroxycyclopropanation of terminal alkenes may be also explored. In our scheme cyclohexylmagnesium bromide[9c] was used as titanium alkylating agent[7].



i) a) ethyl stearate (1equiv), $Ti(O\text{-}Pr^i)_4$ (1 equiv), cyclohexylmagnesium bromide (6 equiv), ether, THF, r. t., b) H_2O / H^+; ii) hydrazine hydrate, KOH, triethylene glycol, 185-190°C; iv) a) P, I_2, 140-150°C; b) Bu^tOK, DMSO, benzene, r. t., 2 h.; v) a) CH_3CO_2Et (1.4 equiv), $Ti(OPr^i)_4$ (1.4 equiv), cyclohexylmagnesium bromide (7.1 equiv), ether, THF, r. t., b) H_2O / H^+; vi) KOH, THF, r. t.

10-Undecen-1-ol (**3**) is available by reduction of 10-undecylenic acid with lithium aluminium hydride in ether, and it was used as a starting material. The reaction of equimolar amounts of ethyl stearate, 10-undecen-1-ol, $Ti(OPr^i)_4$ with 6 equivalents of cyclohexylmagnesium bromide in ether-THF mixture at ambient temperature led, after quenching with aqueous acid and workup, to 1,2-disubstituted cyclopropanol **2**[10, 11]. Treatment of crude product **2** with an excess of hydrazine hydrate and potassium hydroxide in triethylene glycol at 185 - 190 °C for 9 hours gave 10-methyloctacosan-1-ol (**4**)[12] (m. p. 45 - 47 °C after recrystallisation from acetone) in 56% yield based on ethyl stearate. The reaction proceeds through the formation of corresponding α-methyl ketone **5**, followed by Kizhner-Wolf reduction. The primary alcohol **4** was transformed into corresponding iodide by the reaction with iodine and phosphorus without solvent for 8 hours at 140 - 150 °C[13]. Then without further purification the iodide was dehydrohalogenated into 10-methyloctacos-1-ene (**6**) by the treatment with potassium tert-butoxide in the mixture of dimethylsulphoxide and benzene at room temperature for 2 hours [14].

Alkene **6** was isolated after usual workup and column chromatography on alumina (eluent - cyclohexane) in 79% yield based on **4**[15]. Hydroxycyclopropanation of alkene **6** with ethyl acetate (1.4 equiv), $Ti(OPr^i)_4$ (1.4 equiv), and cyclohexylmagnesium bromide (7.1 equiv) in ether-THF mixture at room temperature, according the same procedure as described for **2**[10], gave 1-methyl-2-(8-methylhexacosyl)-1-cyclopropanol (**7**) in 64% yield. The latter was isolated as colourless oil after column chromatography on alumina (eluent - cyclohexane - $CHCl_3$, 5:1)[16]. The treatment of cyclopropanol **7** with equimolar amounts of potassium hydroxide for 12 hours in dry THF at room temperature led to the formation of target 3,11-dimethylnonacosan-2-one (**1**), which was isolated after flash-chromatography on alumina (eluent - cyclohexane) as a waxy solid with m. p. 29 - 31 °C (lit.[4] m. p. 28 - 30 °C) in 67% yield. NMR and IR spectral data of **1** were identical to the data described in the literature[4].

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10. Cyclohexylmagnesium bromide (derived from cyclohexyl bromide (11.08 mL, 90 mmol) and magnesium turnings (2.40 g, 100 mmol) in 65 mL of dry ether) was added to the stirred solution of 10-undecen-1-ol (**3**) (3.00 mL, 15 mmol), ethyl stearate (4.68 g, 15 mmol), and titanium tetraisopropoxide (4.46 mL, 15 mmol) in 45 mL of dry THF over a period of 1 h. Reaction mixture was stirred for an additional 30 min and then poured into 200 mL ice-cold 10% sulfuric acid. The organic layer was separated,and aqueous layer was extracted with ether (2×20 mL). The combined organic extracts were washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated under reduced pressure to leave a pale-yellow oil. The crude 1-heptadecyl-2-(9-hydroxynonyl)-1-cyclopropanol (**2**) was used in the following step without further purification.
11. m. p. 23-24 °C (from acetone). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 0.02 (t, 1H, J=5.5 Hz), 0.79-1.08 (m, 5H), 1.11-1.74 (m, 49H), 2.46-2.76 (m, 2H), 3.61 (t, 2H, J=7 Hz).
12. ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm): 0.78-0.94 (m, 6H), 1.10-1.80 (m, 52H), 3.64 (t, J=7Hz, 2H).
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15. ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm): 0.78-0.94 (m, 6H), 1.10-1.80 (m, 49H), 4.90-5.10 (m, 2H), 5.72-5.96 (m, 1H).
16. ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm): 0.03 (t, J=5Hz, 1H), 0.78-0.94 (m, 8H), 1.10-1.28 (m, 49H), 1.38 (s, 3H), 1.78-1.82 (m, 1H).