SHORT PAPER

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Synthesis of ionone and methylionone analogues from delta-pyronene†

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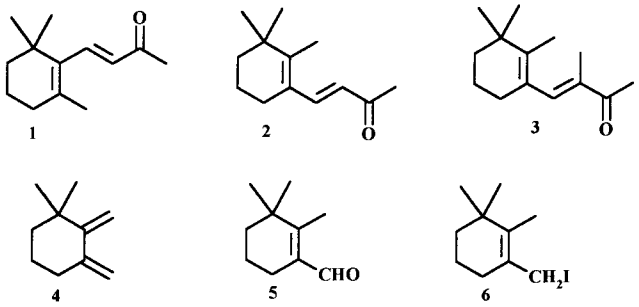
"Iso"-beta-ionone and "iso"-beta-isomethylionone have been prepared from delta-pyronene via 1,6,6-trimethyl-2-methylene cyclohexan-1-ol.

Ionones and methylionones, because of their floral olfactory characteristics are synthetic chemicals with an important impact on the fragrance industry.[1–6]

In connection with our studies directed towards the synthesis of new fragrant compounds,[7] we describe the preparation of ionone and methylionone analogues **2** and **3** respectively from δ-pyronene **4**. The synthesis of "iso"-β-ionone **2** has been reported previously[8,9] from either "iso"-β-cyclocitral **5** or "iso"-β-cyclogeranyl iodide **6** (Scheme 1). These new derivatives ("iso"-series) are distinguished by a change in the substituent positions within the trimethylcyclohexenyl moiety. Thus, by comparison with the natural compound β-ionone **1** (2,6,6-trimethylcyclohexenyl pattern), its analogue "iso"-β-ionone **2** possesses a 2,3,3-trimethycyclohexenyl skeleton.



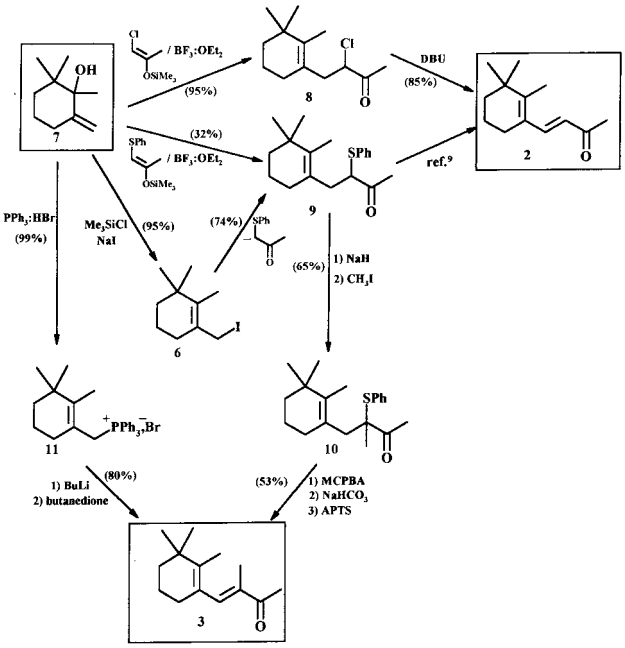
Scheme 1

However, these prior syntheses suffer from the formation of precursors **5** and **6** with only moderate yields from δ-pyronene **4** (28% and 46% respectively).

In order to improve the yield of "iso"-β-ionone **2**, we used a reaction involving an electrophilic addition of enol ethers to allylic alcohols. Such reactions have been developed by several research groups[10–15] and particularly applied to the synthesis of retinoids.[16–18]

In our work, the allylic alcohol **7** (1,6,6-trimethyl-2-methylenecyclohexan-1-ol), which was efficiently obtained from δ-pyronene **4** (60%) by epoxidation (MCPBA) and subsequent reduction ($LiA1H_4$),[8] was the key intermediate for these syntheses (Scheme 2).

Thus, condensation of allylic alcohol **7**, in nitroethane solution with 1-chloro-2-trimethylsiloxy-1-propene, at low temperature in the presence of boron trifluoride etherate catalyst, afforded the α-chloroketone **8**. Dehydrohalogenation of **8** (DBU/CH_2C1_2; room temperature) led to "iso"-β-ionone **2** (overall yield from alcohol **7**: 81%).



Scheme 2

This result prompted us to investigate other hererosubstituted enol ethers and, in particular, 1-phenylthio-2-trimethylsiloxy-1-propene in order to obtain the methylionone analogue **3** ("iso"-β-isomethylionone). In this method, the phenylthio group could be used for, on the one hand the α-carbon activation towards methylation, and on the other hand the generation of a double bond, via the corresponding phenylsulfinyl derivative.

In contrast to the previous result, the condensation of allylic alcohol **7** with 1-phenylthio-2-trimethylsiloxy-1-propene gave the α-keto sulfide **9** in a moderate yield (32%). However this compound, also precursor[9] of "iso"-β-ionone **2**, has been obtained from allylic alcohol **7** via "iso"-β-cyclogeranyl iodide **6** with excellent yields (overall 70%).

Treatment of α-keto sulfide **9** with sodium hydride and then methyl iodide afforded the C_{14}-adduct **10** in 65% yield. Its conversion into methylionone analogue **3** ("iso"-β-isomethylionone), was accomplished by oxidation (MCPBA; -78°C) to a keto sulfoxide, elimination of the sulfoxide moiety ($NaHCO_3$) and treatment with p-toluenesulfonic acid. The methylionone analogue **3** was obtained from allylic alcohol **7** with an overall yield of 24%. We have also developed a more convenient procedure using a Wittig reaction from the triphenylphosphonium bromide **11**, which was quantitatively obtained from allylic alcohol **7** (PPh_3:HBr). The reaction of the triphenylphosphonium bromide **11** with BuLi and then

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butanedione (in excess) gave methylionone analogue **3** (overall yield: 80%).

On the basis of these results, the allylic alcohol **7**, efficiently obtained from δ-pyronene **4** (60% yield; two steps) is a useful key intermediate for the synthesis of "iso"-β-ionone **2** and "iso"-β-isomethylionone **3**. These new fragrant compounds, because of their structural similarity with ionone and methylionone, known as important substances in the perfumery industry, could have some utility in this area.

Experimental

Synthesis of "iso"-β-ionone 2 from allylic alcohol **7**: 1-chloro-2-trimethylsiloxy-1-propene (493 mg, 3 mmol) was added to a solution of allylic alcohol **7**[8] (462 mg, 3 mmol) in nitroethane (15 ml). The mixture was cooled to –25°C then boron trifluoride etherate (426 mg, 3 mmol) was added. After the completion of the reaction (15 min), the reaction mixture was hydrolysed with saturated sodium hydrogencarbonate and extracted three times with pentane. The organic layers were washed with H_2O. After concentration in vacuo 3-chloro-4-(2′,3′,3′-trimethylcyclohex-1′-enyl)butan-2-one **8** was obtained (651 mg, 95% yield):

δ_H ($CDCl_3$) 0.91 (6H, s), 1.55 (3H, s), 2.23 (3H, s), 2.51 (2H, d, J = 7.5 Hz), 4.23 (1H, t); δ_c ($CDCl_3$) 13.8 (CH_3-7′), 19.4 (CH_2-5′), 26.3 (CH_3-1), 28.0 (CH_3-8′ and CH_3-9′), 30.7 (CH_2-6′), 34.9 (C-3′), 38.3 (CH_2-4), 39.3 (CH_2-4′), 82.5 (CH-3), 124.5 (C-1′ or C-2′), 138.4 (C-2′ or C-1′), 203.1 (C-2).

To a solution of chloroketone **8** (400 mg, 1.75 mmol) in methylene chloride (2 ml), 1,8-diazabicyclo[5.4.0]undec-7-ene (560 mg, 3.5 mmol) was added. The resultant reaction mixture was kept 24h at room temperature, hydrolysed with 10% HCl and extracted with ether. The organic layers were washed with H_2O. The solvent was evaporated to give a residue which was chromatographed (silica gel, petroleum ether/ether 85:15) to yield "iso"-β-ionone **2** [4-(2′,3′,3′,-trimethylcyclohex-1′-enyl)but-3-en-2-one] (287 mg, 85% yield):

δ_H ($CDCl_3$) 1.00 (6H, s), 1.84 (3H, s), 2.22 (3H, s), 6.03-7.63 (2H, AX, J_{ax}=16.1 Hz); δ_c ($CDCl_3$) 14.2 (CH_3-7′), 18.7 (CH_2-5′), 26.2 (CH_2-6′), 27.5 (CH_3-1), 27.7 (CH_3-8′ and CH_3-9′), 36.3 (C-3′), 38.7 (CH_2-4′), 125.0 (CH-3), 127.2 (C-1′ or C-2′), 142.4 (CH-4), 151.3 (C-2′ or C-1′), 199.1 (C-2); HRMS ($C_{13}H_{20}O$): calcd. 192.1514; found 192.1511.

(1) *Synthesis of "iso"-β-isomethylionone 3 from allylic alcohol* **7**: (1) Via Wittig reaction: Triphenylphosphonium bromide (686 mg, 2 mmol) was added to a solution of allylic alcohol **7**[8] (308 mg, 2 mmol) in methylene chloride (10 ml). The reaction mixture was stirred for 60h at room temperature. After evaporation of the solvents under reduced pressure, the residue was washed with ether to give phosphonium bromide **11** (461 mg, 99% yield).

n-Butyllithium (0.6 ml of a 2.5M solution in hexane), was added to a solution of phosphonium bromide **11** (733 mg, 1.53 mmol) in THF (15 ml) cooled to 0°C and the mixture was stirred for 15min. Then butanedione (656 mg, 4.6 mmol) was added and stirred for 4h at room temperature. The resultant mixture was quenched with 10% HCl and extracted with ether. The organic layers were washed with saturated sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue purified by chromatography (silicagel, petroleum ether/ether 90:10) gave 4-(2′,3′,3′-trimethylcyclohex-1′-enyl)-3-methylbut-3-en-2-one **3** (252 mg, 80% yield).

δ_H ($CDC1_3$) 0.98 (6H, s), 1.45 (3H, s), 1.61 (3H, s), 2.27 (3H, s), 6.92 (1H, s); δ_C ($CDC1_3$) 12.6 (CH_3-7′), 15.1 (CH_3-5), 19.2 (CH_2-5′), 25.6 (CH_3-1), 28.1 (CH_3-8′ and CH_3-9′), 29.6 (CH_2-6′), 34.5 (C-3′), 39.3 (CH_2-4′), 127.3, 137.1, 138.5, 143.2 (CH-4), 200.5 (C-2); HRMS ($C_{14}H_{22}O$): calcd. 206.1671; found 206.1669.

(2) *Via keto-sulfide* **9**: The keto-sulfide **9** (906 mg, 3 mmol) in THF solution (5 ml), was slowly added to a solution of sodium hydride (79 mg, 3.3 mmol) in THF (10 ml), cooled to 0°C. The mixture was stirred for one hour, the methyl iodide (1.28 g, 9 mmol) was added. After stirring at room temperature for 12 hours, the reaction mixture was hydrolysed with 10% HCl solution and extracted twice with ether. The organic layers were washed with saturated sodium hydrogen carbonate then brine. Evaporation of solvent under reduced pressure afforded a crude product which was purified by a silica-gel column chromatography. Elution with petroleum ether/ether 9/1 provided C_{14}-adduct **10** (613 mg, 65% yield) [3-methyl-3-phenylthio-4-(2′,3′,3′-trimethylcyclohex-1′-enyl)butane-2-one]:

δ_H ($CDCl_3$) 0.91 (6H, s), 1.17 (3H, s), 1.55 (3H, s), 2.35 (3H, s), 7.15-7.45 (5H, m); δ_C ($CHCl_3$) 14.5 (CH_3-7′), 19.4 (CH_2-5′), 20.1 (CH_3-5), 25.3 (CH_3-1), 27.8 (CH_3-8′ or CH_3-9′), 28.5 (CH_3-8′ or CH_3-9′), 31.6 (CH_2-6′), 35.1 (C-3′), 39.3 (CH_2-4′), 40.7 (CH_2-4), 61.0 (C-3), 126.0 (C-1′ or C-2′), 128.8 (2CH, Ph), 129.3 (CH, Ph), 129.6 (C-1′ or C-2′), 136.0 (2CH, pH), 138.2 (C, pH), 206.2 (C-2).

To a cooled (–78 °C) solution of C_{14}-keto sulfide **10** (632 mg, 2 mmol) in methylene chloride, m-chloroperbenzoic acid (475 mg, 2 mmol) in methylene chloride (10 ml) was added. The reaction mixture was stirred for three hours, hydrolysed with 5% sodium bisulfide then extracted three times with methylene chloride. The organic layers were washed with 10% $NaHCO_3$, brine, dried ($MgSO_4$) and concentrated. The crude product in CCl_4 solution was refluxed for five hours in the presence of sodium bicarbonate (520 mg). The solvent was evaporated to give a residue which was stirred for 24 h at room temperature with p-toluenesulfonic acid (30 mg), in ether solution (2 ml). The reaction mixture was hydrolyzed (H_2O) and extracted with ether. The organic layer was washed, dried ($MgSO_4$) and concentrated under reduced pressure to give **3** (220 mg, 53% yield).

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