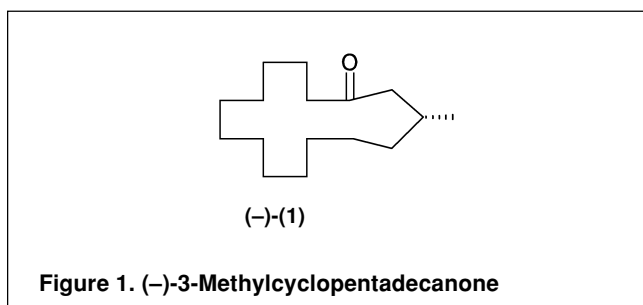


Radical Addition of Acetone to Alkenes: Two Short Routes to Muscone

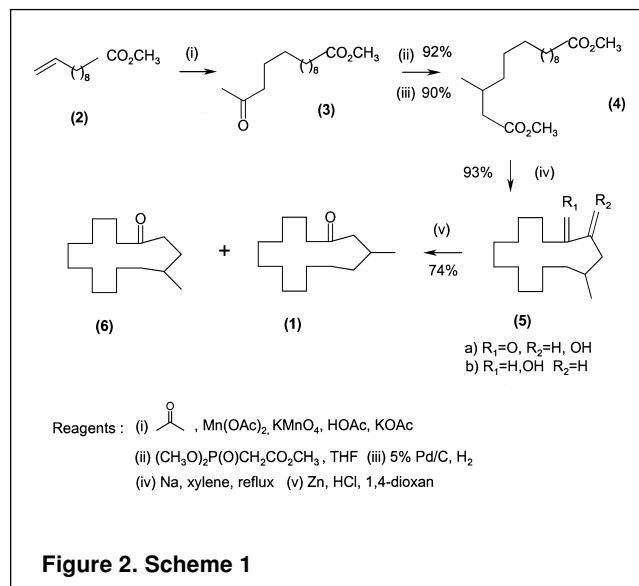
By David Munro and Ken Palmer, Quest International, Ashford, Kent, UK

(-)-3-Methylcyclopentadecanone, known as muscone (Figure 1 [1]) is the principal odorous constituent of the musk deer gland. It represents a benchmark of musk odor that is in great demand for perfumery use. Prior to the elucidation of its structure¹ in 1926, the existence of macrocyclic molecules was not widely accepted. Many syntheses of both the optically active material²⁻¹¹ and racemic muscone¹²⁻²³ have been reported.



Despite the elegance of these syntheses, most suffer the disadvantage of the large number of steps involved in their production. Where ingenious efforts have minimized the synthetic stages, these have still required specialized equipment and processes which have limited their industrial application. There has not been, as yet, a short, safe, and efficient method of production that employs inexpensive and readily accessible starting materials. Herein, we report two such syntheses that feature, in their initial stage, the radical addition of acetone to a suitable alkene through the in situ generation of manganese (III) by a redox reaction.²⁴

Accordingly, the radical reaction of acetone with methyl undecylenate (Figure 2 [2]), mediated by potassium permanganate, gave a good conversion (82% by glc) to methyl 13-oxotetradecanoate (Figure 2 [3]). Wittig-Horner reaction of methyl 13-oxotetradecanoate with trimethyl phosphonoacetate, followed by catalytic hydrogenation, resulted in dimethyl 3-methylpentadecanedioate (Figure



2 [4]). This can be used to give the methyl substituted 15-membered cyclic ketone via intramolecular acyloin condensation, a well-known macrocyclisation technique that, being a heterogenous reaction where both ester groups must come into contact with the metal surface, does not suffer from the usual disadvantage of needing uneconomical high-dilution conditions.

When dimethyl 3-methylpentadecanedioate was treated under nitrogen with sodium in refluxing xylene, an inseparable mixture of acyloin diastereomers (Figure 2 [5a], [5b]) was obtained. Further treatment of these with zinc and hydrochloric acid led to a good overall yield of muscone and 4-methylcyclopentadecanone (Figure 2 [6]) in a ratio of 30/70 (Scheme 1), where isolated yields are shown. Although this mixture had excellent olfactive properties, it was desirable to aim for a shorter and more chemoselective route to muscone, utilizing, if possible, a similarly inexpensive and readily available starting material.

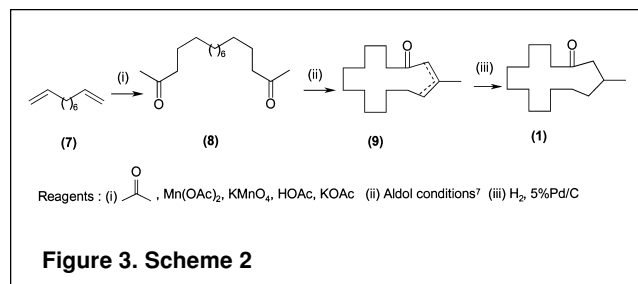
Scheme 1

These aims were fulfilled by 1,9-decadiene (Figure 3 [7]), which is prepared by metathesis of cyclooctene and ethylene. It is applied industrially as a vulcanization catalyst.²⁵ Radical addition of acetone to 1,9-decadiene produces 2,15-hexadecanedione (Figure 3 [8]), a material that has been used to obtain muscone by intramolecular aldol reaction⁷ (Scheme 2).

Scheme 2

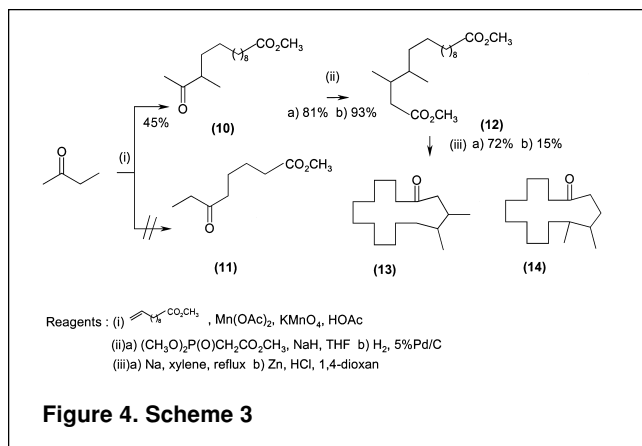
Due to the previous multistage literature syntheses²⁶⁻³⁰ of 2,15 hexadecanedione, such a protocol has, hitherto, been inconvenient and produced a low yield. These problems are overcome by the present procedure. The initial isolated yield of 2,15 hexadecanedione is 29%. Optimization experiments are in progress. A variety of conditions are available for the conversion of 2,15 hexadecanedione to muscone, including catalytic methods³⁰ that enable greater than 60% conversion with high selectivity, making this a candidate for the shortest and least expensive synthesis of racemic muscone reported to date.

The use of ketones other than acetone allows access to



a wide range of related macrocyclic ketones with desirable odor characteristics. The addition of 2-butanone to methyl undecylenate was lower yielding, but noteworthy for its chemoselectivity, producing only methyl 12-methyl-13-oxopentadecanoate (Figure 4 [10]). The isomeric methyl 13-oxopentadecanoate (Figure 4 [11]) was not observed (Scheme 3). The product was converted to the diester (Figure 4 [12]) and observed as two diastereomers (20.3% + 70.5%) from which 3,4-dimethylcyclopentadecanone (Figure 4 [13]) and 4,5-dimethylcyclopentadecanone (Figure 4 [14]) were obtained as an inseparable mixture of four diastereomers (33.6%+14.8%+33.1%+11.5%). These materials possess musk properties.³¹

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Experimental Synthesis of 2,15-Hexadecanedione

A mixture of potassium acetate (70g : 720mmol), manganese(III) acetate tetrahydrate (1.0g : 0.4mmol), acetone (300ml), and glacial acetic acid (150ml) was heated to 70°C under N_2 .

1,9-Decadiene (35g : 0.25mol) was then added, followed by solid potassium permanganate (12.6g : 0.8 equivalent) in very small portions, at 70°C over a period of 4 h. The reaction mixture was then cooled, diluted with water (1500ml) and extracted into dichloromethane. The combined organic extracts were washed with saturated NaHCO_3

(aq), then water, and finally dried over MgSO_4 . The solvent was removed in vacuo to give a pale-yellow oil (58.2g). GLC (SE54 : 100–250°C at 4°C min^{-1}) indicated 70.4% conversion. TLC (silica : hexane 50%, Et_2O 50%) indicated a major product separated by flash chromatography (as TLC) to give a colorless solid (25.2g). This was recrystallized to produce colorless crystals (18.9g : 29%) (mp 80°C [hexane]) (^{13}C NMR [CDCl_3] : δ 209.2[C=O], 43.7[$\text{CH}_2\text{C}=\text{O}$], 29.8[$\text{CH}_3\text{C}=\text{O}$], 29.5[CH_2], 29.4[CH_2], 29.3[CH_2], 29.1[CH_2], 23.8[CH_2]).

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