Synthesis of (*R,S*)-Muscone from 10-Undecenoic Acid[1]

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Muscone (3-methylcyclopentadecanone) is a major macrocyclic ketone found in the solid secretion, commonly known as musk, from the pouch of *Moschus moschiferus*. Herein, we report its synthesis from 10-undecenoic acid, which is the major product of castor oil pyrolysis. Methyl 14-oxotetradecanoate was prepared by radical addition of methyl 10-undecenoate to acrolein. The terminal oxo group was protected as an acetal, and the ester group was treated with the anion of dimethyl methylphosphonate (CH_3-(O)P(OMe)$_2$, DMMP) to give 2-(15-dimethoxyphosphynil-14-oxo-pentadecane)-1,3-dioxolane. The acetal protection was removed and the Emmons-Horner reaction was carried out in K_2CO_3-*t*-butanol to give 2-cyclopentadecenone. The addition of MeMgI in the presence of Cu_2Cl_2 gave muscone.

KEY WORDS: Acrolein, 2-cyclopentadecenone, dimethyl methylphosphonate, Emmons-Horner reagent, methyl 14-oxotetradecanoate, muscone.

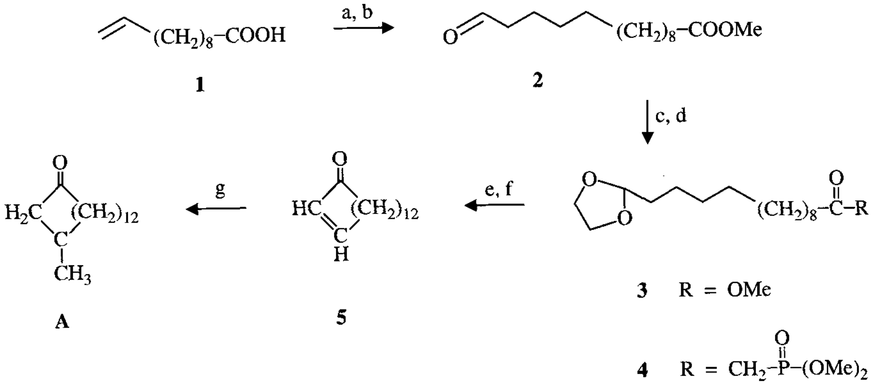
Musk, a widely used perfumery material, is obtained as a solid secretion from the pouches of *Moschus moschiferus*, which is found in the Himalayan region of India. Since the recognition of muscone (3-methylcyclopentadecanone) as the major macrocyclic ketone (1) in musk, many synthetic routes have been reported for its preparation. Most of the strategies begin with the use of cyclododecanone and its expansion by three carbons (2,3). Other approaches pertain to preparation of the appropriately substituted aliphatic chain followed by cyclization in the final step to give muscone (4). Practically all these methods use synthetic starting materials and involve many steps. We report herein a simple route for its preparation by starting from an indigenously available, inexpensive raw material, 10-undecenoic acid, which is obtained as a major product in the pyrolysis of castor oil (5). All the steps in synthesis of racemic muscone and reaction conditions are shown in Scheme 1, where conditions are a) CH_3OH, H_2SO_4, reflux; b) $BH_3 \cdot DMS$, THF, $Hg(OAc)_2$, acrolein, $NaBH_4$; c) $HOCH_2CH_2OH$, PTSA, C_6H_6, reflux; d) CH_3-(O)P-(OMe)$_2$, BuLi, THF, −78°C, 3; e) PPTS, acetone, reflux; f) K_2CO_3, *t*-BuOH; g) MeMgI, Cu_2Cl_2, ether, 0°C, 5.

EXPERIMENTAL PROCEDURES

Materials. Undecylenic acid of 99% purity was procured from Jayant Industrial and Scientific Research (Bombay, India). The reagents diborane-dimethylsulfide, acrolein, dimethyl methylphosphonate, para-toluenesulfonamide (PTSA), and butyllithium and methyl iodide were purchased from Aldrich Chemical Co. (Milwaukee, WI) and used directly. Tetrahydrofuran (THF) was distilled and dried over lithium aluminum hydride. Solvents used were of reagent grade and procured locally. Silica gel (60–120 mesh) was obtained from ACME Synthetic Chemicals (Bombay, India).

Methods. Infrared (IR) spectra were recorded in chloroform on Perkin Elmer 683 or 1310 spectrometers (Perkin Elmer, Norwalk, CT). ^1H NMR spectra were recorded on a Varian FT-80 A spectrometer (Varian Associates, Palo Alto, CA) with tetramethylsilane (TMS) as internal standard. Mass spectra were recorded on a Finnigan MAT 1020B spectrometer (Sunnyvale, CA).

Methyl 14-oxo-tetradecanoate (2). A solution of 10-undecenoic acid (100 mmol) in methanol (100 mL) and H_2SO_4 (1 mL) was refluxed for 2 h. After evaporation of methanol, the crude compound was extracted with diethyl ether and vacuum distilled to yield 97% of methyl 10-undecenoate. Diborane-DMS in THF (3 mmol) was added to methyl 10-undecenoate (10 mmol) in THF (10 mL) under N_2 at 0°C. After 45 min, $Hg(OAc)_2$ (10 mmol) was added and the mixture was allowed to react at 20°C for 30 min. The resulting product was further diluted with CH_2Cl_2 and mixed with acrolein (50 mmol). Rapid addition of $NaBH_4$ (10 mmol suspended in 2 mL water) led to precipitation of metallic Hg within 5 min (6). After the evaporation of supernatant liquid, the compound was



SCHEME 1

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extracted with diethyl ether, washed with water and separated on a silica gel column to yield 43% of methyl 14-oxo-tetradecanoate (2). IR 2920, 1735, 1720 cm^{-1}. ^1H NMR δ 9.8 (*t*, 1H, -CHO), 3.7 (*s*, 3H, O-CH_3), 2.3 (*t*, 4H, CH_2-CO, CH_2-CHO), 1.3–1.6 (*bs*, 20H, -$(CH_2)_{10}$-). Mass *m/e* (relative abundance) 256 (5.0), 225 (8.0).

2-(15-Dimethoxyphosphynil-14-oxo-pentadecane)-1,3-dioxolane (4). To 2 (10 mmol) in benzene, ethylene glycol (15 mmol) and PTSA (0.5 mmol) were added, and the mixture was refluxed in a Dean-Stark apparatus to remove water of reaction. After removal of benzene, the product was extracted with diethyl ether and separated on a silica gel column to yield 95% of 3 [^1H NMR δ 4.9 (*t*, 1H, O-CH-O), 3.9 (*m*, 4H, O-CH_2-CH_2-O)]. To a cold (−78°C) solution of dimethyl methanephosphonate (10 mmol) in 5 mL of THF, butyllithium [15% solution in hexane, 10 mmol] was added over 5 min. After stirring for 15 min, a solution of 3 (10 mmol) in THF was added dropwise over 10 min. After 30 min, additional butyllithium (10 mmol) was added to the reaction mixture (7). After stirring for 2 h, the reaction mixture was quenched with solid NH_4Cl. The crude product was extracted with diethyl ether and separated on a silica gel column to yield 4 in 80% yield. IR 2920, 1720, 1280 cm^{-1}. ^1H NMR δ 4.9 (*t*, 1H, O-CH-O), 3.9 (*m*, 4H, O-CH_2-CH_2-O), 3.8 and 3.9 (*s*, 6H, P-$[OCH_3]_2$), 3.0 and 3.3 (*s*, 2H, OC-CH_2-PO), 2.6 (*t*, 2H, CH_2-CO), 1.3–1.6 (*bs*, 22H, -$CH_2)_{11}$-).

2-Cyclopentadecenone (5). 4 (5 mmol) was taken in acetone containing 5% water (5 mL) and refluxed for 4 h in the presence of pyridinium *p*-toluene sulfonate (PPTS) (0.2 mmol). Acetone was removed, and the product was extracted with diethyl ether and washed with water. The crude product (5 mmol) was taken in *t*-BuOH (25 mL), and the solution was added dropwise to a boiling solution of K_2CO_3 (15 mmol) in *t*-BuOH (25 mL) over 5 h (8). After refluxing for an additional 2 h, the solvent was removed on a rotavapor. The crude product was extracted with diethyl ether, and the ether layer was washed twice with dilute HCl and dried on solid Na_2SO_4. The crude product was purified on a silica gel column to yield 30% of 5. IR 2930, 1680 cm^{-1}. ^1H NMR δ 6.7–6.9 (*m*, 1H, -CH=), 6.1–6.2 (*d*, 1H, =CO-CO, $J = 8$ Hz), 2.5 (*t*, 2H, CH_2-CO), 2.2–2.3 (*m*, 2H, allylic -CH_2-), 1.5–1.8 (*m*, 4H, β-CH_2 to carbonyl and olefin), 1.3 (*bs*, 16H, -$(CH_2)_8$). Mass *m/e* (rel. abund.) 222 (40.0), 41 (100.0).

3-Methylcyclopentadecanone (A). To the solution of MeMgI (1.5 mmol) in ether, Cu_2Cl_2 (2 mmol, freshly prepared) was added at 0°C under inert atmosphere. After stirring for 15 min, 5 (1 mmol) in diethyl ether was added slowly over 1 h (9). The solution was stirred for 3 h and quenched with 1 N HCl. The product was extracted with diethyl ether, washed with water, dried over Na_2SO_4 and purified on a silica gel column to yield 80% of muscone (A). IR 2930, 1720 cm^{-1}. ^1H NMR δ 2.2–2.5 (*t* and *d*, 4H, CH_2-CO), 1.3 (*bs*, 22H, -$(CH_2)_{11}$-), 0.98 (*d*, 3H, -CH_3). Mass *m/e* (rel. abund.) 238 (10.0), 223 (5.0), 70 (100.0).

RESULTS AND DISCUSSION

Methyl 10-undecenoate was found to be 99% pure by gas chromatography (GC) analysis. Methyl 14-oxotetradecanoate (2) was obtained by 1,4-addition of the free radical generated at 11-carbon atom of methyl 10-undecenoate to acrolein. The radical was generated by a sequence of transformations at the double bond, namely, hydroboration of the double bond and decomposition of the borated product with $Hg(OAc)_2$, followed by addition of sodium borohydride. The ^1H NMR spectrum of 2 showed a triplet at 9.8 δ (-CHO), a singlet at 3.7 δ (-OCH_3), an increase in integration of the singlet at 1.3 δ corresponding to four methylene groups, and an absence of peaks for double bond protons. The IR spectrum showed absorption at 1735 cm^{-1} (ester CO group), along with 1720 cm^{-1} (aldehyde CO group), and the mass spectrum showed a molecular ion at 256. The free aldehyde group was protected as acetal to yield substituted 1,3-dioxolane (3). Compound (4), the Emmons-Horner reagent, was prepared by attack of the anion of DMMP [CH_2-(O)P$(OMe)_2$] on the methyl ester. The anion, generated by stirring 1 equivalent of butyllithium and 1 equivalent of DMMP, attacks the electrophilic carbon of the methyl ester with simultaneous displacement of the -OCH_3 group to give activated methylene flanked by carbonyl and phosphonate groups. The addition of excess butyllithium (1 eq) enhanced the yield from 50% to 80%. The ^1H NMR spectrum showed peaks at 3.8 and 3.99 δ (two singlets, due to two P-OCH_3 groups) and 3.0 and 3.3 δ (split singlets due to OC-CH_2-PO), with disappearance of a singlet at 3.7 δ corresponding to methyl ester. The absorption at 1280 cm^{-1} in the IR spectrum confirmed the presence of the phosphonate ester group in compound (4). The removal of acetal protection of 4 regenerated the aldehyde group at the 14-carbon atom. The next step of intramolecular coupling of the aldehyde with activated methylene, as in the Wittig reaction, to offer a 15-carbon α,β-unsaturated cycloketone was carried out in the presence of various combinations of bases such as NaH, $KHCO_3$, $NaHCO_3$ and K_2CO_3, and solvents such as THF, dimethyl formamide (DMF) and *t*-BuOH. The maximum yield of 2-cyclopentadecenone (5) was obtained when phosphonate ester in *t*-BuOH was added dropwise to K_2CO_3 in refluxing *t*-BuOH over a period of 2 h in high dilution. Any deviation from these reaction conditions offers low yield due to dimer formation. The ^1H NMR spectrum showed the absence of the phosphonate ester group and presence of a *trans* double bond. The *J* value of 16 Hz for the proton α to the keto group (doublet at 6.1–6.2 δ) confirmed the *trans* nature of the double bond.

Muscone (A) was obtained from 5 by addition of MeMgI catalyzed by Cu_2Cl_2 at 0°C under inert atmosphere. Addition of the Grignard reagent without Cu salts gave 1,2-addition of methyl to offer allylic alcohol. The IR ^1H NMR and mass spectra matched with the reported data (2). Thus, this offers a simple route to prepare racemic muscone from a low-cost raw material, 10-undecenoic acid, which can be obtained from castor oil in commercial quantities.

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