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Ring Closing Metathesis Directed Synthesis of (*R*)-(–)-Muscone from (+)-Citronellal

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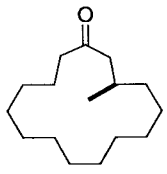
Abstract—A concise and simple synthesis of the valuable perfumery ingredient (*R*)-(−)-muscone **1** has been achieved through ring closing olefin metathesis (RCM) aided macrocyclization protocol as the key step. Commercially available starting material (*R*)-(+)-citronellal **3** has been employed as a building unit in preparing the acyclic diolefinic substrate **16**, which in turn was exposed to bis(tricyclohexylphosphine)benzylideneruthenium dichloride catalyst **2** to afford the cyclic RCM reaction product **17** in 78% yield. Catalytic hydrogenation of **17** furnished enantiomerically pure (*R*)-(−)-muscone **1**.

(*R*)-(−)-Muscone (3-methylcyclopentadecan-1-one) **1** is the main odorous principle of musk pod obtained from the male musk deer *Moschus moschiferus*.[1] Its absolute configuration was established by an asymmetric synthesis[2] via the electrolytic method using monomethyl ester of tridecanedioic acid and β-methylglutaric acid and further confirmed by ORD studies.[3] Owing to its rare occurrence in nature, and its exotic odor, several approaches have been made towards the synthesis of muscone. Being a macrocyclic ketone, muscone in racemic form has been synthesized earlier[4] by several routes involving a variety of conventional procedures such as acyloin condensation, fragmentation reaction of tosyl hydrazones derived from α,β-epoxy ketones, one carbon homologation and ring enlargement protocols. Similarly, a number of reports on the synthesis of (*R*)-muscone **1** have appeared in literature from time to time.[5] Some of the recent syntheses reported for (*R*)-muscone **1** were based on key reactions like free radical macrocyclization,[6] diastereoselective conjugate addition to a cyclic ester followed by Dieckmann condensation reaction[7] and asymmetrically catalyzed macrocyclization of an ω-alkynal in combination with a hydroxyl group directed cyclopropanation of the resulting cyclic allyl alcohol.[8] Though these syntheses have successfully addressed the problem of enantioselectivity, most of them, however, employed the laboriously prepared and not so easily available chiral catalytic systems in order to transfer enantioselectively either the methyl group or a cyclopropyl moiety on a pre-formed functionalized cyclic substrate which in turn was prepared via the multistep synthetic sequence. In order to overcome these limitations, we visualized a simple approach for (*R*)-muscone **1** starting from an acyclic chiral substrate which could be easily accessible in good yield through readily available starting material and then utilizing ring closing olefin metathesis as the key reaction to effect macrocyclization. Recourse to the molybdenum alkylidene catalyst developed by Schrock[9e] gave the same result (Fig. 1).

In recent years, the olefin metathesis has advanced in a widely applicable synthetic method[9] with the development of stable transition metal based catalysts and more particularly, the ring closing olefin metathesis (RCM) guided synthetic protocol continues to yield spectacular success during the natural product synthesis.[10] Among various catalysts available, the ruthenium and the molybdenum alkylidenes are the most frequently used initiators for olefin metathesis.[11]

In principle, muscone **1** could be obtained by RCM reaction involving a suitable diolefinic substrate. In this paper, we



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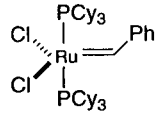

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Figure 1.

Keywords: catalysis; cyclic ketones; cycloalkanes; metathesis; ruthenium and compounds.
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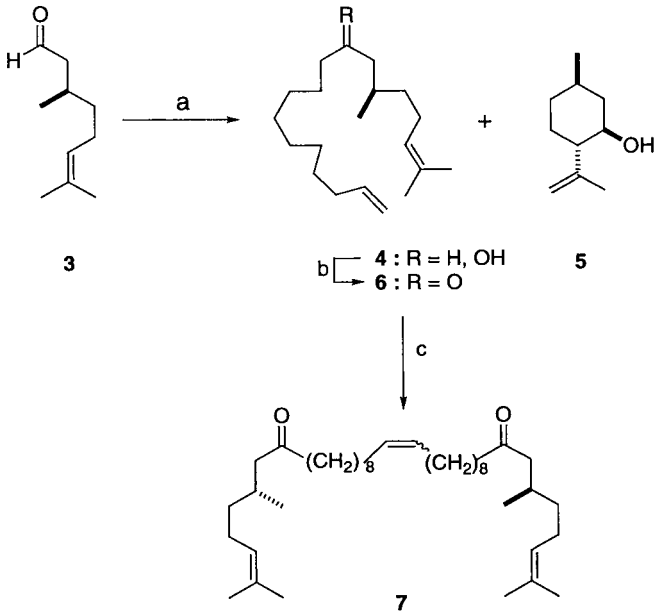
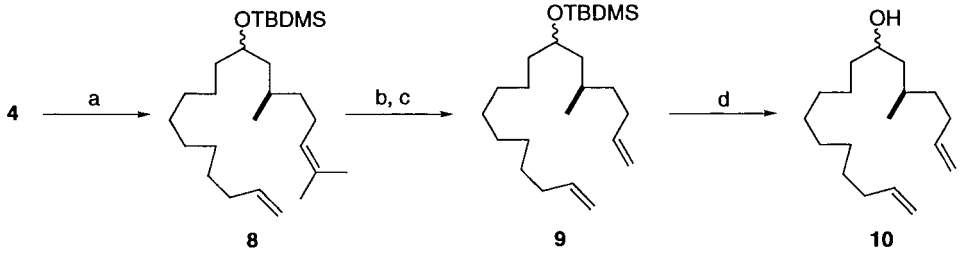


Scheme 1. Reagents and conditions: (a) 10-bromodec-1-ene, Mg, Et_2O, 16 h; (b) Jones reagent, CH_3COCH_3, 10 min; (c) 5 mol% of **2**, 21 h, 45°C.

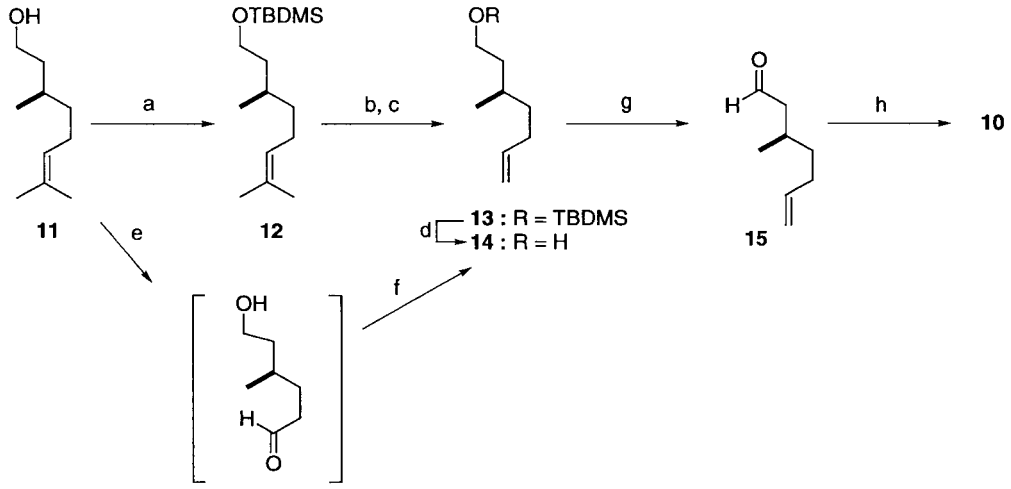
describe in detail[12] the realization of this assumption in practice which leads us to a simple and concise synthesis of (*R*)-muscone **1** in good chemical and optical yields. Although, muscone **1** in optically active form has been synthesized by different routes, none of them employed an RCM protocol for effecting macrocyclization leading to the natural product **1**.

The required acyclic diolefinic RCM substrate was prepared from the commercially available chiral starting material (*R*)-(+)-citronellal **3** (Scheme 1). For this purpose, dec-9-en-1-ol was converted into the corresponding bromide by treatment with carbon tetrabromide in the presence of triphenylphosphine using acetonitrile as a solvent. The Grignard reagent prepared from this bromide was reacted with **3** to give the alcohol **4**. Some quantity of a by-product identified as isopulegol **5**[13] was also isolated during the Grignard reaction. The formation of this by-product can be rationalized on the basis of a carbonyl ene-cyclization of highly reactive citronellal under the experimental conditions employed for the Grignard reaction. Repeated attempts to suppress the formation of this by-product yielded no success. The alcohol **4** was then subjected to Jones oxidation to yield the keto compound **6**. Having the desired diolefinic substrate **6** in hand, we then turned our attention towards the selection of a suitable RCM catalyst. Among the catalysts, we opted for bis(tricyclohexylphosphine)benzylidene ruthenium dichloride **2** as the initiator for the ring closing metathesis after considering its commercial availability, excellent functional group tolerance and the reported retention of catalytic activity even under reaction conditions which did not include rigorous exclusion of moisture and oxygen.[9] Accordingly, the diolefinic substrate **6** was exposed to ruthenium alkylidene **2** under the RCM reaction conditions. However, compound **6** failed to undergo ring closing metathesis and instead provided the corresponding acyclic dimer **7**, formed as a product of intermolecular metathesis reaction. This result further confirms the earlier reported observation that the RCM process is sensitive to steric hindrance close to the double bond to be metathesized in the substrate.[11]

Based on the foregoing result, it was evident that, to induce a productive RCM reaction using ruthenium alkylidene **2**, it is essential to convert the trisubstituted double bond existing in substrate **6** to a terminal olefinic moiety. This was achieved as shown in Scheme 2. When **4** was directly subjected to ozonolysis-Wittig reaction protocol, we were unable to isolate any appreciable quantity of the corresponding olefinic compound **10**. Hence, the alcohol **4** was converted to its TBDMS ether **8** and was then subjected to



Scheme 2. Reagents and conditions: (a) TBDMSCI, imidazole, DMF, 21 h; (b) O_3, CH_2Cl_2, −78°C, Me_2S, −78°C then rt, 12 h; (c) Ph_3PMeBr, *n*-BuLi, THF, −78° then rt, 4 h; (d) TBAF, THF, 24 h.

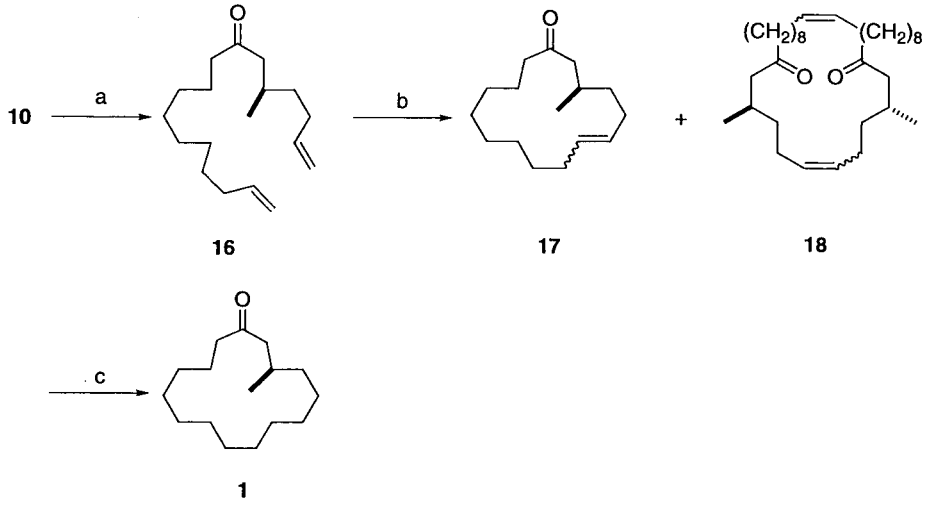


Scheme 3. Reagents and conditions: (a) TBDMSCI, imidazole, DMF, 10 h; (b) O_3, CH_2Cl_2, −78°C, Me_2S, −78°C then rt; 12 h; (c) Ph_3PMeBr, *n*-BuLi, THF, −78°C then rt, 3 h; (d) TBAF, THF, 1 h; (e) OsO_4, dioxane, $NaIO_4$, H_2O, 36 h; (f) Ph_3PMeBr, *n*-BuLi, THF, −78°C then rt, 4 h; (g) SO_3·pyridine, CH_2Cl_2, DMSO, NEt_3, 1.5 h; (h) 10-bromodec-1-ene, Mg, Et_2O, 4 h.

ozonolysis at −78°C followed by Wittig olefination of the resulting dialdehyde to furnish the diolefinic TBDMS ether **9**. Deprotection of the TBDMS group in **9** was achieved with TBAF to provide the alcohol **10**. Alternatively, **10** was also prepared directly by the Grignard reaction on aldehyde **15**, which in turn was made available by repeating the above set of reactions on (*R*)-citronellol **11** (Scheme 3). This approach also helped us to prevent the formation of undesired by-product **5** arising from **3** under the Grignard reaction conditions as observed earlier.

Thus, when (+)-citronellol **11** prepared by sodium borohydride reduction of **3** was subjected to ozonolysis, the reaction provided only trace quantities of the desired aldehyde and hence the hydroxyl group in **11** was protected in the form of its TBDMS ether **12**. The isopropenyl double bond present in **12** was then cleaved smoothly by ozonolysis followed by the Wittig olefination of the derived aldehyde to afford the olefin **13** in good yield. Deprotection of the TBDMS group in **13** was achieved by treatment with TBAF to provide alcohol **14**.

Alternatively, the hydroxyl group protection and deprotection sequence leading to **14** could be avoided by resorting to osmium tetroxide-periodate oxidation (Scheme 3). Thus, (+)-citronellol **11** was treated with a catalytic amount of osmium tetroxide in dioxane, followed by cleavage of the resulting diol with sodium periodate in one pot operation and Wittig olefination of the derived aldehyde directly gave **14** in 67% combined yield. The olefinic alcohol **14** was then converted to aldehyde **15** by oxidation with sulfurtrioxide pyridine complex in dimethyl sulfoxide and triethylamine. Without further purification, the aldehyde **15** was treated with Grignard reagent prepared from 10-bromodec-1-ene as before to yield the alcohol **10** in 66% yield (over two steps) without any contamination of the by-product. Attempts of further improvement in the yield of **10** gave no success apparently due to the labile and volatile nature of aldehyde **15**. Surprisingly, all our efforts to use the previously prepared alcohol **4** or its TBDMS ether **8** as a substrate for osmium tetroxide-periodate oxidation and subsequent Wittig reaction ended up in very poor yields of the corresponding terminal olefins **10** and **9**, respectively.



Scheme 4. Reagents and conditions: (a) Jones reagent, CH_3COCH_3, 5 min; (b) 5 mol% of **2**, CH_2Cl_2, 21 h, 45°C; (c) H_2, 10% Pd-C, MeOH, 3 h.

When **10** was subjected to Jones oxidation, it provided the desired RCM substrate **16** in high yield (Scheme 4). As anticipated, when **16** was exposed to ruthenium alkylidene catalyst **2** in refluxing dichloromethane, it smoothly underwent ring closing olefin metathesis to yield the desired cyclic product **17** in 78% yield as a mixture of *E*/*Z* isomers along with a small quantity of cyclic dimeric compound **18** formed as a result of intermolecular metathesis. Finally, catalytic hydrogenation of **17** over palladium carbon provided pure (*R*)-(−)-muscone **1** which was identical in all respects with an authentic sample.

Thus, a new simple synthesis of the rare and classical perfumery compound (*R*)-(−)-muscone **1** has been achieved starting from readily available synthons by employing ring closing olefin metathesis. The key macrocyclization step involving the acyclic substrate in the present synthesis proceeds under mild reaction condition with moderate catalyst load and in good yield.

Experimental

IR spectra were recorded on a Shimadzu FT/IR-4200 spectrophotometer for solutions in carbon tetrachloride unless otherwise indicated. ^{1}H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectra were obtained for solutions in deuteriochloroform on a Varian Gemini 200H instrument with tetramethylsilane as internal standard. Mass spectra were run on a JEOL HX-110 spectrometer of the Instrumental Analysis Center for Chemistry, Tohoku University or a JEOL GCmate, Niigata University. Specific rotations, $[\alpha]_D$ were determined on a Horiba SEPA-200 polarimeter for solutions in chloroform and are given in 10^{-1} deg cm^2 g^{-1}. Medium pressure liquid chromatographies (MPLC) were carried out on a JASCO PRC-50 instrument with a pre-packed silica gel column. Microanalyses were carried out in the microanalytical laboratory of the Instrumental Analysis Center for Chemistry, Tohoku University. Reactions were run under an atmosphere of nitrogen. Tetrahydrofuran and diethyl ether were distilled over sodium benzophenone ketyl and dichloromethane was distilled over calcium hydride and stored under nitrogen atmosphere. Anhydrous sodium sulfate (Na_2SO_4) was used for drying the organic extracts. The work-up procedure involved dilution of the reaction mixture with water or saturated aqueous sodium hydrogen carbonate or ammonium chloride solution followed by extraction with diethyl ether (*n*-hexane or ethyl acetate or dichloromethane), washing of the combined organic extract with water, brine, drying (Na_2SO_4) and evaporation of the solvent at aspirator pressure. (*R*)-(+)-Citronellal used in this work was procured from Tokyo Kasei Kogyo Co., Ltd.

10-Bromodec-1-ene. Carbon tetrabromide (10.62 g, 32 mmol) was added to a solution of dec-9-en-1-ol (3.15 g, 20 mmol) and triphenylphosphine (8.39 g, 32 mmol) in acetonitrile (30 cm^3) at 0°C. The reaction mixture was stirred at room temperature for 22 h, and the acetonitrile was evaporated under reduced pressure. *n*-Hexane (20 cm^3) was added to the residue and the precipitated triphenylphosphine oxide was filtered off. The filtered residue was washed twice with *n*-hexane (2×10 cm^3) and the *n*-hexane was removed from the combined organic part to leave a pale yellow oil, purified by column chromatography on silica gel using *n*-hexane as eluent followed by distillation in a Kugelrohr short-path apparatus to give 10-bromodec-1-ene (4.42 g, 100%) as a colorless oil; ν_{max}/cm^{-1} 3088, 2930, 1641, 1545, 912 and 744; δ_H (200 MHz) 1.23–1.47 (10H, m), 1.86 (2H, m), 2.02 (2H, m), 2.09 (4H, m), 3.41 (2H, t, *J*=6.9 Hz, CH_2Br), 4.89–5.05 (2H, m, CH_2=CHCH$_2$) and 5.81 (1H, ddt, *J*=16.9, 10.6, 6.7 Hz, CH_2CH=CH_2).

(6*R*)-2,6-Dimethyl-2,17-octadecadien-8-ol 4. A slurry of magnesium powder (121 mg, 5.0 mmol) in diethyl ether (1.3 cm^3) was stirred with a trace quantity of iodine until the solution became colorless. 10-Bromodec-1-ene (1.095 g, 5.0 mmol) in diethyl ether (1 cm^3) was then added dropwise to the slurry. The reaction for the formation of Grignard reagent was initiated by adding a small crystal of iodine and the reaction mixture was refluxed for 5 min. After the exothermic reaction had started, it was stirred at room temperature for 30 min and then diluted with diethyl ether (5 cm^3). A solution of (*R*)-citronellal **3** (771 mg, 5.0 mmol) in diethyl ether (1.3 cm^3) was added slowly to the Grignard reagent at 0°C and then the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was quenched with aqueous ammonium chloride and extracted with diethyl ether. Evaporation of solvent followed by purification of the product by MPLC provided alcohol **4** (926 mg, 63%) as an inseparable diastereomeric mixture (ratio 1:1); ν_{max}/cm^{-1} 3648, 3008, 2964, 1644, 1461, 1450, 1379 and 907; δ_H (200 MHz) 0.91 and 0.92 (total 3H, ratio=1:1, d, *J*=6.5 Hz, C*H*$_3$CH), 1.1–1.5 (19H, m), 1.6 and 1.68 (3H each, s, olefinic methyl), 1.88–2.12 (4H, m), 2.32 (1H, br s, hydroxy), 3.7 (1H, m, C*H*OH), 4.89–5.16 (23H, m, CH$_2$CH=C*H*$_2$), 5.1 (1H, m, CH$_2$C*H*=CMe$_2$) and 5.81 (1H, ddt, *J*=17 Hz, 10.2 and 6.6, CH$_2$C*H*=CH$_2$); *m*/*z* (EI) 294 (M$^+$, 0.2%), 276 (M$^+$−H$_2$O, 0.6), 109 (48), 95 (43), 82 (100), 69 (79) and 67 (38).

The above reaction also gave the by-product **5** (285 mg, 37% based on **3**); ν_{max}/cm^{-1} 3588, 3008, 2953, 2926, 1644, 1460, 1375, 1282 and 901; δ_H (200 MHz) 0.94 (3H, d, *J*=6.5 Hz, C*H*$_3$H), 1.18–1.68 (6H, m), 1.71 (3H, s, olefinic methyl), 1.78–2.11 (3H, m), 3.46 (1H, td, *J*=10 and 4.3 Hz, C*H*OH) and 4.84–4.92 (2H, m, C*H*$_2$=CMe); δ_C (50 MHz) 19.16, 22.21, 29.60, 31.41, 34.29, 42.61, 54.09, 70.29, 112.81 and 146.57.

(6*R*)-2,6-Dimethyloctadeca-2,17-octadien-8-one 6. To a stirred solution of alcohol **4** (120 mg, 0.407 mmol) in acetone (3 cm^3) was added Jones reagent dropwise at ice bath temperature until a slight orange color persisted. After 10 min, the reaction mixture was quenched by the addition of isopropyl alcohol and the product was extracted with ethyl acetate (2×10 cm^3). Evaporation of the combined extracts followed by purification of the residue using MPLC provided ketone **6** (96 mg, 81%) (Found: C, 81.9; H, 12.2. $C_{20}H_{36}O$ requires C, 82.1; H, 12.4%); ν_{max}/cm^{-1} 3008, 2928, 1713, 1644, 1379, 916 and 746; δ_H (200 MHz) 0.88 (3H, d, *J*=6.6 Hz, C*H*$_3$ CH), 1.10–1.45 (12H, m), 1.45–1.57 (3H, m), 1.59 and 1.68 (3H each, s, olefinic methyl), 1.85–2.10 (4H, m), 2.20 (1H, dd, *J*=15.5 and 7.9 Hz), 2.36 (2H, t,

J=7 Hz), 2.38 (1H, dd, J=15.5 and 7.8 Hz), 4.95 (2H, m, $CH_2CH{=}CH_2$), 5.1 (1H, m, $CH_2CH{=}CMe_2$) and 5.81 (1H, ddt, J=17, 10.2 and 6.6 Hz, $CH_2CH{=}CH_2$).

Acyclic dimer 7. To a solution of keto-diolefin **6** (33 mg, 0.11 mmol) in dry degassed dichloromethane (25 cm^3) was added via cannula, a solution of ruthenium alkylidene **2** (6 mg, 0.007 mmol) predissolved in CH_2Cl_2 (6 cm^3). The resulting purple colored solution was heated to 45°C for 21 h and concentrated under reduced pressure to afford an oily brown residue. Purification by MPLC [eluent: *n*-hexane–ethylacetate (5:1)] afforded the dimer **7** (26 mg, 83%) as a diastereomeric mixture (Found: C, 81.8; H, 11.9. $C_{38}H_{68}O_2$ requires C, 81.9; H, 12.3%); ν_{max}/cm^{-1} 2928, 2856, 1715, 1461, 1410, 1377 and 966; δ_H (200 MHz) 0.89 (6H, d, J=6.5 Hz, 2×CH_3CH), 1.10–1.40 (32H, brs), 1.60 and 1.68 (6H each, s, 2×2 olefinic methyls), 1.85–2.10 (6H, m), 2.18 (2H, dd, J=15.5 and 7.9 Hz), 2.37 (4H, t, J=6.7 Hz), 2.40 (2H, dd, J=15.6 and 7.8 Hz), 5.00–5.15 (2H, brt, J=8.8 Hz, 2×$CH_2CH{=}CMe_2$) and 5.30–5.42 (2H, m, olefinic).

(*R*)-11-*tert*-Butyldimethylsiloxy-13,17-dimethyloctadeca-1,16-diene 8. A mixture of alcohol **4** (544 mg, 1.85 mmol), imidazole (377 mg, 5.53 mmol) and *tert*-butyldimethylsilylchloride (833 mg, 5.53 mmol) in *N*,*N*-dimethylformamide (2 cm^3) was stirred at room temperature for 21 h. The reaction mixture was quenched with aqueous ammonium chloride and extracted with ethyl acetate (2×10 cm^3). Purification of the residue after removal of solvent was carried out using silica gel column chromatography to give the silylether **8** (660 mg, 87%) (Found: C, 76.4; H, 12.8. $C_{26}H_{52}OSi$ requires C, 76.4; H, 12.8%); ν_{max}/cm^{-1} 3008, 2955, 1645, 1545, 1462, 1380, 1255, 1070 and 910; δ_H (200 MHz) 0.03 (6H, s, 2×$OSiCH_3$), 0.88 (12H, br s, CH_3CH and 3×$SiCCH_3$), 1.2–1.55 (19H, m), 1.6 and 1.68 (3H each, s, olefinic methyl), 1.9–2.1 (4H, m, allylic), 3.69 (1H, m, CHOSi), 4.89–5.16 (2H, m, $CH_2CH{=}CH_2$), 5.1 (1H, m, $CH_2CH{=}CMe_2$) and 5.81 (1H, ddt, J=17, 10.2 and 6.6 Hz, $CH_2CH{=}CH_2$).

(5*R*)-7-*tert*-Butyldimethylsiloxy-5-methylheptadeca-1,16-diene 9. Ozone (10% in oxygen) was bubbled through a stirred solution of olefin **8** (91 mg, 0.223 mmol) in dichloromethane (10 cm^3) at −78°C for 15 min. Dimethyl sulfide (0.1 cm^3) was added to the resulting pale blue solution and the reaction mixture was stirred at room temperature overnight. After removal of the solvent, the residue was passed through a short silica gel column with a pad of Na_2SO_4 on the top and eluted with a mixture of *n*-hexane–ethyl acetate (1:1). Evaporation of the solvent provided the corresponding dienal of silyl derivative **8**, an oily liquid which was subjected directly to the next reaction without further purification.

To a slurry of methyl(triphenyl)phosphonium bromide (223 mg, 0.624 mmol) in tetrahydrofuran (3 cm^3) at 0°C was added dropwise, a solution of *n*-BuLi (1.6 mol dm^3 in *n*-hexane; 0.37 cm^3, 0.595 mmol) and the resulting orange brown solution was stirred for 30 min. Then, the above dialdehyde (64 mg, 0.166 mmol) dissolved in tetrahydrofuran (1.5 cm^3) was added in the Wittig reagent at −78°C with stirring. The stirring was continued at this temperature for 1 h and then at room temperature for 3 h. The reaction was quenched by the addition of aqueous ammonium chloride and extracted with ethyl acetate. Evaporation of the solvent followed by purification of the product by MPLC gave **9** (62 mg, 73%) as a diastereomeric mixture (Found: C, 75.85; H, 12.4. $C_{24}H_{48}OSi$ requires C, 75.7; H, 12.7%); ν_{max}/cm^{-1} 3008, 2955, 1645, 1255, 1070 and 837; δ_H (200 MHz) 0.04 (6H, s, 2×$OSiCH_3$), 0.88 (12H, br s, CH_3CH and 3×$SiCCH_3$), 1.05–1.5 (19H, m), 1.9–2.1 (4H, m, allylic), 3.7 (1H, m, CHOSi), 4.9–5.5 (4H, m, 2×$CH_2CH{=}CH_2$) and 5.8 (2H, ddt, J=17, 10.2 and 6.6 Hz, 2×$CH_2CH{=}CH_2$).

(5*R*)-5-Methylpentadeca-1,16-diene-7-ol 10. To a stirred solution of **9** (366 mg, 0.961 mmol) in THF (3.5 cm^3) was added tetrabutylammonium fluoride (1.0 mol dm^{-3} in tetrahydrofuran; 2.87 cm^3, 2.87 mmol) at room temperature and stirring was continued for 24 h. Reaction was quenched by the addition of aqueous ammonium chloride. The product was extracted with ethyl acetate and purified by MPLC to give **10** (248 mg, 97%) as an oily liquid.

Alternatively, the Grignard reagent was prepared as in the previous experiment from magnesium powder (43 mg, 1.76 mmol) and 10-bromodec-1-ene (383 mg, 1.75 mmol) in diethyl ether (3.5 cm^3). A solution of the aldehyde **15** (57 mg, 0.46 mmol) in diethyl ether (2 cm^3) was then added at ice bath temperature with stirring. Thereafter, the reaction mixture was stirred at room temperature for 4 h and then quenched by the addition of aqueous ammonium chloride solution. Extraction with diethyl ether, evaporation of the solvent and purification of the product by MPLC furnished alcohol **10** (80 mg, 66%) (Found: C, 81.4; H, 12.9. $C_{18}H_{34}O$ requires C, 81.1; H, 12.9%); ν_{max}/cm^{-1}, 3648, 3008, 2857, 1641, 1462, 1379, 995 and 912; δ_H (200 MHz) 0.91 and 0.92 (total 3H, ratio=1:1, d, J=6.5 Hz, CH_3CH), 1.1–1.5 (19H, m), 1.98–2.2 (4H, m, allylic), 2.35 (1H, br s, hydroxy), 3.7 (1H, m, $W_{1/2}$ 16.6, CHOH), 4.8–5.1 (4H, m, 2×$CH_2CH{=}CH_2$) and 5.81 (2H, ddt, J=17, 10.2 and 6.6 Hz, 2×$CH_2CH{=}CH_2$).

(*R*)-(+)-Citronellol 11. To a stirred suspension of sodium borohydride (1.642 g, 43.4 mmol) in methanol (25 cm^3) maintained at 0°C was added a solution of (*R*)-(+)-citronellal **3** (6.12 g, 7.2 cm^3, 39.7 mmol) in methanol (3 cm^3) and the reaction mixture was stirred for 5 h. The reaction was quenched by careful addition of water followed by extraction with ether. Evaporation of the solvent left behind an oil which was purified by distillation using Kugelrhor apparatus to give **11** (5.63 g, 91%); ν_{max}/cm^{-1} 3638, 2964, 2856, 1452, 1379, 1057, 910 and 801; δ_H (200 MHz) 0.91 (3H, d, J=6.5 Hz, CH_3CH), 1.09–1.51 (6H, m), 1.61 and 1.69 (3H each, s, olefinic methyl), 1.93–2.05 (2H, m, allylic), 3.69 (2H, m, CH_2OH) and 5.10 (1H, t, J=7.1 Hz, olefinic). Spectral data were identical with authentic sample.

(*R*)-2,6-Dimethyl-8-*tert*-butyldimethylsiloxyoct-2-ene 12. To a stirred mixture of TBDMS chloride (181 mg, 1.66 mmol) and imidazole (170 mg, 2.49 mmol) in *N*,*N*-dimethylformamide (0.3 cm^3) was added **11** (156 mg, 1 mmol) at ice bath temperature and then the reaction mixture was stirred at room temperature for 10 h. The reaction mixture was diluted with water and extracted with ethyl

acetate. Removal of the solvent left behind an oily liquid which was purified by silica gel column chromatography using *n*-hexane as the eluent to give TBDMS ether **12** (270 mg, 99%); ν_{max}/cm^{-1} 2959, 2858, 1471, 1255, 1095 and 839; δ_H (200 MHz) 0.05 (6H, s, 2×OSiCH_3), 0.87–0.91 (12H, m, CH_3CH and 3×SiCCH_3), 1.00–1.44 (5H, m), 1.61 and 1.69 (3H each, s, olefinic methyl), 1.91–2.04 (2H, m, allylic), 3.64 (2H, td, *J*=6.7 and 2.5 Hz, CH_2OSi) and 5.11 (1H, t, *J*=6.4 Hz, olefinic).

(*R*)-5-Methyl-7-*tert*-butyldimethylsiloxyoct-1-ene 13. The TBDMS ether **12** (250 mg, 0.925 mmol) in dichloromethane (10 cm^3) was subjected to ozonolysis and worked-up as in the previous experiment to give the corresponding aldehyde which was used as such for the next reaction. To the Wittig reagent prepared from methyl triphenylphosphonium bromide (635 mg, 1.75 mmol) in tetrahydrofuran and *n*-BuLi (1.6 mol dm^{-3} in *n*-hexane; 1.06 cm^3, 1.70 mmol), was added a solution of the above prepared aldehyde (220 mg, 0.91 mmol) in tetrahydrofuran (1.5 cm^3) at −78°C with stirring. The yellow colored reaction mixture was stirred further for 1 h and then continued stirring at room temperature for another 2 h. The reaction mixture was diluted with aqueous ammonium chloride and extracted with ethyl acetate. Removal of the solvent followed by purification of the product by MPLC using only *n*-hexane as the solvent provided the olefin **13** (210 mg, 94%) (Found: C, 69.1; H, 12.4. $C_{14}H_{30}$ OSi requires C, 69.4; H, 12.5%); ν_{max}/cm^{-1} 3008, 2957, 1644, 1462, 1256, 1096 and 908; δ_H (200 MHz) 0.05 (6H, s, 2×OSiCH_3), 0.86–0.89 (12H, m, CH_3CH and 3×SiCCH_3), 1.18–1.47 (5H, m), 1.982.14 (2H, m, allylic), 3.63 (2H, td, *J*=6 and 2.5 Hz, CH_2OSi), 4.89–5.05 (2H, m, CH_2=CHCH_2) and 5.81 (1H, ddt, *J*=17.1, 10.3 and 6.7 Hz, CH_2C*H*=CH_2).

(*R*)-3-Methylhept-6-en-1-ol 14. The TBDMS ether **13** (200 mg, 0.83 mmol) in tetrahydrofuran (2 cm^3) was stirred with tetrabutylammonium fluoride (1 mol l^3 in tetrahydrofuran; 2.47 cm^3, 2.47 mmol) at room temperature for 1 h. The reaction mixture was diluted with water and extracted with diethyl ether. Careful removal of the solvent followed by purification by MPLC provided **14** (103 mg, 98%) as an oil.

Alternatively, a solution of osmium tetroxide (8 mg, 0.03 mmol) in water (1 cm^3) was added to a vigorously stirred solution of (+)-citronellol **11** (159 mg, 1.02 mmol) in 1,4-dioxane (4 cm^3). After stirring for 15 min at room temperature, a solution of sodium periodate (642 mg, 3.0 mmol) in water (3 cm^3) was added. After being stirred for 36 h at room temperature, the reaction mixture was filtered through a pad of celite and the filtrate was poured into saturated solution of ammonium chloride. The aqueous layer was extracted with chloroform and the solvent was removed. The product was purified rapidly, by silica gel column chromatography to give the oily aldehyde (102 mg, 77%); ν_{max}/cm^{-1} 3605, 2955, 2928, 2874, 2736, 1741, 1459, 1373 and 1049; δ_H (200 MHz) 0.94 (3H, d, *J*= 6.2 Hz, CH_3CH), 1.21–1.82 (6H, m), 2.48 (2H, m, CH_2CHO), 3.71 (2H, m, CH_2OH) and 9.79 (1H, t, *J*= 1.7 Hz, CHO) which was used immediately for the next reaction.

The Wittig reagent was prepared as usual from methyl(triphenyl)phosphonium bromide (1.368 g, 3.83 mmol) in tetrahydrofuran (12 cm^3) and *n*-BuLi (1.6 mol dm^{-3} in *n*-hexane; 2.2 cm^3, 3.56 mmol). The aldehyde (102 mg, 0.785 mmol) obtained in the above reaction was added to the Wittig reagent as a solution in THF (2 cm^3) at −78°C with stirring. The reaction mixture was allowed to warm to room temperature over a period of 4 h and then quenched with saturated solution of ammonium chloride. Extraction with ethyl acetate followed by purification of the product by MPLC gave **14** (88 mg, 87%); ν_{max}/cm^{-1} 3638, 3008, 2961, 1641, 1240, 1051 and 910; δ_H (200 MHz) 0.91 (3H, d, *J*=6.5 Hz, CH_3CH), 1.14–1.72 (6H, m), 1.95–2.20 (2H, m, allylic), 3.69 (2H, td, *J*=6.7 and 2.5 Hz, CH_2OH), 4.8–5.1 (4H, m, 2×CH_2CH=CH_2) and 5.81 (2H, ddt, *J*=17.1, 10.2 and 6.7 Hz, 2×CH_2C*H*=CH_2); *m/z* (EI) 110 (M^+-H_2O, 31%), 95 (87), 86 (31), 72 (79), 68 (100), 62 (75) and 55 (91); HR MS *m/z* 128.1196 M^+, $C_8H_{16}O$ requires 128.1201.

(*R*)-3-Methylhept-6-enal 15. To a stirred mixture of alcohol **14** (95 mg, 0.738 mmol) in dichloromethane (5 cm^3) containing dimethyl sulfoxide (3.15 cm^3, 44.4 mmol) and triethylamine (1.31 cm^3, 9.4 mmol) was added a solution of sulfur trioxide pyridine complex (772 mg, 4.85 mmol) in dichloromethane (3 cm^3) at 0°C. The reaction mixture was stirred for 1.5 h by gradually raising the temperature to 25°C and then diluted with *n*-pentane (20 cm^3) followed by successive washing of the organic phase with water, 1 M aqueous hydrochloric acid, aqueous sodium hydrogencarbonate and brine. Careful removal of the solvent followed by purification of the product by passing it through a small silica gel column with a layer of anhydrous sodium sulfate on the top provided the labile aldehyde **15** (79 mg, 85%) which was used immediately for the next reaction; ν_{max}/cm^{-1} 2959, 2928, 2856, 2736, 1730, 1644, 1462, 1379, 1263 and 909; δ_H (200 MHz) 0.98 (3H, d, *J*=6.6 Hz, CH_3CH), 1.22–1.50 (3H, m), 2.0–2.2 (2H, m, allylic), 2.25–2.5 (2H, m, CH_2CHO), 4.92–5.08 (2H, m, CH_2CH=CH_2), 5.80 (1H, ddt, *J*=17, 10.2 and 6.7 Hz, CH_2C*H*=CH_2) and 9.75 (1H, t, *J*=2.3 Hz, CHO).

(*R*)-5-Methylheptadeca-1,16-diene-7-one 16. Jones reagent was added to a stirred solution of alcohol **10** (160 mg, 0.60 mmol) in acetone (3.5 cm^3) at ice bath temperature until a slight orange color persisted. After 5 min, the excess reagent was destroyed by the addition of isopropyl alcohol and the reaction mixture was diluted with water. The aqueous phase was extracted with ethyl acetate followed by evaporation of solvent and purification of the product by MPLC gave the diolefinic ketone **16** (154 mg, 97%) (Found: C, 81.6; H, 12.2. $C_{18}H_{32}O$ requires C, 81.7; H, 12.2%); $[\alpha]_D$=+2.94. (*c* 0.9 in MeOH); ν_{max}/cm^{-1} 3079, 2928, 1715, 1641, 1462, 1367, 993 and 912; δ_H (200 MHz) 0.89 (3H, d, *J*=6.5 Hz, CH_3CH), 1.2–1.45 (12H, brs), 1.5–1.8 (3H, m), 1.9–2.1 (4H, m, allylic), 2.18 (1H, dd, *J*=14.2 and 5.5 Hz), 2.34–2.50 (3H, m), 4.88–5.05 (4H, m, 2×CH_2=CHCH_2) and 5.695.92 (2H, m, 2×CH_2C*H*=CH_2); δ_C (50 MHz) 19.69, 23.76, 28.71, 28.87, 29.04, 29.21, 29.28, 29.34, 31.21, 33.76, 36.03, 43.36, 50.14, 114.09, 114.40, 138.64, 139.14 and 211.15.

(*R*)-3-Methylcyclopentadec-6-en-1-one 17. To a solution of **16** (30 mg, 0.114 mmol) in dry degassed dichloro-

methane (25 cm^3) was added via syringe, a solution of ruthenium alkylidene catalyst **2** (5 mg, 0.006 mmol) predissolved in dichloromethane (6 cm^3). The resulting purple solution was heated to 45°C for 21 h and then concentrated under reduced pressure to afford an oily brown residue. Purification by MPLC [pre-packed silica gel column 2×50 cm, eluent:ethylacetate-*n*-hexane(1:9)] provided **17** (20.9 mg, 78%); ν_{max}/cm^{-1} 3056, 2858, 1705, 1462, 1378, 1265 and 908; δ_H (500 MHz) 0.91 and 0.94 (total 3H, ratio=3:1, d, J=6.5 Hz, $CHCH_3$), 1.2–1.6 (11H, m), 1.8–2.6 (12H, m), and 5.32 (2H, m, olefinic); δ_C (50 MHz) 20.89, 22.62, 24.70, 26.11, 26.74, 26.79, 27.10, 27.17, 27.95, 29.39, 36.58, 41.43, 50.43, 129.68, 130.33 and 211.90; *m/z* (EI) 236 (M^+, 21%), 221 (5), 125 (8), 109 (19), 95 (33), 81 (54), 55 (87) and 41 (100).

The fractions also provided the cyclic dimer **18** (5 mg, 18%) as a solid (Found: C, 81.2; H, 12.1. $C_{32}H_{56}O_2$ requires C, 81.3; H, 11.95%); ν_{max}/cm^{-1} 2928, 2854, 1713, 1462, 1410, 1370 and 970; δ_H (200 MHz) 0.89 (6 H, d, J=6.2 Hz, $2\times CH_3CH$), 1.17–1.43 (24H, brs), 1.47–1.65 (6H, m), 1.9–2.1 (8H, m, $2\times CH_2COCH_2$), 2.15 (2H, dd, J=14.2 and 5.5 Hz, allylic), 2.3–1.47 (6H, m, allylic) and 5.33–5.40 (4 H, m, olefinic).

(*R*)-3-Methylcyclopentadecan-1-one or muscone 1. 5% Palladium on charcoal (5 mg) was added to a stirred solution of **17** (20 mg, 0.08 mmol) in methanol (3 cm^3) and stirred under hydrogen atmosphere at room temperature for 3 h. The catalyst was filtered off and the residue was washed twice with ethanol. The combined washings and the filtrate was concentrated to provide an oily product, purified by MPLC [eluent: ethylacetate–*n*-hexane (1:9)] to give muscone **1** (20 mg, 98%); $[\alpha]_D$=−12.6 (*c* 0.9 in MeOH) (lit.[5h] −12.5 in MeOH); ν_{max}/cm^{-1} 2930, 1713, 1533, 1460 and 1371; δ_H (200 MHz) 0.94 (3H, d, J=6.7 Hz, CH_3CH), 1.1–1.5 (20H, brs, CH_2), 1.5–1.8 (3H, m, CH_2CH_2CO and CH_3CH), 2.18 (1H, dd, J=14.8 and 5.2 Hz, $COCHHCH$) and 2.35–2.50 (3H, m, CH_2COCHH).

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