# Ring closing metathesis guided synthesis of (*R*)-(−)-muscone

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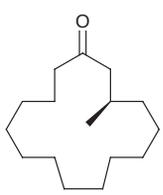
1 PERKIN COMMUNICATION

**A concise synthesis of the valuable perfumery compound (*R*)-(−)-muscone 1 in its natural form by making use of the ring closing olefin metathesis (RCM)-aided macrocyclisation route has been achieved.**

(*R*)-Muscone **1**, the precious and exotic perfumery ingredient, isolated from the male musk deer *Moschus moschiferus*,[1] is perhaps the only perfumery compound to receive wide attention ever since its chemical constitution was established.[2] Because of the exorbitant price that the natural product fetched, several groups concentrated their efforts in synthesising racemic muscone. The literature covering various aspects of macrocyclic musk and related compounds has been excellently reviewed.[3]



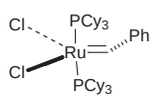
**1**

Being a macrocyclic natural product, muscone in racemic form was synthesized earlier by several routes[4] including a variety of procedures based on acyloin condensation, fragmentation of tosylhydrazones derived from α,β-epoxy ketones, photochemical reaction involving bridged bicyclic ketones, novel one carbon homologation and ring enlargement protocols. Similarly, there have been reports on the synthesis of (*R*)-muscone **1** involving key reactions like free radical macrocyclization,[5] diastereoselective conjugate addition to a cyclic α,β-unsaturated ester of (*R*,*R*)-cyclohexane-1,2-diol followed by a Dieckman condensation reaction[6] and asymmetrically catalysed macrocyclisation of an ω-alkynal[7] followed by a hydroxy group directed cyclopropanation of the resulting cyclic (15*S*)-allyl alcohol.[8]

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

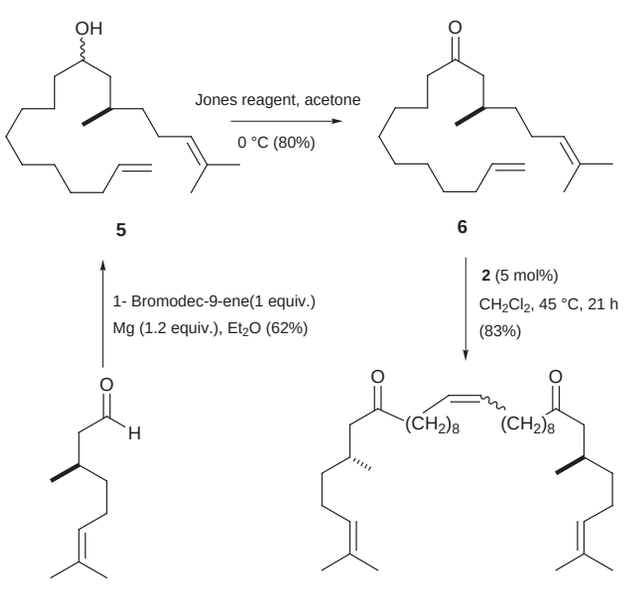
In principle, muscone could be obtained by RCM of an appropriate diene substrate which in turn should be obtainable using readily available starting materials. This has indeed been realized in practice and we describe herein an efficient synthesis of the natural product (*R*)-(−)-muscone **1** by employing an RCM reaction as shown in Scheme 2. Although, several reports on the synthesis of racemic[4] and optically active muscone have appeared in the literature,[8] none of them utilized an RCM protocol for effecting macrocyclization leading to the natural product **1**.

Among the RCM catalysts, we selected bis(tricyclohexylphosphine)benzylidene ruthenium(IV) dichloride **2** as the




**2**

initiator for the 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] The key diene substrate **9** was prepared *via* the initial Grignard reaction involving (*R*)-(+)-citronellal **4**‡ and 1-bromodec-9-ene which in turn was prepared by reacting dec-9-en-1-ol with carbon tetrabromide in the presence of triphenylphosphine using acetonitrile as solvent. In an attempt to effect a short synthesis of the natural product **1**, the keto diene **6** was exposed to ruthenium alkylidene **2** under the RCM reaction conditions.[10] However, we could only isolate the corresponding acyclic dimeric compound **3** derived from **6** as a product of intermolecular metathesis in the form of a waxy solid (Scheme 1). The dimerization of **6** in the present




**Scheme 1**

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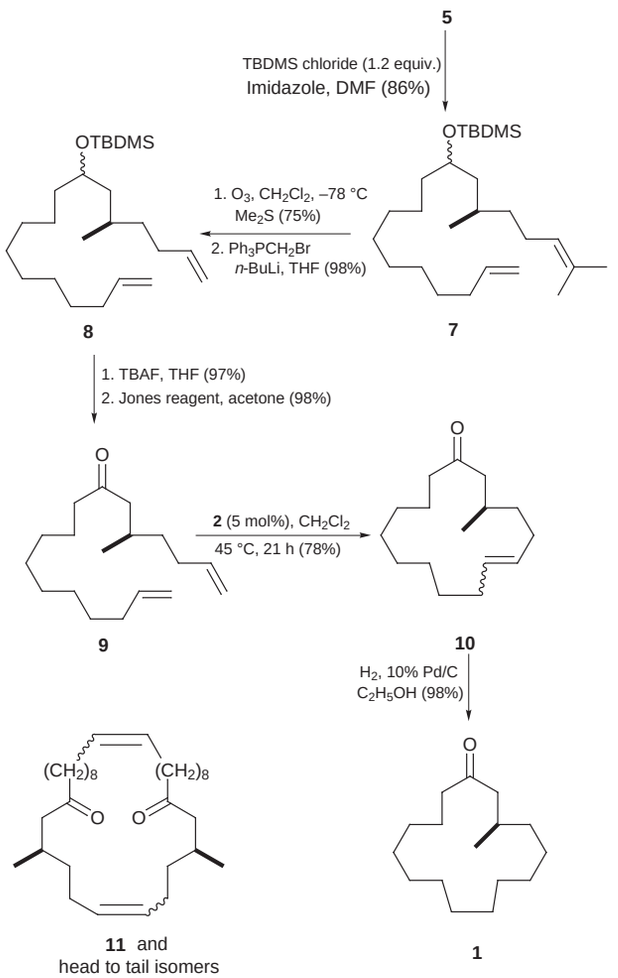
‡ Commercially available (*R*)-(+)-citronellal from Tokyo Kasei Kogyo Co., Ltd. was used.

case is logical by considering the inertness of ruthenium alkylidene **2** towards the RCM of terminally substituted olefins.[11]

Therefore, to induce a productive RCM by using alkylidene **2**, it was necessary to remove the olefinic gem-dimethyl substitution in diene **6**. Accordingly, the alcohol **5**, protected in the form of its TBDMS ether **7**, was subjected to ozonolysis followed by Wittig olefination of the resulting dialdehyde to furnish the desired diene substrate **9** after deprotection and subsequent oxidation (Scheme 2). As anticipated, when **9** was




**Scheme 2**

exposed to ruthenium catalyst **2** under the RCM reaction conditions, it smoothly underwent ring closing olefin metathesis[11] to yield the desired cyclic product **10** in 78% yield as a mixture of *E*/*Z* isomers§ along with a small quantity of a mixture of cyclic dimeric compound **11** obtained as a result of intermolecular metathesis. Finally, catalytic hydrogenation of **10** 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 utilizing ring closing olefin metathesis. The key macrocyclization step in the present synthesis proceeds under mild reaction conditions with moderate catalyst loading in good yield. The evaluation of the olfactory properties of some of the intermediate compounds is currently in progress.

§ All compounds gave satisfactory spectral analysis in agreement with the assigned structures.

¶ $[\alpha]_D^{18}$ −12.6 (*c* 0.9 in MeOH); lit.,[8g] $[\alpha]_D^{18}$ −12.5 (*c* 5.0 in MeOH).

## Experimental

### Procedure for the RCM reaction

To a solution of acyclic diene **9** (30 mg, 0.114 mmol) in dry degassed $CH_2Cl_2$ (25 ml) was added, *via* syringe, a solution of ruthenium catalyst **2** (5 mg, 0.006 mmol) predissolved in $CH_2Cl_2$ (6 ml). The purple solution was heated to 45 °C for 21 h and concentrated under reduced pressure to afford an oily brown residue. Purification by MPLC (pre-packed column 2 × 50 cm, 5% EtOAc–hexane) afforded 20 mg (78%) of **10** as an oil with a musky odor.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