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Synthesis of guaiane sesquiterpenoids by a ring-closing metathesis annulation sequence

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Abstract—A new route for the synthesis of guaiane and nor-guaiane sesquiterpenoids is described, using a ring-closing metathesis annulation reaction sequence on a chiral enantiopure cycloheptenone derived from (*R*)-(−)-carvone.

The guaianes **1** and nor-guaianes **2** are sesquiterpenes with a perhydroazulene carbon skeleton **3** (Fig. 1).[1] Combinations of fused five- and seven-membered ring systems are also common among naturally occurring diterpenes[2] and sesterterpenes.[3] The wide spectrum of biological activities allied with structural complexity make these compounds interesting targets for total synthesis. Traditional synthetic approaches to perhydroazulene structures[4] involve the contraction of six-membered ring starting materials to cyclopentanoids followed by annulation, or more rarely expansion to cycloheptanoids and annulation. Other approaches include intramolecular [3 + 2]Pd-catalyzed cycloaddition,[5] photochemical rearrangement of the eudesmane framework,[6] and dichloroketene cycloaddition-diazoalkane ring expansion.[7]

Among the few annulation methodologies for cycloheptanoids we have not found any examples describing the use of ring-closing metathesis (RCM) reactions for the synthesis of the perhydroazulene carbon skeleton. The Mehta group have however developed methodology for the seven-membered ring annulation of cyclopentanoids utilizing the RCM reaction.[8,9]

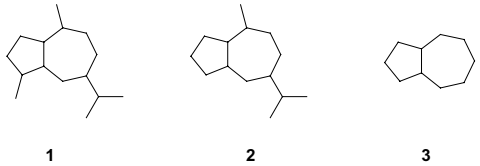

Figure 1. Guaiane **1**, nor-guaiane **2**, and perhydroazulene **3** carbon skeletons.

The RCM reaction[10] has become over the last decade a very powerful tool for the synthesis of many complex ring systems, following upon the development of improved ruthenium carbene complexes.[11] First- **4** and second-generation **5**, **6** Grubbs' catalysts (Fig. 2) are the most frequently used in these olefin metathesis reactions because of their availability, experimental simplicity, efficiency, and functional group tolerance.

In this paper, we describe a new approach to sesquiterpenes of the guaiane group, using the ring-closing metathesis reaction as the key step of the annulation of an enantiopure cycloheptenone.

Previously, we have shown that enantiomeric cycloheptenones can be prepared by enantiodivergent ring expansions of simple *p*-menthane monoterpenes. The (*R*)-(+)-6-isopropenyl-3-methyl-cycloheptenone (**7**) can be readily obtained from (*R*)-(−)-carvone in four

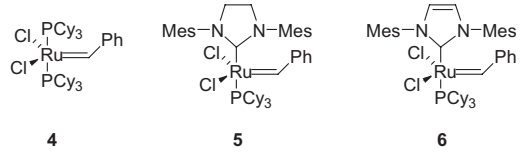

Figure 2. Grubbs' olefin metathesis catalysts.

Keywords: Ring-closing metathesis; Annulation; Guaianes; Chiral cycloheptenone.
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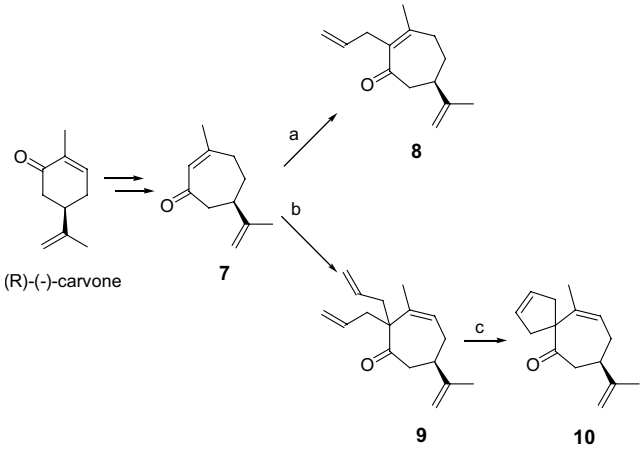


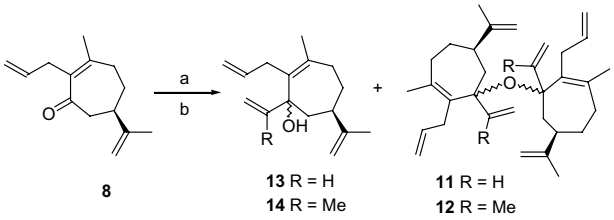
Scheme 1. Reagents and conditions: (a) *t*-BuOK, *t*-BuOH, allyl chloride, rt, 1.5 h; (b) *t*-BuOK, *t*-BuOH, allyl bromide, rt, 1.5 h; (c) Grubbs' catalyst **4** (4 mol%), CH_2Cl_2, rt, 10 h.

steps.[12] Furthermore, treatment of **7** with *t*-BuOK in *t*-BuOH and allyl chloride at room temperature (Scheme 1a) furnished the mono-allylated compound **8** as the major product (43% yield) and trace quantities of the bis-allylated product **9**.[13] Use of more reactive allyl bromide under the same conditions (Scheme 1b) gave the bis-allylated compound **9** in 68% yield.

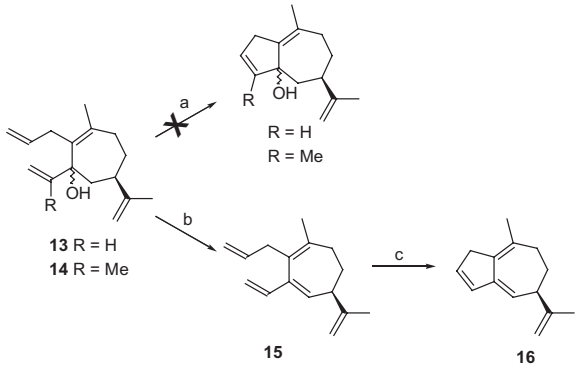
Although mono-allyl **8** is required for elaboration into the guaianes, the easy preparation of bis-allyl **9** lead us to test the RCM reaction (Scheme 1c) with a view to the formation of the spiro[4.6]undecane carbon skeleton as found in ingenol.[14] Reaction of **9** (52 mM) with Grubbs' catalyst **4** (4 mol%) in CH_2Cl_2 at room temperature under N_2 furnished a 90% yield of spiro compound **10** after 10 h of reaction.[15]

Reaction of **8** with standard solutions of vinyl and isopropenylmagnesium bromide in THF gave to our surprise, the symmetrical ethers **11** and **12** as major products (Scheme 2), in 56% and 49% yield, respectively, when the reaction quench was realized with aqueous ammonium chloride. Quenching with water furnished compounds **13** and **14** in 95% and 90% crude yields, and in 25% and 32% yields after purification.[16]

When **13** and **14** were submitted to the RCM reaction (Scheme 3) no products were observed, even under much more drastic conditions, with recovery of starting materials. The presence of free polar groups close to the double bonds is known to inhibit the RCM reaction with Grubbs' catalyst **4**.[17]



Scheme 2. Reagents and conditions: (a) vinylmagnesium bromide, THF, −78 °C, 1 h; (b) isopropenylmagnesium bromide, THF, −78 °C, 1 h.

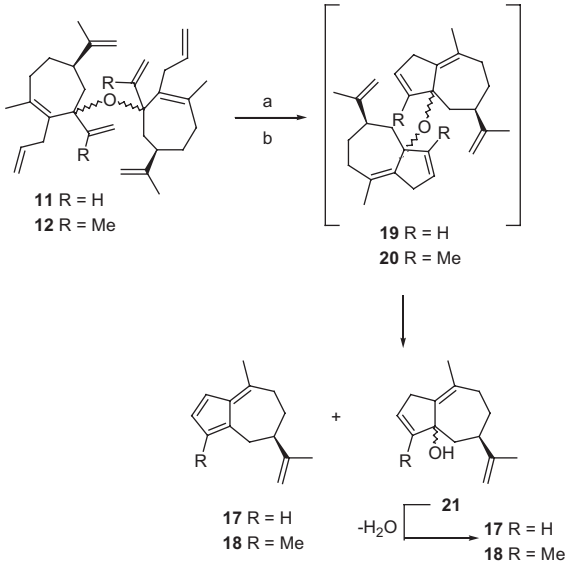


Scheme 3. Reagents and conditions: (a) Grubbs' catalyst **4** (5–20 mol%), CH_2Cl_2, rt, reflux, 24 h; (b) PTSA, acetone, reflux, 3 h; (c) Grubbs' catalyst **4** (5 mol%), CH_2Cl_2, rt, 3 h.

The negative influence of the hydroxyl group in the RCM reaction was confirmed by dehydration (71% yield) of **13** and submitting the product **15** to catalyst **4** in CH_2Cl_2 at room temperature (Scheme 3). Nor-guaiane **16** was obtained in 61% yield after 3 h reaction.

The RCM reaction was also carried out on substrate **11**, using Grubbs' catalyst **4** (5 mol%) and after 4 h no starting material was detected. Purification on silica gel supplied a yellow oil, characterized as nor-guaiane **17** (Scheme 4) in 78% yield.

Compound **12** when subjected to catalyst **4**, using the same conditions but for 24 h, followed by purification by silica gel chromatography afforded guaiane **18** in 63% yield. Increasing the catalyst loading to 15 mol% and raising the reaction temperature to 40 °C, gave no improvement of yield.



Scheme 4. Reagents and conditions: (a) 5 mol% of **4**, CH_2Cl_2, rt, 4 h; (b) 5–15 mol% of **4**, CH_2Cl_2, rt, or reflux, 24 h.

We suggest[18] that compounds **19** and **20** may be formed initially from **11** and **12** by an RCM reaction, and then through a sequence of hydrolysis and dehydration reactions catalyzed by silica gel produce **17** and **18**. The possible intermediates **21** could also be involved in the formation of **17** and **18**. Our interest in the RCM reaction of **11** and **12** to **19** and **20** is due to their structural similarity with dimeric ether guaianolides that have been recently isolated[19] and show strong antidiabetic activity.

In summary, we have developed a new synthetic route for the perhydroazulene ring system using a ring-closing metathesis reaction as a key step. Guaiane and nor-guaiane derivatives **16**, **17**, and **18** were synthesized in enantiomerically pure forms from commercially available (*R*)-(−)-carvone, together with spiro compound **10**. These guaiane derivatives are versatile advanced intermediates for further functionalization, and open a pathway for the synthesis of natural guaianes and related compounds.

Acknowledgements

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