

Ring-closing olefin metathesis reactions; synthesis of iso- β -bisabolol

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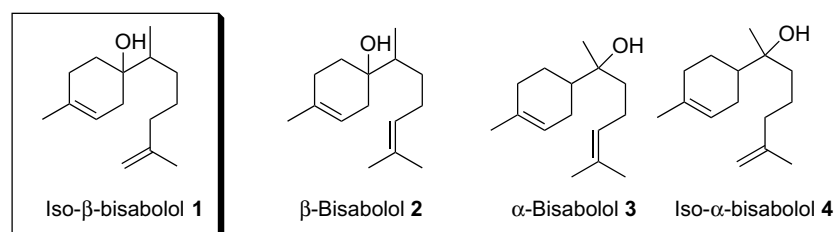
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Abstract—A ring-closing olefin metathesis is the key step in a synthesis of the rare iso- β -bisabolol found in sandalwood oils.
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The bisabolols were isolated from *Santalum* spp. Besides the odourless major bisabolols **2** and **3**, trace constituents possessing the isomeric structures **1** and **4** have been found very recently and synthesized and evaluated for their odour impact. **1** is an interesting odour active compound with a strong floral scent.¹ Herein we report a straightforward synthesis of a mixture of the four stereoisomers of bisabolol **1** using a ring-closing olefin metathesis (RCM) reaction as the key step.²

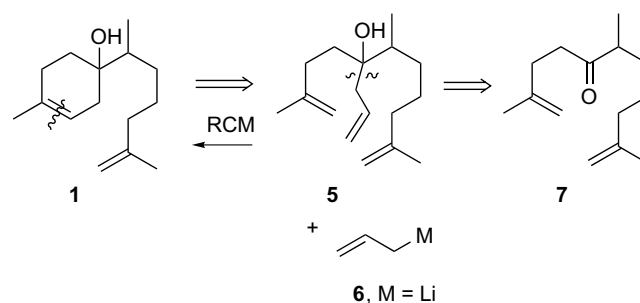
dized with PCC to ketone **7**. The tertiary alcohol **5** was obtained from ketone **7** by the addition of in situ generated allyllithium **6** (from allyltriphenyltin and phenyllithium).^{8,9} Selective ring-closing olefin metathesis was achieved using Grubbs second generation catalyst **11** to yield iso- β -bisabolol **1** as a mixture of all four stereoisomers. This mixture had been separated previously by the DRAGOCO group.¹ The number of stereoisomers of **1** can be reduced by using enantiomerically pure **10**.⁷ This synthetic scheme will be applied to the synthesis of



A retrosynthetic analysis (Scheme 1) leads to tri-olefin **5**, which should be regioselectively cyclized by an olefin metathesis reaction.

2 starting from aldehyde **10a**.^{10,11} Fráter and Müller had previously prepared bisabolol **2** by a different route.¹²

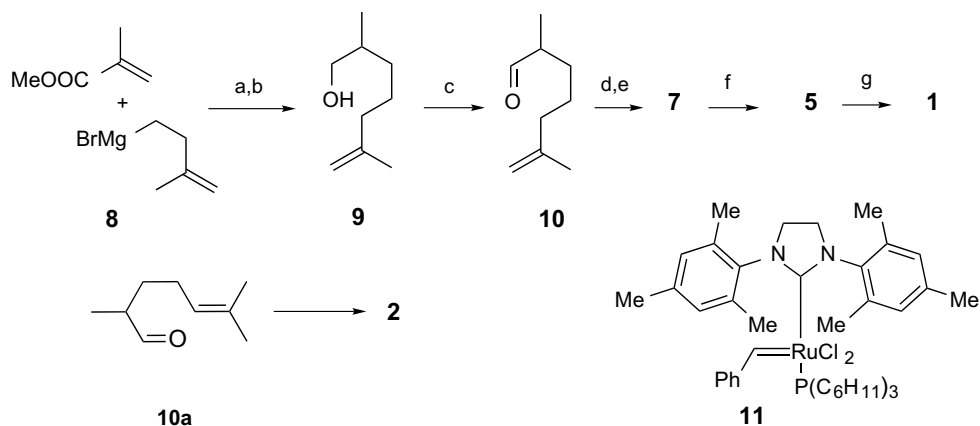
The required tri-olefin **5** was prepared by the sequence described in Scheme 2.³ Conjugate addition⁴ of the Grignard reagent **8** to methyl methacrylate in the presence of CuBr–Me₂S complex and TMSCl yielded an ester, which was reduced to the known alcohol **9**.^{5,6} Oxidation of **9** with PCC gave the unstable aldehyde **10**,⁷ which was reacted with the Grignard reagent **8** to give an intermediate secondary alcohol, which was oxi-



Keywords: Metathesis; Monocyclic sesquiterpenes; Bisabolols.

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Scheme 1.



Scheme 2. Reagents and conditions: (a) CuBr–Me₂S, LiI, TMSCl, Ar, –78 °C, 4 h, 53%; (b) LAH, ether, 2 h, 91%; (c) PCC, CH₂Cl₂, rt, 2 h, 89%; (d) **8**, THF, reflux, 20 min, 55%; (e) PCC, CH₂Cl₂, rt, 2 h, 86%; (f) **6**, ether, reflux, Ar, 80%; (g) **11**, benzene, 80 °C, Ar, 4 h, 93%.

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References and notes

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