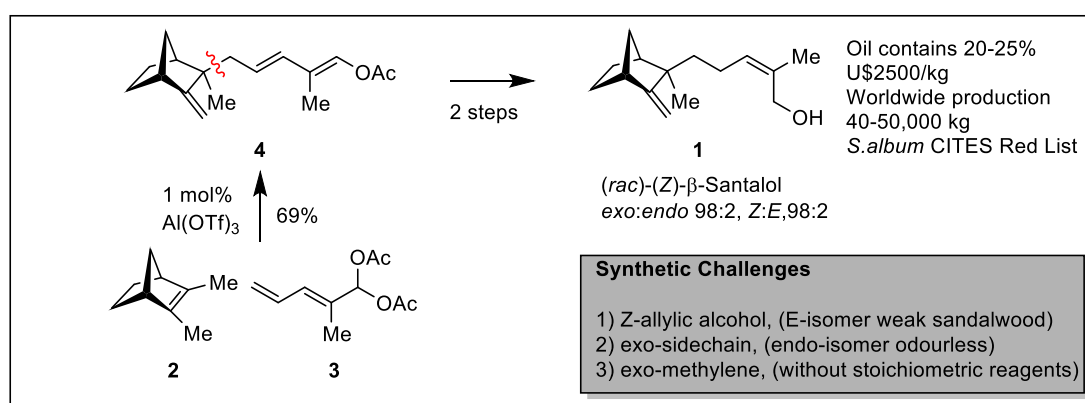


From Leopold Ruzicka in 1935 until now: The Story of (*Z*)- β -Santalol at Firmenich:- Towards an Industrial Synthesis.

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The original structural determination of β -Santalol **1** by Leopold Ruzicka in 1935 spurred a long term interest at Firmenich, in both the constituents of East Indian Sandalwood Oil and synthetic substitutes for this highly prized essential oil.[1] Over the last 40 years, the ever dwindling supply and increasing price of East Indian Sandalwood oil has stimulated extensive research towards both an economical and scalable synthesis of (-)-(*Z*)- β -Santalol **1**, present at 20-25% in the essential oil and largely responsible for its typical, lactonic sandalwood odour.[2] Steam distillation of East Indian Sandalwood (*S.album L.*) gives the essential oil in yields of 5-7%; that oil now fetches *ca.* US\$2,500/kg with an annual worldwide production of 40-50,000 kg. Other isomers present in the oil contribute little to the odour and the (+) enantiomer is odourless, placing challenging demands on the precise stereochemical control of any synthesis. **Figure 1.**[3]



Despite many elegant academic syntheses and industrial efforts, to date, no industrially feasible synthesis of (*Z*)- β -Santalol **1** has been realised on large scale.[4] We herein describe the discovery of a novel coupling reaction between santene **2** and allylidene diacetate **3** giving the key dienol acetate intermediate **4** in one step. Subsequent 1,4 hydrogenation and acetate ester removal furnished *rac*-(*Z*)- β -Santalol **1** in good overall yield, which is not only the shortest synthesis to date but all reactions are economical and scalable. This new synthesis employs an unprecedented coupling reaction and 2 further catalytic transformations with only one redox manipulation necessary to install the pivotal (*Z*)-allylic alcohol.

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