doi:10.2533/chimia.2017.823 Chimia 71 (2017) 823–835

The Synthesis of Fragrant Natural Products from *Santalum album L.*: (+)-(*Z*)-α-Santalol and (–)-(*Z*)-β-Santalol

Anthony A. Birkbeck*

Abstract: The synthetic challenges associated with the selective synthesis of α-Santalene (**1**), (*Z*)-α-Santalol (**2**), β-Santalene (**3**), and most importantly (*Z*)-β-Santalol (**4**) have interested the world's synthetic chemists for decades. These molecules, lovely examples of nature's exquisite creations, have been isolated from East Indian Sandalwood Oil (*Santalum album L.*) and have stimulated chemists to develop new and efficient methodologies to synthesize them. The synthesis and evolution of various approaches to the [2.2.1]bicycloheptane ring system present in β-Santalene (**3**) and the even more challenging selective synthesis of the (*Z*)-allylic alcohol sidechain present in both (*Z*)-α-Santalol (**2**) and (*Z*)-β-Santalol (**4**) will be covered in this review.

Keywords: (*Z*)-Allylic alcohol · Sandalwood oil · α-Santalol · β-Santalol · *Santalum album*

1. Introduction

Perfumes from volatile natural products have been used by humans for millennia for a wide variety of purposes including: to enhance feelings of well-being, to improve health, repel insects, and to cover the undesirable odours of funeral pyres, transpiration and other malodours.[1] Even though nature appears to have a finite number of biosynthetic pathways available to her (*i.e.* isoprenoid, acetate, Shikimic acid, carotenoid, *etc.*) this has not limited the isolation of a wide variety of novel and fascinating odorant structures from natural sources, ranging from *cis*-3-hexenol (C-6) to Civettone (C-17).[2] As a result of this diversity, volatile natural products have also long inspired chemists due both to their interesting odours and novel structures.

Natural essential oils are extensively used in the perfumery industry. Many odoriferous plants, trees and exudates have been successfully cultivated and are harvested to yield their essential oils, using a variety of techniques, including enfleurage, steam distillation, solvent extraction, cold pressing and maceration, depending on the stability of the components contained within them. But variable climatic variations and natural occurrences such as wildfires mean that producers cannot always guarantee a constant supply. Further, climatic variations and geographical origin can also influence the compositions of essential oils. A further challenge is that the conversion of nature's creations – whether in the form of flowers, woods or leaves – by obtaining and processing essential oils is often very time consuming, energy and labour intensive, and often requires solvent extraction, meaning that essential oils are expensive. The extraction of *ca.* 1 kg of rose absolute, for instance, demands inputs of 1 million rose petals.

As an alternative, many synthetic versions of fragrant molecules offer perfumers reliable supply at constant quality and price.[3] Early examples of synthetic versions of natural odorants include coumarin (1866), vanillin (1876), β-ionone (1893), and more recently citral (1959) and menthol (1973). For this reason, chemists have long strived to replicate nature's beautiful odorant creations, focusing in particular on the principle odour vector present in highly appreciated essential oils. The odour of most essential oils is infinitely more rich and complex than the pure odiferous principal. Nonetheless, in many cases one key molecule typically recalls the odour of the essential oil, albeit in a simpler way. While rose absolute will always be more appreciated by perfumers than a carefully-crafted synthetic mixture of phenyl ethanol, geraniol, citronellol, rose oxide and traces of β-damascenone, the mixture will often suffice for less expensive perfumes, especially where price performance is more important.

1.1 *East Indian Sandalwood Oil (Santalum album Linn.)*

The *Santalum* species are hemi-parasitic trees that require a host for survival and are found throughout the Indo-Pacific region. A recent genetic analysis suggested that the ancestor *Santalum sp.* originated in Australia more than 1 million years ago and was subsequently dispersed by birds to Papua New Guinea, New Caledonia, and eventually Hawaii.[4] The constituents of each of the commercially important Sandalwood oils have been compared and comprehensively reviewed by Joulain and Baldovini (Scheme 1).[5] Comparable levels of (+)-(*Z*)-α-Santalol (**2**) and (–)-(*Z*)-β-Santalol (**4**) are present in *Santalum album* and *Santalum austrocaledonicum,* however, *Santalum spicatum* has roughly half the quantity of both (+)-(*Z*)-α-Santalol (**2**) and (–)-(*Z*)-β-Santalol (**4**) and correspondingly higher levels of various bisabolol isomers and farnesol and as thus is not a direct substitute for *Santalum album* Sandalwood oil, despite large scale and sustainable harvesting in Western Australia.[6] *Santalum lanceolatum* (Northern Sandalwood) was also historically of some interest but is no longer commercially produced. Several other woods from a different genus are also known as Sandalwoods, such as West Indian Sandalwood (Jamaican Rosewood, *Amyris balsamifera*), East African Sandalwood (*Osyris lanceolata*) and False Sandalwood (*Eremophila mitchelli*). However the oils derived from these later woods are less commercially interesting.[7] Several *Santalum* species are under threat due to over exploitation and *Santalum album* is currently on the CITES Red List, meaning that the export of the wood from India is banned.[8]

*Correspondence: Dr. A. A. Birkbeck
Firmenich SA, Corporate R&D Division,
P.O. Box 239,
CH-1211 Geneva 8
E-mail: alec.birkbeck@firmenich.com

The exquisite and tenacious East Indian Sandalwood has been widely employed in fine fragrances. However, in recent years, scarce supply and ever increasing prices have hampered use in anything but the most expensive creations.[9] Sandalwood itself is also highly valued (fetching >U$100,000/MT), particularly for use in incense sticks and ornate carving of religious objects. Historically in India, it also found widespread use in fragrancing funeral pyres. Steam distillation of finely chopped East Indian Sandalwood (*Santalum album. Sp*) gives the highly appreciated essential oil in typically 5–7% yield.[10]

The impending lack of supply of East Indian Sandalwood oil was the primary reason behind the plantation of 100 hectares of irrigated *Santalum album* in the Ord River region of north-western Australia in 1999.[11] Such plantations have been touted as a potential solution to the ever-increasing demand for high quality East Indian Sandalwood oil. The Ord River plantation has since grown to over 5000 hectares and the first trees were harvested in the last couple of years.[12]

A further alternative to ensure a sustainable supply of this highly appreciated odour in perfumery and to ensure consistent quality is to devise an industrially-feasible synthetic version of the principal odorant molecule. Efforts have been underway since the late 1970s towards an industrial synthesis of (+/-)-(*Z*)-β-Santalol (**4**) or (–)-(*Z*)-β-Santalol (**4**). This paper traces the evolution of scientific work on the synthesis of both (*Z*)-α-Santalol (**2**) and (*Z*)-β-Santalol (**4**) highlighting how the selectivity challenges were overcome, concluding with a convergent industrially feasible synthesis of (+/-)-(*Z*)-β-Santalol (**4**).

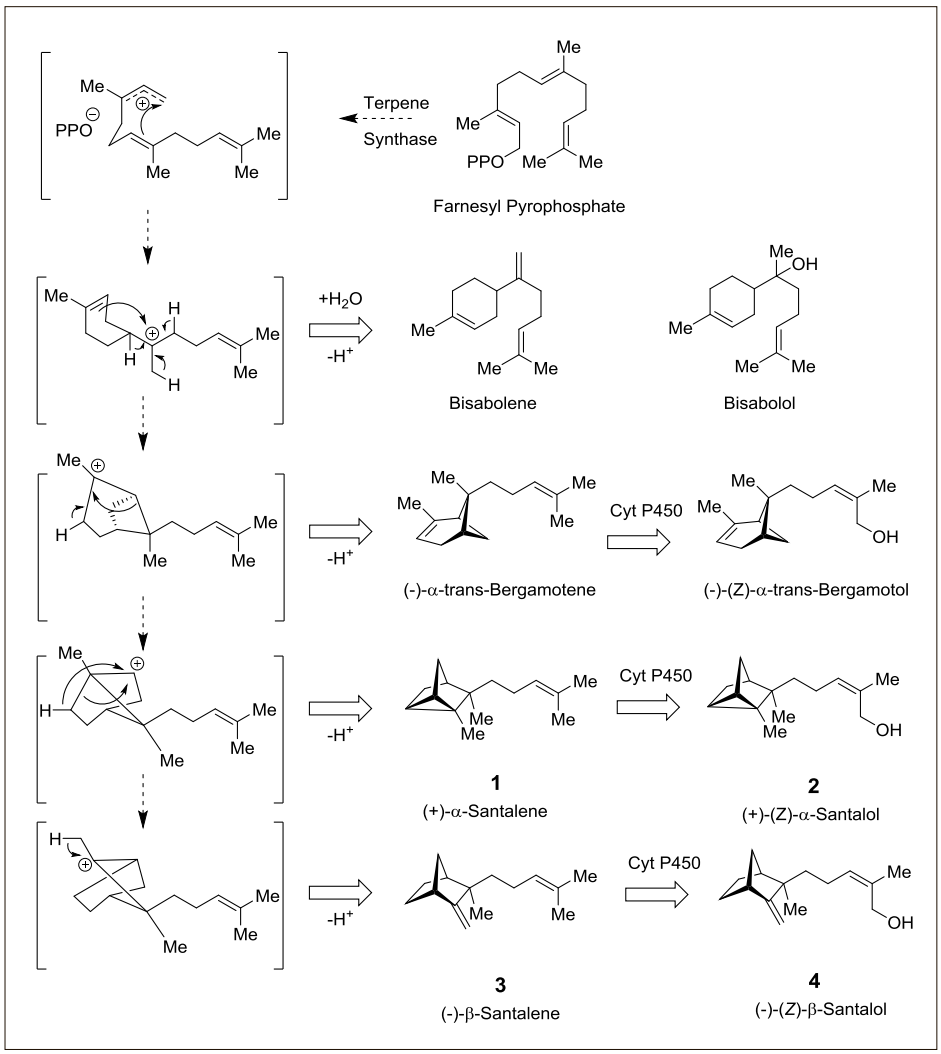
2. Constituents of East Indian Sandalwood Oil

The synthesis of natural products on industrial scale has always been dependent on the structural complexity of the target molecule and the final cost of that molecule. Sesquiterpene alcohols including (*Z*)-α-Santalol (**2**) and (*Z*)-β-Santalol (**4**) actually make up >90% of East Indian Sandalwood oil which currently fetches U$2500/kg. The biosynthesis of the variety of sesquiterpenes including santalene, bergamotene, curcumene, and bisabolene in East Indian Sandalwood oil from farnesyl diphosphate is followed by a separate oxidation step mediated by cytochrome P450 enzymes.[13] This selective oxidation yields the sesquiterpene alcohols that make up the majority of the essential oil which is found in the heartwood of the tree and believed to serve an anti-infective role. In addition to their odours both (*Z*)-α-Santalol (**2**) and (*Z*)-β-Santalol (**4**) and several of their further oxidized derivatives have shown biological activities with significant potential medical applications.[14]

The actual composition of *Santalum album* oil is highly complex and has been investigated in detail by Demole at Firmenich and Brunke at Dragoco.[15] Unambiguous analysis is not simple. The chemical constituents of Sandalwood oil and their relative odour contributions can only be studied using GC-olfactometry when each peak on a GC trace may be smelt in pure form. To completely assign and differentiate the individual components or majority of peaks, two dimensional GC/GC is required.[16] The comprehensive analysis of the *Santalum album* oil by GC olfactometry by Brunke at Dragoco in 1995 showed that (–)-(*Z*)-β-Santalol (**4**) is largely responsible for the highly appreciated creamy, lactonic, sandalwood odour of the oil with a dilution factor of 1024.[17]

The structure of α-Santalol (**2**) was correctly identified by Semmler in 1921 *via* extensive degradation studies.[18] Correlating the chemical degradation studies of β-Santalol (**4**) with a possible structure, however, proved far more challenging. In early 1935, Penfold described the apparent discrepancies between the probable structures of β-Santalol (**4**) and in particular the position of the second alkene and the chemical degradation data at hand.[19]

At the end of 1935, Ruzicka, who went on to win the Nobel prize (1939) for his work in the field of macrocyclic musks and the isoprene rule, elucidated the correct gross structure of β-Santalol (**4**).[20] In 1967, the stereochemistry of the (*Z*)-allylic alcohol present in α-Santalol (**2**) was confirmed by Erman, while that of β-Santalol (**4**) was only confirmed in 1970 by Erman and Kretschmar from P&G who unambiguously prepared and characterised both the (*E*)-β-Santalol (**5**) and (*Z*)-β-Santalol (**4**) isomers.[21] (*Z*)-β-Santalol (**4**) was confirmed as the key odorant. However it was not until 1991 that Helmchen's asymmetric synthesis showed for the first time that the enantiomer (+)-(*Z*)-β-Santalol (**8**) was in fact odourless and the (–)-(*Z*)-β-Santalol



Scheme 1. Postulated biosynthesis of sesquiterpenes and sesquiterpene alcohols present in Sandalwood oil.

(**4**) enantiomer was solely responsible for the highly appreciated odour and highly reminiscent of the essential oil.[22] The rotation of pure (–)-(*Z*)-β-Santalol (**4**) ex. *Santalum album* $[\alpha]_D$ = -109.5° correlated very well with synthetic material $[\alpha]_D$= –109.4°.[5]

2.1 *Synthetic Routes to Sandalwood Constituents*

Devising a synthetic route to the principle odour vector in sandalwood oil has challenged chemists for almost 50 years. The most difficult challenges in the industrially feasible synthesis of (*Z*)-β-Santalol (**4**) is the efficient installation of the (*Z*)-allylic alcohol sidechain. The (*Z*)-configured sidechain is identical in both (*Z*)-α-Santalol (**2**) and (*Z*)-β-Santalol (**4**). As the (*Z*)-configuration was only determined in 1970, all pre-1970 syntheses of β-Santalol (**4**) were made as a mixture of alkene isomers unaware of the exact stereochemistry of the (–)-(*Z*)-β-Santalol (**4**) present in the oil of *Santalum album*. The odour of (*E*)-β-Santalol (**5**) is reminiscent of sandalwood but much weaker and less appreciated than the (*Z*)-isomer. For this reason it is interesting to review the syntheses of both (*Z*)-α-Santalol (**2**) and (*Z*)-β-Santalol (**4**) with particular emphasis on the stereoselective construction of the sidechains. Other challenges include the efficient large scale synthesis of optically active (–)-(*Z*)-β-Santalol (**4**) as the (+)-enantiomer (+)-(*Z*)-β-Santalol (**8**) has been shown to be odourless.[22] In addition, the control of the orientation of the sidechain is essential as *epi*-(*Z*)-β-Santalol (**7**) has been shown to be very weak to odourless (Scheme 2).[10]

As many well renowned synthetic chemists have tackled both (*Z*)-α-Santalol (**2**) and (*Z*)-β-Santalol (**4**) it is nonetheless useful to review the various approaches to the (*Z*)-α-Santalol (**2**) allylic alcohol sidechain in addition to some aspects of various β-Santalene syntheses.

α-(*Z*)-Santalol (**2**) is closely related chemically to both *epi*-(*Z*)-β-Santalol (**7**) and (*Z*)-β-Santalol (**4**). In 1980, interestingly, Brunke from Dragoco showed that treatment of α-Santalyl acetate with anhydrous HCl cleaved the strained cyclopropane ring which upon treatment with a basic alumina resulted in the stereospecific elimination of HCl with concomitant rearrangement of the [2.2.1]bicyclic heptane ring system and yielded a 1:1 mixture of (–)-(*Z*)-β-Santalol (**4**) and (+)-*epi*-(*Z*)-β-Santalol (**7**).[23] In 1966, the specificity of this rearrangement, previously observed in in degradation studies by Bhattacharyya, was used to good effect in the synthesis of (–)-β-Santalene (**3**) and (+)-*epi*-β-Santalene (**6**) by Money and co-workers (*vide infra*).[24]

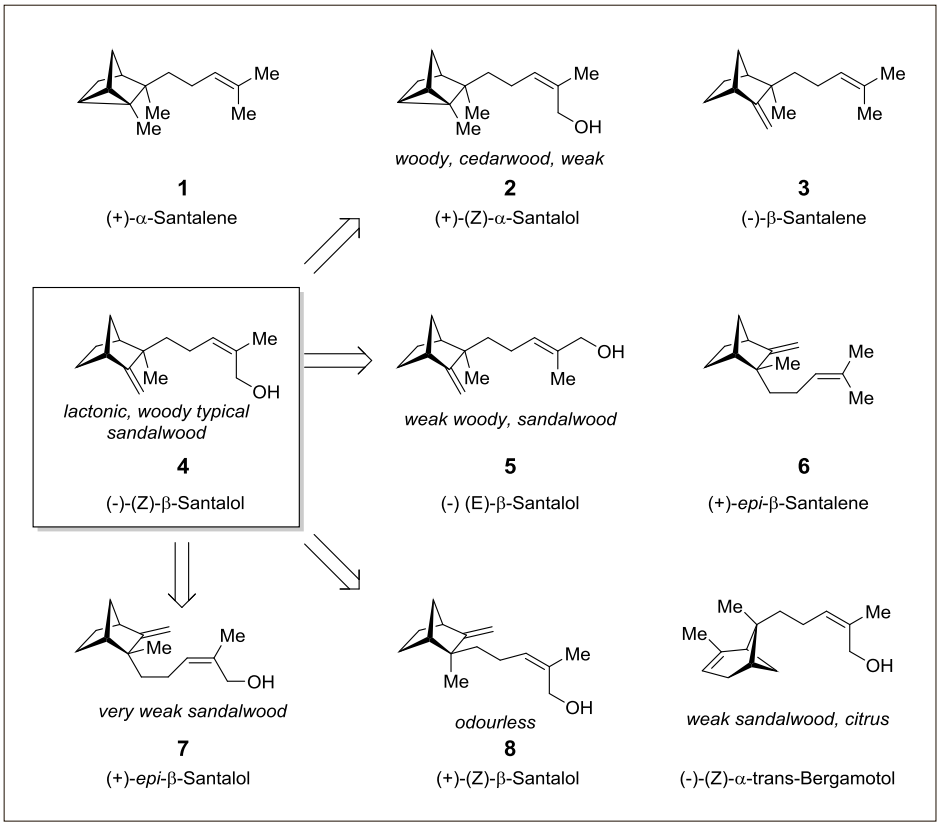
The following review focuses on the syntheses of (*Z*)-α-Santalol (**2**) and (*Z*)-β-Santalol (**4**) with some mention of β-Santalene (**3**) syntheses. The review proceeds in chronological order, with the exception that closely related synthetic approaches are grouped together.

2.2 *(Z)-α-Santalol (2)*

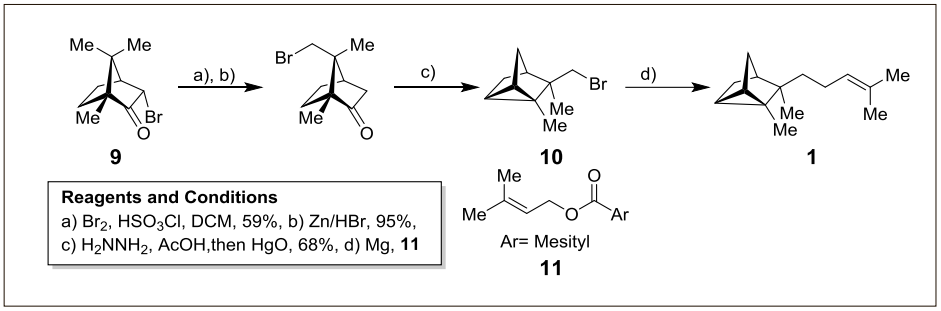
In the late 1950s, advances in the understanding of the propensity of the camphor nucleus to undergo specific and predictable rearrangements spurred new lines of research on α-Santalene (**1**) and (*Z*)-α-Santalol (**2**). In 1957, Corey applied these new insights to the case of α-Santalene (**1**) and synthesized the key starting material from α-bromo camphor **9** (Scheme 3).[25]

In his synthesis of α-Santalene (**1**), Corey reported the straightforward 3–4 step synthesis of the bromotricyclene **10** from α-bromo camphor **9**, which would serve as the preferred starting material for virtually all subsequent syntheses of α-Santalol (**2**) (*vide infra*). Conversion of bromide **10** into the Grignard reagent and then direct coupling with an extremely hindered prenyl mesityl ester **11** furnished α-Santalene (**1**) free of the other possible regio isomers in good yield.

Nearly 10 years later, Collonge described a similar approach *via* the homologation of bromo tricyclene **10**, into the chloride **12** which upon formation of the Grignard reagent was coupled with methacrolein to yield the allylic alcohol **13** (Scheme 4).[26] Treatment of the alcohol **13** with PBr_3 with a catalytic amount of pyridine, followed by treatment with base to effect the S_N2' displacement gave predominantly α-Santalol (**2**) presumably as a mixture of (*E*) and (*Z*) isomers. The authors also noted the formation of β-Santalol (**4**) in the product mixture *via* the ring



Scheme 2. East Indian Sandalwood oil principal constituents and their odours.



Scheme 3. Corey α-Santalene (**1**) (1957).

cleavage and generation of the β-Santalene (**3**) skeleton resulting from the base elimination of HBr (*vide supra*).

In 1967, Erman and Kretschmar at P&G, disclosed a further, novel approach *via* the homologation of the hindered neopentyl-like tricyclene bromide **10** *via* acetylide displacement to give alkyne **14** and then into aldehyde **15** (Scheme 5).[27] Aldehyde **15** was converted into a mixture of (*E*) and (*Z*) unsaturated esters **16** and **17**, which were separated and reduced separately to the corresponding alcohols. The comparison of synthetic (*Z*)-α-Santalol (**2**) with an authentic sample isolated from sandalwood oil confirmed the (*Z*)-allylic sidechain geometry, thus correcting the previous assumed and erroneous (*E*) assignment. This approach – Wittig homologation followed by separation and reduction – was employed in many of the subsequent syntheses of (Z)-β-Santalol (**4**).

In 1970, Corey subsequently disclosed two approaches to (*Z*)-α-Santalol (**2**). The first approach was a modified Wittig-Schlosser olefination in which the intermediate betaine was further treated with *n*-BuLi and then allowed to react with dry formaldehyde (Scheme 6).[28] After stereoselective elimination, this produced the (*Z*)-configured allylic alcohol (*Z*)-α-Santalol (**2**) in good yield. This direct Wittig-Schlosser modification approach from key aldehyde intermediate **15** was subsequently employed by both Willis and Fehr in their syntheses of (*Z*)-β-Santalol (**4**) (*vide infra*).

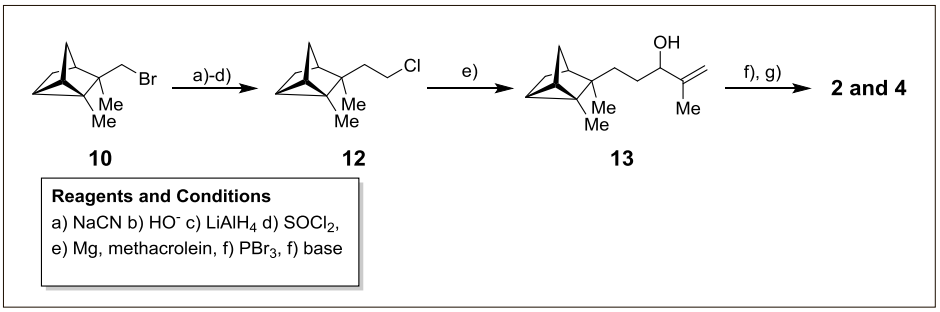
The second approach described by Corey, involved the elaboration of bromotricyclene **10** into propargylic alcohol **18** (Scheme 7).[29] Subsequent treatment with *n*-BuLi then DIBAL-H to effect the *trans*-hydroalumination then addition of iodine gave, stereospecifically, the *trans*-allylic alcohol **19**. A lengthy sequence of manipulations was necessary to deoxygenate the allylic alcohol to the methyl group and to convert the vinyl iodide to the hydroxymethylene functionality to install the (*Z*)-allylic alcohol moiety.

In his syntheses of both α-Santalene (**1**) and (*Z*)-α-Santalol (**2**), Julia converted bromotricyclene **10** into the phenyl sulfone **20**, which was deprotonated and subsequently alkylated with prenyl chloride and desulfonylated to yield α-Santalene (**1**) in good overall yield (Scheme 8).[30]

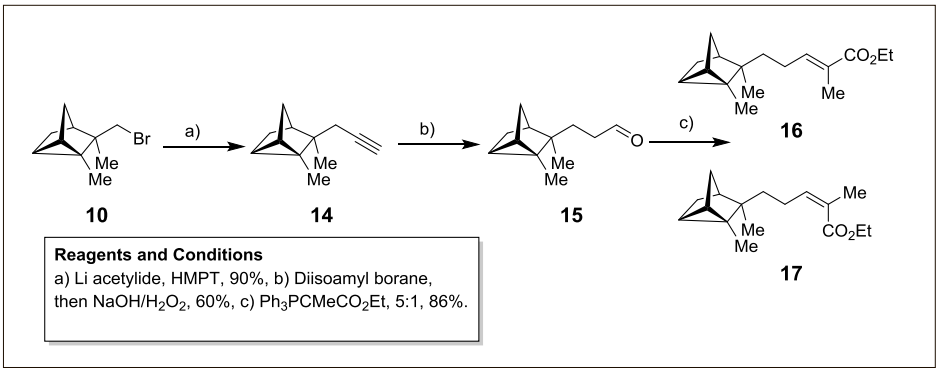
Employing the same sulfone **20** but alkylating the anion this time with the dichloride **21** derived from isoprene, gave completely regioselective alkylation by displacement of the least hindered allylic chloride (Scheme 9). The remaining allylic chloride was displaced by sodium acetate in hot DMF to yield the acetate, which upon desulfonylation by sodium amalgam and acetate deprotection gave (*Z*)-α-Santalol (**2**).

In 1976, Takagi reported the synthesis of α-Santalol (**2**) *via* the stoichiometric Ni coupling with bromotricyclene **10** to yield a (60:40) mixture of (*E*)- and (*Z*)-α-Santalol (**2**) after reductive debenzylation (Scheme 10).[31]

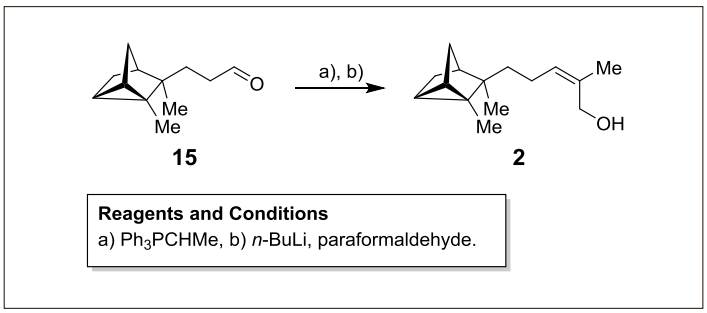
This was followed in 1980 by Still's synthesis of (*Z*)-α-Santalol (**2**), which relied on a stereoselective Wittig approach employing the α-Santalyl phosphonium salt **22** and reaction with the protected hydroxy acetone derivative **23** (Scheme 11).[32] The phosphonium salt was available in several steps from aldehyde **15**. Again the high (*Z*) selectivity was due to



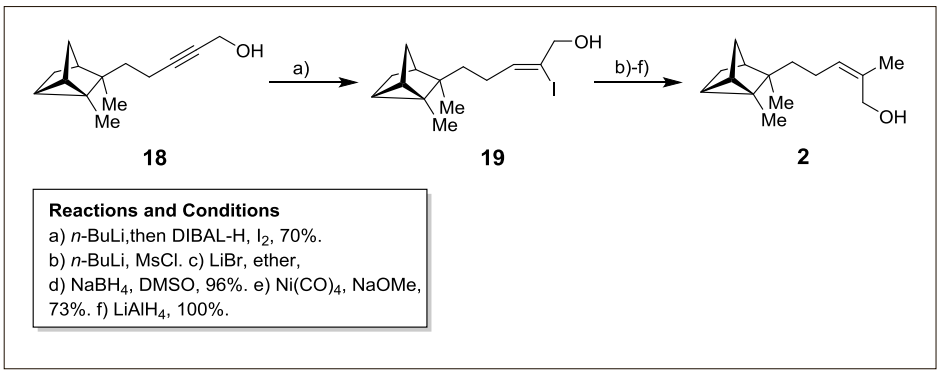
Scheme 4. Collonge α-Santalol (**2**) and α-Santalol (**4**) (1966).



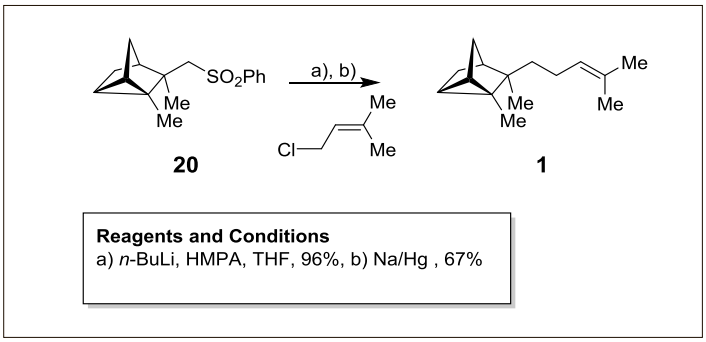
Scheme 5. Erman (*Z*)-α-Santalol (**2**) configuration confirmation (1967).



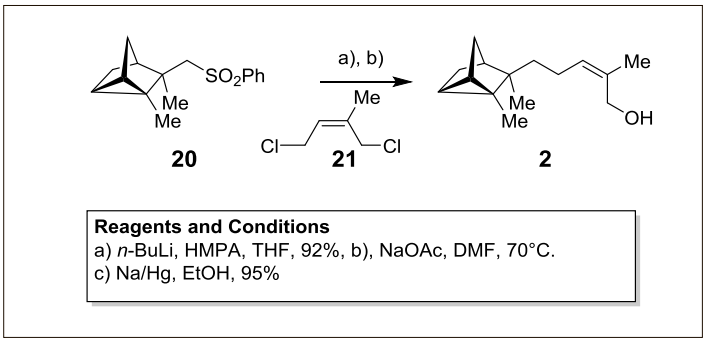
Scheme 6. Corey (*Z*)-α-Santalol (**2**) *via* Wittig-Schlosser Modification (1970).



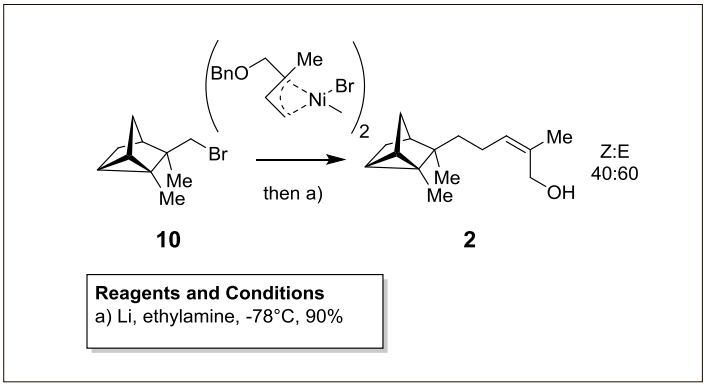
Scheme 7. Corey (*Z*)-α-Santalol (**2**) *via* hydroalumination (1970).



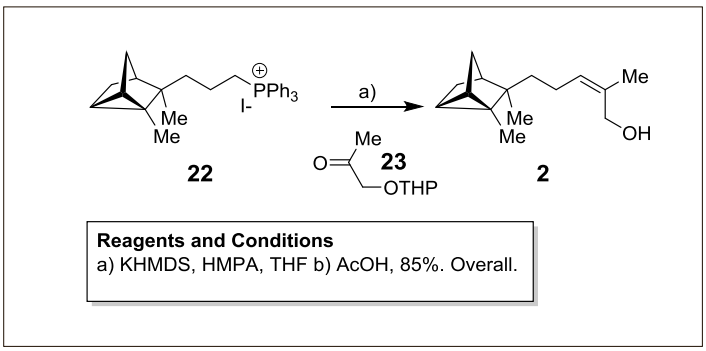
Scheme 8. Julia α-Santalene (**1**) (1973).



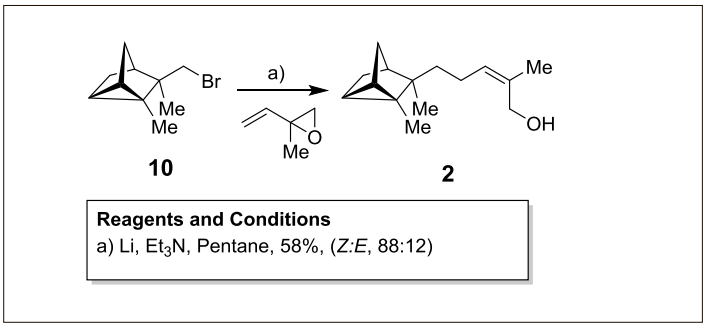
Scheme 9. Julia α-Santalol (**2**) (1973).



Scheme 10. Takagi (*Z*)-α-Santalol (**2**) (1976).



Scheme 11. Still (*Z*)-α-Santalol (**2**) (1980).



Scheme 12. Tamura (*Z*)-α-Santalol (**2**) (1981).

the selective elimination of the intermediate betaine.

The effect of different metal counter ions and their intramolecular complexation on the intermediate betaine was studied in detail by Still with the aim of maximizing (*Z*) selectivity. Comprehensive optimization studies showed that THP was the protecting group that gave the highest (*Z*) selectivity and there was also a noticeable counterion effect. The use of lithium *via n*-BuLi in THF gave lower selectivity (11:1 (*Z*:*E*) when compared to KHMDS in THF/HMPA which gave 41:1 (*Z*:*E*).

In 1981, Tamura presented a novel, concise and interesting approach to (*Z*)-α-Santalol (**2**) (Scheme 12).[33] His approach used the formation of the organo-lithium derived from bromotricyclene **10** and subsequent selective opening of isoprene epoxide in S_N2' like fashion, which gave (*Z*)-α-Santalol (**2**) with the (*Z*)-configured allylic alcohol with good selectivity (88:12, *Z*:*E*) in one step and 58% yield.

Schlosser followed in 1993 with a similarly concise synthesis of both α-Santalene and (*Z*)-α-Santalol from bromotricyclene **10** and 'prenyl potassium' to yield initially β-Santalene (**3**) (Scheme 13).[34] Treatment of α-Santalene (**1**) with potassium *tert*-butoxide and *n*-BuLi gave the allyl potassium intermediate with high (*Z*) selectivity, as predicted based on their previous studies, which was trapped with fluorodimethoxyborane diethyl ether complex and oxidation with hydrogen peroxide liberated the alcohol functionality to yield (*Z*)-α-Santalol (**2**) with very high (*Z*) selectivity.

Before covering the syntheses of (*Z*)-β-Santalol (**4**) and some of β-Santalene (**3**), it is useful to review some semi-synthetic (or relay) approaches from β-Santalene (**3**) isolated from Sandalwood oil to (*Z*)-β-Santalol (**4**).

2.3 *Semi-synthetic Approaches to (Z)-β-Santalol (4)*

In 1985, Willis from Fritzche Dodge Alcott showed that selective chlorination of β-Santalene (**3**) to give allylic chloride **24**, followed by S_N2' displacement with various carboxylate sources would yield the desired (*Z*)-β-Santalol (**4**) isomer as the major product (*E*/*Z* (29:71)) after deprotection of the ester (Scheme 14).[35] This method was applied to a wide variety of trisubstituted alkenes.

In 1994, Unnikrishnan showed that by taking the same allylic chloride **24** as above, chloride displacement with dimethylamine yielded tertiary amine **25** (Scheme 15).[36] Oxidation of the tertiary amine **25** to the *N*-oxide and heating to promote the [2,3] sigmatropic rearrangement followed by reduction of the N-O bond gave (*E*)-β-Santalol (**5**).

2.4 β-Santalene (3) and (Z)-β-Santalol (4) Syntheses

As the bicyclo[2.2.1]heptane ring system is common to both β-Santalene (**3**) and to (*Z*)-β-Santalol (**4**), this section covers the approaches to each, albeit with less emphasis on the β-Santalene (**3**) syntheses.

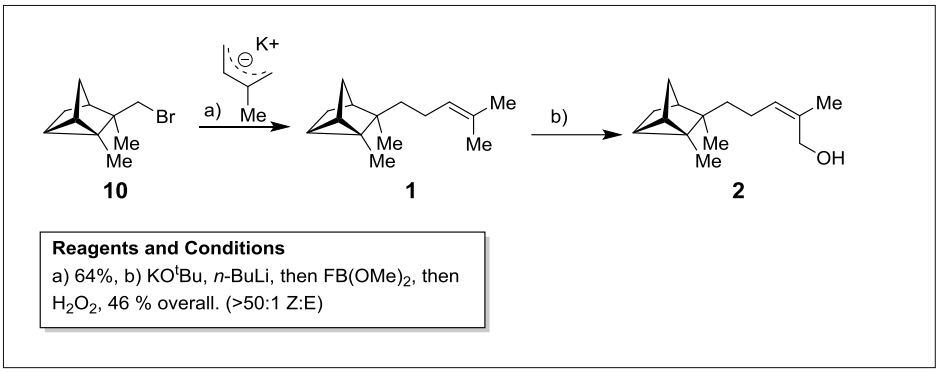
In 1962, Corey reported a stereoselective approach to both β-Santalene (**3**) and *epi*-β-Santalene (**6**) using the inherent preference of the enolate of bicyclic ketone **26** to undergo *exo*-alkylation with iodide **27** in highly specific fashion even if a substituent is present in the α-position (Scheme 16).[37] Simply by changing the order of alkylating agents both *exo* and *endo* sidechain orientations were accessible, ketone **28** was transformed into β-Santalene (**3**) and ketone **29** into *epi*-β-Santalene (**6**).

In 1963, shortly after the publication of the Corey approach, Brieger described the 4-step synthesis of β-Santalene (**3**), from the low yielding (4%) Diels-Alder reaction between Geraniol and cyclopentadiene to give alcohol **30** as a mixture of *exo* and *endo* isomers (Scheme 17).[38] This was followed by dehydration of the alcohol functionality which gave a mixture of β-Santalene (**3**) and *epi*-β-Santalene (**6**).

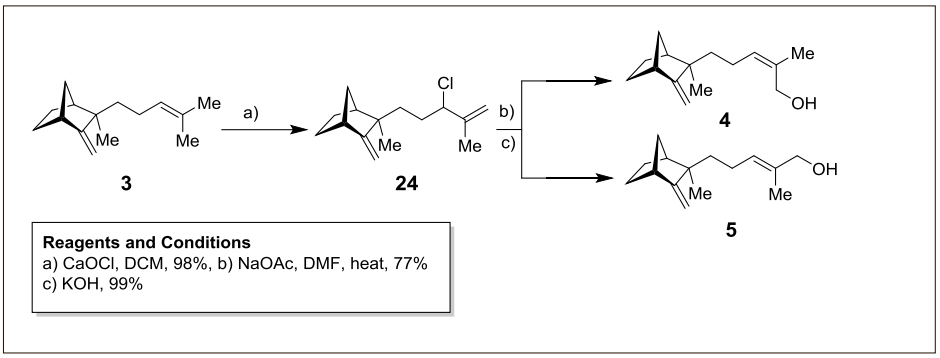
Nearly 20 years later, Weyerstahl re-investigated this simple approach with the aim of improving the yield and selectivity of the initial Diels-Alder reaction by employing stronger electron withdrawing groups such as CHO, CN and CO_2R (Scheme 18).[39] Little improvement in yield (still 2–6%) was seen for adduct **31**, however, and conversion of the CHO, CN or CO_2R into the methyl substituent giving β-Santalene (**3**) was still required. Citral (R=CHO) cyclized under the harsh reaction conditions without giving the desired product. These consistently low yields confirmed the inhibitory effect of β,β-disubstitution in the dienophile in Diels Alder reactions with even highly reactive dienes such as cyclopentadiene.[40]

Having already determined the sidechain geometry for (*Z*)-α-Santalol (**2**) (*vide infra*), Erman *et al*. from P&G published the results of their efforts to determining the β-Santalol (**4**) sidechain geometry *via* synthesis of both (*E*)- and (*Z*)-isomers in 1970 (Scheme 19).[21] Both of the investigated routes involved the highly *exo*-selective alkylation of the bicyclic ketone **32**. The enolate of ketone **32** was alkylated with iodide **33** followed by methyl lithium addition then acetal deprotection gave aldehyde **34**. An alternative route involved alkylation of the same ketone enolate **32** with allyl bromide and subsequent transformation furnished the same aldehyde **34**. Wittig homologation followed by alcohol elimination with $SOCl_2$, gave the (*Z*)- and (*E*)-esters **35** and **36** (*E*:*Z*, 5:1), which were separated by preparative GLC. The reduction of ester **36** furnished (*E*)-β-Santalol (**5**) as the major isomer, reduction of ester **35** gave (*Z*)-β-Santalol (**4**) as the minor component. The pure (*Z*)-β-Santalol (**4**) proved to be analytically identical to the (*Z*)-β-Santalol (**4**) isolated from East Indian Sandalwood oil.

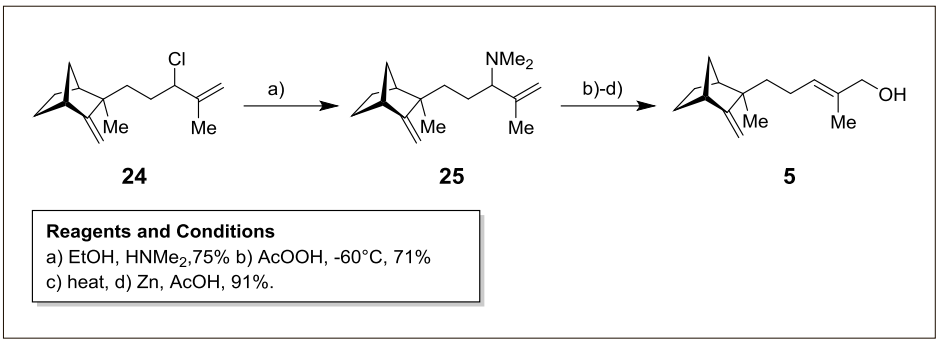
In 1971, in-depth investigations into the relationships between several sesquiterpenes led Money and co-workers to develop



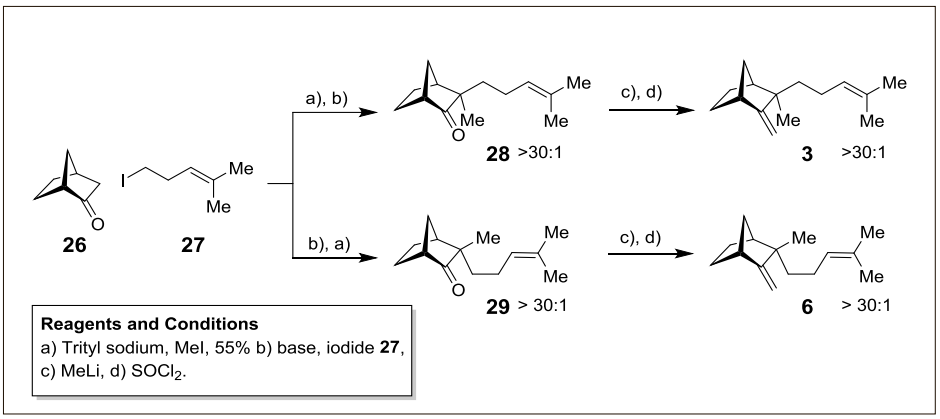
Scheme 13. Schlosser (*Z*)-α-Santalol (**2**) (1993).



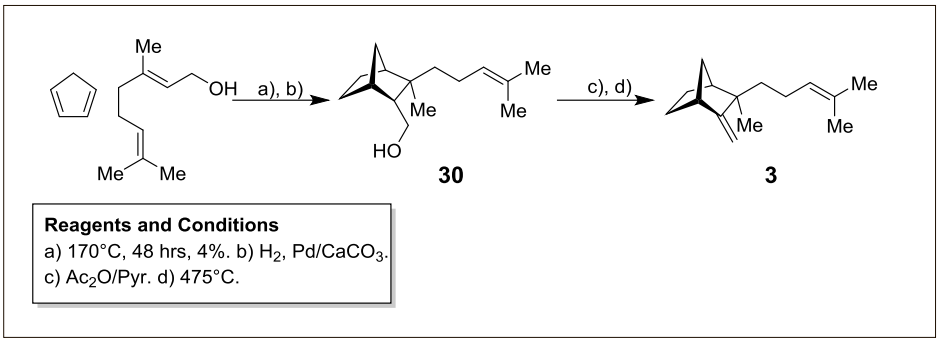
Scheme 14. Willis semi-synthesis of (–)-(*Z*)-α-Santalol (**4**) from (–)-β-Santalene (**3**) (1985).



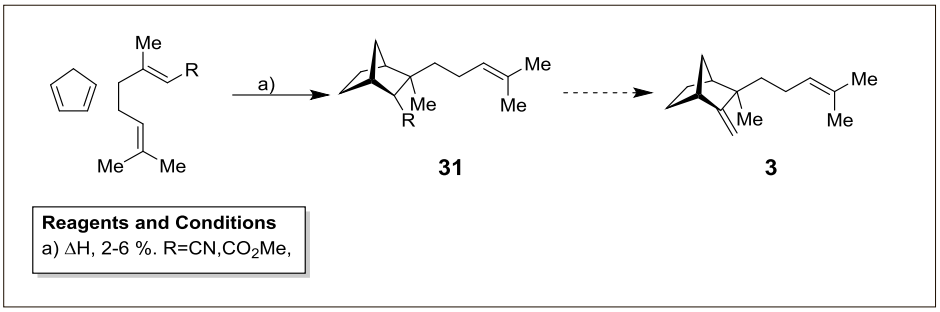
Scheme 15. Unnikrishnan semi-synthesis of (–)-(*E*)-β-Santalol (**5**) from (–)-β-Santalene (**3**) (1994).



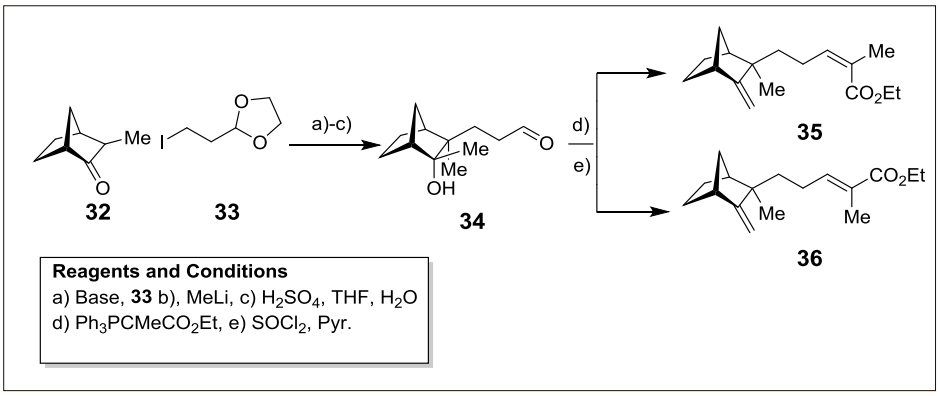
Scheme 16. Corey β-Santalene (**3**) and *epi*-β-Santalene (**6**) (1962).



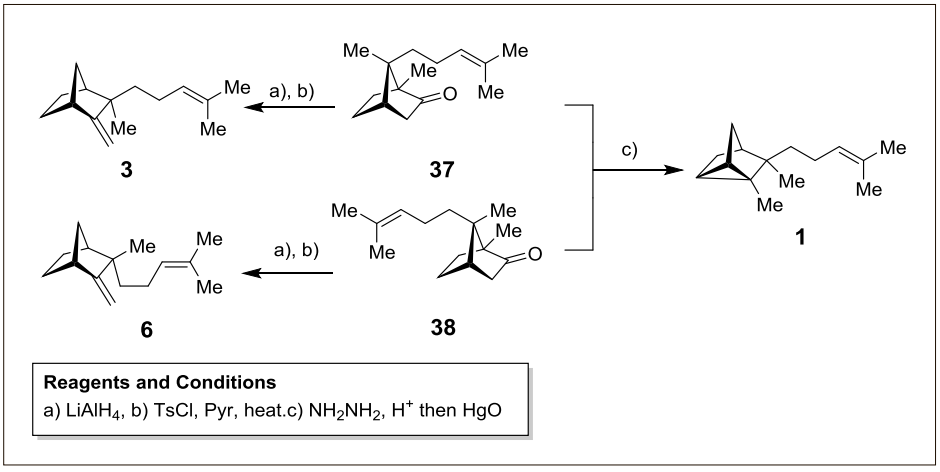
Scheme 17. Brieger β-Santalene (**3**) and *epi*-β-Santalene (**6**) (1963).



Scheme 18. Weyerstahl β-Santalene (**3**) and *epi*-β-Santalene (**6**) (1981).



Scheme 19. Erman (*Z*)-β-Santalol (**4**) and (*E*)-β-Santalol (**5**) (1970).



Scheme 20. Money (+)-α-Santalene (**1**), (–)-β-Santalene (**3**), (+)-*epi*-β-Santalene (**6**) (1971).

a versatile approach from the cyclization of optically active dihydrocarvone acetals to campherenone **37** and *epi*-Campherenone **38** and then further into (+)-α-Santalene (**1**) and (–)-β-Santalene (**3**) or (+)-*epi*-β-Santalene (**6**, Scheme 20).[41] The reduction of campherenone **37** and activation as the tosylate followed by the stereospecific elimination gave (–)-β-Santalene (**3**) in optically active form. Alternatively, using similar conditions *epi*-campherenone **38** was transformed into (+)-*epi*-β-Santalene (**6**).

In 1979, Willis and co-workers at Fritzche Dodge Alcott reported a conceptually different approach to key aldehyde intermediate **39** *via* the Namekin rearrangement of spirolactone **40** (Scheme 21).[42] Treatment of the epoxide-derived optically-active camphene with the dianion of acetic acid followed by acid ring closure gave the spirolactone **40** in reasonable yield. Unfortunately, the subsequent series of methyl migrations, ring openings and rearrangements under the harsh acidic conditions employed, gave racemic product, even though the desired lactone **41** was the major product. This lactone **41** was further treated with ethanolic hydrogen chloride, to open the lactone and eliminate the tertiary alcohol to give the ester, which upon selective reduction with DIBAL-H gave the desired aldehyde **39**. This key aldehyde **39** was converted into both β-Santalene (**3**) and (*Z*)-β-Santalol (**4**). The presence of *epi*-(*Z*)-β-Santalol (**7**) and (*E*)-β-Santalol (**5**) in Sandalwood oil was also confirmed.[43]

In a very efficient and selective approach to aldehyde **44** in 1979, Hoffmann and co-workers from BASF employed building blocks from the industrial synthesis of Vitamin A in a Diels-Alder reaction to construct the [2.2.1]bicycloheptane ring with a leaving group (either Cl, OAc) present to generate selectively the *exo*-methylene functionality (Scheme 22).[44] Several industrially feasible routes were claimed and described, including the aldol/formylation/deprotection/elimination route *via* enone **42** and acetal **43**. In addition the multi-step 2-carbon extension of the bicyclic aldehyde **44** gave key aldehyde **39**, which upon aldol condensation with propanal gave the (*E*)-enal, which upon selective 1,2 reduction gave the less appreciated (*E*)-β-Santalol (**5**) in good yield. Despite the intermediates being readily available and the chemistry being easily scalable, this latter synthesis of the less appreciated (*E*) isomer was lengthy and linear and never commercialised.

Also in 1979, Bertrand reported the synthesis of β-Santalene (**3**) from the *exo*-selective alkylation with iodide **27** of ester **45** which was readily available from the Diels-Alder reaction between cyclopentadiene and an allenic ester (Scheme 23).[45] Conversion of the ester functionality in **46** into the methyl group present in β-Santalene (**3**) was multistep.

In 1981, Ohloff and co-workers from Firmenich reported the hetero Diels-Alder reaction between acrolein and norbornene (**47**), followed by hydration of the vinyl ether to yield the lactol **48** (Scheme 24).[46] The use of the Wittig reaction followed by oxidation and selective *exo*-methylation

delivered the ketone **29**. Methylenation of the ketone **29** gave *epi*-β-Santalene (**6**) and *epi*-(*Z*)-β-Santalol (**7**) was also prepared.

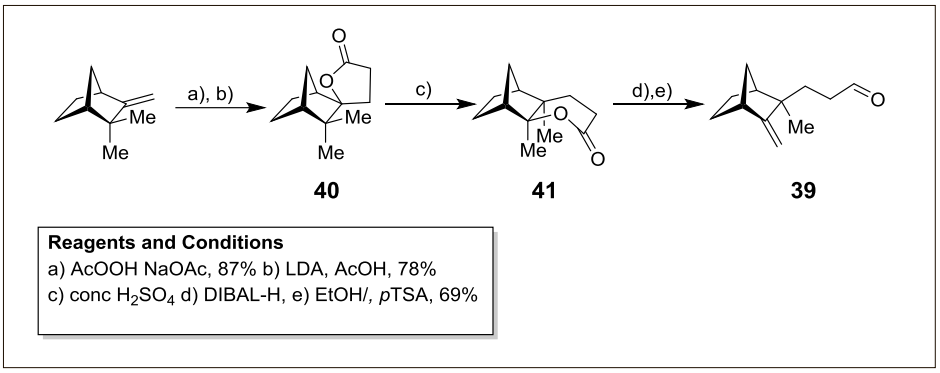
In 1981, Honda reported the highly selective *exo* alkylation of the enolate derived from unsaturated ester **49**, in turn readily synthesized *via* Diels-Alder reaction, which gave the allylic acetate **50** (Scheme 25).[47] The entire side chain was installed *via* bromide **51** in one step with the correct alkene geometry. However, several reduction and activation steps were then needed to convert the ester group to the required methyl group. Honda's work inspired Bertrand to extend his previous synthesis of β-Santalene (**3**) by employing the same ester enolate **52** alkylation and installing entire side chain in one step (Scheme 26).[48] The preparation of the side chain synthon **53**, however, used novel coupling chemistry and conversion of the ester in **54** to the methyl group necessitated several synthetic manipulations.

In 1983, Oppolzer reported a chiral camphor-derived allene ester **55** Diels-Alder reaction with cyclopentadiene to give endo ester **56** in very high *e.e* and *d.e* (Scheme 27).[49] The enolate of ester **56** was alkylated with the iodide **27** then the ester present in **57** transformed into the methyl functionality to give (–)-β-Santalene (**3**) in good overall yield.

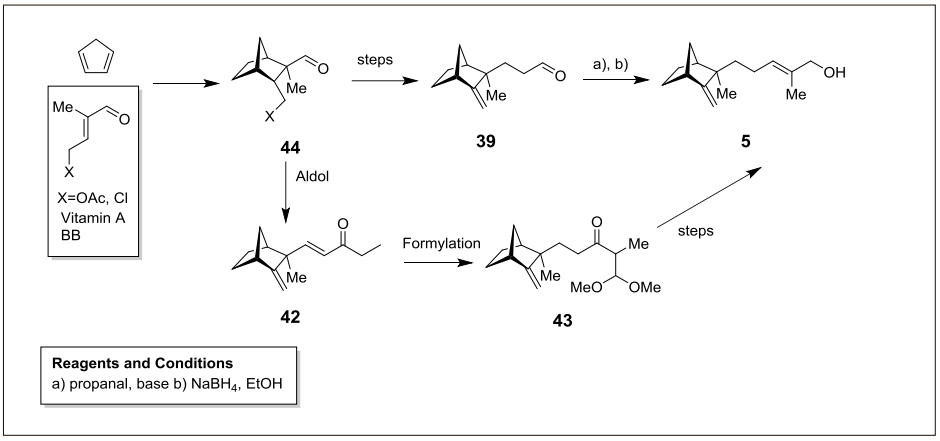
Taking advantage of a Namekin rearrangement of camphor sulfonic acid **58**, Wolinsky reported in 1983 the conversion of cyclic sulfate **59** under thermal conditions into the isomeric cyclic sulfate, which upon alkylation with THP protected bromo ethanol to give acetal **60** (Scheme 28).[50] Desulfonylation and tertiary alcohol elimination, followed by deprotection and oxidation with Collins reagent furnished the key aldehyde **39**, which had previously been converted into (*Z*)-β-Santalol (**4**).

In 1988, Koizumi reported a novel Diels-Alder approach using a chiral sulfoxide dienophile **61** to give intermediates **62**:**63**:**64** (ratio 2:32:66) (Scheme 29).[51] Ester **64** was readily converted into (–)-β-Santalene (**3**) and ester **61** was converted into optically active acetal **65** which had been used by BASF in their syntheses of (+/–)-(*E*)-β-Santalol (**5**).

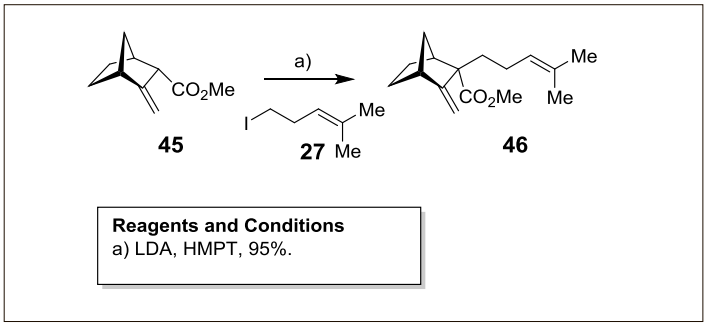
Although absolute configuration was known since 1971 due to approaches by Money, Koizumi and Oppolzer which furnished optically active (–)-β-Santalene (**3**), and the (*Z*) stereochemistry of β-Santalol (**4**) was determined in 1970, no synthesis of either the (+)- or (–)-enantiomer of (*Z*)-β-Santalol (**4**) was reported prior to the Helmchen's 1990 publication (Scheme 30).[22] Helmchen used a chiral auxiliary based on pantothenic acid to synthesize the (–)-methyl norcamphor **32** in optically active form. Highly *exo*-selective alkylation of the ketone enolate derived from



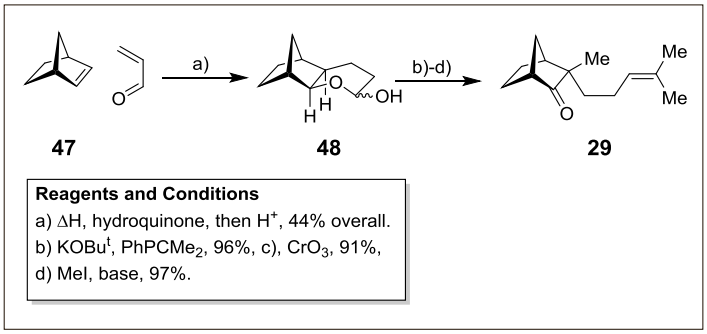
Scheme 21. Willis (*Z*)-β-Santalol (**4**) (1979).



Scheme 22. Hoffmann (*E*)-β-Santalol (**5**) (1979).

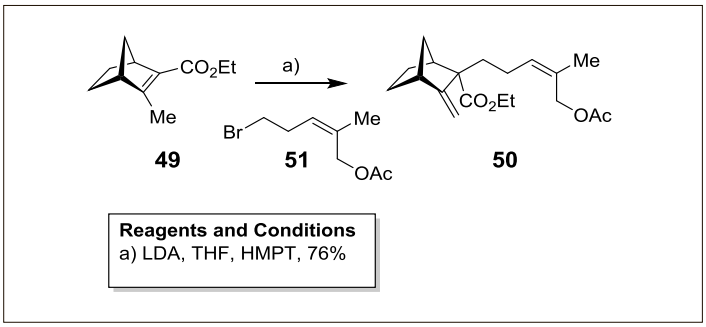


Scheme 23. Bertrand β-Santalene (**3**) (1979).

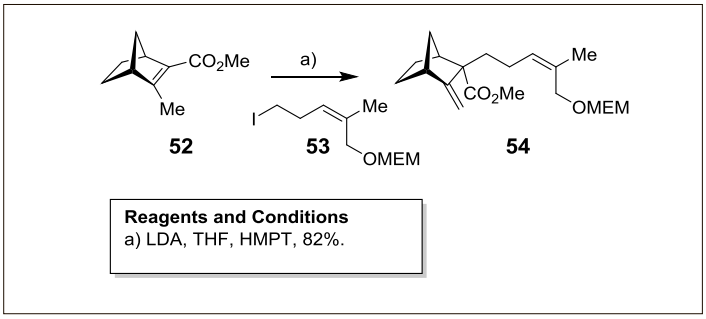


Scheme 24. Ohloff *epi*-β-Santalene (**6**) and *epi*-(*Z*)-β-Santalol (**7**) (1981).

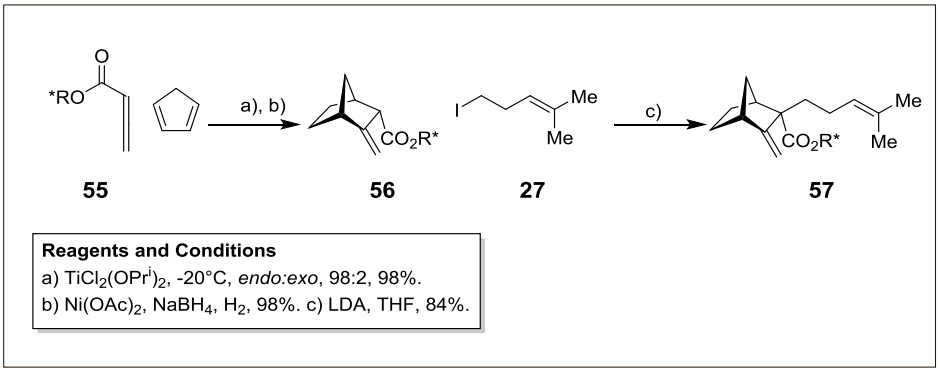
32 with iodide **33** gave the aldehyde **66**. Deprotection followed by (*Z*)-selective Still modification of the Horner-Wittig reaction gave the ester as a mixture (*E*)- and (*Z*)-isomers (*Z*:*E*, 84:16),which were readily separable by HPLC. Methylenation of the ketone and selective reduction of the ester gave (–)-(*Z*)-β-Santalol (**4**) which displayed a very similar optical rotation and odour to the (–)-(*Z*)-β-Santalol (**4**) isolated from East Indian Sandalwood oil. Interestingly synthesis of the opposite antipode (+)-(*Z*)-β-Santalol (**8**) showed it to be completely odourless.



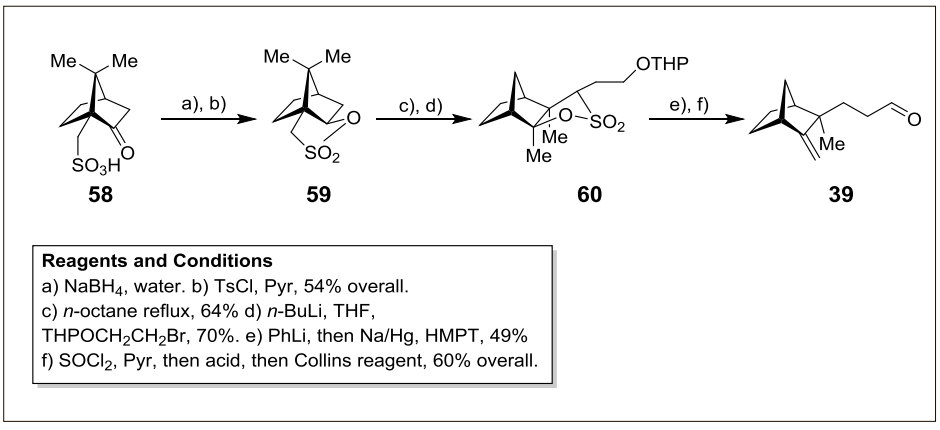
Scheme 25. Honda (*Z*)-β-Santalol (**4**) (1981).



Scheme 26. Bertrand (*Z*)-β-Santalol (**4**) (1982).



Scheme 27. Oppolzer (–)-β-Santalene (**3**) (1983).



Scheme 28. Wolinsky β-Santalol (**4**) (1983).

In 2002, Solladié reported the Diels-Alder reaction of chiral maleate dienophile **67** with cyclopentadiene as a route to furnish optically active β-Santalene (**3**) (Scheme 31).[52] Unfortunately the Diels-Alder reaction was moderately selective and gave the desired diastereisomer together with the undesired isomer in a ratio of 69:31. Separation and reduction of the diester gave the diol **68** which was converted into the dimesylate **69**. Conversion to the methylene and methyl groups was challenging but achieved in good overall yield.

An approach by Stalinski in 2004 showed the feasibility of constructing the [2.2.1] bicycloheptane nucleus using a novel disconnection and radical chemistry (Scheme 32).[53] Cyclization of precursor **70** gave a mixture of the desired target compound **71** in 40% yield in addition to appreciable quantities of the monocyclized silane **72**. Silane **71** was then converted in several steps to a mixture of (*E*)-β-Santalol (**5**) and (*Z*)-β-Santalol (**4**).

Fehr reported in 2009, the 'ene' reaction of optically active alkene **73** to yield propargylic alcohol **74** towards the enantioselective synthesis of (–)-(*Z*)-β-Santalol (**4**) (Scheme 33).[54] A novel Cu-catalysed 'Grob' type fragmentation of intermediate **74** to yield the enal **75**, selective hydrogenation of which gave aldehyde **39**. Optically active aldehyde **39** was then converted into (–)-(*Z*)-β-Santalol (**4**) *via* the Corey-Yamamoto Wittig modification.[28]

Two years later in 2011, Fehr demonstrated that conversion of enal **76** into the dienol acetates **77**/**78** would allow the highly (*Z*)-selective 1,4 hydrogenation yielding the (*Z*)-allylic acetate opened the way for the first industrially feasible synthesis of (*Z*)-β-Santalol (**4**) in either racemic or optically active form from aldehyde **39** (Scheme 34).[55]

Fehr's work inspired intensified activity on the synthesis of (*Z*)-β-Santalol (**4**), drawing on earlier work by Frankel, Shibasaki and Dressen Hölsher on the 1,4 hydrogenation of dienes and dienol acetates (*vide infra*). This built on work initially investigated by Frankel in the late 1960s, namely the 1,4 hydrogenation of 1,3 dienes to give (*Z*)-alkenes, using chromium carbonyl complexes under forcing conditions.[56] In the mid-1980s, Shibasaki extended this concept to the synthesis of prostaglandins including the 1,4 hydrogenation of dienol acetates to yield geometrically pure allylic acetates using the same chromium carbonyl complexes.[57] In 2000, Dreissen Hölsher later disclosed the use of 'naked' Cp*Ru complexes with non-coordinating anions (BARF) for the 1,4 hydrogenation of sorbate esters and sorbyl alcohol to give *cis*-3 hexenyl esters and *cis*-3-hexenol with excellent (*Z*) selectivities (up to 96:4) and under very mild conditions (4 bars H_2 and 60 °C).[58] In 2004, Dupau from Firmenich applied this to the challenges of industrial manufacture of *cis*-3 hexenol and *cis*-3 hexenoate esters.[59] He showed the beneficial effect of carboxylic acids on the selectivity and reactivity of 1,4 hydrogenation of dienes using the more industrially feasible $RuCp^*(COD)BF_4$ catalyst. Treatment of a mixture (1:4, (*E*,*Z*):(*E*,*E*)) dienol acetates **77** and **78** by Fehr with $RuCp^*(COD)BF_4$ (0.05 mol%) in acetone containing maleic acid gave (*Z*)-Santanyl acetate which upon acetyl deprotection yielded (–)-(*Z*)-

β-Santalol (**4**) in good overall yield from aldehyde **39**.[55] This showed that a 4-step sequence from aldehyde **39** to give the installation of the key (*Z*)-allylic alcohol could be catalytic, industrially feasible and efficient.

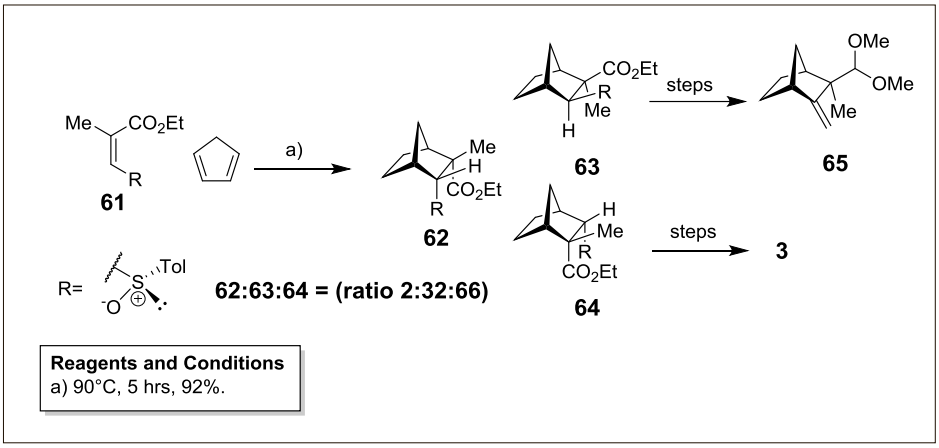
In 2012, Chapuis, also from Firmenich, improved the BASF route to aldehyde **39** *via* the efficient transformation of aldehyde **44** into aldehyde **39** *via* a Meyer-Schuster rearrangement of propargylic alcohol **79** and selective hydrogenation of the enal **73** (Scheme 35).[60] The highly enantioselective (up to 94% ee) Diels-Alder reaction between cyclopentadiene and vitamin A building blocks with Corey's oxaborazoline catalyst was also developed. The dehydro-(*Z*)-β-Santalol was also claimed as a fine sandalwood odorant.

Encouraged by the work of Erman in their synthesis of nor-β-Santalol but aware of the inherent acid sensitivity of both *exo* and *endo* isomers of key aldehyde **39**, Birkbeck and co-workers embarked on a program aimed at extending the Scriabine reaction of aromatic substrates to reactive alkenes and in particular Santene (**80**, Scheme 36).[61] Whilst treatment of Santene (**80**) and allylidene diacetate **81** under Lewis acid catalysis gave the desired product enol acetate **82**, with low *exo*:*endo* (2:1 to 6:1) selectivity, moderate yields and long reaction times, it provided, after deprotection, the key aldehyde **39** intermediate in only two steps from Santene (**80**). During the optimisation of this key coupling reaction, they identified a potential shortcut of three synthetic steps if the entire sidechain was installed in one step using dienyl acetate **83** giving directly the pure dienol acetate **78** product set up for the crucial 1,4 hydrogenation step. This coupling actually worked even better than imagined, giving exquisite *exo*:*endo* (up to 98:2) selectivity and acceptable reaction times with catalyst loadings down to 1 mol%. The additional benefit was that the dienol acetate (*E*,*E*) to (*E*,*Z*) selectivity (>30:1) greatly facilitated the subsequent 1,4 hydrogenation step to yield (*Z*)-β-Santanyl acetate. Catalytic deprotection of the acetate ester was readily achieved using Zemplen conditions to yield (+/–)-(*Z*)-β-Santalol (**4**) (*exo*:*endo*, 98:2, *Z*:*E* 98:2) in good overall yield. The beauty of this approach is evident from the short convergent nature and the simultaneous installation of the entire *exo*-orientated side-chain dienol acetate ready for the crucial 1,4 hydrogenation and the *exo*-methylene motif without stoichiometric reagents in one catalytic coupling reaction.

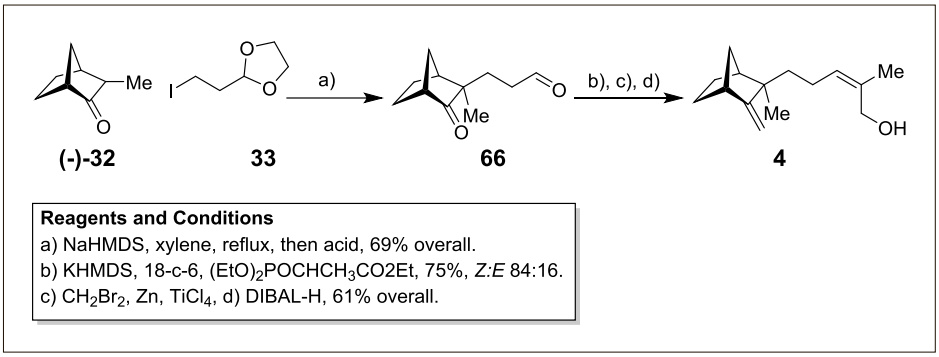
This new convergent synthesis employed an unprecedented coupling reaction and two further catalytic transformations with only one redox manipulation to install the pivotal (*Z*)-allylic alcohol.

3. Conclusion

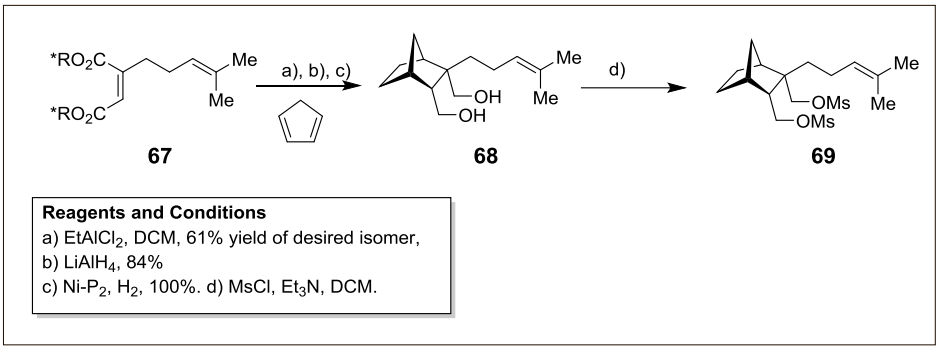
Despite high demand, the ever increasing pressure on natural sources of Sandalwood and its essential oil means that this highly appreciated essential oil is now out of reach for most perfumers. Of the natural smelling Sandalwood odorants, (–)-(*Z*)-β-Santalol (**4**) is certainly the gold standard and highly reminiscent of the essential oil. As efforts to fulfil demand for Sandalwood through plantations grow, this



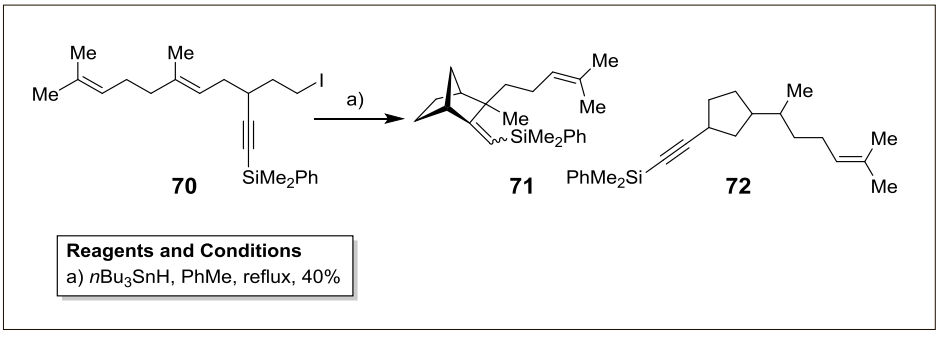
Scheme 29. Koizumi β-Santalene (**3**) (1988).



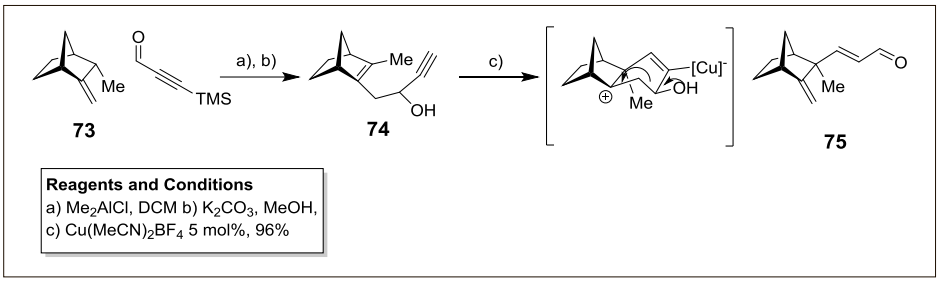
Scheme 30. Helmchen (–)-(*Z*)-β-Santalol (**4**) (1990).



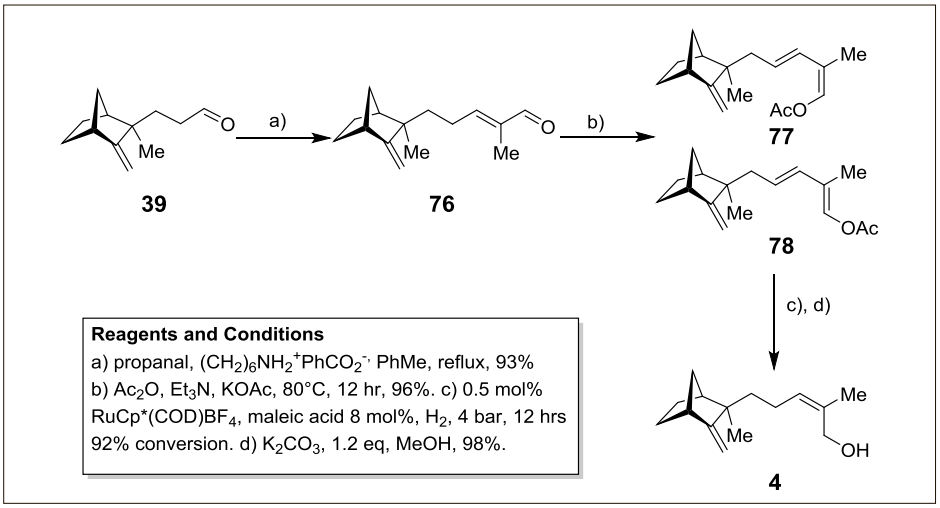
Scheme 31. Solladié (–)-β-Santalene (**3**) (2002).



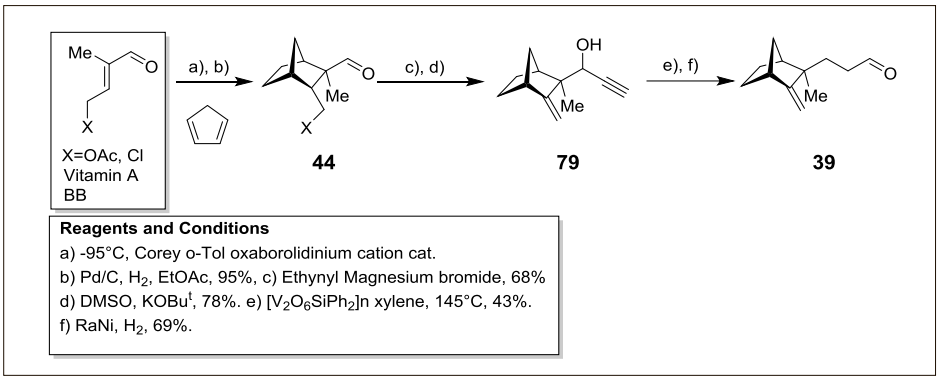
Scheme 32. Stanlinski β-Santalols (2004).



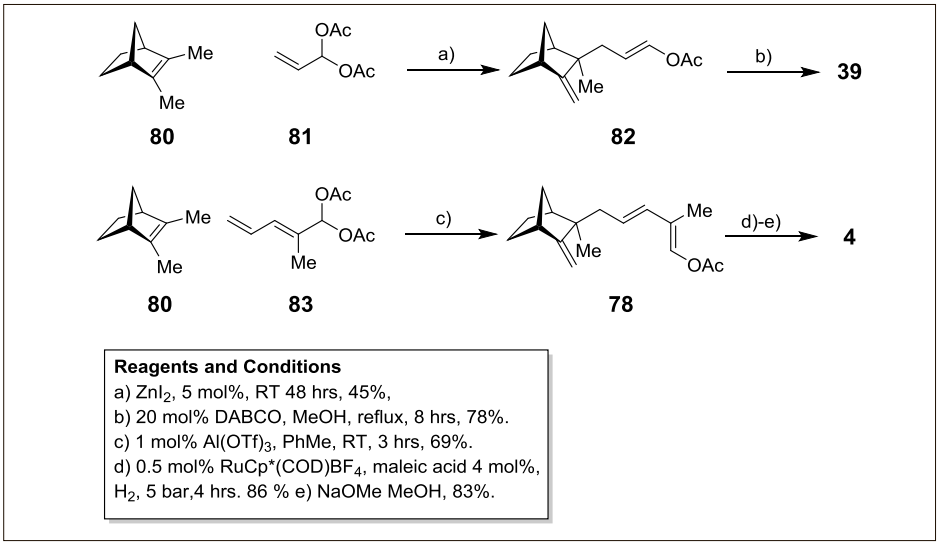
Scheme 33. Fehr (–)-(*Z*)-β-Santalol (**4**) (2009).



Scheme 34. Fehr (–)-(*Z*)-β-Santalol (**4**) (2011).



Scheme 35. Chapuis (–)-(*Z*)-β-Santalol (**4**) (2012).



Scheme 36. Birkbeck 1st and 2nd generation Scriabine-inspired couplings to give (*Z*)-β-Santalol (**4**) (2014).

paper has reviewed the history of efforts to devise an industrially-feasible synthetic version of (*Z*)-β-Santalol (**4**).[62]

The paper has traced the evolution of efforts to synthesize (*Z*)-β-Santalol (**4**) culminating in the catalytic 1,4 hydrogenation of dienol acetate **78** to install the key (*Z*)-allylic alcohol motif present in (*Z*)-β-Santalol (**4**) as reported by Fehr.[55] It highlights that the efforts by Erman from P&G to prepare the correct allylic alcohol geometry in both (*Z*)-α-Santalol (**2**) in 1967 and (*Z*)-β-Santalol (**4**) in 1970 challenged chemists to devise novel and efficient approaches to the selective installation of this key trisubstituted (*Z*)-allylic alcohol motif. The challenge(s) of installing the key (*Z*)-allylic alcohol in both (Z)-α-Santalol (**2**) and (*Z*)-β-Santalol (**4**) elicited many ingenious approaches. Some of these may be envisaged on large scale, particularly those that avoid the use of stoichiometric reagents, such as Grignard organolithiums and Wittig reagents, which result in large amounts of waste when produced on industrial scale. The paper reports that catalytic alternatives have now been found for the introduction of both the sidechain and the crucial (*Z*)-configured allylic alcohol, resulting in a convergent concise, industrially-feasible route to (+/–)-(*Z*)-β-Santalol (**4**).

Acknowledgements

The author would like to thank colleagues and co-workers involved in the (*Z*)-β-Santalol project at Firmenich, in particular Charles Fehr and Christian Chapuis for sharing their experience and advice. Sincere thanks to Jean-François Basset, Philippe Dupau, Alexandre Huboux, Xavier Marquet, Maurus Marty, Pascal Millet, Hervé Pamingle, Julie Quintaine, Lionel Saudan and Eric Walther who contributed throughout this project. Finally thanks also to Gilles Oddon and Maud Reiter for their support and encouragement.

Received: October 19, 2017

[1] M. Koivunen, S. O. Duke, J. C. Coats, J. J. Beck, 'Pest Management with Natural Products', ACS Symposium Series, American Chemical Society, Washington, DC, **2013**; H. Surburg, J. Panten, 'Common Fragrance and Flavour Materials', 5th Ed., Wiley VCH, **2006**; B. Schaefer, 'Natural Products in the Chemical Industry', 2nd Ed., Springer-Verlag, **2014**.

[2] J. D. Roberts, M. C. Caserio, 'Basic Principles of Organic Chemistry', 2nd Ed., Chap. 30, 'Natural Product Biosynthesis', W. A. Benjamin, Inc., Menlo Park, CA. ISBN 0-8053-8329-8, **1977**.

[3] P. de Nicolai, *Chem.& Biodiversity* **2008**, *5*, 1137.

[4] D. T. Harbaugh, B. G. Baldwin, *Am. J. Botany* **2007**, *94*, 1028

[5] N. Baldovini, C. Delasalle, D. Joulain, *Flavor and Fragrance J.* **2011**, *26*, 7. The question of the enantiomeric purity of (*Z*)-β-Santalol in the various *Santalum* species has been raised by Joulain in this review but has not yet been thoroughly investigated.

[6] M. J. Piggott, E. L. Ghisalberti, R. D. Trengrove, *Flavor and Fragrance J.* **1997**, *12*, 43; J. J. Brophy, C. J. R. Fookes, E. V. Lassak, *J. Essent. Oil. Res*. **1991**, *3*, 381; J. Moniodis, C. G. Jones, M. Renton, J. A. Plummer, L. E. Barbour, E. L. Ghisalberti, J. Bohlmann, *Molecules* **2017**, *22*, 940; D. A. Adams, S. P. Bhatnagar, R. C. Cookson, *Phytochemistry* **1975**, *14*, 1459; C. Valder, M. Neugebauer, M. Meier, B. Kohlenberg, F-J. Hammerschmidt, N. A. Braun, *J. Essent. Oil Res*. **2003**, *15*, 178. Despite its significantly lower (–)-(*Z*)-β-Santalol (**4**) content in Australian Sandalwood (*Santalum spicatum sp.*, pre 1930 classified as *Eucaryara spicatum*), the export of Australian Sandalwood had been a key source of export revenue earner in the early days of the fledgling colony, but the export industry collapsed in the early 1970s.

[7] L. N. Owen, *J. Chem. Soc*. **1949**, 1582; A. E. Bradfield, E. M. Francis, *J. Chem. Soc*. **1936**, 1619; T. G. H. Jones, F. B. Smith, *Perfumery and Essent. Oil Rec*. **1931**, *22*, 47; T. G. H. Jones, F. D. Smith, *Proc. Roy. Soc. Queensland*, **1929**, *41*, 17; N. A. Braun, J-F. Butaud, J-P. Bianchini, B. Kohlenberg, F-J. Hammerschmidt, M. Meier, P. Raharivelomanana, *Nat. Prod. Commun*. **2007**, *2*, 695; N. A. Braun, M. Meier, F-J. Hammerschmidt, *J. Essent. Oil Res*. **2005**, *17*, 477; A. Kreipl, W. A. Konig, *Phytochem*. **2004**, *65*, 2045; T. A. Van Beek, R. Kleis, M. P. Posthumus, A. Van Veldhuizen, *Phytochem*. **1989**, *28*, 1909; K. D. Beattie, P. G. Waterman, P. I. Forster, D. R. Thompson, D. N. Leach, *Phytochem*. **2011**, *72*, 400; T. Page, I. Southwell, M. Russell, H. Tate, J. Tungon, C. Sam. G. Dickinson, K. Robson, R. R. B. Leakey, *Chem. & Biodiversity* **2010**, *7*, 1990; N. A. Braun, S. Sim. B. Kohlenberg, B. M. Lawrence, *Nat. Prod. Commun*. **2014**, *9*, 1365.

[8] CITES red list ref *http://www.iucnredlist.org/details/31852/0*. *Santalum album* (India) is listed in CITES Appendix II and the export of the wood from India is banned

[9] G. Ohloff, W. Pickenhagen, P. Kraft, 'Scent and Chemistry: the Molecular World of Odours', Chapter 7.15. Wiley VCH, **2012**.

[10] C. Chapuis, *Chem & Biodiversity* **2004**, *1*, 980; A. A. Birkbeck, 'Challenges in the Synthesis of Natural and Non-Natural Volatiles, The Chemistry of Volatiles', Wiley, VCH, **2010**.

[11] *Perfumer & Flavorist*, Ed. J. Allured, **2015**, *40*, 16.

[12] In Kununurra, Western Australia there are currently 6500 hectares of *S. album* under cultivation (*www//tfsltd.com.au*). A. Brown, J. Eatt, J. Done, D. Raymond, M. Pattison, *Perfumer & Flavorist*, **2011**, *36*, 26; C. G. Jones, J. A. Plummer, E. L. Barbour, *J. Essent. Oil. Res*. **2007**, *19*, 157.

[13] C. G. Jones, E. L. Ghisalberti, J. A. Plummer, E. L. Barbour, *Phytochem.* **2006**, *67*, 2463; J. M. Celedon, A. Chiang, M. M. S Yuen, M. L. Diaz-Chavez, L. L. Madilao, P. M. Finnegan, E. L. Barbour, J. Bohlmann, *Plant J.* **2016**, *86*, 289; M. L. Diaz-Chavez, J. Moniodis, L. L. Madilao, S. Jancsik, C. Keeling, E. L. Barbour, E. L. Ghisalberti, J. A. Plummer, C. G. Jones, J. Bohlmann, *PloS One* **2013**, *8*, e75053; C. G. Jones, J. Moniodis, K. G. Zulak, A. Scaffidi, J. A. Plummer, E. L. Ghisalberti, E. L. Barbour, J. Bohlmann, *J. Biol. Chem*. **2011**, *286*, 17445.

[14] T. Ochi, H. Shibata, T. Higuti, K-H. Kodama, T. Kusumi, Y. J. Takaishi, *J. Nat. Prod*. **2005**, *68*, 819; T. H. Kim, H. Ito, T. Hatano, J. Takayasu, H. Tokuda, H. Nishino, T. Machiguchi, T. Yoshida, *Tetrahedron* **2006**, *62*, 6981; B. Lee, J. Bohmann, T. Reeves, C. Levenson, A. L. Risinger, *J. Nat. Prod* **2015**, *78*, 1357. M. Sharma, C. Levenson, R. H. Bell, S. A. Anderson, J. B. Hudson, C. C. Collins, M. E. Cox, *Phytotherapy Res*. **2014**, *28*, 925; T. H kim, T. Hatano, K. Okamoto, T. Yoshida, H. Kanzaki, M. Arita, H. Ito, *Molecules* **2017**, *22*, 1139.

[15] E. Demole, C. Demole, P. Enggist, *Helv. Chim. Acta*. **1976**, *59*, 737; E.-J.Brunke, K.-G. Fahlbusch, G. Schmaus, J. Vollhardt, *Rivista Italianna EPPOS* **1997**, 48; E.-J. Brunke, G. Schmaus, *Dragoco Report* **1995**, *42*, 195; N. A. Braun, M. Meier, W. Pickenhagen, *J. Essent. Oil Res*. **2003**, *15*, 63; E-J. Brunke, J. Vollhardt, G. Schmaus, *Flavor & Fragrance J*. **1995**, *10*, 211; E-J. Brunke, G. Schmaus, *Dragoco Report*, **1995**, *42*, 197.

[16] R. Shellie, P. J. Marriott, P. Morrison, *J. Chrom. Sci.* **2004**, *42*, 417; D. Sciarrone, R. Costa, C. Ragonese, P. Q. Tranchida, L. Tedone, L. Santi, P. Dugo, G. Dugo, D. Joulain, L. Mondello, *J. Chrom. A*. **2011**, *1218*, 137; S. Panto, D. Sciarrone, M. Maimone, C. Ragonese, S. Giofre, P. Donato, S. Farnetti, L. Mondello, *J. Chrom. A*. **2015**, *1417*, 96.

[17] Dilution factors represent the odour strength of a molecule in an essential oil and is a measure by which the oil is diluted and the component remains detectable by GC-olfactometry. The higher the number, the higher the dilution and the lower concentration present whilst still being perceived. Another key odorant molecule discovered by the Dragoco study with a dilution factor of 256, was Nor-Bergamotenone, described as nutty, sandalwood and essential for the natural top note character of the oil. An independent synthesis of this component by Chapuis and Schulte Elte, however, questioned the importance of this product in Sandalwood oil reconstitutions. C. Chapuis, M. Barthe, B. L. Muller, K. H. Shulte-Elte, *Helv. Chim. Acta* **1998**, *81*, 153.

[18] F. W. Semmler, K. Bode, *Chem. Ber*. **1907**, *40*, 1124; F. W. Semmler, *Chem. Ber*. **1910**, *43*, 1893.

[19] A. E. Bradfield, A. R Penfold, J. L Simonsen, *J. Chem. Soc*. **1935**, 309; The position of the second olefin was difficult to reconcile whilst respecting Bredt's Rule. For a review of anti-Bredt natural products see: J. Y. W. Mak, R. H. Pouwer, C. M. Williams, *Angew. Chem. Int. Ed.* **2014**, *53*, 13664.

[20] L. Ruzicka, G. Thomann, *Helv. Chim. Acta* **1935**, *18*, 355.

[21] H. C. Kretschmar, W. F. Erman, *Tetrahedron Lett*. **1970**, *11*, 41.

[22] A. Krotz, G. Helmchen, *Tetrahedron Asymm*. **1990**, *1*, 537; A. Krotz, G. Helmchen, *Lieb. Ann*. **1994**, 601.

[23] E.-J. Brunke, F-J. Hammerschmidt, H. Struwe, *Tetrahedron Lett*. **1980**, *21*, 2405; E.-J., Brunke, A. Boehme, H. Struwe, *Lieb. Ann*. **1982**, 1105.

[24] S. Ramaswami, S. K. Ramaswami, S. C. Bhattacharyya, *J. Org. Chem*. **1962**, *27*, 2791. See also ref. [41].

[25] E. J. Corey, S. W. Chow, R. A Scherrer, *J. Am. Chem. Soc*. **1957**, *79*, 5773.

[26] J. Collonge, G. Descotes, Y. Bahurel, A. Menet, *Bull. Soc. Chim. Fr*. **1966**, 374.

[27] R. G. Lewis, D. H. Gustefson, W. F. Erman, *Tetrahedron Lett*. **1967**, *5*, 401.

[28] E. J. Corey, H. Yamamoto, *J. Am. Chem. Soc*. **1970**, *92*, 226.

[29] E. J. Corey, H. A. Hirst, J. Katzenellenbogen, *J. Am. Chem. Soc*. **1970**, *92*, 6314.

[30] M. Julia, P. Ward, *Bull. Soc. Chim. Fr*. **1973**, *11*, 3065.

[31] K. Sato, S. Inoue, Y. Takagi, S. Morii, *Bull. Chem. Soc. Jpn*. **1976**, *49*, 3351.

[32] C. Sreekumar, K. P. Darst, W. C. Still, *J. Org. Chem*. **1980**, *45*, 4260; W. C. Still, C. Gennari, *Tetrahedron Lett.* **1983**, *24*, 4405; See also A. D. Buss, S. Warren, *J. Chem. Soc. Chem. Comm*. **1981**, 100; A. D. Buss, S. Warren, *Tetrahedron Lett*. **1983**, *24*, 3931; G. Hutton, T. Jolliff, H. Mitchell, S. Warren, *Tetrahedron Lett.* **1995**, *36*, 7905.

[33] M. Tamura, G. Suzukama, *Tetrahedron Lett*. **1981**, *22*, 577.

[34] M. Schlosser, G. F. Zhong, *Tetrahedron Lett*. **1993**, *34*, 5441.

[35] US 4,510,319 (to Fritzsche Dodge & Alcott Inc), Priority July 1 **1982**.

[36] P. A. Unnikrishnan, *Org. Prep. Proc. Int*. **1994**, *26*, 488. In 2016 Knopff and co-workers from Firmenich described a different approach. They used all the sesquiterpenes present in Sandalwood oil, *via* ozonolysis, to give the mixture of precursor aldehydes, which were transformed *via* the sequence described by Fehr (see ref. [60]) to yield the mixture of (*Z*)-sesquiterpene alcohols found in Sandalwood oil. WO 2016087179 (to Firmenich), Priority December 2 **2014**.

[37] E. J. Corey, R. Hartmann, P. A. Vatakencherry, *J. Am. Chem. Soc*. **1962**, *84*, 2611.

[38] G. Brieger, *Tetrahedron Lett*. **1963**, *30*, 2123; G. Brieger, *Tetrahedron Lett*. **1964**, *31*, 541.

[39] F.-M. Simmross, P. Weyerstahl, *Lieb. Ann*. **1981**, 1089.

[40] F. Friguelli, F. Pizzo, A. Taticchi, E. Wenkert, *J. Org. Chem*. **1983**, *48*, 2802.

[41] C. R. Eck, G. L. Hodgson, D. F. MacSweeney, R. W. Mills, T. Money, *J. Chem Soc. Perkin Trans. 1* **1974**, 1938; G. L. Hodgson, D. F. MacSweeney, R. W. Mills, T. Money, *J. Chem Soc. Chem. Commun*. **1971**, 766; G. L. Hodgson, D. F. MacSweeney, D. W. Mills, T. Money, *J. Chem Soc. Perkin Trans. 1* **1973**, 2113; G. L. Hodgson, D. F. MacSweeney, R. W. Mills, T. Money, *J. Chem Soc. Perkin Trans. 1* **1974**, 3683; T. Money, *Nat. Prod. Rep*. **1985**, *2*, 253.

[42] P. A. Christenson, B. J. Willis, *J. Org. Chem*. **1979**, *44*, 2012; P. A. Christenson, B. J. Willis, *J. Org. Chem*. **1980**, *45*, 3068. Racemisation caused during the acid-catalysed rearrangement of spirolactone **38**, C. Chapuis unpublished results. *Endo* methyl shift see P. T. Lansbury, R. M. Boden, *Tetrahedron Lett*. **1973**, *14*, 5017. See also J. E. Baldwin, T. C. Barden, *J. Org. Chem*. **1983**, *48*, 625.

[43] P. A. Christenson, N. Secord, B. J. Willis, *Phytochem*. **1981**, *20*, 1139.

[44] M. Baumann, W. Hoffmann, *Lieb. Ann*. **1979**, 743.

[45] M. Bertand, H. Monti, K. Chhang Huong, *Tetrahedron Lett*. **1979**, *20*, 15.

[46] R. L. Snowden, P. Sonnay, G. Ohloff, *Helv. Chim. Acta*. **1981**, *64*, 25. Nor-β-Santalol synthesis by P&G for the related thermal hetero Diels Alder reaction between norsantene (methyl-norbornene) and acrolein at 200 °C, gave a 45% yield of a mixture of the desired pyran as major component (92.8%) and the aldehyde (7.2%) corresponding to a formal thermal 'ene' product or hetero Diels Alder followed by elimination, see US 3,673,261. (**1972**) to P&G.

[47] K. Sato, O. Miyamoto, S. Inoue, K. Honda, *Chem. Lett*. **1981**, *8*, 1183.

[48] H. Monti, C. Corriol, M. Bertrand, *Tetrahedron Lett*. **1982**, *23*, 947; H. Monti, C. Corriol, M. Bertrand, *Tetrahedron Lett.* **1982**, *23*, 5539.

[49] W. Oppolzer, C. Chapuis, *Tetrahedron Lett*. **1983**, *24*, 4665; W. Oppolzer, C. Chapuis, D. Dupuis, M. Guo, *Helv. Chim. Acta*. **1985**, *68*, 2100. See also M. Bertrand, J. P. Zahra, *Tetrahedron Lett*. **1989**, *30*, 4117; Z. M. Ismail, H. M. R. Hoffmann, *J. Org. Chem*. **1981**, *46*, 3549.

[50] D. Solas, J. J. Wolinsky, *J. Org. Chem*. **1983**, *48*, 1988.

[51] Y. Arai, M. Yamamoto, T. Koizumi, *Bull. Chem. Soc. Jpn*. **1988**, *61*, 467.

[52] N. Baldovini, G. Solladie, *Tetrahedron Asymm*. **2002**, *13*, 885.

[53] Z. Pianowski, L. Rupnicki, P. Cmoch, K. Stanlinski, *Synlett*. **2005**, 900. In 2015, an improved intramolecular version of this radical

cyclization was reported by K. Ishigami, S. Yamada, H. Watanabe, *Tetrahedron Lett*. **2015**, *56*, 5816. The radical cyclization was greatly improved by tethering the substrate and the yield of the desired cyclized product increased to 86% yield. This intermediate was used to synthesize hydroxy-(*Z*)-β-Santalol, a potent inhibitor of *H. pylori* growth.

[54] C. Fehr, I. Magpantay, J. Arpagaus, X. Marquet, M. Vuagnoux, *Angew. Chem. Int. Ed*. **2009**, *48*, 7221; WO2009/141781 (to Firmenich), Priority 20 May, **2008**.

[55] C. Fehr, I. Magpantay, M. Vuagnoux, P. Dupau, *Chem. Eur. J.* **2011**, *17*, 1257; C. Fehr, *Synlett*. **2012**, *23*, 990.

[56] E. N Frankel, T. L. Mounts, R. O. Butterfield, H. J. Dutton, *Adv. Chem. Ser.* **1968**, *70*, 177; E. N. Fankel, R. O. Butterfield, *J. Org. Chem*. **1969**, *34*, 3930; E. N. Frankel, E. Selke, C. A. Glass, *J. Org. Chem*. **1969**, *34*, 3936.

[57] M. Sodeoka, T. Timori, M. Shibasaki, *Tet. Lett*. **1985**, *26*, 6497; A. Takahashi, M. Shibasaki, *J. Org. Chem*. **1988**, *53*, 1227. (Z)-selective 1,4 hydrogenation of conjugated dienes using chromium complexes see: M. Shibasaki, M. Sodeoka, Y.K. Ogawa, *J. Org. Chem*. **1984**, *49*, 4096; M. Sodeoka, M. Shibasaki, *J. Org. Chem*. **1985**, *50*, 1149; M. Sodeoka, S. Satoh, M. Shibasaki, *J. Am. Chem. Soc*. **1988**, *110*, 4823.

[58] B. Dreissen-Hölscher, J. J Heinen, *Organomet. Chem*. **1988**, 570, 141; S. Steines, U. Englet, B. Dreissen–Hölscher, *J. Chem. Soc. Chem. Commun*. **2000**, 217;EP 1 394170 (**2004** to Degussa),

[59] WO 2008/120175 (to Firmenich) Priority 3rd April, **2007**. For a more detailed discussion see P. Dupau, *Top. Organometallic Chem*. **2012**, *42*, 47.

[60] WO 2012/110375A1 (to Firmenich) Priority 16/02/**2011**; C. Chapuis, D. Skuy, J.-Y. de Saint Laumer, R. Brauchli, *Chem & Biodiv*. **2014**, *11*, 1470; WO2015/067470 (to Firmenich), Priority October 22, **2014**.

[61] A. A. Birkbeck, X. Marquet, P. Millet, H. Pamingle, *Eur. J. Org. Chem*. **2014**, 7582. WO2013/0010126 (to Firmenich) Priority 30 June **2011**; WO2013/0010127 (to Firmenich) Priority 30 June **2011**. For the synthesis of nor-(*Z*)-β-Santalol by P&G see ref. [46]. For the acid-catalysed transformation of *exo* isomer of aldehyde **37** see H. C. Kretschmar, Z. J. Barneis, W. F. Erman, *Tetrahedron Lett*. **1970**, *11*, 37, and for the *endo* isomer see R. L. Snowden, R. Naef, *Tetrahedron Lett*. **1984**, *25*, 2877.

[62] Y. Zhang, H. Yan, M. Niu, Q. Cheng, X. Zhang, J. Teixeira de Silva, G. Ma, *Trees*, **2017**, *https://doi.org/10.1007/s00468-017-1558-y*; F.M. Schempp, L. Drummond, M. Buchhaupt, J. Schrader, *J. Agric. Food. Chem*. **2017**, ASAP.