Chirality and odor perception
Scents of precious woods

ABSTRACT

In the last 25 years, the importance of chiral discrimination in olfaction has come a long way. This paper provides an overview of the progress made in key chiral odorants that represent the scents of precious woods. The effect of chirality on the odor of sandalwood odorants (β-santalols, 3-isocamphylcyclohexanols & Ebanol®s), patchouli odorants (patchoulol & spiropatchoulolone), agarwood (karanone, dihydrokaranone & jinkohol II) as well as the odor active components of other woody fragrance materials (Iso E Super®, Georgywood®, etc.) is reviewed.

From the beginning of recorded history, trading of fragrant oils, spices and precious woods were important items of early commerce. By 3000 BC the Egyptians – when learning to write and make bricks, were already importing large quantities of myrrh. In November 1922, when the archeologist, Howard Carter, discovered the tomb of the boy pharaoh, Tutankhamon, a world of knowledge about an age 3000 years before would unfold. As the painstaking discovery and cataloguing of artifacts proceeded, of the items found were perfume containers filled with spices & aromatic substances (such as frankincense) preserved in fat that still gave off a faint odor. From Japan, China, India to the Middle East, the use of precious woods such as sandalwood, agarwood, patchouli and cedarwood, as well as frankincense and myrrh, have been used from antiquity for religious ceremonies and for pleasure. Aromatic woods and plants were burned during funeral ceremonies, providing a connection between this world and the after-life. The word perfume derives from the Latin "per fumum" (by means of smoke) and refers to the ancient practice of burning aromatic woods and scented material in religious ceremonies to deepen the connection between people and their Gods. It should also be mentioned that burning aromatic woods and resins was also necessary to cover the stench after animals (or even humans - as practiced in India) were sacrificed in the flames so as not to drive away all participants of these religious rituals (1).

Today, in the Middle East, the aroma of sandalwood and patchouli still permeates coffee shops and bazaars as a mixture of these aromatics are used in the tobacco paste called "Jurak" smoked by men (and only rarely by women) in a water-pipe (or Shisha, Narghile or Hookha).

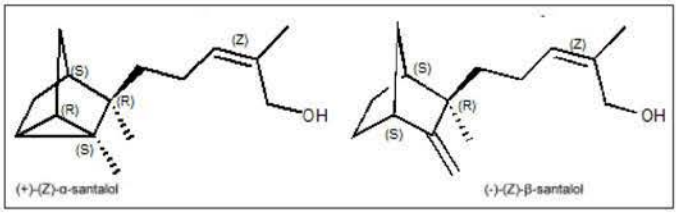
The use of aromatics derived from such woods (or in the case of patchouli, the sweet, heavy woody scent derived from the leaves of the herbaceous shrub, Pogostemon cablin (Blanco) Benth.), remains popular in modern perfumes.

SANDALWOOD

Although several species of sandalwood are available in commerce, the prized wood is that of *Santalum album L.* which is today in short supply. Historically, India was a major producer, but this wood has been over harvested and the government now bans exports, although illegal harvesting and smuggling continues to exacerbate the problem. *Santalum album* appears on the 2004 IUCN Red List of Threatened Species.

East Indian Sandalwood oil, produced by steam distillation, is a highly valued perfume raw material, but with a current price close to US $1600/Kg and because of its threatened status, it has largely been replaced by synthetic substitutes.

The two major constituents of E.I. Sandalwood oil are (+)-(*Z*)-α-santalol and (-)-(*Z*)-β-santalol (which together comprise 70-90 percent of the oil in a ratio of ~ 70:30, respectively). While both possess heavy woody-sandal odors, only the (-)-(*Z*)-β-santalol isomer is considered the "gold standard" for sandalwood odor as it adds a urinaceous, animalic

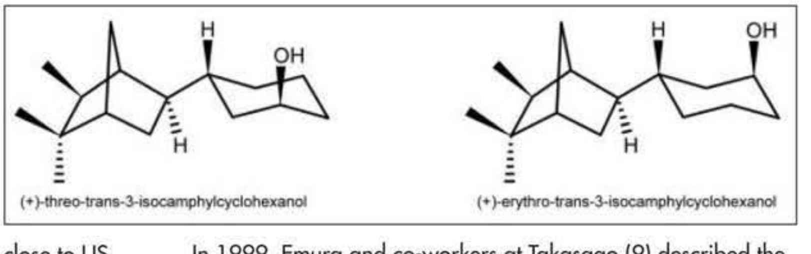


(+)-(Z)-α-santalol (-)-(Z)-β-santalol

sandalwood tonality to the oil.

In 1990, Helmchem's group at the University of Heidelberg first synthesized both enantiomers of (*Z*)-β-santalol and found that the (-)-enantiomer possessed the typical sandalwood odor of the natural material while (+)-(*Z*)-β-santalol was odorless. Unfortunately, no economical synthesis of β-santalol has yet been developed. In the same study, (-)-(E)-β-santalol, a minor constituent of sandalwood, was also prepared. In this case, the nature identical (-)-enantiomer possessed a scent similar to (-)-(*Z*)-β-santalol (but less intense) while its ent-form again was odorless (2).

Of the synthetic sandalwood odorants, the first commercially successful material was derived from the BF_3-catalyzed condensation of camphene and phenol (3), which provides at least nine isomeric terpenyl-phenols (4). The major components are o- (*p*-) (2,2,3-trimethyl- exo-5-norbornyl)-phenols, accompanied by some o- (*p*-) (exo-2-bornyl)-phenols and smaller amounts of o- (*p*-) (1,3,3-trimethyl-exo-6-norbornyl)-phenols. Only very small amounts (>1 percent) of the three corresponding meta-substituted phenols are formed in the condensation mixture. On catalytic hydrogenation, these *m*-isomers lead to 3-terpenyl-cyclohexanols (isocamphylcyclohexanols) characterized by a powerful odor of sandalwood. Surprisingly, the 2- and 4-terpenyl-cyclohexanols obtained in the same way from the o- and *p*-terpenyl-phenols are almost odorless. In a series of papers during the 1960's, Demole unequivocally demonstrated that only the erythro and threo trans-3-isocamphylcyclohexanols with the axial alcohol configuration had the desired powerful sandalwood character (4-6). Following Demoles work, several groups were able to increase the amount of isocamphylcyclohexanols to above 10 percent by replacing phenol with guaiacol (7) or catechol (8) in the initial condensation, and today commercial grades containing between 5-20 percent are available.

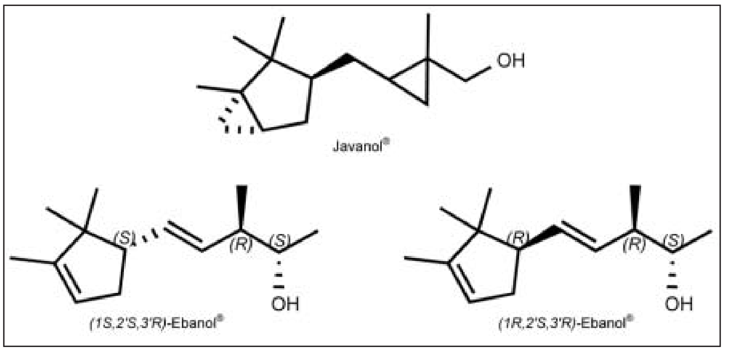


(+)-threo-trans-3-isocamphylcyclohexanol (+)-erythro-trans-3-isocamphylcyclohexanol

In 1999, Emura and co-workers at Takasago (9) described the synthesis and odor properties of the enantiomers of both the threo and erythro trans-3-isocamphylcyclohexanols as shown in Table 1. As will be noted, the (+)-threo enantiomer possesses the most desirable odor and strength followed by the erythro enantiomers, while the (-)-threo enantiomer possesses no sandalwood character.

Enantiomer	Odor Threshold	Odor Description
(+)-threo	0.2 ppb	Strong, diffusive, and sandalwood-like odor; natural sandalwood odor, very strong and keen
(-)-threo	200 ppb	Weak, moldy and woody odor
(+)-erythro	7 ppb	Sandalwood like odor without moldy feeling, and it is sufficiently diffusive
(-)-erythro	3 ppb	Strong, warm sandalwood odor

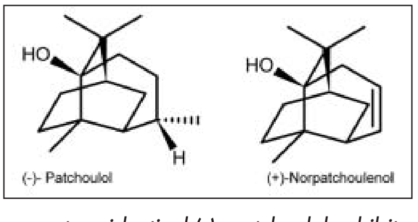
Table 1. The trans-3-isocamphylcyclohexanols



Other popular synthetic sandalwood odorants (e.g. Javanol®) have primarily been based on materials derived from α-campholenic aldehyde. As the enantiomeric versions of this aldehyde are easily prepared from the (+)- or (-)-α-pinene epoxides, there are many examples of odor evaluations of enantiomers from materials such as Ebanol (8 diastereomers), where only the (*1S,2'S,3'R*)-Ebanol and (*1R,2'S,3'R*)-Ebanol have powerful sandalwood odors (10).

PATCHOULI

The powerful woody odor of patchouli is due to primarily to (-)-patchoulol, (+)-norpatchoulenol and pogostol (which comprise about 30-40 percent, 0.3-0.5 percent and 1.0-2.5 percent of patchouli oil, respectively). The stereoselective synthesis of (+)- and (–)-patchoulol was achieved at Firmenich by Naf et al. in 1981 and the odor evaluations of the enantiomers carried out (11).



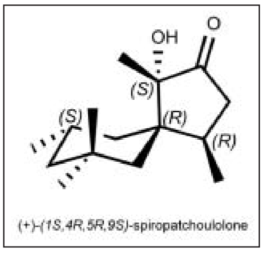
"The synthetic, nature-identical (-)- patchoulol exhibits a strong, typical patchouli scent with an earthy, slightly camphoraceous, powdery cellar note which is practically indistinguishable from natural patchouli alcohol. In contrast to the odour profile of the (-)-enantiomer, the 'unnatural (+)-patchoulol is much weaker, less characteristic, nearly indefinable and by no means reminiscent of patchouli. It might however have a β-santalol odour with a green undertone."

Although a stereospecific synthesis of (+)-norpatchoulenol was developed by Oppolzer (12, 13) that is also amenable to the preparation of the unnatural (-)-enantiomer, the odor comparison of these appears not to have been carried out.

OTHER WOODY ODORANTS

Before examining the subject of the key odorants of Agarwood, lets examine the role of enantioselectivity in odor perception on the enantiomers of 1-hydroxy-1,4,7,7,9-pentamethylspiro[4.5]decan-2-one (a patchouli-like odorant), Arborone (the odor active component of the popular Iso E Super®), desmethyl-Arborone, and Georgywood®.

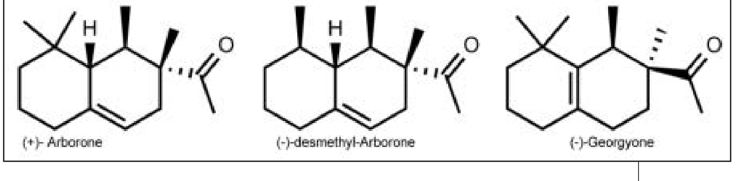
In 2005, Kraft and co-workers reported the synthesis and odor evaluation of the enantiomeric forms of 1-hydroxy-1,4,7,7,9-pentamethylspiro[4.5]decan-2-one (which we will hereafter refer to as "spiropatchoulolone") in which the stereocenters of the odor active (+)-(*1S,4R,5R,9S*)-enantiomer superimpose well with those of (-)-patchoulol (14).



While (+)-spiropatchoulone possesses a powerful woody patchouli character (with an odor threshold of 0.067 ng/L in air for the racemate), the ent-form is essentially odorless.

In 2006, Hong & Corey (15) reported the first stereospecific syntheses and provided odor evaluations of the enantiomers of Aborone, desmethyl-Arborone and Georgyone.

Racemic Arborone, which comprises only ~5 percent of commercial Iso E Super®, has been shown by Fráter et. al. (14) to have an intense warm, woody, ambery character and an odor threshold as low as 5 pg/l (in air) and is the primary contributor to Iso E Super's odor profile. Hong & Corey have shown that desmethyl-Arborone provides a similar odor profile.



In the case of Georgywood®, which was introduced into fragrances by Givaudan in the late 1990's (for example – "Golden Moments" by P. Presley, where Georgywood is used at about 5 percent), the enantiomers have been examined by both Corey's group (15) and Fráter's group (17).

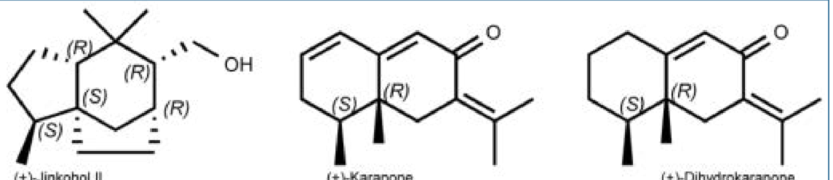
The enantiomeric odor profiles of these three structurally similar woody odorants appear in Table 2.

Enantiomer	Odor Description
(+)Arborone	Possesses an intense woody odor that is clean and very pleasant. Comparative tests in Corey's laboratory indicated that the odor threshold for (+)-Arborone is 20 to 30 times lower than that for (–)-Georgyone. Comparatively, Fráter, et. al., have reported an odor threshold of 5 pg/L for racemic Arborone
(-)Arborone	A very faint odor.
(-)-desmethyl-Arborone	Possesses an intense warm woody-amber odor in common with (-)-Georgyone and (+)-Arborone. Its odor also has a slight fresh minty note.
(+)-desmethyl-Arborone	Possesses a relatively weak odor.
(-)-Georgyone	Woody-ambery; Bottom note: Fresh, minty, green, sweet (Fráter, et. al.); Hong & Corey describe the odor as "an intense clean woody odor". Odor threshold - 20 pg/L (in air).
(+)-Georgyone	Weakly woody; Bottom note: musty (Fráter, et. al.); Hong & Corey found this enantiomer to possess a relatively weak odor which is best described as distinctly unpleasant-acrid-musty. Odor threshold - 3.5 ng/L (in air).

Table 2.Other Synthetic Woody Odorants

AGARWOOD

Is perhaps the most valued wood for a perfume material in the world. According to statistics the trade in agarwood exceeds a


(+)-Jinkohol II (+)-Karanone (+)-Dihydrokaranone

billion dollars U.S. In fact, agarwood is only the "resinous" portion of wood from trees belonging to the *Aquilaria* genus, *Thymelaeceae* family. At least fifteen species of *Aquilaria* trees are known to produce agarwood. A whole range of qualities and products are on the market and prices range from a few dollars per kilo for the lowest quality to over thirty thousand US dollars for top quality oil and resinous wood. Aquilaria trees are native to Asia from Northern India to Vietnam and Indonesia. Only by cutting trees down and extracting the valued sections can agarwood be harvested in commercially attractive quantities. This has resulted in the rapid demise of *Aquilaria* in the natural forests of tropical South and Southeast Asia. Several species of Aquilaria are considered endangered due to over harvesting. *Aquilaria crassna* Pierre ex Lecomte is listed as an endangered species in Vietnam, and Aquilari malaccensis Lam. is listed as endangered by the World Conservation Union, IUCN and is protected worldwide under the (CITES) convention (although illegal trading is still prevalent) (18).

The healthy wood of Aquilaria trees is white, soft, even-grained, and not scented when freshly cut. Under certain pathological conditions, the heartwood becomes saturated with resin, and eventually becomes hard. The best grade of *agarwood* is nearly black and sinks when placed in water. In general, *agarwood* is considered inferior if it is lighter in tone, with diminishing amounts of resin. It was long thought that agar deposits were created as an immune response by the tree, the result of an attack by a fungus. But recent experiments by Blanchette (19) (as part of The Rainforest Project Foundation's effort to preserve endangered species of the world's forests) indicate that open wounds subject to aeration can create the agarwood resin. Today, as part of this project, several Aquilaria plantations in Vietnam, are beginning to produce "cultivated" agarwood.

Enantiomer	Odor Description
(+)-Jinkohol II	The woody note characteristic of sesquiterpenes in combination with a somewhat camphoraceous odor and, when heated or burnt, the characteristic odor of agarwood is strengthened (21).
(-)-Jinkohol II	Very similar to (+)-Jinkohol II (21).
(+)-Karanone	A strong bright woody-amber note (22).
(-)-Karanone	A weak woody note with a citrus-atmosphere (22).
(+)-Dihydrokaranone	A remarkable and intense woody note (23).
(-)-Dihydrokaranone	A citrus and mild woody note; it lacks in sharpness and brightness, and is deficient in charm as compared to its enantiomer, but is pleasant in another aroma direction (23).

Table 3. Agarwood Odorant Enantiomers

The aromatic part of agarwood consists primarily of a complex mixture of oxygenated sequiterpenoids and chromones (20), a number of which appear to contribute to the woody oriental-incense aroma. Three important naturally occurring aroma constituents of agarwood - (+)-Jinkohol II (21), (+)-Karanone (22) and (+)-Dihydrokaranone (23) have been evaluated for their odor properties versus their enantiomers.

The odors of the enantiomeric forms are shown in Table 3.

CONCLUSIONS

This short overview of the role of chirality on key odorants responsible for scents of precious woods used in perfumery provides clear evidence of enantioselectivity in odor perception. However, as in the case of Jinkohol II, such enantioselectivity is certainly not universal. Nevertheless, the potential use of molecular modeling against olfactory receptor models (as well as biological work involving the odorant activation of olfactory glomerulus using optical detection fluorescence microscopy) as described by Hong and Corey (15), as well as the more classical approach of using molecular overlays of new (woody) odorants as used by Kraft (14) provide screening and modeling tools of promise for odor prediction. For additional reading, the articles of Brenna et. al. (24) and Kraft et. al. (25) are recommended.

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