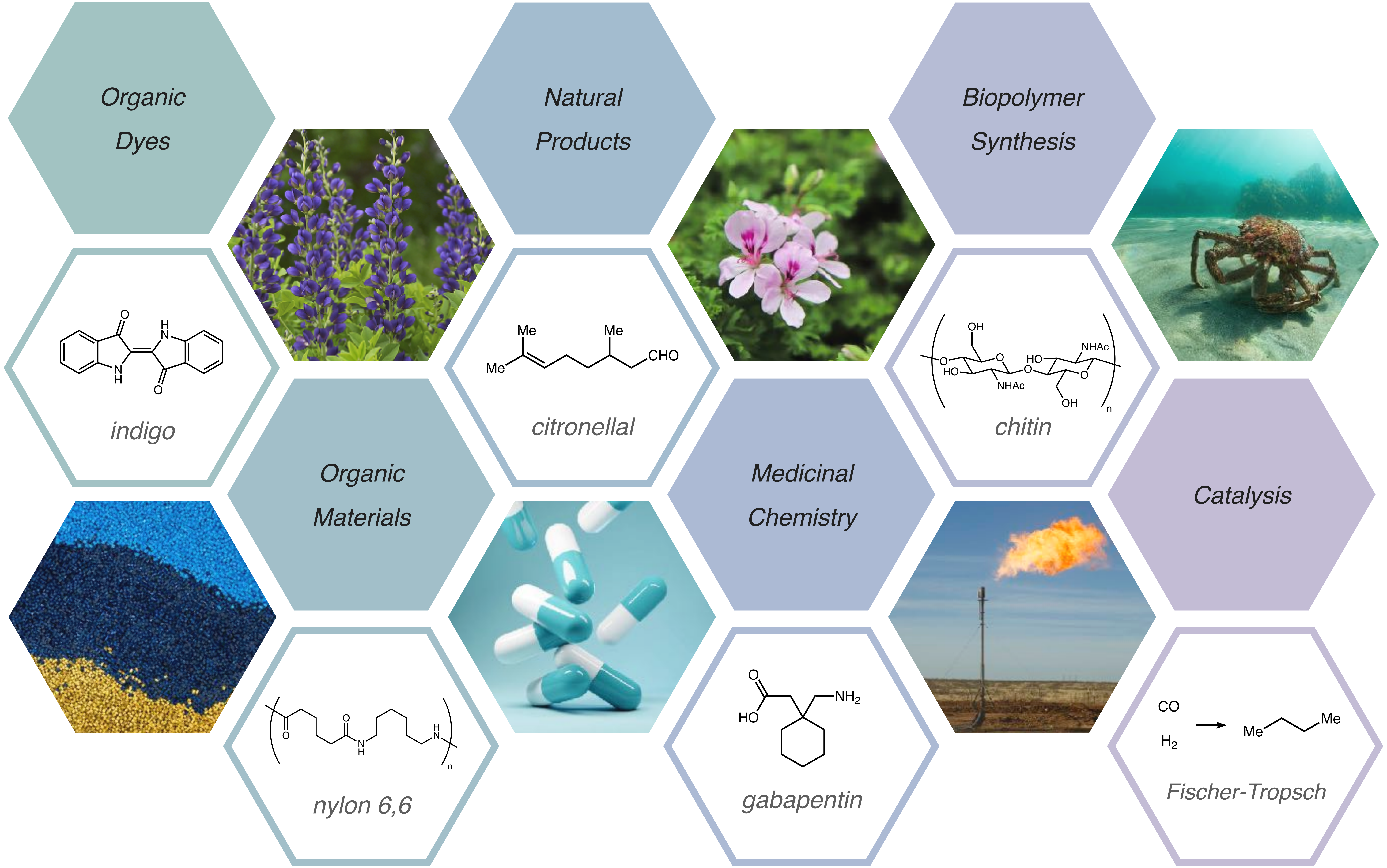
Fragrance Chemistry

Literature Talk

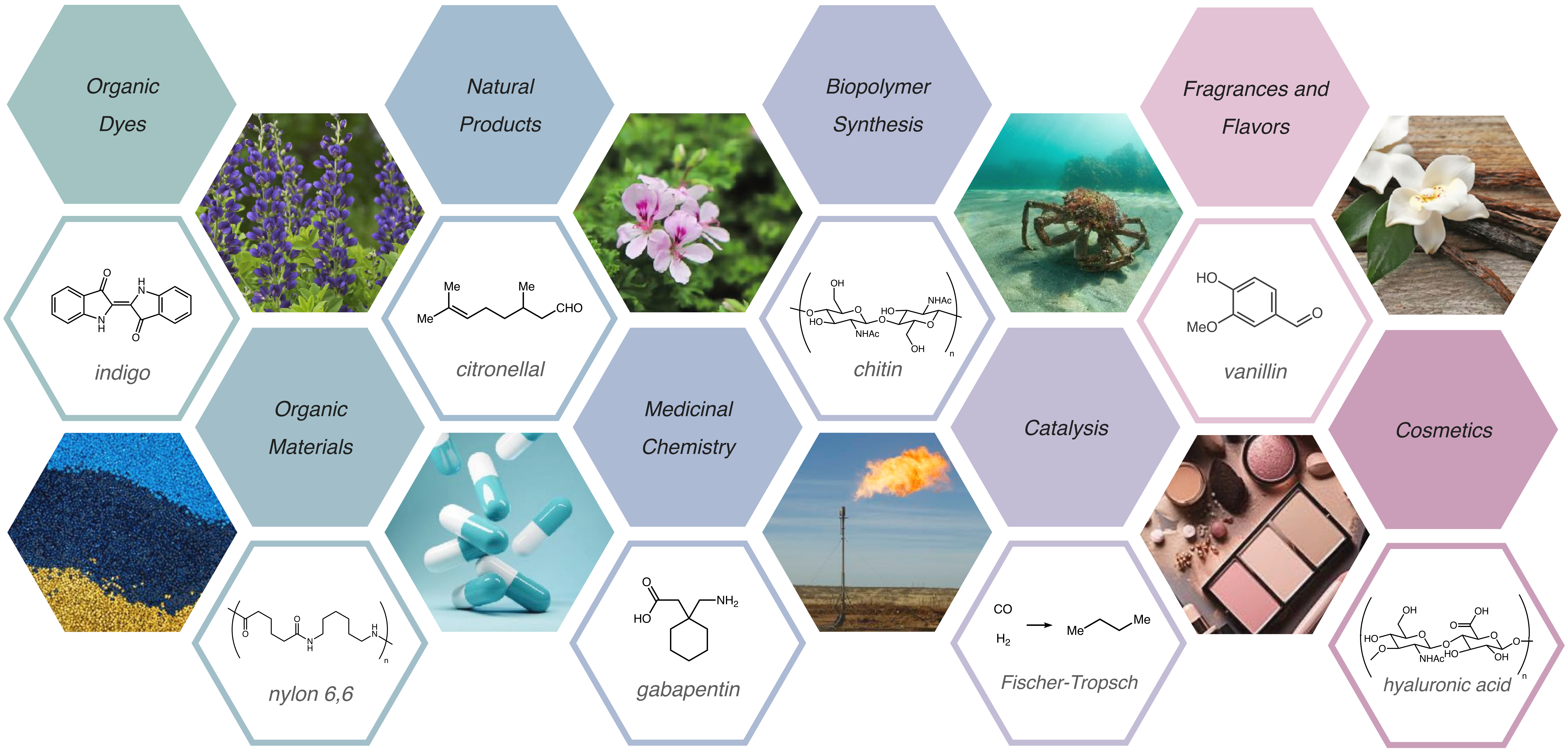
November 1st, 2024

Iona Mathis McWhinnie
MacMillan Group
Princeton University

Organic Synthesis in Society



Organic Synthesis in Society

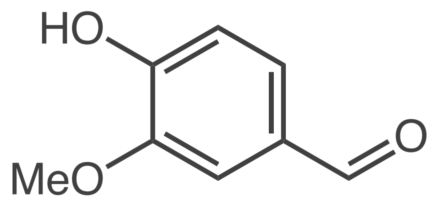


Organic Synthesis in Society

Fragrances and Flavors

Cleaning Products $255.7 Billion

$30.61 Bilion Industry



vanillin

Personal Hygiene & Grooming $592.6 Billion

Cosmetics $308.7 Billion

Outline

The Olfactory Sense

Natural Fragrances

Synthetic Fragrances

- Vanillin
- (–)-Ambrox
- (–)-β-Santalol

Fragrance Discovery

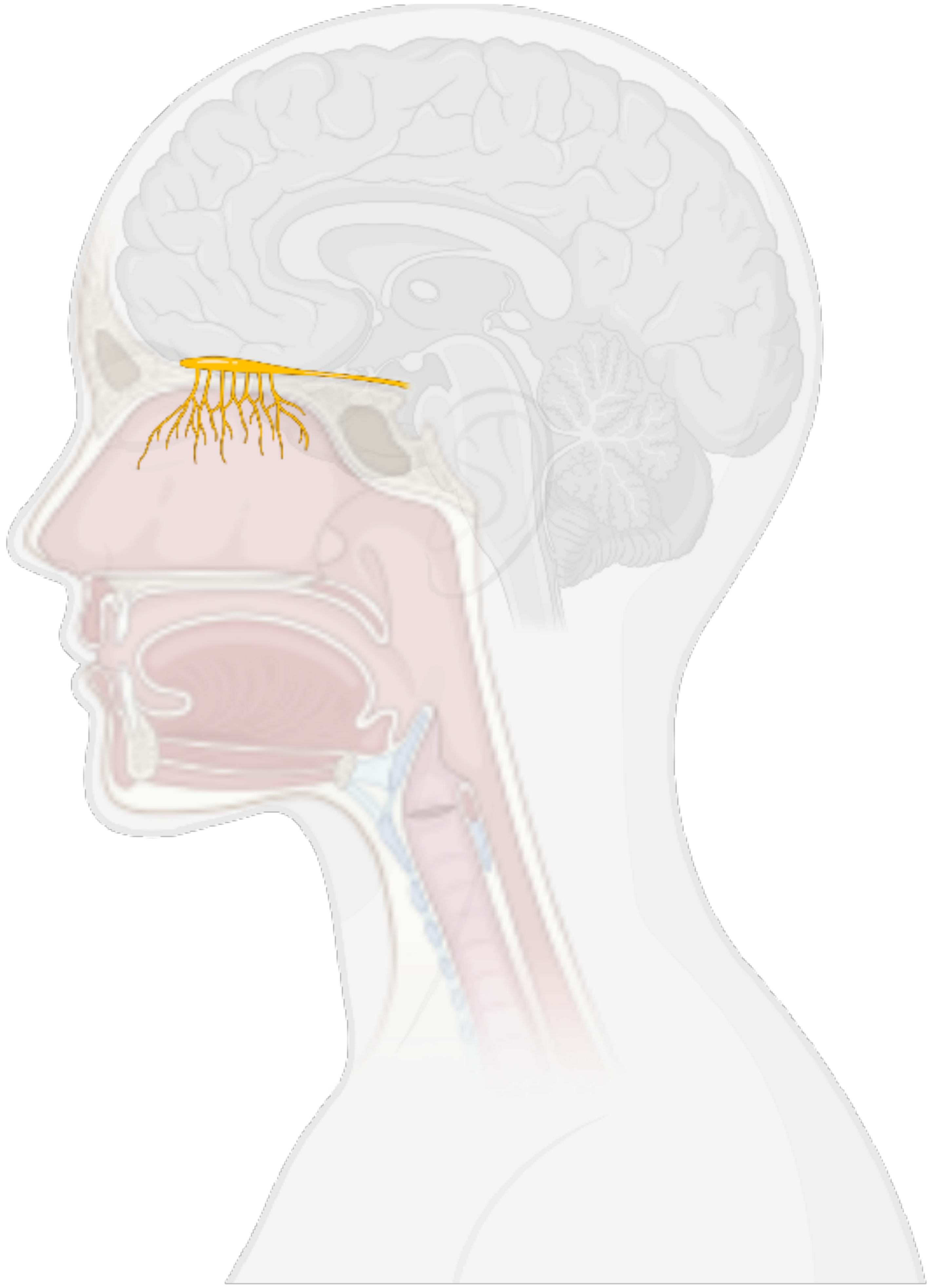
- Discovery of Nympheal

Conclusion and Outlook

The Olfactory Sense

Importance of Olfaction

- food quality
- warning signals
- communication



Requirements for an odorant

- ✓ volatile
- ✓ <300 Da
- ✓ hydrophobic

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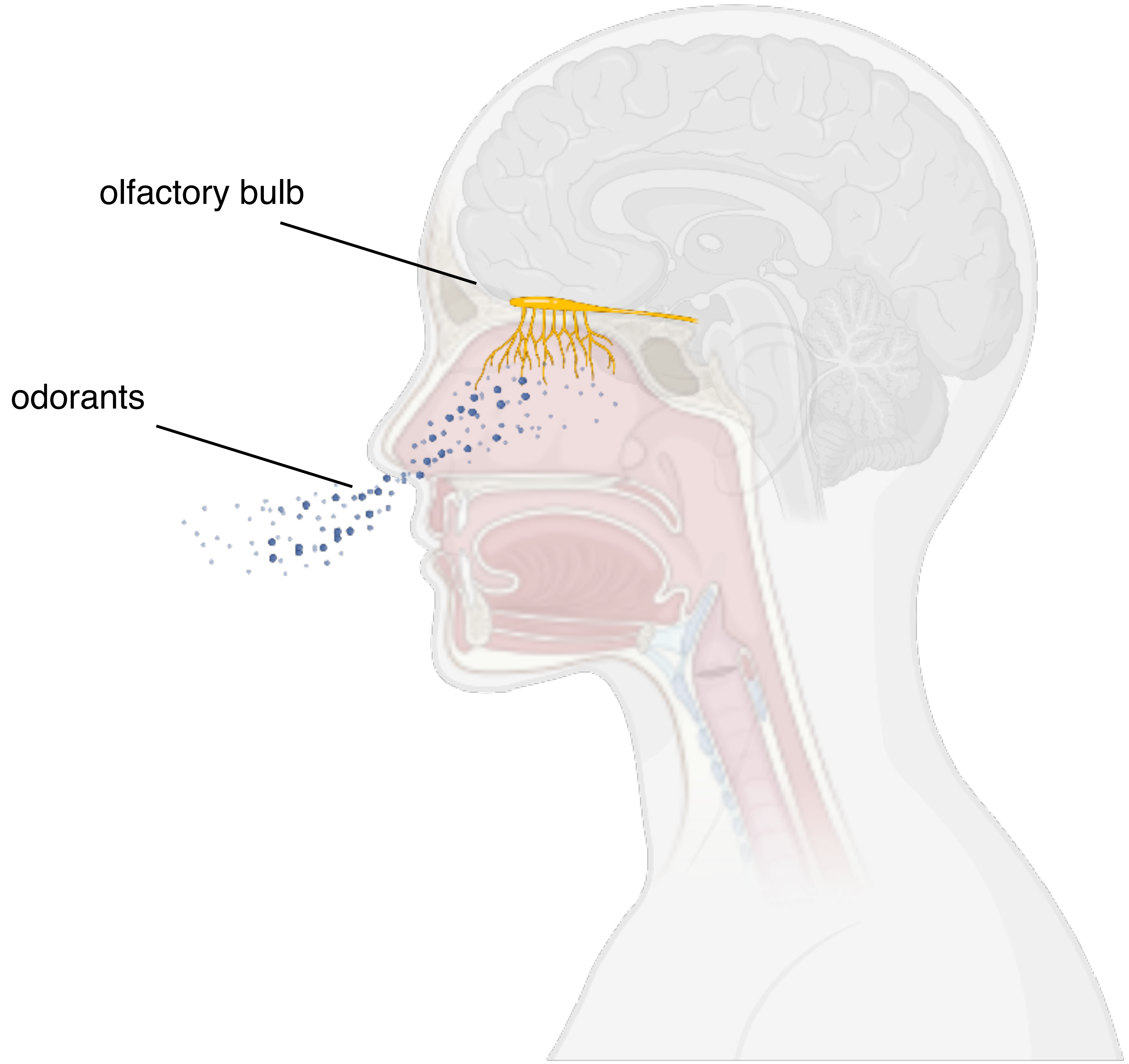
Sell, C. S., *Chemistry of Fragrances*. The Royal Society of Chemistry: 2006.

The Olfactory Sense



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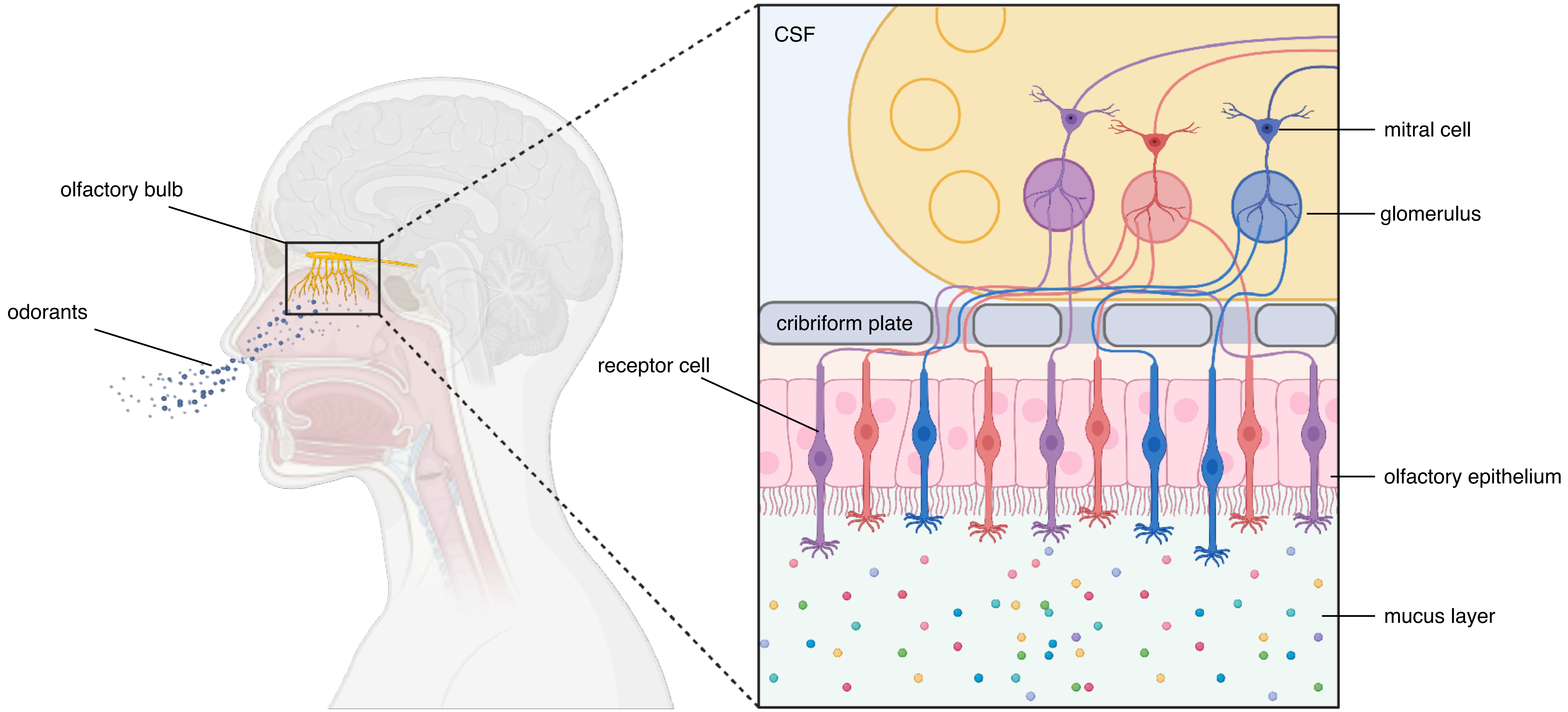
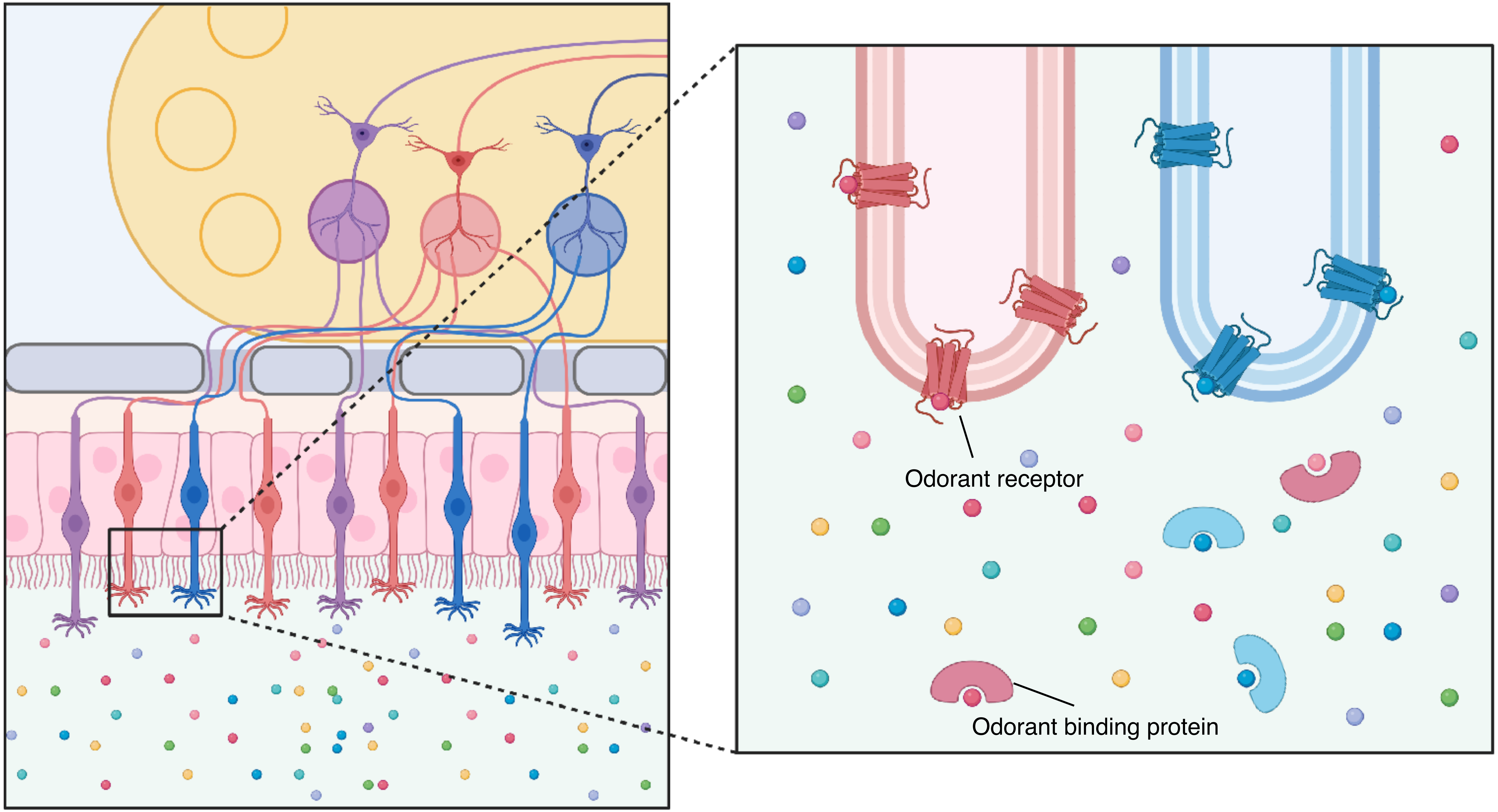


Sharma, A.; Kumar, R.; Aier, I.; Semwal, R.; Tyagi, P.; Varadwaj, P. *Curr Neuropharmacol* **2019,** *17* (9), 891-911.

The Olfactory Sense



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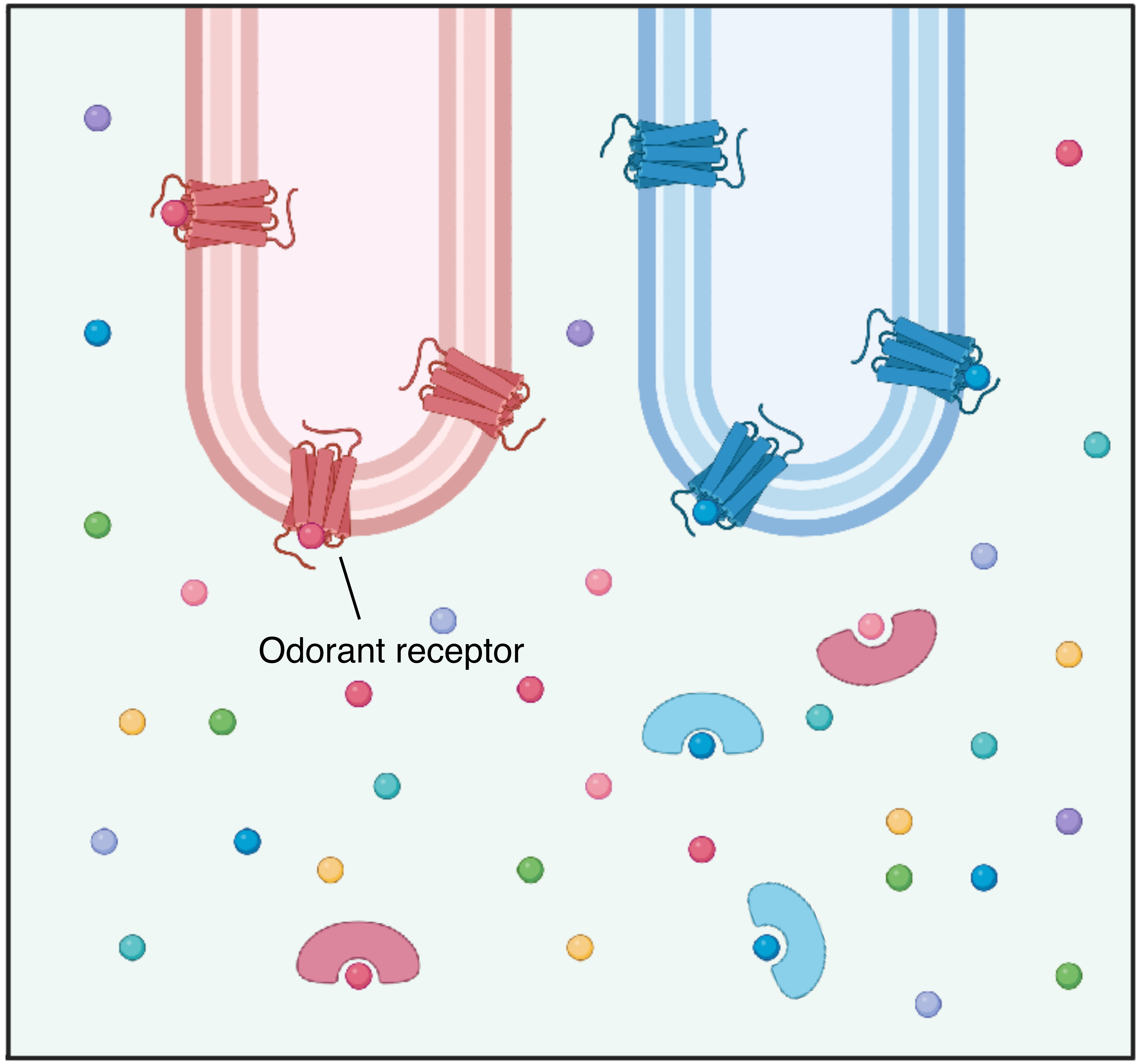


Richard Axel

Linda B. Buck

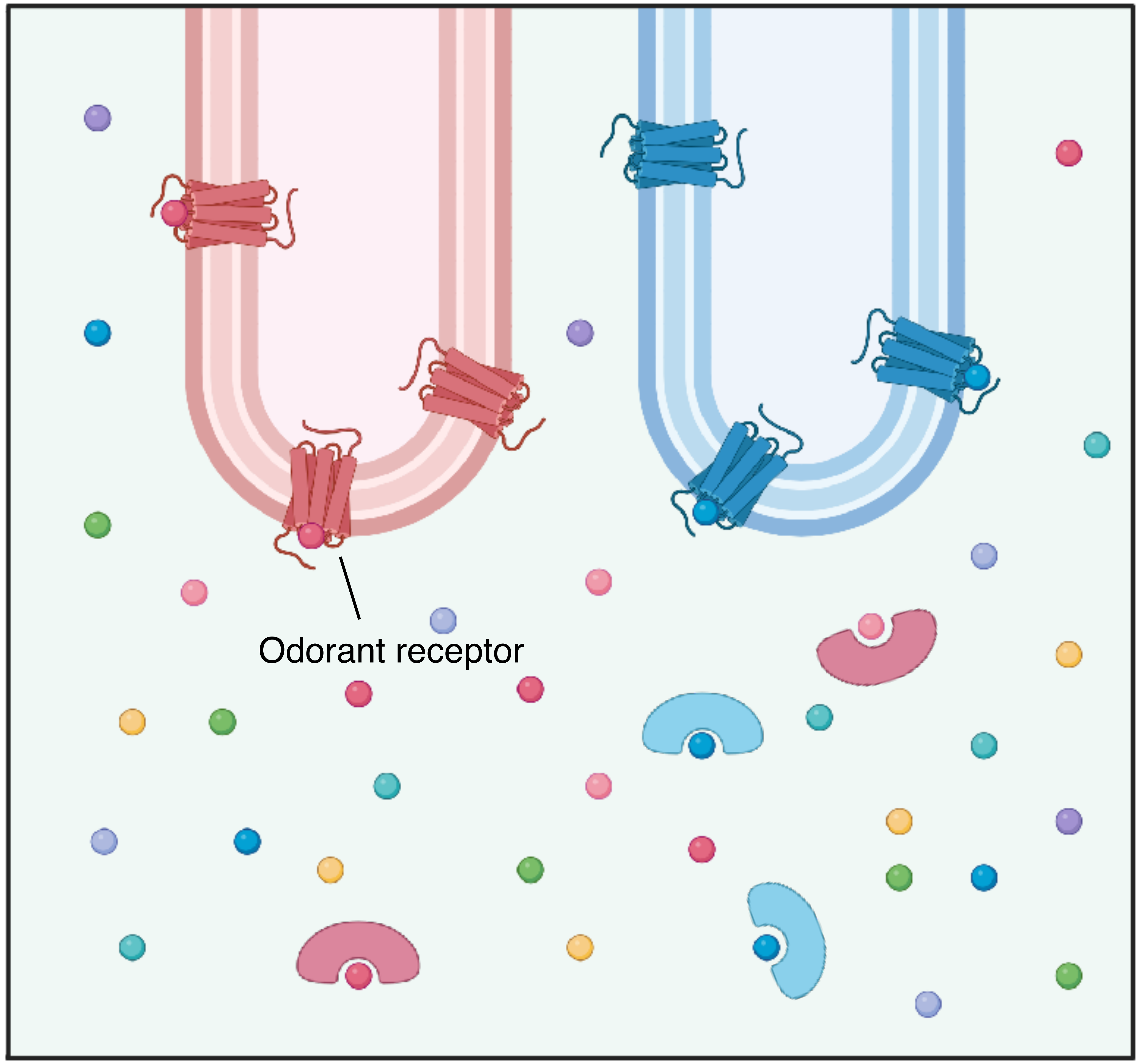
2004 Nobel Prize
in Medicine

"for their discoveries of odorant receptors and the organization of the olfactory system"

Buck L. and Axel R. *Cell*. **1991**, **65**(1),175-187.

https://www.nobelprize.org/prizes/medicine/2004/press-release/

The Olfactory Sense



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"for their discoveries of odorant receptors and the organization of the olfactory system"

- each olfactory cell posses one type of olfactory receptor
- 1000 genes coding for olfactory GPCRs, each responding to a select range of structural features
- a single molecule can activate multiple receptors
- olfactory signaling is combinatorial in nature

Buck L. and Axel R. *Cell*. **1991**, **65**(1),175-187.

https://www.nobelprize.org/prizes/medicine/2004/press-release/

Odorant Receptor Activation

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Odorant Receptor Deactivation

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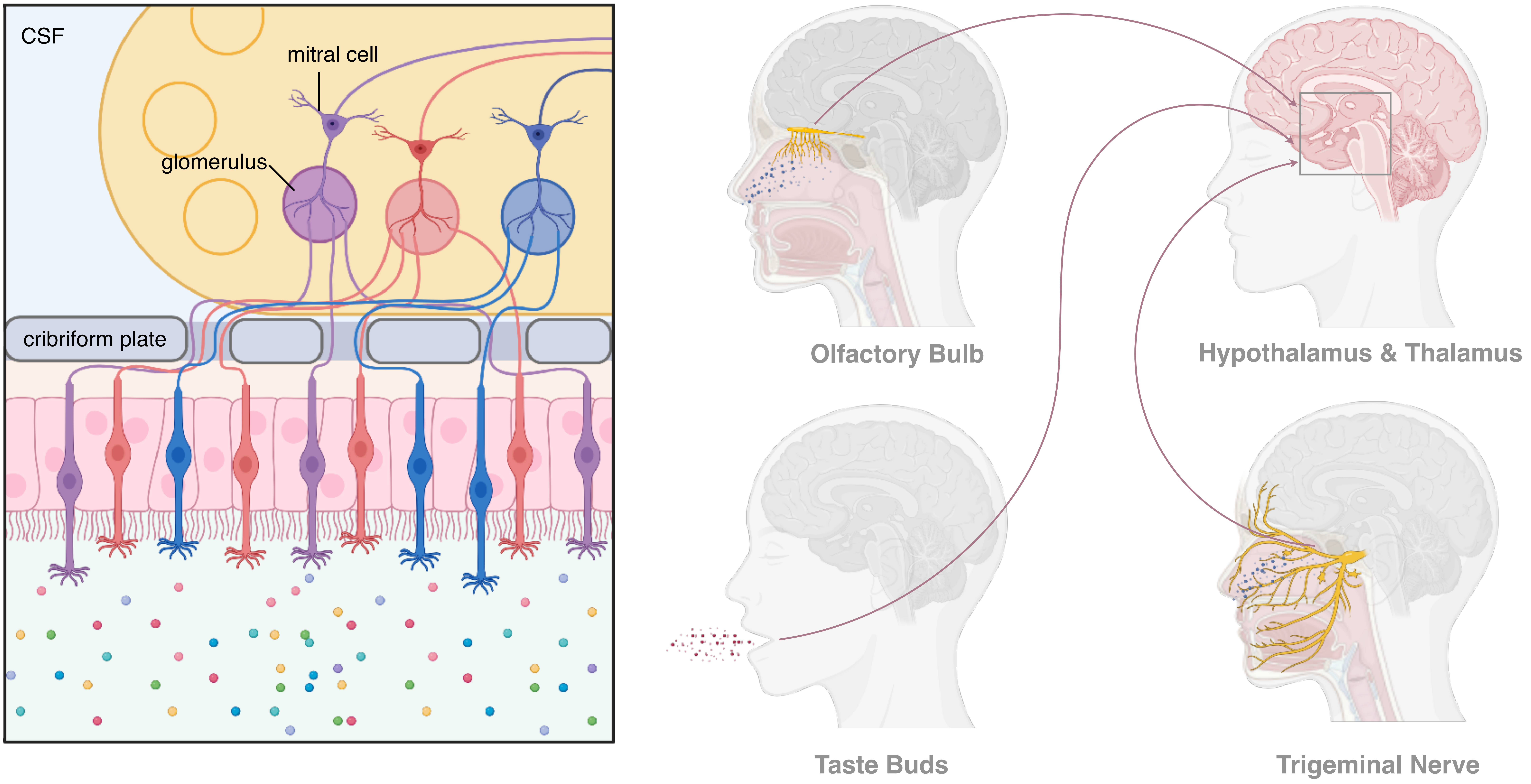

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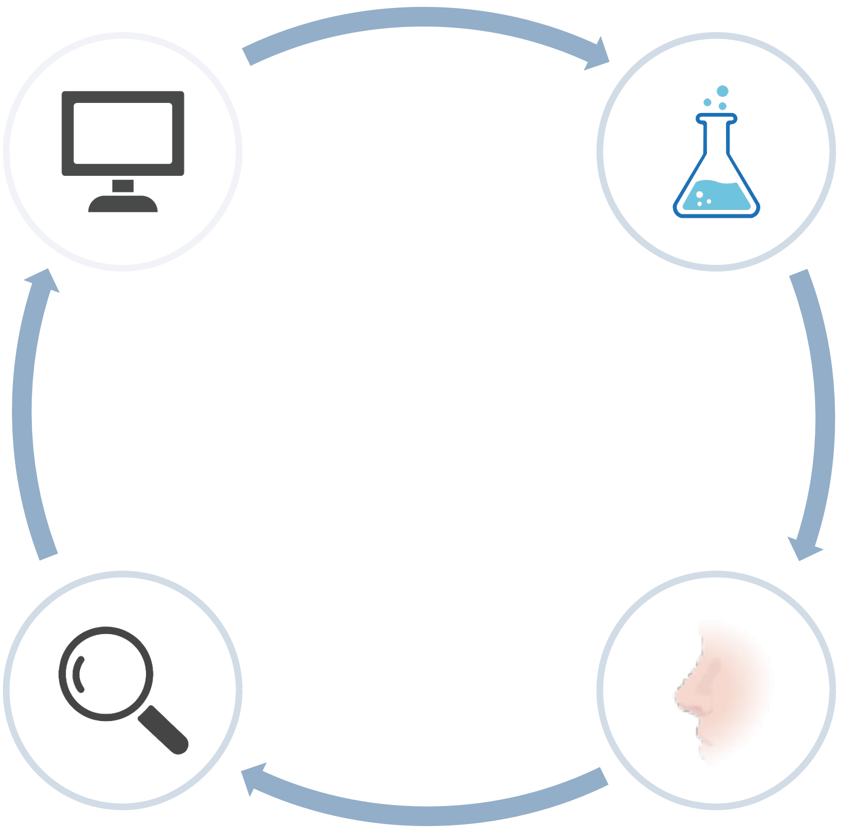
Fragrance Ingredients

Natural Sources

Synthesis



Fragrance Discovery

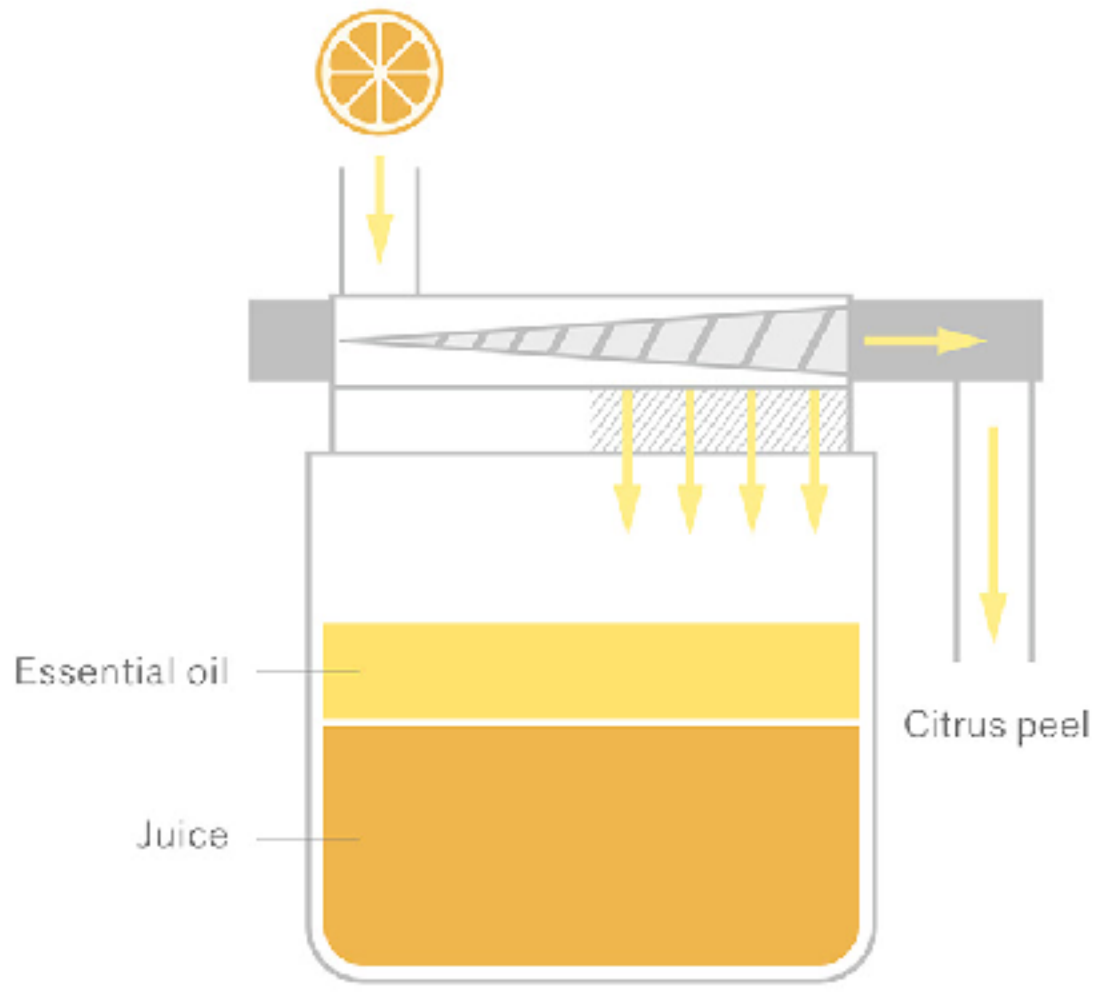
Fragrance Ingredients

Natural Sources

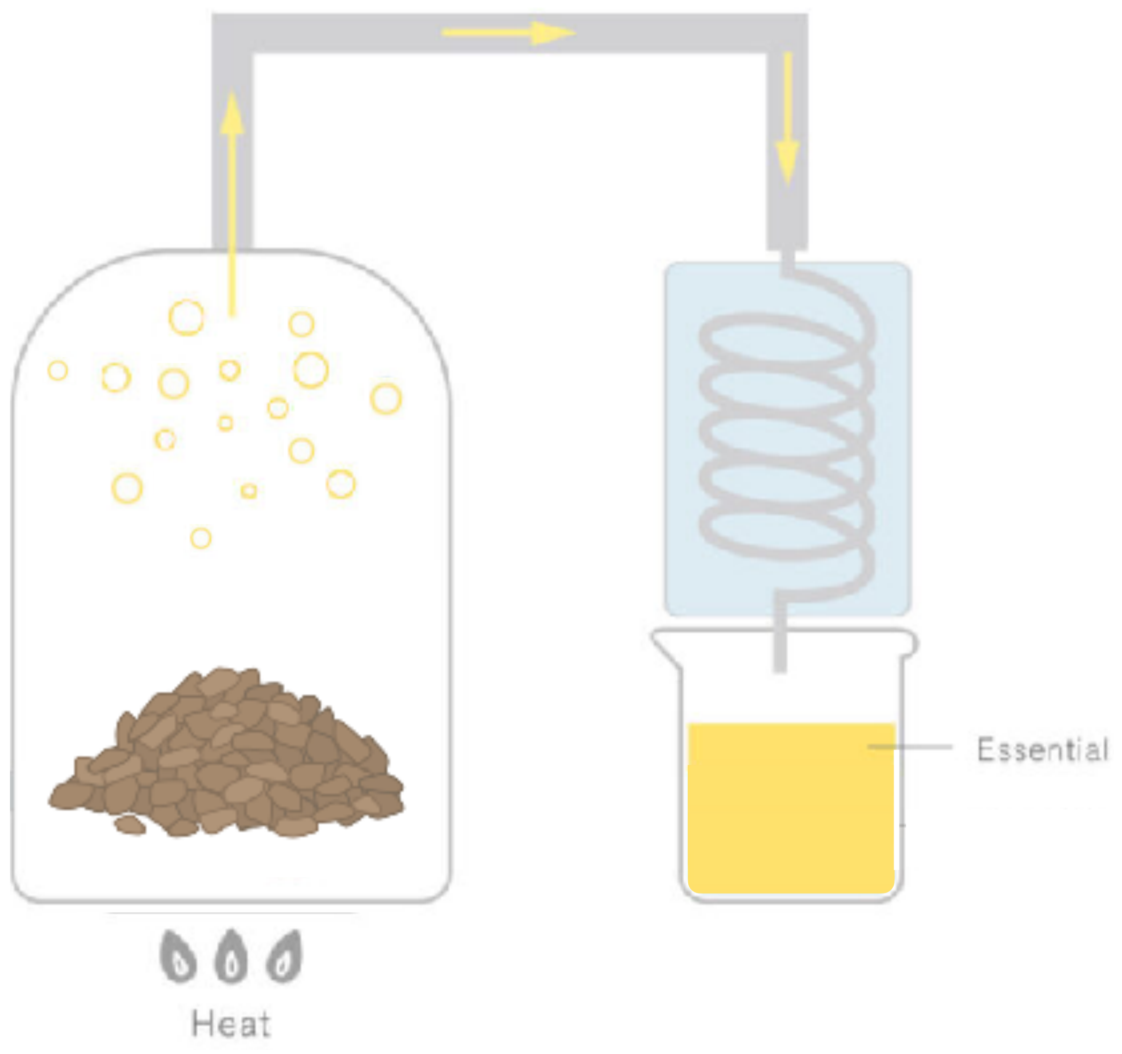
Synthesis

Fragrance Discovery

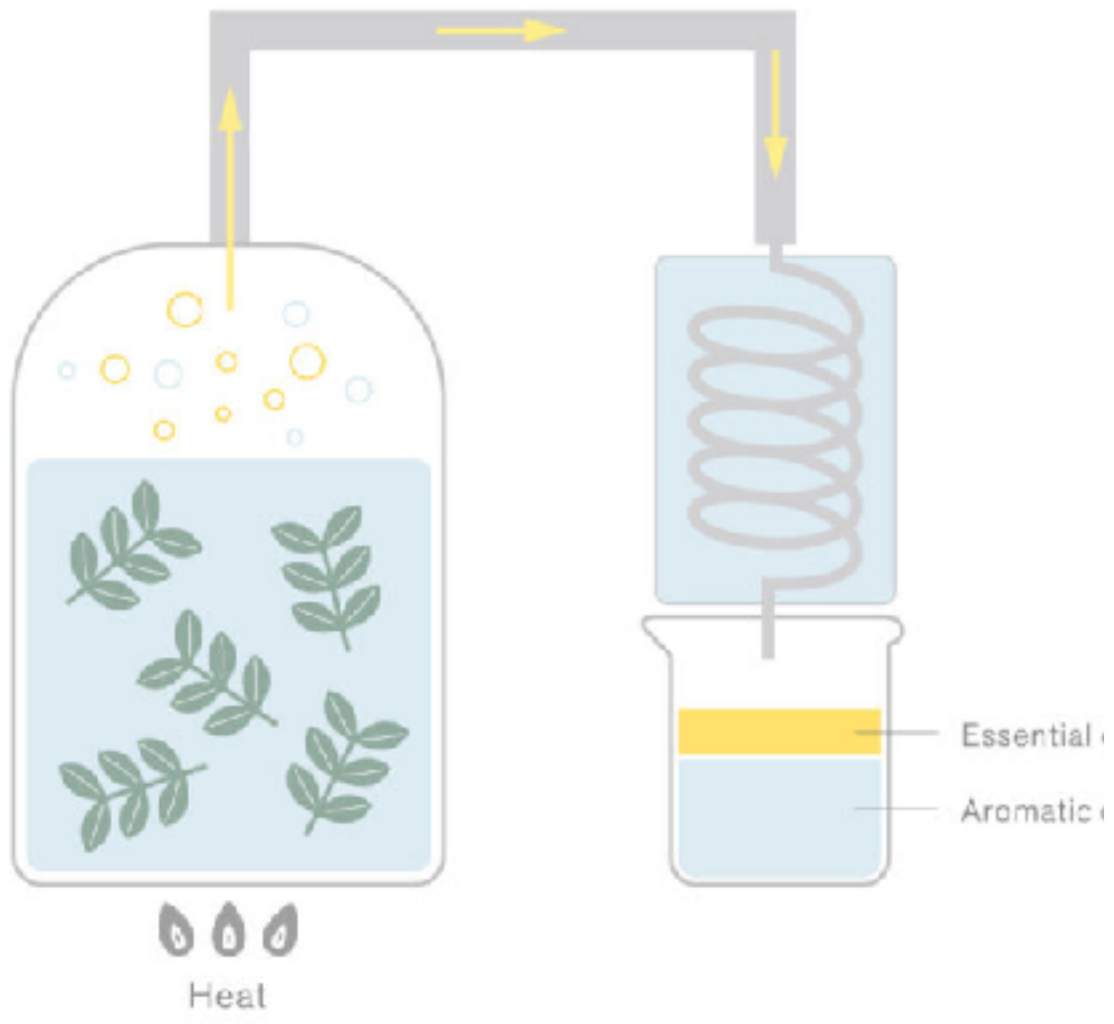
Natural Sources



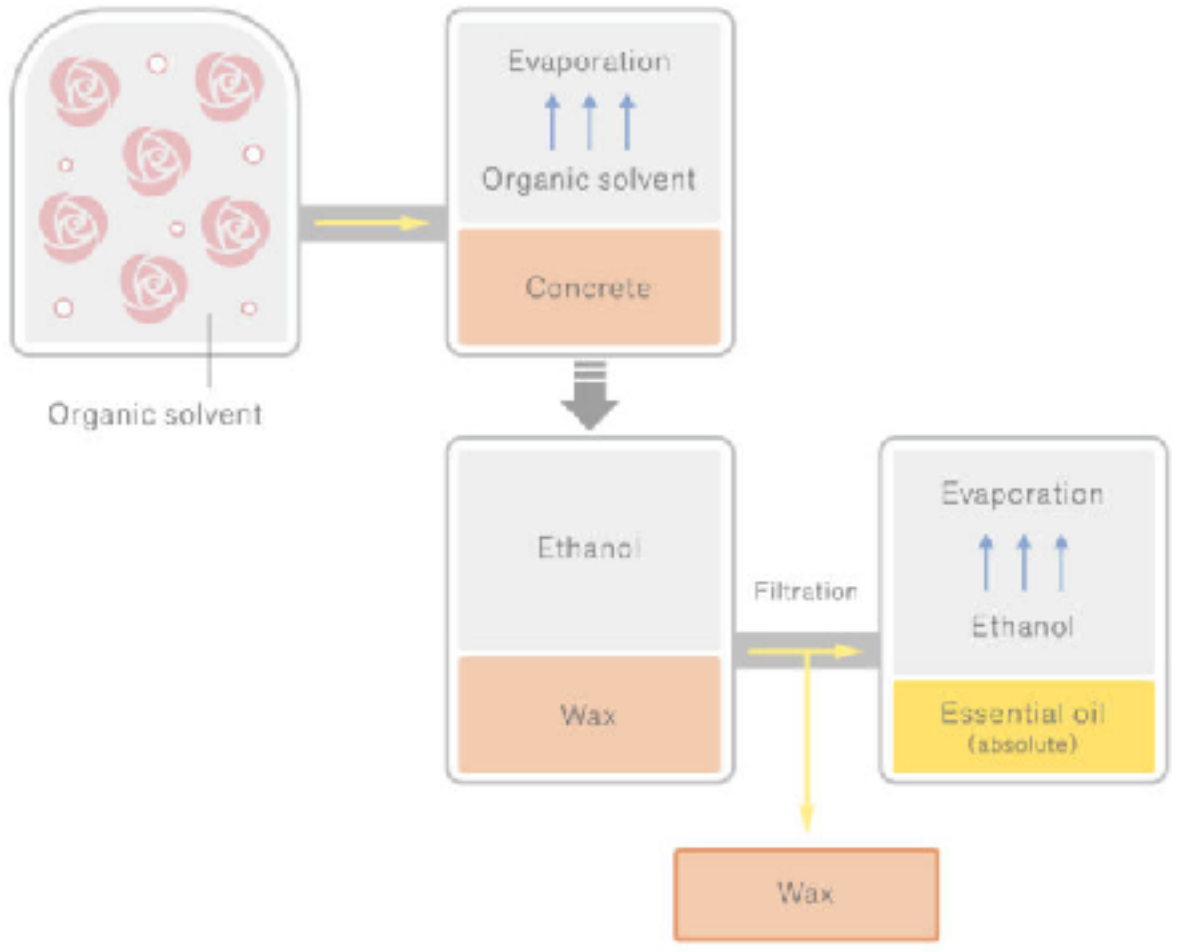
Oil Expression



Dry Distillation



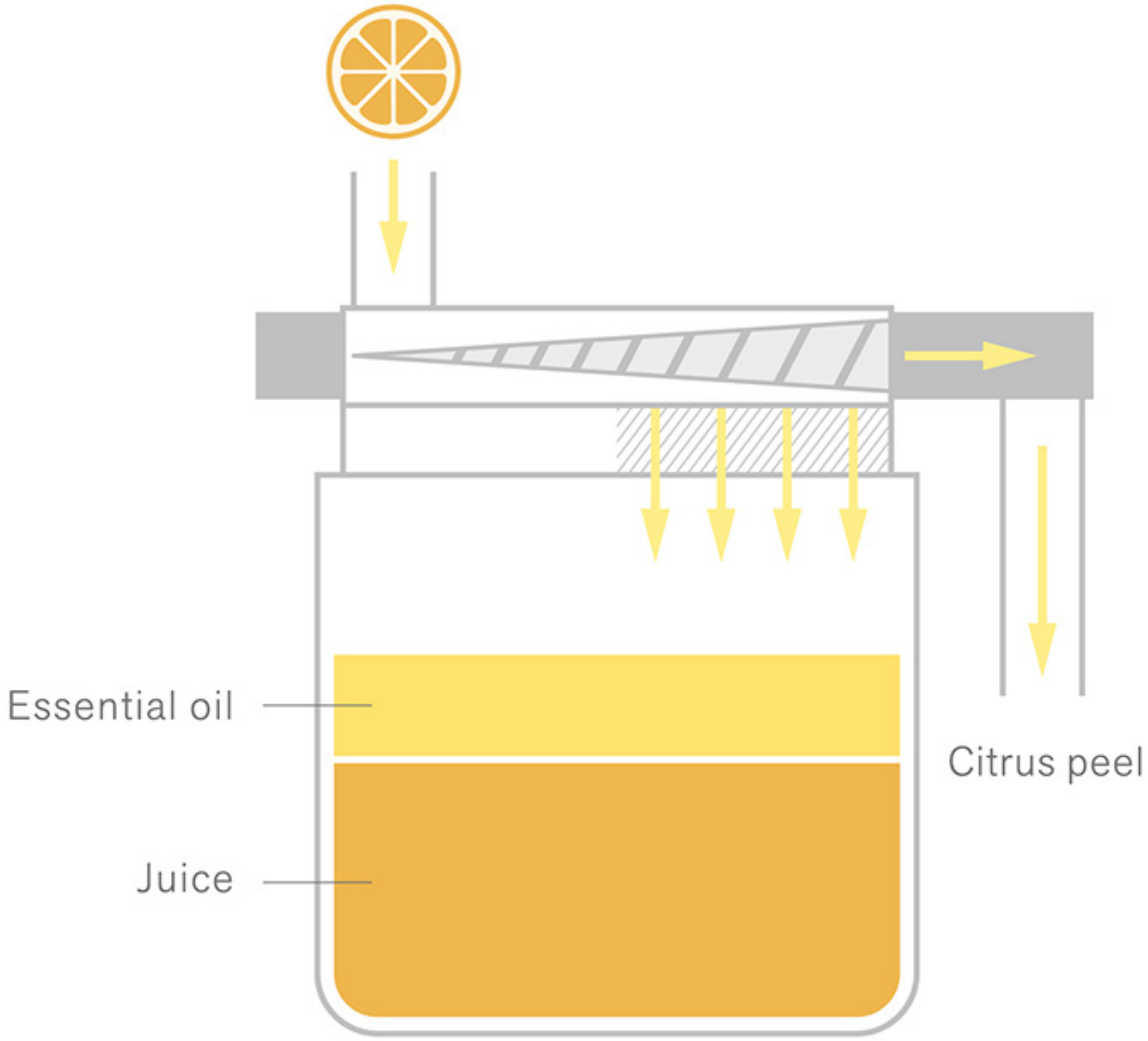
Steam Distillation



Solvent Extraction

Sell, C. S., *Chemistry of Fragrances*. The Royal Society of Chemistry: 2006.

Oil Expression



- Physical pressure applied to produce expressed oil
- Commercial citrus oils

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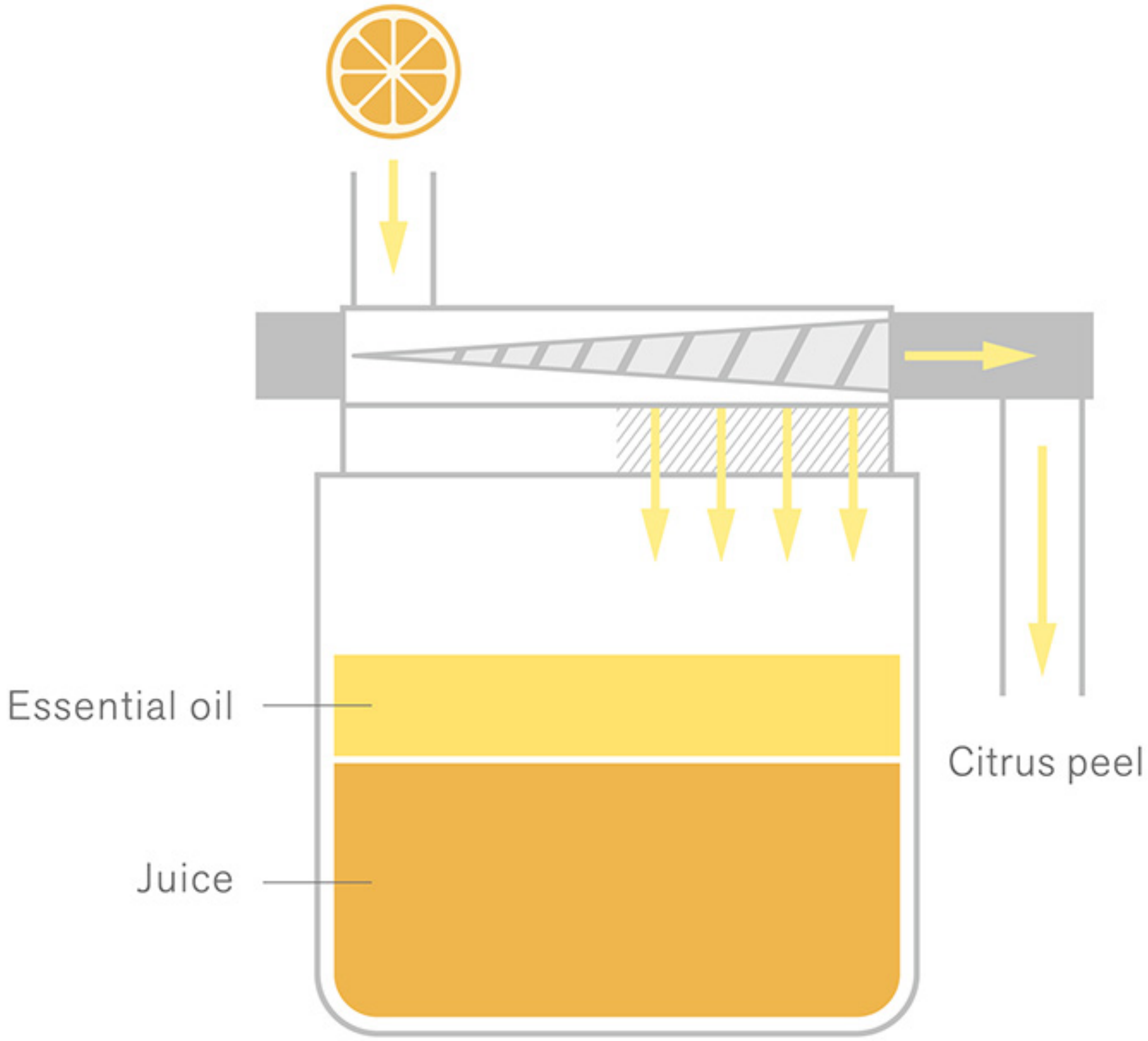
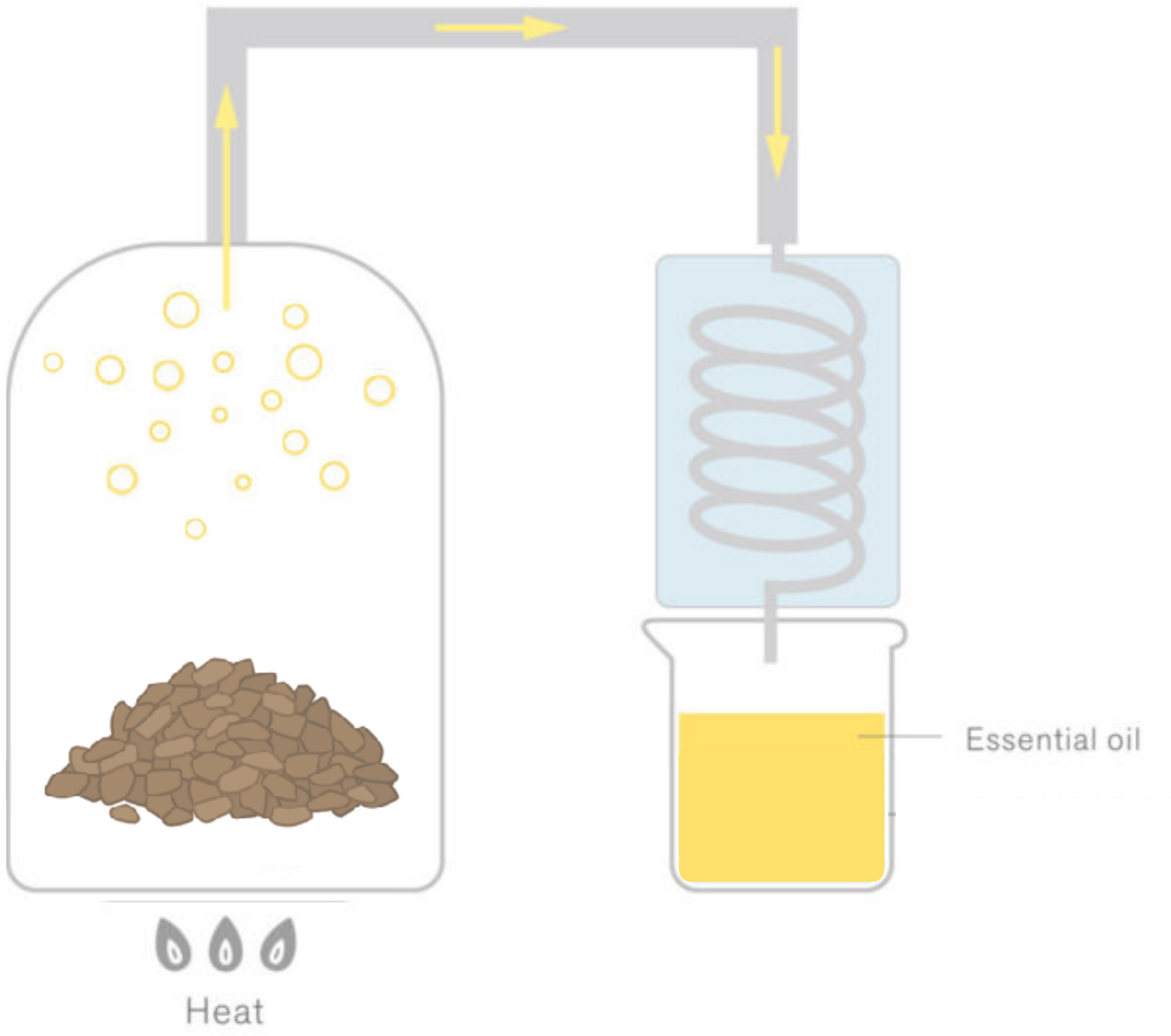
Oil Expression



Dry Distillation



- Heat applied directly to plant material
- Usually reserved for high boiling point wood oils

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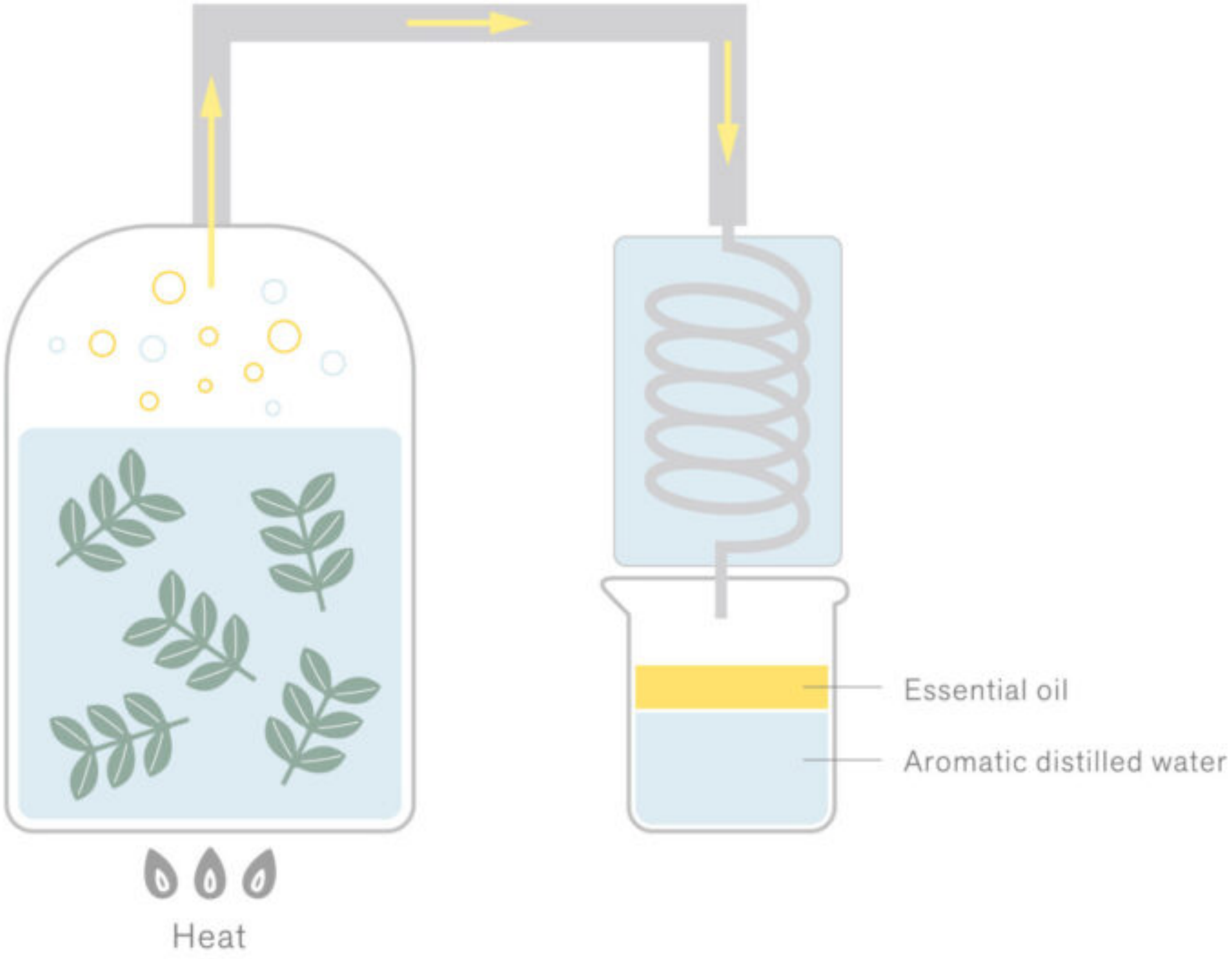
Steam Distillation



- Water or steam added to material, co-distilled with oil
- Minimal degradation due to temperature ceiling

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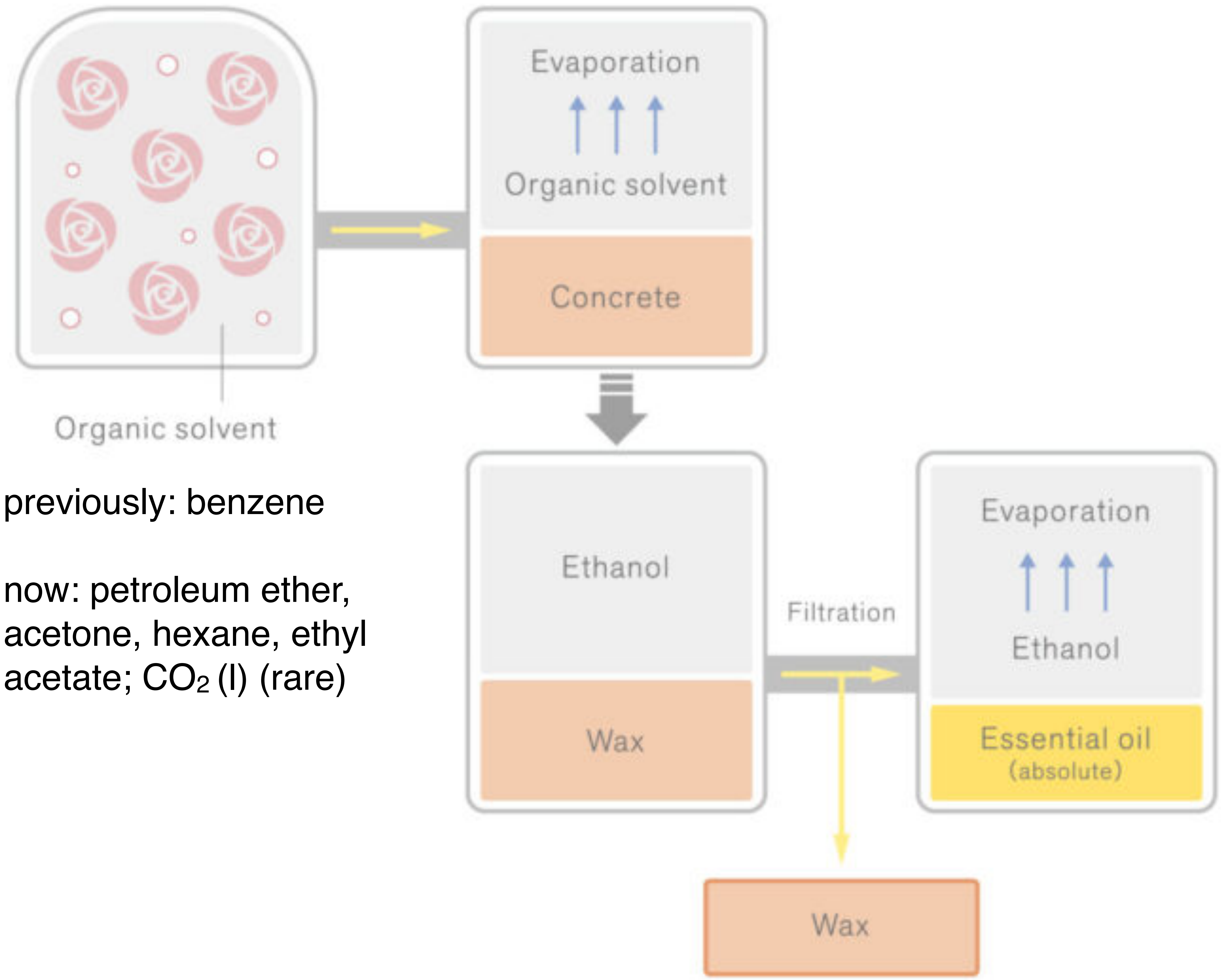
Solvent Extraction

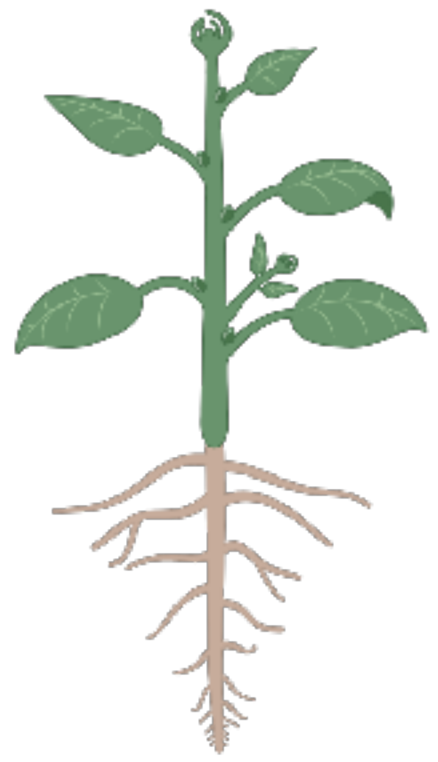


- previously: benzene
- now: petroleum ether, acetone, hexane, ethyl acetate; CO_2 (l) (rare)

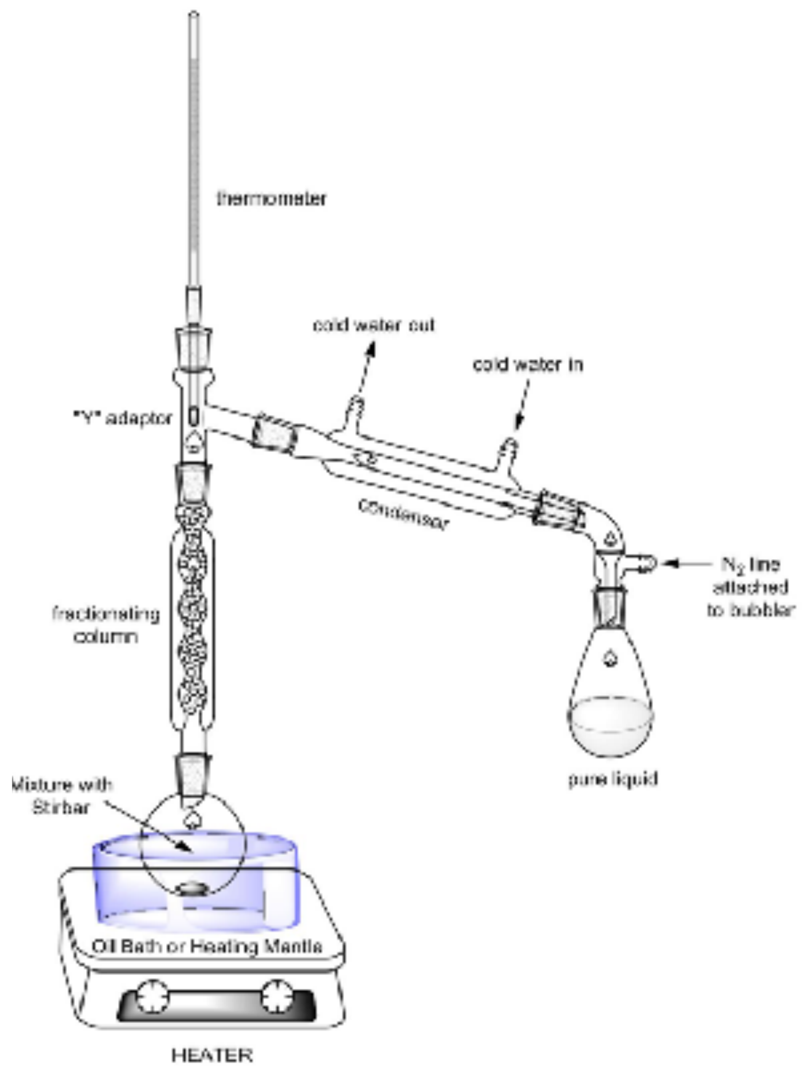
- most important extraction method
- produces an absolute (residual solvent may be present)

Sell, C. S., *Chemistry of Fragrances*. The Royal Society of Chemistry: 2006.

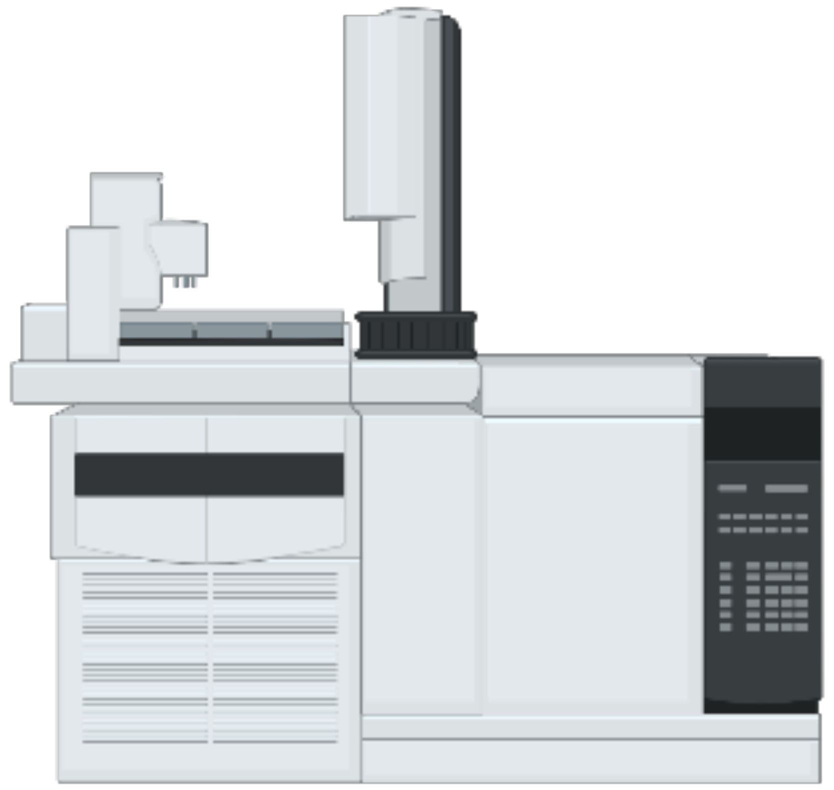
Essential Oil Analysis



Plant material



Fractional distillation



GC–MS

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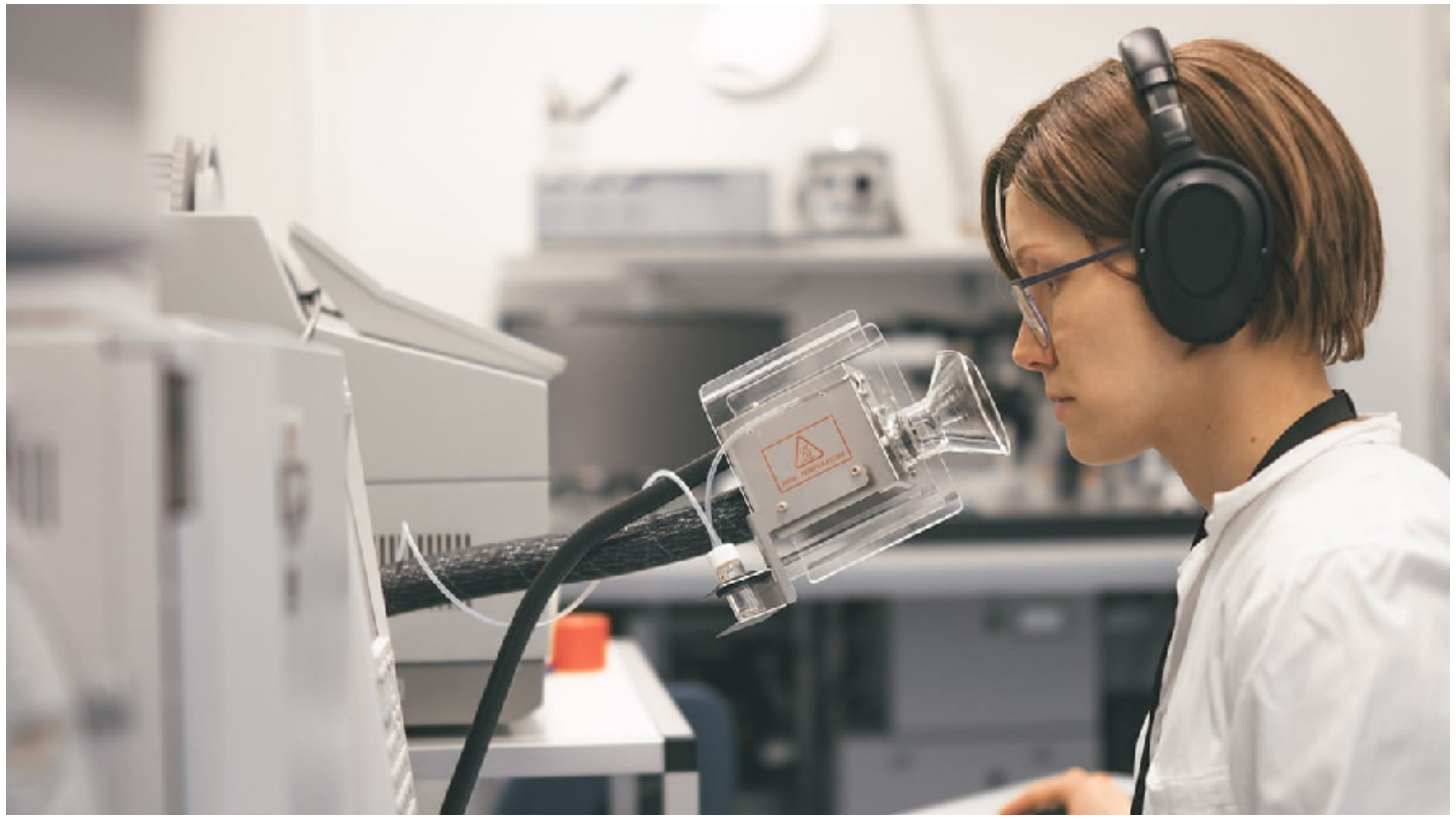
GC-Sniffing



GC-Olfactometry or GC-Sniffing

- Column effluent split between detector and smelling port
- Human nose can be more sensitive to certain materials than some detectors

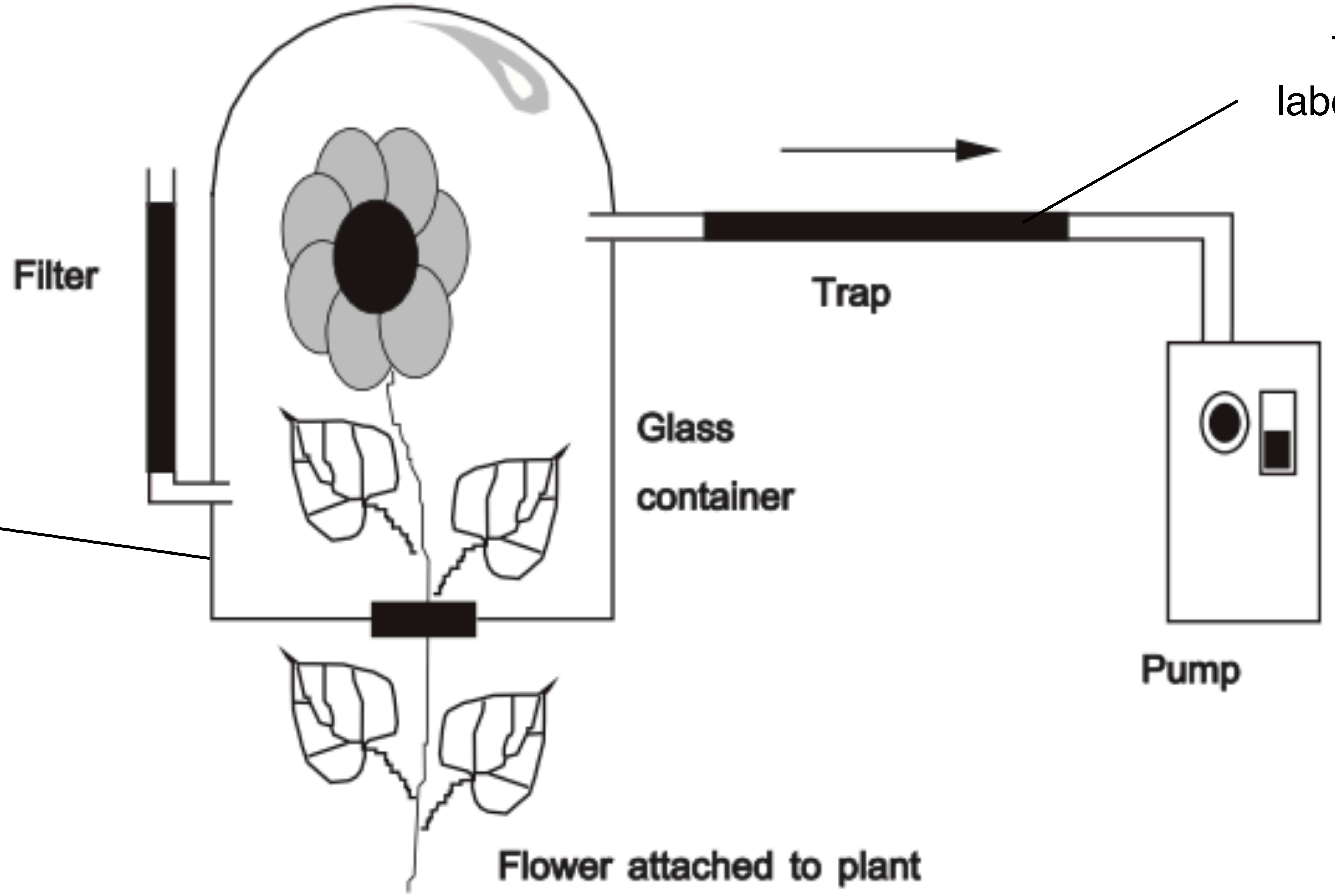
Sell, Charles S. *Fundamentals of fragrance chemistry*. John Wiley & Sons, 2019.

Headspace Analysis

Headspace: air above or around a fragrant substance that contains volatile compounds

Transported back to laboratory for GC analysis

Portable device allows for non-destructive analysis



- Fragrance can be collected on-site anywhere in the world
- Useful when solvent extracts cannot reproduce natural scent

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Fragrance Ingredients

Natural Sources

Synthesis

Fragrance Discovery

Why Make Synthetic Fragrances?

Sustainability

- unfavorable carbon footprints
- Low yielding and unsustainable land and water usage

Cost

- Significant material burden; not atom economical
- Manual labor costs for growing and harvesting

Security of Supply

- Limited availability for plants growing in select regions
- Supply dependent on weather and affected by natural disasters

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Why Make Synthetic Fragrances?

Sustainability

Cost

Security of Supply

"Natural isn't always better"

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Vanillin

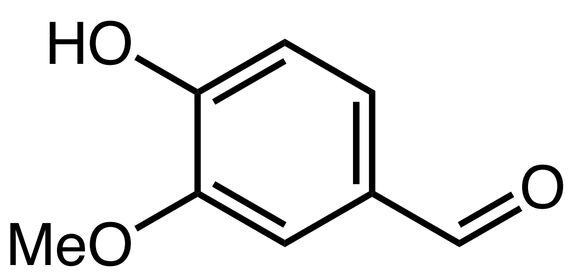
From Vanilla to Vanillin

Vanilla planifolia

Native to the tropical forests of Mexico, Central and and northern south Africa

Vanilla Pods (1.7-2.8% vanillin)

Dried, cured, and extracted for the production of vanilla extract



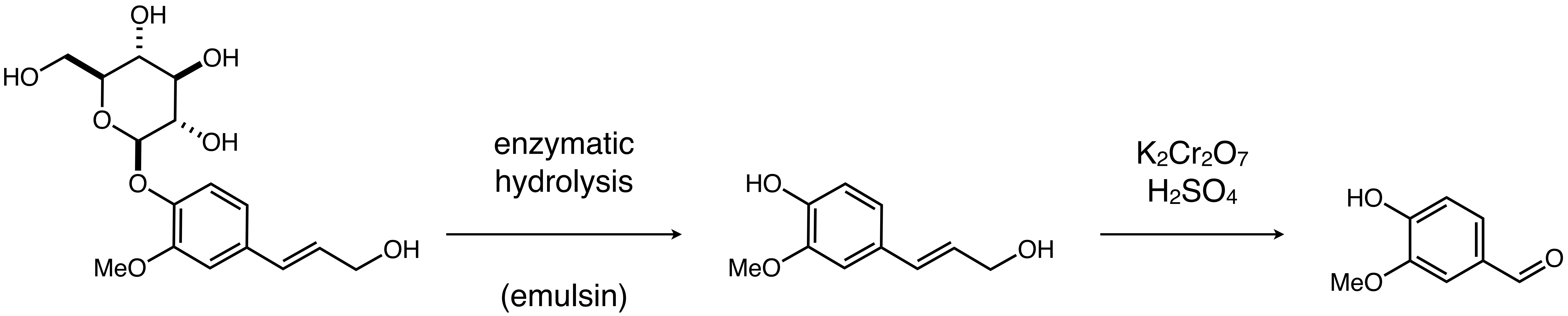
Vanillin

First isolated in 1858
by Théodore Nicolas Goblet

D'Arrigo, P.; Rossato, L. A. M..; Serra, S. *Molecules*. **2024**, *29*(2), 442.

First Synthesis of Vanillin – 1874

Wilhelm Haarmann
1847–1931



coniferin *coniferyl alcohol* *vanillin*

Beta-D-glucopyranoside

Haarmann & Reimer

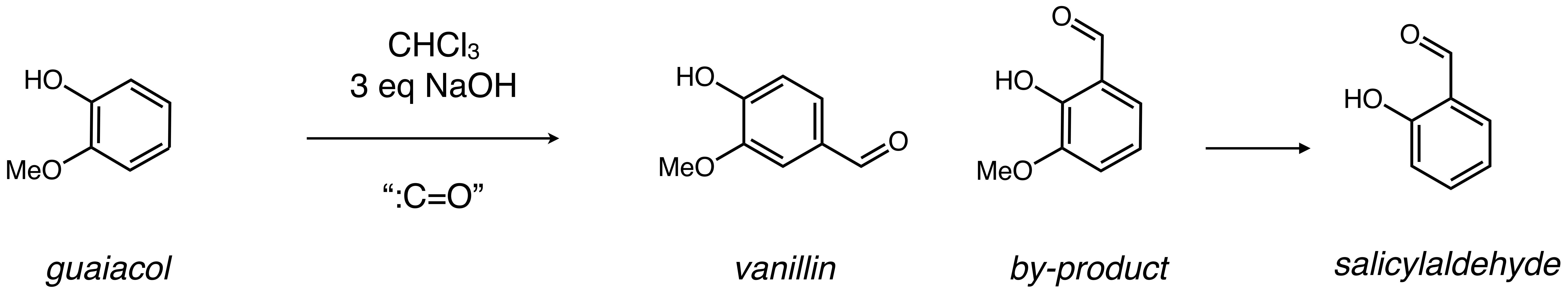
First Route for the Industrial Production of Vanillin

- ✗ Labor intensive
- ✗ Minimal cost benefits

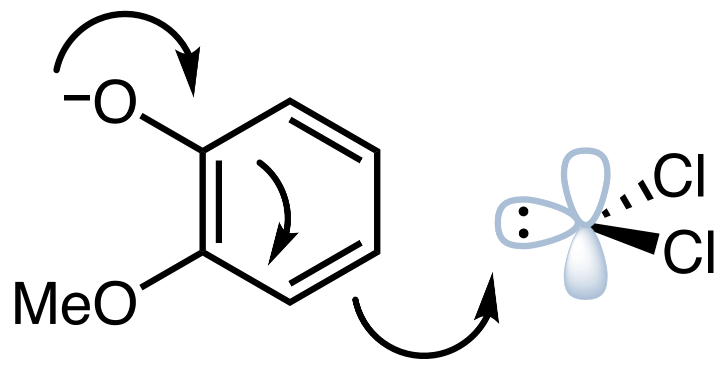
Elterlein, F.; Bugdahn, N.; Kraft, P. *Chem. Eur. J.* **2024**, *30*, e202400006.

Petrochemical Vanillin – 1876

Karl Ludwig Reimer
1845-1883



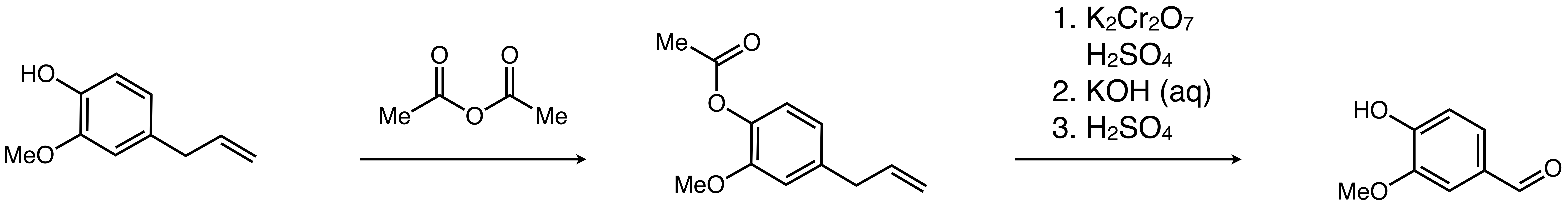
Reimer–Tiemann Reaction



- ✗ Difficult to separate
- ✗ Salicylate odor

Elterlein, F.; Bugdahn, N.; Kraft, P. *Chem. Eur. J.* **2024**, *30*, e202400006.

Haarmann–Reimer Collaboration – 1876



eugenol

70-95% in clove oil
Easily isolated by distillation

eugenyl acetate

vanillin

✓ Abundant starting material

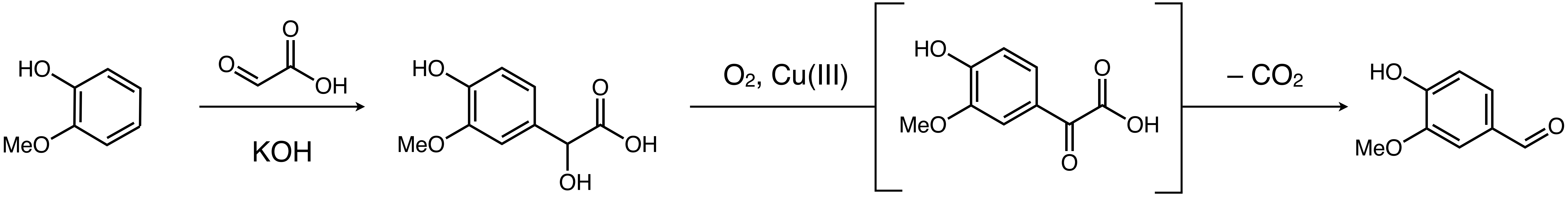
✗ Chromium

Produced on an Industrial Scale

Elterlein, F.; Bugdahn, N.; Kraft, P. *Chem. Eur. J.* **2024**, *30*, e202400006.

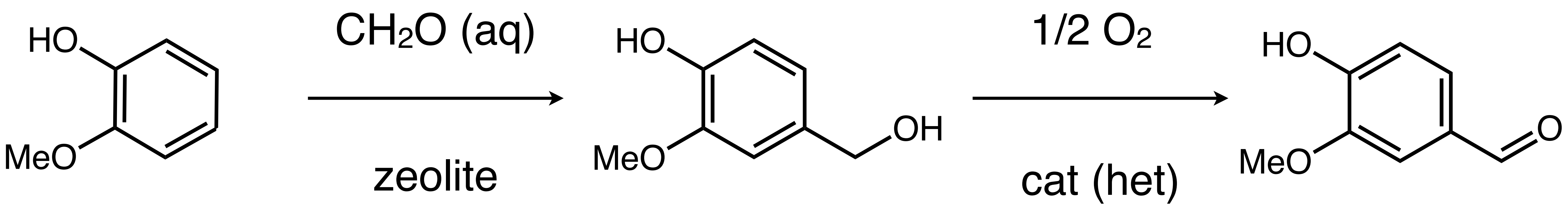
Modern Routes

Rhône-Poulenc (now Solvay)



guaiacol *vanillylmandelic acid* *vanilglycolic acid* *vanillin*

Solvay



guaiacol *vanillyl alcohol* *vanillin*

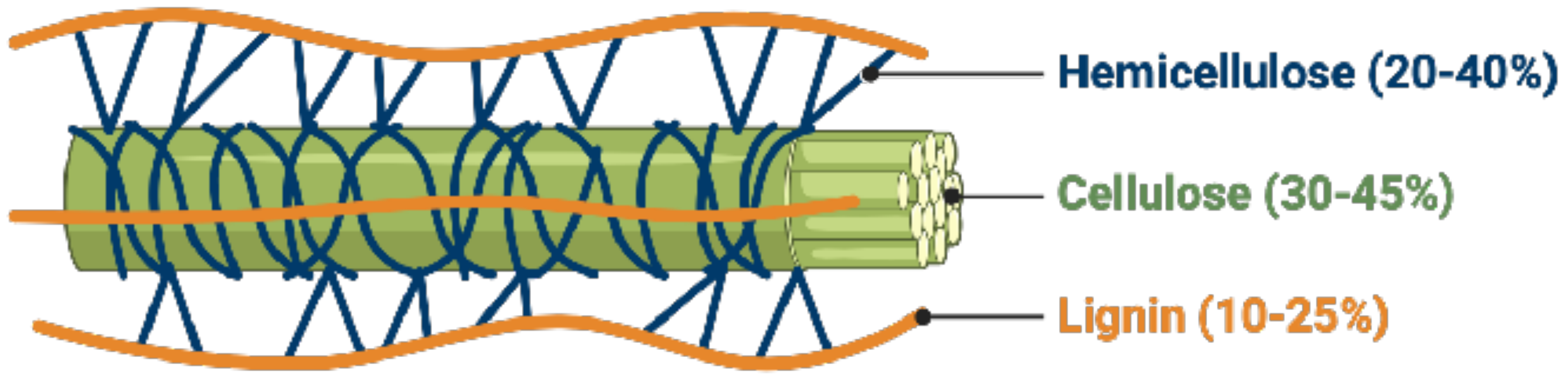
✓ Atom economical

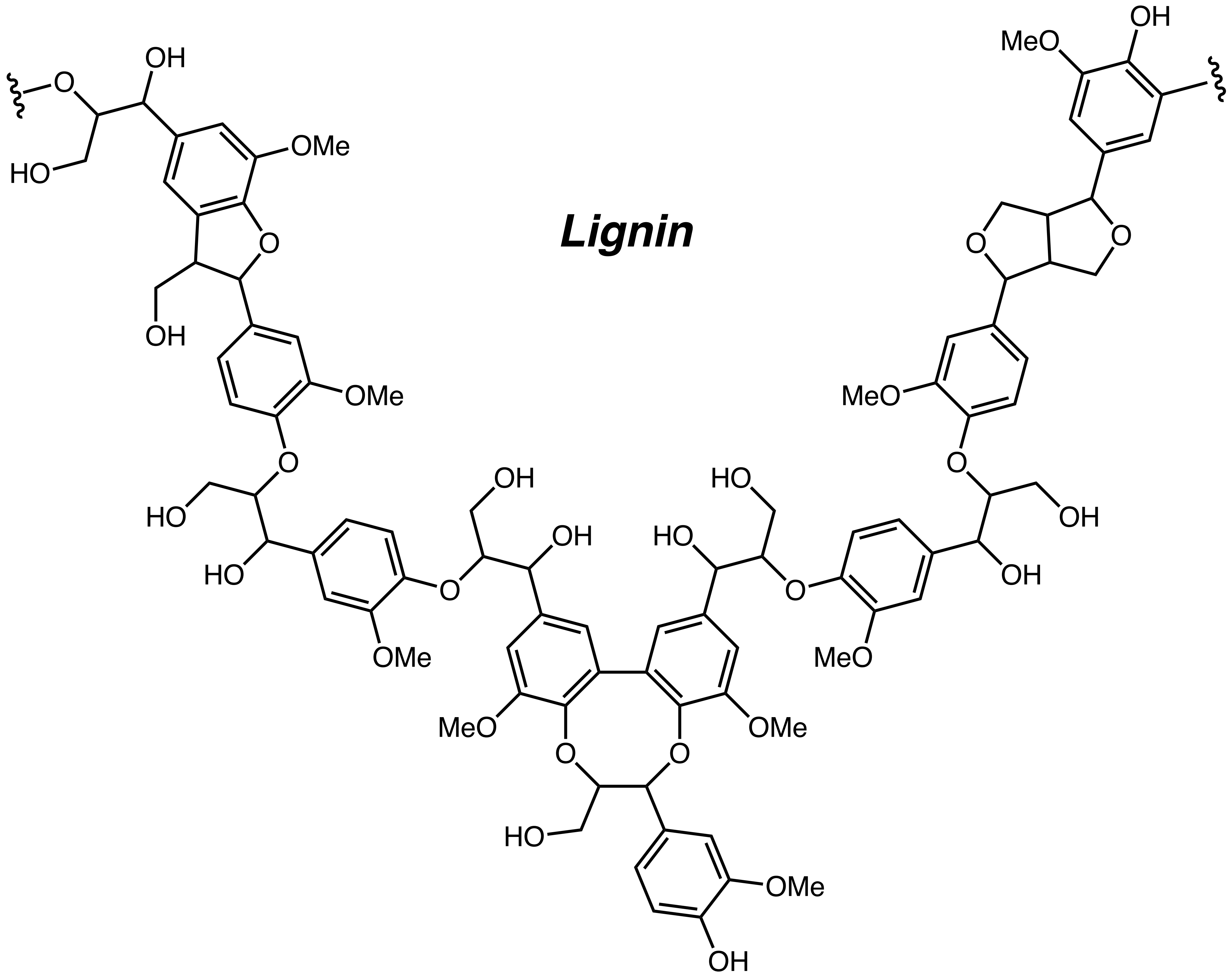
✗ Non-renewable starting material

Schaefer, Bernd. Natural products in the chemical industry. Vol. 831. Heidelberg: Springer, 2014.

D'Arrigo, P.; Rossato, L. A. M..; Serra, S. *Molecules*. **2024**, *29*(2), 442.

Modern Syntheses of Vanillin – Lignin

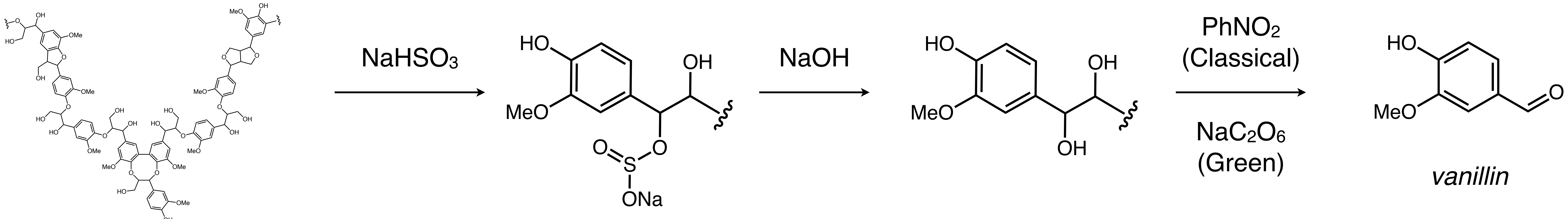




undesired waste material in paper and pulp industry

D'Arrigo, P.; Rossato, L. A. M.; Serra, S. *Molecules*. **2024**, *29*(2), 442.

Modern Syntheses of Vanillin – Lignin



Lignin

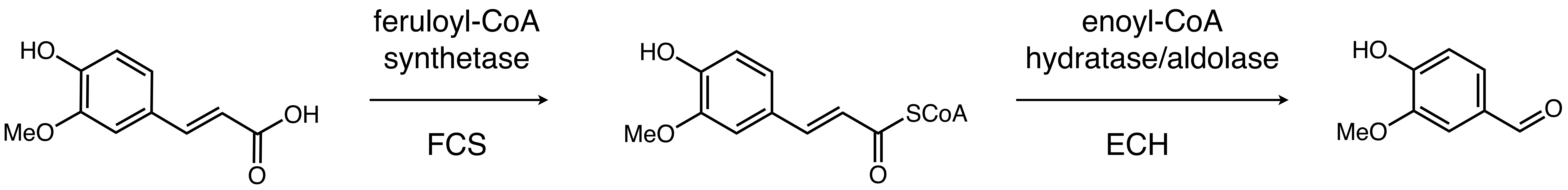
sodium lignosulfate

- ✓ Renewable starting material
- ✓ Cost effective

D'Arrigo, P.; Rossato, L. A. M..; Serra, S. *Molecules*. **2024**, *29*(2), 442.

Enzymatic Productions

The Rhodia Process



ferulic acid *feruloyl CoA* *vanillin*

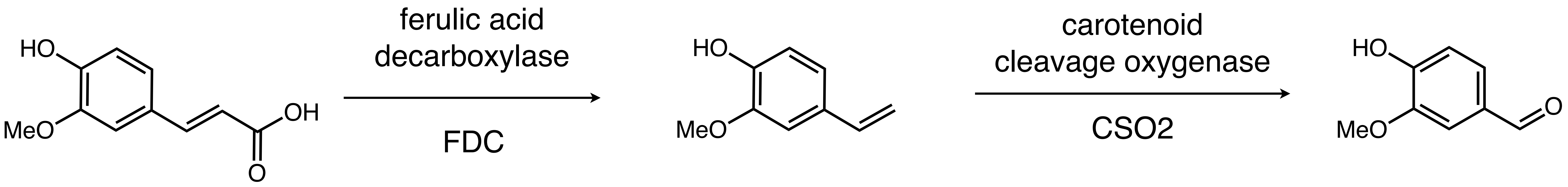
Rhovanil Natural

- whole cell *E. coli* catalyst

✗ Expensive co-factor

✓ can be labeled as natural flavoring

Cost-Efficient Upgrade



ferulic acid *genome mining* *4-vinylguaiacol* *vanillin*

✓ No co-factor

Lee, E.G.; Yoon, S.H.; Das, A.; Lee, S.H.; Li, C.; Kim, J.Y.; Choi, M. S.; Oh, E. K.; Kim, S. W. *Biotechnol Bioeng*. **2009**, *102*(1), 200.

Furuya, T.; Miura, M.; Kuroiwa, M.; Kino, K. *New Biotechnology*. **2015**, *32*(3), 335.

(–)-Ambrox

Ambergris to Ambrox

Digestive Tract Injuries

Sperm Whale (*Physeter macrocephalus)*

Ambergris – "floating gold"

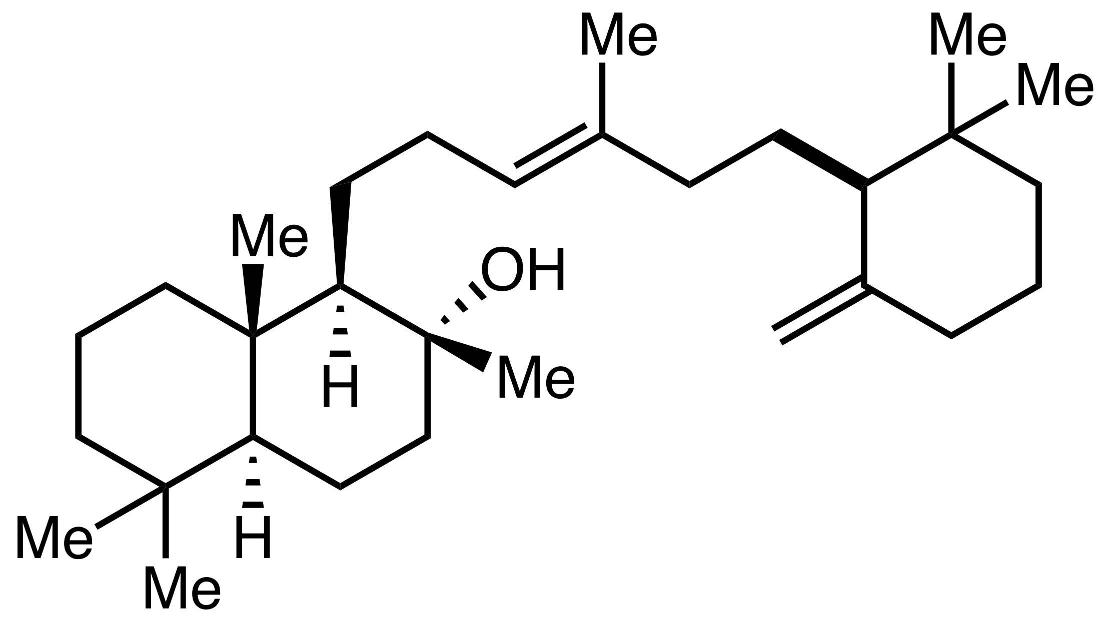
up to $40,000 per kg

Elterlein, F.; Bugdahn, N.; Kraft, P. *Chem. Eur. J.* **2024**, *30*, e202400006.

Ambergris to Ambrox

Max Stoll
1899–1969

ambergris tincture



ambreine (odorless)
25-45% in ambergris

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Ambergris to Ambrox

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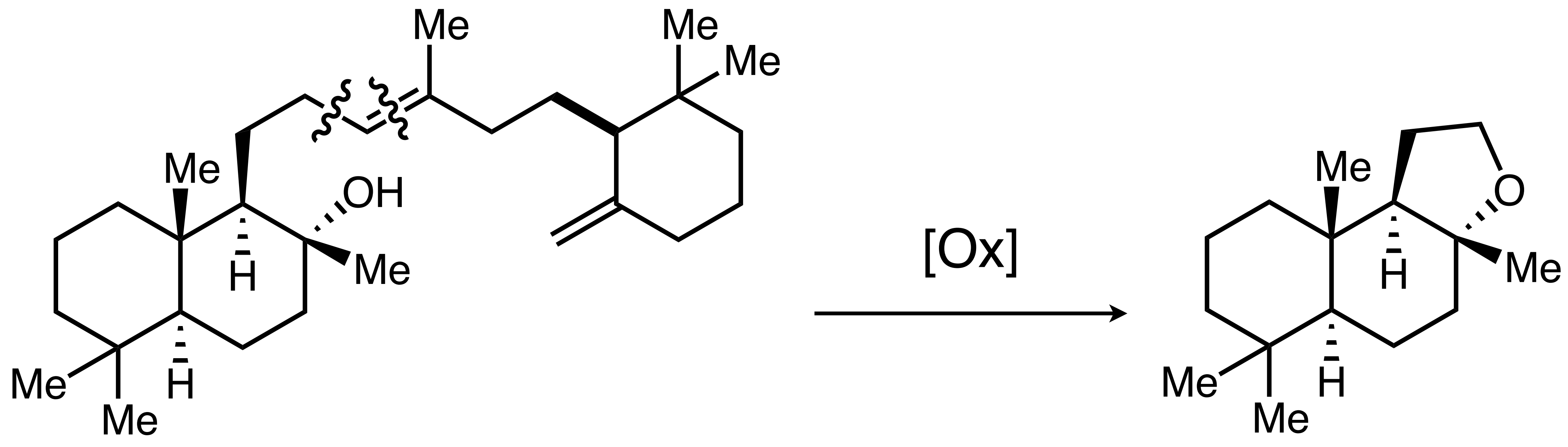

ambreine (odorless)
25-45% in ambergris

(–)-Ambrox (smelling principle)
trace in ambergris

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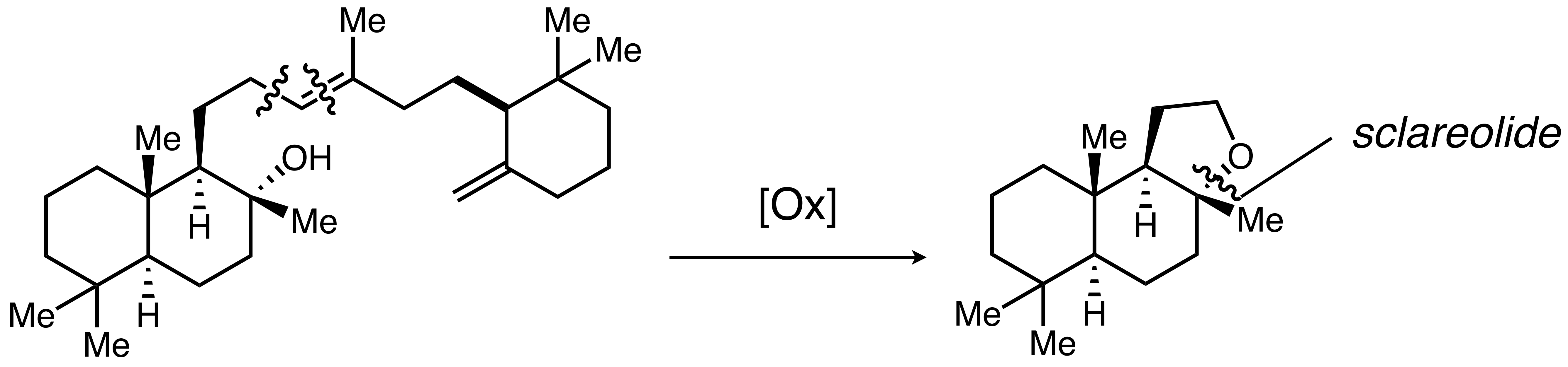
Ambergris to Ambrox

Max Stoll
1899–1969

ambergris tincture



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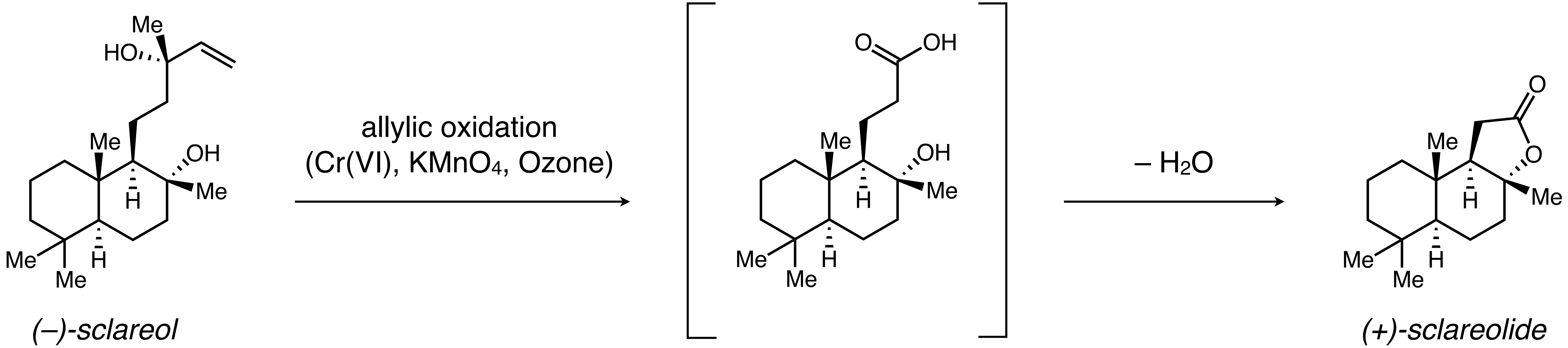
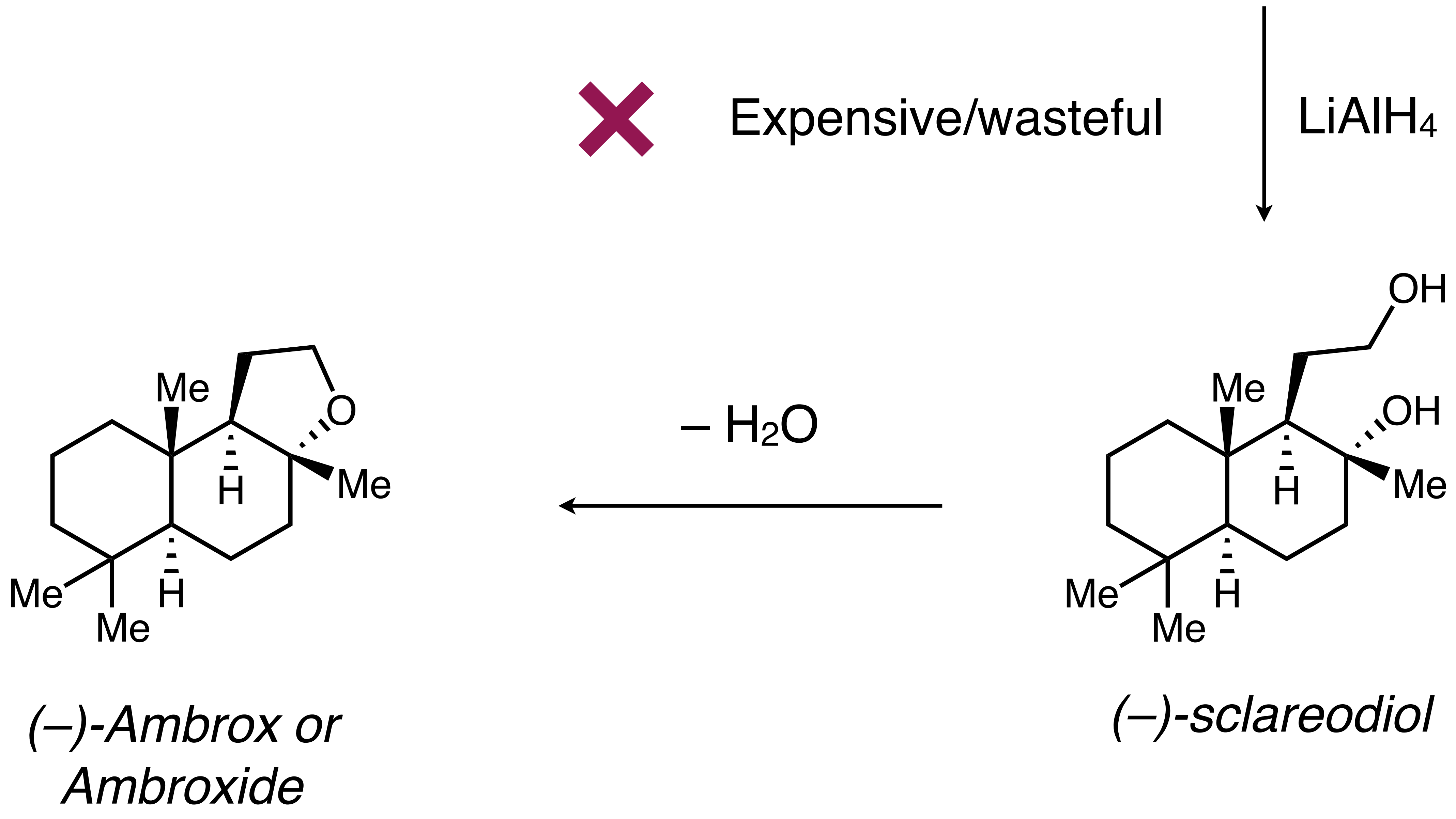
Ambergris to Ambrox: initial route

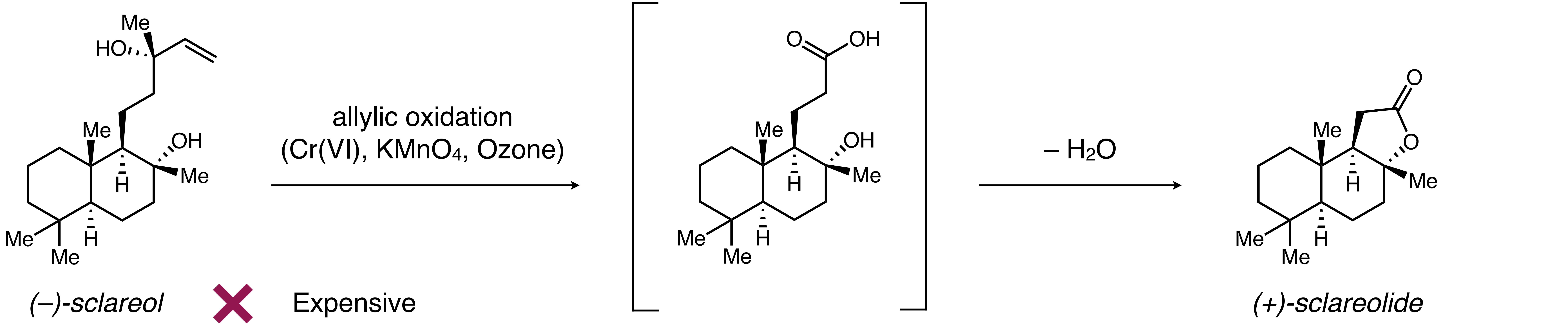


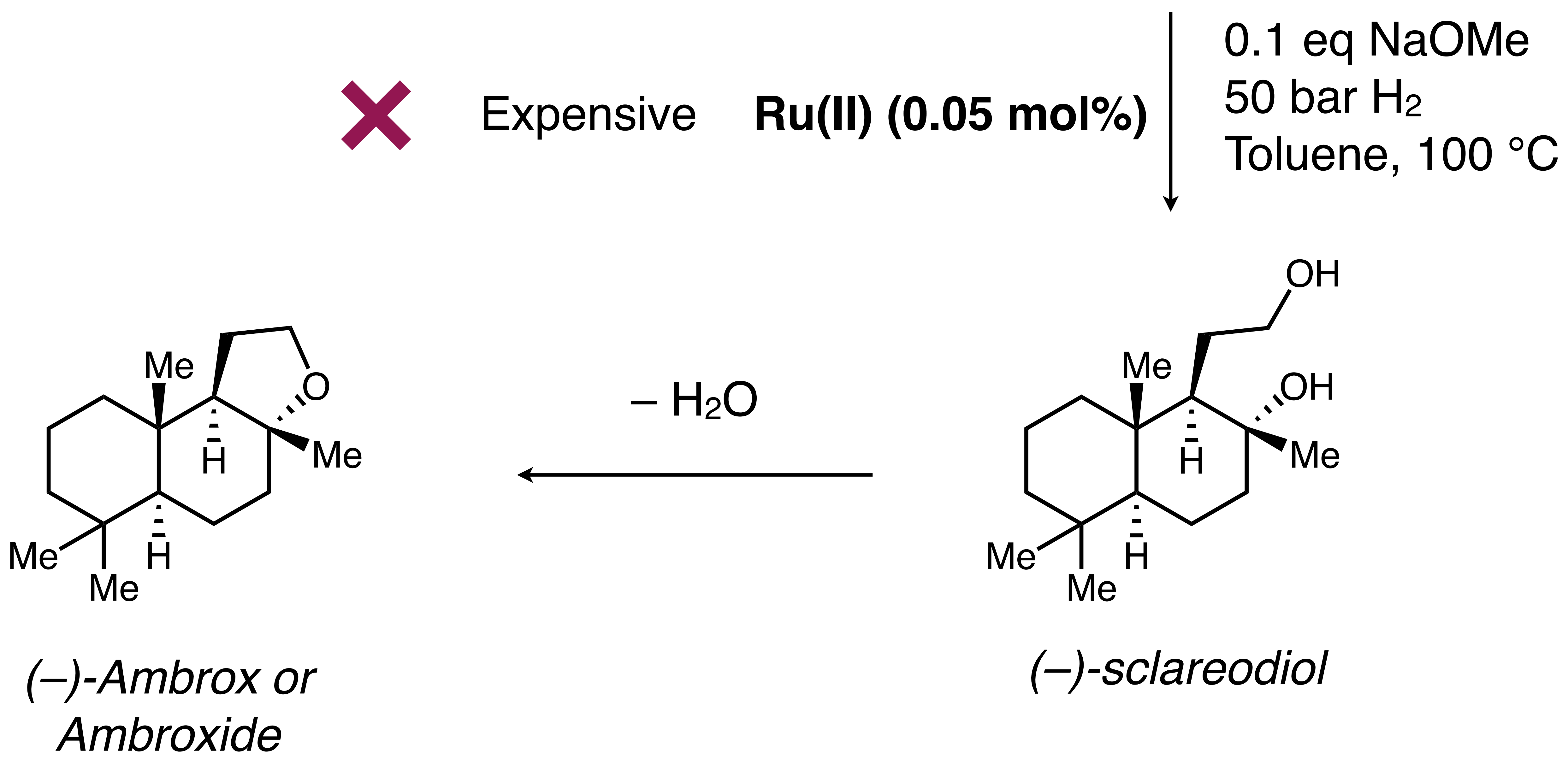


Clary Sage (*Salvia sclarea)*

Elterlein, F.; Bugdahn, N.; Kraft, P. *Chem. Eur. J.* **2024**, *30*, e202400006.

Ambergris to Ambrox: initial route

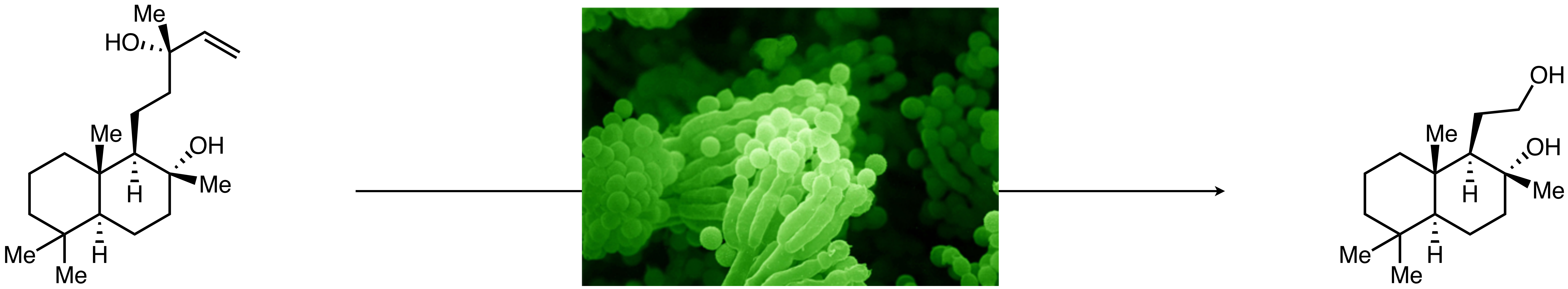




Clary Sage (*Salvia sclarea)*

GIVAUDAN - US2016/326199, 2016, A1

Biosynthesis of (–)-Sclareodiol



(–)-sclareol

Cytotoxic to many cells

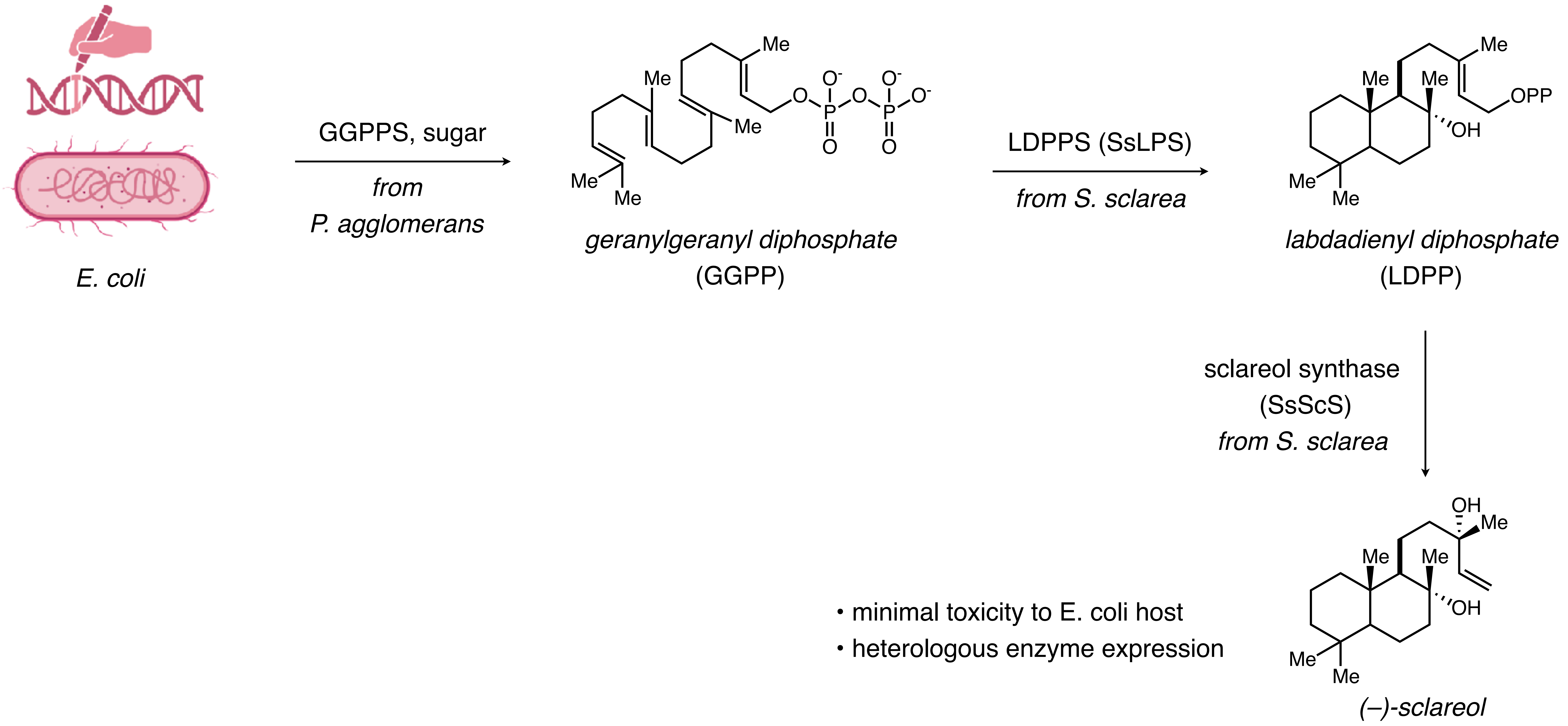
Hard to obtain commercially

Hyphozyma roseonigra

(–)-sclareodiol

Ncube, E.N.; Steenkamp, P.A.; van der Westhuyzen, C.W.; Steenkamp, L.H.; Dubery, I.A. *Catalysts* **2022**, *12*, 55.

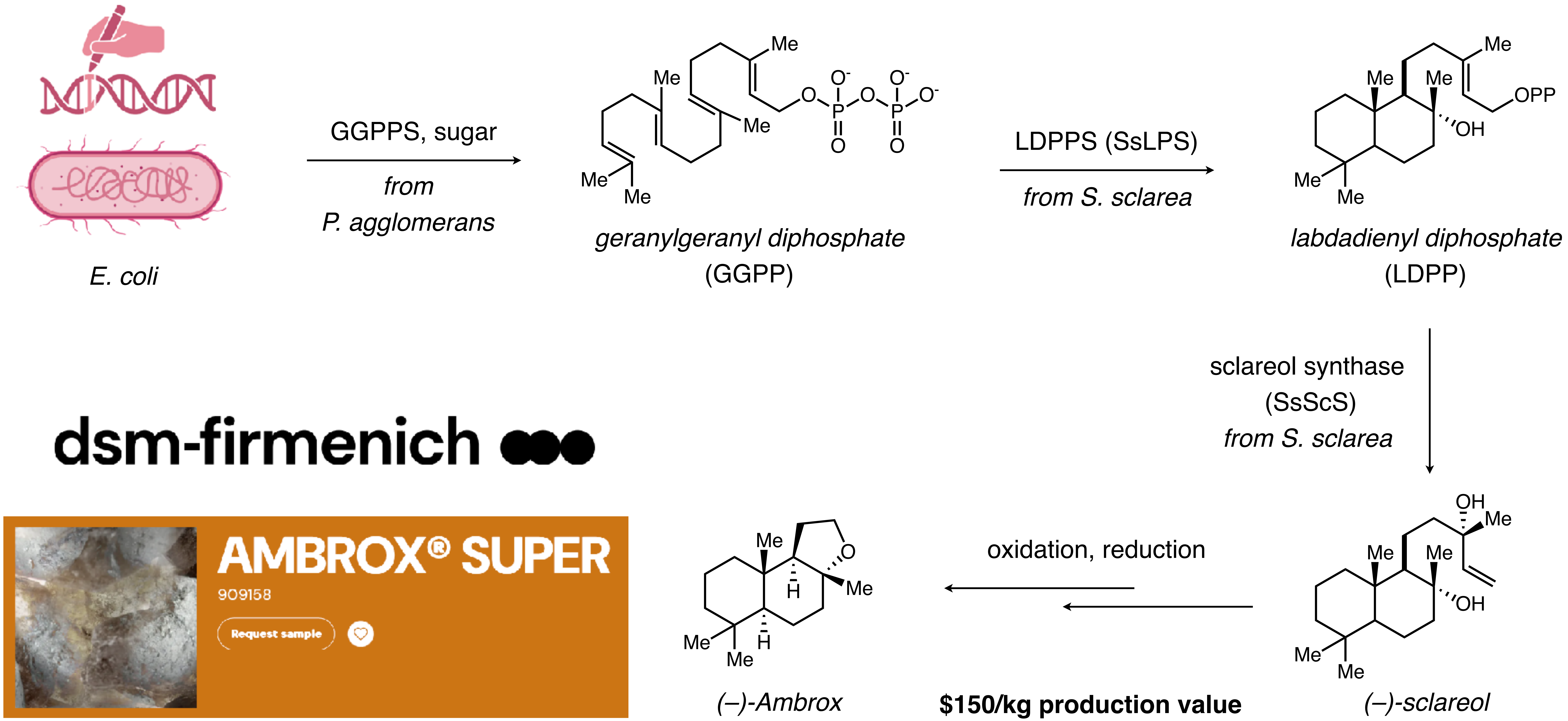
Biosynthesis of (–)-Sclareol



- minimal toxicity to E. coli host
- heterologous enzyme expression

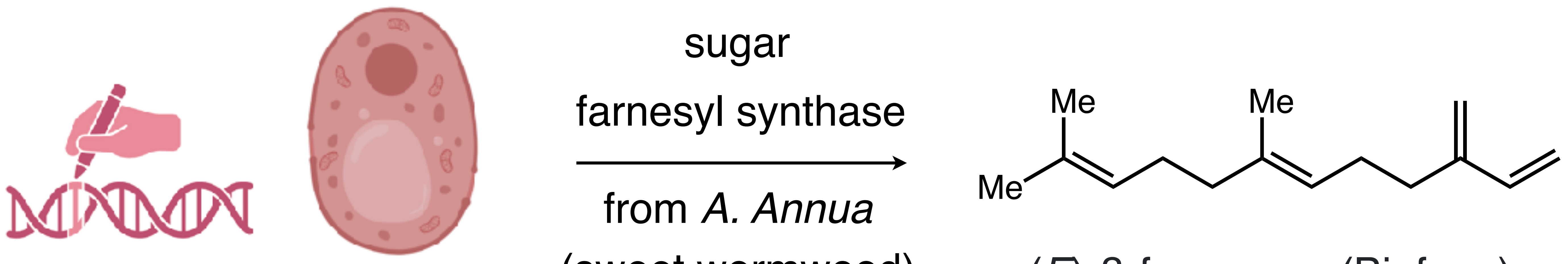
Schalk, M.; Pastore, L.; Mirata, M.A.; Khim, S.; Schouwey, M.; Deguerry, F.; Pineda, V.; Rocci, L.; Daviet, L. **2012**. *J. Am. Chem. Soc. 134*(46), 18900

Biosynthesis of (–)-Sclareol



Schalk, M.; Pastore, L.; Mirata, M.A.; Khim, S.; Schouwey, M.; Deguerry, F.; Pineda, V.; Rocci, L.; Daviet, L. **2012**. *J. Am. Chem. Soc. 134*(46), 18900

Biosynthesis of (–)-Ambrox



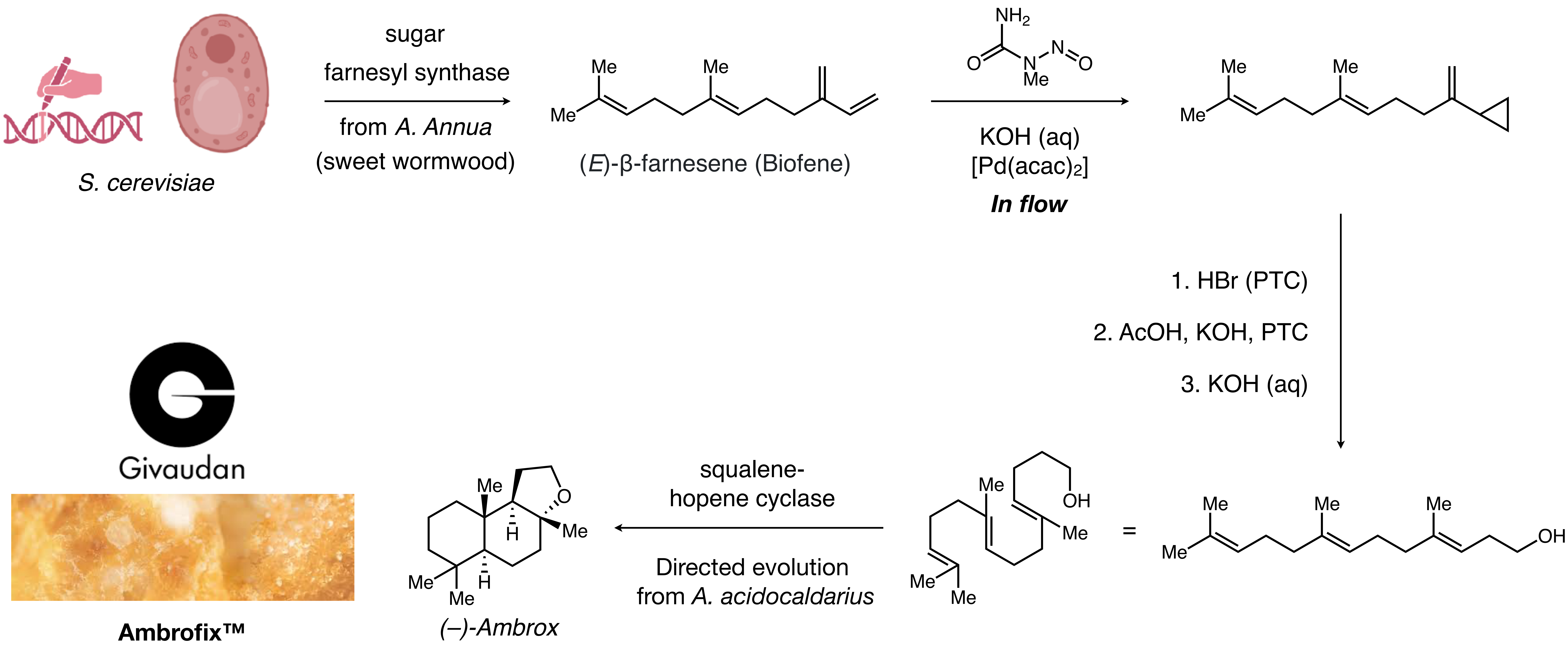
S. cerevisiae

(*E*)-β-farnesene (Biofene)

amyris

Eichhorn, E., & Schroeder, F. *Journal of Agricultural and Food Chemistry*, 2023, *71*(13), 5042-5052.

Biosynthesis of (–)-Ambrox



Eichhorn, E., & Schroeder, F. *Journal of Agricultural and Food Chemistry*, 2023, *71*(13), 5042-5052.

(–)-β-Santalol

Sandalwood to (–)-β-Santalol

East Indian Sandalwood (*Santalum album)*

Steam Distillation

Sandalwood oil (5-7% yield) $3000-8000 per L

https://www.acs.org/molecule-of-the-week/archive/s/santalols.html

Sandalwood to (–)-β-Santalol

East Indian Sandalwood (*Santalum album)*

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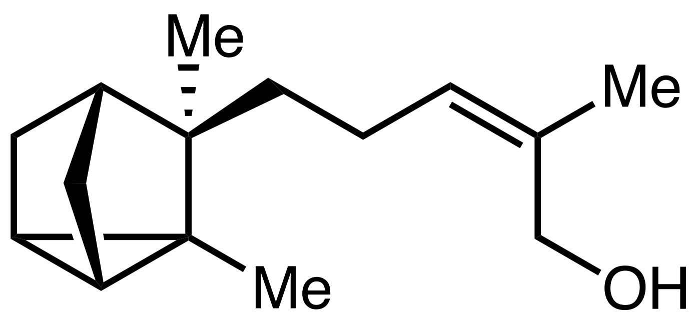
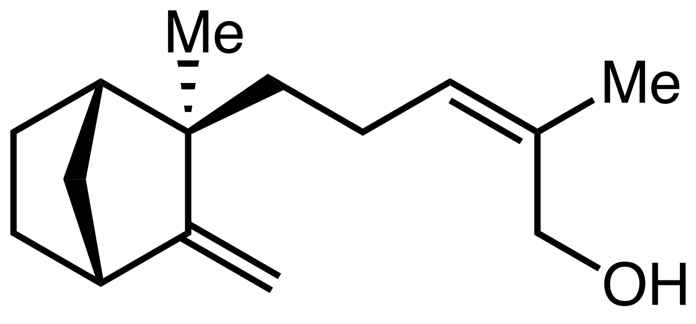
Sandalwood oil (5-7% yield) $3000-8000 per L



α-santalol

(41-55%)

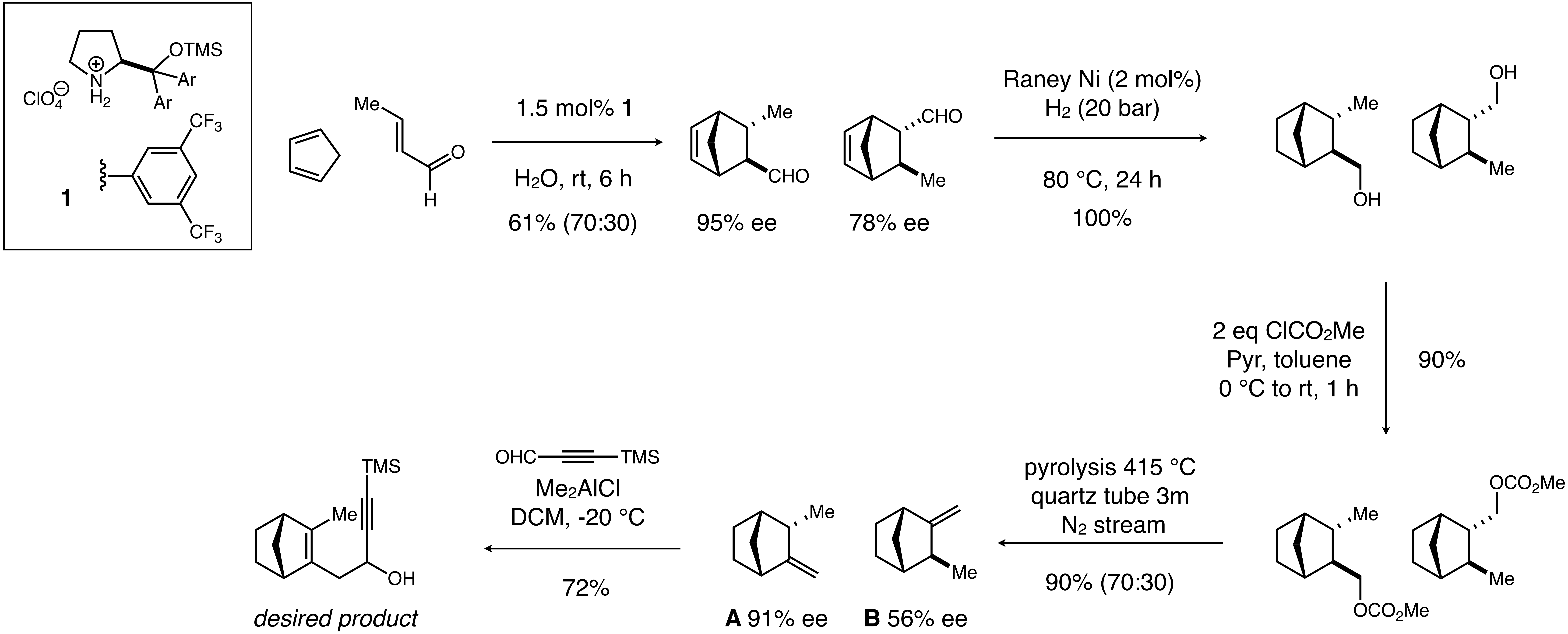


(–)-β-santalol

(16-24%)

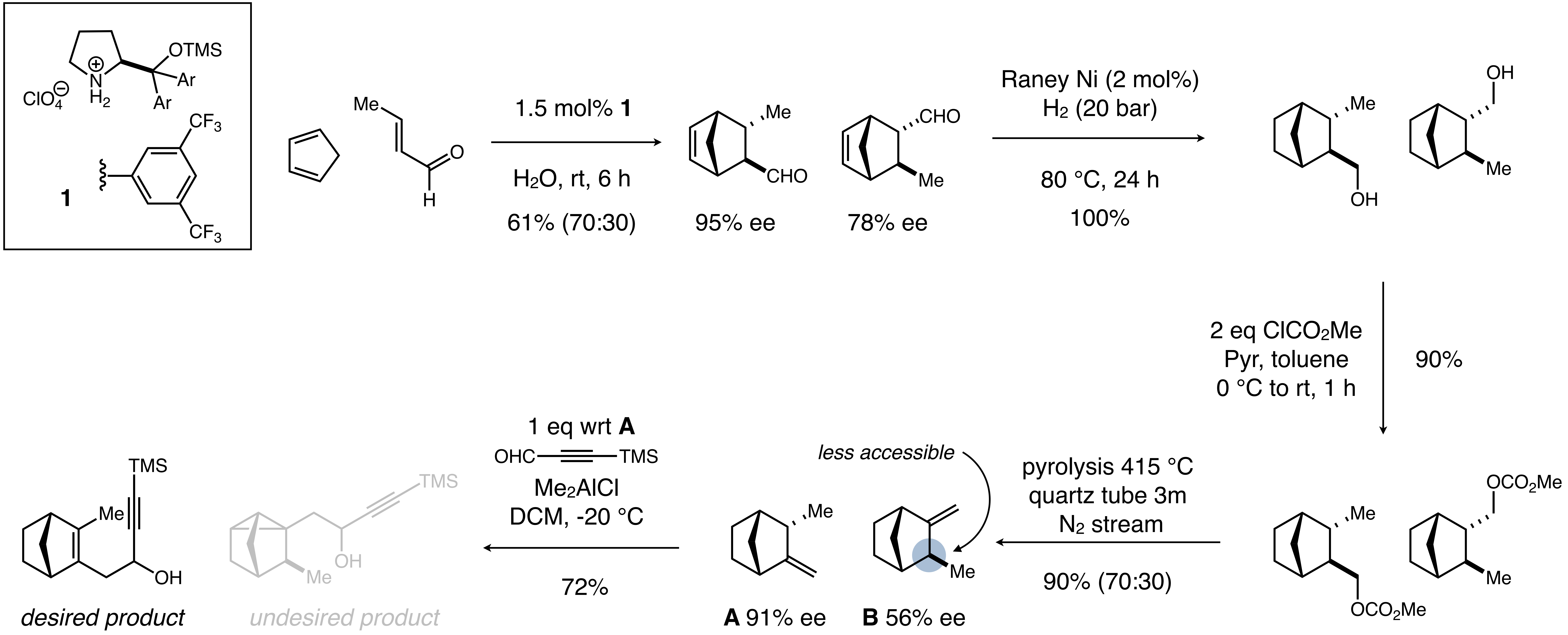
https://www.acs.org/molecule-of-the-week/archive/s/santalols.html

Sandalwood to (–)-β-Santalol – First Asymmetric Synthesis



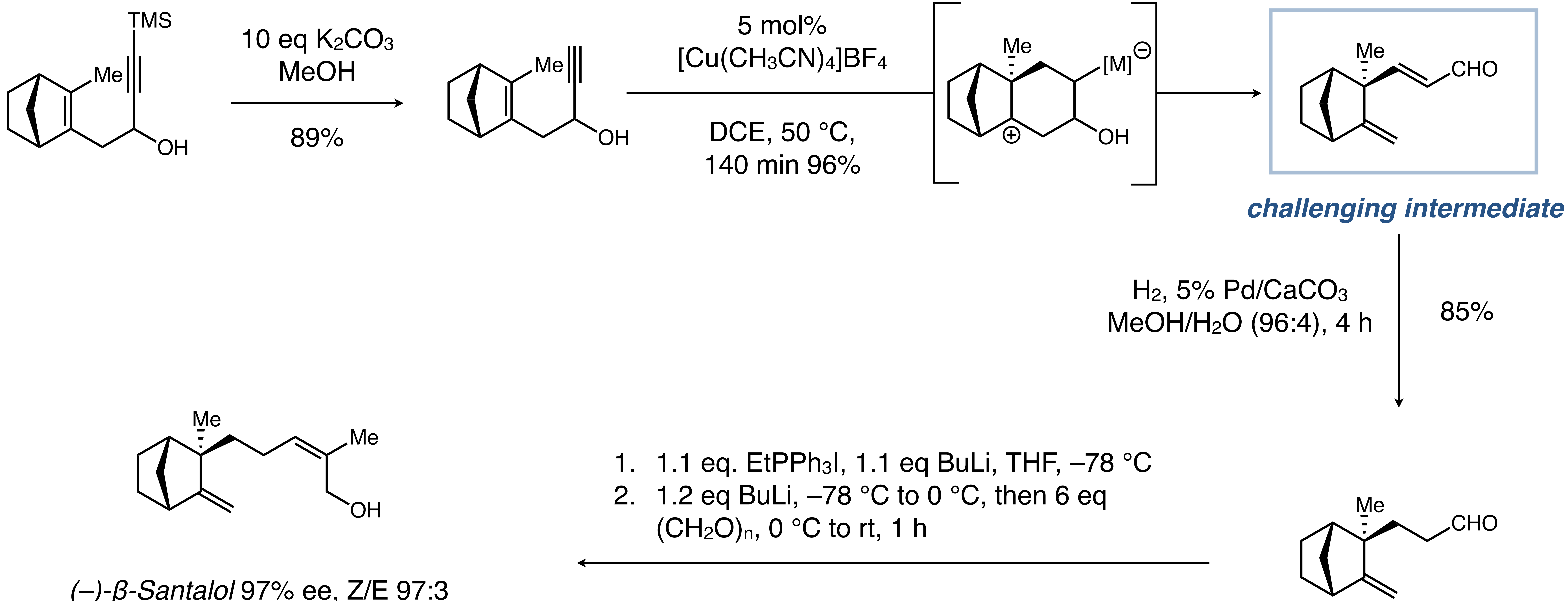
Schalk, M.; Pastore, L.; Mirata, M. A.; Khim, S.; Schouwey, M.; Deguerry, F.; Pineda, V.; Rocci, L.; Daviet, L.. *Journal of the American Chemical Society* **2012,** *134* (46), 18900-18903

Sandalwood to (–)-β-Santalol – First Asymmetric Synthesis



Schalk, M.; Pastore, L.; Mirata, M. A.; Khim, S.; Schouwey, M.; Deguerry, F.; Pineda, V.; Rocci, L.; Daviet, L.. *Journal of the American Chemical Society* **2012,** *134* (46), 18900-18903

Sandalwood to (–)-β-Santalol – First Asymmetric Synthesis

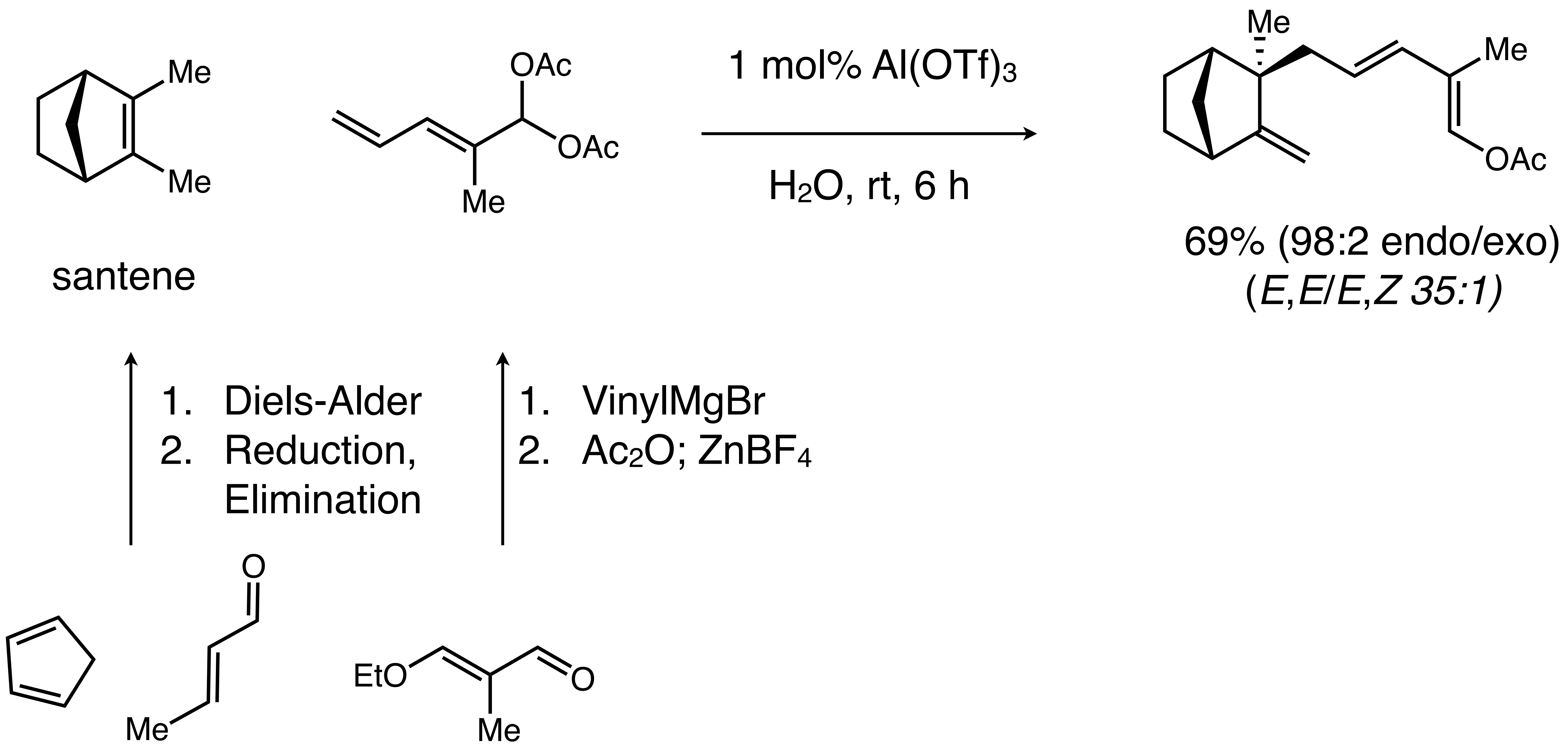


(–)-β-Santalol 97% ee, Z/E 97:3

after low temp pentane recrystallization

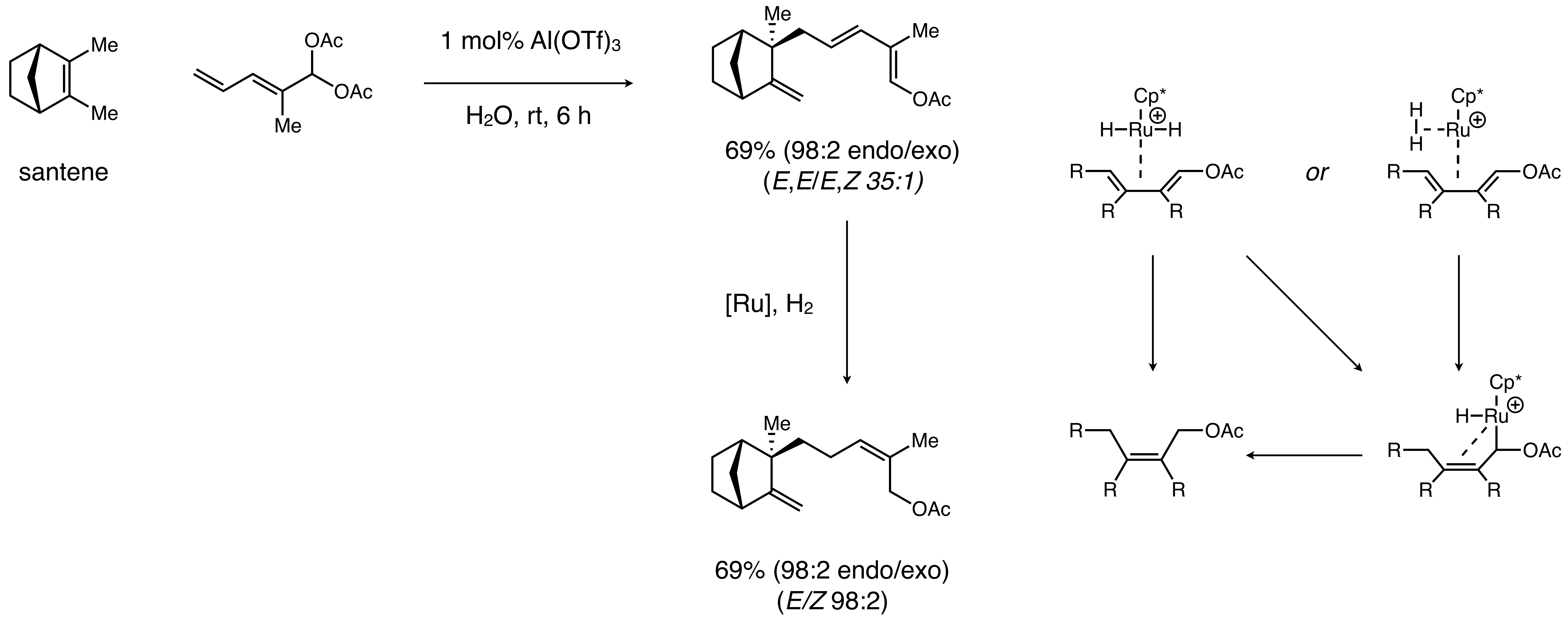
Schalk, M.; Pastore, L.; Mirata, M. A.; Khim, S.; Schouwey, M.; Deguerry, F.; Pineda, V.; Rocci, L.; Daviet, L.. *Journal of the American Chemical Society* **2012,** *134* (46), 18900-18903

Sandalwood to β-Santalol – Industrial Route



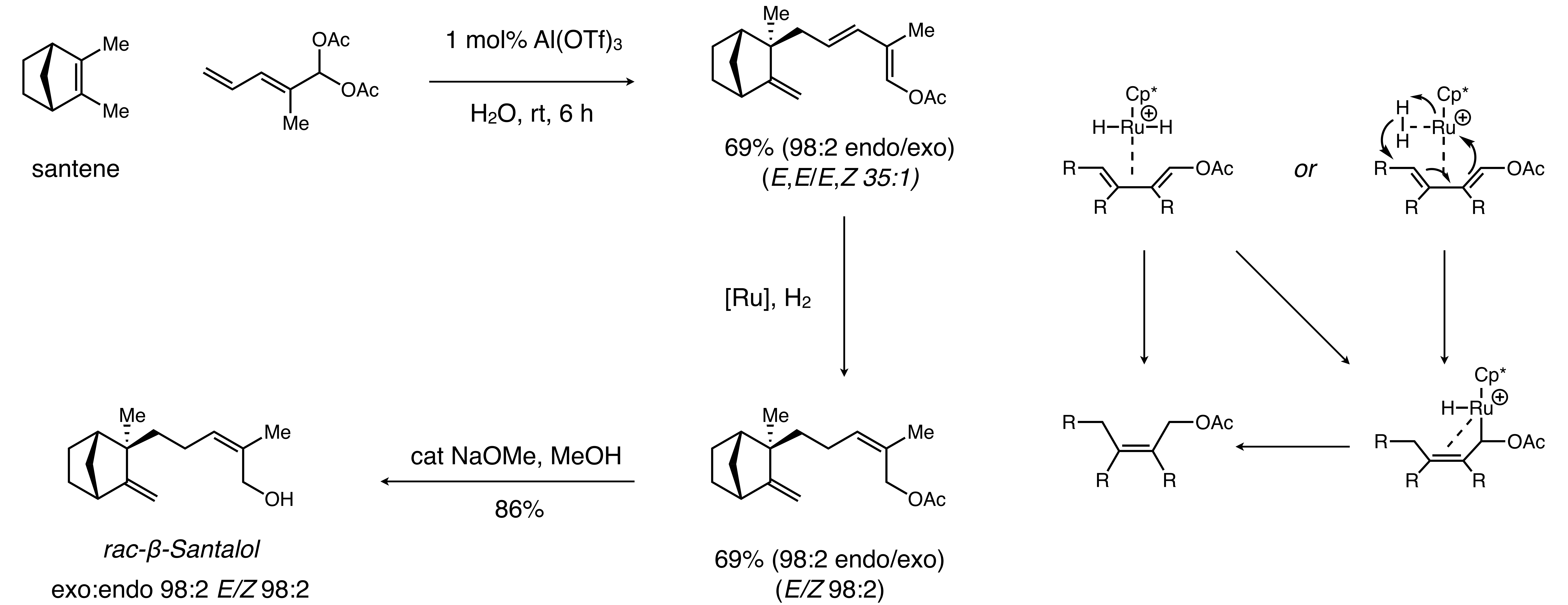
Fehr, C.; Magpantay, I.; Vuagnoux, M.; Dupau, P. *Chemistry – A European Journal* **2011,** *17* (4), 1257-1260.

Sandalwood to β-Santalol – Industrial Route



Fehr, C.; Magpantay, I.; Vuagnoux, M.; Dupau, P. *Chemistry – A European Journal* **2011,** *17* (4), 1257-1260.

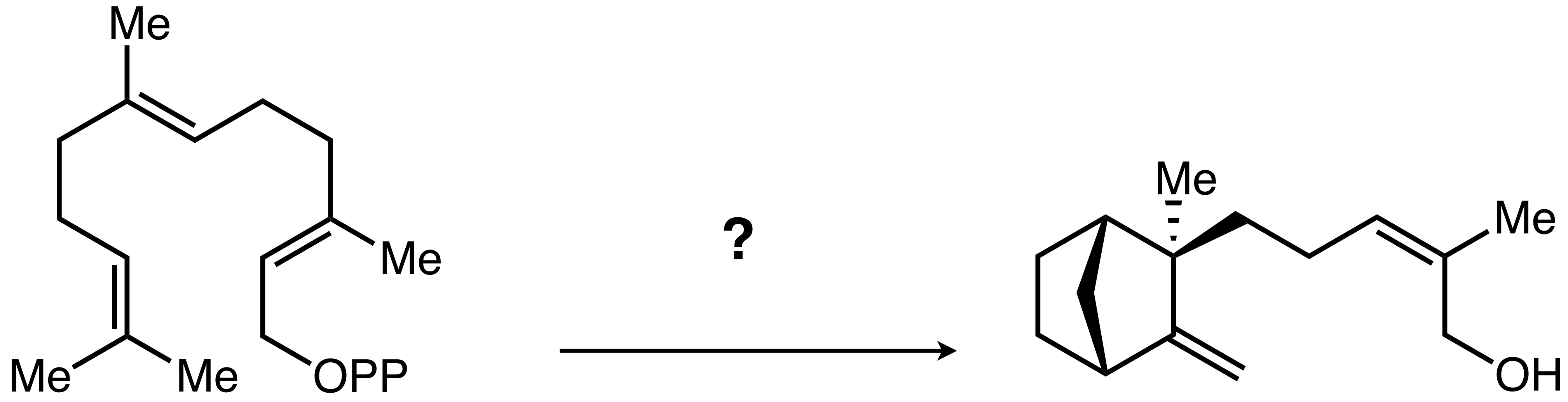
Sandalwood to β-Santalol – Industrial Route



Fehr, C.; Magpantay, I.; Vuagnoux, M.; Dupau, P. *Chemistry – A European Journal* **2011,** *17* (4), 1257-1260.

Sandalwood to β-Santalol – Biosynthetic Route

Jörg Bohlmann
University of British Columbia



farnesyl pyrophosphate *(–)-β-Santalol*

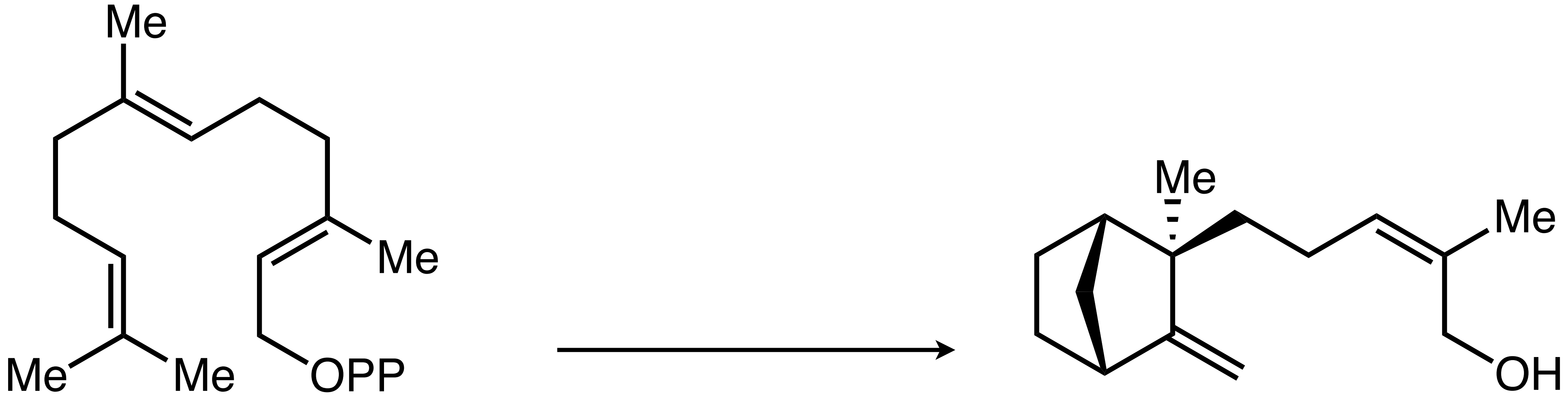
Jones, C. G.; Moniodis, J.; Zulak, K. G.; Scaffidi, A.; Plummer, J. A.; Ghisalberti, E. L.; Barbour, E. L.; Bohlmann, J. *Journal of Biological Chemistry* **2011,** *286* (20), 17445-17454.

Jones, C. G.; Keeling, C. I.; Ghisalberti, E. L.; Barbour, E. L.; Plummer, J. A.; Bohlmann, J., *Archives of Biochemistry and Biophysics* **2008,** *477* (1), 121-130.

Sandalwood to β-Santalol – Biosynthetic Route

Jörg Bohlmann
University of British Columbia

East Indian Sandalwood
(*Santalum album)*



farnesyl pyrophosphate *(–)-β-Santalol*

New Caledonia Sandalwood
(*Santalum austrocaledonicum)*

Austrailian Sandalwood
(*Santalum spicatum)*

- Cloned and characterized three orthogolous terpene synthases

Jones, C. G.; Moniodis, J.; Zulak, K. G.; Scaffidi, A.; Plummer, J. A.; Ghisalberti, E. L.; Barbour, E. L.; Bohlmann, J. *Journal of Biological Chemistry* **2011,** *286* (20), 17445-17454.
Jones, C. G.; Keeling, C. I.; Ghisalberti, E. L.; Barbour, E. L.; Plummer, J. A.; Bohlmann, J., *Archives of Biochemistry and Biophysics* **2008,** *477* (1), 121-130.

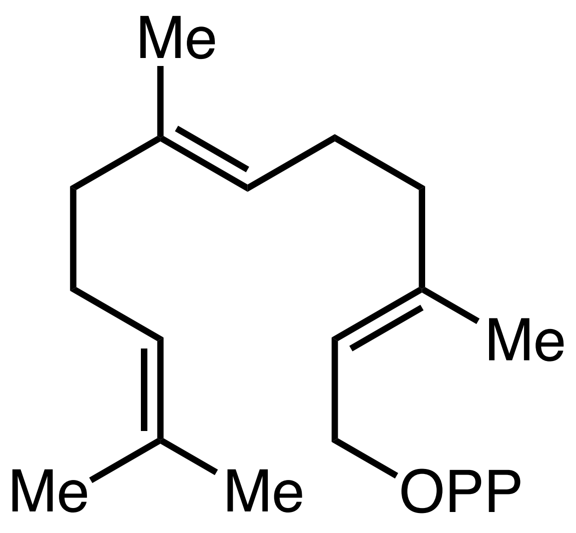
Sandalwood to β-Santalol – Biosynthetic Route

Jörg Bohlmann
University of British Columbia

East Indian Sandalwood
(*Santalum album)*

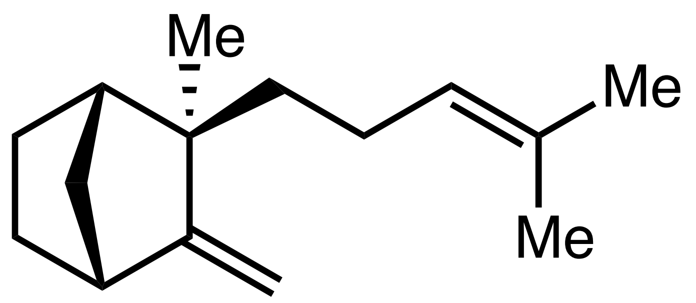
New Caledonia Sandalwood
(*Santalum austrocaledonicum)*

Austrailian Sandalwood
(*Santalum spicatum)*



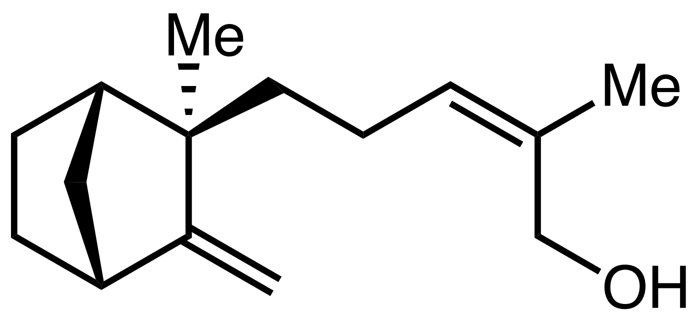
farnesyl pyrophosphate

santalene synthase →



santalene
and other terpenes

P450 ↓



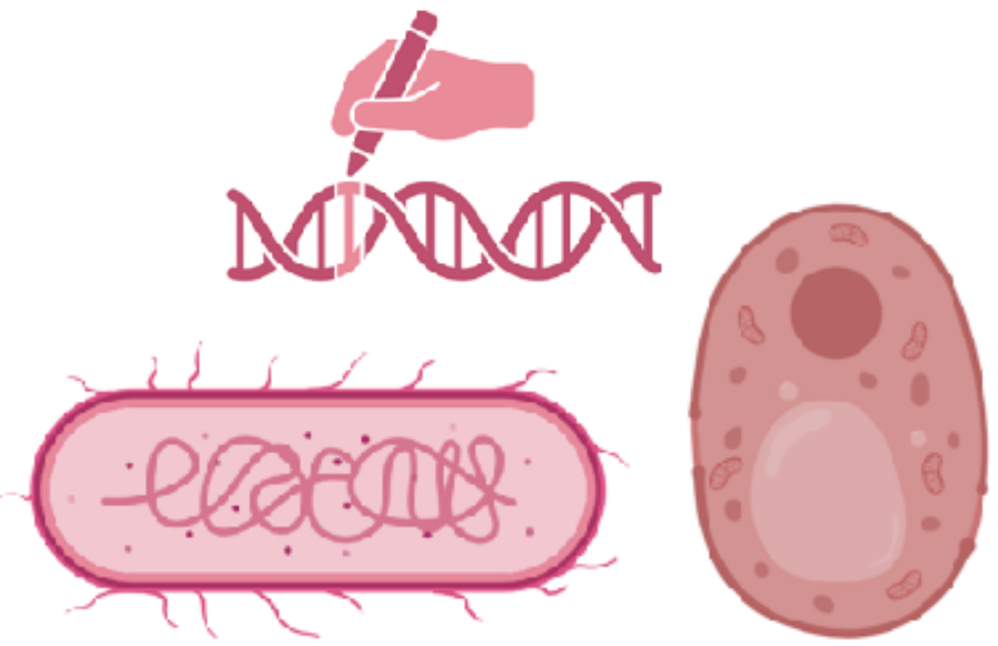
(–)-β-Santalol
minor component

- Cloned and characterized three orthogolous terpene synthases

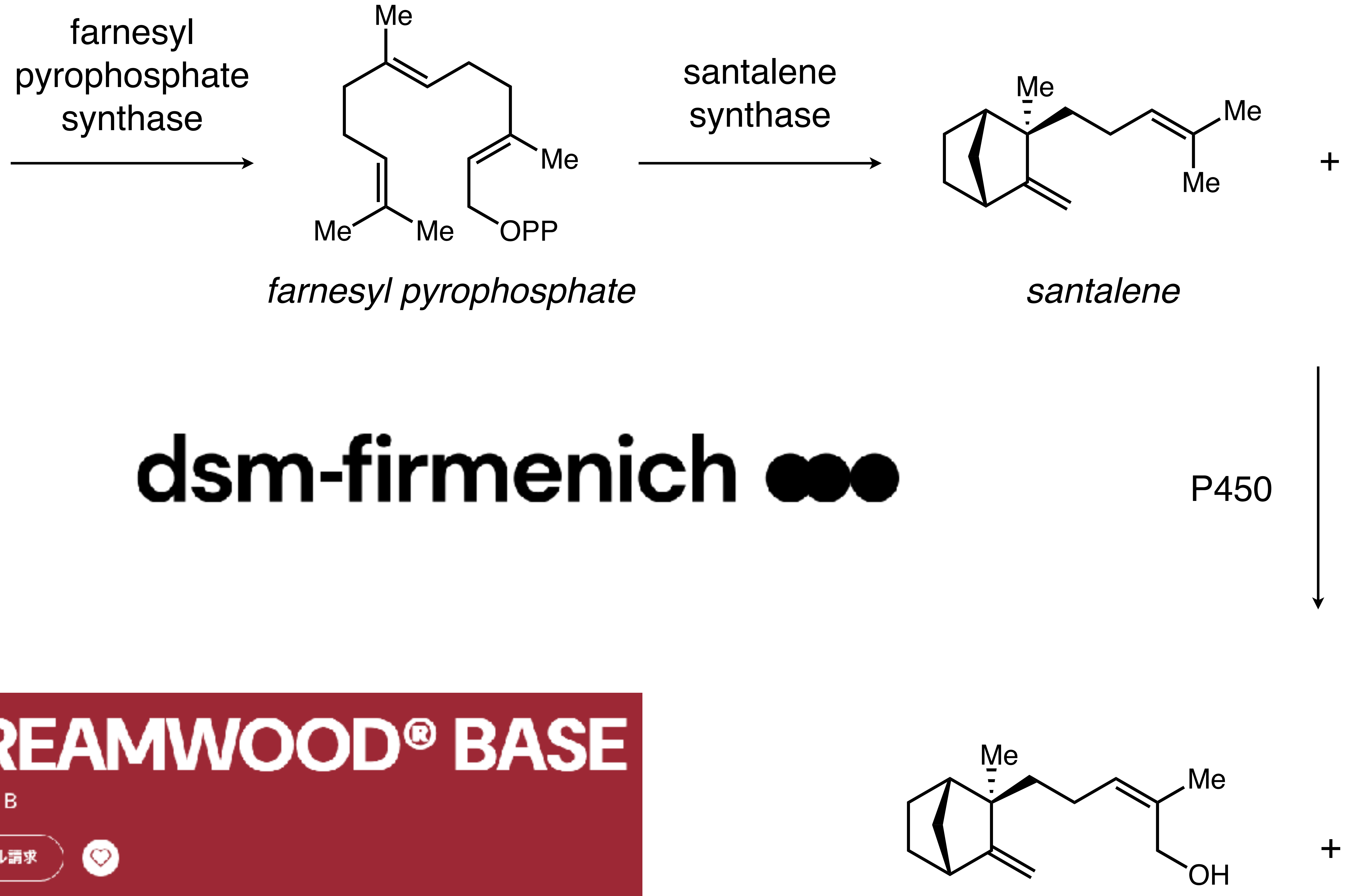
Jones, C. G.; Moniodis, J.; Zulak, K. G.; Scaffidi, A.; Plummer, J. A.; Ghisalberti, E. L.; Barbour, E. L.; Bohlmann, J. *Journal of Biological Chemistry* **2011,** *286* (20), 17445-17454.

Jones, C. G.; Keeling, C. I.; Ghisalberti, E. L.; Barbour, E. L.; Plummer, J. A.; Bohlmann, J., *Archives of Biochemistry and Biophysics* **2008,** *477* (1), 121-130.

Sandalwood to β-Santalol – Biosynthetic Route



E. coli or S. cerevisiae



+ α-, β-, epi-β-santalene
α-exo-bergamotene

Co expressed genes coding for:

- Farnesyl pyrophosphate synthase
- Santalene synthase
- P450 santalene oxidase
- P450 reductase

dsm-firmenich

(–)-β-Santalol

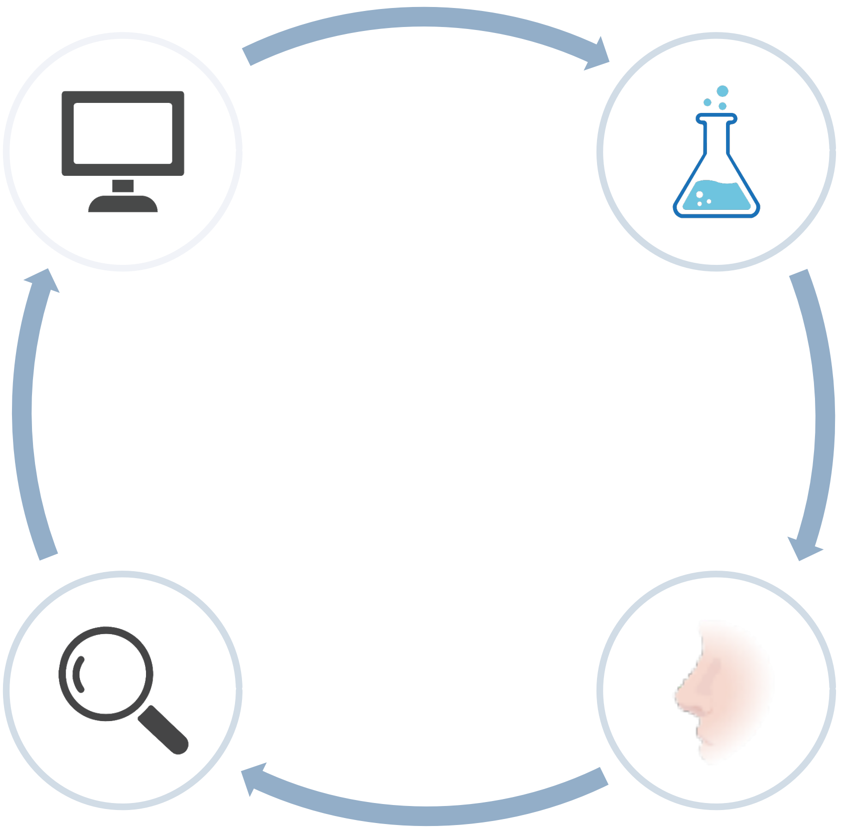
+ other santalols
and bergamatols

M. Schalk, A. Taglieber, L. Daviet, *Perfum. Flavor.* 2020, 45 (May), 38–44

Fragrance Ingredients

Natural Sources

Synthesis



Fragrance Discovery

Fragrance Discovery

Major Players in Fragrance Production

dsm-firmenich

Switzerland & Netherlands

iff

International Flavors & Fragrances Inc.
NY, USA

Unilever

England, UK

L'ORÉAL

Clichy, France

Givaudan

Switzerland

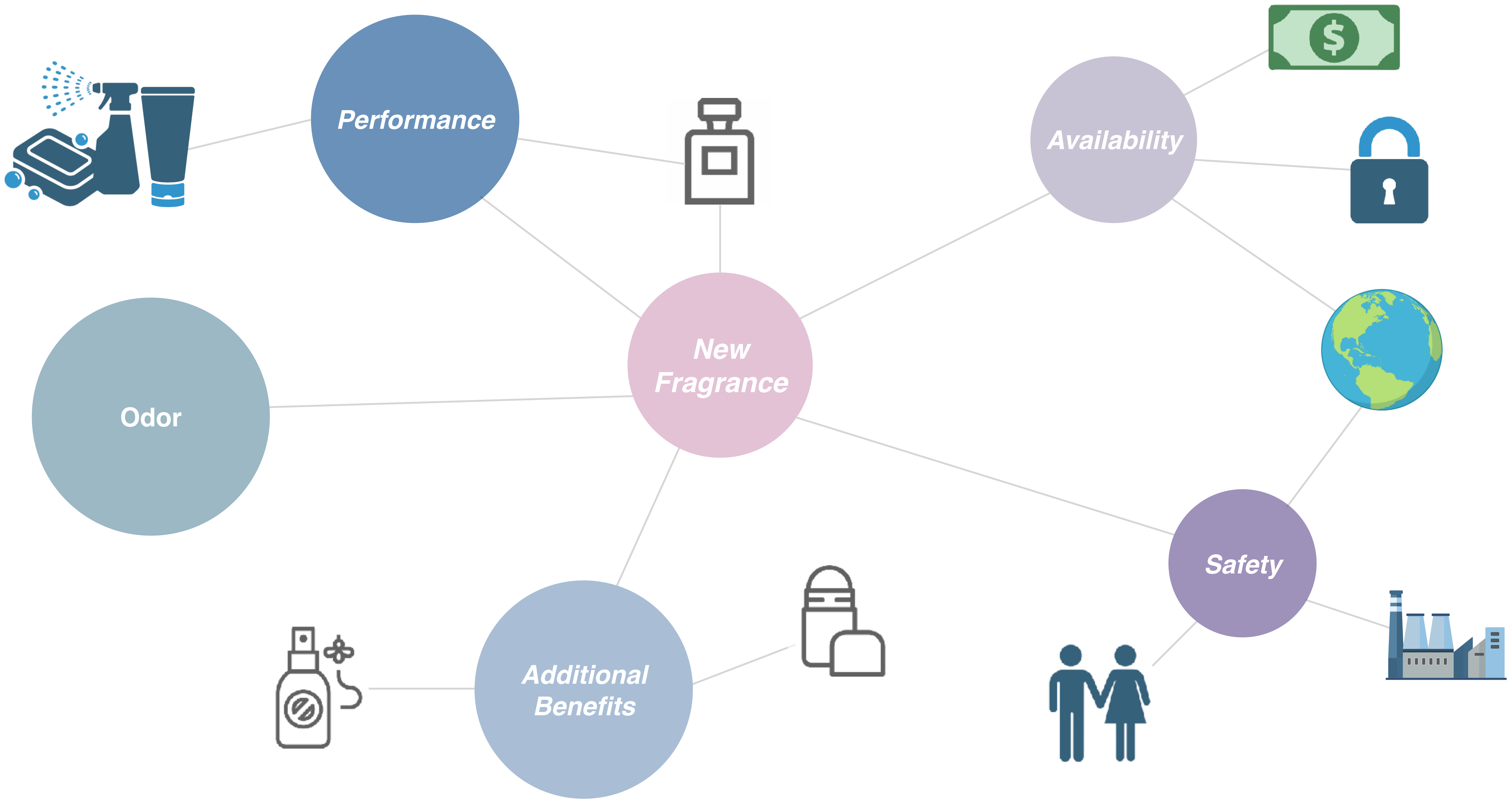
P&G

Procter & Gamble
OH, USA

COLGATE-PALMOLIVE

NY, USA

Fragrance Discovery



Sell, C. S., *Chemistry of Fragrances*. The Royal Society of Chemistry: 2006.

Odor Characteristics

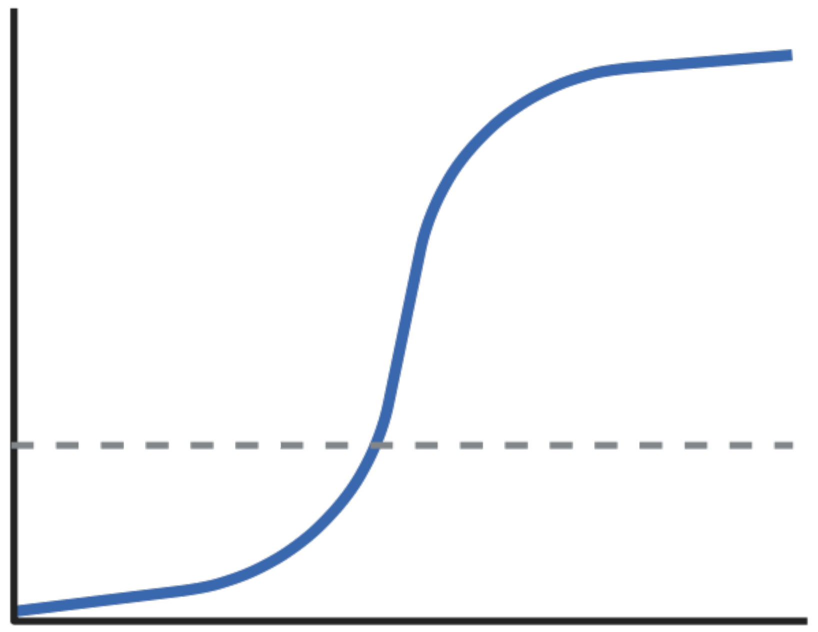
Persistence/Tenacity

- *Ability of odor to stick to hair or fabric*
- *Dependent upon volatility and log(P)*

Sell, C. S., *Chemistry of Fragrances*. The Royal Society of Chemistry: 2006.

Odor Characteristics

Persistence/Tenacity



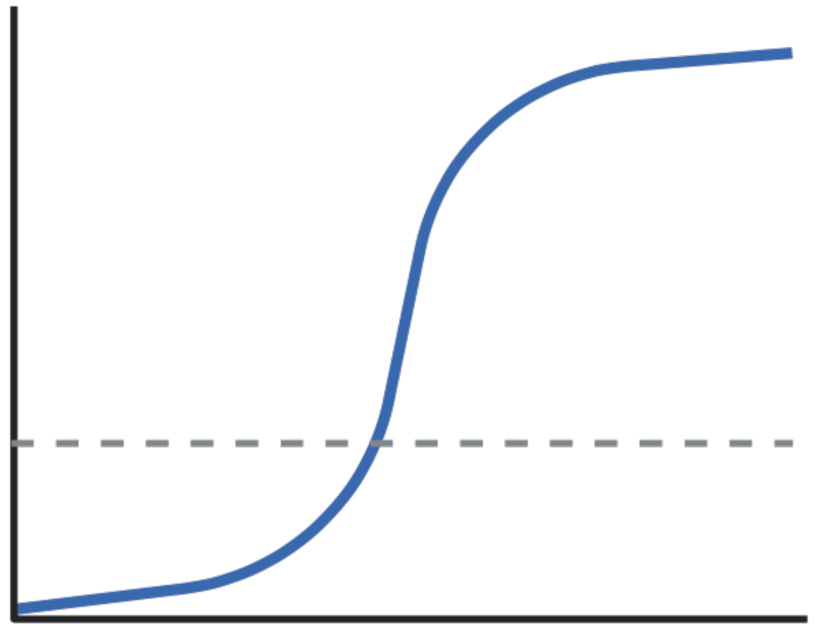
Threshold

- *Lowest concentration at which odor can be perceived*
- *Less material required, lower costs*

Sell, C. S., *Chemistry of Fragrances*. The Royal Society of Chemistry: 2006.

Odor Characteristics

Persistence/Tenacity



Threshold

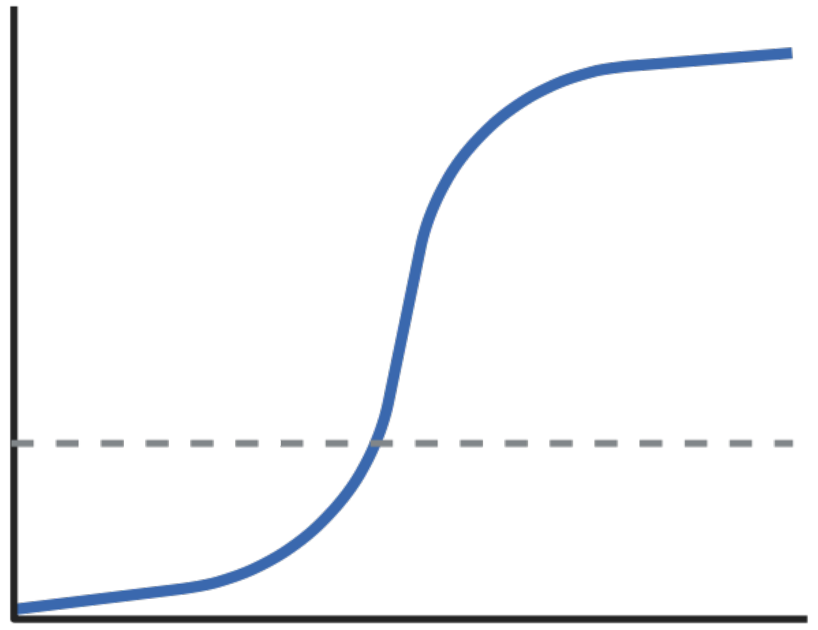
Impact

- *Subjective phenomenon*
- *Intensity of perceived sensation*

Sell, C. S., *Chemistry of Fragrances*. The Royal Society of Chemistry: 2006.

Odor Characteristics

Persistence/Tenacity



Threshold

Impact

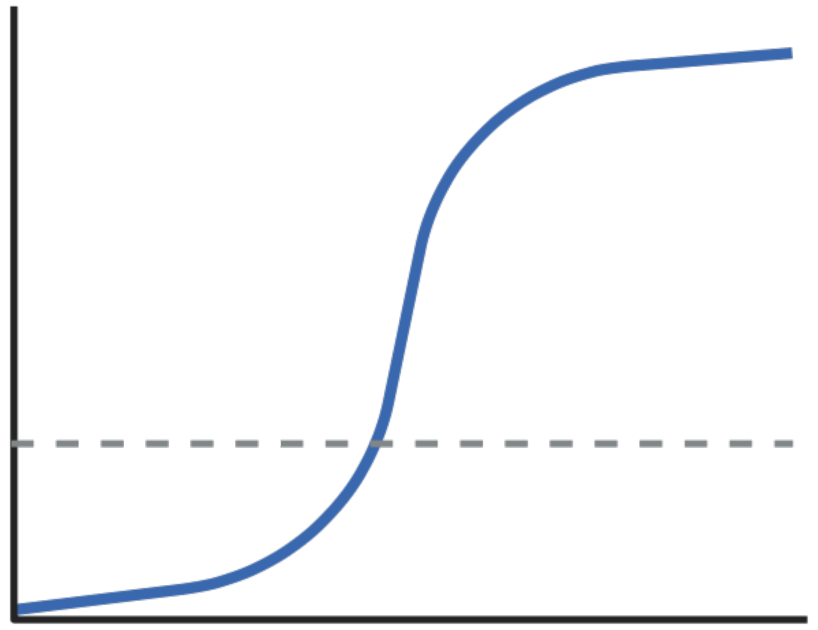
Radiance

- *The ability of a fragrance to fill a space*
- *Requires low recognition threshold*

Sell, C. S., *Chemistry of Fragrances*. The Royal Society of Chemistry: 2006.

Odor Characteristics

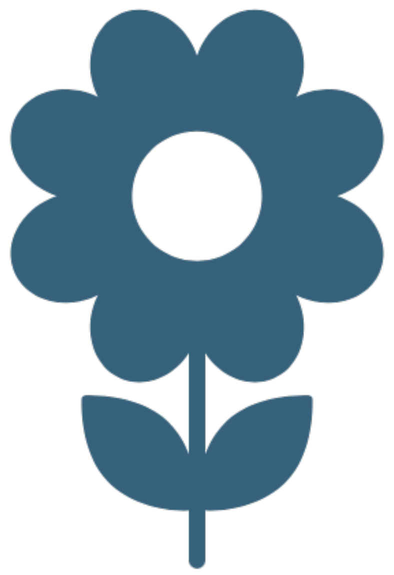
Persistence/Tenacity



Threshold

Impact

Radiance



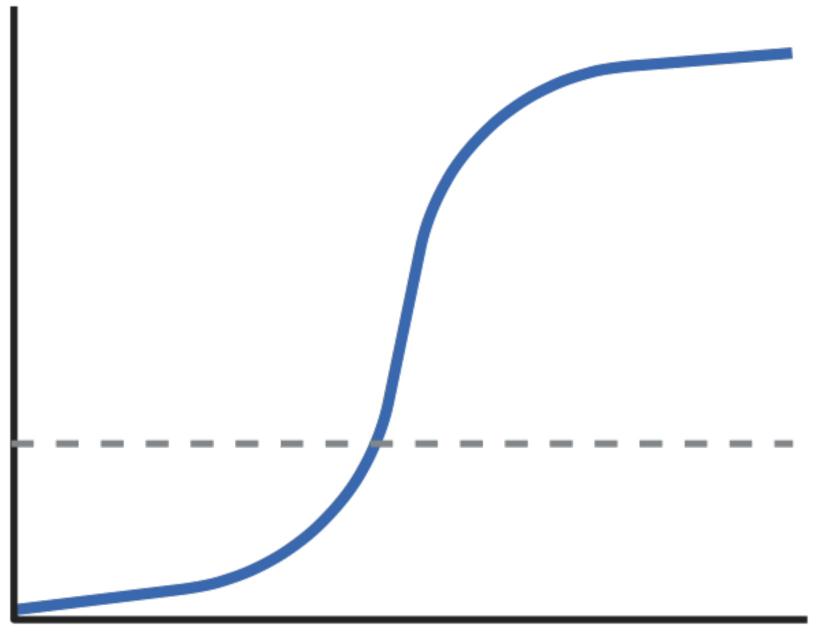
Bloom

- *The ability of a fragrance to perfume a room when introduced as a solid*
- *Relevant for soap fragrances*

Sell, C. S., *Chemistry of Fragrances*. The Royal Society of Chemistry: 2006.

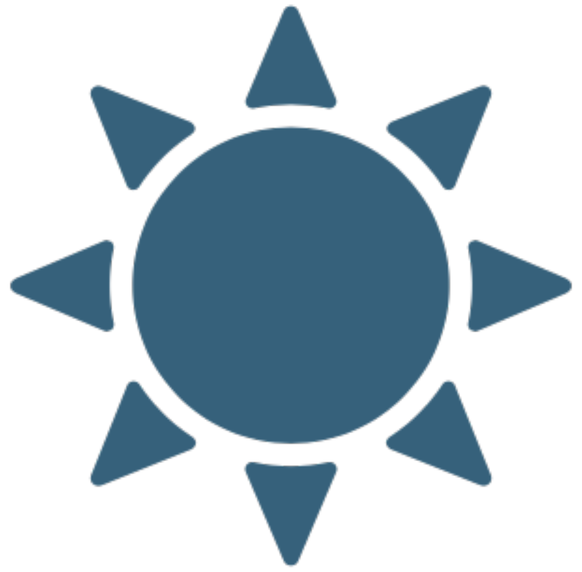
Odor Characteristics

Persistence/tenacity

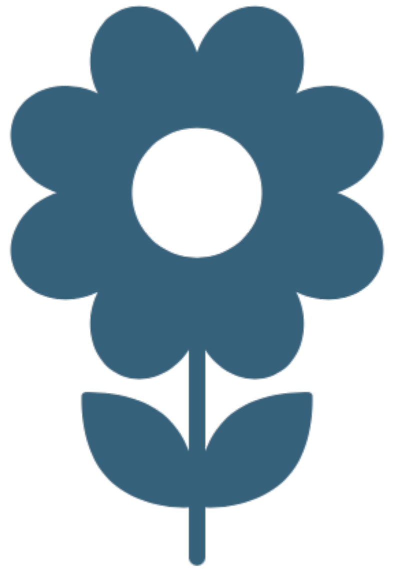


Threshold

Impact



Radiance

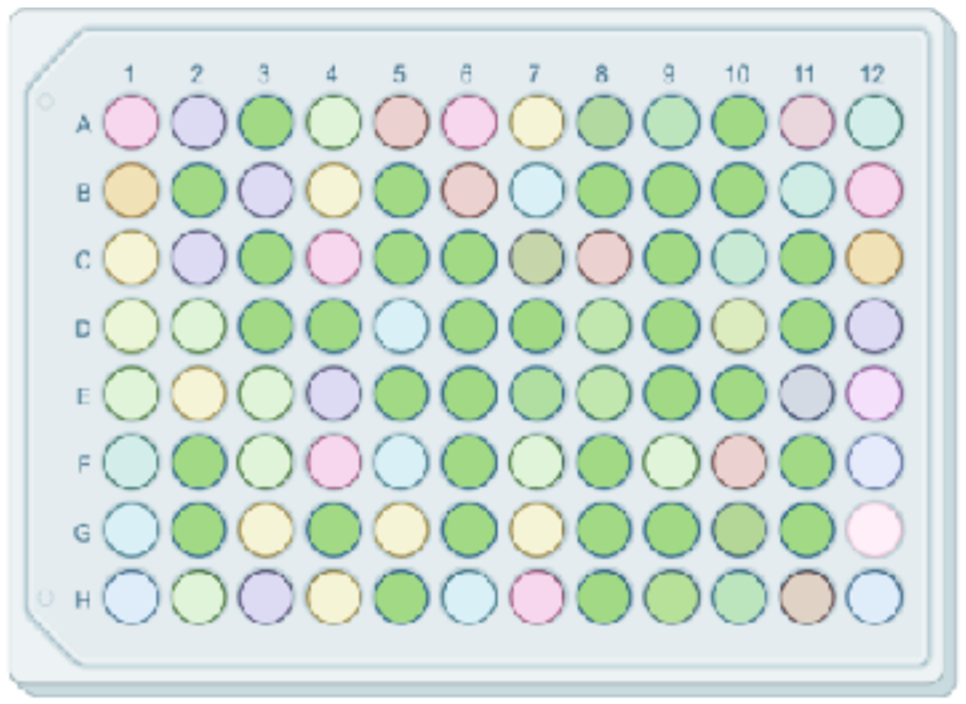


Bloom

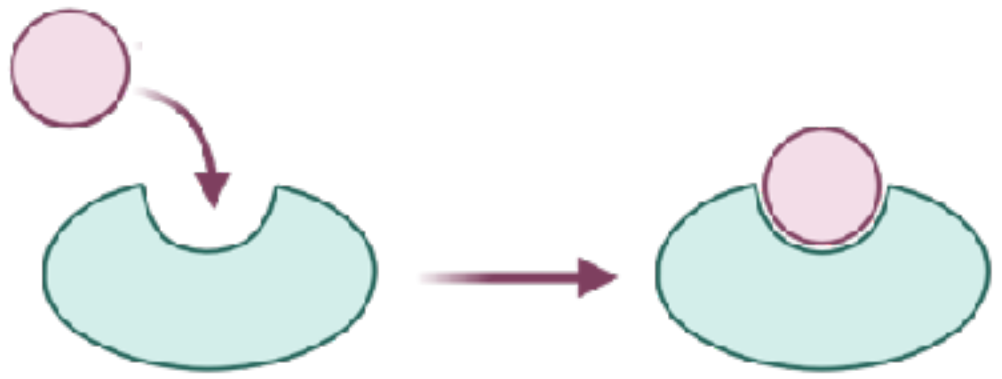
Trail

Sell, C. S., *Chemistry of Fragrances*. The Royal Society of Chemistry: 2006.

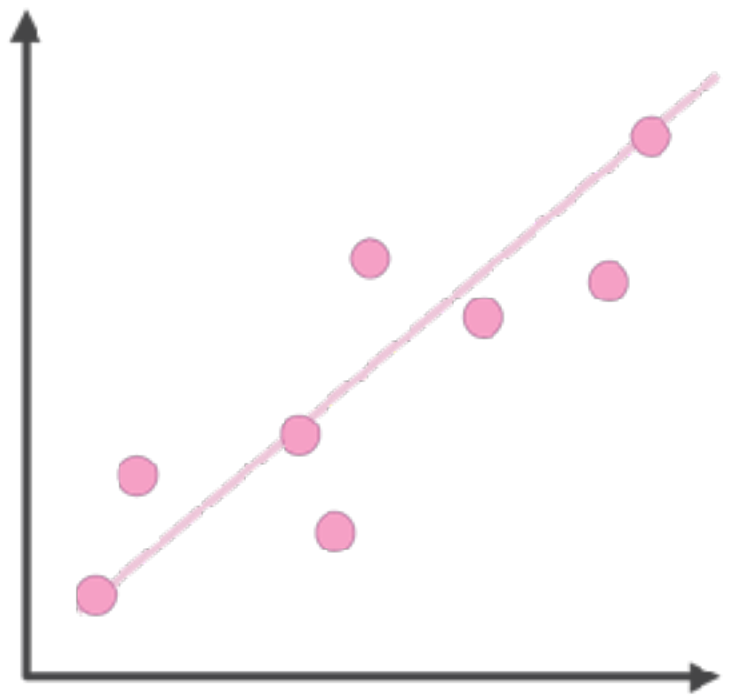
Strategies for Novel Fragrance Design



Random Screening



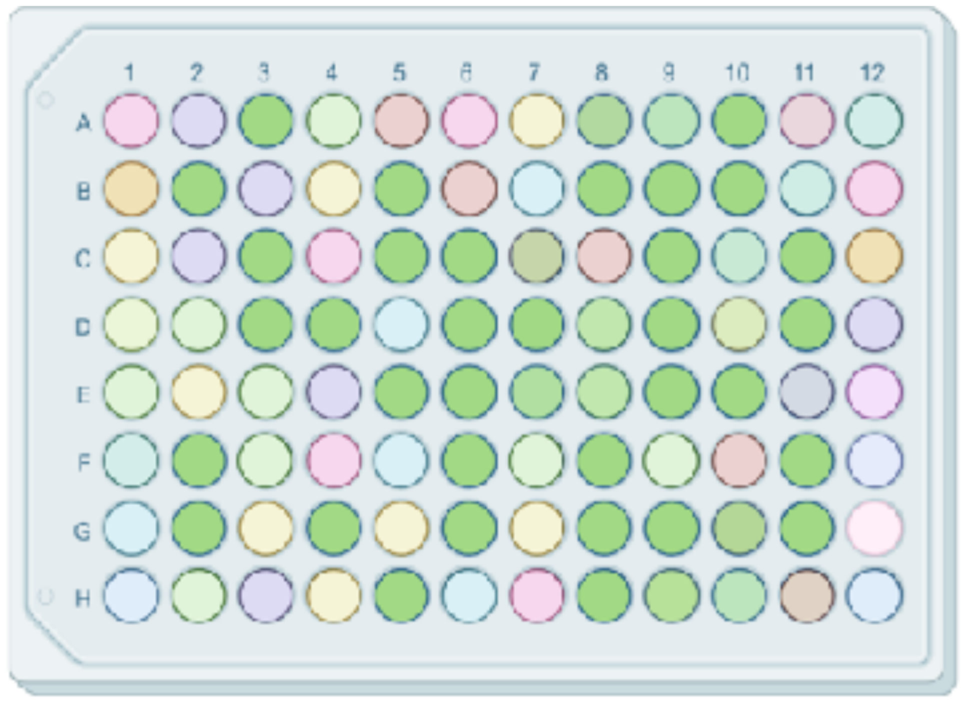
Mechanism of Action



Statistical Design

Sell, C. S., *Chemistry of Fragrances*. The Royal Society of Chemistry: 2006.

Strategies for Novel Fragrance Design



Random Screening

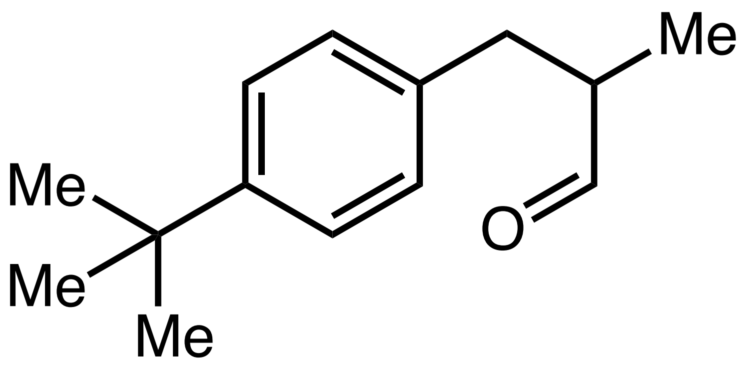
Mechanism of Action

Statistical Design

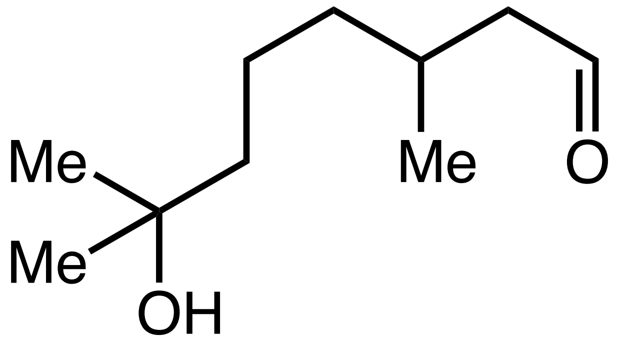
Sell, C. S., *Chemistry of Fragrances*. The Royal Society of Chemistry: 2006.

Random Screening

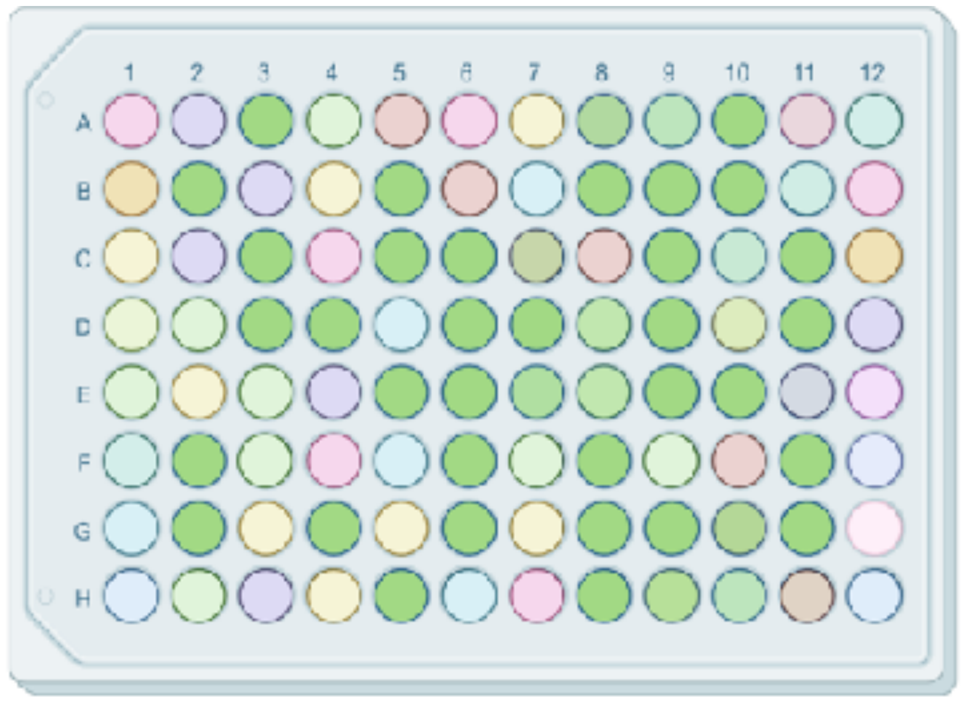
Lily of the Valley



Lilial



hydroxycitronellal

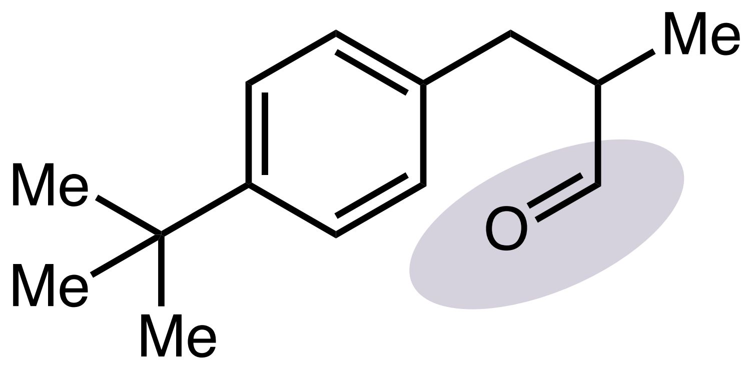


Random Screening

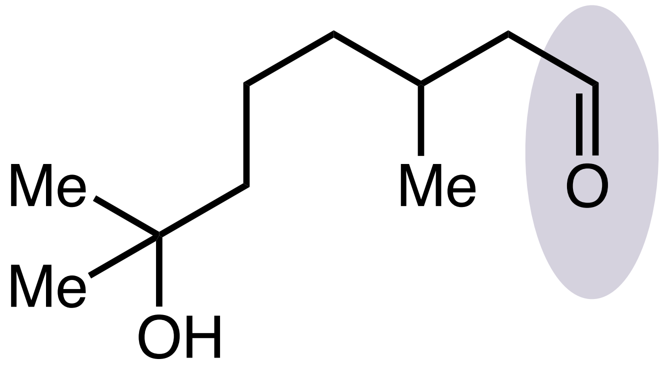
Anselmi, C.; Centini, M.; Mariani, M.; Sega, A.; Pelosi, P. *Journal of Agricultural and Food Chemistry* **1992,** *40* (5), 853-856.

Random Screening

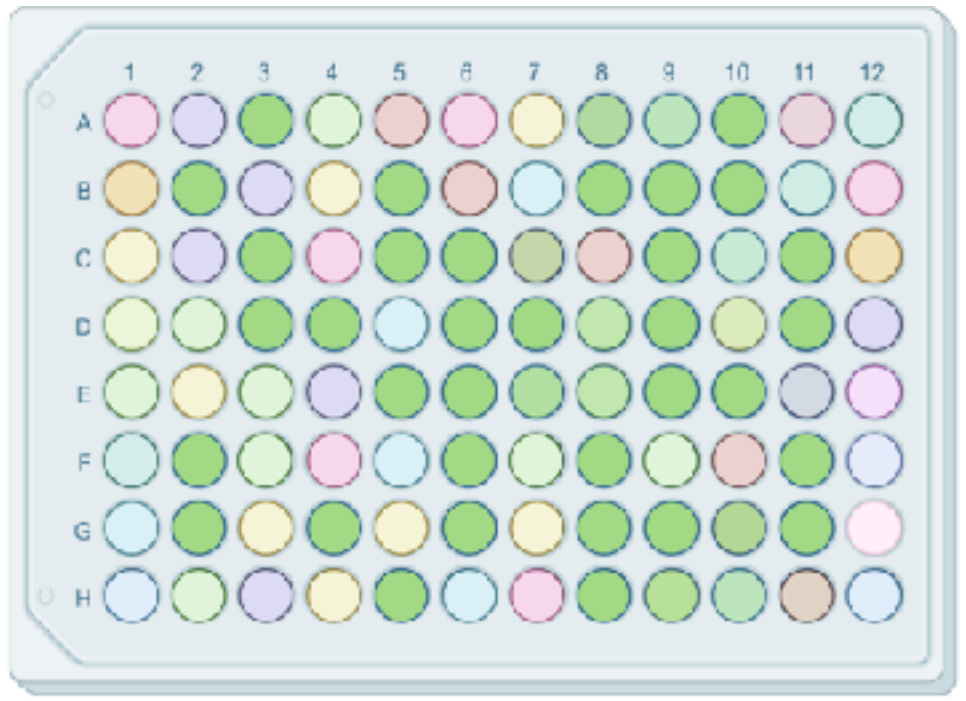
Lily of the Valley



Lilial



hydroxycitronellal



Random Screening

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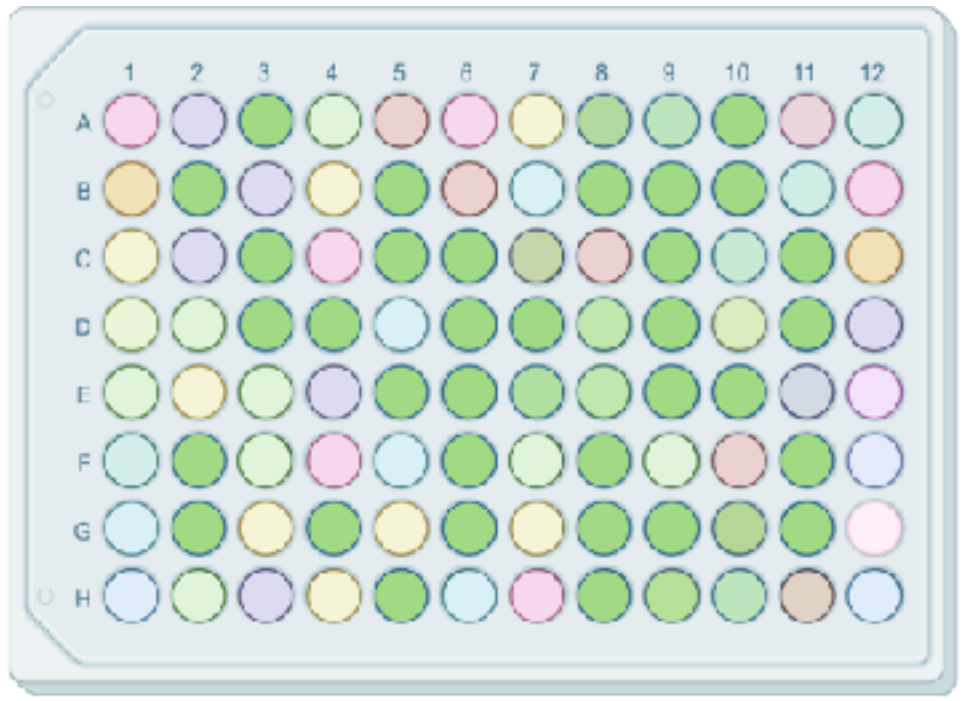
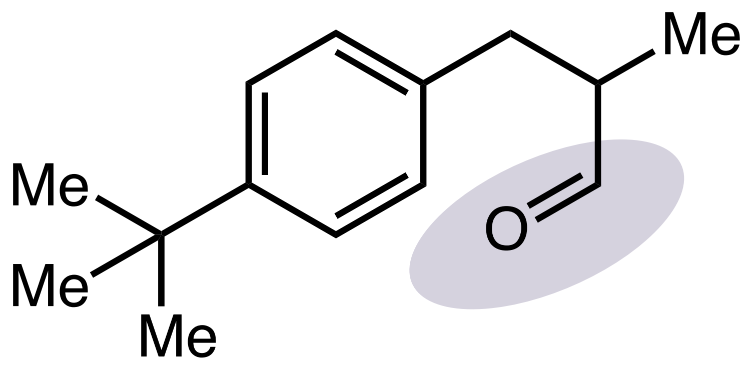
Random Screening

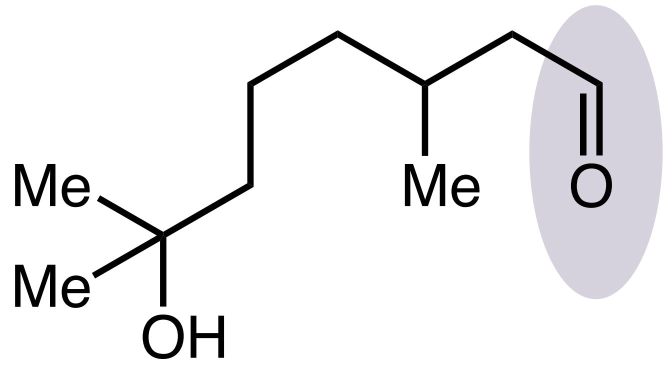
Lily of the Valley



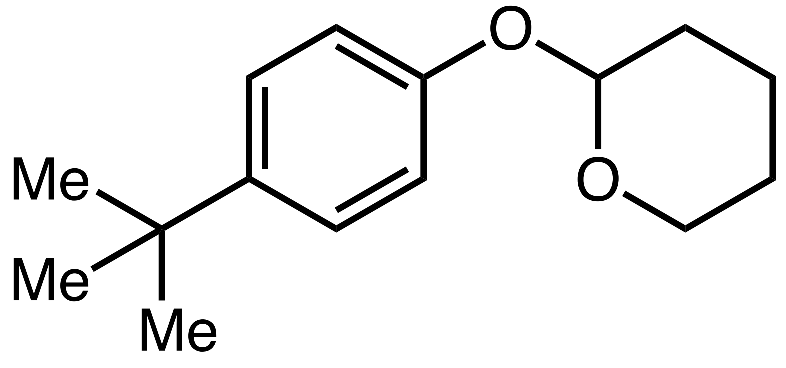
Random Screening



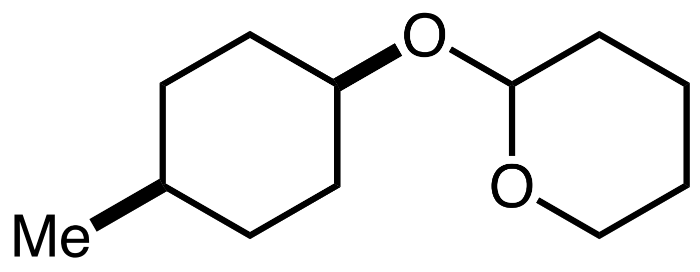
Lilial



hydroxycitronellal



33

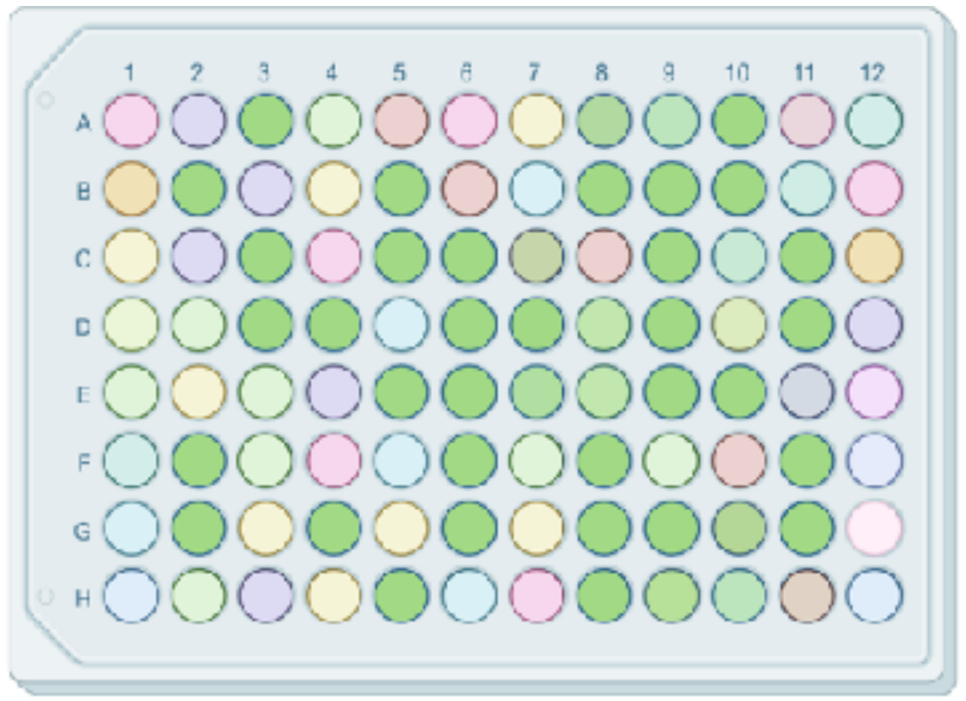


34

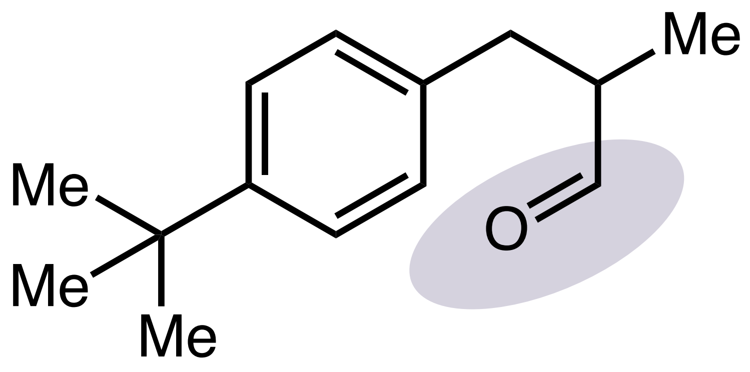
Anselmi, C.; Centini, M.; Mariani, M.; Sega, A.; Pelosi, P. *Journal of Agricultural and Food Chemistry* **1992,** *40* (5), 853-856.

Random Screening

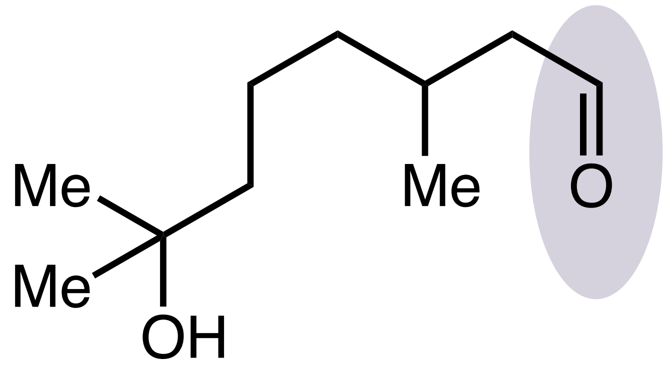
Lily of the Valley



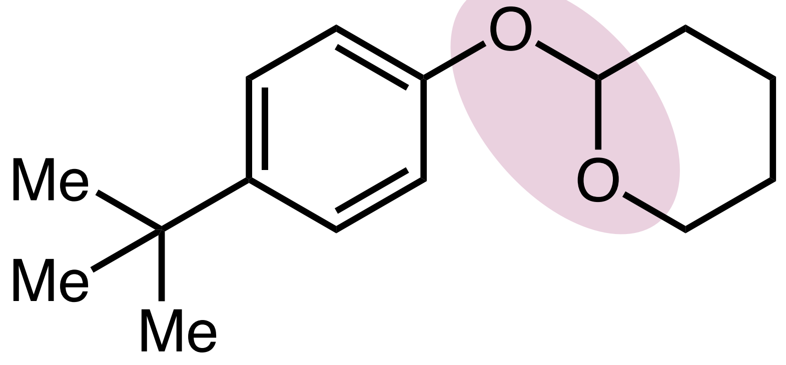
Random Screening



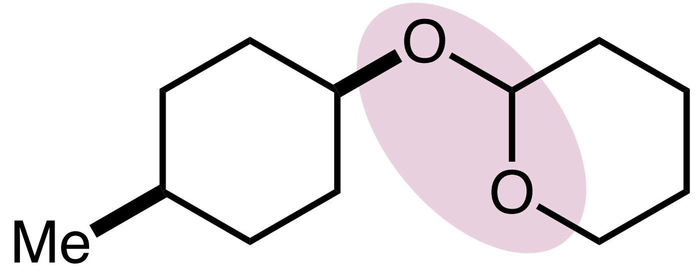
Lilial



hydroxycitronellal



33

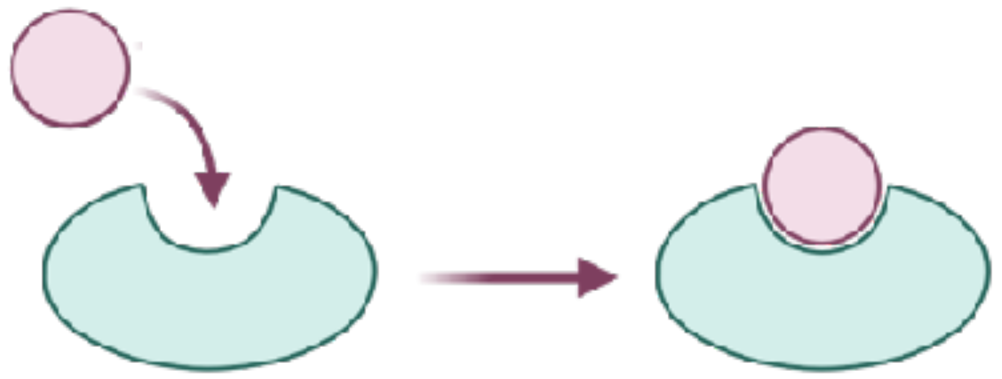


34

Anselmi, C.; Centini, M.; Mariani, M.; Sega, A.; Pelosi, P. *Journal of Agricultural and Food Chemistry* **1992,** *40* (5), 853-856.

Strategies for Novel Fragrance Design

Random Screening

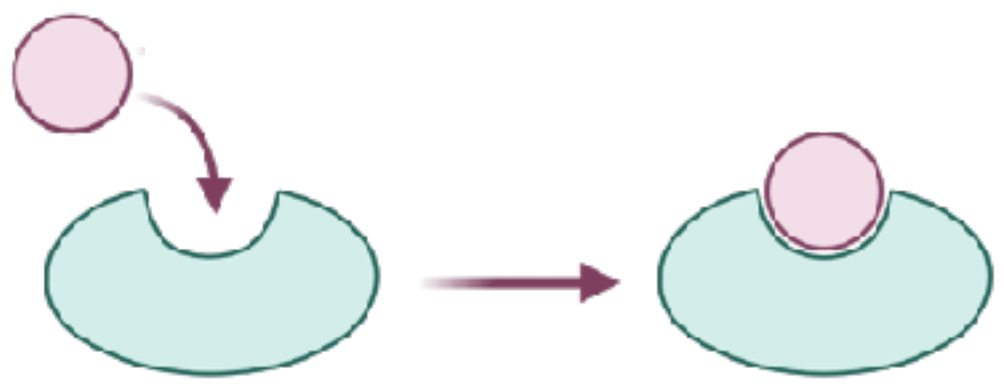


Mechanism of Action

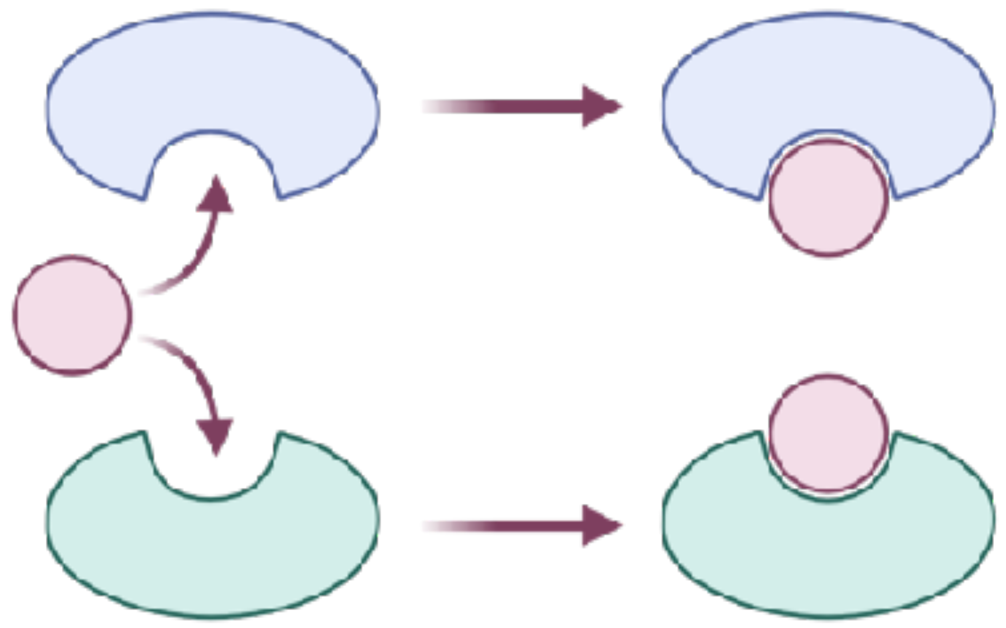
Statistical Design

Sell, C. S., *Chemistry of Fragrances*. The Royal Society of Chemistry: 2006.

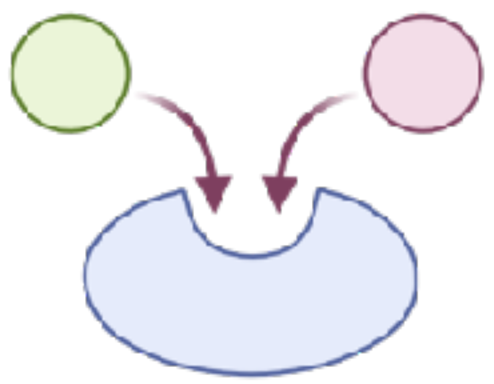
Mechanism of Action



Mechanism of Action



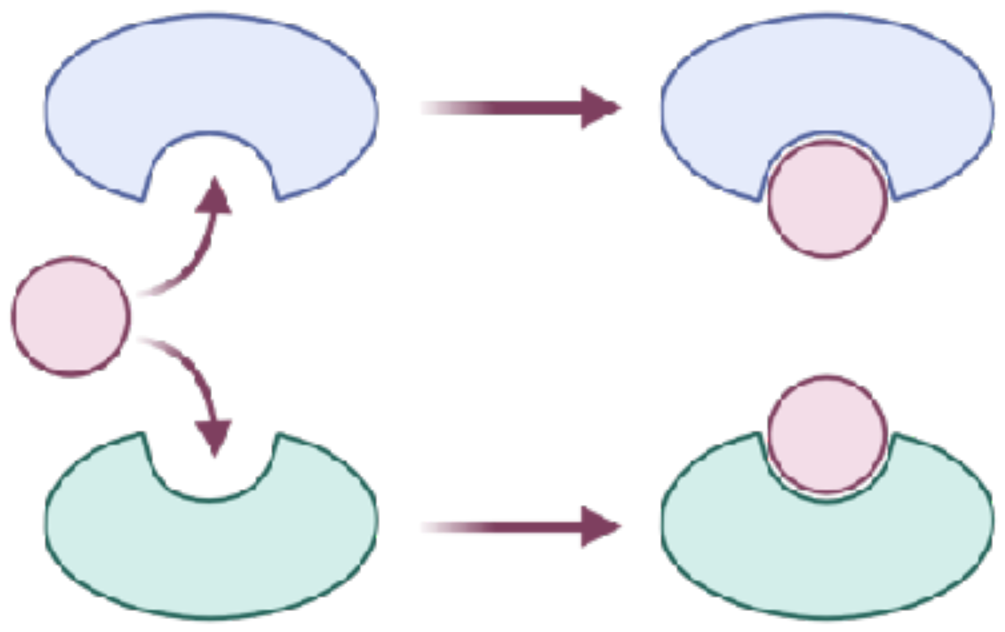
Odorant Promiscuity



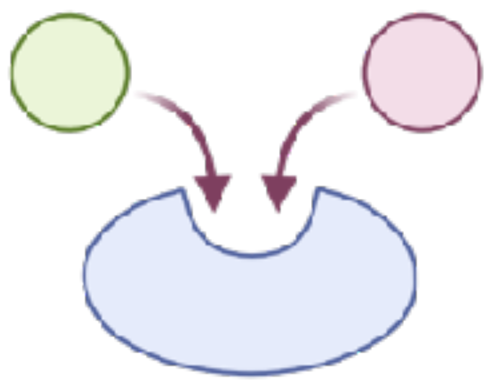
Binding Site Promiscuity

Sell, C. S., *Chemistry of Fragrances*. The Royal Society of Chemistry: 2006.

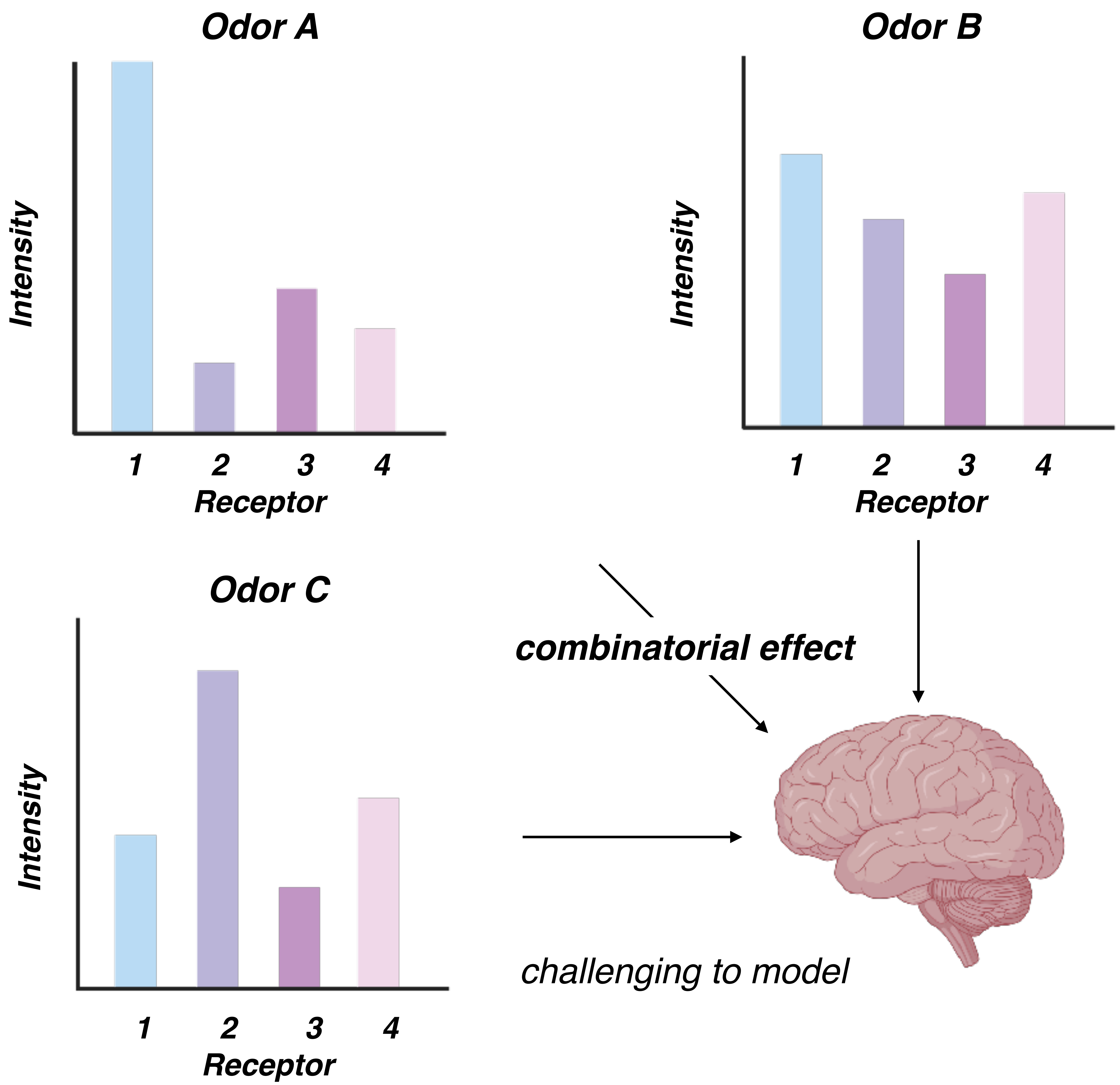
Mechanism of Action



Odorant Promiscuity



Binding Site Promiscuity

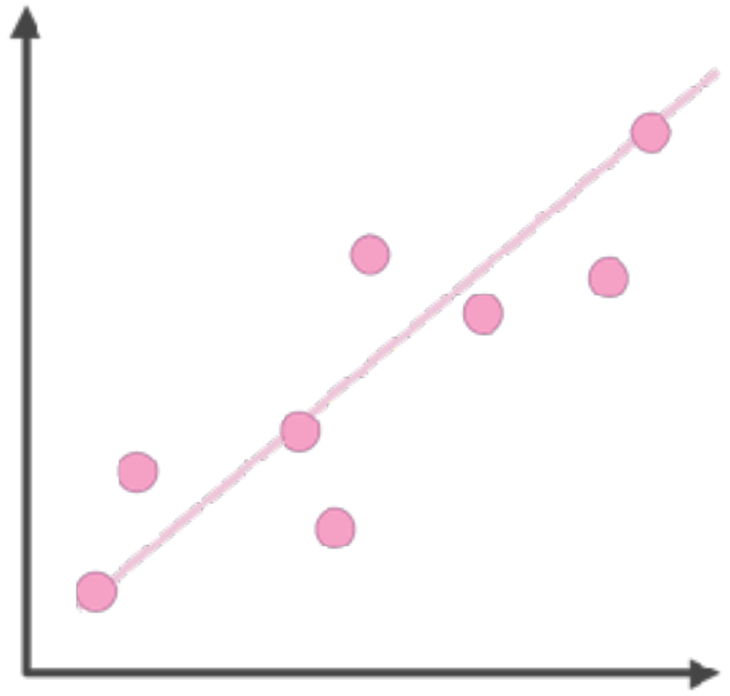


Sell, C. S., *Chemistry of Fragrances*. The Royal Society of Chemistry: 2006.

Strategies for Novel Fragrance Design

Random Screening

Mechanism of Action

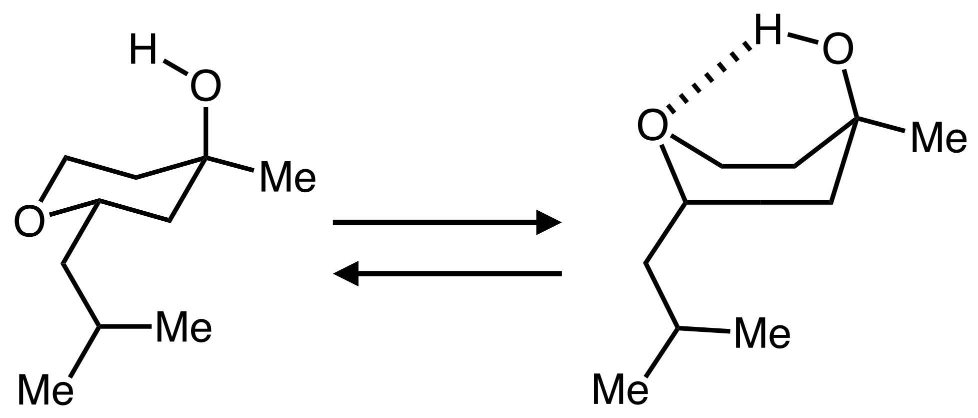


Statistical Design

Sell, C. S., *Chemistry of Fragrances*. The Royal Society of Chemistry: 2006.

Statistical Design

$$\log(\text{activity}) = f(\text{electronic}) + f(\text{steric}) + f(\log P)$$



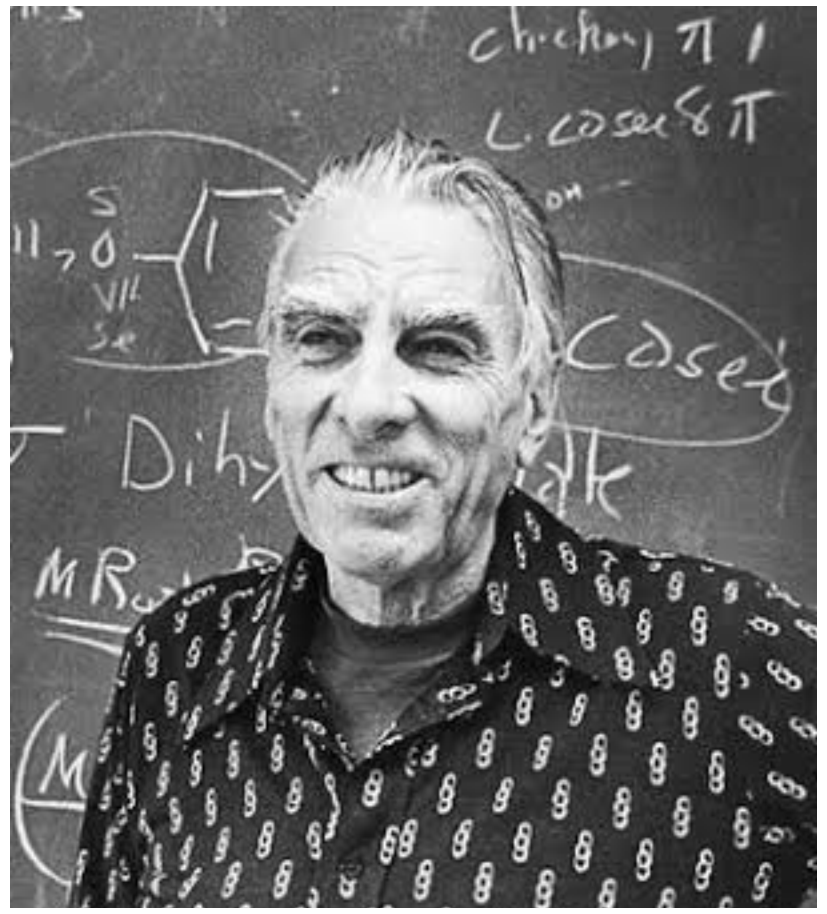
The Hansch Approach

Pattern Recognition

Olfactophores

Sell, C. S., *Chemistry of Fragrances*. The Royal Society of Chemistry: 2006.

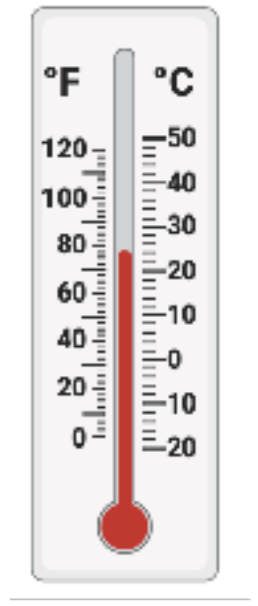
The Hansch Approach



Corwin Hansch (1918-2011)

log(activity) = *f*(electronic) + *f*(steric) + *f*(log *P*)

Physical Features

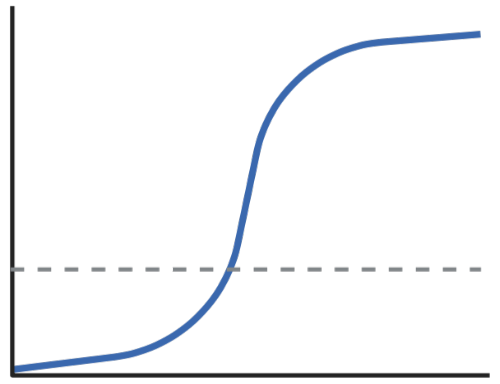


boiling point

vapor pressure

log(P)

Odor Properties



Threshold

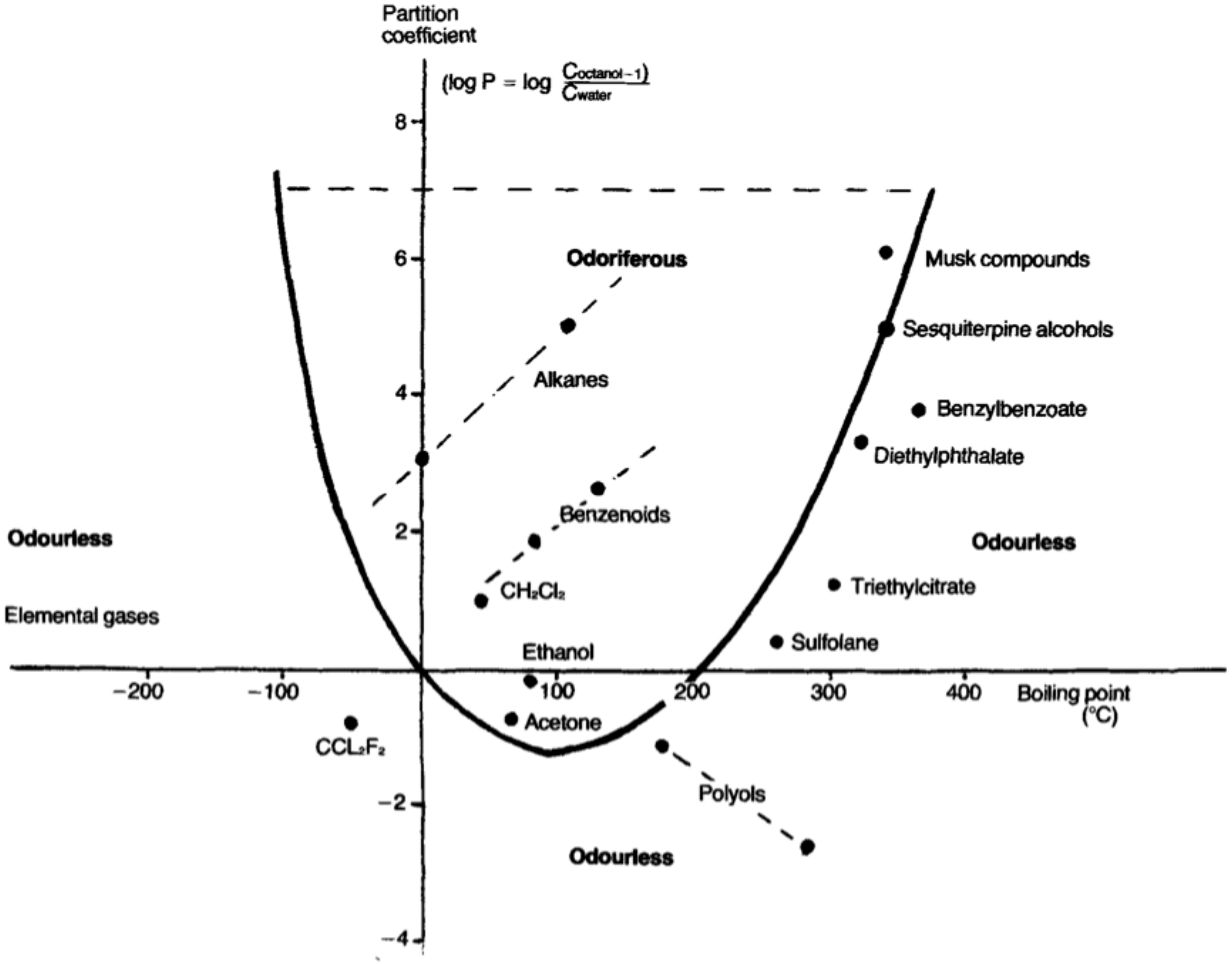
Impact

Similarity

Sell, C. S., *Chemistry of Fragrances*. The Royal Society of Chemistry: 2006.

The Hansch Approach

Odor correlated with boiling point and log(P)

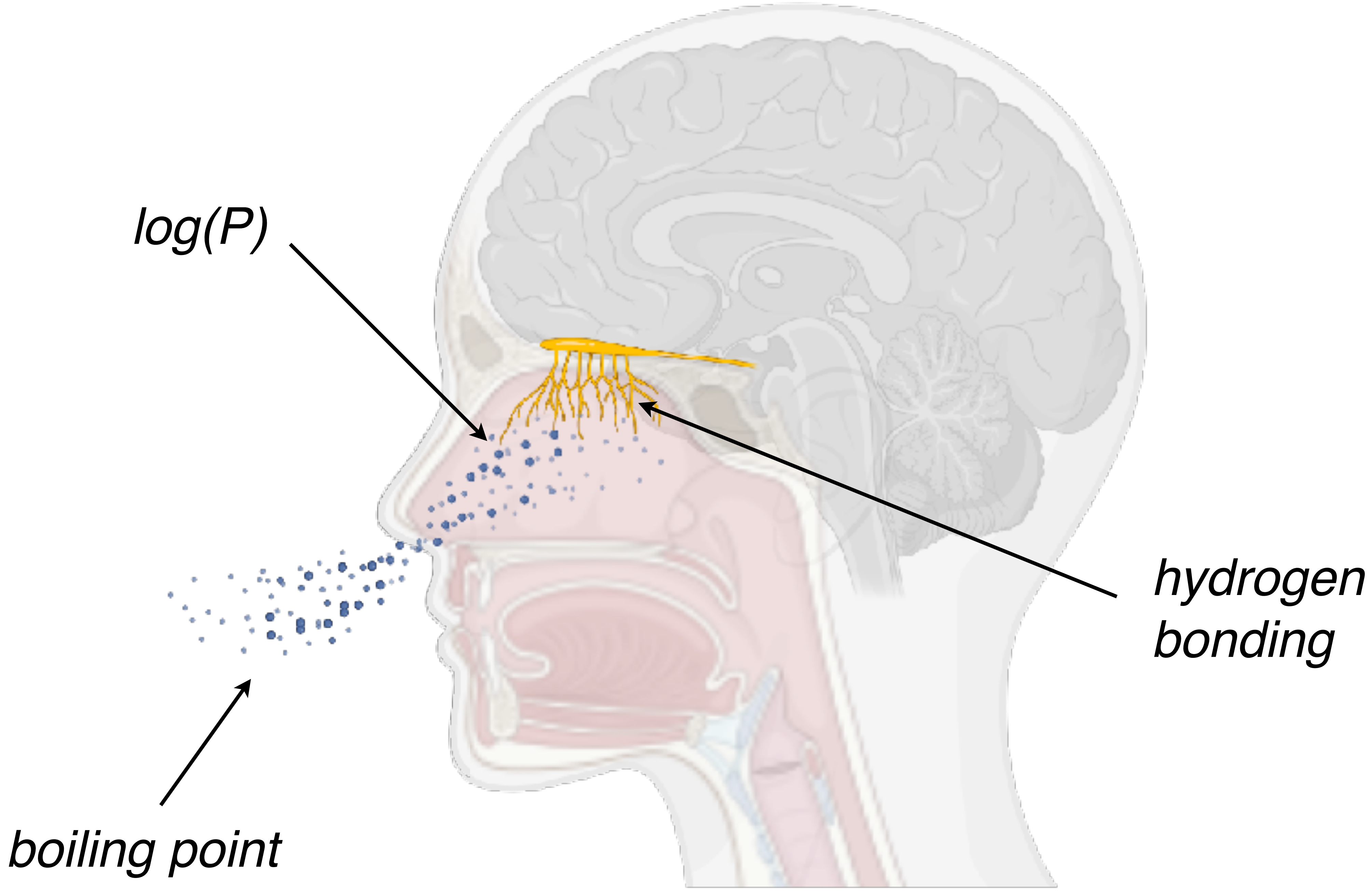


Odor intensity correlated with log(P) and hydrogen bonding

For a total of 50 ethers, alcohols, hydrocarbons, benzenoids

$$\log(1/c) = -0.38 + (0.19)(\mathbf{log\ P})^2 + 2.12 \pm (0.74)\ \mathbf{log\ P} + 1.18(0.48)\boldsymbol{HB} - 5.23 \pm (0.45)$$

$$n = 50,\ r^2 = 0.80,\ SD = 1.17$$

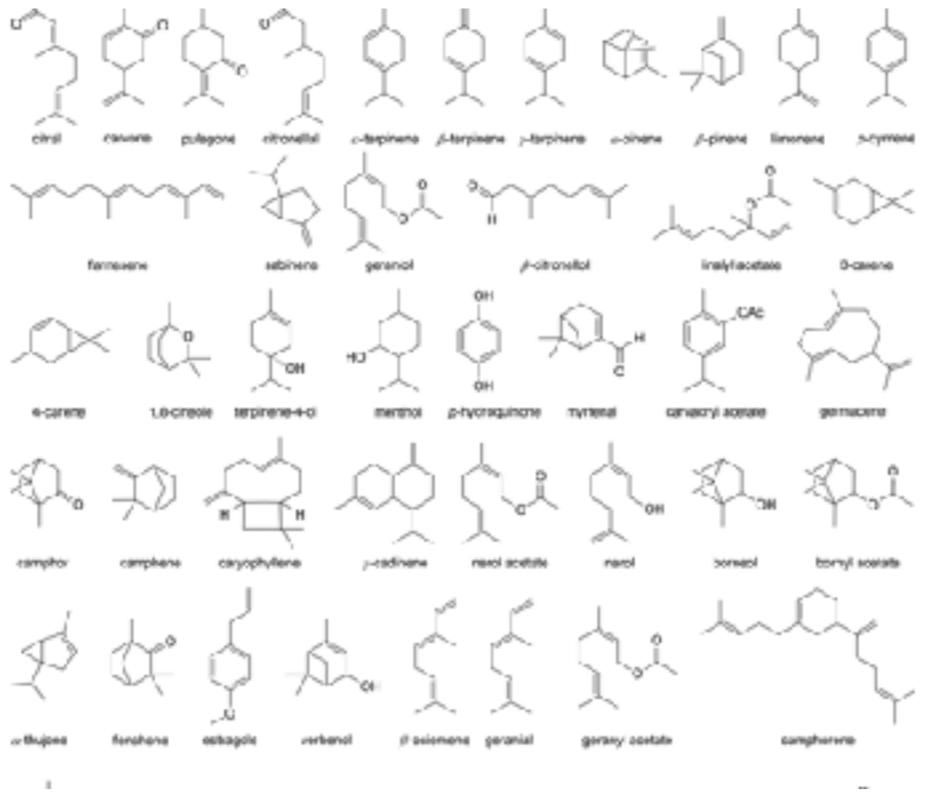


Greenberg, M. J. *Journal of Agricultural and Food Chemistry* **1979,** *27* (2), 347-352.

Boelens, H. *Trends in Pharmacological Sciences.* **1983**, 4, 421-426.

Pattern Recognition

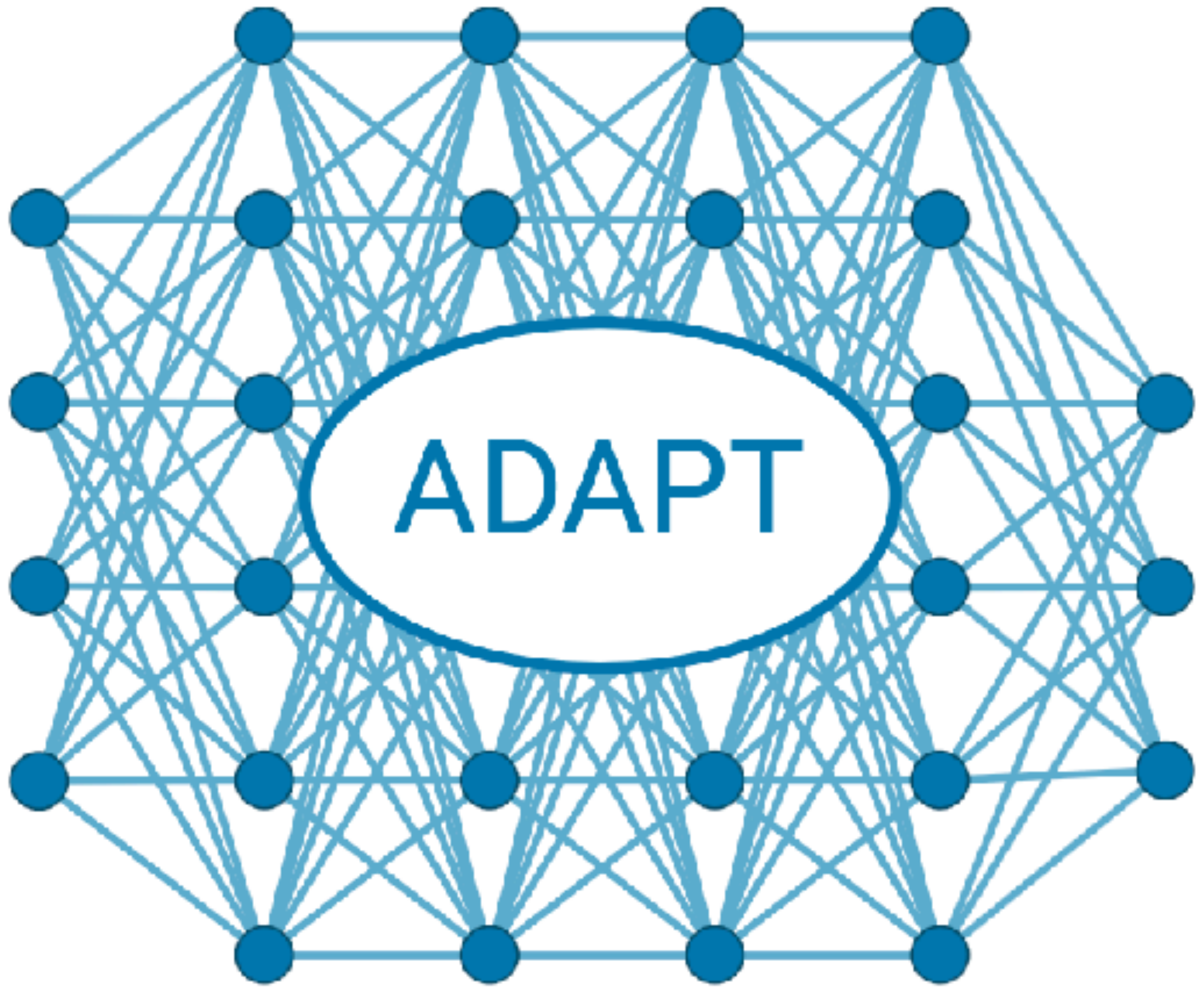
large number of compounds with structural diversity



+

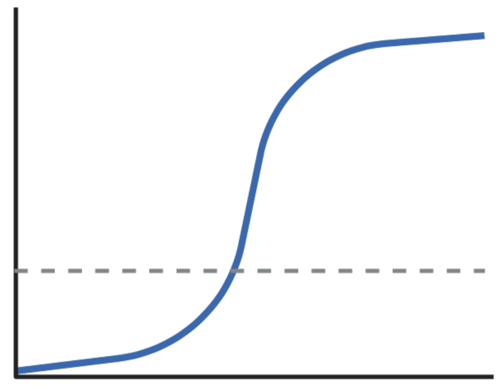
Molecular Descriptors

topological
geometrical
electronic
physicochemical



Automated Data Analysis using Pattern recognition Techniques

Molecular Classes



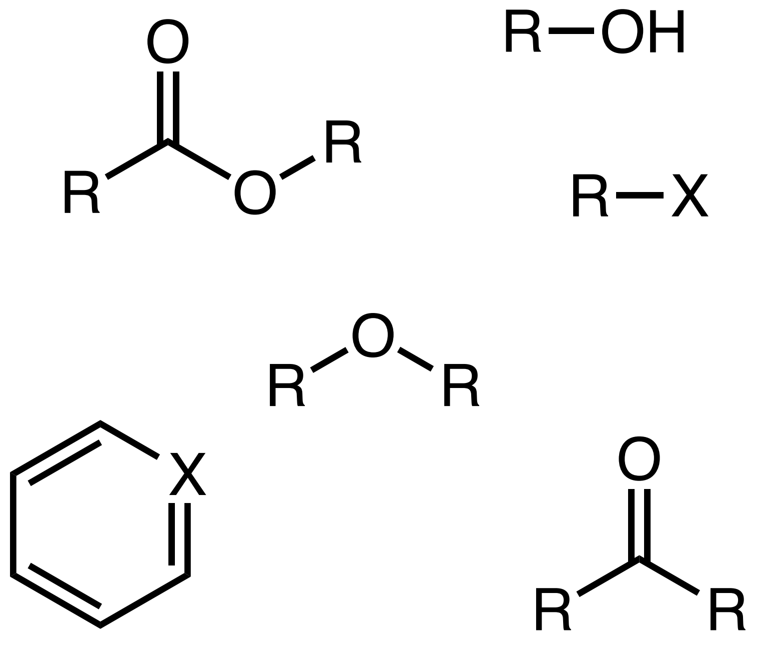
Threshold

Quantitative *or* Qualitative

Fragrance Classes

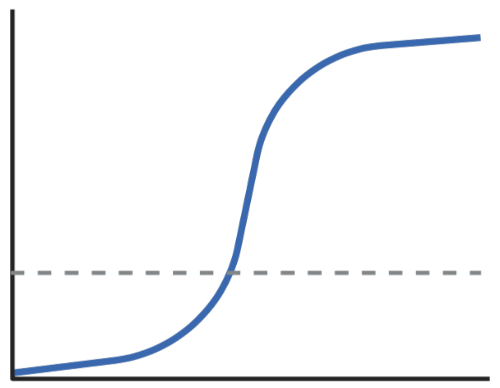
Sell, C. S., *Chemistry of Fragrances*. The Royal Society of Chemistry: 2006.

Pattern Recognition



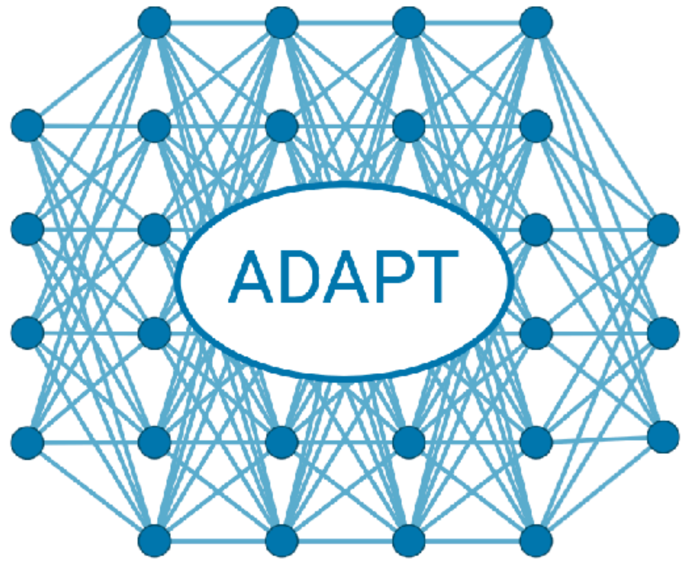
55 structures

+



Threshold

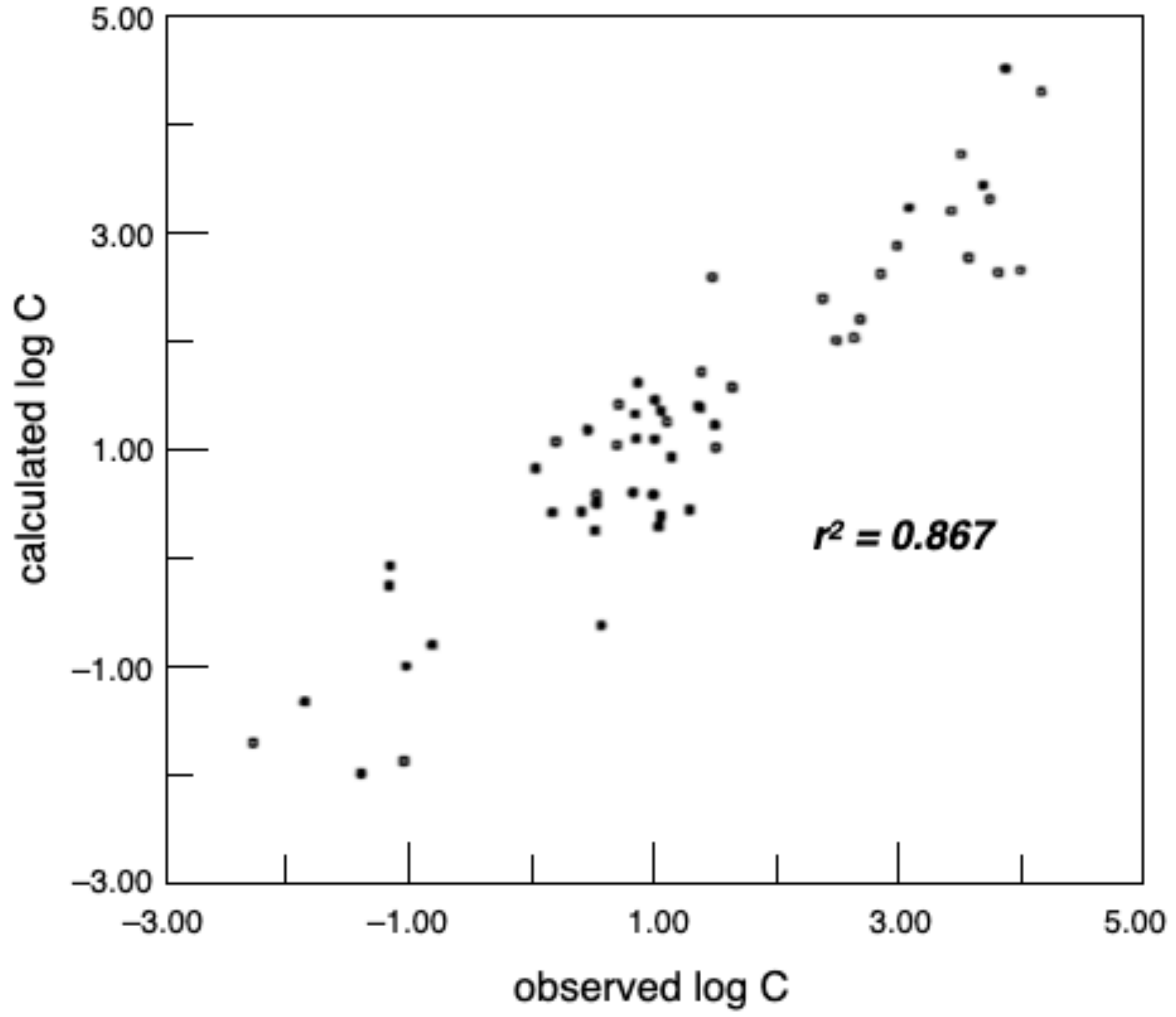
log C = log of concentration to produce odor equivalent to 87 ppm 1-butanol in air



85 molecular descriptors

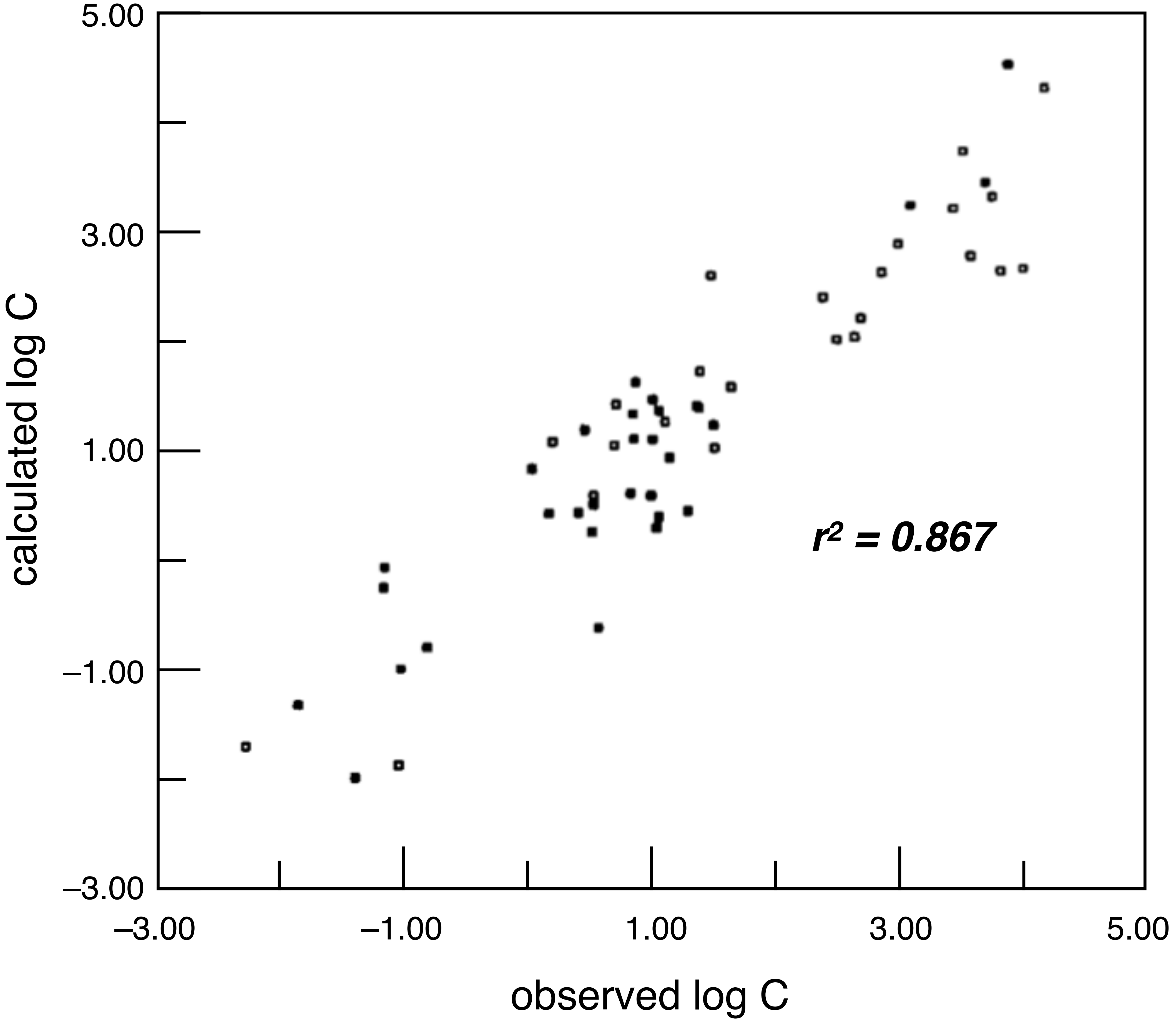
topological, structural, substructural, geometrical, electronic

Model developed



Edwards, P.A. and Jurs, P.C. Jurs, *Chem. Senses.* **1989**, *14*(2), 281.

Pattern Recognition



Descriptor	Coefficient (error)
log mol wt.	–7.02 (0.82)
charge on most negative atom	+3.93 (0.65)
polarity parameter (Δ)	+1.64 (0.32)
measure of unsaturation	–0.53 (0.14)
average distance sum connectivity	–0.74 (0.28)

Edwards, P.A. and Jurs, P.C. Jurs, *Chem. Senses.* **1989**, *14*(2), 281.

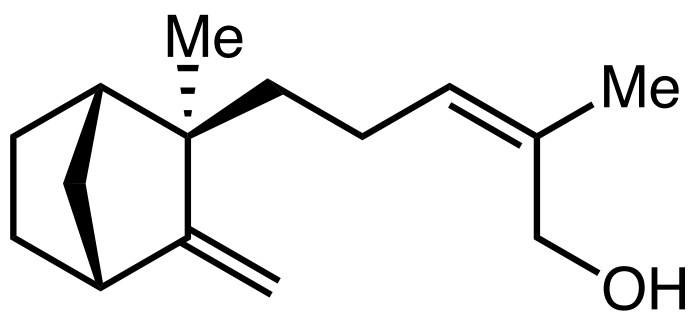
Olfactophores

olfactophore (or osmophore): 3-dimensional arrangement of chemical features in a molecule that is responsible for its olfactory activity

Sell, C. S., *Chemistry of Fragrances*. The Royal Society of Chemistry: 2006.

Olfactophores

Sandalwood Oil

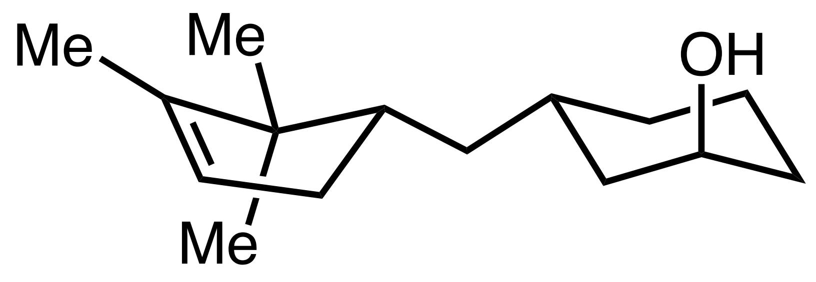


(–)-β-Santalol
principle smelling component

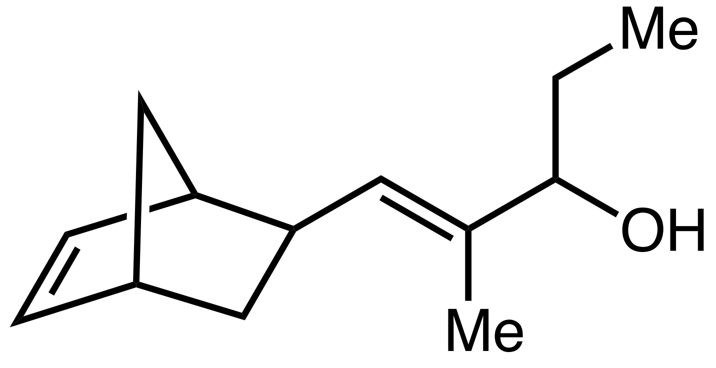
Active Analogue Approach: *assume a common conformation among an active series is responsible for odor*

Buchbauer, G.; Hillisch, A.; Mraz, K.; Wolschann, P. *Helvetica Chimica Acta* **1994,** *77* (8), 2286-2296.

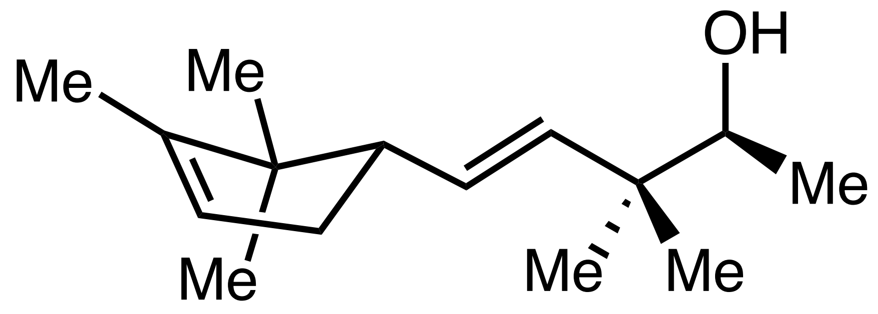
Sandalwood odor molecules



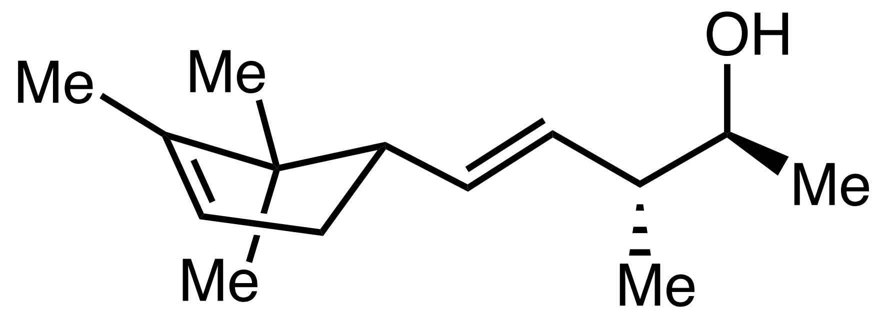
E



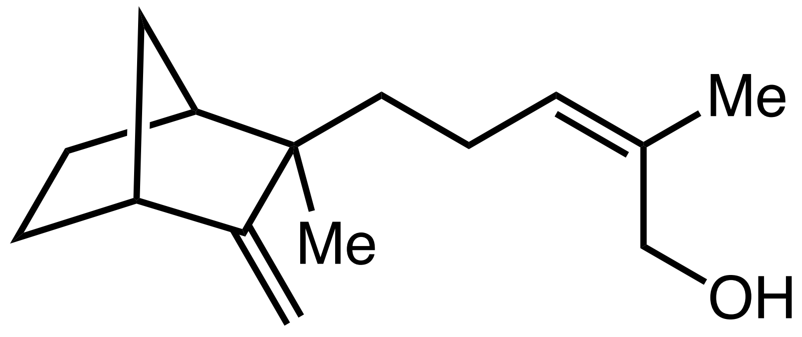
F



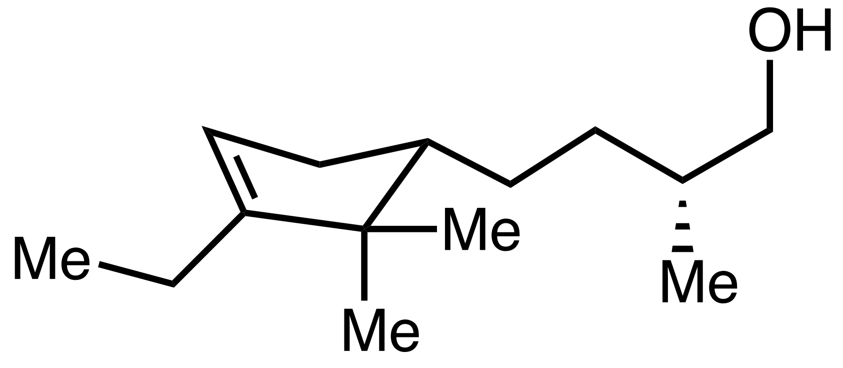
G



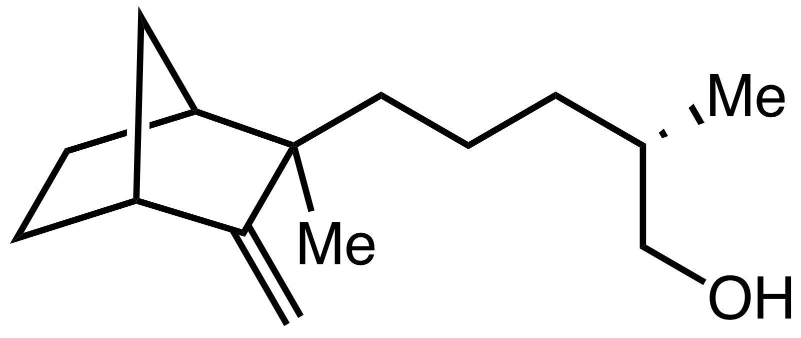
H



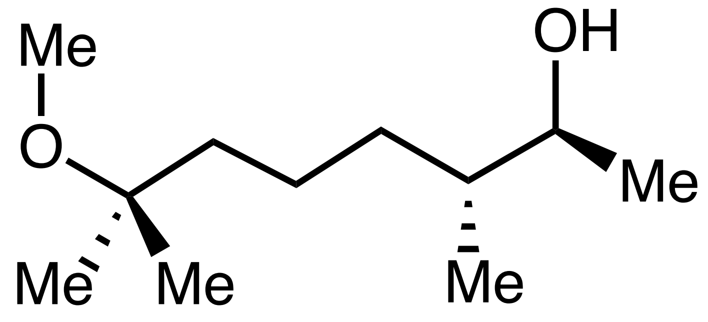
I *(–)-β-Santalol*



J



K

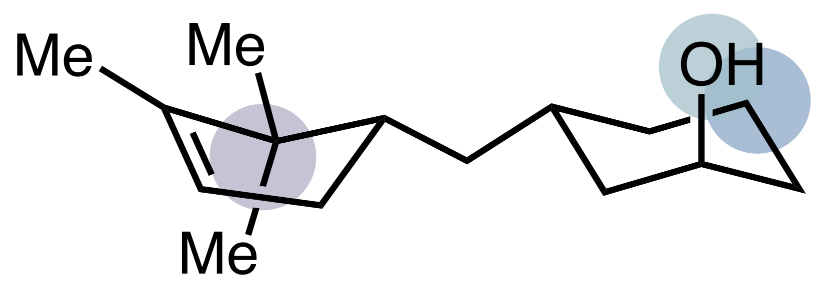


L

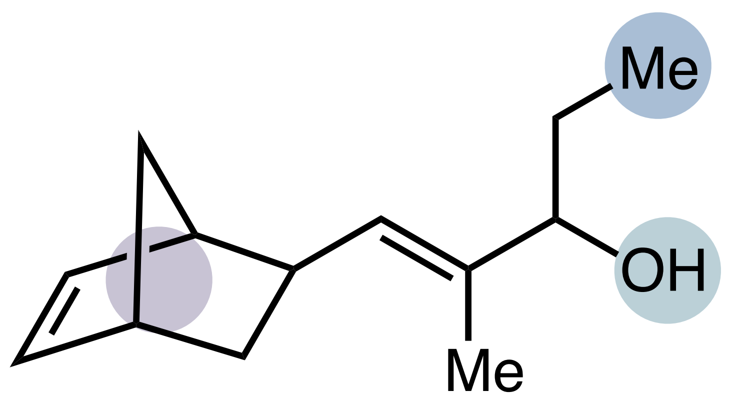
Buchbauer, G.; Hillisch, A.; Mraz, K.; Wolschann, P. *Helvetica Chimica Acta* **1994,** *77* (8), 2286-2296.

Olfactophores – Sandalwood

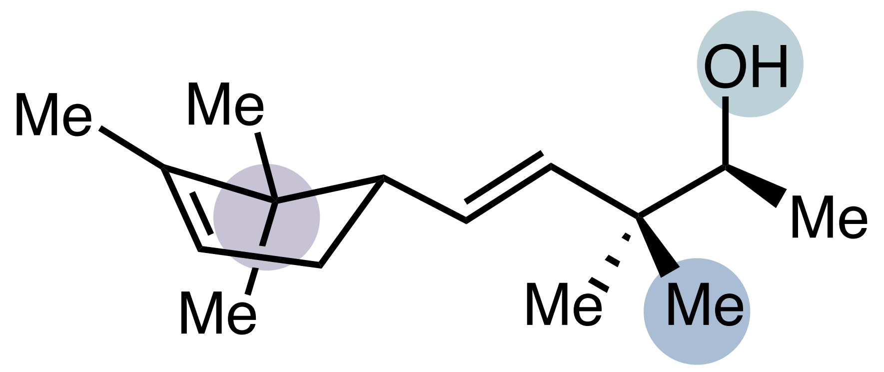
Sandalwood odor molecules



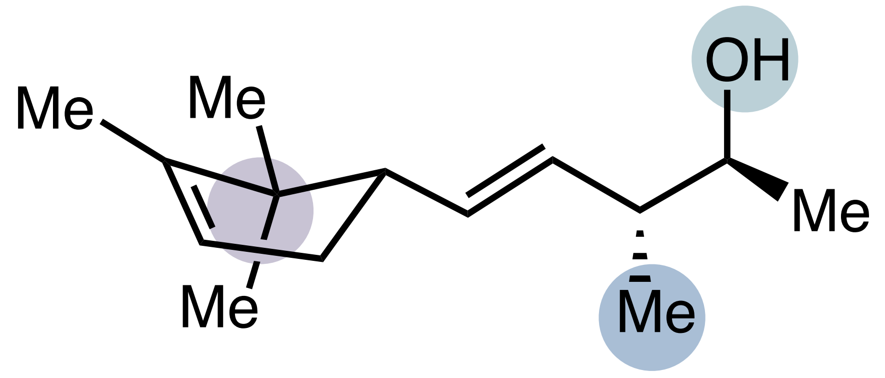
E



F



G



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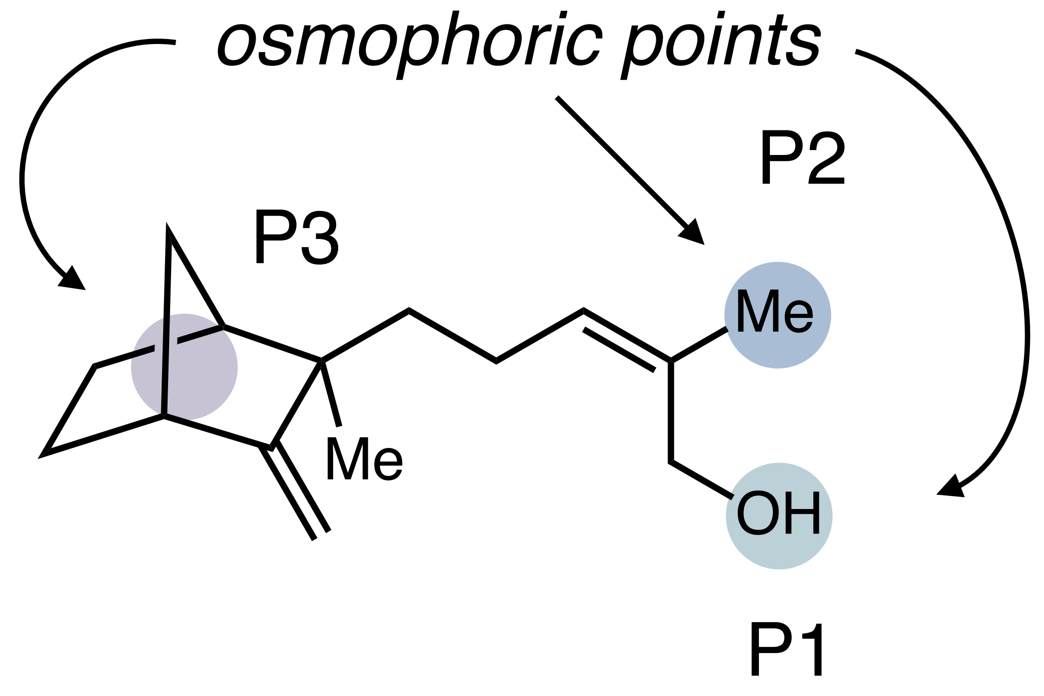
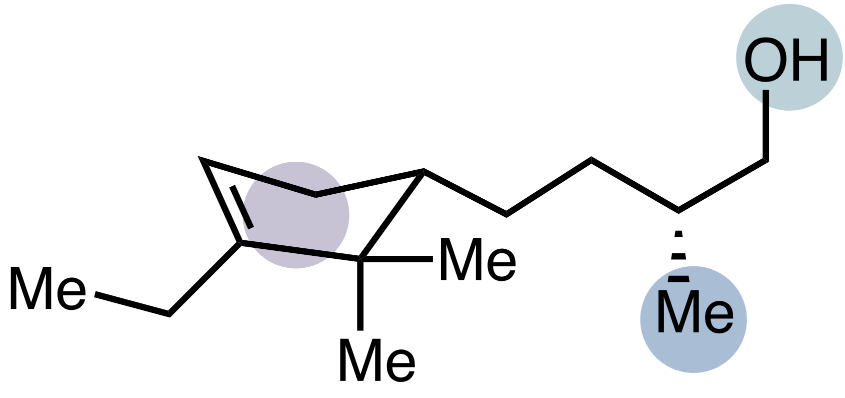
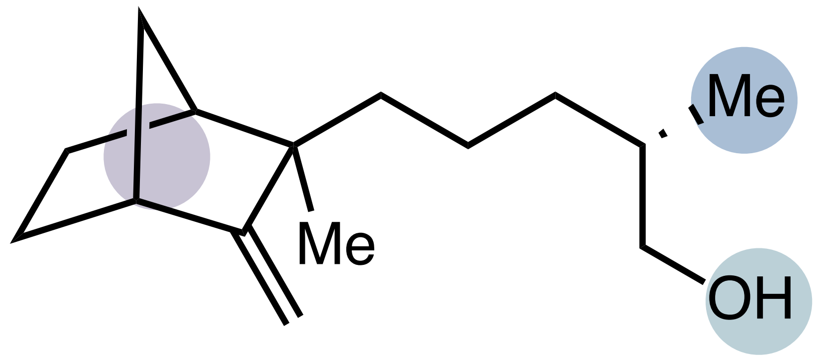


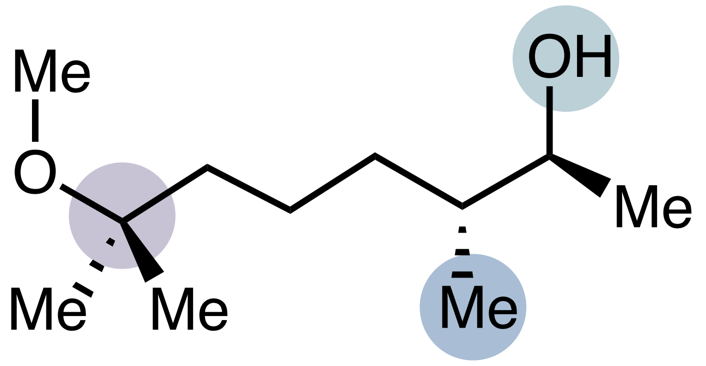
I *(–)-β-Santalol*



J



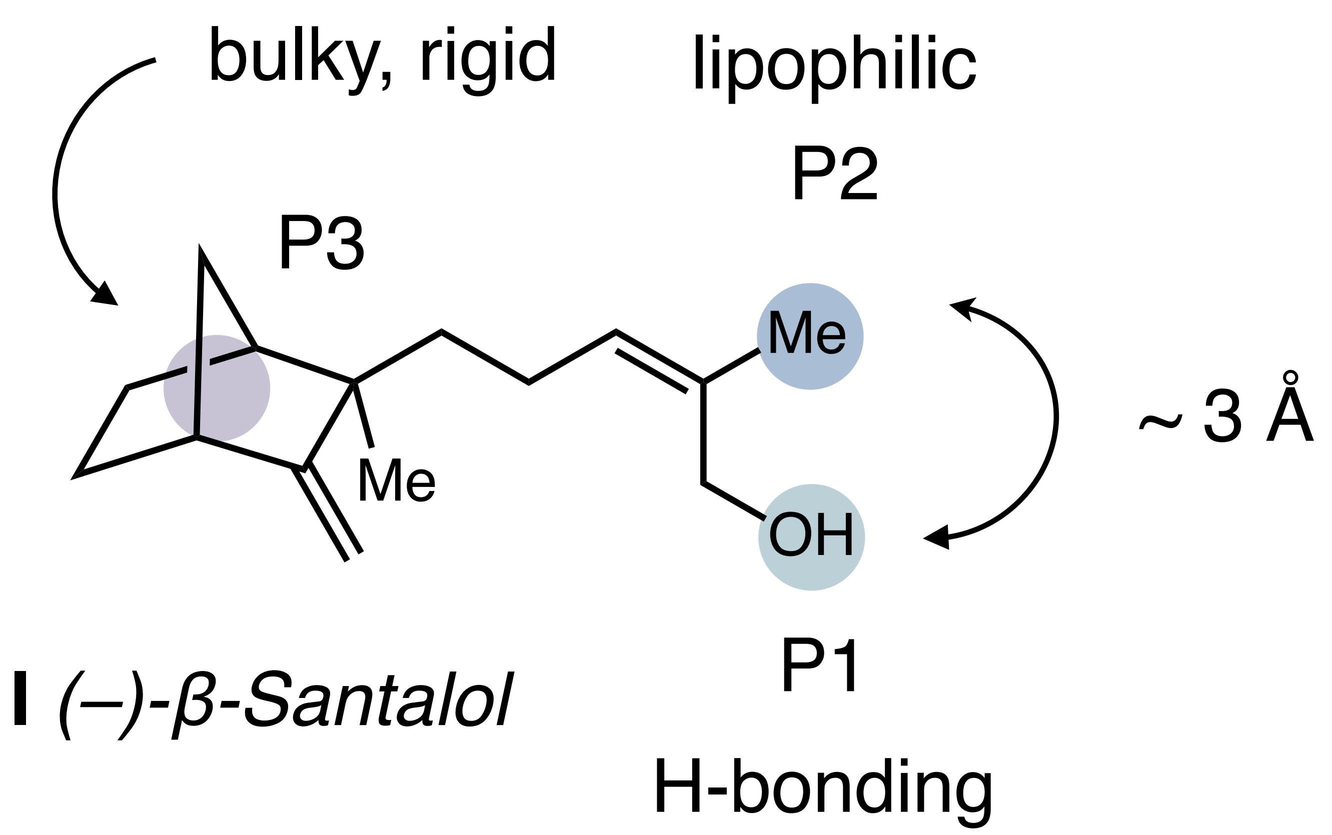
K



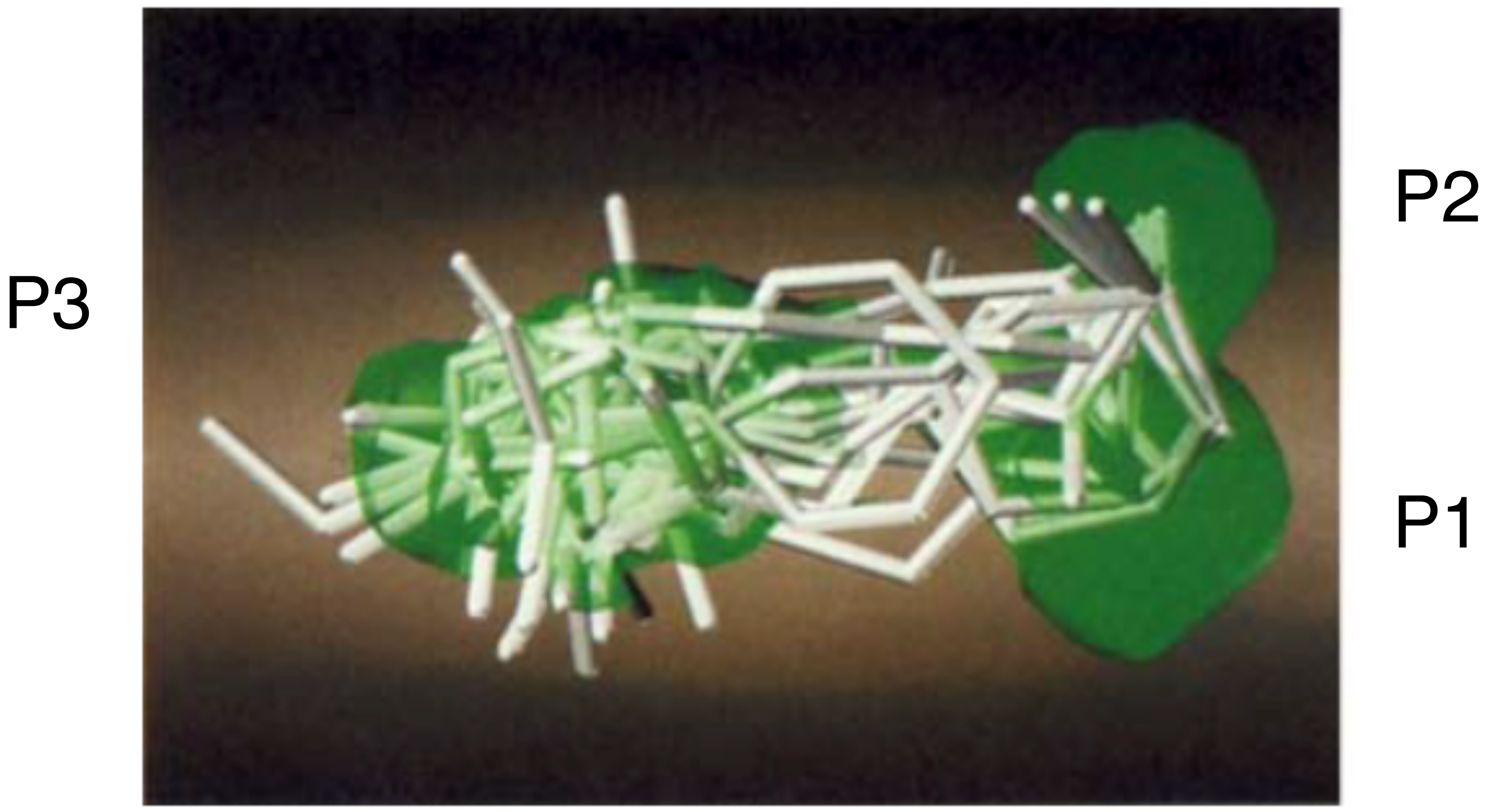
L

Buchbauer, G.; Hillisch, A.; Mraz, K.; Wolschann, P. *Helvetica Chimica Acta* **1994,** *77* (8), 2286-2296.

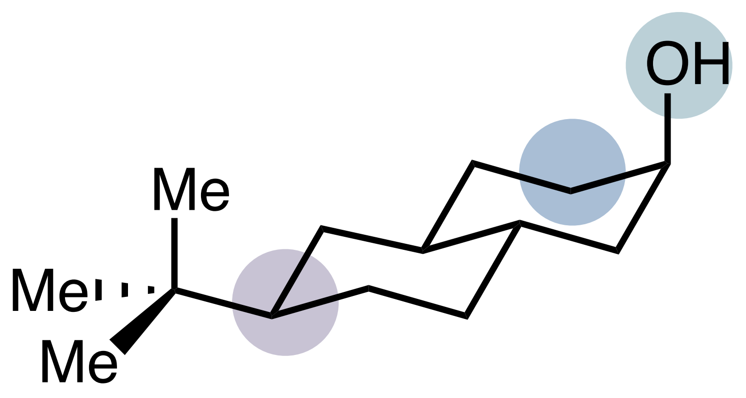
Olfactophores



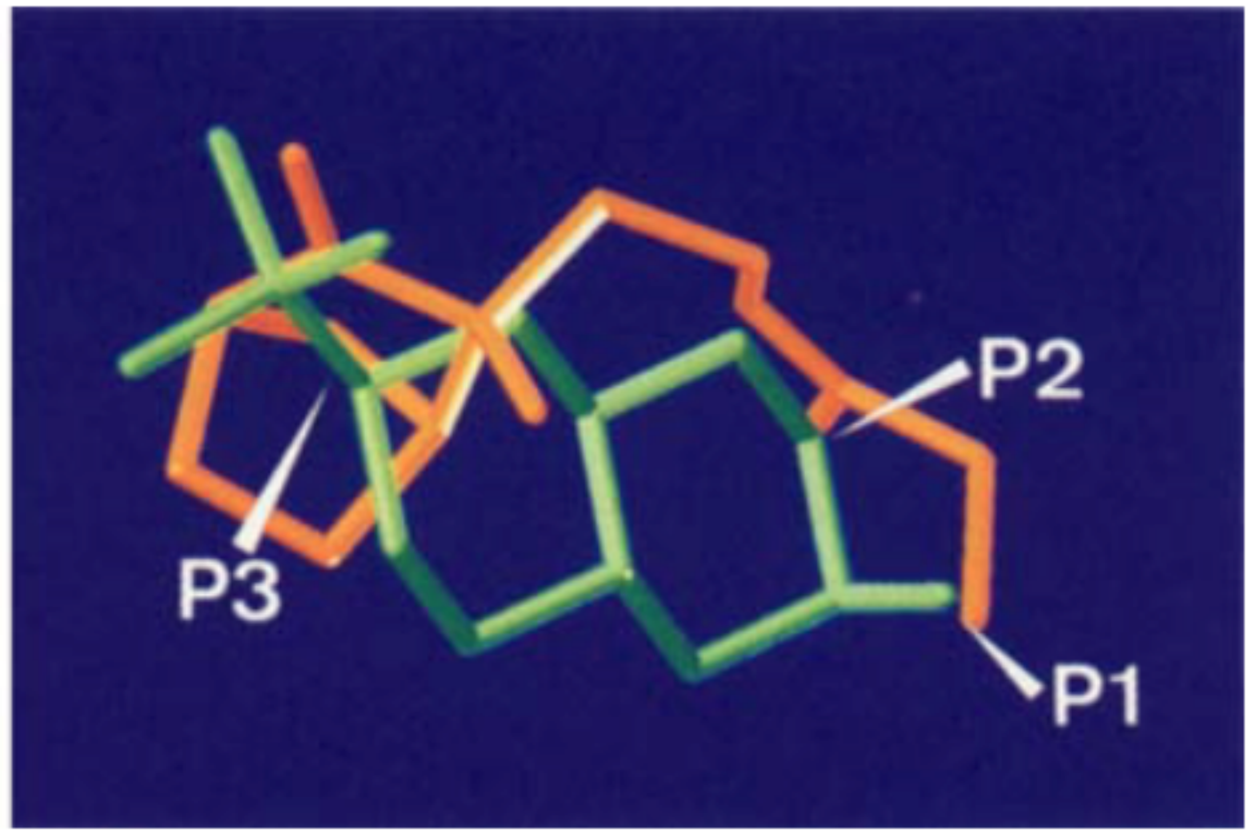
I *(–)-β-Santalol*



E-L overlay



A

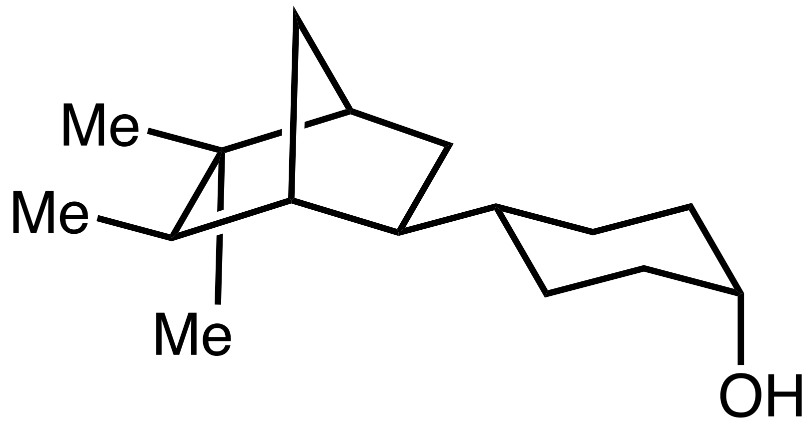


A-I overlay

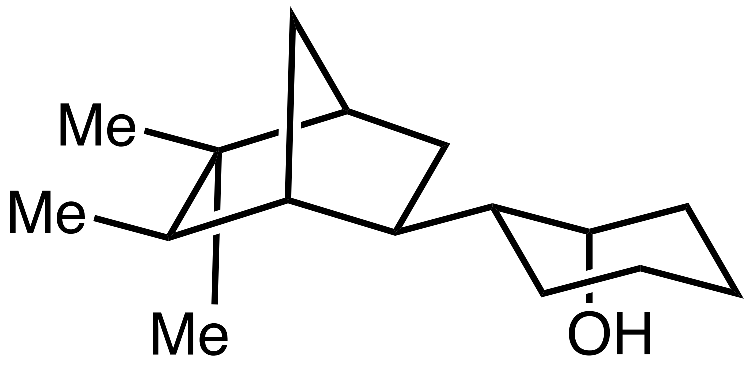
Buchbauer, G.; Hillisch, A.; Mraz, K.; Wolschann, P. *Helvetica Chimica Acta* **1994,** *77* (8), 2286-2296.

Olfactophores

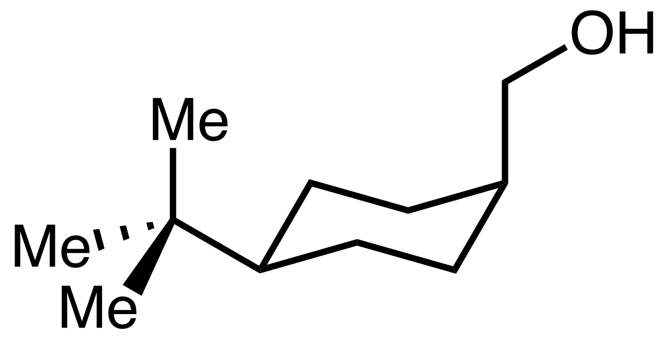
Odorless molecules



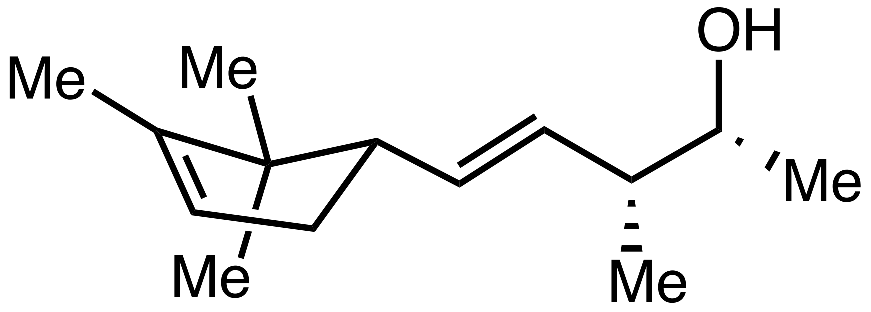
a



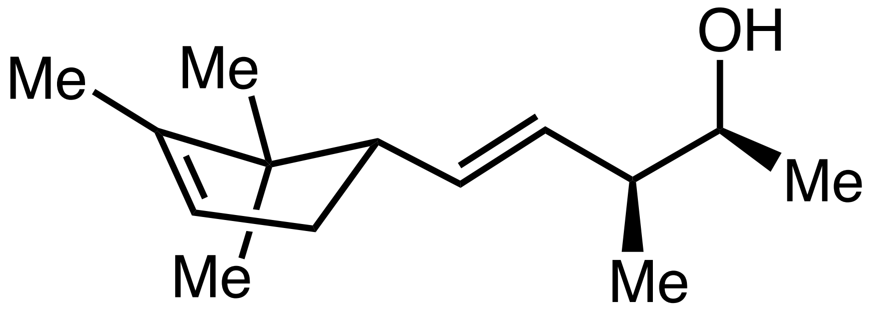
b



c



d



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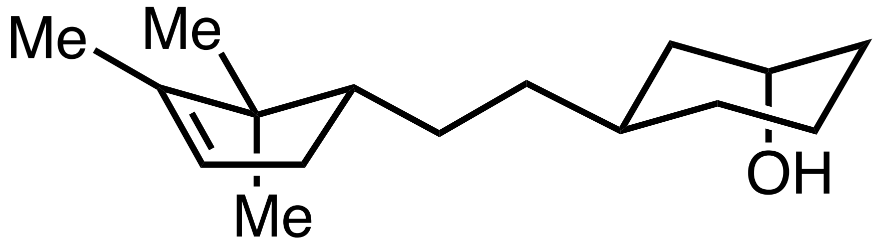
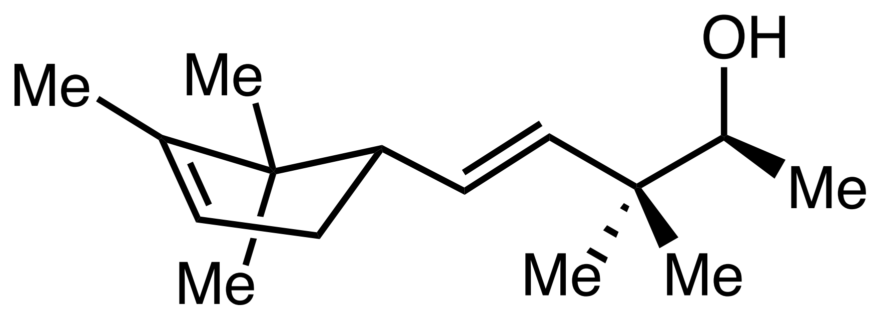


f

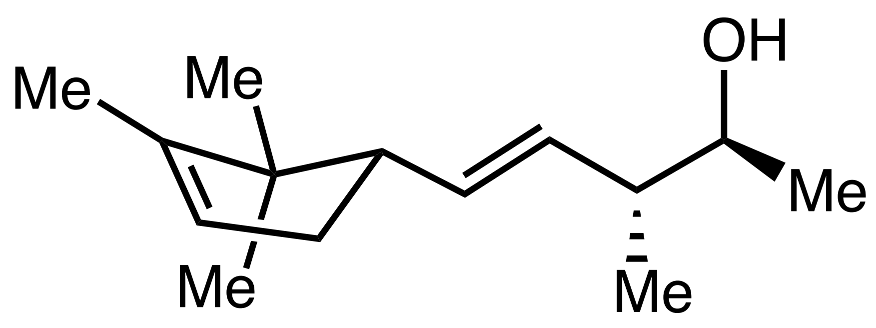
Buchbauer, G.; Hillisch, A.; Mraz, K.; Wolschann, P. *Helvetica Chimica Acta* **1994,** *77* (8), 2286-2296.

Olfactophores

Sandalwood Odor

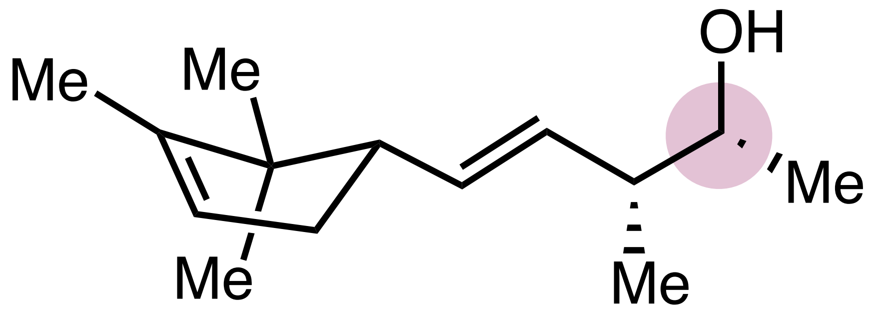


G



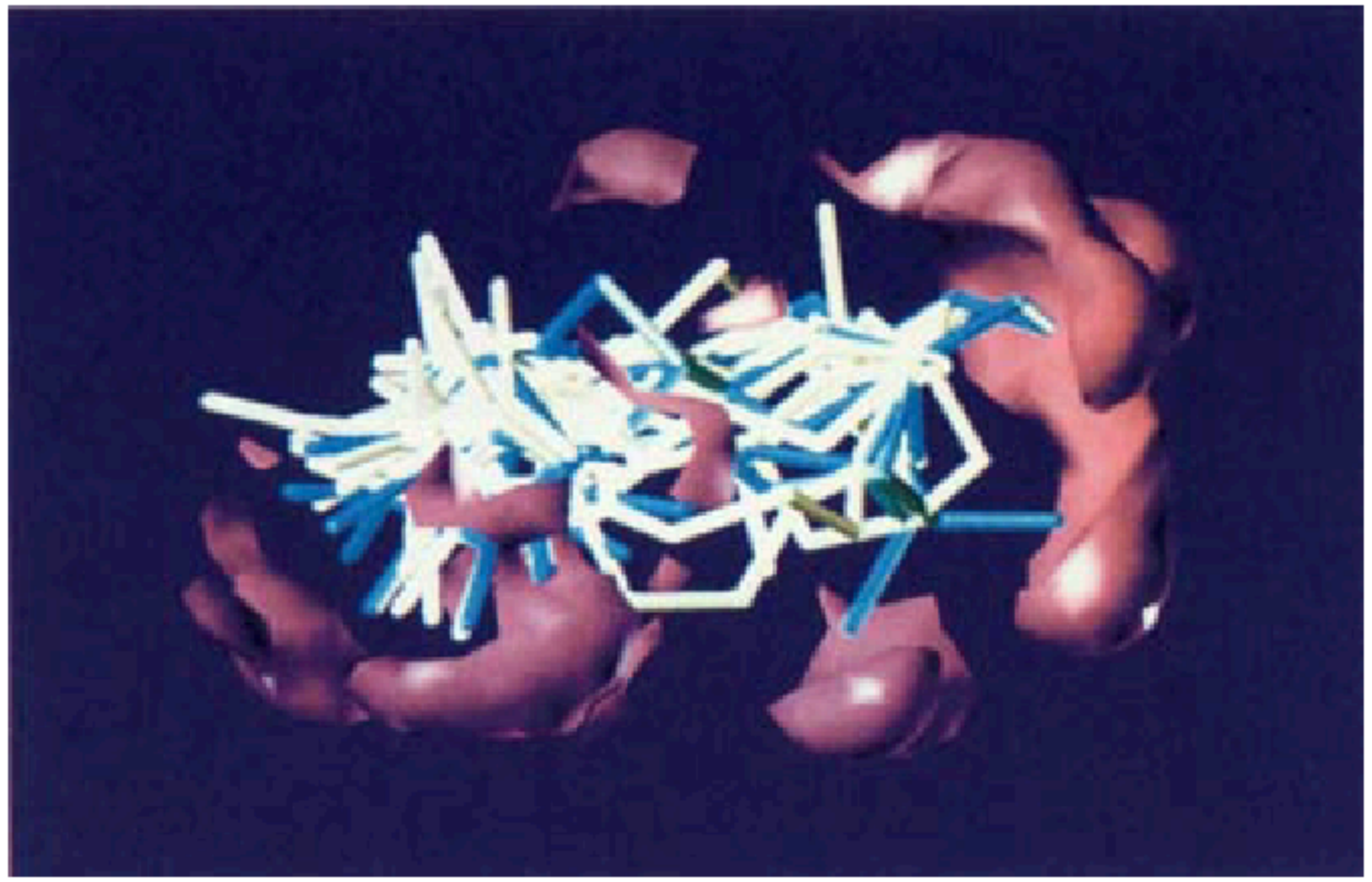
H

Odorless molecules



d

e



Overlay of Odor and Odorless Compounds

purple bulks represent deviations of odorless compounds

Buchbauer, G.; Hillisch, A.; Mraz, K.; Wolschann, P. *Helvetica Chimica Acta* **1994,** *77* (8), 2286-2296.

The Discovery of Nympheal

Lily of the Valley (Convallaria majalis)

Nympheal™ — Floral and Muguet scent by Givaudan

Goeke, A.; Kraft, P.; Lelievre, D.; Alchenberger, A. *Perfum. Flavor* **2018,** *43*, 25-40.

The Discovery of Nympheal

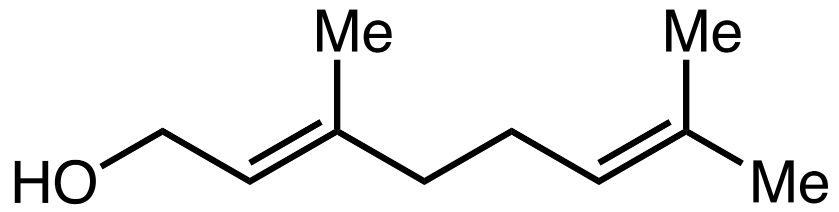
Lily of the Valley (Convallaria majalis)

- Very delicate odor mixture
- No commercial essential oil exists
- Even CO_2 (l) extraction destroys odor
- No principle natural odorant exists

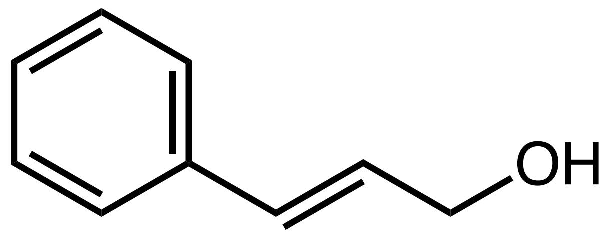
Goeke, A.; Kraft, P.; Lelievre, D.; Alchenberger, A. *Perfum. Flavor* **2018,** *43*, 25-40.

The First Synthetic Muguet Oil

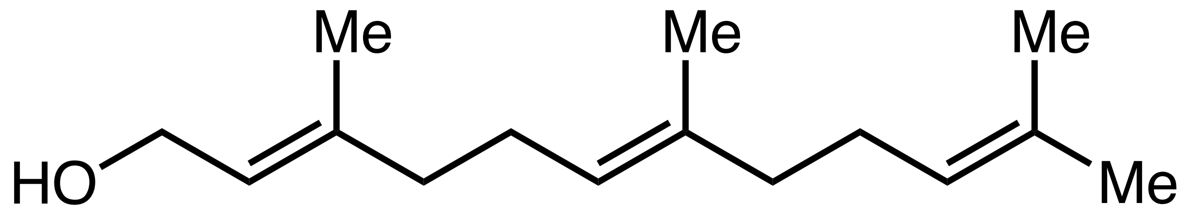
"Synthetic muguet oil"
1902 by Haarmann&Reimer



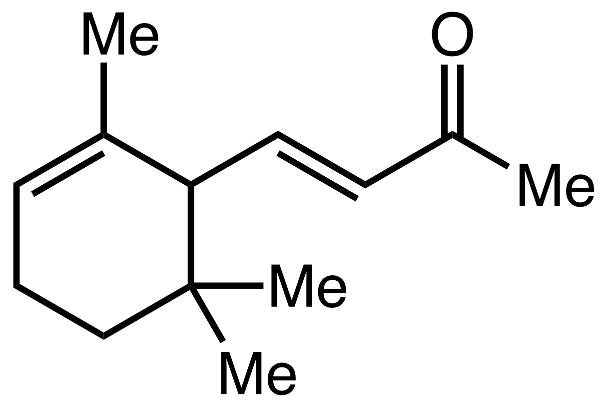
geranoil or geranium oil (50)



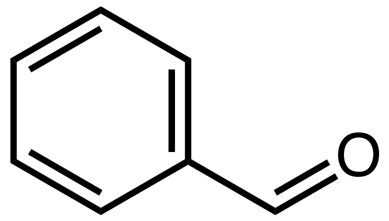
cinnamic alcohol (30)



farnesol (20)



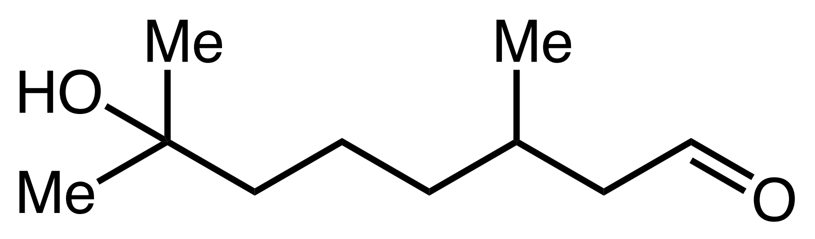
α-ionone (2)



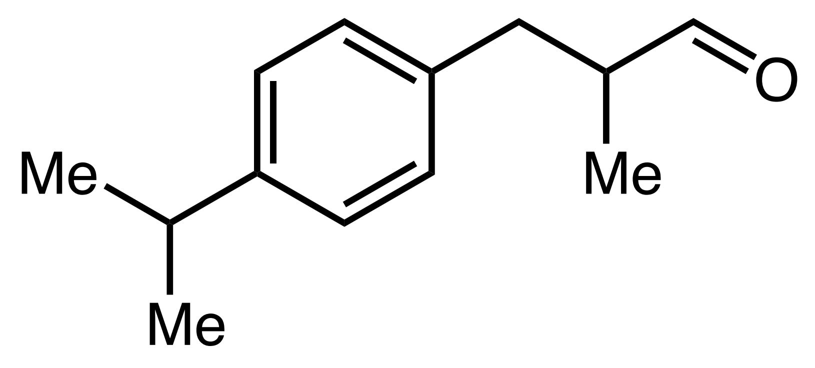
benzaldehyde (1)

Goeke, A.; Kraft, P.; Lelievre, D.; Alchenberger, A. *Perfum. Flavor* **2018,** *43*, 25-40.

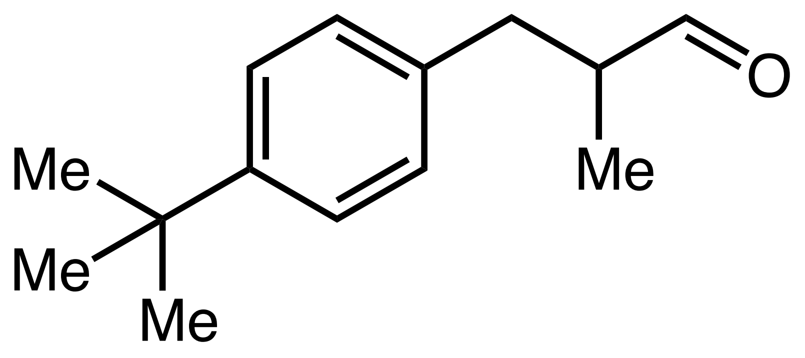
The Discovery of Nympheal



hydroxycitronellal
th 4.8 ng/L air
(1905)



cyclamen aldehyde
("Aldehyde B")
th 2.5 ng/L air
(1919)



Lilial
th 0.45 ng/L air
(1956)

potential reprotoxin

Goeke, A.; Kraft, P.; Lelievre, D.; Alchenberger, A. *Perfum. Flavor* **2018,** *43*, 25-40.

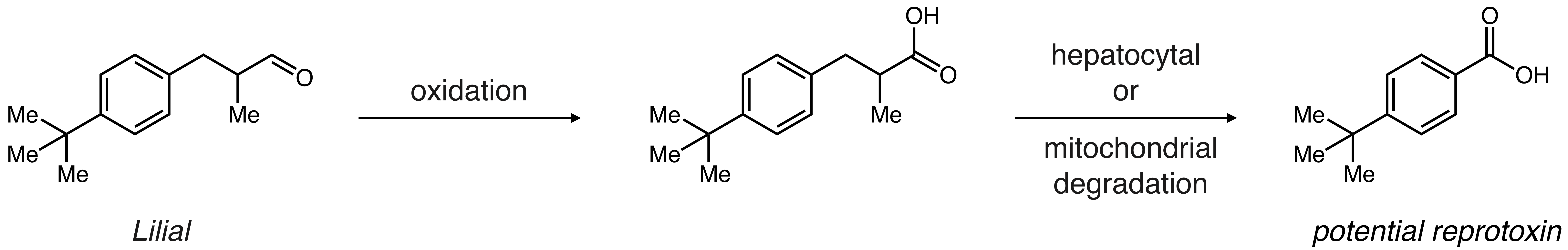
The Discovery of Nympheal – Goals

1. olfactory properties to be close as possible to Lilial

2. molecule should be free of structural elements that could cause reprotoxictiy issues

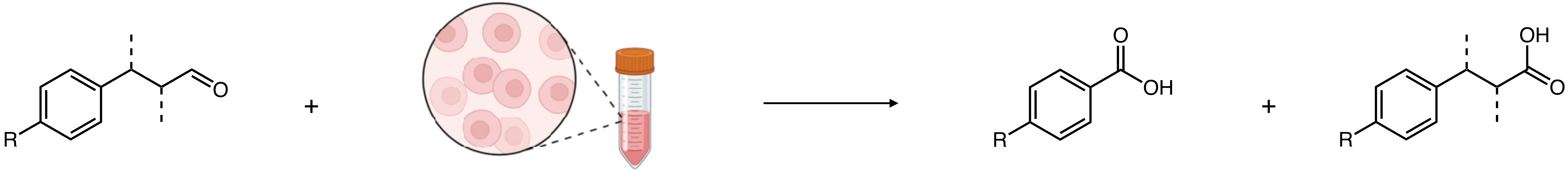
Goeke, A.; Kraft, P.; Lelievre, D.; Alchenberger, A. *Perfum. Flavor* **2018,** *43*, 25-40.

Lilial Degradation Pathway



Goeke, A.; Kraft, P.; Lelievre, D.; Alchenberger, A. *Perfum. Flavor* **2018,** *43*, 25-40.

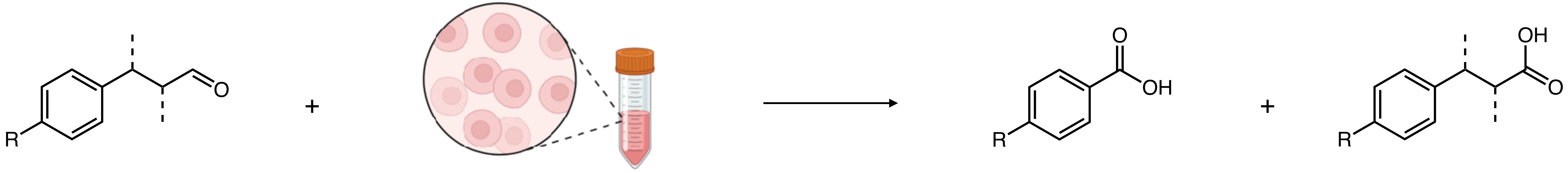
Degradation Assay



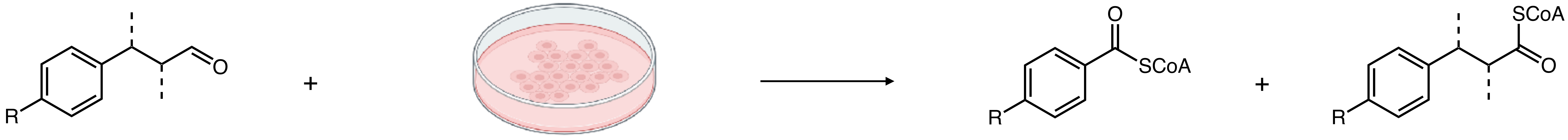
p-alkyl-phenylpropanals + rat hepatocyte suspension → minor metabolite + major metabolite

Laue, H.; Kern, S.; Badertscher, R. P.; Ellis, G.; Natsch, A.. *Toxicological Sciences* **2017,** *160* (2), 244-255.

Degradation Assay



p-alkyl-phenylpropanals | rat hepatocyte suspension | minor metabolite | major metabolite

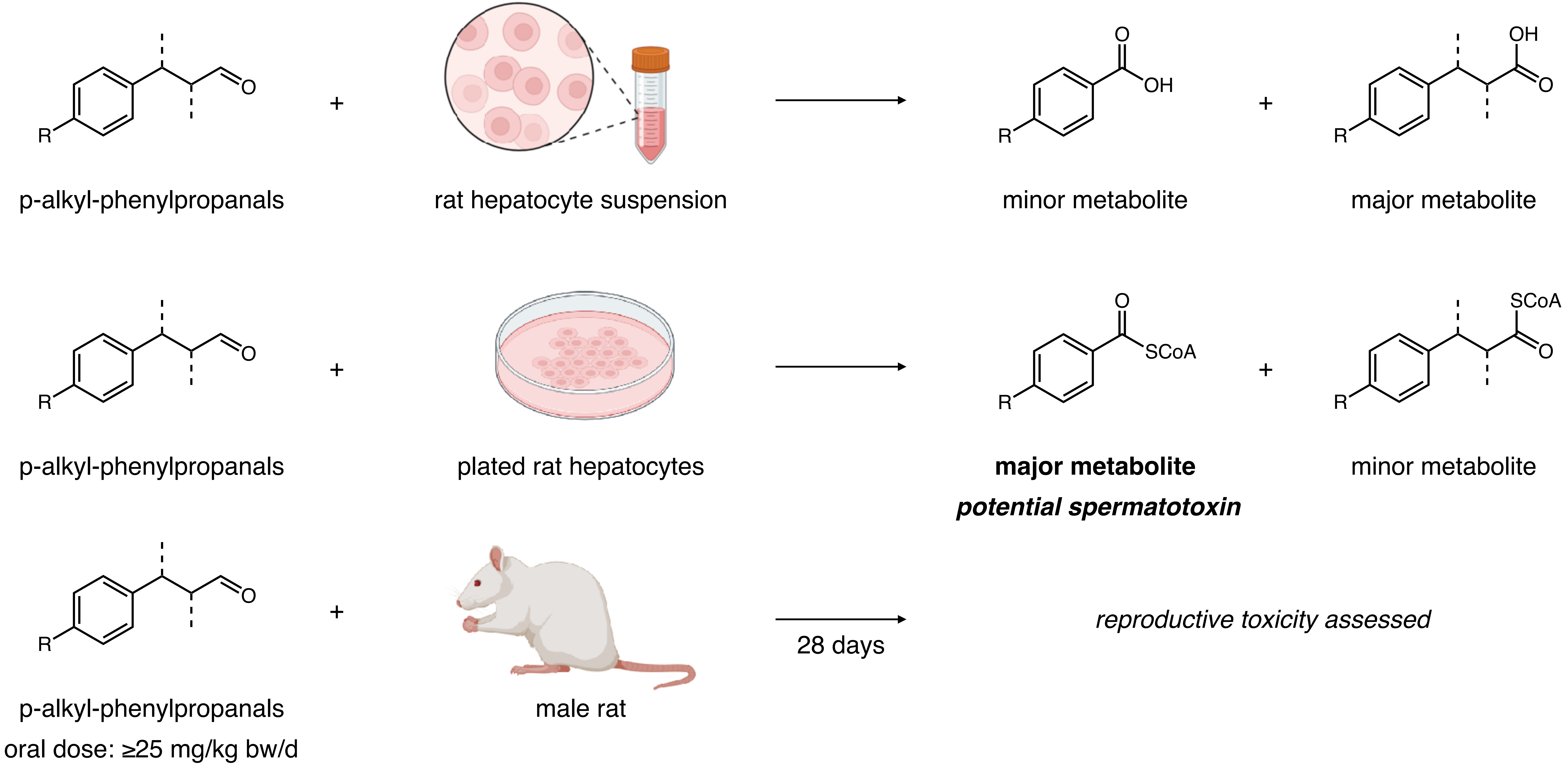


p-alkyl-phenylpropanals | plated rat hepatocytes | **major metabolite** | minor metabolite

potential spermatotoxin

Laue, H.; Kern, S.; Badertscher, R. P.; Ellis, G.; Natsch, A.. *Toxicological Sciences* **2017,** *160* (2), 244-255.

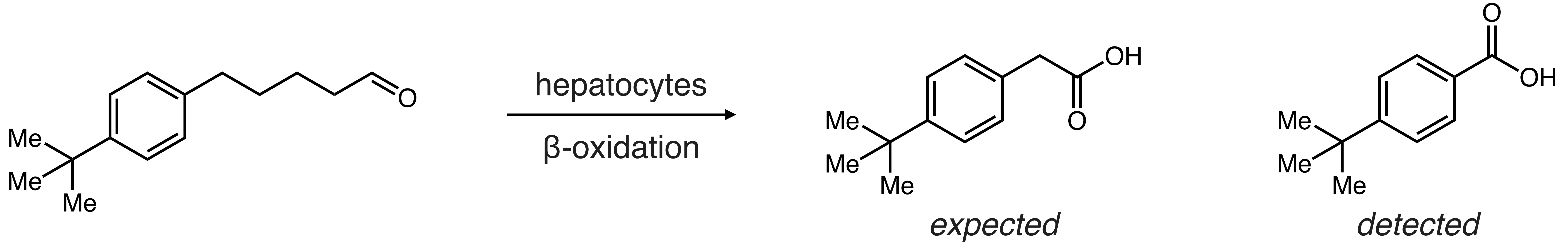
Degradation Assay



Laue, H.; Kern, S.; Badertscher, R. P.; Ellis, G.; Natsch, A.. *Toxicological Sciences* **2017,** *160* (2), 244-255.

The Discovery of Nympheal

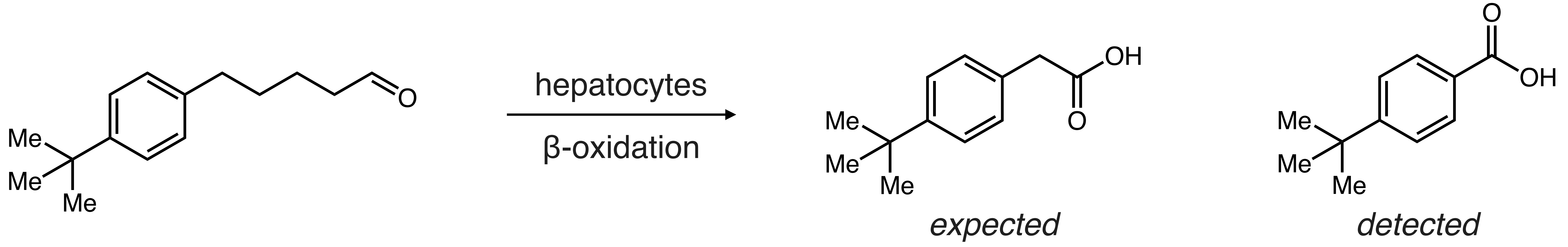
Strategy I: synthesis of unexplored phenyl butanals



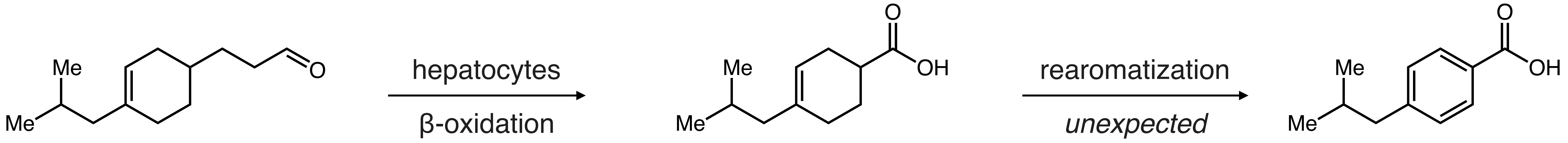
Goeke, A.; Kraft, P.; Lelievre, D.; Alchenberger, A. *Perfum. Flavor* **2018,** *43*, 25-40.

The Discovery of Nympheal

Strategy I: synthesis of unexplored phenyl butanals



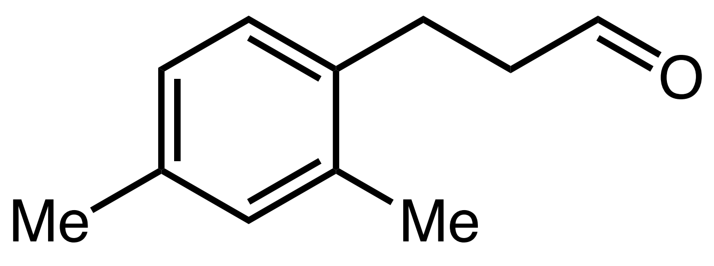
Strategy II: introduction of cyclohexenyl derivatives of similar substitution

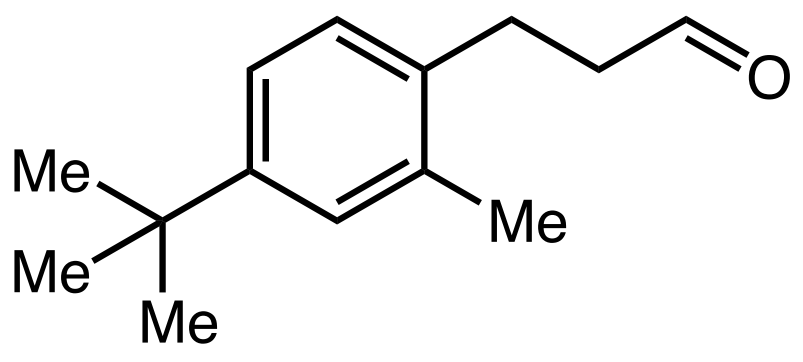


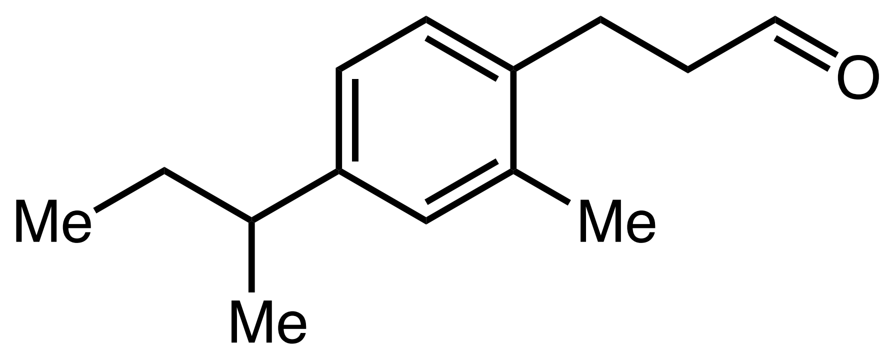
Goeke, A.; Kraft, P.; Lelievre, D.; Alchenberger, A. *Perfum. Flavor* **2018,** *43*, 25-40.

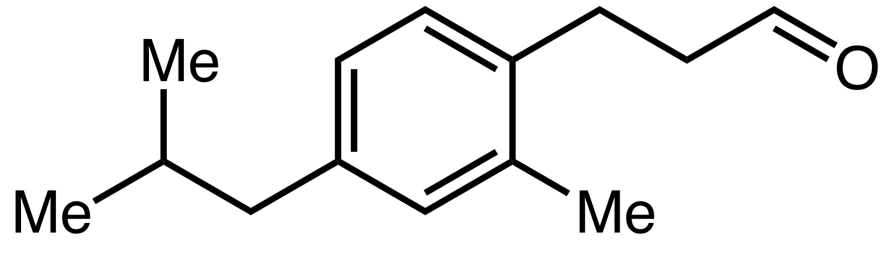
The Discovery of Nympheal

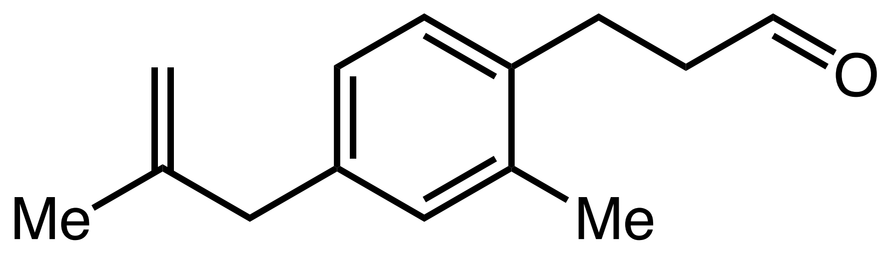
Strategy III: ortho-substitution

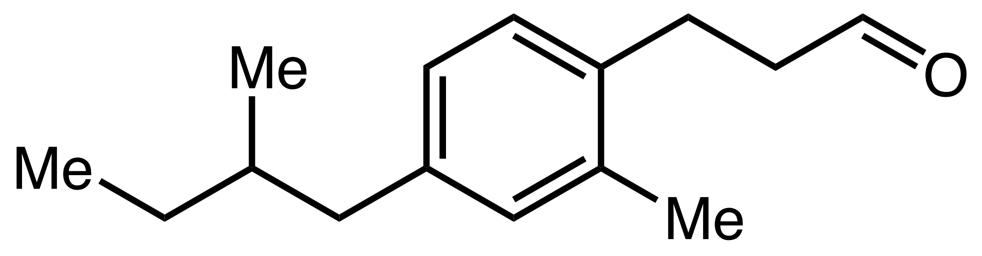


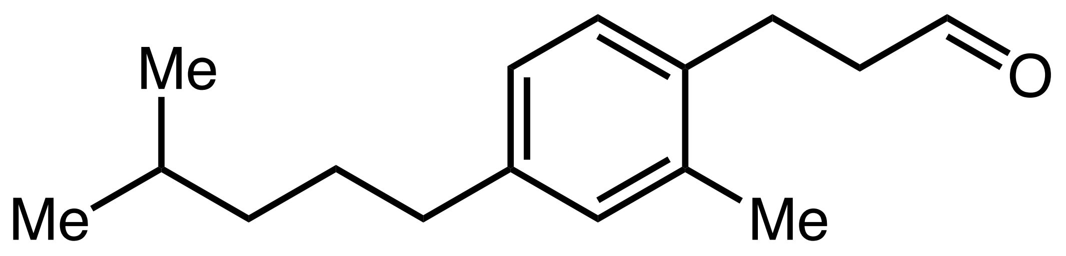


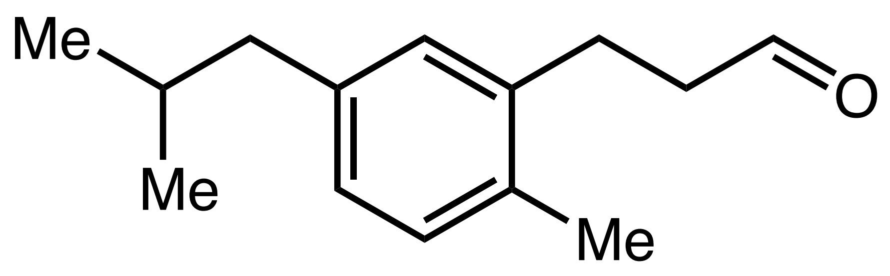








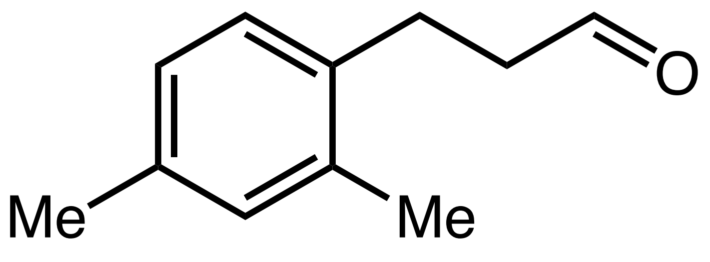


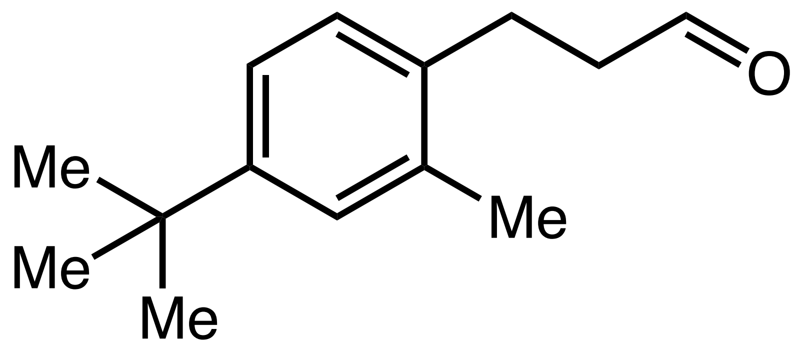


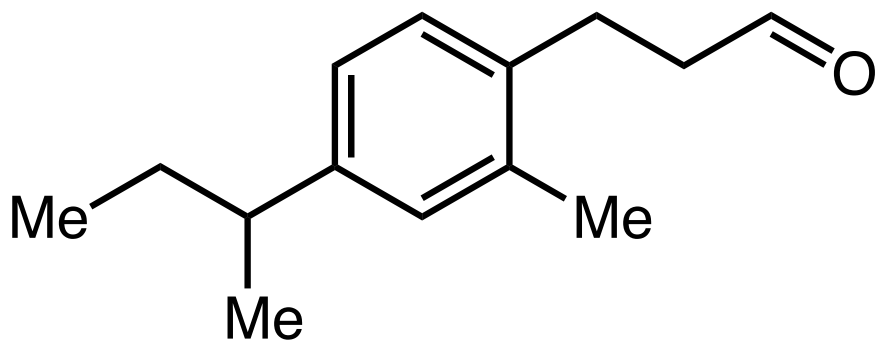
Goeke, A.; Kraft, P.; Lelievre, D.; Alchenberger, A. *Perfum. Flavor* **2018,** *43*, 25-40.

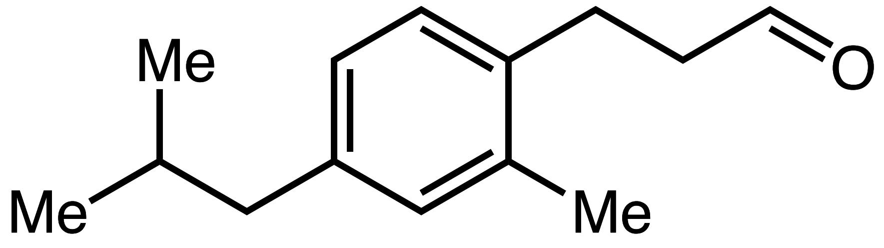
The Discovery of Nympheal

Strategy III: ortho-substitution

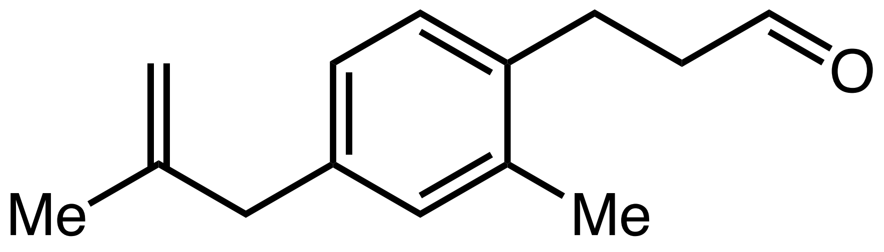


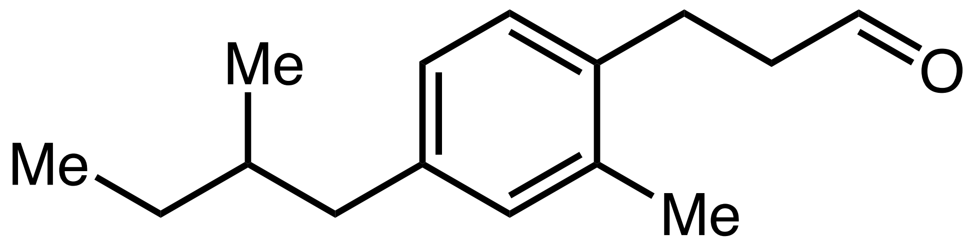


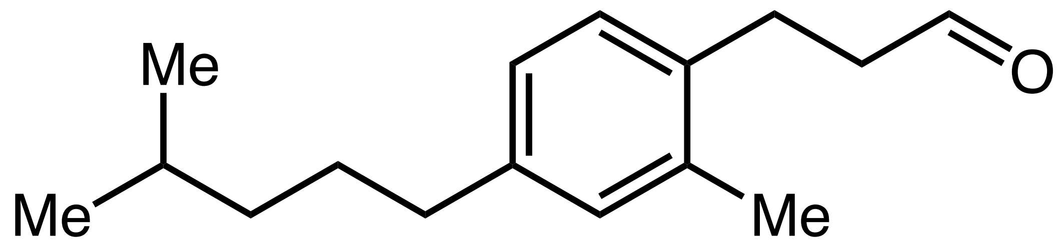


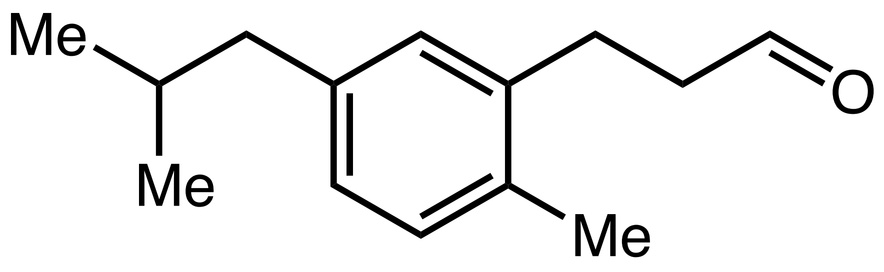


Nympheal





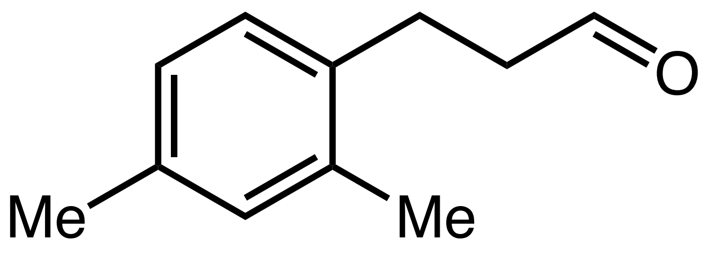


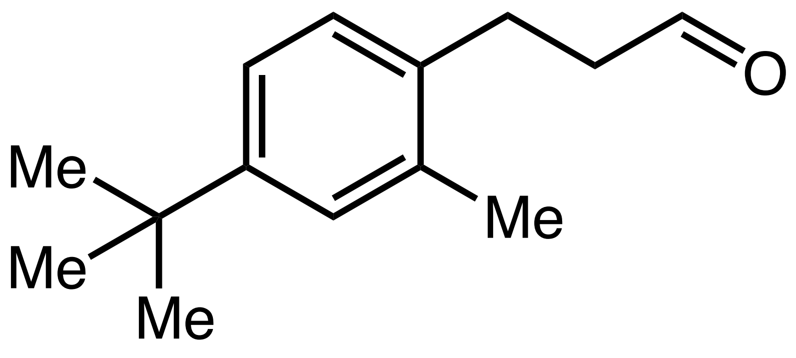


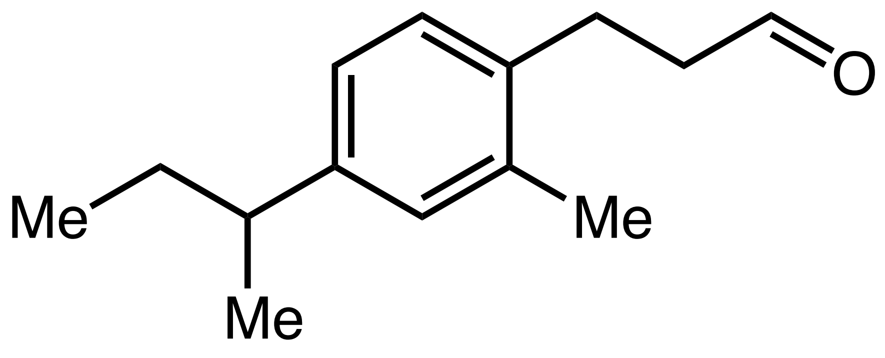
Goeke, A.; Kraft, P.; Lelievre, D.; Alchenberger, A. *Perfum. Flavor* **2018,** *43*, 25-40.

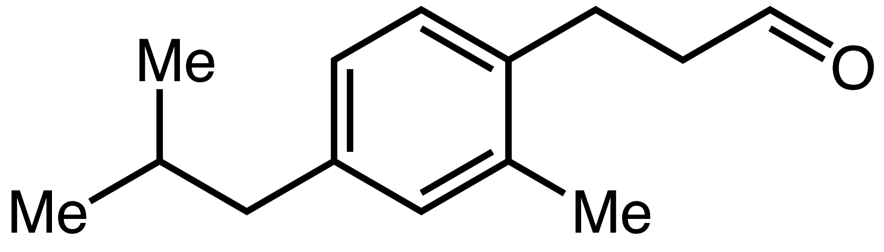
The Discovery of Nympheal

Strategy III: ortho-substitution



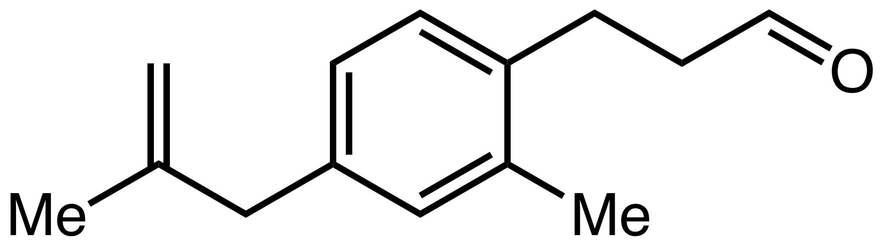


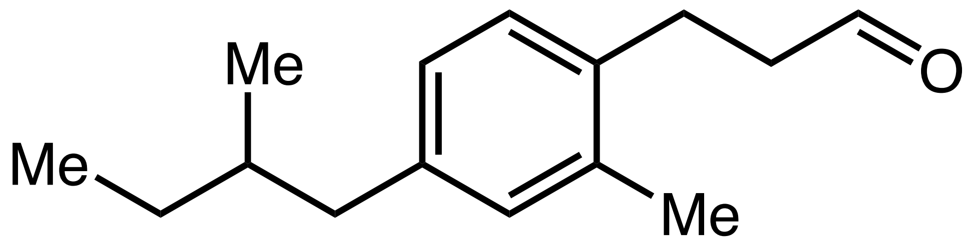


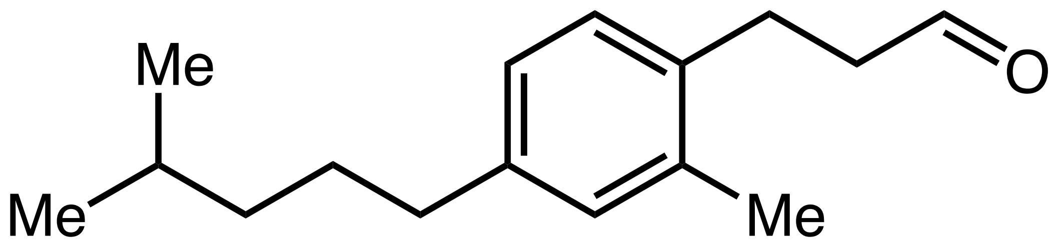


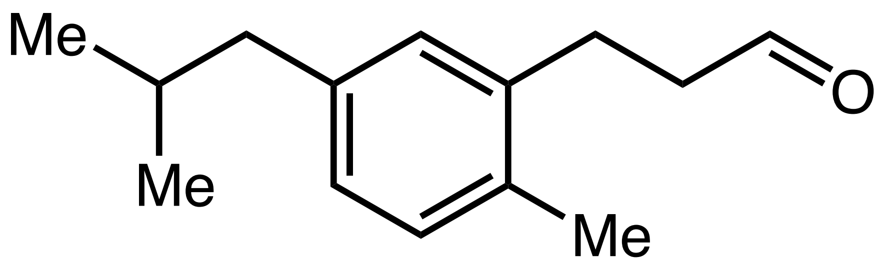
Nympheal

No reproductive toxicity





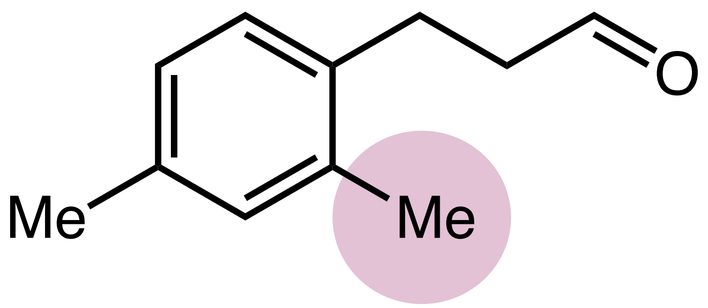


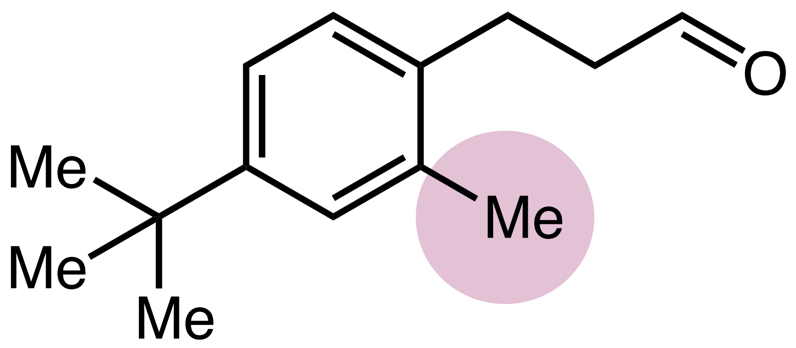


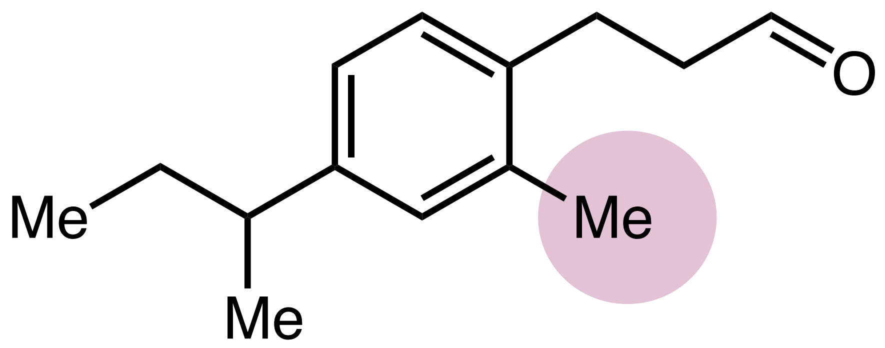
Goeke, A.; Kraft, P.; Lelievre, D.; Alchenberger, A. *Perfum. Flavor* **2018,** *43*, 25-40.

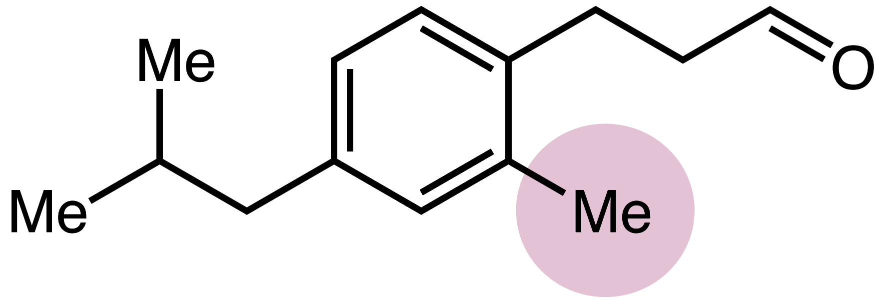
The Discovery of Nympheal

Strategy III: ortho-substitution



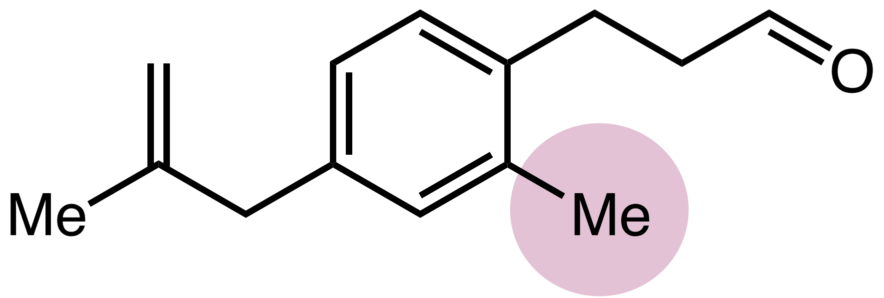


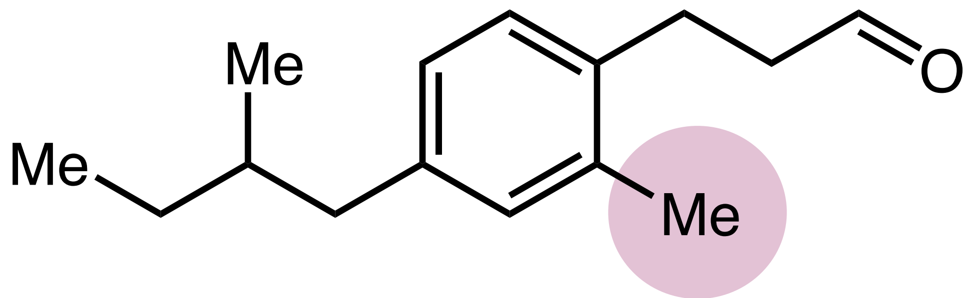


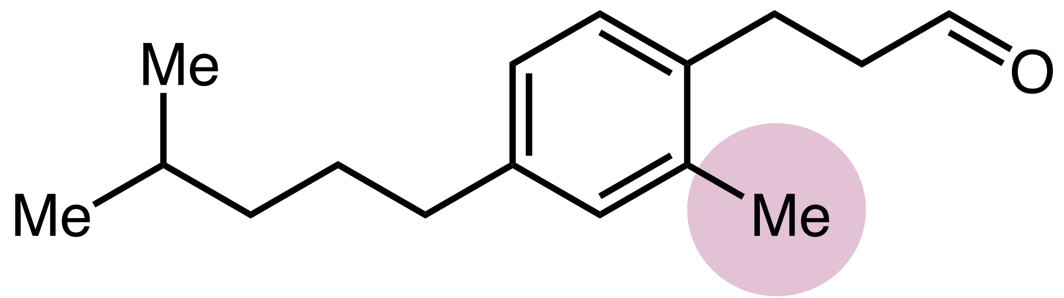


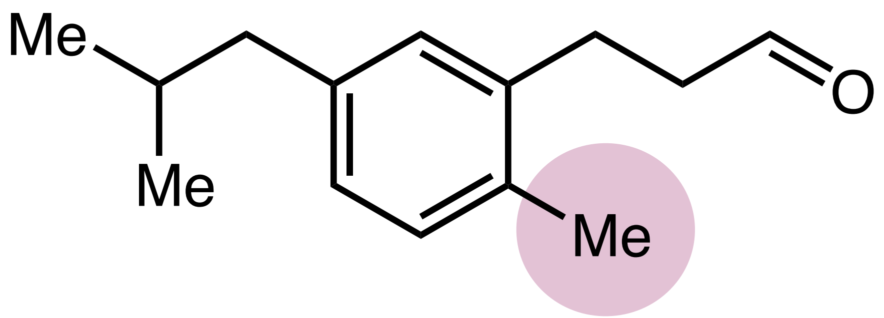
Nympheal

"Magic Methyl Effect"









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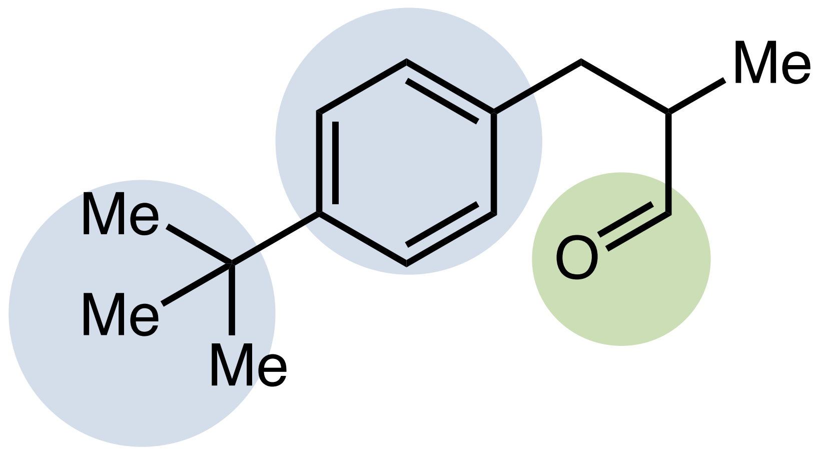
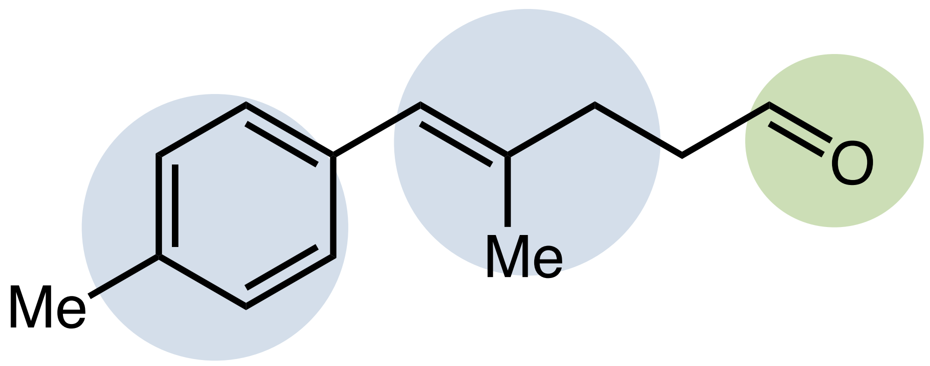
Olfactophores

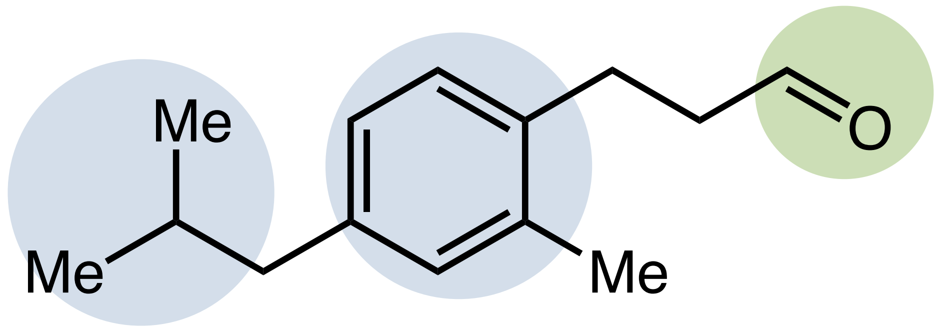
Lily of the Valley



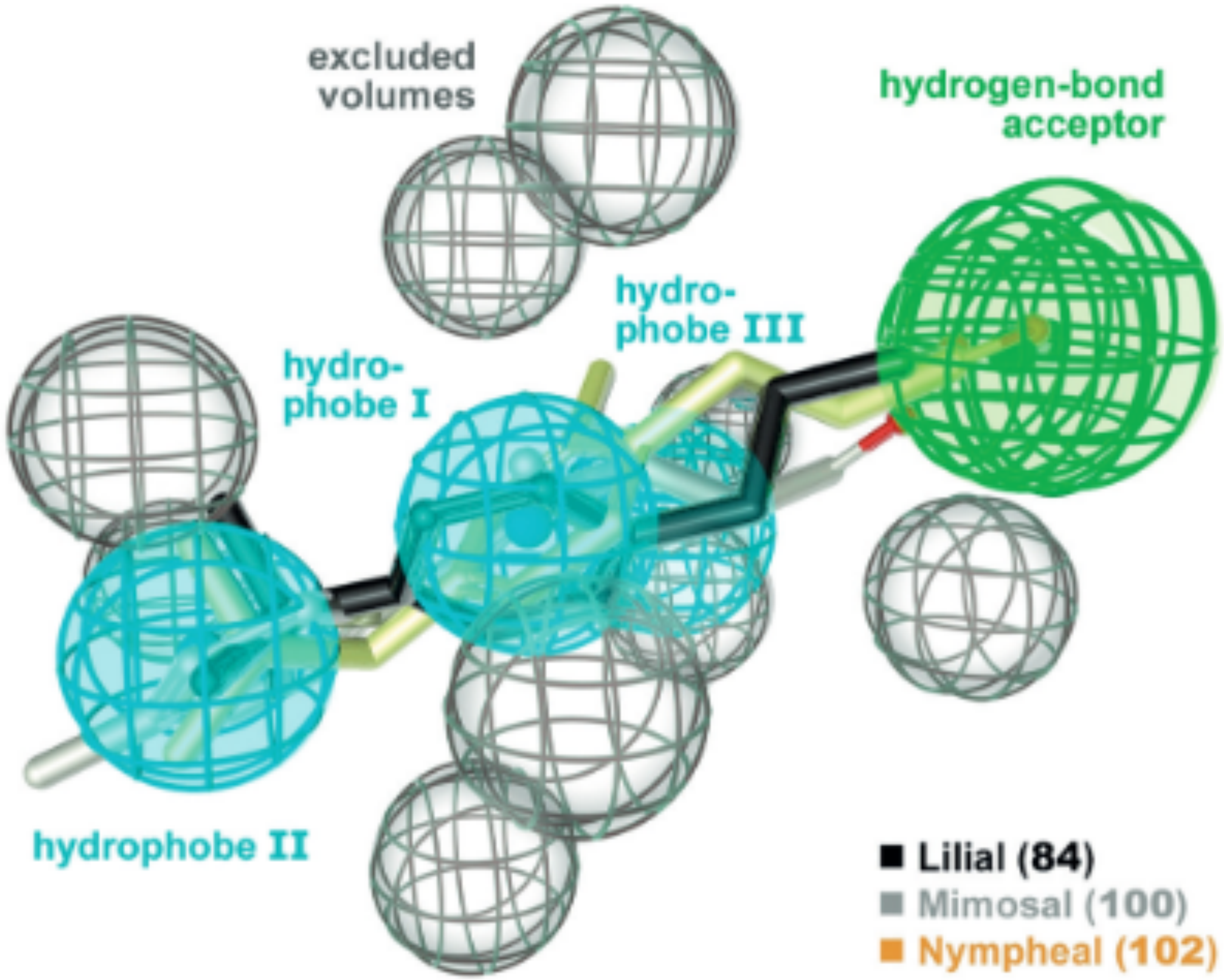
Lilial



Mimosal



Nympheal



Conclusion & Outlook

Sustainability

Biodegradability

Renewability

Elterlein, F.; Bugdahn, N.; Kraft, P. *Chem. Eur. J.* **2024**, *30*, e202400006.

Conclusion & Outlook

Sustainability

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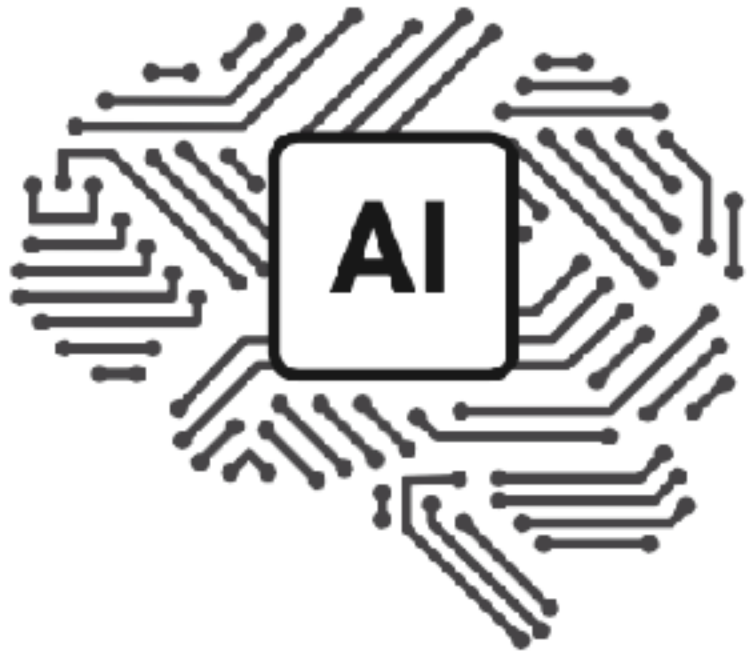


Machine Learning

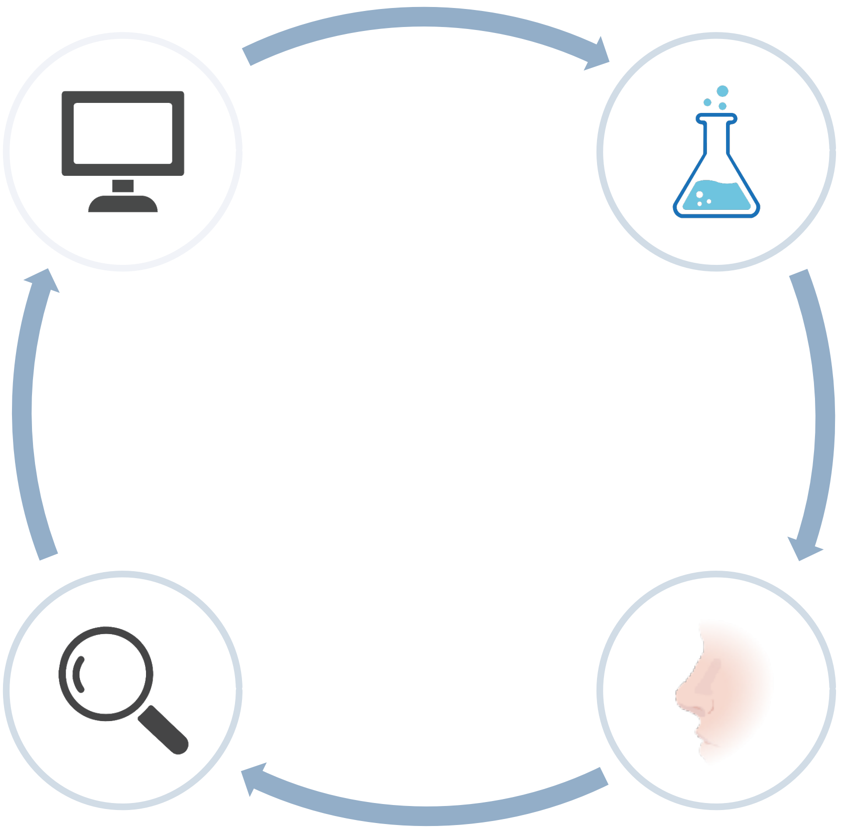
Biotechnology

Elterlein, F.; Bugdahn, N.; Kraft, P. *Chem. Eur. J.* **2024**, *30*, e202400006.

Questions?

Natural Sources

Synthesis



Fragrance Discovery