Molecular Fragrance Celebrities
Ruben Martinez

FROM TIME IMMEMORIAL, HUMAN KIND HAS ENJOYED SMELLING THINGS…

Shenvi Lab Group Meeting
1/16/2017

- Perfumes were historically sourced from animals and plants

Civet, from civet cats

Musk, from musk deer

Ambergris, from sperm whales

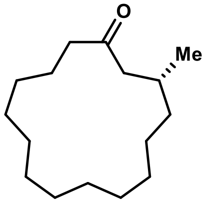
Sandalwood oil

Patchouli Oil

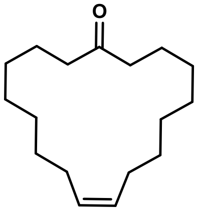
Rose Oil

Jasmine Oil

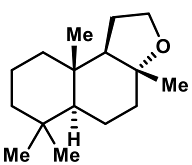
Grapefruit Oil



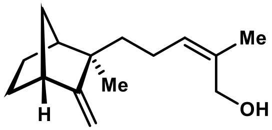
(–)-muscone



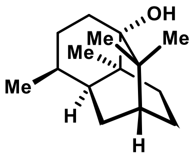
civetone



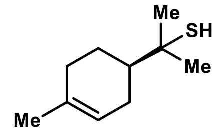
(–)-ambroxide



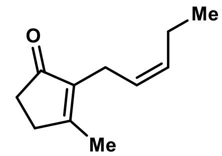
(*Z*)-(–)-β-santalol



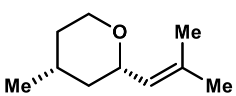
(–)-patchoulol



(+)-1-p-8-menthenethiol "grapefruit mercaptan"



cis-jasmone

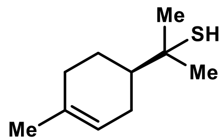


(–)-*cis*-rose oxide

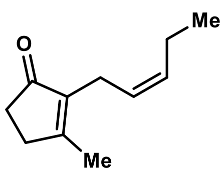
1. Musk deer CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=657641
2. Civet cat https://commons.wikimedia.org/w/index.php?curid=6944629
3. Ambergris CC BY-SA 4.0. https://commons.wikimedia.org/w/index.php?curid=53967605
4. Sandalwood CC BY 2.5, https://commons.wikimedia.org/w/index.php?curid=11886489
5. Patchouli CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=875908
6. Grapefruit CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=30814891
7. Jasmine CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=48516945
8. Rose CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=8434

Why make new compounds?

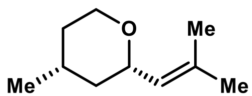
- Customizability and Profitability
  - Changing preferences
  - Patent protection: “captive scents”
  - Improved technology
  - Toxicology – allergens and sensitization



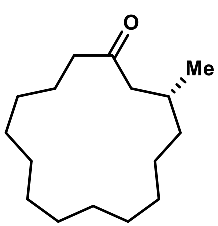
(+)-1-p-8-menthenethiol
"grapefruit mercaptan"



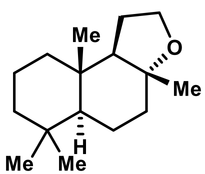
cis-jasmone



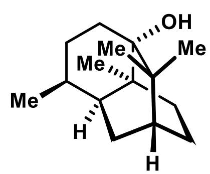
(–)-*cis*-rose oxide



(–)-muscone

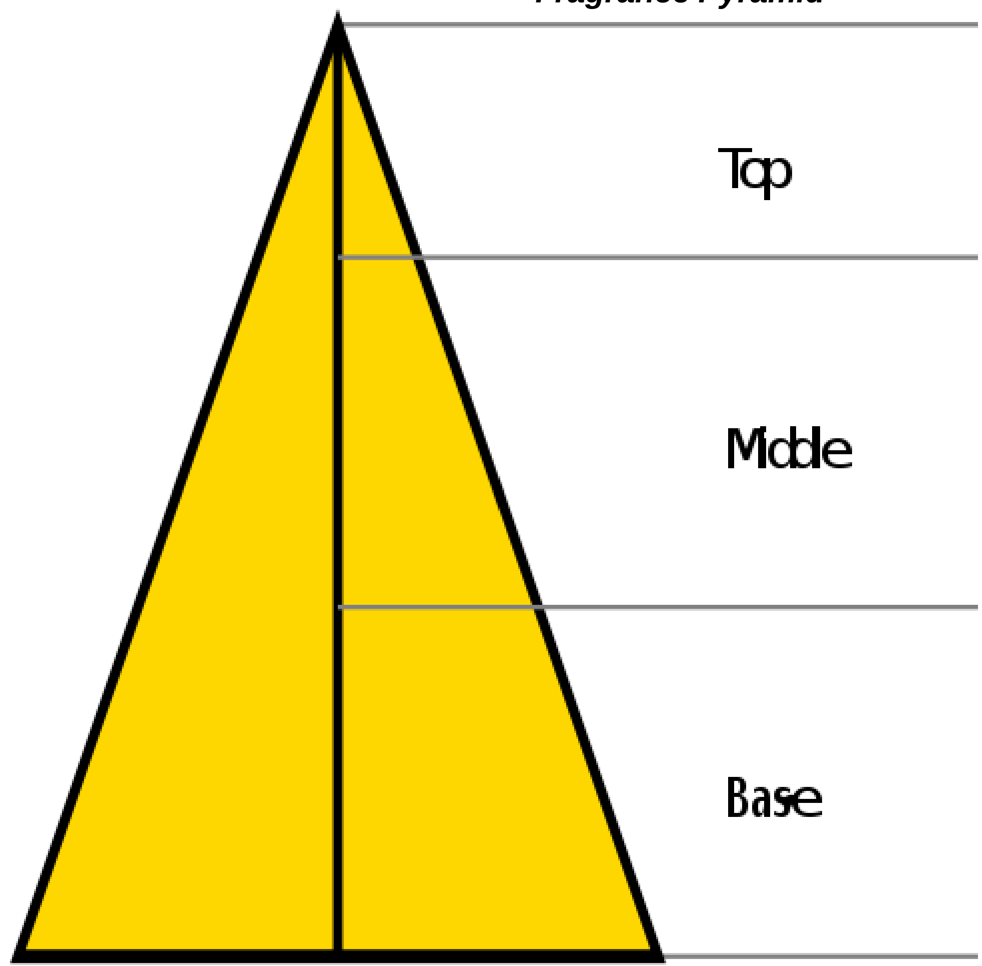


(–)-ambroxide



(–)-patchoulol

Fragrance Pyramid

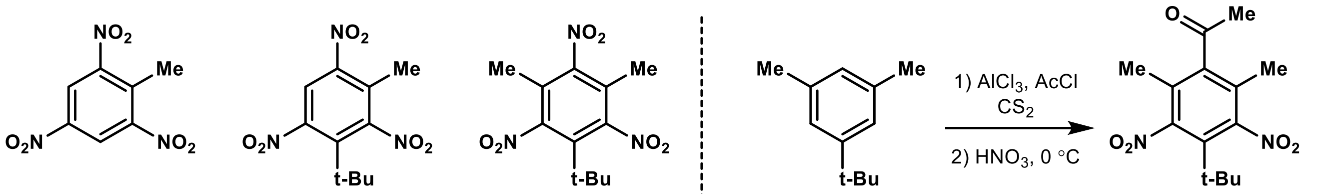


1. Gautschi, M.; Bajgrowicz, J. A.; Kraft, P. *CHIMIA Int. J. Chem.* ***2001, 55, 379.*** **(Review)**
2. Fráter, G.; Bajgrowicz, J. A.; Kraft, P. *Tetrahedron* ***1998, 54, 7633. (Review)***
3. Fragrance Pyramid - Public Domain, https://commons.wikimedia.org/w/index.php?curid=11272358

Synthetic Musks

- First industrial synthetic musk discovered by chance in explosives research (1898)

Nitro Musks, ~ 1900s (obsolete)

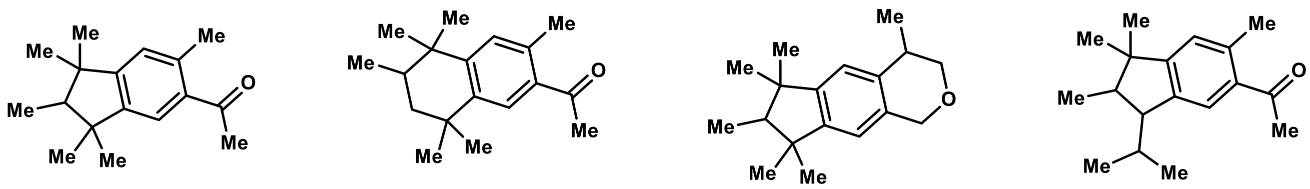


trinitrotoluene | **"Musk Baur"** | **"Musk Xylene"** | **butylated xylene** | **"Musk Ketone"**

+ Powerful musk fragrances (odor threshold 0.1 ng/L)
+ Easily produced on scale

– **Phototoxicity + Alkaline instability**

- Search for non-nitro benzenoid musks resulted in the polycyclic musks (i.e. Phantolide®, 1951)



Phantolide® Polak's Fruit Works, 1951

Fixalide® Givaudan, 1955

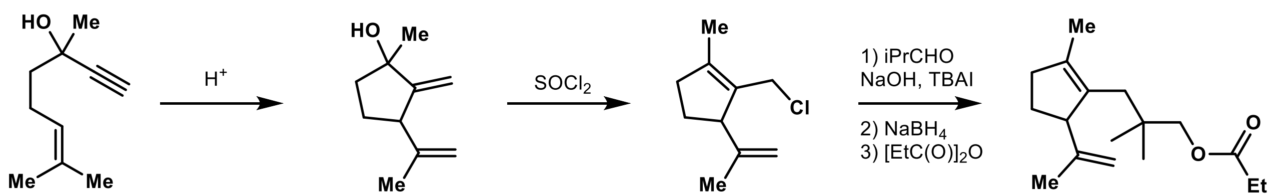
Galaxolide® IFF, 1967

Traseolide® Quest, 1977

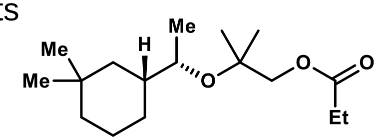
+ Hydrophobicity makes excellent laundry additive
+ Excellent chemical and photochemical stability

– **Environmental bioaccumulation, concerns about deposition in human fat cells**

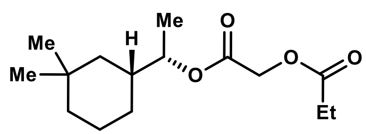
- Discovery of Cyclomusk in 1975 (BASF) brought biodegradable musks with new crossover scents



Cyclomusk



Helvetolide®

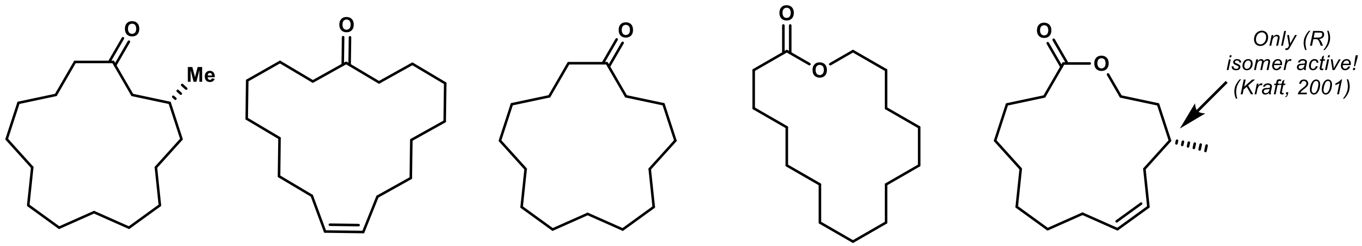


Romandiolide®

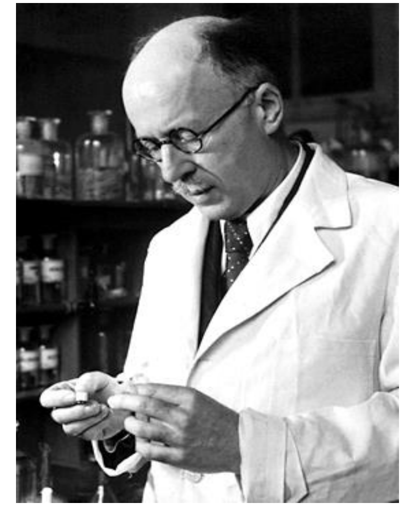
1. Baur-Thurgar, A. *Ber. Dtsch Chem. Ges.* ***1898, 31, 1344.***
2. Fuchs, K. (Polak's Frital Works), *US Patent 2759022*, **1956.**
3. Hoffmann, W.; Von Fraunberg, K. (BASF) *Ger. Patents DE 2513995, DE 2513996*
4. Eh, M. *Chemistry & Biodiversity* ***2004, 1, 1975.***
5. Gautschi, M.; Bajgrowicz, J. A.; Kraft, P. *CHIMIA Int. J. Chem.* ***2001, 55, 379.*** **(Review)**
6. Fráter, G.; Bajgrowicz, J. A.; Kraft, P. *Tetrahedron* ***1998, 54, 7633. (Review)***

Macrocyclic Musks and the Boss of Basenotes

- Muscone and civetone – natural macrocycles which begot a whole perfumery class



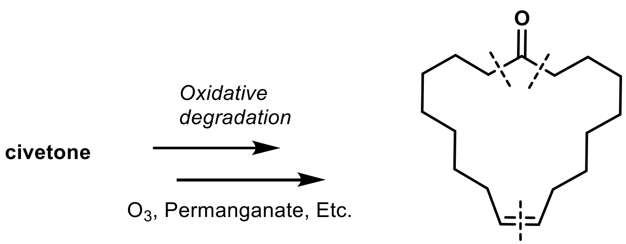
(–)-muscone **civetone** **Exaltone®** **Exaltolide®** **Nirvanolide®**



Leopold Ruzicka
Nobel Prize, Chemistry
1939

" In the original experiments, which were carried out on civetone, I was hindered less by the caprices of the substance itself than by the general prejudice, shared by my self, against the probability of the existence of a 15- and a 17-membered ring."

- Pioneering work on muscone and civetone done by Ruzicka



Logic to solve:

1) **Harsh** = Mixture of various normal-chain dicarboxylates resulted
2) *Gentle* = Dicarboxylate with ketone
3) Hydrogenation / ox. degradation and Wolff-Kishner / ox. deg. give *same product*
4) Confirmed via synthesis
-Ruzicka macrocyclization

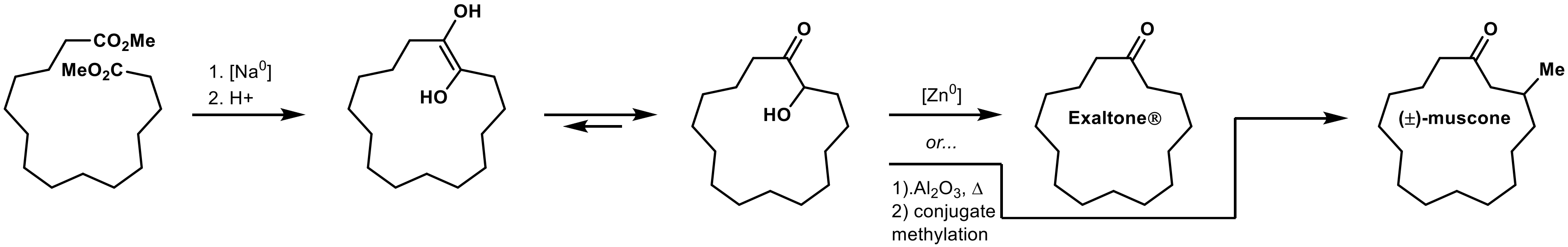
- Disproved Baeyer ring strain theory, showed anti-Bredt ring systems, numerous other contributions

Number of units in the polymethylene	2	3	4	5	6–8	15	30
Heat of combustion in kcal per CH_2-group	170	168	165	159	158	157	156

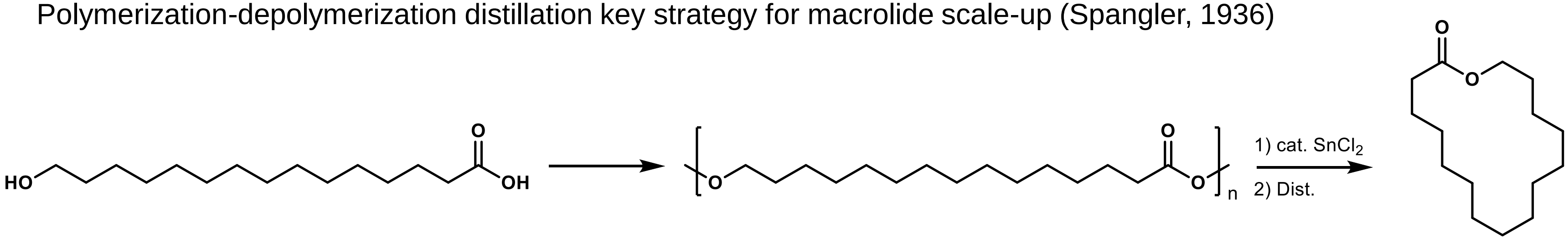
1. Photo By Nobel Foundation - http://nobelprize.org/, Public Domain, https://commons.wikimedia.org/w/index.php?curid=9713540
2. Leopold Ruzicka - Nobel Lecture. ***Nobel Lectures**, Chemistry 1922-1941*, Elsevier Publishing Company, Amsterdam, 1966
3. Kraft, P.; Fráter, G. *Chirality* ***2001, 13, 388.***

More Fun with Musks

- Industrial syntheses: Acyloin condensation allowed high concentration (Prelog, Stoll, 1947)

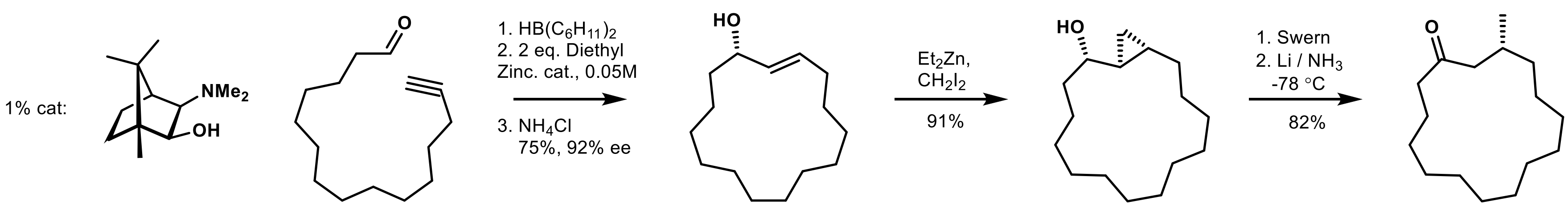


- Polymerization-depolymerization distillation key strategy for macrolide scale-up (Spangler, 1936)



Exaltolide®

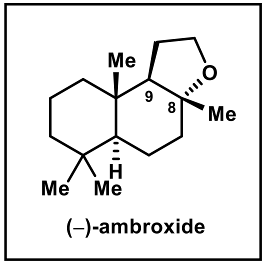
- Although not amenable to industrial scale, Oppolzer demonstrated excellent chiral induction



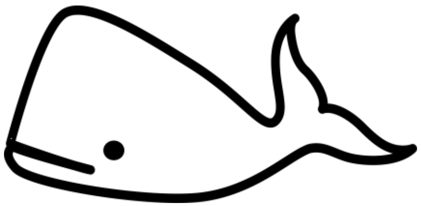
(–)-muscone

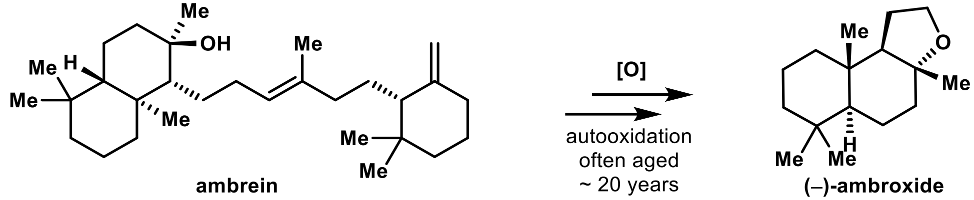
1. Prelog, V.; Frenkiel, L.; Kobelt, M.; Barman, P. *Helv. Chim. Acta* ***1947, 30, 1741.***
2. Stoll, M.; Rouvé, A. *Helv. Chim. Acta* ***1947, 30, 1822.***
3. Spanagel, E. W.; Carothers, W. H. *J. Am. Chem. Soc.* ***1935, 57, 929.***
4. Oppolzer, W.; Radinov, R. N. *J. Am. Chem. Soc.* ***1993, 115, 1593.***
5. Fráter, G.; Bajgrowicz, J. A.; Kraft, P. *Tetrahedron* ***1998, 54, 7633. (Review)***

Ambroxide aka Ambrofix® aka Ambroxan®

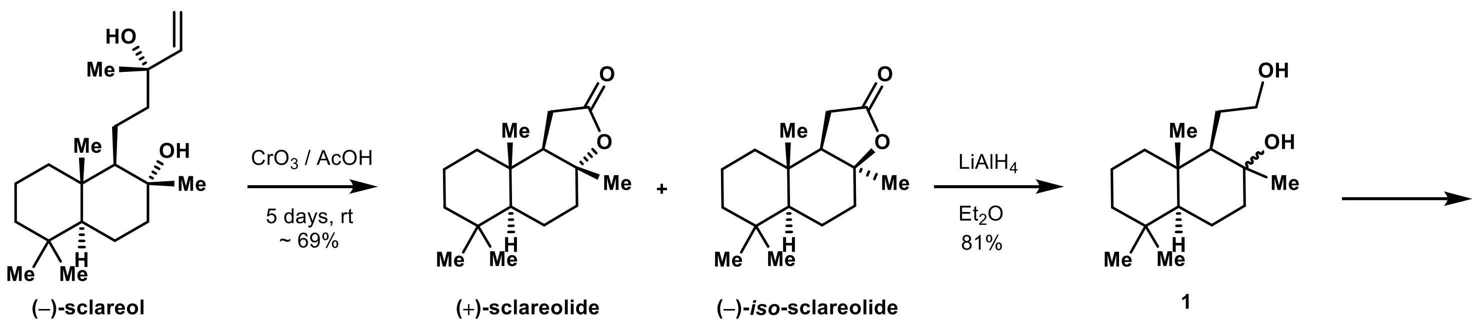


- Historically important back to ancient perfumers – most important molecule out of natural sperm whale *ambergris*



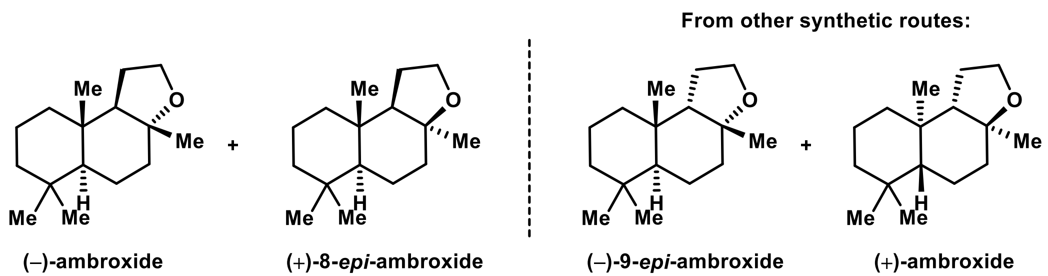


- Structural elucidation and chemical synthesis reported in 1950, Max Stoll's group at <u>*Firmenich*</u>



- Potency of epimers can vary greatly

Amber Odorant	*Odor Threshold*
(–)-ambroxide	**0.3 ppb**
(+)-8-*epi*-ambroxide	**34 ppb**
(–)-9-*epi*-ambroxide	**0.15 ppb**
(+)-ambroxide	**2.4 ppb**

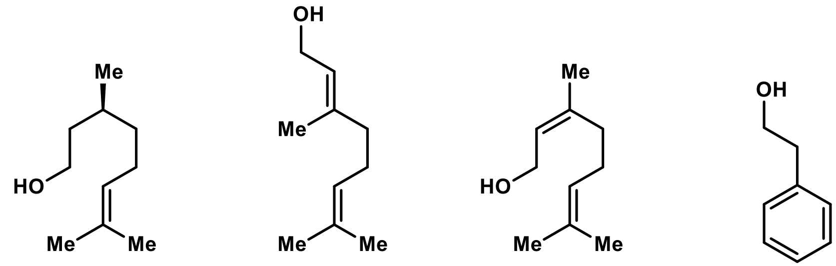


1. Ruzicka, L.; Janot, M. M. *Helv. Chim. Acta* ***1931, 14, 645.***
2. Hinder, M.; Stoll, M. *Helv. Chim. Acta* ***1950, 33, 1308.***
3. Fráter, G.; Bajgrowicz, J. A.; Kraft, P. *Tetrahedron* ***1998, 54, 7633. (Review)***

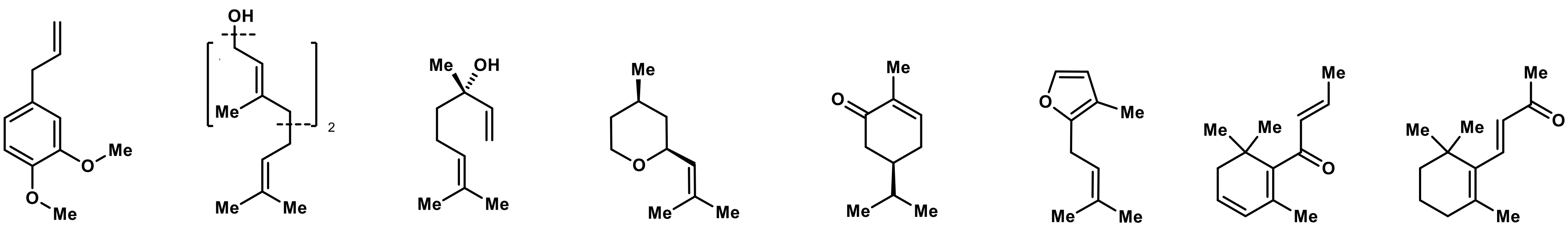
The Importance of Minor Constituents

- Ohloff (Firmenich) reported relative thresholds of Bulgarian rose oil vs constitutional percentage

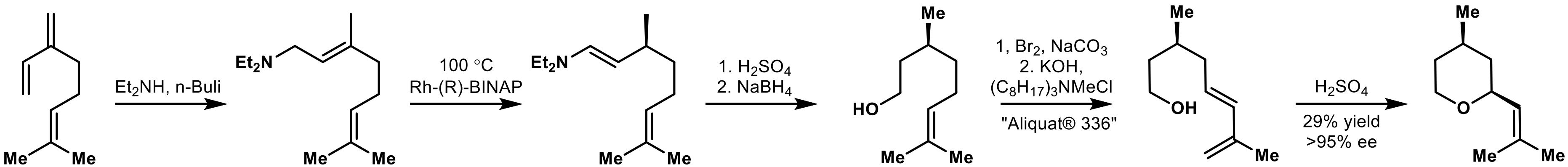
Constituent	% constitution	odor threshold, ppb	10^3 x odor units (conc/ppb)*1000	rel. % odor contribution
(–)-citronellol	38	40	95,000	62
paraffins	16	--	0	0
geraniol	14	75	1,860	1.2
nerol	7	300	233	0.15
phenylethanol	2.8	750	37	0.024
methyl eugenol	2.4	820	29	0.019
farnesol	1.2	30	400	0.26
linalool	1.2	20	600	0.39
(–)-rose oxide	1.4	6	2,300	1.5
(–)-carvone	0.46	0.05	9,200	6
rose furan	0.41	50	82	0.05
β-damascenone*	0.16	200	8	0.005
β-ionone	0.14	10*	140*	0.09*
	0.03	0.07	42,860	28



(–)-citronellol **geraniol** **nerol** **phenyl ethanol**



methyl eugenol **farnesol** **linalool** **(–)-*cis*-rose oxide** **(–)-carvone** **rose furan** **β-damascenone** **β-ionone**



myrcene **(–)-citronellol** **(–)-*cis*-rose oxide**

1. Ohloff, G. *Perfum. Flavor.* ***1978b, 3(2-3), 11.***
2. Matsuda, H.; Yamamoto, T. (Takasago.) US Patent 5858348
3. Fráter, G.; Bajgrowicz, J. A.; Kraft, P. *Tetrahedron* ***1998, 54, 7633. (Review)***
4. **** Ohloff noted this value was incorrect, due to the impact of olfactory fatigue. The actual numbers for threshold and odor units are 0.009 ppb, and 156,000, respectively.***