



Cooling Compounds

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Presentation to the Society of Flavor Chemists

Newark, 12.04.03



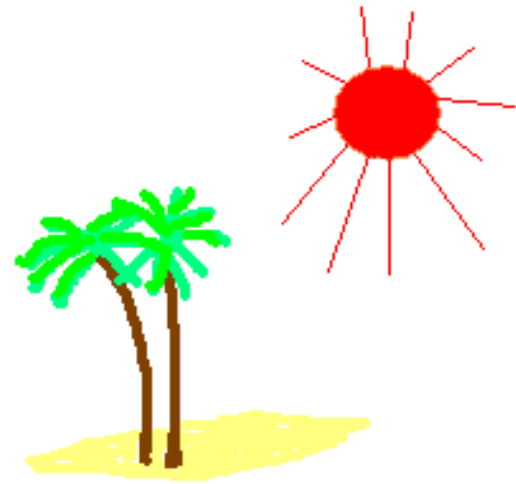


is a major producer of fragrance and flavor chemicals from turpentine and one of the leaders in synthetic cooling agents.

Headquarters in Jacksonville, Florida



It must have been Florida weather
that predetermined Millennium's
active research in the WS type
coolants





People and Chemistry



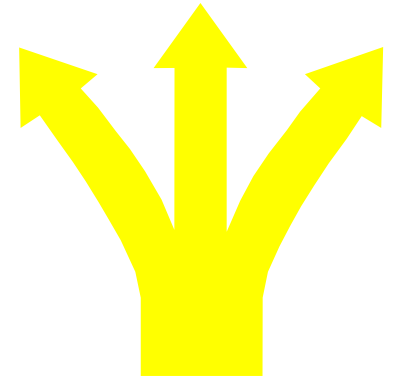
- Most people do not like the Chemical Sciences.
- But Life is Chemistry!
- Chemicals have accompanied human Civilization from the cradle.

- Ethanol - a surprisingly simple molecule with a strong and versatile physiological activity.
- A recent patent granted to Procter & Gamble lists ethanol as a physiological **warming** agent for throat soothing compositions.

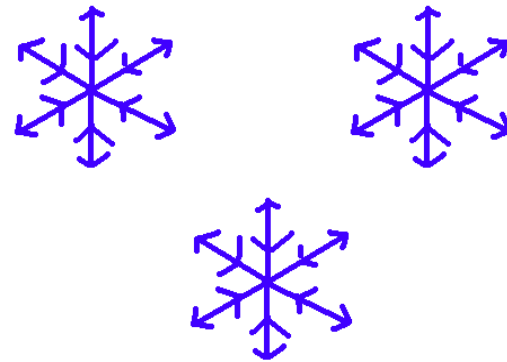
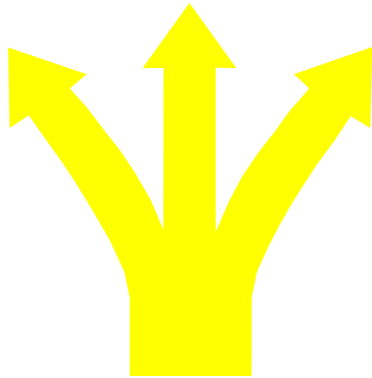
See: Bealin-Kelly, Hanke & Nienaber. US 6,432,441(2002).

Evaporative cooling

- Applied on skin, ethanol is rather cooling.
- Most common explanation: cooling through evaporation.
- Lower-boiling compounds like ether or acetaldehyde cool even stronger.
- This kind of cooling action is not *physiological*, it is *physical*.



Evaporative cooling versus “true,” physiological cooling



Unlike ether or ethanol, true, physiological coolants “exert chemical action at or near nerve endings associated with the sensation of cold.”

(see: Watson, Hems, Rowsell & Spring. *J. Soc. Cosmet. Chem.* 1978, **29**, 185-200)



Further, cooling action of the true coolants is explained through an influx of Ca^{2+} ions into the nerve cell. This calcium influx is converted into an electrical signal in the brain resulting in the perception of cooling.

See: Givaudan's brochure on "Evercools". Page 7.



Differences in the Perception of Cooling

'...the perception of cooling varies depending on the type of cooling ingredient, the product base (or vehicle) and the ability of the consumer to identify the experience. Therefore the measurement of cooling is subjective. We also need to be aware of the potential differences between east and west.'

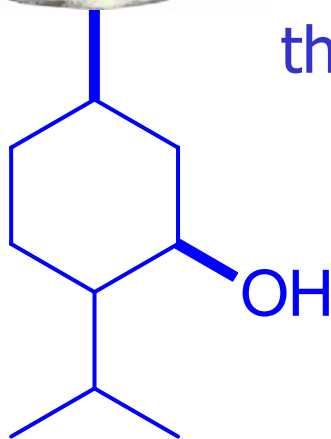
(from: Jacobs and Johncock (H&R), "Some like it cool", Parf. und Kosmetik, 1999, N4, p. 26)

- An excellent review on the perception and mechanism of cooling action with numerous literature references can be found on Dr. John Leffingwell's website
- ([www/leffingwell.com/cooler_than_menthol](http://www.leffingwell.com/cooler_than_menthol))





His Majesty *l*-Menthol,
the King of True Coolants



The Kingdom of *l*-Menthol

- The Kingdom of *l*-Menthol is as old as the Civilization.
- It is immense.
- In volume, Menthol is coolant #1, and will certainly continue to be in this position for a long time.
- Menthol is irreplaceable in many (but not all) applications.
- Menthol produced a lot of offspring - synthetic coolants.

Disadvantages of Menthol

- Volatility
- Strong smell
- Bitter taste
- Burning sensation in higher concentrations
- Often interferes with the composition

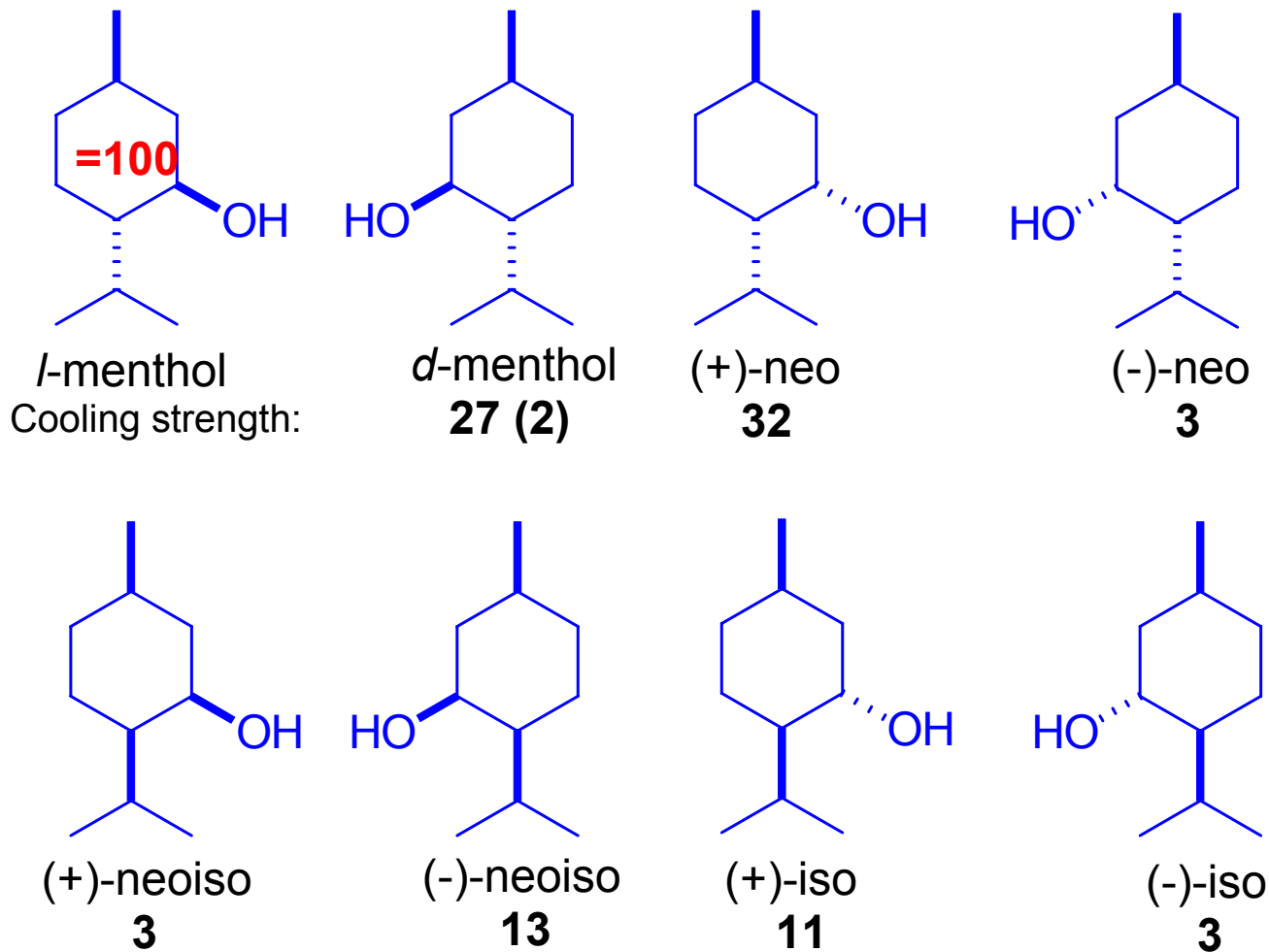


Q. How to avoid these disadvantages, but preserve cooling effect?

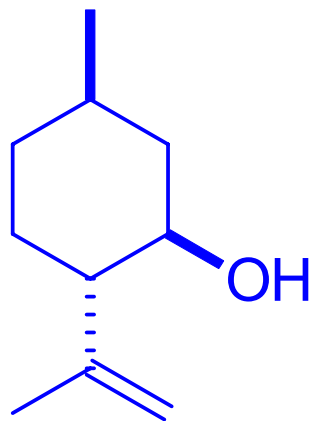
Approach 1

Search within the Menthol Royal Family
- oxygenated p-Menthane derivatives

Royal Family: Great Dukes - Menthol isomers

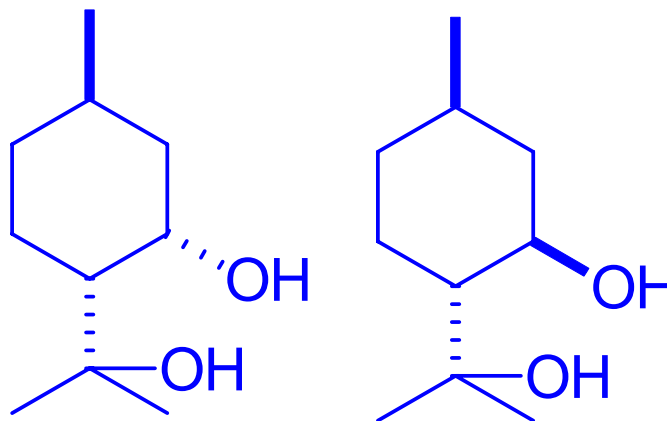


Royal Cousins: other p-menthane alcohols



(-)-isopulegol
20-30

Marketed as
Coolact P^R by
Takasago

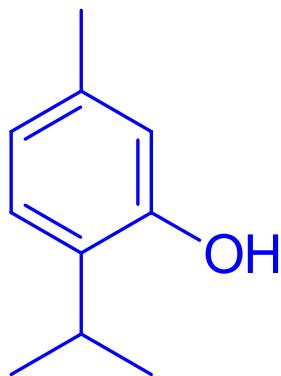


p-Menthane-3,8-diol
10-12

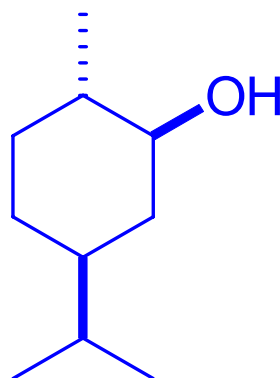
Isomeric mixture marketed as
Coolact 38D^R by Takasago

Syntheses by cyclization of (+)-citronellal
See, for example US 5,773,410 & US 5,959,161 (TIC)
Cooling strength data from US 6,328,982 (TIC), column 3.

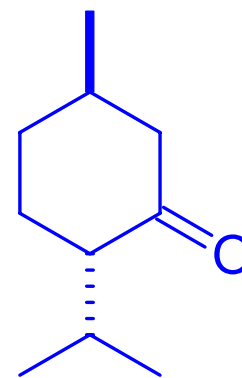
Remote relatives: other oxygenated p-menthanes & camphor



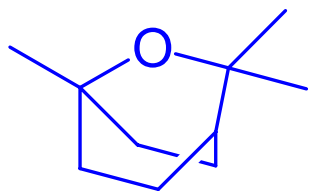
Thymol



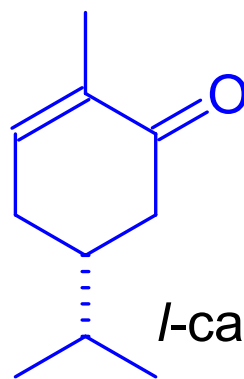
Carvomenthol
(mild cooling)



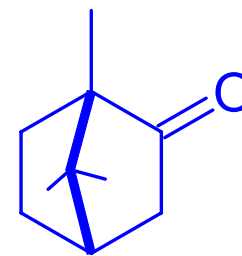
l-Menthone



1,8-Cineol
(mild cooling)



l-carvone



d-camphor
(cooling)

Conclusions from “Approach 1”

- Search inside Menthol family produced two commercially successful coolants: Coolact P[®] (FEMA GRAS **2962**) and Coolact 38D[®] (FEMA **4053**).
- Most of other p-menthane derivatives are not free of disadvantages similar to *l*-Menthol: strong smell, taste, volatility, etc.
- p-Menthane carbon skeleton is not an absolute pre-requisite for cooling properties.

Approach 2

Modification of the α -menthol molecule
making it "heavier."



Interestingly enough, initial steps along this path were made during a search for tobacco flavor additives that would allow controlled menthol release from burning tobacco into the cigarette smoke.

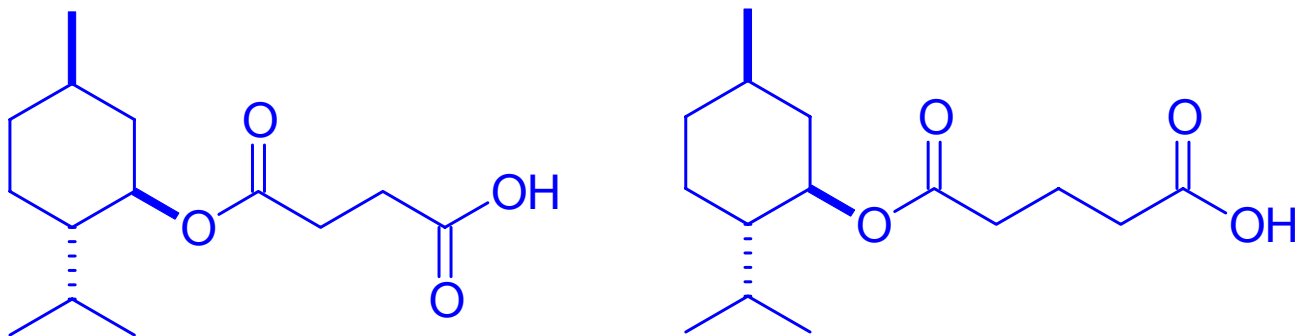




Thus, Monomethyl succinate was patented first as a tobacco additive in 1963, and patented as a cooling agent 35 years later by V. Mane Fils.

See: Jarboe. US 3,111,127 (1963) to Brown & Williamson Tobacco Corp.
Mane & Ponge. US 5,725,865 and 5,843,466 (1998) to V.Mane Fils

Monomenthyl Succinate FEMA GRAS 3810 & Monomenthyl Glutarate FEMA GRAS 4006 represent an interesting class of coolants - Monomenthyl Esters of di- and polycarboxylic acids.



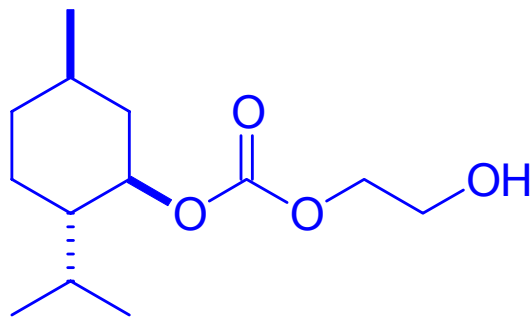
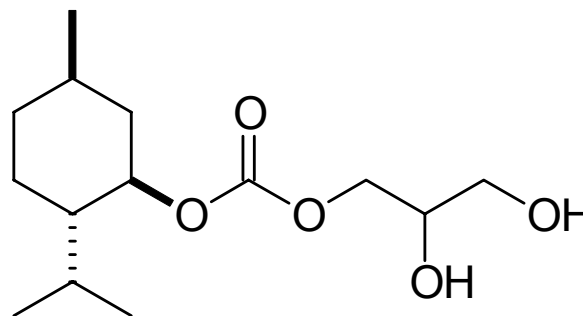
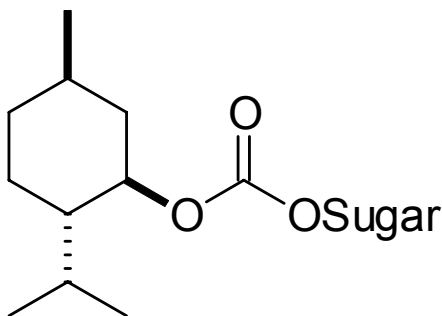
Examples of application:

Pelan, Vermeulen, & Wemmenhoven. Water continuous food product with cooling flavor. WO 2003/043431 to Unilever.

Flammer, Grainger, Boden & Christensen.

Anti-dandruff compositions... EP 1,332,772 (2003) to IFF.

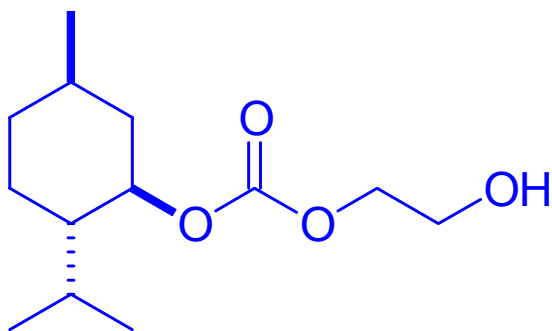
In 1968, Liggett & Myers obtained a patent for the use of carbonate esters of menthol and polyols in tobacco. Examples included:



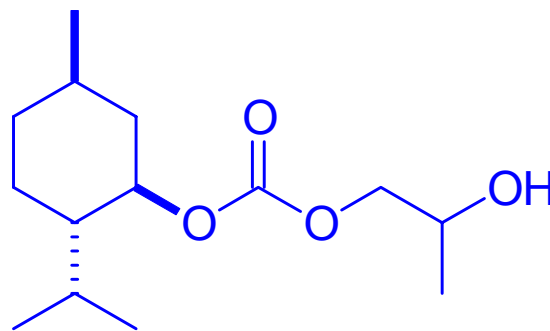
Menthol ethylene glycol carbonate

Mold, Kallianos & Shelburne. US 3,419,543

Much later (1994), H&R patented this compound - Menthol Ethylene Glycol Carbonate - as a physiological cooling agent, which is now known as Frescolat[®] type MGC (FEMA GRAS **3805**). Another patented compound was Menthol Propylene Glycol Carbonate (Frescolat[®] type MPC), FEMA **3806**.



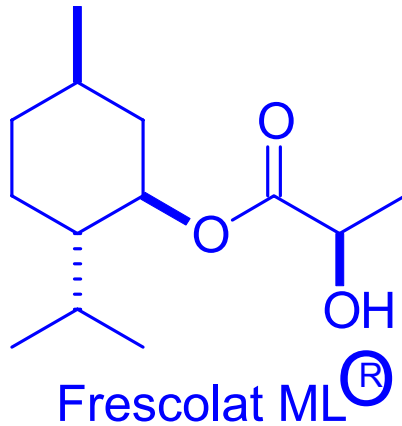
Frescolat type MGC



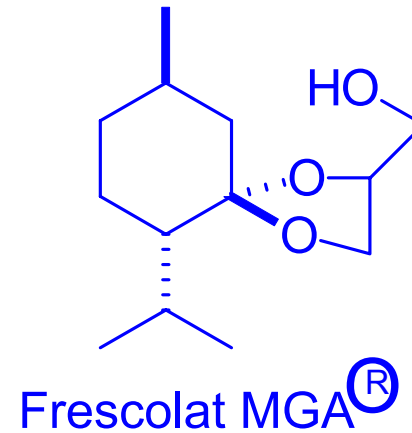
Frescolat type MPC

Pelzer, Surburg & Hopp. DE 4,226,043 (1994) to H&R

Commercially successful coolants by H&R: Frescolat ML[®]
(Menthyl lactate, FEMA **3748**) and Frescolat MGA[®],
(Menthone Glycerin Acetal, FEMA **3807** and **3808**).

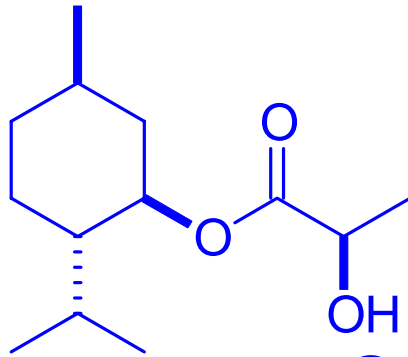


Obtained by
esterification
of lactic acid with
menthol



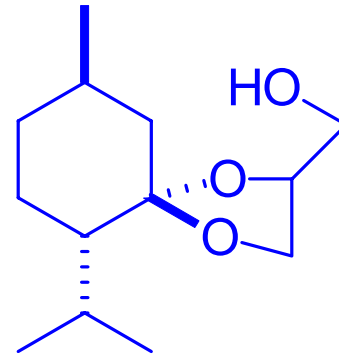
Obtained by acetalization
of menthone with glycerin

Bauer, Brüning & Grüb. DE 2,608,226 (1977) to H&R



Frescolat ML[®]

**Cooling strength
33-50**

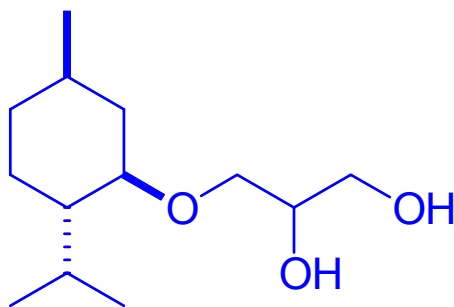


Frescolat MGA[®]

**Cooling strength
about same as ML,
maybe little stronger**

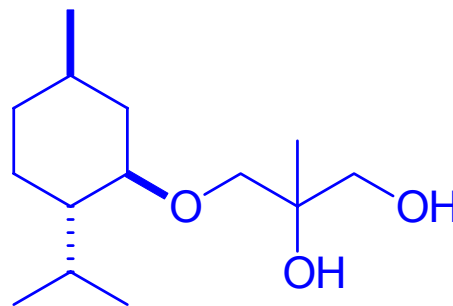
Another widely used physiological coolant is 3-(*l*-Menthoxo)-1,2-propanediol by Takasago, also known as Cooling Agent 10. FEMA **3784**.

A similar coolant by Takasago has an additional methyl group in the glycerin part of the molecule. FEMA **3849**.



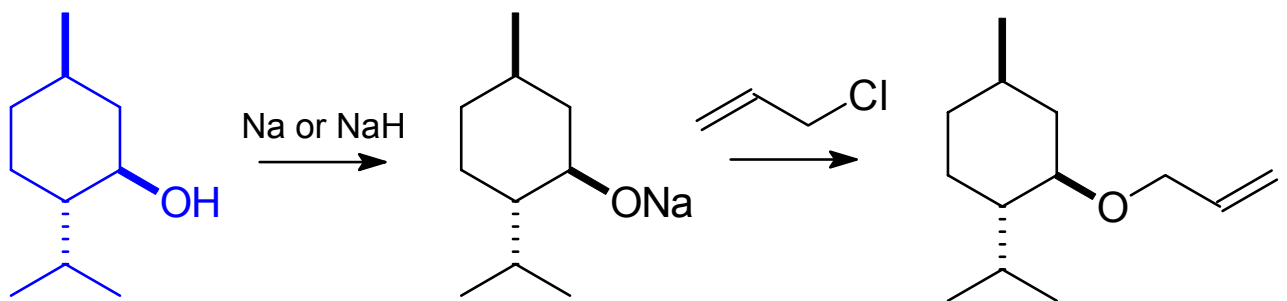
Cooling Agent 10

Cooling strength **20-25**
(US 6,328,982 to TIC)

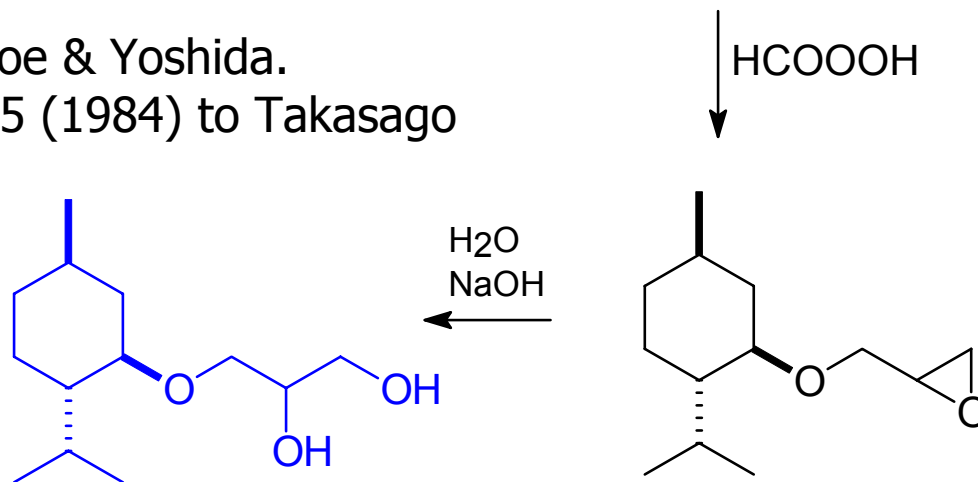


l-Menthoxo-2-methyl
1,2-propanediol

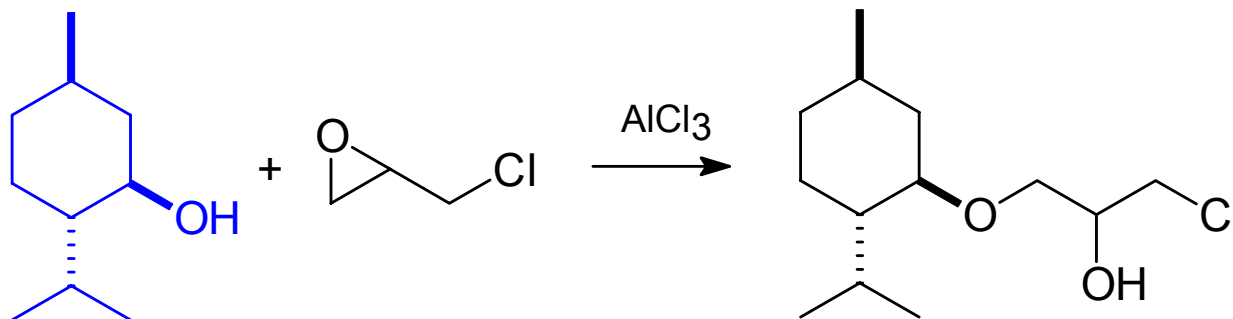
Synthesis of Cooling Agent 10. Method A.



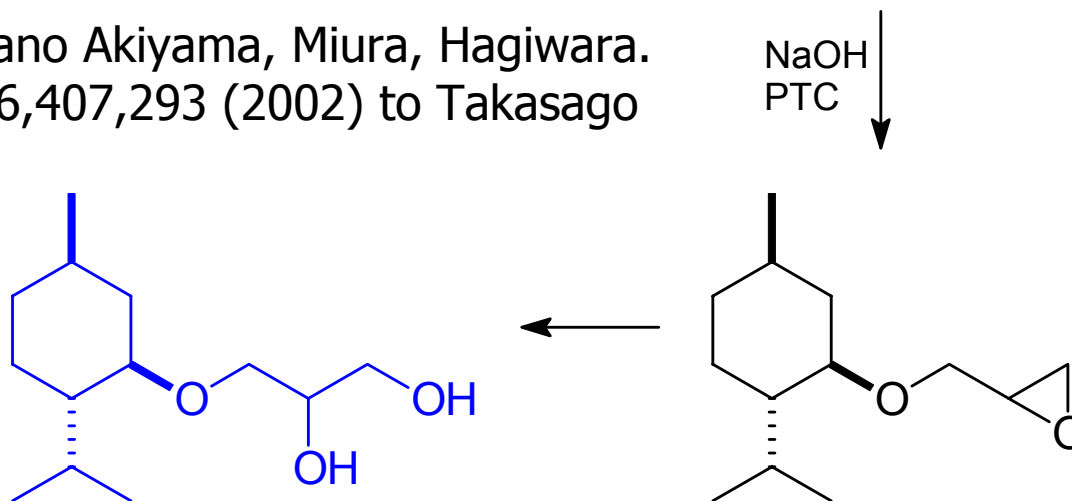
Amano, Moroe & Yoshida.
US 4,459,425 (1984) to Takasago



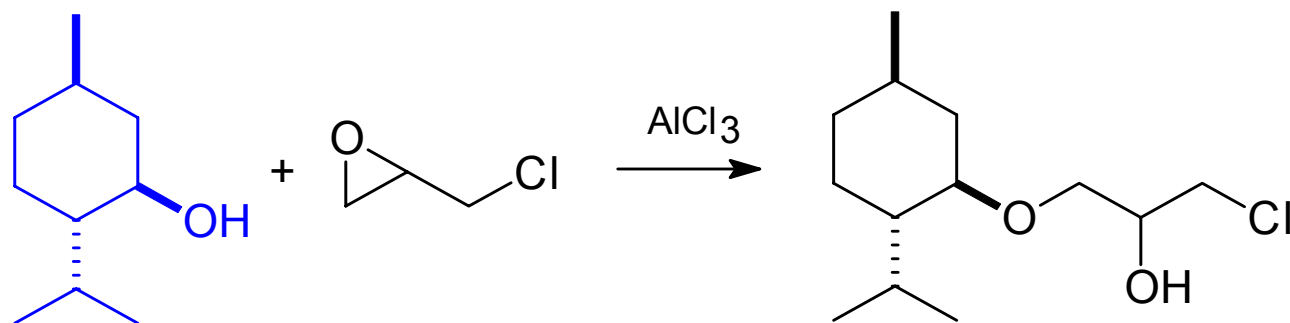
Synthesis of Cooling Agent 10. Method B.



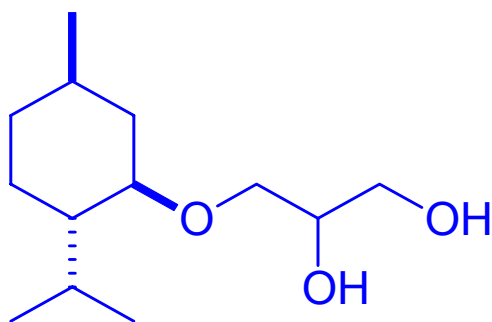
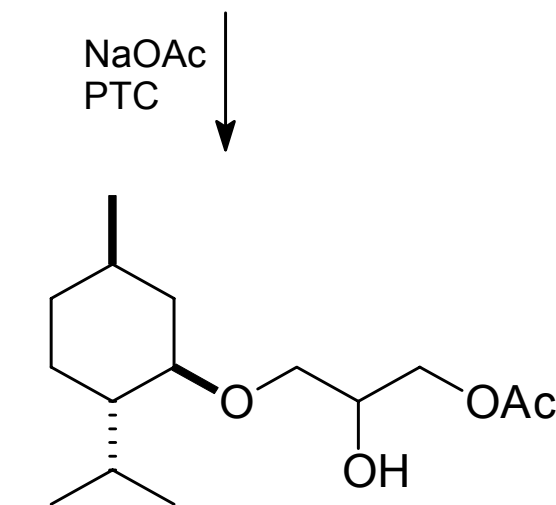
Amano Akiyama, Miura, Hagiwara.
US 6,407,293 (2002) to Takasago



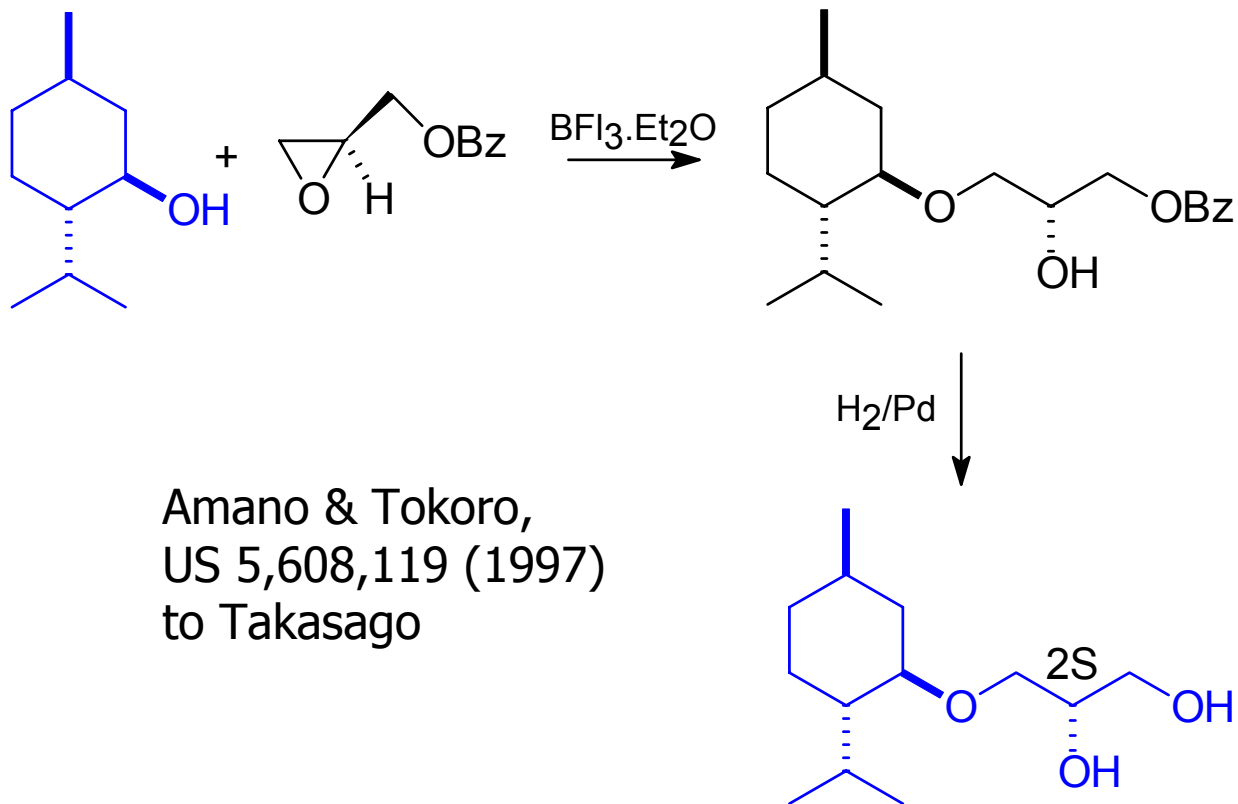
Synthesis of Cooling Agent 10. Method C.



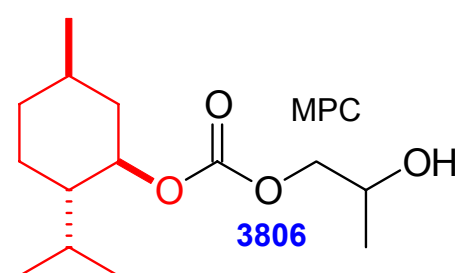
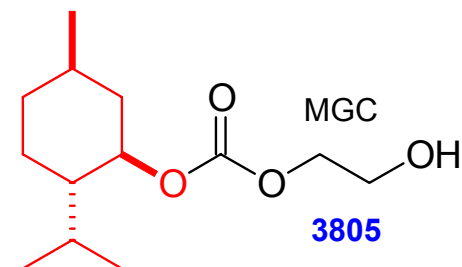
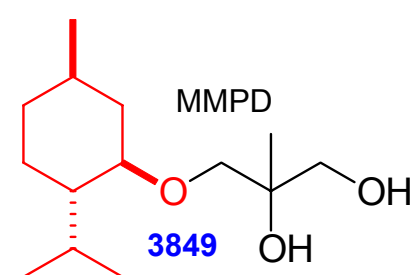
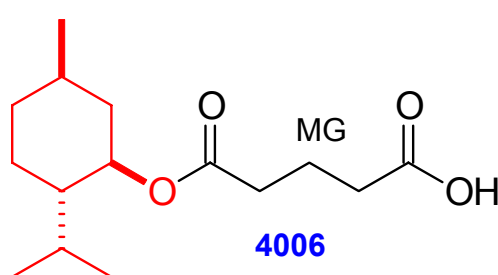
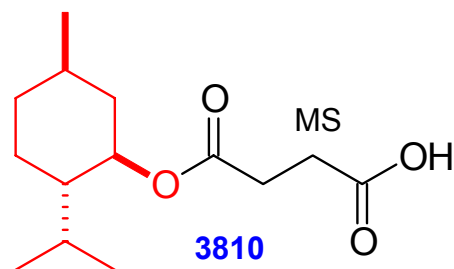
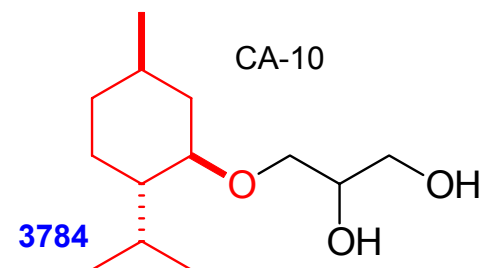
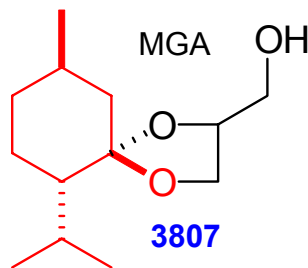
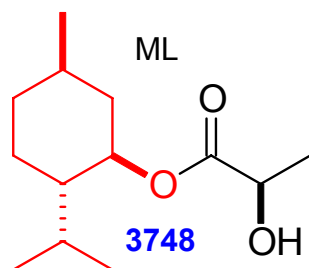
Amano, Akiyama, Miura, Hagiwara.
US 6,515,188 (2003) to Takasago



Synthesis of "2S"-Cooling Agent 10

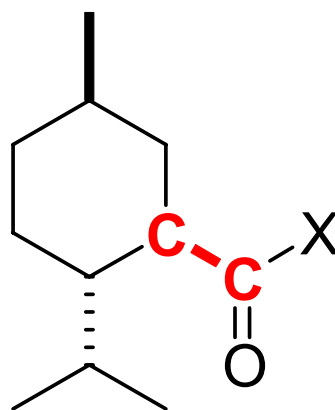


Overview of Coolants "Heavier than Menthol" containing a C-O bond ("Menthoxy-coolants")



In the 70's, Wilkinson Sword patented a great number of *l*-menthol based physiological coolants containing a C-C bond in the 3^d position.

WS type coolants

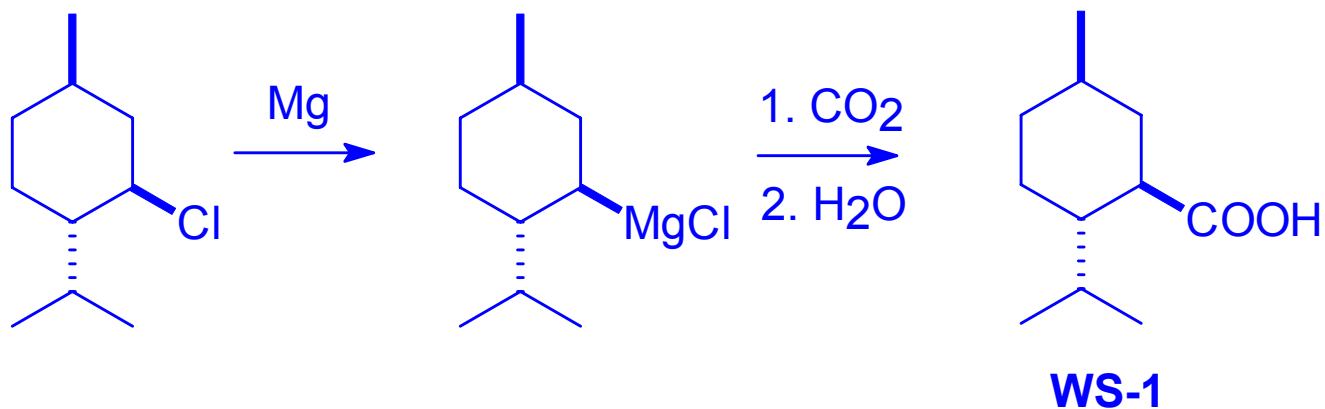


Key patents (Watson, Rowsell, et al.):

DE 2,202,535 (1972); DE 2,205,255 (1972); DE 2,503,555 (1975);
GB 1,351,761 (1974); GB 1,351,762 (1974); US 4,033,994 (1977); US
4,059,118 (1977); US 4,060,091 (1977); US 4,136,163 (1979); US
4,150,052 (1979); US 4,157,384 (1979); US 4,178,459 (1979); US
4,193,936 (1980); US 4,226,988 (1980).

WS-1: Key Synthetic Intermediate

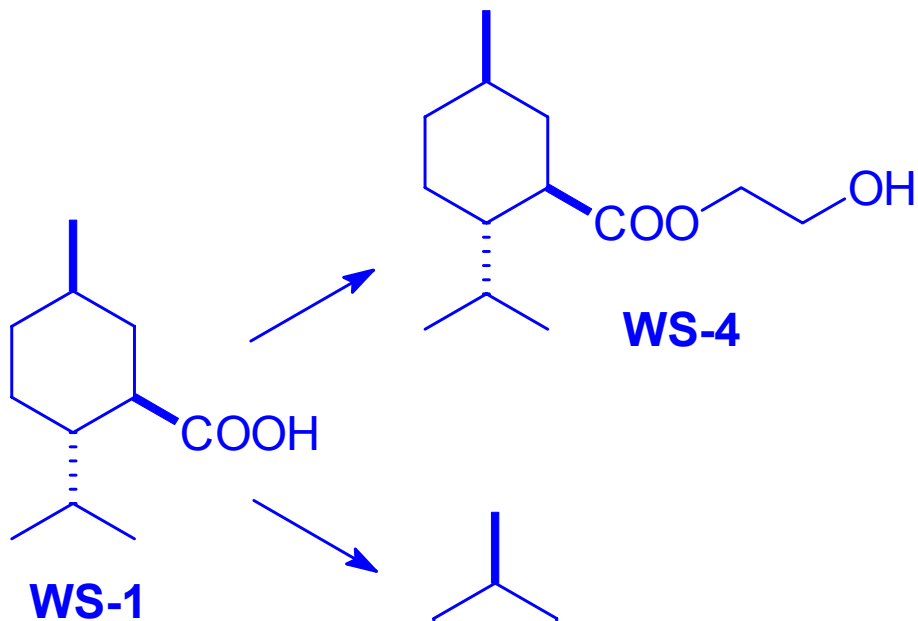
For synthesis of WS-1, see Rowsell. GB 1,392,907 (1975)



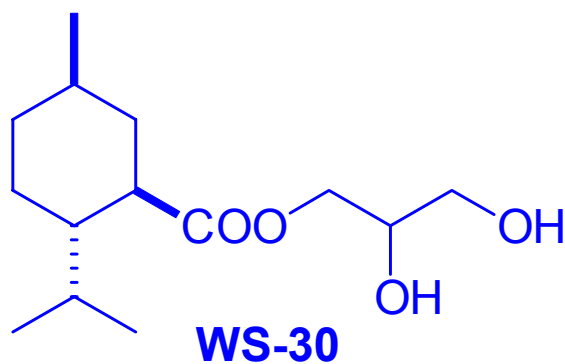
16 times weaker than
l-menthol (see Watson, Rowsell
& Browning, US 4,157,384)

Esters of WS-1

(US 4,157,384)

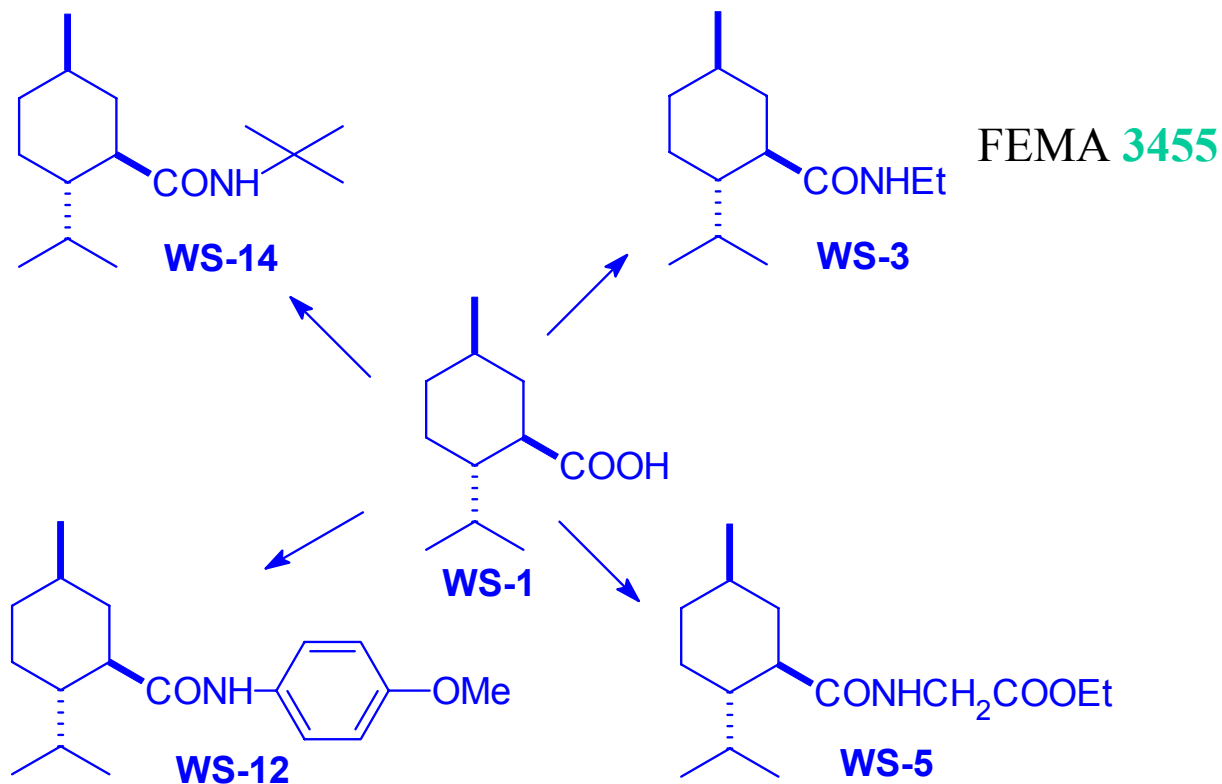


Cooling strength **16-33**



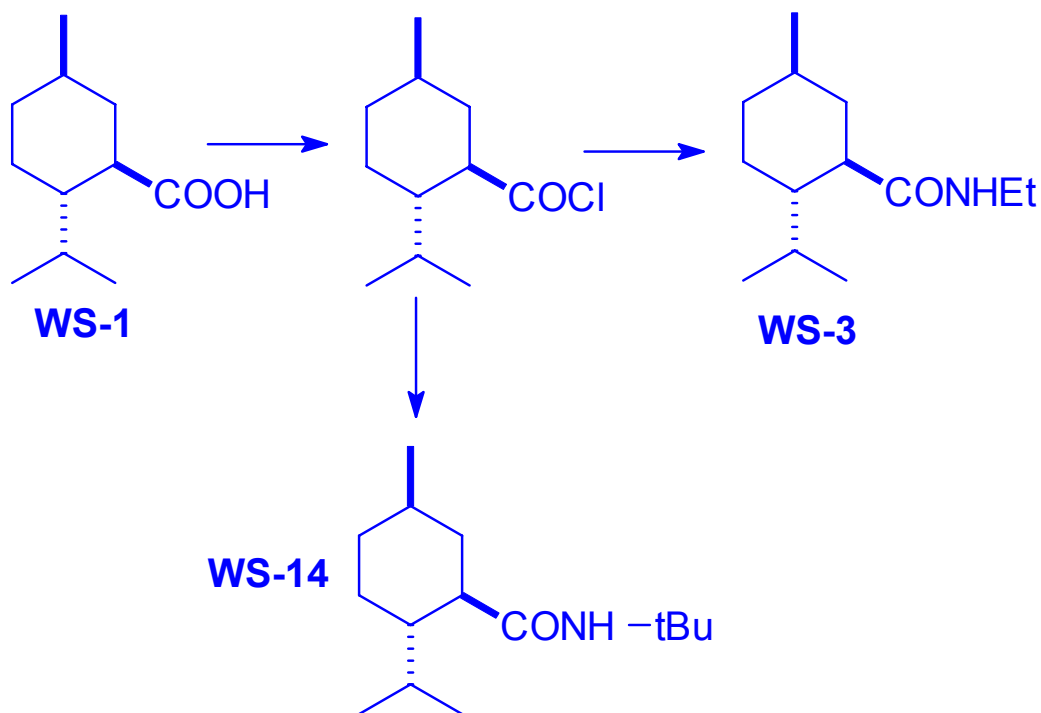
Cooling strength **20-25**
Could be a less expensive alternative for Cooling Agent 10!

N-Substituted Amides of WS-1



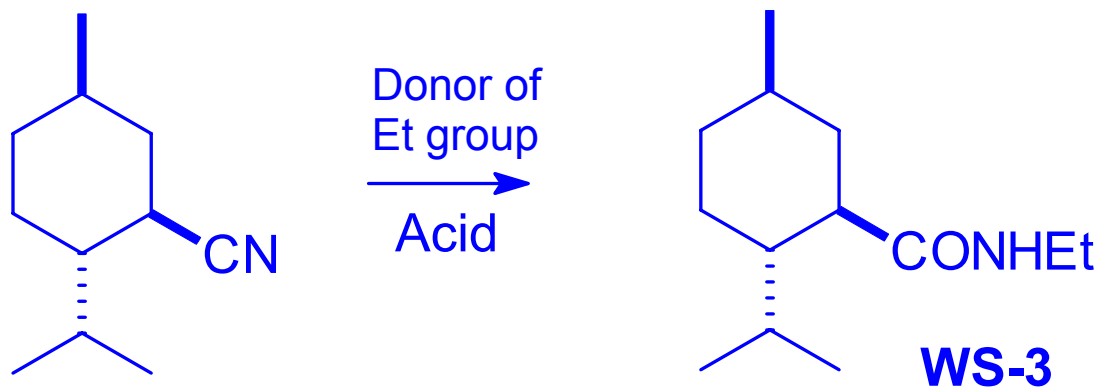
Cooling strength: WS-3, **150**; WS-5, **230**, WS-12, **150**; WS-14, **75**.
Data from: Watson, Hems, Rowsell & Spring,
J.Soc.Cosmet.Chem., 1978, pp. 185-200.

Synthesis of WS-3 and WS-14



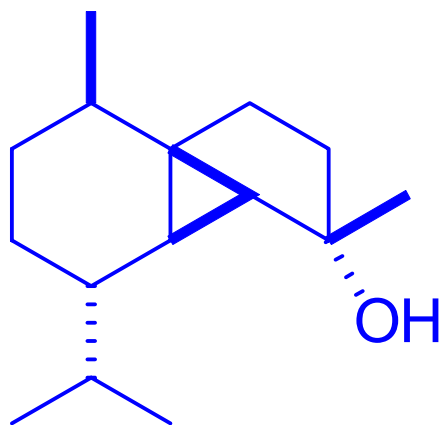
Watson, Rowsell & Spring, US 4,178,459 to Wilkinson Sword

Alternative Synthesis of WS-3



Lebedev & Erman. US 6,482,983 (2002) to Millennium Specialty Chemicals

Cubebol - another example of a "heavier-than-menthol" coolant with a C-C bond in the 3d position of p-menthane

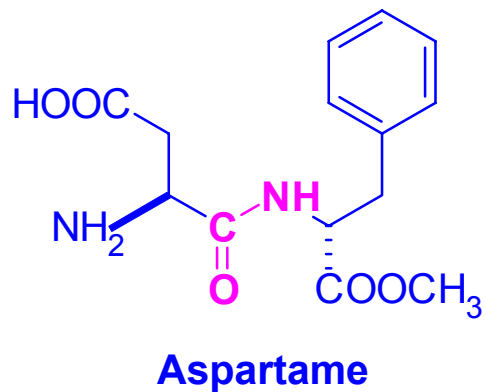
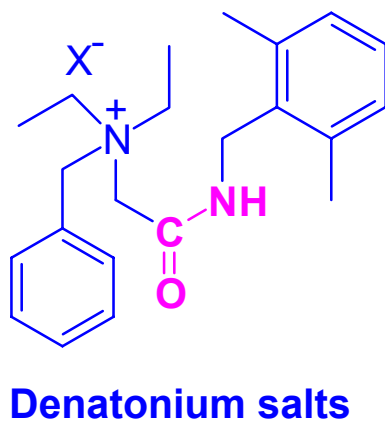
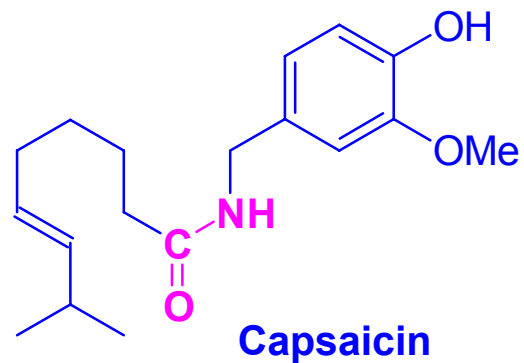
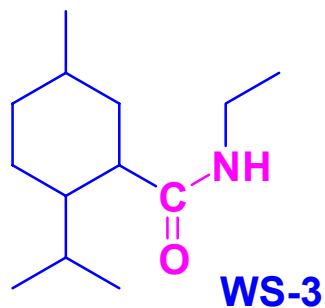


Velazco, Wuensche & Deladoey. US 6,214,788 (2001) to Firmenich

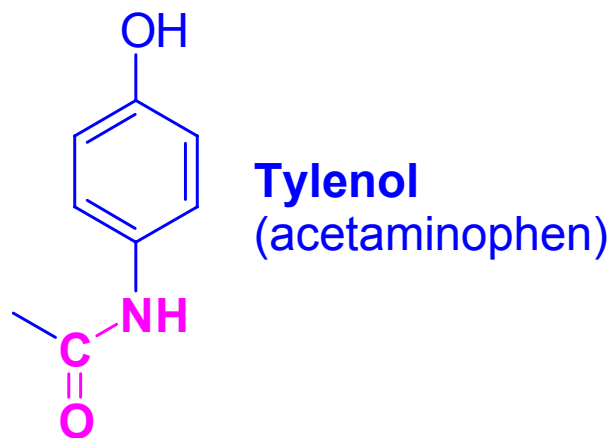
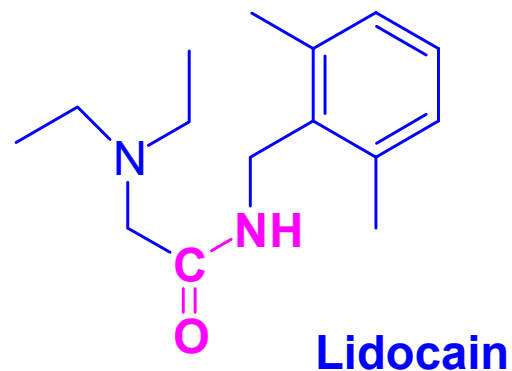
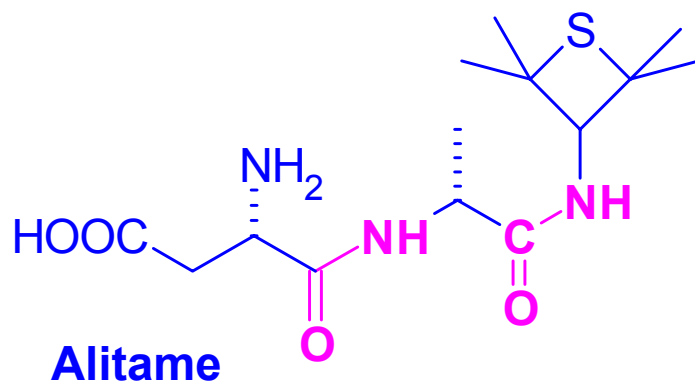
Summary of "Approach 2"- Modification of the /-menthol molecule, making it "heavier."

- This approach produced at least 3 commercially successful physiological coolants of the **Menthoxy** type, and several promising candidates.
- Also, at least one commercially successful N-monosubstituted **Amide** type coolant, and several promising candidates.
- N-Monosubstituted Amides are typically stronger coolants than "Menthoxy."

The Magic of N-Monosubstituted Amides



The Magic of N-Monosubstituted Amides



Approach 3

Search among molecules structurally unrelated to *l*-menthol

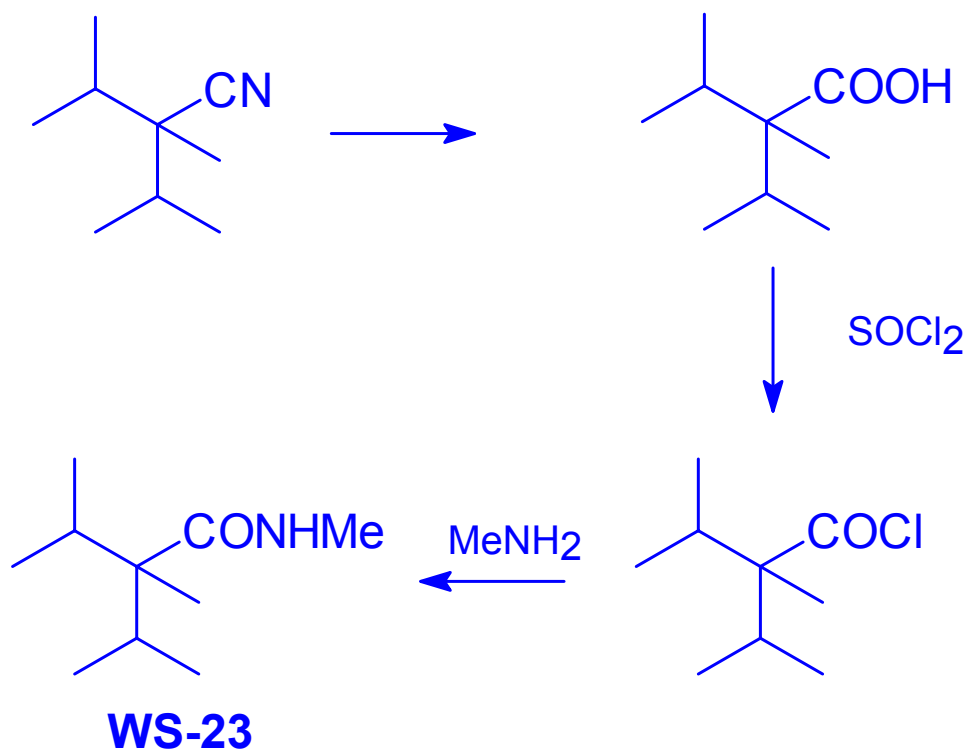


Approach 3: Scope of the Search - Molecular Requirements for Cooling

- Presence of a hydrogen-bonding group
- “Compact” hydrocarbon skeleton
- Correct hydrophilic/hydrophobic balance: $\log P = 3.0 \pm 1.0$
- MW within the range 150-350

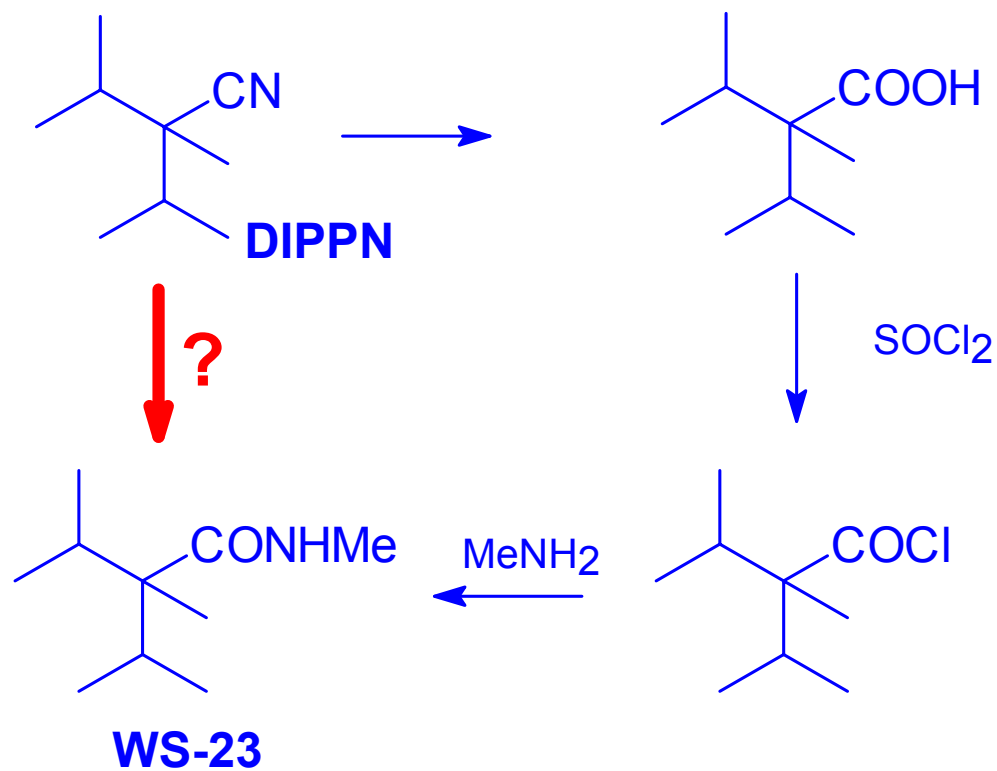
see: **Watson, Hems, Rowsell & Spring.**
***J. Soc. Cosmet. Chem.* 1978, 29, 185-200**

Approach 3: Wilkinson Sword's search among different classes of organic compounds resulted in another commercially successful **amide** type coolant: WS-23.

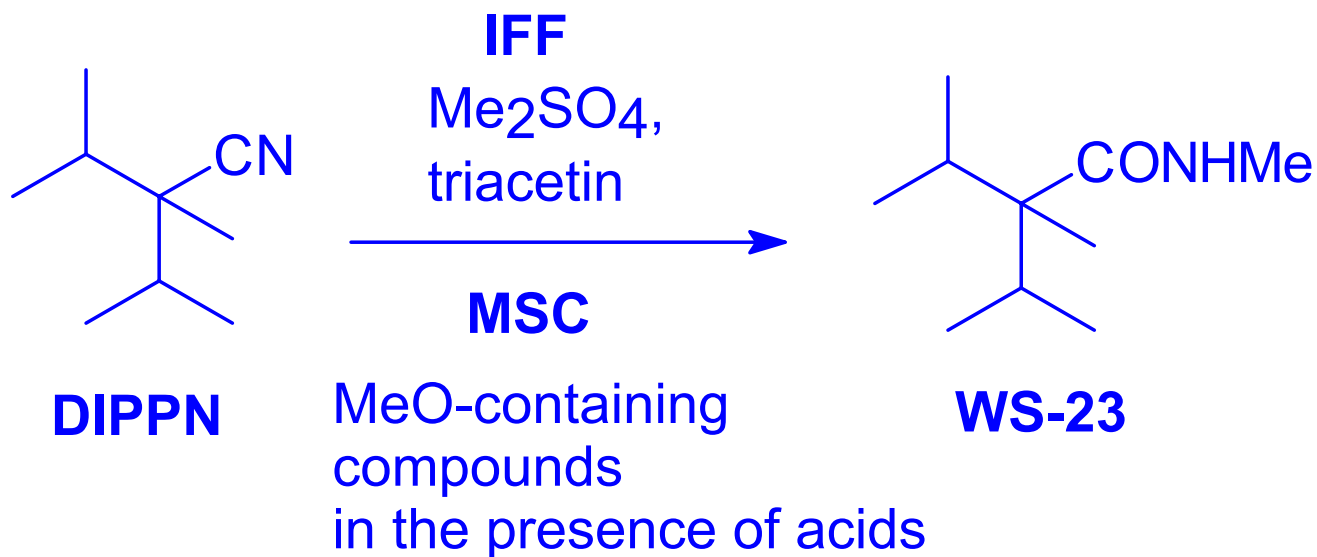


Rowsell, Spring & Hems. GB 1,421,744 (1976) to Wilkinson Sword

Is there a shorter synthesis of WS-23?

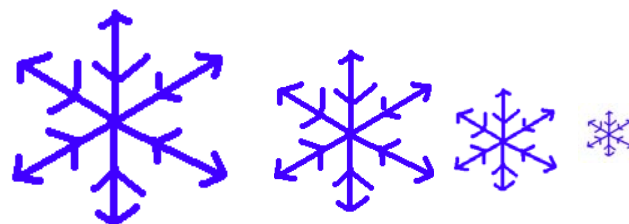
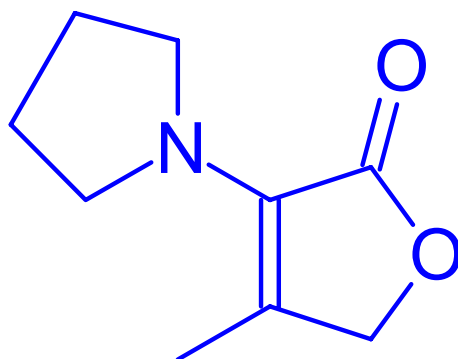


New Syntheses of WS-23 by IFF and MSC



Boden & Ramirez. US 6,303,817 (2001) to IFF.
Lebedev & Erman. US 6,482,983 (2002) to MSC.

MPF coolant 4-Methyl-3-(1-pyrrolidinyl)-2[5H]-furanone - reportedly 35 times more cooling than menthol!



Ottinger, Soldo & Hoffmann. *J.Agric.Food.Chem.*, 2001, Vol. 49, pp. 5383-90.
Hoffmann, Ottinger, Frank, Soldo, Cerny, Robert & Blank. US 6,592,884 (2003)
to Nestec S.A.

Summary of “Approach 3”- Search among molecules structurally unrelated to /-menthol

- This approach produced at least 1 commercially successful physiological coolant of the **Amide** type (WS-23).
- Also, a great number of promising candidates, including the MPF (methyl pyrrolidinyl furanone).



Applications of Cooling Agents

General: provide cooling sensation on contact with human body. Edible and Potable compositions, compositions for Inhalation, application on Skin and Mucous membranes.

Compositions for food, confectionery, soft and alcoholic beverages, tobacco products, chewing gums, toothpaste, dental floss, mouthwash, anti-plaque, anti-gingivitis compositions, shampoos, antidandruff shampoos, lotions, deodorants, after shave lotions, shaving gels, shaving aid composites, fragrances, skin sanitizing compositions, pharmaceutical compositions, including those for treatment of nasal symptoms, of upper gastrointestinal tract distress, for treating cold symptoms; chewable antacid tablets, throat lozenges, throat drops, cough relief, alleviating discomfort of hot flash, foot therapy, etc.

Cooling Agents: Patent Coverage

- In the 70's, Wilkinson Sword obtained a number of patents covering practically all possible uses of WS-compounds. By now, WS patents expired.*
- Frescolat ML has been patented by H&R in 1977.**
- US patent for Cooling Agent 10 obtained by Takasago in 1984***.

***For WS patents see references cited before**

**** Bauer, Brüning & Grüb. DE 2,608,226 (1977) to H&R**

*****Amano, Moroe & Yoshida. US 4,459,425 (1984) to TIC**

Cooling Agents: Patent Coverage

- H&R obtained a US patent for Frescolat MGA in 1993.*
- Monomethyl succinate patented by Mane in 1998.**

***Grub, Pelzer, Hopp, Emberger & Bertram. US 5,266,592 (1993) to H&R**

****Mane & Ponge. US 5,725,865 and 5,843,466 (1998) to V.Mane Fils.**

Recent Patenting Trend - Combinations of Coolants

- Chewing gum, long-lasting effect: menthol + WS-3^{a, b}
- Enhanced cooling properties: Frescolat MGA + menthol and/or WS-3 and/or WS-23^c
- Coolant 10 and WS-3 and/or WS-23 in treatment of nasal symptoms ^d
- Monomenthyl Succinate with other coolants ^e

^a Cheruruki et al. US 5,009,893 (1991) to Warner-Lambert.

^b Luo. US 5,698,181 (1997) to Warner-Lambert.

^c Furman. US 5,451,404 (1995) to Procter & Gamble.

^d Beck. US 5,622,992 (1997) to Procter & Gamble.

^e Mane & Ponge. US 5,725,865 and 5,843,466 (1998) to V.Mane Fils.

Recent Patenting Trend - Combinations of Coolants

- Topical decongestant - mixtures of CA 10, WS-3, WS-23 ^a
- Oral compositions having improved consumer aesthetics: menthol + WS-3 ^b
- Pharmaceutical compositions with cooling agents: WS-3 + menthyl acetate ^c

^a **Bech & Mitra. US 5,760,085 (1998) to Procter & Gamble.**

^b **Lee. US 6,391,886 (2002) to Procter & Gamble.**

^c **Zanone & Stier. US 6,497,859 (2002) to Noville Inc.**

Recent Patenting Trend - Combinations of Coolants

- Coolant composition with reduced stinging: WS-3 + WS-23 + aqueous vehicle + C1-C6 alcohol^a
- Nasal composition: mixtures of CA-10, WS-3 & WS-23^b
- Chewing gum: mixing at least two physiological cooling agents (WS-3, WS-23, ML, MGA, CA-10, MS) with a release modification material^c
- Long lasting and cooling enhancing effect on skin: ML, Isopulegol & CA-10^d

^a **Luke & Reed. WO 93/25177 to Procter & Gamble**

^b **Beck & Reed. WO 94/25003 to Procter & Gamble (claims 3,4).**

^c **Wolf et al. WO 99/12734 to Wrigley.**

^d **Suares et al. WO 00/62737 to Unilever.**

Combinations of Cooling and Warming Agents!!!

- “Emollient” effect: Coolants - menthol, CA-10, WS-3, ML, etc. + “Hotacts” - Vanillyl butyl ether, Capsaicin, etc.^a
- Warming compositions comprising a cooling agent and VBE^b, including compositions for food & drinks^c

^a Nakatsu et al. EP Appl. 1,121,927 (2001) to Takasago

^b Kumamoto. EP Appl. 1,215,257 (2002) to Takasago

^c Kumamoto, EP Appl. 1,215,258 (2002) to Takasago



Acknowledgement

Many thanks to our Senior Perfumer Mr. Pat Whelan for professional evaluations of the activity of cooling agents.

Thank you for attention!

