

F&F Formulation

Progress in Physiological Cooling Agents^a

Development, classification, synthetic approaches, strength, patents and trends

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Physiological cooling agents continue to gain popularity for use in various consumer applications due to their recognized ability of improving desirable sensate properties in consumer products. These properties are generally explained by the chemical action of these agents on the nerve endings responsible for the sensation of cold.¹ Common applications and uses for cooling agents include foods, beverages, flavors, pharmaceuticals, perfumes, and miscellaneous cosmetic goods.

One of the most well known physiological cooling agents is *l*-menthol, which has been used for a very long time in practically all of the above-mentioned applications. Menthol has an excellent cooling strength, low sensitivity threshold, and is relatively inexpensive. *l*-Menthol is available from natural sources such as cornmint oil from *Mentha arvensis*, as well as synthetically, primarily by the well-known methods practiced by Symrise (then Haarmann & Reimer) and Takasago.

On the other hand, *l*-menthol also exhibits some undesirable properties, such as strong “stinging” smell, a somewhat bitter taste and burning sensation in higher concentrations, and high volatility. These undesirable properties, to a certain extent, have limited *l*-menthol’s utility in many applications, and therefore have stimulated an intense search for suitable synthetic substitutes — physiological cooling agents that possess a low volatility and have a relatively weak odor or even no odor at all. Therefore, beginning in the 1960s, mainstream research into synthetic physiological cooling agents began to concentrate on the modification of the *l*-menthol molecule in order to decrease its volatility by attaching a heavy group to the hydroxy group, or *instead* of the hydroxy group of menthol.

Menthoxy-Type Cooling Agents

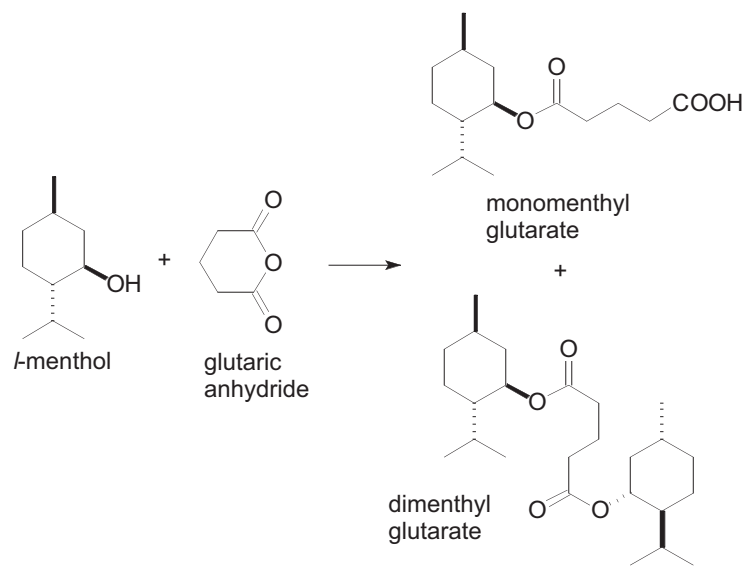
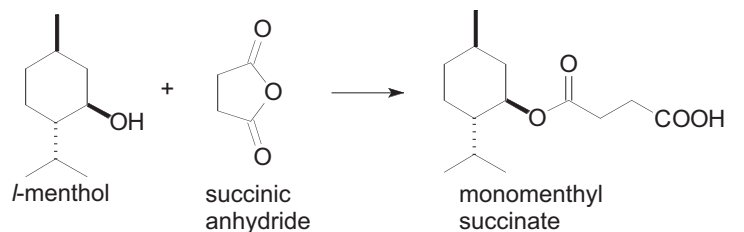
Menthyl esters: First steps along this research path were made during a search for tobacco flavor additives that would allow controlled menthol release from burning tobacco into resulting smoke. Such an example, monomenthyl succinate, was patented in 1963 by Brown & Williamson Tobacco, and 35 years later as a general use physiological cooling agent by V. Mane Fils.^{2,3} Monomenthyl succinate has FEMA GRAS status (FEMA# 3810). A very similar cooling agent, monomenthyl glutarate, has recently been approved by FEMA (FEMA# 4006). Curiously, the literature on this material’s use is very scarce. Monomenthyl glutarate is briefly mentioned in a PCT Application as a component of a flavor blend available from IFF, and also in a US patent as a 70:30 mixture of a monoester monomenthyl glutarate and diester dimenthyl glutarate.^{4,5} Both monomenthyl succinate and glutarate can be obtained by a direct esterification of succinic or glutaric acid with menthol, or by a reaction of menthol with, respectively, succinic or glutaric anhydride (F-1). According to the literature, formation of the undesirable diester is higher in the case of glutaric anhydride.^{2,6}

In 1968, Liggett & Myers patented mixed carbonate esters of *l*-menthol and polyols as tobacco additives, including menthyl glyceryl carbonate and menthyl hydroxyethyl carbonate.⁷ These materials’ syntheses involve a reaction of menthol with phosgene to give an intermediate menthyl chlorocarbonate, which is further reacted with glycerin or ethylene glycol (F-2). Repeating the story of monomenthyl succinate, menthyl hydroxyethyl carbonate was, much later, in 1994, patented as a cooling agent that is now known as Frescolat MGC (Symrise, FEMA# 3805), along with its close analog Frescolat MPC (Symrise, FEMA# 3806).^{8,9} However,

^aParts of this article were presented at a December 2003 Society of Flavor Chemists meeting in Newark, NJ, and a June 2004 central regional meeting of the American Chemical Society in Indianapolis.

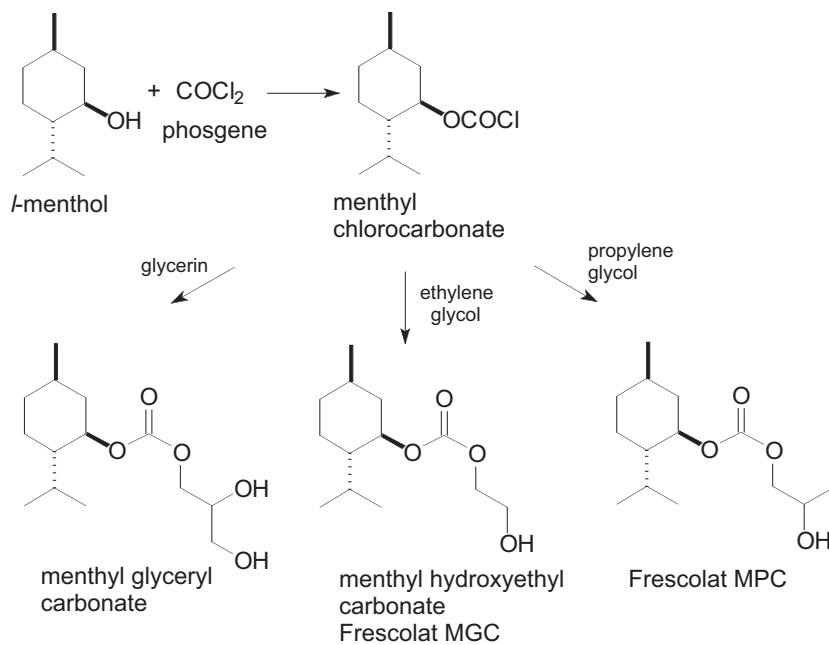
Both monomethyl succinate and glutarate can be obtained by a reaction of menthol with, respectively, succinic or glutaric anhydride

F-1



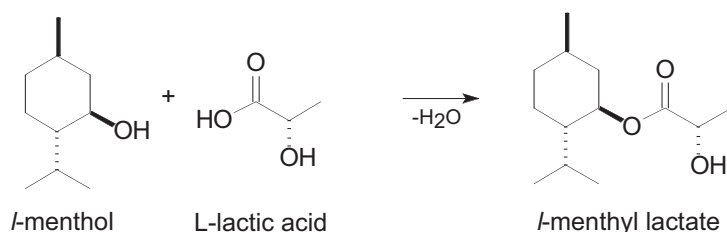
In 1968, Liggett & Myers patented mixed carbonate esters of *l*-menthol and polyols as tobacco additives, including menthyl glyceryl carbonate and menthyl hydroxyethyl carbonate; their synthesis involves a reaction of menthol with phosgene to give an intermediate menthyl chlorocarbonate, which is further reacted with glycerin or ethylene glycol⁷

F-2



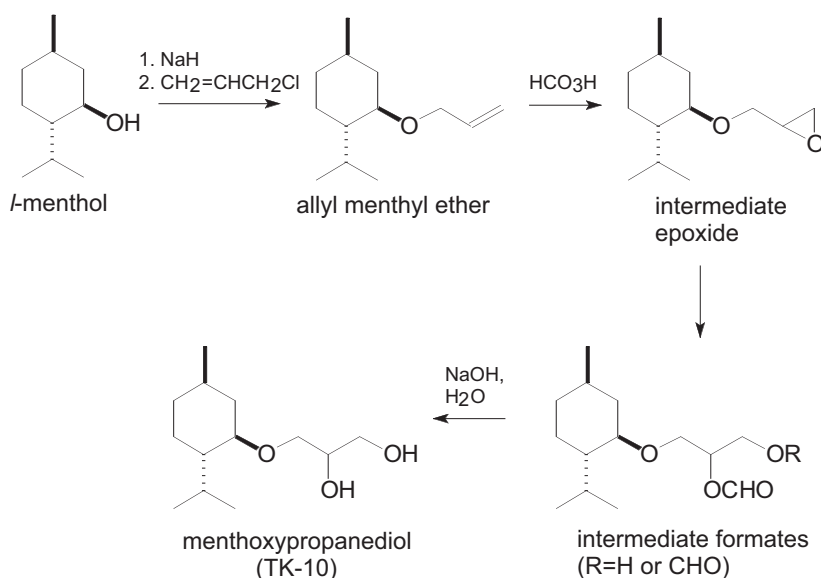
FEMA# 3748, *l*-menthyl lactate, can be obtained by a direct esterification of L-lactic acid with *l*-menthol

F-3



The synthesis of menthyl glyceryl ether (FEMA# 3784) is rather complex and involves an O-allylation of menthol through its Na-alcoholate with allyl chloride followed by epoxidation with performic acid and epoxide opening

F-4

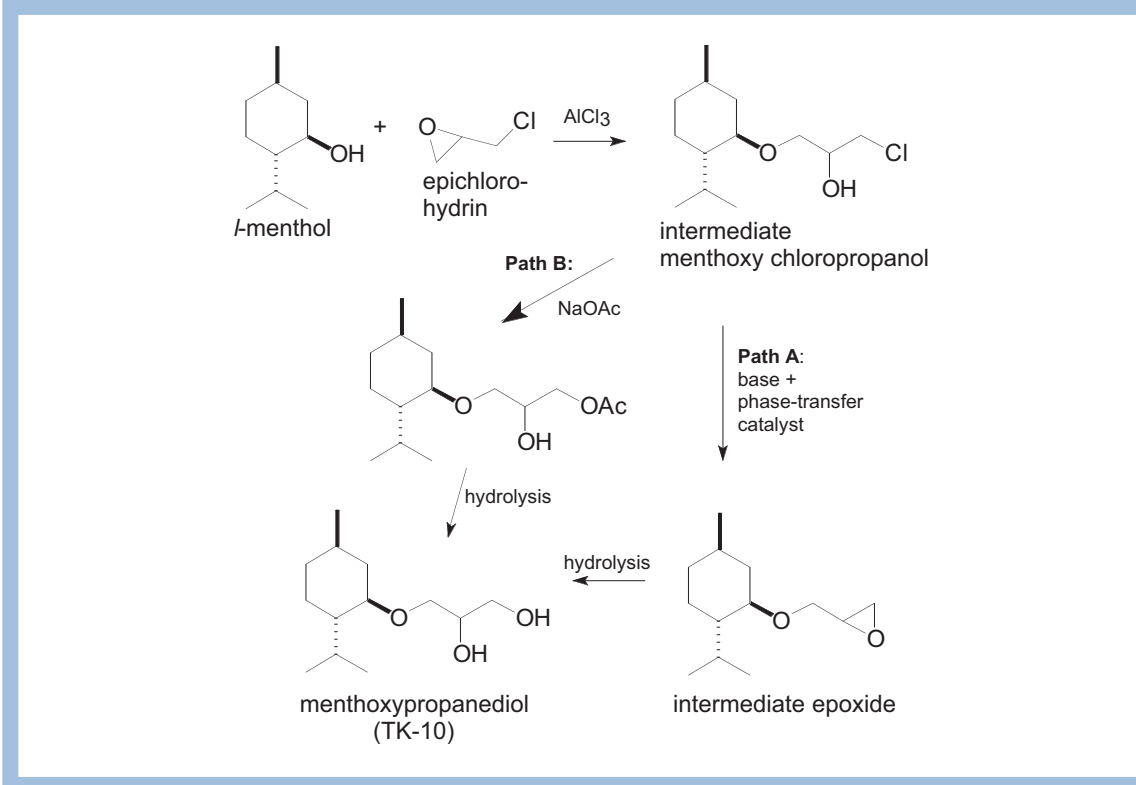


there is no indication that these two ester-type cooling agents are widely used in the industry.

Another ester-type cooling agent, *l*-menthyl lactate, or Frescolat ML (Symrise, FEMA# 3748), is very well known and commercially successful. The material can be obtained by direct esterification of L-lactic acid with *l*-menthol (F-3).¹⁰ Menthyl lactate was obtained for the first time almost 100 years ago, but again its useful cooling properties went unnoticed until much later.^{11,12} Symrise produces two grades of menthyl lactate: one of them, Frescolat ML, can exist as either a clear liquid or a fused solid; another grade, Frescolat ML Crystal, is a fine crystalline material with a congealing point of 42°C minimum. As disclosed in a US Patent, the crystalline material is somewhat unstable on storage, developing a pungent smell, and therefore has to be stabilized with Na or K bicarbonate (0.01 percent to 5 percent).¹³ According to Symrise's

product data sheet, Frescolat ML Crystal additionally contains about 0.05 percent of tocopherol.

Menthyl ethers: The most significant role in the development of the menthyl ether-type of synthetic cooling agent belongs to Takasago International Corp. In the early 1980s, Takasago introduced a new commercially successful cooling agent, menthyl glyceryl ether, also known as TK-10, Cooling Agent 10, Coolact 10 (Takasago, FEMA# 3784), and menthoxypropanediol (or MPD).^{14,15} The synthesis of this molecule is rather complex and involves an O-allylation of menthol through its Na-alcoholate with allyl chloride, followed by epoxidation with performic acid and epoxide opening (F-4).



Although the material's patent suggests that the intermediate epoxide opens by its reflux with an excess of 20 percent aqueous NaOH , there are reasons to believe that the reaction proceeds via intermediate formates, which are hydrolyzed with NaOH (as shown in F-4).¹⁴

Recently, Takasago patented two new modifications of the synthesis of TK-10, apparently looking for a simpler method. In one modification (F-5, Path A), the epoxy ring of epichlorohydrin is opened by menthol in the presence of a Lewis acid giving an intermediate menthoxy chloropropanol, which is further treated with a base in the presence of a phase-transfer catalyst giving the intermediate epoxide, whose hydrolysis results in the formation of TK-10.¹⁶ In another modification (F-5, Path B), the intermediate menthoxy chloropropanol is reacted with Na acetate, thus substituting an acetoxy group for Cl; the resulting acetoxy menthoxy propanol is hydrolyzed to TK-10.¹⁷

When starting with the optically pure (2R)-epichlorohydrin, Path B allows for obtaining optically pure TK-10 with an S-configuration at the middle carbon atom of the glycerin moiety.¹⁷ Optically pure (2S)-TK-10 is considered a better cooling

agent than the racemic product, and there are indications that Takasago has been working on its synthesis at least since mid 1990s.¹⁸

To conclude the discussion of the menthyl ether-type cooling agents, it is worth mentioning that an analog of TK-10 exists that contains an additional methyl group attached to the middle atom of the glycerin moiety. This cooling agent was first patented in 1997, and has a FEMA registration (FEMA# 3849), though there is not much information available on its commercial use.¹⁹

Ketals and Acetals Containing a Paramenthane Group

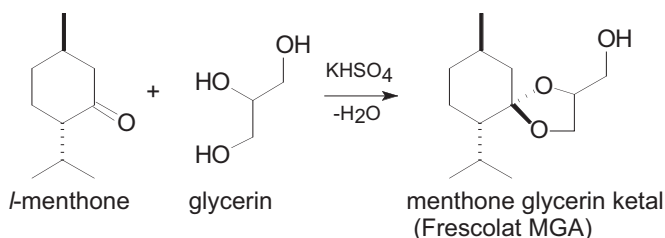
The most important representative of the ketal group of synthetic cooling agents is menthone glycerin ketal, commonly known as menthone glycerin acetal, or Frescolat MGA (Symrise).^{8,20} The synthesis of this compound is very simple, consisting of the acetalization of menthone with glycerin in the presence of an acid catalyst, for example K bisulfate (F-6).²⁰

Commercial menthone glycerin ketal usually contains significant amounts of isomenthone ketal. The product has two FEMA designations: FEMA# 3807 for the *l*-menthone derivative, and FEMA# 3808 for the product obtained from racemic *d,l*-menthone.²¹ However, only the *laevo*-form (FEMA# 3807) appears to be the item of commerce.

Menthone glycerin ketal can be formally classified as a menthoxy-type cooling agent because it contains

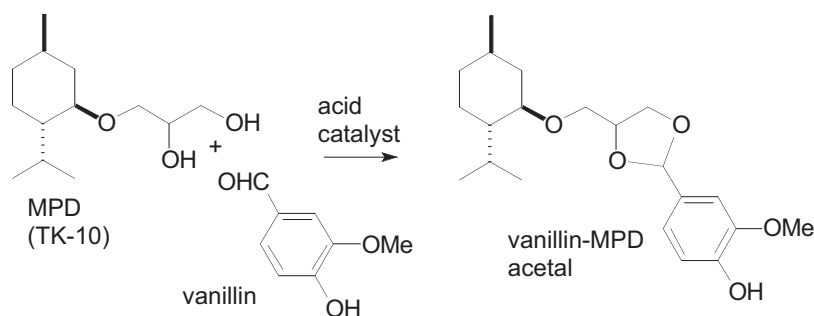
Menthone glycerin acetal synthesis is very simple, consisting of the acetalization of menthone with glycerin in the presence of an acid catalyst, for example K bisulfate

F-6



A flavor ingredient whose molecule is derived from the cooling agent menthoxypropanediol and sweet vanillin by the means of acetalization

F-7



-O-C groups attached to the third carbon atom of the para-menthane system.

Looking at the structures of TK-10, methyl glyceryl carbonate and Frescolat MGA, one could readily find a similarity between these three molecules: they all contain a glycerin fragment in one or another way bound to a paramenthane. Continuing and developing this theme, Takasago suggested a new flavor ingredient whose molecule is derived from the cooling agent menthoxypropanediol (TK-10) and the sweet vanillin by the means of acetalization (F-7).^{22,23} In an unexpected turn, the materials' constituents — MPD and vanillin — impart a long-lasting hot, burning and tingling taste to this new MPD-vanillin acetal. However, when used in a combination with a coolant such as menthol or TK-10, MPD-vanillin acetal assists in achieving a longer-lasting cooling effect.²³

Menthol Analogs: Isopulegol and 3,8-Paramenthane-diols

Isopulegol is an interesting exemption from the rule that in order to meet the

“odorless” criterion, cooling compounds should be significantly heavier than menthol. Isopulegol has the same carbon skeleton as menthol, but is “lighter” by two hydrogen atoms. As menthol, isopulegol exists in eight stereoisomeric forms. It was found that optically and chemically pure (-)-*n*-isopulegol ($[\alpha]_D^{25} = -22.2^\circ\text{C}$) obtained by the cyclization of (+)-citronellal (F-8) is practically odorless and possesses cooling properties.²⁴

Purification can be achieved by crystallization at -40°C followed by distillation. Takasago sells isopulegol under trade name Coolact P (FEMA# 2962).

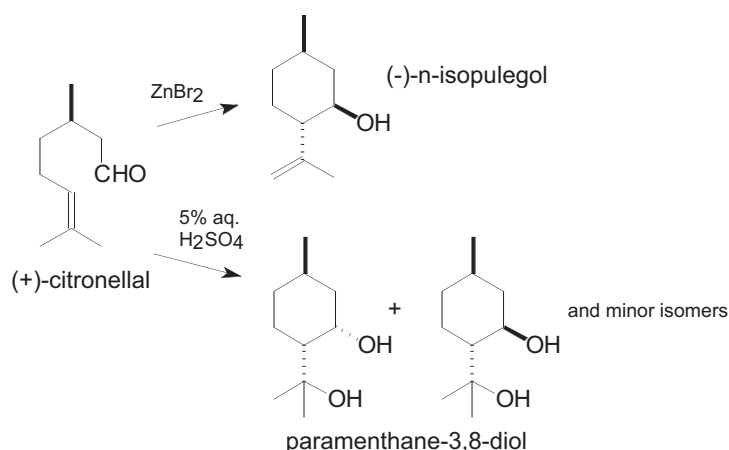
One more cooling agent, also obtained by the cyclization of citronellal, is Coolact 38D (Takasago), or paramenthane-3,8-diol,²⁵ recently approved by FEMA (FEMA# 4053). The difference in synthetic procedures leading from (+)-citronellal to (-)-*n*-isopulegol and paramenthane-3,8-diol is that the former is obtained in the presence of a Lewis acid catalyst, preferably under anhydrous conditions, while the latter materials are obtained by using an aqueous protonic acid (F-8).

WS Type Cooling Agents

All cooling agents discussed in the previous section have an oxygen atom linked to the third position of the paramenthane skeleton. The compounds reviewed in

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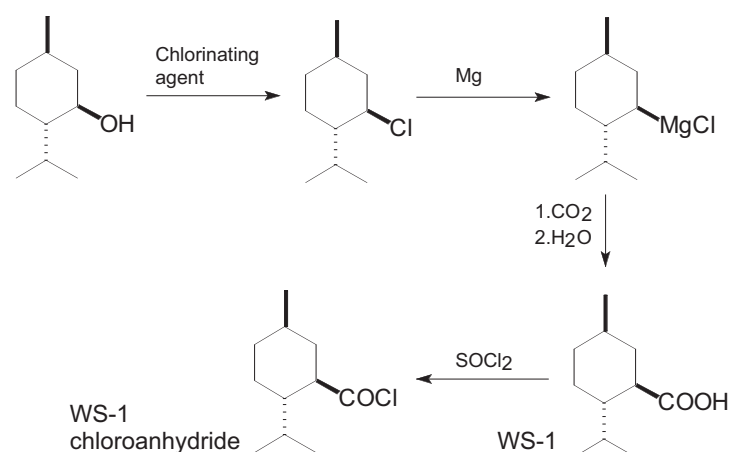
F-8



41

An intermediate for the synthesis of WS compounds is WS-1 chloroanhydride, usually obtained by the reaction of WS-1 with thionyl chloride

F-9



the following section have a carbonyl group linked to the C-3 of the paramenthane, and include esters and amides of the paramenthane-3-carboxylic acid. Cooling agents of this type were proposed and thoroughly investigated in the 1970s by the Wilkinson Sword, and therefore are commonly known as WS compounds.^{1,26-31}

The key intermediate for WS cooling agents is the paramenthane-3-carboxylic acid, or WS-1, whose synthesis involves conversion of menthol into menthyl chloride, then menthyl magnesium chloride (Grignard reagent), and carboxylation of the Grignard reagent with carbon dioxide.³¹ The next intermediate for the synthesis of WS compounds is WS-1 chloroanhydride, usually obtained by the reaction of WS-1 with thionyl chloride (F-9).^{28,30}

Further, the chloroanhydride can be readily converted into WS esters — for example, into ethylene

glycol ester WS-4 by a direct reaction with the corresponding glycol. In the case of WS-30 (glyceryl ester), due to the multifunctional character of glycerin molecules, the synthesis employs solketal, which is a protected form of glycerin, and involves an additional step of deprotection by hydrolysis (F-10).²⁸

Preparation of amide-type WS compounds is based on the reaction of WS-1 chloroanhydride with the corresponding amines. Several examples of such syntheses, including the synthesis of commercially important WS-3 (FEMA# 3455), are provided in F-11. The amine part of the molecule can contain an additional functional group, such as the ethoxycarbonyl

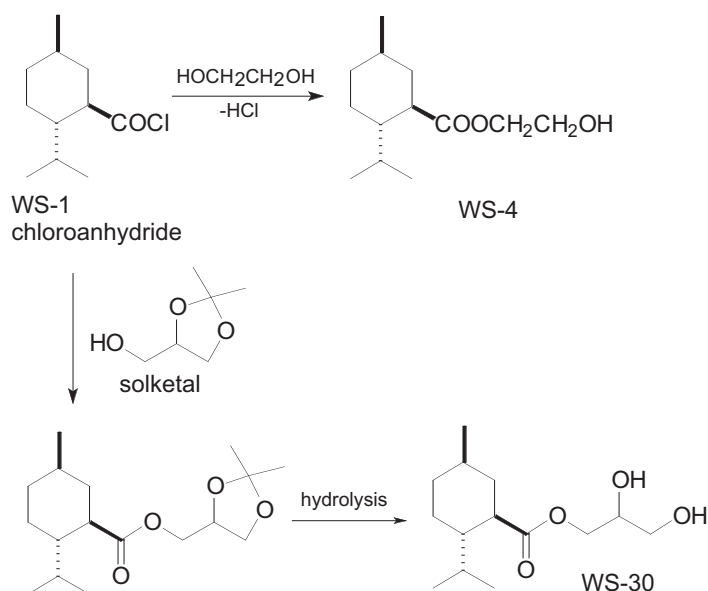
Chloroanhydride can be readily converted into WS esters, and in the case of WS-30 (glyceryl ester), due to the multifunctional character of glycerin molecule, the synthesis employs solketal, which is a protected form of glycerin, and which involves an additional step of deprotection by hydrolysis

F-10

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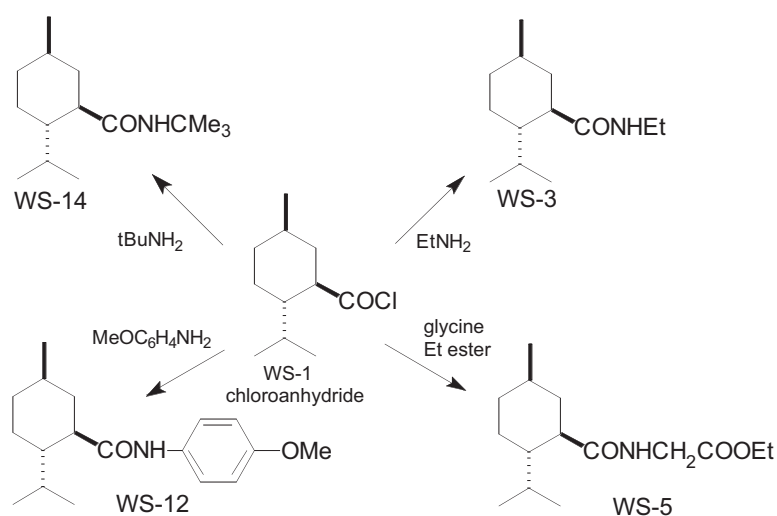
VOL. 29 NOVEMBER | DECEMBER 2004

PERFUMER & FLAVORIST



Several examples of the preparation of amide-type WS compounds based on the reaction of WS-1 chloroanhydride with the corresponding amines, including the synthesis of commercially important WS-3 (FEMA# 3455)

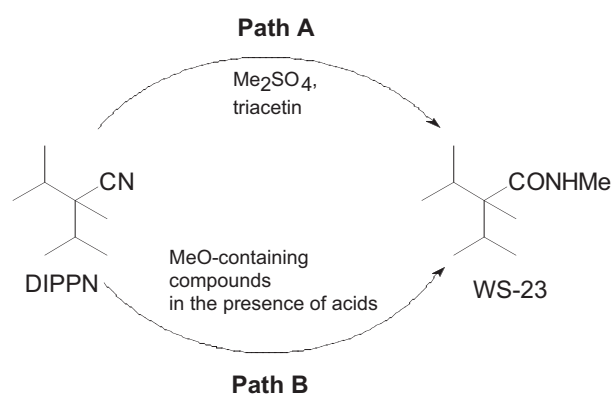
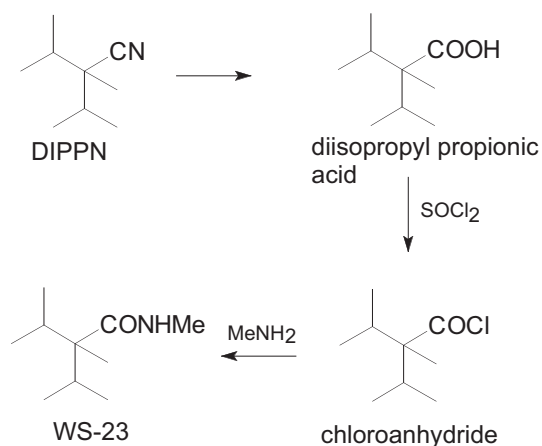
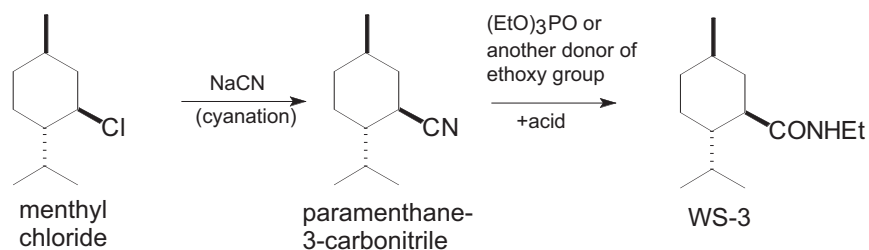
F-11



group in WS-5, and can be a linear alkyl (ethyl in WS-3), branched alkyl (tertiary butyl in WS-14) or aryl (p-methoxyphenyl in WS-12).³⁰

An alternative route to WS-14 exists, which consists of a reaction of menthyl magnesium chloride (Grignard reagent) with tertiary-butyl isocyanate, but there is no indication that this method has been used commercially.³² Also, there is an

alternative synthesis of WS-3 that has been developed by the Millennium Specialty Chemicals based on the reaction of paramenthane-3-carbonitrile with triethyl phosphate in the presence of an acid, for example polyphosphoric acid.^{33,34} According to the method, not only triethyl phosphate, but any compound that contains an ethoxy group C₂H₅O-, can be used, including ethanol, diethyl carbonate, diethyl sulfate, etc. (F-12).^{33,34} The prospects of commercialization of this method depend strongly on the cost and availability



of the starting paramenthane-3-carbonitrile, which can be obtained by a cyanation of menthyl chloride, shown in F-12.

Importantly, paramenthane, or menthol-like structure, is not a “pre-requisite” for a compound to possess cooling properties. Indeed, Wilkinson Sword has patented a broad variety of cooling agents having no structural similarity to *l*-menthol whatsoever. These cooling agents include carboxamides, ureas, phosphine oxides, sulfonamides and sulfinamides, sulfides and sulfones, acyclic secondary and tertiary alcohols, branched-chain primary alcohols, acyclic carboxylic acids, their salts and esters, and many others.³⁵ Other examples of menthol-unrelated cooling agents include icilin (same as AG-3-5), whose strong cooling properties were discovered in the early 1980s by E. Wei, 2(5H)-MPF, with its extremely low cooling threshold, and other similar compounds from malt patented by T. Hoffmann et al.³⁶⁻³⁹ However, according to the available sources of information, only one menthol-unrelated cooling compound is now produced commercially: an acyclic branched-chain carboxamide WS-23 (FEMA# 3804), which was also synthesized for the first time and patented by Wilkinson Sword Ltd.^{40,41} The original method for the synthesis of WS-23 consisted of the conversion of diisopropyl propionitrile (DIPPN) into the corresponding diisopropyl propionic acid, chlorination of the acid producing its chloroanhydride, and finally amination of the chloroanhydride with methylamine according to F-13.⁴¹

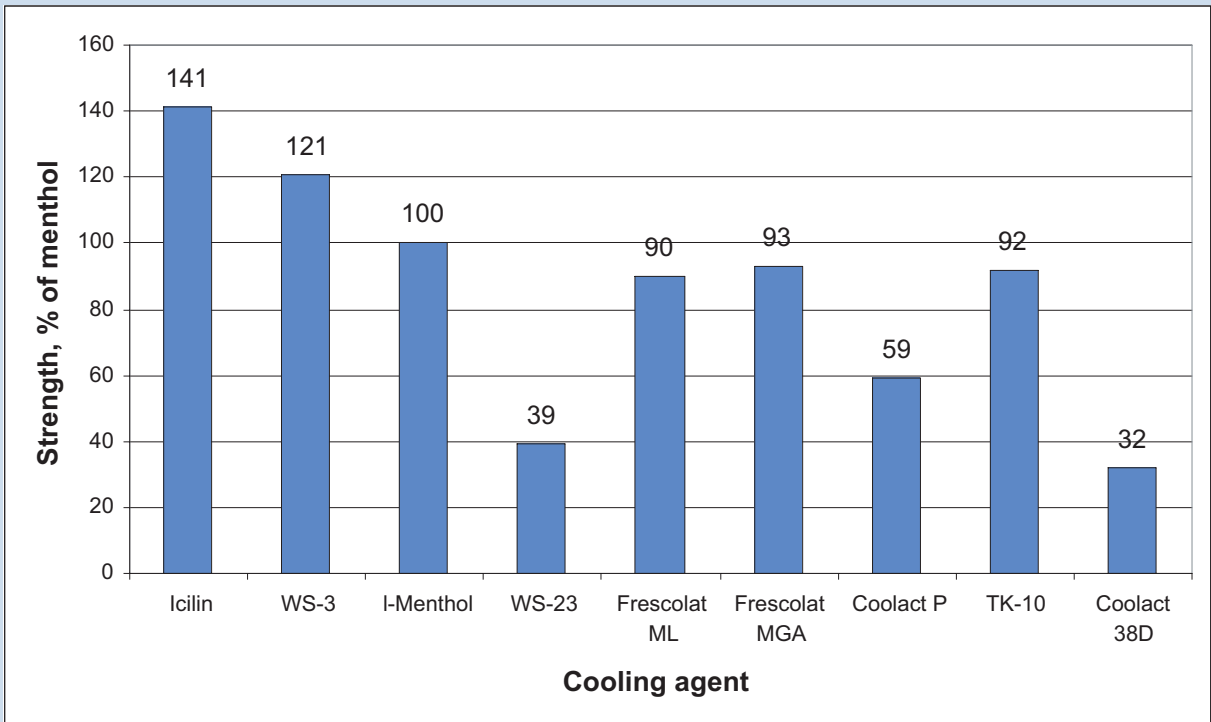
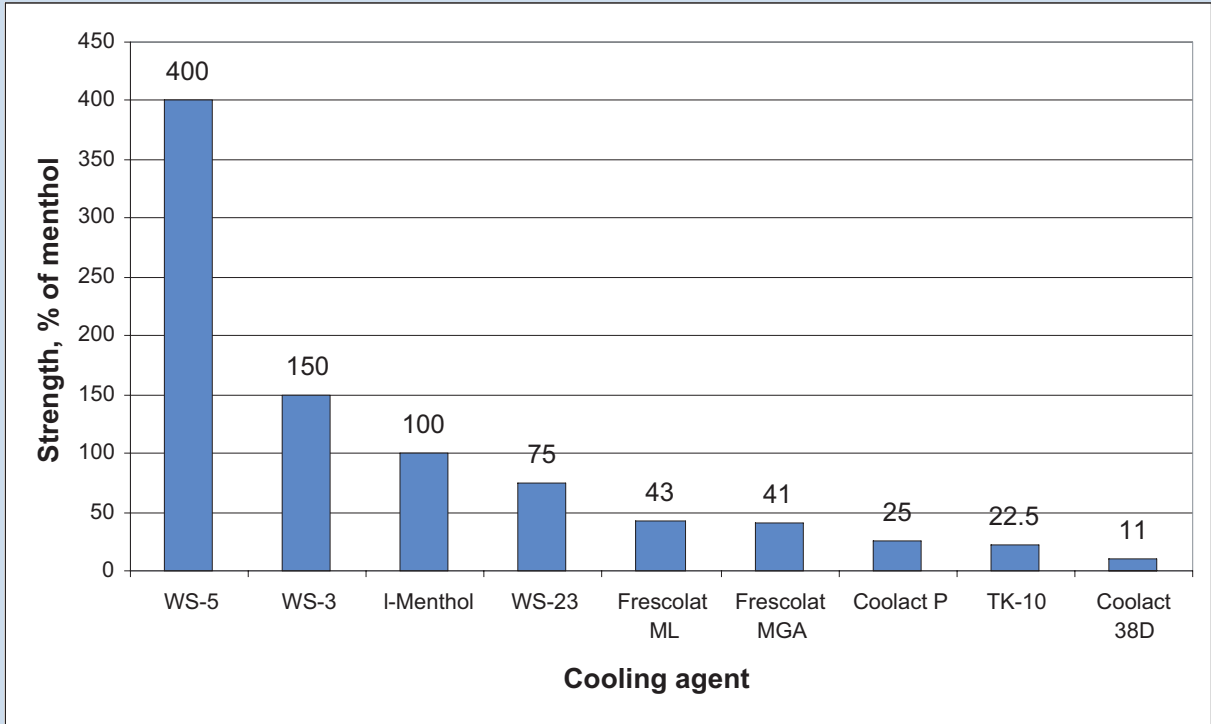
Of course, it was very attractive to find a method that would allow a direct conversion of DIPPN into WS-23. As a result of intense research in this area, a number of procedures for such direct conversion have recently been patented. Thus, IFF's method consists in heating DIPPN in an excess of triacetin, continuously adding dimethyl sulfate and removing byproduct methylacetate by distillation (F-14, Path A).⁴² The yield of WS-23 by this method, according to the patent, is approximately 70 percent of the theory.⁴² A higher yield of WS-23 (over 90 percent of the theory) is obtained using the broad method patented by Millennium Specialty Chemicals.^{33,34} This method, already mentioned above in conjunction with WS-3, consists in reacting DIPPN with any methoxy-containing compound in the presence of an acid, wherein the methoxy-containing compound can be methanol, dimethyl carbonate, trimethyl phosphate, trimethyl borate and the like; the acid can be polyphosphoric, chlorosulfonic, and sulfuric, among others (F-14, Path B). One of the most efficient versions uses methanol and polyphosphoric acid.

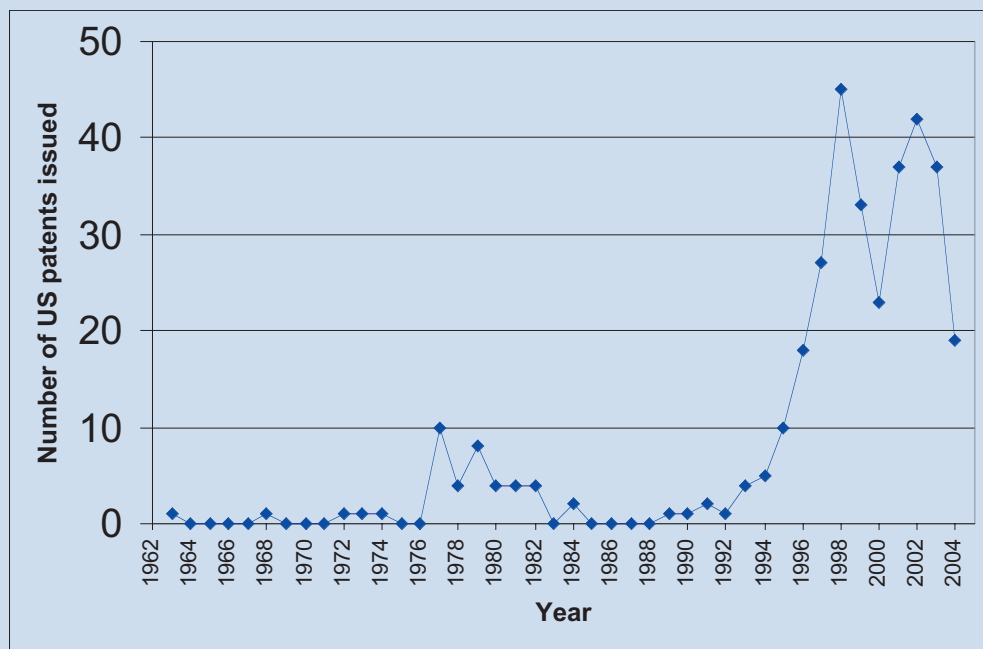
Strong competition in the field of the synthesis of amide cooling agents can be illustrated by the fact that, probably unaware of the publications, DSM Fine Chemicals GmbH later filed a PCT Application that is very similar to Millennium's method with methanol and polyphosphoric acid.^{33,34,43}

Cooling Strength

Obviously, the very concept and measurements of "cooling strength" are subjective. The perception of cooling varies very broadly from person to person, and depends not only on one's training, but also on the method of measurement, product base (or vehicle), concentration of the cooling agent, purity and isomeric composition of the cooling agent, presence of other active ingredients, and many other factors. Furthermore, it has been found that cooling-strength perception varies from one global region to another.⁴⁴ There is some fragmentary information on cooling strength in the literature. For example, one US patent gives average oral threshold values in μg for *l*-menthol (0.25), WS-3 (0.3), WS-5 (0.2), WS-12 (0.1) and WS-14 (0.4).³⁰ An article from the same group of authors gives somewhat corrected data: *l*-menthol (0.3), WS-3 (0.2), WS-5 (0.13), WS-12 (0.2), and WS-14 (0.4).¹ Thus, according to the US patent, cooling strength increases as follows: WS-14 < WS-3 < *l*-menthol < WS-5 < WS-12, while according to the article it increases in the following manner: WS-14 < *l*-menthol < WS-3 < WS-12 < WS-5. In a Takasago patent, cooling strength of *l*-menthol is assumed as 1.0, and measured strengths for TK-10, Coolact P, and Coolact 38D are respectively in the following ranges: 0.20-0.25, 0.20-0.30 and 0.10-0.12.⁴⁵ However, as stated in the same patent, in a vaseline ointment, TK-10 showed a cool feeling 2.0 to 2.5 times stronger than that of *l*-menthol.

Partly based on the literature information and numerous personal communications and discussions,





in addition to comparison tests conducted for dilute (10 ppm) aqueous solutions of individual coolants by the Millennium Specialty Chemicals' flavor panel, the author of this article suggests the sequence of cooling agent strengths presented in T-1.⁴⁶ Cooling strength in T-1 is expressed in percentage points compared to *l*-menthol, whose strength is assumed as 100 percent.

In a recent paper, Behrendt et al. reported cooling efficacies for a number of cooling agents on the basis of measurements of fluorescence from Ca²⁺ ions on cloned mouse receptors TRPM8.⁴⁷ The results of this work, for better comparison arranged in the same order and expressed in percentage points in relation to *l*-menthol, are presented in T-2 (note that icilin is missing from T-1, and WS-5 from T-2). Although one can easily find a strong similarity between trends shown in T-1 and T-2, it also appears that human receptors have lower sensitivity to the menthoxy-type coolants, compared with the mice receptors TRPM8.

Patent Coverage and Current Trends

The fact that cooling agents, their synthesis and applications have become "hot" topics is obvious from the rapidly growing patent coverage. In June 2004, the total number of issued US patents concerning synthetic physiological cooling agents was approximately 350. This number includes not only patents directly related to cooling agents, their synthesis and applications, but also patents only briefly mentioning cooling agents in the specification.⁴⁸ T-3 represents the rate of patent issuance from 1963 to the present. After a nearly flat

initial period in patent progress, a "spike" in patent activity emerged in the late 1970s and early 1980s, a result of the Wilkinson Sword activity. Following another plateau period between 1986 and 1992, the number of patents rapidly grew to an average of about 30 per year.

Regarding the ownership of the patents, 196 — or more than half of the ca 350 patents — belong to Procter & Gamble Co. Wilkinson Sword Ltd. is in second place with 26 US patents, followed by the Wrigley Co. (12), Takasago (11), Avon (nine), Gillette (nine), L'Oreal (eight), Warner-Lambert (seven), Symrise (five), and IFF (four).⁴⁹ The remaining balance belongs to the companies possessing between one and three patents on cooling agents.

Wilkinson Sword's patents have covered practically all possible uses of the individual WS-type compounds. Symrise patents have covered Frescolat cooling agents, while Takasago covered individual Coolacts. More recently, a major trend is finding and patenting combinations of cooling agents that provide a different effect than the components taken separately, and thus further improve the consumer qualities of the final product. For instance, a combination of menthol and WS-3 in chewing gums provides a long-lasting

cooling effect without the bitterness.^{50,51} Combinations of Frescolat MGA and a secondary coolant, such as menthol or carboxamide, in various goods improve overall performance.⁵² Compositions of TK-10, WS-3 and WS-23 were found useful for treatment of nasal symptoms.⁵³ One patent claims usefulness of monomethyl succinate as a primary coolant in the presence of a secondary coolant chosen from a group consisting of carboxamides, Frescolat ML and other materials.³ Combinations of WS-3, Frescolat MGA and TK-10 improve the consumer aesthetics of cough treatment compositions.⁵⁴ One chewing gum, according to a patent, contains a mixture of at least two cooling agents combined with a release modification material.⁵⁵ Cooling enhancement on skin has been noticed in cosmetic compositions containing menthyl lactate combined with TK-10 and Coolact P.⁵⁶ Interestingly, the presence of a warming agent, such as vanillyl butyl ether, can enhance the perception of cooling agents such as TK-10 and Coolact P.⁴⁵

Another new trend is the search for convenient liquid sellable forms of cooling agents with little or no solvent. Thus, Takasago patented liquid solvent-free

blends of *l*-menthol and Coolact P.⁵⁷ A liquid solvent-free 50:50 blend of *l*-menthol and menthyl lactate solidifies at +8°C.⁵⁸ Paramenthane carboxamides are very much prone to crystallization from their solutions in other cooling agents, and therefore menthol-free compositions of WS-3 and menthyl lactate still require propylene glycol as a solvent.⁵⁹ Finally, Millennium Specialty Chemicals found that certain solvent-free blends of WS-3, WS-23, and menthyl lactate exist as stable liquids.⁶⁰

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