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The Search for New Fragrance Ingredients[a,b]

by Anubhav P.S. Narula, International Flavor and Fragrances Inc.

The purpose of this paper is to give an overview of our intense synthetic efforts that have been expended in the quest for novel fragrance ingredients. Carbon-carbon bond formation is at the heart of organic synthesis.[1] Several examples will be presented, which will highlight the utility of diverse synthetic reactions such as Diels-Alder, Mannich, ene reactions, etc. that have been used to uncover highly desirable aroma chemicals (Iso E Super, Lyral, Triplal [or Aldehyde AA], Isocyclocitral and so forth; F-1). Some recent synthetic work will illustrate how these powerful reactions provide substrates that can be elaborated into novel polycyclic structures with interesting odor profiles. In the course of this research investigation, three new proprietary fragrance molecules were discovered and commercialized: Cassiffix, a fresh herbal, long-lasting cassis note; Prismantol, a woody, spicy, ginger, cardamom note; and Prismylate, a woody, amber, vetivert odorant. These are presented in F-2.[2,3]

Background Research in Pursuit of Cassiffix

The Diels-Alder reaction was discovered in 1928 while Kurt Alder was working with Otto Diels.[4] They showed that when butadiene, a diene, is allowed to react with acrolein, a dienophile, under thermal conditions, it produces a (4 + 2) cycloaddition product — 3-cyclohexene carboxaldehyde (F-3) — in high yields, thus offering a simple way to prepare cyclic structures. This reaction played a crucial role in the synthesis of reserpine, morphine and cantharedine, to name a few. Since its discovery, the Diels-Alder reaction has been used in the synthesis of numerous complex natural products. In fact, the Nobel Prize in chemistry was awarded to Kurt Alder and Otto Diels in 1950 because of the enormous utility of their discovery.

[a] This paper was originally presented at the IFEAT International Conference in Warsaw, Poland, October 13-17, 2002.

[b] All trademarked materials noted in this article are assigned to International Flavor and Fragrances Inc., unless noted to the contrary. Sandalore and Ebanol are registered trademarks of Givadaun SA Corp.; Ambrox and Polysantol are registered trademarks of Firmenich Inc.; Brahamanol is a registered trademark of Symrise; Ambroxan is a registered trademark of Henkel KGAA.

Diels–Alder Adducts as Templates

As stated above, the Diels-Alder adducts were employed as templates for further elaboration into new chemicals. This can be achieved easily by first reducing these adducts with an appropriate reducing agent, such as sodium borohydride, followed by cyclization with an acid to furnish a cyclic ether. A series of novel cyclic ethers were prepared for odor evaluation. F-4 also shows how these adducts can be used to prepare new structures by functional group transformation.

Important Ethers in Perfumery

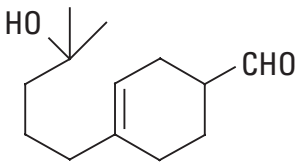
It may be pointed out that ether functionality is an essential feature of some very important fragrance ingredients in perfumery.[5] These structures are delineated in F-5. It is well known that conversion of an alcohol to an ether linkage enhances the diffusiveness of a fragrance ingredient viz. cedrol to Cedramber. It is worth mentioning that when ethyl alcohol (b.p. 78°C) is converted into diethylether (b.p. 34.8°C) its vapor pressure increases; this invariably enhances odor. This is yet another motive for synthesizing carbocyclic ethers.

Ethers from Iso E Super, Isocylogeraniol, Triplal and Wondral

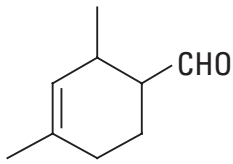
In order to test the stated research idea, commercially available aroma chemicals were tried as substrates for

Aroma chemicals arising from Diels-Alder chemistry

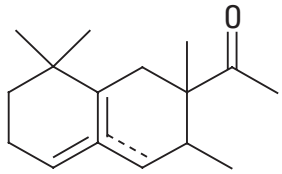
F-1



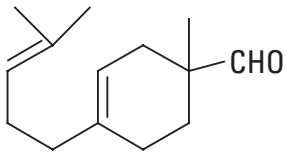
Lyral, 1957
floral, muguet



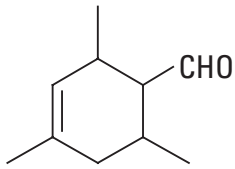
Triplal, 1965
green, citrus



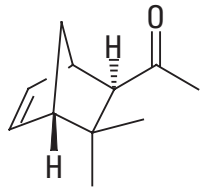
Iso E Super, 1972
woody, floral, ambery



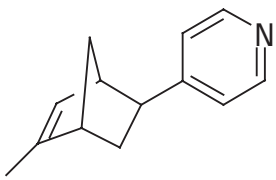
Precyclemone B, 1951
ozone, (freshe air), floral, muguet



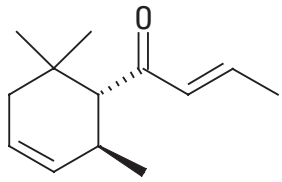
Isocyclocitral, 1980
green, herbal, aldehydic



Camek, 1956
herbal, camphoraceous



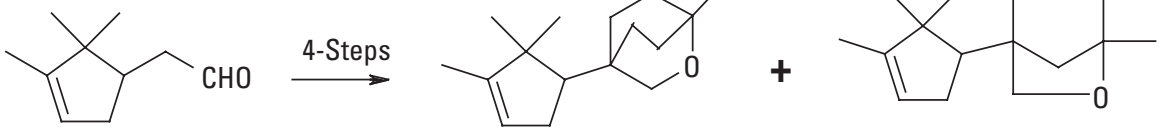
Orriniff, 1983
orris, green, violet



Delta Damascone, 1977
fruity, cassis, floral

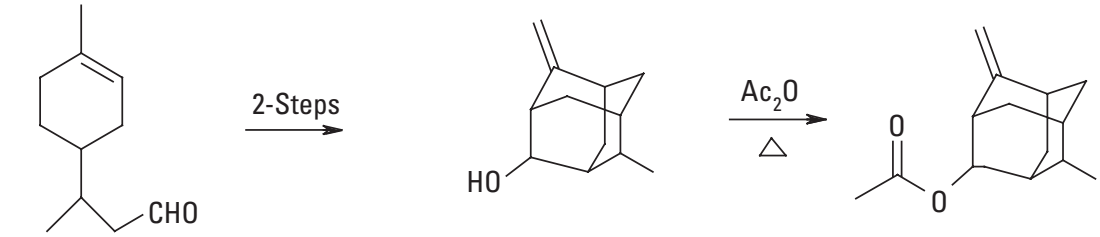
New proprietary fragrance ingredients

F-2



campholenic ald.

Cassiffix, 1991



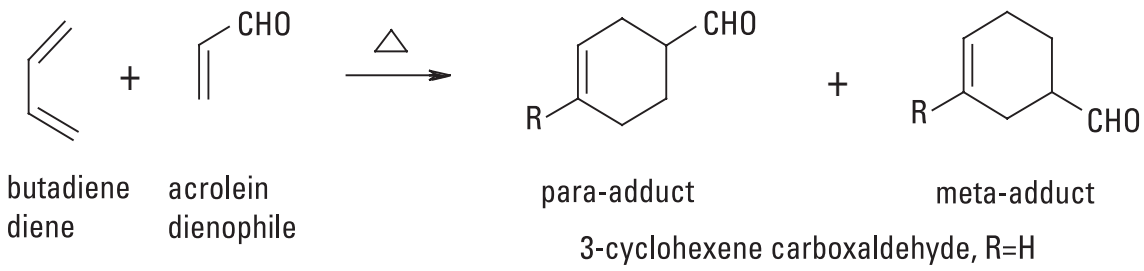
limonene ald.

Prismantol, 1987
spicy (ginger), woody, cardamom

Prismylate, 1988
woody, amber, vertivert

Diels-Alder reaction

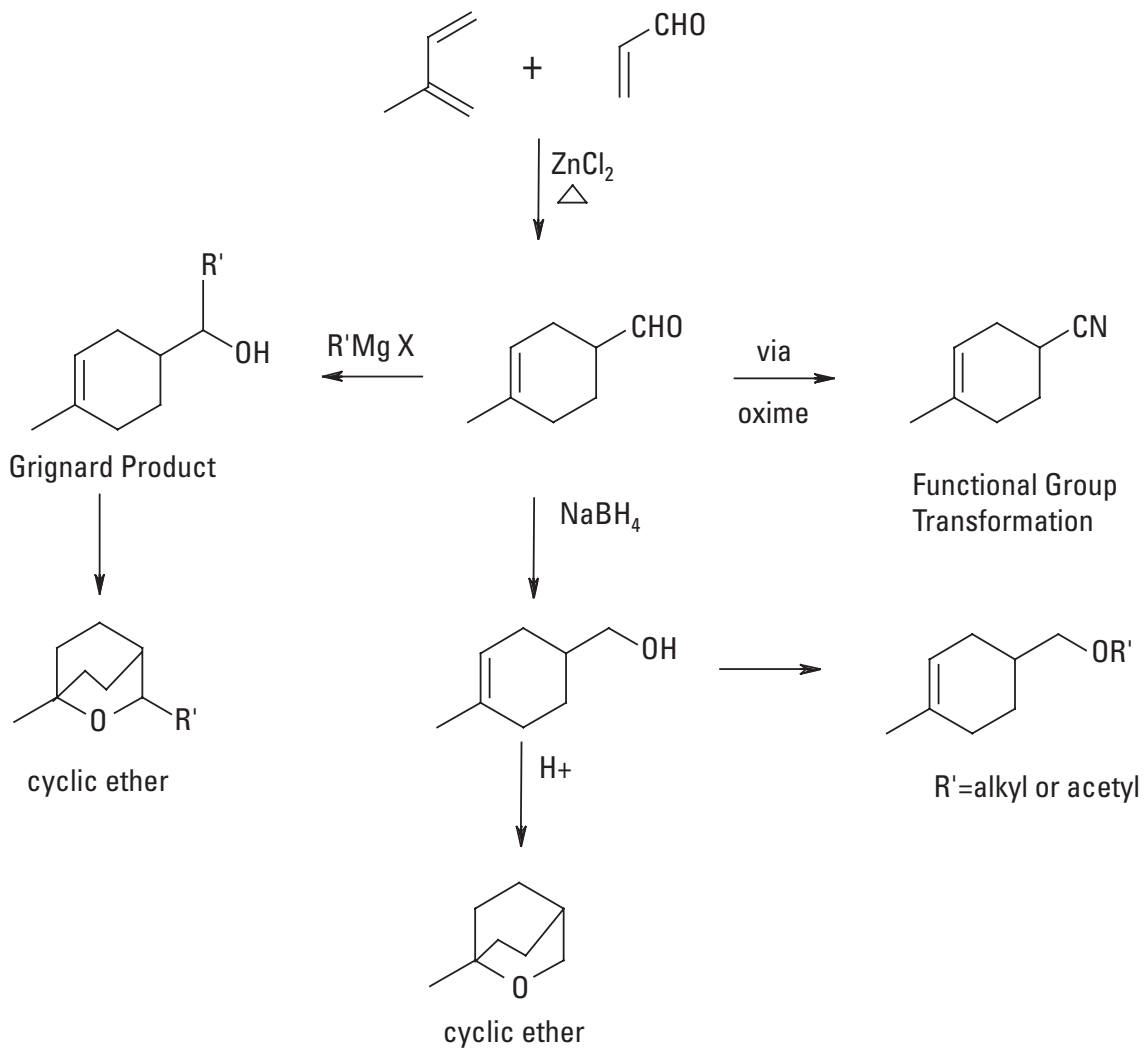
F-3



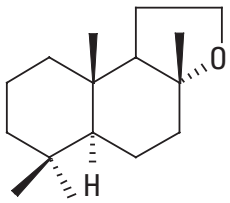
1. Regioselectivity: para-isomer, favored over meta-isomer, when R=alkyl.
2. Diene: butadiene, substituted dienes: isoprene, piperylene, dimethylbutadiene, Cyclicdienes, etc.
3. Dienophile: unsaturated aldehyde, ketone, ester, nitrile, acid, anhydride, etc.

Diels-Alder adducts as templates for new chemicals

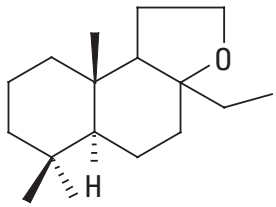
F-4



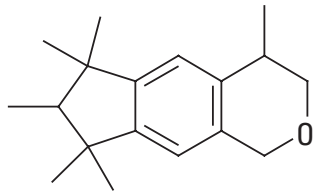
Examples of important cyclic ethers **F-5**



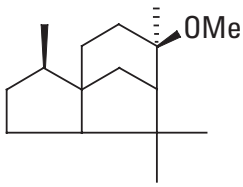
Ambrox
Ambroxan
Amberiff
ambergris



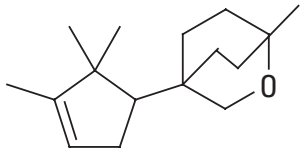
Grisalva
ambergris



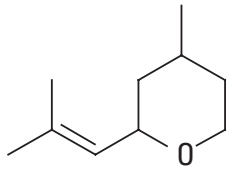
Galaxolide
musk



Cedramber
woody, ambery



Cassiffix
cassis, herbal



Rose Oxide
floral, rose, geranium

exploratory work. Iso E Super was reduced with lithium aluminiumhydride to give the corresponding alcohol. Cyclization with methanesulphonic acid in nitromethane offered a novel tricyclic ether in good yield, having a dry, woody odor. Similarly, Isocyclogeraniol, a green, herbal rosy fragrance ingredient underwent a rapid cyclization to furnish 1,3,5-trimethyl-2-oxabicyclo (2,2,2) octane with a woody, eucalyptus, cineol odor. Two additional cyclic ethers, 1,3-dimethy-2-oxabicyclo (2,2,2) octane and 1-methyl-2-oxabicyclo (2,2,2) octane, were prepared starting from the corresponding alcohols obtained by the reduction of Triplal and Wondral, respectively.[6] Their structure and odor are shown in F-6.

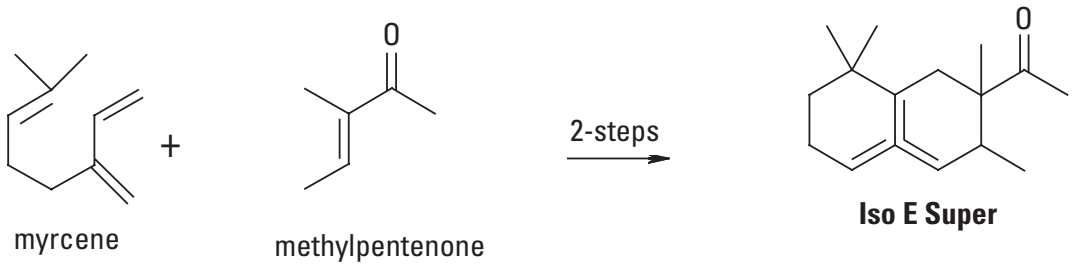
Ethers from Diverse Grignard Products of Isocyclocitral, Triplal and Wondral

Since both primary and secondary alcohol substrates cited above underwent a smooth cyclization to cyclic ethers, the question arose whether diverse substituted secondary alcohol substrates would undergo cyclization to cyclic ethers as observed previously. These substrates are easily amenable by addition of different Grignard reagents — i.e., methyl, cyclohexyl, phenyl, benzyl, and phenyethyl group — to commercially available aldehydes such as Isocyclocitral, Triplal, and Wondral. This was indeed found to be the case. F-7 delineates the structure as well as the odor of these new cyclic ethers. [7]

Discovery of Cassiffix — a Long-Lasting Cassis Note

It is well known in perfumery that campholenic aldehyde provides an excellent backbone to build new structures, in particular when it comes to synthetic mimics of sandalwood odor. Several useful sandalwood odorants, such as Bacdanol, Sandalore, Ebanol, Polysantol, Brahmanol, and Madrol or Santaliff have been developed from it (see F-8).[5] Therefore, the standard methodology was extended, as described earlier, towards the preparation of cyclic ethers from diverse Grignard addition products obtained from (-)-campholenic aldehyde. These alcohols gave excellent yields of desired carbocyclic ethers.[8]

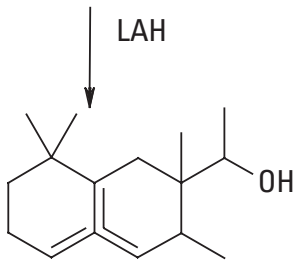
F-9 describes these novel structures and their odor descriptors.

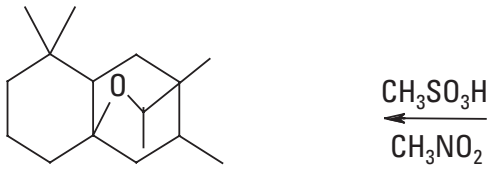


myrcene

methylpentenone

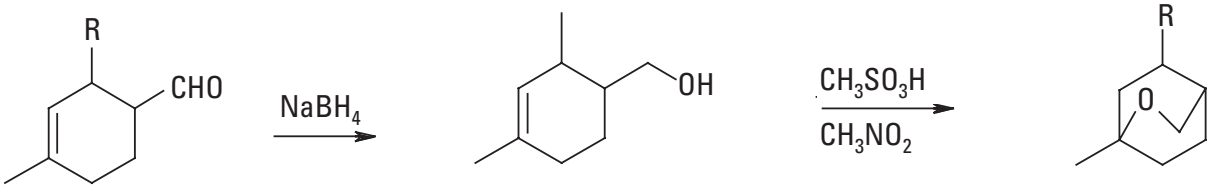
Iso E Super





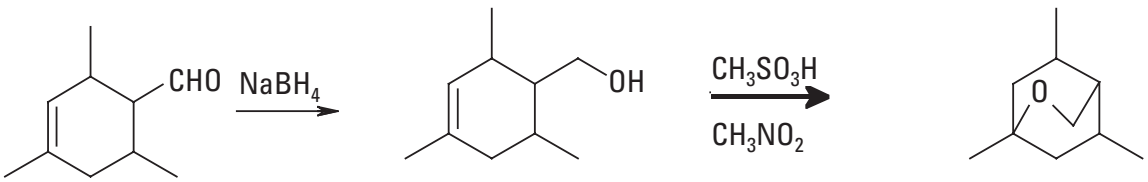
Iso E Super Ether
dry, woody

Iso E Super Alcohol
weak, woody



Triplal, R = CH3
Wondral, R = H

1, 3 - dimethyl -2- oxa-
bicyclo [2,2,2] octane
cineol/borneal, turpentine, woody

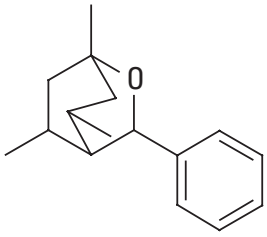


Isocyclocitral
melon, green

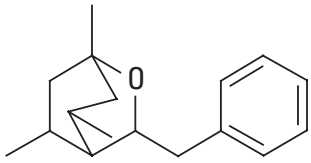
Isocyclogeraniol
green, woody, spicy

1,3,5 - trimethyl -2- oxa
bicyclo [2,2,2] octane
cineol, eucalyptus, woody

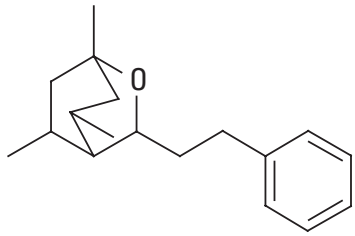
Some examples of novel ethers: 2-oxabicyclo [2,2,2] octane derivatives **F-7**



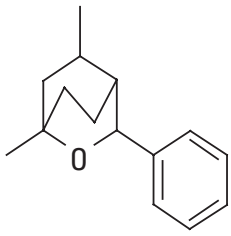
sl. Cassis note



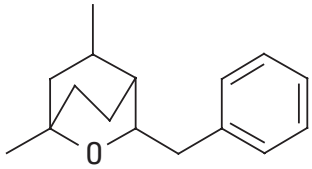
sl. Cassis note



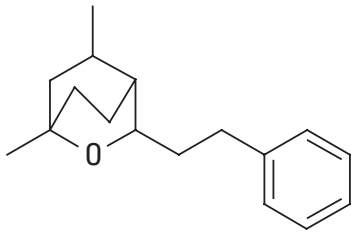
floral (rose/peony) green, honey-like



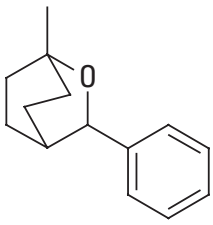
green, sl. galbanum carrot oil



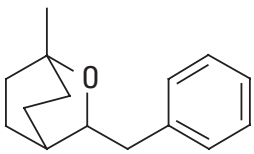
green, natural chamomile, floral (muguet), fruity (pear)



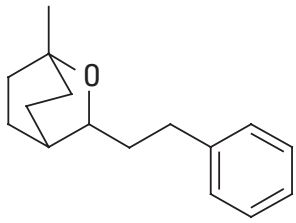
warm, sweet, cinnamic, honey, woody, rosy



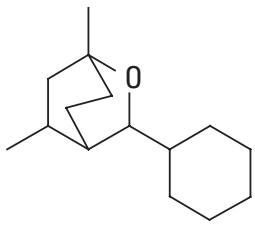
green, styryl, mushroom grapefruit



cassis, woody, fruity, citrus (grapefruit)



balsamic, cinnamic rosy



woody, green

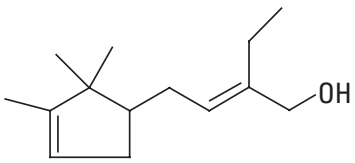
Extending this idea further, there appeared to be some worth, from the odor perspective, in preparing a carbocyclic ether from the Diels-Alder adduct of α-methylenecamphlenic aldehyde and isoprene by using the stated standard methodology. Therefore, α-methylenecampholenic aldehyde was prepared from (-)-campholenic aldehyde via the Mannich reaction with formaldehyde in 88 percent yield and reacted with isoprene thermally. As expected, this produced a mixture of para- and meta- Diels-Alder adducts. Reduction with sodium borohydride followed by cyclization with methanesulphonic in nitromethane produced a mixture of novel carbocyclic ethers, which exhibited a fresh, herbal, and a strong long-lasting cassis odor (see F-10).[2] Besides the formation of anticipated cyclic ethers from the corresponding para- and meta- Diels-Alder adducts, the formation of a spiro- carbocyclic ether in substantial amounts was also observed. This spiro-ether is formed by the rearrangement of α-campholenic skeleton to β-campholenic skeleton, followed by usual cyclization.[7]

Other Structural Analogues of Cassiffix

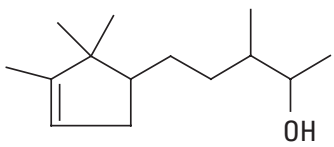
In order to broaden the structural diversity of carbocyclic ethers, this strategy was extended towards

Sandalwood odorants from α-campholenic aldehyde

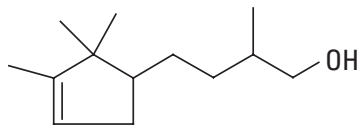
F-8



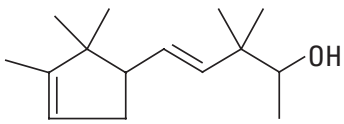
Bacdanol



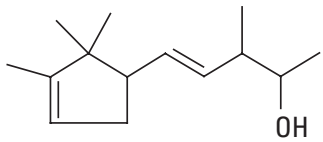
Sandalore



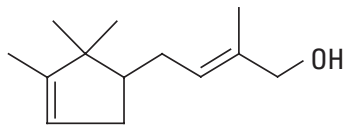
Brahmanol



Polysantol



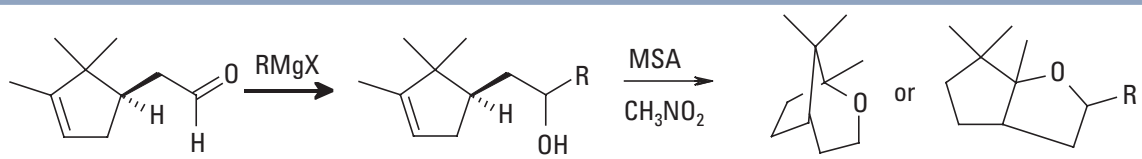
Ebanol



Santaliff

Novel ethers from α-campholenic aldehyde Grignard addition products

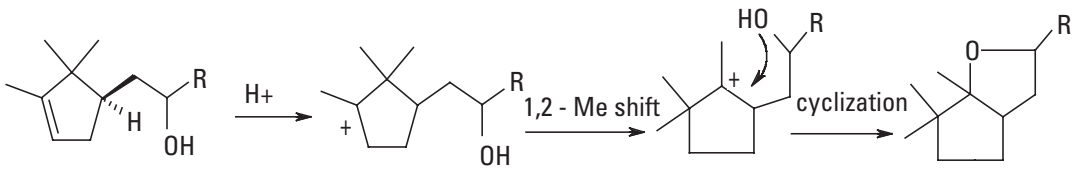
F-9

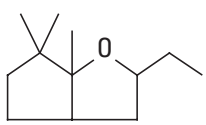


(-)-α - campholenic ald.

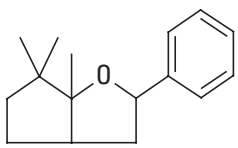
sweet, woody, cineol, eucalyptus

Mechanism of Ether Derivative Formation:

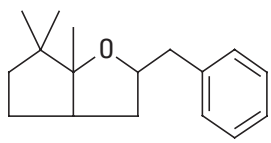




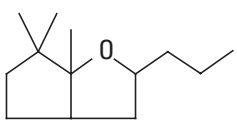
sweet, castoreum, animalic, piney



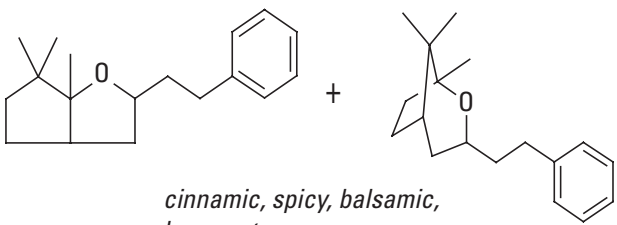
woody, spicy, sweet



borneol, green

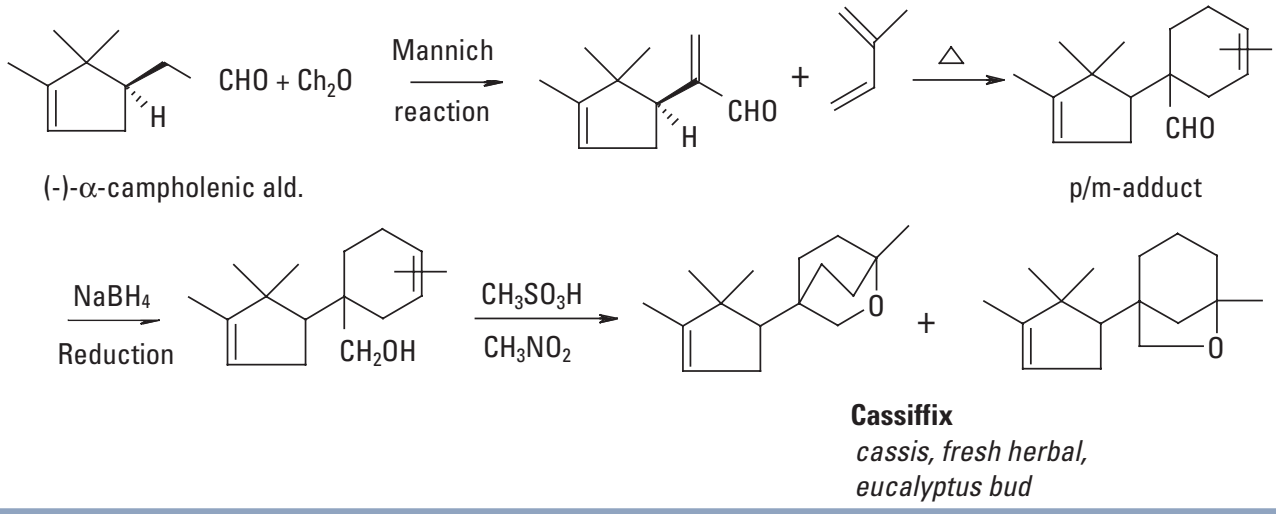


borneol, fruity



cinnamic, spicy, balsamic, honey, styrax

Route to Cassiffix **F-10**



Cassiffix
cassis, fresh herbal, eucalyptus bud

the preparation of a series of ethers by carrying out thermal Diels-Alder reaction of α-methylene-campholenic aldehyde with a wide variety of dienes: butadiene, dimethylbutadiene, methyl-pentadiene, piperylene, etc. These reactions gave good yields of the expected Diels-Alder adducts, which on reduction with sodium borohydride gave alcohols that underwent smooth cyclization with methanesulphonic acid and gave various substituted analogues of Cassiffix in good yields. F-11 depicts the structure and odor of these new Cassiffix analogues.[8,9]

Following the same methodology, several more substituted oxabicyclooctanes or carboccyclic ethers were prepared in excellent yields.[10] The structures of these new chemicals are shown in F-13 along with their odor descriptors.

Discovery of Prismantol and Prismylate

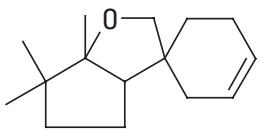
Finally, presented herein, is one more example of how an intermediate, prepared by the Mannich reaction of limonene aldehyde, led serendipitously to the discovery of two new fragrance ingredients: Prismantol and Prismylate.[3] Limonene aldehyde was originally prepared in the laboratory in 1981 by the oxo reaction of limonene. While studying the chemistry of α-methylene limonene aldehyde, it was observed that it undergoes a facile intramo–lecular ene reaction producing an intermediate, a bicyclic aldehyde, which further suffers another ene reaction to produce a tricyclic alcohol with an adamantane skeleton (see F-14).[11,12] This alcohol has a spicy, gingery, cardamom, woody odor and is commercially known by the name of Prismantol. Several derivatives of Prismantol were prepared for exploratory purposes. Its acetate derivative, Prismylate, was also developed as it has an inter–esting odor comprising of amber, woody, and vetivert note.

Conclusion

This paper provides just a glimpse of ongoing, relentless research efforts, which were expended in the discovery of three new fragrance molecules. It is refreshing to note that a perfumer's need for new notes never wanes, despite that they have about 3,000 fragrance ingredients in their palette. Therefore, perfumers worldwide can bank on the ingenuity of synthetic organic chemists to provide them with new fragrance ingredients, which will enhance their creativity as well as address their toxicological

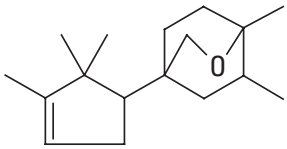
Other structural analogues of Cassiffix

F-11



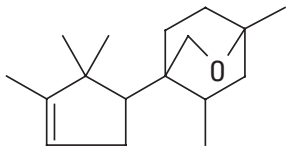
ex.

butadiene
very cassis, fruity
(black currant), piney, balsamic



ex.

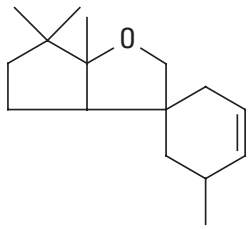
2,3 - dimethylbutadiene
weak cassis, borneol



ex.

methyl pentadiene
woody, ambery
low keyed fruity, floral

* For the sake of brevity, only one isomer is shown

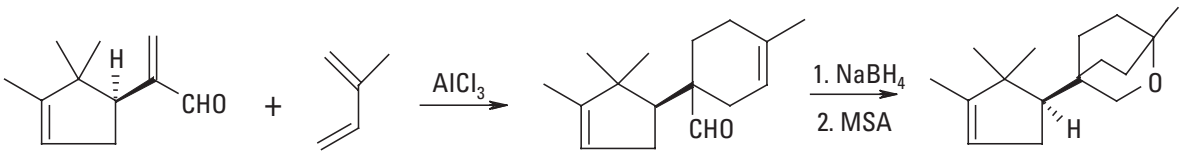


ex.

peperylene
weak cassis, pine needle,
woody

Cassiffix para-isomer and ent-Cassiffix

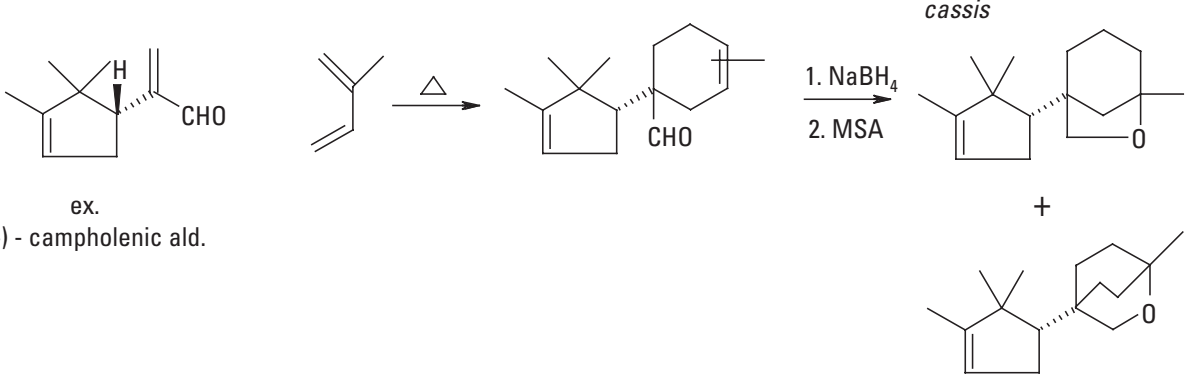
F-12



ex.
(-) - campholenic ald.

para - product >93%

Cassiffix: para- isomer
floral, narciss, woody
cassis

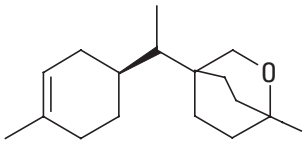


ex.
(+) - campholenic ald.

ent - Cassiffix
weak, dusty, woody
fruity, cassis

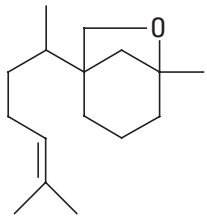
Some more examples of substituted oxabicyclooctanes

F-13



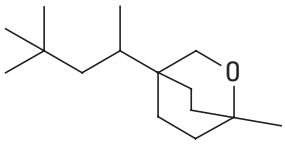
ex.

α-methylene limonene ald.
limoneneoxabicyclooctane mix
earthy, green, sappy



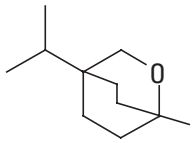
ex.

Bergamal
methyl heptenyloxabicyclooctane



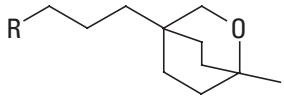
ex.

α-methylene vandor B
6-Oxabicyclo [3,2,1] octane
5-methyl-1-(1,3,3-trimethylbutyl)
weak, ambery, woody, cedarwood



ex.

α-methylene isovaleraldehyde
isopropylmethyloxabicyclooctane
green, earthy, minty, camphoraceous

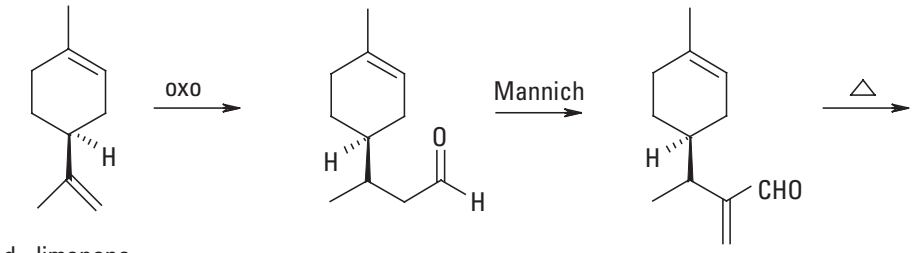


ex.

α-methylene hexanal
green, fruity (peach), cycloprop aspects
R=H, *green, hearbal, fruity (fig like)*

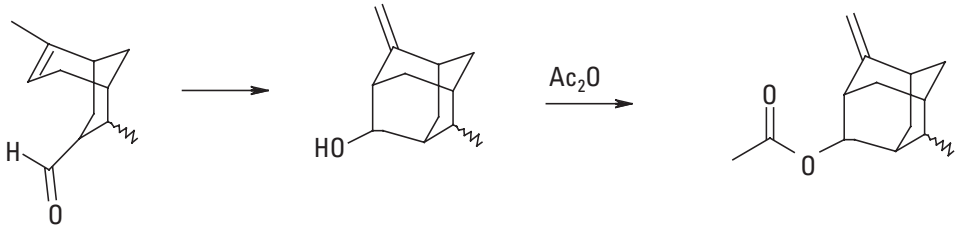
Route to Prismantol and Prismylate

F-14



d - limonene

limonene aldehyde
citrus (orange), ozone, aldehydic, fatty, green



Intermediate

Prismantol
spicy (ginger), cardamon, woody

Prismylate
woody, ambery, vertivert

and environmental concerns for some known fragrance ingredients. Towards that aim, an organic chemist's quest in the pursuit of new fragrance molecules will continue unabated.

Acknowledgements

The author wishes to acknowledge his colleagues at International Flavors and Fragrances Inc. whose names are cited in the references for their dedicated synthetic work, and to several renowned perfumers for their expert fragrance evaluations of all the new chemicals disclosed in this article.

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