Aldehydes*

Aliphatic, unsaturated, acetals, aromatics and more

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Aliphatic

The simplest aldehyde in use is acetaldehyde **1**, which is ubiquitous in fruit formulations; a dilute solution of acetaldehyde has a pleasant apple taste (F-1). As the chain extends, a fatty character develops, which is exhibited by the C12 lauric aldehyde **2** and the synthetic material methylnonylacetaldehyde **3** (aldehyde MNA) (F-1); this fatty, "animalic" character has been used to effect in perfumery, most famously in the aldehyde cocktail of "Chanel No. 5."

An interesting aldehyde is 12-methyltridecanal **4** (F-2). This compound, which is FEMA GRAS, is found in beef fat and appears to originate from microorganisms in the rumen of cattle.[1] It is absorbed by the gut as plasmanogens, and released only when the beef is heated over a long period of time (e.g. stewing). Briefly roasting the meet does not release the material. Hence, this gives the potential to create a boiled or stewed beef flavour well differentiated from fried or roasted beef.

Unsaturated

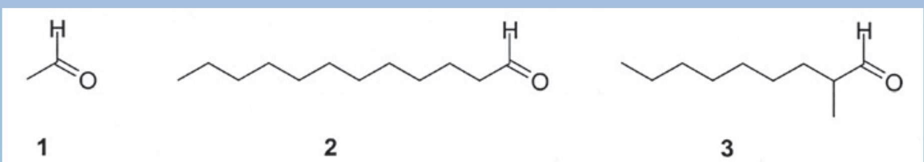
The most important materials in this category are the "*trans*-2-alkenals," in particular *trans*-2-hexenal 5 (leaf aldehyde, F-3). A Union Carbide patent revealed a route using ethyl vinyl ether as "vinylic synthon."[2]

A subsequent development of this reaction uses the acetal derivative of the aldehyde as the precursor, which overcomes the need to use two equivalents of the starting aldehyde, one of which is simply regenerated (F-4). Reaction of the acetal (usually the ethyl acetal) with ethyl vinyl ether in the presence of a Lewis acid, such as boron trifluoride or the clay catalyst Montorillonite K10, produces the triethoxy alkane.[3] When heated with a mixture of aqueous formic acid with an alkali metal formate, this undergoes hydrolysis of the acetal function followed by elimination of the alkoxide group via the $E1_{CB}$ pathway to form the unsaturated aldehyde.

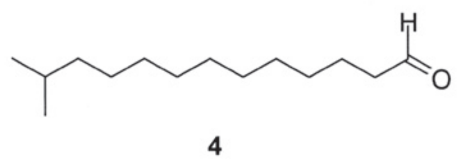
There have been many reports of synthesis of these materials via Wittig chemistry. A recent report shows that alcohols, which are in general more readily available than aldehydes, can be used as precursors via in situ oxidation and Wittig coupling (F-5).[4]

The character of the aldehydes changes significantly as the chain extends, and in general the odor threshold falls, as shown in F-1. In particular, *trans*-2-dodecenal has an intense, persistent coriander aroma, which tends to live with anyone who has handled it for several days!

Simple aldehydes **F-1**



A very fatty aldehyde **F-2**



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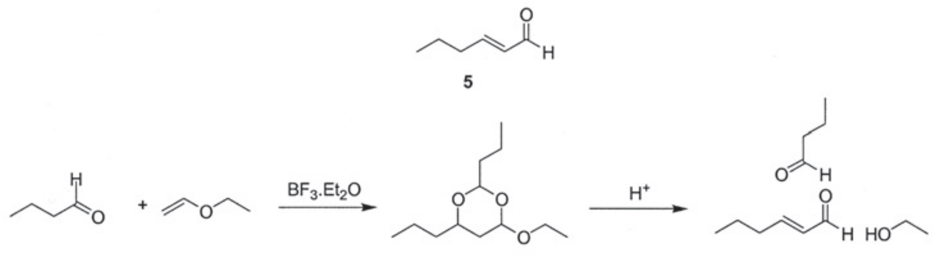
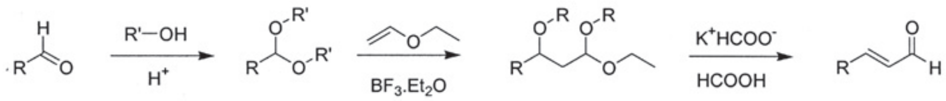
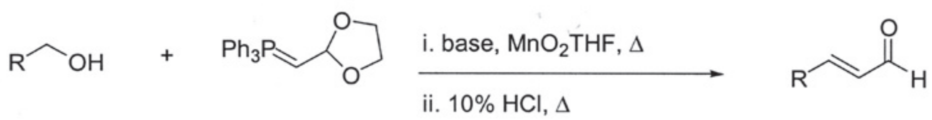
Classical synthesis of *trans*-2-alkenals **F-3**



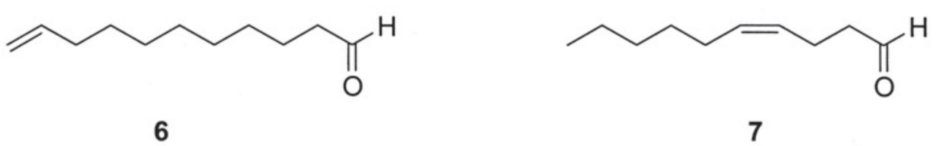
A modification of the classical synthesis of *trans*-2-alkenals **F-4**



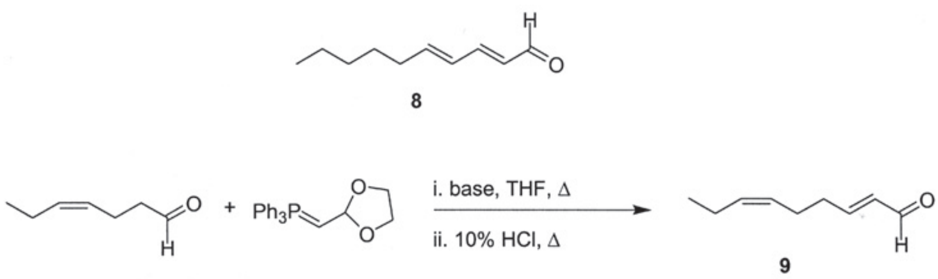
Wittig synthesis of *trans*-2-alkenals **F-5**



Non-conjugated alkenals **F-6**



Polyunsaturated aldehydes **F-7**



Two non-conjugated aldehydes of importance are 10-undecanal 6 and *cis*-4-decenal 7 (F-6). The former is derived from the "cracking" of castor oil; it is claimed that commercially available materials that contain isomers rather than simply the 10- isomer are more powerful.

The most important polyunsaturated aldehyde is *trans*-2,*trans*-4-decadeienal 8, which has a powerful fatty-citrus, chicken aroma. *trans*-2,*cis*-6-Nonadienal 9 (violet leaf aldehyde) has been prepared by "one-pot" homologation using the phosphonium salt (F-7).[4]

Among the terpenoids, aldehydes are less important than the alcohols. Most significant is citral, which is actually a mixture of the isomers geranial **10**, neral **11** and citronellal **12** (F-8).

There are more compounds that may be considered relatives of the terpenes which are important. 2,6-Dimethyl-5-heptenal **13** (melonal) contributes a fresh, green, melon note to both flavors and fragrances. Several, such as the citronellol derivative **14** (Muguet Aldehyde 50, IFF) and the cyclic aldehydes **15** (Melafleur, IFF) and especially **16** (Lyral, IFF) are important for floral, muguet/lily-of-the-valley notes (F-9).

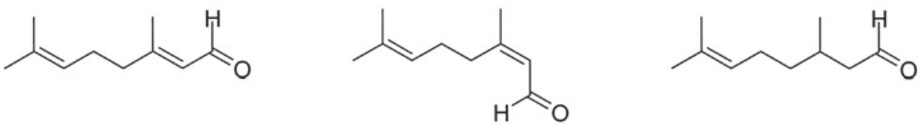
Acetals

One problem that occurs in using aldehydes, especially in some demanding fragrance media, is that they are prone to oxidation, the formation of Schiff's bases with amines, and, if they have an α hydrogen, condensation reactions such as the aldol reaction. Perhaps surprisingly, the tendency towards oxidation decreases with conjugation. Whereas

Organoleptic properties of *trans*-2-alkenals — T-1

Aldehyde	Odor threshold	Character
trans-2-pentenal	1500	Sharp, acrid
trans-2-hexenal	17	Sharp, green, almond on dilution
trans-2-heptenal	13	Green
trans-2-octenal	3	Fatty, citrus — "fatty lemon"
trans-2-nonenal	0.1	Intensely fatty, cucumber on dilution
trans-2-decenal	0.3	Oily, citrus — "orange beef"
trans-2-undecenal		Citrus, herbaceous
trans-2-dodecenal		Herbaceous, intense coriander

Terpenoid aldehydes — F-8



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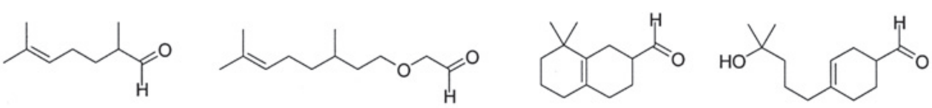
Aliphatic muguet aldehydes — F-9



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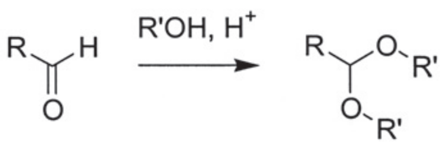
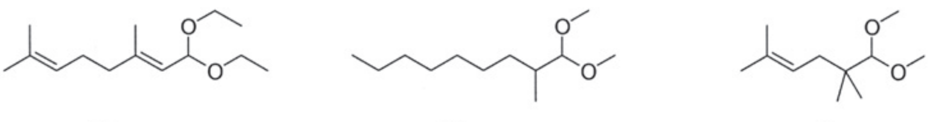
Synthesis of acetals — F-10



Acetals as "protected" aldehydes — F-11



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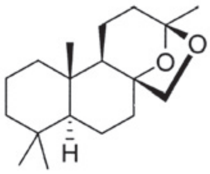
simple aliphatic alcohols such as hexanal are commonly "stabilized" by the addition of an anti-oxidant such as butylated hydroxytoluene (BHT) or butylated hydroxyanisole (BHA), this is not necessary with unsaturates such as *trans*-2-hexenal; *trans*-2,*trans*-4-decadienal shows little tendency towards oxidation. Oxidation products are often detected by the acid value of the aldehyde; this is a simple test involving titration with potassium hydroxide solution, and is defined as the number of milligrams of potassium hydroxide needed to neutralize 1 g of the analyte. Typically, the maximum value of an aldehyde would be 10. The test is also used for esters, as any hydrolysis will lead to the formation of an acid and hence a rise in acid value.

These reactions can be prevented if the aldehyde function is "protected" by the formation of an acetal (F-10).

Many acetals have odors similar to their aldehyde precursors and can be used in their stead; examples include citral diethyl acetal **17** and 2-methylnonylacetaldehyde dimethyl acetal **18** (aldehyde MNA DMA) (F-11). Several acetals are used in their own right, including the wonderfully named grapefruit fragrance ingredient **19** Methyl Pamplemousse (Givaudan) (F-11).

Acetals include a number of "amber" chemicals.[5] These materials are so-called due to their resemblance to ambergris, a material formed in the stomach of whales, probably as a protection against intestinal damage by the "shelly" parts of plankton. The material is occasionally found washed up on beaches, but the major source has traditionally been the whaling industry. Unsurprisingly, this is now a rare and expensive material, driving the search for synthetic alternatives. Ambergris mostly consists of steroidal

Amber acetals **F-12**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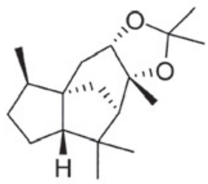
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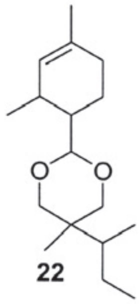
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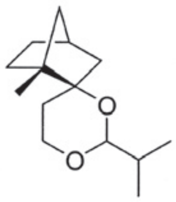
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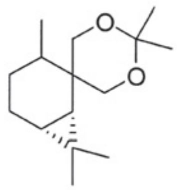
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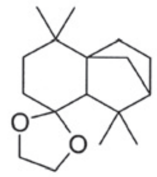
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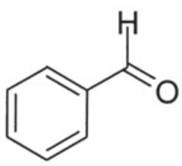
Simple aromatic aldehydes **F-13**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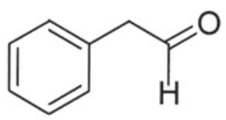
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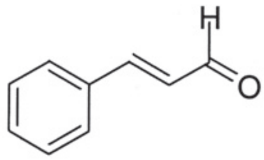
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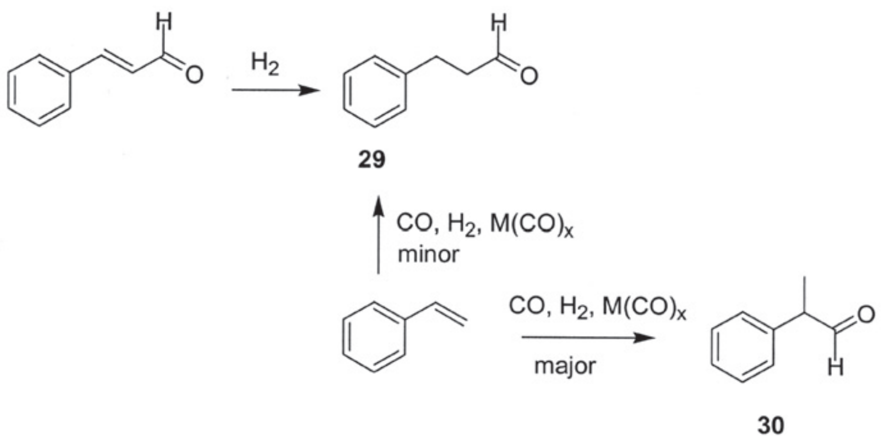
Aromatic aldehydes from styrene **F-14**



materials, and hence this structure was the first to be looked at. Amberketal **20** resembles the ABC ring fragment of the steroids, and Amberconide **21** (Symrise) could be considered a distorted version of this. More recently, molecules have been developed which have the amber tonality but have no steroidal character, e.g. Kranal **22** (Quest), Belambre (Givaudan) **23**, Spirambrene (Givaudan) **24** and Ysamber K (Symrise) **25** (F-12).

Aromatics

The identification of benzaldehyde **26** in oil of bitter almonds is one of the milestones in aroma chemistry (F-13). It has a powerful cherry-marzipan odor, and is widely used in cherry flavors, even though it is not actually a significant aroma chemical in cherries. Phenylacetaldehyde **27** has a floral aroma common to all the "phenyl C2" compounds (F-13). Cinnamaldehyde **28**, found in many essential oils, was another milestone aroma chemical (F-13).

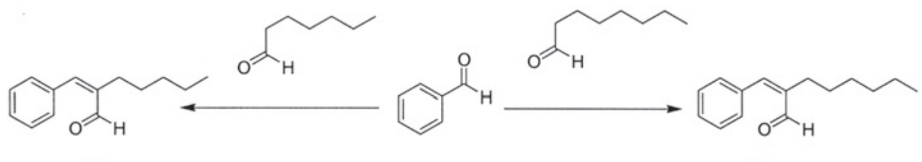
3-Phenylpropionaldehyde **29** (dihydrocinnamaldehyde), with a powerful hyacinth-like aroma, is obtained by the selective reduction of the alkene bond in cinnamaldehyde (F-14). It is also a by-product in the synthesis of its isomer 2-phenylpropionaldehyde **30** (hydratropaldehyde), which is obtained from styrene via hydroformylation (the oxo process); a recent patent claims less than 2 percent linear isomer when a rhodium catalyst is used (F-14).[6] This also has a powerful hyacinth aroma for floral fragrances.

A large number of aromatic aldehydes can be considered to be cinnamaldehyde derivatives. Amylcinnamaldehyde **31** and hexylcinnamaldehyde **32** have sweet, floral jasmine notes, and are widely used for domestic fragrances, especially as inexpensive alternatives to Hedione (Firmenich) (*vide infra*), which they resemble. These materials can be prepared by the condensation of benzaldehyde with the appropriate aldehyde (F-15).

Similarly, condensation of phenylacetaldehyde with acetaldehyde, isobutyraldehdye and isovaleraldehyde produces, respectively, 2-phenyl-2-butenal **33**, 4-methyl-2-phenyl-2-pentenal **34** and 5-methyl-2-phenyl-

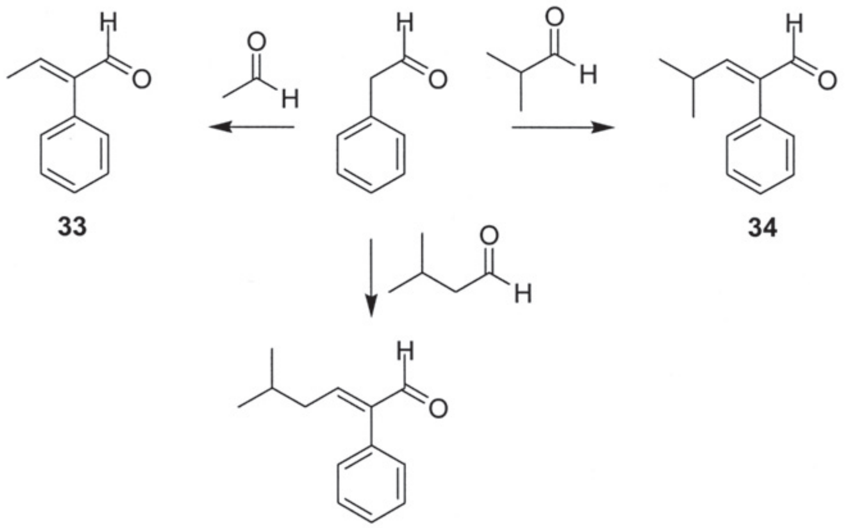
Cinnamaldehyde derivatives

F-15



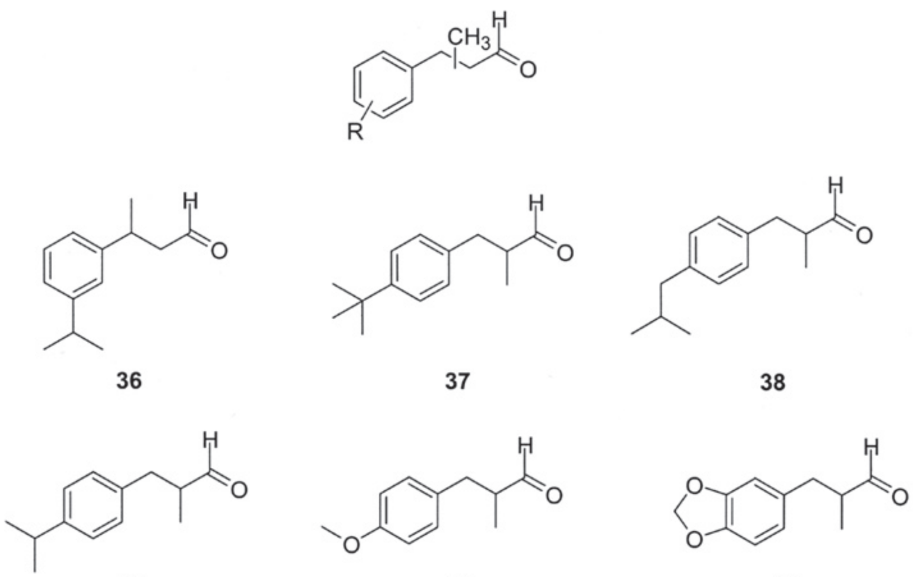
Aromatic aldehydes derived from phenylacetaldehyde

F-16



Aromatic muguet aldehydes

F-17



2-hexenal **35** (Cocal, IFF), which have sweet, vanilla-like aromas that make them valuable in chocolate and sweet formulations for both flavor and fragrance (F-16).

There are several important materials used in fragrance, especially for muguet notes, which have similar structures: an aromatic ring with a methylpropanal chain and an C3 or C4 alkyl group meta- or para- to it; examples are Florhydral **36** (Givaudan), Lilial **37** (Givaudan), Sylvial **38** (Givaudan) and cyclamen aldehyde **39**; Canthoxal **40** (IFF) and Helional (IFF)/Tropional (Givaudan) **41** are closely related with an alkoxy groups replacing the alkyl (F-17).

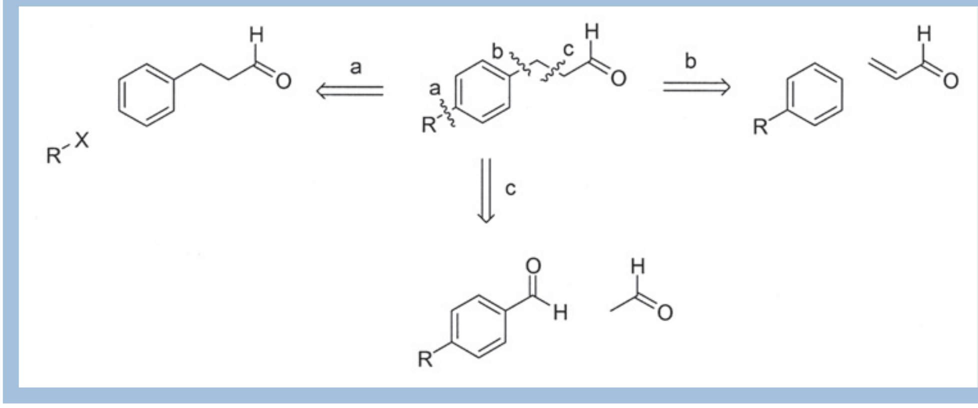
All three possible retrosynthetic disconnections have been used in the synthesis of these compounds (F-18); note the methyl group on the propanal chain is omitted for clarity (the ring alkyl is shown para for the same reason).

i. In F-19, disconnection a (at the alkyl group) is illustrated in a synthesis of Lilial **37**. Alkylation of methyldihydrocinnamic alcohol **42** (available from the reduction of methylcinnamaldehyde, which in turn is prepared from the aldol condensation of benzaldehyde with propionaldehyde, c.f. hexylcinnamaldehyde above) gives the tert-butyl derivative **43**, which is oxidized to the aldehyde.[7,8]

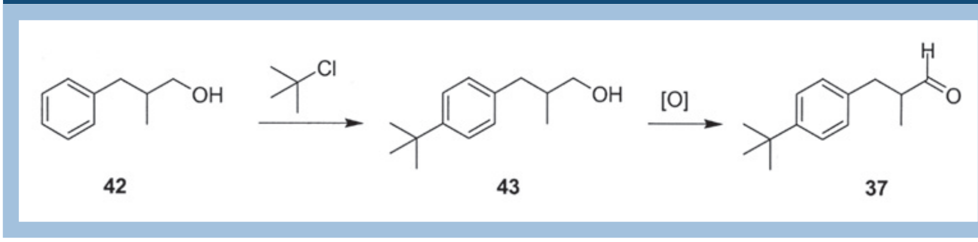
ii. Disconnection b (F-20), at the ring-aldehyde chain bond, is illustrated in a synthesis of cyclamen aldehyde **39**. Isopropylbenzene **44** undergoes a Friedel-Crafts reaction with a protected form of methacrolein, the diacetate, to form an enol acetate **45** that is readily hydrolyzed to the aldehyde.[9]

iii. Disconnection c (F-21), to the carbonyl, is the

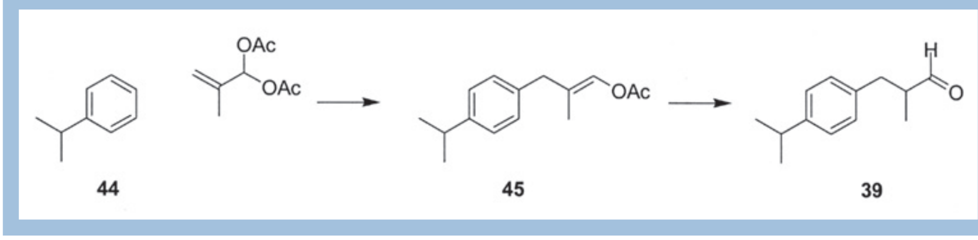
Retrosynthetic analysis of the aromatic muguet aldehydes F-18



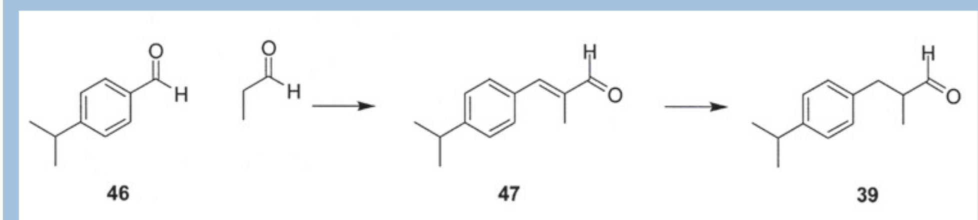
Disconnection a F-19



Disconnection b F-20



Disconnection c F-21



characteristic aldol disconnection, and is illustrated by another approach to cyclamen aldehyde **39**. Cumene aldehyde **46** condenses with propionaldehyde to give the unsaturated aldol product **47**, which is hydrogenated to the saturated aldehyde.[10]

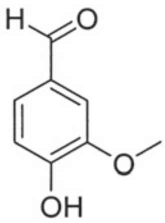
The most important aromatic aldehyde is surely vanillin **48** (F-21). Its synthesis by Wilhelm Haarmann and Ferdinand Tiemann was the cornerstone of Haarmann and Reimer (now Symrise). Vanillin is the single most important component of vanilla, though not the only material of importance; vanilla extract has been estimated to be some [10] times stronger than the vanillin content would indicate. The synthesis of vanillin has been reported by many routes, including carbonylation of guaiacol and via the degradation of lignins obtained as waste from paper production; since the latter is a natural material, it is also a source for natural vanillin. Vanillin is widely used in both flavors and fragrances; it is generally stable, but there can be a problem with discoloration. As a phenol, it reacts with traces of iron to give a purple coloration, and indeed this could be used as a test for the metal. The isobutyl ester Isobutavan **49** (F-22) overcomes this by "protecting" the phenolic hydroxyl. The vanillin homologue ethyl vanillin **50** (F-22) has a more powerful aroma than vanillin, though it is not found in nature.

Methylenedioxybenzaldehyde (heliotropin, piperonal) **51** is found in a number of essential oils, and is used for spicy, floral notes in both flavors and fragrances (F-23). Aldol condensation of heliotropin with propionaldehyde, followed by hydrogenation, produces the synthetic derivative Helional (IFF) **52**, which has a greener, hay-like odor.

Acknowledgements

Thanks go to the many people with whom I have worked over the past dozen years. Chemistry is a social discipline, and I have learned from many people; I hope that, in a way, my work here is giving

Vanillin and related compounds **F-22**



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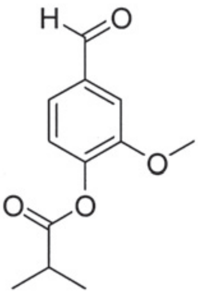

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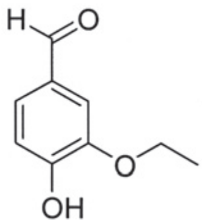

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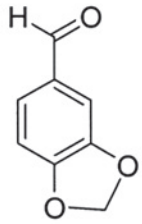
Heliotropin and its relative **F-23**



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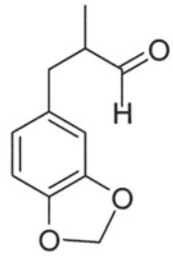

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something back. A particular mention goes to Mark Dewis, Simon Jameson, John Heffernan, Kevin Auty, Peter Setchell, Lee Morgan, Gareth Jones, John Johnson, Tracy Brown, Peter Cannon, Martin Gill, Rob Gregory, others who I've now offended by not mentioning, and finally to Duncan Mullis, who first employed me in the F&F industry; in a way, Duncan, "Aldehydes" is your fault! I should add special thanks should go to Mark Dewis and Philip Kraft, who made time to make valuable and constructive comments, and to Paul Sayer at Blackwell Publishing for his help and for arranging permission to publish this extract.

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