

The Design and Synthesis of Novel Muguet Fragrance Ingredients: The Discovery of a Series of 3-Alkylcycloalkanols

Karen Rossiter*

Abstract: A number of novel muguet fragrance ingredients have been discovered with the support of qualitative structure-activity relationships and molecular modelling. These belong to the following chemical families; 3-alkylcycloalkanols, 3-alkylcyclohexylmethanols and 4-(2-methylpropyl)cyclohexanols. It has also been shown that within the 3-alkylcycloalkanols, the alcohol group is not necessarily a prerequisite for a muguet odour, but that conversion to other functional groups does lead to weaker odorants. Chirality also appears to play an important role on the odour properties of 3-alkylcycloalkanols.

Keywords: 3-Alkylcycloalkanols · Fragrance ingredient · Molecular modelling · Muguet · Structure-activity relationships

1. Introduction

The perfumers of today have at their disposal over 3000 fragrance ingredients to choose from when creating a perfume. These include natural oils, nature-identical materials and synthetic compounds. With such a large number to choose from, it might at first be thought that the perfumer does not require any more novel materials. However, the number of ingredients available to a perfumer creating a fragrance for relatively cheap and hostile products, such as strongly alkaline bleach or acidic antiperspirant, is significantly lower than the number available for use in alcoholic fine fragrances. The perfumer's freedom of choice is considerably restricted by factors such as stability and cost. Other advantages that new ingredients might offer over existing aroma chemicals include better olfactory properties, uniqueness of odour, im-

proved biodegradability, and additional functionality (such as insect repellency or antimicrobial activity).

One odour area where there is a need for more stable fragrance ingredients is that of muguet (lily of the valley): a note often used to enrich the character of a fragrance whilst giving, in modern functional perfumery, a 'freshness' which is particularly appealing to consumers. The odour description 'muguet', like rose and jasmine, comes from the flower. However, since flowers from the muguet plant are very small and difficult to extract, it is impossible to produce a commercially feasible oil. Therefore, perfumers have to rely on synthetic substitutes to create this odour type (Fig. 1).

The odour of muguet flowers is best represented by 3,7-dimethyl-7-hydroxyoctanal, commonly known as hydroxycitronellal (**1**). However, the use of this material is restricted because of concerns regarding skin sensitisation. Today, the most widely used muguet fragrance materials are the *p*-alkylphenylpropanals; Bourgeonal® (**2**), Lilial® (**3**), and cyclamen aldehyde (**4**). However, the presence of the aldehyde group makes them unstable in the more hostile products [1]: common side reactions include autoxidation to the corresponding carboxylic acid and, in some cases, the lower homologous ke-

tone; reaction with alcohols to form the corresponding acetals; aldol condensations; and the formation of aldehyde trimers. Thus, in more recent years attention has been focused towards the discovery of non-aldehydic muguet materials such as Florosa® (**5**), Mayol® (**6**) and Mugetanol® (**7**). However, although the muguet alcohols are chemically very stable they tend to have a more rosy odour, and lack both the impact and the green and watery notes associated with materials such as Lilial® (**3**). They are also less substantive and as a result tend to be used for different applications. Ideally, the perfumer needs a new fragrance ingredient with the chemical stability of Florosa and the odour impact properties of Lilial® (**3**) and Bourgeonal® (**2**).

The search for new stable muguet odorants has led to the investigation of other chemical classes including the tetrahydropyranyl and tetrahydrofuranyl ethers of alcohols and phenols [2], acetals [3] and 1,3,4,5-tetrahydro-2-benzoxepin derivatives [4]. Often the structures have been designed as potential conformational mimics of the *p*-alkylphenylpropanals (Fig. 2). However, this approach has not been too successful to date. Compound **10** has a 'weak and vague' odour with no aspects of muguet [4], whereas **8** and **9**, in our opinion, are more rose and jasmine

*Correspondence: Dr. K.J. Rossiter
Quest International
Ashford, Kent
TN24 OLT, UK
Tel.: +44 1233 644687
Fax.: +44 1233 644134
E-Mail: karen.rossiter@questintl.com

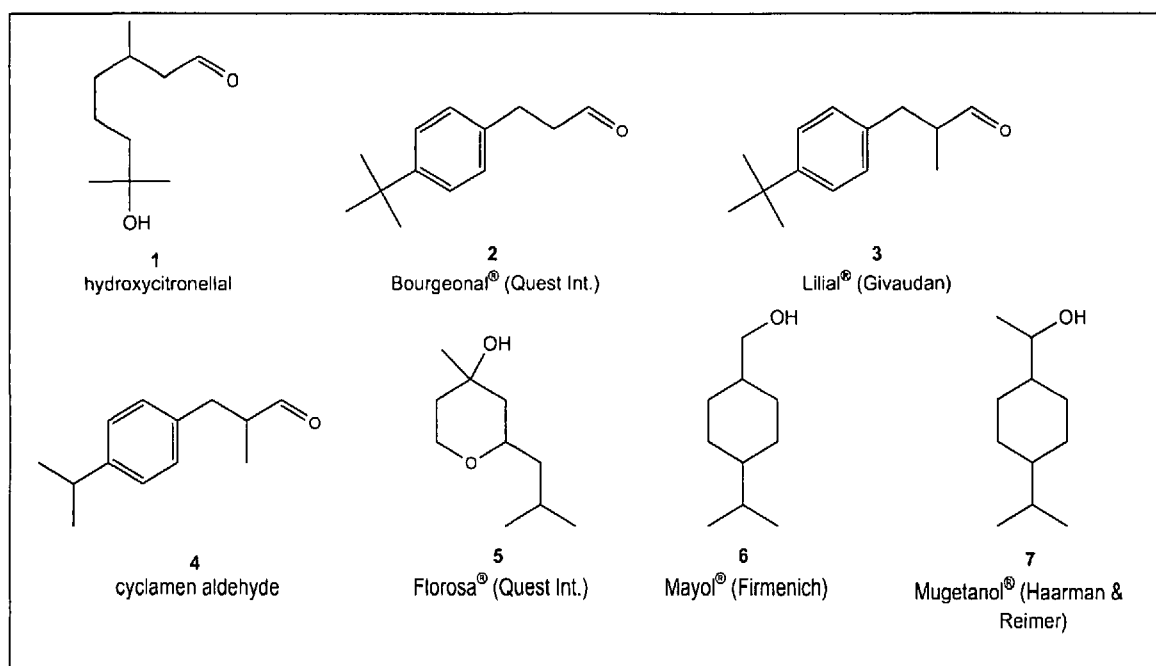


Fig. 1. Synthetic muguet odorants

in character than muguet. Thus, the best chances of finding a novel stable muguet material probably remains within the alcohol chemical class.

In earlier work, we identified a number of novel muguet smelling 3-alkoxy-2,2-dimethylpropanols using a qualitative hybrid approach that involved the hybridisation of two structural fragments found in two different known muguet odorants [5] (Fig. 3). An investigation into the effect of the methyl substitution pattern led to the conclusion that in the 3-(3-methylbutoxy)propan-1-ol series dimethylation at position two is very important for a good muguet odour. Successive replacement of the methyl groups by hydrogen leads to a gradual decrease in the muguet character and the introduction of a fruity note. Introduction of a methyl group at position one, whilst retaining dimethylation at C(2), results in a very weak muguet odorant.

We postulated that the muguet aspects of 2,2,7-trimethyl-4-oxaoctan-1-ol (**11**) are associated with a cyclic-type conformation that closely resembles that of *cis*-Florosa (**5a**, hydroxyl and *iso*-butyl group on same side of ring) (Fig. 4). However, because **11** is a flexible molecule it can easily adopt a large number of conformations including one which resembles the less active *trans*-Florosa (**5b**, hydroxyl and *iso*-butyl group on opposite side of ring). Thus if the structure of 2,2,7-trimethyl-4-oxaoctan-1-ol (**11**) could be modified in such a way that the desired active cyclic-type conformation was preferred, it is reasonable to assume that the resulting compound should have an improved muguet odour profile.

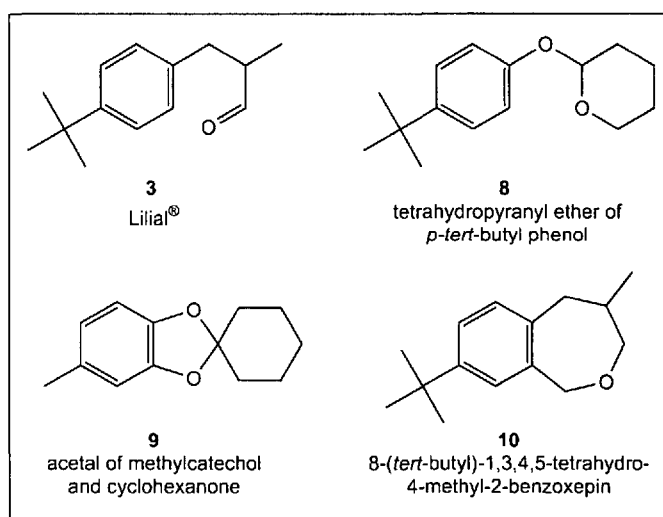


Fig. 2. Structures designed to mimic a conformation of Lilia®

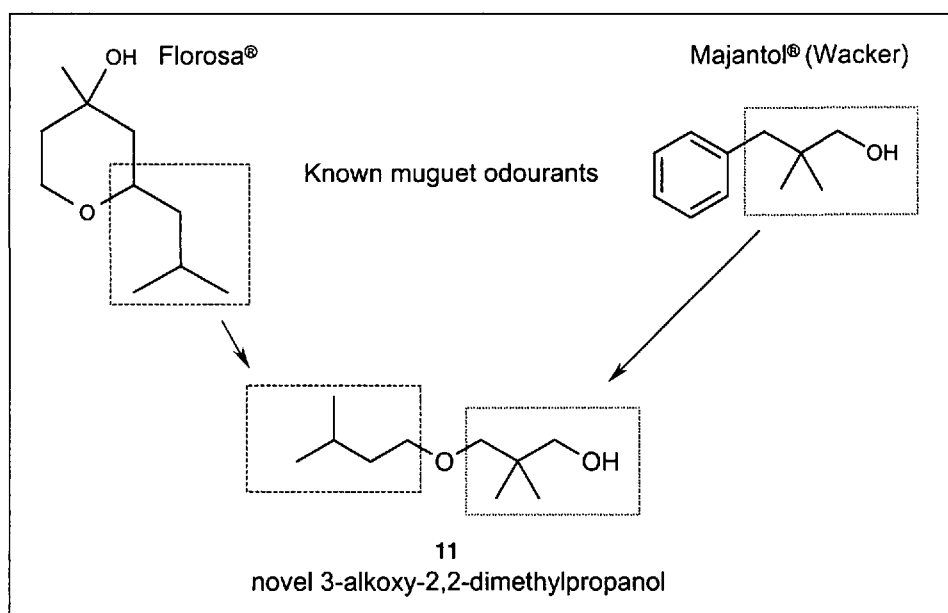


Fig. 3. Design of novel muguet odorant using the hybrid approach

Here we report our work on cyclic versions of **11** and describe how the results of this work led to the discovery of a powerful high-performing muguet fragrance ingredient, 1-methyl-3-(2-methylpropyl)cyclohexanol. The odour properties of a large number of analogues and derivatives are also reported and the structural requirements for a material in this family to possess a muguet odour discussed.

2. Synthesis and Evaluation of Novel Tetrahydropyran-4-ols

The most obvious way of modifying the structure of 2,2,7-trimethyl-4-oxaocan-1-ol (**11**) so that it more closely resembles the organoleptically active conformation of *cis*-Florosa, is by insertion of a methylene bridge between C(1) and C(5) to give 5,5-dimethyl-2-(2-methylpropyl)tetrahydropyran-4-ol (**12**) (Fig. 5). The latter has only one substituent at position 4 and thus one would expect the *cis*-isomer (**12a**, both OH and *iso*-butyl equatorial) to be thermodynamically more stable than the *trans*-isomer (**12b**, OH axial) (Fig. 6). In contrast, one would expect there to be little difference between the stability of the two isomers of Florosa (**5a** and **b**). Indeed, a *cis/trans* ratio of 55:45 is typically obtained from the acid catalysed reaction of 3-methyl-3-butenol with 3-methylbutanal.

Calculated heats of formation predict that **12a** is slightly more stable than **12b** but that for Florosa this pattern is reversed (*i.e.* *trans* more stable than *cis*) (Fig. 6). This suggests that under thermodynamically controlled reaction conditions, the resulting mixture of **12** may be more enriched in the postulated active *cis*-isomer and potentially a more potent muguet odorant than Florosa. One might also expect the same to be true for 2-(2-methylpropyl)-tetrahydropyran-4-ol (**13**, Fig. 7) provided, of course, that the methyl group at position four is not a critical feature for a good muguet odour in this series of compounds. For completeness 4,5,5-trimethyl-2-(2-methylpropyl) tetrahydropyran-4-ol (**14**) was also prepared. Thus the set of four compounds in Fig. 7 allowed an investigation into the effect of both the methyl group at position 4 and *gem*-dimethyl substitution at position 5 on the odour properties of 2-(2-methylpropyl) tetrahydropyran-4-ols.

Tetrahydropyrans **12** and **14** were prepared in six steps according to Scheme 1 and **13** (*cis/trans* 85:5) by the acid-catalysed Prins reaction of but-3-en-

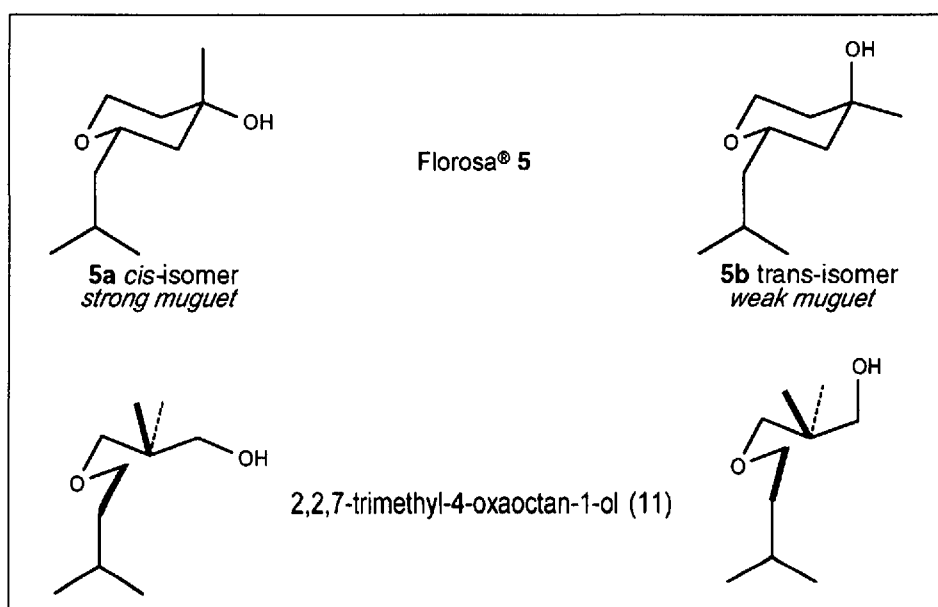


Fig. 4. Comparison of the conformational arrangement of **11** with that of Florosa® (**5**)

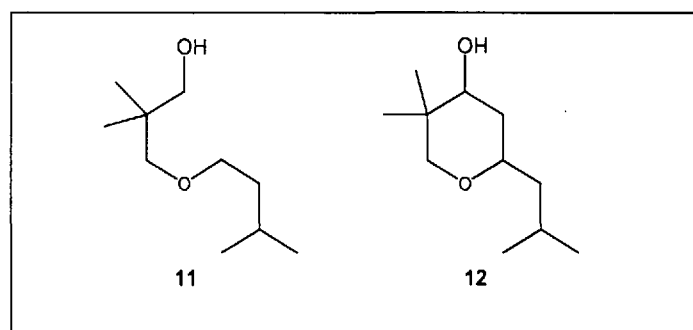


Fig. 5. The novel acyclic alcohol **11** and its cyclic equivalent **12**

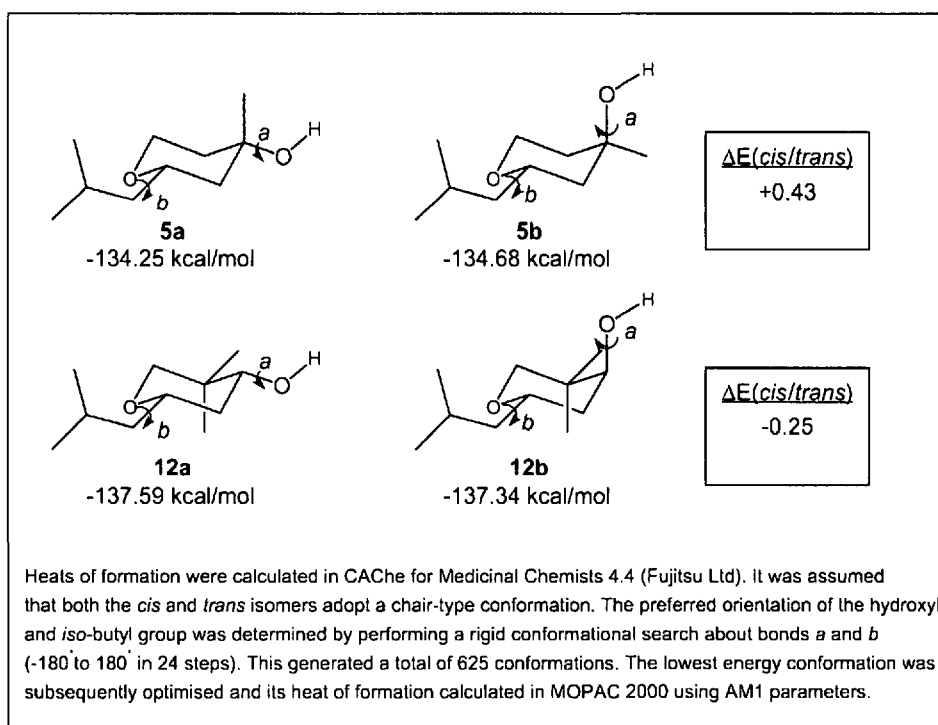


Fig. 6. Relative stability of the *cis*- and *trans*-isomers of Florosa® and **12**

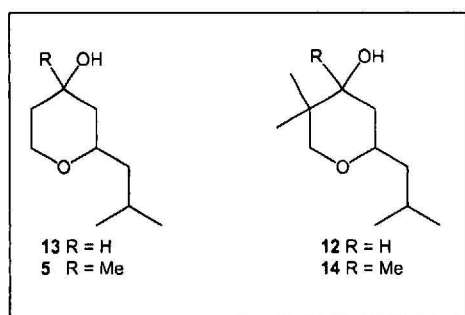


Fig. 7. Novel pyranols designed to investigate the effect of the methyl substitution pattern at C(4) and C(5)

1-ol and 3-methylbutanal. The *cis*- and *trans*-isomers were separated by column chromatography, their stereochemistry determined by NMR and their odours evaluated and compared with the isolated isomers of Florosa (Table 1).

The only novel pyranol to exhibit any muguet character was 2-(2-methylpropyl)-tetrahydropyran-4-ol (13). Like Florosa, the *cis*-isomer (13a) was found to be more potent than the *trans*-isomer (13b), but less potent than the *cis*-isomer of Florosa (5a). Thus replacing the methyl group of Florosa by a hydrogen atom led to a decrease in odour intensity.

Dimethylation at position 5 in the pyrane ring destroys the muguet character; the *cis*-isomers 12a and 14a possess a strong sulphurous note and the *trans*-isomers 12b and 14b are odourless. The surprising sulphurous note in the *cis*-isomers was confirmed by GC olfactometry to be due to the *cis*-pyranols themselves

and not due to any trace impurities. In cycloaddition reactions it is known that a sulphur atom can sterically act as a *gem*-dialkylated atom [6]. Perhaps in 12a and 14a the *gem*-dimethyl atom is organoleptically behaving like a sulphur atom. After all, it has been observed that a sulphur atom can replace a *cis* carbon-carbon double bond in *cis*-3-hexenol and *cis*-3-hexenyl acetate with no significant effect on the green odour profile of these materials [7]. Similar replacements are also possible within the macrocyclic musk family [8].

The most striking observation in this series of tetrahydropyranols is that the *trans*-isomer of each of the four compounds studied is either very weak in

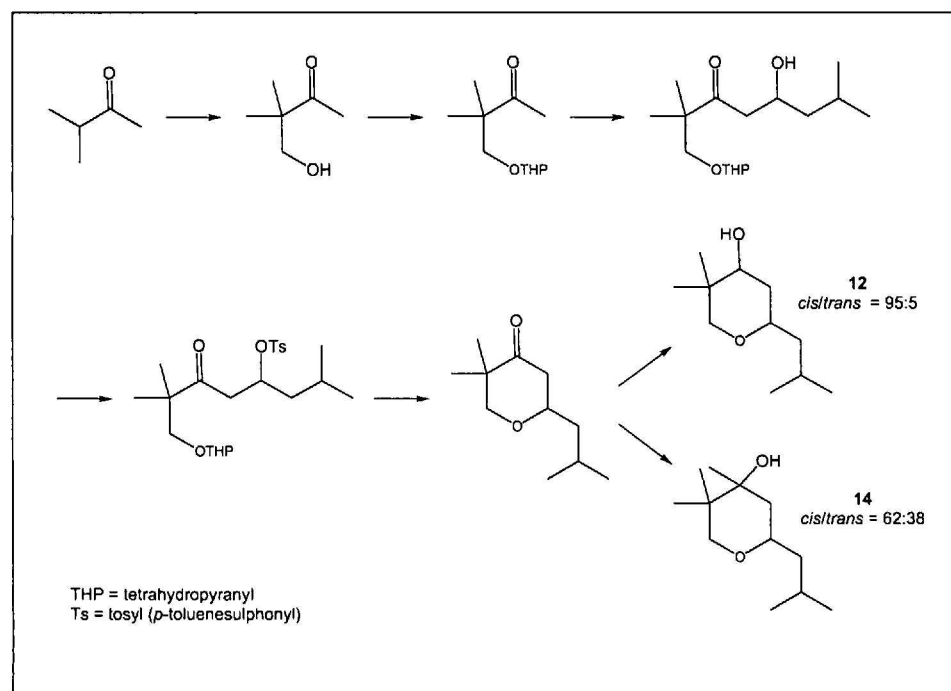
odour or odourless. One possible explanation for this is that the *trans*-isomers may exist in a boat conformation with the OH group intramolecularly hydrogen-bonded to the ether oxygen atom to form a stable six-membered ring (Fig. 8). If this were the case, the alcohol group might not be as free to interact with the olfactory receptors thus rendering the *trans*-isomers weak or odourless. For the *cis*-isomers the preferred conformation is likely to be that of a chair with the OH group free for interaction.

The idea that six-membered heterocycles may, when suitably substituted, adopt a boat form is not new. Lyle [9] concluded that significant amounts of the boat form of 1,2,2,6,6-pentamethyl-4-hy-

Table 1. Odour qualities of the isomers of Florosa and pyranols 12-14

Compound ^{a)}	Odour
5a	Strong, muguet, rose
5b	Weak, muguet
12a	Sulphurous, rubbery, fruity, rhubarb
12b	Odourless
13a	Moderate, muguet, Florosa-like
13b	Weak, muguet, rhubarb, rose
14a	Sulphurous, rubbery, oily
14b	Odourless

^{a)} a = *cis*-isomer with regard to OH and iso-butyl group; b = *trans*-isomer with regard to OH and iso-butyl group



Scheme 1. The synthesis of tetrahydropyranols 12 and 14

droxy-4-phenylpiperidine exist in the pure state and in solution. His conclusions were based upon the observed reduced reactivity of the hydroxyl group and the infrared absorption spectra of dilute solutions of 1,2,2,6,6-pentamethyl-4-hydroxy-4-phenylpiperidine. Borsdorf [10] also used IR spectroscopy to investigate the existence of a boat form in a range of 2,2,6,6-tetramethyltetrahydropyran-4-ols. However, we found no IR evidence to support the existence of intramolecular hydrogen bonding in either the *trans*- or *cis*-isomer of Florosa (5). At high concentrations in carbon tetrachloride the individual isomers each showed intermolecular hydrogen bonding with a broad O-H band at 3439 and 3398 cm^{-1} , respectively. On dilution these broad bands disappeared and sharp bands, attributed to a non-bonded OH group, appeared at frequencies of 3615 cm^{-1} (*trans*-isomer) and 3609 cm^{-1} (*cis*-isomer). Neither isomer produced a broad

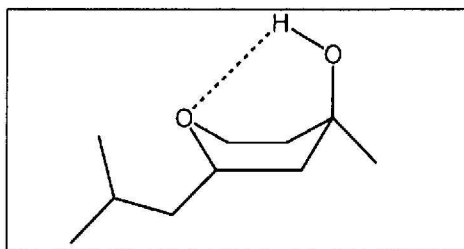


Fig. 8. Postulated conformation for the weak-smelling or odourless *trans*-pyranols

band at high dilution that was indicative of intramolecular hydrogen bonding.

It is generally accepted, in both drug-receptor interactions and olfactory perception, that the active conformation does not necessarily correspond to the lowest energy one or to the one that exists in solution. Consequently we used molecular modelling to investigate whether or not the tetrahydropyran-4-ols could potentially exist in an intramolecularly hydrogen-bonded boat form, and if so whether this form was more favoured in the *trans*-isomers than in the *cis*. Initially each isomer was drawn in the chair conformation with the hydroxyl group orientated towards the ring ether oxygen atom. The conformational arrangement of the isobutyl group was identical for both the *trans*- and *cis*-isomers. The structure was optimised and its heat of formation calculated in MOPAC 2000 using AM1 and (PM3) parameters (CACHe for Medicinal Chemists 4.4, Fujitsu Ltd.). The boat forms were generated from the corresponding chair forms by dragging either the ether oxygen atom or C(4) to approximately the desired position and then minimising the structure and calculating the heats of formation as before (Fig. 9). In all cases minimisation led to a twist boat form with the hydroxyl group still pointing towards the ether oxygen atom.

Table 2 shows that the energy difference between the two forms is relatively small for both the *cis*- and *trans*-isomers of the four pyranols studied (< 4 kcal/mol). Indeed it is less than the estimated thermodynamic strength of a hydrogen bond [11], which suggests that both the *cis*- and *trans*-isomers could, in theory, adopt an intramolecular hydrogen bonded boat form. However, perhaps of greater significance is the O–H distance in the chair forms. This is substantially smaller in the *trans*-isomers (3.07–3.22 Å) than in the *cis* (4.11–4.30 Å) and well within the criteria for a weak hydrogen bond (< 3.4 Å). Thus the attraction between the ether oxygen atom and the hydroxyl hydrogen atom in the *trans*-isomers may act as the driving force for conversion of the chair form to a boat/twist boat.

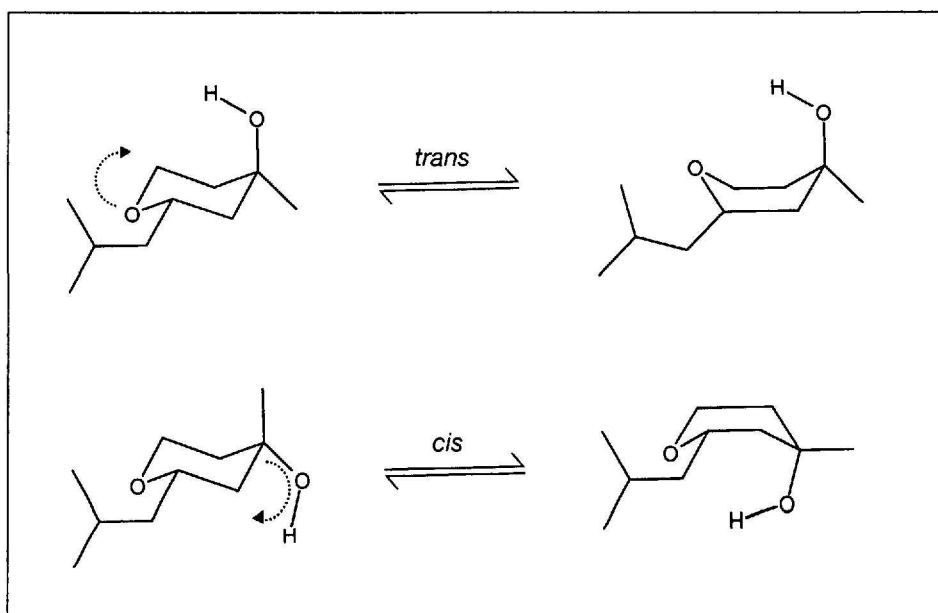


Fig. 9. Modelling investigations into the relative stability of the chair and boat conformations for *trans*- and *cis*-pyranols

Table 2. Calculated heats of formation in kcal/mol for the chair and twist boat forms of pyranols 5, 12, 13, and 14. The optimised geometry was calculated in MOPAC 2000 using AM1 and (PM3) parameters.

Compound	Chair form	Boat form	Difference (boat – chair)
5a	-134.39 (-124.36)	-133.43 (-122.25)	+0.96 (+2.11)
5b	-134.88 (-124.84)	-134.14 (-123.66)	+0.74 (+1.18)
12a	-139.80 (-129.86)	-138.02 (-126.50)	+1.78 (+3.36)
12b	-139.42 (-128.88)	-137.57 (-125.11)	+1.85 (+3.77)
13a	-133.50 (-119.97)	-131.37 (-116.98)	+2.13 (+2.99)
13b	-132.93 (-119.65)	-132.07 (-118.41)	+0.86 (+1.24)
14a	-138.73 (-132.00)	-137.69 (-129.94)	+1.04 (+2.06)
14b	-139.05 (-132.34)	-137.25 (-128.53)	+1.80 (+3.81)

3. The Design of a New Target, 1-Methyl-3-(2-methylpropyl)cyclohexanol (15)

Although not convincing, molecular modelling did provide some supporting theoretical evidence that the *trans*-tetrahydropyran-4-ols might more easily adopt an intramolecularly hydrogen bonded boat form than the *cis*-isomers. In order to investigate experimentally whether this might explain the weak

odour of the *trans* isomers compared to their corresponding *cis*-isomers we designed a target molecule that was not capable of intramolecular hydrogen bonding, *i.e.* the ether oxygen was replaced with a methylene group. It was anticipated that both isomers of 1-methyl-3-(2-methylpropyl)cyclohexanol (15, Fig. 10) would have a strong odour. It was felt that the chances of 15 having a pure muguet odour rather than the rosy, muguet character of *Florosa* were quite high for

the following reasons. Rose oxide (**16**) has no muguet aspects but is rosy and green. Drawing an analogy with the structure and odour of Florosa (**5**), we postulated that the ether oxygen in Florosa might be responsible for its rose note and the tertiary alcohol for its muguet note.

1-Methyl-3-(2-methylpropyl)cyclohexanol was conveniently prepared in the laboratory in two steps; 1,4-conjugate addition of isobutyl magnesium bromide to 2-cyclohexen-1-one in the presence of a copper salt followed by the 1,2-addition of a methyl Grignard reagent (Scheme 2). The isomeric mixture obtained using Grignard chemistry typically consisted of 70% *trans*-1-methyl-3-(2-methylpropyl)cyclohexanol and 30% *cis*-1-methyl-3-(2-methylpropyl)cyclohexanol. The mixture possesses an extremely powerful muguet odour with additional citrus and rhubarb notes. Sensory profiling of the individual isomers, which are easily separated by either column chromatography or efficient fractional distillation, and the determination of their relative odour thresholds revealed that both geometric isomers are comparable in odour strength with the *trans* isomer having a more rhubarb, citrus character and the *cis* isomer being more muguet.

The association of the muguet character with the *cis*-isomer **15a** fitted well with our predictions based on Florosa. The orientation of the alcohol group in relation to the alkyl side chain is also consistent with Pelzer's postulated active conformation for *cis*-Muguetanol (**7**, Fig. 11) [12]. However somewhat surprising was the discovery that chirality had a more pronounced effect on the odour character than did the configuration of the molecule. GC olfactometry, using a chiral GC column, revealed that the first enantiomer to elute for both *trans*- and *cis*-1-methyl-3-(2-methylpropyl)cyclohexanol has predominantly a citrus character and that the second isomer is floral (Fig. 12). The relative strength of the enantiomers governs the overall impression perceived for the two racemic mixtures. The four enantiomers of Muguetanol, on the other hand, all have a muguet note with the (-)-*cis*-isomer being the more potent [12]. Presumably chirality is less important in this case because the molecule is more symmetrical, whereas for the 3-alkyl substituted cyclohexanols it appears that the side of the cyclohexane ring to which the substituent is attached is crucial in determining whether the material is citrus or floral in character.

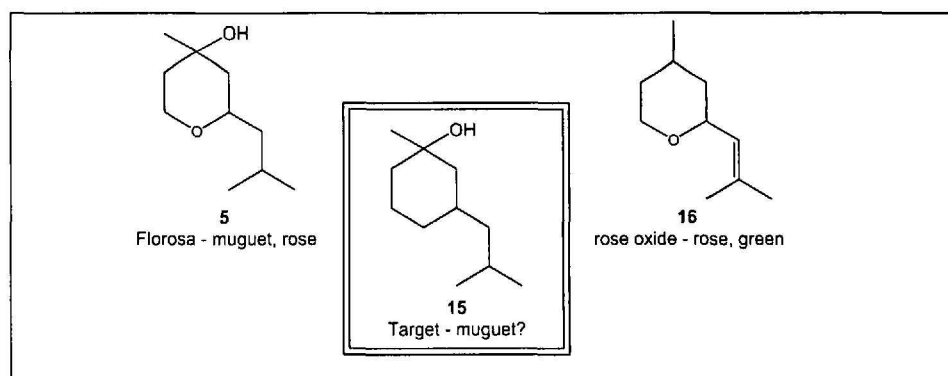
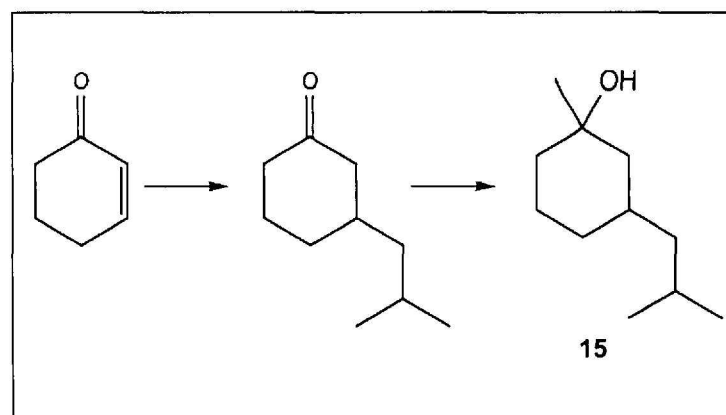


Fig. 10. The design of a new target, 1-methyl-3-(2-methylpropyl)cyclohexanol (**15**)



Scheme 2. Two-step synthesis of **15**

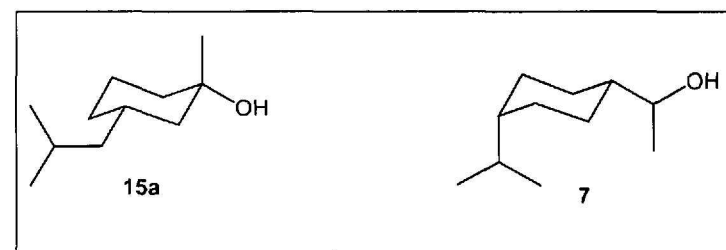


Fig. 11. A comparison of the configurations of *cis*-**15** and Muguetanol (**7**)

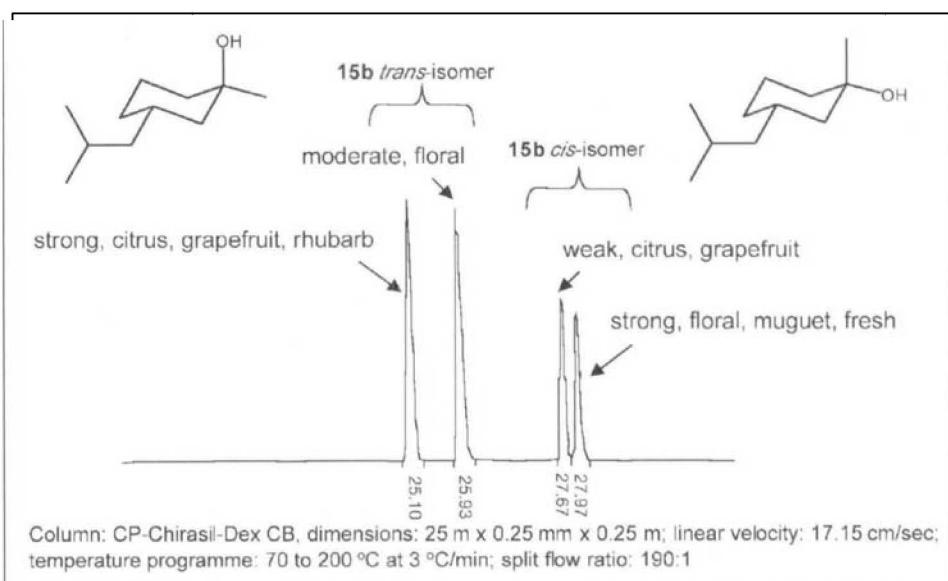


Fig. 12. Chiral GC trace with odour descriptors for the isomeric mixture of 1-methyl-3-(2-methylpropyl)cyclohexanol (**15**)

4. Analogues and Derivatives of 1-Methyl-3-(2-methylpropyl)cyclohexanol

4.1. 3-Alkylcyclohexanols

A large number of analogues were prepared to investigate the effect of the alkyl substitution pattern and ring size on the odour properties of 3-alkylcycloalkanol (Fig. 13). The alkyl substitution patterns at R¹ and R³ were varied by changing the Grignard reagents used in steps 1 and 2, respectively, of Scheme 2. A hydrogen was introduced at R¹ by replacing step 2 with a sodium borohydride reduction. Methyl substitution at R², R³, R⁵ and R⁶ was introduced by the use of suitable commercially available cyclohexenones such as 3-methyl-2-cyclohexen-1-one and isophorone. The ring size was varied by use of the commercially available 2-cyclopenten-1-one and 2-cyclohepten-1-one. The C₈ unsaturated ketone was synthesised by the rearrangement of cyclooctene oxide and subse-

quent oxidation of the resulting 2-cycloocten-1-ol. For the C₅, C₇ and C₈ cyclic analogues it was found that the first step proceeded more smoothly if carried out in the presence of trimethylsilyl chloride and hexamethylphosphoric triamide; additives well known for increasing the rate and selectivity of 1,4-conjugate additions [13].

Table 3 lists the analogues prepared with their odour descriptors. For brevity, only the odour descriptors for the isomeric mixtures are provided. However, it was generally observed that the odours of the individual isomers are different. For example, the *cis*-isomer of **23** has a rhubarb and terpenic odour whereas the *trans*-isomer is more floral. In the case of **26** the *trans*-isomer is muguet and rhubarb while the *cis*-isomer is more woody. Interestingly, these two examples go against the trend seen for **15**, where the *cis*-isomer has the more dominant muguet character. Again, this probably reflects the importance of the relative

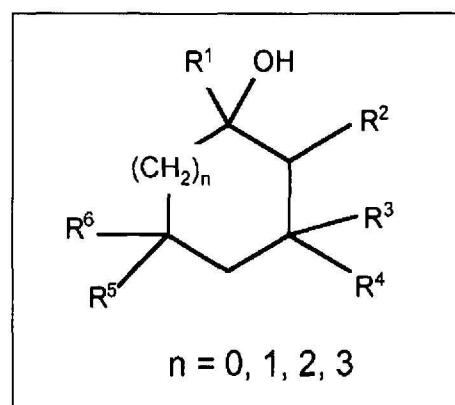


Fig. 13. Structural modifications investigated for the 3-alkylcycloalkanol

contribution of the enantiomers to the perceived odour profile of the geometric isomers and the total isomeric mixture.

For the mixtures, it was found that the floral, citrus character associated with 1-methyl-3-(2-methylpropyl)cyclohexanol was retained in analogues with the following structural requirements [14]:

Table 3. Odour descriptors for a series of 3-alkylcycloalkanol

Compound	n	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	Odour
15	1	Me	H	<i>i</i> -Bu	H	H	H	strong, muguet, lilac, terpenic, citrus
16	1	H	H	<i>i</i> -Bu	H	H	H	floral, herbal, woody
17	1	<i>i</i> -Bu	H	<i>i</i> -Bu	H	H	H	fatty, candlewax
18	2	octyl	H	<i>i</i> -Bu	H	H	H	odourless
19	0	Me	H	<i>i</i> -Bu	H	H	H	strong, muguet, lactonic
20	1	Me	H	<i>i</i> -Pr	H	H	H	minty, anisic, terpenic
21	1	octyl	H	Me	H	H	H	fatty
22	3	Me	H	Me	H	H	H	weak, oakmoss
23	1	Et	H	<i>i</i> -Bu	H	H	H	muguet, freesia, fruity, rhubarb, peach, herbal
24	1	Pr	H	<i>i</i> -Bu	H	H	H	floral, geranium, metallic
25	1	vinyl	H	<i>i</i> -Bu	H	H	H	muguet, metallic, citrus
26	1	Me	H	cyclohexyl	H	H	H	muguet, rhubarb, grapefruit, woody
27	1	Me	Me	<i>i</i> -Bu	H	H	H	muguet, terpenic, dirty, woody
28	1	Me	H	Me	H	H	H	minty, earthy, terpenic, medicinal
29	1	Me	H	octyl	H	H	H	weak, floral, terpenic
30	1	H	H	<i>i</i> -amyl	H	H	H	strong, muguet, rose, jasmine, grapefruit, rhubarb
31	1	Me	H	<i>i</i> -amyl	H	H	H	strong, muguet, rhubarb, grapefruit
32	1	Me	H	benzyl	H	H	H	harsh, citrus, rubbery
33	CHMe	Me	H	<i>i</i> -propenyl	H	H	H	minty, lilac, terpenic
34	CHMe	Me	H	<i>i</i> -Pr	H	H	H	minty, terpenic
35	1	Me	H	<i>i</i> -Bu	Me	H	H	rhubarb, muguet
36	1	Me	H	<i>i</i> -Bu	Me	Me	Me	earthy, musty
37	2	Me	H	<i>i</i> -Bu	H	H	H	muguet, rhubarb, dirty
38	3	Me	H	<i>i</i> -Bu	H	H	H	moderate, rhubarb, terpenic, lilac, muguet
39	1	Me	H	<i>i</i> -butenyl	H	H	H	floral, terpenic, rhubarb, camphor
40	1	H	H	<i>i</i> -butenyl	H	H	H	rose, muguet, fatty, metallic
41	1	Me	H	<i>s</i> -Bu	H	H	H	muguet, terpenic, green
42	1	Me	H	<i>t</i> -Bu	H	H	H	grapefruit, rhubarb, floral

1. R^1 = hydrogen, methyl, ethyl, propyl. A further increase in the size of R^1 leads to the introduction of fatty notes (17 and 21) and a decrease in odour intensity.
2. R^3 = *iso*-butyl, *sec*-butyl, *tert*-butyl, cyclohexyl, *iso*-amyl. If R^3 becomes too small the odour character shifts to minty and terpenic (20, 28, 33) and if it becomes too big the odour of the resulting compound is weak (29).
3. For the 1-methyl-3-(2-methylpropyl) disubstituted derivatives, the ring size can be C_5 , C_6 or C_7 . The 8-membered ring analogue (38) still has the characteristic rhubarb, floral character but is less intense.
4. Introduction of one extra methyl group at position 2 or 3 (27, 35) does not destroy the floral, citrus odour, whereas introduction of three extra methyl groups leads to a very uninteresting musty, earthy smelling compound (36).
5. Introduction of a double bond in the R^3 side chain appears to increase the odour strength but the muguet note is harsher (39, 40).

4.1. 2/4-Alkylcyclohexanols and 3/4-Alkylcyclohexylmethanols

1-Methyl-2-(2-methylpropyl) cyclohexanol (43) and 1-methyl-4-(2-methylpropyl)cyclohexanol (44) were prepared

to determine the importance of the position of the 2-methylpropyl group (Fig. 14). The precursor 2- and 4-alkylcyclohexanones, respectively, were prepared by alkylation of cyclohexanone and by the hydrogenation and subsequent oxidation of 4-isobutylphenol [15]. Compound 43 has an uninteresting minty odour, while 44 is a good muguet odorant [16].

Drawing an analogy with the structure and odour of Mayol (6) and Mugetanol (7), led to the synthesis of 45, 46, and 47 (Fig. 14). These were prepared from the corresponding alkylated cyclohexanone or pyranone in two steps: conversion to the corresponding homologous aldehyde according to the procedure of Miwa *et al.* [17] followed by either reduction or treatment with a methyl Grignard reagent. 2-(2-Methylpropyl)tetrahydropyran-4-one was obtained from Florosa (5) by pyrolysis of the corresponding acetate [18] and subsequent oxidative cleavage of the exocyclic alkene [19]. In general, it was found that the isopropyl group in the 4-alkylsubstituted cyclohexylmethanols 6 and 7 could be replaced by an isobutyl group (45) and the muguet odour retained. Pelzer *et al.* [12] have already shown that replacement by an ethyl or methyl group also leads to floral odorants but that substitution by a tertiary-butyl group leads to a sandalwood material, 1-[4-(1,1-dimethylethyl)cyclo-

hexyl]ethanol. In the case of the 3-alkyl-substituted cyclohexylmethanols (46) it was found that only the isobutyl analogue has a muguet odour; 1-[3-(1-methyl-ethyl)cyclohexyl]ethanol, for example, is weak green and hay-like. However, moving the hydroxyl group away from the ring (47, *cf.* 5 and 46, *cf.* 15) leads to a decrease in the odour strength and a greater shift towards a rosy as opposed to muguet odour.

4.2. Derivatives in which the OH Group Has Been Replaced by an Alternative Functional Group

In order to determine the importance of the presence of the hydroxyl group, 1-methyl-3-(2-methylpropyl)cyclohexanol (15) was converted to the corresponding acetate 48 by treatment with a mixture of pyridine and acetic anhydride and to the methyl ether 49 by successive treatment with a strong base (sodium hydride) and methyl iodide. The epoxide 50 was prepared from 3-(2-methylpropyl)cyclohexanone by treatment with trimethyl-oxosulphonium iodide [20] and the nitriles 51 by treatment with tosylmethylisocyanide [21] to give 3-(2-methylpropyl)cyclohexylcarbonitrile and subsequent methylation (Fig. 15).

Interestingly, the muguet character of 1-methyl-3-(2-methylpropyl)cyclohexanol (15) is also present in the correspond-

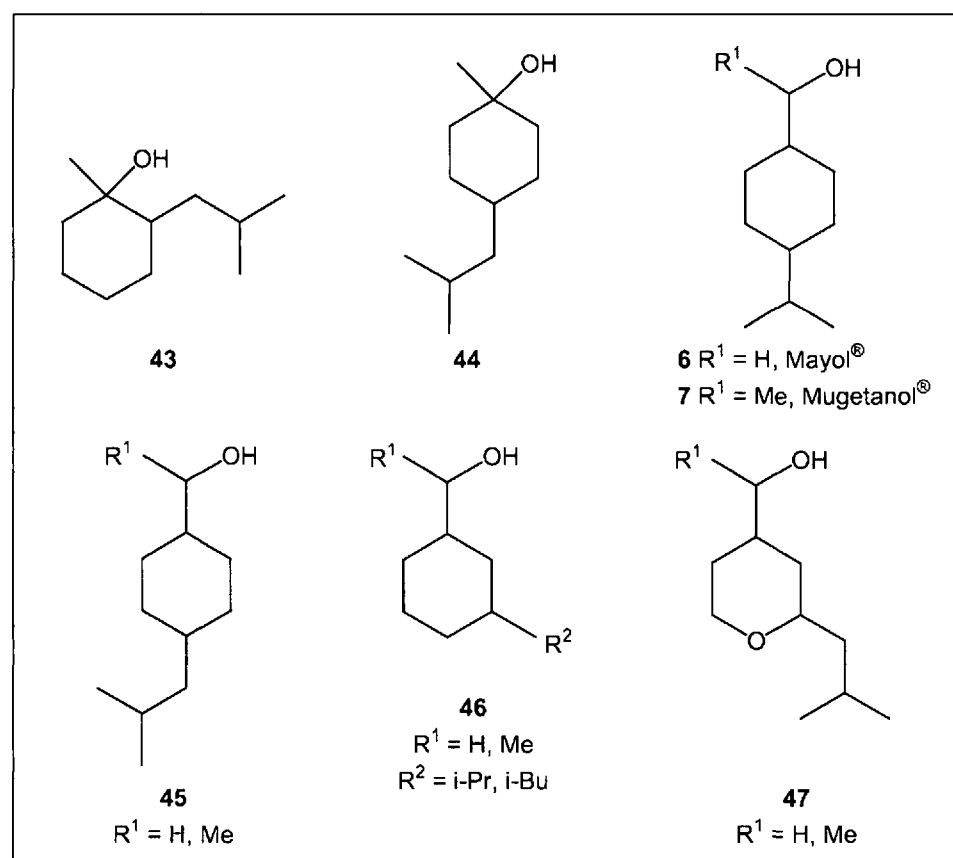


Fig. 14. An investigation into the effect on odour of the position of the alkyl C_3 - C_4 side chain and the position of the hydroxyl group

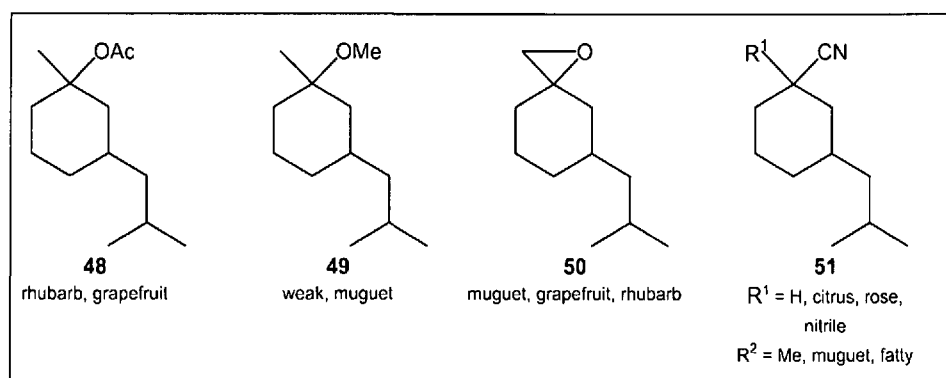


Fig. 15. The effect of replacing the OH group with other functional groups on the muguet odour of 3-(2-methylpropyl)cyclohexyl derivatives

ing ether, epoxide and nitrile derivative but not in the acetate, which is predominantly fruity. However, 49–51 all have weaker odours than the alcohol derivative, and the nitrile (51b) also has an unpleasant fatty note.

5. Summary

A number of novel muguet fragrance ingredients have been discovered with the support of qualitative structure-activity relationships and molecular modelling. Although the first generation of targets, the 5,5-dimethyl-2-(2-methylpropyl) tetra-hydropyranols, did not exhibit any muguet character, trying to understand why these compounds did not fit the model inspired the design and discovery of an excellent muguet fragrance ingredient, 1-methyl-3-(2-methylpropyl)cyclohexanol. The empirical analogue synthesis approach led to the findings that the muguet character is present in 1,3-dialkylcycloalkanols when R¹ is preferably methyl or ethyl, R³ is preferably a C₄–C₆ alkyl group and the ring size is C₅–C₇. It was also found that the alcohol group is not necessarily a prerequisite for a muguet odour, although replacement by an epoxide, methyl ether or nitrile group does lead to weaker floral odorants. 3-(2-Methylpropyl)cyclohexylmethanols and 4-(2-methylpropyl)cyclohexanols were also shown to exhibit good muguet odours. Replacement of the 2-methylpropyl group by a smaller group leads to a loss in the muguet character in the 3-alkyl series but not in the 4-alkyl series.

The work reported here has shown how molecular modelling can help the fragrance chemist in his search for novel molecules, in particular in providing theoretical support for an idea or hypothesis. However, it is also clear that the field of fragrance research is full of surprises. We

could not have predicted that chirality would have had a more pronounced effect on the odour properties of 3-alkylcyclohexanols than the configuration of the molecule nor, based on our hypothesis, would we have expected the corresponding epoxides, nitriles and methyl ethers to exhibit some muguet character. Indeed, the synthesis of derivatives and analogues is the only means of fully defining the structural requirements for a particular family to exhibit a specific odour whilst at the same time being essential for lead optimisation. The empirical approach, computer-aided design, the analysis of natural products, and serendipity all have an important role to play in the discovery of new fragrance ingredients. Similar conclusions have been made by Fráter, Bajgrowicz and Kraft [22] who have also explored the use of molecular modelling as a tool for rational odorant design.

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