SYNTHESIS AND FRAGRANCE PROPERTIES OF MACROCYCLIC MUSKS

Reported by Terry Moore   April 14, 2005

INTRODUCTION

Of the three strikingly different compound classes possessing musky odors[1-3]—nitroarenes,[4] polycyclic benzenoids,[4] and macrocyclic ketones and lactones[4-7]—the last group has been used for the longest time in fragrance formulations. Owing to the relatively high cost of production, however, less than 25% of the musks produced worldwide in 1998 were macrocyclic; this number has been projected to grow to 60-65% by 2008,[3] mainly because of risks associated with bioaccumulation of polycyclic musks and nitroarenes.[8-10] This review will cover key points in the history of macrocyclic musks, will provide an analysis of various structure-odor relationships (SORs), and will examine approaches to design and synthesize novel, structurally diverse macrocyclic musks.

BACKGROUND

Discovery and Structural Elucidation

Although Tonkin musk—the dried secretions from the male Asian musk deer (*Moschus moschiferus* L.)—had been known as a fragrance and traditional medicine for 800 years,[5] nothing was understood of the chemical constitution of the natural compounds imparting the musky odor until Ružička's 1926 structural elucidation of the 15- and 17-membered macrocycles muscone (**1**) and civetone (**2**).[11] His confirming experiment that these compounds have macrocyclic structures was the oxidation of both dihydrocivetone and the unsaturated Wolff-Kishner product of civetone with KMnO$_4$ or ozone to the same dicarboxylic acid, HO$_2$C-(CH$_2$)$_{15}$-CO$_2$H. Ružička's structural elucidation of these macrocycles effectively squelched von Baeyer's 1885 theory that rings containing more than 8 members were too unstable to exist[12] and paved the way to his Nobel Prize in chemistry in 1939.

Prior to Ruzicka's discovery, Baur, in a search for synthetic explosives, had serendipitously found in 1891 that the tri-nitro compound **3** (musk Baur) possessed a musk-like odor.[13] The lower cost of producing **3** and its derivatives, relative to the natural macrocycles, led to the preeminence of nitromusks in the fragrance industry until the development of the polycyclic musks, such as Galaxolide® (**4**), in the

Chart 1: Structures of some musk compounds.

(*R*)-Muscone (1)   Civetone (2)   Musk Baur (3)   Galaxolide (4)

1950s and 1960s.[2] Recently, however, it was reported that both nitromusks and polycyclic musks bioaccumulate in fish and in human fat and breast milk.[8-10] The potential risks associated with this bioaccumulation have spawned a newfound interest in synthesis of macrocyclic musks for the fragrance industry.

Approaches to Macrocycle Synthesis

The first synthesis of a macrocyclic musk was completed in 1926 by Ružička,[14] who synthesized Exaltone® (**5**) in 2% yield by pyrolysis of the thorium salt of hexadecanedioic acid (Scheme 1).   Although this

Scheme 1. Ruzicka's Synthesis of Exaltone (5).[14]
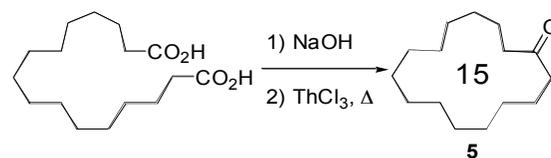
approach was later optimized by others to achieve yields of 60-70%, it was still impractical to use in an industrial setting because of the high dilution needed to favor the intramolecular reaction.   To circumvent this problem, Prelog[15] and Stoll[16,17] independently developed acyloin condensation approaches for the production of muscone (**1**). Because the reductive coupling occurs on the surface of sodium metal, there was no longer a need for high dilution. For macrocyclic lactones, another way to overcome this problem was developed by Spanagel and Carothers in 1935.[18] They obtained macrocyclic lactones in good yield and high purity by polymerizing an ω-hydroxy acid by dehydration, then subsequently depolymerizing it under carefully controlled conditions of temperature, pressure, and catalyst.

One common strategy for obtaining macrocycles is ring expansion of cyclododecanone (**6**), an inexpensive starting material available from the trimerization of 1,3-butadiene, hydrogenation and oxidation.[7] One of the earliest examples of this ring-expansion approach was reported by Ohloff et al.[19] in 1967 (Scheme 2).   Enone **7** was formed by Stobbe condensation of cyclododecanone with diethyl succinate, followed by cyclization and acid-catalyzed hydrolysis and decarboxylation. Enone **7** was reduced to the tetra-substituted alkene, which was oxidatively cleaved with ozone to give the dione **8**. Macrocyclic ketone **5** was formed from **8** by partial reduction and dehydration to unsaturated ketone **9** followed by hydrogenation.

Scheme 2: Ohloff's Synthesis of Exaltone.[19]
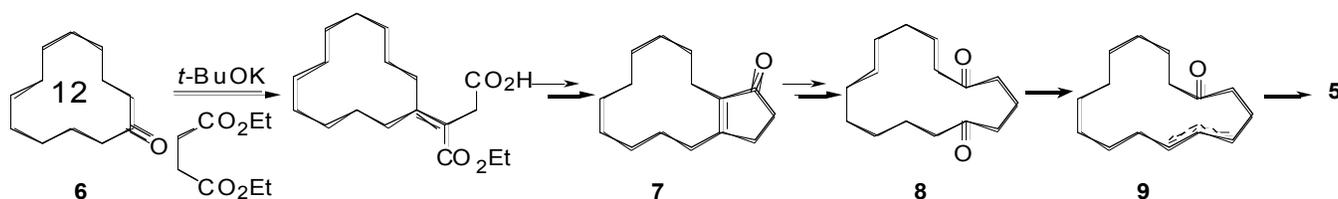
More recently, ring-closing metathesis has been used in the construction of macrocycles. In 1996, Fürstner and Langemann[20] reported the synthesis of Exaltolide® (**11**), a widely produced macrocyclic musk (>200 tons/year), in three steps from commercially available starting materials (Scheme 3). Metathesis of diene ester **10** with Grubbs' ruthenium catalyst provided the unsaturated macrocycle, which was hydrogenated to Exaltolide® **11**.

In 1964, Mamdapur et al.[21] synthesized (-)-(R)-muscone, the natural enantiomer, starting from (+)-citronellal, which was transformed to keto ester **12** over seven steps. The double bond of **12** was oxidatively cleaved, and functionalization gave the keto diester **13**. Keto diester **13** underwent acyloin cyclization, followed by ketalization and reduction to the ketal diol **14**, which was converted to the unsaturated protected ketone, which was hydrogenated and deprotected to give (-)-(R)-muscone (Scheme 4).

Scheme 4. Mamdapur's Synthesis of (-)-(R)-1.[21]
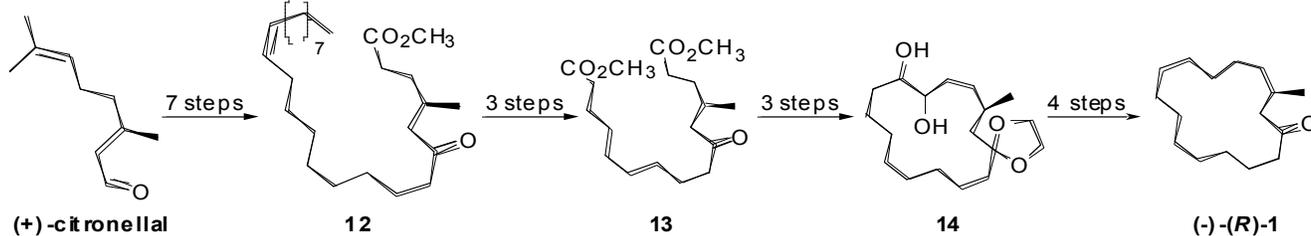
STRUCTURE-ODOR RELATIONSHIPS

Nearly every commercially available perfume contains some amount of a musk compound.[22] Given this importance of musks to the fragrance industry, chemists have invested considerable effort to understand the structural basis for musk odor.[22,23] The first to posit structural requirements for the musk odor was Stoll,[24] who suggested in 1936 that macrocyclic musks must contain rings of 14-19 members and have at least one C=O or NH group. Additionally, he postulated that methyl substituents have almost no influence on odor, that lactones and keto ethers have the strongest musk odor, and that more than one oxygen linkage in the ring decreases the intensity of the odor. Stoll's empirical rules, while helpful as guidelines, were not without flaws.

Stoll's theory applied only to macrocyclic musks, but more recently, scientists have wondered whether there might be some common structural determinant across all three classes of musks (nitroarenes, polycyclic benzenoids and macrocyclic ketones and lactones); a necessary corollary is that

all three compounds bind to a similar set of odorant receptors responsible for the perception of the musk odor. The other possibility is that the slight differences in musk odors arise from different sets of receptors, in which case the search for a common olfactophore—the set of structural determinants for a particular odor—among all three structural classes would be considered pointless.[2] At present, there are no X-ray crystal structures of any of the predicted 1,000 odorant receptors, although there are some models based on rhodopsin, a similar G-protein coupled receptor (GPCR).[25] Further, it is not known which odorant receptors bind musk molecules. Since this lack of information makes it nearly impossible to define the atomic-level interaction of musk odorants with receptors, all musk SOR models are based on ligand structural similarity.

An expert in the musk field, Beets[26] in 1957 suggested, based on his experience, that musks must have a molecular weight of 200-300, a closely packed structure and a polar functional group. Theimer and Davies[27] found correlation between the odor of a musk molecule and both its desorption rate from a water surface into air and its molecular dimensions. They proposed that musks must have a desorption rate from 0.4 to 1.7 (units unspecified), a cross-sectional area of 40-57 Å^2 and a length-to-width ratio from 2.8 to 3.3.

Bersuker et al.[28] established an olfactophore model across all three musk classes by analyzing electron-topologic matrices of contiguity (ETMCs)—matrices of electronic charge, bond order, and interatomic distance resulting from studies of electronic structure and a single conformation determined by Bersuker's in-house software—for 362 compounds possessing and lacking musk odor. This study found two structural requirements for musk odor: 1) a polar oxo functional group (N=O or C=O) the O atom of which is located 6.7 ± 0.5 Å from two CH_2 or CH_3 groups, which are located 2.5 ± 0.5 Å from each other and 2) two CH_2 or CH_3 groups located 5.5 ± 0.5 Å from each other. While these structural features are necessary, they are not sufficient; additional steric hindrance that prevents the interaction of the odorant with its receptors might cause a molecule to lack musk odor, although no detail outlining the scope of these steric interactions was given. Bersuker reported that within the set, there is a probability of prediction of P = 0.96 for correctly predicting a compound's musk odor.

In 1995 Kansy et al.,[29] using Bersuker's compound set, reported, in opposition to Bersuker's claim, that the odors of only 54.4% of the compounds were correctly predicted using a single conformer approach (MOLOC), and 64.7% were correctly predicted using a multiconformer approach (CATALYST). Kansy et al. proposed a model wherein three hydrophobic groups reside 5.5, 6.7, and 8.0 Å from a hydrogen bond acceptor; however, no predictive information was given for this model.

Chart 2. Structure of 13-(*R*)-Methyl-oxacyclo tetradecan-2-one.
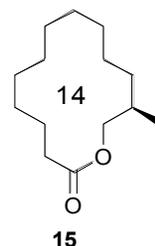
Since a given macrocycle could occupy numerous conformations with little change in free energy, determining the active conformer is difficult. Kraft and Cadalbert[30] devised a strategy around this dilemma by restricting the conformational freedom of some macrocyclic musks through the introduction of methylene bridges into analogues of the 14-membered macrocyclic lactone **15**. Since **15** and its enantiomer possess different odors, and since a methylene bridge could be incorporated without increasing the molecular weight over 300—the observed upper boundary for macrocyclic musk molecular weight—**15** seemed a good choice for conformation-odor correlation studies. Kraft and Cadalbert synthesized the 14-membered rings by hydrogenation of the bicyclic bridgehead enones **16**, alkylation of the resulting ketone, cyclization to the enol ether **17**, oxidative cleavage of the double bond, and selective reduction of the resultant ketone to afford bridged lactones **18** (Scheme 5). The researchers found that the [7.5.1]-bicycle **19** gave the strongest musk odor.

Scheme 5. Synthesis of Bridged Macrocyclic Lactones.[30]
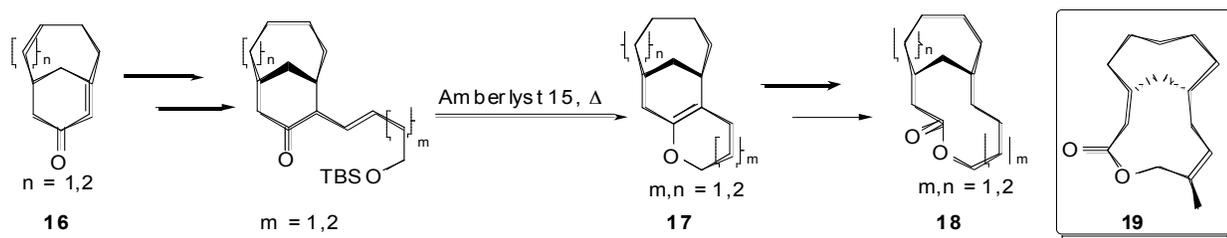
DESIGN OF NOVEL MACROCYCLIC MUSKS

In designing novel macrocyclic musks, researchers have considered a limited number of options for structurally diverse compounds. First, saturated carbon atoms within the ring can be replaced by heteroatoms or multiple bonds. Second, substituents can be placed on the macrocyclic ring, and third, the ring size can be varied. As this last option is a common feature of most designs, it will not be discussed separately.

Heteroatom and Multiple Bond Substitution for Macrocyclic CH_2

Kraft and Cadalbert[31] have introduced oxygen atoms into rings of various sizes. They found that the (*R*)-enantiomer of the 15-membered 7-oxamacrolide **20** possessed "musky, floral, woody, myrrh, fresh, powdery" tones, whereas the (*S*)-enantiomer was odorless. Eh[32] reported a similar set of compounds in 4-oxamacrolides, with the (*R*)-enantiomers of compounds **21** and **22** producing strong musky odors. Michrowska et al.[33] synthesized a series of carbonates **23** as potential

Chart 3. Novel oxygen-containing macrocycles 17-20.

macrocyclic musks using ring-closing metathesis; however, no information was given on the quality of the musk odor of the compounds.

It has long been known that benzene and thiophene are bioistosteric, meaning that, in some cases, the benzene ring of a given compound can be substituted with a thiophene group with little to no loss in biological activity.[34] Assuming this principle could be applied to (Z)-double bonds, Kraft and Cadalbert[35] replaced the (Z)-double bond of ambrettolide **24** with a sulfur atom. The odor of the 16-membered thia macrocycle **25** was described as resembling that of ambrettolide, but "more green-mossy" than **24**; however, the odor threshold of **25** is about ten times lower.

Chart 4. Ambrettolide (24) and its thia-analog (25).

The last of these so-called "in-ring" variations introduces a multiple bond. Lehmann and Tochtermann[36] synthesized a series of 16-membered macrocycles with double (**26**) and triple bonds (**27**) at various positions on the ring. They found all of the alkynes **27** to be only slightly musky, whereas all of the (Z)-alkenes **26** were classified as "strong musks."

Fehr and coworkers[37] introduced novel di- and mono-unsaturated 15-membered macrocyclic ketones **28-30** by iterative Grob fragmentations of a 6,7,6-tricyclic keto diol. The odors of these compounds were all reported as musky, but **29**, particularly, was described as "an excellent, powerful, musk odorant."

Chart 5. Unsaturated Macrocycles 26-30.

26
m = 5-8
n = 10 - m

27

28: *E*; X = CH₂
29: *Z*; X = CH₂
30: *Z*; X = (*Z*)-CH=

Scheme 6. Synthesis of Saturated and Unsaturated Macrocyclic Lactones.[38]

Alkyl, Alkenyl, and Oxo Substitution for Macrocyclic H

In addition to substitution for ring methylene units, macrocycle hydrogens have also been substituted by alkyl, alkenyl, and oxo substituents. Rodefeld et al.[38] synthesized a series of keto lactones **31** that were subsequently converted

31
m = 1,2
n = 1,2,3

to exo-methylene lactones **32**, which were then further transformed into their endocyclic isomers **33** and saturated lactones **34** (Scheme 6). The oxo lactones **31** did not possess a musky odor, but unsaturated lactones **32** and **33** and saturated lactones **34** had intense musky odors. Bollbuck and Tochtermann[39] reported varying degrees of musk odor for macrocyclic lactones **35**.
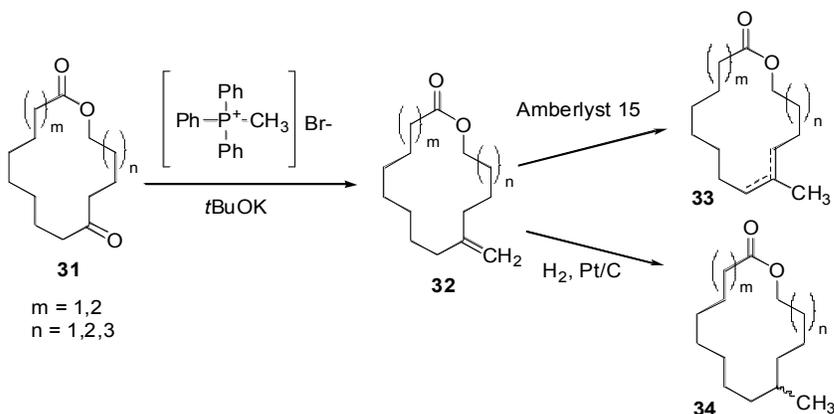
Nicolaou and coworkers[40] synthesized a small library of muscone analogs by a solid-phase approach that incorporated points of diversity both within and on the ring. A polymer-supported phosphonate was coupled with olefinic esters **36** (Scheme 7). Cross olefin metathesis afforded the homoallylic alcohols, which were oxidized using the Dess-Martin reagent to the phosphino aldehydes **37**. Intramolecular condensation between the keto phosphonate and aldehyde gave the free dienones **38**. Off-bead conjugate addition with alkyl lithium cuprates, followed by hydrogenation gave the final racemic muscone analogs **39** in moderate yield and good purity. The odors of the compounds were not given.

Chart 6. Structure of Lactones 35.

35

R_1 = Me, Et
R_2 = H, Me
R_3 = H, Me, Et

Scheme 7. Solid-Phase Synthesis of Muscone Analogs.[40]
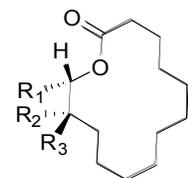
CONCLUSION

Due to a risk associated with bio-persistence of the long-used nitromusks and polycyclic musks, chemists in the fragrance industry have turned their synthetic efforts to the historically more costly, but presumably more easily biodegraded, macrocyclic musks. Analogs synthesized thus far have incorporated structural diversity in ring size, ring constitution, or ring substitution. Since efforts have relied mainly on producing analogs by a trial and error approach, it is surprising that combinatorial methods, capable of generating large numbers of analogs quickly, have not been utilized more often. SOR studies undertaken thus far have not yielded highly predictive models; to be more effective in creating novel fragrances, researchers need to know more about the structural basis of the musk scent, and particularly the atomic-level interactions of macrocyclic musks with their odorant receptors.

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