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Efficient Macrocyclization by a Novel Oxy-Oxonia-Cope Reaction: Synthesis and Olfactory Properties of New Macrocyclic Musks

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Dedicated to Dr. Roman Kaiser

Musk odorants are indispensable in perfumery to lend sensuality to fine fragrances, a nourishing effect to cosmetics, and a comforting feeling to laundry.[1] Due to a certain phototoxicity of nitro musks, and the lack of biodegradation of polycyclic musks,[1] the two most important musk families at present are macrocycles **1**–**5** (Figure 1), derived from the natural lead muscone (**1**), and linear alicyclic musks such as **6**–**7**, the odor of which has been attributed to horseshoe-shaped conformers that mimic macrocyclic rings on the odorant receptors.[1]

Both musk families, linear[1c] as well as macrocyclic,[2] comprise highly flexible structures, which make double bonds and methyl groups ideal design elements to rigidify and conformationally constrain them. The two most powerful macrocyclic musks, (+)-(3*R*,5*Z*)-5-muscenone (**2**)[3] and (13*R*,10*Z*)-Nirvanolide (**3**) both feature a double bond and a methyl substituent, and Cosmone (**4**) can be regarded as a "*nor*-muscenone". By introduction of two double bonds such as in **5**, the conformational freedom can be further restricted, enabling a targeted design of potent musk odorants.[4] Methyl substituents determine the conformational space of linear musks to a great extend; yet, as apparent from the two dehydro-derivatives **6** and **7** of Serenolide (Figure 1), a shift of a double bond can change the odor threshold by a factor of over 150.[5]

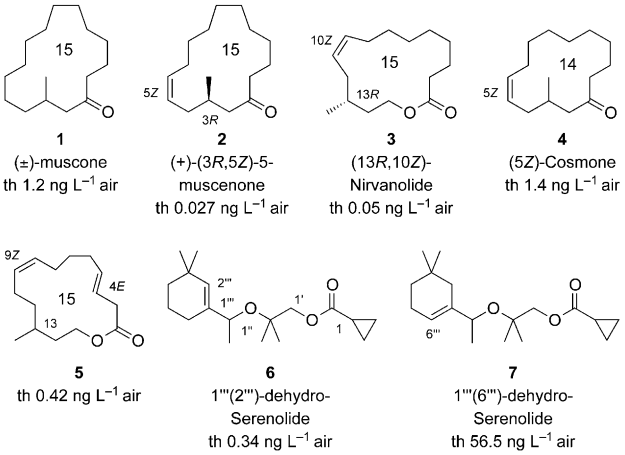

Figure 1. Macrocyclic musks **1**–**5**, and linear musk structures **6** and **7**.

The synthesis of further unsaturated macrocyclic musks can shed light upon similarities in the structure–odor correlation of these two musk families, and to this purpose we herein report on the intramolecular application of a new reaction[6] of β,γ-unsaturated aldehydes with different aldehydes in the presence of Lewis acids. The projected macrocyclization can be regarded as an oxy-version of the established 2-oxonia Cope rearrangement,[7,8] but as illustrated in Scheme 1, could as well proceed through compound **11** in a Prins-type[9,10] manner by coordination of the Lewis acid to the opposite formyl function. Both pathways would however lead to the same macrocyclic alk-3-en-1-yl formates **10**. Hydride reduction and subsequent oxidation of **10** should provide β,γ-unsaturated macrocyclic ketones, which could then be hydrogenated to the saturated macrocycles; thus, could then also open up a new route to (±)-muscone (**1**).[11]

As delineated in Scheme 2, the dicarbonyl substrates **8a**–**g** were prepared from commercial bromo alcohols **12a**–**g** by protection as *tert*-butyldiphenylsilyl (TBDPS) ethers **13a**–**g**, and subsequent Finkelstein reaction[12] with KI in acetone to afford iodides **14a**–**g** in excellent yields. Deconjugated α-alkylation[13] of the Weinreb amide **15**[14] with **14a**–**g** afforded alkylated amides **16a**–**g** in 39–60% yield, with unreacted **14a**–**g** being recovered. Deprotection of the Weinreb amides **16a**–**g** with tetrabutylammonium fluoride (TBAF) in THF

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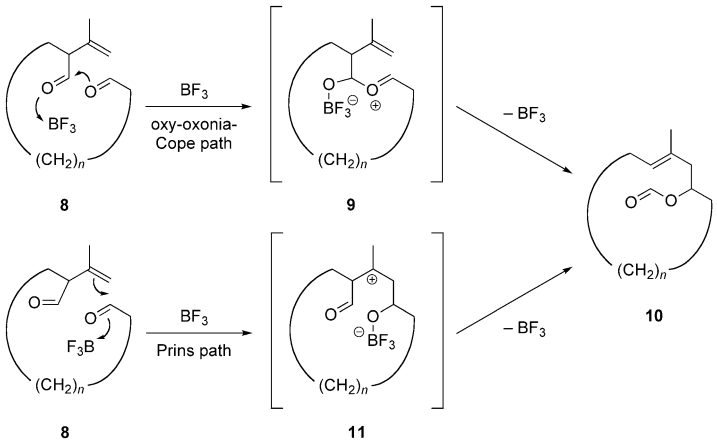
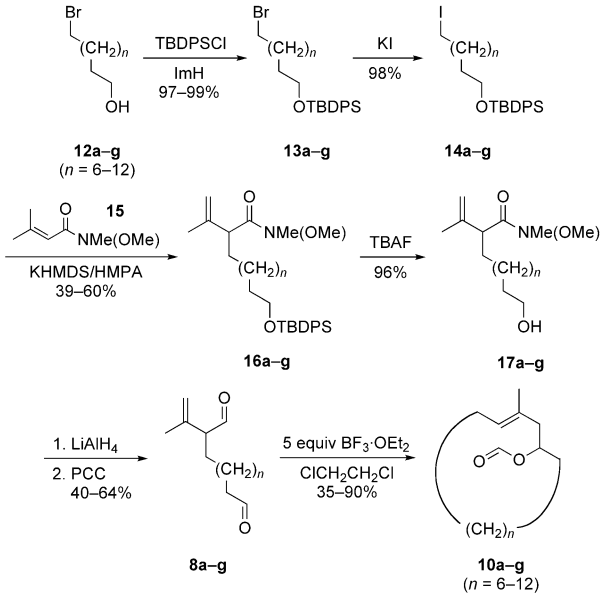


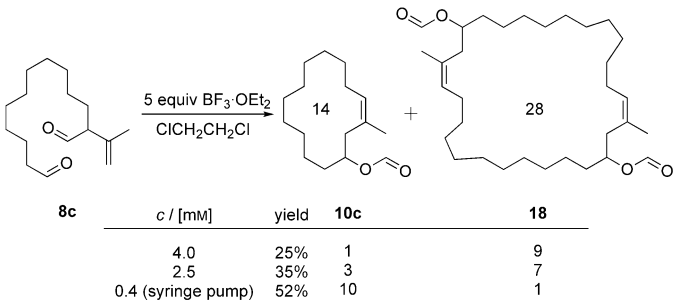
Scheme 1. The two possible pathways of the new macrocyclization.



Scheme 2. Synthetic route to the dicarbonyl substrates **8a–g**, and macrocyclization to large-ring cycloalk-3-en-1-yl formates **10a–g**.

provided the corresponding hydroxyamides **17a–g**, free of any α,β-double-bond isomers. Hydride reduction of **17a–g**, and subsequent pyridinium chlorochromate (PCC) oxidation then furnished the dicarbonyl substrates **8a–g** in yields of 40–64%.

2-(Prop-1-en-2-yl)tridecanedial (**8c**) was chosen as the test substrate for the projected macrocyclization; however, treatment with BF_3OEt_2 (0.3 equiv) in dichloroethane afforded **10c** in trace amounts only. As delineated in Scheme 3, the dimer **18** was the major isolated product. Dimerization was suppressed under high-dilution conditions (Scheme 3), with the best yield of **10c** (52%) being obtained at 0.4 mM by slow addition of **8c** to the BF_3OEt_2 solution through a syringe pump. All attempts to increase the yields by use of other Lewis acids or Amberlyst 15 were unsuccessful.



c / [mM]	yield	10c	18
4.0	25%	1	9
2.5	35%	3	7
0.4 (syringe pump)	52%	10	1

Scheme 3. Effect of the dilution on the macrocyclization of **8c**.

By using a syringe pump at 1.0 mM on a preparative scale, compound **10c** was isolated in 45% yield with a *Z*/*E* ratio of 99:1. As summarized in Table 1, the yield and *Z*/*E* ratio of this new macrocyclization strongly depended upon the ring size, with **8a** and **8b** affording no cyclization products.

Table 1. Correlation of ring size and yield for the cyclization of the dialdehydes **8a–g** to cycloalk-3-en-1-yl formates **10a–g**.[a]

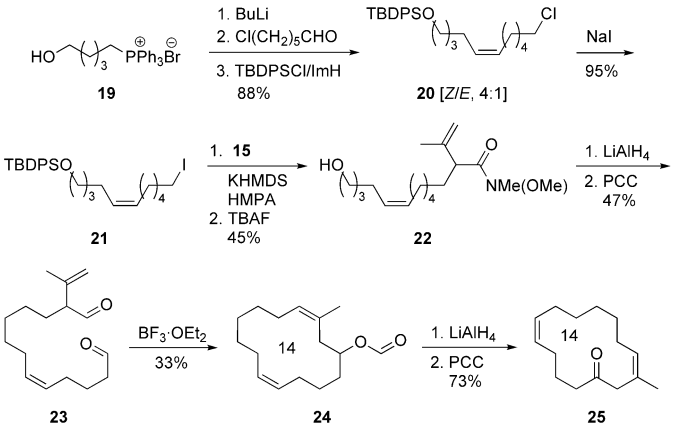
Entry	*n*	Ring size [*n*+6]	Product	*Z*/*E* ratio[b]	Yield [%][c]
a	6	12	**10a**	–	0
b	7	13	**10b**	–	0
c	8	14	**10c**	99:1	45
d	9	15	**10d**	82:18	43
e	10	16	**10e**	95:5	91
f	11	17	**10f**	98:2	35
g	12	18	**10g**	85:15	90

[a] Reaction conditions: BF_3·OEt_2 (5 equiv), syringe pump, $c = 1.0$ mM in 1,2-dichloroethane at RT. [b] Determined by GC and NMR spectroscopy. [c] Isolated product yields after flash chromatography.

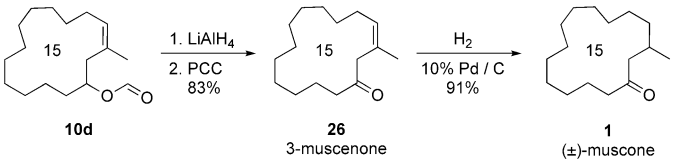
Yields for the 16- and 18-membered rings both reached 90%, whereas those for 14-, 15- and 17-membered rings were in the 40% region.

Next, it was envisaged to further constrain the conformational freedom of the smallest attainable ring by introduction of another *Z*-configured double bond, thereby constructing a double-unsaturated structural isomer **25** of (5*Z*)-Cosmone (**4**). The synthesis of **25** by reaction of the Wittig salt **19** of 5-bromopentanol with 6-chlorohexanal, TBDPS protection, Finkelstein *trans* halogenation, alkylation of the Weinreb amide **15**, hydride reduction/PCC oxidation, BF_3-mediated cyclization, and concluding hydride reduction/PCC oxidation is summarized in Scheme 4. Due to the additional ring strain of **24**, the yield of the macrocyclization was 33% (slightly lower than that for the cyclization of **10c**); however, both double bonds were exclusively *Z*-configured.

As in the synthesis of **25**, the cycloalk-3-en-1-yl formates **10a–g** are transformed to the corresponding unsaturated macrocyclic ketones by simple hydride reduction/PCC oxidation. This is exemplified in Scheme 5 for the synthesis of 3-muscenone (**26**) from **10d**. Catalytic hydrogenation of **26** completes a straightforward synthesis of (±)-muscone (**1**).[11]



Scheme 4. Synthesis of the double-unsaturated structural isomer **25** of (5*Z*)-Cosmone (**4**).



Scheme 5. Synthesis of (±)-muscone (**1**) from **10d**.

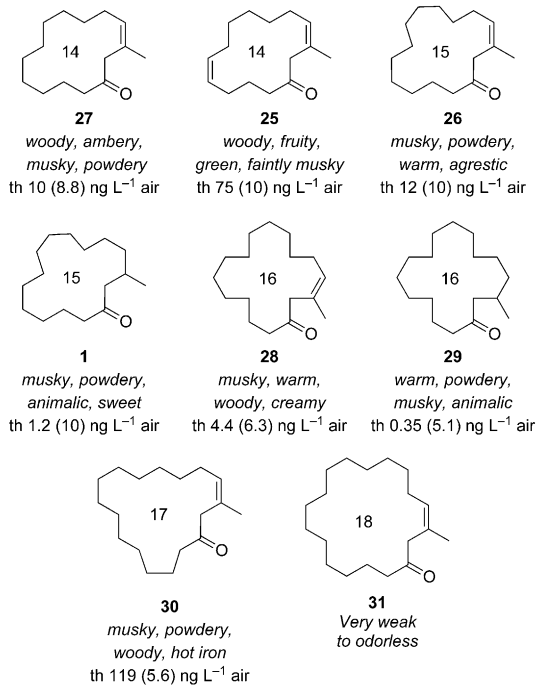


Figure 2. Overview of the olfactory properties of the compounds with measured odor thresholds. The thresholds calculated according to the olfactophore model in Figure 3 are given in brackets.

The olfactory data of the β,γ-unsaturated macrocyclic ketones synthesized are summarized in Figure 2, together with their detection thresholds (th) as determined by GC-olfactometry. In contrast to a (5*Z*)-double bond of **2**,[11f] the β,γ-double bond generally decreases the musk character and intensity of these macrocyclic ketones. Within their respective series, the 16-membered rings **28** and **29** turned out to be the most potent and the most musky, which also indicates that a β,γ-double bond does rather populate inactive conformers. Usually only observed for unsubstituted 13-membered rings,[15] woody facets prevail in the 3-methyl-substituted 14-membered rings **25** and **27**, whereas the molecular dimensions of the musk receptors are reached with the faint-to-odorless 18-membered analogues. The (10*Z*)-double bond in **25** also has a negative influence on the odor threshold, and makes the musk facets in the odor of **27** almost disappear, indicating a negative but critical influence.

This critical influence makes the macrocyclic odorants **25**–**30** ideal candidates for the generation of an olfactophore model to test whether or not macrocyclic and linear alicyclic musks could bind to the same set of receptors. The respective musk olfactophore model, derived with the Discovery Studio 3.0 software package,[16] is depicted in Figure 3, and albeit with a correlation of 0.54 it is not entirely convincing, it still suggests that both families indeed should address the same receptor sets. In Figure 3a, one can recognize how **25** (gold color) sticks out from the binding pocket that is nicely filled up by macrolide **5**. The estimated 10 ng L^{-1} threshold for **25** still is too optimistic, but goes in the right direction. On the other hand, Figure 3b convincingly illustrates how the linear musk **6** mimics the shape of the Nirvanolide stereoisomer **3** on the olfactophore model, both constituting potent musks. However, **6** is only about five times more intense than **7** in the model, far less than in reality. Yet, while in reality the hydrophobes are polarizable, in the olfactophore model the double bond shift can only be accounted for by the respective difference in conformational space. A further comparison of the experimental data with the calculated values, as well as the geometric parameters for the olfactophore model, can be found in the Supporting Information.

Finally, it remains to decide on the mechanistic path for the BF_3-catalyzed macrocyclization of **8** (Scheme 1). Therefore, the reaction was investigated by density functional theory at the B3LYP/6-31G(d) level using the Gaussian 03 program package.[17] The transition states (TS) were optimized using the Berny algorithm,[18] whereas harmonic frequency calculations were carried out to verify the nature of the stationary points. Altogether, 16 TS were obtained and energetically compared in Figure 4a, differentiated into those yielding (*Z*)-**10c** [TS-(*Z*)] and (*E*)-**10c** [TS-(*E*)], respectively, with the oxy-oxonia-Cope TS depicted in red, and the Prins-type TS in blue. The lowest TS for the oxy-oxonia-Cope TS-**9**-(*Z*)-1 (Figure 4b, 44.80 kJ mol^{-1}) and the Prins-type case TS-**11**-(*Z*)-1 (Figure 4c, 87.49 kJ mol^{-1}) are shown as well, both leading to the *Z*-configured product (*Z*)-**10c**.

In accordance with the experimental results (*Z*/*E*, 99:1), the three lowest energy TS all afford the *Z*-configured product (*Z*)-**10c**. The lowest transition state affording the *E*-con-

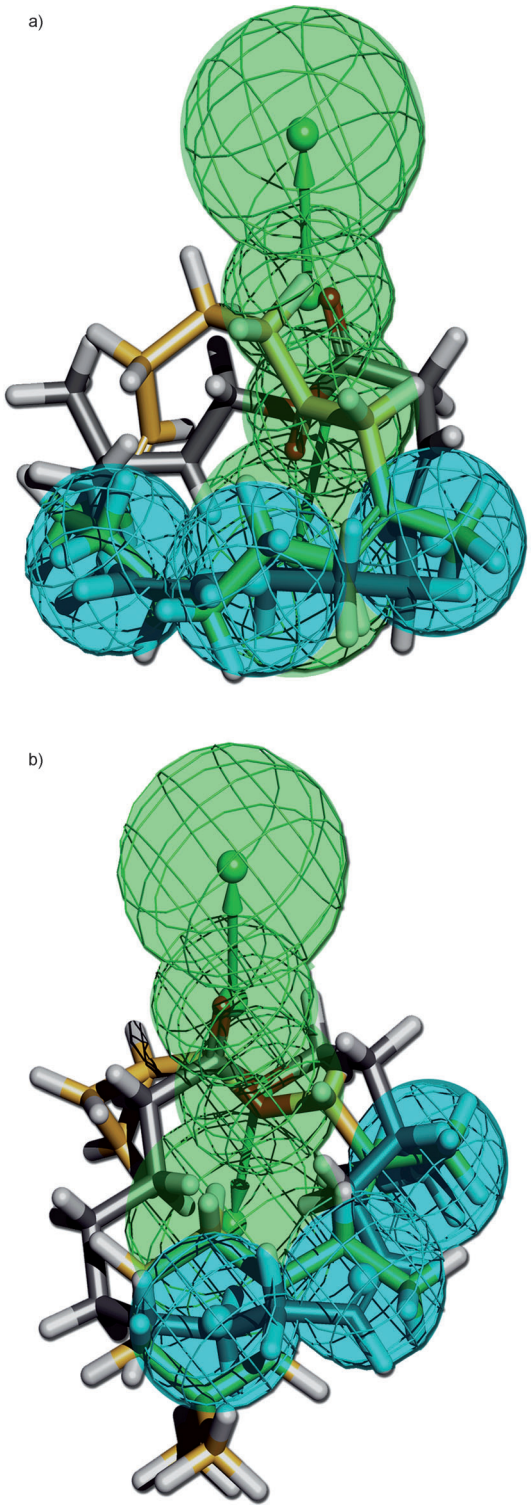


Figure 3. Musk olfactophore model derived with the Discovery Studio 3.0 software package,[16] featuring three aliphatic hydrophobes (cyan) and two hydrogen-bond acceptors (green), with a) macrocycles **5** (steel, calcd detection threshold (th) 0.21 ng L^{-1}) and **25** (gold), and b) linear musk **6** (gold, calcd th 0.52 ng L^{-1}) and macrolide **3** (steel, calcd th 0.06 ng L^{-1}).

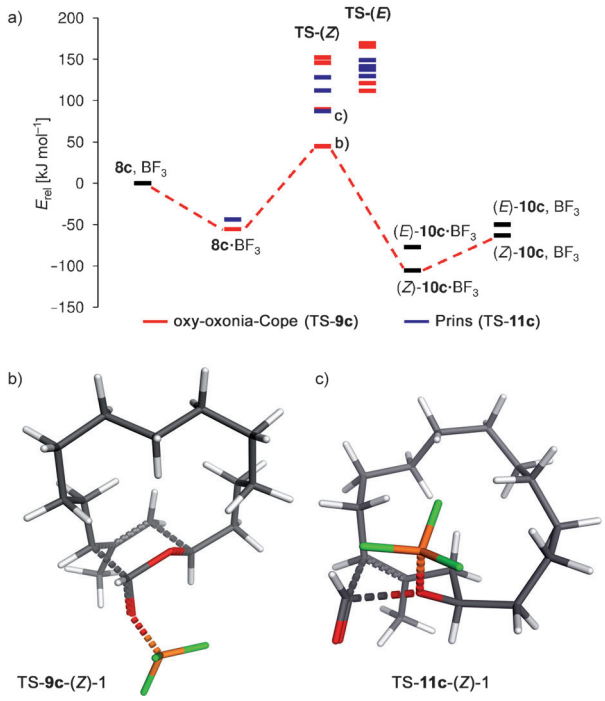


Figure 4. a) Gas-phase relative energies (using the sum of electronic and zero-point energies in kJ mol^{-1}) for the oxy-oxonia-Cope (red) and the Prins (blue) macrocyclization of **8c** at the B3LYP/6-31G(d) level. b) Lowest oxy-oxonia-Cope TS [TS-**9**-(*Z*)-1], and c) lowest Prins-type TS [TS-**11**-(*Z*)-1] for the macrocyclization of **8c** to **10c**.

figured product (*E*)-**10c** is 67.29 kJ mol^{-1} higher in energy than the lowest transition state TS-**9**-(*Z*)-1, with both proceeding according to an oxy-oxonia-Cope mechanism. Both, the lowest oxy-oxonia-Cope TS-**9**-(*Z*)-1 (Figure 4b) and the lowest Prins TS-**11**-(*Z*)-1 (Figure 4c) are in a chair-type conformation, with the chair necessarily occupying *gauche*-corner positions. In TS-**9**-(*Z*)-1, the macrocyclic ring adapts a rectangular [3434] diamond-lattice conformation[19] of all-*trans* edges, and as one would expect to be energetically most favorable, the chair is situated in the *gauche*-corner of the longest all-*trans* edge. Such a favorable position is not possible for the Prins case, in which the 14-membered macrocyclic ring is forced into a [23333] conformation.[19] This additionally favors the oxy-oxonia-Cope path over the Prins path, especially for even-membered ring systems. We cannot completely rule out the existence of further transition states with slightly different conformations of the macrocyclic ring system, but this should not change the overall picture. These calculations are, however, only valid in the gas phase, and solvent effects can exert some influence. But even then, one would expect complete *Z*-selectivity at room temperature, as according to simple Boltzmann statistics N[TS-**9c**-(*E*)-1]/N[TS-**9c**-(*Z*)-1)] = 1.56 × 10^{-12}, or 1 in 2/3 trillion transition states would lead to (*E*)-**10c** only, whereas 1 in 30 million reactions would run according to the Prins-type mechanism.

It therefore seems likely that the observed *E* isomers of **10c–g** resulted from a subsequent isomerization reaction. To verify this hypothesis, **10d** (*Z*/*E* = 82:18) was reduced, the

resulting *Z*- and *E*-isomeric cyclopent-3-en-1-ols separated by flash chromatography, and transformed into isomerically pure formates (*Z*)-**10d** and (*E*)-**10d** that were then treated separately with $BF_3{\cdot}OEt_2$ in dichloroethane under exactly the same conditions as in the cyclization reaction. After 24 h of stirring, (*Z*)-**10d** partially isomerized to (*E*)-**10d**, whereas (*E*)-**10d** did not isomerize to (*Z*)-**10d**. Thus, it is indeed most likely that the (*E*)-**10c–g** isomers result from a subsequent isomerization reaction. The new macrocyclization **8**→(*Z*)-**10** accordingly proceeds almost exclusively on an oxy-oxonia-Cope path.

We have reported on a new efficient macrocyclization of 2-isopropenyl dialdehydes **8** to (3*Z*)-configured cycloalk-3-en-1-yl formats (*Z*)-**10** in the presence of Lewis acids. These findings proved useful in the synthesis of several unsaturated and saturated macrocyclic ketones, including (±)-muscone (**1**), and allowed additional insight into the structure–odor correlation of musks, resulting in an olfactophore model, which makes it likely that macrocyclic and linear alicyclic musks address the same set of olfactory receptors.

Experimental Section

General procedure: *Cyclization of 2-(prop-1-en-2-yl)heptadecanedial (**8g**) to (3Z)-3-methylcyclooctadec-3-enyl formate (**10g**)*: At room temperature, under N_2 atmosphere, and with the aid of a syringe pump, a solution of dialdehyde **8g** (308 mg, 1.00 mmol) in 1,2-dichloroethane (200 mL) was added at a rate of 2 mL h^{-1} to a vigorously stirred solution of $BF_3{\cdot}OEt_2$ (710 mg, 5.0 mmol) in 1,2-dichloroethane (800 mL). After 100 h, the addition was complete, and the reaction mixture was stirred at room temperature for another 1 h, prior to quenching by addition of saturated aq. $NaHCO_3$ (10 mL). The organic layer was separated and dried with $MgSO_4$, the solvent evaporated under reduced pressure, and the crude product purified by flash chromatography (hexane/MTBE, 25:1, R_f = 0.30) to furnish **10g** (277 mg, 90 %).

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Keywords: fragrances · ketones · macrocycles · Prins reaction · rearrangement · structure–odor relationship

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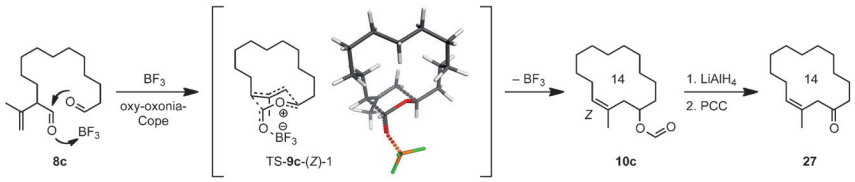

Musk made to odor: A new oxy-oxonia-Cope macrocyclization to (3*Z*)-configured cycloalk-3-en-1-yl formates is reported, which is useful in the synthesis of unsaturated and saturated macrocyclic ketones (see scheme). The synthesized structures provide new insight into the structure–odor correlation of musks, making it likely for macrocyclic and linear alicyclic musks to address the same olfactory receptors.

Macrocycles

No More Musk Suicides!
A poem by Shangyin Li (813–858) from the late Tang Dynasty reported the tragic case of a musk deer that committed suicide rather than let his hunters have his musk pods. On page ■■ ff., P. Kraft and co-workers report a versatile macrocyclization, which utilizes an unprecedented oxy-oxonia-Cope reaction. This novel macrocyclization can also be employed for a new synthesis of muscone. The book featuring the ancient drawing is held by a Tibetan Alchi Lama Monk.