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Three-Carbon Ring Expansion by Cyclopropane Insertion: Macrocyclic Musks from Readily Available C-12 Starting Materials

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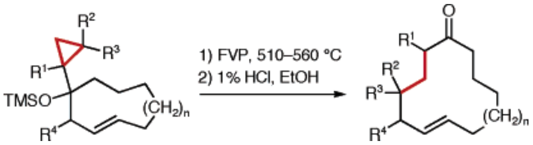
ABSTRACT



A thermal three-carbon ring expansion based on side chain ring insertion of a cyclopropane moiety is described. Flash vacuum pyrolysis (FVP) of 1-cyclopropyl-cycloalk-3-enol derivatives leads to the three-carbon ring expanded enones with clean retention of double bond geometry. Substrates bearing methyl groups on the cyclopropane ring undergo regioselective bond cleavage, allowing for the systematic preparation of selectively substituted macrocyclic musks from low-priced C-12 starting compounds.

Macrocyclic musks are of central importance in fragrance chemistry, particularly for their excellent odor properties and biodegradability.[1] In recent years, intensive efforts have been made to develop efficient methods that are capable of producing substituted 15-carbon macrocyclic ketones having an unsaturation of defined double bond geometry.[2] However, well-established macrocyclization methodologies suffer from inherent high-dilution conditions and often produce *E*/*Z* mixtures, whereas fragmentation procedures are limited in the variability of appropriately substituted bicyclic precursors.[3] Herein, we report a fundamentally new approach based on side chain ring insertion of a cyclopropane moiety that allows for the systematic preparation of both specifically substituted and specifically unsaturated C-15 macrocycles from inexpensive C-12 starting materials in a single synthetic operation. In addition, we demonstrate that this concept is also applicable to other ring sizes.

Recently we reported a diradical-mediated two-carbon ring expansion of 1-vinylcycloalkanols by means of flash vacuum pyrolysis (FVP).[4,5] The instigating question of the current study was directed at whether the vinyl group might be replaced with a cyclopropane ring to yield the corresponding three-carbon ring-expanded cycloalkanones **2** by means of a 1,4-C shift.[6] The design of this proposed reaction **1** → **2** was predicated on the well-known fact that cyclopropylcarbinyl radicals **a** immediately rearrange into homoallyl radicals **b**, once they have been generated (Scheme 1).[7,8]

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(1) For leading references on musk odorants, see: (a) Fráter, G.; Bajgrowicz, J. A.; Kraft, P. *Tetrahedron* **1998**, *54*, 7633. (b) Williams, A. S. *Synthesis* **1999**, 1707. (c) Fráter, G.; Bajgrowicz, J. A.; Denis, C.; Kraft, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 2980. (d) Fráter, G.; Lamparsky, D. In *Perfumes: Art, Science and Technology*; Müller, P. M., Lamparsky, D., Eds.; Elsevier: London, New York, 1991; Chapter 20, pp 533−555. (e) Ohloff, G. *Riechstoffe und Geruchssinn. Die Molekulare Welt der Düfte*; Springer: Berlin, 1990; Chapter 9, pp 195−219. (f) Mookherjee, B. D.; Wilson, R. A. In *Fragrance Chemistry: The Science of the Sense of Smell*; Theimer, E. T., Ed.; Academic Press: New York, 1982; Chapter 12, pp 433−494.

(2) Fehr, C.; Galindo, J.; Etter, O.; Thommen, W. *Angew. Chem., Int. Ed.* **2002**, *41*, 4523.

(3) Recent examples: (a) Kamat, V. P.; Hagiwara, H.; Katsumi, T.; Hoshi, T.; Suzuki, T.; Ando, M. *Tetrahedron* **2000**, *56*, 4397. (b) Louie, J.; Bielawski, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 11312.

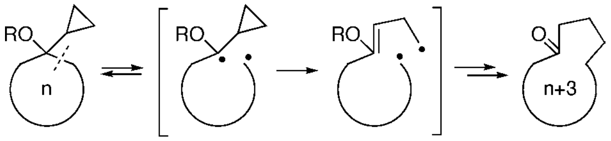
(4) (a) Nagel, M.; Fráter, G.; Hansen, H.-J. *Synlett* **2002**, 275. (b) Nagel, M.; Fráter, G.; Hansen, H.-J. *Synlett* **2002**, 280.

(5) For reviews on FVP, see: (a) McNab, H. *Contemp. Org. Synth.* **1996**, *3*, 373. (b) Wiersum, U. E.; Jenneskens, L. W. In *Gas-Phase Reactions in Organic Synthesis*; Vallé, Y., Ed.; Gordon and Breach: Amsterdam, 1997; pp 143−194. (c) McNab, H. *Aldrichimica Acta* **2004**, *37*, 19.

(6) Rüedi, G.; Hansen, H.-J. *Tetrahedron Lett.* **2004**, *45*, 5143.

10.1021/ol0487027 CCC: $27.50

Scheme 1

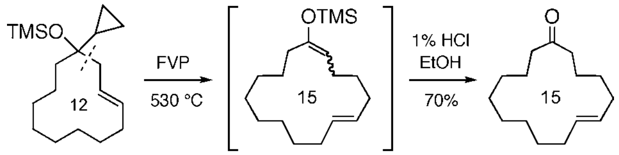


1 a b 2

Our initial attempts to effect the diradical-mediated three-carbon ring expansion with a series of substrates **1** of different ring size (*n* = 10−15; R = TMS) proved unsatisfactory. Only traces of the desired ring-expanded products **2** could be detected when samples of **1** were subjected to FVP (550−700 °C) followed by hydrolysis of the intermediate silylenol ethers. Apparently, the overall radical stabilizing ability of a cyclopropyl and a silyloxy group at a common carbon atom is too low to effect clean homolytic breakage.[9]

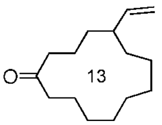
To reduce the activation barrier, a radical stabilizing functionality was introduced adjacent to the bond to be broken. Thus, an endocyclic allylic double bond gave rise to a clearly defined weakest single bond, facilitating the intended breakage of the C1−C2 bond.[10] As a result, FVP of **3**[11] at 530 °C proceeded smoothly to give the ring-expanded silylenol ether **4** as a 1:1 mixture of diastereoisomers (Scheme 2).[12] For ease of characterization and handling **4** was hydrolyzed by brief treatment of the crude product with 1% HCl in EtOH to give enone **5** in 70% isolated yield. It is noteworthy to state that the endocyclic double bond suffered no *E*/*Z* isomerization by passage from **3** to **5**.

Scheme 2



3 4 5

Interestingly, we observed a minor amount of another isomer (**6**, 10%), which was ascertained to be 5-vinylcyclotridecanone.[13] This byproduct of mechanistic significance presumably arises through a competing homo silyloxy-Cope rearrangement (3,4-C shift).[14]



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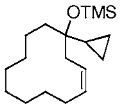
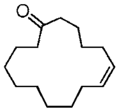
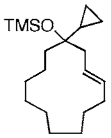
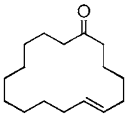
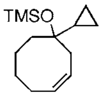
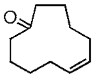
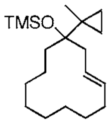
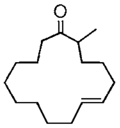
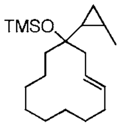
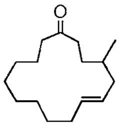
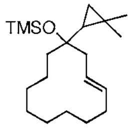
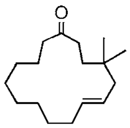
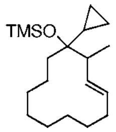
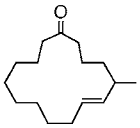
To study the generality of this new three-carbon ring expansion, we examined the influence of the double bond geometry and the ring size (Table 1, entries 1−3). FVP of **7a** possessing a (*Z*)-double bond produced exclusively (*Z*)-6-cyclopentadecenone (**8a**). In agreement with **3** the homologous compound **7b** underwent clean homolysis to give

Table 1. Three-Carbon Ring Expansion with Various Substrates **7a−g**

entry		substrate **7**	product **8**	*T* (°C)	yield (%)[a,b]
1	**a**			530	74 (69)
2	**b**			530	77 (71)
3	**c**			560	30[c]
4	**d**			520	78 (72)
5	**e**			520	62 (41)
6	**f**			510	56 (50)
7	**g**			520	68 (61)

[a] Overall yields for ring expansion and hydrolysis step. [b] GC yield (isolated yield). [c] Not separated from byproducts.

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(7) For a review, see: Newcomb, M. *Tetrahedron* **1993**, *49*, 1151.

(8) (a) Effio, A.; Griller, D.; Ingold, K. U.; Beckwith, A. L. J.; Serelis, A. K. *J. Am. Chem. Soc.* **1980**, *102*, 1734. (b) Newcomb, M.; Glenn, A. G. *J. Am. Chem. Soc.* **1989**, *111*, 275. (c) Martinez, F. N.; Schlegel, H. B.; Newcomb, M. *J. Org. Chem.* **1996**, *61*, 8547. (d) Martinez, F. N.; Schlegel, H. B.; Newcomb, M. *J. Org. Chem.* **1998**, *63*, 3618. (e) Halgren, T. A.; Roberts, J. D.; Horner, J. H.; Martinez, F. N.; Tronche, C.; Newcomb, M. *J. Am. Chem. Soc.* **2000**, *122*, 2988. (f) Choi, S.-Y.; Horner, J. H.; Newcomb, M. *J. Org. Chem.* **2000**, *65*, 4447. (g) Horner, J. H.; Newcomb, M. *J. Am. Chem. Soc.* **2001**, *123*, 4364. (h) Takekawa, Y.; Shishido, K. *J. Org. Chem.* **2001**, *66*, 8490. (i) Cooksy, A. L.; King, H. F.; Richardson, W. H. *J. Org. Chem.* **2003**, *68*, 9441.

(9) (a) McMillen, D. F.; Golden, D. M. *Annu. Rev. Phys. Chem.* **1982**, *33*, 493. (b) Smith, D. M.; Nicolaides, A.; Golding, B. T.; Radom, L. *J. Am. Chem. Soc.* **1998**, *120*, 10223.

(10) Brocks, J. J.; Beckhaus, H.-D.; Beckwith, A. L. J.; Rüchardt, C. *J. Org. Chem.* **1998**, *63*, 1935.

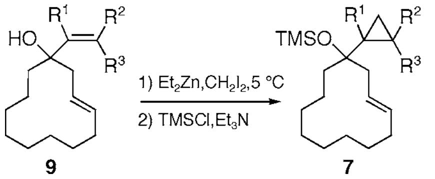
(11) Compound **3** was prepared on a multigram scale by dehydrochlorination of 2-chlorocyclododecanone to give the thermodynamically more stable 3-enone, followed by Grignard reaction and silylation (70% over three steps).

(12) Only tar formation was observed when **3** was heated under static conditions in a sealed glass tube at 200−400 °C.

6-cyclohexadecenone (**8b**) in comparable yield. As expected from general ring strain effects in medium ring systems the eight-membered substrate **7c** was reluctant to react in this manner. However, at more elevated temperatures (560 °C) the 11-membered product **8c** was obtained in 30% yield.

The scope was further explored with methyl-substituted substrates **7d**−**g**, as they would provide enones **8d**−**g**, representing new compounds of possible value in fragrance chemistry. The key step for the preparation of the precursors **7d**−**f** includes the regioselective cyclopropanation of the exocyclic allylic double bond in dienols **9d**−**f** (Scheme 3).

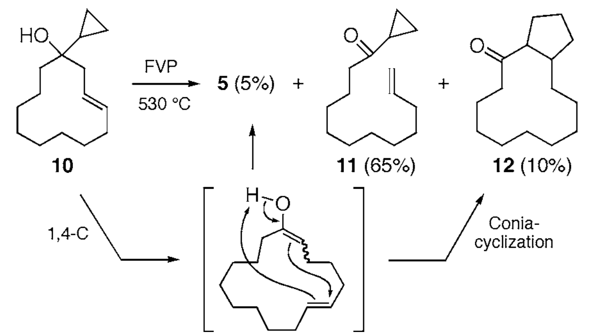
Scheme 3



	R^1	R^2	R^3	
d:	Me	H	H	(91%)
e:	H	H	Me	(81%)
f:	H	Me	Me	(78%)

As summarized in Table 1 (entries 4−7) the desired muscenones **8d**−**g** were obtained in good yields. The lower yield observed in the case of **7e** with a *cis*-substituted cyclopropane moiety having energetically unequal bonds may be ascribed to competing cleavage and H-transfer reactions.[15] As expected, however, the more highly substituted bond turned out to be the main site of breakage to give 4-methyl enone **8e**.[16] The same result was obtained when the *trans*-analogue of **7e** was submitted to FVP.[17] Product **8f** possessing a *gem*-dimethyl group was obtained in the same manner from the sterically crowded precursor **7f**. Finally, we investigated the effect of a methyl group in the 2-position. Subjecting substrate **7g** to FVP at 520 °C afforded **8g** bearing the substituent at C5.[18] As observed in the case of **3**, neither of the substrates **7a**−**g** underwent *E*/*Z* isomerization during the short thermal impact.

Scheme 4



According to Scheme 4 the TMS-protecting group proved to be crucial. As exemplified with cyclopropyl alcohol **10**, prolysis under comparable conditions produced three isomeric compounds. The major component turned out to be ring-opened cyclopropyl ketone **11** (65%), the product of a retro-ene fragmentation, instead of the ring expansion product **5** (5%). In addition, we found a 5,12 fused bicyclic ketone **12** (10%).[19] A reasonable explanation for the formation of the latter involves a six-electron oxa-ene process of the Conia type within the initially formed enol form of **5**.[20]

In summary, we have developed a new type of three-carbon ring expansion offering a strategically novel and practical route to an otherwise difficult-to-achieve but common ring system. Both the low price and the easy accessibility of C-12 precursors allow for the synthesis of specifically substituted C-15 macrocyclic musks. Enones **8d**−**g** are new and reveal the typical musk odor. It is of further synthetic significance that the FVP reactions can be run as a continuous, solvent-free process, rendering this procedure very promising for large-scale operations. Further studies are in progress.

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Supporting Information Available: Experimental conditions and complete spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[13] For related silyloxy-Cope reactions, see: (a) Thies, R. W.; Billigmeier, J. E. *J. Am. Chem. Soc.* **1974**, *96*, 200. (b) Thies, R. W.; Bolesta, R. E. *J. Org. Chem.* **1976**, *41*, 1233. (c) Thies, R. W.; Darwula, K. P. *J. Chem. Soc., Chem. Commun.* **1985**, *17*, 1188. (d) Thies, R. W.; Darwula, K. P. *J. Org. Chem.* **1987**, *52*, 3798.

[14] Although many silyloxy-Cope reactions can be found in the literature, the involvement of a cyclopropyl moiety is unprecedented so far. For a recent review on silyloxy-Cope rearrangements, see: Schneider, C. *Synlett* **2002**, 1079.

[15] Recent examples: (a) Rüedi, G.; Nagel, M.; Hansen, H.-J. *Org. Lett.* **2003**, *5*, 2691. (b) Rüedi, G.; Nagel, M.; Hansen, H.-J. *Org. Lett.* **2003**, *5*, 4211. (c) Rüedi, G.; Nagel, M.; Hansen, H.-J. *Synlett* **2003**, 1210.

[16] (a) Takekawa, Y.; Shishido, K. *Tetrahedron Lett.* **1999**, *40*, 6817. (b) Takekawa, Y.; Shishido, K. *J. Org. Chem.* **2001**, *66*, 8490.

[17] At temperatures above 450 °C, both pure substrates interconverted to give a 1:1 mixture of *cis*/*trans* isomers.

[18] The relative configuration of compound **7g** was determined to be (1*R**,2*R**).

[19] The formation of the *cis*- as well as the *trans*-isomer of **12** would generally be possible. Although only a single isomer had been formed, its relative configuration could not be assigned by NOE measurements because of overlapping ^{1}H signals.

[20] (a) Conia, J. M.; Le Perchec, P. *Synthesis* **1975**, 1. (b) Conia, J. M.; Lange, G. L. *J. Org. Chem.* **1978**, *43*, 564.