

Diradical-Promoted ($n + 2 - 1$) Ring Expansion: An Efficient Reaction for the Synthesis of Macrocyclic Ketones

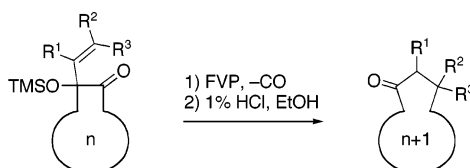
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ABSTRACT



A diradical-promoted ($n + 2 - 1$) ring expansion reaction based on vinyl side chain insertion (+2C) and decarbonylation (−1C) has been developed. Flash vacuum pyrolysis (FVP) of medium- and large-ring 2-trimethylsilyloxy-2-vinyl-cycloalkanones at 500–600 °C affords the one-carbon ring-expanded cycloalkanones in good yields. Methyl groups on the vinyl moiety are transformed regiospecifically as corresponding α - and β -substituents, respectively. 2-Ethynyl precursor analogues react in a manner similar to give α,β -unsaturated cyclic ketones.

The design and development of synthetic methods providing access to functionalized macrocyclic target molecules by means of free-radical-mediated ring expansion represents a major challenge in contemporary organic synthesis.¹ Among these processes the class of reactions running through *diradical* intermediates is very sparsely populated. Apart from the well-established vinylcyclopropane-to-cyclopentene rearrangement² only very few examples involving conformationally or otherwise constrained substrates have been reported so far.³ Considering the significance of functionalized medium- and large-ring carbocyclic systems, we have initiated a program directed at developing diradical-mediated ring expansion reactions by means of flash vacuum pyrolysis

(FVP). These investigations have thus far produced fundamentally new two-⁴ and three-carbon ring expansions⁵ suitable for the synthesis of such compounds. In continuation of these studies, we describe herein a remarkable one-carbon ring expansion and its application to the synthesis of muscone and related macrocyclic ketones.

Recently, we have reported that 1-vinylcycloalkanols (**1a**) undergo clean homolysis of the weakest single bond when submitted to FVP at 650 °C (Scheme 1).^{4a,b} Recombination within the generated diradical intermediate **2a** provided the two-carbon ring-expanded ketones **3a** in good-to-excellent yields.⁶ On the basis of this finding, we envisioned that 2-hydroxy-2-vinylcycloalkanones (**1b**) having an adjacent carbonyl group would react in a similar manner to give an open-chain α -hydroxyallyl ω -acyl intermediate **2b**, which under the high thermal impact would immediately lose carbon monoxide. Driven by ring strain release gained by

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(1) For reviews, see: (a) Dowd, P.; Zhang, W. *Chem. Rev.* **1993**, 93, 2091. (b) Yet, L. *Tetrahedron* **1999**, 55, 9649. (c) McCarroll, A. J.; Walton, J. C. *Angew. Chem., Int. Ed.* **2001**, 40, 2224.

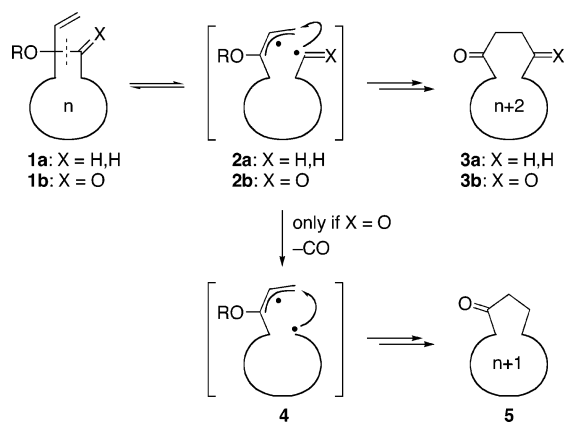
(2) For a recent review, see: Baldwin, J. E. *Chem. Rev.* **2003**, 103, 1197. (3) (a) Reich, H. J.; Cram, D. J. *J. Am. Chem. Soc.* **1967**, 89, 3078. (b) Reich, H. J.; Cram, D. J. *J. Am. Chem. Soc.* **1969**, 91, 3517. (c) Muthuramu, K.; Sundari, B.; Ramamurthy, V. *J. Org. Chem.* **1983**, 48, 4482. (d) Sarobe, M.; Kwint, H. C.; Fleer, T.; Hevenith, R. W. A.; Jenneskens, L. W.; Vlietstra, E. J.; Van Lenthe, J. H.; Wesseling, J. *Eur. J. Org. Chem.* **1999**, 5, 1191. (e) Paquette, L. A.; Zhao, Z.; Gallou, F.; Liu, J. *J. Am. Chem. Soc.* **2000**, 122, 1540. (f) von Doering, W.; Cheng, Y.; Lee, K.; Lin, Z. *J. Am. Chem. Soc.* **2002**, 124, 11642.

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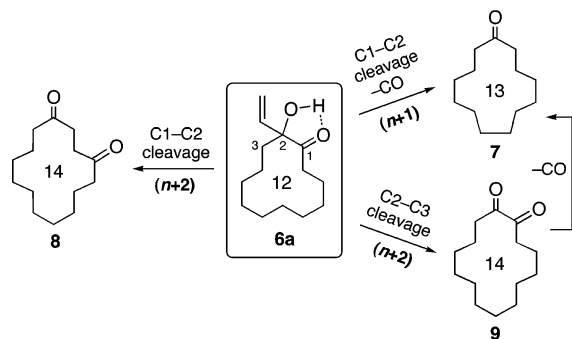
(6) In a recent paper, we provided evidence that vinyl insertion occurs via open-chain diradical intermediate states, rather than via formally disallowed 1,3-sigmatropic shifts; see: Rüedi, G.; Hansen, H.-J. *Helv. Chim. Acta* **2004**, 87, 1628.

Scheme 1



passing to increasingly large ring systems the resulting α -hydroxyallyl ω -alkyl diradical **4** would ring expand to an enol ether precursor, from which the cyclic ketone **5** would be derived by an overall $(n + 2 - 1)$ ring expansion.

We started our investigations with 2-hydroxy-2-vinylcyclododecanone (**6a**), which was readily prepared by vinylmagnesium bromide addition to cyclododecane-1,2-dione.⁷ As illustrated in Scheme 2, FVP of **6a** at 500 °C and 2–4

Scheme 2. FVP of 2-Hydroxy-2-vinylcyclododecanone **6a**

$\times 10^{-2}$ mbar produced three products, **7–9**, in 98% combined yield (GC). Apart from the expected one-carbon ring-expanded cyclotridecanone **7** (26%), the other components turned out to be 14-membered 1,4-dione **8** (28%) and 1,2-dione **9** (44%), respectively. Apparently, the formation of **8** involves the insertion of the vinyl moiety in diradical intermediate **2b** before CO can leave the molecule. On the other hand, the additional five-membered ring, formed by the intramolecular hydrogen bridge in 2-hydroxy ketone **6a**,⁸ makes the C1–C2 bond breakage a bit more difficult, thus allowing for partial C2–C3 cleavage to give 1,2-dione **9**.

(7) In connection with this study, we have developed a practical and user-friendly method for the selenium-free one-step preparation of 1,2-diketones by treating the corresponding cycloalkanones with sodium nitrite and HCl in THF at low temperatures.

(8) The ¹H NMR showed a low field shifted singlet at 4.19 ppm accounting for a OH group being part of a hydrogen bridge.

In an effort to determine whether the product ratio could be shifted to the desired one-carbon ring expansion product **7**, the effect of the reaction temperature and the role of a protecting group were investigated (Table 1). A temperature

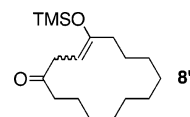
Table 1. Temperature and Protecting Group Effects

entry	R	T (°C)	7 (% yield)	8 (% yield)	9 (% yield)
1	H	500	26	28	44
2	H	560	38	26	27
3	H	600	46	22	5
4	TMS	520	48 ^a	48 ^a	0
5	TMS	540	59 ^a	36 ^a	0
6	TMS	560	68 ^a	25 ^a	0
7	TMS	580	75 ^a	14 ^a	0
8	TMS	600	73 ^a	6 ^a	0
9	TMS	480	31 ^a	51 ^a	0

^a After treatment of the crude silylenol ether precursor with 1% HCl in EtOH.

increase from 500 to 560 °C was found to be only marginally beneficial. The unwanted 1,4-diketone **8** proved to be rather unaffected while the yield of **9** decreased in favor of **7** (entry 2). As depicted in Scheme 2, the higher yield of **7** may be ascribed to decarbonylation of initially formed 1,2-dione **9** under increasingly high reactor temperatures (≥ 560 °C).⁹ This effect was found to be even more pronounced at 600 °C (entry 3).¹⁰

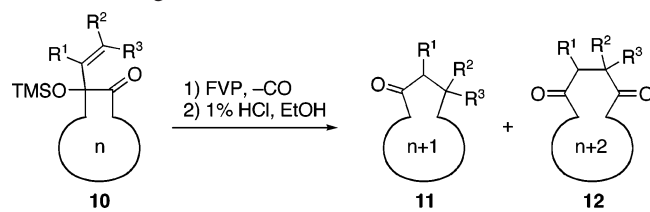
To suppress competing C2–C3 bond breakage the tertiary alcohol functionality was protected with a TMS group. Hence, subjecting silyl ether **6b** to FVP at 520 °C provided upon hydrolysis (1% HCl in EtOH) of the resulting silylenol ether intermediates a 1:1 mixture of **7** and **8** in 96% combined yield with no traces of **9** (entry 4).¹¹ Gradually increasing the temperature by 20 °C steps eventually led to a value of 580 °C at which the conversion to cyclotridecanone (**2**) was found to be optimal (entry 7). On the other hand 1,4-diketone **8** could be obtained in 51% yield when the reaction was conducted at 480 °C (entry 9).¹² This finding suggested that the formation of **7** might also involve decarbonylation of the initially formed silylenol ether precursor of **8**. Indeed, FVP of an independently synthesized sample of (*E/Z*)-4-trimethylsilyloxycyclotetradec-3-enone (**8'**) at 600 °C afforded upon hydrolysis cyclotridecanone (**7**) in 60% yield, whereas FVP at 480 °C resulted in essentially no reaction.



With optimized conditions in hand, the next issue to be addressed was the effect of the ring size on the $(n + 2 - 1)$

ring expansion reaction. Toward this end, a series of cyclic 2-trimethylsilyloxy-2-vinyl precursors **10a–c** was submitted to FVP (Table 2, entries 1–3). The reactions proceeded

Table 2. Ring Size and Substituent Effects



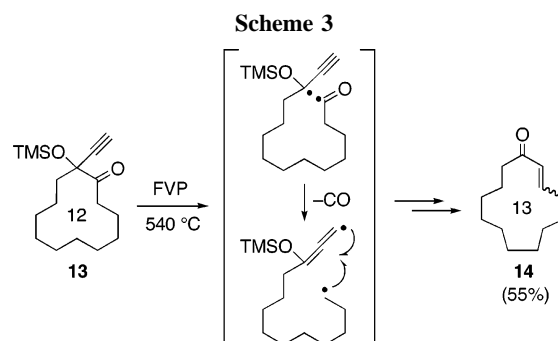
entry	<i>n</i>	R ¹	R ²	R ³	<i>T</i> (°C) ^a	11 (% yield)	12 (% yield)
1	10	a	H	H	590	63	12
2	11	b	H	H	580	71	17
3	15	c	H	H	560	70	18
4	12	d	H	CH ₃ /H	560	71	15
5	14	e	H	CH ₃ /H	570	73	19
6	12	f	CH ₃	H	580	60	12
7	12	g	CH ₃	CH ₃ /H	580	81 ^c	11 ^c
8	12	h	H	CH ₃	580	70	14

^a Optimized temperature. ^b Substrate used as a 1:1 mixture of (*E/Z*)-isomers. ^c Obtained as a 1:1 mixture of diastereoisomers.

equally well to give after hydrolysis of the crude product mixtures the one-carbon ring-expanded ketones **11a–c** in good yields (63–71%) along with their respective 1,4-diketone counterparts **12a–c** (12–18%). Given the good performance and the ready availability of the 12-membered parent system **6b**, the influence of substituents on the vinyl side chain was investigated with selected substrates **10d–h** bearing variable 1-alkenyl groups in the 2-position.¹³ Replacing the vinyl moiety with a 1-propenyl group had little effect on the efficiency of the reaction (entries 4 and 5). It is noteworthy to state that FVP of the 14-membered substrate **10e** followed by hydrolysis of the silylenol ether intermediate directly afforded the valuable musk odorant (±)-muscone (**11e**) in 73% yield.¹⁴ Given the ready accessibility of **10e**, this sequence represents a short and very efficient synthesis of this natural product from low-priced C-12 starting material.¹⁵ On the other hand, exchanging the vinyl func-

tionality for an isopropenyl group resulted in slightly lower yield, providing a 5:1 mixture of 2-methylcyclotridecanone (**11f**) and 2-methylcyclotetradecane-1,4-dione (**12f**) (entry 6). Best results were obtained in the case of **10g**, which upon FVP at 580 °C and subsequent hydrolysis produced 2,3-dimethylcyclotridecanone **11g** in 81% yield (entry 7). In remarkable contrast to previous studies, the *gem*-dimethyl group on the recombination center in substrate **10h** did not adversely affect the course of the reaction in terms of producing open chain disproportionation products via intramolecular hydrogen abstraction.¹⁶ Instead, the desired 3,3-dimethyl ketone **11h** was formed in 70% yield accompanied with its 1,4-dione counterpart **12h** (14%) (entry 8).

A final study was directed at whether 2-ethynyl analogue **13** might react under FVP in a similar manner to yield the corresponding α,β-unsaturated ketones. As illustrated in Scheme 3, pyrolysis of **13** at 540 °C produced a 1:1 mixture



of (*E/Z*)-2-cyclotridecenone (**14**) in 55% yield (based on recovered material). The spectroscopic data provided no evidence for the presence of unsaturated dione side products. Although the conversion rate could be increased at elevated temperatures, the yield of **14** decreased as a result of the formation of low-boiling side products, which were not further characterized.

To conclude, we have developed a conceptually new one-carbon ring expansion reaction providing access to specifically substituted cycloalkanones based on a diradical cascade mechanism. In view of the ready availability of appropriately substituted substrates, this sequence represents a short and very efficient route to naturally occurring macrocyclic musks such as, e.g., (±)-muscone, as well as a variety of synthetic analogues from cheap C-12 starting compounds. 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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(9) As a control experiment 1,2-dione **9** was subjected to FVP at 600 °C to give **7** (67%), doubly decarbonylated cyclododecane (16%), and unreacted starting material (10%). In contrast, **9** remained unaffected when treated at temperatures below 540 °C.

(10) The lower overall yield may be attributed to double decarbonylation and dehydration.

(11) The initially formed silylenol ether compounds were each obtained as 1:1 mixture of *E/Z*-isomers.

(12) Lower temperatures gave rise to incomplete conversion.

(13) Compounds **10d–h** were prepared in good yields by addition of the corresponding 1-alkenylmagnesium bromide reagent to the appropriate 1,2-diketone, followed by silylation.

(14) For recent reviews on macrocyclic musks, 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.

(15) Precursor **10e** was obtained on a multigram scale from low-priced cyclododecanone through a five-step synthesis in ca. 60% overall yield. For details, see refs 4a,b and 6.

(16) 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.