

Cyclopropylcarbinyl radicals as three-carbon insertion units: easy synthesis of C-15 macrocyclic ketones by three-carbon ring expansion[☆]

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Abstract—Thermal isomerization of cyclic 3-cyclopropyl ketones under FVP conditions at 620 °C provides a new and convenient route to δ,ϵ -unsaturated cycloalkanones. The synthetic potential of this novel three-carbon ring expansion has been demonstrated by the synthesis of (\pm)-muscone from inexpensive C-12 starting material.

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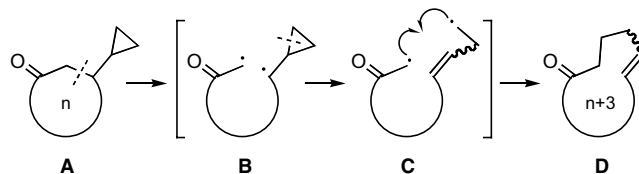
The extraordinary odor qualities of macrocyclic musks places them among the most demanded constituents in fragrance chemistry.¹ However, most synthetic approaches include uneconomical macrocyclization procedures or multi-step annelation–fragmentation sequences.² Therefore, it is important to explore new synthetic routes to this exciting class of compounds.

In a recent paper we reported a diradical-mediated two-carbon ring expansion reaction operating in 3-vinylcycloalkanones of different ring size under flash vacuum pyrolysis (FVP) conditions at 600–630 °C.³ The current study was directed at exploring whether a cyclopropyl moiety as three-carbon building block might be capable of undergoing a similar transformation to effect ring expansion by three carbon atoms.⁴ This approach would provide a new method for the synthesis of valuable C-15 macrocyclic musk odorants in a rapid and efficient way by easy transformation of inexpensive C-12 starting compounds.

In contrast to alkyl substituents, a cyclopropyl group stabilizes a neighboring radical center by about 3

kcal mol⁻¹,⁵ facilitating thus the intended homolytic cleavage in its α -position. As outlined in Scheme 1, the design of this new three-carbon ring expansion was formulated around the expectation that cyclopropylcarbinyl radicals, once they are formed, suffer immediate breakage of one of the adjacent cyclopropyl bonds to form the relaxed homoallyl radicals (in situ generation of the three-carbon component).⁶ Driven by the generation of a stabilized α -acyloyl ω -cyclopropylcarbinyl diradical **B**, regioselective homolysis of the weakest single bond in substrate **A** would be expected to occur under FVP conditions. Intramolecular coupling within the resulting open-chain homoallyl diradical **C** under insertion of the previously attached C₃-unit would then lead to cyclic ketone **D** having a specific unsaturation in δ,ϵ -position.

Our test of this hypothetical cascade reaction **A** → **D** started with 3-cyclopropylcyclohexanone (**2a**), which was obtained in good yields by cuprous iodide assisted

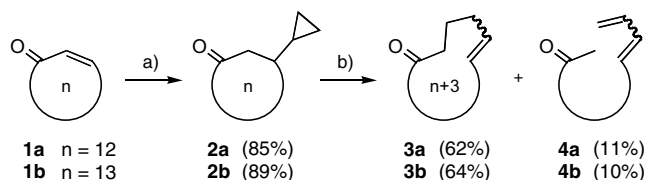


Scheme 1. General strategy for the diradical-mediated three-carbon ring expansion.

Keywords: Ring expansion; Vacuum pyrolysis; Cyclopropylcarbinyl radicals; Rearrangement; Musk odorants.

[☆] Supplementary data associated with this article, can be found, in the online version, at doi: 10.1016/j.tetlet.2004.04.148

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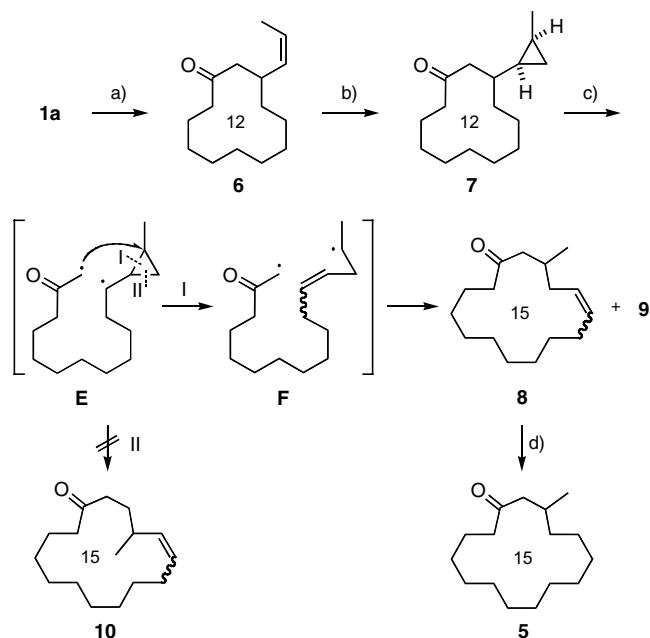


Scheme 2. Three-carbon ring expansion of cyclopropyl ketones **2a** and **2b**. Reagents and conditions: (a) cyclopropyl lithium, CuI, Et₂O, -78 °C; (b) FVP, 620 °C, 2–4 × 10⁻² mbar, N₂ flow (0.8–1.2 L/h).

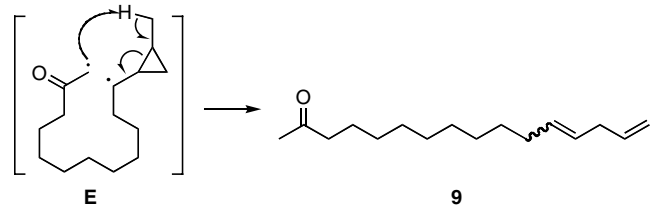
conjugate addition of cyclopropyl lithium to (*E*)-2-cyclododecanone (**1a**). According to Scheme 2, pyrolysis of **2a** in a flow reactor under reduced pressure (2–4 × 10⁻² mbar) at temperatures in the range of 600 °C gave rise to the formation of two major isomeric products **3a** and **4a**. Although careful adjustment of the reactor temperature revealed optimal conversion to occur at 620 °C, the reaction did not go to completion. The desired enone **3a** was formed in 62% yield based on 63% recovered starting material.⁷ The perfume qualities of this compound were classified as musky, fruity (type prune), animal, and light metallic.⁸ Interestingly, a minor amount of the ring-opened dienone **4a** was also formed, presumably via intramolecular H-transfer reaction. Fortunately, the conversion rate could be raised when the crude pyrolysate was subjected once again to the same reaction conditions (recycling procedure). However, due to rapid rotation around the cyclopropyl bond and unselective cleavage in intermediate **B** all products were obtained as a 1:1 mixture of *E/Z* isomers.

To gain further insight into this three-carbon ring expansion we cursorily examined the influence of the ring size on this transformation by subjecting also the homologous 3-cyclopropylcyclotridecanone (**2b**) to FVP at 620 °C. The resulting hexadecacyclic enone **3b** and its open-chain counterpart **4b** were formed in comparable yields in comparison to the former ring expansion reaction, confirming thus the generality of the above observed finding.

Encouraged by these results, we next turned our attention toward an application of this concept to the synthesis of (±)-muscone (**5**) from low-priced **1a** (Scheme 3). Treatment of the latter with freshly prepared (*Z*)-1-propenyl lithium in the presence of cuprous iodide afforded **6** (98% yield) with high retention of the (*Z*)-configuration (>50:1).⁹ Subsequent cyclopropanation using diiodomethane and diethyl zinc led to crystalline *cis*-**7** in 88% yield. As observed in the case of substrates **2a,b**, pyrolysis of *cis*-**7** would presumably lead to the primary diradical intermediate **E**. Although both bond I and bond II cleavage in **E** would result in the relief of cyclopropane ring strain, the higher substituted bond I was expected to be the main site of breakage, as this would give the more stable diradical intermediate **F**.¹⁰ Indeed, thermal isomerization at 620 °C produced a 1:1 mixture of the desired muscenone **8** in 34% yield (based on recovered **7**, 44%) along with the acyclic methyl ketone **9** (32% yield).¹¹ Even though the product mixture has been thoroughly purified by chromatographic



Scheme 3. Straightforward synthesis of (±)-muscone via regioselective cyclopropane ring cleavage. Reagents and conditions: (a) (*Z*)-1-bromopropene, CuI, Et₂O, -78 °C; 98%; (b) CH₂I₂, Et₂Zn, Et₂O, 0 °C, 88%; (c) FVP, 620 °C, 2–4 × 10⁻² mbar, N₂ flow, **8** (34%), **9** (32%); (d) H₂, Pd/C, EtOH, 23 °C, 90%.



Scheme 4. Competing intramolecular H-transfer reaction.

means, the spectral data provided no evidence for the existence of the isomeric 4-methyl analogue **10**. Therefore, competing breakage of cyclopropyl bond II in diradical **E** can be ruled out under the applied conditions. As depicted in Scheme 4, the concomitant formation of considerable amounts of the open-chain product **9** can be rationalized by the fact that the additional methyl group is ideally suited for intramolecular disproportionation by H-transfer. Finally, hydrogenation of **8** in the presence of Pd/C proceeded smoothly to give the targeted (±)-muscone (**5**) in 90% yield.

In conclusion, we have presented a very short two-step ring expansion protocol leading to specifically unsaturated C-15 macrocyclic ketones based on a diradical-mediated side-chain ring isomerization of a cyclopropyl moiety as C₃-building block. A methyl group on the three-membered ring proved to be transferred regioselectively into β-position of the ring expanded product, which enables the direct access to muscone. The low overall-yield (<40%) as well as the lack on diastereoselectivity (*E/Z* mixtures) are compensated by both the preparative convenience of this method (solvent-free

procedure, no work-up, continuous process) and the low price of the C-12 starting material. Our future efforts are directed at enhancing the scope and selectivity of this novel ($n + 3$) ring expansion reaction.

Supplementary material: Experimental details and complete spectral data of the compounds **2a–4a**, and **6–8** are given as Supplementary material.

Acknowledgement

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- The following procedure is illustrative: The thermo-isomerization device consists of an electrically heatable tube furnace (1 m long), a condenser unit with a cooling trap at the outlet side and a Kugelrohr oven as the evaporation unit at the inlet side. A quartz tube (110 cm long, 2.5 cm i.d.) which fitted into the furnace, was connected to a trap (cooled with liquid N₂) on one side and to a bulb placed in the Kugelrohr oven on the other. The starting material **2a** (2.10 g, 9.4 mmol) was placed in the bulb equipped with a capillary inlet device for the inert flow gas (N₂ flow 0.8–1.2 L/h) and a magnetic stirrer. After evacuation of the apparatus with a high-vacuum oil pump ($2\text{--}4 \times 10^{-2}$ mbar) **2a** was distilled directly through the preheated reactor tube (620 °C reactor temperature; estimated contact time <1 s). After all of the starting material had been distilled (ca. 30 min), the apparatus was vented and the frozen products were transferred to a bulb using Et₂O as solvent. The resulting solution was dried over anhydrous MgSO₄, filtered, and evaporated under reduced pressure (>95% recovery). Purification by flash chromatography on silica gel (hexane/AcOEt 60:1) afforded recovered starting material **2a** (1.32 g, 63%), **3a** (0.48 g, 23%), and **4a** (84 mg, 4%). Data of (*E/Z*)-**3a**: ¹H NMR (300 MHz, CDCl₃): δ 5.33–5.20 (m, 2H, H–C(5,6)), 2.61–2.27 (m, 4H, CH₂(2,15)), 2.05–1.95 (m, 4H, CH₂(4,7)), 1.67–1.55 (m, 4H, CH₂(3,14)), 1.38–1.23 (m, 12H); ¹³C NMR (75 MHz, CDCl₃): δ 212.4, 211.7, 132.2, 131.4, 130.1, 129.2, 42.0, 41.5, 41.2, 40.8, 31.3, 30.0, 28.2, 27.1, 26.9, 26.8, 26.4, 26.2, 25.2, 24.7, 24.5, 24.0, 22.4, 22.3, 21.9; Elemental analysis: calcd for C₁₅H₂₆O (222.37): C 81.02, H 11.78; found: C 80.92, H 11.75. Data of (*E/Z*)-**4a**: mp 15 °C. ¹H NMR (300 MHz, CDCl₃): δ 6.38–6.19 (m, 1H, H–C(14)), 6.10–5.91 (m, 1H, H–C(13)), 5.72–5.50 (m, 1H, H–C(12)), 5.12–4.89 (m, 2H, CH₂(15)), 2.41 (t, *J* = 7.6 Hz, 2H, CH₂(3)), 2.12 (s, 3H, H₃C(1)), 2.10–1.98 (m, 2H, CH₂(11)), 1.56 (m, 2H, CH₂(4)), 1.37–1.26 (m, 12H); ¹³C NMR (75 MHz, CDCl₃): δ 209.3, 137.3, 137.2, 135.5, 135.4, 130.8, 130.5, 114.5, 114.3, 43.8, 32.5, 32.3, 29.8, 29.6, 29.38, 29.35, 29.34, 29.30, 29.13, 29.08, 23.8.
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