## A Novel, Short and Repeatable Two-Carbon Ring Expansion Reaction by Thermo-Isomerization: Easy Synthesis of Macrocyclic Ketones

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**Abstract:** A novel two-carbon ring enlargement procedure, in which medium- and large-ring 1-vinylcycloalkanols are thermoisomerized in a flow reactor system at temperatures of 600 °C to about 650 °C, produces the isomeric ring-expanded cycloalkanones directly and efficiently. This two-step ring expansion protocol can easily be applied several times successively. For e.g., the musk odorant cyclopentadecanone (*Exaltone*<sup>®</sup>) is prepared from cycloundecanone in two repetitive cycles. Thermo-isomerization of the corresponding ethynylic cycloalkanols gives in moderate yields the bishomologous  $\alpha$ , $\beta$ -unsaturated macrocyclic (*E*)-2-cycloalkenones. A reaction mechanism via alkyl hydroxyallyl biradical intermediates is proposed.

**Key words:** ring expansions, macrocyclic ketones, thermo-isomerization, ring-insertion reactions, hydroxyallyl radicals





On search on new access to  $\alpha$ -campholenic derivatives by pyrolysis of borneol precursors,<sup>1</sup> a novel two-carbon ring expansion reaction has been discovered.

In our thermo-isomerization experiments with medium and large ring-sized 1-vinylcycloalkan-1-ols of type **A**, which were performed at temperatures in the range of 600-650 °C, we obtained not the expected open-chain alkenone isomers **C** (hypothetically formed via an intramolecular [1,5]H shift reaction<sup>2</sup> and the subsequent enol intermediate **B**). Instead the ring-expanded isomeric cyclic ketones **E** were formed as the main products in good yields. According to Scheme 1, the reaction pathway for the formation of ketones **E** from allylic alcohols **A** would formally include the reorganization of the involved bonds, which corresponds to a [1,3]C shift reaction via enol intermediate **D**.

Thermo-isomerization of 1-vinylcyclododecanol<sup>3,4</sup> **6** (which is derived in one step from ketone **5** by addition of vinylmagnesium reagent) in a flow reactor system<sup>5</sup> under reduced pressure (1-4 mbar) and at temperatures around 650 °C gave directly cyclotetradecanone (7) in average yields of 75% (Scheme 2).<sup>6</sup> Cycloalkanone 7 could easily be separated from by-products (mostly more volatile and less polar alkene fractions formed by dehydration of the starting material) either by crystallization of **7** from hex-

ane solution at -20 °C or by column chromatography on silica gel (eluant, hexane–*t*-BuOMe, 97:3-95:5).

The cyclic ketone **7** was directly used as the starting material for a subsequent ring enlargement step, analogous to the first expansion cycle. Indeed, allylic alcohol **8**, obtained from ketone **7**,<sup>3</sup> was transformed into the isomeric 16-membered homologous cycloalkanone<sup>7</sup> **9** in comparably good yields by application of the same thermo-isomerization conditions. This repeatable<sup>11</sup> ring-enlargement procedure<sup>4,5</sup> was also applied to the corresponding vinyl-cycloalkanols derived from odd-membered cyclic ketones (Scheme 2). In this way, the 17-membered cycloalkanone **13** ("dihydrocivetone")<sup>8</sup> was obtained by three iterative ring expansion cycles, starting from commercially available cycloundecanone via cyclotridecanone<sup>9</sup> (**11**) and cyclopentadecanone<sup>10</sup> (**12**).

No reaction or only the formation of olefins was observed previously when **4** was submitted to a static thermolysis at  $420 \,^{\circ}C.^{12}$  The thermo-isomerization of the same alcohol **4** under the dynamic high temperature conditions which we applied in our experiments, proceeded smoothly to give the bishomologous cycloalkanone **5** in excellent average yields of more than 80% (Scheme 2). We also tested the transformation of vinylcyclooctanol (**2**) into cyclodecanone (**3**). However, the corresponding isomerization experiments under different conditions gave only moderate conversion rates. Besides ca. 50% recovered starting material plus further dehydration and disproportionation products, the expected ketone **3** was formed in yields of

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Scheme 2 Reagents and Conditions: a) 1. Anhyd CeCl<sub>3</sub>, THF, r.t., 0.5 h; 2. Vinyl magnesium bromide (THF solution.), 25 °C, 0.5 h. *b*) Dynamic gas phase thermo-isomerization (DGPTI, FVP conditions, ~ 650 °C, 1–4 mbar,  $N_2$  flow).

only 25–30%. Whereas experiments with prolonged contact times in the flow reactor system led only to an increase of the undesired dehydration products,<sup>5</sup> the yields of **3** could be raised significantly when the crude isomerization mixture was subjected to the thermo-isomerization process at least a second time (recycling procedure). However, only starting material and dehydration products were obtained, when the corresponding six- or sevenmembered ring systems were subjected to the same reaction conditions.

In sharp contrast to the smooth rearrangement reactions of the macrocyclic vinylcycloalkanols, the thermolysis experiments involving comparable acyclic (open-chained) allylic alcohols, such as **14** (Scheme 3),<sup>4</sup> resulted, under the same reaction conditions, in the formation of complex product mixtures with mainly low molecular mass components, apparently generated by predominantly destructive fragmentation processes of the "retro-Grignard" type (mainly formation of alkenes, polymers, tars).<sup>13</sup>



Scheme 3 Conditions: Flash vacuum pyrolysis (FVP, ~ 650 °C, 1–4 mbar,  $N_2$  flow)

With regard to the reactor temperatures of more than about 600 °C that are necessary for the thermo-isomerization processes, a plausible pathway for the reaction involves a biradical intermediate<sup>5b</sup> in analogy to the well investigated vinylcyclopropane-to-cyclopentene rearrangement.<sup>14–17</sup>



Scheme 4

According to the mechanism shown in Scheme 4, a homolytic cleavage of the C(1)-C(2) bond in **15** results in an open-chained biradical intermediate **16** with an alkyl radical at the one end and a resonance-stabilized hydroxyallyl species at the opposite of the chain. Intramolecular recombination of the biradical **16** in the terminal vinylogous position leads via the ring-expanded cyclic enol intermediate **17** and subsequent tautomerization to the cycloalkanones **18** as a formal [1,3]C shift product under insertion of the C<sub>2</sub>-unit of the former vinylic side chain. Intramolecular hydrogen abstraction reaction within the biradical intermediate **16** (disproportionation by H-transfer) leads to open-chain vinyl alkyl ketone derivatives<sup>6a</sup> **19**, which are also identified as rearranged by-products with identical molecular masses in the thermo-isomerization reactions.<sup>18</sup>

The dynamic thermo-isomerization procedure is also applicable to 1-ethynyl cycloalkanols (Scheme 5), e.g. **20** and **21**, which are easily accessible in excellent yields from the correspondig cyclic ketones by CeCl<sub>3</sub> mediated addition of ethynyl magnesium bromide.<sup>19</sup> The product mixtures contained the  $\alpha$ , $\beta$ -unsaturated ring-expanded cyclic ketones **22** and **24**, respectively,<sup>20,21</sup> in about 20-25%

yields, besides nearly equal amounts of the open-chained  $\alpha, \omega$ -dienone isomers<sup>22</sup> 23 and 25, respectively. Highly volatile by-products and also the starting saturated ketones 5 and 11, respectively, which seem to be the products of a retro-Grignard fragmentation process at the high reactor temperatures, have been observed. The NMR spectra show that the 2-cycloalkenones 22 and 24, respectively, which were separated by column chromatography from the thermolysates, possess the thermodynamically favorable (*E*)-configuration.<sup>20,21</sup>



Scheme 5 Reagents and conditions: *a*) Dynamic gas phase thermoisomerization (FVP conditions, ~ 640–670 °C, 1–4 mbar, N<sub>2</sub> flow). *b*) 1. Anhyd CeCl<sub>3</sub>, r.t., 0.5 h; 2. vinyl magnesium bromide (THF solution), 25 °C, 0.5 h (85–95%). *c*) Cf. Scheme 2. d) 1. Anhyd CeCl<sub>3</sub>, r.t., 0.5 h; 2. ethynyl magnesium bromide (THF solution), 25 °C, 0.5 h (90–95%). *e*) H<sub>2</sub>, Pd/C (~quant.).

The musk odorant cyclopentadecanone **12** (*Exaltone*<sup>®</sup>, cf. Scheme 2)<sup>10</sup> can easily be obtained from 2-cyclopentadecenone **24** by catalytic hydrogenation. On the other hand, **24** is the well established direct precursor for the synthesis of the valuable musk odorant muscone (3-methylcyclopentadecanone) which is easily accessible from **24** by reported short procedures.<sup>23,24</sup> The straightforward synthesis of muscone-precursor **24** starting from commercial available cycloundecanone via cyclotridecanone (**11**) as intermediate is outlined in Scheme 5. A muscone synthesis via a one-carbon homologation with cyclotetradecanone **7** as the precursor ketone was also reported earlier.<sup>25</sup> Useful extensions in the application of this novel ring-expanding bishomologation methodology by thermoisomerization reactions to the synthesis of alkyl substituted macrocyclic ketones, e.g. a new short and straightforward synthesis of  $(\pm)$ -muscone, will be presented in a subsequent communication.

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reaction mixture was poured into cold water (1 L ) and t-BuOMe (500 mL) were added. With stirring, a 10% aqueous HCl solution was added until the slimy or gel-like consistency of the mixture disappeared, and the mixture became clear and two-phased (pH < 3). The organic phase was washed several times with water, then with sat. NaHCO<sub>3</sub> solution, and brine. After drying (MgSO<sub>4</sub>) and evaporation of the solvent under reduced pressure, the crude 1vinylcyclododecanol 6 (GC purity about 90%) was purified either by bulb-to-bulb distillation (HV) and subsequent crystallization from hexane-t-BuOMe (95:5, v/v) or by chromatography on a short column (silica gel, eluent, hexane-t-BuOMe 97:3-95:5). Allylic alcohol 6 was obtained in yields of 75-85% as a colorless waxy solid (mp 53 °C). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): 5.98 (*dd*, *J* = 10.8, 17.4 Hz, 1 H), 5.20 (*dd*, *J* = 1.4, 17.4 Hz, 1 H), 5.01 (*dd*, *J* = 1.4, 10.8 Hz, 1 H), 1.9–1.2 (m, 23 H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): 145.3 (*d*); 111.0 (*t*); 75.3 (*s*); 34.6(2), 26.3(2), 25.9, 22.5(2), 22.1(2), 19.5(2)(6 t). EI-MS (GC/MS): 210.2 (2, M<sup>+</sup>), 192.2 (50, M – 18), 77.7(98), 67(100), 55(97). Also see: (c) Marcou, A.; Normant, H. Bull. Soc. Chim. Fr. 1965, 3491. (d) Herz, W.; Juo, R.-R. J. Org. Chem. 1985, 50, 618. (e) Ref. 6a.

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MHz, CDCl<sub>3</sub>): 202.1 (*s*), 148.2, 130.3 (2 *d*), 40.4, 31.4, 26.6, 26.3, 26.2, 26.0, 25.8, 25.7, 25.4, 25.0, 24.9 (11 *t*). For **24**: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): 6.81 (*td*, J = 15.7, 7.5 Hz, 1 H), 6.19 (*dt*, J = 15.7, 1.3 Hz, 1 H), 2.52-2.47 (*m*, 2 H), 2.30-2.23 (*m*, 2 H), 1.72-1.44 (*m*, 4H), 1.4-1.2 (*m*, 16 H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): 201.7 (*s*), 147.9, 130.7 (2 *d*), 40.0, 31.6, 26.9, 26.8, 26.7, 26.6, 26.5, 26.2, 26.0, 25.4, 25.2 (12 *t*)..

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