

Synthesis of Macrocyclic Ketones by Repeatable Two-Carbon Ring Expansion Reactions

Matthias Nagel*, Georg Fráter^a and Hans-Jürgen Hansen^b

Abstract: A novel and short method for the synthesis of macrocyclic alkanones has been developed: medium- and large-ring 1-vinylcycloalkanols can be transformed directly and efficiently into the isomeric, ring-expanded bishomologous macrocyclic ketones by a thermal 1,3-C shift rearrangement reaction in the gas phase, carried out under dynamic conditions in a flow reactor system at high temperatures. This two-carbon ring enlargement protocol involves only two steps and is easily repeatable, since the obtained cyclic ketones can directly be used as starting materials for the subsequent analogous two-carbon ring insertion reactions. Alkyl substituents at the vinylic side chain are transferred to the ring-expanded ketone as corresponding α - and β -substituents, respectively. Therefore, this thermo-isomerization process provides not only a short route to cycloalkanones but also to many alkyl-substituted macrocyclic ketones, such as, e.g. the musk odorant (\pm)-muscone. A reaction mechanism *via* alkyl hydroxyallyl biradical intermediates is proposed.

Keywords: Dynamic gas phase thermo-isomerization · Hydroxyallyl radicals · Macrocyclic ketones · Ring expansions

Introduction

Gas phase reactions performed under dynamic conditions at high temperatures (typically in the range of *ca.* 400 to 700 °C) and with short exposure times in flow reactor systems can be applied as a preparatively useful tool in organic synthesis. This technique is usually called flash vacuum pyrolysis (FVP) [1]. In a conventional FVP set-up, the starting material is evaporated or sublimed under reduced pressure through a hot zone, e.g. a quartz tube heated in an appropriate electrically heated furnace, and

the products formed are trapped at low temperatures immediately after passing the hot zone. Due to the high thermal energy impact during the short residence time of the substrate in the hot reactor zone, elemental processes with high activation barriers are accessible. In some cases ‘exotic’ (or ‘non-classical’) reaction pathways *via* highly reactive intermediates can be involved in such gas phase transformations and can therefore lead to the formation of unexpected reaction products [1][2]. By careful selection of the reaction parameters for this dynamic process, *i.e.* by adjustment of the dimensions of the reactor and by choosing the appropriate temperature, flow and pressure conditions, the substrate can be exposed to a controlled thermal energy, which is required for the desired chemical conversion. With regard to our successful applications of FVP techniques in the synthesis of azulene precursor compounds *via* a high-temperature cycloisomerization process [3], we were interested in further research on the preparative applicability of *non-destructive* thermal transformations in the gas phase. Therefore, we extended our studies specifically to rearrangement or thermo-isomerization reactions, with respect to their implicitly high degree of atomic economy and synthetic efficiency. Since gas

phase reactions normally can be performed without solvents and as continuous processes, they also might have an impact on industrial synthetic processes.

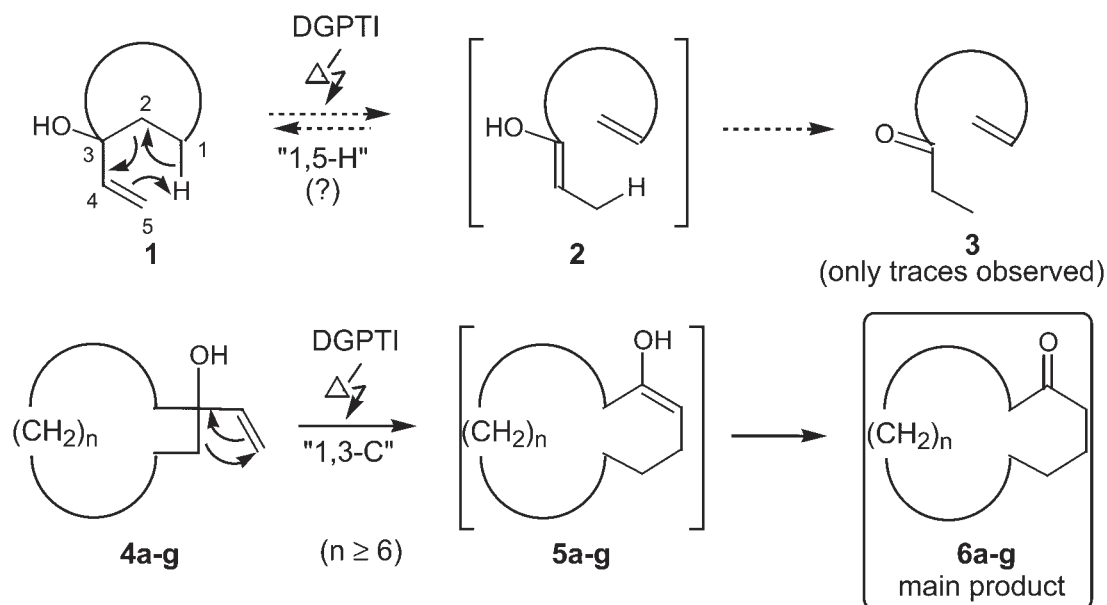
An Unexpected Experimental Observation

One of our key interests was focused on thermal ring-opening reactions of 1-vinyl-substituted cycloalkanols **1** under flash thermolysis conditions. Initially, we expected the formation of open-chain alkenones **3** by fragmentation *via* an intramolecular [1,5]-H shift reaction of the retro-ene type, according to the mechanism depicted in Scheme 1.

However, we found in our experiments, which were performed in a flow reactor system under reduced pressure (1–4 mbar) and at temperatures around 650 °C an unexpected result as we have reported already [4]: We did not observe the formation of the corresponding open-chain alkenone derivatives **3** as the products of a formal ring-opening process, but instead we obtained the ring-expanded isomeric cycloalkanones **6**. Starting from 1-vinylcyclododecan-1-ol (**4d**), which was prepared in one step from cyclododecanone (**6b**) by addition of vinyl-

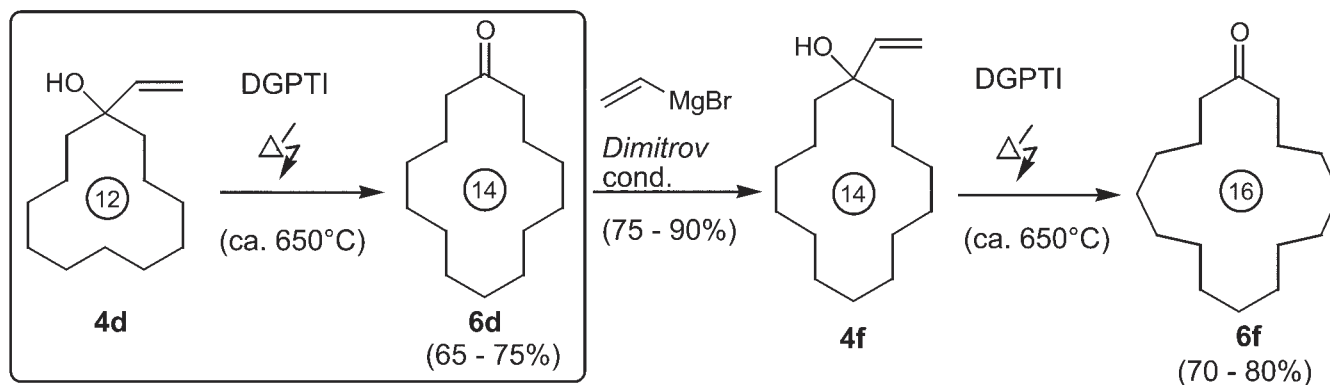
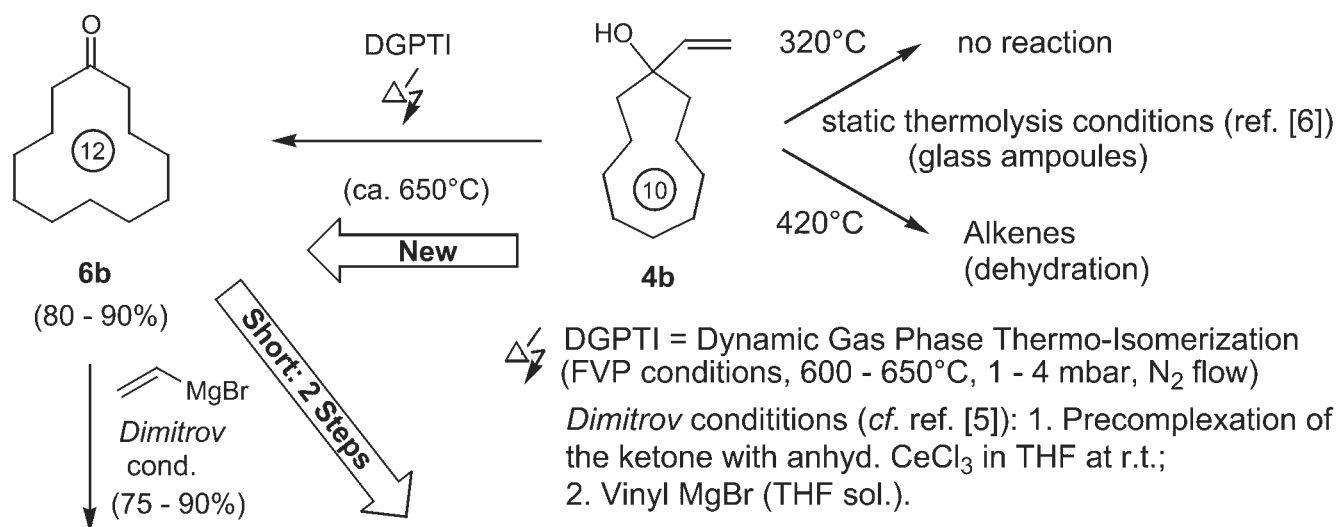
*Correspondence: Dr. M. Nagel
Swiss Federal Laboratories for Materials Testing and Research (EMPA)
Überlandstrasse 129
CH-8600 Dübendorf
Tel.: +41 1 823 47 70
Fax: +41 1 823 15 40
E-Mail: matthias.nagel@empa.ch
www.empa.ch

^aGivaudan Dübendorf Ltd
Überlandstrasse 138
CH-8600 Dübendorf
^bUniversity of Zürich
Winterthurerstr. 190
CH-8057 Zürich



a: $n = 5$; b: $n = 6$; c: $n = 7$; d: $n = 8$; e: $n = 9$; f: $n = 10$; g: $n = 11$

Two-Carbon Ring Expansion Sequence



Repeatable

Scheme 1

magnesium bromide after precomplexation with anhydrous CeCl_3 [5], the isomeric cyclic ketone, cyclotetradecanone (**6d**) was formed in average yields of 70% after passing the reactor. Evidently, the formation of the main product **6d** by the dynamic gas phase thermo-isomerization (DGPTI) reaction is based on a ring expansion reaction by insertion of the two C-atoms of the vinylic side chain into the resulting macrocyclic ketone [4]. We then used the ring-expanded ketone **6d** as starting material for a subsequent two-carbon ring enlargement protocol, analogous to the first two-step expansion procedure. And, indeed, the allylic alcohol **4f** was transformed into the isomeric 16-membered cycloalkanone **6f** in comparably good yields by application of the same thermo-isomerization conditions. This two-carbon ring expansion reaction was also applicable to the corresponding vinylcycloalkanones derived from odd-membered cyclic ketones. In this way, cycloheptadecanone (**6g**) was obtained by three iterative ring expansion cycles, starting from the commercially available 11-membered cycloalkanone **6a**. To the best of our knowledge, this two-carbon ring enlargement procedure is one of the shortest repeatable ring expansion reactions realized with carbocyclic systems (for more details, cf. [4]).

The advantage of the dynamic gas phase thermo-isomerization procedure becomes evident by comparison with similar thermolysis experiments performed under static conditions: No reaction or only the formation of olefins has been observed previously, when **4b** was heated in sealed glass ampoules at 420 °C [6]. Under the dynamic high temperature conditions which we applied in our thermo-isomerization experiments, the same alcohol **4b** was transformed smoothly into the bishomologous cycloalkanone **6b** in excellent average yields of > 80%.

Development of the Thermo-Isomerization Device

During the course of our experimental studies on scope and limitations of the two-carbon ring expansion reaction by DGPTI for the synthesis of macrocyclic ketones, we developed an appropriate apparatus in our laboratories with regard to the application of this novel method on a preparative scale. The apparatus is depicted in Fig. 1 and consists of an electrically heatable, one meter-long tube furnace as the central unit, a modified Büchi kugelrohr oven as the evaporation unit and a condenser unit with cooled product traps at the outlet side.

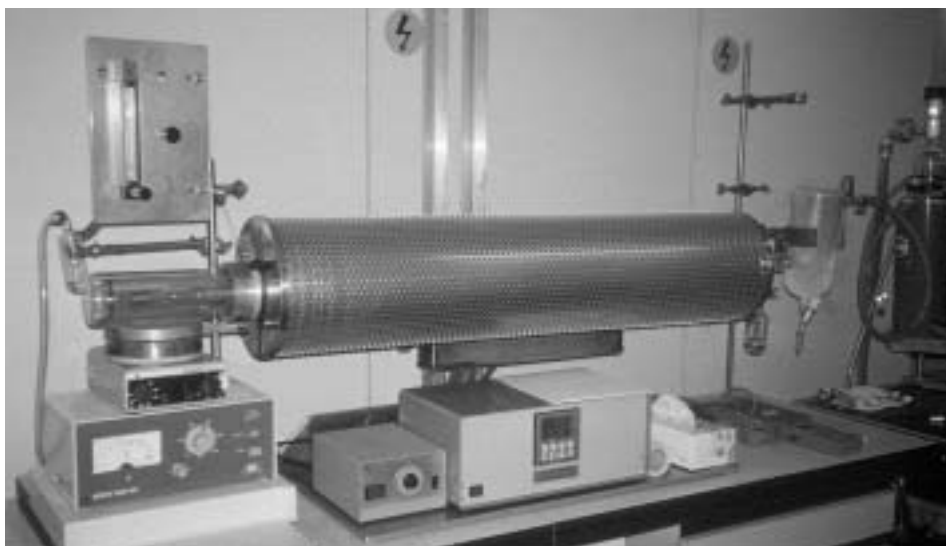


Fig. 1

The tube furnace consists inside of six separate sectors, each individually heatable by a temperature control unit. This equipment allows for the application of different temperatures, and temperature gradients, respectively, along the reactor tube inside the furnace. The bulb in the evaporation unit is equipped with a capillary inlet device for the inert flow gas (N_2 or Ar) and a magnetic stirrer. The isomerization reactions were carried out with a quartz tube reactor (1 m long, 25 mm i.d.), which fitted into the furnace. The outlet part of the reactor is connected to at least two cooling traps, which allow the selective condensation of the reaction products at different temperatures. After evacuation of the apparatus with a high-vacuum oil pump, the starting materials were evaporated directly into the reactor tube and the flow of the inert gas was adjusted by a precision needle

valve from 15 to > 50 ml/min (1 to > 3 l/h), depending on the individual contact times necessary for the isomerization processes. The rate of distillation of the starting material (about 5 up to ca. 20 g/h) was controlled by regulation of the evaporation temperature. At the end of the reactor unit the high boiling main fraction of the isomerization products was collected in the first cooling trap at about 0 °C, and the more volatile side products (mainly apolar dehydration products) in subsequent traps, which were cooled to lower temperatures (see Fig. 2). By using filling materials for the reactor, the contact times may be raised, but simultaneously the inner surface is enlarged and surface-catalyzed side reactions at high temperatures (e.g. dehydration) can become predominant, depending on the specific properties of the fillings and the degree of their packing.

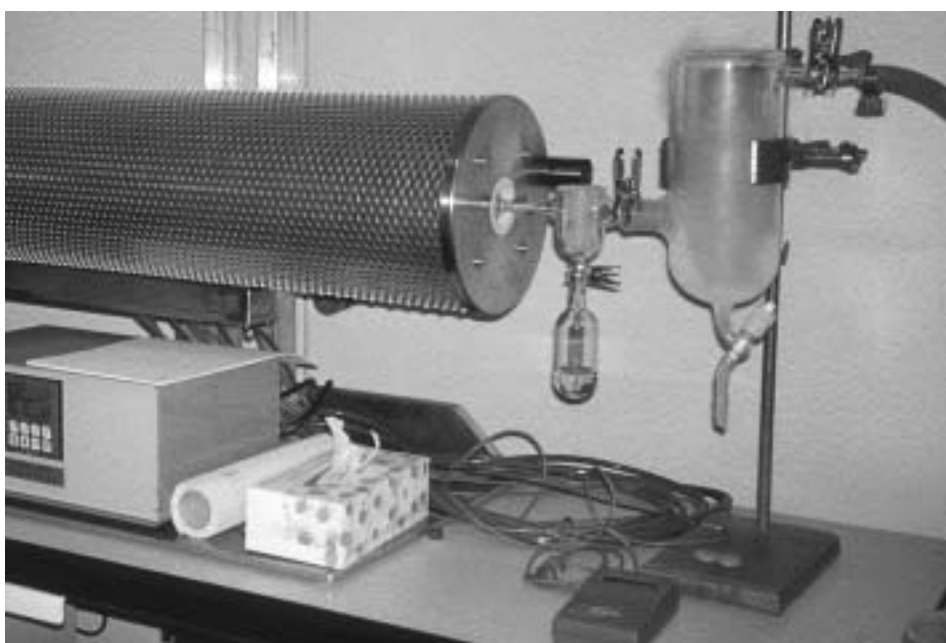


Fig. 2

Synthesis of Alkylated Macrocyclic Ketones

In order to gain more insight into the general applicability of the described bishomologization procedure, we investigated systematically the influence of alkyl substituents at the vinyl moiety of the cycloalkanols. For example, a homologous series of macrocyclic 3-methyl substituted cycloalkanones **8a–e** could be prepared in a similar manner starting from the corresponding 1-(propen-1-yl)cycloalkanols **7a–e** by DGPTI in 45–55% yields (Scheme 2) [4].

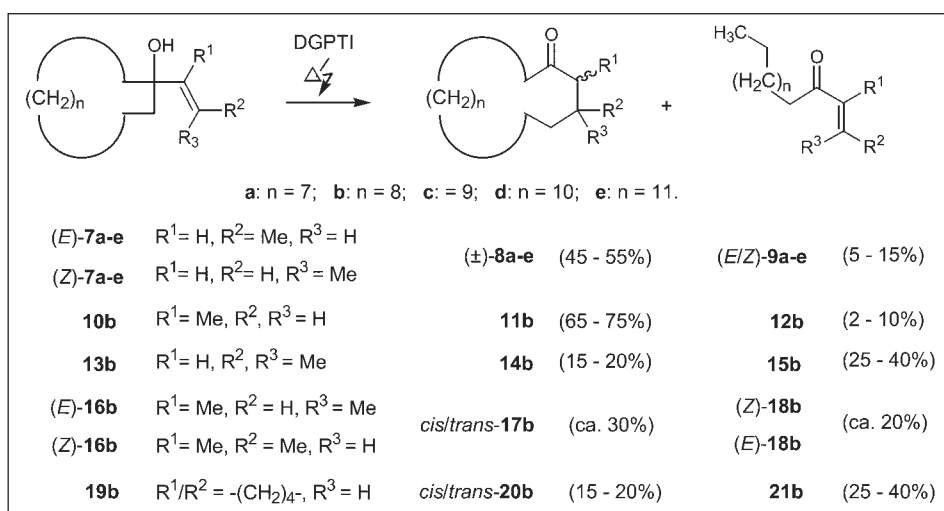
In this way, the valuable musk odorant (\pm)-muscone **8c** could easily be prepared from cyclotridecanone (**6c**). In general, alkyl substituents at the vinylic moiety are transferred locospecifically to the ring-expanded ketones as corresponding α - and β -substituents, respectively. Some typical examples are given in Scheme 2. In all our DGPTI experiments, the open-chained enone-isomers were also formed alongside with the ring-expanded ketones in varying amounts, depending on the degree of substitution at the vinylic moiety and the size of the ring system [4].

Mechanistic Considerations

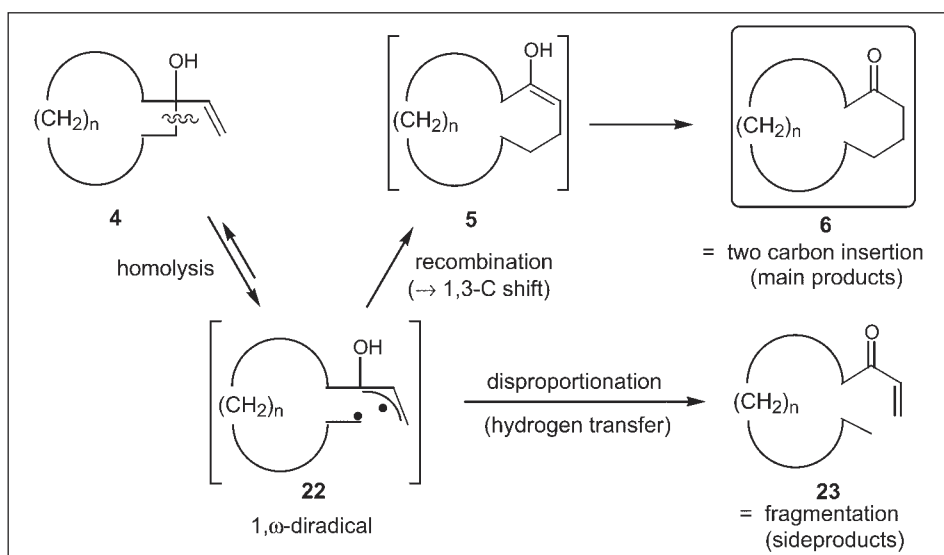
In analogy to the well-investigated vinylcyclopropane-to-cyclopentene rearrangement (*cf.* literature cited in [4]) and with regard to the reactor temperatures of more than about 600 °C that are necessary for the thermo-isomerization processes, a plausible pathway for the reaction involves a biradical intermediate.

According to the assumed mechanism depicted in Scheme 3, a homolytic cleavage of the C(1)–C(2) bond in **4** results in the formation of the open-chain hydroxyallyl-alkyl biradical **22**. Intramolecular recombination of the alkyl radical at the opposite end of the chain at the terminal vinylogous position of the resonance-stabilized hydroxyallyl species leads *via* the ring-expanded cyclic enol intermediate **5** and subsequent tautomerization to the cycloalkanone **6** as a formal 1,3-C shift product. Intramolecular hydrogen abstraction reaction within the biradical intermediate **22** (disproportionation by H-transfer) leads to the open-chain alkenone derivatives **23**. More detailed studies on the mechanism and further applications of DGPTI processes to other substrates are under investigation in our laboratories and will be published elsewhere.

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Scheme 2



Scheme 3

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