Short and Versatile Two-Carbon Ring Expansion Reactions by Thermo-Isomerization: Novel Straightforward Synthesis of (±)-Muscone, Nor- and Homomuscones, and Further Macrocyclic Ketones

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Abstract: Thermo-isomerization of 1-vinyl substituted medium- and large-ring cycloalkanol derivatives in a flow reactor system at temperatures of 600 °C to about 650 °C leads directly to the ring-expanded macrocyclic ketones. Alkyl substituents at the vinylic moiety are transferred locospecifically to the ring-expanded ketone as corresponding α-, and β-substituents, respectively. This novel thermal 1,3-C shift reaction therefore provides a new access to short syntheses of many alkyl-substituted macrocyclic ketone derivatives [e.g. (±)-muscone and analogues] in a systematic manner.

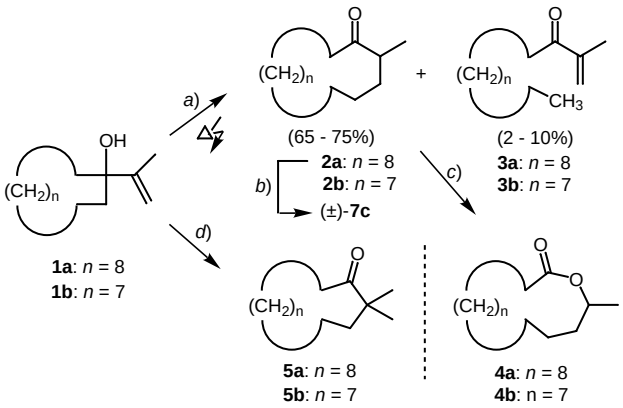
Key words: ring expansions, macrocyclic ketones, dynamic gas phase thermo-isomerization, two- carbon ring insertion reactions, (±)-muscone syntheses

In the preceding communication[1] we described a novel thermo-isomerization process under flash vacuum pyrolysis conditions, in which 1-vinylcycloalkanols (or their corresponding ethynyl forms) can directly be transformed into the isomeric macrocyclic ketones (or their α,β-unsaturated forms) expanded by two C-atoms.[2] In order to get more insight into the general applicability of this two-carbon ring expansion procedure, we investigated systematically the influence of alkyl substituents at the vinyl moiety of the cycloalkanols.

Thermo-isomerization of the allylic alcohols[3] **1** with a 1-methylethen-1-yl substituent (Scheme 1) in the same manner as described[2] gave the known 2-methylcycloalkanones[4,7] **2** in yields of 65-75%, as well as about 2-10% of the open-chained alkenone isomers **3**.[8a]

The macrocyclic 2-methylketones **2** were used previously as the precursors for the synthesis of the naturally occurring vegetable macrolides **4** (compounds with musky odor)[5a] which were synthesized from **2** by employing a Baeyer-Villiger oxidation (60-70% yield) as final transformation in multistep ring-enlargement procedures.[4a,f] Ketone **2a** was also the intermediate in an earlier synthesis of (±)-muscone (**7c**) by a two-step regioselective one-carbon ring homologation sequence.[7]

A novel one-carbon insertion reaction was also observed, when alcohol **1a** was heated in the presence of basic alumina which led to the isomeric ketone 2,2-dimethylcyclotridecanone[8b] (**5a**).[4f,9] Both ketones **5** can easily be prepared in about 60% isolated yield by heating the corresponding allylic alcohols **1** adsorbed on basic alumina in a kugelrohr oven to 160 °C for 15-30 min under an inert atmosphere at normal pressure. This remarkable [1,2]C shift reaction[10] with formation of the geminal α-alkylated ketones[11] **5** represents a new type of a solvent-free ("dry"), surface-catalyzed[12] thermo-isomerization process.



Scheme 1 *Reaction conditions*: *a*) Dynamic gas phase thermo-isomerization (FVP conditions, ~ 650 °C, 1-4 mbar, N_2 flow). *b*) Transformation of **2a** into (±)-**7c**: ref.[7] (one-carbon homologation). *c*) Baeyer-Villiger oxidation, see refs.[5,6]. *d*) Alumina (Alox basic), 160 °C, 15-30 min.

The ring-expanded 13- to 17-membered 3-methylcycloalkanones **7a–e** were easily obtained by the dynamic gas phase thermo-isomerization procedure from both isomers of the corresponding 1-(propen-1-yl)cycloalkanols **6a-e** in about 45-55% yields (Scheme 2). With (*E/Z*)-1-(propen-1-yl)cyclotridecanol **6c** as starting material, the valuable musk odorant[13] (±)-musone **7c** (3-methylcyclopentadecanone)[14] is directly formed (45-55%). The homologous 16-membered macrocyclic 3-methylketones **7d** ("homomuscone"),[15] as well as the 17-membered **7e** ("dihomomuscone"),[13g,15c] were easily obtained in the same manner. The corresponding lower muscone homologues, cyclotetradecanone derivative **7b** ("normuscone"),[14k,15c,16] as well as the cyclotridecanone derivative **7a** ("dinormuscone"),[7,15b,c,17] are each accessible analogously from the alcohols **6a** and **6b**, respectively. In all

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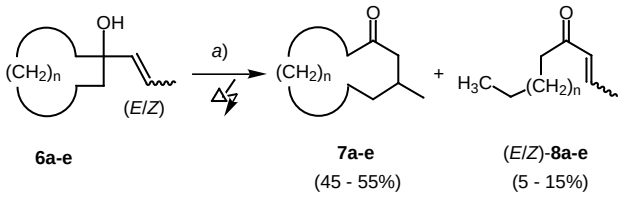
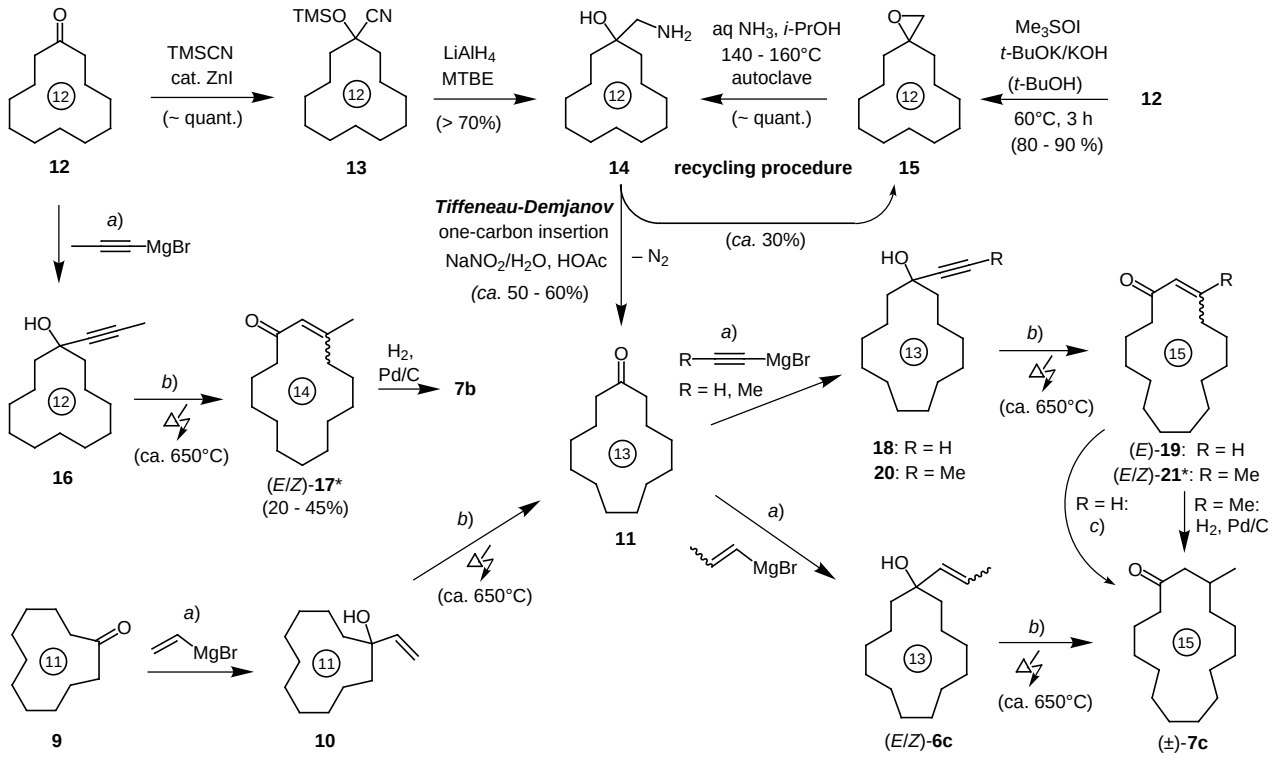
cases, the open-chained enone-isomers **8a**–**e** (Scheme 2) were also formed as side-products [predominantly the (*E*)-isomer] in average yields of 5-15%.[18]



a: n = 7; **b**: n = 8; **c**: = 9; **d**: n = 10; **e**: n = 11.

Scheme 2 *Reaction conditions*: *a*) Dynamic gas phase thermo-isomerization (FVP conditions, ~ 650 °C, 1-4 mbar, N_2 flow).

Cyclotridecanone (**11**) is the essential precursor for the synthesis of 15-membered cyclic ketones by the two-carbon insertion procedure.[1] In consideration of the prohibitively high prices of the odd-membered homologous ketones **11** and also **9**, compared with the much lower price of **12**, a one-carbon ring-expansion method starting from **12** was thought to be a more attractive approach for the synthesis of larger amounts (200-500 g) of **11** under economical aspects. We tried to use the known Tiffeneau-Demjanov homologation procedure[19] for this purpose (Scheme 3), via the protected cyanohydrin **13** and subsequent reduction with $LiAlH_4$.[20] The yields of aminoalcohol **14** could be raised by changing the solvent (higher boiling *t*-BuOMe instead of Et_2O), which also made the work-up procedure more efficient.[20d] When aminoalcohol **14** was treated with sodium nitrite and acetic acid according to the literature procedures for Tiffeneau-Demjanov ring expansion reactions,[19b–19d] ketone **11** was formed in about 50-60% yield, but the isomeric oxirane **15** (about 30%) and the starting ketone **12** (about 5-10%) were also found and could not be separated efficiently from **11**. Since these unsatisfactory results could not be circumvented by systematic variations of the experimental conditions, a method for the separation of the spirooxirane **15** from ketone **11** was developed by selective chemical modification to form a more polar derivative. A straightforward method for directly recovering the aminoalcohol **14** from the reaction mixtures of the Tiffeneau-Demjanov procedure involves reaction with ammonia.[21] By heating the raw reaction mixtures, which contained the ketone **11** and oxirane **15** (besides minor amounts of **12**), in concd. aqueous ammonia solution (excess) and *i*-PrOH in an autoclave at 140-160 °C for 2-4 h, the by-product **15** was transformed back into starting material **14** almost quantitatively. The β-aminoalcohol **14** could now easily be separated from the ketones, either by crystallization in nonpolar solvents, or by filtration after transformation into its hydrochloride by bubbling gaseous HCl into a stirred anhydrous *t*-BuOMe solution of the components. Finally, cyclotridecanone (**11**) can be separated from homologous ketone **12** by distillation over a Vigreux column under reduced pressure (GC purity > 98%). Since aminoalcohol



Scheme 3 *Reaction conditions*: *a*) 1. Anhyd $CeCl_3$ (0.1-0.4 mol-equiv), THF, r.t. 0.5-1 h (precomplexation of the ketone); 2. Grignard reagent (THF solution), r.t., 0.5 h. *b*) Dynamic gas phase thermo-isomerization (FVP conditions, ~ 650 °C, 1-4 mbar, N_2 flow). *c*) See ref. 4 and literature therein. **17*** and **21***: (*E*)/(*Z*)-Isomers not separated.

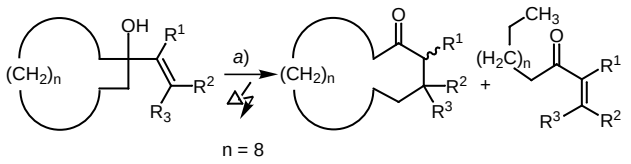
14 could be obtained very efficiently from the spiroepoxide **15**, we tried to use the latter as a main precursor of **14**. The methylene transfer reaction to ketone **12** from the ylide obtained from trimethylsulfoxonium iodide (Me_3SOI) under basic conditions[22] takes place in one step and in excellent yields to **15**. Encouraged by similar literature procedures,[23] this step could be improved further to nearly solvent-free conditions, so that the use of DMSO as solvent was not longer necessary.[24]

A further approach to the synthesis of (±)-muscone **7** from cycloalkanone **11** via the 3-methyl-2-cyclopentadecenone ("2-muscenone") intermediate **21** is also outlined in Scheme 3. The thermo-isomerization of 1-prop-1-ynylcyclotridecanol **20** gave the ring-enlarged cycloalkenone isomers **21** in a complex mixture,[25] together with open-chained isomers, starting ketone **11**, and dehydration products. Hydrogenation of the raw thermolysate resulted in the formation of three main compounds which were separable by column chromatography (SiO_2, hexane–*t*-BuOMe, 97:3): (±)-muscone **7c** (about 20% isolated yield), 4-hexadecanone (about 15%), and cyclic ketone **11** (about 10%) as well as non-polar hydrocarbon fractions. In the same manner, the homologous (*E*/*Z*)-3-methyl-2-cyclotetradecenone isomers[25a] **17** (20-45%, based on NMR spectra) were obtained under equivalent conditions from 1-prop-1-ynylcyclododecanol (**16**), and gave, also after hydrogenation of the product mixture, the cyclic ketone 3-methylcyclotetradecanone **7b** (about 25%) as well as the open-chained isomer 4-pentadecanone (about 25%) as the main products of the isomerization process.

As outlined in Scheme 4, thermo-isomerization of the 2-methyl-1-propenyl derivative **22** led in 50–60% average yield to almost 1:2 mixtures of 3,3-dimethylcyclotetradecanone **23** and its open-chain isomer **24**. A similar behavior was observed with the (*E*/*Z*)-2-buten-2-yl-substituted isomers **25** as starting material. Both isomers gave mixtures of the two racemic *cis*/*trans*-isomers **26** (ca. 30%) and the open-chain (*E*/*Z*)-isomers **27** (ca. 20%). With the cyclohexen-1-yl substituent[26] in **28**, the ring expansion process led to mixtures (about 1:1:4, 45-55% average yields) of the known *cis*/*trans* isomers of bicyclo[12.4.0]hexadecan-2-one (**29**)[27] and also the cylohexen-1-yl undecyl ketone (**30**)[28] which were not fully separable by column chromatography.

During the past 75 years, since Ruzicka had established the molecular structure of naturally occurring muscone, a huge number of syntheses of either (±)-muscone **7c** or also its enantiomers have been published,[14] but ring expansion procedures by two carbon atoms are rare among them. Only limited examples have been described in earlier reports, where **7c** was synthesized in multistep protocols via [1,3]C shift reactions from more complex 13-membered cyclic precursor systems by two-carbon insertion reactions.[29]

Effects of substituents at C(2) as well as further applications and extensions of this versatile bis-homologation procedure by dynamic gas phase thermo-isomerization for the synthesis of macrocyclic musk compounds are under investigation and will be published elsewhere.



22	R^1= H, R^2, R^3 = Me	**23**	**24**
(*E*)-**25**	R^1= Me, R^2 = H, R^3 = Me	**26** (*cis*/*trans*)	(*Z*)-**27**
(*Z*)-**25**	R^1= Me, R^2 = Me, R^3 = H		(*E*)-**27**
28	R^1/R^2 = -$(CH_2)_4$-, R^3 = H	**29** (*cis*/*trans*)	**30**

Scheme 4 *Reaction conditions*: *a*) Dynamic gas phase thermo-isomerization (FVP conditions, ~ 650 °C, 1-4 mbar, N_2 flow).

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(2) For a description of the thermo-izomerization procedure and the experimental setup, see ref.[1] and references therein.
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(8) Selected characteristic spectroscopic data of (a) **3a**: ^{1}H NMR (300 MHz, $CDCl_3$): 5.94 and 5.74 [br *s*, H_2-C(1)], 1.86 [br *s*, Me-C(2)], 0.87 [*t*-type *m*, $H_3C(\omega)$]. ^{13}C NMR (75 MHz, $CDCl_3$): 202.3 [*s*, C(3)], 144.6 [*s*, C(2)], 124.1 [*t*, C(1)], 17.7 [*q*, Me-C(2)], 13.5 [*q*, C(ω)]. (b) **5a**: ^{1}H NMR (300 MHz, $CDCl_3$): 2.52 [*t*-type *m*, 2 H, H_2-C(13)], 1.68-1.63 (*m*, 2 H), 1.54-1.49 (*m*, 2 H), 1.33-1.15 (*m*, 16 H), 1.12 [*s*, 6 H, Me_2-C(2)]. ^{13}C NMR (75 MHz, $CDCl_3$): 216.0 (*s*), 47.84 (*s*), 40.83, 35.68, 26.96, 26.69, 26.63, 25.45, 25.26 (7 *t*), 24.70 (*q*, 2), 24.56, 24.48, 22.27, 21.86 (4 *t*).

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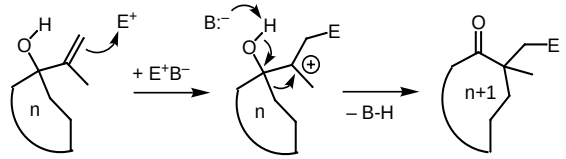

Scheme 5

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(18) Selected characteristic data of enones **8**: ^{1}H NMR (300 MHz, $CDCl_3$): (*E*)-**8a**: 6.84 [*dq*, *J* = 15.5, 7 Hz, H-C(2)], 6.12 [*dq*, *J* = 15.5, 1.7 Hz, H-C(3)], 1.87 (*dd*, *J* = 7, 1.5 Hz). (*Z*)-**8a**: 6.19 [*m*, 2 H, H-C(2,3)], 2.11 (*d*, *J* = 7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 200.4 [*s*, C(4)], (*E*)-**8a**: 141.9 [*d*, C(2)], 131.9 [*d*, C(3)], 18.0 [*q*, C(1)]. (*Z*)-**8a**: 142.2 [*d*, C(2)], 127.6 [*d*, C(3)], 15.9 [*q*, C(1)].

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(24) Cyclododecanone (**12**, 60 g, 0.33 mol) was melted by keeping it at 65-70 °C, then *t*-BuOH (15 mL) and trimethyl sulfoxonium iodide (117 g, 0.52 mol, 1.6 mol equiv.) were added with stirring. The resulting pulpy suspension was kept at 70 °C and potassium *t*-butoxide (56 g, 0.5 mol) were added in several portions. After an induction period of several minutes the insoluble precipitates slowly dissolved, due to the formation of equimolar amounts of DMSO during the spiroepoxide formation. After stirring for 1.5 h, powdered KOH (2 g) was added to the mixture. The course of the reaction was then followed by GC (conversion up to 95%). When further addition of KOH resulted in no additional epoxide formation, the mixture was allowed to cool to r.t. and water (100 mL) was added slowly with stirring. The mixture was diluted with *t*-BuOMe and then washed several times with water and brine. The organic layer was dried on $MgSO_4$ and the solvent removed. After bulb-to-bulb distillation, oxirane **15** was obtained as a colorless oil (61 g, containing 5-10% **12**) and was used for the transformation into **14** without further purification.

(25) The mixture of the (*E/Z*)-isomers **17**, and **21**, respectively, was found already earlier to be difficult to separate, cf. ref.[14k] For **21** see also: (a) Stoll, M.; Rouvé, A. *Helv. Chim. Acta* **1947**, *30*, 2019. (b) Ito, Y.; Saegusa, T. *J. Org. Chem.* **1977**, *42*, 2326. (c) Ref.[17a] (d) Flieri, H. G.; Scholz, D.; Stütz, A. *Monatsh. Chem.* **1979**, *110*, 245. (e) Torii, S.; Inokuchi, T.; Mizuguchi, K.; Yamazaki, M. *J. Org.Chem.* **1979**, *44*, 2303. (f) See ref.[19c] (g) Tsuji, J.; Yamada, T.; Kaito, M.; Mandai, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1417. (h) Rautenstrauch, V.; Snowden, R. L.; Linder, S. M. *Helv. Chim. Acta* **1990**, *73*, 896. (i) See ref.[14b]

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