Synthesis of Macrocyclic Carbonates with Musk Odor by Ring-Closing Olefin Metathesis

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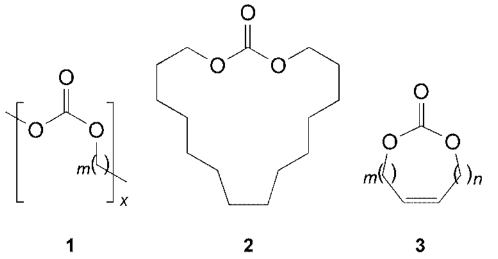
This study shows the efficiency of modern well-defined ruthenium catalysts for the formation of musk-odored macrocyclic carbonates with ring sizes between 15–23 atoms. It also reveals that, in these cases, geometric factors are very important and that smaller ring carbonates are difficult to access by ring closing metathesis, even with highly active second-generation ruthenium catalysts.

Introduction

Cyclic carbonates are valuable industrial chemicals.[1] A wide variety of cyclic carbonates have been successfully used for ring-opening polymerizations.[1] Polycarbonates of the general formula **1** have found many commercial applications, including packaging, transparent glasses and structural foams (Scheme 1).[2] Recently, polycarbonates have become promising materials for a variety of biomedical applications because of their biocompatibility, biodegrability and low toxicity.[1]



Scheme 1. Organic carbonates of industrial interest

The large-ring cyclic carbonates, such as Astrotone™ **2** prepared by Carothers et al.,[3] are valuable synthetic musks.[4] Natural macrocyclic musks, especially muscone and civetone, are attractive ingredients in many perfumes. Natural sources of musks mainly originate from animals, whose death is sometimes a prerequisite for the harvesting of musk. The Washington Convention[5] proclaims this to be ill treatment of wild animals. Furthermore, the use of more readily accessible synthetic nitro-containing and polycyclic musks has been reduced in recent years because of their health damaging properties. Hence, there is a need for the development of new biodegradable non-toxic odorants.[4]

Olefin metathesis is an efficient carbon-carbon bond-forming method that can be applied to the synthesis of various carbo- and heterocycles.[6] The ring-closing metathesis (RCM) approach has been used by Wiegers et al. to prepare a series of musky-odored macrocyclic carbonates **3** (*m*, *n* = 1−8) using the $WCl_6/SnMe_4$ catalytic system.[7] However, this ill-defined catalyst required rather harsh reaction conditions, and gave only low conversions and low yields of isolated musk macrocycles **3**.[7]

The stable and active well-defined ruthenium carbene complex $Cl_2(Cy_3P)_2Ru{=}CHPh$ (**I**)[8] and its "second- generation" successor **II**, recently developed at Caltech,[9] allow olefin metathesis under much more controlled conditions (Scheme 2).[6]

Results and Discussion

To the best of our knowledge metathesis cyclization of unsaturated carbonates catalyzed by the modern ruthenium precatalysts **I**−**II** has not been described.[10,11] Herein, we wish to report our results concerning the preparation of medium- and large-ring cyclic carbonates by olefin metathesis.

To our surprise under standard metathesis conditions (5 mol % of **I**, CH_2Cl_2, 20−40 °C, c = 0.01−0.02 M) we were unable to isolate any of the expected cyclic product **5** (Scheme 3 and Table 1, Entry b). Under more forcing conditions (80 °C, 10−25 mol % of catalysts **I** and **II** in toluene) we observed slow consumption of the substrate, lead-

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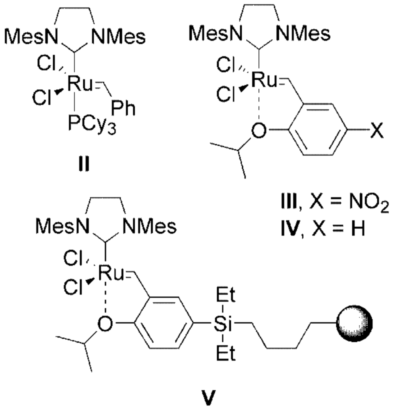
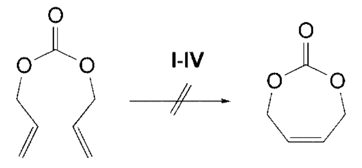
Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.



Scheme 2. The second-generation ruthenium precatalysts for alkene metathesis. Cy = cyclohexyl; Mes = 2,4,6-trimethylphenyl

ing to formation of undefined products. Even application of the highly active Hoveyda-type catalyst **III**,[12] recently developed in our group, did not produce any detectable amount of the monomeric product **5**. Prolonged stirring with carbenes **III** and **IV**[13,14] (2.5 mol %, CH_2Cl_2, 40 °C, 24 h) resulted in nearly quantitative consumption of **4** and formation of (cyclo)oligomeric and polymeric products, as suggested by TLC, NMR spectroscopy and ESI analyses.[15,16] This result was intriguing, as it is well established that seven-membered cyclic products are easily formed by RCM.[17] It is known that some allylic substrates, such as ethers, amines or tosylamides, undergo a double-bond isomerization under RCM conditions.[18] In order to establish the synthetic rules, we decided to undertake a study to determine the number of methylene spacers (*m, n* values, cf. Scheme 1) required to allow a successful RCM reaction of these substrates.



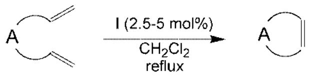
4 **5**

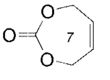
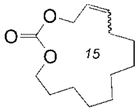
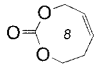
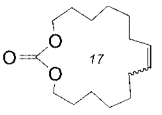
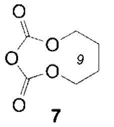
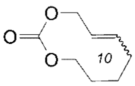
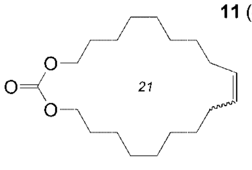
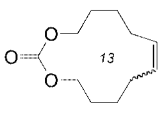
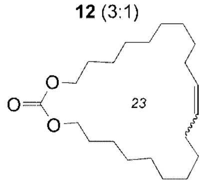
Scheme 3

Table 1 summarizes representative ring-closure reactions mediated by the commercially available Grubbs catalyst **I**. Interestingly, no products of ring sizes 8−10 were found in RCM reactions of the corresponding di(alkenyl) carbonates and the di(allyl) pyrocarbonate. A 13-membered product **9** was formed, albeit in very low yield (6%). In most cases significant amounts of polar by-products were isolated, consisting of cyclic "dimers" and higher oligomers, as determined by ESI mass spectroscopy.

In contrast to the above mentioned results the cyclization of the larger 15-membered ring **10** proceeded in a good yield. This shows that the allyl carbonate fragment *is well tolerated* by the ruthenium catalyst and does not undergo isomerization.

Table 1. RCM of di(alkenyl) carbonates; A = −OC(O)O− or −OC(O)OC(O)O−



Product (isomers ratio)	Yield[a]	Product (isomers ratio)	Yield[a]
 **5**	0	 **10** (5:1)	80[e] 79[f]
 **6**	0[b]	 **11** (4:1)	60[g] 29[h]
 **7**	0		
 **8**	0[c]	 **12** (3:1)	49
 **9** (n.d.)	6[d]	 **13** (3:1)	91

[a] Yields of isolated pure products. The (*E*) and (*Z*) stereochemistry was not assigned. Reaction conditions: *c* = 0.02 M, CH_2Cl_2, 40 °C, 5 mol % (for **5**−**9**) or 2.5 mol % (for **10**−**13**) of **I**, 2−24 h. [b] 29% of a cyclic dimer was isolated. [c] 84% of a cyclic dimer and trimer were formed. [d] 57% of a cyclic dimer was formed. [e] 20% of a cyclic dimer was formed as a by-product. [f] Reaction with the polymeric catalyst **V**. [g] 19% of a cyclic dimer was formed as a by-product. [h] Reaction with the $WCl_6/SnMe_4$ system. Reaction conditions: catalyst (10 mol %), PhCl, 90 °C, 7 h. ref.[7]

We used this transformation to further optimize the reaction conditions. The following salient observations emerged: (i) increasing concentration of the reaction solution ($c \geq 0.05$ M) apparently decreased the yield of **10**, (ii) running the reaction under higher dilution (≤ 0.01 M) at room temperature produced considerable amounts of oligomeric by-products, (iii) the highest yield of **10** (80%) can be obtained even in a more concentrated solution (*c* = 0.02 M) when a higher temperature is applied.[19]

Having established the optimum reaction conditions: *c* = 0.02 M, CH_2Cl_2, 40 °C, 2.5 mol % of **I**, 2−24 h, we were able to obtain cyclic carbonates of ring sizes between 15−23 atoms (Table 1) in good to excellent yields. The analytical data for the representative 17-membered cyclic carbonate **11** are in agreement with those published in the literature.[7] We also found that in this transformation a recyclable Hoveyda-type catalyst **V**, recently developed in our laboratory,[20] can be successfully used.

Conclusion

In summary, this study shows the efficiency of modern well-defined ruthenium catalysts for the formation of musk-odored macrocyclic carbonates with ring sizes between 15−23 atoms. It also reveals that, in these cases, geometric factors are very important and that smaller ring carbonates are difficult to access by RCM, even with highly active catalysts such as **III**.

Experimental Section

General Remarks: All RCM reactions were carried out under argon in pre-dried glassware using Schlenk techniques. CH_2Cl_2 was dried by distillation over CaH_2 and transferred under argon. Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F254 precoated plates (0.25 mm thickness) with a fluorescent indicator. Flash column chromatography was performed with Merck silica gel 60 (230−400 mesh). NMR spectroscopy: Spectra were recorded with Bruker AVANCE 500, Varian Gemini 200 and 400 spectrometers in $CDCl_3$; chemical shifts (δ) are given in ppm relative to TMS, coupling constants (*J*) in Hz. IR: Perkin−Elmer Spectrum 2000 FT-IR, wavenumbers in cm^{-1}. MS (EI, LSIMS): AMD 604 Intectra GmbH. MS (ESI): Mariner Perseptive Biosystems, Inc.

Starting Materials: Di(alkenyl) carbonates were prepared according to the literature procedures (cf. Supporting Information; for Supporting Informations see also the footnote on the first page of this article).[2,21] Catalysts **I**, **II** and **IV** are commercially available from Aldrich Chemical Co. Other chemicals were purchased from Aldrich or Fluka and used without further purification.

A Representative Procedure for RCM of Di(alkenyl) Carbonates

1,3-Dioxa-10-cycloheptadecen-2-one (11): A solution of catalyst **I** (15.4 mg, 0.0187 mmol, 2.5 mol %) in CH_2Cl_2 (5 mL) was added to a solution of di(7-octenyl) carbonate (211.8 mg, 0.75 mmol) in CH_2Cl_2 (35 mL). The resulting solution was stirred at 45 °C for 16 h. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*c*-hexane, then *c*-hexane/ethyl acetate, 8:1) to give carbonate **11** (114 mg, 60%) as a colorless oil possessing a strong sweet musky aroma[7] (4:1 isomeric mixture).[22] IR (film): $\tilde{\nu}$ = 2928, 2856, 1745, 1461, 1401, 1260, 1055, 1028, 970 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.20−1.39 (m, 16 H), 1.55−1.64 (m, 2 H), 1.85−2.01 (m, 2 H), 4.02−4.08 (m, 4 H), 5.20−5.37 (m, 2 H) ppm. MS (EI): *m*/*z* (%) = 254 (0.9), 163 (0.9), 149 (2), 135 (7), 121 (9), 110 (9), 108 (10), 96 (24), 95 (17), 94 (17), 93 (17), 82 (26), 81 (40), 79 (27), 66 (24), 67 (71), 55 (52), 54 (39), 53 (18), 42 (21), 41 (100), 38 (39). HRMS (ESI) $[M + Na]^+$ ($C_{15}H_{26}O_3Na$): calcd. 277.1774; found 277.1761. The analytical data are in agreement with those published in literature.[7]

1,3-Dioxa-8-cyclotridecen-2-one (9): Colorless oil (8.9 mg, 6%). IR (KBr): $\tilde{\nu}$ = 2932, 2857, 1745, 1459, 1403, 1256, 1040, 971 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.38−1.50 (m, 8 H), 1.60−1.73 (m, 2 H), 1.92−2.09 (m, 2 H), 4.03−4.12 (m, 4 H), 5.30−5.42 (m, 2 H) ppm. MS (EI): *m*/*z* (%) = 198 (0.9), 155 (7), 137 (34), 136 (100), 121 (30), 108 (59), 107 (39), 95 (91), 94 (56), 93 (61), 81 (80), 80 (47), 79 (62), 68 (37), 67 (77), 55 (44), 54 (16), 43 (9), 41 (32), 39 (5). HRMS (ESI) $[M + Na]^+$ ($C_{11}H_{18}O_3Na$): calcd. 221.1148; found 221.1140.

1,3-Dioxa-5-cyclopentadecen-2-one (10): Colorless waxy solid possessing a strong musky aroma (136.2 mg, 80%). A 5:1 isomeric mixture (GC).[22] IR (film): $\tilde{\nu}$ = 2927, 2855, 1745, 1457, 1391, 1246, 1010, 969 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.10−1.49 and 1.53−1.72 (2m, 14 H), 2.00−2.11 (m, 2 H), 4.22−4.32 (m, 2 H), 4.48−4.58 (m, 2 H), 5.53−5.72 (m, 1 H), 5.74−5.88 (m, 1 H) ppm. MS (EI): *m*/*z* (%) = 227 (15), 221 (13), 198 (13), 176 (11), 165 (43), 154 (79), 147 (16), 138 (33), 137 (58), 136 (63), 123 (27), 117 (30), 110 (50), 108 (30), 98 (41), 96 (91), 92 (33), 85 (81), 84 (100), 83 (34). HRMS (ESI) $[M + Na]^+$ ($C_{13}H_{22}O_3Na$): calcd. 249.1461; found 249.1447.

1,3-Dioxa-12-cyclohenicosen-2-one (12): Colorless, low melting waxy solid possessing a noticeable musky aroma (114 mg, 49%). A 2.8:1 isomeric mixture (GC).[22] IR (film): $\tilde{\nu}$ = 2927, 2855, 1746, 1461, 1400, 1259, 967 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.23−1.45 (m, 24 H), 1.61−1.70 (m, 2 H), 1.93−2.06 (m, 2 H), 4.10−4.14 (t, *J* = 6.5 Hz, 4 H), 5.35−5.41 (m, 2 H) ppm. HRMS (ESI) $[M + Na]^+$ ($C_{19}H_{34}O_3Na$): calcd. 333.2400; found 333.2396.

1,3-Dioxa-13-cyclotricosen-2-one (13): Colorless, low melting waxy solid, possessing a weak musky aroma (211.5 mg, 91%). A 3:1 isomeric mixture (GC).[22] IR (KBr): $\tilde{\nu}$ = 2925, 2853, 1746, 1467, 1395, 1261, 1166, 964 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.13−1.40 (m, 28 H), 1.59−1.70 (m, 2 H), 1.88−2.03 (m, 2 H), 4.16−4.21 (m, 4 H), 5.28−5.40 (m, 2 H) ppm. MS (EI): *m*/*z* (%) = 338 (7), 164 (2), 152 (4), 149 (5.5), 138 (10), 137 (9.5), 135 (14), 124 (17.5), 123 (15), 121 (19), 111 (8), 110 (29), 109 (26), 107 (10), 97 (19), 96 (79), 95 (50), 94 (18), 93 (14), 83 (26), 84 (100), 81 (65), 80 (32), 79 (16), 69 (31), 68 (31), 67 (59), 57 (10), 55 (60), 54 (23), 43 (16), 41 (42), 39 (5). HRMS (ESI) $[M + Na]^+$ ($C_{21}H_{38}O_3Na$): calcd. 361.2713; found 361.2709.

Acknowledgments

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