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Optimization of Ring-Closing Metathesis: Inert Gas Sparging and Microwave Irradiation

Bernd Nosse, Andreas Schall, Won Boo Jeong, Oliver Reiser *

Institut für Organische Chemie der Universität Regensburg, Universitätsstrasse 31, 93053 Regensburg, Germany
Fax: (+49)-941-943-4121, e-mail: oliver.reiser@chemie.uni-regensburg.de

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Abstract: A systematic study of a ring-closing metathesis towards a tetrasubstituted double bond as part of a seven-membered ring in a 5.7.5-tricyclic guaianolide system is described. By combining two techniques, namely sparging an inert gas through the solution together with dielectric heating *via* microwave irradiation a high-yielding ring-closing metathesis reaction in this particularly challenging case was achieved. The results obtained compare favorably with conventional heating conditions or with microwave irradiation in a closed system. The key aspects seem to be that rapid microwave irradiation diminishes catalyst decay by allowing the required high reaction temperature to be reached quickly and homogeneously and thereby providing enough energy for a successful metathesis reaction, while inert gas sparging is purging off evolving ethylene to shift the equilibrium to the product.

Keywords: homogeneous catalysis; metathesis; microwave irradiation; ring-closing metathesis; ruthenium; tetrasubstituted olefin

Introduction

The construction of various small, medium and macrocyclic ring systems has been accomplished by ring-closing metathesis (RCM) as the key step in numerous natural product syntheses.[1] Nevertheless, optimization studies of the RCM with respect to catalyst loading and reaction conditions are scarce,[2] and, especially, the formation of tetrasubstituted double bonds in such reactions remains difficult and leaves room for improvement. Five- and six-membered ring cyclizations forming tetrasubstituted double bonds, which benefit by the Thorpe–Ingold effect, have met with some success.[3] In contrast, only few RCM examples for tetrasubstituted double bonds with other ring sizes have been reported,[4] and new approaches such as relay ring-closing metathesis[5] have been devised to overcome current problems.[6]

In the course of our investigations toward the total synthesis of guaianolides such as Arglabin or Ixerin Y, we employed ring-closing metathesis as the key step to construct the typical 5.7.5-tricyclic ring system **1**.[7] However, RCM of **2** employing various commercially available ruthenium catalysts suffered from low conversion, long reaction times, and the need for high catalyst loading and reaction temperatures, as generally encountered in the synthesis of tetrasubstituted alkenes by olefin metathesis.

Herein, we report a short systematic study on the enhancement of such RCM reactions by a combination of inert gas sparging together with microwave heating.

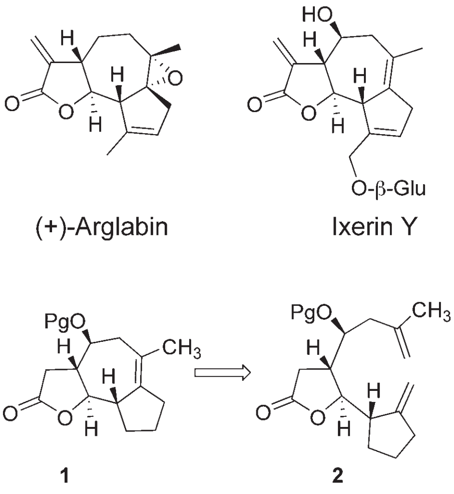
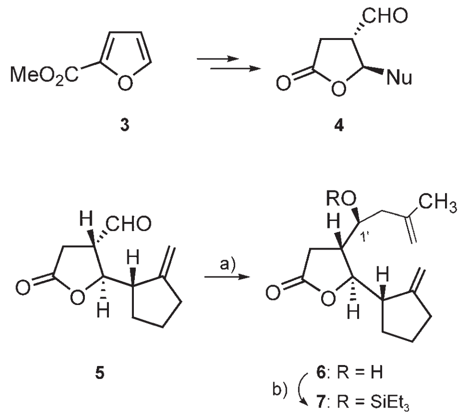


Figure 1. Retrosynthetic analysis of tricyclic 5.7.5-sesquiterpene lactones.

Results and Discussion

Conventional RCM

Recently we described a convenient asymmetric route that allows the synthesis of either enantiomer of substituted γ-butyrolactones **4** starting from furan-2-carboxylic ester **3**.[8] Following this strategy, aldehyde **5** was syn-



Scheme 1. *Reaction conditions:* a) (2-methallyl)-trimethylsilane (2.0 equivs.), $BF_3 \cdot OEt_2$ (1.05 equivs.), CH_2Cl_2, −50 °C, 17 h, 61%, dr (1'*R*/1'*S*) = 72:28; b) chlorotriethylsilane (1.7 equivs.), NEt_3 (1.9 equivs.), CH_2Cl_2, room temperature, 2.75 days, quant., dr (1'*R*/1'*S*) = 71:29.

thesized and subsequently allylated to obtain **6**, serving as the starting point in our metathesis study, as a 3:1 diastereomeric mixture at C1' following the Felkin–Anh[9] paradigm. Although a number of reports have shown that unprotected hydroxy groups do not disturb or even accelerate a RCM being mediated by ruthenium-based metathesis catalysts,[10] we were not able to achieve this transformation with **6**. Consequently, several protecting groups were screened, revealing that the triethylsilyl ether **7** showed best results in subsequent metathesis reactions. The TES group could be introduced quantitatively, proved to be stable throughout the RCM[11] – in contrast, we observed partial deprotection of the corresponding trimethylsilyl derivative – and was readily cleaved by fluoride.

Orienting experiments with the ruthenium(II)-alkylidene complexes **8**,[12] **9**,[13] or **10**[14] (Fig. 2) revealed that the most suitable catalysts with respect to reaction time and yields for the RCM 5.7.5-tricyclic ring system **1** proved to be **9**, which was therefore used throughout this investigation.

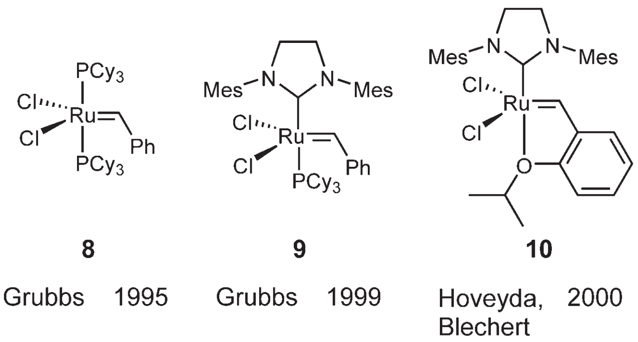
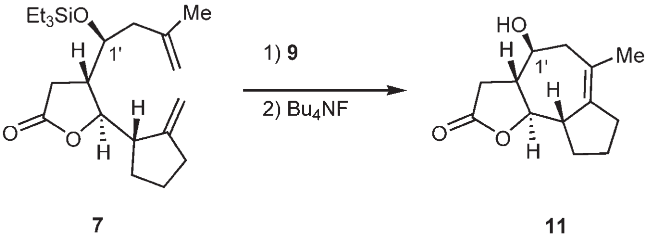


Figure 2. Commonly used commercially available ruthenium olefin-metathesis catalysts.

Nevertheless, the yield of the RCM product **11** employing 10 mol % of catalyst **9** under standard conditions and performing the reaction under an inert atmosphere of nitrogen did not exceed 35% (Table 1, entry 1). Our initial screening experiments also showed that the application of an ethylene atmosphere, which was found to be beneficial in many metathesis processes,[15] completely inhibits the transformation of **7** to **11**. We therefore attempted to actively remove the evolving ethylene during the RCM by sparging the reaction mixture with a gentle stream of an inert gas. Indeed, using the identical catalyst loading of 10 mol % as before, the yield could be almost doubled (Table 1, entries 1 and 3) when introducing nitrogen through a cannula during the metathesis reaction. Even with only 5 mol % of catalyst the yield was already significantly improved (Table 1, entry 2), while an optimum was reached when 15 mol % of **9** was employed, giving rise to **11** in 80% yield (Table 1, entry 4).

Prolonging the reaction time to seven days even with a concurrent increase of catalyst did not significantly improve the yield of the title reaction. Apparently, the unimolecular thermolytic decomposition of the catalytically active ruthenium methylidene complex as described by Grubbs and co-workers[16] proceeds at elevated temperatures (80 °C, Table 1; 110 °C, Table 2) sufficiently fast to render **9** catalytically inactive for the title transformation in much less than one day. The decomposition of the metathesis catalyst is also visually observed by a color change from brown-red to green-brown. Since

Table 1. RCM-reactions under conventional heating conditions.[a]



Entry	Conditions	Time	Yield [%][b]
1	10 mol % **9**, N_2 atmosphere	1 d	35
2	5 mol % **9**, N_2 sparging	1 d	49
3	10 mol % **9**, N_2 sparging	1 d	66
4	15 mol % **9**, N_2 sparging	1 d	80
5[c]	22.5 mol % **9**, N_2 sparging	7 d	82

[a] All reactions were carried out in toluene at 80 °C. 5 mol% of **9** were added at the beginning of the reaction, followed by additional 5 mol % every 3 hours.

[b] Yields of isolated products, the diastereomeric ratio (1'*S*/1'*R* = 71:29) did not change in the course of the reaction.

[c] 5 mol % of **9** were added at the beginning of the reaction, followed twice by 5 mol % of **9** after 1 and 2 days, and 7.5 mol % of **9** after 4 days.

high temperatures were necessary to run the RCM of **7**[17] the thermal instability of the metathesis catalysts obviously represents the limiting factor of this sterically demanding RCM reaction.

RCM under Microwave Irradiation

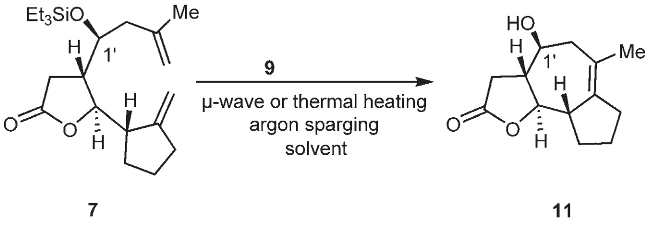
Although dielectric heating has been established as a yield-enhancing method for many different reactions,[18] its application in ring-closing metathesis is still a recent field of research. Nevertheless, under microwave conditions the conversion of metathesis reactions in the liquid phase, of reactions employing polymer-bound olefins or ruthenium catalysts, as well as of domino reactions was improved considerably.[19]

Due to the high reaction temperatures required for the RCM of **7**, the application of microwave irradiation seemed to be especially suitable. In our study we used a microwave reactor emitting a focused irradiation at 2.45 GHz with a maximum power of 300 W. The reactions were performed in an open system with simultaneous introduction of a gentle stream of argon by means of a small teflon tube (Table 2, entries 1–6). This way, an external stirring device could be avoided and, even more important, the reaction could be run under an inert atmosphere together with concurrent removal of evolving ethylene. To allow a direct comparison of the results so obtained, control experiments under identical conditions but with conventional heating were performed as well (Table 2, entries 7–9).

Similar to conventional heating no change in the diastereomeric ratio of starting material and product could be detected, but yields of the intramolecular metathesis reaction were significantly higher and completion of the reaction was achieved in shorter times (Tables 1 and 2).

While dichloromethane proved to be unsatisfactory as solvent (Table 2, entry 1), the yield could be raised to over 80% using mesitylene or toluene (10 mol % **9**, entries 2 and 5). The heating rate for the two latter solvents in the absence of catalyst and starting material is rather slow due to their small dipole moment. However, performing the microwave reaction in the presence of **7** and **9** leads at 300 W in less than 10 minutes to a temperature around 100 °C which reached a maximum of 110 °C for both solvents after approx. 20 minutes, demonstrating the energy uptake by the reaction partners. Since toluene can be removed more easily it was taken for all subsequent experiments. Further optimization revealed that by applying a 15 mol % loading of **9**,[20] the RCM of **7** could be accomplished with an isolated yield of 98% (entry 6), which, to the best of our knowledge, represents one of the most efficient examples for an RCM towards a highly substituted cycloalkene. Conventional

Table 2. RCM reactions under microwave irradiation or conventional heating.



Entry	Catalyst loading [mol %]	Conditions[a]	Deprotection	Yield [%]
1[b]	10	CH_2Cl_2, 300 W, 40 °C, 75 min	–	27[f]
2[b]	10	mesitylene, 300 W, 110 °C, 75 min	–	81[f]
3[c]	10	toluene, 225 W, 95 °C, 150 min	–	63[g]
4[d]	5	toluene, 300 W, reflux (110 °C), 60 min	–	54[f]
5[b]	10	toluene, 300 W, reflux (110 °C), 75 min	Bu_4NF	82[h]
6[e]	15	toluene, 300 W, reflux (110 °C), 90 min	Bu_4NF	98[h]
7[e, i]	15	toluene, reflux (110 °C), 120 min, glass vessel	Bu_4NF	60[h]
8[e, i]	15	toluene, reflux (110 °C), 120 min, quartz vessel	Bu_4NF	57[h]
9[e, i]	15	toluene, reflux (110 °C), 250 min, glass vessel	Bu_4NF	82[h]

[a] All microwave reactions were carried out in a quartz vessel.
[b] Ruthenium catalysts **9** in toluene was added during 30 min *via* syringe pump.
[c] 5 mol % of **9** were added at the beginning of the reaction, followed by additional 5 mol % after 60 min.
[d] 5 mol % of **9** were added at the beginning of the reaction.
[e] 5 mol % of **9** were added at the beginning of the reaction, followed by additional 5 mol % every 30 min.
[f] Yield determined by NMR as the protected TES-derivative of **11**.
[g] Yield determined by GC as the protected TES-derivative of **11**.
[h] Yield of isolated product, the diastereomeric ratio (1′*S*/1′*R* = 71 : 29) did not change in the course of the reaction.
[i] Reactions were initiated by putting the reaction vessel into a preheated oil bath at 120 °C.

heating using a preheated oil bath set at 120 °C gave much slower conversion (entries 7 and 8), and even at prolonged reaction times (entry 9) the yield does not reach the value obtained under microwave conditions. It was also checked that the yield of the reaction is not significantly influenced by the reaction vessel used, i.e., that in a glass vessel about the same results are obtained as in the quartz vessel that was used in the microwave experiments.

Besides the solvent, the power of the microwave irradiation, reflecting the maximum temperature reached in the reaction vessel, had a strong influence on the course of the reaction. For example, reduction of the output power from 300 W (entry 5) to 225 W (entry 3) lowers the temperature maximum of the solution to 95 °C and led to a drop in yield to 63% yield despite doubling the reaction time.

Since no decomposition of starting material was observed in any case, the formation of **11** seems to be only dependent on the catalytically active ruthenium species, which is also reflected in the correlation of yield with the relative amount of the employed ruthenium complex **9**. Consequently, when dielectric heating is applied, the thermolytic decay of the catalyst appears again to be decisive for the outcome of the reaction.

To shed further light on the catalytic activity of **9** under microwave conditions, a time-dependent analysis for the conversion of **7** was performed, increasing the catalyst loading of **9** in three steps each by 5 mol % to a total amount of 15 mol % (Fig. 3). After each addition of the catalyst the microwave irradiation was continued for 60 minutes and the ratio of product **11** and starting material **7** was determined *via* GC in 30-minute intervals. This experiment clearly showed that under the reaction conditions the Grubbs catalyst **9** rapidly decays and that within 30 minutes at most it is completely inactivated.

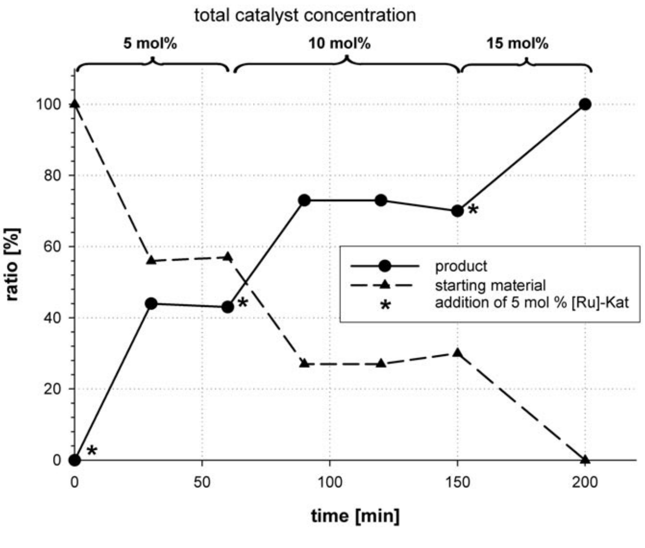


Figure 3. Time-dependent conversion of the metathesis reaction under microwave irradiation.

In comparison with conventional heating, these results make clear the advantage of dielectric heating and are in accordance with the line of argument put forward by Undheim[19e] and co-workers: While catalyst decomposition processes still take place, rapid microwave irradiation diminishes these processes by allowing the required high reaction temperature to be reached quickly and homogeneously and thereby providing enough energy for a successful metathesis reaction.

Noteworthy, passing an inert gas through the reaction solution in order to expel ethylene plays a crucial role in the microwave-assisted RCM. Attempts to achieve a ring-closure using a closed microwave system (monomode Discover from CEM) failed completely and starting material could be recovered almost quantitatively.

Conclusion

Combining two techniques, namely sparging an inert gas in order to purge off evolving ethylene together with dielectric heating *via* microwave irradiation enabled a powerful ring-closing metathesis reaction in a particularly challenging case, i.e., the construction of a tetrasubstituted double bond as a part of a constrained seven-membered ring system. The almost quantitative yield of the metathesis reaction of the TES-protected diene **7** to the cycloalkene **11** could not be achieved under conventional heating conditions or under microwave irradiation in a closed system.

Experimental Section

General Remarks

Reactions with moisture-sensitive chemicals were performed under nitrogen or argon in a flame-dried reaction flask. Solvents were dried by standard methods. Chromatography: Macherey-Nagel silica gel (0.03–0.06 mm). Diastereomeric ratios were determined by integration of the respective diastereomeric peaks in ^{13}C NMR. TLC: commercial precoated aluminium sheets 60 F 254 (Merck). IR: Mattson Genesis series FT-IR, Perkin Elmer 298, Bruker IFS 66, ν in cm^{-1}. ^{1}H NMR and ^{13}C NMR: Bruker Avance 600, ARX 400, Avance 300, δ in ppm, *J* in Hz. Multiplicities were determined by DEPT (distortionless enhancement by polarization transfer) measurements. MS: Finnigan MAT 95, Varian MAT 311A. GC: Fisons GC 8130 (split-injector, CromJet Integrator), column: J&W Scientific DBWAX (length 30 m, inner diameter 0.25 mm), injector temperature 200 °C, oven temperature 230 °C, carrier gas helium. Experiments under microwave heating were performed with a Synthewave S402 from Prolab, France (open system, focused irradiation at 2.45 GHz, maximum power 300 W) with a simultaneous gentle stream of argon introduced *via* a teflon tube.

Typical Procedure for Metathesis Reaction under "Conventional" Conditions

In a 100-mL Schlenk-flask equipped with a condenser, diene **7** (350 mg, 0.960 mmol, dr = 71:29, 1.0 equiv.) was dissolved in dry toluene (32 mL). A gentle stream of nitrogen was introduced into the solution *via* cannula and the solution was heated to 80 °C by means of an oil bath. The catalyst **9** (41 mg, 0.048 mmol, 5 mol %) was added, followed by an additional 5 mol % after 4 h. After an additional 2 h of stirring 5 mol % of **9** was added once more (total catalyst loading 15 mol %) and stirring at 80 °C was continued overnight maintaining the inert gas introduction and adding solvent to keep the volume constant if required. After cooling to 40 °C Bu_4NF (757 mg, 2.40 mmol, 2.5 equivs.) was added and the reaction mixture was stirred for 45 min at this temperature. Subsequently the solvent was removed under vacuum and the residue was purified by column chromatography (gradient hexanes/EtOAc, 5:1 to 1:1) to afford **11** as a colorless solid; yield: 171 mg (0.769 mmol, 80%), *dr* (4*S*/4*R*) = 71:29.

Typical Procedure for Metathesis Reaction under Microwave Irradiation

Diene **7** (60 mg, 0.165 mmol, dr = 71:29) was dissolved in dry toluene (9 mL, $c = 0.02$ M) in a quartz vessel and brought into the microwave reactor which was equipped with a condenser. Argon was gently introduced into the solution *via* a teflon tube. By means of an additional teflon tube a solution of catalyst **9** (7 mg, 8.25×10^{-6} mol, 5 mol %) in dry toluene (0.4 mL) was added and irradiation with microwaves (300 W) was started. After 30 min and again after altogether 60 min, 5 mol % of the ruthenium catalyst as a solution in dry toluene (0.4 mL) was inserted *via* the teflon tube, while the irradiation was continued permanently. Following the last addition, the reaction mixture was irradiated for additional 30 min (total time 90 min). Subsequently the solvent was removed under vacuum, the residue was redissolved in THF (5 mL) and treated with Bu_4NF (65 mg, 0.206 mmol, 1.25 equivs.). Stirring was continued for 30 min at room temperature and the solvent was removed under vacuum. After chromatography on silica (hexanes/EtOAc = 3:1) **11** was obtained as a colorless solid; yield: 36 mg (0.162 mmol, 98%), dr (4*S*/4*R*) = 72:28.

(3a*R*,4*S*/*R*,9a*S*,9b*R*)-4-Hydroxy-6-methyl-3a,4,5,7,8,9,9a,9b-octahydro-3*H*-azuleno[4,5-*b*]furan-2-one (11): $R_f = 0.18$ (hexanes/EtOAc, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$, major diastereomer): $\delta = 1.40–1.55$ (m, 1H), 1.60–1.72 (m, 1H), 1.70–1.84 (m, 1H), 1.75 (s, 3H), 2.08–2.18 (m, 1H), 2.18–2.27 (m, 2H), 2.28–2.48 (m, 2H), 2.42–2.51 (m, 1H), 2.46 (dd, $J = 16.4$, 12.9 Hz, 1H), 2.60–2.70 (m, 1H), 2.77 (dd, $J = 16.4$, 6.5 Hz, 1H), 3.54 (dt, $J = 10.1$, 2.5 Hz, 1H), 3.67 (t, $J = 10.2$ Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$, major diastereomer): $\delta = 24.05$ (+, CH_3), 24.77 (–, C-8), 32.01 (–, C-9), 32.92 (–, C-7), 35.54 (–, C-3), 45.49 (–, C-5), 46.77 (+, C-9a), 54.65 (+, C-3a), 69.67 (+, C-4), 84.53 (+, C-9b), 124.18 (C_{quart}, C-6), 138.92 (C_{quart}, C-6a), 175.77 (C_{quart}, C-2); IR (KBr): $\nu = 3446$, 2930, 2866, 1776, 1421, 1184, 1039, 976, 732 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%) = 222.2 (44) [M^+], 120.2 (21), 109.2 (100), 95.2 (41), 67.2 (32); HRMS (EI, 70 eV): *m*/*z* = 222.1258 (calcd. for $C_{13}H_{18}O_3$: 222.1256 [M^+]).

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