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Exploiting the Reversibility of Olefin Metathesis. Syntheses of Macrocyclic Trisubstituted Alkenes and (*R*,*R*)-(–)-Pyrenophorin

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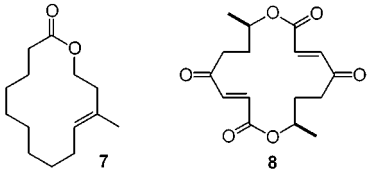
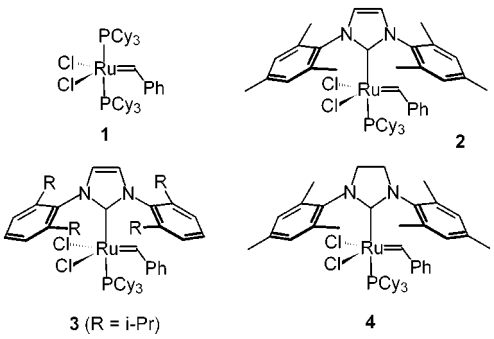
ABSTRACT



The formation of the trisubstituted cycloalkene 7 by RCM of diene 5 proceeds via the acyclic dimer 6, thus demonstrating the ready reversibility of olefin metathesis if catalyzed by "second generation" ruthenium carbene complexes such as 2–4. When applied to acrylate 11, these catalysts trigger a cyclooligomerization process that evolves with time and serves as key step en route to the lactide antibiotic (–)-pyrenophorin 8.

According to the generally accepted mechanism, (ring closing) olefin metathesis is—in principle—a reversible process.[1] In practice, however, the retro-reaction is kinetically hindered and usually does not come into play because the alkene entity of the product is more highly subsituted than the olefinic sites of the substrate and standard metathesis catalysts such as **1** are rather senstitive toward this parameter.[2] As a consequence, deliberate uses of this a priori reversibility are scarce.[3−5]



We now report two examples illustrating the preparative potential of the retro-metathesis mode of action. Both of them rely on the superior reactivity of "second generation" ruthenium carbene complexes such as **2**−**4**.[6−8] These catalysts were recently found to cyclize tri- and even tetrasub-

(1) Reviews: (a) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (c) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036. (d) Fürstner, A. *Top. Catal.* **1997**, *4*, 285.

(2) Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62*, 7310.

(3) For another example, see: Smith, A. B.; Adams, C. M.; Kozmin, S. A., *J. Am. Chem. Soc.* **2001**, *123*, 900−991. We thank Prof. Smith for informing us on his results prior to publication.

(4) Recently, the increased stereoselectivity of macrocyclizations using **2** or **4** as the catalyst has been ascribed to the reversibility of the reaction, cf.: (a) Lee, C. W.; Grubbs, R. H. *Org. Lett.* **2000**, *2*, 2145. (b) Fürstner, A.; Thiel, O. R.; Kindler, N.; Bartkowska, B. *J. Org. Chem.* **2000**, *65*, 7990.

(5) (a) Xu, Z.; Johannes, C. W.; Houri, A. F.; La, D. S.; Cogan, D. A.; Hofilena, G. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 10302. (b) Hoveyda, A. H., *Top. Organomet. Chem.* **1998**, *1*, 105.

(6) (a) Huang, J.; Stevens, E. D.; Nolan, S. P.; Petersen, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674. (b) Jafarpour, L.; Stevens, E. D.; Nolan, S. P. *J. Organomet. Chem.* **2000**, *606*, 49.

(7) (a) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247. (b) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953. (c) Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1751.

(8) (a) Ackermann, L.; Fürstner, A.; Weskamp, T.; Kohl, F. J.; Herrmann, W. A. *Tetrahedron Lett.* **1999**, *40*, 4787. (b) Weskamp, T.; Kohl, F. J.; Hieringer, W.; Gleich, D.; Herrmann, W. A. *Angew. Chem.* **1999**, *111*, 2573. (c) Ackermann, L.; El Tom, D.; Fürstner, A. *Tetrahedron* **2000**, *56*, 2195.

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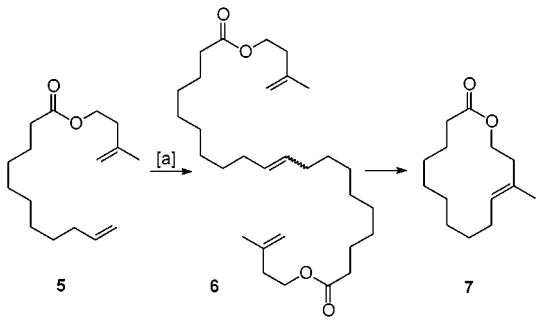
stituted products,[7−9] but all examples reported to date deal with five−eight-membered rings only. Since direct access to trisubstituted cycloalkenes of larger ring sizes via RCM is of eminent importance but known to be very difficult,[5,10] we tried to determine if **2**−**4** could bring compounds of this type into reach. In an attempt to cyclize diene **5** to the 14-membered lactone **7** (Scheme 1), however, we noticed that

Scheme 1[a]



[a] [a] See Table 1.

the desired ring is only formed in small amounts after a 4 h reaction time, while the acyclic dimer **6** prevails. On prolonged heating (40 h), however, **6** almost disappears while **7** becomes the major product (Table 1).

Table 1. Dimerization versus Cyclization of Diene **5**[a]

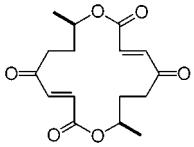
substrate	catalyst	*t* (h)	product[c]
5	**1** (10%)	17	**6** (79%)
	2 (10%)	40	**7** (65%)[b]
	3 (3%)	4	**5** (25%), **6** (29%), **7** (10%)
	3 (6%)	40	**7** (57%)[b]
	4 (6%)	40	**7** (57%)[b]
6	**3** (10%)	28	**7** (60%)[b]

[a] All reactions are carried out in refluxing CH_2Cl_2. [b] In addition to **7**, traces of **5** and **6** are detected by GC. [c] The product **7** is invariably obtained as a 7:1 mixture of isomers.

To corroborate that the cyclic monomer **7** is formed via the acyclic dimer **6**, substrate **5** was treated with the standard Grubbs carbene **1**.[11] As expected, this catalyst effects a smooth dimerization at the least substituted site but does not cause any subsequent cyclization, irrespective of the catalyst loading and the reaction time. Triene **6** thus obtained in 79% yield was then exposed to complex **3** in refluxing CH_2Cl_2 and was thereby cleanly converted into the cyclic monomer **7**.[12] This example demonstrates that the reversibility of olefin metathesis is key to success of the formation of highly substituted macrocycles and illustrates again the superior performance of **2**−**4** as compared to **1**.

"Second generation" ruthenium carbene complexes also react with electron-deficient alkenes such as acrylic acid derivatives which are problematic substrates for the parent Grubbs catalyst **1**.[9,13] Notably, however, compounds of this type undergo either a regular cyclization or a cyclodimerization[14] depending on the tether length between the alkene groups. If the latter pathway is operative, high selectivity for head-to-tail connected monomer units and (*E*)-configured double bonds in the products was observed. This behavior warrants further study because it may open a novel entry into lactide antibiotics incorporating these structural elements.

The 16-membered macrodiolide (−)-pyrenophorin **8**, an antifungal agent produced by the plant pathogenic fungi *Pyrenophora avenae* and *Stemphylium radicinum*,[15] is a prototype member of this family of natural products. Numer-



ous syntheses of this γ-oxo-α,β-unsaturated dilactone have been reported (for a compilation, see Table S-1 in the Supporting Information).[16] Despite the fact that all but one cleverly exploit the C_2-symmetry of the target and employ rather diverse methodology for the construction of the macrocyclic ring, most syntheses are rather lengthy and poor yielding (Table S-1, Supporting Information).

(9) Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. P. *J. Org. Chem*. **2000**, *65*, 2204. (b) Fürstner, A.; Thiel, O. R.; Blanda, G. *Org. Lett.* **2000**, *2*, 3731.

(10) For a prototype example, see RCM approaches to epothilone B: (a) Meng, D.; Bertinato, P.; Balog, A.; Su, S.-D.; Kamenecka, T.; Sorensen, E. J.; Danishefsky, S. J. *J. Am. Chem. Soc*. **1997**, *119*, 10073. (b) May, S. A.; Grieco, P. A. *Chem. Commun*. **1998**, 1597. (c) Review: Mulzer, J. *Monatsh. Chem*. **2000**, *131*, 205.

(11) (a) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc*. **1996**, *118*, 100. (b) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 2039.

(12) The closest precedent to the result reported herein is described by Hoveyda et al., cf. ref 5. In the course of their synthesis of the antifungal agent Sch 38516, the formation of a trisubstituted 14-membered lactam is outlined by using $Mo(=NAr)(=CHCMe_2Ph)[OCMe(CF_3)_2]_2$ as metathesis catalyst. Although no direct proof has been gained that this particular cyclization occurs via a discrete intermediate, the authors were also able to effect a *stepwise* conversion by first exposing the substrate to the ruthenium carbene **1**. This leads to an acyclic dimer which—in a separate step—can be converted into the desired cyclic monomer by means of Schrock's molybdenum catalyst.

(13) For related cross-metathesis reactions of acrylates, see: Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc*. **2000**, *122*, 3783.

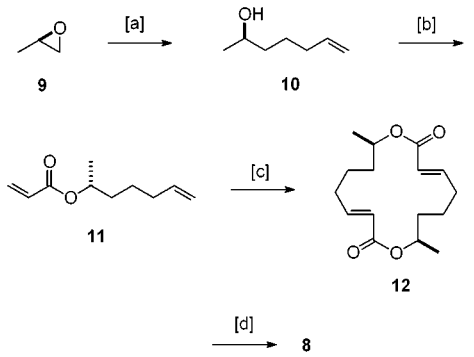
(14) For an elegant application of a RCM-based macrodimerization reaction to a natural product synthesis, see: Smith, A. B.; Kozmin, S. A.; Adams, C. M.; Paone, D. V. *J. Am. Chem. Soc*. **2000**, *122*, 4984.

(15) (a) Isolation: Ishibashi, K. *J. Agric. Chem. Soc. Jpn*. **1961**, *35*, 257. (b) Structure elucidation: Nozoe, S.; Hirai, K.; Tsuda, K.; Ishibashi, K.; Shirasaka, M.; Grove, J. F. *Tetrahedron Lett*. **1965**, 4675.

(16) Syntheses of rac-**8** as well as formal total syntheses are compiled in the Supporting Information. For syntheses of (−)-**8**, see: (a) Seebach, D.; Seuring, B.; Kalinowski, H.-O.; Lubosch, W.; Renger, B. *Angew. Chem*. **1977**, *89*, 270. (b) Seuring, B.; Seebach, D. *Liebigs Ann. Chem*. **1978**, 2044. (c) Mali, R. S.; Pohmakotr, M.; Weidmann, B.; Seebach, D. *Liebigs Ann. Chem*. **1981**, 2272. (d) Hatakeyama, S.; Satoh, K.; Sakurai, K.; Takano, S. *Tetrahedron Lett*. **1987**, *28*, 2717. (e) Baldwin, J. E.; Adlington, R. M.; Ramcharitar, S. H. *Synlett* **1992**, 875. (f) Machinaga, N.; Kibayashi, C. *Tetrahedron Lett*. **1993**, *34*, 841. (g) Matsushita, Y.-I.; Furusawa, H.; Matsui, T.; Nakayama, M. *Chem. Lett*. **1994**, 1083. (h) Nokami, J.; Taniguchi, T.; Gomyo, S.; Kakihara, T. *Chem. Lett*. **1994**, 1103. (i) Sugai, T.; Katoh, O.; Ohta, H. *Tetrahedron* **1995**, *51*, 11987.

The metathesis-based approach pursued in our laboratory (Scheme 2) accounts for a total synthesis of (−)-**8** which is

Scheme 2[a]

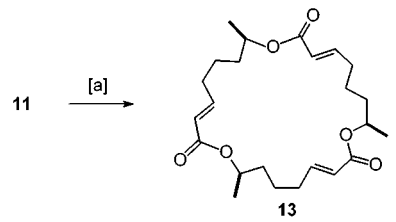


[a] [a] 3-Butenylmagnesium bromide, CuCl(COD) cat., THF, −78 °C → rt, 75%; [b] acrylic acid chloride, Et_3N, CH_2Cl_2, rt, 14 h, 82%; [c] complex **4** (5 mol %), CH_2Cl_2, reflux, 50 min, 37%; [d] CrO_3, Ac_2O, AcOH, benzene, 0 °C, 30 min, 54%.

much shorter than all previous ones yet equally or even more efficient. We used enantiomerically pure (*R*)-propenoxide **9** as the starting material, which is commercially available or can be readily prepared by Jacobsen's excellent resolution method.[17] Reaction with but-3-enylmagnesium bromide in the presence of catalytic amounts of CuCl(COD) (COD = cyclooctadiene)[18] delivers alcohol **10** in good yield which is esterified with acrylic acid chloride under standard conditions to provide ester **11**.

Surprisingly, however, on treatment with the ruthenium complex **4** as the catalyst this diene undergoes a *cyclooligomerization which evolves with time*: if the reaction is quenched by addition of EtOCH=CH_2 immediately after TLC indicates complete consumption of the substrate (ca. 50 min), a 37% yield of the desired cyclodimeric compound **12** as the major kinetic product is obtained after standard workup.[19] On prolonged stirring, however, this compound almost disappears and the corresponding cyclotrimer **13** starts to prevail, together with higher cyclooligomers. We are unaware of any precedent to such a rapid evolution of a product mixture formed by an RCM-based macrocyclization process. Even more surprising is the fact that catalyst **2** containing an imidazol-2-ylidene rather than the imidazolidin-2-ylidene ligand in **4** gives very little dimer (<10%) at any time but affords directly the cyclotrimeric compound **13** as the major product of the reaction in excellent yield (Scheme 3).

Scheme 3[a]



[a] [a] Complex **2** (5 mol %), CH_2Cl_2, reflux, 15 h, 81%.

The as yet limited understanding of the mode of action of such "second generation" ruthenium catalysts makes an unambiguous explanation of this subtle but distinct behavior presently impossible. Care, however, should be taken in trying to interpret this result simply by calculating and comparing the thermodynamic stability of **13** and **12** that seem to be similar in energy. Accurate data are difficult to obtain in view of the tremendous number of conformational minima of **13** and its higher oligomers, and the fact that standard programs do not account for the different entropic terms encountered during the formation of dimeric, trimeric, or oligomeric products, respectively.

The final allylic oxidation of diene **12** was carried out as previously described,[16a] providing (−)-**8** in 54% yield. Although the efficiency of the metathesis-based macrodimerization step may seem low, one must keep in mind that the overall yield obtained over the entire sequence (12%) compares well with the most productive previous syntheses of this particular fungicide because it is significantly shorter than any of the recorded approaches (cf. Table S-1). Therefore, this application represents an additional example for a new "economy of steps" enabled by metathetic conversions.[20]

Acknowledgment. Generous financial support by the DFG (Leibniz Award to A. F.) and the Fonds der Chemischen Industrie (Kekulé Stipend to L. A.) is gratefully acknowledged. We thank Dr. K. Angermund for his help with the computation and Prof. A. B. Smith III, University of Pennsylvania, for an exchange of information.

Supporting Information Available: Compilation of all previous syntheses of pyrenophorin, experimental details, and analytical and spectroscopic data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936.

(18) For further applicatons of the CuCl(COD)-catalyzed propenoxide ring opening reaction, see: (a) Fürstner, A.; Konetzki, I. *J. Org. Chem.* **1998**, *63*, 3072. (b) Fürstner, A.; Konetzki, I. *Tetrahedron* **1996**, *52*, 15071. (c) Fürstner, A.; Kindler, N. *Tetrahedron Lett.* **1996**, *37*, 7005. (d) Fürstner, A.; Seidel, G.; Kindler, N. *Tetrahedron* **1999**, *55*, 8215.

(19) In addition to **12**, the product mixture contains the cyclic trimer **13** (27%) and several higher cyclic oligomers (ca. 11%) that were identified by GC/MS.

(20) For a discussion, see: Fürstner, A. *Synlett* **1999**, 1523.