Total Syntheses of (*S*)-(−)-Zearalenone and Lasiodiplodin Reveal Superior Metathesis Activity of Ruthenium Carbene Complexes with Imidazol-2-ylidene Ligands

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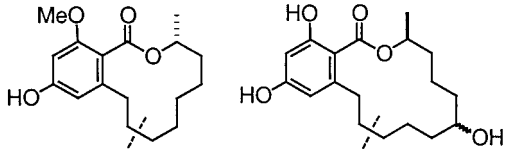
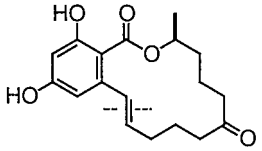
Total syntheses of the bioactive orsellinic acid derivatives zearalenone **3** and lasiodiplodin **1** are reported based on a ring-closing metathesis (RCM) reaction of styrene precursors as the key steps. These and closely related macrocyclizations are catalyzed with high efficiency by the "second generation" ruthenium carbene catalyst **5** bearing a N-heterocyclic carbene ligand, whereas the standard Grubbs carbene **4** fails to afford any cyclized product. Only the (*E*)-isomer of the macrocyclic cycloalkene is formed in all cases. The substrates for RCM can be obtained either via a Stille cross-coupling reaction of tributylvinylstannane or, even more efficiently, by Heck reactions of the aryl triflate precursors with pressurized ethene. Furthermore, the synthesis of **1** via RCM is compared with an alternative approach employing a low-valent titanium-induced McMurry coupling of dialdehyde **47** for the formation of the large ring. This direct comparison clearly ends in favor of metathesis which turned out to be superior in all preparatively relevant respects.

Introduction

As part of our program on the application of ring-closing metathesis (RCM) to the synthesis of biologically active natural products[1] we have previously reported efficient entries into various orsellinic acid derivatives including (*R*)-(+)-lasiodiplodin **1**[2,3,4] and the animal growth promoting agent zeranol **2** (Ralgro, Ralabol).[2a,5] In both cases, the macrocyclic rings had to be closed at the *allylic* sites where RCM proceeds readily in the presence of catalytic amounts of the Grubbs ruthenium carbene complex **4**.[2]





The important anabolic, estrogenic, and antibacterial macrolide (*S*)-(−)-zearalenone **3**,[6,7] however, remained beyond reach of this approach simply because complex **4** was found totally ineffective for attempted cyclizations of the required *styrenyl* precursor.[8] We now report that this situation is easily rectified by using the "second generation" ruthenium carbene complex **5** bearing a N-heterocyclic carbene (NHC) ligand for the crucial ring closure. Moreover, it will be shown that this powerful new catalyst upgrades the performance of RCM to such an extent as to make this transformation significantly more effective, reliable, and economical than the McMurry coupling which was previously considered a prime tool for handicapped macrocyclization events.

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(1) Selected references: (a) Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130. (b) Fürstner, A.; Müller, T. *J. Am. Chem. Soc.* **1999**, *121*, 7814. (c) Fürstner, A.; Grabowski, J.; Lehmann, C. W. *J. Org. Chem.* **1999**, *64*, 8275. (d) Fürstner, A.; Gastner, T.; Weintritt, H. *J. Org. Chem.* **1999**, *64*, 2361. (e) Fürstner, A.; Thiel, O. R. *J. Org. Chem.* **2000**, *65*, 1738. (f) Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 8746. (g) Fürstner, A.; Müller, T. *J. Org. Chem.* **1998**, *63*, 424. (h) Fürstner, A.; Müller, T. *Synlett* **1997**, 1010. (i) Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 3942. (j) Fürstner, A.; Langemann, K. *Synthesis* **1997**, 792.

(2) (a) Fürstner, A.; Seidel, G.; Kindler, N. *Tetrahedron* **1999**, *55*, 8215. (b) Fürstner, A.; Kindler, N. *Tetrahedron Lett.* **1996**, *37*, 7005.

(3) Isolation of **1** and its de-*O*-methyl congener: (a) Aldridge, D. C.; Galt, S.; Giles, D.; Turner, W. B. *J. Chem. Soc. (C)* **1971**, 1623. (b) Cambie, R. C.; Lal, A. R.; Rutledge, P. S.; Woodgate, P. D. *Phytochemistry* **1991**, *30*, 287. (c) Lee, K.-H.; Hayashi, N.; Okano, M.; Hall, I. H.; Wu, R.-Y.; McPhail, A. T. *Phytochemistry* **1982**, *21*, 1119. (d) Xin-Seng, Y.; Ebizuka, Y.; Noguchi, H.; Kiuchi, F.; Iitaka, Y.; Sankawa, U.; Seto, H. *Tetrahedron Lett.* **1983**, *24*, 2407. (e) For the isolation of new lasiodiplodin derivatives, see: Matsuura, H.; Nakamori, K.; Omer, E. A.; Hatakeyama, C.; Yoshihara, T.; Ichihara, A. *Phytochemistry* **1998**, *49*, 579. (f) Barrow, C. J. *J. Nat. Prod.* **1997**, *60*, 1023.

(4) Previous syntheses: (a) Gerlach, H.; Thalmann, A. *Helv. Chim. Acta* **1977**, *60*, 2866. (b) Danishefsky, S.; Etheredge, S. J. *J. Org. Chem.* **1979**, *44*, 4716. (c) Takahashi, T.; Kasuga, K.; Tsuji, J. *Tetrahedron Lett.* **1978**, 4917. (d) Braun, M.; Mahler, U.; Houben, S. *Liebigs Ann.* **1990**, 513. (e) Jones, G. B.; Huber, R. S. *Synlett* **1993**, 367. (f) Fink, M.; Gaier, H.; Gerlach, H. *Helv. Chim. Acta* **1982**, *65*, 2563. (g) Solladié, G.; Rubio, A.; Carreño, M. C.; Garcia Ruano, J. L. *Tetrahedron: Asymmetry* **1990**, *1*, 187. (h) Bracher, F.; Schulte, B. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2619.

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(6) Isolation and structure: (a) Stob, M.; Baldwin, R. S.; Tuite, J.; Andrews, F. N.; Gillette, K. G. *Nature* **1962**, *196*, 1318. (b) Urry, W. H.; Wehrmeister, H. L.; Hodge, E. B.; Hidy, P. H. *Tetrahedron Lett.* **1966**, 3109. (c) Cordier, C.; Gruselle, M.; Jaouen, G.; Hughes, D. W.; McGlinchey, M. J. *Magn. Res. Chem.* **1990**, *28*, 835.

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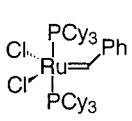
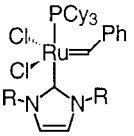


4



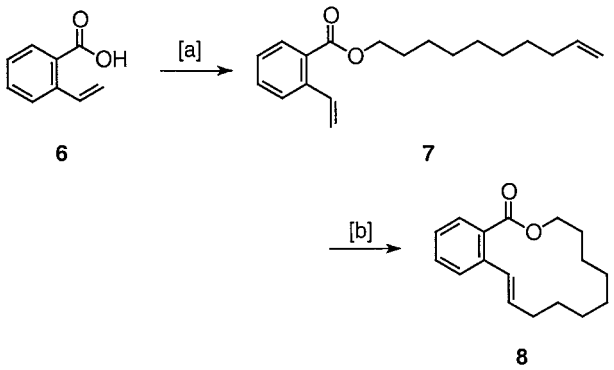
5 (R = mesityl)

Results and Discussion

Model Studies and Synthesis of *rac*-Zearalenone. Recently it has been shown that the replacement of one PCy_3 group in **4**[9] by strongly electron-donating and sterically encumbered N,N′-disubstituted 2,3-dihydro-1*H*-imidazol-2-ylidene ligands or the fully saturated analogues thereof imparts a significantly improved stability to the active species in solution and leads to a substantially increased catalytic activity as well.[10,11] Advantage can be taken from this excellent application profile of the resulting complexes such as **5** in many cases which were previously difficult to achieve or even impossible. This includes the formation of tetrasubstituted cycloalkenes,[10,11] metathetic conversions of acrylates and related electron poor substrates,[12,13] and RCM of conformationally restricted dienes.[14] In light of this encouraging precedent, we were prompted to reinvestigate the macrocyclization of stryrene derivatives related to zearalenone **3**.

A suitable model for the core structure of this macrolide is available by esterification of 2-vinylbenzoic acid **6**[15] with 9-decenol under Mitsunobu conditions (Scheme 1).[16]

Scheme 1[a]

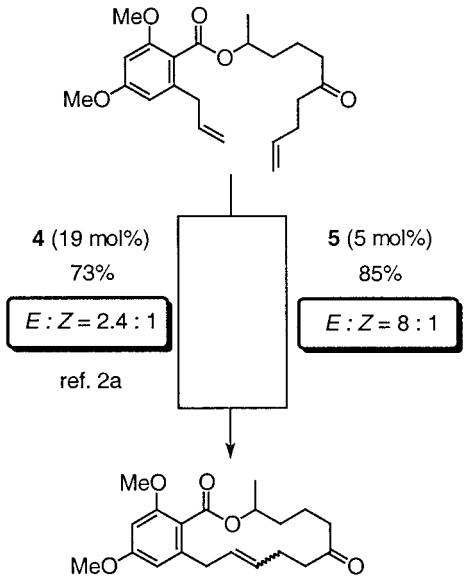


6 **7** **8**

[a] (a) 9-Decenol, PPh_3, DEAD, Et_2O, rt, 3 h, 75%; (b) Complex **5** (5 mol %), toluene, 80 °C, 23 h, 75%.

In line with our expectations, the resulting diene **7** readily cyclizes on exposure to catalytic amounts of complex **5** in toluene at 80 °C. Surprisingly, however, the 14-membered cycloalkene **8** which is isolated in 75% yield was found to consist of the *E*-isomer only.[17] This gratifying result contrasts to most RCM-based macrocyclizations previously reported in the literature in which mixtures of both stereoisomers are usually obtained.[1,18]

Next, we investigated if alkoxy substituents on the arene ring, which significantly alter the electronic prop-



Therefore a similar explanation may apply to the examples reported in this paper. The question, however, why *all* styrenyl substrates described herein *exclusively* afford the macrocyclic *E*-cycloalkenes is not yet solved.

(7) For previous syntheses of **3** and related compounds see the following for leading references: (a) Keinan, E.; Sinha, S. C.; Sinha-Bagchi, A. *J. Chem. Soc., Perkin 1* **1991**, 3333. (b) Hitchcock, S. A.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1323. (c) Takahashi, T.; Nagashima, T.; Ikeda, H.; Tsuji, J. *Tetrahedron Lett.* **1982**, *23*, 4361. (d) Takahashi, T.; Ikeda, H.; Tsuji, J. *Tetrahedron Lett.* **1981**, *22*, 1363. (e) Kalivretenos, A.; Stille, J. K.; Hegedus, L. S. *J. Org. Chem.* **1991**, *56*, 2883. (f) Rama Rao, A. V.; Deshmukh, M. N.; Sharma, G. V. M. *Tetrahedron* **1987**, *43*, 779. (g) Takahashi, T.; Kasuga, K.; Takahashi, M.; Tsuji, J. *J. Am. Chem. Soc.* **1979**, *101*, 5072. (h) Solladié, G.; Maestro, M. C.; Rubio, A.; Pedregal, C.; Carreno, M. C.; Garcia Ruano, J. L. *J. Org. Chem.* **1991**, *56*, 2317. (i) Taub, D.; Girotra, N. N.; Hoffsommer, R. D.; Kuo, C. H.; Slates, H. L.; Weber, S.; Wendler, N. L. *Tetrahedron* **1968**, *24*, 2443. (j) Vlattas, I.; Harrison, I. T.; Tökés, L.; Fried, J. H.; Cross, A. D. *J. Org. Chem.* **1968**, *33*, 4176. (k) Windholz, T. B.; Brown, R. D. *J. Org. Chem.* **1972**, *37*, 1647. (l) Hurd, R. N.; Shah, D. H. *J. Org. Chem.* **1973**, *38*, 390. (m) Hurd, R. N.; Shah, D. H. *J. Med. Chem.* **1973**, *16*, 543. (n) Peters, C. A.; Hurd, R. N. *J. Med. Chem.* **1975**, *18*, 215. (o) Bass, R. J.; Banks, B. J.; Leeming, M. R. G.; Snarey, M. *J. Chem. Soc., Perkin Trans. 1* **1981**, 124. (p) Nicolaou, K. C.; Winssinger, N.; Pastor, J.; Murphy, F. *Angew. Chem. Int. Ed.* **1998**, *37*, 2534. (q) Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614.

(8) Attempts to isomerize the double bond of the RCM product formed in our previous route to zeranol **2** from the allylic into the vinylic position have failed, cf. ref 2a. Therefore, no viable entry into zearalenone itself was found during these investigations.

(9) (a) Nguyen, S. T.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 9858. (b) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100.

(10) These complexes have been independently and almost simultaneously reported by three different research groups, cf: (a) Huang, J.; Stevens, E. D.; Nolan, S. P.; Petersen, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674. (b) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247. (c) Ackermann, L.; Fürstner, A.; Weskamp, T.; Kohl, F. J.; Herrmann, W. A. *Tetrahedron Lett.* **1999**, *40*, 4787. (d) Weskamp, T.; Kohl, F. J.; Hieringer, W.; Gleich, D.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **1999**, *38*, 2416.

(11) For closely related complexes with fully "saturated" NHC-ligands, see: (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953. (b) Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1751.

(12) Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204.

(13) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783.

(14) Ackermann, L.; El Tom, D.; Fürstner, A. *Tetrahedron* **2000**, *56*, 2195.

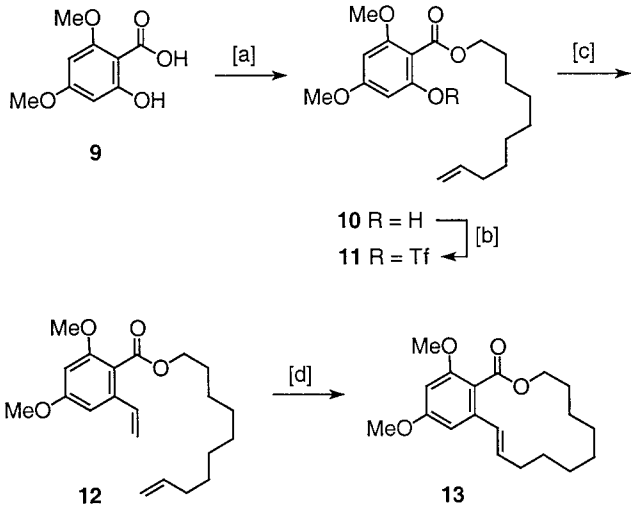
(15) Dale, W. J.; Starr, L.; Strobel, C. W. *J. Org. Chem.* **1961**, *26*, 2225.

(16) Mitsunobu, O. *Synthesis* **1981**, 1.

(17) After this paper had been submitted, one example of a macrocyclization was published in which the use of the "fully saturated" analogue of complex **5** affords a much higher *E*/*Z* ratio than the use of the "standard" Grubbs carbene **4**. This result is caused by the ability of the former catalyst to isomerize the initial product under the reaction conditions, thereby progressively enriching the mixture in the thermodynamically favored *E*-isomer, cf. Lee, C. W.; Grubbs, R. H. *Org. Lett.* **2000**, *2*, 2145. This increased propensity of **5** to give macrocyclic *E*-alkenes is also evident from the following comparison:

(18) Reviews: (a) Fürstner, A. *Angew. Chem.* **2000**, *112*, 3140; *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (c) Fürstner, A. *Top. Catal.* **1997**, *4*, 285. (d) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036. (e) Fürstner, A. *Top. Organomet. Chem.* **1998**, *1*, 37. (f) Ivin, K. J.; Mol, J. C. *Olefin Metathesis and Methathesis Polymerization*, 2nd ed.; Academic Press: New York, 1997.

Scheme 2[a]



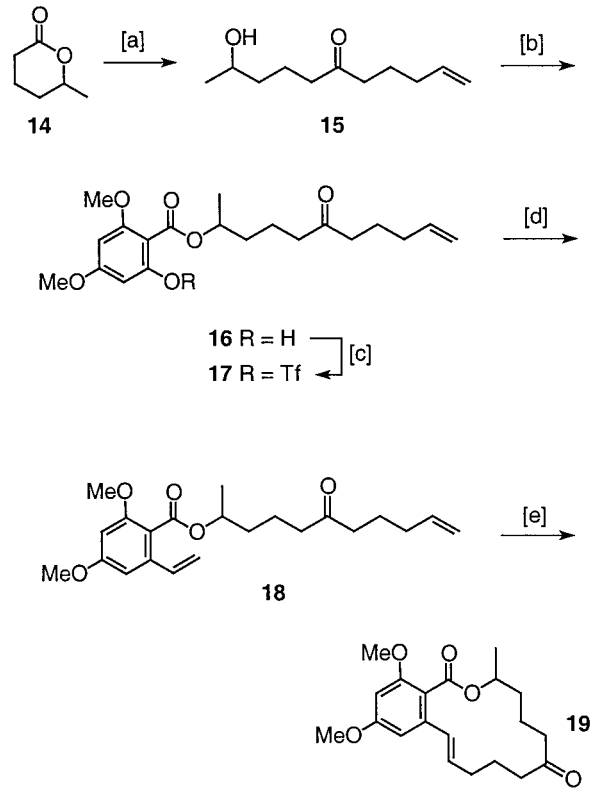
[a] (a) 9-Decenol, PPh_3, DEAD, Et_2O, rt, 3 h, 67%; (b) Tf_2O, pyridine, CH_2Cl_2, 3 h, 90%; (c) (i) tributylvinylstannane, LiCl, $PdCl_2(PPh_3)_2$ (5 mol %), DMF, rt, 14 h, 82%; *or* (ii) ethylene (50 bar), LiCl, triethylamine, $PdCl_2(PPh_3)_2$ (5 mol %), DMF, 90 °C, 20 h, 88%; (d) Complex **5** (5 mol %), toluene, 80 °C, 15 h, 93%.

erties of the cyclization precursor, have any influence on the outcome of RCM (Scheme 2). Esterification of the readily accessible salicylic acid **9**[2a] with 9-decenol, conversion of the resulting product **10** into the aryl triflate **11**, and a subsequent Stille cross coupling with tributylvinylstannane affords an appropriate model compound.[19] This diene cyclizes even more readily in the presence of ruthenium complex **5** than compound **7**. Product **13** thus obtained was isolated in 93% yield in stereomerically pure form as the (*E*)-isomer. It is also worth mentioning that a Heck reaction[20] of triflate **11** with ethylene (50 bar) affords an even higher yield of the required diene **12** and therefore constitutes an attractive, inexpensive, and nontoxic alternative to the Stille coupling outlined above.

This sequence is readily adapted to the synthesis of zearalenone itself (Scheme 3). Reaction of commercially available lactone **14** with 4-pentenylmagnesium bromide at low temperature provides hydroxyketone **15** in good yield. Esterification of this compound with acid **9** and formation of the corresponding triflate **17** followed by Heck reaction with ethylene (55 bar) and ring closure of the resulting diene **18** in the presence of ruthenium complex **5** delivers zearalenone dimethyl ether **19** which can be deprotected to the natural product with BCl_3/BBr_3 according to a literature procedure.[7a] The efficiency of the Heck coupling as well as of the RCM cyclization step account for the remarkable overall yield of this sequence. Finally, it is emphasized that neither styrene **7** nor **12** or **18** give any cyclized material if the "standard" Grubbs carbene **4** is used instead of **5** as the catalyst for the RCM reactions.

***(S)*-(−)-Zearalenone**. The approach to (±)-**3** depicted in Scheme 3, however, cannot be adapted to the synthesis of enantiomerically pure zearalenone due to the fact that

Scheme 3[a]



[a] (a) 4-Pentenylmagnesium bromide, Et_2O, THF, −78 °C → rt, 77%; (b) acid **9**, PPh_3, DEAD, Et_2O, rt, 3 h, 64%; (c) Tf_2O, pyridine, CH_2Cl_2, 3 h, 92%; (d) (i) tributylvinylstannane, LiCl, $PdCl_2(PPh_3)_2$ (5 mol %), DMF, rt, 14 h, 83%; *or* (ii) ethylene (55 bar), LiCl, triethylamine, $PdCl_2(PPh_3)_2$ (5 mol %), DMF, 90 °C, 20 h, 93%; (e) Complex **5** (5 mol %), toluene, 80 °C, 15 h, 91%.

Scheme 4

enantiomerically pure alcohol **15** suffers from rapid loss of optical activity. This behavior has been recognized earlier[7i] and is caused by the fast and reversible intramolecular hydride shift depicted in Scheme 4. Therefore we were forced to develop alternative entries avoiding this scrambling process.

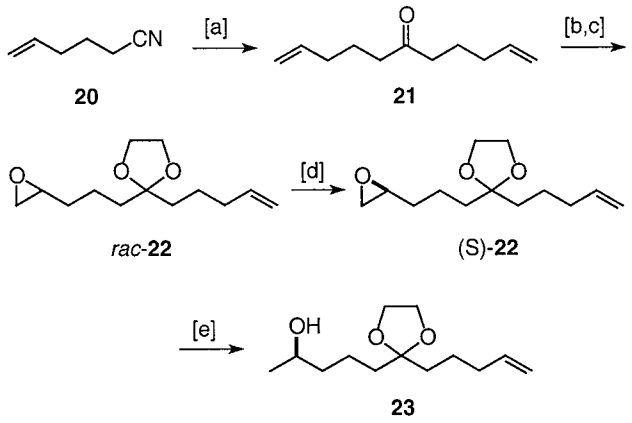
Two independent routes have been pursued toward this end. The first one (Scheme 5) starts from commercial 1-cyano-4-pentene **20** which reacts with 4-pentenylmagnesium bromide in refluxing Et_2O to provide the symmetrical ketone **21** after aqueous workup. Protection of the carbonyl group as dioxolane followed by reaction with *m*-chloroperbenzoic acid delivers monoepoxide (±)-**22** in 41% yield. Resolution of this compound according to Jacobsen's excellent procedure turned out to be very practical, delivering the required epoxide (*S*)-**22** in optically pure form (ee > 99%).[21] Its reaction with $LiBEt_3H$ affords the required (*R*)-configured alcohol **23** ready for esterification with salicylic acid **9** under Mitsunobu conditions.

The attractive stereochemical outcome of this approach, however, is somewhat compromised by the rather poor yield of the mono-epoxidation step. Therefore we

(19) (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (b) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1. (c) Mitchell, T. N. In *Metal-Catalyzed Cross Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; p 167.

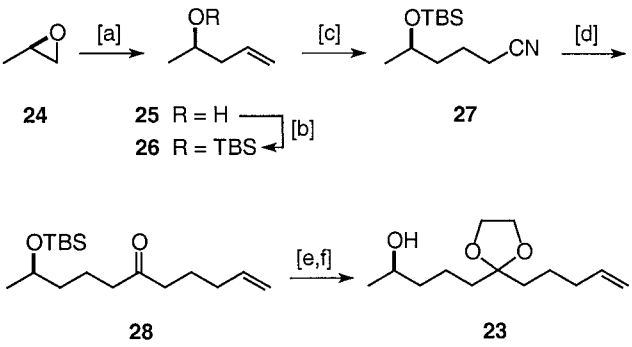
(20) (a) Heck, R. F. *Org. React.* **1982**, *27*, 345. (b) Bräse, S.; de Meijere, A. In *Metal-Catalyzed Cross Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; p 99.

Scheme 5[a]



[a] (a) 4-Pentenylmagnesium bromide, Et_2O, reflux, 3 h, 70%; (b) ethylene glycol, pyridinium *p*-toluenesulfonate cat., toluene, reflux, 4 h, 98%; (c) m-CPBA (1.5 equiv), CH_2Cl_2, 16 h, 41%; (d) (*S*,*S*)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamino-Co^{III} acetate (2.5 mol %)[21], H_2O (2 equiv), THF, 67 h, 41%, ee ≥ 99%; (e) $LiBEt_3H$, THF, 1 h, 95%.

Scheme 6[a]

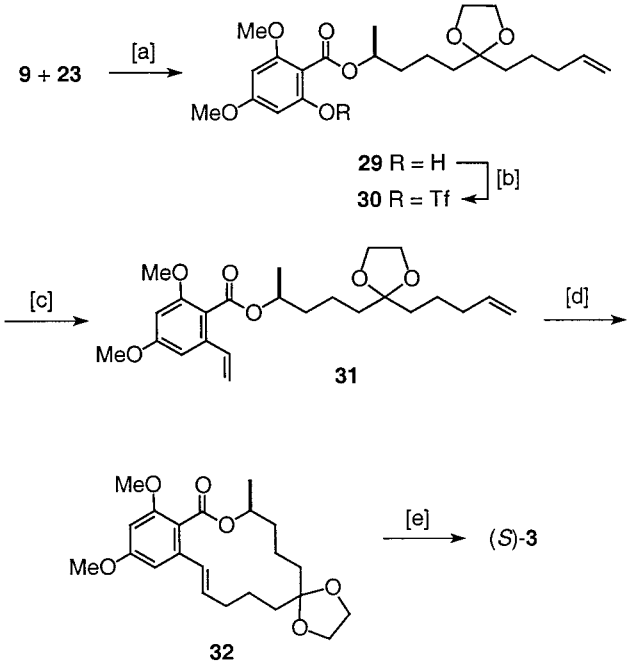


[a] (a) Vinylmagnesium bromide, CuCl(COD) (10 mol %), THF, −78 °C → rt; (b) TBSCl, imidazole, DMF, 16 h, 63% (over both steps); (b) (i) Cp_2ZrHCl, CH_2Cl_2, 2 h; (ii) t-BuNC, 2 h; (iii) I_2, benzene, 30 min, 77%; (d) 4-pentenylmagnesium bromide, Et_2O, reflux, 4 h, 68%; (e) ethylene glycol, pTsOH·H_2O cat., benzene, reflux, 12 h, 73%; (f) n-Bu_4NF, THF, 89%.

pursued an alternative route to the same alcohol employing (*R*)-propenoxide **24** as the starting material which is commercially available or can again be prepared on a large scale using the Jacobsen method[21] (Scheme 6). Ring opening with vinylmagnesium bromide in the presence of catalytic amounts of CuCl(COD) (COD = cyclooctadiene)[22] gives alcohol **25** which is immediately protected as TBS-ether **26** under standard conditions. Hydrozirconation of its double bond followed by reaction with t-BuNC and I_2 as described by Buchwald et al.[23] delivers nitrile **27** in 77% yield. Treatment of **27** with 4-pentenylmagnesium bromide then affords ketone **28** which is converted into (*R*)-**23** by two routine protecting group manipulations.

Having secured good access to this key building block, the completion of the total synthesis of (*S*)-(−)-**3** turned

Scheme 7[a]



[a] (a) PPh_3, DEAD, Et_2O, rt, 3 h, 88%; (b) Tf_2O, pyridine, CH_2Cl_2, 3 h, 89%; (c) ethylene (40 bar), LiCl, triethylamine, $PdCl_2(PPh_3)_2$ (5 mol %), DMF, 90 °C, 82%; (d) complex **5** (5 mol %), toluene, 80 °C, 4 h, 91%; (e) ref 7a.

out to be straightforward and highly satisfactory. Esterification of (*R*)-**23** with **9** under Mitsunobu conditions delivers ester (*S*)-**29** in 88% yield, which is converted into aryl triflate **30** under standard conditions. Heck-reaction of this substrate with ethylene (40 bar) catalyzed by $PdCl_2(PPh_3)_2$ (5 mol %) in the presence of LiCl and Et_3N proceeds with excellent yield and sets the stage for the crucial ring closure. Thus, exposure of the resulting styrene derivative **31** to catalytic amounts of complex **5** in toluene at 80 °C affords (*E*)-**32** as the only product in 91% isolated yield.[17] The deprotection of this compound can be carried out as described in the literature. The nearly quantitative cyclization effected by the NHC-complex **5** is in striking contrast to the complete failure if the standard carbene **4** is employed as the catalyst. Therefore, this and the other examples reported herein illustrate the superior reactivity of **5** and further substantiate the notion that NHC-containing ruthenium complexes will likely set new standards in the field of olefin metathesis.[10−14]

Lasiodiplodin: Comparison of RCM and McMurry Coupling. The very same sequence of reactions using acid **9** and alcohol **33** also gives access to lasiodiplodin **1** and its naturally occurring de-*O*-methyl congener.[3,4] These macrolides are efficient inhibitors of prostaglandin biosynthesis and exhibit reasonably high anticancer activity.[24] As can be seen from Scheme 8, all individual steps proceed well, including the key cyclization of styrene **36** which affords (*E*)-**37** as the only product in 69% yield. The selective deprotection of this compound to **1** was previously described.[4d,g]

Although this result is slightly inferior to our previous approach to lasiodiplodin,[2] in which the macrocyclic ring has been formed by RCM in essentially quantitative yield

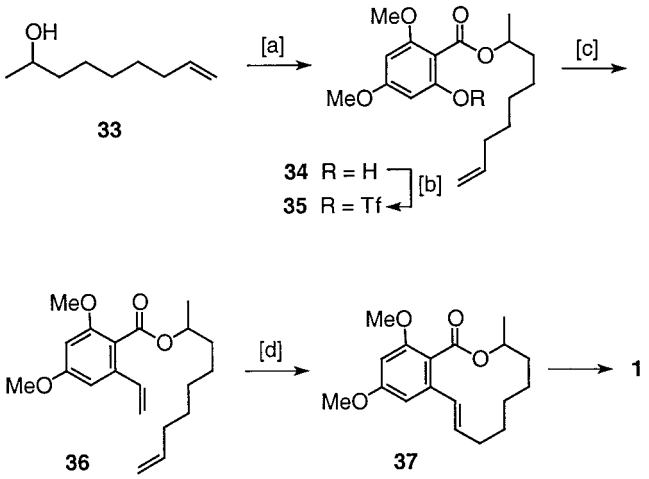
(21) (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936. (b) Furrow, M. E.; Schaus, S. E.; Jacobsen, E. N. *J. Org. Chem*. **1998**, *63*, 6776.

(22) Previous natural product syntheses from our laboratory employing a CuCl(COD)-catalyzed propenoxide ring opening reaction: (a) Fürstner, A.; Konetzki, I. *J. Org. Chem*. **1998**, *63*, 3072. (b) Fürstner, A.; Konetzki, I. *Tetrahedron* **1996**, *52*, 15071.

(23) Buchwald, S. L.; LaMaire, S. J. *Tetrahedron Lett*. **1987**, *28*, 295.

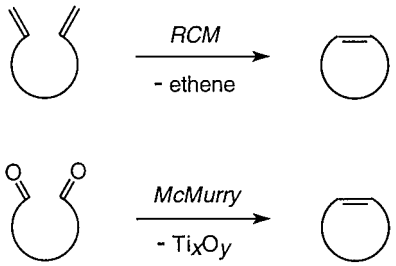
(24) Detailed in vitro cytotoxicity data of a lasiodiplodin derivative are reported in ref 2a.

Scheme 8[a]



[a] (a) Acid **9**, PPh_3, DEAD, Et_2O, rt, 3 h, 63%; (b) Tf_2O, pyridine, CH_2Cl_2, 3 h, 92%; (c) (i) tributylvinylstannane, LiCl, $PdCl_2(PPh_3)_2$ (5 mol %), DMF, rt, 14 h, 78%; *or* (ii) ethylene (40 bar), LiCl, triethylamine, $PdCl_2(PPh_3)_2$ (5 mol %), DMF, 90 °C, 20 h, 92%; (d) complex **5** (5 mol %), toluene, 80 °C, 15 h, 69%.

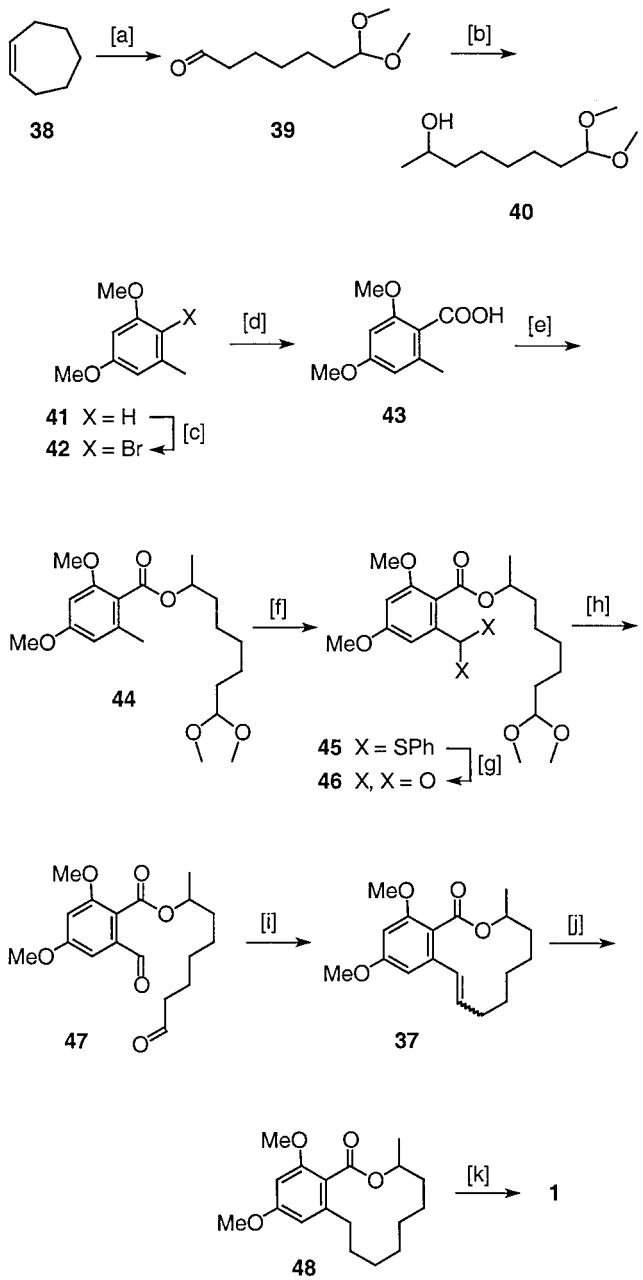
Scheme 9



at the allylic rather than the vinylic site, a comparison with an entirely different approach to this target is more revealing. It is well established in the literature that the reductive coupling of carbonyl compounds mediated by low-valent titanium [Ti] ("McMurry coupling") constitutes a fairly general and efficient entry into medium and macrocyclic rings, even if high enthalpic barriers have to be overcome during cyclization.[25] The formal resemblance of carbonyl coupling and RCM (Scheme 9) as well as the fact that a direct comparison of these mechanistically unrelated olefin forming reactions has not yet been carried out so far prompted us to pursue a McMurry approach to lasiodiplodin as well.

The required cyclization precursor, i.e., dialdehyde **47** is assembled as depicted in Scheme 10. Dimethylation of 3,5-dihydroxytoluene followed by regioselective bromination of the resulting product **41** leads to compound **42**, which is converted into orsellinic acid dimethyl ether **43** by metal/halogen exchange with n-BuLi at low temperature and quenching of the aryllithium species thus formed.[4d] The aliphatic fragment is conveniently obtained by ozonolysis of cycloheptene **38** under Schreiber's conditions[26] followed by reaction of the monoprotected dialdehyde **39** with MeLi. Compounds **40** and **43** are then

Scheme 10[a]



[a] (a) (i) O_3, MeOH, CH_2Cl_2, −78 °C → rt, (ii) Me_2S, $NaHCO_3$, rt, 16 h, 82%; (b) MeMgCl, Et_2O, 0 °C, 20 h, 95%; (c) NBS, $CHCl_3$, 0 °C, 1.5 h, 97%; (d) (i) n-BuLi, THF, −78 °C; (ii) CO_2 (solid), −78 °C → rt, 86%; (e) (i) oxalyl chloride, toluene, reflux, 16 h; (ii) alcohol **40**, pyridine, DMAP cat., CH_2Cl_2, rt, 26 h, 86%; (f) (i) LDA (3 equiv), THF, −78 °C, 10 min; (ii) PhSSPh (2 equiv), −78 °C → rt, 5 h, 96%; (g) NBS, lutidine, aq acetone, 0 °C → rt, 40 min, 82%; (h) Amberlyst-15 (H-form), aq acetone, 24 h, 75%; (i) Ti-graphite, DME, rt, 24 h, 60−82%, (j) Pd/C (5% w/w), EtOH, EtOAc, rt, 20 h, 93%; (k) ref 4d,g.

esterified, and the resulting product **44** is converted into bis(phenylthio)acetal **45** by double deprotonation of its benzylic CH_3 group and trapping of the organometallic intermediate with diphenyl disulfide.[27] While attempted deprotection of this dithioacetal with Hg(II) failed, the use of NBS in the presence of 2,6-lutidine effected the cleavage with formation of aldehyde **46** in 79% yield.[28]

(25) Reviews: (a) Fürstner, A.; Bogdanovic, B. *Angew. Chem.* **1996**, *108*, 2582; *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2442. (b) McMurry, J. E. *Chem. Rev.* **1989**, *89*, 1513. (c) Lectka, T. In *Active Metals. Preparation, Characterization, Applications*; Fürstner, A., Ed.; VCH: Weinheim, 1996; p 85.

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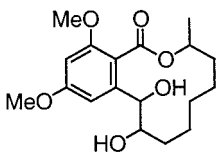
The subsequent liberation of the aliphatic aldehyde group was best achieved with Amberlyst-15 in aqueous acetone[29] which sets the stage for the formation of the 12-membered ring by reductive carbonyl coupling.

Despite our experience with low-valent titanium [Ti] chemistry,[30] this key transformation turned out to be fairly problematic. We noticed that a large excess of [Ti] and rather high dilution conditions (syringe pump) are necessary to achieve good yields. The best results were achieved with titanium−graphite formed from $TiCl_3$ and 2 equiv of C_8K[31] in DME at ambient temperature.[32,33] Even under these optimized conditions, however, the yield remained somewhat variable, ranging between 60−82%.[34] In all cases variable amounts of pinacol **49** and phthalide **50** were formed as byproducts. In contrast to RCM, the McMurry coupling delivers alkene **37** as a mixture of both stereoisomers (*E*:*Z* ≈ 3.5:1). For the stuctures of these alkenes in the solid-state, consult the Supporting Information.

Conclusions. A concise synthesis of the macrolide (*S*)-(−)-zearalenone **3** is described which is based on the formation of the macrocyclic ring by RCM of a styrene derivative. The use of the second generation metathesis catalyst **5** bearing an NHC-ligand is key to success since the classical Grubbs ruthenium carbene **4** fails to afford any cyclized product.[35] Successful preparations of several other macrocycles as well as a straightforward synthesis of the cytotoxic natural product lasiodiplodin **1** show the generality and scope of this transformation. Furthermore, the RCM−based approach to **1** is compared with a synthesis of the same lactone via McMurry coupling of a dialdehyde precursor. *This direct comparison unequivocally ends in favor of metathesis which is superior in all relevant preparative aspects* including the overall yield, accessibility of substrates, total number of steps, stability of intermediates, stereoselectivity, atom economy, reproducibility, flexibility, and ease of handling of the reagents.[36] Further applications meant to illustrate the superb features of metathesis in general are underway and will be reported in due course.



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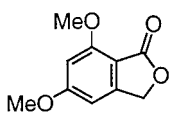

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Supporting Information Available: The entire Experimental Section including adequate characterization of all new compounds and the X-ray structures of compounds (*E*)-**37** and (*Z*)-**37**. This material is available free of charge via the Internet at http://pubs.acs.org.

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