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Macrocycle Formation by Ring-Closing-Metathesis. 2.[1] An Efficient Synthesis of Enantiomerically Pure (*R*)-(+)-Lasiodiplodin

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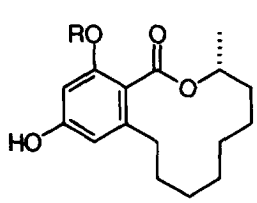
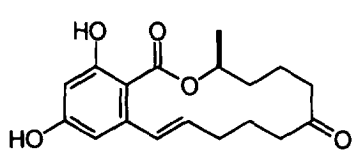
Abstract: A highly efficient and flexible route to the macrolide (*R*)-(+)-lasiodiplodin **1** and its de-O-methyl congener **2** is outlined, which is based on the formation of the 12-membered ring by ring-closing metathesis (RCM) as the key step.

The 12-membered ring lactones lasiodiplodin (**1**) and de-O-methyl lasiodiplodin (**2**) isolated from a culture broth of the fungus *Botrysdiplodia theobromae* (formerly *Lasiodiplodia theobromae*) exhibit plant growth regulating properties.[2] Macrolide **2** has also been found in the roots of *Arnebia euchroma*, which is used in traditional Chinese medicine.[3] This metabolite may well be responsible, at least in part, for the pharmacological properties of the plant extracts, because it efficiently inhibits the prostaglandin biosynthesis.[3] The structural relationship of **1** and **2** with other orsellinic acid type macrolides such as zearalenone (**3**), curvularin (**4**), resorcylide (**5**) and monocillin I (**6**) is obvious.[4-6]



1 R = Me
2 R = H



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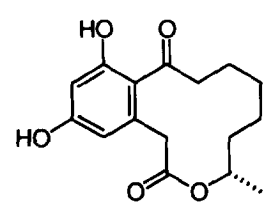

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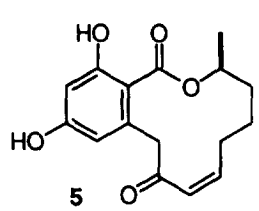

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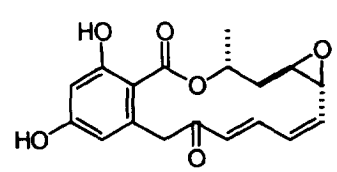
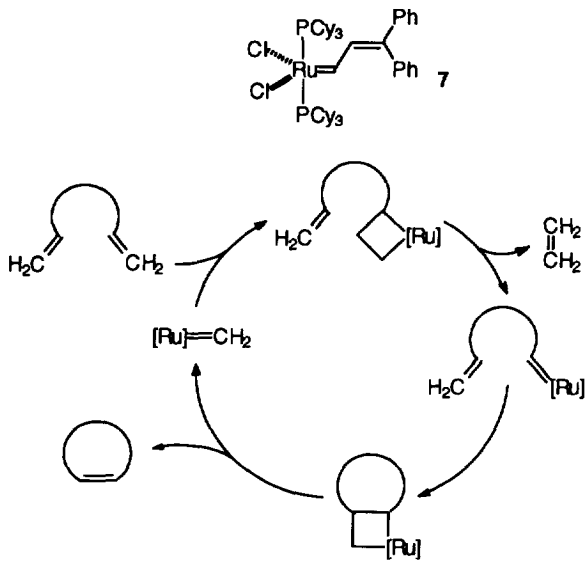


6

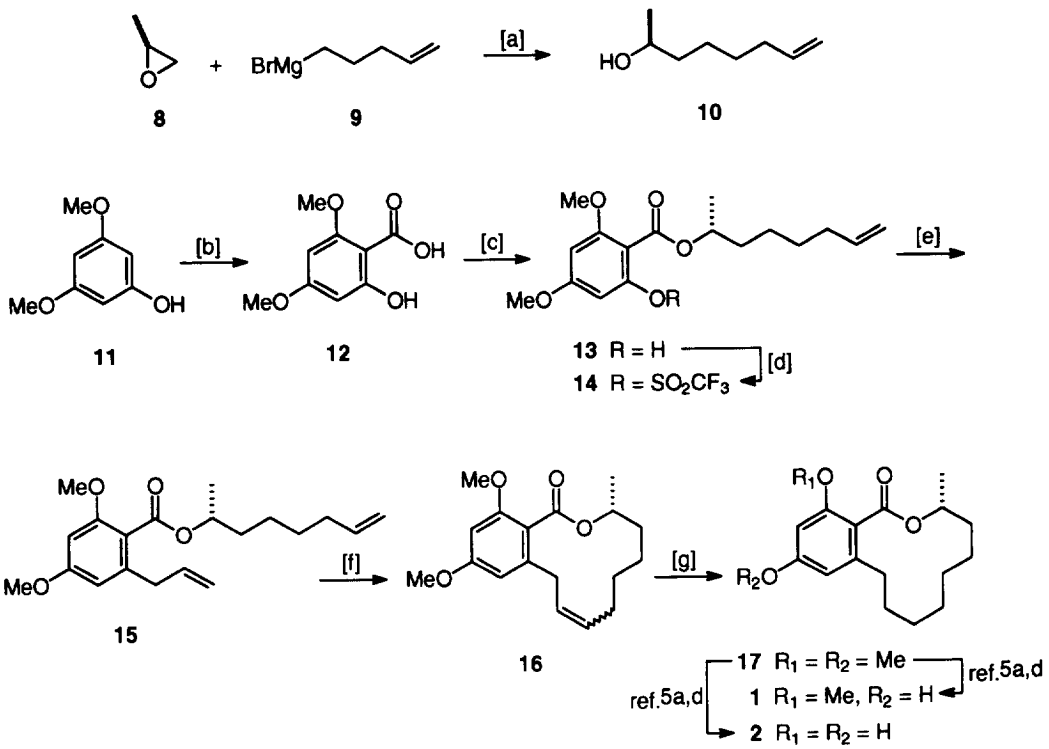
In the following we describe an efficient entry into this class of physiologically active natural products which is based on ring-closing-metathesis (RCM) (Scheme 1) as the key step to form the macrocyclic ring. RCM is presently evolving into a mature preparative method since well defined transition metal complexes have been launched as catalysts, which tolerate a wide spectrum of functional groups.[7] Among them, the ruthenium carbene $(PCy_3)_2Cl_2Ru{=}CHCH{=}CPh_2$ (**7**)[8] introduced by *Grubbs* et al. is particularly noteworthy, as it is rather insensitive towards oxygen and moisture, yet highly reactive in metathetic reactions of monosubstituted olefins.



Scheme 1.

This propensity has been elegantly used for the synthesis of a fairly large number of functionalized 5-, 6- and 7-membered carbo- and heterocycles from 1,ω-diene precursors.[7,9] In contrast, macrocyclization reactions by RCM are still largely unexplored and were supposed to be successful with conformationally biased substrates only.[10,11] This is, however, not the case. As we have recently shown by the formation of odoriferous macrolides, RCM is amongst the most efficient entries into macrocyclic systems even if the diene precursor is devoid of any conformational constraints, provided that the site of ring closure is adequately chosen.[1] The versatility of this concept is now further substantiated by the total synthesis of lasiodiplodin outlined below.

Our synthesis (Scheme 2) starts with the cheap 3,5-dimethoxyphenol **11**, which was converted into the salicylic acid derivative **12** on a multigram scale via a Kolbe-Schmitt reaction of its sodium salt with pressurized CO_2.[12] Esterification of **12** under Mitsunobu conditions[14] with the enantiomerically pure (*S*)-alcohol **10** (obtained upon CuCl(COD)-catalyzed reaction of 4-pentenylmagnesium bromide **9** with commercially available (*S*)-propenoxide **8**)[13] proceeds with inversion of the configuration affording ester (*R*)-**13**. Its treatment with $(F_3CSO_2)_2O$ in pyridine led to the corresponding aryltriflate **14**, which was subjected to a Stille reaction with allyltributylstannane using $Pd_2(dba)_3$/tris(2-furyl)phosphane as catalyst in the presence of LiCl.[15] Thus, a slow but clean reaction gave the cross-coupling product **15** in excellent yield which serves as the cyclization precursor. Gratifyingly, the crucial macrocycle formation by RCM was smoothly achieved by slowly combining the solutions of this diene and of the ruthenium carbene **7** (6 mol%), both in CH_2Cl_2, via two dropping funnels, while argon was bubbled through the resulting reaction mixture in order to ensure complete evaporative loss of the ethene formed as the by-product and hence to drive the conversion. This set-up resulted reproducibly (4 runs) in an *essentially quantitative formation of the 12-membered alkene* (*R*)-**16** as a mixture of the (*E*) and (*Z*) isomers ((*E*):(*Z*)≈2.3:1), which can be separated by flash chromatography for analytical purposes.[16] In order to complete the synthesis, however, the mixture of geometrical isomers was hydrogenated to the known dimethylether (*R*)-**17**,[5a,17] which can be deprotected either to lasiodiplodin **1** or to de-O-methyl lasiodiplodin **2**, respectively, according to the protocols described in the literature.[5a,d] The unnatural enantiomer (*S*)-**17** has been prepared analogeously from (*R*)-propenoxide as the starting material.



Scheme 2. Syntheses of (*R*)-(+)-lasiodiplodin (**1**) and of de-O-methyl lasiodiplodin (**2**): [a] CuCl(COD) (10 mol%), THF, -78°C→r.t., 81%; [b] (i) NaOMe in MeOH; (ii) CO_2 (40 atm), 120°C, 80%; [c] EtOOC-N=N-COOEt, PPh_3, Et_2O, r.t., 83%; [d] $(CF_3SO_2)_2O$, pyridine, 0°C→r.t., 91%; [e] allyltributylstannane, LiCl (3 eq.), $Pd_2(dba)_3$ (3 mol%), tris(2-furyl)phosphane (12 mol%), N-methyl-2-pyrrolidinone, 40°C, 93%; [f] $(PCy_3)_2Cl_2Ru$=CHCH=CPh_2 (**7**) (6 mol%), CH_2Cl_2, r.t., 94%, (*E*):(*Z*)≈2.3:1 (GC); [g] H_2 (1atm), Pd/C, EtOH, r.t., 94%.

Acknowledgement. We would like to thank the Volkswagen-Stiftung, Hannover, and the Fonds der Chemischen Industrie, Frankfurt, for generous financial support.

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This paper is dedicated to the memory of Wolfgang Oppolzer

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16. Selected data of (*E*)-**16**: $[\alpha]_D^{20}$ +72 (c 0.46, acetone); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.34 (d, 1H, *J* = 2.3), 6.32 (d, 1H, *J* = 2.3), 5.41 (dddd, 1H, *J* = 1.9, 4.5, 10.2, 14.9), 5.20 (dddd, 1H, *J* = 1.6, 3.2, 10.2, 14.9), 5.10 (qdd, 1H, *J* = 2.8, 6.3, 10.0), 3.80 (s, 3H), 3.78 (s, 3H), 3.36 (d, 1H, *J* = 6.3), 3.07 (ddd, 1H, *J* = 2.9, 5.0, 14.2), 2.22 (m, 1H), 1.21-1.71 (m, 6H), 1.31 (d, 3H, *J* = 6.2), 1.09 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.1, 161.1, 158.3, 140.8, 132.7, 128.7, 117.6, 107.1, 96.9, 68.8, 56.0, 55.3, 38.3, 34.6, 32.8, 24.7, 20.1, 20.0. IR: 1714 cm^{-1}. MS *m/z* (%): 304 (24, [M^+]), 217 (10), 207 (100), 205 (15), 196 (32), 191 (11), 189 (10), 178 (12).
17. (*R*)-**17**: $[\alpha]_D^{20}$ +8.7 (c 1.63, $CHCl_3$); lit.: $[\alpha]_D$ +9 (c 1, $CHCl_3$)[5d]; $[\alpha]_D^{25}$ +4.2 (c 0.18, EtOH).[5a]

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