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Macrocycles by Ring-Closing-Metathesis, XI[1]: Syntheses of (*R*)-(+)-Lasiodiplodin, Zeranol and Truncated Salicylihalamides

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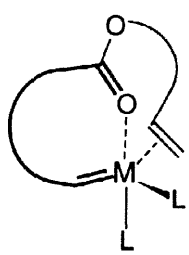
Abstract: Concise, flexible and high yielding approaches to the orsellinic acid type macrolides lasiodiplodin **1** and zeranol **3** are described which involve only metal-assisted or metal-catalyzed C-C-bond formations. Key steps are the efficient allylation of aryl triflates **14** and **25** either by Stille or by modified Suzuki coupling reactions, and the high yielding ring closure of the macrocyclic rings by RCM using the ruthenium carbene **18** as the catalyst. One of the synthesis intermediates, *i. e.* cycloalkene **16**, can also be regarded as a truncated analogue of the potent anti-tumor agent salicylihalamide A **7**. From the in-vitro cytotoxicity data of **16** it is possible to deduce first insights into the structure/activity relationship of salicylihalamide.

INTRODUCTION

Our recent studies on ring-closing-metathesis (RCM) have contributed to define the remarkable scope of this method for the synthesis of carbo- and heterocycles of various ring sizes and have provided insights into the essential parameters for successful macrocyclization.[1] Compelling evidence has accumulated that the formation of large rings by RCM requires the assistance of a properly positioned „relay" functionality (e. g. ester, amide, ketone, ether) on the diene substrate. Coordination of this polar group onto the emerging carbene unit (leading to complexes of type **A** or similar) helps to assemble the reacting sites within the coordination sphere of the metal and thus favors cyclization over competing oligomerization pathways. If, however, such a chelate structure becomes too stable, the catalyst may be sequestered in an unproductive form and RCM is likely to cease.



A

Therefore the ***distance*** between the alkene units and the polar groups as well as their relative ***orientation*** and ***affinity*** are key parameters that have to be properly assessed in retrosynthetic planning. Although conformational predisposition towards ring closure is not a basic requirement for productive RCM, one has to keep in mind that these

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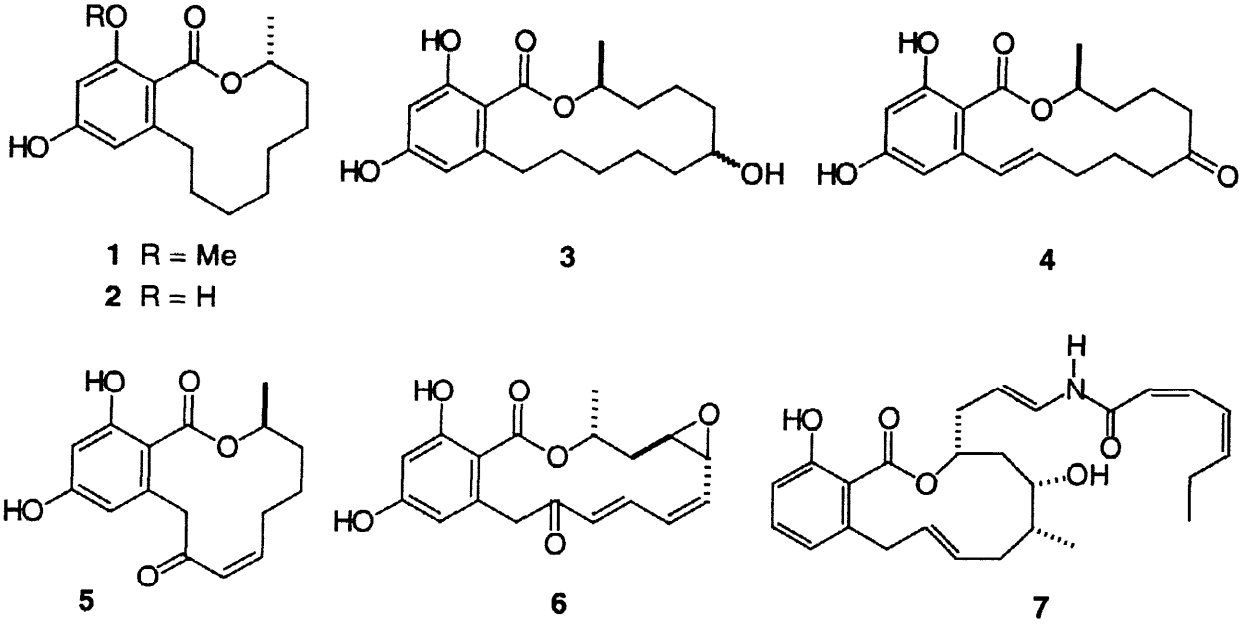
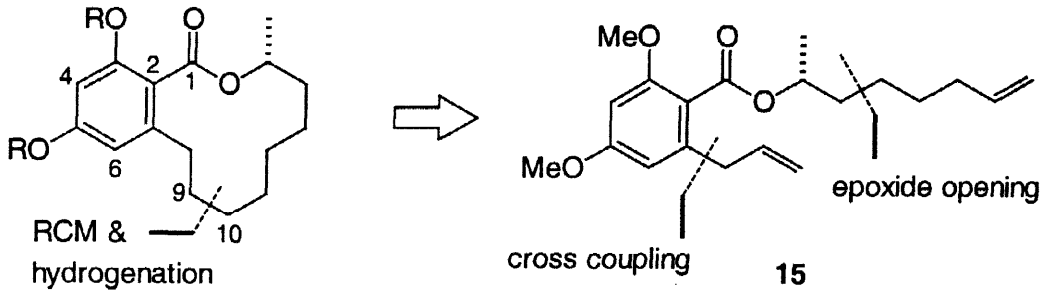
macrocyclizations are essentially driven by the gain in entropy upon bisecting the diene substrates and that the ability to build up strain in the molecule is therefore rather limited.[1,2,3]



The syntheses of lasiodiplodin **1** and zeranol **3** outlined below corroborate these notions. Like most other resorcylic acid type macrolides[4] such as zearalenone **4**, resorcylide **5**, monocillin I **6**, and the closely related salicylihalamide A **7**, these compounds elicit pronounced physiological responses and serve as an attractive testing ground for probing the efficiency of new synthetic methods.

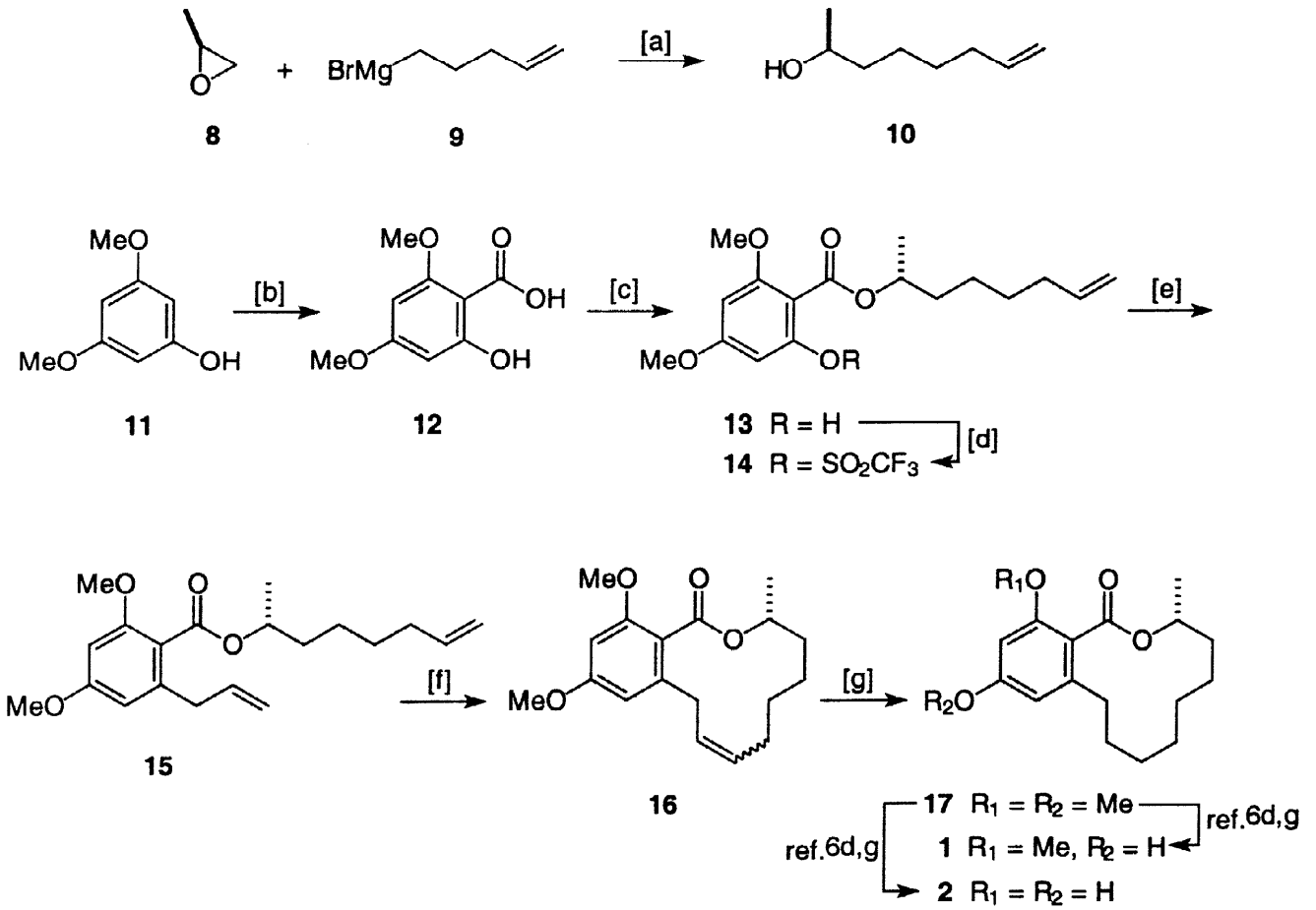
RESULTS AND DISCUSSION

(*R*)-(+)-Lasiodiplodin.[1c] Lactone **1** together with its de-O-methyl congener **2** have been isolated from the fungus *Botrysdiplodia theobromae* (formerly *Lasiodiplodia theobromae*) as well as from the wood of *Euphorbia splendens* and *E. fidjiana*.[5,6] **2** is also one of the secondary metabolites of *Arnebia euchroma*, a plant which serves in traditional Chinese medicine for the treatment of human hepatitis and abdominal oedema.[5d] Both macrolides were found to be efficient inhibitors of prostaglandin biosynthesis and exhibit significant antileukemic activity.



Scheme 1. Lasiodiplodin: Retrosynthetic Analysis

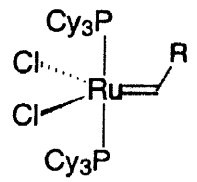
Upon considering the crucial parameters for successful macrocyclization by RCM outlined above, we identify the 9,10-bond as the strategic site for cyclizing the 12-membered ring. It is likely that stable chelate intermediates can be avoided, independent of which olefinic group of the diene **15** is activated by the metathesis catalyst. Because compound **15** is easily assembled from well accessible starting materials as indicated in Scheme 1, a short and flexible approach to enantiomerically pure **1** and **2** is likely to emerge.



Scheme 2. Syntheses of (*R*)-(+)-lasiodiplodin (**1**) and 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] **10**, 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)phosphine (12 mol%), N-methyl-2-pyrrolidinone, 40°C, 93%; [f] **18b** (6 mol%), CH_2Cl_2, reflux, 94%, (*E*):(*Z*)≈2.3:1 (GC); [g] H_2 (1atm), Pd/C, EtOH, r.t., 94%.

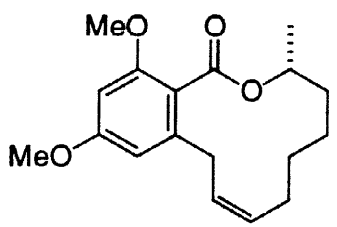
This plan was reduced to practice as shown in Scheme 2. 3,5-Dimethoxyphenol **11** is converted into the salicyclic acid derivative **12** on a multigram scale via a Kolbe-Schmitt reaction of its sodium salt with pressurized CO_2.[7] The aliphatic segment is obtained by reaction of 4-pentenylmagnesium bromide **9** with (*S*)-propenoxide **8**[8] in the presence of catalytic amounts of CuCl(COD).[9] Esterification of the resulting enantiomerically pure alcohol (*S*)-**10** with **12** under Mitsunobu conditions[10] proceeds with complete inversion of the configuration to afford (*R*)-**13**. The phenolic OH group of the latter is then transformed into the

corresponding triflate **14** which undergoes a slow but rather clean Stille cross coupling reaction with allyltributylstannane in the presence of $Pd_2(dba)_3$/tris(2-furyl)phosphine as the catalyst and LiCl as a stabilizing agent.[11] Gratifyingly, the resulting diene **15** cyclizes smoothly when exposed to the ruthenium carbene **18b** (6 mol%) developed by *Grubbs et al.*[12] under high dilution conditions in refluxing CH_2Cl_2 as the preferred solvent. We observed an essentially quantitative and very well reproducible formation of the 12-membered cycloalkene **16**, which is obtained as a mixture of the geometrical isomers [(*E*) : (*Z*) ≈ 2.3 : 1]. Hydrogenation of the double bond provides enantiomerically pure lasiodiplodin methyl ether (*R*)-**17**, which can be deprotected either to lasiodiplodin **1** itself or to de-O-methyl-lasiodiplodin **2**, respectively, according to literature procedures.[6] It is noteworthy that our approach delivers this key component in only 7 synthetic operations starting from inexpensive and commercially available starting materials and is therefore considerably more productive than any of the alternative syntheses of this specific compound described in the literature.[6]

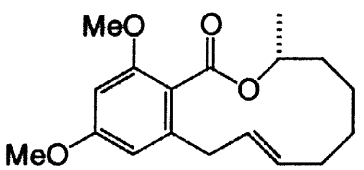


18a R = Ph
18b R = CH=CPh2

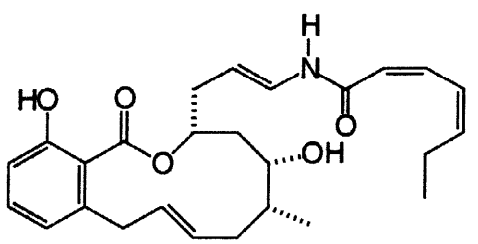
Anti-Tumor Activity of 16. Very recently it has been disclosed that the sponge metabolite salicylihalamide A **7**[13] exhibits a potent and unique differential cytotoxicity profile in the NCI 60-cell line human tumor assay. The mean panel GI_{50} concentration is ≈ 15 nM, with melanoma cell lines showing the highest sensitivity (GI_{50} 7 ± 2 nM). Since the activity of **7** does not display any significant correlations to the profiles of known antitumor agents, this macrolide constitutes a very attractive new lead structure in the search for anti-cancer drugs.



(*Z*)-**16**



(*E*)-**16**



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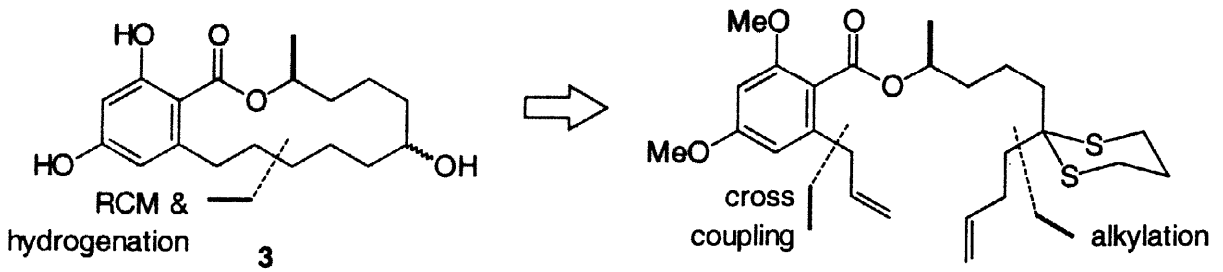
Because of the obvious structural relationship of our synthetic intermediate (*E*)-**16** with salicylihalamide A **7**, an assessment was called for to determine the anti-tumor activity of this compound. **16** exhibits a rather uniform in-vitro activity, with GI_{50} values in the range of ≈ 0.2-50 μM. However, no particular specificity has been noticed for any of the cell lines tested.[14] Since **16** may be regarded as a truncated analogue of **7**, these data provide a first hint to the structure/activity relationship of salicylihalamide. They suggest that the cytotoxicity of **7** stems to a significant extent from the peculiar enamide side chain of this interesting marine natural product.[13,15]

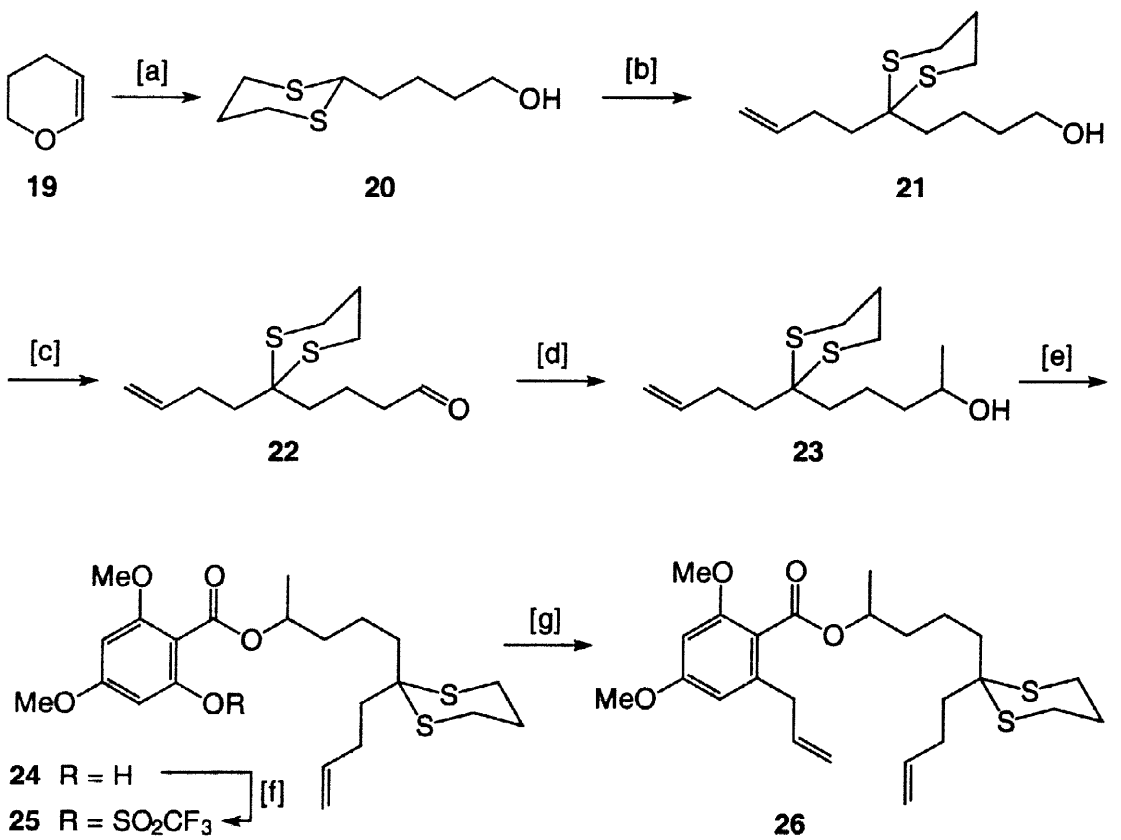
Zeranol. The anabolic, estrogenic and antibacterial properties of zearalenone **4** and related mycotoxins isolated from the fungus *Gibberella zeae* (*Fusarium graminearum*) have led to a systematic investigation of their activity profile.[16] During these studies zeranol **3** has been identified as a potent animal growth promotor for

cattle and sheep and has been marketed under various trade names (Ralgro®, Ralabol® etc.).[16a] Industrially, this compound is obtained by reduction of zearalenone, which itself is produced by fermentation.[17]



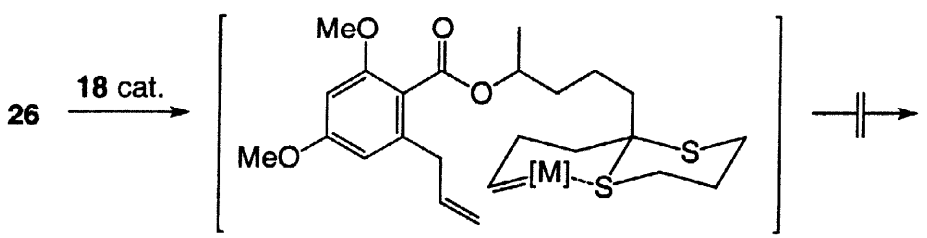
Scheme 3. Zeranol 3: Retrosynthetic Analysis

We became interested in whether a purely chemical approach to 3 based on RCM as the key step may rival this established semi-synthetic route.[18] In close analogy to the synthesis of lasiodiplodin outlined above, the "allylic" C-C-bond of the 14-membered ring has been chosen as the strategic site of disconnection (Scheme 3). This leads back to the salicylic acid derivative already used in the lasiodiplodin series esterified with a 6-hydroxy-9-decene-2-ol derivative which may be readily assembled via dithiane alkylation.



Scheme 4. [a] $HS(CH_2)_3SH$, $BF_3{\cdot}Et_2O$, MeOH, 87%; [b] (i) *sec*-BuLi (2 equiv.), THF,-15°C, 4h; (ii) 4-bromo-1-butene, 16h, 85%; [c] PCC, CH_2Cl_2, 51-62%; [d] MeMgI, Et_2O, -30°C, 97%; [e] **12**, EtOOC-N=N-COOEt, PPh_3, Et_2O, 84%; [f] $(CF_3SO_2)_2O$, pyridine/CH_2Cl_2, 0°C→r.t., 91%; [g] 9-allyl-9-BBN, KOMe, $PdCl_2$(dppf) (3 mol%), THF, reflux, 86%.

Our synthesis (Scheme 4) uses 3,4-dihydro-2H-pyrane as a well accessible starting material. Treatment of **19** with propane-1,3-dithiol in the presence of $BF_3{\cdot}Et_2O$ provides the known dithioacetal **20**.[18f,26] Its deprotonation with 2 equiv. of *sec*-BuLi followed by quenching of the resulting dianion with 4-bromo-1-butene cleanly affords the C-alkylated derivative **21**. The oxidation of the primary alcohol in **21** to the corresponding aldehyde **22** turned out to be somewhat delicate, with the best result being obtained by means of PCC in CH_2Cl_2.[19] Treatment of the latter with MeMgI and subsequent esterification of the resulting alcohol **23** with salicylic acid **12** under standard Mitsunobu conditions[10] delivers ester **24** in excellent yield. This compound is converted into the corresponding aryltriflate **25**, which undergoes a Stille coupling reaction with allyltributylstannane in the presence of $Pd_2(dba)_3$/tris(2-furyl)phosphine as the catalyst and LiCl as a stabilizing agent.[11] Although this reaction provides the desired allylated product **26** in reasonable yields, it proceeds very slowly (NMP, 40°C, 48h, 41%; or 60°C, 24h, 60%). Therefore we took recourse to an alternative allylation protocol which has been recently delevoped in our laboratory.[20] Thus, a modified Suzuki cross coupling[21] of aryltriflate **25** with the borate formed from 9-allyl-9-BBN and KOMe catalyzed by $PdCl_2$(dppf) (3 mol%) in refluxing THF affords product **26** on a multigram scale in 86% isolated yield after only 30 min reaction time.

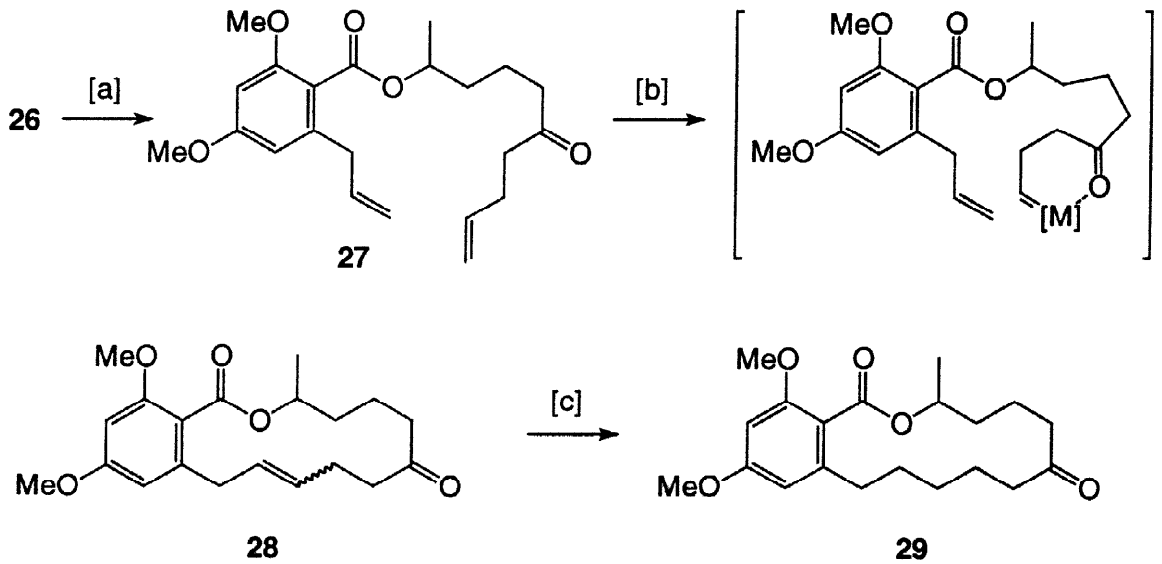


Scheme 5. Rationale for the Unsuccessful Macrocyclization of **26** by RCM; [M] = Ru(II) template.

Attempted cyclization of diene **26** bearing the intact dithioacetal moiety by RCM with the Grubbs catalyst **18** failed completely; the substrate was recovered unchanged. This is likely interpreted in terms of chelation of the emerging ruthenium carbene by the proximate sulfur atoms, which sequesters the catalyst in an unproductive form as formally depicted in Scheme 5. Similar problems with RCM reactions of dienes containing thioether functions have been reported in the recent literature, even in cases of kinetically more favorable ring sizes.[22] These reports together with our findings indicate a quite general incompatibility of the ruthenium based metathesis catalysts with substrates containing sulfur(II) donor sites.

For our preparative purposes, however, this situation is easily rectified by deprotecting the dithiane group prior to ring closure. Among the various methods tested, the excellent protocol of *Stork et al.* using commercially available (trifluoroacetoxy)iodobenzene turned out to be by far the best.[23] It provides the desired ketone **27** in very well reproducible 84% isolated yield, which serves as the appropriate precursor for the crucial RCM process. Since a ketone is a weaker ligand to Ru(II) than sulfur(II) it may be well suited to bring the reacting sites in vicinity as formally depicted in Scheme 6. In fact, diene **27** cyclizes smoothly on treatment with catalytic amounts of **18** in dilute CH_2Cl_2 solutions to afford the desired 14-membered cycloalkene **28** in 73% yield on a gram scale [(*E*) : (*Z*) ≈ 2.4 : 1]. The crude product was pure enough for further elaboration. Thus, hydrogenation of the mixture over Pd on charcoal in EtOH delivers zearalanone dimethylether **29** in

quantitative yield, which has repeatedly served as a key intermediate for the synthesis of various members of the zearalenone family of natural products including zeranol.[16-18] Despite considerable experimentation and contrary to our expectations, however, we were unable to find conditions for the seemingly trivial isomerization of the allylic double bond of **28** into the thermodynamically more stable vinylic position which would result in a formal total synthesis of zearalenone **4** itself.[24]



Scheme 6. [a] $(CF_3CO_2)_2IPh$, $MeOH/H_2O$ (9/1), 84%; [b] **18** (19 mol%), CH_2Cl_2, reflux, 73%; [c] H_2 (1 atm), Pd/C, EtOH, quant.

In summary, it has been shown that RCM opens up highly straightforward entries into orsellinic acid type macrolides. The intrinsic flexibility of these approaches, their economy of steps and high overall efficieny are particularly noteworthy. If compared to more conventional syntheses of these bioactive target molecules,[6,18] they nicely substantiate our previous claim that RCM is amongst the most promising avenues to large ring systems and favorably compares to all current alternatives, provided that the essential parameters for successful ring closure are properly assessed.[1,3]

EXPERIMENTAL

General. All reactions were carried out under Ar using Schlenk techniques. The ruthenium carbene **18b** was prepared according to the literature procedure.[12] All commercially available reagents (Aldrich, Fluka) were used as received. The solvents were dried by distillation over the following drying agents and were transferred under Ar: CH_2Cl_2 (CaH_2), Et_2O, THF (Mg-anthracene), toluene (Na), pyridine (KOH). Flash chromatography: Merck silica gel 60 (230 - 400 mesh). Melting points: Gallenkamp apparatus, uncorrected. NMR: Spectra were recorded on a Bruker AC 200, AMX 300, DPX 300, AMX 400 or DMX 600 spectrometer in $CDCl_3$ unless stated otherwise. Chemical shifts (δ) are given in ppm relative to TMS, coupling constants (J) in Hz. The multiplicity in the ^{13}C NMR spectra refers to the geminal protons (DEPT). IR: Nicolet FT-7199, wavenumbers

in cm^{-1}. MS: Finnigan MAT 8200 (70 eV); HR-MS: Finnigan MAT SSQ 7000 (70 eV). Elemental analyses: Dornis & Kolbe, Mülheim.

***(S)-(+)-7-Octen-2-ol* (10).** – A solution of 4-pentenylmagnesium bromide **9** [freshly prepared from 5-bromo-1-pentene (2.34 g, 15.7 mmol) and Mg (420 mg, 17.3 mmol) in THF (30 mL)] is added over 30 min to a suspension of (*S*)-(+)-methyloxirane **8** (830 mg, 14.2 mmol)[8] and CuCl(COD) (296 mg, 1.42 mmol) in THF (23 mL) at –78°C. The mixture is allowed to warm to ambient temperature overnight, the reaction is quenched by addition of aq. sat. NH_4Cl (30 mL) and the aqueous layer is repeatedly extracted with Et_2O (90 mL). Drying of the combined organic phases (Na_2SO_4), evaporation of the solvent and flash chromatography of the crude product with pentane/Et_2O (10/1) as the eluent affords the product as a colorless liquid (1.47 g, 81%). $[\alpha]_D^{20}$ = +11.2 (c 4.30, acetone); (ref.[25]: $[\alpha]_D$ = +7.88) – IR [cm^{-1}]: 3347, 3078, 2968, 2935, 2858, 1641, 1463, 1415, 1347, 1306, 1185, 1122, 1097, 1056, 991, 940, 910, 841, 730, 636, 554. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.81 (ddt, 1 H, *J* = 17.1, 10.3, 6.7 Hz), 5.00 (dt, 1 H, *J* = 17.1, < 1 Hz), 4.94 (dt, 1 H, *J* = 10.3, < 1 Hz), 3.79 (sext, 1 H, *J* = 6.2 Hz), 2.06 (q, 2 H, *J* = 6.6 Hz), 1.69 (br. s, 1 H), 1.35-1.48 (br. m, 6 H), 1.18 (d, 3 H, *J* = 6.2 Hz). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 138.8, 114.3, 68.0, 39.1, 33.7, 28.9, 25.2, 23.4. – MS (EI): *m/z* (rel. intensity): 128 (0.01) [M^+], 110 (2), 95 (16), 82 (23), 81 (19), 71 (10), 69 (21), 68 (25), 67 (23), 56 (26), 55 (19), 54 (32), 45 (100), 43 (21), 42 (10), 41 (35), 39 (13), 29 (10), 27 (10).

***2,4-Dimethoxy-6-hydroxybenzoic Acid* (12).**- A solution of 3,5-dimethoxyphenol **11** (5.00g, 32.4 mmol) in MeOH (20 mL) is treated with a solution of NaOMe (1.84 g, 34.1 mmol) in MeOH (20 mL). After stirring for 5 min, the solvent is evaporated and the remaining salt dried *in vacuo* (10^{-2} mbar, 50°C). An autoclave (100 mL) is flushed with Ar and charged with this salt. The autoclave is then pressurized with CO_2 (≈ 5.4 g, ≈ 40 atm) and kept at 120°C for 12 h. After venting the reactor, the crude product is dissolved in boiling water and the resulting solution treated with HCl until pH ≈ 8 is reached. The aqueous solution is repeatedly extracted with Et_2O in order to remove unreacted starting material. Dropwise addition of HCl (→ pH ≈ 1) leads to the precipitation of **12**, which was filtered off, rinsed with water and dried *in vacuo*. Colorless solid (5.14 g, 80%).- mp = 152-153°C (ref.[7]: 159°C; ref.[6d]: 152-154°C). – IR [cm^{-1}]: 3213, 3045, 3007, 2954, 2845, 2792, 2673, 2580, 1671, 1636, 1592, 1580, 1499, 1473, 1443, 1410, 1369, 1315, 1293, 1219, 1195, 1164, 1123, 1101, 1048, 987, 935, 856, 829, 796, 760, 690, 619, 538, 479. – ^{1}H-NMR (200 MHz): δ = 12.47 (s, 1 H), 11.01 (s, 1 H), 6.19 (d, 1 H, *J* = 2.3 Hz), 6.04 (d, 1 H, *J* = 2.3 Hz), 4.02 (s, 3 H), 3.83 (s, 3 H). – ^{13}C-NMR (50 MHz): δ = 170.7, 166.3, 165.6, 159.6, 95.1, 94.9, 91.3, 56.9, 55.7. – MS (EI): *m/z* (rel. intensity): 198 (41) [M^+], 181 (15), 180 (100), 152 (30), 137 (42).

***(R)-(–)-4,6-Dimethoxy-2-hydroxybenzoic acid (1-methyl-hept-2-enyl)ester* (13).**- To a suspension of acid **12** (1.21 g, 6.1 mmol) and diethyl azodicarboxylate (0.99 mL, 6.3 mmol) in Et_2O (25 mL) is added over 1 h a solution of PPh_3 (2.10 g, 8.0 mmol) and alcohol **10** (680 mg, 6.1 mmol) in Et_2O (25 mL). After TLC indicates quantitative conversion, the precipitates are filtered off, the solvent is evaporated and the crude product purified by flash chromatography using hexanes/ethyl acetate (12/1) as the eluent. This affords ester **13** as a colorless syrup (1.56 g, 83%). $[\alpha]_D^{20}$ = –35.2 (c = 8.15, acetone). – IR [cm^{-1}]: 3076, 2975, 2937, 2858, 1647, 1613, 1582, 1465, 1440, 1420, 1396, 1355, 1317, 1268, 1217, 1206, 1160, 1115, 1052, 994, 943, 912, 821, 782, 706, 622, 536. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 12.05 (s, 1 H), 6.09 (d, 1 H, *J* = 2.4 Hz), 5.95 (d, 1 H, *J* = 2.4 Hz), 5.80 (ddt, 1 H, *J* = 17.1, 10.3, 6.7 Hz), 5.14 (sext, 1 H, *J* = 6.3 Hz), 4.99 (dq, 1 H, *J* = 17.1, 1.9 Hz),

4.93 (ddt, 1 H, J = 10.3, 2.0, 1.1 Hz), 3.80 (s, 3 H), 3.79 (s, 3 H), 2.06 (q, 2 H, J = 6.7 Hz), 1.37-1.84 (br. m, 6 H), 1.34 (d, 3 H, J = 6.2 Hz). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 170.7, 165.7, 165.0, 152.3, 138.7, 114.4, 97.3, 93.3, 91.5, 72.0, 55.8, 55.3, 35.7, 33.6, 28.7, 24.6, 19.9. – MS (EI): *m/z* (rel. intensity): 308 (11) [M^+], 198 (12), 181 (21), 180 (100). – $C_{17}H_{24}O_5$ (308.37): *calcd.* C 66.21, H 7.84; *found* C 65.83, H 7.79.

(R)-(–)-2,4-Dimethoxy-6-trifluoromethylsulfonyloxybenzoic acid (1-methyl-hept-7-enyl)ester (**14**).- Triflic anhydride (0.81 mL, 4.8 mmol) was added via syringe to a solution of phenol **13** (1.23 g, 4.0 mmol) in pyridine (8 mL) at 0°C. The solution was allowed to reach ambient temperature before the reaction is quenched with water (10 mL). The aqueous phase is repeatedly extracted with Et_2O, the combined organic layers are washed with aq. HCl (5 %, *v/v*) and brine, dried over Na_2SO_4 and evaporated. Flash chromatography of the crude product with hexanes/ethyl acetate (15/1) affords triflate **14** as a pale yellow syrup (1.60 g, 91%). – $[\alpha]_D^{20}$ = –11.9; (c = 5.25, acetone). – IR [cm^{-1}]: 3081, 2980, 2943, 2847, 1727, 1623, 1580, 1501, 1466, 1424, 1382, 1332, 1276, 1247, 1217, 1161, 1142, 1112, 1064, 974, 916, 832, 763, 607, 499. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 6.46 (d, 1 H, J = 2.1 Hz), 6.44 (d, 1 H, J = 2.2 Hz), 5.80 (ddt, 1 H, J = 17.1, 10.3, 6.7 Hz), 5.15 (sext, 1 H, J = 6.3 Hz), 4.99 (ddt, 1 H, J = 17.1, 2.0, 1.6 Hz), 4.93 (ddt, 1 H, J = 10.3, 2.0, 1.2 Hz), 3.83 (s, 6 H), 2.06 (q, 2 H, J = 6.9 Hz), 1.38-1.79 (br. m, 6 H), 1.34 (d, 3 H, J = 6.3 Hz). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 162.9, 162.1, 159.2, 147.8, 138.8, 118.5 (q, J_{CF} = 321 Hz), 114.4, 111.1, 98.7, 98.4, 73.2, 56.3, 55.8, 35.6, 33.6, 28.7, 24.7, 19.7. – MS (EI): *m/z* (rel. intensity): 440 (3) [M^+], 332 (12), 331 (80), 330 (57), 314 (12), 313 (100), 181 (10), 180 (46), 179 (25), 137 (12), 110 (10), 69 (13), 55 (10), 41 (14).

(R)-(–)-2-Propen-1-yl-4,6-dimethoxybenzoic acid (1-methyl-hept-6-enyl)ester (**15**). A solution of $Pd_2(dba)_3$ (32 mg, 3 mol%) and tris(2-furyl)phosphine (65 mg, 0.28 mmol) in N-methyl-2-pyrrolidone (NMP, 1.5 mL) is stirred for 10 min prior to the addition of LiCl (144 mg, 3.41 mmol), triflate **14** (500 mg, 1.14 mmol; dissolved in NMP (3 mL)) and allytributylstannane (0.42 mL, 1.37 mmol). The mixture is kept at 40°C for 5 d. For work-up, aqueous KF (10%, *w/w*) is added, the aqueous layer is extracted with EtOAc, the combined organic phases are washed with brine, dried over Na_2SO_4 and evaporated. Flash chromatography (hexanes/Et_2O, 20/1) of the crude material provides the title compound as a colorless syrup (352 mg, 93%). – $[\alpha]_D^{20}$ = –20.5 (c 4.60, acetone). – IR [cm^{-1}]: 3077, 3001, 2976, 2936, 2859, 2841, 1720, 1640, 1605, 1587, 1490, 1462, 1423, 1378, 1327, 1270, 1232, 1208, 1160, 1099, 1047, 994, 950, 912, 832, 783, 744, 641, 610. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 6.33 (s, 2 H), 5.92 (ddt, 1 H, J = 16.9, 10.2, 6.6 Hz), 5.80 (ddt, 1 H, J = 17.1, 10.2, 6.7 Hz), 5.14 (sext, 1 H, J = 6.6 Hz), 5.07 (dq, 1 H, J = 16.9, 1.7 Hz), 5.05 (dq, 1 H, J = 10.2, 1.7 Hz), 4.99 (dq, 1 H, J = 17.1, 2.1 Hz), 4.93 (dq, 1 H, J = 10.3, 2.2 Hz), 3.79 (s, 3 H), 3.78 (s, 3 H), 3.36 (d, 2 H, J = 6.6 Hz), 2.06 (q, 2 H, J = 6.8 Hz), 1.37-1.76 (br. m, 6 H), 1.32 (d, 3 H, J = 6.3 Hz). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 167.7, 161.3, 158.0, 139.7, 138.7, 136.3, 117.2, 116.3, 114.4, 105.8, 96.7, 71.7, 55.7, 55.3, 37.7, 35.8, 33.7, 28.7, 24.9, 20.0. – MS (EI): *m/z* (rel. intensity): 332 (19) [M^+], 222 (53), 208 (12), 207 (100), 205 (50), 177 (13), 41 (11). – $C_{20}H_{28}O_4$ (332.44): *calcd.* C 72.26, H 8.49; *found* C 72.19, H 8.48.

(R)-(+)-2,4-Dimethoxy-7-methyl-7,8,9,10,11,14-hexahydro-6-oxa-benzocyclododecen-5-one (**16**). – Solutions of diene **15** (100 mg, 0.30 mmol) and of the ruthenium carbene **18b** (17 mg, 6 mol%) in CH_2Cl_2 (30 mL each) are slowly added via two dropping funnels to refluxing CH_2Cl_2 (60 mL). A stream of Ar is slowly bubbled through the resulting reaction mixture until TLC indicates complete conversion of the starting material. Evaporation of the solvent and flash chromatography (hexanes/Et_2O, 20/1) of the residue [(*E*) : (*Z*) ≈ 2.3 : 1,

GC] afford a pure sample of (*E*)-**16** (56 mg, 61%). A second fraction (30 mg, 33%) consists of a mixture of (*E/Z*)-**16**. Analytical and spectroscopic data of (*E*)-**16**: $[\alpha]_D^{20}$ = +72 (c 0.46, acetone). – IR [cm^{-1}]: 2972, 2932, 2866, 2843, 1714, 1604, 1586, 1490, 1458, 1422, 1376, 1328, 1284, 1262, 1228, 1208, 1161, 1133, 1107, 1094, 1047, 971, 899, 883, 848, 831, 779, 744, 727, 640, 622. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 6.34 (d, 1 H, *J* = 2.3 Hz), 6.32 (d, 1 H, *J* = 2.3 Hz), 5.41 (dddd, 1 H, *J* = 14.9, 10.2, 4.5, 1.9 Hz), 5.20 (dddd, 1 H, *J* = 14.9, 10.2, 3.2, 1.6 Hz), 5.10 (dqd, 1 H, *J* = 10.0, 6.3, 2.8 Hz), 3.80 (s, 3 H), 3.78 (s, 3 H), 3.36 (d, 1 H, *J* = 6.3 Hz), 3.07 (ddd, 1 H, *J* = 14.2, 5.0, 2.9 Hz), 2.22 (m, 1 H), 1.21-1.71 (br. m, 6 H), 1.31 (d, 3 H, *J* = 6.2 Hz), 1.09 (m, 1 H). – ^{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. – MS (EI): *m/z* (rel. intensity): 304 (24) [M^+], 217 (10), 208 (17). 207 (100), 205 (15), 204 (10), 196 (32), 191 (11), 189 (10), 178 (12). – $C_{18}H_{24}O_4$ (304.38): *calcd.* C 71.03, H 7.95; *found* C 71.22, H 7.71; HR-MS: *calcd.* 304.167460, *found* 304.167393. Characteristic data of (*Z*)-**16**: ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 168.0, 161.3, 157.7, 140.6, 129.8, 129.7, 126.6, 105.9, 96.5, 71.3, 55.8, 55.3, 31.9, 26.5, 24.5, 18.5, 18.3.

(R)-(+)-2,4-Dimethoxy-7-methyl-7,8,9,10,11,12,13,14-octahydro-6-oxa-benzocyclododecene-5-one (**17**). – A suspension of cycloalkene **16** (71 mg, 0.23 mmol) and Pd/C (5% *w/w*, 9 mg) in EtOH (10 mL) is stirred under H_2 (1 atm) for 20 h. The catalyst is filtered off, the solvent is evaporated and the product is purified by flash chromatography (hexanes/ethyl acetate, 12/1) affording lasiodiplodin dimethyl ether **17** as a colorless syrup (63 mg, 94%). $[\alpha]_D^{20}$ = +8.7 (c 1.63, $CHCl_3$); ref.[6g] $[\alpha]_D$ = +9 (c 1, $CHCl_3$), ref.[6d] $[\alpha]_D$ = +4.2 (c 0.18, EtOH). IR [cm^{-1}]: 3005, 2979, 2927, 2844, 1716, 1604, 1586, 1490, 1457, 1420, 1372, 1351, 1326, 1285, 1263, 1231, 1203, 1161, 1132, 1106, 1089, 1057, 1001, 975, 946, 931, 909, 874, 843, 830, 801, 777, 727, 646, 606, 533. – ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.32 (d, 1 H, *J* = 2.2 Hz), 6.30 (d, 1 H, *J* = 2.2 Hz), 5.28 (quintd, 1 H, *J* = 6.5, 3.2 Hz), 3.80 (s, 3 H), 3.79 (s, 3 H), 2.72 (dt, 1 H, , *J* = 13.5, 7.9 Hz), 2.54 (dt, 1 H, *J* = 13.5, 6.7 Hz), 1.93 (m, 1 H), 1.65 (m, 4 H), 1.35-1.60 (br. m, 5 H), 1.32 (d, 3 H, *J* = 6.5 Hz), 1.26 (m, 2 H). – ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 168.5, 161.1, 157.7, 142.8, 118.1, 105.8, 96.3, 72.0, 55.9, 55.3, 32.4, 30.7, 30.2, 26.5, 25.5, 24.2, 21.3, 19.5. – MS (EI): *m/z* (rel. intensity): 307 (19), 306 (97) [M^+], 207 (12), 206 (14), 205 (15), 197 (11), 196 (100), 195 (13), 192 (16), 191 (49), 178 (17), 177 (10), 165 (14), 152 (83), 151 (22), 120 (10), 69 (19), 55 (12), 41 (12).

4-[1,3]Dithian-2-yl-butan-1-ol (**20**). To a solution of dihydropyran **19** (7.0 g, 83 mmol) and MeOH (6.7 mL) in $CHCl_3$ (35 mL) is added $BF_3{\cdot}Et_2O$ (8.8 g) over 20 min at 0°C. After stirring for 15 min, propane-1,3-dithiol (8.97 g, 83 mmol) is introduced and the resulting mixture stirred at ambient temperature for 4 h. A standard extractive work-up followed by distillation of the crude product furnishes the title compound as a colorless syrup (13.82 g, 87%). – bp = 106-110°C/0.02 torr; ref.[26]: 120°C/0.1 torr. – IR [cm^{-1}]: 3398, 2935, 2860, 1453, 1422, 1377, 1347, 1276, 1243, 1185, 1139, 1116, 1070, 981, 941, 908, 883, 867, 841, 817, 761, 683, 664, 642. – ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 4.06 (t, 1 H, *J* = 6.8 Hz), 3.65 (m, 2 H), 2.83-2.90 (m, 4 H), 1.72-1.96 (m, 4 H), 1.59 (m, 4 H). – ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 62.5, 47.4, 35.1, 32.4, 30.4 (2 CH_2), 25.9, 22.8. – MS (EI): *m/z* (rel. intensity): 192 (47) [M^+], 119 (100), 85 (37), 84 (8), 74 (13), 73 (12), 67 (10), 45 (16), 41 (17).

4-(2-But-3-enyl-[1,3]dithian-2-yl)-butan-1-ol (**21**). A solution of *sec*-BuLi (1.16 M in cyclohexane, 19.8 mL, 23 mmol) is slowly added to a solution of compound **20** (2.15 g, 11.2 mmol) in THF (25 mL) at –15°C. The mixture is stirred at that temperature for 4 h prior to the addition of 4-bromo-1-butene (0.80 mL, 7.9 mmol) and

stirring is continued for another 16 h. The reaction is quenched with aq. sat. $NaHCO_3$ (20 mL), the aqueous layer is repeatedly extracted with Et_2O, the combined organic phases are successively washed with aq. sat. Na_2CO_3, water and brine, dried over Na_2SO_4 and evaporated. Flash chromatography (hexanes/ethyl acetate, 4/1) then affords dithiane **21** as a colorless syrup (2.35 g, 85%). – IR [cm^{-1}]: 3382, 3075, 2939, 2909, 2865, 1738, 1640, 1451, 1423, 1374, 1346, 1274, 1238, 1171, 1111, 1068, 1033, 997, 909, 867, 795, 744, 710, 677, 646. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.83 (ddt, 1 H, *J* = 17.0, 10.3, 6.6 Hz), 5.06 (m, 1 H), 4.98 (ddt, 1 H, *J* = 10.1 Hz), 3.67 (t, 2 H, *J* = 6.2 Hz), 2.81 (m, 4 H), 2.18 (m, 2 H), 1.87-2.00 (m, 6 H), 1.69 (s, 1 H), 1.47-1.65 (m, 4 H). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 137.9, 114.8, 62.6, 53.0, 38.2, 37.3, 32.7, 28.6, 26.0 (2 CH_2), 25.4, 20.4. – MS (EI): *m/z* (rel. intensity): 247 (11), 246 (63) [M^+], 205 (26), 191 (69), 175 (12), 174 (12), 173 (100), 172 (13), 171 (55), 157 (10), 153 (19), 139 (43), 138 (12), 137 (10), 127 (13), 121 (12), 119 (14), 117 (39), 114 (11), 113 (11), 111 (16), 107 (67), 106 (48), 101 (22), 99 (53), 97 (28), 95 (11), 93 (24), 91 (19), 87 (16), 85 (15), 84 (13), 81 (25), 79 (44), 77 (17), 75 (25), 74 (10), 73 (38), 71 (17), 69 (13), 67 (30), 65 (16), 59 (12), 57 (17), 55 (29), 53 (17), 47 (16), 45 (24), 43 (19), 41 (72), 39 (19), 31 (16), 29 (14), 28 (12). – $C_{12}H_{22}OS_2$ (246.44): *calcd.* C 58.97, H 9.07, S 26.24; *found* C 58.59, H 8.83, S 26.11.

4-(2-But-3-enyl-[1,3]dithian-2-yl)-butyraldehyde (**22**). – A solution of alcohol **21** (5.56 g, 22.6 mmol) in CH_2Cl_2 (80 mL) is added over 1 h to a suspension of PCC (7.31 g, 33.9 mmol) in CH_2Cl_2 (120 mL) at 0°C. The mixture is stirred for 5 h at ambient temperature. The precipitates are filtered off through a pad of silica, the residues are carefully washed with CH_2Cl_2 (ca. 100 mL in several portions), the combined filtrates are evaporated and the crude product purified by flash chromatography with hexanes/ethyl acetate (10/1) as the solvent affording analytically pure **22** as a colorless syrup (2.825 g, 51%). When the reaction is carried out on a smaler scale, yields of up to 62% have been obtained. IR [cm^{-1}]: 3427, 3076, 2940, 2909, 2827, 2722, 1723, 1640, 1451, 1417, 1389, 1275, 1239, 1186, 1113, 1079, 998, 910, 868, 796, 733, 676, 648. – ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 9.79 (t, 1 H, *J* = 1.4 Hz), 5.83 (ddt, 1 H, *J* = 16.9, 10.4, 6.5 Hz), 5.07 (m, 1 H), 4.99 (m, 1 H), 2.82 (m, 4 H), 2.49 (t, 2 H, *J* = 6.0 Hz), 2.21 (m, 2 H), 1.71-2.01 (m, 8 H). – ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 201.8, 137.7, 114.9, 52.7, 43.6, 37.6, 37.4, 28.4, 25.9 (2 CH_2), 25.2, 16.9. – MS (EI): *m/z* (rel. intensity): 244 (52) [M^+], 216 (14), 203 (32), 190 (10), 189 (77), 175 (11), 173 (76), 171 (10), 170 (10), 169 (45), 151 (11), 145 (66), 141 (17), 137 (15), 136 (12), 125 (17), 120 (11), 119 (26), 116 (14), 114 (17), 113 (13), 111 (15), 109 (11), 108 (13), 107 (65), 106 (52), 100 (17), 99 (42), 97 (25), 93 (27), 92 (12), 91 (24), 87 (18), 85 (24), 81 (22), 79 (31), 77 (18), 75 (11), 74 (11), 73 (38), 71 (30), 67 (34), 65 (17), 59 (17), 57 (10), 55 (53), 53 (18), 47 (18), 45 (34), 43 (15), 41 (100), 39 (29), 29 (20), 27 (18). – $C_{12}H_{20}OS_2$ (244.42): *calcd.* C 58.97, H 8.25, S 26.24; *found* C 58.40, H 7.78, S 26.27; HR-MS: *calcd.* 244.095561; *found* 244.096608.

5-(2-But-3-enyl-[1,3]dithian-2-yl)-pentan-2-ol (**23**). – A solution of aldehyde **22** (2.825 g, 11.6 mmol) in Et_2O (30 mL) is added dropwise to a solution of MeMgI (34.8 mmol) in Et_2O (60 mL) at –30°C and the mixture is kept at that temperature for 14 h. Quenching the reaction with sat. aq. NH_4Cl followed by a standard extractive work-up affords analytically pure **23** as a colorless syrup (2.939 g, 97%). IR [cm^{-1}]: 3395, 3076, 2942, 2909, 2867, 2231, 1828, 1640, 1451, 1423, 1376, 1299, 1274, 1239, 1191, 1133, 1026, 996, 910, 869, 834, 814, 793, 733, 678, 647, 621, 559. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.83 (ddt, 1 H, *J* = 16.9, 10.4, 6.5 Hz), 5.05 (dt, 1 H, *J* = 17.0, < 1 Hz), 4.97 (dt, 1 H, *J* = 10.2, < 1 Hz), 3.82 (sext, 1 H, *J* = 6.1 Hz), 2.81 (m, 4 H), 2.19 (m, 2 H), 1.83-2.00 (m, 7 H), 1.37-1.65 (m, 4 H), 1.20 (d, 3 H, *J* = 6.2 Hz). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 137.8, 114.7, 67.6, 52.9, 39.2, 38.3, 37.2, 28.5, 25.9 (2 CH_2), 25.3, 23.4, 20.3. – MS (EI): *m/z* (rel. intensity): 260 (51)

[M^+], 219 (20), 205 (41), 186 (11), 185 (35), 175 (14), 174 (11), 173 (100), 171 (10), 167 (25), 153 (73), 152 (11), 147 (21), 145 (17), 135 (24), 127 (15), 125 (16), 119 (15), 113 (17), 112 (11), 111 (33), 109 (13), 107 (62), 106 (45), 101 (17), 99 (36), 97 (57), 95 (25), 94 (33), 93 (41), 91 (17), 87 (16), 85 (17), 81 (21), 79 (41), 77 (15), 75 (17), 73 (31), 71 (42), 69 (12), 67 (35), 65 (13), 59 (11), 55 (30), 53 (14), 47 (14), 45 (40), 43 (51), 41 (65), 39 (15), 29 (13), 27 (10). – $C_{13}H_{24}OS_2$ (260.46): *calcd.* C 59.95, H 9.29; *found* C 60.18, H 9.19; HR-MS: *calcd.* 260.126861, *found* 260.125972.

4,6-Dimethoxy-2-hydroxybenzoic acid [4-(2-but-3-enyl-[1,3]dithian-2-yl)-1-methyl-butyl]ester (**24**).- A solution of alcohol **23** (1.576 g, 6.1 mmol) and PPh_3 (1.592 g, 6.1 mmol) in Et_2O (40 mL) is added dropwise to a solution of salicyclic acid **12** (1.202 g, 6.1 mmol) and diethyl azodicarboxylate (1.082 g, 6.2 mmol) in Et_2O (40 mL). Work-up of the reaction mixture after 5 h as described above for compound **13** followed by flash chromatography of the crude product (hexanes/ethyl acetate, 15/1) provides analytically pure **24** as a colorless syrup (2.264 g, 84%). IR [cm^{-1}]: 2940, 1643, 1611, 1581, 1420, 1314, 1267, 1216, 1159, 1113, 1051, 820. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 12.05 (s, 1 H), 6.09 (d, 1 H, *J* = 2.4 Hz), 5.94 (d, 1 H, *J* = 2.4 Hz), 5.79 (ddt, 1 H, *J* = 17.1, 10.2, 6.6 Hz), 5.16 (m, 1 H), 5.01 (dq, 1 H, *J* = 17.2, 1.7 Hz), 4.95 (ddt, 1 H, *J* = 10.2, 1.9, 1.2 Hz), 3.80 (s, 6 H), 2.79 (m, 4 H), 2.18 (m, 2 H), 1.87-1.99 (m, 4 H), 1.57-1.78 (m, 6 H), 1.36 (d, 3 H, *J* = 6.2 Hz). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 170.8, 165.8, 165.1, 162.4, 137.8, 114.8, 97.2, 93.3, 91.6, 71.8, 56.0, 55.4, 52.9, 38.3, 37.3, 36.0, 28.6, 26.0, 25.9, 25.4, 20.0, 19.8. – MS (EI): *m/z* (rel. intensity): 440 (25) [M^+], 385 (12), 243 (11), 242 (29), 199 (39), 188 (14), 187 (24), 181 (76), 180 (20), 173 (55), 169 (12), 168 (24), 167 (100), 143 (10), 145 (18), 135 (33), 126 (11), 125 (20), 107 (20), 106 (13), 93 (18), 79 (11), 55 (16), 41 (17). –HR-MS ($C_{22}H_{32}O_5S_2$): *calcd.* 440.169119, *found* 440.169501.

2,4-Dimethoxy-6-trifluormethylsulfonyloxybenzoic acid [4-(2-but-3-enyl-[1,3]dithian-2-yl)-1-methyl-butyl] ester (**25**).- To a solution of phenol **24** (4.04 g, 9.2 mmol) in CH_2Cl_2 (30 mL) and pyridine (30 mL) is slowly added a solution of triflic anhydride (4.73 g, 16.8 mmol) in CH_2Cl_2 (20 mL) at 0°C. The mixture is stirred at ambient temperature until TLC indicates complete consumption of the starting material. A standard extractive work-up as described above for triflate **14** followed by flash chromatography (hexanes/ethyl acetate, 10/1) affords compound **25** as a pale yellow syrup (4.77 g, 91%). IR [cm^{-1}]: 2943, 1728, 1622, 1579, 1274, 1217, 1161, 1142, 1063, 974, 833, 606. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 6.46 (d, 1 H, *J* = 2.2 Hz), 6.43 (d, 1 H, *J* = 2.1 Hz), 5.81 (ddt, 1 H, *J* = 17.1, 10.2, 6.6 Hz), 5.16 (sext, 1 H, *J* = 6.2 Hz), 5.03 (dq, 1 H, *J* = 17.1, 1.6 Hz), 4.96 (ddt, 1 H, *J* = 10.2, 1.9, 1.2 Hz), 3.85 (s, 3 H), 3.83 (s, 3 H), 2.80 (t, 4 H, *J* = 6.7 Hz), 2.19 (m, 2 H), 1.87-2.04 (m, 6 H), 1.49-1.83 (m, 4 H), 1.36 (d, 3 H, *J* = 6.3 Hz). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 162.8, 162.2, 159.4, 147.9, 137.9, 118.5 (q, J_{CF} = 320 Hz), 114.8, 111.0, 98.7, 98.4, 72.9, 56.5, 55.8, 53.0, 38.3, 37.5, 35.8, 28.6, 26.0, 25.4, 19.9, 19.6. – MS (EI): *m/z* (rel. intensity): 572 (23) [M^+], 531 (11), 517 (17), 331 (33), 313 (519), 242 (17), 187 (26), 181 (18), 180 (34), 173 (70), 169 (12), 168 (30), 167 (100), 153 (16), 145 (22), 136 (11), 135 (27), 126 (16), 125 (18), 107 (18), 106 (14), 93 (17), 79 (13), 73 (10), 55 (14), 41 (15). –HR-MS ($C_{23}H_{31}F_3O_7S_3$): *calcd.* 572.118405, *found* 572.119099.

4,6-Dimethoxy-2-(propen-1-yl)-benzoic acid [4-(2-but-3-enyl-[1,3]dithian-2-yl)-1-methyl-butyl]ester (**26**).- To a solution of B-allyl-9-BBN (1.35 g, 8.3 mmol)[20] in THF (120 mL) is added KOMe (582 mg, 8.3 mmol) and the mixture is stirred for 10 min until a clear solution is formed. Triflate **25** (3.98 g, 6.9 mmol) and $PdCl_2$(dppf) (171 mg, 3 mol%) are introduced and the mixture is refluxed under Ar for 30 min. After that time the ^{11}B NMR

of an aliquot shows a single peak at δ = 56.6 ppm (external standard: $BF_3{\cdot}Et_2O$). For work-up the volatiles are removed *in vacuo*, the residue is suspended in CH_2Cl_2 (120 mL) and the undissolved salts are filtered off over a short pad of silica. Evaporation of the solvent and drying of the residue at 10^{-2} torr affords **26** (purity by NMR and GC ≥ 93%, rest: cyclooctanone) as a colorless syrup (2.97g, 86%). An analytically pure sample is obtained by flash chromatography using hexane/Et_2O (20/1) as the eluent. IR [cm^{-1}]: 3077, 2940, 2840, 1719, 1689, 1639, 1605, 1456, 1423, 1379, 1327, 1271, 1208, 1160, 1096, 1047, 995, 912, 833, 734, 622.- ^1H NMR (300 MHz, $CDCl_3$): δ = 6.33 (s, 2H), 5.92 (ddt, 1H, *J* = 16.4, 10.5, 6.4 Hz), 5.82 (ddt, 1H, *J* = 17.0, 10.4, 6.6 Hz), 5.18 (sext., 1H, *J* = 6.2 Hz), 5.07 (dq, 1H, *J* = 17.2, 1.6 Hz), 5.06 (dq, 1H, *J* = 10.1, 1.4 Hz), 5.04 (dq, 1H, *J* = 17.1, 1.6 Hz), 4.96 (dq, 1H, *J* = 10.2, 1.4 Hz), 3.80 (s, 3H), 3.79 (s, 3H), 3.37 (dd, 2H, *J* = 6.6, 1.3 Hz), 2.80 (m, 4H), 2.20 (m, 2H), 1.86-1.99 (m, 6H), 1.49-1.76 (m, 4H), 1.34 (d, 3H, *J* = 6.3 Hz).- ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.7, 161.3, 156.1, 139.8, 137.9, 136.3, 117.1, 116.4, 114.9, 105.8, 96.7, 71.5, 55.9, 55.3, 53.0, 38.4, 37.7, 37.5, 36.1, 28.6, 26.0, 25.4, 20.2, 20.1.- MS (EI): *m/z* (rel. intensity): 464 (14, [M^+]), 243 (50), 223 (30), 207 (12), 206 (14), 205 (100), 204 (26), 187 (19), 177 (14), 173 (45), 168 (16), 167 (76), 145 (15), 135 (25), 125 (14), 107 (14), 93 (13), 55 (11), 41 (12).- HR-MS ($C_{25}H_{36}O_4S_2$): *calcd.* 464.20551; *found* 464.20384.

4,6-Dimethoxy-2-(propen-1-yl)-benzoic acid (1-methyl-5-oxo-non-8-enyl)ester **(27)**. – Solid $(CF_3COO)_2IPh$ (2.70 g, 6.2 mmol) is added to a turbid solution of dithiane **26** (1.92 g, 4.13 mmol) in MeOH (40 mL) and H_2O (4 mL). After stirring for 15 min, the mixture is diluted with Et_2O (100 mL) and aq. sat. $NaHCO_3$ (30 mL). A standard extractive work-up followed by flash chromatography (hexanes/ethyl acetate, 10/1) affords ketone **27** as a colorless syrup (1.298 g, 84%). ^1H-NMR (600 MHz, $CDCl_3$): δ = 6.31 (s, 2 H), 5.89 (ddt, 1 H, *J* = 16.9, 10.2, 6.6 Hz), 5.77 (ddt, 1 H, *J* = 17.0, 10.3, 6.6 Hz), 5.12 (m, 1 H), 5.04 (dq, 1 H, *J* = 17.0, 1.7 Hz), 5.03 (dq, 1 H, *J* = 10.1, 1.6 Hz), 5.00 (dq, 1 H, *J* = 17.1, 1.7 Hz), 4.95 (ddt, 1 H, *J* = 10.2, 1.7, 1.4 Hz), 3.77 (s, 3H), 3.76 (s, 3 H), 3.34 (m, 2 H), 2.38-2.48 (m, 4 H), 2.30 (m, 2 H), 1.53-1.75 (m, 4 H), 1.30 (d, 3 H, *J* = 6.3 Hz). – ^{13}C-NMR (150 MHz, $CDCl_3$): δ = 209.8, 167.8, 161.4, 158.1, 139.9, 137.1, 136.3, 117.0, 116.4, 115.2, 105.9, 96.7, 71.3, 55.8, 55.4, 42.4, 41.8, 37.7, 35.3, 27.8, 20.0, 19.5. – MS (EI): *m/z* (rel. intensity): 374 (0.36) [M^+], 222 (10), 207 (78), 206 (13), 205 (85), 204 (42), 186 (11), 177 (31), 175 (12), 159 (13), 154 (11), 153 (100), 147 (11), 83 (34), 69 (24), 55 (70), 41 (13).- $C_{22}H_{30}O_5$: *calcd.* C 70.55, H 8.06; *found* C 70.35, H 8.08.

2,4-Dimethoxy-7-methyl-7,8,9,10,13,16-hexahydro-12H-6-oxa-benzocyclotetradecene-5,11-dione **(28)**. – Solutions of diene **27** (1.148 g, 3.1 mmol) and ruthenium carbene **18b** (478 mg, 0.58 mmol) in CH_2Cl_2 (80 mL each) are added over a period of 10 h via syringe pumps to refluxing CH_2Cl_2 (500 mL). Reflux is continued for another 48 h until TLC shows complete conversion. The solution is concentrated to ≈ 20 mL and filtered through a pad of silica. This affords cycloalkene **28** as a highly viscous syrup which is pure enough for further elaboration (876 mg, GC purity: ≥ 90%; corresponds to 73% yield). An analytically pure sample was obtained by chromatography, which consists of an inseparable mixture of (*E,Z*)-**28** [GC and GC-MS: (*E*) : (*Z*) ≈ 2.4 : 1]. Characteristic data of the major isomer: ^{13}C-NMR (150 MHz, $CDCl_3$): δ = 212.0, 167.6, 161.4, 158.7, 140.4, 130.6, 128.9, 117.0, 107.0, 97.0, 71.2, 56.0, 55.4, 43.9, 40.6, 36.3, 33.6, 28.2, 19.4, 19.1. – MS (EI): *m/z* (rel. intensity): 346 (3) [M^+], 328 (17), 235 (15), 218 (15), 217 (96), 207 (14), 204 (17), 192 (17), 191 (11), 190 (16), 189 (100), 158 (13), 151 (44), 55 (11).

***Zearalanone Dimethylether* (29).**- A suspension of compound **28** (83 mg, 0.24 mmol) and Pd/C (5% *w/w*, 5 mg) in EtOH (10 mL) is stirred under H_2 (1 atm) for 3h at ambient temperature. The catalyst is filtered off and the solvent is evaporated affording analytically pure **29** (83 mg, quant.) as a syrup which solidifies upon standing. Analytical data are identical to those reported in the literature.[16d] Previously unreported spectroscopic data: ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 6.32 (s, 2H), 5.32 (tq, 1 H, *J* = 3.7, 6.5), 3.80 (s, 3 H), 3.78 (s, 3H), 2.26-2.65 (m, 6 H), 2.19 (dt, 1 H, *J* = 6.5, 15.1), 1.22-1.87 (m, 8 H), 1.34 (d, 3 H, *J* = 6.5), 1.55 (dt, 1 H, *J* = 3.8, 6.7).- ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 212.3, 167.9, 161.3, 158.0, 142.4, 116.9, 105.7, 96.4, 70.2, 55.8, 55.2, 43.5, 38.6, 34.4, 33.7, 30.7, 27.6, 23.1, 19.8, 19.3.- MS (EI): *m/z* (rel. intensity): 348 (63) [M^+], 330 (13), 279 (11), 261 (16), 233 (11), 219 (14), 207 (13), 206 (18), 205 (26), 196 (21), 192 (35), 191 (100), 178 (48), 165 (15), 152 (34), 151 (25), 135 (14), 125 (33), 83 (11), 69 (15), 55 (49).

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Cancer type	HL-60	EKVX	COLO 205	SK-MEL-5	OVCAR-3	TK-10	PC-3	T-47D
	leukemia	lung	colon	melanoma	ovarian	renal	prostate	breast
GI_{50} (μM)	0.82	1.56	3.58	1.73	1.42	1.86	1.85	0.81
LC_{50} (μM)	>100	5.62	>100	7.07	5.43	7.93	6.88	>100

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