Total Syntheses of (+)-Ricinelaidic Acid Lactone and of (−)-Gloeosporone Based on Transition-Metal-Catalyzed C−C Bond Formations

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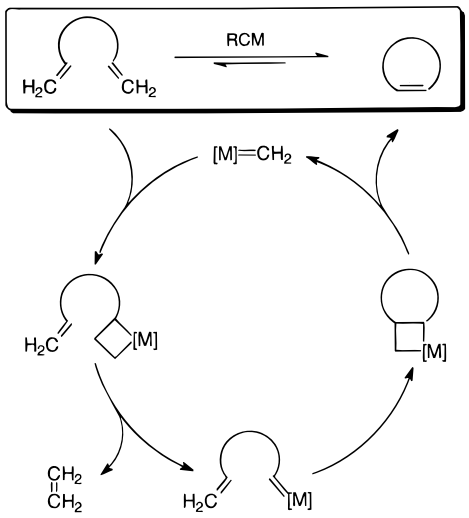
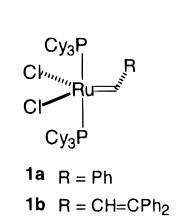
Abstract: Total syntheses of the macrolides (*R*)-(+)-ricinelaidic acid lactone (**6**) and (−)-gloeosporone (**7**), a fungal germination self-inhibitor, are presented, which are distinctly shorter and more efficient than any of the previous approaches to these targets reported in the literature. Both of them benefit from the remarkable ease of macrocyclization of 1,ω-dienes by means of ring-closing olefin metathesis (RCM) using the ruthenium carbene **1a** as catalyst precursor. The diene substrates are readily formed via the enantioselective addition of dialkylzinc reagents to aldehydes in the presence of catalytic amounts of $Ti(OiPr)_4$ and bis-triflamide **18** and/or the stereoselective allylation of aldehydes developed by Keck et al. using allyltributylstannane in combination with a catalyst formed from $Ti(OiPr)_4$ and (*S*)-(−)-1,1′-bi-2-naphthol. Comparative studies show this latter procedure to be more practical than the stoichiometric allylation reaction employing the allyltitanium−α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanol complex **3b**. Finally, a method for the efficient ring closure of 4-pentenoic acid esters by RCM is presented that relies on the joint use of **1a** and $Ti(OiPr)_4$ as a binary catalyst system. These results not only expand the scope of RCM to previously unreactive substrates but also provide additional evidence for the important role of ligation of the evolving ruthenium carbene center to a polar relay substituent on the substrate which constitutes the necessary internal bias for the RCM-based macrocyclization process.

Introduction

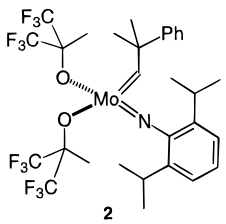
Our recent investigations on ring-closing olefin metathesis (RCM) using either **1a**,**b** or **2** as catalyst precursors have revealed the remarkable scope of this method for the preparation of medium-sized and macrocyclic products (Scheme 1).[1−4] These reactions are essentially driven by the gain in entropy upon bisecting the diene substrate.

Scheme 1





1a R = Ph
1b R = CH=CPh$_2$



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It was discovered that neither a conformational predisposition of the starting material toward ring closure nor the ring size formed are particularly relevant factors,[1] although this had been previously assumed.[2b] However, the mere presence of a functional group (ester, ketone, ether, urethane, etc.) in the starting material was found to be of utmost importance, as well as the proper distance between this key substituent and the alkenes to be metathesized.[1a,d] These results are interpreted in

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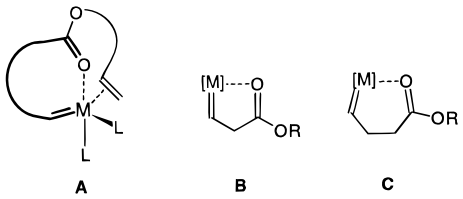
(2) For general reviews on olefin metathesis in organic synthesis, see the following for leading references: (a) Ivin, K. J.; Mol, J. C. *Olefin Metathesis and Metathesis Polymerization*; Academic Press: New York, 1997. (b) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446. (c) Fürstner, A. *Topics in Catalysis* In press.

(3) For other examples of macrocyclization reactions via RCM using various catalysts, see: (a) Borer, B. C.; Deerenberg, S.; Bieräugel, H.; Pandit, U. K. *Tetrahedron Lett.* **1994**, 3191. (b) Miller, S. J.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 5855. (c) Miller, S. J.; Blackwell, H. E.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 9606. (d) Clark, T. D.; Ghadiri, M. R. *J. Am. Chem. Soc.* **1995**, *117*, 12364. (e) König, B.; Horn, C. *Synlett* **1996**, 1013. (f) McKervey, M. A.; Pitarch, M. *J. Chem. Soc., Chem. Commun.* **1996**, 1689. (g) Yang, Z.; He, Y.; Vourloumis, D.; Vallberg, H.; Nicolaou, K. C. *Angew. Chem.* **1997**, *109*, 170. (h) Nicolaou, K. C.; He, Y.; Vourloumis, D.; Vallberg, H.; Yang, Z. *Angew. Chem.* **1996**, *108*, 2554. (i) Schinzer, D.; Limberg, A.; Bauer, A.; Böhm, O. M.; Cordes, M. *Angew. Chem.* **1997**, *109*, 543. (j) Bertiano, P.; Sorensen, E. J.; Meng, D.; Danishefsky, S. J. *J. Org. Chem.* **1996**, *61*, 8000. (k) Houri, A. F.; Xu, Z.; Cogan, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1995**, *117*, 2943. (l) Martin, S. F.; Liao, Y.; Chen, H.-J.; Pätzel, M.; Ramser, M. N. *Tetrahedron Lett.* **1994**, 6005. (m) Tsuji, J.; Hashiguchi, S. *Tetrahedron Lett.* **1980**, 2955. (n) Villemin, D. *Tetrahedron Lett.* **1980**, 1715. (o) Plugge, M. F. C.; Mol, J. C. *Synlett* **1991**, 507. (p) Descotes, G.; Ramza, J.; Basset, J.-M.; Pagano, S.; Gentil, E.; Banoub, J. *Tetrahedron* **1996**, *52*, 10903.

(4) For the preparation of the ruthenium carbenes **1a**,**b**, see: (a) Nguyen, S. T.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 9858. (b) Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3974. (c) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem.* **1995**, *107*, 2179. (d) For the preparation of **2**, see: Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875.

S0002-7863(97)01994-X CCC: $14.00

terms of ligation, with the polar group acting as a relay for the evolving carbene species which assembles the reacting sites within the coordination sphere of the metal (e.g., complexes of type **A** or similar). However, if such an array becomes too



stable, as might be the case in certain 5- or 6-membered chelate structures (e.g., **B** and **C**), the catalyst can be sequestered in the form of unproductive complexes and cyclization will not take place.[1] Finally, macrocyclizations by RCM turned out to be sensitive to steric hindrance near the double bonds. This finding is deemed to reflect the bulk of the residual ligands L in chelate complexes such as **A**, which are formed *in situ* on reaction of a diene substrate with one of the standard catalyst precursors **1a**,**b** or **2**.[1]

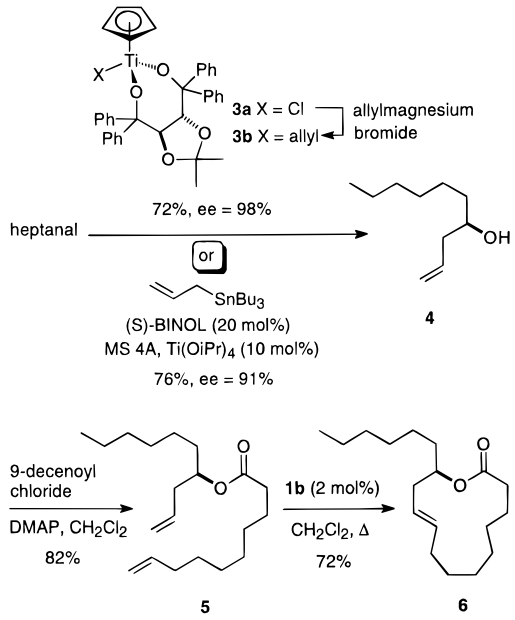
The total syntheses of enantiomerically pure (+)-ricinelaidic acid lactone (**6**) and (−)-gloeosporone (**7**) reported below show that the proper assessment of these key parameters provides a safe guidance for retrosynthetic planning. Moreover, they illustrate that RCM in combination with asymmetric catalysis for the formation of sp^3 centers can open up straightforward avenues to complex target molecules that rival the existing methodology in all preparative respects. Since the number of "unproductive" protection/deprotection steps can be reduced to a minimum, these syntheses are short, flexible, "atom economical",[5] and remarkably efficient. Finally, we have found a binary catalyst system that leads to the cyclization of those diene substrates which are *a priori* handicapped by an inadequate distance between the "relay" substituent and the alkene entities.

Results and Discussion

(*R*)-(+)-Ricinelaidic Acid Lactone. Since ricinelaidic acid lactone (**6**) has frequently served as a model to test the efficiency of macrolactonization reactions,[6] we have selected this 13-membered macrolide as our target in order to probe whether C−C bond formation can be a competitive strategy for the formation of large ring compounds. Starting from heptanal, the synthesis of **6** in enantiomerically pure form has been achieved in only three steps with an overall yield of ∼45% (Scheme 2).

Specifically, the catalytic asymmetric allylation protocol developed by Keck et al.[7] was employed to install the (*R*)-configurated stereogenic center. The desired homoallylic

Scheme 2



alcohol **4** was formed in good yield with an enantiomeric excess (ee) of 91% upon consecutive addition of heptanal and allyltributylstannane to a solution of a catalyst formed in situ from $Ti(OiPr)_4$ and (*S*)-(−)-1,1′-bi-2-naphthol ((*S*)-BINOL) (1:2 ratio) in the presence of 4 Å molecular sieves (MS). We noticed, however, that it is essential to use *freshly distilled* $Ti(OiPr)_4$ for the preparation of the catalytically active species in order to get a high ee and reproducible results. Esterification of **4** with 9-decenoyl chloride provided compound **5**, which was then subjected to the macrocyclization by RCM. In line with our previous experiences,[1] the reaction of this diene with the ruthenium carbene **1a** (2 mol %) in a dilute, refluxing CH_2Cl_2 solution led to the very clean formation of the title compound. Pure (*E*)-**6** was isolated in 72% yield by flash chromatography of the crude product on silica impregnated with $AgNO_3$.[8]

In order to evaluate the preparative significance of Keck's catalytic allylation reaction in more detail, we have also prepared alcohol **4** by an independent route. Treatment of heptanal with 1.1 equiv of the allyltitanium complex **3b** developed by Duthaler and Hafner[9] afforded the desired product in an excellent ee (98%). Although this optical purity is slightly higher than that obtained according to Keck's method, we nevertheless prefer the latter procedure since it can be conveniently scaled up, uses only commercially available reagents, and requires just catalytic amounts of expensive chiral ligands.

(−)-Gloeosporone. After having established by this route to **6** that esters of homoallylic alcohols are suitable starting materials for RCM, we tackled the total synthesis of (−)-gloeosporone (**7**), a germination self-inhibitor isolated from *Colletotrichum gloeosporioides*.[10]

Spores of this fungus germinate poorly when crowded due to a specific response to an endogeneous secondary metabolite which seems to regulate the dispersion of the species. The oxocane structure **8** had been assigned to the biologically active principle isolated from a culture broth;[11,12] this original formula,

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(7) (a) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc*. **1993**, *115*, 8467. (b) Keck, G. E.; Geraci, L. S. *Tetrahedron Lett*. **1993**, *34*, 7827. (c) Keck, G. E.; Krishnamurthy, D.; Grier, M. C. *J. Org. Chem*. **1993**, *58*, 6543.

(8) Gupta, A. S.; Dev, S. *J. Chromatogr*. **1963**, *12*, 189.

(9) (a) Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, G.; Rothe-Streit, P.; Schwarzenbach, F. *J. Am. Chem. Soc*. **1992**, *114*, 2321. (b) For a review, see: Duthaler, R. O.; Hafner, A. *Chem. Rev*. **1992**, *92*, 807.

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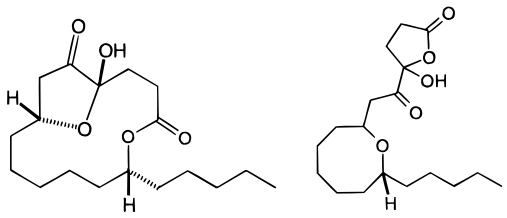


(-)-gloeosporone (**7**) **8**

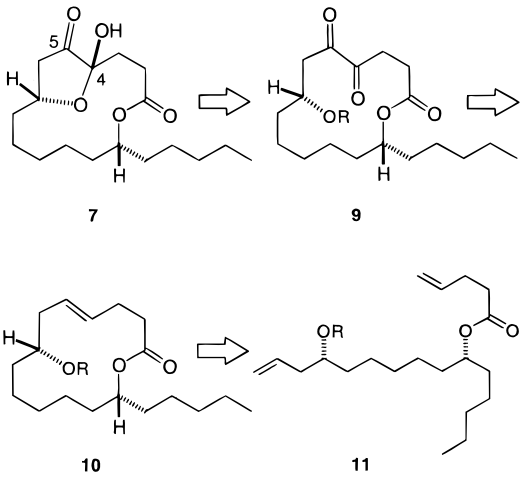
however, was found to be wrong. The actual structure of (−)-gloeosporone (**7**) was unambiguously established in 1987 with high-field NMR studies, X-ray crystallography,[13] and total syntheses.[14] The latter also proved the absolute configuration to be 4*S*,7*R*,13*R*. The biological activity of synthetic **7** has been assayed in some detail, showing that this metabolite exhibits a high activity against several fungi but does not inhibit the growth of bacteria.[14c,f]

Our retrosynthetic analysis of this target is shown in Scheme 3. It is well established in the literature that the 7-hydroxy 4,5-diketone precursor **9** (R = H) cyclizes spontaneously to the correct 4*S*-configurated hemiketal.[14] Since an α-diketone can be obtained by oxidation of an alkene entity, the obvious site for ring closure by RCM is the C4−C5 bond. This leads to the rather simple diene **11** as the starting material, the homoallylic alcohol part of which can be prepared in optically active form by one of the allylation protocols for aldehydes outlined above.

However, keeping in mind that a proper *distance* of the alkene to be metathesized and the polar "relay" functions is a fundamental requirement for successful macrocyclizations by RCM,[1] a more detailed evaluation of this concept is appropriate. If a chelation of the evolving carbene with the ester group plays a crucial role, the 4-pentenoate substructure in **11** may pose problems, since it will lead to a 6-membered chelate of the general type **C**, which may likely be too stable to be productive for a RCM event. The model reactions shown in Scheme 4 fully confirm this anticipation: while the 5-hexenoate **12** reacts without incident to the corresponding macrolide **13**,[1a,d] the conversion of the 4-pentenoate **14** to the desired 14-membered ring **15** (which may be considered as a truncated model for alkene **10** *en route* to gloeosporone) is poor even after prolonged reaction time. We therefore faced the problem of finding appropriate conditions for the cyclization of 4-pentenoates prior to embarking on the synthesis of (−)-gloeosporone.

In order to destabilize a presumably unproductive chelate of type **C**, we ran the cyclization of **14** in the presence of Lewis acids, which may compete with the ruthenium carbene for the coordination onto the ester group (Table 1). Such an additive must be compatible with the RCM catalyst, should provoke a minimum of undesirable acid-induced side reactions, and has to undergo a *kinetically labile* coordination with the "relay"

Scheme 3



Scheme 4

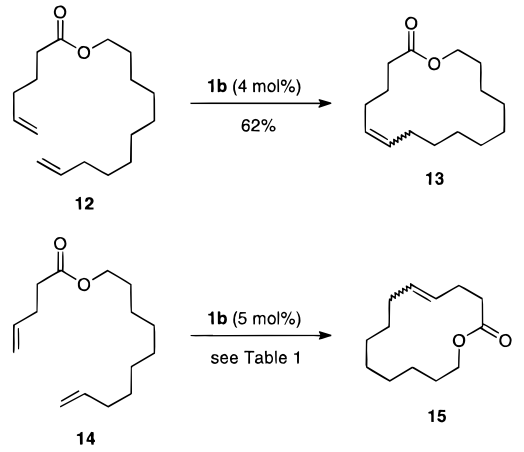


Table 1. Cyclization of the 4-Pentenoate **14** in the Presence of Additives

entry	*t* (d)	*T* (°C)	additive	**14** (%)[a]	**15** (%)[a]
1	3	25		67	22
2	3	25	$Ti(OiPr)_4$ (2 equiv)	49	40
3	3	40	$Ti(OiPr)_4$ (5 mol %)	7	55
4	3	25	LiBr (5 equiv)	79	14

[a] Determined by GC.

substituent. Strong Lewis acids such as $TiCl_4$ or $SnCl_4$ were soon ruled out, since they decompose the catalyst, whereas the addition of LiBr seems to retard rather than promote the cyclization (entry 4).[15] However, $Ti(OiPr)_4$ might meet these criteria: it is well established that esters do coordinate weakly *trans* to alkoxides on a Ti(4+) template and that this lability secures the catalytic activity of titanium alkoxides in many cases.[16,17] In fact, the yield of the macrolide **15** was almost doubled when the cyclization reaction of the 4-pentenoate **14** was carried out in the presence of 2 equiv of $Ti(OiPr)_4$ under otherwise identical conditions (cf. entries 1 and 2). When the temperature was raised to 40 °C, even catalytic amounts of $Ti(OiPr)_4$ were found to be sufficient (entry 3). This binary

(12) For syntheses directed to the proposed oxocane **8** structure, see: (a) Carling, R. W.; Clark, J. S.; Holmes, A. B.; Sartor, D. *J. Chem. Soc., Perkin Trans. 1* **1992**, 95. (b) Carling, R. W.; Holmes, A. B. *Tetrahedron Lett.* **1986**, *27*, 6133. (c) Mortimore, M.; Cockerill, G. S.; Kocienski, P.; Treadgold, R. *Tetrahedron Lett.* **1987**, *28*, 3747.

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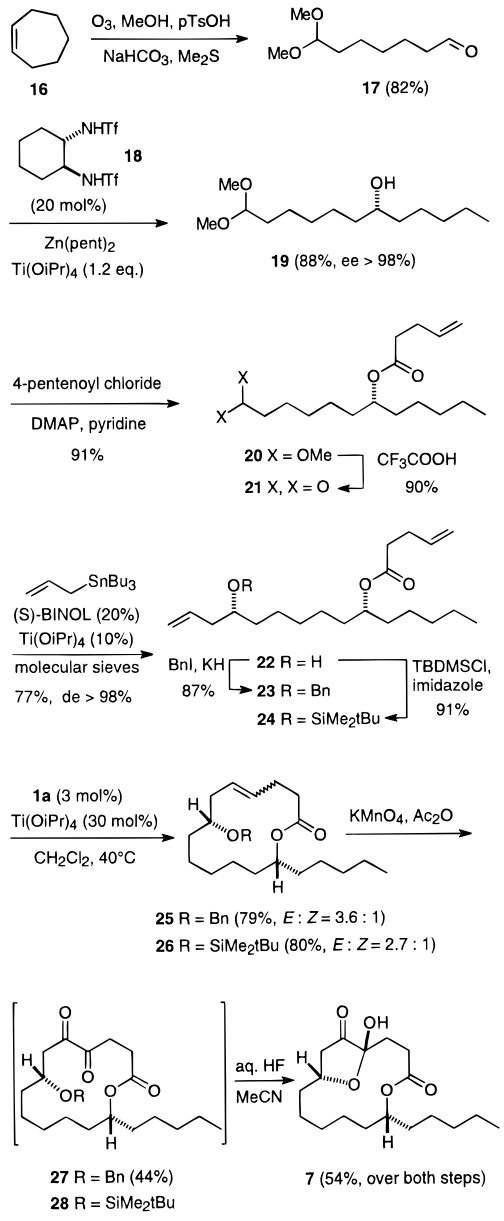
(15) LiBr may lead to the exchange of the Cl ligands for Br on the catalyst and thus diminish its activity, cf.: Dias, E. L.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1997**, *119*, 3887.

(16) For a detailed study on the bonding order of various ligands to titanium, see *inter alia*: Gau, H.-M.; Lee, C.-S.; Lin, C.-C.; Jiang, M.-K.; Ho, Y.-C.; Kuo, C.-N. *J. Am. Chem. Soc.* **1996**, *118*, 2936.

(17) For a review on $Ti(OiPr)_4$, see: Banwell, M. G. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: New York, 1995; p 4932.

Scheme 5



system, therefore, not only expands the scope of the RCM-based macrocyclization reaction to those substrates that are handicapped by an inappropriate distance between the alkene groups and the relay substituent but also provides further evidence for the assumed coordination of the emerging carbene on the polar functional group of the starting material, which enforces a proximity of the reacting centers and thereby facilitates the macrocyclization process.[1]

This new protocol was then successfully implemented into our approach to (−)-gloeosporone (**7**) as depicted in Scheme 5. Ozonolysis of cycloheptene (**16**) according to Schreiber's procedure readily afforded the monoprotected dialdehyde **17**.[18] The enantioselective addition of dipentylzinc to this substrate in the presence of $Ti(OiPr)_4$ and catalytic amounts of (*S,S*)-bistrifluoromethanesulfonamide **18**[19] was highly satisfactory, providing the corresponding secondary alcohol **19** in 88% chemical yield with an ee of >98%.

We then again employed Keck's allylation method[7] for introducing the 7*R*-configurated homoallylic alcohol part (gloeosporone numbering): Esterification of **19** with 4-pentenoyl chloride followed by deprotection of the dimethyl acetal **20** under standard conditions led to the rather labile aldehyde **21**. Reaction of this substrate with allyltributylstannane in the presence of a catalyst formed in situ from freshly distilled $Ti(OiPr)_4$, (*S*)-BINOL and 4 Å MS furnished the desired product **22** in 77% yield in diastereomerically pure form (diastereomeric excess (de) > 98%) as evident from careful analysis on chiral GC columns and the ^{19}F NMR inspection of the corresponding Mosher ester[20] (for details, see the Supporting Information). For comparative reasons, the allylation of **21** was also carried out using the Duthaler−Hafner reagent **3b**,[9] which proved to be similarly effective for this transformation as far as the conversion and the optical purity (de > 98%) are concerned. However, in this case it turned out to be difficult to separate the product **22** from the TADDOL auxiliary ligand by flash chromatography because of their very similar retention times. Therefore, the mixture had to be carried through and purification could be achieved only after the next step.

Alcohol **22** was then converted into the *O*-benzyl- and *O*-tBu-Me_2Si-protected compounds **23** and **24**, respectively. These compounds failed to cyclize when treated with the ruthenium carbene **1a**; however, both of them reacted smoothly when exposed to catalytic amounts of **1a** *in the presence of catalytic amounts of Ti(OiPr)*$_4$. This example clearly features the performance of the new binary catalyst system in RCM-based macrocyclization reactions. Alkenes **25** and **26** were obtained in excellent yields as a mixture of the *E*- and *Z*-isomers, which were oxidized without separation to the corresponding 1,2-diketones **27** and **28** when exposed to $KMnO_4/Ac_2O$.[21] Attempted deprotection of the OBn group led to the decomposition of compound **27**. Gratifyingly, however, oxidation and deprotection could be conveniently carried out using the *O*-tBuMe_2-Si-protected cycloalkene **26** as the substrate, with no need to purify the diketone **28** prior to its desilylation with HF in aqueous MeCN. The analytical data and in particular the spectroscopic characteristics of (−)-gloeosporone (**7**) thus obtained at 600 MHz perfectly match those reported in the literature[14] (see the Supporting Information).

In summary, we have achieved a total synthesis of the germination self-inhibiting macrolide (−)-gloeosporone (**7**) in enantiomerically pure form in only eight synthetic operations with an overall yield of 18%. This approach is distinctly shorter and more efficient than those reported in the literature and seems to be flexible enough for the synthesis of various analogues of this macrobicyclic fungizide. Finally, it is worth mentioning that (i) all C−C bond formations in this sequence are transition-metal-catalyzed, (ii) the chiral centers are thereby formed in stereomerically pure form, and (iii) the macrocyclization by C−C coupling employing the newly developed binary RCM catalyst system is significantly more productive than the well-established macrolactonization strategies previously employed. These aspects highlight the notion that a well-orchestrated interplay of RCM and other transition-metal-catalyzed reactions opens up highly flexible, modular and performant avenues to complex target molecules. Work in our laboratory to further substantiate these features is in progress.

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Experimental Section

General. All reactions were carried out under Ar using Schlenk techniques. The Grubbs carbene **1a** was purchased from Strem Chemical Inc.[4] Ac_2O and $Ti(OiPr)_4$ were distilled under Ar immediately prior to use. All other 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: Et_2O (Na/K), CH_2Cl_2 (P_4O_{10}), THF (magnesium/anthracene), toluene (Na/K), DMF (Desmodur, dibutyltin dilaurate). Flash chromatography was on Merck silica gel 60 (230−400 mesh) using hexanes/ethyl acetate in various proportions as the eluent. For the instrumentation used, see the Supporting Information. Elemental analyses were performed by Dornis & Kolbe, Mülheim.

(*R*)-Dec-1-en-4-ol (4). Method A. A solution of allylmagnesium bromide (1 M in Et_2O, 702 μL, 0.702 mmol) was added dropwise over a period of 10 min at 0 °C to the titanium complex **3a** (500 mg, 0.82 mmol)[9] in Et_2O (12 mL). The resulting dark-green mixture was stirred at that temperature for 1 h. It was then cooled to −78 °C, and heptanal (72 mg, 0.63 mmol, 88 μL) was added. After an additional 4 h of stirring at that temperature, aqueous saturated NH_4F (8 mL) was added and the mixture was hydrolyzed for 12 h. A standard extractive work-up followed by flash chromatography (hexanes/ethyl acetate 12:1) yielded compound **4** as a colorless syrup (71 mg, 72%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.94−5.74 (m, 1H), 5.18−5.09 (m, 2H), 3.70−3.58 (m, 1H), 2.30−2.10 (m, 2H), 1.70 (s, 1H), 1.46−1.29 (m, 10H), 0.92−0.85 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 135.0, 118.0, 70.7, 42.0, 36.9, 31.8, 29.4, 25.6, 22.6, 14.1; $[\alpha]_D^{rt} = -3.2°$ (c = 6.4, CH_2Cl_2), [lit.[23] $[\alpha]_D^{rt} = -4.2°$ (c = 0.5, $CHCl_3$)]. The enantiomeric excess (ee) was determined by GC using a chiral column to be 98% (see the Supporting Information). **Method B.** A solution of (*S*)-BINOL (31 mg, 0.11 mmol, 20 mol %) in CH_2Cl_2 (500 μL) and $Ti(OiPr)_4$ (freshly distilled, 16 mg, 0.056 mmol, 17 μL, 10 mol %) were added to powdered molecular sieves (4 Å, 1 g, activated at 160 °C, 10^{-2} bar for 12 h) in CH_2Cl_2 (10 mL), and the red suspension was refluxed for 1 h. The mixture was cooled to room temperature (rt), and a solution of heptanal (63 mg, 0.55 mmol, 71 μL) in CH_2Cl_2 (2 mL) was added. Stirring was continued for 10 min at that temperature prior to the addition of allyltributylstannane (201 mg, 0.66 mmol) at −78 °C. After an additional 10 min at that temperature, the flask was sealed and kept at −18 °C for 15 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL), and the mixture was hydrolyzed for 3 h. A standard extractive work-up followed by flash chromatography (hexanes/ethyl acetate 10:1) afforded alcohol **4** as a colorless syrup (66 mg, 76%): $[\alpha]_D^{rt} = -3.1°$ (c = 5.9, CH_2Cl_2). The ee was determined as above to be 91%.

(*R*)-Dec-1-en-4-yl Dec-9-enoate (5). 9-Decenoic acid (187 mg, 1.1 mmol) in CH_2Cl_2 (5 mL) was added dropwise at ambient temperature to a solution of *N*,*N*-(dimethyl)-1-amino-1-chloro-2-methyl-1-propene (146 mg, 1.1 mmol)[22] in CH_2Cl_2 (10 mL). After 1 h of stirring at that temperature, alcohol **4** (170 mg, 1.09 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (DMAP, 159 mg, 1.3 mmol) in CH_2Cl_2 (10 mL) were added to the flask at 0 °C. The reaction was complete after 4 h of stirring at ambient temperature as indicated by TLC. The mixture was filtered through a plug of silica gel, which was washed with CH_2Cl_2. The solvent was evaporated, and the residue was purified by flash chromatography (hexanes/ethyl acetate 20:1) to afford ester **5** as a colorless syrup (280 mg, 82%): R_f 0.65 (hexanes/ethyl acetate 10:1); $[\alpha]_D^{rt} = +17.3°$ (c = 7.2, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.91−5.65 (m, 2H), 5.11−4.90 (m, 5H), 2.33−2.24 (m, 4H), 2.05−1.99 (m, 2H), 1.64−1.52 (m, 4H), 1.41−1.27 (m, 16H), 0.88 (t, 3H, J = 6.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) resolved signals δ 173.4, 139.1, 133.9, 117.5, 114.2, 73.0, 38.7, 34.7, 33.8, 33.7, 31.8, 29.1, 29.0, 28.9, 25.3, 25.1, 22.6, 14.1; IR (neat) 3078, 2929, 2857, 1735, 1642, 1465, 1439, 1417, 1378, 1246, 1174, 993, 912, 725 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 308 ([M$^+$], 1), 153 (28), 135 (100), 97 (9), 83 (13), 69 (17), 55 (18), 41 (9). Anal. Calcd for $C_{20}H_{36}O_2$ (308.50): C, 77.87; H, 11.76. Found: C, 77.65; H, 11.66.

(*R*)-(+)-Ricinelaidic Acid Lactone (6). A solution of the ruthenium carbene **1a** (10 mg, 0.012 mmol, 2 mol %) in CH_2Cl_2 (2mL) was added to a solution of ester **5** (180 mg, 0.58 mmol) in CH_2Cl_2 (100 mL) at reflux temperature. Stirring was continued for 24 h, after which the solvent was evaporated and the residue was purified by flash chromatography (hexanes/diethyl ether 30:1) using silica gel impregnated with $AgNO_3$.[8] Compound **6** was obtained as a colorless syrup (119 mg, 72%) which is admixed with only ≤2% of the (*Z*)-isomer: R_f 0.50 (hexanes/diethyl ether 30:1); $[\alpha]_D^{rt} = +46.7°$ (c = 0.95, $CHCl_3$) [lit.[6d] $[\alpha]_D^{rt} = +45.7°$ (c = 1.0, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.54−5.26 (m, 2H), 4.98−4.92 (m, 1H), 2.38−2.15 (m, 4H), 2.02 (q, 2H, J = 6.5 Hz), 1.69−1.27 (m, 20H), 0.86 (t, 3H, J = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 134.3, 126.4, 73.1, 37.8, 35.0, 34.1, 32.2, 31.7, 29.2, 27.6, 27.2, 27.0, 25.4, 23.8, 23.1, 22.6, 14.0; IR (neat) 3024, 2929, 2857, 1733, 1460, 1447, 1375, 1337, 1246, 1223, 1179, 1148, 1125, 1077, 1038, 970, 806 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 280 ([M$^+$], 31), 166 (14), 137 (12), 124 (13), 109 (17), 98 (100), 81 (31), 67 (35), 55 (41), 41 (42).

(6*R*)-12,12-Dimethoxydodecan-6-ol (19). The chiral ligand (*1S*,*2S*)-1,2-(*N*,*N*′-bis(trifluoromethanesulfonylamino))cyclohexane (**18**)[19] (189 mg, 0.5 mmol, 2 mol %) and $Ti(OiPr)_4$ (8.53 g, 30 mmol, 8.86 mL) were dissolved in toluene (10 mL), and the mixture was stirred at 40 °C for 30 min. The solution was then cooled to −78 °C, and Zn-$(C_5H_{11})_2$[24] (6.23 g, 30 mmol) in toluene (2 mL) was added dropwise followed by a solution of 7,7-dimethoxyheptanal (**17**)[18] (4.35 g, 25 mmol) in toluene (2 mL). Stirring was continued for 30 min at −78 °C, 2 h at −50 °C, and 2 h at −20 °C, after which the reaction was quenched with aqueous saturated NH_4Cl (20 mL). The mixture was extracted with Et_2O (3 × 50 mL), and the combined organic phases were dried over Na_2SO_4, filtered, and evaporated to dryness. Flash chromatography (hexanes/ethyl acetate 10:1 → 8:1) of the residue afforded **19** as a colorless liquid (5.44 g, 88%): R_f 0.39 (hexanes/ethyl acetate 2:1); $[\alpha]_D^{rt} = -0.34°$ (c = 4.7, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.36 (t, 1H, J = 5.7 Hz), 3.57 (bs, 1H), 3.11 (s, 6H), 1.61−1.30 (m, 19H), 0.89 (t, 3H, J = 6.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 104.5, 71.9, 52.6, 37.5, 37.4, 32.4, 31.9, 29.5, 25.6, 25.3, 24.6, 22.7, 14.0; IR (neat) 3444, 2930, 2858, 2678, 1462, 1384, 1366, 1192, 1126, 1074, 1054, 960, 915, 805, 727 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 245 ([M$^+$ − 1], 10), 215 (9), 143 (10), 111 (8), 83 (8), 75 (100), 71 (19). Anal. Calcd for $C_{14}H_{30}O_3$ (246.39): C, 68.25; H, 12.27. Found: C, 68.40; H, 12.27. The ee was determined by inspection of the ^{19}F NMR spectrum of the corresponding Mosher ester[20] to be >98% (see the Supporting Information).

(6*R*)-12,12-Dimethoxy-6-dodecyl Pent-4-enoate (20). 4-Pentenoic acid (1.45 g, 14.5 mmol, 1.48 mL) in CH_2Cl_2 (5 mL) was added dropwise at ambient temperature to a solution of *N*,*N*-(dimethyl)-1-amino-1-chloro-2-methyl-1-propene (1.9 g, 14.22 mmol)[22] in CH_2Cl_2 (10 mL). After 1.5 h of stirring at that temperature, the alcohol **19** (3.94 g, 16 mmol), pyridine (5 mL), and 4-(*N*,*N*-dimethylamino)pyridine (DMAP, 20 mg) in CH_2Cl_2 (10 mL) were added to the flask at 0 °C. The reaction was complete after 5 h of stirring at ambient temperature as indicated by TLC. Water (20 mL) was added, and most of the pyridine was removed by extraction with aqueous saturated NH_4Cl (4 × 30 mL). The organic phase was washed with brine and dried over Na_2SO_4. Removal of the solvent and flash chromatography (hexanes/ethyl acetate 12:1) of the residue gave **20** as a colorless oil (4.26 g, 91%): R_f 0.55 (hexanes/ethyl acetate 4:1); $[\alpha]_D^{rt} = +0.12°$ (c = 34.8, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.93−5.76 (m, 1H), 5.11−4.97 (m, 2H), 4.88 (t, 1H, J = 6.3 Hz), 4.35 (t, 1H, J = 5.7 Hz), 3.31 (s, 6H), 2.39−2.36 (m, 4H), 1.56−1.44 (m, 6H), 1.35−1.27 (m, 12H), 0.88 (t, 3H, J = 6.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.9, 136.8, 115.4, 104.5, 74.3, 52.6, 34.1, 34.1, 33.9, 32.4, 31.7, 29.4, 29.0, 25.3, 25.0, 24.5, 22.6, 14.0; IR (neat) 3080, 2931, 2861, 2830, 1734, 1642, 1463, 1380, 1366, 1290, 1254, 1178, 1128, 1078, 1055, 994, 960, 914, 727 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 297 (2), 197 (12), 165 (11), 75 (100), 71 (16), 55 (22). Anal. Calcd for $C_{19}H_{36}O_4$ (328.49): C, 69.47; H, 11.05. Found: C, 69.36; H, 11.15.

(6*R*)-12-Oxododec-6-yl Pent-4-enoate (21). Trifluoroacetic acid (2 mL) and water (2 mL) were added at 0 °C to a solution of the acetal

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20 (500 mg, 1.52 mmol) in CH_2Cl_2 (10 mL), and the resulting mixture was stirred at that temperature for 6 h. After the solution was neutralized with aqueous saturated $NaHCO_3$, the product was isolated by a standard extractive work-up and purified by flash chromatography (hexanes/ethyl acetate 15:1) to afford **21** as a colorless syrup (387 mg, 90%) (aldehyde **21** should be processed immediately since it was rather unstable): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.76 (t, 1H, J = 1.8 Hz), 5.90−5.75 (m, 1H), 5.09−5.01 (m, 2H), 4.88 (quint., 1H, J = 6.6 Hz), 2.45−2.36 (m, 6H), 1.65−1.49 (m, 6H), 1.34−1.24 (m, 10H), 0.88 (t, 3H, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) resolved signals δ 202.5, 172.8, 136.8, 115.4, 74.1, 43.8, 34.2, 34.0, 33.9, 31.7, 29.0, 25.1, 25.0, 22.6, 22.0, 14.0; IR (neat) 3080, 2932, 2861, 2718, 1731, 1642, 1463, 1416, 1378, 1343, 1291, 1256, 1178, 1111, 997, 915, 729 cm^{-1}; MS (EI) *m/z* (rel intensity) 280 (1), 199 (30), 181 (27), 127 (68), 100 (82), 83 (100), 69 (21), 55 (94), 43 (30).

(4*R*,10*R*)-4-Hydroxypentadec-1-en-10-yl Pent-4-enoate (22). Method A. Allylmagnesium bromide (1 M in Et_2O, 7.01 mL, 7.01 mmol) was added within 2 min at 0 °C to a solution of titanium complex **3a**[9] (0.218 M in Et_2O, 35.7 mL, 7.79 mmol). After 1 h of stirring, the mixture was cooled to −78 °C and aldehyde **21** (1.65 g, 5.84 mmol) in Et_2O (10 mL) was slowly added. After 4 h at that temperature, aqueous saturated NH_4F was added and the mixture was stirred at room temperature for 12 h. A standard extractive work-up and flash chromatography (hexanes/ethyl acetate 10:1) yielded 3.67 g of a colorless syrup which consists of a 1:1 mixture of the homoallylic alcohol **22** and of the ligand (4*R*,*trans*)-2,2-dimethyl-α,α,α′,α′-tetraphenyl-1,3-dioxolane-3,4-dimethanol which has the same mobility as **22**. This material can be used directly for the synthesis of either the benzyl ether **23** or the silyl ether **24**, since the ligand is unreactive under the conditions stated.

Method B. $Ti(OiPr)_4$ (16 mg, 0.056 mmol, 17 μL, 10 mol %) was added to a stirred suspension of (*S*)-BINOL (31 mg, 0.11 mmol, 20 mol %) and molecular sieves (4 Å, 1.0 g, powdered, activated at 160 °C, 10^{-2} mbar) in CH_2Cl_2 (8 mL). The mixture was refluxed for 1 h and then cooled to ambient temperature. Aldehyde **21** (155 mg, 0.55 mmol) was added to the red suspension, and the solution was stirred for an additional 10 min. After the flask was cooled to −78 °C, allyltributylstannane (201 mg, 0.61 mmol, 188 μL) was added dropwise via canula. After an additional 10 min at that temperature, the flask was sealed with stoppers and kept at −18 °C for 14 h. The green-greyish suspension was then treated with aqueous saturated $NaHCO_3$ (20 mL) for 3 h. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated. Flash chromatography (hexanes/ethyl acetate 10:1) afforded product **22** as a colorless syrup (136 mg, 77%): $[\alpha]_D^{rt} = -1.48°$ (c = 7.3, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90−5.78 (m, 2H), 5.16−4.98 (m, 4H), 4.91−4.82 (m, 1H), 3.65 (s, 1H), 2.39−2.22 (m, 5H), 2.20−2.03 (m, 1H), 1.60−1.27 (m, 19H), 0.90−0.86 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 136.8, 134.9, 118.1, 115.4, 74.3, 70.6, 42.0, 36.7, 34.1, 34.1, 33.9, 31.7, 29.5, 29.0, 25.6, 25.3, 25.0, 22.6, 14.0; IR (neat) 3451, 3078, 2932, 2860, 1734, 1641, 1459, 1437, 1418, 1378, 1342, 1258, 1179, 1119, 996, 914, 728, 642 cm^{-1}; MS (EI) *m/z* (rel intensity) 283 (12), 265 (5), 225 (6), 183 (57), 165 (72), 135 (18), 109 (52), 101 (77), 95 (66), 83 (85), 67 (34), 55 (100), 41 (32). Anal. Calcd for $C_{20}H_{36}O_3$ (324.50): C, 74.03; H, 11.18. Found: C, 74.20; H, 11.13. The diastereomeric excess (de) was determined by GC analysis with a chiral column and by inspection of the ^{19}F NMR spectrum of the corresponding Mosher ester[20] to be >98% (see the Supporting Information).

(4*R*,10*R*)-4-(Benzyloxy)pentadec-1-en-10-yl Pent-4-enoate (23). The homoallylic alcohol **22** (580 mg, 1.79 mmol) in THF (5 mL) was added to a suspension of KH (107 mg, 2.69 mmol, 1.5 equiv) in THF (20 mL) at 0 °C. After the evolution of H_2 ceased (ca. 10 min), a solution of benzyl iodide (586 mg, 2.69 mmol, 1.5 equiv) in THF (5 mL) was added and the mixture was stirred at ambient temperature for 2 h. The reaction was quenched by addition of aqueous saturated NH_4Cl (30 mL), and the product was extracted into Et_2O (3 × 30 mL). The combined organic phases were dried over Na_2SO_4, filtered, and evaporated. Flash chromatography (hexanes/ethyl acetate 15:1) afforded **23** as a colorless syrup (264 mg, 87%): R_f 0.31 (hexanes/ethyl acetate 10:1); $[\alpha]_D^{rt} = +14.5°$ (c = 2.85, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.37−7.15 (m, 5H), 5.92−5.75 (m, 2H), 5.13−4.97 (m, 4H), 4.88 (quintet, 1H, J = 6.8 Hz), 4.57 (d, 1H, J = 11.8 Hz), 4.41 (d, 1H, J = 11.8 Hz), 3.43 (quintet, 1H, J = 5.5 Hz), 2.42−2.28 (m, 6H), 1.59−1.19 (m, 18H), 0.88 (t, 3H, J = 6.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) resolved signals δ 172.9, 139.0, 136.9, 135.1, 128.3, 127.8, 127.5, 116.9, 115.4, 78.5, 74.3, 70.9, 38.3, 34.2, 33.9, 33.8, 31.8, 29.6, 29.1, 25.3, 25.3, 25.0, 22.6, 14.0; IR (neat) 3078, 3030, 2931, 2860, 1733, 1641, 1497, 1455, 1378, 1347, 1255, 1176, 1096, 1069, 1028, 993, 914, 734, 697 cm^{-1}; MS (EI) *m/z* (rel intensity) 414 ([M$^+$], <1), 191 (16), 173 (19), 91 (100), 83 (11), 55 (9). Anal. Calcd for $C_{27}H_{42}O_3$ (414.63): C, 78.21; H, 10.21. Found: C, 78.32; H, 10.16.

(8*R*,14*R*)-2-Oxo-8-(benzyloxy)-14-pentyl-1-oxacyclotetradec-5-ene (25). Compound **24** (200 mg, 0.48 mmol) and $Ti(OiPr)_4$ (41 mg, 0.14 mmol, 43 μL, 0.3 equiv) were dissolved in CH_2Cl_2 (150 mL), and the mixture was refluxed for 1 h. A solution of the ruthenium carbene **1a** (8 mg, 0.001 mmol, 2 mol %) in CH_2Cl_2 (2 mL) was added, and reflux was continued for 96 h, after which all of the starting material was consumed as indicated by TLC. The mixture was filtered through a short pad of silica gel, and the solvent was removed *in vacuo*. Flash chromatography (hexanes/ethyl acetate 15:1) afforded the product **25** as a colorless syrup (147 mg, 79%): R_f 0.38 (hexanes/ethyl acetate 10:1); $[\alpha]_D^{rt} = +25.0°$ (c = 1.6, CH_2Cl_2); ratio of isomers E:Z = 3.6:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.16 (m, 5H), 5.55−5.41 (m, 2H), 4.99−4.86 (m, 1H), 4.59 (d, 0.75 H, J = 11.8 Hz), 4.57 (d, 0.25H, J = 11.8 Hz), 4.50 (d, 0.25H, J = 11.8 Hz), 4.46 (d, 0.75H, J = 11.8 Hz), 3.45−3.39 (m, 0.25H), 3.37−3.32 (m, 0.75H), 2.47−2.26 (m, 5H), 2.11−2.03 (m, 1H), 1.61−1.15 (m, 18H), 0.89−0.83 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) (*E*)-isomer δ 173.0, 139.1, 131.4, 128.3, 127.9, 127.7, 127.4, 77.5, 74.3, 70.6, 36.1, 34.4, 34.3, 33.9, 31.7, 29.8, 27.6, 26.5, 25.3, 22.6, 22.5, 21.9, 14.0; (*Z*)-isomer (resolved signals) δ 139.0, 130.4, 127.6, 126.7, 78.1, 74.6, 70.4, 35.3, 34.7, 32.7, 31.8, 30.8, 27.5, 25.1, 23.6, 23.4, 23.1; IR (neat) 3064, 3029, 2930, 2859, 1731, 1605, 1586, 1496, 1455, 1439, 1355, 1341, 1248, 1222, 1160, 1095, 1068, 1028, 974, 908, 735, 697 cm^{-1}; MS (EI) *m/z* (rel intensity) 386 ([M$^+$], 4), 204 (53), 183 (14), 165 (15), 144 (11), 113 (54), 91 (100), 71 (13), 55 (13), 41 (13). Anal. Calcd for $C_{25}H_{38}O_3$ (386.57): C, 77.68; H, 9.91. Found: C, 77.54; H, 9.86.

(8*R*,14*R*)-2,5,6-trioxo-8-(benzyloxy)-14-pentyl-1-oxacyclotetradecane (27). Finely ground $KMnO_4$ (278 mg, 1.76 mmol, 4 equiv) was added in portions at 0 °C to a stirred solution of cycloalkene **25** (170 mg, 0.44 mmol) in freshly distilled Ac_2O (10 mL). After 4 h of stirring at that temperature, chilled ethyl acetate was added and the reaction was quenched with aqueous saturated $NaHSO_3$ (5 mL). The organic phase was treated for 10 min with aqueous saturated $NaHCO_3$ (50 mL), washed with brine, dried over Na_2SO_4, and evaporated. Flash chromatography (hexanes/ethyl acetate 20:1 → 15:1) yields the diketone **27** as a bright yellow syrup (81 mg, 44%): R_f 0.58 (hexanes/ethyl acetate 4:1); $[\alpha]_D^{rt} = -1.71°$ (c = 2.1, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.37−7.27 (m, 5H), 4.95−4.83 (m, 1H), 4.61 (d, 1H, J = 11.8 Hz), 4.50 (d, 1H, J = 11.8 Hz), 3.93−3.81 (m, 1H), 3.32−2.68 (m, 6H), 1.56−1.02 (m, 18H), 0.90−0.84 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 198.0, 197.4, 171.5, 138.3, 128.4, 127.8, 127.7, 75.0, 74.8, 70.8, 40.3, 33.9, 32.8, 32.1, 32.0, 31.7, 28.7, 26.8, 25.2, 22.5, 22.3, 21.8, 14.0; IR (neat) 2932, 2857, 1727, 1497, 1456, 1399, 1356, 1256, 1190, 1159, 1089, 1068, 1028, 982, 736, 698 cm^{-1}; MS (EI) *m/z* (rel intensity) 416 ([M$^+$], <1), 310 (2), 165 (5), 91 (100), 81 (11), 55 (16).

(4*R*,10*R*)-4-((*tert*-Butyldimethylsilyl)oxy)pentadec-1-en-10-yl Pent-4-enoate (24). Substrate **22** (100 mg, 0.31 mmol) in DMF (10 mL) was treated with $tBuMe_2SiCl$ (60 mg, 0.40 mmol, 1.3 equiv) and imidazole (27 mg, 0.40 mmol, 1.3 equiv) at ambient temperature for 7.5 h. The mixture was poured into water (30 mL), and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic phases were dried over Na_2SO_4, filtered, and evaporated. Flash chromatography (hexanes/ethyl acetate 30:1) afforded the silyl ether **24** as a colorless syrup (124 mg, 91%): R_f 0.58 (hexanes/ethyl acetate 15:1), 0.40 (hexanes/ethyl acetate 30:1); $[\alpha]_D^{rt} = +10.52°$ (c = 1.35, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.90−5.71 (m, 2H), 5.11−4.98 (m, 4H), 4.88 (quintet, 1H, J = 6.1 Hz), 3.67 (quintet, 1H, J = 5.5 Hz), 2.43−2.33 (m, 4H), 2.20 (t, 2H, J = 6.8 Hz), 1.52−1.20 (m, 18H), 0.91−0.85 (m, 12H), 0.04 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) resolved signals δ 172.9, 136.8, 135.5, 116.6, 115.4, 74.4, 72.0, 42.0, 36.7, 34.1, 33.9, 31.7, 29.7, 29.1, 25.9, 25.3, 25.3, 25.0, 22.6, 18.1, 14.0, −4.3, −4.5; IR (neat) 3078, 2932, 2858, 1735,

1642, 1471, 1463, 1437, 1362, 1255, 1177, 1094, 1065, 1004, 913, 836, 807, 774 cm^{-1}; MS (EI) *m/z* (rel intensity) 397 (22), 297 (26), 175 (76), 157 (100), 109 (30), 95 (32), 83 (34), 81 (22), 75 (39), 73 (43), 69 (18), 67 (14), 55 (26). Anal. Calcd for $C_{26}H_{50}O_3Si$ (438.77): C, 71.17; H, 11.49; Si, 6.40. Found: C, 71.28; H, 11.36; Si, 6.54.

(8*R*,14*R*)-8-((*tert*-Butyldimethylsilyl)oxy)-2-oxo-14-pentyl-1-oxacyclotetradec-5-ene (26). The silyl ether **24** (200 mg, 0.46 mmol) and $Ti(OiPr)_4$ (39 mg, 0.14 mmol, 41 μL, 0.3 equiv) were dissolved in CH_2Cl_2 (180 mL), and the mixture was refluxed for 1 h. The ruthenium carbene **1a** (8 mg, 0.001 mmol, 2 mol %) in CH_2Cl_2 (2 mL) was then added, and reflux was continued for 24 h after which an additional 4 mg (0.0005 mmol, 1 mol %) of **1a** in CH_2Cl_2 (2 mL) was added. After an additonal 24 h, the mixture was cooled to ambient temperature and filtered through a short pad of silica gel. The solvent was removed *in vacuo*, and the residue was purified by flash chromatography (hexanes/ethyl acetate 100:1) to give the macrolide **26** as a colorless syrup (151 mg, 80%): R_f 0.26 (hexanes/ethyl acetate 30:1); $[\alpha]_D^{rt} = +9.9°$ (c = 4.85, $CHCl_3$) [lit.[14b] $[\alpha]_D^{27} = +13.5°$ (pure (*E*)-isomer, c = 1.2, $CHCl_3$)]; ratio of isomers *E*:*Z* = 2.7:1; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.51−5.39 (m, 2H), 4.99−4.88 (m, 1H), 3.96−3.51 (m, 1H), 2.46−2.02 (m, 6H), 1.63−1.09 (m, 18H), 0.86−0.79 (m, 12H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) (*E*)-isomer δ 173.1, 131.0, 128.3, 74.2, 71.0, 40.5, 34.4, 34.3, 33.7, 32.5, 31.7, 27.7, 26.5, 25.9, 25.4, 23.3, 22.6, 21.8, 18.1, 14.0, −4.3, −4.7; (*Z*)-isomer (resolved signals) δ 129.9, 127.1, 74.6, 71.5, 35.4, 35.0, 34.8, 34.5, 32.8, 31.7, 27.5, 25.1, 23.7, 23.5; IR (neat) 3020, 2956, 2929, 2858, 1735, 1471, 1462, 1376, 1362, 1342, 1254, 1222, 1158, 1091, 1065, 1053, 1007, 974, 940, 836, 774, 665 cm^{-1}; MS (EI) *m/z* (rel intensity) 353 (65), 335 (58), 297 (31), 261 (28), 243 (33), 219 (12), 171 (100), 165 (38), 109 (49), 95 (51), 75 (75), 73 (96), 67 (23), 55 (20), 41 (13). Anal. Calcd for $C_{24}H_{46}O_3Si$ (410.71): C, 70.19; H, 11.29; Si, 6.84. Found: C, 70.11; H, 11.21; Si, 6.72.

(−)-Gloeosporone (7). Finely ground $KMnO_4$ (353 mg, 2.24 mmol, 6 equiv) was added in portions to a solution of the cycloalkene **26** (153 mg, 0.37 mmol) in freshly distilled Ac_2O (10 mL) at 0 °C. The mixture was stirred at 0 °C for 2 h and at ambient temperature for 1 h. Ethyl acetate (10 mL) was then added, and the reaction was quenched with aqueous saturated $NaHSO_3$ (5 mL). The phases were separated, and the organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The remaining Ac_2O was removed under high vacuum. The resulting bright yellow oil was dissolved in CH_3CN (5 mL) and treated at ambient temperature with 2 mL of a solution of aqueous HF (40%) in CH_3CN (1:10 v/v). After 45 min, the yellow color faded and the reaction was quenched with aqueous saturated $NaHCO_3$. A standard extractive work-up followed by flash chromatography (hexanes/ethyl acetate 8:1 → 6:1) afforded **7** as a colorless solid (66 mg, 54%): mp 117−118 °C (lit.[14b] 117−118 °C); R_f 0.19 (hexanes/ethyl acetate 4:1), 0.44 (hexanes/ethyl acetate 3:1), 0.55 (hexanes/ethyl acetate 2:1); $[\alpha]_D^{rt} = -63.6°$ (c = 1.4, acid free $CHCl_3$) [lit.[14b] $[\alpha]_D^{27} = -63.2°$ (c = 0.34, acid free $CHCl_3$)]; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.09−5.03 (m, 1H), 4.45−4.41 (m, 1H), 3.54 (bs, 1H), 2.74 (dd, 1H, J = 18.7, 6.2 Hz), 2.44 (ddd, 1H, J = 16.5, 8.5, 3.9 Hz), 2.35 (ddd, 1H, J = 14.3, 9.0, 3.8 Hz), 2.28 (ddd, 1H, J = 15.2, 8.9, 3.6 Hz), 2.10 (ddd, 1H, J = 14.3, 8.3, 3.5 Hz), 2.04 (dd, 1H, J = 18.8, 8.3 Hz), 1.71−1.43 (m, 10H), 1.30−1.20 (m, 8H), 0.89−0.86 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.0, 174.4, 98.9, 74.4, 73.4, 40.4, 34.6, 32.3, 32.2, 31.7, 30.0, 29.5, 25.9, 25.3, 25.0, 22.5, 21.1, 14.0; IR (KBr) 3337, 2935, 2902, 2870, 2850, 1752, 1715, 1463, 1448, 1422, 1386, 1341, 1238, 1201, 1178, 1150, 1078, 1038, 1002, 967 cm^{-1}; IR (CCl_4) 3445, 2956, 2932, 2860, 1772, 1726, 1711, 1277, 1239, 1220, 1144, 1073 cm^{-1}; MS (EI) rel intensity 308 ([M^+ − 18], 4), 180 (18), 152 (13), 119 (100), 109 (21), 101 (76), 96 (35), 82 (29), 67 (24), 55 (45), 41 (23).

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Supporting Information Available: Compilation of the instrumentation used and the spectra formats; copies of the ^{1}H and ^{13}C NMR spectra of new compounds; and details on the determination of the ee and de, respectively, of compounds **4**, **19**, and **22** (45 pages). See any current masthead page for ordering and Internet access instructions.

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