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# Ring-Closing Metathesis and Photo-Fries Reaction for the Construction of the Ansamycin Antibiotic Kendomycin: Development of a Protecting Group Free Oxidative Endgame

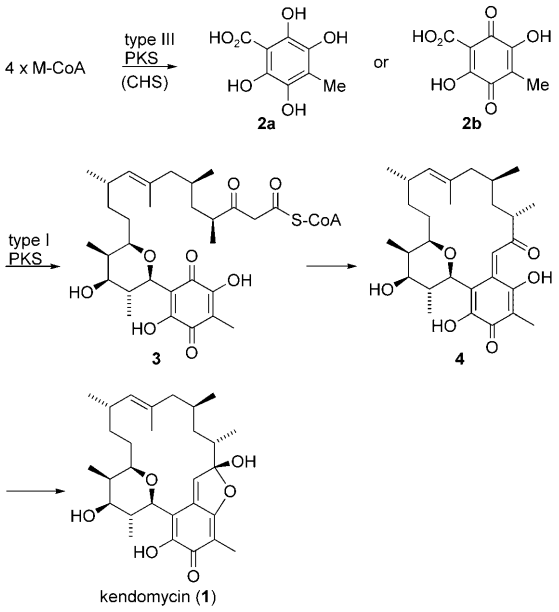
**Thomas Magauer, Harry J. Martin, and Johann Mulzer*[a]**

**Abstract:** Two convergent total syntheses of the *ansa*-polyketide (−)-kendomycin (**1**) are described. The syntheses benefit from the use of readily available and cheap starting materials. Highly complex diastereoselective Claisen–Ireland rearrangements were used to introduce the (*E*)-double bond and the C16-Me group. The ring closure of the strained *ansa* macrocycle was achieved by ring-closing metathesis and a highly efficient combination of macrolactonization and photo-Fries reaction. A protecting group free endgame via an unstable *o*-quinone is presented. Additionally some unsuccessful synthetic efforts towards the total synthesis of **1** are described.

**Keywords:** Claisen–Ireland rearrangement · metathesis · natural products · polyketides

## Introduction

Kendomycin [(−)-TAN 2162] (**1**) was first reported in 1996,[1] and re-isolated in 2000 by Zeeck and Bode during their screening program for new metabolites from *Actinomycetes*.[2] Biological testing revealed **1** to be a potent endothelin receptor antagonist and antiosteoperotic compound with remarkable antibacterial and cytostatic activity,[2,3] most likely through proteasome inhibition.[3a] Beside the diverse pharmacological qualities, which have attracted (bio)-chemists in the last years, kendomycin discloses an unique molecular architecture with a fully carbogenic *ansa*-polyketide chain, nine stereogenic centers, a pentasubstituted tetrahydropyran ring and a remarkable *p*-quinone-methide chromophore. The biosynthesis (Scheme 1)[2b,4] implies the formation of benzoic acid **2a** or the corresponding quinoid nucleus **2b** from malonate subunits under the mediation of chalcone synthase (CHS). This core unit is then loaded onto the type I polyketide synthase (PKS) to form keto acid **3** which undergoes cyclization to ketone **4** under decarboxylation. Ketalization leads to **1** eventually.




Scheme 1. Biosynthesis of kendomycin.

The challenging framework and the promising pharmacological profile of **1** motivated us[5] and sometime later, a number of other groups[6–8] to carry out studies towards its synthesis. Thus far four total syntheses[6] and one formal one[7] have been reported, along with a number of fragment preparations.[8] All these approaches loosely follow the biogenetic pathway by starting with an aromatic polyphenol

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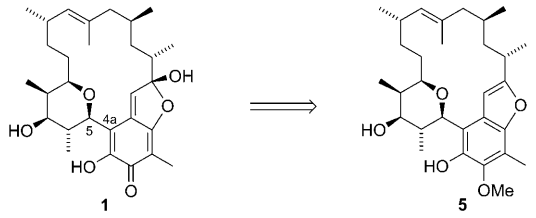
subunit, attaching a polyketide chain and then aiming for cyclization. The main challenge has thus been the formation of the strained macrocyclic *ansa*-ring and the late stage generation of the quinone and lactol units. So far, macrocyclizations have been performed via RCM,[6b] C-glycosidation,[6a] Barbier-type organometal addition,[6d] Prins reaction[7] and Horner–Wadsworth–Emmons olefination.[8e] In continuation of earlier reports[5] we now want to disclose our recent efforts, which have culminated in two successful syntheses.[6e]

## Results and Discussion

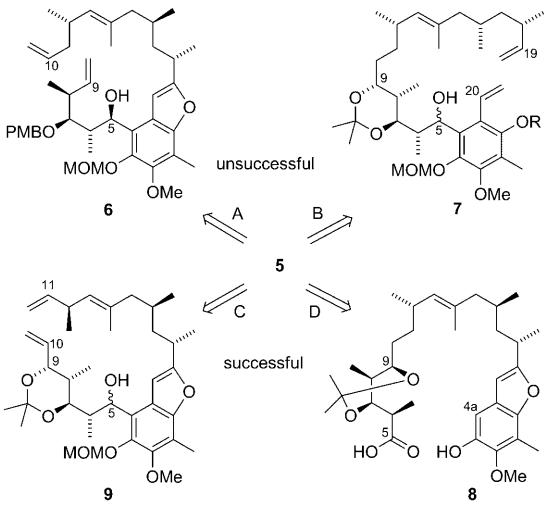
It is obvious that the formation of the quinone methide chromophore should be deferred to the end of the synthesis, via the oxidation of known[6a] benzofuran **5** (Scheme 2). A further general consideration concerns the tetrahydropyran ring which preferably should be installed after the macrocyclization—mainly because of restricted rotation around the C4a–C5 bond[5d] which might be disadvantageous for subsequent ring closures.




Scheme 2. Benzofuran precursor of kendomycin.

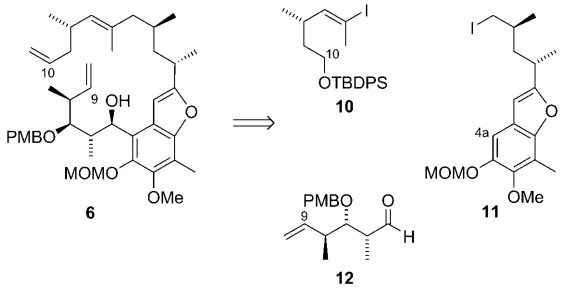
In this report we present four general approaches toward the synthesis of the common precursor **5** (Scheme 3). Three of them address the ring-closing metathesis (RCM) at different sites as key steps. In the first approach (A), we intended to combine olefinic carbons C9 and C10 of compound **6** through RCM, followed by an addition of C5-OH to C9 for tetrahydropyran ring formation. In approaches B and C using compounds **7** and **9**, respectively, as RCM precursors, the tetrahydropran ring should be generated by diastereoselective $S_N1$ reaction of the C9-OH with an in situ generated benzylic cation at C5.[9] The final approach (D) focuses on the macrolactonization of compound **8** followed by a photo-Fries reaction, and the tetrahydropyran should be formed by C5-carbonyl reduction and $S_N1$ cyclization. It should be noted at this point, that only approaches C and D have been successful, in contrast to route A where the RCM did not work and B, where the RCM precursor **7** could not be made at all.

**RCM and trans-etherification (route A)**: Retrosynthetically, the RCM precursor **6** was disconnected into vinyl iodide **10**, alkyl iodide **11** and aldehyde **12** (Scheme 4). The synthesis of the Northern diene portion should be achieved by a Negishi cross-coupling of iodides **10** and **11**, followed by chain




Scheme 3. Precursors for macrocyclizations.

elongation to the 10-olefin. *ortho*-Directed lithiation of C4a and addition to aldehyde **12** should set the stage for the envisaged RCM reaction.

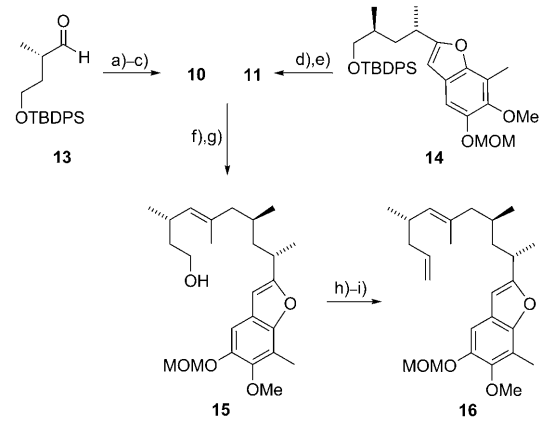



Scheme 4. Retrosynthetic disconnections for route A.

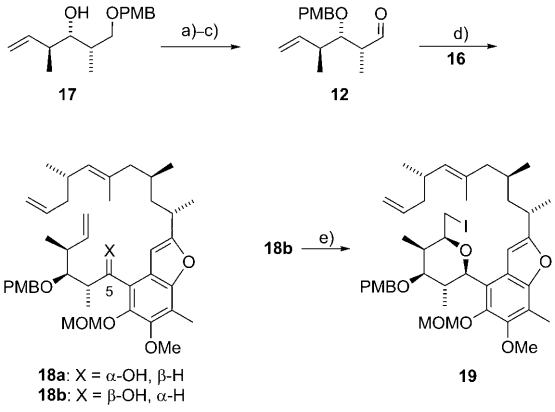
Vinyliodide **10** was easily available from known aldehyde **13**.[10] Colvin's one carbon chain elongation[11] afforded the corresponding alkyne, which was alkylated with MeI and converted to **10** by hydrozirconation/iodination. Iodide **11** was prepared from known compound **14**[9] via a two step standard procedure. $Pd^0$-assisted Negishi coupling[12] of iodides **10** and **11**, followed by deprotection gave (*E*)-olefin **15** which was converted to 1,4-diene **16** via IBX oxidation and Wittig methylenation (Scheme 5).

Aldehyde **12** was available from known alcohol **17**[13] via 1,3 shift of the PMB protecting group and oxidation of the primary alcohol with IBX (Scheme 6). MOM-directed *ortho*-lithiation of **16** followed by nucleophilic addition to aldehyde **12** afforded benzylic alcohols **18a** and **18b** as a 1.5:1 diastereomeric mixture. The configuration at the benzylic carbon C5 was assigned by converting compound **18b** into cyclic iodoether **19**. 2D NMR experiments (NOESY) revealed that **19** and hence **18b** have the desired *R* configuration at C5.



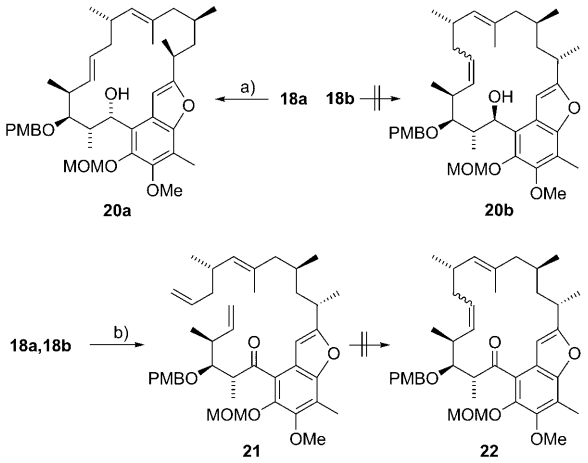

Scheme 5. Synthesis of compound **16**. a) $TMSCHN_2$, LDA, THF, −78 °C → RT, 82 %; b) BuLi, MeI, THF, −78 °C → RT, 95 %; c) $[Cp_2ZrClH]$, benzene, THF, $I_2$, 83 %; d) TBAF, THF, 94 %; e) $I_2$, $PPh_3$, $CH_2Cl_2$, 88 %; f) **11**, *t*BuLi, $ZnCl_2$, $Et_2O$/THF, 5 mol % $[Pd(PPh_3)_4]$, −78 °C → RT, add **10** in THF; g) TBAF, THF, 67 % 2 steps; h) IBX, DMSO, RT, 97 %; i) $MePPh_3Br$, *t*BuOK, THF, 0 °C, 90 %.




Scheme 6. a) DDQ, $CH_2Cl_2$, 3 Å MS, 0 °C, 74 %; b) DIBAL, $CH_2Cl_2$, −78 → −10 °C, 93 %; c) $CH_2Cl_2$, DMSO, $(COCl)_2$, $NEt_3$, −78 °C, 99 %; d) **16**, *n*BuLi, TMEDA, THF, −40 °C then **12**, −78 → −25 °C, 75 % (d.r. 1.5:1); e) *tert*-butyl-4-methylpyridine, $I_2$, $CH_2Cl_2$, −78 → −10 °C, 50 %.

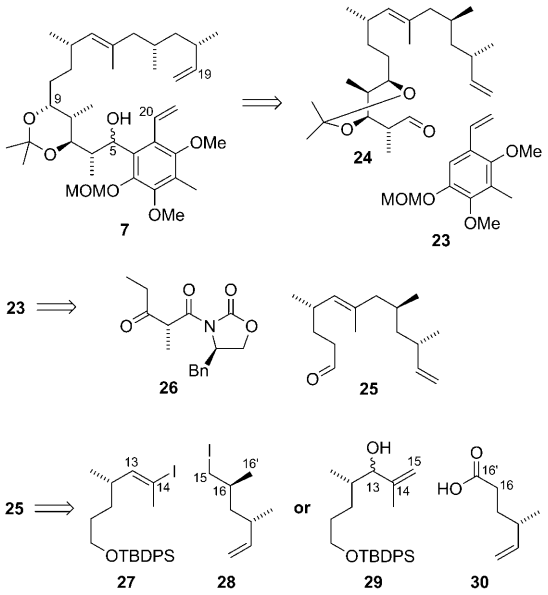
Subjecting **18b** to Grubbs' II catalyst[14] did not result in the desired cyclization to **20b**, but only decomposition of starting material was observed (Scheme 7). In contrast, **18a** underwent the cyclization and afforded macrocyle **20a** which was used for test purposes. Unfortunately all attempts to form the tetrahydropyran by iodination, oxymercuration or selenocyclization failed. Additionally, as RCM of ketone **21** was not successful, we abandoned approach A at this point[15] and turned to route B.

**RCM reaction at C19/C20 (route B)**: Installation of the 13,14-(*E*)-double bond via Negishi coupling and C4/5 connection via an *o*-lithiation aldehyde addition sequence have proven to be reliable and efficient. Additionally, we envisaged the Ireland–Claisen rearrangement[16] as an appropriate tool for generating the 13,14-(*E*)-olefin along with the C-16 methyl group. Thus *seco*-compound **7** should be available




Scheme 7. a) Grubbs' II catalyst, 15 mol %, $CH_2Cl_2$, reflux, 16 h, 46 %; b) IBX, DMSO, RT, 96 %.

from styrene **23** and aldehyde **24**, which could be formed by an Evans aldol addition of aldehyde **25** and ketoimide **26** (Scheme 8). The installation of the C14/C15 double bond should then be achieved by either Negishi coupling of iodides **27**[7] and **28** or by esterification of acid **30** with alcohol **29** followed by an Ireland–Claisen rearrangement.

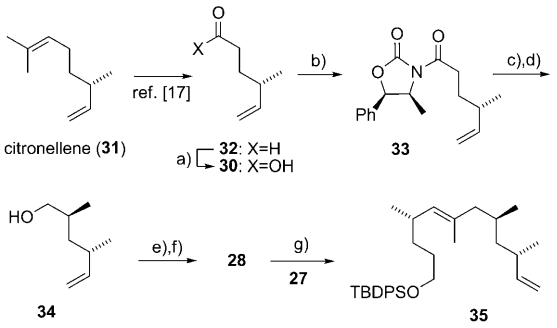



Scheme 8. Retrosynthetic disconnections for route B.

The synthesis started with known[6a] aldehyde **32**, easily available from citronellene **31** in two steps.[17] Pinnick oxidation[18] to the corresponding acid **30** followed by amidation afforded oxazolidinone **33** in good yield (Scheme 9). The second methyl group was introduced via diastereoselective alkylation with methyl iodide, and reductive removal of the auxiliary afforded primary alcohol **34**. Subsequent Finkelstein reaction delivered gram quantities of alkyl iodide **28** in

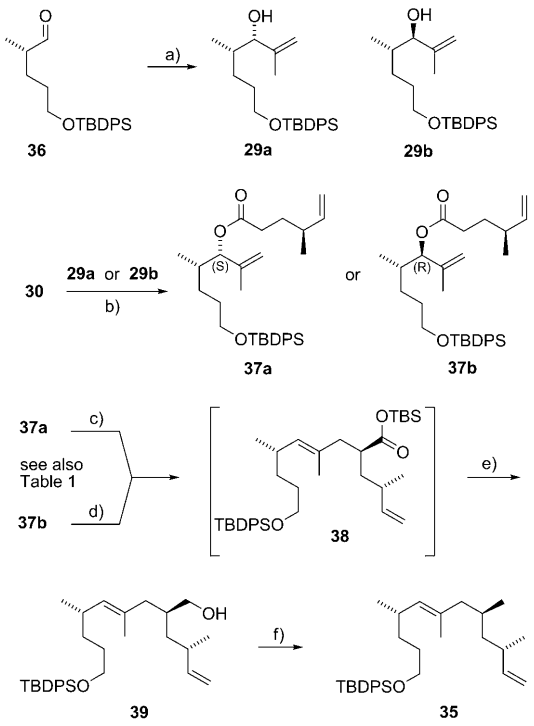
excellent yield. Coupling of known vinyl iodide **27** with **28** smoothly afforded diene **35** as a key fragment.




Scheme 9. a) $NaClO_2$, $NaH_2PO_4$, *t*BuOH, $H_2O$, 73% from **31**; b) DIC, DMAP, Evans' oxazolidinone, $CH_2Cl_2$, 82%; c) LHMDS, MeI, THF, −78°C → RT, 74% (d.r. 10:1); d) $LiAlH_4$, $Et_2O$, 0°C, 80%; e) MsCl, $NEt_3$, $CH_2Cl_2$, 0°C; f) NaI, acetone, RT, 86% from **34**; g) 2.2 equiv *t*BuLi, $ZnCl_2$, −78 → 0°C, then **27**, $Et_2O$/THF, 5 mol% $[Pd(PPh_3)_4]$, 0°C, 95%.

In another approach (Scheme 10) for the synthesis of **35** we decided to use an Ireland–Claisen reaction. This should give access to the trisubstituted (*E*)-olefin and generate the stereocenter at C16 with the desired configuration. For this purpose, known aldehyde **36**[6a] was treated with isopropenyl bromide in a Hiyama–Kishi reaction to give a 1.4:1 mixture of allylic alcohols **29**.[19] The alcohols were separated and esterified with carboxylic acid **30** to afford compounds **37a** and **37b**, respectively. Treatment of **37a** with LDA in THF/HMPA afforded a (*Z*)-silyl ketene acetal, which was rearranged to the corresponding silyl ester **38** in good yield and acceptable diastereoselectivity (see also Table 1).[20] Reaction with potassium fluoride and subsequent reduction with $LiAlH_4$ furnished alcohol **30** which was reduced to give the C16-methyl group in **35**. Since the ester enolate geometry strongly depends on the solvents, treatment of **37b** with LDA in THF should give the corresponding (*Z*)-enolate, and thus, the rearrangement should likewise provide compound **39** after desilylation and reduction. Disappointingly, all attempts to rearrange the (*Z*)-enolate of **37b** proved to be low yielding.

Nevertheless, the rearrangement of **37a** had provided us with gram quantities of diene **35** and so we focused on the elongation sequence (Scheme 11). Deprotection and IBX oxidation furnished aldehyde **25** in 77% yield over two steps. Extended Evans aldol methodology[21] followed by 1,3-reduction[22] afforded stereotetrad (C6 to C9) **40** in good yield and high diastereoselectivity. Base induced hydrolysis to remove the auxiliary and treatment with camphorsulfonic acid in 2,2-dimethoxypropane and methanol afforded the methyl ester. Reduction with $LiAlH_4$ and oxidation of the resulting primary alcohol to aldehyde **24** paved the way for testing the final key steps. Thus, known aryl bromide **41**[23] was formylated and then converted to styrene **23** via Wittig methylenation. To obtain the desired RCM precursor **7**, **23**



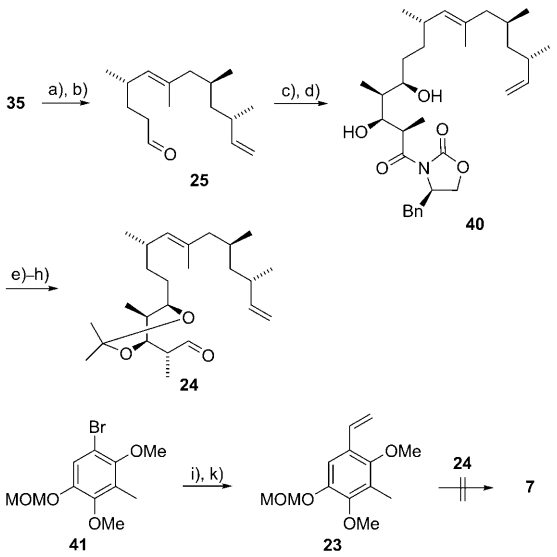

Scheme 10. a) $CrCl_2$ (4 equiv), $NiCl_2$ (0.04 equiv), DMF, 0°C → RT, 86% (d.r. 1.4:1); b) DIC, DMAP, $CH_2Cl_2$, then **29a** or **29b**, 92%; c) LDA, THF/HMPA (23%) then TBSCl, −78°C → reflux; d) LDA, THF, then TBSCl-HMPA, −78°C → reflux; e) i) HMPA, $KHCO_3$, KF, MeI, 0°C; ii) $LiAlH_4$, $Et_2O$, 0°C, 63% from **37a** (d.r. 5:1), 8% from **37b**; f) i) MsCl, $NEt_3$, $CH_2Cl_2$, 0°C; ii) $LiAlH_4$, THF, 0°C → RT, 90%.

and **24** had to be coupled as before, but unfortunately, addition of *n*BuLi to **23** did not give the expected *ortho*-lithiated[24] product but led to polymerization of the styrene unit. So, with a heavy heart after so much experimentation, we abandoned route B.

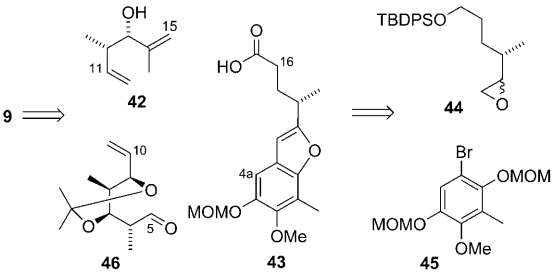
**RCM reaction at C10/C11 (route C)**: In our final RCM approach we aimed for the generation of a C10/C11 olefin which has subsequently to be reduced in presence of the 13,14-olefin. For the formation of the 13,14-trisubstituted double bond we wanted to reapply the Ireland–Claisen approach using the known allylic alcohol **42**[25] and carboxylic acid **43** as simple precursors. Carboxylic acid **43** should be assembled from epoxide **44** and known aryl bromide **45**.[8e] The missing tetrahydropyran side chain should be introduced in the usual way by *ortho*-lithiation of the C4a position and addition of aldehyde **46** (Scheme 12).

For the enantioselective preparation of allylic alcohol **42**, a Duthaler–Hafner crotylation[26] of methacrolein proved to be the method of choice, as the asymmetric crotylation protocols by Roush[27] or Brown[28] lacked enantio- or diastereoselectivity in this case. The synthesis of acid **43** started from aldehyde **32** (available from citronellene **31** in two steps, see Supporting Information), which was reduced to the corresponding alcohol and converted into silylether **47** (Scheme 13) and then into epoxide **44**. Treatment of **44** with



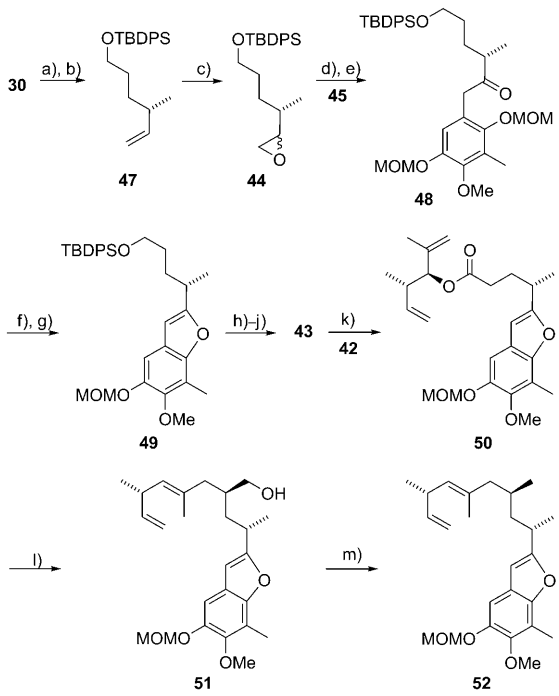

Scheme 11. a) TBAF, THF, RT, 87%; b) IBX, DMSO, RT, 95%; c) **26**, $Sn(OTf)_2$, $CH_2Cl_2$, $NEt_3$, −35, then −78°C, then add **25**, 76% (d.r. 10:1); d) $Me_4NBH(OAc)_3$, $CH_3CN$/AcOH 1.9:1, −32°C, 76% (d.r. 20:1); e) LiOH, $H_2O_2$, THF/$H_2O$ 3:1, 92%; f) 2,2-dimethoxypropane, CSA, 16 h, RT, 90%; g) $LiAlH_4$, $Et_2O$, 0°C, 99%; h) IBX, DMSO, RT, 99%; i) *t*BuLi, DMF, 1 N HCl, −78°C → RT, 83%; k) $MePPh_3Br$, *t*BuOK, THF, 0°C, 98%.




Scheme 12. Retrosynthetic disconnections for route C.

a cuprate reagent derived from bromide **45** gave the corresponding alcohol as a mixture of diastereomers (ca. 1:1). Oxidation led to ketone **48**, which after treatment with triflic acid and reprotection with MOMCl furnished benzofuran **49** in good yield. Desilylation and two-step oxidation of the primary alcohol afforded carboxylic acid **43** which was esterified with alcohol **42** to provide the rearrangement precursor **50**. To our dismay, the Ireland–Claisen conditions we had used for Route B did not work out as expected. In our first tries, we had to struggle with moderate yields and very low diasteroselectivities. Fortunately, after a lot of optimization (see Table 1), yield and diasteroselectivity were improved considerably. Subsequent reduction of the 16′-OH finished the synthesis of 1,3-diolefin **52**.

Aldehyde **46** was obtained via Evans aldol addition of ketoimide **26** and acrolein (Scheme 14) to give adduct **53** in good yield and diastereoselectivity. Lactonization to **54** was performed via stereoselective carbonyl reduction and subse-

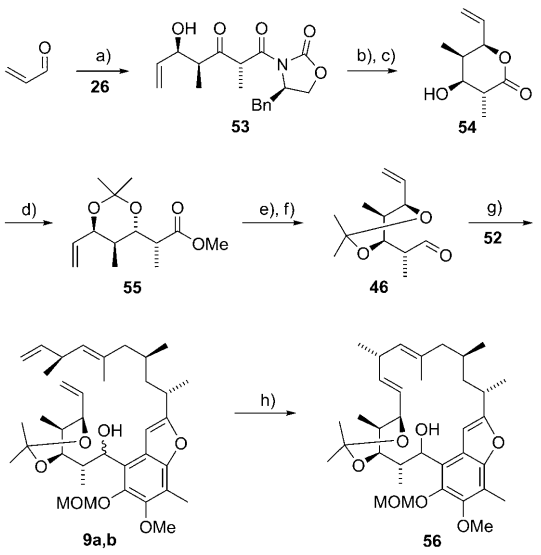



Scheme 13. a) $LiAlH_4$, $Et_2O$, 0°C, 77% from citronellene **31**; b) TBDPSCl, imidazole, THF, RT, 90%; c) *m*CPBA, $CH_2Cl_2$, 0°C, 96%; d) **45**, Mg, THF, reflux 2 h, −40°C, CuI, then **44**, −40 → 0°C, 4 h, 87%; e) DMSO, $(COCl)_2$, $NEt_3$, $CH_2Cl_2$, −78°C, 95%; f) TfOH, toluene, 80°C; g) MOMCl, NaH, DMF, 95% from **47**; h) TBAF, THF, RT, 89%; i) IBX, DMSO, RT, 97%; j) $NaClO_2$, $NaH_2PO_4$, *t*BuOH, $H_2O$, 99%; k) DMAP, EDCI·HCl, $CH_2Cl_2$, RT, 81%; l) i) LHMDS (4 equiv), HMPA, THF, then **50** dissolved in THF/TBSCl, −78°C → RT, then DMF, microwave, 15 min, 180°C; ii) $LiAlH_4$, $Et_2O$, 0°C, 89% (d.r. 4:1); m) i) MsCl, $CH_2Cl_2$, 0°C; ii) $LiAlH_4$, $Et_2O$, 0°C, 89%.

quent removal of the auxiliary. Treatment with camphorsulfonic acid in dimethoxypropane furnished ester **55** which was converted into aldehyde **46** by a reduction–oxidation sequence. *ortho*-Directed lithiation of **52** and addition of aldehyde **46** gave triolefin **9** as a 3.5:1 mixture of diastereomers **9a**/**9b**, which was separated by chromatography. RCM of the major diastereomer **9a** with Grubbs' second generation catalyst induced smooth ring closure to 10,11-(*E*)-olefin **56** exclusively.

Site selective reduction of the 10,11-olefin with diimide,[29] followed by acid-induced formation of the tetrahydropyran ring and concomitant removal of the MOM group led to key intermediate **5**. Since the minor diastereomer **9b** did not undergo the RCM reaction and the $S_N1$ tetrahydropyran formation is independent of the configuration at C5 we concluded that it might be advantageous to change the order of the cyclization reactions (Scheme 15). Treatment of the **9a**,**b** mixture with HCl resulted in clean formation of tetrahydropyran **59**, which, not surprisingly showed the typical atropisomerism (1.5:1) of those compounds. Pleasingly, the subsequent RCM afforded the desired macrocyle in excellent yield and almost exclusively as the (*E*)-isomer **60** (15:1).[30] The success of this RCM came totally unexpected, as we had anticipated major problems from the tetrahydropyran

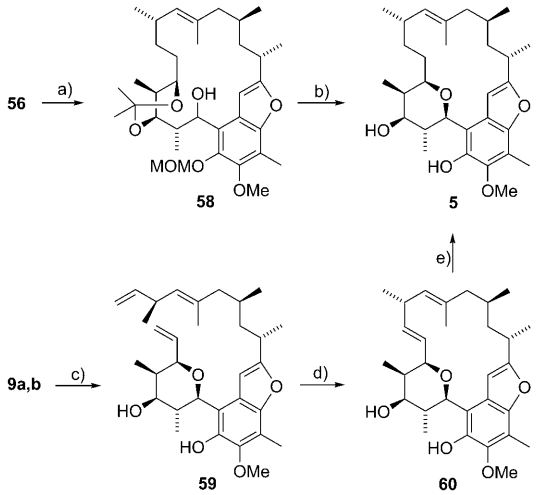
  




Scheme 14. a) $Sn(OTf)_2$, $CH_2Cl_2$, $Et_3N$, $-20 \rightarrow -78\,^{\circ}C$, then acrolein, 91% (d.r. 5:1); b) $Me_4NBH(OAc)_3$, $CH_3CN$/AcOH 2:1, $-32 \rightarrow 0\,^{\circ}C$, 70% (d.r. 6:1); c) LiOH, $H_2O_2$, THF/$H_2O$ 2:1, RT, 72%; d) $(CH_3)_2C(OMe)_2$, CSA, RT, 91%; e) $LiAlH_4$, $Et_2O$, $0\,^{\circ}C$, 96%; f) pyridine·$SO_3$, $NEt_3$, $CH_2Cl_2$/DMSO, $-5\,^{\circ}C$, 99%; g) *n*BuLi, TMEDA, THF, then **52**, $-78 \rightarrow -30\,^{\circ}C$, 90% (d.r. 3.5:1); h) Grubbs' II catalyst, 20 mol%, $CH_2Cl_2$, reflux, 16 h, 62% ((*E*) only).

ring. Diolefin **59** was reduced with high site selectivity to compound **5** with diimide.

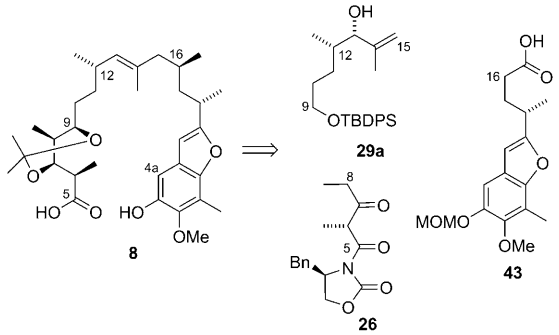
**Macrolactonization and photo-Fries reaction to close the C4a/C5 bond (route D)**: This approach (Scheme 16) was centered around *seco*-acid **8** as a key intermediate. The carbon skeleton should be assembled from the established building blocks **43** and **29a** which would give the (*E*)-13,14-olefinic unit via Claisen–Ireland rearrangement. Evans aldol




Scheme 15. Synthesis of benzofuran **5** via RCM. a) $N_2(COOK)_2$, AcOH, $CH_2Cl_2$, 40 h, reflux, 58%; b) 3 N HCl, MeOH, RT, 96%; c) 3 N HCl, MeOH, RT, 71%; d) Grubbs' II catalyst, 20 mol%, $CH_2Cl_2$, reflux, 16 h, 83% (*E*/*Z* 15:1); e) $N_2(COOK)_2$, AcOH, $CH_2Cl_2$, 5 h, reflux, 71%.

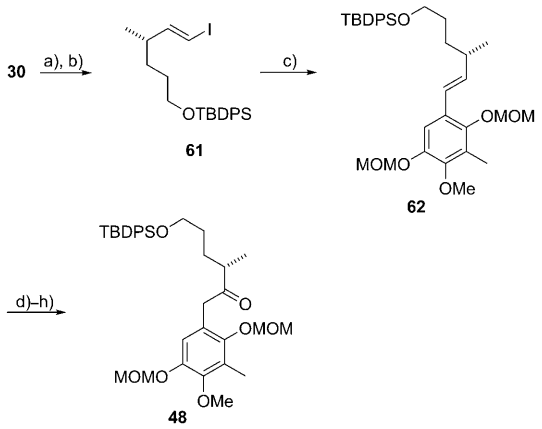
addition of a C9-aldehyde with ketoimide **26** should be used for the C8–C5 chain elongation.

For ketone **48**, which serves as the precursor of acid **43**, we developed a new route (Scheme 17). Starting with alde-




Scheme 16. Retrosynthesis for route D.

hyde **30**, Colvin's chain elongation furnished the corresponding alkyne which was converted into vinyl iodide **61**. Negishi coupling with aryl bromide **45** furnished styrene **62**, which, after epoxidation was subjected to a $Pd^0$-mediated rearrangement[31] to ketone **48**.

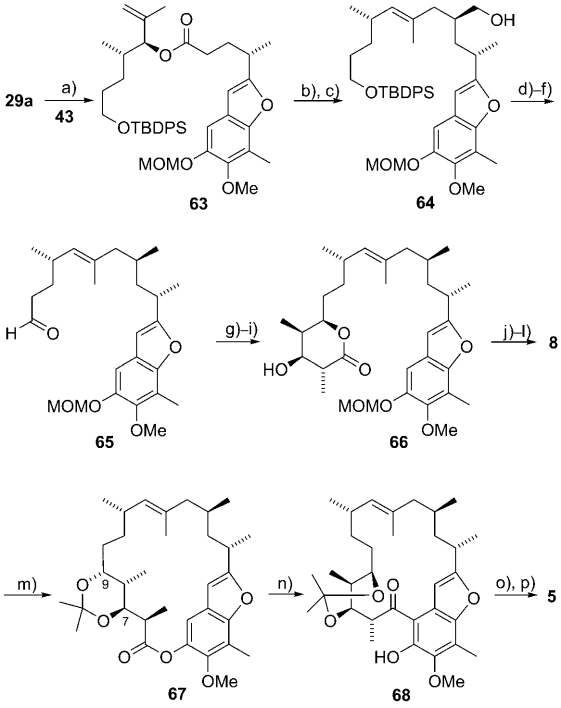



Scheme 17. Synthesis of compound **48**. a) $TMSCHN_2$, *n*BuLi, THF, $-78\,^{\circ}C \rightarrow$ RT, 83%; b) [$Cp_2ZrHCl$], benzene, $50\,^{\circ}C$; $I_2$, $0\,^{\circ}C$, 76%; c) **45**, *t*BuLi, $ZnCl_2$, $Et_2O$/THF, $-78 \rightarrow 0\,^{\circ}C$, [$Pd(PPh_3)_4$], then add **61**, 67%; d) DMDO, acetone, RT, 99%; e) $Pd(OAc)_2$, $PBu_3$, *t*BuOH, reflux, 81%.

Allylic alcohol **29a** was connected with acid **43** to furnish ester **63** as the substrate of an Ireland–Claisen rearrangement (Scheme 18). Treatment with excess LHMDS and reductive work-up led to primary alcohol **64** as an easily separable 4:1 diastereomeric mixture. Subsequent reduction of the carboxyl to the methyl group followed by desilylation and oxidation gave aldehyde **65** which was subjected to an aldol addition with ketoimide **26**. Diastereoselective 1,3-reduction followed by acid catalyzed lactonization furnished lactone **66** which was converted into *seco*-acid **8** via the 7,9-acetonide protected methyl ester. Macrolactonization of **8**

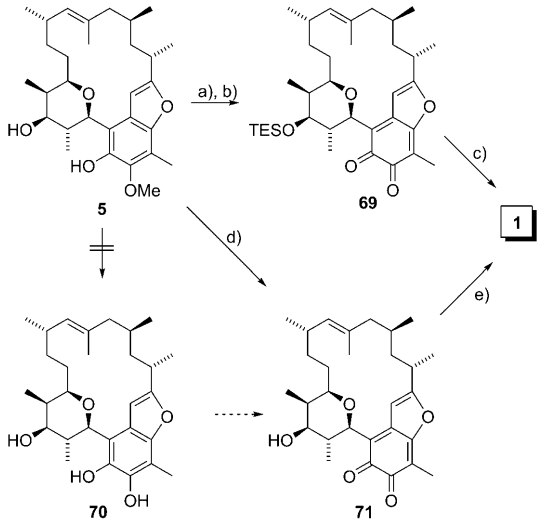
  

under modified Boden–Keck conditions[32] worked nicely to give 55% of monomer **67**, which underwent clean photo-Fries rearrangement to ketone **68**. Reduction of the ketone to the alcohol (diastereomeric mixture) followed by removal of the acetonide and $S_N1$ cyclization furnished key intermediate **5**.




Scheme 18. Synthesis of benzofuran **5** via photo-Fries rearrangement. a) EDCI, DMAP, **43**, $CH_2Cl_2$, 85%; b) LHMDS, HMPA, TBSCl, −78°C → reflux; c) $LiAlH_4$, $Et_2O$, 0°C, 84% from **63** (d.r. 4:1); d) i) MsCl, $Et_3N$, $CH_2Cl_2$, 0°C; ii) $LiAlH_4$, $Et_2O$, 0°C, 94% (2 steps); e) TBAF, THF, RT, 93%; f) IBX, DMSO, RT, 93%; g) **26**, $Sn(OTf)_2$, $CH_2Cl_2$, $Et_3N$, −20°C, then −78°C, then **65**, 87% (d.r. 6:1); h) $Me_4NBH(OAc)_3$, $CH_3CN$/AcOH 2:1, −32 → 0°C, 72% (d.r. 20:1); i) LiOH, $H_2O_2$, THF/$H_2O$ 3:1, 96%; j) 3N HCl, dioxane, 50°C; k) $(CH_3)_2C(OMe)_2$, CSA, RT, 85% 2 steps; l) LiOH, THF/MeOH/$H_2O$ 2:1:1, 12 h, RT, 84%; m) EDCI, DMAP, DMAP·HCl, $CHCl_3$, reflux, 20 h, 55%; n) *hν*, 254 nm, cyclohexane, 50 min, 75%; o) $NaBH_4$, MeOH, RT, then 0.5N HCl; p) TsOH, toluene, 60°C, 71% from **68**.

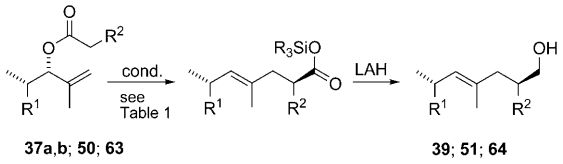
**Completion of the total synthesis**: With two successful approaches for benzofuran intermediate **5** in our hands, we focused on the crucial oxidative endgame (Scheme 19). Firstly, we reproduced Lee's endgame[6a] by starting with protection of the C7-OH to give the corresponding TES ether which was then oxidized with IBX to provide the unstable yet isolable *o*-quinone **69**. On treatment of **69** with aqueous HF, the silyl group was removed and 1,6-conjugate addition of water occurred to furnish the target molecule **1**. In an alternative approach we tried to avoid the OTES protecting group. For this purpose we envisaged a biomimetic pathway, by first converting **5** into catechol **70**, followed by oxidation to quinone **71** and spontaneous addition of water. Unfortunately we could not remove the phenolic methyl ether even under a variety of conditions. Still convinced that it should be possible to work out a protecting group free endgame we tried the direct oxidation of **5** with different oxidants, for instance Fremy's salt ($(KSO_3)_2NO$), CAN, $Ag_2O$, PIDA, $NaIO_4$ and IBX. These experiments all failed, but finally we discovered that DDQ in $CH_2Cl_2/H_2O$ cleanly oxidized **5** to *o*-quinone **71**, which was immediately hydrolyzed to kendomycin (**1**) on treatment with diluted hydrochloric acid.




Scheme 19. Oxidation of **5**. a) TESOTf, $Et_3N$, $CH_2Cl_2$, 0°C, 82%; b) IBX, DMF, RT, 24 h c) 0.1M HF, MeCN, RT, 30% (2 steps); d) DDQ, $CH_2Cl_2$/$H_2O$ 10:1, RT, 52%; e) aq. HCl (1%), MeCN, 50%.

## Conclusions

In conclusion we have presented four synthetic approaches, two of which resulted in convergent total syntheses of kendomycin (**1**). For the stereoselective installation of the (*E*)-13,14-olefin we investigated the experimental conditions for three Ireland–Claisen reactions of unusual complexity, summarized in Scheme 20 and Table 1, respectively.




Scheme 20. Ireland–Claisen rearrangements.

For the formation of the tetrahydopyran ring a remarkably efficient $S_N1$ cyclization was used either before or after the macrocyclization. Regarding the crucial issue of ring closure, our work not only demonstrates the so far unrecognized capability of the photo-Fries ring contraction for the formation of macrocycles, but also reemphasizes the unparalleled potential of RCM for connecting monosubstituted olefin residues. Additionally a protecting group free end-

Table 1. Reaction conditions for Ireland–Claisen rearrangements.

| Compound | Base (equiv)/$SiR_3X$ (equiv)[a] | Reaction conditions[b] | Product | Yield [%][c] | d.r.[d] |
|---|---|---|---|---|---|
| **37a** | LDA (1.2)/TBSCl (1.1) | THF/HMPA, 2 h | **39** | 63 | 5:1 |
| **37b** | LDA (1.2)/TBSCl (1.1) | THF, 2 h | **39** | traces | n.d. |
| **50** | LDA (1.25)/TBSCl (1.1) | THF/HMPA, 3 h | **51** | 20 | n.d. |
| **50** | LDA (1.25)/TBSOTf (1.1) | THF/HMPA, 15 h | **51** | 35 | 5:1 |
| **50** | LDA (3.0)/TMSCl (3.0) | THF/HMPA, 14 h, RT | **51** | 17 | n.d. |
| **50** | LDA (3.0)/TBSCl (10.0) | THF/HMPA/toluene,[e] 1 h | **51** | 59 | 1.1:1 |
| **50** | LDA (3.2)/TBSCl (5.5) | THF, 2 h | **51** | 19 | 4:1 |
| **50** | LDA (5.0)/TBSCl (7.0) | THF/HMPA, 3 h | **51** | 46 | 10:1 |
| **50** | LHMDS (1.25)/TBSCl (1.2) | THF/HMPA, 3 h[f] | **51** | traces | n.d. |
| **50** | LHMDS (4.0)/TBSCl (6.0) | THF/HMPA, 3 h | **51** | 64 | 1:1 |
| **50** | LHMDS (4.0)/TBSCl (6.0) | THF/HMPA, 3 h[f] | **51** | 84 | 4:1 |
| **63** | LDA (1.25)/TBSCl (6.0) | THF/DMPU, 2 h[f] | **64** | n.d. | n.d. |
| **63** | LDA (5.0)/TBSCl (5.5) | THF/DMPU, 2 h | **64** | n.d. | n.d. |
| **63** | LHMDS (4.0)/TBSCl (6.0) | THF/HMPA, 3 h[f] | **64** | 47 | 2:1 |
| **63** | LHMDS (5.0)/TBSCl (6.0) | THF/HMPA, 4 h[f] | **64** | 63 | 2:1 |
| **63** | LHMDS (6.0)/TBSCl (7.0) | THF/HMPA, 2 h[f] | **64** | 58 | 2:1 |
| **63** | LHMDS (4.0)/TBSCl (6.0) | THF/HMPA; DMF[f,g] | **64** | 89 | 4:1 |

[a] Enolization and silylketene acetal formation were performed at −78 °C. [b] The reactions were refluxed, unless otherwise stated. All rearrangement products were treated with $LiAlH_4$ after workup. [c] Yields were determined after reductive workup. [d] The diastereomeric ratio (d.r.) was determined by $^1H$ NMR. [e] Internal quench conditions. [f] The silylketene acetal was isolated before rearrangement. [g] The starting material was added as a solution in THF/TBSCl. The rearrangement was performed under microwave irradiation at 180 °C.

game for converting **5** into **1** was developed, which saves another synthetic step.

## Experimental Section

All solvents were distilled prior to use, except THF, which was purchased from Acros Organics (99.85%, $H_2O$ < 50 ppm) and used without further purification. $Et_2O$, toluene and benzene were distilled from sodium. $CH_2Cl_2$ and $CHCl_3$ were passed through an $Al_2O_3/MgSO_4$ column or distilled over $P_2O_5$. Acetone was distilled over $P_2O_5$. DMF, DMSO, $NEt_3$, $iPr_2NH$, $iPr_2NEt$, TMEDA, HMPA and 2,6-lutidine were distilled from $CaH_2$. TBSCl was dissolved in hexane or THF (3 M), treated with $Et_3N$ (3%) and transferred via a syringe filter to the reaction mixture. [CpZrHCl] was prepared according to the Negishi procedure.[33] Solvent degassing was achieved by repeated (at least four cycles) freeze–pump–thaw cycles. All non-aqueous reactions were performed under an atmosphere of argon using oven-dried or flame-dried glassware and standard syringe/septa techniques. $^1H$- and $^{13}C$ NMR spectra were measured in $CDCl_3$ on a Bruker Avance DRX-400 or DRX-600 at 400.13 MHz (100.61 MHz) or 600.13 MHz (150.90 MHz), respectively. Chemical shifts are given in ppm and were referenced to residual $CHCl_3$ ($^1H$, $\delta$ = 7.26 ppm, $^{13}C$, $\delta$ = 77.00 ppm) or toluene ($^1H$, $\delta$ = 7.09, 7.00, 6.98 ppm, $^{13}C$, $\delta$ = 137.9, 129.2, 128.3, 125.5, 20.4 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant in Hz, integration. Assignments of proton resonances were confirmed by correlated spectroscopy. IR spectra were recorded as thin films on a silicon plate on a Perkin–Elmer 1600 FT-IR spectrometer. Mass spectra were measured on a Micro mass, trio 200 Fisions Instruments. High-resolution mass spectra (HRMS) were performed with a Finnigan MAT 8230 with a resolution of 10000. Optical rotations were measured on a Perkin–Elmer 351 polarimeter at 20 °C (reported as follows: concentration ($c$ in g per 100 mL), solvent). The reaction progress was monitored on precoated TLC plates (Merck Kieselgel 60 F254). Spots were visualized under UV light (254 nm) and/or were stained with ceric ammonium molybdate (CAM), *p*-anisaldehyde or potassium permanganate stain. Column chromatography was performed with Merck silica gel 60 (230–400 mesh). Analytical HPLC was performed on a Jasco System (PU-980 pump, UV 975 and RI 930) using a Nucleosil 50 column (5 μm, Ø 4 mm × 241 mm) at ambient temperature. Preparative HPLC was performed on a Dynamix Model SD-1 equipped with a Model UV-1 absorbance detector using a Supershere (60 Å pore size, 4 μm particle size, Ø 25 mm × 250 mm) at ambient temperature. Yields refer to chromatographically purified compounds, unless otherwise stated.

**(*S*)-*tert*-Butyl-(4-methylhex-5-enyloxy)-diphenylsilane (47)**: β-(+)-Citronellene (20.3 g, 147 mmol, 1.0 equiv) and sodium acetate (12.6 g, 154 mmol, 1.05 equiv) were dissolved in $CH_2Cl_2$ (490 mL) and cooled to −20 °C. *m*-CPBA (75%, 35.4 g, 154 mmol, 1.05 equiv) was added in small portions and stirring was continued for 1.5 h, allowing the suspension to warm to 0 °C. The reaction was quenched by careful addition of saturated aqueous $NaHCO_3$ (200 mL) and extracted with $CH_2Cl_2$ (3 × 70 mL). The combined organic fractions were washed with 1 N NaOH (100 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude product was dissolved in $Et_2O$ (245 mL), cooled to 0 °C and $H_5IO_6$ (50 g, 220 mmol, 1.5 equiv) in THF (220 mL) was added within 45 min. Stirring was continued until TLC analysis showed complete consumption of the starting material. The mixture was diluted with $Et_2O$ (500 mL), $H_2O$ (300 mL) was added and the phases were separated. The organic layer was washed twice with brine, dried over $MgSO_4$ and filtered. This solution was recooled to 0 °C and $LiAlH_4$ (4 M in $Et_2O$, 44 mL, 176 mmol, 1.2 equiv) was added via a dropping funnel over 2 h. The solution was slowly quenched with ethyl acetate (10 mL), 1 N $KHSO_4$ (200 mL) was carefully added and the aqueous layer was extracted with $Et_2O$ (3 × 100 mL). The organic fraction was dried over $MgSO_4$, filtered and evaporated to dryness. Purification of the residue by flash chromatography (pentane/diethyl ether 5:1) afforded the alcohol as a colorless oil (13.0 g, 77% over 3 steps). $[\alpha]_D^{20} = +18.8$ ($c$ = 1.25, $CH_2Cl_2$); $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 5.69 (ddd, $J$ = 17.4, 10.2, 7.4 Hz, 1H), 4.99–4.90 (m, 1H), 3.63 (t, $J$ = 6.3 Hz, 2H), 2.20–2.07 (m, 1H), 1.62–1.51 (m, 2H), 1.40–1.32 (m, 2H), 1.31–1.25 (br, OH), 1.00 ppm (d, $J$ = 6.6 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 144.4, 112.8, 63.1, 37.6, 32.6, 30.5, 20.2 ppm; IR (film): $\tilde{\nu}$ = 3331, 3077, 2935, 1640, 1455, 1419, 1374, 1058 $cm^{-1}$; HRMS (ESI): $m/z$: calcd for $C_7H_{12}$: 96.0939, found: 96.0919 $[M-H_2O]^+$.

Above-prepared alcohol (3.30 g, 28.8 mmol, 1.0 equiv) in DMF (29 mL) was cooled to 0 °C and imidazole (3.92 g, 57.6 mmol, 2 equiv) was added. After 5 min TBDPSCl (7.4 mL, 28.8 mmol, 1.0 equiv) was transferred to the solution via cannula and stirring was continued for 1 h at ambient temperature. The reaction mixture was diluted with $Et_2O$ (200 mL), quenched with $NH_4Cl$ (100 mL) and the phases were separated. The aqueous layer was extracted with $Et_2O$ (3 × 50 mL), the organic layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (hexane/ethyl acetate 10:1) afforded compound **47** as a colorless oil (9.10 g, 90%). $[\alpha]_D^{20} = +6.7$ ($c$ = 1.10, $CH_2Cl_2$); $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.71–7.64 (m, 4H), 7.45–7.33 (m, 6H), 5.68 (ddd, $J$ = 17.3, 10.1, 7.3 Hz, 1H), 4.96–4.88 (m, 1H), 3.65 (t, $J$ = 6.6 Hz, 2H), 2.16–2.04 (m, 1H), 1.62–1.52 (m, 2H), 1.39–1.32 (m, 2H), 1.05 (s, 9H), 0.98 ppm (d, $J$ = 6.6 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 144.7, 135.6, 134.2, 129.5, 127.6, 112.5, 64.1, 37.4, 32.7, 30.2, 26.9, 20.2, 19.2 ppm; IR (film): $\tilde{\nu}$ = 2932, 1639, 1589, 1473, 1427, 1389, 1361, 1112 $cm^{-1}$; HRMS (ESI): $m/z$: calcd for $C_{19}H_{23}OSi$: 295.1518, found: 295.1522 $[M-t\text{Bu}]^+$.

**(*S*)-*tert*-Butyl(4-(oxiran-2-yl)pentyloxy)diphenylsilane (44)**: Alkene **47** (5.91 g, 16.74 mmol, 1.0 equiv) was dissolved in $CH_2Cl_2$ (57 mL) and cooled to 0 °C. *m*-CPBA (75%, 9.3 g, 40.17 mmol, 2.4 equiv) was added

in small portions and stirring was continued for 3 h. The reaction was filtered over Celite, quenched by the careful addition of saturated aqueous $NaHCO_3$ (70 mL) and extracted with $CH_2Cl_2$ (3×70 mL). The combined organic fractions were dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash chromatography (hexane/ethyl acetate 10:1 → 5:1) afforded epoxide **44** as a colorless oil (mixture of diastereomers) (5.91 g, 96%). $^1$H NMR (The asterisk denotes the minor diastereomer, 400 MHz, $CDCl_3$): $\delta$ = 7.69–7.65 (m, 4H), 7.45–7.35 (m, 6H), 3.70–3.63 (m, 2H), 2.75–2.64 (m, 2H), 2.51–2.47(m, 1H), 2.47–2.44* (m, 1H), 1.72–1.55 (m, 2H), 1.52–1.40 (m, 1H), 1.40–1.19 (m, 2H), 1.06 (s, 9H), 1.02 (d, $J$ = 6.6 Hz, 3H), 0.92* ppm (d, $J$ = 6.8, 3H); $^{13}$C NMR (The asterisk denotes the minor diastereomer, 100 MHz, $CDCl_3$): $\delta$ = 135.6, 134.1*, 134.0, 129.6, 129.5*, 127.6, 64.1*, 64.0, 57.0, 56.9*, 46.9, 45.6*, 36.0, 35.8*, 30.7*, 30.1, 29.9*, 29.7, 26.9, 19.2, 17.1, 15.6* ppm; IR (film): $\tilde{\nu}$ = 3071, 3048, 2932, 1590, 1472, 1428, 1390, 1361, 1268, 1189, 1112 cm$^{-1}$; HRMS (ESI): $m/z$: calcd for $C_{21}H_{25}O_2Si$: 311.1467; found: 311.1464 $[M-t\mathrm{Bu}]^+$.

**(*S*)-6-(*tert*-Butyldiphenylsilyloxy)-1-(4-methoxy-2,5-bis(methoxymethoxy)-3-methylphenyl)-3-methylhexan-2-one (48)**: Bromide **45** (11.3 g, 35.18 mmol, 3 equiv) was dissolved in THF (50 mL). Mg (855 mg, 35.18 mmol, 3 equiv), a crump of iodine and 2 drops of dibromoethane were added and the mixture was heated to reflux until the Mg has been completely consumed (1.5 h). The reaction was allowed to cool to room temperature and transferred to a solution of CuI (223 mg, 1.17 mmol, 0.1 equiv) in THF (12 mL) at −50 °C. The resulting grey suspension was stirred for 30 min at −30 °C and then cooled to −45 °C. Epoxide **44** (4.3 g, 11.7 mmol, 1 equiv) in THF (23 mL) was added dropwise and the temperature was raised to 0 °C within 4 h. The reaction was quenched by the addition of saturated aqueous $NH_4Cl$ (100 mL) and the phases were separated. The aqueous layer was extracted with $Et_2O$ (4×50 mL), the combined organic phases were dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography (hexane/ethyl acetate 10:1 → 3:1) gave a diastereomeric mixture of the alcohols (6.2 g, 87%).

Oxalylchloride (1.72 mL, 20.30 mmol, 2 equiv) was dissolved in $CH_2Cl_2$ (50 mL), cooled to −78 °C and DMSO (2.88 mL, 40.60 mmol, 4 equiv) was added dropwise. After 40 min, above alcohol (6.2 g, 10.15 mmol, 1 equiv) in $CH_2Cl_2$ (20 mL) was added via syringe and stirring was continued for additional 45 min. DIPEA (10.6 mL, 60.90 mmol, 6 equiv) was added and the solution was warmed to 0 °C. The reaction was hydrolyzed with saturated aqueous $NH_4Cl$ (100 mL), extracted with $CH_2Cl_2$ (3×50 mL), washed with brine, dried over $MgSO_4$ and filtered. Purification by column chromatography (hexane/ethyl acetate 5:1 → 3:1) afforded ketone **48** (5.8 g, 95%). $[\alpha]_D^{20}$ = +9.1 ($c$ = 0.95, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.68–7.63 (m, 4H), 7.45–7.34 (m, 6H), 6.74 (s, 1H), 5.14 (s, 2H), 4.83 (s, 2H), 3.80 (s, 3H), 3.73 (d, $J$ = 3.8 Hz, 2H), 3.63 (t, $J$ = 6.2 Hz, 2H), 3.51 (s, 3H), 3.48 (s, 3H), 2.68–2.58 (m, 1H), 2.20 (s, 3H), 1.80–1.70 (m, 1H), 1.56–1.47 (m, 2H), 1.48–1.39 (m, 1H), 1.09 (d, $J$ = 6.8 Hz, 3H), 1.04 ppm (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 211.8, 150.0, 148.0, 146.9, 135.5, 134.0, 129.5, 127.6, 125.8, 123.5, 116.2, 99.7, 95.5, 63.7, 60.4, 57.4, 56.2, 45.0, 43.3, 30.1, 29.1, 26.8, 19.2, 16.5, 10.4 ppm; IR (film): $\tilde{\nu}$ = 2933, 1710, 1559, 1481, 1237, 1155, 1112, 967 cm$^{-1}$; HRMS (ESI): $m/z$: calcd for $C_{35}H_{48}O_7Si$: 608.3169; found: 608.3186 $[M]^+$.

**(*S*)-*tert*-Butyl(4-(6-methoxy-5-(methoxymethoxy)-7-methylbenzofuran-2-yl)pentyloxy)diphenylsilane (49)**: Ketone **48** (15.8 g, 25.95 mmol, 1.0 equiv) and molecular sieves (4 Å, 15.8 g) in of toluene/EtOH 4:1 (500 mL) were heated to 80 °C. After the addition of TfOH (689 μL, 7.79 mmol, 0.3 equiv) stirring was continued at 80 °C for 5 min and then the mixture was rapidly cooled to 0 °C. The reaction was quenched by the addition of saturated $NaHCO_3$ (300 mL), filtered over Celite and the mixture was extracted with $Et_2O$ (3×100 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was removed in vacuo affording crude furan (13 g, 100%), which was used without further purification in the next step. A small sample was purified by column chromatography (hexane/ethyl acetate 5:1 → 3:1) to obtain an analytically pure sample. $[\alpha]_D^{20}$ = +12.1 ($c$ = 2.45, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.70–7.65 (m, 4H), 7.45–7.33 (m, 6H), 6.90 (s, 1H), 6.23 (d, $J$ = 0.5 Hz, 1H), 5.52 (s, 1H), 3.84 (s, 3H), 3.69 (t, $J$ = 6.3 Hz, 2H), 2.96–2.86 (m, 1H), 2.45 (s, 3H), 1.93–1.82 (m, 1H), 1.74–1.63 (m, 1H), 1.67–1.57 (m, 2H), 1.31 (d, $J$ = 6.8 Hz, 3H), 1.07 ppm (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 164.0, 147.9, 145.1, 142.4, 135.6, 134.0, 129.5, 127.6, 124.1, 113.8, 102.0, 100.7, 63.8, 61.4, 33.3, 31.6, 30.0, 26.9, 19.2, 19.1, 9.3 ppm; IR (film): $\tilde{\nu}$ = 3529, 2933, 2858, 1607, 1459, 1427, 1360, 1111, 864 cm$^{-1}$; HRMS (ESI): $m/z$: calcd for $C_{31}H_{38}O_4Si$: 502.2539; found: 502.2537 $[M]^+$.

Crude furan (13 g, 25.95 mmol, 1.0 equiv) in DMF (130 mL) was cooled to 0 °C. Then NaH (1.5 g, 38.85 mmol, 1.5 equiv) was added in small portions, followed by the careful addition of neat MOMCl (2.75 mL, 36.26 mmol, 1.4 equiv). The dark-brown solution was stirred for 1 h, diluted with $Et_2O$ (200 mL) and quenched with saturated aqueous $NH_4Cl$ (150 mL). The product was extracted with $Et_2O$/hexane 1:1 (3×50 mL), washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated and the pale yellow oil was purified by column chromatography (hexane/ethyl acetate 3:1) to furnish furan **49** (13.4 g, 95%). $[\alpha]_D^{20}$ = +12.6 ($c$ = 1.40, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.68–7.62 (m, 4H), 7.44–7.31 (m, 6H), 7.07 (s, 1H), 6.22 (s, 1H), 5.21 (s, 2H), 3.84 (s, 3H), 3.67 (t, $J$ = 6.2 Hz, 2H), 3.55 (s, 3H), 2.93–2.86 (m, 1H), 2.40 (s, 3H), 1.90–1.80 (m, 1H), 1.71–1.59 (m, 1H), 1.63–1.54 (m, 2H), 1.29 (d, $J$ = 7.1 Hz, 3H), 1.04 ppm (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 164.0, 149.2, 146.9, 145.5, 135.5, 134.0, 129.5, 127.6, 123.4, 115.3, 105.0, 100.8, 96.2, 63.8, 61.0, 56.1, 33.3, 31.6, 30.0, 26.8, 19.2, 19.1, 9.1 ppm; IR (film): $\tilde{\nu}$ = 2932, 1684, 1653, 1559, 1473, 1427, 1260, 1153, 1112, 1044 cm$^{-1}$; HRMS (ESI): $m/z$: calcd for $C_{33}H_{42}O_5Si$: 546.2802; found: 546.2792 $[M]^+$.

**(*S*)-4-(6-Methoxy-5-(methoxymethoxy)-7-methylbenzofuran-2-yl)pentanoic acid (43)**: A solution of benzofuran **49** (7.63 g, 13.93 mmol, 1.0 equiv) in THF (280 mL) was treated with TBAF (1 M in THF, 15.33 mL, 15.33 mmol, 1.1 equiv) and stirred overnight at room temperature. Finally the reaction was quenched with $NH_4Cl$ (150 mL) and the aqueous layer was extracted with $Et_2O$ (3×100 mL). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated to dryness. Purification by column chromatography using gradient elution (hexane/ethyl acetate 3: 1 → 1:1) furnished the alcohol as a pale yellow oil (3.84 g, 89%). $[\alpha]_D^{20}$ = +13.4 ($c$ = 1.60, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.07 (s, 1H), 6.27 (s, 1H), 5.21 (s, 2H), 3.84 (s, 3H), 3.64 (t, $J$ = 6.3 Hz, 2H), 3.54 (s, 3H), 2.99–2.89 (m, 1H), 2.42 (s, 3H), 1.88–1.77 (m, 1H), 1.73–1.63 (m, 1H), 1.65–1.54 (m, 2H), 1.32 ppm (d, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 163.7, 149.2, 146.9, 145.6, 123.4, 115.3, 105.0, 101.0, 96.2, 62.9, 61.0, 56.1, 33.5, 31.6, 30.3, 19.1, 9.1 ppm; IR (film): $\tilde{\nu}$ = 3854, 3676, 2935, 1653, 1559, 1457, 1153, 1043 cm$^{-1}$; HRMS (ESI): $m/z$: calcd for $C_{17}H_{24}O_5$: 308.1624; found: 308.1620 $[M]^+$.

A 100 mL Schlenk flask was charged with above alcohol (3.57 g, 11.58 mmol, 1.0 equiv) and DMSO (60 mL, 0.2 M). IBX (8.1 g, 28.94 mmol, 2.5 equiv) was added over a period of 20 min and stirring was continued for 2 h at ambient temperature. The solution was diluted with $Et_2O$/hexane 1:1 (100 mL) and $H_2O$ (100 mL). The mixture was filtered over Celite, the layers were separated and the aqueous layer was extracted with $Et_2O$/hexane 1:1 (3×50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The crude product was filtered over a plug of silica to give pure aldehyde as a pale orange oil (3.43 g, 97%). $[\alpha]_D^{20}$ = +17.2 ($c$ = 0.75, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 9.74 (t, $J$ = 1.4 Hz, 1H), 7.08 (s, 1H), 6.28 (s, 1H), 5.21 (s, 2H), 3.84 (s, 3H), 3.54 (s, 3H), 3.03–2.93 (m, 1H), 2.47 (dt, $J$ = 7.5, 1.4 Hz, 2H), 2.41 (s, 3H), 2.10–1.93 (m, 2H), 1.34 ppm (d, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 202.0, 162.3, 149.3, 147.1, 145.8, 123.2, 115.4, 105.1, 101.6, 96.1, 61.0, 56.1, 41.6, 33.0, 27.7, 19.0, 9.1 ppm; IR (film): $\tilde{\nu}$ = 2932, 1723, 1653, 1559, 1457, 1340, 1219, 1153, 1119, 1090, 1042 cm$^{-1}$; HRMS (ESI): $m/z$: calcd for $C_{17}H_{22}O_5$: 306.1467; found: 306.1464 $[M]^+$.

Above aldehyde (3.43 g, 11.19 mmol, 1.0 equiv) was dissolved in $t$BuOH (75 mL, 0.15 M), treated with 2-methyl-2-butene (1 mL mmol$^{-1}$, 11.2 mL), and cooled to 5 °C. $NaClO_2$ (18.9 g, 167.85 mmol, 15 equiv) and 18.9 g $NaH_2PO_4$ were dissolved in $H_2O$ (110 mL, 1.5 M), transferred to a 250 mL dropping funnel, and added over a period of 20 min. After 50 min at RT. TLC analysis showed complete consumption and the reaction mixture was partitioned between $CH_2Cl_2$ (150 mL) and brine (100 mL). The aqueous layer was extracted with three portions of $CH_2Cl_2$ (50 mL) and the

combined organic extracts were dried over $MgSO_4$. Evaporation of the solvent gave crude acid, which was purified by flash chromatography (hexane/ethyl acetate 3:1 → 1:1) to give acid **43** as an orange-viscous oil (3.60 g, 99%). $[\alpha]_D^{20} = +35.5$ ($c = 0.65$, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 7.08$ (s, 1H), 6.29 (s, 1H), 5.21 (s, 2H), 3.85 (s, 3H), 3.54 (s, 3H), 3.04–2.94 (m, 1H), 2.42–2.35 (m, 2H), 2.41 (s, 3H), 2.12–1.92 (m, 2H), 1.34 ppm (d, $J = 6.8$ Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta =$ 177.7, 162.4, 149.3, 147.0, 145.7, 123.2, 115.4, 105.1, 101.6, 96.2, 61.0, 56.1, 33.0, 31.4, 30.2, 19.0, 9.1 ppm; IR (film): $\tilde{\nu} = 3629, 2933, 1707, 1653, 1607, 1559, 1457, 1420, 1261, 1153, 1117, 1043\ cm^{-1}$; HRMS (ESI): $m/z$: calcd for $C_{17}H_{22}O_6$: 322.1416; found: 322.1421 $[M]^+$.

**(*S*)-((3*S*,4*S*)-2,4-Dimethylhexa-1,5-dien-3-yl) 4-(6-methoxy-5-(methoxymethoxy)-7-methylbenzofuran-2-yl)pentanoate (50)**: A mixture of acid **43** (2.55 g, 7.91 mmol, 1.0 equiv), alcohol **42** (1.20 g, 9.51 mmol, 1.2 equiv), EDCI·HCl (1.97 g, 10.28 mmol, 1.3 equiv) and DMAP (1.26 g, 10.31 mmol, 1.3 equiv) in $CH_2Cl_2$ (30 mL) was stirred at room temperature for 1.5 h. The reaction was diluted with $CH_2Cl_2$ (100 mL), quenched with 1% HCl (20 mL) and washed with brine (2×50 mL). The organic layer was dried over $MgSO_4$, concentrated in vacuo and the residue was purified by flash chromatography (hexane/ethyl acetate 15:1 → 5:1) to give ester **50** (2.75 g, 81%). $[\alpha]_D^{20} = +26.8$ ($c = 1.30$, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 7.07$ (s, 1H), 6.27 (s, 1H), 5.70 (ddd, $J = 17.2$, 10.2, 8.0 Hz, 1H), 5.21 (s, 2H), 5.06–4.98 (m, 2H), 5.05 (d, $J = 7.8$ Hz, 1H), 4.96–4.91 (m, 2H), 3.84 (s, 3H), 3.54 (s, 3H), 3.02–2.91 (m, 1H), 2.52–2.43 (m, 1H), 2.41 (s, 3H), 2.36–2.30 (m, 2H), 2.10–1.99 (m, 1H), 1.99–1.89 (m, 1H), 1.72 (s, 3H), 1.32 (d, $J = 7.1$ Hz, 3H), 0.96 ppm (d, $J =$ 7.1 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 172.5$, 162.7, 149.3, 147.0, 145.7, 141.8, 139.8, 123.3, 115.2, 114.4, 113.4, 105.1, 101.4, 96.2, 80.3, 61.0, 56.1, 40.0, 33.0, 32.1, 30.5, 18.9, 18.2, 16.6, 9.1 ppm; IR (film): $\tilde{\nu} = 2967, 1734, 1700, 1684, 1653, 1559, 1457, 1152, 1117\ cm^{-1}$; HRMS (ESI): $m/z$: calcd for $C_{25}H_{34}O_6Na$: 453.2253; found: 453.2269 $[M+Na]^+$.

**(2*S*,6*S*,*E*)-2-((*S*)-2-(6-Methoxy-5-(methoxymethoxy)-7-methylbenzofuran-2-yl)propyl)-4,6-dimethylocta-4,7-dien-1-ol (51)**: LHMDS (1M in THF, 11.1 mL, 12.08 mmol, 4 equiv) was diluted with THF (12 mL), cooled to −78°C and freshly distilled HMPA (7.5 mL) was slowly added via cannula. After 5 min ester **50** (2.3 g, 3.28 mmol, 1.0 equiv) in THF (2.1 mL, 0.5 mL rinse) was transferred to a freshly prepared TBSCl solution (3M in THF, 6.56 mL, 19.68 mmol, 6 equiv) and added dropwise to the above LHMDS/HMPA mixture. The reaction mixture was stirred for 40 min at −78°C, allowed to warm to 0°C over 15 min, stirred for additional 5 min at room temperature and partitioned between $H_2O$ (100 mL) and $Et_2O$ (3×70 mL). The combined organic fractions were washed with brine, dried over $MgSO_4$ and evaporated to dryness. The crude ketene silyl acetal was dissolved in DMF (12 mL) and heated under microwave irradiation at 180°C for 15 min. The mixture was partitioned between $H_2O$ (100 mL) and $Et_2O$ (100 mL), extracted with $Et_2O$ (3×50 mL), washed with brine (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude ester was dissolved in $Et_2O$ (30 mL), transferred to an ice-bath and $LiAlH_4$ (4M in $Et_2O$, 1.51 mL, 6.04 mmol, 2 equiv) was added carefully via cannula. After 30 min at room temperature TLC analysis showed complete consumption of the starting material and the reaction mixture was quenched at 0°C by slow addition of ethyl acetate, diluted with $Et_2O$ (100 mL) and washed with 1% HCl (100 mL). The aqueous layer was extracted with $Et_2O$ (3×50 mL), and the combined organic fractions were washed with brine (50 mL), dried over $MgSO_4$ and the solvent was removed in vacuo. Purification by column chromatography (hexane/ethyl acetate 10:1 → 5:1) afforded alcohol **51** as a colorless oil (1.11 g, 89%, d.r. 4:1 as determined by $^1$H NMR). (*S*)-**51**: $[\alpha]_D^{20} =$ +9.5 ($c = 1.95$, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 7.07$ (s, 1H), 6.28 (s, 1H), 5.74 (ddd, $J = 17.1$, 10.5, 6.4 Hz, 1H), 5.21 (s, 2H), 5.05 (d, $J = 8.8$ Hz, 1H), 4.95 (dt, $J = 17.2$, 1.6 Hz, 1H), 4.89 (dt, $J = 10.2$, 1.5 Hz, 1H), 3.84 (s, 3H), 3.54 (s, 3H), 3.49 (d, $J = 5.1$ Hz, 2H), 3.12–2.97 (m, 2H), 2.41 (s, 3H), 2.13–1.99 (m, 2H), 1.88–1.78 (m, 1H), 1.78–1.69 (m, 1H), 1.62 (d, $J = 1.3$ Hz, 3H), 1.49–1.41 (m, 1H), 1.42–1.36 (br, OH), 1.31 (d, $J = 7.1$ Hz, 3H), 1.05 ppm (d, $J = 6.8$ Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 163.9$, 149.2, 146.9, 145.6, 142.9, 133.3, 130.7, 123.4, 115.3, 112.0, 105.0, 100.9, 96.2, 66.1, 61.0, 56.1, 42.8, 37.7, 36.4, 36.2, 31.5, 20.5, 20.1, 16.2, 9.1 ppm; IR (film): $\tilde{\nu} = 3451, 2927, 1559, 1449, 1340, 1219, 1154, 1116, 1091, 1044\ cm^{-1}$; HRMS (ESI): $m/z$: calcd for $C_{25}H_{36}O_5$: 416.2563; found: 416.2569 $[M+Na]^+$. (*R*)-**51**: $[\alpha]_D^{20} = -18.4$ ($c = 1.10$, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta\ \delta = 7.07$ (s, 1H), 6.26 (s, 1H), 5.75 (ddd, $J = 17.0$, 10.4, 6.4 Hz, 1H), 5.21 (s, 2H), 5.04 (dd, $J = 8.8$, 1.0 Hz, 1H), 4.98 (dt, $J = 17.2$, 1.6 Hz, 1H), 4.91 (dt, $J = 10.1$, 1.5 Hz, 1H), 3.84 (s, 3H), 3.57–3.52 (m, 2H), 3.54 (s, 3H), 3.11–3.00 (m, 2H), 2.41 (s, 3H), 2.05 (dd, $J = 14.4$, 6.8 Hz, 2H), 1.97 (dd, $J = 13.5$, 6.4, 1H), 1.79–1.69 (m, 2H), 1.62–1.51 (m, 1H), 1.55 (d, $J = 1.3$ Hz, 3H), 1.30 (d, $J = 6.8$ Hz, 3H), 1.04 ppm (d, $J = 6.8$ Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta =$ 163.8, 149.2, 147.0, 145.6, 142.9, 133.2, 130.7, 123.4, 115.3, 112.0, 105.0, 101.0, 96.2, 65.7, 61.0, 56.1, 42.7, 36.9, 36.3, 36.0, 31.4, 20.6, 20.3, 16.1, 9.1 ppm; IR (film): $\tilde{\nu} = 3451, 2928, 1606, 1451, 1340, 1219, 1154, 1117, 1090, 1044\ cm^{-1}$; HRMS (ESI): $m/z$: calcd for $C_{25}H_{36}O_5$: 416.2563; found: 416.2565 $[M]^+$.

**6-Methoxy-5-(methoxymethoxy)-7-methyl-2-((2*S*,4*S*,8*S*,*E*)-4,6,8-trimethyldeca-6,9-dien-2-yl)benzofuran (52)**: Alcohol **51** (370 mg, 0.89 mmol, 1.0 equiv) was dissolved in $CH_2Cl_2$ (5 mL), cooled to 0°C and treated with $Et_3N$ (150 µL, 1.06 mmol, 1.2 equiv). After 5 min MsCl (80 µL, 1.06 mmol, 1.2 equiv) was added and stirring was continued for 30 min. The solution was poured onto $H_2O$ (20 mL), extracted with $CH_2Cl_2$ (3× 10 mL), washed with brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude mesylate was immediately redissolved in $Et_2O$ (9 mL). $LiAlH_4$ (4M in $Et_2O$, 670 µL, 2.67 mmol, 3 equiv) was carefully added to the ice cooled solution and the cloudy mixture was allowed to warm to room temperature over 30 min. After 2 h the reaction mixture was quenched at 0°C by slow addition of ethyl acetate, diluted with $Et_2O$ (40 mL) and washed with 1% HCl (10 mL). The aqueous layer was extracted with $Et_2O$ (3×10 mL), and the combined organic fractions were washed with brine (10 mL), dried over $MgSO_4$ and the solvent was removed in vacuo. Purification by flash chromatography (hexane/ethyl acetate 5:1) afforded diolefin **52** as a an oil (310 mg, 89%). $[\alpha]_D^{20} = +3.0$ ($c = 1.35$, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 7.07$ (s, 1H), 6.24 (s, 1H), 5.76 (ddd, $J = 17.2$, 10.4, 6.1 Hz, 1H), 5.21 (s, 2H), 4.99–4.94, m 1H), 4.96 (dt, $J = 17.3$, 1.7 Hz, 1H), 4.88 (dt, $J = 10.4$, 1.6 Hz, 1H), 3.84 (s, 3H), 3.54 (s, 3H), 3.11–2.95 (m, 2H), 2.42 (s, 3H), 2.07 (dd, $J = 13.3$, 5.2 Hz, 1H), 1.79 (dd, $J = 12.6$, 8.1 Hz, 1H), 1.74–1.64 (m, 1H), 1.59–1.44 (m, 2H), 1.57 (d, $J = 1.3$ Hz, 3H), 1.27 (d, $J = 6.8$ Hz, 3H), 1.05 (d, $J = 6.8$ Hz, 3H), 0.83 ppm (d, $J =$ 6.3 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 164.7$, 149.1, 146.8, 145.8, 142.9, 133.3, 130.1, 123.5, 115.3, 111.7, 105.0, 100.4, 96.2, 61.0, 56.1, 48.0, 43.0, 36.3, 31.3, 28.3, 20.6, 19.5, 19.1, 16.1, 9.1 ppm; IR (film): $\tilde{\nu} = 2926, 1684, 1653, 1559, 1507, 1458, 1153, 1117, 1044\ cm^{-1}$; HRMS (ESI): $m/z$: calcd for $C_{25}H_{36}O_4$: 400.2614; found: 400.2607 $[M]^+$.

**2*R*,4*S*,5*R*)-1-((*R*)-4-Benzyl-2-oxooxazolidin-3-yl)-5-hydroxy-2,4-dimethylhept-6-ene-1,3-dione (53)**: A 250 mL Schlenk flask was charged with acid-free $Sn(OTf)_2$ (5.3 g, 12.71 mmol, 1.1 equiv) and $CH_2Cl_2$ (42 mL, 0.3M). The white suspension was treated at −20°C with $Et_3N$ (1.76 mL, 12.71 mmol, 1.1 equiv) whereupon the mixture turned pale yellow. After 5 min β-ketoimide **26** (3.34 g, 11.54 mmol, 1.0 equiv) in $CH_2Cl_2$ (19 mL, 0.6M) was added dropwise and the clear solution was stirred for 1 h at −20°C. Freshly distilled acrolein (2.31 mL, 34.62 mmol, 3 equiv) was dissolved in $CH_2Cl_2$ (35 mL, 1M) and slowly added at −78°C. After 30 min at −78°C, the yellow-orange solution was poured onto a cooled (0°C) and vigorously stirred mixture of $CH_2Cl_2$/1M $NaHSO_4$ 1:1 (150 mL). After 20 min at room temperature the aqueous phase was extracted with $CH_2Cl_2$ (3×50 mL), the organic phase was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$ and concentrated. Purification of the residue by gradient flash chromatography (hexane/ethyl acetate 3:1 → 1:1) yielded **53** as a viscous oil (3.64 g, 91%, d.r. 5:1 as determined by HPLC and $^1$H NMR). $[\alpha]_D^{20} = -115.3$ ($c = 1.6$, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 7.37$–7.27 (m, 3H), 7.23–7.17 (m, 2H), 5.82 (ddd, $J = 16.9$, 10.7, 5.9 Hz, 1H), 5.31 (d, $J = 17.2$ Hz, 1H), 5.20 (d, $J = 10.6$ Hz, 1H), 4.87 (q, $J = 7.2$ Hz, 1H), 4.80–4.72 (m, 1H), 4.49–4.43 (br, 1H), 4.30–4.24 (m, 1H), 4.19 (dd, $J = 9.1$, 3.0 Hz, 1H), 3.30 (dd, $J = 13.5$, 3.2 Hz, 1H), 2.93–2.84 (m, 1H), 2.78 (dd, $J = 13.5$, 9.6 Hz, 1H), 2.46(d, $J = 3.3$ Hz, OH), 1.48 (d, $J = 7.3$ Hz, 3H), 1.24 ppm (d, $J = 7.1$ Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 210.8$, 170.4, 153.3, 137.5, 135.0, 129.3, 129.0, 127.4, 116.3, 72.7, 66.5, 55.3, 52.0, 48.9, 38.0, 12.8, 10.9 ppm; IR (film): $\tilde{\nu} = 3629, 3510, 2984, 1773, 1684, 1653, 1559, 1456, 1362, 1214,$

1121 $cm^{-1}$; HRMS (ESI): *m/z*: calcd for $C_{19}H_{23}O_5NNa$: 368.1473; found: 368.1477 $[M+Na]^+$.

**(3*R*,4*S*,5*R*,6*R*)-4-Hydroxy-3,5-dimethyl-6-vinyltetrahydro-2*H*-pyran-2-one (54)**: $Me_4NBH(OAc)_3$ (2.85 g, 10.85 mmol, 5 equiv) was dissolved in MeCN/AcOH 1.9:1 (360 mL), cooled to −32 °C and aldol product **53** (750 mg, 2.17 mmol, 1.0 equiv) in MeCN (6 mL) was added dropwise. The reaction was stirred for 3 h at −32 °C, allowed to warm to 0 °C overnight, diluted with $CH_2Cl_2$ (100 mL) and quenched by the addition of saturated aqueous Rochelle's salt (150 mL). Saturated aqueous $NaHCO_3$ was carefully added to the vigorously stirred solution over 20 min. After 1 h no more gas evolution was observed and the two-phase mixture was partitioned between $CH_2Cl_2$ (400 mL) and $H_2O$ (100 mL). The aqueous layer was extracted with $CH_2Cl_2$ (3×100 mL), and the combined organic fractions were dried over $MgSO_4$, filtered and concentrated in vacuo. Purification of the residue by flash chromatography (hexane/ethyl acetate 3:1) afforded the diol as a viscous oil (527 mg, 70 %, d.r. ≥ 6:1 as determined by $^1$H NMR). $[\alpha]_D^{20}$ = −30.5 (*c* = 0.80, $CH_2Cl_2$); $^1$H NMR (600 MHz, $CDCl_3$): δ = 7.36–7.31 (m, 2H), 7.30–7.27 (m, 1H), 7.22–7.18 (m, 2H), 5.97 (ddd, *J* = 16.9, 10.9, 5.8 Hz, 1H), 5.32 (d, *J* = 17.4 Hz, 1H), 5.21 (d, *J* = 10.6 Hz, 1H), 4.73–4.68 (m, 1H), 4.34–4.30 (br, 1H), 4.27–4.22 (m, 1H), 4.20 (dd, *J* = 8.7, 2.6 Hz, 1H), 3.98 (d, *J* = 9.8 Hz, 1H), 3.84 (dq, *J* = 7.1, 1.9 Hz, 1H), 3.80–3.76 (br, OH), 3.41–3.34 (br, OH), 3.24 (dd, *J* = 13.5, 3.4 Hz, 1H), 2.80 (dd, *J* = 13.5, 9.3 Hz, 1H), 2.03–1.96 (m, 1H), 1.28 (d, *J* = 7.2 Hz, 3H), 0.84 ppm (d, *J* = 7.2 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): δ = 178.0, 152.8, 137.9, 134.9, 129.4, 129.0, 127.5, 115.7, 75.7, 73.4, 66.2, 55.0, 39.3, 39.2, 37.8, 12.1, 9.7 ppm; IR (film): $\tilde{\nu}$ = 3448, 2976, 1780, 1700, 1559, 1456, 1388, 1211 $cm^{-1}$; HRMS (ESI): *m/z*: calcd for $C_{19}H_{25}O_5NNa$: 370.1630; found: 370.1644 $[M+Na]^+$.

A solution of the diol (1.98 g, 5.71 mmol, 1.0 equiv) in THF/$H_2O$ 3:1 (80 mL) was treated at 0 °C with $H_2O_2$ (30 % in $H_2O$, 2.3 mL). LiOH (383 mg, 9.14 mmol, 1.6 equiv) was added and stirring was continued for 1 h at ambient temperature. The reaction was acidified by the addition of 1 N HCl (20 mL) and stirred for further 5 min. The biphasic mixture was diluted with $H_2O$ (100 mL), extracted with $Et_2O$ (3×70 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (hexane/ethyl acetate 3:1 → 1:1) gave lactone **54** (700 mg, 72 %). $[\alpha]_D^{20}$ = +103.8 (*c* = 0.60, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): δ = 5.85 (ddd, *J* = 17.2, 11.0, 5.7 Hz, 1H), 5.40 (d, *J* = 17.2 Hz, 1H), 5.3 (d, *J* = 10.6 Hz, 1H), 4.80–4.74 (m, 1H), 3.88 (dd, *J* = 9.6, 4.0 Hz, 1H), 2.57–2.48 (m, 1H), 2.27–2.19 (m, 1H), 2.09–2.01 (br, OH), 1.41 (d, *J* = 7.1 Hz, 3H), 0.97 ppm (d, *J* = 7.1 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 173.2, 133.6, 117.4, 79.9, 73.7, 60.4, 40.1, 37.9, 21.0, 14.4, 14.2, 5.5 ppm; IR (film): $\tilde{\nu}$ = 3446, 2977, 1718, 1700, 1653, 1559, 1507, 1458, 1213, 1094 $cm^{-1}$; HRMS (ESI): *m/z*: calcd for $C_9H_{12}O_2$: 152.0837; found: 152.0844 $[M-H_2O]^+$.

**(*R*)-Methyl 2-((4*S*,5*S*,6*R*)-2,2,5-trimethyl-6-vinyl-1,3-dioxan-4-yl)propanoate (55)**: Lactone **54** (700 mg, 4.11 mmol, 1.0 equiv) was dissolved in 2,2-dimethoxypropane (40 mL), treated with camphorsulfonic acid (96 mg, 0.41 mmol, 0.1 equiv) and stirred overnight at room temperature. The solution was diluted with $Et_2O$ (100 mL), neutralized with saturated aqueous $NaHCO_3$ (50 mL), extracted with $Et_2O$ (3×50 mL), washed with brine (70 mL) and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by flash chromatography (hexane/ethyl acetate 10:1) to yield ester **55** (903 mg, 91 %). $[\alpha]_D^{20}$ = −20.3 (*c* = 1.05, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): δ = 5.79 (ddd, *J* = 17.1, 10.7, 6.1 Hz, 1H), 5.25 (dt, *J* = 17.3, 1.7 Hz, 1H), 5.16 (dt, *J* = 10.5, 1.6 Hz, 1H), 4.39–4.35 (m, 1H), 3.71–3.66 (m, 1H), 3.69 (s, 3H), 2.59 (dq, *J* = 6.99, 4.99 Hz, 1H), 2.00–1.90 (m, 1H), 1.34 (s, 3H), 1.33 (s, 3H), 1.21 (d, *J* = 7.1 Hz, 3H), 0.83 ppm (d, *J* = 7.1 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 174.8, 134.7, 115.7, 100.7, 75.1, 70.8, 51.7, 42.9, 37.4, 25.2, 23.7, 12.8, 11.4 ppm; IR (film): $\tilde{\nu}$ = 2988, 1740, 1700, 1653, 1559, 1458, 1301, 1226, 1176, 1025, 1001 $cm^{-1}$; HRMS (ESI): *m/z*: calcd for $C_{12}H_{19}O_4$: 227.1283; found: 227.1289 $[M-Me]^+$.

**(*R*)-2-((4*S*,5*S*,6*R*)-2,2,5-Trimethyl-6-vinyl-1,3-dioxan-4-yl)propanal (46)**: Ester **55** (900 mg, 3.71 mmol, 1.0 equiv) in $Et_2O$ (40 mL) was cooled to 0 °C and $LiAlH_4$ (4 M in $Et_2O$, 1.49 mL, 5.57 mmol, 1.5 equiv) was carefully added via cannula. After 30 min at 0 °C TLC analysis showed complete consumption of the starting material and the reaction mixture was quenched by slow addition of ethyl acetate, diluted with $Et_2O$ (80 mL) and washed with 1 % HCl (100 mL). The aqueous layer was extracted with $Et_2O$ (3×50 mL), and the combined organic fractions were washed with brine (50 mL), dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography (hexane/ethyl acetate 3:1) afforded the alcohol as a colorless oil (761 mg, 96 %). $[\alpha]_D^{20}$ = +11.8 (*c* = 0.80, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): δ = 5.80 (ddd, *J* = 17.1, 10.1, 6.2 Hz, 1H), 5.26(dt, *J* = 17.3, 1.6 Hz, 1H), 5.16 (dt, *J* = 10.8, 1.6 Hz, 1H), 4.39–4.34 (m, 1H), 3.70–3.65 (m, 2H), 3.57 (dd, *J* = 8.1, 2.7 Hz, 1H), 2.36 (t, *J* = 5.4 Hz, OH), 2.01–1.92 (m, 1H), 1.90–1.81 (m, 1H), 1.38 (s, 3H), 1.35 (s, 3H), 0.99 (d, *J* = 7.0 Hz, 3H), 0.83 ppm (d, *J* = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 135.7, 115.7, 100.6, 76.8, 71.1, 67.1, 37.2, 36.5, 25.4, 23.8, 13.0, 10.6 ppm; IR (film): $\tilde{\nu}$ = 3423, 2987, 1684, 1653, 1559, 1507, 1457, 1380, 1226, 1180, 1027 $cm^{-1}$; HRMS (ESI): *m/z*: calcd for $C_{11}H_{19}O_3$: 199.1334; found: 199.1332 $[M-Me]^+$.

A solution of the above prepared alcohol (23 mg, 0.107 mmol, 1.0 equiv) in $CH_2Cl_2$ (0.5 mL, 0.2 M) was cooled to −5 °C. $Et_3N$ (45 μL, 0.321 mmol, 3 equiv) and subsequently $SO_3$·Pyr (51 mg, 0.321 mmol, 3 equiv) in DMSO (0.5 mL, 0.6 M) were added dropwise. The mixture was stirred for 1.5 h at −5 °C and quenched with aqueous 1 M $KHSO_4$ solution (0.5 mL). The phases were partitioned between brine and $Et_2O$ (1:1, 40 mL) and the aqueous layer was extracted with $Et_2O$ (3×10 mL). The combined organic fractions were concentrated to 5 mL under reduced pressure, filtered over a plug of silica and excess solvent was removed in vacuo to afford aldehyde **46** (23 mg, 99 %). $[\alpha]_D^{20}$ = −39.0 (*c* = 0.70, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): δ = 9.71 (d, *J* = 1.0 Hz, 1H), 5.80 (ddd, *J* = 17.1, 10.7, 6.2 Hz, 1H), 5.27(dt, *J* = 17.3, 1.7 Hz, 1H), 5.18 (dt, *J* = 10.6, 1.6 Hz, 1H), 4.40–4.35 (m, 1H), 3.84 (dd, *J* = 8.1, 3.3 Hz, 1H), 2.44 (ddq, *J* = 7.0, 3.2, 0.9 Hz, 1H), 2.04–1.94 (m, 1H), 1.36 (s, 3H), 1.33 (s, 3H), 1.17 (d, *J* = 7.0 Hz, 3H), 0.87 ppm (d, *J* = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 204.2, 135.4, 115.9, 100.8, 73.2, 70.9, 48.6, 36.7, 25.1, 23.8, 12.7, 7.8 ppm; IR (film): $\tilde{\nu}$ = 2986, 1734, 1684, 1653, 1559, 1507, 1458, 1380, 1225 $cm^{-1}$; HRMS (ESI): *m/z*: calcd for $C_{11}H_{17}O_3$: 197.1178; found: 197.1171 $[M-Me]^+$.

**(*S*)-1-(6-Methoxy-5-(methoxymethoxy)-7-methyl-2-((2*S*,4*S*,8*S*,*E*)-4,6,8-trimethyldeca-6,9-dien-2-yl)benzofuran-4-yl)-2-((4*R*,5*S*,6*R*)-2,2,5-trimethyl-6-vinyl-1,3-dioxan-4-yl)propan-1-ol (9a,b)**: To a solution of benzofuran 52 (100 mg, 0.250 mmol, 1.4 equiv) in THF (0.6 mL) freshly distilled TMEDA (80 μL, 0.535 mmol, 3 equiv) was added at ambient temperature. The solution was cooled to −78 °C and *n*BuLi (156 μL, 0.250 mmol, 1.4 equiv) was added dropwise. After 1.5 h at −30 °C the orange solution was recooled to −78 °C and aldehyde 46 (38 mg, 0.178 mmol, 1.0 equiv) in THF (0.5 mL) was added via cannula. The reaction mixture was warmed to −25 °C over 2 h, diluted with $Et_2O$ (40 mL) and finally quenched with saturated aqueous $NH_4Cl$ solution (10 mL). The reaction mixture was extracted with diethyl ether (3×10 mL), dried over $MgSO_4$ and the solvent was removed in vacuo. The residue was purified by column chromatography (hexane/ethyl acetate 20:1 → 5:1) to furnish alcohols **9a** and **9b** (97 mg, 90 %, d.r. 4:1 as determined by $^1$H NMR). Separation of the diastereomers for analytical purpose was done by HPLC, yielding diastereomer **9a** and **9b** as light orange, viscous oils. **9a**: $[\alpha]_D^{20}$ = −3.9 (*c* = 0.95, $CH_2Cl_2$); $^1$H NMR (600 MHz, $CDCl_3$): δ = 6.63 (s, 1H), 5.79–5.72 (m, 2H), 5.21 (dt, *J* = 17.0, 1.7 Hz, 1H), 5.17 (dd, *J* = 6.0, 4.9 Hz, 1H), 5.13 (dt, *J* = 10.6, 1.7 Hz, 1H), 5.10 (d, *J* = 5.7 Hz, 1H), 5.09 (d, *J* = 5.7 Hz, 1H), 4.98–4.95 (m, 1H), 4.95 (dt, *J* = 17.4, 1.7 Hz, 1H), 4.88 (dt, *J* = 10.2, 1.5 Hz, 1H), 4.33 (t, *J* = 5.7 Hz, 1H), 3.77 (s, 3H), 3.56 (s, 3H), 3.44 (d, *J* = 4.5 Hz, OH), 3.32 (d, *J* = 8.5, 1.3 Hz, 1H), 3.09–3.03 (m, 1H), 3.03–2.96 (m, 1H), 2.39 (s, 3H), 2.35–2.29 (m, 1H), 2.09 (dd, *J* = 12.8, 5.7 Hz, 1H), 1.98–1.91 (m, 1H), 1.78 (dd, *J* = 13.2, 7.9 Hz, 1H), 1.72–1.65 (m, 1H), 1.61–1.54 (m, 1H), 1.58 (d, *J* = 1.1 Hz, 3H), 1.50–1.44 (m, 1H), 1.33 (s, 3H), 1.26 (d, *J* = 6.8 Hz, 3H), 1.13 (d, *J* = 6.8 Hz, 3H), 1.11 (s, 3H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.4 Hz, 3H), 0.72 ppm (d, *J* = 6.8 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): δ = 164.0, 150.1, 147.0, 144.0, 143.3, 135.8, 133.3, 130.1, 125.1, 123.0, 115.5, 114.2, 111.7, 101.3, 100.5, 99.9, 76.8, 74.2, 71.7, 60.6, 57.4, 47.9, 43.0, 40.7, 37.1, 36.3, 31.2, 28.3, 25.3, 23.7, 20.6, 19.5, 19.1, 16.0, 12.4, 9.1, 8.8 ppm; IR (film): $\tilde{\nu}$ = 3497, 2965, 2930, 1844, 1636, 1458, 1381, 1224, 1159, 1116, 1054 $cm^{-1}$; HRMS (ESI): *m/z*: calcd for $C_{37}H_{56}O_7Na$: 635.3924; found: 635.3919 $[M+Na]^+$. **9b**: $[\alpha]_D^{20}$ = −13.1 (*c* = 0.90, $CH_2Cl_2$); $^1$H NMR (600 MHz, $CDCl_3$): δ = 6.51-

(s, 1H), 5.85 (ddd, $J$=17.1, 10.7, 6.3 Hz, 1H), 5.76 (ddd, $J$=17.2, 10.4, 6.0 Hz, 1H), 5.27 (dt, $J$=17.4, 1.7 Hz, 1H), 5.17 (dd, $J$=10.8, 1.6 Hz, 1H), 5.13–5.08 (m, 3H), 4.98–4.95 (m, 1H), 4.96 (dt, $J$=17.4, 1.7 Hz, 1H), 4.88 (dt, $J$=10.2, 1.7 Hz, 1H), 4.40 (t, $J$=5.5 Hz, 1H), 3.97 (dd, $J$=7.9, 1.5 Hz, 1H), 3.79 (s, 3H), 3.60 (s, 3H), 3.24–3.10 (br, OH), 3.10–3.03 (m, 1H), 3.03–2.97 (m, 1H), 2.40 (s, 3H), 2.35–2.29 (m, 1H), 2.07 (dd, $J$=13.0, 5.9 Hz, 1H), 2.03–1.97 (m, 1H), 1.79 (dd, $J$=12.8, 8.3 Hz, 1H), 1.73–1.67 (m, 1H), 1.58–1.54 (m, 1H), 1.57 (d, $J$=1.5 Hz, 3H), 1.53–1.49 (m, 1H), 1.44 (s, 3H), 1.39 (s, 3H), 1.28 (d, $J$=6.8 Hz, 3H), 1.05 (d, $J$=6.8 Hz, 3H), 0.87 (d, $J$=6.8 Hz, 3H), 0.84 (d, $J$=6.4 Hz, 3H), 0.72 ppm (d, $J$=6.8 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$=164.2, 150.1, 147.5, 144.4, 143.3, 136.1, 133.3, 130.1, 125.5, 123.0, 115.6, 114.4, 111.7, 100.6, 100.4, 100.2, 73.5, 71.4, 70.7, 60.7, 57.7, 48.0, 42.8, 41.0, 36.8, 36.3, 31.2, 28.2, 25.6, 24.1, 20.6, 19.4, 18.9, 16.0, 12.9, 10.7, 9.1 ppm; IR (film): $\tilde{\nu}$ = 3469, 2965, 2930, 1457, 1380, 1340, 1226, 1160, 1116, 1023 cm$^{-1}$; HRMS (ESI): $m/z$: calcd for $C_{37}H_{56}O_7Na$: 635.3924; found: 635.3915 $[M+Na]^+$.

**Macrocycle 56**: Compound **9a** (80 mg, 0.131 mmol, 1.0 equiv) was dissolved in degassed $CH_2Cl_2$ (130 mL) and heated to reflux. Grubbs' II catalyst (22 mg, 0.026 mmol, 0.2 equiv) in degassed $CH_2Cl_2$ (15 mL) was added via syringe pump within 16 h. After completion of the addition the mixture was stirred for another 30 min. The temperature was lowered to room temperature and air was bubbled through the solution to destroy excess catalyst. The solvent was evaporated and purification by column chromatography (hexane/ethyl acetate 10:1 → 5:1) afforded macrocycle **56** (47 mg, 62%, rotamers) as a white foam. $[\alpha]_D^{20}$ = +53.9 ($c$ = 1.20, $CH_2Cl_2$); $^1$H NMR (600 MHz, $CDCl_3$): $\delta$=6.42 (s, 1H), 5.78 (dd, $J$=15.5, 4.2 Hz, 1H), 5.31 (dd, $J$=15.5, 9.1 Hz, 1H), 5.10 (dd, $J$=9.3, 4.7 Hz, 1H), 5.09 (d, $J$=5.7 Hz, 1H), 5.03–4.95 (br, 1H), 4.82 (d, $J$=8.7 Hz, 1H), 4.16 (dd, $J$=8.7, 6.0 Hz, 1H), 3.78 (s, 3H), 3.58 (s, 3H), 3.54 (dd, $J$=9.6, 3.6 Hz, 1H), 3.11–3.04 (m, 1H), 3.04–2.98 (m, 1H), 2.46–2.37 (m, 1H), 2.42 (s, 3H), 2.21 (d, $J$=14.7 Hz, 1H), 2.11–2.03 (br, 1H), 2.02–1.92 (br, 1H), 1.72–1.58 (br, 2H), 1.51 (s, 3H), 1.48–1.41 (m, 1H), 1.29–1.18 (m, 12H), 1.01–0.95 (m, 6H), 0.72–0.53 ppm (br, 3H); $^1$H NMR (400 MHz, $C_7D_8$, 350 K): $\delta$=6.44 (s, 1H), 5.65 (ddd, $J$=15.5, 4.9 Hz, 1H), 5.44 (ddd, $J$=15.5, 8.2, 1.7 Hz, 1H), 5.32 (d, $J$=8.2 Hz, 1H), 5.03 (d, $J$=5.6 Hz, 1H), 4.99 (d, $J$=5.6 Hz, 1H), 4.88 (d, $J$=8.8 Hz, 1H), 4.23 (dd, $J$=8.0, 6.1 Hz, 1H), 3.69 (dd, $J$=8.8, 4.5 Hz, 1H), 3.66 (s, 3H), 3.33 (s, 3H), 2.99–2.89 (m, 2H), 2.72–2.63 (br, OH), 2.59–2.49 (m, 1H), 2.40 (s, 3H), 2.16–2.07 (m, 2H), 1.94 (ddd, $J$=13.7, 8.9, 5.4 Hz, 1H), 1.80–1.70 (m, 1H), 1.70–1.60 (m, 1H), 1.52–1.41 (m, 1H), 1.50 (s, 3H), 1.47 (d, $J$=6.6 Hz, 3H), 1.34 (s, 3H), 1.26 (d, $J$=6.9 Hz, 3H), 0.99 (d, $J$=6.4 Hz, 3H), 0.94 (d, $J$=6.8 Hz, 3H), 0.90 (s, 3H), 0.70 ppm (d, $J$=7.0 Hz, 3H); $^{13}$C NMR (100 MHz, $C_7D_8$, 350 K): $\delta$=163.6, 149.0, 146.6, 139.5, 137.9, 133.4, 128.6, 127.9, 127.2, 122.8, 114.9, 102.5, 100.9, 99.1, 75.2, 71.9, 60.6, 57.5, 45.4, 43.4, 40.4, 35.4, 34.8, 32.6, 30.0, 29.2, 26.1, 21.4, 21.2, 21.0, 19.3, 17.0, 13.2, 11.8, 9.5 ppm; IR (film): $\tilde{\nu}$ = 3440, 2960, 1683, 1652, 1557, 1455, 1378, 1163, 1113 cm$^{-1}$; HRMS (ESI): $m/z$: calcd for $C_{35}H_{52}O_7Na$: 607.3612; found: 607.3616 $[M+Na]^+$.

**4-((2*R*,3*R*,4*S*,5*R*,6*R*)-4-Hydroxy-3,5-dimethyl-6-vinyltetrahydro-2*H*-pyran-2-yl)-6-methoxy-7-methyl-2-((2*S*,4*S*,8*S*,*E*)-4,6,8-trimethyldeca-6,9-dien-2-yl)benzofuran-5-ol (59)**: A mixture of **9a,b** (200 mg, 0.326 mmol) was dissolved in MeOH (7 mL) and treated with 3 drops of 3 N HCl. The reaction mixture was stirred at room temperature overnight, diluted with $H_2O$ (50 mL) and extracted with $CH_2Cl_2$ (4×20 mL). The organic extracts were dried over $MgSO_4$, concentrated in vacuo and purified by flash chromatography (hexane/ethyl acetate 5:1 → 3:1) to afford tetrahydropyran **59** (120 mg, 72%, 1.5:1 rotamers) as a white foam. $[\alpha]_D^{20}$ = +87.2 ($c$ = 1.75, $CH_2Cl_2$); $^1$H NMR (rotamers, 600 MHz, $CDCl_3$): $\delta$= 7.67 (br, 0.5OH)+5.60 (br, 0.5OH), 6.55(br, 0.5H)+6.18(br, 0.5H), 5.88–5.79 (m, 1H), 5.76 (ddd, $J$=17.4, 10.2, 6.0 Hz, 1H), 5.27 (d, $J$=16.6 Hz, 1H), 5.17 (br, 1H), 4.98–4.93 (m, 2H), 4.90–4.87 (m, 1H), 4.75 (br, 0.5H)+4.49 (br, 0.5H), 4.23 (dd, $J$=4.0, 1.7 Hz, 1H), 3.84 (br, 3H), 3.70 (br, 1H), 3.10–3.02 (m, 1H), 3.02–2.96 (m, 1H), 2.42 (s, 3H), 2.25–1.95 (br, 1H), 2.16–2.11 (br, 1H), 2.08 (dd, $J$=13.0, 5.5 Hz, 1H), 1.78 (dd, $J$=12.3, 8.5 Hz, 1H), 1.73–1.65 (m, 1H+OH), 1.63–1.55 (m, 1H), 1.57 (s, 3H), 1.51–1.45 (m, 1H), 1.27 (d, $J$=6.8 Hz, 3H), 1.09 (br, 3H), 1.05 (d, $J$=6.8 Hz, 3H), 0.83 (d, $J$=6.4 Hz, 3H), 0.82 ppm (d, $J$=6.4 Hz, 3H); $^{13}$C NMR (The asterisk denotes signals not apparent in the $^{13}$C-spectrum, 150 MHz, $CDCl_3$): $\delta$=163.7, 146.9*, 143.3, 136.4*, 133.3, 130.1, 115.2*, 114.3*, 111.7, 98.9*, 82.8*, 80.2*,76.8*, 61.3*, 48.1*, 47.9, 42.9, 39.1, 37.7*, 36.3, 31.3, 28.3, 20.6, 19.5, 19.2, 16.0, 13.6*, 9.2, 6.6* ppm; IR (film): $\tilde{\nu}$ = 3391, 2964, 2927, 1636, 1604, 1455, 1405, 1384, 1284, 1114, 1048 cm$^{-1}$; HRMS (ESI): $m/z$: calcd for $C_{32}H_{46}O_5$: 510.3345; found: 510.3331 $[M]^+$.

**Diolefin 60**: Compound **59** (50 mg, 0.098 mmol, 1.0 equiv) was dissolved in degassed $CH_2Cl_2$ (100 mL) and heated to reflux (45 °C outside temperature). Grubbs' II catalyst (16.6 mg, 0.020 mmol, 0.2 equiv) in degassed $CH_2Cl_2$ (13 mL) was added via syringe pump within 16 h. After completion of the addition the mixture was stirred for another 30 min. The temperature was lowered to room temperature and air was bubbled through the solution to destroy excess catalyst. The solvent was evaporated and purification by column chromatography (hexane/ethyl acetate 5:1 → 3:1) afforded macrocycle **60** (39 mg, 83%, $E$/$Z$ 15:1). The mixture was used in the next step without further purification. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=6.66 (s, 1H), 5.59 (ddd, $J$=15.6, 8.7, 2.0 Hz, 1H), 5.54 (s, OH), 5.33 (dd, $J$=15.5, 2.1 Hz, 1H), 4.92 (d, $J$=9.1 Hz, 1H), 4.74 (d, $J$=10.1 Hz, 1H), 4.27 (dd, $J$=4.4, 2.1 Hz, 1H), 3.81 (s, 3H), 3.76–3.69 (m, 1H), 3.17–3.04 (m, 1H), 3.04–2.93 (m, 1H), 2.44 (s, 3H), 2.12–2.04 (m, 1H), 1.95 (dd, $J$=12.8, 4.9 Hz, 2H), 1.87–1.79 (m, 1H), 1.79–1.71 (m, 1H), 1.69 (s, 3H), 1.66–1.45 (m, 2H), 1.55 (br, OH), 1.33 (d, $J$=7.1 Hz, 3H), 1.04 (d, $J$=7.1 Hz, 3H), 1.00 (d, $J$=6.8 Hz, 3H), 0.97 (d, $J$=6.8 Hz, 3H), 0.95 ppm (d, $J$=6.8 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=162.0, 148.3, 141.8, 136.8, 133.0, 130.2, 125.2, 122.4, 115.5, 112.9, 104.6, 76.7, 75.7, 61.4, 44.4, 43.4, 38.9, 38.4, 35.8, 31.0, 28.8, 22.1, 21.3, 19.2, 18.1, 12.8, 9.4, 7.0 ppm; IR (film): $\tilde{\nu}$ = 3450, 2967, 1683, 1653, 1456, 1404, 1380, 1321, 1109 cm$^{-1}$; HRMS (ESI): $m/z$: calcd for $C_{30}H_{42}O_5$: 482.3032; found: 482.3023 $[M]^+$.

**Tetrahydropyran 5**: To a vigorously stirred refluxing solution of **60** (37 mg, 0.076 mmol, 1.0 equiv) and AcOH (11 μL, 0.192 mmol, 2.5 equiv) in $CH_2Cl_2$ (7 mL) was added dipotassium azodicarboxylate (89 mg, 0.460 mmol, 6 equiv) over a period of 6 h. The mixture was cooled to room temperature, filtered over Celite and concentrated in vacuo. The crude product was purified by HPLC (hexane/ethyl acetate 4:1) to give **5** as a white foam (28 mg, 76%). All analytical data matched with those reported by Lee[6a] and Rychnovsky.[7] $[\alpha]_D^{20}$ = +19.4 ($c$ = 0.17, $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$): $\delta$=6.55 (s, 1H), 5.53 (s, 1H), 4.60 (d, $J$=9.5 Hz, 1H), 4.54 (d, $J$=10.2 Hz, 1H), 3.83 (s, 3H), 3.67–3.62 (m, 1H), 3.44 (ddd, $J$=11.0, 2.3, 1.1 Hz, 1H), 3.11–3.04 (m, 1H), 2.47–2.41 (m, 1H), 2.45 (s, 3H), 2.26–2.19 (m, 1H), 1.93–1.88 (m, 1H), 1.84–1.77 (m, 1H), 1.62 (s, 3H), 1.61–1.54 (m, 1H), 1.53–1.49 (br, OH), 1.48–1.41 (m, 2H), 1.38 (d, $J$=6.8 Hz, 3H), 1.35–1.18 (m, 5H), 1.04 (d, $J$=7.0 Hz, 3H), 0.90 (d, $J$=6.6 Hz, 3H), 0.81 ppm (d, $J$=6.4 Hz, 3H), 0.76 (d, $J$=6.4 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$=159.7, 148.2, 141.6, 141.5, 131.5, 129.0, 122.1, 115.7, 112.5, 104.7, 77.8, 77.3 (2×CH), 61.4, 43.8, 41.8, 39.6, 38.6, 33.7, 32.5, 31.5, 31.1, 27.5, 21.8, 21.0, 19.6, 18.7, 12.8, 9.4, 6.6 ppm; IR (film): $\tilde{\nu}$= 3463, 2924, 2854, 1457, 1375, 1325, 1109, 1001 cm$^{-1}$; HRMS (ESI): $m/z$: calcd for $C_{30}H_{44}O_5Na$: 507.3086; found: 507.3082 $[M+Na]^+$.

***O*-quinone 71**: Macrocycle **5** (6 mg, 0.012 mmol, 1 equiv) was dissolved in $CH_2Cl_2/H_2O$ 10:1 (1 mL) and treated with DDQ (4.2 mg, 0.019 mmol, 1.5 equiv) at room temperature. The color of the solution turned dark purple within 15 min, whereas TLC analysis showed complete consumption of the starting material. The mixture was directly loaded onto a silica column and eluted (hexane/ethyl acetate 3:1 → 2:1), to collect purple-blue fractions. The solvent was carefully evaporated to afford labile *o*-quinone **71** (3 mg, 52%) as a violet-blue compound. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=6.11 (s, 1H), 4.72 (d, $J$=9.8 Hz, 1H), 4.17 (d, $J$=10.0 Hz, 1H), 3.55–3.48 (m, 1H), 3.32–3.26 (m, 1H), 2.97–2.87 (m, 1H), 2.34–2.27 (m, 1H), 2.27–2.21 (m, 1H), 1.90 (s, 3H), 1.88–1.80 (m, 1H), 1.81–1.73 (m, 1H), 1.68–1.54 (m, 3H), 1.62 (s, 3H), 1.47–1.37 (m, 1H), 1.44–1.31 (m, 1H), 1.36–1.24 (m, 2H), 1.19–1.09 (m, 1H), 1.25 (d, $J$=6.8 Hz, 3H), 0.91 (d, $J$=6.1 Hz, 3H), 0.90 (d, $J$=6.8 Hz, 3H), 0.89 (d, $J$=6.5 Hz, 3H), 0.80 ppm (d, $J$=6.5 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=177.2, 173.7, 164.3, 147.4, 131.3, 129.1, 125.4, 113.7, 105.3, 78.3, 76.4, 75.8, 42.1, 41.7, 39.4, 38.2, 33.8, 32.5, 32.1, 29.7, 27.7, 21.8, 21.0, 19.6, 17.9, 17.0, 13.0, 8.2, 6.4 ppm; IR (film): $\tilde{\nu}$ = 3625, 2924, 2359, 17.32, 1699, 1652, 1584, 1455, 1377, 1326, 1094 cm$^{-1}$; HRMS (ESI): $m/z$: calcd for $C_{31}H_{43}O_5NNa$: 532.3039; found: 532.3058 $[M+MeCN+Na]^+$.

**Kendomycin (1)**: *O*-quinone **71** (2 mg, 0.0043 mmol) was dissolved in MeCN (2 mL) and treated with one drop of 1 % HCl. The initial blue solution turned yellow within 15 min and the reaction mixture was partitioned between etyhlacetate (50 mL) and brine (15 mL). The aqueous phase was extracted with ethyl acetate (3×10 mL), the organic layer was dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (hexane/ethyl acetate 3:1 → 2:1) gave kendomycin **1** (1 mg, 50 %) as a yellow solid. M.p. 226–227 °C (authentic sample: 235–236 °C); $[\alpha]_D^{20} = -76.4$ ($c = 0.11$, MeOH), (lit. $[\alpha]_D^{20} = -80$ ($c = 2.71$, MeOH),[2] $[\alpha]_D^{20} = -79.3$ ($c = 0.135$, MeOH),[2b–d] $[\alpha]_D^{20} = -82.4$ ($c = 0.514$, MeOH)[2a]), $^1$H NMR (600 MHz, $CD_3COCD_3$): $\delta = 8.10$ (s, 1H), 7.19 (s, 1H), 6.54 (s, 1H), 4.64 (d, $J = 10.0$ Hz, 1H), 4.36 (d, $J = 10.3$ Hz, 1H), 3.95 (d, $J = 4.5$ Hz, 1H), 3.56 (m, 1H), 3.53 (ddd, $J = 11.0$, 2.3, 1.1 Hz, 1H), 2.42 (m, 1H), 2.36 (m, 1H), 2.12 (br d, $J = 17.0$ Hz, 1H), 1.96 (m, 1H), 1.88 (m, 1H), 1.84 (s, 3H), 1.71 (m, 1H), 1.67 (m, 1H), 1.64 (m, 1H), 1.61 (s, 3H), 1.57 (m, 1H (10-H$^a$)[34]), 1.45 (ddd, $J = 12.9$, 11.4, 2.9 Hz, 1H), 1.33 (m, 2H (11-$H_2$)), 1.25 (m, 10-H$^b$), 0.95 (d, $J = 7.0$ Hz, 3H), 0.94 (d, $J = 6.5$ Hz, 3H), 0.89 (d, $J = 6.5$ Hz, 3H), 0.87 (d, $J = 6.5$ Hz, 3H), 0.71 ppm (d, $J = 7.0$ Hz, 3H); $^{13}$C NMR (150 MHz, $CD_3COCD_3$): $\delta = 182.1$, 168.6, 146.8, 141.3, 132.1, 130.2, 129,9, 119.1, 111.0, 104.2, 78.7, 77.8, 76.2, 46.1, 41.4, 40.8, 39.8, 38.1, 35.9, 33.6, 33.5, 26.5, 22.7, 19.9, 19.7, 13.3, 12.7, 7.6, 7.2 ppm; IR (film): $\tilde{\nu} = 3322$, 2926, 1670, 1614, 1585, 1329, 1098 cm$^{-1}$; HRMS (ESI): *m*/*z*: calcd for $C_{29}H_{42}O_6$: 486.2981; found: 486.2975 $[M]^+$.

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[1] a) Y. Funahashi, N. Kawamura, T. Ishimaru, JP Patent 08231551A2960910, **1996** [*Chem. Abstr.* **1997**, *126*, 6553]; b) Y. Funahashi, N. Kawamura, JP Patent 08231552A2960910, **1996** [*Chem. Abstr.* **1996**, *125*, 326518]; c) M. H. Su, M. I. Hosken, B. J. Hotovec, T. L. Johnston, US Patent 5728727A980317, **1998** [*Chem. Abstr.* **1998**, *128*, 239489].

[2] a) H. B. Bode, A. Zeeck, *J. Chem. Soc. Perkin Trans. 1* **2000**, 323; b) H. B. Bode, A. Zeeck, *J. Chem. Soc. Perkin Trans. 1* **2000**, 2665.

[3] a) Y. A. Elnakady, M. Rohde, F. Sasse, C. Backes, A. Keller, H.-P. Lenhof, K. J. Weissman, R. Müller, *ChemBioChem* **2007**, *8*, 1261; b) C. O. Janssen, S. Lim, E. P. Lo, K. F. Wan, V. C. Yu, M. A. Lee, S. B. Ng, M. J. Everett, A. D. Buss, D. P. Lane, R. S. Boyce, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5771.

[4] S. C. Wenzel, H. B. Bode, I. Kochems, R. Mueller, *ChemBioChem* **2008**, *9*, 2711.

[5] a) M. P. Green, S. Pichlmair, M. M. B. Marques, H. J. Martin, O. Diwald, T. Berger, J. Mulzer, *Org. Lett.* **2004**, *6*, 3131; b) M. M. B. Marques, S. Pichlmair, H. J. Martin, J. Mulzer, *Synthesis* **2002**, 2766; c) H. J. Martin, M. Drescher, H. Kählig, S. Schneider, J. Mulzer. *Angew. Chem.* **2001**, *113, 3287; Angew. Chem. Int. Ed.* **2001**, 40, 3186; *Angew. Chem. Int. Ed.* **2001**, *40*, 3186.

[6] a) Y. Yu, H. Men, C. Lee, *J. Am. Chem. Soc.* **2004**, *126*, 14720; b) A. B. Smith III, E. F. Mesaros, E. Meyer, *J. Am. Chem. Soc.* **2006**, *128*, 5292; c) A. B. Smith III, E. F. Mesaros, E. Meyer, *J. Am. Chem. Soc.* **2005**, *127*, 6948; d) J. T. Lowe, J. S. Panek, *Org. Lett.* **2008**, *10*, 3813; e) T. Magauer, H. J. Martin, J. Mulzer, *Angew. Chem.* **2009**, *121*, 6148; *Angew. Chem. Int. Ed.* **2009**, *48*, 6032.

[7] K. B. Bahnck, S. D. Rychnovsky, *J. Am. Chem. Soc.* **2008**, *130*, 13177.

[8] a) T. Sengoku, D. Uemura, H. Arimoto, *Chem. Lett.* **2007**, *36*, 726; b) T. Sengoku, H. Arimoto, D. Uemura, *Chem. Commun.* **2004**, 1220; c) J. D. White, H. Smits, *Org. Lett.* **2005**, *7*, 235; d) D. Williams, K. Shamim, *Org. Lett.* **2005**, *7*, 4161; e) J. Mulzer, S. Pichlmair, M. P. Green, M. M. B. Marques, H. J. Martin, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 11980.

[9] S. Pichlmair, M. M. B. Marques, M. P. Green, H. J. Martin, J. Mulzer, *Org. Lett.* **2003**, *5*, 4657.

[10] J. Uenishi, R. Kawahama, O. J. Yonemitsu, *J. Org. Chem.* **1997**, *62*, 1691.

[11] E. W. Colvin, B. J. Hamill, *J. Chem. Soc. Chem. Commun.* **1973**, 151.

[12] a) E. Negishi, C. Kotora, C. Xu, *J. Org. Chem.* **1997**, *62*, 8957; b) Review: E. Negishi, Q. Hu, Z. Huang, M. Qian, G. Wang, *Aldrichimica Acta* **2005**, *38*, 71.

[13] W.-H. Jung, C. Harrison, Y. Shin, J.-H. Fournier, R. Balachandran, B. S. Raccor, R. P. Sikorski, A. Vogt, D. P. Curran, B. W. Day, *J. Med. Chem.* **2007**, *50*, 2951.

[14] a) M. Scholl, S. Ding, C. W. Lee, R. H. Grubbs, *Org. Lett.* **1999**, *1*, 953; b) B. Schwab, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1996**, *118*, 100.

[15] At that time we became aware that the White group had unsuccessfully pursued a related approach for the tetrahydropyran formation: H. Smits, PhD Thesis, Oregon State University, **2007**.

[16] a) R. E. Ireland, D. Habich, D. W. Norbeck, *J. Am. Chem. Soc.* **1985**, *107*, 3271; b) R. E. Ireland, P. Wipf, J. D. Armstrong, *J. Org. Chem.* **1991**, *56*, 650; c) R. E. Ireland, R. H. Mueller, A. K. Willard, *J. Am. Chem. Soc.* **1976**, *98*, 2868; d) A. M. M. Castro, *Chem. Rev.* **2004**, *104*, 2939.

[17] a) K. Mori, *Tetrahedron* **2008**, *64*, 4060; b) A. G. M. Barrett, R. A. E. Carr, S. V. Attwood, G. Richardson, N. D. A. Walshe, *J. Org. Chem.* **1986**, *51*, 4840.

[18] B. S. Bal, W. E. Childers, H. W. Pinnick, *Tetrahedron* **1981**, *37*, 2091.

[19] a) Y. Okude, S. Hirano, T. Hiyama, H. Nozaki, *J. Am. Chem. Soc.* **1976**, *98*, 3179; b) A. Fürstner, N. Shi, *J. Am. Chem. Soc.* **1996**, *118*, 12349; c) **29a** and **29b** were obtained as an easily separable 1.4:1 mixture. **29b** was recycled by oxidation to the ketone and reduction with $NaBH_4$ (d.r. 2:1).

[20] Claisen–Ireland rearrangements of this dimension are rare in the literature; we are aware of three examples of similar complexity: a) C. E. Stivala, A. Zakarian, *J. Am. Chem. Soc.* **2008**, *130*, 3774; b) M. J. Fisher, C. D. Myers, J. Joglar, S. H. Chen, S. J. Danishefsky, *J. Org. Chem.* **1991**, *56*, 5826; c) R. E. Ireland, D. Habich, D. W. Norbeck, *J. Am. Chem. Soc.* **1985**, *107*, 3271.

[21] a) J. S. Clark, R. Metternich, V. J. Novack, G. S. Sheppard, D. A. Evans, *J. Am. Chem. Soc.* **1990**, *112*, 866; b) D. A. Evans, J. S. Clark, D. L. Rieger, *Tetrahedron* **1992**, *48*, 2127.

[22] D. A. Evans, K. T. Chapman, E. M. Carreira, *J. Am. Chem. Soc.* **1988**, *110*, 3578.

[23] S. Pichlmair, PhD Thesis, University of Vienna, **2004**.

[24] a) M. R. Winkle, R. C. Ronald, *J. Org. Chem.* **1982**, *47*, 2101; b) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879.

[25] E. Merifield, E. J. Thomas, *J. Chem. Soc. Perkin Trans. 1* **1999**, 3269.

[26] a) A. Hafner, R. O. Duthaler, R. Marti, G. Rihs, P. Rothe-Streit, F. Schwarzenbach, *J. Am. Chem. Soc.* **1992**, *114*, 2321; b) Review: A. Hafner, R. O. Duthaler, *Chem. Rev.* **1992**, *92*, 807.

[27] a) W. R. Roush, K. Ando, D. B. Powers, A. D. Palkowitz, R. L. Halterman, *J. Am. Chem. Soc.* **1990**, *112*, 6339; b) W. R. Roush, R. L. Halterman, *J. Am. Chem. Soc.* **1986**, *108*, 294.

[28] H. C. Brown, S. K. Bhat, *J. Am. Chem. Soc.* **1986**, *108*, 5919.

[29] D. J. Pasto, R. T. Taylor, *Organic Reactions, Vol. 40* (Ed.: L. A. Paquette), Wiley, New York, **1991**, pp. 91–155.

[30] Replacement of $CH_2Cl_2$ with benzene gave a *E*/*Z* 2.5:1 mixture in 80 % yield.

[31] S. Kulasegaram, R. J. Kulawiec, *J. Org. Chem.* **1997**, *62*, 6547.

[32] E. P. Boden, G. E. Keck, *J. Org. Chem.* **1985**, *50*, 2394.

[33] Z. Huang, E. Negishi, *Org. Lett.* **2006**, *8*, 3675.

[34] 2D-NMR experiments with natural and synthetic Kendomycin showed that protons 10-$H_2$ and 11-$H_2$ have been misassigned (compare ref. [2;6a–d]).

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