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Model Studies for a Ring-Closing Metathesis Approach to the Bafilomycin Macrolactone Core from a 2,2-Dimethoxy Tetraenic Ester Precursor

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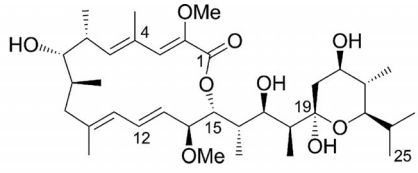
A ring-closing metathesis strategy is reported for the construction of the 16-membered macrolactone core of the bafilomycins. One decisive key feature is the presence of a 2,2-dimethoxyketal functionality at C-2 that provides the required flexibility to the tetraenic ester precursor, allowing the ring-closing metathesis reaction to take place. Three different model esters of increasing complexity were successfully subjected to the 1,3-diene-ene ring-closing metathesis reaction. The best promoter for the simplest esters was the Grubbs first-generation precatalyst. A Hoveyda–Grubbs-type trifluoromethylamido-containing precatalyst developed by Mauduit's group gave satisfactory results for the most complex ester. In all experiments, the 12-*Z*-configured isomer was obtained as the major product. Subsequent microwave-promoted methanol elimination was achieved on the simplest model compound using camphorsulfonic acid (CSA) as a catalyst. Under these conditions, a *E* to *Z* isomerization of the double bond at C-4, as well as ca. 50 % isomerization of the 12-*Z* double bond into the corresponding 12-*E* isomer, were observed.

Introduction

Bafilomycin A_1 **1** is a 16-membered macrolide first isolated from the broth of Streptomyces griseus in 1984 by Werner et al.[1] Its structure was confirmed in 1987 by X-ray analysis.[2] Due to its potent specific inhibitory effect on vacuolar-type proton-translocating ATPases (V-ATPases) at the nanomolar level,[3] it was immediately recognized that bafilomycin A_1 had potential pharmaceutical applications in combatting disorders involving the dysfunction of V-ATPases. However, the ubiquity of V-ATPases precluded rapid therapeutic applications of natural bafilomycin A_1. One of the first diseases to be targeted was osteoporosis, and extensive structure–activity relationship studies led to the identification of several optimized analogues, some of which were patented.[4] Analogues such as SB-242784 from GSK[5] or FR167356 from Fujisawa Pharmaceuticals[6] are currently under clinical investigation. Today, increased understanding of the regulation of V-ATPases, as well as increasing knowledge about the diversity of the isoforms of the different subunits of this enzymatic complex, make the prospects for the development of specific inhibitors for therapeutic purposes promising.[7]



Bafilomycin A_1 **1**

More recently, the bafilomycins have been the subject of further research, due to their promising anticancer potential. New bafilomycin metabolites from *Streptomyces* sp. strains of marine origin have been shown to act as potent inhibitors of autophagy,[8] a catabolic process that represents an attractive target for cancer therapy.[9] Moreover, in combination with other anticancer drugs, bafilomycin A_1 has been shown to have potential anticancer properties. This has been demonstrated in combination with taxol for Bcl-2/Bcl-xL-overexpressing malignancies.[10] In a similar vein, in combination with anticancer drug Bortezomib, it has been claimed that bafilomycin A_1 can optimize some cancer treatments.[11] A recent patent deals with a new bafilomycin-like metabolite from *Micromonospora* sp. with antiproliferative properties.[12] In addition to these potential applications, bafilomycin A_1 has been shown to have antimalarial activity.[13]

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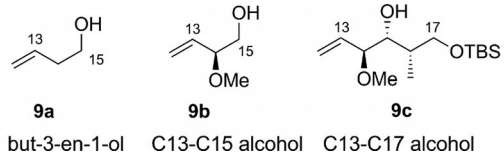
Its challenging structure and pharmaceutical potential stimulate organic chemists to work towards the synthesis of this molecule, as well as other plecomacrolide congeners. Several total syntheses of **1** have been published since the pioneering work of Evans et al. in 1993.[14] These studies were reviewed in 2005.[15] More recently, some more partial[16] or total syntheses[17] have been published.

In our group, work towards the synthesis of bafilomycin A_1 had been undertaken previously. This approach was based on the synthesis of an intermediate seco ester by a Stille cross-coupling reaction involving a classical C-12–C-13 disconnection.[18] Due to the increasing importance of the ring-closing metathesis (RCM) reaction for the formation of cyclic compounds − and especially macrocycles − in the last decade,[19] it appeared to us that an alternative and more direct strategy involving RCM would give a more efficient alternative for the construction of the macrocyclic core of the bafilomycins at the C-12–C-13 junction. We were initially dissuaded from undertaking such an approach when we became aware of the negative preliminary results obtained by the Yang group in 2006.[20] These authors failed in their attempt to construct the 16-membered macrolactone core of the bafilomycins by RCM using an analogous C-12–C-13 disconnection when the C-2–C-4 diene was already present in the polyenic ester precursor.

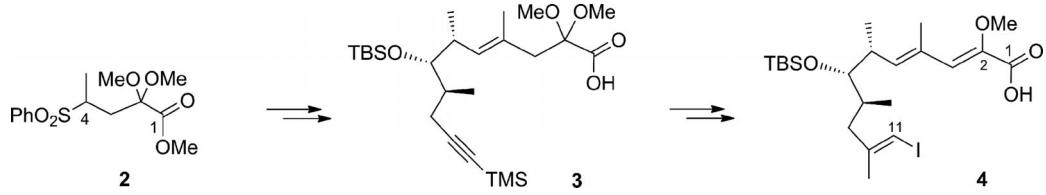
We thought that it would be possible to take advantage of the strategy we had already developed for the synthesis of C-1–C-11 subunit **4** via functionalized 2,2-dimethoxyketal **3** according to Scheme 1. The presence of a tetrasubstituted centre at C-2 in **3** could facilitate the transformation into the macrolactone by RCM. This approach starts from the easy to prepare, crystalline C_4 sulfonyl ester **2**.[21]

We therefore decided to test whether the increased flexibility at C-2 could be enough to enable cyclization to form the bafilomycin macrolide ring by a ring-closing metathesis strategy.[22] The overall strategy we initially adopted is summarized in Scheme 2. The key step would be the late formation of the C-2 double bond of **5**. This would take place after the RCM step that would transform tetraenic ester **7** into 2,2-dimethoxy macrocycle **6**. A simple Julia olefination between sulfone **2** and aldehyde diene **10** would give C-1–C-12 acid subunit **8**.

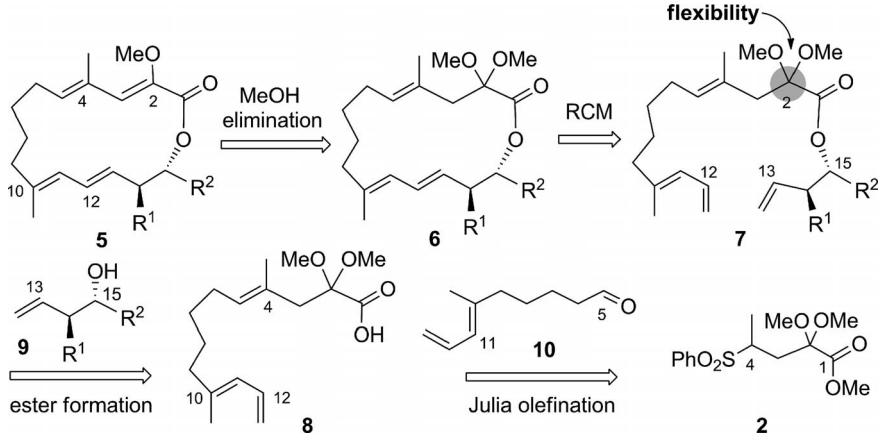
The convergence of this strategy is attractive from the point of view of the synthesis of small libraries of bafilomycin analogues from a variety of alcohols **9** of increasing structural complexity. As well as the simplest commercially available 3-buten-1-ol (**9a**), two more ω-unsaturated alcohols were tested: alcohol **9b**, with an allylic methoxy group that may have an influence on the outcome of the RCM step,[23] and the more complex alcohol **9c**, which already has the functional groups and stereogenic centres required for the synthesis of bafilomycin A_1.



In this paper, we report the results of our work using the strategy described above for the construction of the bafilomycin 16-membered core.



Scheme 1. Synthesis of the C-1–C-11 subunit of bafilomycins.[21] TMS = trimethylsilyl; TBS = *tert*-butyldimethylsilyl.



Scheme 2. Retrosynthesis of bafilomycin macrocycle model compounds.

Results and Discussion

Synthesis of Alcohols 9

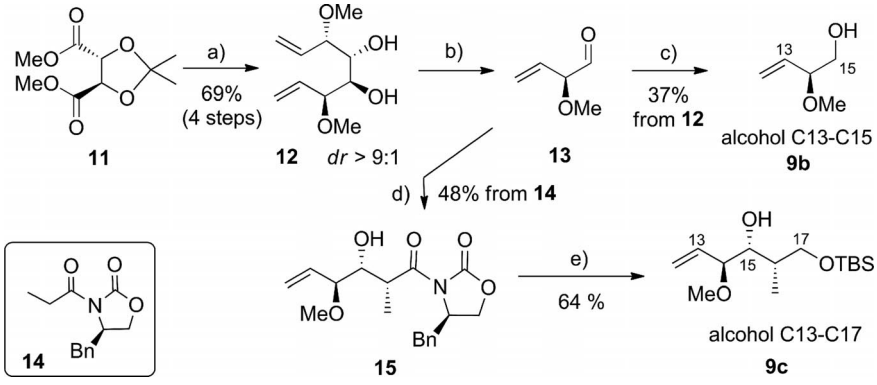
For the sake of a convergent synthetic route, we chose to prepare alcohols **9b** and **9c** from a common aldehyde **13**. We decided to synthesize **13** in enantiopure form in anticipation of the final synthetic project.

For the synthesis of intermediate aldehyde **13**, we followed a sequence described by Danishefsky in 2004 during the synthesis of migrastatin, starting from (–)-dimethyl 2,3-*O*-isopropylidene-L-tartrate (**11**; Scheme 3).[24] Reduction of **11** with DIBAL-H (diisobutylaluminium hydride), followed by in situ addition of divinylzinc gave, after dimethyl ether formation and acetonide deprotection, the expected product (i.e., **12**) with a diastereomeric ratio of >9:1 (69% yield over four steps).[25] Oxidative scission of **12** gave volatile aldehyde **13**, which was immediately used for the next steps without purification. Reduction of **13** with sodium borohydride gave enantioenriched alcohol **9b** (37% yield from **12**).

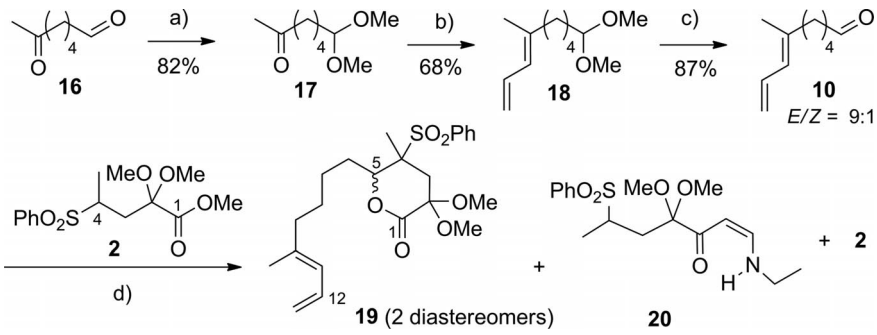
For the synthesis of hydroxy synthon **9c** that is required for the bafilomycins, crude aldehyde **13** was subjected to a $TiCl_4$-mediated *syn* Evans/Crimmins aldol condensation with enantiopure (*R*)-(–)-4-benzyl-3-propionyl-2-oxazolidinone (**14**).[26] As anticipated, in the presence of an excess of TMEDA, the *syn* Evans aldol product **15** was obtained in 48% yield from **14** (*dr* = 15:1). The configuration of **9c** was deduced to be as shown based on literature precedent for *syn* Evans condensation of the same propionyloxazolidinone **14** with an enantiopure α-methoxy aldehyde.[27] Compound **15** was easily purified by chromatography. It was transformed into TBS-mono-protected alcohol **9c** by reduction with sodium borohydride[26] followed by selective protection of the primary hydroxy group of the resulting diol as a TBS ether (64% yield from **15**).

Synthesis of the Tetraenic Ester RCM Precursors

A crucial step in the synthesis of acid intermediate **8** was a Julia olefination between sulfone **2** and diene aldehyde **10**. Compound **10** was easily synthesized in three steps from known keto aldehyde **16**, which was prepared by ozonolysis of 1-methylcyclohexene.[28] A Yamamoto olefination of **17** using allyldiphenylphosphine oxide followed by acid hydrolysis allowed the synthesis of **10** via **18** with a 9:1 *E*/*Z* stereoselectivity (Scheme 4).[29] The subsequent condensation reaction between **2** and **10** proved to be more problematic than expected. Although the starting aldehyde was completely consumed, separation of δ-lactone **19** from the excess of starting sulfone **2** proved to be particularly difficult,



Scheme 3. Reagents and conditions: a) i: DIBAL-H, toluene –78 °C; ii: vinylmagnesium bromide, $ZnCl_2$, THF, room temp., 4 h; iii: NaH, MeI, DMF, room temp., 2 h; iv: HCl (2 M), MeOH, reflux, 2 h; b) $Pb(OAc)_4$, Na_2CO_3, CH_2Cl_2, 0 °C; c) $NaBH_4$, Et_2O; d) **14**, $TiCl_4$, CH_2Cl_2, 0 °C, 5 min; TMEDA (tetramethylethylenediamine), 0 °C, 30 min, then crude **13**, 0 °C, 1 h; e) i: $NaBH_4$, THF/H_2O overnight; ii: TBSCl, DMAP (4-dimethylaminopyridine), Et_3N, CH_2Cl_2, overnight.



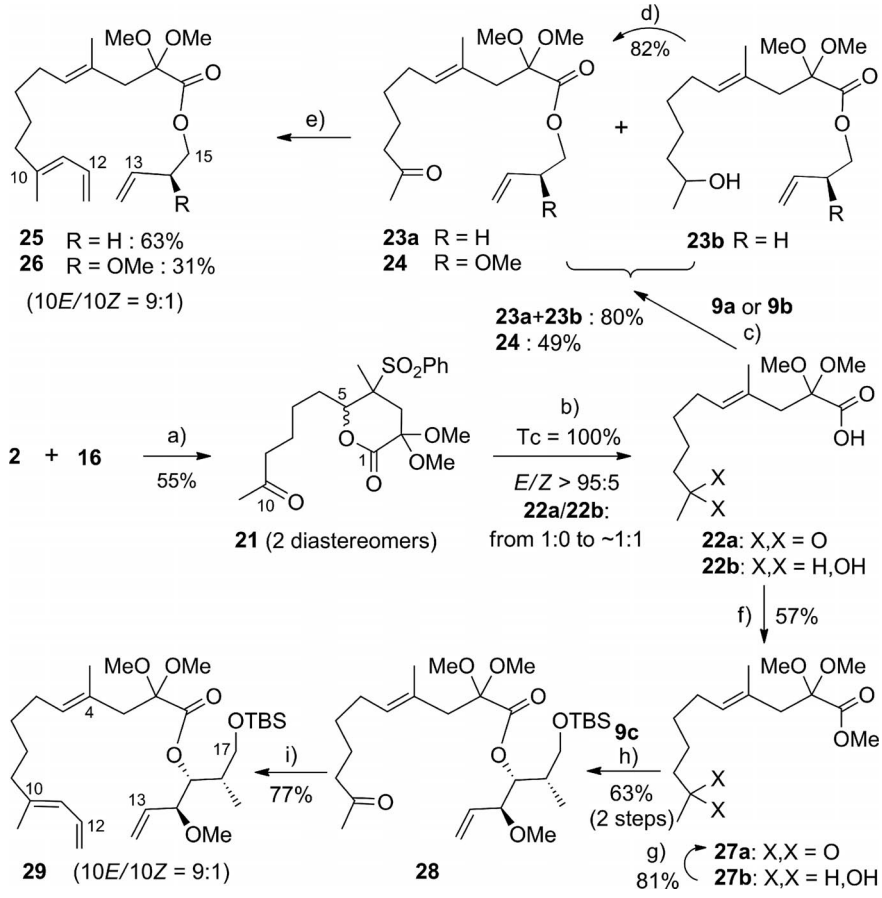
Scheme 4. Reagents and conditions: a) MeOH, *p*TsA (cat.), room temp., 30 min; b) allyldiphenylphosphine oxide, BuLi, THF/HMPA (hexamethylphosphoramide), –78 °C, 30 min, then room temp., 2 h, 70%. c) H_2O/HCO_2H, room temp., overnight; d) **2** (5 equiv.), LDA, THF, –78 °C, 5 min, –55 °C, 40 min, then **10** (THF), –78 °C, 25 min, then 0 °C, 20 min.

as these compounds had the same polarity. Unfortunately, all attempts to crystallize the remaining sulfone from the crude reaction product mixture failed. Moreover, a variable amount of enaminone **20** was produced in this reaction, arising from the undesired addition of oxidized LDA (lithium diisopropylamide) onto the ester functionality of sulfone **2**.[30]

Despite much effort, this route proved to be unfeasible from a practical point of view. We therefore decided to develop a slightly less convergent route to the required tetraenic ester precursors of the RCM reaction by carrying out the stereoselective Yamamoto condensation with allyldiphenylphosphine oxide after the Julia condensation reaction. The results are shown in Scheme 5. Direct condensation of sulfone **2** with ketoaldehyde **16** led, after aqueous hydrogenosulfite quenching and chromatography, to 10-oxo δ-lactone **21** as a 1:1 mixture of diastereomers in 55% yield. Reductive elimination with Na/Hg led to the formation of the expected acid (i.e., **22**) with an excellent *E*/*Z* stereoselectivity in the formation of the trisubstituted double bond (*E*/*Z* > 95:5).[31] However, a variable mixture of ketoacid **22a** and hydroxyacid **22b** was formed, depending on the origin of the batch of amalgam used (see Experimental Section). For instance, a crude mixture of **22a/22b** (ca. 1:1 ratio) was directly subjected to an esterification reaction with alcohol **9a** under Steglich conditions to give a mixture of esters **23a/23b** (70% yield from **21**). Also, compound **24** was obtained in 49% yield starting from **22a**.

At this stage, when necessary, an IBX oxidation of the 10-hydroxy derivatives allowed their easy conversion into the corresponding 10-keto compounds (exemplified for **23b**). Subsequent Yamamoto olefination of keto esters **23a** or **24a** as described above delivered tetraenic model compounds **25** and **26** in 63 and 31% yields, respectively.

This approach was ineffective in the case of bulky secondary alcohol **9c**, required for the synthesis of the bafilomycins. Steglich conditions failed to give the expected ester (i.e., **28**). Two modifications led to the formation of required ester. The esterification reaction was achieved under Yamaguchi–Yonemitsu lactone formation conditions in the presence of 2,4,6-trichlorobenzoyl chloride and an excess of DMAP.[32] Moreover, in contrast to the Steglich reactions described above, it proved to be necessary to purify acids **22** before carrying out the esterification reaction, probably

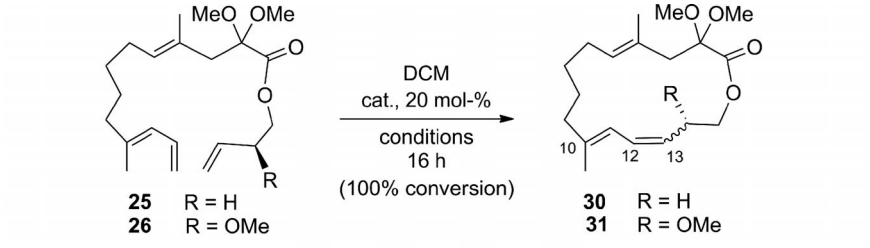


Scheme 5. Reagents and conditions: a) **2**, LDA, THF, –78 °C, 5 min, then –55 °C, 40 min, ketoaldehyde **16**, –78 °C, 25 min, then 0 °C, 20 min; b) Na/Hg (6%), $NaHCO_3$, THF/MeOH, –40 °C; c) **9a** or **9b**, EDC, DMAP, CH_2Cl_2, room temp., overnight; d) IBX (2-iodoxybenzoic acid), DMSO, THF, room temp., overnight; e) allyldiphenylphosphine oxide, BuLi, THF/HMPA, –78 °C, then room temp., 2 h; f) $TMSCHN_2$, MeOH/Et_2O, 25 min, room temp.; g) IBX, DMSO, THF, room temp., overnight; h) i: KOH (10% aq.), reflux, 2 h; ii: 2,4,6-trichlorobenzoyl chloride, DMAP (3 equiv.), Et_3N, toluene, **9c**, room temp., 30 h; i) allyl diphenylphosphine oxide, BuLi, THF/HMPA, –78 °C then room temp., 2 h.

to remove the interfering residual phenylsulfinic acid still present in the crude product of the reductive elimination reaction. Treatment of the crude acid mixture **22a/22b** with diazomethane followed by IBX oxidation led to methyl keto ester **27a**. Subsequent alkaline hydrolysis of **27a** followed by esterification under Yamaguchi–Yonemitsu conditions gave keto ester **28** in 63% yield. Yamamoto olefination as described above gave tetraene **29** in good yield as a single enantiopure 4*E*,10*E* stereoisomer.

RCM Reactions

With tetraenic esters **25**, **26**, and **29** in hand, we turned to the RCM reactions. With the simplest esters **25** and **26**, we tested the Grubbs I first-generation,[33] Grubbs II second-generation,[34] and Hoveyda–Grubbs[35] precatalysts, and the results are summarized in Scheme 6. In all cases, the starting material had been consumed when the reaction was stopped. In the first experiments, significant degradation occurred upon direct evaporation of the reaction mixture. Better results were obtained by adding activated charcoal at the end of the reaction before removal of the solvent.[36] All subsequent RCM reactions were carried out with this post-reaction activated charcoal treatment. Under these conditions, the best results for **25** were obtained using the Grubbs I precatalyst at room temp., and compound **30** was formed in 66% yield. 14-Methoxy analogue **31** was obtained in 51% yield from **26**, as a 9:1 mixture of *Z*/*E* isomers at C-12.



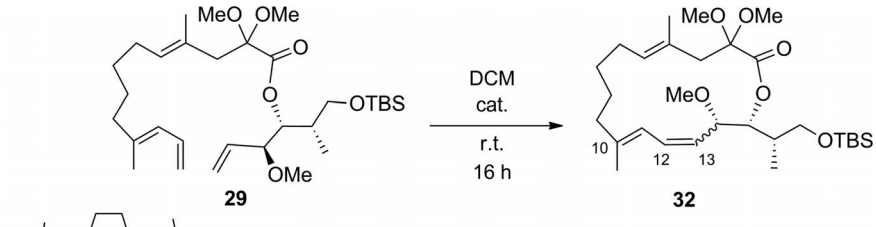
25 R = H
26 R = OMe

30 R = H
31 R = OMe

S.M.	precatalyst	*T*	results		
			comments	*Z*/*E* *	Yield
25	Grubbs-I	r.t.	clean	>95:5	66 %
	"	reflux	some degradation	80:20	–
	Grubbs-II	r.t.	some degradation	>95:5	–
	Hoveyda-Grubbs	r.t., then reflux	some degradation	>95:5	–
26	Grubbs-I	r.t.	clean	90:10	51 %

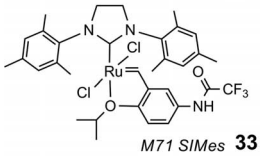
* Evaluated from the ^{1}H NMR spectrum of the crude product

Scheme 6. RCM reactions with tetraenic esters **25** and **26**.

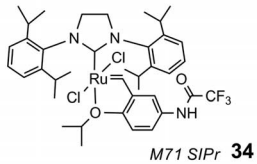


29

32



M71 SIMes **33**



M71 SIPr **34**

precatalyst	mol-%	results			
		conversion*	comments	*Z*/*E* *	yield
Grubbs I	20	~10%	low degrad.	1:1	–
"	20+20	>90%	medium degrad.	7:3	–
33	5	~35%	high degrad.	7:3	–
34	5	~35%	medium dégrad.	7:3	–
35	5	~35%	low degrad.	7:3	–
"	10+10	>90%	medium degrad.	7:3	48%

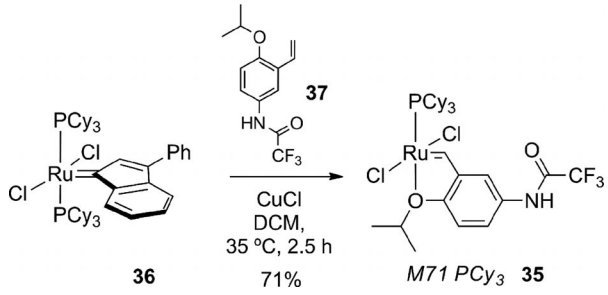
* Evaluated from the ^{1}H NMR spectra of the crude products

Scheme 7. RCM reactions with tetraenic ester **29**.

The *Z* isomers were greatly predominant when the reactions were run at room temperature, and often they were the only products detectable by ^{1}H NMR spectroscopic analysis of the crude product mixtures. When the Grubbs I precatalyst was used at reflux temperature, 20% of the *E* isomer of **30** was formed. Various attempts to improve the formation of the *E* isomer by further treatment of the *Z* isomer with Grubbs II or Hoveyda–Grubbs precatalysts did not alter the *Z*/*E* ratio or led to different levels of degradation products.

We next turned to the RCM reaction of the more complex ester **29** (Scheme 7). When this compound was heated at reflux for 16 h in CH_2Cl_2 in the presence of the Grubbs I precatalyst, macrolactone **32** was formed as a ca. 1:1 mixture of *Z* and *E* isomers, but the conversion was low. Under more drastic conditions (increased catalyst loading or temperature), the reaction mixture became more complex, and the amount of degradation products increased. We decided to test Mauduit's modified Hoveyda–Grubbs ruthenium precatalysts M71-SIMes (**33**) and M71-SIPr (**34**),[37] as well as the new phosphine-based parent carbene complex M71-PCy_3 (**35**). Precatalyst **35** was prepared in one step from the known Ru-indenylidene complex, $RuCl_2(PCy_3)_2$(Ind) (**36**),[38] by exchange with 2,2,2-trifluoro-*N*-(4-isopropoxy-3-vinylphenyl)acetamide (**37**) according to Scheme 8.

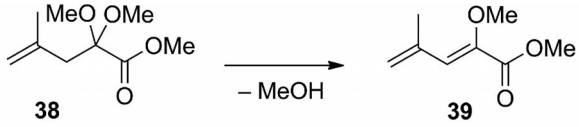
Of all the precatalysts tested for the formation of **32**, M71-PCy_3 (**35**) gave the best result. A 48% yield was obtained with an acceptable level of degradation (with two successive additions of 10 mol-% of the precatalyst). Considering the *Z*/*E* selectivity at the C-12 double bond, although the preliminary RCM reactions described above for the simpler model compounds **25** and **26** led to the exclusive formation of the *Z* isomer (the unnatural isomer), it clearly appeared that although increasing the bulk of the alcohol subunit in **29** had a deleterious effect on the kinetics of the reaction (10% conversion with the Grubbs I precatalyst), it had a favourable effect on the *E*-selectivity for the formation of the C-12 double bond. The *E*/*Z* ratios obtained varied from 3:7 with precatalyst **35** to 1:1 with the Grubbs I precatalyst.



Scheme 8. Synthesis of M71-PCy3 (**35**).

At this point, it was important to test the remaining crucial MeOH elimination reaction at C-2 to validate the synthetic approach to the bafilomycin core. A similar elimination reaction had been already tested successfully in these laboratories during a previous synthesis of a C-1–C-11 bafilomycin precursor, using camphorsulfonic acid in refluxing benzene. It must be pointed out that these conditions only led to the expected elimination product (with the required *Z* configuration) when the free seco acid was used; no elimination occurred when the corresponding esters were tested.[39] As the present RCM approach to the bafilomycins would require the elimination of MeOH to occur after the formation of the macrolide core, we decided to test the elimination reaction with 2,2-dimethoxy ester **38**, which we anticipated would be a reasonable model for our purposes. The most significant results are summarized in Scheme 9.

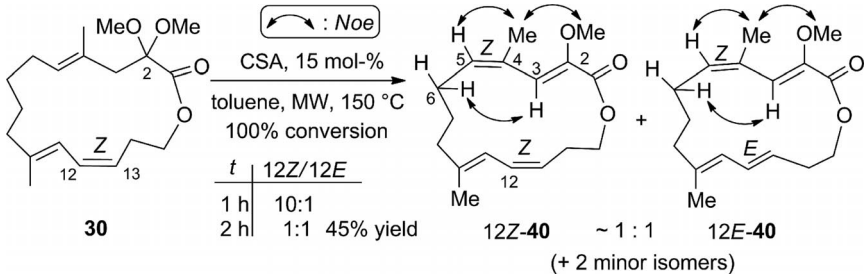
Under various conventional thermal conditions, either in toluene, or in methanol as described by the group of Terashima,[40] no reaction occurred (Scheme 9, entries 1 and 2). The triflate conditions for the synthesis of enol ethers from acetals developed by Gassman et al. also failed (Scheme 9, entry 3; DIPEA = diisopropylethylamine).[41] We next turned to microwave irradiation.[42] Microwave -promoted trifluoroacetic acid (TFA) conditions adapted from Nakabayashi et al.[43] led to partial degradation of the starting



Entry	Solvent	Promoter	Conditions*	*T*	Results	Ref.
1	toluene	CSA (0.1 equiv.)	110 °C	72 h	no reaction	
2	MeOH	CSA (0.25 equiv.)	70 °C	72 h	no reaction	[38]
3	DCM	TMSOTf/DIPEA	r.t.	2 h	no reaction	[39]
4	toluene	TFA (0.1 equiv.)	MW, 190 °C	2 h	partial degradation	[41]
5	"	CSA (0.05 equiv.)	MW, 150 °C	2 h	10% conversion	
6	"	CSA (3 x 0.05 equiv.)	"	3 x 2 h	100% conversion, 67% yield	

* For MW irradiations a CEM-Discover apparatus was used at 300 W

Scheme 9. Model studies for the MeOH elimination.



Scheme 10. MeOH elimination reaction on macrolactone **30**.

material (i.e., **38**; Scheme 9, entry 4). When camphorsulfonic acid was used at 150 °C, slow conversion into the desired diene (i.e., **39**) was observed (Scheme 9, entry 5). The best results g followed by a 2 h period of irradiation (Scheme 9, entry 6). Compound **38** was completely and cleanly converted into diene **39**, which was formed in 67% yield as a single product, which was deduced from literature data to have the expected *Z* configuration.[44]

These conditions were then tested on pure 12-*Z*-configured 16-membered macrolactone **30**. After some experimentation, in the presence of 15 mol-% CSA in toluene at 150 °C under microwave irradiation, the expected elimination of MeOH took place quantitatively to give an inseparable mixture of tetraenic products **40**, with only traces of decomposition products (Scheme 10).

Macrolactone **40** was obtained as a mixture of four stereoisomers in a ca. 4:4:1:1 ratio.[45] Surprisingly, careful ^{1}H NMR spectroscopic analysis of this mixture (600 MHz) showed important modifications of the stereochemistry of the double bonds at C-4 and C-12. First of all, the double bond at C-4 had *Z* stereochemistry for the two major isomers, indicating that a total inversion of the initial *E* configuration obtained in the Julia olefination reaction had taken place. Moreover, a ca. 50% isomerization of the 12-*Z*-configured double bond was observed when the reaction time was extended to 2 h. One of the two major isomers (12-*E*) showed a signal at δ = 6.52 ppm, J = 14.6 and 11.2 Hz in its ^{1}H NMR spectrum. This observed acid-promoted isomerization at C-12 could indicate that the thermodynamic stability of the final tetraenic macrolactone 12-*E*-**40** could be similarly greater than its 12-*Z*-configured isomer. Further studies will be needed to explain the isomerization of the double bond at C-4, although it is reasonable to claim that the mechanism of formation of the more stable isomer of the 2,4-diene could proceed via an intermediate allyl cation.

Conclusions

The approach reported here allows the formation of the macrolactone core of the bafilomycins by RCM starting from 2,2-dimethoxyketal ester precursors, using either Grubbs I or PCy_3-type ruthenium precatalysts. Grubbs first-generation precatalyst, in the case of esters **25** and **26**, as well as the new phosphine-based M71-PCy_3 (**35**), in the case of **29**, gave the best results. The macrocyclic products predominantly had a 12-*Z* configuration, and this stereoisomer can be assumed to be the kinetic product.

In 2009, during the course of this study, Dai's group used a strategy similar to ours to carry out the first synthesis of the macrocyclic core of the bafilomycins using an RCM strategy.[46] These authors used an ester precursor with a vicinal diol functionality at C-2–C-3 to bring the flexibility necessary for the formation of the macrolide. In their study, the RCM cyclization using the Grubbs second-generation precatalyst led to the formation of the bafilomycin macrocycle in 89% yield and with a 12*Z*/12*E* ratio of 82:18. Thus, in both cases tested so far, either by us or by Dai's group, the formation of the 12-*Z* isomer is favoured in the formation of trienic macrolide precursors of the bafilomycins by RCM.

Interestingly, under the microwave-activated acidic conditions used for the methanol elimination reaction of macrolactone **30** to give **40**, partial isomerization of the 12-*Z* to the 12-*E* configured double bond was observed. It is possible, based on the results of the various unsuccessful isomerization attempts performed with trienic macrocycles **30**–**32** in the presence of different RCM precatalysts (see above), that the less rigid 2,2-dimethoxy intermediate lactones are more thermodynamically stable when the double bond at C-12 has a *Z* configuration. In contrast, the final tetraenic macrolide **40**, with a 12-*E* configuration, could be claimed to be the more stable isomer once the C-2–C-4 diene is installed, although the fact that we observed a concomitant isomerization of the double bond at C-4 makes this less certain. Further studies are clearly required in two directions: 1) to validate and optimize the 12-*Z* to 12-*E* equilibration as a possible stereochemical bias for the synthesis of the final tetraenic lactone; 2) to preserve the *E*-configuration of the initially formed double bond at C-4. In the bafilomycins, where a methyl substituent is present at C-6 (which is not the case for model compound **30**), it seems reasonable to expect that the unwanted Z isomer would be disfavoured, due to additional allylic strain.

We are currently working towards the application of this approach to the synthesis of bafilomycins, with particular attention being paid to the control of the stereochemistry at C-12.

Experimental Section

General Methods: ^{1}H NMR spectra were recorded with Bruker DPX 250 (250 MHz), DRX-300 (300 MHz), AV-360 (360 MHz),

Avance DPX 400 (400 MHz), or DRX B600 (600 MHz) instruments. Molecular sieves and K_2CO_3 were added to stock deuterated chloroform. The following abbreviations are used to describe peak patterns: br. = broad, ap. = apparent, s = singlet, d = doublet, t = triplet, q = quartet, quint = quintuplet, and m = multiplet. Coupling constants (J) are reported in Hz to ±0.5 Hz. ^{1}H chemical shifts are expressed in parts per million (ppm), and are referenced to the residual ^{1}H signal of deuterochloroform (δ = 7.26 ppm). ^{13}C chemical shifts are expressed in parts per million, and are referenced to the central peak of deuterochloroform (δ = 77.00 ppm). When measured, DEPT-135 experiments are described according to + (primary and tertiary C atoms, positive signals) or – (secondary C atoms, negative signals). Infrared spectra were recorded with a Perkin–Elmer Spectrum One FTIR instrument, using the thin film method on NaCl plates, prepared from solutions in CH_2Cl_2. Absorption maxima ($\tilde{\nu}$) are reported in wavenumbers (cm^{-1}). High-resolution mass spectra were recorded using electrospray ionization (ESI) with a TSQ (Thermo Scientific 2009) mass spectrometer with direct introduction. The quoted masses are accurate to ±5 ppm. Flash chromatography was performed using silica gel (Merck Geduran Si60 40–63 μm) as the stationary phase. Analytical TLC was performed on aluminium plates precoated with silica gel (Merck silica gel, 60 F254), which were visualized by UV fluorescence when applicable (λ_{max} = 254 nm), and/or by staining with vanillin or *p*-anisadehyde ethanolic sulfuric acid solutions followed by heating. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium–benzophenone. All air- and/or water-sensitive reactions were carried out under a nitrogen atmosphere using a dual manifold high-vacuum line with dry, freshly distilled solvents, using standard syringe–cannula/septa and purge-and-refill techniques. All glassware was dried with a flameless heatgun and kept under vacuum before use. Optical rotations were determined with a Perkin–Elmer 241-instrument operating at the D-line of Na, and are reported as follows: $[\alpha]_D^{25}$ (concentration [g/100 mL], solvent). Except for alcohols **9b** and **9c**, which were synthesized in an enantiopure form in anticipation of a future synthesis of bafilomycin analogues, neither optical rotations nor enantiomeric excess determinations were carried out for the compounds synthesized in this model study. Ozonolysis reactions were carried out using a BMT 802 X ozone generator. Microwave-assisted reactions were carried out using a CEM Discover apparatus. Sulfone **2** was prepared as described previously.[21] (*R*)-(–)-4-Benzyl-3-propionyl-2-oxazolidinone (**14**) is commercially available, and was also prepared on a multigram scale according to a published procedure.[47]

(3*R*,6*R*)-3,6-Dimethoxyocta-1,7-diene-4,5-diol (12): Anhydrous $ZnCl_2$ (20.1 g, 147.8 mmol, 3.9 equiv., dried three times by melting under vacuum until constant mass) was dissolved in dry THF (90 mL), and a commercially sourced solution of vinylmagnesium bromide (1.0 M in THF; 271 mL, 271 mmol, 7.1 equiv.) was slowly added. A dark green solution with some precipitate was formed. (–)-Dimethyl 2,3-*O*-isopropylidene-L-tartrate **11** (8 g, 37.4 mmol, 1.0 equiv.) was dissolved in dry toluene (100 mL), the solution was cooled to –78 °C, and DIBAL-H (1.0 M in toluene; 86 mL, 86 mmol, 2.3 equiv.) was added slowly. This mixture was stirred for 3 h at –78 °C, then the solution of divinylzinc was slowly added to the aldehyde solution by cannula at –78 °C. After 30 min, the mixture was allowed to warm to room temperature, and it was stirred for a further 4 h. The reaction mixture was then cooled to 0 °C, and NH_4Cl (satd. aq.) and Rochelle salt solution (satd. aq., excess) were added carefully. The mixture was stirred overnight. EtOAc and brine were added, and usual extraction followed by purification by flash chromatography on silica gel (petroleum ether/EtOAc, 4:1 to 1:1) gave intermediate (1*R*,1′*R*)-1,1′-[(4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-diyl]bis(prop-2-en-1-ol) (7.1 g, 89%) as a pale yellow liquid. R_f 0.4 (petroleum ether/Et_2O, 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.97 (ddd, J = 5.9, 10.5, 17.2 Hz, 2 H), 5.37 (br. d, J = 17.2 Hz, 2 H), 5.27 (br. d, J = 10.5 Hz, 2 H), 4.15 (m, 2 H), 3.88 (br. d, J = 4.3 Hz, 2 H), 1.41 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100.63 MHz): δ = 136.8, 117.2, 109.5, 81.7, 73.6, 26.9 ppm.

The above diol (3.0 g, 14.0 mmol, 1.0 equiv.) was put into DMF (50 mL), and the mixture was cooled to 0 °C. NaH (60 wt.-% in mineral oil, 1.2 g, 30.8 mmol, 2.2 equiv.) was added portionwise, followed, after 10 min, by commercially sourced methyl iodide (2.1 mL, 33.6 mmol, 2.4 equiv.). The resulting solution was allowed to warm to room temp. It was stirred for a further 45 min, and then NH_4OH (2 N aq.) was added. Usual extraction with EtOAc (washing with brine) gave, after evaporation, a crude product. This material was dissolved in a mixture of MeOH (50 mL) and HCl (2 N aq.; 15 mL). This solution was heated under reflux for 2.5 h, then it was allowed to cool to room temp. and Na_2CO_3 (satd. aq.) was added. Usual extraction with EtOAc followed by purification of the crude extract by flash chromatography on silica gel (petroleum ether/EtOAc, 2:1) gave diol **12** (2.2 g, 77%) as a pale yellow oil. R_f 0.3 (petroleum ether/Et_2O, 1:1). $[\alpha]_D$ = +30.9 (c = 1.8, $CHCl_3$), ref. +31.0 (c = 1.77, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.75 (ddd, J = 7.0, 11.1, 16.6 Hz, 2 H), 5.34 (m, 4 H), 3.71 (m, 2 H), 3.82 (m, 2 H), 3.33 (s, 6 H, OCH_3), 3.02 (br., 2 H, OH) ppm. ^{13}C NMR ($CDCl_3$, 100.63 MHz): δ = 135.2 (2 C), 119.2 (2 C), 84.7 (2 C), 71.3 (2 C), 57.2 (2 OCH_3) ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3448, 3078, 2982, 2937, 2904, 2824, 1740, 1643 cm^{-1}. HRMS (DI, EI): calcd. for $[C_{10}H_{18}O_4]^+$ 202.1205; found 202.1207. These data are in agreement with the literature.[24]

(*S*)-2-Methoxybut-3-en-1-ol (9b): Diol **12** (550.0 mg, 2.7 mmol, 1.0 equiv.) was put into dry Et_2O (30 mL), and commercially sourced $Pb(OAc)_4$ (1.3 g, 2.8 mmol, 1.05 equiv.) and $NaHCO_3$ (240.0 mg, 2.8 mmol, 1.05 equiv.) were added. The reaction mixture was stirred for 5 min at 0 °C, then at room temperature for 25 min, and then ethylene glycol (70.0 μL) was added. The mixture was stirred rapidly for 5 min, then it was filtered through a Celite pad. Et_2O and brine were added to the filtrate. The organic phase was decanted and combined with ethereal washings of the aqueous phase (small volumes). The combined organic phases were dried with $MgSO_4$. Without evaporation of the solvent, the crude organic phase containing aldehyde **13** was cooled to 0 °C, and $NaBH_4$ (306.0 mg, 8.1 mmol, 1.5 equiv.) was added. The reaction mixture was stirred at 0 °C until no starting material remained (about 30 min). Then water and Et_2O were added slowly. The mixture was extracted with Et_2O, and the solvent was evaporated carefully in vacuo (cooled water bath). The residue was purified by flash chromatography on silica gel (pentane/Et_2O, 4:1 to 1:1) to give volatile alcohol **9b** (125 mg, 37% over two steps). $[\alpha]_D$ = +37.9 (c = 1.05, $CHCl_3$), ref. for the corresponding (*R*) isomer = –41.4 (c = 1.05, $CHCl_3$).[48] ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.67 (ddd, J = 7.3, 10.3, 17.5 Hz, 1 H), 5.31 (dd, J = 7.6, 13.8 Hz, 2 H), 3.70 (m, 1 H), 3.55 (m, 2 H), 3.33 (s, 3 H, OCH_3), 2.10 (br. s, 1 H, OH) ppm. ^{13}C NMR ($CDCl_3$, 100.63 MHz): δ = 134.7, 119.2, 83.3, 65.2, 56.5 ppm. HRMS (DI, EI): calcd. for $[C_5H_{10}O_2 + Na]^+$ 125.0578; found 125.0573.

4-Benzyl-3-[(2*R*,3*R*,4*S*)-3-hydroxy-4-methoxy-2-methylhex-5-enoyl]-oxazolidin-2-one (15): A solution of crude aldehyde **13** was prepared from diol **12** (2.5 g, 12.4 mmol, 1.0 equiv.) by oxidation with $Pb(OAc)_4$ (6.3 g, 12.9 mmol, 1.05 equiv.) as described above, except that the final extraction was carried out with CH_2Cl_2, with no evaporation of the solvent. (*R*)-(–)-4-Benzyl-3-propionyl-2-oxazolidinone **14** (2.8 g, 12.02 mmol, 0.5 equiv.) was dissolved in dry

CH_2Cl_2 (150 mL) at 0 °C, and commercially sourced $TiCl_4$ (1.5 mL, 13.6 mmol, 0.55 equiv.) was added. The resulting solution was stirred for 5 min. Distilled TMEDA (3.5 mL, 23.2 mmol, 0.94 equiv.) was added to this orange mixture, and the resulting dark-brown mixture was stirred for 30 min at 0 °C. The CH_2Cl_2 solution of aldehyde **13** was then added by cannula. The reaction mixture was stirred for 1 h at 0 °C, then NH_4Cl (satd. aq.) was added. Usual extraction was carried out to give a crude aldol product (*dr* = 15:1 from ^1H NMR spectroscopy). This material was purified by flash chromatography on silica gel (EtOAc/petroleum ether, 1:4 to 4:1) to give compound **15** (1.9 g, 48% from **14**) as a pale yellow oil. $[\alpha]_D$ = –38.9 (*c* = 1.7, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.34–7.19 (m, 5 H), 5.77 (ddd, *J* = 8.0, 10.3, 18.1 Hz, 1 H), 5.32 (m, 2 H), 4.68 (ddd, *J* = 3.5, 6.9, 13.5 Hz, 1 H), 4.17 (m, 2 H), 3.95 (m, 2 H), 3.54 (m, 1 H), 3.26 (s, 3 H, OCH_3), 3.23 (dd, *J* = 3.2, 13.4 Hz, 1 H), 2.93 (br. s, 1 H, OH), 2.79 (dd, *J* = 9.4, 13.4 Hz, 1 H), 1.33 (d, *J* = 6.5 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100.63 MHz; DEPT): δ = 176.4, 152.6, 135.4 (+), 135.0, 129.4 (+), 128.7 (+), 127.1 (+), 119.7 (–), 83.7 (+), 72.9 (+), 65.9 (–), 56.2 (+), 54.9 (+), 39.5 (+), 37.6 (–), 12.7 (+) ppm. HRMS (DI, EI): calcd. for $[C_{18}H_{23}NO_5 + Na]^+$ 356.1474; found 356.1468.

(2*S*,3*R*,4*S*)-1-(*tert*-Butyldimethylsilyloxy)-4-methoxy-2-methylhex-5-en-3-ol (9c): $NaBH_4$ (930 mg, 24.6 mmol, 4.6 equiv.) was added to a solution of oxazolidinone **15** (1.7 g, 5.3 mmol, 1.0 equiv.) in a mixture of THF/H_2O (5:1; 70 mL) at 0 °C. The mixture was stirred overnight at room temp., then HCl (2 N aq.) was added, and stirring was continued for 5 min. Extraction as usual with Et_2O (washing with brine) followed by flash chromatography (Et_2O/pentane, 50:50 to 100:0) gave intermediate (2*S*,3*R*,4*S*)-4-methoxy-2-methylhex-5-ene-1,3-diol (C-13–C-17 diol; 787 mg, 83%) as a colourless oil. $[\alpha]_D$ = +29.6 (*c* = 1.8, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 5.90 (br. s, 2 H, exch. H), 5.76 (ddd, *J* = 8.0, 10.4, 17.1 Hz, 1 H), 5.39 (m, 2 H), 3.76–3.65 (m, 2 + 1 H), 3.55 (t, *J* = 7.5 Hz, 1 H), 3.29 (s, 3 H, OCH_3), 2.0 (m, 1 H), 0.99 (d, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100.63 MHz, DEPT): δ = 135.7 (+), 120.7 (–), 84.1 (+), 74.7 (+), 67.2 (–), 56.4 (+), 35.9 (+), 10.5 (+) ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3395, 3079, 2969, 2935, 2881, 2824, 1743, 1712, 1643 cm^{-1}. HRMS (DI, EI): calcd. for $[C_8H_{16}O_3 + Na]^+$ 183.0997; found 183.0992.

This diol (560.0 mg, 3.5 mmol, 1.0 equiv.) was dissolved in distilled CH_2Cl_2 (30 mL), and distilled triethylamine (600 µL, 4.3 mmol, 1.24 equiv.), DMAP (30.0 mg, 0.2 mmol, 0.06 equiv.), and TBSCl (580.0 mg, 3.9 mmol, 1.1 equiv.) were added. The reaction mixture was stirred overnight at room temp. Then NH_4Cl (satd. aq.) was added, and extraction was carried out with Et_2O. The crude material was purified by flash chromatography on silica gel (pentane/EtOAc, 100:0 to 40:60) to give mono-TBS ether **9c** (740 mg, 77%) as a colourless liquid. $[\alpha]_D$ = +9.7 (*c* = 1.8, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 5.78 (ddd, *J* = 7.7, 10.4, 17.2 Hz, 1 H), 5.36 (m, 2 H), 3.78–3.48 (m, 2 + 1 H), 3.52 (m, 1 H), 3.28 (s, 3 H), 3.06 (d, *J* = 2.5 Hz, 1 H, OH), 1.98 (dq, *J* = 2.8, 7.0 Hz, 1 H), 0.99 (d, *J* = 7.0 Hz, 3 H), 0.88 (s, 9 H), 0.05 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100.63 MHz, DEPT): δ = 136.1 (+), 119.3 (–), 83.7 (+), 75.5 (+), 68.3 (–), 56.3 (+), 35.5 (+), 25.9 (+), 18.2, 10.5 (+), –5.6 (+) ppm. IR (NaCl): $\tilde{\nu}$ = 3490, 3077, 2956, 2930, 2884, 2858, 1642, 1472 cm^{-1}. HRMS (DI, EI): calcd. for $[C_{14}H_{30}O_3Si + Na]^+$ 297.1862; found 297.1856.

6-Oxoheptanal (16): Methylcyclohexene (1.23 mL, 10.4 mmol, 1.0 equiv.) was put into CH_2Cl_2 (75 mL), MeOH (19 mL) was added, and the mixture was cooled to –78 °C. A stream of O_3 was bubbled through the solution until a pale blue colour persisted (about 1 h). A stream of N_2 was bubbled through the solution to remove residual O_3 until the solution become colourless. Then, Me_2S (1.2 mL, 16.6 mmol, 1.6 equiv.) was added at –78 °C. After 10 min, the mixture was allowed to warm to room temperature, and it was stirred overnight under a well-ventilated hood. H_2O and CH_2Cl_2 were added. The usual work-up was carried out with CH_2Cl_2. The organic phase was concentrated in vacuo using an aqueous KOH trap. The residue was purified by flash chromatography on silica gel (petroleum ether/Et_2O, 3:2) to give 6-oxoheptanal **16** (1.25 g, 94%) as a colourless liquid (stable for 1 month at –20 °C). R_f 0.4 (petroleum ether/Et_2O, 7:3). ^1H NMR ($CDCl_3$, 400 MHz): δ = 9.75 (t, *J* = 1.5 Hz, 1 H), 2.46–2.42 (m, 4 H), 2.12 (s, 3 H), 1.60 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 208.4, 202.1, 43.6, 43.2, 29.9, 23.1, 21.5 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3418, 2944, 2729, 1710, 1411, 1363, 1161, 1086, 1000 cm^{-1}. HRMS (DI, EI): calcd. for $[C_7H_{12}O_2]^+$ 128.0837; found 128.0839. These data are in agreement with published ones.[49]

7,7-Dimethoxyheptan-2-one (17): A solution of crude 6-oxoheptanal **16** (6.0 g, 46.8 mmol, 1.0 equiv.) prepared as described above and *p*TsA (133.0 mg, 0.4 mmol, 0.01 equiv.) in MeOH (60 mL) was stirred for 30 min at room temperature. $NaHCO_3$ (5% aq.) was added to this reaction mixture, and work-up was carried out with EtOAc. The crude material was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 95:5) to give **17** (7.9 g, 82%) as a colourless liquid. R_f 0.5 (petroleum ether/Et_2O, 7:3). ^1H NMR ($CDCl_3$, 400 MHz): δ = 4.34 (t, *J* = 5.7 Hz, 1 H), 3.30 (s, 6 H), 2.42 (t, *J* = 7.4 Hz, 2 H), 2.12 (s, 3 H), 1.62–1.55 (m, 4 H), 1.35 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, DEPT): δ = 208.7, 104.4 (–), 52.8 (+, 2 C), 43.6 (+), 32.4 (+), 29.9 (–), 24.2 (+), 23.6 (+) ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 2950, 1713, 1364, 1127, 1051 cm^{-1}. HRMS (DI, EI): calcd. for $[C_9H_{18}O_3 + Na]^+$ 197.1154; found 197.1148.

(*E*)-6-Methylnona-6,8-dienal (10): Commercially sourced allyldiphenylphosphine oxide (5.4 g, 22.3 mmol, 2.3 equiv.; dried 3 times by azeotropic distillation with toluene) was dissolved in dry THF (1000 mL), and the mixture was cooled to –78 °C. Distilled HMPA (6.7 mL, 38.8 mmol, 4.0 equiv.) and BuLi (1.3 M in hexanes; 175 mL, 22.3 mmol, 2.3 equiv.) were added with rapid stirring. The resulting red solution was stirred for 30 min at –78 °C, then a solution of **17** (1.70 g, 9.7 mmol, 1.0 equiv.) in dry THF (10 mL) was added dropwise by syringe. The reaction mixture was stirred for a further 30 min at –78 °C, then at room temperature for 2 h. NH_4Cl (satd. aq.) was added. Usual extraction with EtOAc followed by flash chromatography on silica gel (petroleum ether/Et_2O, 98:2) gave (*E*)-9,9-dimethoxy-4-methylnona-1,3-diene **18** (1.3 g, 68%; 9:1 mixture of *E* and *Z* isomers), as well as recovered starting material (0.5 g, 29%). Data for **18**: R_f 0.8 (9:1 petroleum ether/Et_2O). ^1H NMR ($CDCl_3$, 400 MHz; *E* isomer reported): δ = 9.76 (s, 1 H), 6.57 (td, *J* = 10.5, 16.8 Hz, 1 H), 5.85 (d, *J* = 10.9 Hz, 1 H), 5.08 (dd, *J* = 1.8, 16.8 Hz, 1 H), 4.98 (dd, *J* = 1.8, 10.2 Hz, 1 H), 4.36 (t, *J* = 5.7 Hz, 1 H), 3.31 (s, 6 H), 2.06 (t, *J* = 7.5 Hz, 2 H), 1.74 (s, 3 H), 1.60 (m, 2 H), 1.45 (m, 2 H), 1.34 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz; *E* isomer reported): δ = 139.5, 133.4, 125.5, 114.5, 104.6, 52.6 (2 C), 39.7, 32.4, 27.6, 24.3, 16.5 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3086, 2939, 1648, 1463, 1126, 1073 cm^{-1}. HRMS (DI, EI): calcd. for $[C_{12}H_{22}O_2]$ 198.1620; found 198.1629.

Distilled water (0.5 mL) and formic acid (0.5 mL) were added to pure diene acetal **18** (200.0 mg, 1.1 mmol, 1.0 equiv.), and the mixture was stirred at room temperature for 14 h. Then Et_2O and NaOH (5% aq.) were added. Usual work-up followed by rapid flash chromatography on silica gel (petroleum ether/EtOAc, 99:1) gave dienal **10** (133 mg, 87%) as a colourless liquid containing a 90:10 mixture of *E* and *Z* isomers (unstable compound). R_f 0.2 (1:1

petroleum ether/Et_2O). ^1H NMR ($CDCl_3$, 400 MHz): δ = 9.76 (t, J = 1.7 Hz, 1 H), 6.56 (td, J = 10.5, 16.5 Hz, 1 H), 5.84 (d, J = 10.6 Hz, 1 H), 5.08 (dd, J = 1.8, 16.8 Hz, 1 H), 4.99 (dd, J = 1.8, 10.1 Hz, 1 H), 2.44 (dt, J = 1.7, 7.2 Hz, 2 H), 2.07 (t, J = 7.5 Hz, 2 H), 1.75 (s, 3 H), 1.62 (m, 2 H), 1.48 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 202.4, 138.8, 133.2, 125.8, 114.8, 43.7, 39.4, 27.2, 21.7, 16.5 ppm.

3,3-Dimethoxy-5-methyl-6-(5-oxohexyl)-5-(phenylsulfonyl)tetrahydro-2*H*-pyran-2-one (21): BuLi (1.5 M in hexanes; 10.4 mL, 15.6 mmol, 2.9 equiv.) was added to freshly distilled diethylamine (1.6 mL, 15.6 mmol, 2.9 equiv.) in dry THF (10 mL) at –78 °C. The resulting mixture was stirred for 10 min at this temperature, and then for 15 min at 0 °C. This cold basic solution was added by cannula to a solution of sulfone **2** (5.1 g, 16.1 mmol, 3.0 equiv.; dried three times by azeotropic distillation with toluene and under high vacuum overnight) in dry THF (70 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 5 min, then at –55 °C for 40 min. The reaction mixture was then cooled to –78 °C and a solution of 6-oxoheptanal **16** (690.0 mg, 5.4 mmol, 1.0 equiv.) in dry THF (5 mL, followed by a further 2 mL for rinsing) was added dropwise. The mixture was stirred for 25 min at –78 °C. Then the reaction mixture was allowed to warm to 0 °C, and after 20 min, $NaHSO_4$ (2 N aq.) and Et_2O were added. Usual extraction with Et_2O followed by purification by flash chromatography on silica gel (Et_2O/petroleum ether, 70:30 to 95:5) gave, in order of elution, starting sulfone **2** (3.2 g), and **21** (875 mg, 51%; 1:1 mixture of two diastereomers) as a pale yellow oil. R_f 0.3 (petroleum ether/Et_2O, 2:8).

Data for the first diastereomer, pure aliquot fraction: ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.88–7.56 (m, 5 H), 4.61 (dd, J = 1.7, 11.3 Hz, 1 H), 3.31 (s, 3 H), 3.22 (s, 3 H), 2.71 (d, J = 15.4 Hz, 1 H), 2.47 (m, 2 H), 2.21 (m, 1 H), 2.15 (s, 3 H), 2.11 (d, J = 15.4 Hz, 1 H), 1.99 (m, 1 H), 1.68–1.60 (m, 4 H), 1.56 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 208.5, 165.8, 137.0 134.4, 130.5, 129.3, 95.8, 81.7, 64.4 52.2, 49.0, 43.3, 39.2, 29.9, 29.6, 26.7, 23.0, 22.2 ppm.

Data for the second diastereomer, pure aliquot fraction: ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.88–7.60 (m, 5 H), 4.84 (dd, J = 1.7, 11.3 Hz, 1 H), 3.24 (s, 3 H), 3.21 (d, J = 14.8 Hz, 1 H), 3.12 (s, 3 H), 2.92 (d, J = 14.8 Hz, 1 H), 2.45 (m, 2 H), 2.19 (m, 1 H), 2.13 (s, 3 H), 1.70–1.56 (m, 5 H), 1.50 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 208.4 165.4, 135.6, 134.5, 130.4, 129.1, 94.8 78.9 64.1, 50.5, 49.3, 43.2, 39.9, 30.0, 29.9, 25.5, 23.1, 16.7 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3057, 2945, 1773, 1717, 1639, 1448, 1362, 1316 cm^{-1}. HRMS (DI, EI): calcd. for $[C_{19}H_{25}O_7S]^+$ ($[M - CH_3]^+$) 397.1321; found 397.1317.

(*E*)-2,2-Dimethoxy-4-methyl-10-oxoundec-4-enoic Acid (22a and 22b): A mixture of methanol (7 mL) and dry THF (8 mL) was cooled to –40 °C, and Na/Hg (6%; 2.8 g, 5.8 mmol, 10.0 equiv., freshly reduced in powder), $NaHCO_3$ (490.0 mg, 5.8 mmol, 10.0 equiv.), and the diastereomeric mixture of δ-lactones **21** (240.0 mg, 0.6 mmol, 1.0 equiv.; dried twice by azeotropic distillation with toluene) were added. The reaction mixture was stirred at –40 °C for ca. 2 h until no starting material remained (TLC monitoring: Et_2O/petroleum ether, 9:1). Water and Et_2O were then slowly added, and the phases were separated. The aqueous phase was then acidified until pH = 1 and extracted three times using the salting out protocol with brine/Et_2O. The latter organic phases were combined, washed with brine, and concentrated to give a ca. 1:1 mixture of **22a** and **22b**, which were neither separated nor fully characterized at this stage (175 mg) as a pale yellow oil. ^1H NMR ($CDCl_3$, 400 MHz, selected significant signals): δ = 5.26 (t, J = 5.3 Hz, 1 H), 3.33 (s, 6 H), 2.59 (s, 2 H), 2.42 (t, J = 2.4 Hz, 2 H), 2.15 (s, 3 H), 2.00 (q, J = 7.2, 14.3 Hz, 2 H), 1.66 (s, 3 H), 1.54 (m, 2 H), 1.32 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, selected significant signals): δ = 210.6, 170.5, 129.9, 128.9, 103.1, 68.4, 49.8, 43.4, 43.0, 29.8, 29.5, 28.6, 27.3, 22.9, 16.3, 14.0 ppm. This crude mixture was used directly in the next reaction.

This reaction was repeated several times, and it was observed that with commercially sourced Na/Hg amalgam (beads; 6%) alcohol **22b** was not formed, probably due to this amalgam having a lower reactivity than the amalgam we prepared ourselves.

(*E*)-But-3-enyl 2,2-Dimethoxy-4-methyl-10-oxoundec-4-enoate (23a) and (*E*)-But-3-en-1-yl 10-Hydroxy-2,2-dimethoxy-4-methylundec-4-enoate (23b): The crude ca. 1:1 mixture of **22a** and **22b** (50 mg, ca. 0.2 mmol, contaminated by some amount of phenylsulfinic acid) prepared as described above was dissolved in CH_2Cl_2 (4 mL), and 3-buten-1-ol (**9a**; 57 μL, 0.4 mmol, 2.2 equiv.), DMAP (7.0 mg, 0.05 mmol, 0.3 equiv.), and 1-ethyl-3(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC; 89.0 mg, 0.5 mmol, 2.5 equiv.) were added at room temp. with rapid stirring. The resulting pale orange solution was stirred overnight at room temperature, then $NaHSO_4$ (2 N aq.) and EtOAc were added (pH must be <4). Usual extraction followed by silica gel flash chromatography (EtOAc/petroleum ether, 20:80 to 60:40) gave, in order of elution, keto ester **23a** (23 mg, 40% from **21**), and hydroxy alcohol **23b** (23 mg 40% from **21**).

Data for **23a**, R_f 0.5 (petroleum ether/Et_2O, 1:1). ^1H NMR ($CDCl_3$, 400 MHz): δ = 5.79 (tdd, J = 6.7, 10.2, 17.4 Hz, 1 H), 5.18 (t, J = 6.9 Hz, 1 H), 5.10 (m, 2 H), 4.16 (t, J = 6.9 Hz, 2 H), 3.27 (s, 6 H), 2.54 (s, 2 H), 2.44–2.37 (m, 4 H), 2.11 (s, 3 H), 1.95 (q, J = 7.4 Hz, 2 H), 1.62 (s, 3 H), 1.53 (quint, J = 7.6 Hz, 2 H), 1.30–1.23 (quint, J = 7.5 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 208.9, 168.7, 133.7, 129.5, 129.2, 117.4, 103.0, 64.4, 49.8 (2 C), 43.6, 43.3, 32.9, 29.8, 29.1, 27.7, 23.5, 16.4 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 2941, 2991, 2859, 1747, 1713, 1643, 1459, 1360, 1323, 1200, 1137, 1109 cm^{-1}. HRMS (DI, EI): calcd. for $[C_{18}H_{30}O_5]^+$ 326.2093; found 326.2093.

Data for **23b**, R_f 0.3 (petroleum ether/Et_2O, 1:1). ^1H NMR ($CDCl_3$, 400 MHz): δ = 5.80 (ddt, J = 6.7, 10.3, 17.0 Hz, 1 H), 5.20 (t, J = 6.7 Hz, 1 H), 5.10 (m, 2 H), 4.18 (t, J = 6.9 Hz, 2 H), 3.75 (m, 1 H), 3.27 (s, 6 H), 2.55 (s, 2 H), 2.43 (q, J = 6.9 Hz, 4 H), 1.96 (q, J = 5.9 Hz, 4 H), 1.62 (s, 3 H), 1.42–1.30 (m, 6 H), 1.17 (d, J = 6.2 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 168.8, 133.7, 129.7, 117.5, 103.0, 68.0, 64.3, 49.8 (2 C), 43.4, 39.3, 32.9, 29.5, 27.9, 25.3, 23.5, 16.4 ppm.

2-Methoxybut-3-enyl (*E*)-2,2-Dimethoxy-4-methyl-10-oxoundec-4-enoate (24): Compound **22a** (140.0 mg, 0.5 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (15 mL), and alcohol **9b** (102.0 mg, 1.1 mmol, 2.2 equiv.), DMAP (18.9 mg, 0.1 mmol, 0.3 equiv.), and EDC (246.6 mg, 1.3 mmol, 2.5 equiv.) were added with rapid stirring. The resulting pale orange solution was stirred overnight at room temp., and then $NaHSO_4$ (2 N aq.) and EtOAc were added (pH must be <4). Extraction with Et_2O followed by purification by flash chromatography on silica gel (Et_2O/pentane, 20:80 to 60:40) gave compound **24** (89 mg, 49%). R_f 0.3 (petroleum ether/Et_2O, 1:1). ^1H NMR ($CDCl_3$, 400 MHz): δ = 5.70 (ddd, J = 7.2, 10.2, 17.4 Hz, 1 H), 5.32 (m, 2 H), 5.21 (t, J = 6.8 Hz, 1 H), 4.11 (d, J = 5.4 Hz, 2 H), 3.86 (dd, J = 6.0, 11.8 Hz, 1 H), 3.31 (s, 3 H), 3.27 (s, 6 H), 2.55 (s, 2 H), 2.38 (t, J = 7.4 Hz, 2 H), 2.11 (s, 3 H), 1.95 (q, J = 7.1 Hz, 2 H), 1.62 (s, 3 H), 1.54 (quint, J = 7.6 Hz, 2 H), 1.28 (quint, J = 7.1 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 208.9, 168.6, 134.5, 129.4, 129.2, 119.2, 103.0, 80.1, 66.8, 56.6, 49.8 (2 C), 43.6, 43.3, 29.6, 29.1, 29.7, 23.5, 16.4 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 2939, 2859, 1748, 1715, 1454, 1360, 1323, 1284, 1200, 1137,

1108 cm^{-1}. HRMS (DI, EI): calcd. for $[C_{19}H_{32}O_6Na]^+$ 379.2097; found 379.2091.

But-3-enyl (4*E*,10*E*)-2,2-Dimethoxy-4,10-d~imethyltrideca-4,10,12-trienoate (25): Commercially sourced allyldiphenylphosphine oxide (49.0 mg, 0.20 mmol, 2.2 equiv.;, dried 3 times by azeotropic distillation), freshly distilled HMPA (64 μL, 0.37 mmol, 4.0 equiv.), and BuLi (1.1 M in hexanes; 176 μL, 0.13 mmol, 2.2 equiv.) were added to dry THF (2 mL) at –78 °C with rapid stirring. The resulting red solution was stirred for 10 min at –78 °C, and then a solution of ketone **23a** (30.0 mg, 0.09 mmol, 1.0 equiv.) in dry THF (1 mL) was added. The reaction mixture was stirred for 10 min at –78 °C, then at room temp. for 2 h, and then EtOAc and NH_4Cl (satd. aq.) were added. Usual extraction followed by flash chromatography on silica gel (Et_2O/petroleum ether, 40:60) gave tetraene **25** (20 mg, 63%, 9:1 mixture of *E*/*Z* isomers), and also recovered starting material (10 mg, 33%). Data for **25**: R_f 0.7 (petroleum ether/Et_2O, 1:1). ^1H NMR ($CDCl_3$, 400 MHz): δ = 6.56 (td, *J* = 10.5 Hz, 16.8 1 H), 5.84–5.73 (m, 2 H), 5.21 (t, *J* = 6.9 Hz, 1 H), 5.15–4.93 (m, 4 H), 4.17 (t, *J* = 6.5 Hz, 2 H), 3.28 (s, 6 H), 2.55 (s, 2 H), 2.42 (q, *J* = 6.0 Hz, 2 H), 2.02 (t, *J* = 7.6 Hz, 2 H), 1.96 (q, *J* = 7.2 Hz, 2 H), 1.73 (s, 3 H), 1.63 (s, 3 H), 1.43–1.35 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 168.7, 139.6, 133.7, 133.4, 129.7, 129.1, 125.4, 117.4, 114.4, 103.0, 64.4, 49.8 (2 C), 43.4, 39.7, 33.0, 29.2, 27.9, 27.4, 16.5, 16.3 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3064, 2956, 1727, 1642, 1478, 1445, 1375, 1284, 1129 cm^{-1}. HRMS (DI, EI): calcd. for $[C_{21}H_{34}O_4]^+$ 350.2457; found 350.2461.

2-Methoxybut-3-enyl (4*E*,10*E*)-2,2-Dimethoxy-4,10-dimethyltrideca-4,10,12-trienoate (26): Commercially sourced allyldiphenylphosphine oxide (31.0 mg, 0.12 mmol, 3.0 equiv.; dried 3 times by azeotropic distillation), freshly distilled HMPA (29 μL, 0.17 mmol, 4.0 equiv.), and BuLi (2.2 M in hexanes; 67 μL, 0.14 mmol, 3.5 equiv.) were added to dry THF (5 mL) at –78 °C with rapid stirring. After 10 min at –78 °C, the red solution was mixed with a solution of ketone **24a** (15.0 mg, 0.04 mmol, 1.0 equiv.) in dry THF (1 mL). The reaction mixture was stirred for 10 min at –78 °C, then at room temp. for 2 h. Extraction as described above followed by purification by flash chromatography on silica gel (Et_2O/petroleum ether, 40:60) gave tetraene **26** (5 mg, 31%; 9:1 mixture of *E*/*Z* isomers), and also recovered starting material (5 mg, 33%). Data for **26**: R_f 0.7 (petroleum ether/Et_2O, 1:1). ^1H NMR ($CDCl_3$, 400 MHz): δ = 6.56 (dt, *J* = 16.7, 10.3 Hz, 1 H), 5.83 (d, *J* = 11.0 Hz, 1 H), 5.68 (ddd, *J* = 7.3, 10.3, 17.4 Hz, 1 H), 5.34 (m, 2 H), 5.22 (t, *J* = 8.1 Hz, 1 H), 5.00 (m, 2 H), 4.12 (d, *J* = 5.6 Hz, 2 H), 3.86 (dd, *J* = 6.2, 12.4 Hz, 1 H), 3.32 (s, 3 H), 3.29 (s, 6 H), 2.57 (s, 2 H), 1.98 (m, 4 H), 1.74 (s, 3 H), 1.63 (s, 3 H), 1.30 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = (no CO signal detected due to bad signal to noise ratio), 168.7, 139.6, 134.3, 133.4, 129.8, 129.0, 125.4, 119.5, 114.5, 102.9, 82.2, 66.9, 56.9, 49.8 (2 C), 43.6, 39.8, 29.7, 27.9, 27.2, 16.6, 16.4 ppm. HRMS (DI, EI): calcd. for $[C_{22}H_{36}O_5]^+$ 380.2563; found 380.2566.

Methyl (*E*)-2,2-Dimethoxy-4-methyl-10-oxoundec-4-enoate (27a): The crude mixture of **22a** and **22b** (250.0 mg, ca. 1.0 equiv.; partially contaminated with phenylsulfinic acid) prepared as described above was dissolved in Et_2O (10 mL) under N_2 at room temp. MeOH (2.5 mL) was added, and then commercially sourced (trimethylsilyl)diazomethane (2.0 M in Et_2O; 1.2 mL, 2.5 equiv.) was added slowly. Due to its toxicity, care was taken to use a well-ventilated hood.[50] The yellow reaction mixture was stirred for 20 min, then it was evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel (Et_2O/pentane, 20:80 to 80:20) to give keto ester **27a** (75 mg) and hydroxy ester **27b** (75 mg; 57% combined yield).

Data for **27a**: R_f 0.5 (Et_2O/pentane, 1:1). ^1H NMR ($CDCl_3$, 400 MHz): δ = 5.20 (t, *J* = 6.6 Hz, 1 H), 3.74 (s, 3 H), 3.29 (s, 6 H), 2.56 (s, 2 H), 2.40 (t, *J* = 7.4 Hz, 2 H), 2.13 (s, 3 H), 1.96 (q, *J* = 7.2 Hz, 2 H), 1.63 (s, 3 H), 1.55 (m, *J* = 7.4 Hz, 3 H), 1.29 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, DEPT): δ = 208.9, 169.1, 129.3 (+), 128.9, 103.2, 52.0 (+), 49.8 (2 C, +), 43.5 (–), 43.4 (–), 29.7 (+), 29.0 (–), 27.6 (–), 23.3 (–), 16.2 (+) ppm. HRMS (DI, EI): calcd. for $[C_{15}H_{26}O_5 + Na]^+$ 309.1678; found 309.1672.

Data for **27b**: R_f 0.2 (Et_2O/pentane, 1:1). ^1H NMR ($CDCl_3$, 400 MHz): δ = 5.15 (t, *J* = 7.0 Hz, 1 H), 3.74 (m, 1 H), 3.70 (s, 3 H), 3.24 (s, 6 H), 2.51 (s, 2 H), 1.92 (m, 2 H), 1.58 (s, 3 H), 1.36–1.24 (m, 6 H), 1.13 (d, *J* = 6.2 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 169.1, 129.8 (+), 129.0, 103.3, 67.8 (+), 52.0 (+), 49.7 (2 C, +), 43.4 (–), 39.1 (–), 29.4 (–), 27.8 (–), 25.2 (–), 23.4 (+), 16.2 (+) ppm. HRMS (DI, EI): calcd. for $[C_{15}H_{28}O_5 + Na]^+$ 311.1834; found 311.1831.

2-Iodoxybenzoic acid (218.0 mg, 0.8 mmol, 3.0 equiv.) was dissolved in DMSO (1 mL), and a solution of alcohol **27b** (85.0 mg, 0.3 mmol, 1.0 equiv.) in dry THF (5 mL) was added at room temperature. The reaction mixture was stirred overnight in the dark at room temperature, then water (5 mL) was added. The resulting mixture was stirred for 4 h, and a white precipitate was formed. The mixture was then filtered through Celite (rinsing several times with Et_2O). Usual extraction of the filtrate with EtOAc followed by flash chromatography on silica gel (EtOAc/petroleum ether, 20:80 to 60:40) gave keto ester **27a** (68 mg, 81%). Spectroscopic data were in agreement with those of **27a** isolated as described above.

(*E*)-[(2*S*,3*R*,4*S*)-1-(*tert*-Butyldimethylsilyloxy)-4-methoxy-2-methylhex-5-en-3-yl] 2,2-Dimethoxy-4-methyl-10-oxoundec-4-enoate (28): KOH (10% aq.; 5 mL) was added to keto ester **27a** (90.0 mg, 0.31 mmol). The reaction mixture was heated at reflux until no more starting material remained (2 h). HCl (2 N aq.) was added to the reaction mixture until the pH reached ca. 1. The aqueous phase was saturated with NaCl, then extraction was carried out with Et_2O to give crude acid **22a** (90 mg). Commercially sourced DMAP (34.0 mg; 0.27 mmol, 3.0 equiv.) and then dry toluene (1 mL) were added to this crude product (25.0 mg, 0.09 mmol, 1.0 equiv.; dried by azeotropic distillations with toluene) at room temp. under N_2. The mixture was stirred for 5 min, then freshly distilled triethylamine (50 μL, 0.37 mmol, 4.0 equiv.), commercially sourced 2,4,6-trichlorobenzoyl chloride (43 μL, 0.27 mmol, 3.0 equiv.), and a solution of alcohol **9c** (76.0 mg; 0.27 mmol, 3.0 equiv.; dried by azeotropic distillation 3 times with toluene) in toluene (1 mL) were added. The resulting orange mixture was stirred for 30 h at room temp., then Et_2O and $NaHCO_3$ (satd. aq.) were added. Extraction was carried out with Et_2O, and purification on silica gel (Et_2O/pentane, 10:90 to 50:50) gave, in order of elution, unconsumed alcohol **9c**, and keto ester **28** (30.0 mg, 63% over two steps) as a pale yellow oil. ^1H NMR ($CDCl_3$, 400 MHz): δ = 5.76 (ddd, *J* = 7.8, 11.3, 16.8 Hz, 1 H), 5.26 (m, 2 H), 5.15 (t, *J* = 4.6 Hz, 1 H), 3.77 (dd, *J* = 4.4, 7.8 Hz, 1 H), 3.59–3.38 (m, 2 H + 1 H), 3.26 (s, 9 H), 2.58 (s, 2 H), 2.40 (t, *J* = 7.4 Hz, 2 H), 2.13 (s, 3 H), 1.96 (m, 2 H + 1 H), 1.62 (s, 3 H), 1.55 (m, 2 H), 1.30 (m, 2 H), 0.92 (d, *J* = 6.9 Hz, 3 H), 0.88 (s, 9 H), 0.03 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, DEPT): δ = 209.0, 168.3, 134.6 (+), 129.1, 128.1 (+), 119.5 (–), 102.1, 82.8 (+), 76.1 (+), 65.4 (–), 56.3 (+), 49.9 (+), 49.7 (+), 43.7 (–), 42.5 (–), 36.4 (+), 29.8 (+), 29.0 (–), 27.8 (–), 25.9 (3 C, +), 23.6 (–), 18.2, 16.8 (+), 12.4 (+), –5.4 (2 C) ppm. HRMS (DI, EI): calcd. for $[C_{28}H_{52}O_7Si + Na]^+$ 551.3380; found 551.3375.

(4*E*,10*E*)-[(2*S*,3*R*,4*S*)-1-(*tert*-Butyldimethylsilyloxy)-4-methoxy-2-methylhex-5-en-3-yl] 2,2-Dimethoxy-4,10-dimethyltrideca-4,10,12-

trienoate (29): Commercially sourced allyldiphenylphosphine oxide (43.0 mg, 0.17 mmol, 3.0 equiv.; dried three times by toluene azeotropic distillation), freshly distilled DMPU (21 μL, 0.17 mmol, 3.0 equiv.), and BuLi (2.1 M in hexanes; 84 μL, 0.17 mmol, 3.0 equiv.) were added to dry THF (5 mL) at –78 °C with rapid stirring. This red solution was stirred for 10 min at –78 °C, and then a solution of keto ester **28** (31.0 mg, 0.059 mmol, 1.0 equiv.) in dry THF (1 mL) was added. The reaction mixture was stirred for 10 min at –78 °C, then at room temp. for 2 h, and then EtOAc and NH_4Cl (satd. aq.) were added. Usual extraction with EtOAc followed by purification by flash chromatography on silica gel (Et_2O/petroleum ether, 40:60) gave diene ester **29** (25 mg, 77%; 9:1 mixture of *E*/*Z* isomers), as well as recovered starting material **28** (5 mg, 16%). Data for **29**: R_f 0.9 (petroleum ether/Et_2O, 1:1). ^1H NMR ($CDCl_3$, 400 MHz): δ = 6.56 (dt, *J* = 10.5, 16.7 Hz, 1 H), 5.76 (m, 2 H), 5.32 (m, 2 H), 5.15 (t, *J* = 4.7 Hz, 1 H), 5.00 (m, 2 H), 3.77 (dd, *J* = 4.4, 7.8 Hz, 1 H), 3.59–3.38 (m, 2 + 1 H), 3.29 (s, 6 H), 3.28 (s, 3 H), 2.58 (s, 2 H), 2.06–1.95 (m, 5 H), 1.73 (s, 3 H), 1.63 (s, 3 H), 1.40–1.30 (m, 4 H), 0.94 (d, *J* = 6.9 Hz, 3 H), 0.88 (s, 9 H), 0.03 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, DEPT): δ = 168.3, 139.8, 134.7 (+), 133.4 (+), 128.8, 128.6 (+), 125.3, 119.5 (–), 114.4 (–), 102.1, 82.8 (+), 76.1 (+), 65.4 (–), 56.4 (+), 49.9 (+), 49.7 (+), 42.6 (–), 39.7 (–), 36.4 (+), 29.2 (–), 27.9 (–), 27.5 (–), 25.9 (3 C, +), 18.2, 16.8 (+), 16.5 (+), 12.4 (+), –5.4 (2 C) ppm. HRMS (DI, EI): calcd. for $[C_{31}H_{56}O_6Si + Na]^+$ 575.3744; found 575.3745.

(5*E*,11*E*,13*Z*)-3,3-Dimethoxy-5,11-dimethyloxacyclohexadeca-5,11,13-trien-2-one (*Z*-30) and (5*E*,11*E*,13*E*)-3,3-Dimethoxy-5,11-dimethyloxacyclohexadeca-5,11,13-trien-2-one (*E*-30): Typical conditions for RCM experiments: Before use, CH_2Cl_2 was degassed using a freeze–pump–thaw technique (4×). Benzylidene-bis(tricyclohexylphosphine)dichlororuthenium (Grubbs I precatalyst; 34.0 mg, 0.023 mmol, 0.2 equiv.) was added to a solution of tetraenic ester **25** (40 mg, 0.11 mmol, 1.0 equiv.) in degassed CH_2Cl_2 (90 mL). The reaction mixture was stirred at room temperature for 16 h. After this time, TLC showed that all of the starting material had been consumed. Activated charcoal (1.7 g, 50-fold excess w/w with respect to the catalyst) was added to the reaction mixture, which was then stirred for 20 h at room temp. The mixture was filtered through a Celite pad (rinsing several times with CH_2Cl_2). The solvent was evaporated under reduced pressure, and the residue was purified by flash chromatography on silica gel (Et_2O/pentane, 0:100 to 50:50) to give macrolactone **30** (23 mg, 66%) as an unseparated mixture of *E* and *Z* isomers (*E*/*Z* > 95:5 based on ^1H NMR spectroscopy). R_f 0.7 (pentane/Et_2O, 7:3).

Data for *Z*-**30** (major isomer): ^1H NMR ($CDCl_3$, 400 MHz): δ = 6.35 (t, *J* = 10.8 Hz, 1 H), 5.99 (d, *J* = 10.8 Hz, 1 H), 5.38 (app q, *J* = 8.2 Hz, 1 H), 5.16 (t, *J* = 6.4 Hz, 1 H), 3.93 (m, 2 H), 3.30 (s, 6 H), 2.54 (m, 4 H), 2.12 (m, 2 H), 2.00 (m, 2 H), 1.72, 1.69 (2 s, 2×3 H), 1.55 (m, 2 H), 1.30 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, DEPT): δ = 168.8, 138.6, 130.0 (+), 129.4, 129.0 (+), 121.7 (+), 119.4 (+), 104.2, 64.6 (–), 50.0 (2 C, +), 44.0 (–), 37.0 (–), 27.0 (–), 26.9 (–), 26.8 (–), 17.2 (+), 16.5 (+) ppm. IR CH_2Cl_2): $\tilde{\nu}$ = 2940, 2858, 1791, 1748, 1709, 1455, 1378, 1325, 1288, 1199, 1139, 1099, 1063 cm^{-1}. HRMS (DI, EI): calcd. for $[C_{19}H_{30}O_4]^+$ 322.2144; found 322.2149.

Data for *E*-**30** (minor isomer): ^1H NMR spectral assignments deduced from spectra of mixtures containing different *E*/*Z* ratios. ^1H NMR ($CDCl_3$, 400 MHz): δ = 6.26 (dd, *J* = 10.6, 16.0 Hz, 1 H), 5.86 (d, *J* = 10.8 Hz, 1 H), 5.63–5.56 (m, 1 H), 5.22 (t, *J* = 6.4 Hz, 1 H), 4.33 (t, *J* = 5.3 Hz, 2 H), 3.25 (s, 6 H), 2.57 (s, 2 H), 2.47 (m, 2 H), 2.15 (m, 2 H), 1.99 (m, 2 H), 1.75 (s, 3 H), 1.65 (s, 3 H), 1.46–1.41 (m, 4 H) ppm.

(5*E*,11*E*,13*E*,15*S*)-3,3,15-Trimethoxy-5,11-dimethyloxacyclohexadeca-5,11,13-trien-2-one (31*Z*): Grubbs I precatalyst (1.0 mg, 0.003 mmol, 0.18 equiv.) was added to a solution of ester **26** (5 mg, 0.013 mmol, 1.0 equiv.) in degassed CH_2Cl_2 (80 mL), and the reaction mixture was stirred at room temperature for 22 h. After this time, TLC showed no remaining starting material. Activated charcoal (50 mg) was added to the reaction mixture, which was then stirred for 20 h at room temp. The mixture was filtered through a Celite pad, rinsing with CH_2Cl_2. The solvent was evaporated in vacuo, and the residue was purified by flash chromatography on silica gel (Et_2O/pentane, 0:100 to 50:50) to give macrolactone **31** (2.5 mg, 51%, 12*Z*/12*E* >95:5) as a mixture of unseparated isomers, contaminated with starting material. Data for **31*Z***: R_f 0.9 (petroleum ether/Et_2O, 1:1). ^1H NMR ($CDCl_3$, 400 MHz): δ = 6.38 (t, *J* = 10.8 Hz, 1 H), 5.85 (d, *J* = 10.8 Hz, 1 H), 5.26 (dd, *J* = 8.5, 11.2 Hz, 1 H), 5.17 (t, *J* = 6.9 Hz, 1 H), 4.41 (m, 1 H), 4.12 (d, *J* = 5.6 Hz, 2 H), 3.32 (s, 3 H), 3.29 (s, 6 H), 2.57–2.51 (m, 2 H), 1.72 (s, 3 H), 1.70 (s, 3 H), 1.56–1.51 (m, 4 H), 1.33–1.25 (m, 4 H) ppm. HRMS (DI, EI): calcd. for $[C_{20}H_{32}O_5 + Na]^+$ 375.2147; found 375.2151.

(5*E*,11*E*,13*E*,15*S*,16*R*)-16-[(*S*)-1-(*tert*-Butyldimethylsilyloxy)-propan-2-yl]-3,3,15-trimethoxy-5,11-dimethyloxacyclohexadeca-5,11,13-trien-2-one (32*Z*): Precatalyst M71-PCy_3 (**35**; 2 mg, 0.003 mmol, 0.1 equiv.) was added to a solution of ester **29** (15 mg, 0.03 mmol, 1 equiv.) in degassed CH_2Cl_2 (15 mL). The reaction mixture was stirred for 22 h at room temperature. After this time, TLC showed some remaining starting material. and Further M71-PCy_3 (**35**; 2 mg, 0.003 mmol, 0.1 equiv.) was then added to the reaction mixture, which was then stirred for a further 22 h at room temperature. Activated charcoal (50-fold excess w/w with respect to the catalyst) was added to the reaction mixture. The mixture was stirred for 20 h at room temp., then it was filtered through a Celite pad, rinsing with CH_2Cl_2. The solvent was evaporated in vacuo, and the residue was purified by flash chromatography on silica gel (Et_2O/pentane, 0:100 to 50:50) to give macrolactone **32** (7 mg, 48%) as a 7:3 mixture of *Z* and *E* isomers at C-12 (contaminated with some starting material). Data for **32*Z***: R_f 0.9 (petroleum ether/Et_2O, 1:1). ^1H NMR ($CDCl_3$, 400 MHz, main signals for the major 12*Z* isomers reported): δ = 6.37 (t, *J* = 11.1 Hz, 1 H), 5.95 (d, *J* = 11.7 Hz, 1 H), 5.39 (t, *J* = 6.9 Hz, 1 H), 5.25 (dd, *J* = 8.3, 10.5 Hz, 1 H), 4.34–4.22 (m, 2 H), 3.47 (m, 2 H), 3.37 (s, 3 H), 3.30 (s, 6 H), 2.65–2.49 (m, 2 + 1 H), 2.06–1.95 (m, 4 H), 1.71 (s, 3 H), 1.55 (s, 3 H), 1.40–1.30 (m, 4 H), 1.02 (d, *J* = 6.9 Hz, 3 H), 0.84 (s, 9 H), 0.01 (s, 6 H) ppm. HRMS (DI, EI): calcd. for $[C_{29}H_{52}O_6Si + Na]^+$ 547.3431; found 547.3425.

M71-PCy_3 Complex 35: Ru indenylidene catalyst **36** (4.16 g, 4.51 mmol, 1 equiv.) and copper chloride (447 mg, 4.51 mmol, 1 equiv.) were dissolved in dry CH_2Cl_2 (90 mL), and 2,2,2-trifluoro-*N*-(4-isopropoxy-3-vinylphenyl)acetamide **37** (1.23 g, 4.51 mmol, 1 equiv.) was added. The resulting mixture was stirred at 35 °C for 2 h 30 min. The volatiles were removed under reduced pressure, pentane/acetone, 9:1 was added to the residue, and the resulting mixture was filtered through a plug of Celite. The filtrate was concentrated in vacuo. Acetone was added to the residue, and the resulting mixture was filtered through a plug of Celite. The filtrate was concentrated in vacuo to give M71-PCy_3 (**35**) as a brown microcrystalline solid (2.27 g, 71%). ^1H NMR (400 MHz, $CDCl_3$): δ = 17.29 (d, *J* = 4.5 Hz, 1 H), 8.00 (d, *J* = 2.5 Hz, 1 H), 7.91 (br. s, 1 H), 7.67 (dd, *J* = 8.9, 2.5 Hz, 1 H), 7.01 (d, *J* = 8.9 Hz, 1 H), 5.22–5.13 (m, 1 H), 2.34–2.18 (m, 3 H), 2.00 (t, *J* = 8.5 Hz, 6 H), 1.84–1.66 (m, 20 H), 1.29–1.12 (m, 10 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 276.5, 154.7, 150.6, 143.8, 130.0, 121.0, 117.1, 114.8, 113.6, 76.1, 35.8 (3 C), 35.5 (3 C), 30.1 (3 C), 27.8 (3

C), 27. (3 C), 26.9, 26.2 (2 C), 22.0 (2 C) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –75.58 ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 58.84 ppm. HRMS (MALDI-TOF) calcd. for $C_{30}H_{46}{}^{35}Cl^{37}ClF_3NO_2PRu$ $[M]^+$ 713.1531; found 713.1712. $C_{30}H_{45}Cl_2F_3NO_2PRu$ (711.63): calcd. C 50.63, H 6.37, N 1.97; found C 51.18, H 6.49, N 1.97, S 0.

Methyl 2,2-Dimethoxy-4-methylpent-4-enoate (38):[51] A solution of LDA was prepared by dropwise addition of BuLi (2.1 M in hexanes; 3.7 mL, 4.9 mmol, 1.0 equiv.) to a stirred solution of freshly distilled diisopropylamine (692 μL, 4.9 mmol, 1.0 equiv.) in THF (6 mL) at –78 °C, and the mixture was stirred for 15 min. A solution of methyl dimethoxyacetate (605 μL, 4.9 mmol, 1 equiv.) in THF (6 mL) was added dropwise. The reaction mixture was stirred for 15 min at –78 °C, and then for 10 min at 0 °C. Commercially sourced 3-bromo-2-methylpropene (498 μL, 4.9 mmol, 1.0 equiv.) was then added. The mixture was stirred for 20 min at 0 °C, then it was allowed to warm to room temperature, and it was stirred for a further 30 min. Water was added, and usual extraction was carried out with EtOAc. The crude material was purified by flash chromatography (EtOAc/petroleum ether, 20:80 to 50:50) to give **38** (699 mg, 75%), and also *N*,*N*-diisopropyl-2,2-dimethoxyacetamide (80 mg, 8%) as a by-product.[52] Data for **38**: ^1H NMR ($CDCl_3$, 400 MHz): δ = 4.82 (m, 2 H), 3.76 (s, 3 H), 3.29 (s, 6 H), 2.61 (s, 2 H), 1.75 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 161.9, 139.5, 114.9, 102.8, 52.2, 49.8 (2 C), 41.6, 22.9 ppm. HRMS (DI, EI) Calc for $[C_9H_{16}O_4]^+$ 188.1049; found 188.1047.

Methyl (*Z*)-2-Methoxy-4-methylpenta-2,4-dienoate (39): Camphorsulfonic acid (22 mg, 0.05 equiv.) was added to acetal **36** (360 mg, 1.9 mmol, 1.0 equiv.) in dry toluene (3 mL) at room temperature. The reaction mixture was stirred at 150 °C under 300 W microwave irradiation. Every 2 h, the progress of the reaction was checked by ^1H NMR spectroscopy, and additional amounts of acid were added after 2 h and 4 h of reaction time (2× 22 mg). After 6 h, the reaction mixture was cooled to room temp., and solid $NaHCO_3$ was added. The mixture was stirred for 30 min, and then usual extraction with EtOAc followed by flash chromatography on silica gel (EtOAc/petroleum ether, 10:90) gave dienoic ester **39** (201 mg, 67%). ^1H NMR ($CDCl_3$, 400 MHz): δ = 6.62 (s, 1 H), 5.27 (s, 1 H), 5.13 (s, 1 H), 3.80 (s, 3 H), 3.67 (s, 3 H), 2.05 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.0, 144.7, 139.5, 126.6, 122.0, 60.1, 52.0, 21.5 ppm. HRMS (DI, EI) Calc for $[C_8H_{12}O_3]^+$ 156.0786; found 156.0787. ^1H NMR signals were in agreement with literature data for the *Z* isomer.[42]

(5*E*,11*E*,13*E*)-3-Methoxy-5,11-dimethyloxacyclohexadeca-3,5,11,13-tetraen-2-one (*E*-40) and (5*E*,11*E*,13*Z*)-3-Methoxy-5,11-dimethyloxacyclohexadeca-3,5,11,13-tetraen-2-one (*Z*-40): Camphorsulfonic acid (1 mg, 0.001 mmol, 0.05 equiv.) was added to pure macrolactone *Z*-**30** (10 mg, 0.03 mmol, 1 equiv.) in dry toluene (1 mL) at room temperature. The reaction mixture was stirred at 150 °C under microwave irradiation (300 W) for 1 h. Then solid $NaHCO_3$ was added to the reaction mixture, and extraction was carried out with EtOAc. Analysis by NMR spectroscopy showed no consumption of the starting material. The remaining major starting macrolactone *Z*-**30** was dissolved in dry toluene (1 mL), and camphorsulfonic acid (2 mg, 0.02 mmol, 0.1 equiv.) was added. The reaction mixture was stirred for 2 h at 150 °C under microwave irradiation (300 W). Then solid $NaHCO_3$ was added, and extraction was carried out with EtOAc as before. The residue was purified by flash chromatography on silica gel (Et_2O/pentane, 0:100 to 30:70) to give pure elimination products **40** (4 mg, 45%) as a 4:4:1:1 mixture of isomers, of which 12-*E*-**40** and 12-*Z*-**40** were the major isomers. All attempts to separate these isomers proved fruitless. ^1H NMR ($CDCl_3$, 600 MHz, selective NOESY and TOCSY measurements, signals for the two major isomers): δ = 7.02, 6.93 (2 s, 2×1 H, 2 3-H), 6.52 (dd, *J* = 14.6, 11.2 Hz, 1 H, *E*-**40** 12-H), 6.40 (dd, *J* = 11.1 Hz, 1 H, *Z*-**40** 12-H), 6.32 (d, *J* = 11.7 Hz, 1 H, *Z*-**40** 11-H), 5.91 (d, *J* = 11.1 Hz, 1 H, *E*-**40** 11-H), 5.57–5.49 (m, 2 H, *E*-**40** 13-H and 1×5-H), 5.44 (dd, *J* = 8.0, 8.0 Hz, 1 H, 1×5-H), 5.35 (ddd, *J* = 9.8, 9.4, 8.6 Hz, 1 H, *Z*-**40** 13-H), 4.20 (m, 2×2 H, 2 15-H_2), 3.68, 3.67 (2 s, 6 H, 2 OMe), 2.59 (m, 2 H, *Z*-**40** 14-H), 2.46 (ddd, *J* = 6.3, 6.0, 6.0 Hz, 2 H, *E*-**40** 14-H), 2.31 (m, 2 H, 9-H_2), 2.25 (m, 2 H, 9-H_2), 2.09 (m, 2 + 4 H, 2×6-H_2 and 1×H_2), 2.01 (s, 6 H, 2 Me-C-4), 1.72, 1.71 (2 s, 2×3 H, 2 Me-C-10), 1.61 (m, 6 H) ppm. HRMS (DI, EI): calcd. for $[C_{18}H_{26}O_3 + Na]^+$ 313.1780; found 313.1778.

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectra for all reported compounds.

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