Total Synthesis of (−)-Salicylihalamide

Alois Fürstner,* Thorsten Dierkes, Oliver R. Thiel, and Gaetano Blanda[a]

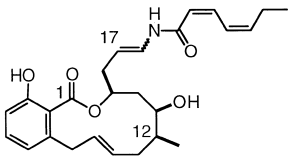
Abstract: A concise total synthesis of the potent cytotoxic marine natural products salicylihalamide A and B (**1a**, **b**) is reported. Key steps of our approach were the asymmetric hydrogenation reactions of β-keto esters **18** and **32** catalyzed by $[((S)\text{-BINAP})RuCl_2]_2 \cdot NEt_3$ and the cyclization of the macrolide core by ring closing olefin metathesis (RCM) using the "second-generation" ruthenium carbene complex **24** as the catalyst which bears an imidazol-2-ylidene ligand. The *E*/*Z* ratio obtained in this macrocyclization reaction was determined by the protecting groups at the remote phenolic OH group of the cyclization precursor. The elaboration of the resulting cycloalkene **37** into the final target involved a $CrCl_2$-mediated synthesis of vinyliodide **49** which, after deprotection, did undergo a copper-catalyzed cross-coupling process with the (*Z*,*Z*)-configurated carboxamide **42** to form the labile enamide moiety of **1**. Compound **42** was derived from a palladium-catalyzed Negishi coupling between butynylzinc chloride and 3-iodoacrylate **39** followed by a Lindlar reduction of enyne **40** thus obtained and a final aminolysis of the ester group.

Keywords: cross-coupling · macrocycles · metathesis · natural products · ruthenium

Introduction

Bioassay-guided fractionation of the extracts of an unidentified sponge of the *Haliclona* genus collected off the Southwestern Australian coast led to the discovery of two novel macrolide antibiotics called salicylihalamide A (**1a**) and B (**1b**).[1, 2] These compounds exhibited remarkably potent cytotoxicity in the 60-cell-line human tumor assay from the National Cancer Institute (NCI), with a mean GI_{50} concentration of only about 15 nM. The melanoma cell lines showed the highest average sensitivity ($GI_{50} = 7$ nM, $TGI = 60$ nM). Most notably, however, the activity profile of salicylihalamide in this assay showed no significant correlation to other compounds in the NCI database, indicating a novel mechanism of action.[1] From subsequent biochemical studies it was concluded that **1** does inhibit mammalian vacuolar-type (H^+)-ATPases (V-ATPases) with an unprecedented selectivity; this suggests that these proton-translocating pumps may constitute a novel molecular target for cancer therapeutic agents.[3]

The most striking structural motif of **1** is the labile enamide linkage connecting a polyunsaturated domain with a salicylic acid derived macrolactone core. Since the discovery of **1a**, **b** in 1997, several closely related natural products have been reported, including oximidine I (**2**),[4] apicularene A (**3**),[5]



Salicylihalamide A (**1a**): 17(*E*)
Salicylihalamide B (**1b**): 17(*Z*)

lobatamide A (**4**),[6] or CJ-12950 (**5**).[7] In addition to the obvious constitutional and topological resemblance, these novel enamides also show pronounced cytotoxic activities against various human cancer cell lines and share with **1** a common mode of action.[3]

While the promising biological properties render salicylihalamide and congeners relevant targets for total synthesis, their unusual structural features provide an excellent forum for the validation of new synthetic methods. In this context, a truncated version of **1** was synthesized using olefin metathesis for the cyclization of the 12-membered ring and its biological activity has been evaluated.[8] Our study has provided strong evidence that the cytotoxicity of **1** is intimately related to the presence of an intact enamide bond and has also clearly featured the relevance of ring closing metathesis (RCM) as a strategic manoeuvre en route to this family of natural products. In fact, RCM later became the key transformation in all preparative approaches towards **1** and analogues thereof reported so far, including the first total syntheses of this rewarding target.[9–11] A particularly noteworthy spin-off of

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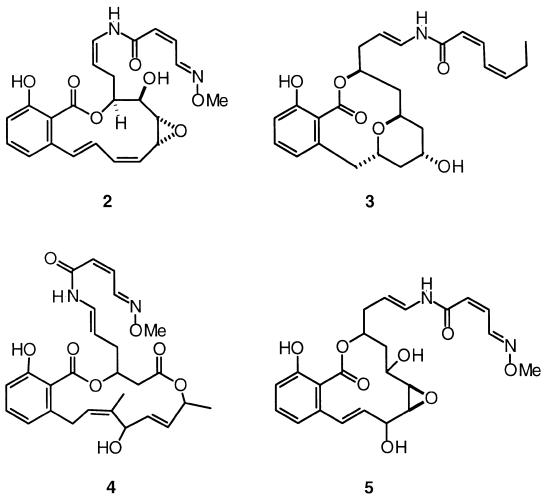


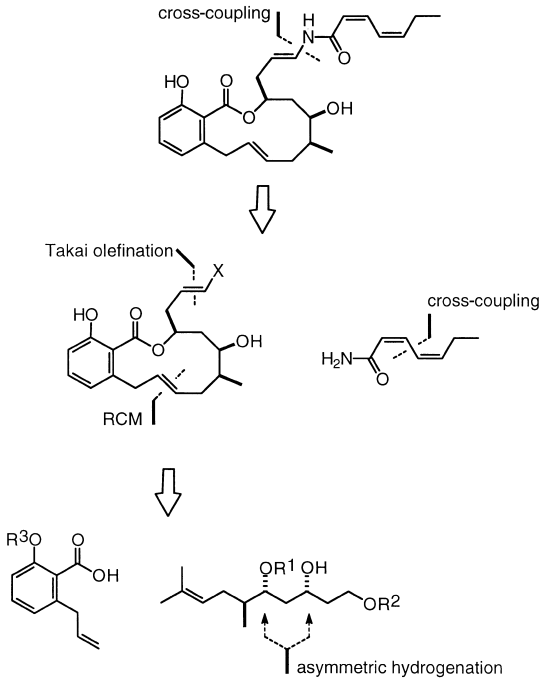
these studies is the fact that the absolute stereochemistry of salicylihalamide had to be revised and is now assigned as it appears in structure **1** (12*S*,13*R*,15*S*).[9a, 12]

Described below is a full account of our work in this field. Specifically, we outline a concise and inherently flexible approach to the core segment of **1** which relies on asymmetric hydrogenation reactions for the formation of the chiral centers. The efficient cyclization of the macrolide ring by RCM lends further credence to the notion that "second-generation" ruthenium carbene complexes are superior catalysts for this type of transformation. Finally, the enamide moiety of the target was formed by a copper-catalyzed cross coupling process which delivered this rather labile structural motif in good yield.

Results and Discussion

Retrosynthetic analysis: Anticipating the formation of the macrolide ring by RCM,[13] salicylihalamide can be deconvoluted into three synthons as shown in Scheme 1. Among the different possible disconnections for the enamide linkage,[14] we opted for a cross-coupling approach aiming at the direct formation the C–N bond, which led back to a suitably functionalized vinyl halide core and an unsaturated amide side chain as the precursors. This strategy expands on model studies that were recently disclosed;[15] it holds the promise to be straightforward and flexible and may therefore outperform the methodology previously used en route to **1**.[9] Since the enamide certainly constitutes a fragile linkage, its formation was postponed to the very end of the synthesis. Preferentially, it should be installed in the presence of the free OH groups because any deprotection step after the enamide formation might destroy this labile moiety. It was by no means clear at the beginning of this study whether the envisaged cross-coupling methodology would meet this serious constraint.

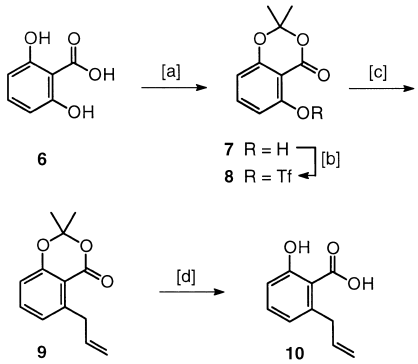
Although the aliphatic segment carrying the chiral centers of the molecule is certainly accessible by various routes, the application of asymmetric hydrogenation reactions seemed to be particularly appealing.[16] This strategy can i) deliver the target by two iterative cycles of β-keto ester formations/



Scheme 1. Retrosynthetic analysis of salicylihalamide **1**.

reductions, ii) promises reagent control over the absolute stereochemistry of the chiral centers formed, and hence iii) provides access to all possible diastereoisomers of **1**, if desirable, simply by changing the chiral ligands to the hydrogenation catalysts.

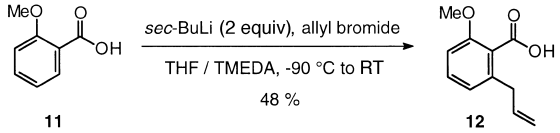
Preparation of the salicylic acid part: Two different syntheses of the required salicylic acid part of **1a**, **b** have been developed. The first one used cheap 2,6-dihydroxybenzoic acid (**6**) as the starting material which was converted on a multigram scale into triflate **8** by formation of the isopropylidene derivative **7**[17] and subsequent reaction with triflic anhydride under standard conditions (Scheme 2).[18] This compound was allylated in high yield by a modified Suzuki-type reaction[19] according to a procedure previously developed in this laboratory.[20] Specifically, 9-allyl-9-BBN was treated with KOMe to afford a mixture of borate complexes



Scheme 2. [a] Acetone, $SOCl_2$, DMAP, DME, 96%; [b] triflic anhydride, pyridine, 85%; [c] 9-allyl-9-BBN, KOMe, cat. [$PdCl_2$(dppf)], THF, 83%; [d] BCl_3, CH_2Cl_2, 96%. BBN = 9-borabicyclo[3.3.1]nonane, dppf = Fe(η^5-$C_5H_4PPh_2)_2$, DMAP = dimethylaminopyridine, DME = dimethoxyethane.

which rapidly transfer the allyl group to the triflate in the presence of catalytic amounts of [$PdCl_2$(dppf)]. Subsequent cleavage of the isopropylidene moiety of **9** was best achieved with BCl_3 in CH_2Cl_2 at 0 °C, affording the desired salicylic acid **10** in almost quantitative yield.

Alternatively, the corresponding methyl ether **12** can be conveniently prepared from commercial 2-methoxybenzoic acid (**11**) by *ortho*-metalation using *s*BuLi followed by trapping of the resulting aryllithium species with allyl bromide at low temperature (Scheme 3).[21] Although the yield of this reaction amounted only to 48%, this approach was appealing in terms of its unrivaled "economy of steps".[22]



Scheme 3. Synthesis of the required salicylic acid part by *ortho*-metalation.[21]

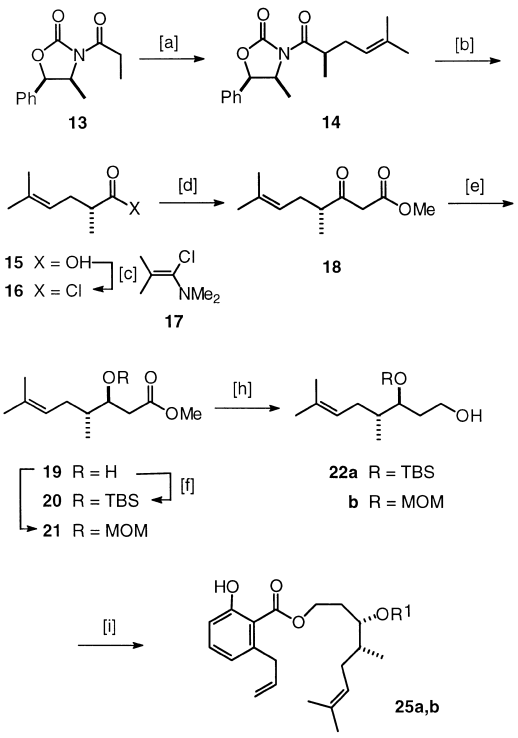
Model studies on RCM: At the outset of our project, the enantiomer of **1** was targeted because of the incorrect assignment of the absolute stereochemistry of salicylihalamide in the original publication (see above).[1, 12] Therefore, the model studies reported below concerning the crucial RCM step have been conducted in the wrong enantiomeric series.

Our synthesis began with an asymmetric alkylation reaction of the oxazolidinone derivative **13** with prenyl bromide (Scheme 4), delivering product **14** in good yield.[23] Hydrolytic cleavage of the chiral auxiliary in the presence of H_2O_2[24] afforded acid **15** which was converted into acid chloride **16** under strictly neutral conditions using the chloroenamine reagent **17**.[25] Reaction of crude **16** with the lithium enolate of methyl acetate at low temperature provided β-keto ester **18**,[26] which did undergo a ligand controlled asymmetric hydrogenation using [((*R*)-BINAP)$RuCl_2]_2 \cdot NEt_3$ as the catalyst (4 atm H_2, 80 °C).[16, 27] This carbonyl reduction occured with almost perfect diastereoselectivity (*de* > 99%). In line with literature precedence,[27a] the trisubstituted double bond of the substrate remained fully intact under these conditions.[28]

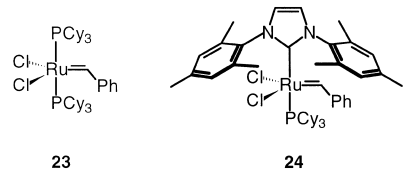
We were well aware, however, that metathesis catalysts such as the classical Grubbs ruthenium carbene complex **23**[29] are rather sensitive to the substitution pattern of the olefin.[30] Therefore the trisubstituted alkene in **22** which was necessary to impose a chemoselective path on the hydrogenation,[28] would likely impede the projected macrocyclization by RCM.

To evaluate this aspect prior to launching the actual total synthesis program, a model study was necessary. For this purpose, the secondary hydroxyl group in compound **19** was silylated and the resulting product **20** was reduced with $LiBEt_3H$ to afford primary alcohol **22a**. Subsequent esterification with acid **10** under Mitsunobu conditions[31] afforded diene **25a** which allowed to test the crucial RCM step.

In fact, the reluctance of complex **23** to react with highly substituted alkenes[30] was responsible for the failure in converting diene **25** into the desired macrocyclic product **26**. It has recently been shown, however, that the exchange of one



Scheme 4. [a] i) LiHMDS, THF, −78 °C, 30 min; ii) dimethylallyl bromide, 0 °C, 16 h, 85%; [b] LiOH, H_2O_2, THF/H_2O, 0 °C, 99%; [c] **17**, CH_2Cl_2, 90 min; [d] i) LDA, methyl acetate, THF, −78 °C, 1 h; ii) addition of crude **16**, RT, 2 h, 81%; [e] [((*R*)-BINAP)$RuCl_2]_2 \cdot NEt_3$ (0.8 mol%), H_2 (4 atm), MeOH, 80 °C, 4 h, 96%; [f] TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 1 h, 95%; [g] MOMCl, iPr_2NEt, DMAP cat., CH_2Cl_2, 40 h, 90%; [h] $LiBEt_3H$, THF, RT, 83% (R = TBS), 98% (R = MOM); [i] DEAD, PPh_3, Et_2O, 96% (**25a**), 81% (**25b**). DEAD = diethyl azodicarboxylate, MOMCl = methoxymethyl chloride.



PCy_3 ligand in **23** for a *N*-heterocyclic carbene up-graded the performance of the catalyst to a significant extent and rendered the catalyst suitable for the cyclization of tri- and even tetrasubstituted cycloalkenes.[32] Gratifyingly, reaction of diene **25** with the "second-generation" ruthenium carbene complex **24** in toluene at 80 °C afforded the 12-membered ring **26** in excellent yield (Scheme 5).[33] While this result suggested that the envisaged cyclization of the macrolide core of salicylihalamide itself was feasible, we were surprised to find that the product was formed as a single isomer which was assigned the (*Z*)-configuration based on a careful analysis of its NMR data.

This stereochemical outcome was certainly unexpected for the following reasons:

i) The vast majority of RCM-based macrocylizations reported in the literature provided (*E*,*Z*)-mixtures, with the (*E*)-isomer usually prevailing;[13]

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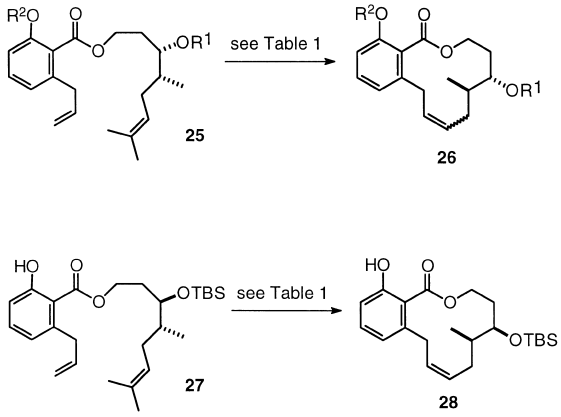
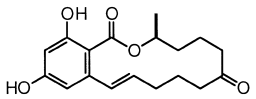


Scheme 5. Model study concerning the formation of the core segment by RCM.

ii) This trend pertained to our previous approach to a truncated salicylihalamide core which was obtained in a ratio of $E:Z = 2.3:1$;[8]

iii) NHC-containing metathesis catalysts were recently shown to be particularly (*E*)-selective;[34, 35]

iv) Complex **24**, when applied to the total synthesis of zearalenone **29**, a fungal metabolite that is closely related to the salicylihalamide core in structural terms, led to the exclusive formation of the desired (*E*)-isomer in excellent yield.[35a]



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Since it is mandatory to form the (*E*)- rather than the (*Z*)-isomer en route to **1**, we studied whether the stereochemical outcome of the RCM reaction can be rectified (see Table 1). A simple means might be the use of "participating" protecting groups.[36] Unfortunately, however, replacement of the TBS group by a more strongly ligating methoxymethyl (MOM) ether had no effect on the course of the reaction, delivering (*Z*)-**26b** as the only product of RCM in 72% yield. Similarly, inversion of the stereocenter at C-13 of the cyclization precursor (easily achieved by reducing ketoester **18** with a ruthenium catalyst containing (*S*)-BINAP rather than (*R*)-BINAP as the ligand) did not change the outcome of the reaction; thus, cyclization of diene **27** again led to the exclusive formation of the (*Z*)-configurated product **28**.[37]

In trying to rationalize this surprising yet seemingly invariable stereochemical course, we speculated whether a hydrogen bond between the phenolic OH and the COOR group in the substrates prevented free rotation in this part of the molecule and hence enforced a strongly preferred conformation of the cyclization precursors. While addressing this issue, it was noticed that protection of the phenolic OH as a TBS ether further increased the efficiency of the cyclization (97% yield) and led to appreciable amounts of the desired (*E*)-isomer **26c**. Although the $E:Z = 30:70$ ratio was far from optimal, this result suggested that it might be possible to approach salicylihalamide **1** by RCM, if the substituent at the remote phenolic OH group was properly chosen.[38]

Table 1. Model study on RCM. All reactions were carried out using complex **24** (5 mol%) as the catalyst in toluene at 80 °C unless stated otherwise.

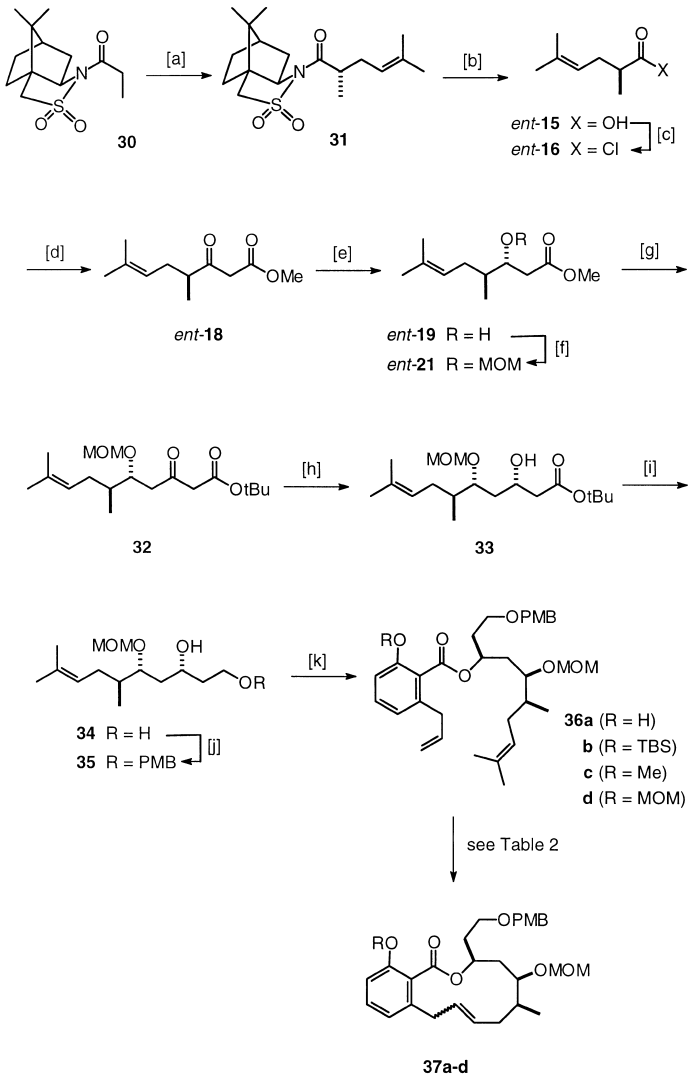
Entry	Substrate	R^1	R^2	Product	Yield [%]	*E*:*Z*
1	**25a**	TBS	H	**26a**	89	0:100
2	**25b**	MOM	H	**26b**	72[a]	0:100
3	**25c**	MOM	TBS	**26c**	97	30:70
4	**27**	TBS	H	**28**	80[a]	0:100

[a] Using 7.5 mol% of the catalyst.

Synthesis of the fully functional core of salicylihalamide: Based on the insights gained in this model study and learning from the literature that the absolute stereochemistry of **1** had originally been assigned incorrectly,[9, 12] we embarked into the total synthesis of this promising antitumor agent.

The first steps simply translate the sequence outlined above into the other enantiomeric series. For this purpose, however, it turned out advantageous to use Oppolzer's bornanesultam auxiliary to control the diastereoselectivity of the prenylation step.[39] Since compound **31** is crystalline (while the corresponding oxazolidinone derivative **14** is not) the purification of the crude product and hence the up-scaling of the reaction to multigram amounts was greatly facilitated. Saponification of **31**, conversion of the resulting acid *ent*-**15** into the acid chloride *ent*-**16** as described, followed by chain extension with lithio methyl acetate provided β-oxo ester *ent*-**18** which did undergo a chemo- and stereoselective hydrogenation in the presence of $[((S)\text{-BINAP})RuCl_2]_2 \cdot NEt_3$ as the catalyst (4 atm H_2, 80 °C). Protection of the resulting OH function in *ent*-**19** by a MOM group sets the stage for the iterative construction of the remaining stereocenter. For this purpose, a chain extension was carried out using the lithium enolate of *tert*-butyl acetate as the reagent, followed by a diastereoselective reduction of the resulting β-keto ester **32** using the same catalyst, that is $[((S)\text{-BINAP})RuCl_2]_2 \cdot NEt_3$. This hydrogenation provided best results under slightly modified conditions by lowering the temperature to 25 °C but increasing the hydrogen pressure to 80 atm. Product **33** thus formed (*de* >98%) was reduced with $LiAlH_4$ and the resulting diol **34** was converted into the mono-PMB ether derivative **35** by double deprotonation with excess NaH followed by addition of one equivalent of PMBCl; under these conditions, the alkylation of the primary alkoxide was strongly favored over the competing protection of the secondary one.[40] Esterification of alcohol **35** with acid **10** under Mitsunobu conditions gave the desired ester **36** which served as a substrate for the envisaged macrocyclization.

In line with the observations made in the model studies, the stereochemical outcome of RCM depends on the remote substituents on the phenolic OH group (Table 2). Thus, the unprotected derivative **36a** led to the exclusive formation of the (*Z*)-configurated product **37a**, the TBS-protected analogue **37b** afforded a $E:Z = 40:60$ mixture of both isomers, whereas the (*E*)-isomer prevailed when a methyl- (**37c**) or a MOM group (**37d**) blocked the phenolic site. We are unaware of any precedence, in which the choice of a remote protecting group allowed to alter the course of RCM to a similar extent.[38]



Scheme 6. [a] Lithium (cyclohexyl)(isopropyl)amide, THF, $-78\,^{\circ}C$, 60 min; then dimethylallyl bromide, HMPA, $-78\,^{\circ}C \rightarrow RT$, 79%; [b] LiOH, H_2O_2, THF/H_2O 4:1, 24 h, 95%; [c] chloroenamine **17**, CH_2Cl_2, 90 min; [d] lithio methyl acetate, THF, $-78\,^{\circ}C \rightarrow RT$, 81%; [e] [((*S*)-BINAP)$RuCl_2]_2 \cdot NEt_3$ (0.4 mol%), H_2 (4 atm), MeOH, 80 °C, 4 h, 94%; [f] MOMCl, iPr_2NEt, cat. DMAP, CH_2Cl_2, 40 h, 89%; [g] lithio *tert*-butyl acetate, THF, $-40\,^{\circ}C$, 3 h, 95%; [h] [((*S*)-BINAP)$RuCl_2]_2 \cdot NEt_3$ (1.2 mol%), H_2 (80 atm), MeOH, 25 °C, 6.5 h, 93%; [i] $LiAlH_4$, Et_2O, 0 °C, 6 h, 90%; [j] NaH, PMBCl, DMF, 90 min, 76%; [k] acid **12**, PPh_3, DEAD, Et_2O, 20 h, 93%. PMB-Cl = *para*-methoxybenzyl chloride.

Table 2. RCM-based cyclization of diene **36** to cycloalkene **37**. All reactions were carried out using complex **24** (5 mol%) as the catalyst in toluene at 80 °C unless stated otherwise.

Entry	Substrate	R	Product	*t* [h]	Yield [%]	*E*:*Z*
1	**36a**	H	**37a**	20	69[a]	0:100
2	**36b**	TBS	**37b**	1	91	40:60
3	**36c**	Me	**37c**	1.5	93	66:34
4	**36d**	MOM	**37d**	3	91[a]	68:32

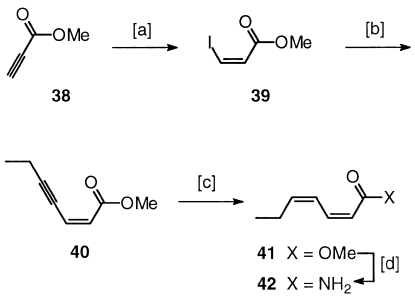
[a] Using 10 mol% of the catalyst.

It should be pointed out that the pronounced stereochemical preferences observed during these RCM reactions cannot be correlated with the thermodynamic stabilities of the isomeric products formed.[38d] Moreover, it is most unlikely that a direct interaction between the unprotected OH group of substrate **36a** with the ruthenium catalyst (e.g. via phenolate complex formation)[50] accounted for the observed (*Z*)-selectivity in this particular case. Thus, cyclization of the methoxy protected diene **36c** *in the presence of one equivalent of salicylic acid methyl ester takes the same course* as the cyclization of this substrate in the absence of the phenol in terms of yield and stereoselectivity. Since we are presently not able to provide a conclusive explanation for the observed stereochemical results, we take this case as an excellent opportunity to initiate in-depth theoretical investigations. The results of these studies will be reported in due course.

For the sake of the synthesis, it was fortunate to find that the methyl ether derivative **36c** afforded macrolide **37c** in excellent yield and reasonable selectivity in favor of the desired (*E*)-alkene. Substrate **36c** was particularly well accessible by direct esterification of fragment **35** with acid **12** (prepared in only one step as described above). Moreover, the retention times of (*E*)-**37c** and (*Z*)-**37c** were sufficiently different to allow separation of these isomers by conventional flash chromatography. (*E*)-**37c** constituted the fully functional core of salicylihalamide and was converted into the target as outlined below.

Synthesis of (*Z*,*Z*)-2,4-heptadienoic acid amide and model studies on the copper-catalyzed enamide formation: Encouraged by a recent report on enamide formations by copper catalyzed cross-coupling reactions of vinyl iodides with carboxylic acid amides,[15] we envisaged to use this strategy for the final assembly of salicylihalamide. This publication, however, left open whether this method would be compatible with ester and unprotected OH groups; this aspect is not obvious as rather high loadings of the copper(I)thiophenecarboxylate (CuTC)[41] catalyst and excess base are required. Moreover, it was not clear if a fairly labile (*Z*,*Z*)-configured $\alpha,\beta,\gamma,\delta$-unsaturated amide can be used without loss of configurational integrity.[42] These issues were addressed by the model studies summarized below.

The required amide **42** was prepared as outlined in Scheme 7. Addition of iodide to methyl propynoic acid afforded (*Z*)-**39** in good yield according to a literature procedure.[43] A subsequent Negishi coupling with butynylzinc chloride in the presence of catalytic amounts of $[Pd(PPh_3)_4]$ furnished product **40**,[44] which did undergo Lindlar reduction to afford the (*Z*,*Z*)-configurated ester **41**. This step required



Scheme 7. [a] LiI, CH_3CN, HOAc, 70 °C, 12 h, 80%; [b] butynylzinc chloride, cat. $[Pd(PPh_3)_4]$, THF, 3 h, 90%; [c] H_2 (1 atm), Lindlar catalyst, cat. quinoline, CH_2Cl_2, 50 min, 80%; [d] NH_4OH, NH_4Cl, 4 d, 62%.

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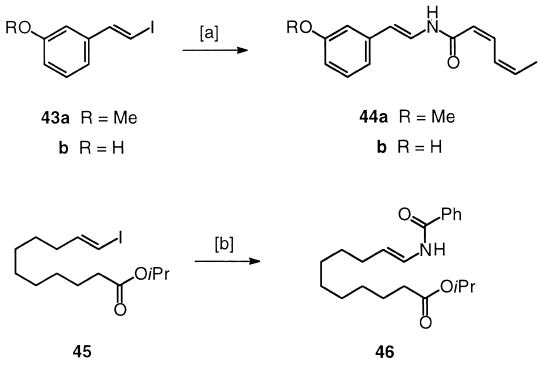
careful monitoring by TLC to avoid overreduction. Aminolysis of ester **41** then provided the required amide **42** which was immediately used for the cross-coupling experiments.

We were pleased to see that this amide did undergo a smooth reaction with vinyl iodide **43a** bearing a methoxy substituent on the arene ring in the presence of CuTC (50 mol%) and excess Rb_2CO_3 as the base in anhydrous dimethylacetamide (DMA) at 90 °C (Scheme 8). Note, however, that an excess of **42** was necessary to drive the

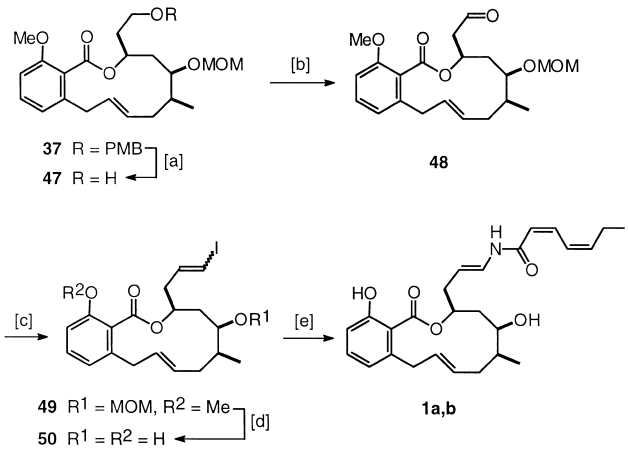


Scheme 8. [a] amide **42** (5 equiv), copper(I) thiophene-2-carboxylate (50 mol%), Rb_2CO_3 (3 equiv), DMA, 90 °C, 2 h, 89% (R = Me, $E:Z$ = 2:1)), 86% (R = H, only E); [b] benzamide, copper(I) thiophene-2-carboxylate (30 mol%), Cs_2CO_3 (1.5 equiv), NMP, 90 °C, 70%. NMP = *N*-methylpyrrolidone, DMA = dimethyl acetamide.

conversion. The cross-coupling of substrate **43b** containing an unprotected phenol group proceeded similarly well. In the latter case, the resulting enamide **44b** was obtained as a single diastereoisomer in high yield. This result proved that the (*Z*)-configuration of both alkene groups in the amide part was fully retained, whereas isomerization of the double bond of vinyl iodide **43b** ($E:Z$ = 8:1) obviously could not be avoided. A third model reaction probing the stability of an ester group under the reaction condition also gave a satisfactory result (**45** → **46**).

Completion of the total synthesis: Since these model studies provided an encouraging outlook on the end game of the total synthesis of **1**, the macrolide core **37** prepared by RCM was converted into a suitable vinyl iodide as shown in Scheme 9. For this purpose, the -OPMB group was cleaved off by means of DDQ,[45] the resulting primary alcohol **47** was oxidized with Dess–Martin periodinane,[46] and aldehyde **48** thus formed was subjected to a Takai olefination.[47] Specifically, treatment of **48** with CHI_3 and $CrCl_2$ in a mixed solvent system (THF/1,4-dioxane 1:6)[48] furnished the desired vinyl iodide **49** as an inseparable mixture of isomers ($E:Z$ = 9:1, as determined by NMR). This material was fully deprotected on exposure to BBr_3, since cleavage of the -OMe and the -OMOM group after the installation of the enamide might have endangered the valuable product (c.f. retrosynthetic analyis).

With the iodide **50** at hand, the stage was set for the final assembly of the target by the copper-catalyzed cross coupling technique. Gratifyingly, reaction of **50** with amide **42** (3 equiv) in the presence of CuTC (50 mol%) and Rb_2CO_3 (3 equiv) proceeded cleanly, affording a mixture of salicylihalamide A

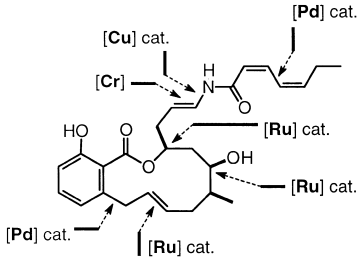


Scheme 9. [a] DDQ, H_2O/CH_2Cl_2 1:18, RT, 12 h, 94%; [b] Dess–Martin periodinane, CH_2Cl_2, 0 °C → RT, 18 h, 87%; [c] CHI_3, $CrCl_2$, THF/1,4-dioxane 1:6, RT, 16 h, 87% ($E:Z$ = 9:1); [d] BBr_3, CH_2Cl_2, −78 °C → RT, 1 h, 88%; [e] amide **42** (3 equiv), copper(I) thiophene-2-carboxylate (50 mol%), Rb_2CO_3 (3 equiv), DMA, 90 °C, 2 h, 57%. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

and B in 57% isolated yield (**1a**:**1b** ca. 2.5:1). The isomers could be separated by HPLC and were identical in all respects to the natural products.[1, 9, 12] It is worth mentioning, however, that the copper-catalyzed enamide formation leading to **1** proceeded if Rb_2CO_3 was employed as the base. Although we can presently provide no satisfactory explanation, the use of Cs_2CO_3 failed to afford any of the desired target molecule under otherwise identical conditions, despite the fact that this base had worked well in model studies.[15]

Conclusion

A concise and inherently flexible approach to the potent antitumor agent salicylihalamide **1** was outlined. This strongly cytotoxic agent was assembled from three well accessible fragments by relying on the power of transition metal catalyzed C–C and C–X bond forming reactions. Scheme 10 illustrates this aspect. Particularly noteworthy are the rigorously chemo- and stereoselective hydrogenation reactions



Scheme 10. Summary of the total synthesis of salicylihalamide **1**.

which guarantee reagent-control over the configuration of the newly formed chiral centers, the high yielding closure of the macrocyclic ring by RCM, and the use of the yet largely unexplored copper-catalyzed cross-coupling technique allowing the direct attachment of amides to unsaturated fragments. Importantly, it has been shown that this reaction tolerates

sensitive functional groups and therefore holds promise for further applications to complex targets in the future.

Finally, this total synthesis highlights once again the excellent performance of "second-generation" ruthenium carbenes for olefin metathesis. At the same time, however, it revealed that we still lack proper insight into the stereodetermining step of this transformation, as the configuration of the newly formed olefin may depend on subtle factors that are difficult to rationalize and foresee. Therefore it is obvious that further in-depth studies on this powerful transformation are necessary. The accompanying paper in this issue reporting the total synthesis of another potent antitumor agent, that is epothilone A and C, will further illustrate this notion.[49] Extensions of our studies on metathesis in general as well as additional syntheses of bioactive target molecules are currently underway and will soon be disclosed.

Experimental Section

General: All reactions were carried out under Ar. The solvents used were purified by distillation over the drying agents indicated and were transferred under Ar: THF, Et_2O (Mg/anthracene), CH_2Cl_2 (P_4O_{10}), CH_3CN, Et_3N (CaH_2), MeOH (Mg), DMF, DMA (Desmodur, dibutyltin dilaurate), hexane, toluene (Na/K). Flash chromatography: Merck silica gel 60 (230–400 mesh). NMR: Spectra were recorded on a DPX 300 or DMX 600 spectrometer (Bruker) in the solvents indicated; chemical shifts (δ) are given in ppm relative to TMS, coupling constants (J) in Hz. IR: Nicolet FT-7199 spectrometer, wavenumbers in cm^{-1}. MS (EI): Finnigan MAT 8200 (70 eV), HRMS: Finnigan MAT 95. Melting points: Gallenkamp melting point apparatus (uncorrected). Optical rotation: Perkin Elmer 343 at $\lambda =$ 589 nm (Na-D line). Elemental analyses: Kolbe, Mülheim/Ruhr. All commercially available compounds (Lancaster, Aldrich) were used as received.

Starting materials and model studies

2-Allyl-6-hydroxy-benzoic acid (10): A solution of BCl_3 (1M in CH_2Cl_2, 30 mL, 30 mmol) was slowly added to a solution of compound **9** (1.00 g, 4.54 mmol)[20] in CH_2Cl_2 (80 mL) at 0 °C and the resulting mixture was stirred for 5 h at ambient temperature. The organic phase was diluted with ethyl acetate (50 mL), washed with brine and dried over Na_2SO_4. Evaporation of the solvent and flash chromatography (hexanes/ethyl acetate/acetic acid 10:1:1) afforded acid **10** as colorless crystals (0.78 g, 96 %). M.p. 98–99 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 11.15-10.75$ (br s, 1H), 7.38 (dd, $J = 8.2$, 7.7 Hz, 1H), 6.90 (dd, $J = 8.2$, 0.9 Hz, 1H), 6.79 (dd, $J = 7.7$, 0.9 Hz, 1H), 6.02 (ddt, $J = 17.0$, 10.2, 6.3 Hz, 1H), 5.07–4.96 (m, 2H), 3.76 (d, $J = 6.3$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 175.2$, 163.6, 144.3, 137.3, 135.6, 122.7, 116.5, 115.7, 110.6, 40.1; IR (KBr): $\nu = 3047$, 2853, 2704, 2589, 1643, 1606, 1576, 1441, 1410, 1309, 1293, 1275, 1237, 1193, 1169, 1124, 1068, 1014, 1002, 915, 814, 792, 757, 707, 573 cm^{-1}; MS (EI): m/z (%): 178 (33) $[M]^+$, 160 (100), 132 (24), 115 (3), 104 (26), 77 (12), 63 (4), 51 (11); HR-MS (EI): ($C_{10}H_{10}O_3$) calcd 178.0630; found 178.0632; elemental analysis calcd (%) for $C_{10}H_{10}O_3$ (178.20): C 67.41, H 5.66; found C 67.53, H 5.75.

(3*S*,4*R*)-3-(*tert*-Butyldimethylsilanyloxy)-4,7-dimethyl-oct-6-enoic methyl ester (20): 2,6-Lutidine (303 µL, 2.60 mmol) and TBSOTf (360 µL, 1.56 mmol) were added at 0 °C to a solution of alcohol **19** (260 mg, 1.3 mmol)[10] in CH_2Cl_2 (20 mL). After stirring for 1 h, the reaction was quenched with aq. NaOH (2N, 10 mL), the mixture was extracted with CH_2Cl_2 (80 mL), the organic layer was washed with aq. sat. NH_4Cl (2 × 10 mL) and brine (10 mL), dried over Na_2SO_4 and evaporated. Flash chromatography of the crude product (hexanes/ethyl acetate 20:1) afforded product **20** as a colorless syrup (389 mg, 95 %). $[\alpha]_D^{20} = -22.8$ ($c = 1.34$, CH_2Cl_2); ^{1}H NMR (CD_2Cl_2, 300 MHz): $\delta = 5.18-5.10$ (m, 1H), 4.16–4.08 (m, 1H), 3.63 (s, 3H), 2.36 (d, $J = 6.6$ Hz, 2H), 2.04–1.92 (m, 1H), 1.83–1.72 (m, 1H), 1.71–1.62 (m, 1H), 1.70 (s, 3H), 1.60 (s, 3H), 0.87 (s, 9H), 0.86 (d, $J = 6.7$ Hz, 3H), 0.06 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz): $\delta = 173.0$, 132.8, 123.3, 73.2, 51.7, 40.4, 38.5, 31.6, 25.9, 25.8, 18.3, 17.9, 14.3, −4.5, −4.7; IR (film): $\nu = 2956$, 2929, 2894, 2857, 1744, 1473, 1463, 1437, 1408, 1378, 1362, 1341, 1290, 1255, 1193, 1172, 1134, 1078, 1034, 1006, 982, 947, 886, 835, 812, 776, 665 cm^{-1}; MS (EI): m/z (%): 314 (<1) $[M]^+$, 299 (3), 283 (2), 257 (100), 225 (8), 199 (2), 182 (17), 147 (9), 131 (10), 115 (7), 109 (18), 89 (30), 73 (23), 69 (53), 41 (16); HR-MS (CI): ($C_{17}H_{34}O_3Si + H$) calcd 315.2355; found 315.2358; elemental analysis calcd for $C_{17}H_{34}O_3Si$ (314.54): C 64.92, H 10.90; found C 65.04, H 11.03.

(3*S*,4*R*)-3-(*tert*-Butyldimethylsilanyloxy)-4,7-dimethyl-oct-6-en-1-ol (22a): $LiBEt_3H$ (1M in THF, 1.62 mL, 1.62 mmol) was added at 0 °C to a solution of ester **20** (255 mg, 0.81 mmol) in THF (20 mL). After stirring for 2 h at ambient temperature, the reaction was quenched with water, the aqueous layer was extracted with Et_2O (3 × 20 mL), the combined organic phases were dried over Na_2SO_4 and evaporated. Flash chromatography of the residue (hexanes/ethyl acetate 1:1) afforded product **22a** as a colorless syrup (193 mg, 83 %). $[\alpha]_D^{20} = -20.9$ ($c = 0.91$, CH_2Cl_2); ^{1}H NMR (CD_2Cl_2, 300 MHz): $\delta = 5.17-5.09$ (m, 1H), 3.78 (dt, $J = 6.8$, 4.7 Hz, 1H), 3.69 (t, $J =$ 6.2 Hz, 2H), 2.06–1.94 (m, 1H), 1.83–1.58 (m, 11H), 0.90 (s, 9H), 0.86 (d, $J = 6.7$ Hz, 3H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz): $\delta = 132.5$, 123.6, 74.7, 61.0, 40.0, 34.2, 32.0, 26.0, 25.8, 18.3, 17.9, 14.1, −4.3, −4.6; IR (KBr): $\nu = 3364$, 2958, 2929, 2885, 2857, 1472, 1463, 1407, 1377, 1361, 1256, 1083, 1062, 1034, 1005, 967, 938, 836, 774, 735, 666 cm^{-1}; MS (EI): m/z (%): 286 (<1) $[M]^+$, 229 (18), 189 (6), 173 (3), 154 (11), 137 (26), 105 (11), 95 (24), 89 (13), 81 (40), 75 (38), 69 (100), 55 (10), 41 (20); HR-MS (CI): ($C_{16}H_{34}O_2Si + H$) calcd 287.2406; found 287.2406; elemental analysis calcd for $C_{16}H_{34}O_2Si$ (286.53): C 67.07, H 11.96; found C 67.14, H 11.99.

(3*S*,4*R*)-3-Methoxymethyl-4,7-dimethyl-oct-6-en-1-ol (22b): Prepared in 98 % yield as described above starting from ester **21** (366 mg, 1.5 mmol).[10] ^{1}H NMR (CD_2Cl_2, 300 MHz): $\delta = 5.17-5.09$ (m, 1H), 4.66 (d, $J = 6.8$ Hz, 1H), 4.60 (d, $J = 6.8$ Hz, 1H), 3.98–3.52 (m, 3H), 3.34 (s, 3H), 2.50–1.62 (m, 6H), 1.68 (s, 3H), 1.60 (s, 3H), 0.86 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz): $\delta = 132.5$, 123.5, 96.5, 78.7, 60.7, 55.8, 37.4, 32.5, 31.8, 25.9, 17.9, 14.5; IR (film): $\nu = 3436$, 2962, 2931, 2886, 1672, 1460, 1405, 1377, 1343, 1218, 1151, 1100, 1038, 918, 860, 825, 764 cm^{-1}; MS (EI): m/z (%): 216 (<1) $[M]^+$, 184 (14), 154 (11), 139 (6), 121 (10), 109 (13), 97 (22), 87 (22), 69 (39), 55 (24), 45 (100) 41 (27); HR-MS (CI): ($C_{12}H_{24}O_3 + H$) calcd 217.1804; found 217.1803; elemental analysis calcd for $C_{12}H_{24}O_3$ (216.32): C 66.63, H 11.18; found C 66.72, H 11.16.

(3*S*,4*R*)-2-Allyl-6-hydroxybenzoic acid 3-(*tert*-butyldimethylsilanyloxy)-4,7-dimethyloct-6-enyl ester (25a): A solution of alcohol **22a** (175 mg, 0.66 mmol) and PPh_3 (194 mg, 0.74 mmol) in Et_2O (25 mL) was added dropwise to a suspension of acid **10** (132 mg, 0.74 mmol) and DEAD (116 µL, 0.74 mmol) in Et_2O (35 mL). After stirring for 20 h, the suspension was concentrated to a total volume of ca. 10 mL, the precipitates were filtered off, the filtrate was dried over Na_2SO_4 and evaporated, and the residue was purified by flash chromatography (hexanes/ethyl acetate 30:1) to afford ester **25a** as a colorless syrup (265 mg, 96 %). $[\alpha]_D^{20} = -26.4$ ($c =$ 1.10, CH_2Cl_2); ^{1}H NMR (CD_2Cl_2, 300 MHz): $\delta = 11.18$ (s, 1H), 7.33 (dd, $J =$ 8.3, 7.5 Hz, 1H), 6.85 (dd, $J = 8.3$, 0.7 Hz, 1H), 6.76 (dd, $J = 7.5$, 0.7 Hz, 1H), 6.01 (ddt, $J = 16.6$, 10.2, 6.2 Hz, 1H), 5.18–5.09 (m, 1H), 5.03 (dd, $J = 10.2$, 1.6 Hz, 1H), 4.97 (dd, $J = 16.6$, 1.7 Hz, 1H), 4.53–4.38 (m, 2H), 3.84–3.76 (, m, 1H), 3.72 (dd, $J = 6.1$, 1.3 Hz, 2H), 2.07–1.65 (m, 5H), 1.67 (s, 3H), 1.59 (s, 3H), 0.91 (s, 9H), 0.88 (d, $J = 6.8$ Hz, 3H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz): $\delta = 171.8$, 163.1, 143.3, 138.1, 134.6, 132.7, 123.4, 122.7, 116.4, 115.6, 112.7, 72.6, 64.1, 40.6, 40.1, 31.8, 31.0, 26.0, 25.8, 18.3, 17.9, 14.0, −4.3, −4.5; IR (film): $\nu = 3079$, 3060, 2958, 2929, 2886, 2857, 1730, 1662, 1608, 1579, 1451, 1409, 1377, 1342, 1312, 1296, 1219, 1194, 1165, 1119, 1097, 1067, 1006, 912, 867, 836, 817, 774, 713, 667 cm^{-1}; MS (EI): m/z (%): 446 (<1) $[M]^+$, 389 (5), 314 (4), 269 (2), 235 (12), 171 (5), 161 (100), 133 (9), 69 (12), 41 (6); HR-MS (CI): ($C_{26}H_{42}O_4Si + H$) calcd 447.2931; found 447.2930; elemental analysis calcd for $C_{26}H_{42}O_4Si$ (446.70): C 69.91, H 9.48; found C 70.18, H 9.12.

(3*S*,4*R*)-2-Allyl-6-hydroxybenzoic acid 3-methoxymethyl-4,7-dimethyloct-6-enyl ester (25b): Prepared as described above from alcohol **22b** (382 mg, 1.77 mmol) and acid **10** (315 mg, 2.12 mmol). Colorless syrup (537 mg, 81 %). $[\alpha]_D^{20} = -39.0$ ($c = 1.85$, CH_2Cl_2); ^{1}H NMR (CD_2Cl_2, 300 MHz): $\delta =$ 11.09 (s, 1H), 7.33 (dd, $J = 8.3$, 7.5 Hz, 1H), 6.85 (dd, $J = 8.3$, 1.0 Hz, 1H), 6.76 (dd, $J = 7.5$, 0.9 Hz, 1H), 6.01 (ddt, $J = 16.4$, 10.2, 6.1 Hz, 1H), 5.17–4.93 (m, 3H), 4.67 (d, $J = 6.8$ Hz, 1H), 4.60 (d, $J = 6.8$ Hz, 1H), 4.58–4.42 (m, 2H), 3.72 (d, 6.1 Hz, 2H), 3.67–3.58 (m, 1H), 3.36 (s, 3H), 2.08–1.81 (m, 5H), 1.68 (s, 3H), 1.59 (s, 3H), 0.89 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz): $\delta = 171.6$, 162.9, 143.3, 138.2, 134.6, 132.9, 123.1, 122.7,

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116.3, 115.5, 112.8, 96.6, 78.7, 63.8, 56.0, 40.5, 37.2, 31.7, 29.4, 25.8, 17.9, 14.2; IR (film): ν = 3385, 3077, 2965, 2931, 2889, 2823, 1727, 1661, 1607, 1578, 1451, 1377, 1343, 1313, 1296, 1249, 1220, 1165, 1142, 1121, 1100, 1038, 987, 916, 817, 769, 713 cm^{-1}; MS (EI): *m*/*z* (%): 376 (<1) $[M]^+$, 344 (15), 205 (13), 183 (13), 160 (100), 133 (10), 121 (24), 93 (8), 69 (22), 55 (7), 45 (37); HR-MS (CI): ($C_{22}H_{32}O_5$ + H) calcd 377.2328; found 377.2325; elemental analysis calcd for $C_{22}H_{32}O_5$ (376.49): C 70.19, H 8.57; found C 70.28, H 8.52.

(3*S*,4*R*)-2-Allyl-6-(*tert*-butyldimethylsilanyloxy)-benzoic acid 3-methoxymethyl-4,7-dimethyloct-6-enyl ester (25c): A solution of compound **25b** (113 mg, 0.3 mmol), imidazole (204 mg, 3 mmol) and TBSCl (362 mg, 2.4 mmol) in DMF (20 mL) was stirred for 18 h at ambient temperature. The mixture was diluted with EtOAc (50 mL) and washed with brine (3 × 20 mL). Drying of the organic phase over Na_2SO_4, evaporation of the solvent followed by flash chromatography of the residue (hexanes/ethyl acetate 20:1) afforded product **25c** as a colorless syrup (145 mg, 99%). $[\alpha]_D^{20} = -21.3$ (c = 1.47, CH_2Cl_2); ^{1}H NMR (CD_2Cl_2, 300 MHz): δ = 7.20 (dd, J = 8.2, 7.6 Hz, 1H), 6.82 (dd, J = 7.6 Hz, 1H), 6.73 (dd, J = 8.2 Hz, 1H), 5.92 (ddt, J = 16.2, 9.5, 6.6 Hz, 1H), 5.14–5.01 (m, 3H), 4.65 (d, J = 6.8 Hz, 1H), 4.60 (d, J = 6.8 Hz, 1H), 4.47–4.37 (m, 1H), 4.33–4.24 (m, 1H), 3.57–3.52 (m, 1H), 3.36 (s, 3H), 3.32 (d, 6.6 Hz, 2H), 2.07–1.94 (m, 1H), 1.90–1.77 (m, 4H), 1.67 (s, 3H), 1.57 (s, 3H), 0.97 (s, 9H), 0.88 (d, J = 6.4 Hz, 3H), 0.23 (s, 6H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz): δ = 168.3, 152.7, 138.9, 137.0, 132.8, 130.3, 127.2, 123.2, 122.2, 117.2, 116.3, 96.6, 78.9, 63.1, 55.9, 37.9, 37.4, 31.7, 29.7, 25.8, 25.7, 18.3, 17.9, 14.4, −4.3; IR (film): ν = 3078, 2962, 2931, 2887, 2859, 2823, 1731, 1662, 1640, 1594, 1584, 1464, 1409, 1377, 1363, 1285, 1264, 1211, 1142, 1108, 1064, 1039, 994, 969, 917, 841, 806, 783, 741, 719, 669, 578, 555 cm^{-1}; MS (EI): *m*/*z* (%): 490 (<1) $[M]^+$, 433 (16), 401 (7), 275 (44), 249 (37), 235 (100), 199 (27), 167 (17), 137 (19), 81 (21), 69 (41), 57 (8), 45 (57); HR-MS (CI): ($C_{28}H_{46}O_5Si$ + H) calcd 491.3193; found 491.3193; elemental analysis calcd for $C_{28}H_{46}O_5Si$ (490.76): C 68.53, H 9.45; found C 68.62, H 9.54.

Representative procedure for RCM

(*Z*)-(9*S*,10*R*)-9-(*tert*-Butyldimethylsilanyloxy)-4-hydroxy-10-methyl-7,8,9,10,11,14-hexahydro-6-oxa-benzocyclododecen-5-one [(*Z*)-26a]: Complex **24** (4.2 mg, 0.005 mmol) was added to a solution of diene **25a** (44.6 mg, 0.1 mmol) in toluene (50 mL). After stirring for 3 h at 80 °C, the reaction was quenched with ethyl vinyl ether (1 mL). Evaporation of the solvent followed by flash chromatography (hexanes/ethyl acetate 50:1) of the crude product afforded cycloalkene (*Z*)-**26a** as a colorless syrup (34.7 mg, 89%). $[\alpha]_D^{20} = -63.7$ (c = 1.02, CH_2Cl_2); ^{1}H NMR (C_6D_6, 300 MHz): δ = 12.12 (s, 1H), 7.02–6.92 (m, 2H), 6.48 (dd, J = 6.6, 2.1 Hz, 1H), 5.32–5.13 (m, 2H), 4.42–4.32 (m, 1H), 4.17 (dd, J = 15.0, 9.3 Hz, 1H), 3.85 (dt, J = 10.1, 3.2 Hz, 1H), 3.81–3.75 (m, 1H), 2.85 (dd, J = 15.0, 2.4 Hz, 1H), 2.08–1.92 (m, 1H), 1.70–1.52 (m, 3H), 1.35–1.24 (m, 1H), 0.94 (s, 9H), 0.86 (d, J = 6.7 Hz, 3H), 0.00 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (C_6D_6, 75.5 MHz): δ = 172.1, 164.5, 144.8, 134.8, 131.2, 127.8, 123.1, 116.8., 111.9, 71.7, 64.8, 39.8, 35.4, 31.8, 31.3, 26.0, 18.1, 13.6, −4.4; IR (KBr): ν = 3425, 3057, 3022, 3006, 2957, 2930, 2895, 2857, 1658, 1631, 1607, 1574, 1471, 1448, 1386, 1347, 1311, 1289, 1251, 1216, 1158, 1127, 1089, 1071, 1052, 1017, 1005, 965, 932, 904, 876, 862, 836, 819, 791, 775, 714, 699, 662, 592 cm^{-1}; MS (EI): *m*/*z* (%): 390 (<1) $[M]^+$, 375 (1), 333 (100), 315 (6), 285 (9), 241 (10), 205 (12), 171 (14), 161 (15), 149 (12), 131 (16), 93 (28), 73 (34), 59 (7), 41 (9); HR-MS (CI): ($C_{22}H_{34}O_4Si$ + H) calcd 391.2305; found 391.2307; elemental analysis calcd for $C_{22}H_{34}O_4Si$ (390.60): C 67.65, H 8.77; found C 67.57, H 8.84.

The following products were obtained analogously:

(*Z*)-(9*S*,10*R*)-4-Hydroxy-9-methoxymethyl-10-methyl-7,8,9,10,11,14-hexahydro-6-oxa-benzocyclododecen-5-one [(*Z*)-26b]: Colorless syrup. $[\alpha]_D^{20} = -82.5$ (c = 0.89, CH_2Cl_2); ^{1}H NMR (C_6D_6, 300 MHz): δ = 12.23 (s, 1H), 7.01–6.93 (m, 2H), 6.46 (dd, J = 6.3, 2.5 Hz, 1H), 5.26–5.07 (m, 2H), 4.46 (d, J = 6.9 Hz, 1H), 4.37 (d, J = 6.9 Hz, 1H), 4.38–4.28 (m, 1H), 4.08 (dd, J = 14.7, 8.9 Hz, 1H), 3.85 (dt, J = 10.9, 3.1 Hz, 1H), 3.66–3.60 (m, 1H), 3.11 (s, 3H), 2.89–2.80 (m, 1H), 2.04–1.49 (m, 4H), 1.41–1.30 (m, 1H), 0.87 (d, J = 6.7 Hz, 3H); ^{13}C NMR (C_6D_6, 75.5 MHz): δ = 172.1, 164.5, 144.8, 134.8, 131.3, 127.6, 123.1, 116.8., 112.0, 95.9, 77.8, 65.2, 55.0, 36.6, 35.5, 31.9, 28.9, 13.7; IR (KBr): ν = 3419, 3051, 2961, 2934, 1750, 1716, 1659, 1606, 1575, 1450, 1385, 1312, 1295, 1250, 1220, 1166, 1152, 1125, 1100, 1068, 1038, 916, 818, 775, 738, 711, 542 cm^{-1}; MS (EI): *m*/*z* (%): 320 (16) $[M]^+$, 288 (7), 258 (29), 240 (3), 214 (5), 201 (14), 172 (22), 160 (13), 134 (8), 115 (8), 99 (4), 85 (44), 81 (6), 69 (1), 55 (12), 45 (100); HR-MS (EI): ($C_{18}H_{24}O_5$) calcd 320.1624; found 320.1625; elemental analysis calcd for $C_{18}H_{24}O_5$ (320.39): C 67.48, H 7.55; found C 67.35, H 7.62.

(9*S*,10*R*)-4-(*tert*-Butyldimethylsilanyloxy)-9-methoxymethyl-10-methyl-7,8,9,10,11,14-hexahydro-6-oxa-benzocyclododecen-5-one (26c): Colorless syrup. *E*:*Z* = 30:70; $[\alpha]_D^{20} = -10.4$ (c = 0.73, CH_2Cl_2); data of (*E*)-**26c**: ^{1}H NMR (C_6D_6, 300 MHz): δ = 6.94 (dd, J = 8.2, 7.6 Hz, 1H), 6.68–6.53 (m, 2H), 5.45–4.96 (m, 2H), 4.62 (s, 2H), 4.40–3.57 (m, 4H), 3.32–3.23 (m, 1H), 3.21 (s, 3H), 2.21–1.48 (m, 5H), 0.98 (s, 9H), 0.87 (d, J = 6.5 Hz, 3H), 0.13 (s, 6H); ^{13}C NMR (C_6D_6, 75.5 MHz): δ = 168.5, 153.2, 140.4, 130.8, 129.9, 128.3, 128.0, 123.2, 117.4, 96.4, 76.3, 63.0, 55.2, 38.3, 37.8, 34.4, 31.9, 25.7, 18.2, 14.0, −4.4.

Data of (*Z*)-**26c**: ^{1}H NMR (C_6D_6, 300 MHz): δ = 6.97 (dd, J = 8.2, 7.6 Hz, 1H), 6.68–6.53 (m, 2H), 5.45–4.96 (m, 2H), 4.50 (d, J = 6.8 Hz, 1H), 4.44 (d, J = 6.8 Hz, 1H), 4.40–3.57 (m, 4H), 2.96–2.88 (m, 1H), 3.12 (s, 3H), 2.21–1.48 (m, 5H), 0.99 (s, 9H), 0.84 (d, J = 6.5 Hz, 3H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (C_6D_6, 75.5 MHz): δ = 168.1, 152.5, 139.8, 130.1, 129.6, 128.4, 128.3, 122.6, 116.7, 96.3, 78.9, 62.3, 55.1, 36.3, 32.1, 30.5, 29.5, 25.7, 18.2, 13.8, −4.4; IR (KBr): ν = 3068, 2957, 2931, 2887, 2858, 2822, 1729, 1660, 1592, 1583, 1464, 1378, 1363, 1284, 1261, 1211, 1153, 1106, 1065, 1040, 974, 939, 919, 902, 842, 783, 739, 701, 670, 574 cm^{-1}; MS (EI): *m*/*z* (%): 434 (<1) $[M]^+$, 377 (75), 315 (19), 247 (22), 221 (24), 207 (42), 141 (10), 73 (32), 57 (9), 45 (100); HR-MS (CI): ($C_{24}H_{38}O_5Si$ + H) calcd 435.2567; found 435.2562; elemental analysis calcd for $C_{24}H_{38}O_5Si$ (434.65): C 66.32, H 8.81; found C 66.28, H 8.88.

(*Z*)-(9*R*,10*R*)-9-(*tert*-Butyldimethylsilanyloxy)-4-hydroxy-10-methyl-7,8,9,10,11,14-hexahydro-6-oxa-benzocyclododecen-5-one [(*Z*)-28]: Colorless syrup. $[\alpha]_D^{20} = -54.2$ (c = 0.99, CH_2Cl_2); ^{1}H NMR (C_6D_6, 600 MHz): δ = 12.32 (s, 1H), 6.99 (dd, J = 8.3, 7.2 Hz, 1H), 6.95 (dd, J = 8.3, 1.6 Hz, 1H), 6.50 (dd, J = 7.2, 1.6 Hz, 1H), 5.52–5.46 (m, 1H), 5.35–5.30 (m, 1H), 4.49–4.42 (m, 1H), 4.14–4.05 (m, 2H), 3.32–3.27 (m, 1H), 3.26–3.19 (m, 1H), 2.37–2.31 (m, 1H), 1.98–1.93 (m, 1H), 1.59–1.56 (m, 1H), 1.54–1.45 (m, 2H), 0.98–0.94 (m, 3H), 0.92 (s, 9H), −0.01 (s, 3H), −0.06 (s, 3H); ^{13}C NMR (C_6D_6, 151 MHz): δ = 172.4, 164.8, 144.2, 134.7, 130.7, 126.5, 122.9, 116.7, 111.9, 74.4, 62.6, 40.1, 34.6, 33.6, 30.7, 26.0, 18.2, 17.5, −4.2, −4.5; IR (KBr): ν = 3450, 3009, 2956, 2930, 2895, 2857, 1734, 1655, 1605, 1576, 1471, 1463, 1449, 1389, 1360, 1337, 1309, 1295, 1251, 1217, 1177, 1166, 1117, 1073, 1037, 995, 905, 886, 862, 837, 816, 773, 721, 710, 669, 598 cm^{-1}; MS (EI): *m*/*z* (%): 390 (<1) $[M]^+$, 375 (1), 333 (100), 315 (6), 285 (9), 241 (10), 205 (12), 171 (14), 161 (15), 149 (12), 131 (16), 93 (28), 73 (34), 59 (7), 41 (9).

Total synthesis of salicylihalamide

***N*-Acylsultam (31)**:[39] A solution of *n*BuLi (1.6 M in hexane, 14.20 mL, 22.7 mmol) and cyclohexylisopropylamine (382 μL, 2.27 mmol) was added over 60 min at −78 °C to a solution of *N*-acylsultam (**30**) (6.17 g, 22.7 mmol) in THF (120 mL, 0.19 M). The resulting lithium enolate was stirred at −78 °C for 1 h before freshly distilled dimethylallyl bromide (7.94 mL, 68.2 mmol) in HMPA (11.92 mL, 68.2 mmol) was added. The reaction mixture was allowed to warm to ambient temperature, was quenched with water (150 mL) and extracted with Et_2O (3 × 150 mL). Drying (Na_2SO_4) of the combined organic phases and evaporation of the solvents gave the crude product which was crystallized from methanol to afford pure **31** (6.09 g, 79%) as a colorless solid. $[\alpha]_D^{20} = -52.5$ (c = 2.2, CH_2Cl_2); m.p. 87–89 °C; ^{1}H NMR (CD_2Cl_2, 300 MHz): δ = 5.09 (t, J = 7.5 Hz, 1H), 3.85 (dd, J = 4.8, 7.5 Hz, 1H), 3.43 (q, J = 11.1 Hz, 2H), 3.12–3.05 (m, 1H), 2.76 (d, 2H), 2.44–2.34 (m, 2H), 2.13–1.82 (m, 3H), 1.63 (s, 3H), 1.57 (s, 3H), 1.42–1.15 (m, 2H), 1.11 (dd, J = 6.8 Hz, 6H), 0.96 (s, 3H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz): δ = 176.5, 134.4, 121.5, 65.6, 54.7, 53.3, 48.7, 48.2, 45.4, 40.6, 34.5, 33.3, 26.9, 26.1, 21.1, 20.2, 18.0, 16.7; IR (KBr): ν = 2970, 2930, 2882, 1689, 1461, 1394, 1336, 1272, 1239, 1220, 1166, 1135, 1120, 1062, 1037, 976, 769 cm^{-1}; MS (EI): *m*/*z* (%): 339 (27) $[M]^+$, 271 (57), 152 (16), 136 (11), 135 (78), 134 (27), 125 (10), 107 (12), 97 (70), 96 (100), 81 (15), 79 (10), 69 (40), 67 (11), 55 (61), 43 (11), 41 (37); HR-MS (EI): ($C_{18}H_{29}NO_3S$) calcd 339.1868; found 339.1867.

(2*S*)-2,5-Dimethyl-hex-4-enoic acid (*ent*-15): Aqueous H_2O_2 (30% *w*/*w*, 22.7 mL) and a suspension of $LiOH \cdot H_2O$ (7.89 g, 188.3 mmol) in water (40 mL) were added at 0 °C to a solution of compound **31** (15.98 g, 47.1 mmol) in THF (400 mL) and water (100 mL). The reaction was first stirred for 60 min at 0 °C and then at ambient temperature for 24 h. Acidification with HCl (2 M, 500 mL), extraction with CH_2Cl_2 (3 × 300 mL), drying of the combined organic layers over Na_2SO_4, evaporation of the

solvents and trituration of the residue with pentane furnished the insoluble auxiliary. The soluble carboxylic acid was purified by column chromatography (pentane/Et_2O 4:1, 1% acetic acid) affording compound *ent*-**15** (6.36 g, 95%) as a colorless liquid. $[\alpha]_D^{20} = +7.4$ ($c = 2.08$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 10.50-10.00$ (br s, 1H), 5.12–5.04 (m, 1H), 2.52–2.28 (m, 2H), 2.19–2.08 (m, 1H), 1.67 (s, 3H), 1.59 (s, 3H), 1.14 (d, $J =$ 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 183.0$, 134.0, 120.9, 39.8, 31.8, 25.8, 17.8, 16.3; IR (KBr): $\nu = 2975$, 2935, 2661, 1710, 1463, 1417, 1378, 1338, 1287, 1245, 1226, 1185, 1125, 1083, 1049, 933, 856, 812, 778, 625 cm^{-1}; MS (EI): *m*/*z* (%): 142 (24) $[M]^+$, 124 (2), 109 (1), 97 (3), 87 (5), 81 (5), 74 (17), 69 (100), 55 (10), 41 (55); HR-MS (EI): ($C_8H_{14}O_2$) calcd 142.0994; found 142.0993.

(2*S*)-2,5-Dimethylhex-4-enoyl chloride (*ent*-16): Chloroenamine **17** (7.30 g, 54.88 mmol)[25] was slowly added through a syringe to a solution of acid *ent*-**15** (6.50 g, 45.78 mmol) in CH_2Cl_2 (80 mL). After stirring for 90 min, the solvent was evaporated in vacuo affording acid chloride *ent*-**16** as a colorless oil. The crude product was dissolved in THF (80 mL) and was directly used in the next step.

(4*S*)-4,7-Dimethyl-3-oxo-oct-6-enoic methyl ester (*ent*-18): A solution of *n*BuLi (1.6 M in hexane, 109.0 mL, 174.4 mmol) was slowly added at $-78\,^\circ$C to a solution of diisopropylamine (22.60 mL, 159.4 mmol) in THF (400 mL). The reaction mixture was stirred for 30 min at $-20\,^\circ$C prior to the slow addition of methyl acetate (12.70 mL, 159.4 mmol) at $-78\,^\circ$C. After stirring for 1 h, a solution of acid chloride *ent*-**16** (45.78 mmol, crude) in THF (80 mL) was added and the reaction mixture was quickly warmed to ambient temperature. After 2 h the reaction was quenched by addition of aq. sat. NH_4Cl. Extraction with Et_2O, drying of the combined organic phases over Na_2SO_4, evaporation of the solvent and flash chromatography (hexanes/ethyl acetate 15:1) afforded keto ester *ent*-**18** as a colorless oil (7.31 g, 81%). $[\alpha]_D^{20} = +35.1$ ($c = 1.54$, CH_2Cl_2); according to NMR, the product consists of a 9:1 mixture of keto-enol tautomers. NMR Data for major form: ^{1}H NMR (CD_2Cl_2, 300 MHz): $\delta = 5.09-5.02$ (m, 1H), 3.69 (s, 3H), 3.47 (s, 2H), 2.69–2.58 (m, 1H), 2.36–2.24 (m, 1H), 2.14–2.02 (m, 1H), 1.69 (s, 3H), 1.61 (s, 3H), 1.07 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz): $\delta = 206.6$, 168.1, 134.4, 121.2, 52.4, 48.1, 47.2, 31.5, 25.8, 17.9, 15.8; IR (KBr): $\nu = 2971$, 2934, 1752, 1715, 1653, 1626, 1450, 1438, 1405, 1377, 1318, 1237, 1195, 1155, 1119, 1039, 1006, 849, 842, 805, 778, 739, 703, 658 cm^{-1}; MS (EI): *m*/*z* (%): 198 (18) $[M]^+$, 180 (8), 166 (4), 143 (13), 130 (54), 125 (31), 109 (20), 101 (29), 96 (25), 81 (14), 74 (15), 69 (100), 55 (38), 41 (56); HR-MS (EI): ($C_{11}H_{18}O_3$) calcd 198.1256; found 198.1254.

(3*R*,4*S*)-3-Hydroxy-4,7-dimethyl-oct-6-enoic methyl ester (*ent*-19): A stainless steel autoclave (200 mL) was charged with a solution of compound *ent*-**18** (2.80 g, 14.12 mmol) in MeOH (80 mL). After addition of [((*S*)-BINAP)$RuCl_2]_2 \cdot NEt_3$ (3.1 mM in THF, 18.4 mL, 0.057 mmol, 0.4 mol%) the autoclave was pressurized with H_2 (4 atm) and the reaction mixture was stirred for 4 h at 80 °C. After venting the autoclave, the solvent was removed in vacuo and the residue was purified by flash chromatography (hexanes/ethyl acetate 6:1) affording product *ent*-**19** (2.654 g, 94%) as a colorless oil. $[\alpha]_D^{20} = +20.5$ ($c = 1.29$, CH_2Cl_2); ^{1}H NMR (CD_2Cl_2, 300 MHz): $\delta = 5.14$ (ddsept, $J = 7.8$, 6.8, 1.4 Hz, 1H), 3.83 (dddd, $J = 9.5$, 6.1, 4.0, 2.6 Hz, 1H), 3.68 (s, 3H), 2.82 (d, $J = 4.0$ Hz, 1H), 2.50 (dd, $J = 16.1$, 2.9 Hz, 1H), 2.38 (dd, $J = 16.1$, 9.6 Hz, 1H), 2.15 (ddd, $J = 14.2$, 6.8, 4.8 Hz, 1H), 1.89 (ddd, $J = 14.2$, 8.6, 7.8 Hz, 1H), 1.70 (q, 1.3 Hz, 3H), 1.61 (d, $J =$ 0.8 Hz, 3H), 1.59 (dddq, $J = 8.4$, 6.1, 4.8, 6.8 Hz, 1H), 0.86 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz): $\delta = 174.1$, 133.0, 123.0, 72.0, 52.0, 39.6, 38.5, 31.2, 25.9, 17.9, 15.3; IR (neat): $\nu = 3472$, 2964, 2925, 2881, 1739, 1438, 1405, 1377, 1339, 1288, 1260, 1196, 1170, 1113, 1051, 1018, 990, 880, 846 cm^{-1}; MS (EI): *m*/*z* (%): 200 (11) $[M]^+$, 182 (55), 167 (9), 150 (14), 122 (40), 109 (62), 107 (56), 103 (24), 93 (25), 81 (22), 69 (84), 55 (57), 41 (100), 29 (37); HR-MS (EI): ($C_{11}H_{20}O_3$) calcd 200.1412; found 200.1413.

(3*R*,4*S*)-3-Methoxymethyl-4,7-dimethyl-oct-6-enoic methyl ester (*ent*-21): *N*,*N*-Dimethylaminopyridine (284 mg, 2.33 mmol), diisopropylethylamine (12.20 mL, 70.0 mmol) and MOMCl (5.31 mL, 70.0 mmol) were added to a solution of compound *ent*-**19** (4.67 g, 23.3 mmol) in CH_2Cl_2 (500 mL). Stirring at ambient temperature was continued for 40 h. After dilution with ethyl acetate (600 mL), the organic phase was washed with brine (3 × 200 mL), dried over Na_2SO_4, evaporated, and the crude product was purified by flash chromatography (hexanes/ethyl acetate 10:1) affording *ent*-**21** as a colorless syrup (5.11 g, 89%). $[\alpha]_D^{20} = +15.6$ ($c = 1.90$, CH_2Cl_2); ^{1}H NMR (CD_2Cl_2, 300 MHz): $\delta = 5.15-5.08$ (m, 1H), 4.61 (s, 2H), 3.95–3.87 (m, 1H), 3.65 (s, 3H), 3.30 (s, 3H), 2.44 (d, $J = 7.4$ Hz, 1H), 2.43 (d, 4.9 Hz, 1H), 2.08–1.95 (m, 1H), 1.88–1.75 (m, 2H), 1.70 (s, 3H), 1.60 (s, 3H), 0.86 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz): $\delta = 172.7$, 133.0, 123.0, 96.7, 78.8, 55.8, 51.8, 37.7, 36.7, 31.5, 25.9, 17.9, 14.5; IR (KBr): $\nu = 2962$, 2932, 2889, 2824, 1742, 1673, 1437, 1378, 1343, 1290, 1272, 1214, 1194, 1173, 1150, 1100, 1043, 976, 919, 857, 821 cm^{-1}; MS (EI): *m*/*z* (%): 244 (<1) $[M]^+$, 212 (12), 194 (3), 182 (18), 167 (3), 155 (4), 139 (6), 121 (19), 103 (23), 81 (9), 69 (33), 55 (24), 45 (100), 41 (25), 29 (9); HR-MS (CI): ($C_{13}H_{24}O_3 + H$) calcd 245.1753; found 245.1754.

(5*R*,6*S*)-5-Methoxymethyl-6,9-dimethyl-3-oxo-dec-8-enoic *tert*-butyl ester (32): A solution of *tert*-butyl acetate (8.37 mL, 62.40 mmol) in THF (20 mL) was slowly added to a solution of LiHMDS (10.44 g, 62.40 mmol) in THF (200 mL) at $-45\,^\circ$C. The temperature was raised to $-30\,^\circ$C over a period of 90 min. A solution of compound *ent*-**21** (2.55 g, 10.43 mmol) in THF (40 mL) was then added at $-40\,^\circ$C. Stirring was continued for 3 h while the temperature was increased to $-30\,^\circ$C. Quenching of the reaction with aq. sat. NH_4Cl, extraction with Et_2O, drying of the combined organic phases over Na_2SO_4, evaporation of the solvent and flash chromatography (hexanes/ethyl acetate 10:1) afforded product **32** as a colorless syrup (3.26 g, 95%). $[\alpha]_D^{20} = +18.1$ ($c = 1.29$, CH_2Cl_2); according to NMR, the product consists of a 13:1 mixture of the keto-enol tautomers. NMR Data for the major keto form: ^{1}H NMR (CD_2Cl_2, 300 MHz): $\delta = 5.16-5.08$ (m, 1H), 4.58 (s, 2H), 4.01–3.94 (m, 1H), 3.37 (s, 2H), 3.29 (s, 3H), 2.73 (dd, $J = 16.2$, 8.7 Hz, 1H), 2.52 (dd, $J = 16.2$, 3.2 Hz, 1H), 2.04–1.92 (m, 1H), 1.87–1.76 (m, 2H), 1.70 (s, 3H), 1.59 (s, 3H), 1.45 (s, 9H), 0.86 (d, $J =$ 6.4 Hz, 3H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz): $\delta = 202.5$, 166.7, 133.0, 122.9, 96.7, 81.9, 77.7, 55.9, 51.9, 44.4, 37.6, 31.7, 28.1, 25.9, 18.0, 14.5; IR (neat): $\nu =$ 2975, 2931, 2824, 1738, 1717, 1643, 1456, 1408, 1393, 1369, 1319, 1286, 1253, 1212, 1150, 1099, 1040, 944, 919, 840 cm^{-1}; MS (EI): *m*/*z* (%): 328 (<1) $[M]^+$, 296 (2), 266 (1), 240 (25), 223 (5), 210 (15), 181 (9), 139 (15), 123 (14), 109 (22), 97 (15), 81 (10), 69 (32), 57 (72), 45 (100), 41 (31), 29 (13); HR-MS (CI): ($C_{18}H_{32}O_5 + H$) calcd 329.2328; found 329.2328.

(3*S*,5*R*,6*S*)-3-Hydroxy-5-methoxymethyl-6,9-dimethyl-dec-8-enoic *tert*-butyl ester (33): A stainless steel autoclave (50 mL) was charged with a solution of keto ester **32** (827 mg, 2.52 mmol) in MeOH (20 mL). After addition of [((*S*)-BINAP)$RuCl_2]_2 \cdot NEt_3$ (3.1 mM in THF, 10 mL, 0.031 mmol, 1.3 mol%) the autoclave was pressurized with H_2 (80 atm) and the reaction mixture was stirred for 6.5 h at 25 °C. After the autoclave had been vented, the solvent was removed in vacuo and the residue was purified by flash chromatography (hexanes/ethyl acetate 4:1) affording product **33** (777 mg, 93%) as a colorless syrup. $[\alpha]_D^{20} = +41.5$ ($c = 1.20$, CH_2Cl_2); ^{1}H NMR (CD_2Cl_2, 300 MHz): $\delta = 5.16-5.08$ (m, 1H), 4.67 (d, $J =$ 6.8 Hz, 1H), 4.60 (d, $J = 6.8$ Hz, 1H), 4.15–4.06 (m, 1H), 3.67–3.60 (m, 1H), 3.55–3.30 (br s, 1H), 3.36 (s, 3H), 2.41 (dd, $J = 15.7$, 4.6 Hz, 1H), 2.32 (dd, $J = 15.7$, 7.9 Hz, 1H), 1.98–1.78 (m, 3H), 1.70 (s, 3H), 1.69–1.41 (m, 2H), 1.60 (s, 3H), 1.44 (s, 9H), 0.86 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz): $\delta = 172.0$, 132.8, 123.2, 96.0, 81.0, 80.5, 67.8, 56.1, 43.2, 36.8, 36.5, 31.7, 28.2, 25.9, 18.0, 14.1; IR (KBr): $\nu = 3468$, 2971, 2932, 1729, 1632, 1455, 1392, 1368, 1340, 1302, 1258, 1214, 1151, 1097, 1034, 951, 917, 844, 774 cm^{-1}; MS (EI): *m*/*z* (%): 330 (<1) $[M]^+$, 242 (29), 224 (14), 212 (42), 183 (20), 145 (38), 123 (13), 115 (61), 95 (21), 81 (14), 69 (44), 57 (63), 45 (100); HR-MS (CI): ($C_{18}H_{34}O_5 + H$) calcd 331.2484; found 331.2485.

(3*R*,5*R*,6*S*)-5-Methoxymethyl-6,9-dimethyl-dec-8-ene-1,3-diol (34): $LiAlH_4$ (1.72 g, 45.3 mmol) was added to a solution of compound **33** (5.01 g, 15.1 mmol) in Et_2O (600 mL) at 0 °C. Careful addition of aq. sat. NH_4Cl (100 mL) after 6 h, extraction with Et_2O (3 × 150 mL), drying of the combined organic phases over Na_2SO_4, evaporation of the solvent and flash chromatography of the residue (hexanes/ethyl acetate 1:1 → 1:2) afforded diol **34** as a colorless syrup (3.56 g, 90%). $[\alpha]_D^{20} = +51.1$ ($c = 1.19$, CH_2Cl_2); ^{1}H NMR (CD_2Cl_2, 300 MHz): $\delta = 5.15-5.07$ (m, 1H), 4.67 (d, $J = 6.6$ Hz, 1H), 4.62 (d, $J = 6.6$ Hz, 1H), 4.05–3.95 (m, 1H), 3.81–3.65 (m, 4H), 3.37 (s, 3H), 3.20–2.85 (br s, 1H), 1.98–1.78 (m, 3H), 1.74–1.61 (m, 3H), 1.70 (s, 3H), 1.59 (s, 3H), 1.55–1.46 (m, 1H), 0.86 (d, $J = 6.0$ Hz, 3H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz): $\delta = 132.9$, 123.1, 95.9, 81.9, 72.2, 61.6, 56.2, 39.3, 36.8, 36.7, 31.9, 25.8, 17.9, 13.8; IR (neat): $\nu = 3386$, 2961, 2931, 2888, 1658, 1442, 1377, 1212, 1151, 1097, 1037, 969, 918, 864, 822, 724 cm^{-1}; MS (EI): *m*/*z* (%): 260 (<1) $[M]^+$, 228 (5), 210 (2), 198 (8), 183 (10), 165 (2), 141 (7), 124 (8), 110 (14), 101 (43), 95 (17), 83 (17), 69 (34), 55 (29), 45 (100), 41 (25), 29 (12); HR-MS (CI): ($C_{14}H_{28}O_4 + H$) calcd 261.2066; found 261.2065.

(3*S*,5*S*,6*R*)-1-(4-Methoxybenzyl)-5-methoxymethyl-6,9-dimethyl-dec-8-en-3-ol (35): A solution of diol **34** (2.074 g, 7.96 mmol) in DMF (70 mL) was added to a suspension of NaH (768 mg, 32.0 mmol) in DMF (100 mL). The

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mixture was stirred for 75 min before PMBCl (1080 μL, 7.96 mmol) was added through a syringe. After stirring for another 90 min, the reaction was quenched with diethylamine (1 mL), the mixture was diluted with ethyl acetate (200 mL) and the organic phase was washed with brine (3 × 50 mL). Drying over Na_2SO_4, evaporation of the solvent and flash chromatography (hexanes/ethyl acetate 2:1) gave product **35** as a colorless syrup (2.29 g, 76 %). $[\alpha]_D^{20} = +26.0$ ($c = 1.32$, CH_2Cl_2); ^{1}H NMR (CD_2Cl_2, 300 MHz): $\delta =$ 7.25 (d, $J = 8.6$ Hz, 2H), 6.86 (d, $J = 8.6$ Hz, 2H), 5.16–5.07 (m, 1H), 4.67 (d, $J = 6.7$ Hz, 1H), 4.60 (d, $J = 6.6$ Hz, 1H), 4.42 (s, 2H), 3.94–3.84 (m, 1H), 3.79 (s, 3H), 3.69–3.53 (m, 3H), 3.50–3.25 (br s, 1H), 3.36 (s, 3H), 1.97–1.49 (m, 7H), 1.71 (s, 3H), 1.59 (s, 3H), 0.86 (d, $J = 6.3$ Hz, 3H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz): $\delta = 159.6$, 132.7, 131.0, 129.6, 123.3, 114.0, 95.9, 81.1, 73.1, 69.7, 68.3, 56.1, 55.5, 37.5, 37.1, 36.8, 31.8, 25.9, 17.9, 14.1; IR (KBr): $\nu = 3463$, 2930, 1613, 1586, 1514, 1463, 1442, 1375, 1302, 1248, 1210, 1173, 1152, 1096, 1036, 969, 917, 821, 773, 756, 707, 637, 571, 518 cm^{-1}; MS (EI): m/z (%): 380 (<1) $[M]^+$, 348 (1), 247 (1), 227 (2), 197 (4), 176 (2), 151 (1), 137 (13), 121 (100), 101 (7), 69 (7), 55 (4), 45 (15); HR-MS (CI): ($C_{22}H_{36}O_5 + H$) calcd 381.2641; found 381.2640.

2-Allyl-6-methoxy-benzoic acid (1*S*,3*R*,4*S*)-1-[2-(4-methoxybenzyl)-ethyl]-3-methoxymethyl-4,7-dimethyl-oct-6-enyl ester (36c): A solution of alcohol **35** (1.582 g, 4.16 mmol) and PPh_3 (1.63 g, 6.21 mmol) in Et_2O (40 mL) was added dropwise to a solution of the carboxylic acid **12** (1.20 g, 6.21 mmol)[21] and DEAD (970 μL, 6.21 mmol) in Et_2O (50 mL). After stirring for 20 h, the mixture was concentrated to a volume of ca. 10 mL and precipitated triphenylphosphine oxide was filtered off. Drying of the filtrate over Na_2SO_4, evaporation of the solvent, and flash chromatography (hexanes/ethyl acetate 20:1) afforded ester **36c** as a colorless syrup (2.10 g, 93 %). $[\alpha]_D^{20} = +15.1$ ($c = 1.02$, CH_2Cl_2); ^{1}H NMR (CD_2Cl_2, 300 MHz): $\delta =$ 11.09 (s, 1H), 7.31 (dd, $J = 8.0$, 7.5 Hz, 1H), 7.21 (d, $J = 8.6$ Hz, 2H), 6.84 (d, $J = 8.0$ Hz, 1H), 6.81 (d, $J = 8.6$ Hz, 2H), 6.73 (d, $J = 7.5$ Hz, 1H), 5.98 (ddt, $J = 17.1$, 10.2, 6.1 Hz, 1H), 5.62–5.53 (m, 1H), 5.12–5.05 (m, 1H), 5.01 (dd, $J = 10.2$, 1.6 Hz, 1H), 4.93 (dd, $J = 17.1$, 1.6 Hz, 1H), 4.64 (d, $J = 6.8$ Hz, 1H), 4.55 (d, $J = 6.8$ Hz, 1H), 4.38 (s, 2H), 3.76 (s, 3H), 3.69 (d, $J = 6.0$ Hz, 1H), 3.64 (d, $J = 6.0$ Hz, 1H), 3.60–3.49 (m, 3H), 3.33 (s, 3H), 2.12–1.48 (m, 7H), 1.63 (s, 3H), 1.56 (s, 3H), 0.87 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz): $\delta = 171.1$, 162.7, 159.6, 143.0, 138.3, 134.3, 132.8, 130.8, 129.6, 123.1, 122.7, 116.3, 115.5, 113.9, 113.3, 96.9, 78.5, 73.0, 72.4, 66.8, 55.5, 54.5, 40.3, 37.4, 35.5, 35.2, 31.8, 25.7, 17.9, 13.8; IR (neat): $\nu = 3374$, 3059, 2960, 2928, 1723, 1656, 1608, 1578, 1514, 1450, 1374, 1302, 1249, 1222, 1165, 1098, 1039, 999, 917, 818, 767, 712, 573 cm^{-1}; MS (EI): m/z (%): 540 (<1) $[M]^+$, 508 (2), 387 (1), 330 (1), 298 (2), 211 (2), 179 (3), 161 (7), 139 (1), 121 (100), 109 (1), 69 (4), 45 (10); HR-MS (ESI pos): ($C_{33}H_{46}O_7 + Na$) calcd 577.3141; found 577.3143.

(7*S*,9*R*,10*S*)-4-Methoxy-7-[2-(4-methoxybenzyl)-ethyl]-9-methoxymethyl-10-methyl-7,8,9,10,11,14-hexahydro-6-oxa-benzocyclododecen-5-one (37c): Complex **24** (68 mg, 10 mol %) was added to a solution of diene **36c** (R = Me, 450 mg, 0.811 mmol) in toluene (600 mL) at 80 °C. The reaction was stopped after 90 min upon addition of ethoxy-ethene (5 mL). Evaporation of the solvent and chromatography (hexanes/Et_2O 4:1) on a pre-packed column (LiChroprep Si 60, size A, E. Merck, Darmstadt, Germany) afforded compound (*E*)-**37c** (246 mg, 61 %) and (*Z*)-**37c** (130 mg, 32 %). (*E*)-**37c**: $[\alpha]_D^{20} = -21.0$ ($c = 1.0$, benzene); ^{1}H NMR (C_6D_6, 300 MHz): $\delta = 7.40$ (d, $J = 8.6$ Hz, 2H), 7.05 (t, $J = 8.0$ Hz, 1H), 6.91 (d, $J = 8.5$ Hz, 2H), 6.66 (d, $J = 7.6$ Hz, 1H), 6.45 (d, $J = 8.5$ Hz, 1H), 6.01–5.90 (m, 1H), 5.58–5.31 (m, 2H), 5.13 (d, $J = 6.7$ Hz, 1H), 4.91 (d, $J = 6.7$ Hz, 1H), 4.54 (m, 1H), 4.42 (s, 2H), 3.88–3.76 (m, 3H), 3.45 (s, 3H), 3.41 (s, 3H), 3.33–3.20 (m, 1H), 3.28 (s, 3H), 2.25–2.08 (m, 4H), 1.84–1.67 (m, 3H), 0.97 (d, $J = 6.0$ Hz, 3H); ^{13}C NMR (C_6D_6, 75.5 MHz): $\delta = 168.5$, 160.2, 157.6, 140.1, 132.1, 132.0, 130.3, 129.5, 126.4, 123.5, 97.7, 80.1, 73.3, 72.6, 67.3, 55.9, 55.5, 55.3, 38.6, 38.5, 37.7, 36.9, 34.9, 27.6, 14.1; IR (neat): $\nu =$ 3067, 2956, 2932, 2839, 1724, 1584, 1513, 1468, 1301, 1274, 1249, 1204, 1154, 1117, 1085, 1040, 972 cm^{-1}; MS (EI): m/z (%): 498 (<1) $[M]^+$, 300 (10), 189 (6), 187 (7), 176 (10), 121 (100), 95 (3), 45 (26); HR-MS (ESI pos): ($C_{29}H_{38}O_7 + Na$) calcd 521.2515; found 521.2514. (*Z*)-**37c**: $[\alpha]_D^{20} = -18.5$ ($c = 1.0$, benzene); ^{1}H NMR (C_6D_6, 300 MHz): $\delta = 7.41$ (d, $J = 8.5$ Hz, 2H), 7.11 (t, $J = 7.7$ Hz, 1H), 6.92 (d, $J = 8.5$ Hz, 2H), 6.72 (d, $J = 7.7$ Hz, 1H), 6.50 (d, $J = 8.5$ Hz, 1H), 5.94–5.89 (m, 1H), 5.52–5.36 (m, 2H), 4.98 (d, $J = 6.7$ Hz, 1H), 4.84 (d, $J = 6.7$ Hz, 1H), 4.45 (s, 2H), 4.20–4.12 (m, 2H), 3.72–3.60 (m, 2H), 3.42 (s, 3H), 3.39 (s, 3H), 3.36 (s, 3H), 2.23–1.98 (m, 4H), 1.90–1.67 (m, 3H), 1.02 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (C_6D_6, 75.5 MHz): $\delta = 167.0$, 160.1, 158.1, 140.8, 131.9, 130.9, 130.1, 130.0, 129.5, 123.4, 114.5, 110.5, 97.7, 78.4, 73.5, 72.6, 67.2, 60.6, 56.1, 55.8, 55.2, 37.2, 37.1, 36.6, 33.4, 32.7, 14.1; IR (neat): $\nu = 3068$, 2957, 2933, 1730, 1612, 1598, 1584, 1514, 1469, 1440, 1374, 1265, 1250, 1154, 1115, 1066, 1039 cm^{-1}; MS (EI): m/z (%): 498 (<1) $[M]^+$, 330 (5), 317 (8), 300 (10), 189 (7), 176 (12), 121 (100), 45 (27); HR-MS (CI): ($C_{29}H_{38}O_7$) calcd 499.269; found 499.2697.

(*Z*)-Hept-2-en-4-ynoic methyl ester (40): A suspension of 1-butynyllithium (0.78 g, 13.0 mmol) in THF (15 mL) was treated at −50 °C with a solution of anhydrous zinc chloride (2.04 g, 15.0 mmol) in THF (20 mL). The resulting mixture was allowed to warm to ambient temperature. Ester **39** (2.12 g, 10.0 mmol) and a solution of $[Pd(PPh_3)_4]$ (232 mg, 0.2 mmol, 2 mol %) in THF (20 mL) were subsequently added. The reaction mixture was stirred for 3 h and quenched by the addition of water. The aqueous layer was repeatedly extracted with Et_2O, the combined organic phases were washed with brine, dried over Na_2SO_4 and evaporated. Flash chromatography (pentane/Et_2O 30:1) afforded product **40** (1.24 g, 90 %) as a colorless liquid. ^{1}H NMR (CD_2Cl_2, 300 MHz): $\delta = 6.13$ (dt, $J = 11.5$, 2.3 Hz, 1H), 6.01 (d, $J = 11.5$ Hz, 1H), 3.71 (s, 3H), 2.43 (qd, $J = 7.5$, 2.3 Hz, 2H), 1.19 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz): $\delta = 165.4$, 127.4, 124.2, 105.4, 77.3, 51.5, 14.0, 13.7; IR (neat): $\nu = 3018$, 2980, 2950, 2918, 2880, 2211, 1730, 1717, 1611, 1437, 1404, 1291, 1234, 1195, 1177, 817 cm^{-1}; MS (EI): m/z (%): 138 (100) $[M]^+$, 137 (28), 123 (31), 110 (14), 107 (48), 95 (36), 79 (38), 77 (41), 67 (37), 78 (12), 77 (41), 67 (37), 63 (13), 51 (20), 39 (12); HR-MS (EI): ($C_8H_{10}O_2$) calcd 138.0681; found 138.0681; elemental analysis calcd for $C_8H_{10}O_2$ (138.17): C 69.55, H 7.30; found C 69.50, H 7.26.

(2*Z*,4*Z*)-Hepta-2,4-dienoic methyl ester (41): Quinoline (21 μL, 8 mol %) and alkyne **40** (291 mg, 2.109 mmol) were dissolved in CH_2Cl_2 (30 mL). Commercially available Lindlar catalyst (105 mg, 3 mol %) was added and the resulting suspension was stirred for 50 min under an atmosphere of H_2 (1 atm). The catalyst was filtered off through a pad of Celite, the solvent was evaporated and the residue was purified by flash chromatography (pentane/Et_2O 30:1) affording diene **41** (237 mg, 80 %) as a colorless liquid. ^{1}H NMR (CD_2Cl_2, 300 MHz): $\delta = 7.21$ (dd, $J = 11.4$, 1.2 Hz, 1H), 6.95 (dd, $J = 11.7$, 0.8 Hz, 1H), 5.98–5.86 (m, 1H), 5.66 (d, $J = 11.4$ Hz, 1H), 3.69 (s, 3H), 2.36–2.22 (m, 2H), 1.03 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz): $\delta = 167.1$, 143.6, 139.2, 124.0, 117.2, 51.3, 21.2, 14.1; IR (neat): $\nu = 3053$, 2968, 2876, 1720, 1631, 1592, 1444, 1365, 1231, 1194, 1175, 1132 cm^{-1}; MS (GC-EI): m/z (%): 140 (17) $[M]^+$, 111 (100), 109 (19), 81 (48), 80 (12), 79 (39), 53 (20), 41 (18), 39 (20), 27 (10); HR-MS (EI): ($C_8H_{12}O_2$) calcd 140.0837; found 140.0837.

(2*Z*,4*Z*)-Hepta-2,4-dienoic acid amide (42): Compound **41** (300 mg, 2.141 mmol) was added to aq. ammonium hydroxide (50 mL, 30 %). The reaction mixture was stirred at ambient temperature for 4 days. The resulting mixture was extracted with ethyl acetate, the combined organic layers were dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography (ethyl acetate) to afford amide **42** (167 mg, 62 %) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.22–7.12$ (m, 1H), 6.77 (dd, $J = 11.6$, 1.1 Hz, 1H), 5.95–5.55 (br s, 2H), 5.88–5.77 (m, 1H), 5.62 (d, $J =$ 11.5 Hz, 1H), 2.23 (dtd, $J = 15.2$, 7.5, 1.6 Hz, 2H), 1.02 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 168.6$, 141.9, 136.2, 123.6, 119.3, 20.7, 13.9; IR (KBr): $\nu = 3403$, 3198, 3009, 2967, 2933, 1653, 1607, 1591, 1457, 1327, 808 cm^{-1}; MS (GC-EI): m/z (%): 125 (6) $[M]^+$, 110 (3), 96 (100), 81 (15), 67 (12), 53 (12), 41 (17), 27 (12); elemental analysis calcd for $C_7H_{11}NO$ (125.17): C 67.17, H 8.86, N 11.19; found C 67.26, H 8.81, N 11.12.

(7*S*,9*R*,10*S*,12*E*)-7-(2-Hydroxyethyl)-4-methoxy-9-methoxymethoxy-10-methyl-7,8,9,10,11,14-hexahydro-6-oxa-benzocyclododecen-5-one (47): A solution of compound **37c** (420 mg, 0.843 mmol) and DDQ (239 mg, 1.053 mmol) in water (1 mL) and CH_2Cl_2 (18 mL) was stirred at ambient temperature for 12 h. The reaction was diluted with ethyl acetate (40 mL) and filtered through a pad of Celite, the filtrate was evaporated and the residue was purified by flash chromatography (hexane/ethyl acetate 1:1) affording compound **47** as a colorless syrup (300 mg, 94 %). $[\alpha]_D^{20} = -34.5$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (CD_2Cl_2, 300 MHz): $\delta = 7.14$ (t, $J = 7.7$ Hz, 1H), 6.73 (d, $J = 7.7$ Hz, 1H), 6.68 (d, $J = 7.7$ Hz, 1H), 5.36–5.30 (m, 2H), 5.25–5.20 (m, 2H), 4.68 (q, $J = 6.7$ Hz, 2H), 4.02–3.93 (m, 2H), 3.69 (s, 2H), 3.68–3.52 (m, 2H), 3.30 (s, 3H), 3.25–3.22 (m, 1H), 1.79–1.58 (m, 4H), 1.36–1.27 (m, 2H), 1.15–1.06 (m, 2H), 0.74 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz): $\delta = 168.5$, 156.6, 139.5, 131.8, 130.4, 128.8, 125.0, 123.4, 109.7, 97.0, 79.6, 73.1, 59.5, 56.0, 55.7, 39.5, 38.1, 38.0, 36.2, 34.4, 13.5; IR (neat): $\nu = 3438$, 3068, 2956, 2930, 2843, 1723, 1597, 1584, 1468, 1439, 1275, 1119, 1085, 1071, 1038, 972 cm^{-1}; MS (EI): m/z (%): 378 (3) $[M]^+$, 346 (9),

316 (12), 315 (10), 260 (9), 259 (13), 228 (16), 215 (21), 204 (12), 189 (18), 187 (49), 186 (13), 177 (11), 175 (24), 174 (20), 163 (15), 162 (39), 161 (27), 159 (13), 153 (11), 148 (12), 115 (16), 55 (18), 45 (100), 43 (13); HR-MS (ESI pos): ($C_{21}H_{30}O_6$ + Na) calcd 401.1940; found 401.1942.

(7*S*,9*R*,10*S*,12*E*)-(4-Methoxy-9-methoxymethoxy-10-methyl-5-oxo-7,8,9,10,11,14-hexahydro[5*H*]-6-oxa-benzocyclododecen-7-yl)-acetaldehyde (48): Dess–Martin periodinane (403 mg, 0.950 mmol) was added at 0 °C to a solution of alcohol **47** (300 mg, 0.793 mmol) in CH_2Cl_2 (60 mL). The solution was allowed to warm to room temperature and stirred for 18 h. The reaction was diluted with ethyl acetate (50 mL) and quenched by the addition of sat. aq. $NaHCO_3$ (50 mL) and sat. aq. $Na_2S_2O_3$ (50 mL). The mixture was vigorously stirred until a clear solution resulted. The aqueous layer was repeatedly extracted with ethyl acetate, the combined organic phases were washed with brine, dried over Na_2SO_4 and evaporated. Flash chromatography (hexane/ethyl acetate 4:1) furnished aldehyde **48** (260 mg, 87 %) as a colorless syrup. $[\alpha]_D^{20} = -42.7$ ($c = 2.0$, benzene); ^{1}H NMR (C_6D_6, 300 MHz): $\delta = 9.65$ (dd, $J = 4.0$, 0.8 Hz, 1H), 7.00 (t, $J = 7.8$ Hz, 1H), 6.62 (d, $J = 7.8$ Hz, 1H), 6.38 (d, $J = 7.8$ Hz, 1H), 6.11 (m, 1H), 5.41 (m, 1H), 5.10 (d, $J = 6.8$ Hz, 1H), 4.94 (d, $J = 6.8$ Hz, 1H), 4.50 (m, 1H), 4.01 (q, 7.3 Hz, 1H), 3.84 (m, 1H), 3.42 (s, 3H), 3.39 (s, 3H), 2.52 (m, 1H), 2.23–2.06 (m, 3H), 1.75–1.65 (m, 2H), 1.43–1.33 (m, 2H), 0.93 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (C_6D_6, 75.5 MHz): $\delta = 199.9$, 168.4, 156.7, 139.8, 132.1, 130.5, 129.6, 123.2, 109.9, 97.9, 80.0, 70.2, 55.9, 55.5, 49.9, 38.5, 38.4, 36.5, 35.1, 27.6, 14.0; IR (neat): $\nu = 3497$, 3068, 2957, 2930, 2733, 1728, 1597, 1584, 1469, 1439, 1274, 1254, 1147, 1116, 1085, 1037, 971 cm^{-1}; MS (EI): *m*/*z* (%): 376 (3) $[M]^+$, 314 (22), 259 (17), 228 (11), 215 (18), 188 (10), 187 (47), 186 (13), 175 (11), 174 (14), 163 (11), 162 (13), 161 (14), 159 (12), 148 (11), 115 (13), 55 (11), 45 (100); HR-MS (ESI pos): ($C_{21}H_{28}O_6$ + Na) calcd 399.1784; found 399.1783.

(7*S*,9*R*,10*S*,12*E*)-7-(3-Iodoallyl)-4-methoxy-9-methoxymethoxy-10-methyl-7,8,9,10,11,14-hexahydro-6-oxa-benzocyclododecen-5-one (49): To a slurry of flame-dried $CrCl_2$ (1018 mg, 8.283 mmol) in THF (5 mL) was added a solution of aldehyde **48** (260 mg, 0.691 mmol) and iodoform (1.10 g, 2.794 mmol) in 1,4-dioxane (30 mL). The resulting brown solution was stirred at ambient temperature for 16 h, diluted with Et_2O (40 mL), and poured into water (ca. 40 mL). The aqueous layer was separated, saturated with NaCl, and extracted with Et_2O (50 mL, in several portions). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and evaporated. Purification of the residue by flash chromatography (hexanes/ethyl acetate 10:1) gave product **49** (302 mg, 87 %) as a syrup (9:1 mixture of *E*:*Z* isomers). $[\alpha]_D^{20} = -37.5$ ($c = 1.0$, benzene); ^{1}H NMR (C_6D_6, 300 MHz): $\delta = 7.05$ (t, $J = 7.6$ Hz, 1H), 7.01–6.89 (m, 1H), 6.65 (d, $J = 7.6$ Hz, 1H), 6.47 (d, $J = 7.6$ Hz, 1H), 5.89 (d, $J = 5.5$ Hz, 1H), 5.57 (m, 1H), 5.49–5.39 (m, 1H), 5.08 (d, $J = 6.8$ Hz, 1H), 4.88 (d, $J = 6.8$ Hz, 1H), 4.46 (d, $J = 6.8$ Hz, 1H), 3.90 (q, $J = 7.0$ Hz, 1H), 3.85 (m, 1H), 3.53 (s, 3H), 3.40 (s, 3H), 2.36–2.07 (m, 3H), 1.79–1.32 (m, 5H), 0.95 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (C_6D_6, 75.5 MHz): $\delta = 168.4$, 157.7, 143.2, 139.9, 132.0, 130.4, 129.4, 123.4, 110.2, 97.8, 97.7, 80.0, 77.9, 73.8, 56.3, 55.9, 43.2, 38.5, 38.4, 34.9, 35.1, 14.0; IR (neat): $\nu = 3425$, 2956, 2929, 2840, 1726, 1658, 1597, 1584, 1468, 1438, 1424, 1274, 1117, 1085, 1040, 972; MS (EI): *m*/*z* (%): 500 (5) $[M]^+$, 455 (22), 438 (19), 307 (12), 275 (10), 260 (13), 259 (34), 245 (15), 229 (10), 228(13), 227 (18), 215 (24), 213 (11), 204 (10), 199 (13), 189 (11), 187 (41), 186 (13), 185 (11), 177 (11), 175 (13), 174 (12), 173 (10), 163 (17), 162 (13), 161 (23), 159 (13), 148 (10), 115 (15), 91 (11), 67 (12), 55 (13), 45 (100); elemental analysis calcd for $C_{22}H_{29}IO_5$ (500.38): C 52.81, H 5.84; found C 52.70, H 5.77.

(7*S*,9*R*,10*S*,12*E*)-4,9-Dihydroxy-7-(3-iodoallyl)-10-methyl-7,8,9,10,11,14-hexahydro-6-oxa-benzocyclododecen-5-one (50): A solution of BBr_3 (1 M in CH_2Cl_2, 450 μL) was added dropwise at −78 °C to a solution of compound **49** (90 mg, 0.179 mmol) in CH_2Cl_2 (20 mL). The resulting brownish red solution was stirred at that temperature for 1 h and allowed to warm to room temperature. The reaction was quenched by the addition of water (50 mL). The aqueous layer was extracted with CH_2Cl_2, the organic extracts were washed with brine, dried over Na_2SO_4 and evaporated. Purification of the residue by flash chromatography (hexanes/ethyl acetate 4:1) afforded product **50** (70 mg, 88 %) as a colorless wax. $[\alpha]_D^{20} = -31.5$ ($c = 1.0$, benzene); ^{1}H NMR (CD_3OD, 300 MHz): $\delta = 7.20$ (t, $J = 7.6$ Hz, 1H), 6.91–6.37 (m, 3H), 6.36 (d, $J = 14.5$ Hz, 1H), 5.44–5.40 (m, 3H), 4.92 (s, 2H), 4.25 (d, $J = 8.5$ Hz, 1H), 3.72–3.62 (m, 2H), 2.58–2.48 (m, 3H), 1.89–1.81 (m, 3H), 1.42 (m, 1H), 0.94 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (CD_3OD, 75.5 MHz): $\delta = 172.7$, 158.5, 145.4, 142.3, 140.6, 133.7, 133.2, 132.2, 125.1, 124.1, 116.9, 79.4, 76.8, 73.7, 44.9, 40.7, 40.2, 38.9, 15.2; IR (neat): $\nu = 3433$, 2958, 2914, 1691, 1652, 1605, 1589, 1465, 1295, 1268, 1249, 1216, 1126, 1066, 1028, 968; MS (EI): *m*/*z* (%): 442 (12) $[M]^+$, 425 (12), 424 (17), 295 (10), 276 (14), 275 (12), 257 (14), 251 (25), 239 (11), 232 (31), 231 (519), 230 (14), 213 (17), 203 (11), 202 (14), 201 (18), 192 (14), 191 (24), 190 (20), 185 (15), 176 (17), 175 (32), 175 (38), 173 (68), 172 (100), 167 (13), 163 (11), 162 (16), 161 (27), 160 (23), 159 (15), 152 (11), 151 (14), 150 (14), 149 (29), 148 (33), 147 (25), 145 (22), 144 (11), 135 (11), 134 (17), 133 (10), 132 (11), 131 (15), 128 (13), 127 (22), 117 (11), 116 (20), 115 (28), 109 (11), 107 (14), 105 (17), 95 (19), 91 (17), 83 (23), 81 (21), 79 (17), 78 (10), 77 (17), 69 (16), 68 (13), 67 (31), 66 (21), 65 (11), 57 (17), 55 (40), 53 (14), 43 (31), 41 (41), 39 (19), 29 (19); HR-MS (EI): ($C_{19}H_{23}IO_4$) calcd 442.0641; found 442.0637.

Salicylihalamide (1a, b): An oven-dried Schlenk flask was charged with amide **42** (25 mg, 0.202 mmol), CuTC (13 mg, 0.068 mmol) and Rb_2CO_3 (46 mg, 0.202 mmol). Anhydrous DMA (1 mL) was added, the resulting suspension was carefully degassed in vacuo, compound **50** (30 mg, 0.068 mmol) was introduced, and degassing was repeated prior to heating the mixture to 90 °C for 2 h under argon. The red slurry was cooled to room temperature and diluted wit Et_2O, the organic phase was washed with pH 7 buffer, the aqueous layer was extracted twice with Et_2O, the combined organic phases were dried over Na_2SO_4 and evaporated. The residue was purified by preparative HPLC (Shimadzu LC-8; column: 125/20 mm BIAX; eluent: MeOH/H_2O 7:3) giving both isomers of the title compound (17 mg, 57 %, **1a**:**1b** ≈ 2.5:1) as colorless solids. Spectroscopic data of **1a**: $[\alpha]_D^{20} = -33.0$ ($c = 1.0$, benzene); ^{1}H NMR (CD_3OD, 300 MHz): $\delta = 7.34$ (t, $J = 10.8$ Hz, 1H), 7.17 (t, $J = 7.5$ Hz, 1H), 6.91 (t, $J = 11.8$ Hz, 1H), 6.87 (d, $J = 13.3$ Hz, 1H), 6.77 (d, $J = 7.8$ Hz, 1H), 6.70 ($J = 7.5$ Hz, 1H), 5.85 (m, 1H), 5.73 (d, $J = 11.5$ Hz, 1H), 5.52–5.34 (m, 4H), 4.15 (dd, $J = 8.7$, 3.3 Hz, 1H), 3.59 (dd, $J = 16.4$, 7.3 Hz, 1H), 3.39 (m, 1H), 2.46 (m, 1H), 2.37–2.28 (m, 4H), 1.97–1.74 (m, 3H), 1.41 (m, 1H), 1.07 (t, $J = 7.5$ Hz, 3H), 0.90 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (CD_3OD, 75.5 MHz): $\delta = 172.3$, 167.1, 158.4, 143.8, 141.9, 141.2, 138.9, 132.9, 132.8, 131.9, 127.4, 126.5, 123.6, 121.5, 116.5, 111.6, 77.2, 73.2, 40.1, 40.0, 39.7, 38.7, 37.8, 22.7, 15.5, 14.8; MS (EI) *m*/*z* (%) 439 (14) $[M]^+$, 192 (20), 191 (19), 173 (9), 149 (9), 127 (9), 109 (100), 108 (13), 83 (27), 82 (33), 81 (73), 79 (20), 57 (12), 56 (15), 55 (15), 53 (13), 41 (17); spectroscopic data of **1b**: $[\alpha]_D^{20} = -65.0$ ($c = 0.5$, benzene); ^{1}H NMR (C_6D_6, 300 MHz): $\delta = 8.03$ (t, $J = 11.8$ Hz, 1H), 7.86 (d, $J = 11.2$, 1H), 7.38 (t, $J = 10.5$ Hz, 1H), 7.04 (m, 1H), 6.73 (t, $J = 11.6$ Hz, 1H), 6.57 (dd, $J = 7.0$, 3.0 Hz, 1H), 5.73 (m, 1H), 5.59 (d, $J = 11.4$, 1H), 5.45–5.17 (m, 3H), 4.69 (q, $J = 8.2$ Hz, 1H), 3.64 (dd, $J = 16.6$, 5.1 Hz, 1H), 3.53 (d, $J = 7.7$ Hz, 1H), 3.43 (d, $J = 16.5$ Hz, 1H), 2.30–2.00 (m, 4H), 1.91–1.73 (m, 3H), 1.65 (m, 1H), 1.45 (s, 1H), 1.34 (dd, $J = 15.0$, 8.0 Hz, 1H), 0.93 (d, $J = 6.8$ Hz, 3H), 0.87 (m, 3H). The analytical data are in full agreement with those previously reported.[1, 9]

Enamide formation—Model reactions

(2*Z*,4*Z*)-Heptadienoic acid [2-(3-methoxyphenyl)-vinyl]-amide (44a): An oven-dried Schlenk flask was charged with amide **42** (43 mg, 0.345 mmol), CuTC (7 mg, 0.035 mmol) and Rb_2CO_3 (32 mg, 0.138 mmol). Anhydrous DMA (1 mL) was added, the resulting suspension was degassed, vinyl iodide **43a** (18 mg, 0.069 mmol) was introduced and the degassing procedure was repeated prior to heating the mixture to 90 °C for 3 h under argon. The red slurry was cooled to room temperature, diluted with Et_2O and washed with pH 7 buffer. The aqueous phase was extracted twice with Et_2O, the combined organic layers were dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography (hexanes/ethyl acetate 10:1) affording compound **44a** (16 mg, 89 %) as a colorless oil. Mixture of isomers (*E*:*Z* = 2:1); data of the major isomer: ^{1}H NMR (CD_2Cl_2, 300 MHz): $\delta = 7.63–7.51$ (m, 2H), 7.39–7.31 (m, 1H), 7.19 (t, 1H), 6.95–6.87 (m, 2H), 6.72 (d, $J = 7.9$ Hz, 1H), 6.12 (d, $J = 14.1$ Hz, 1H), 5.92 (q, $J = 9.6$ Hz, 1H), 5.64 (d, $J = 11.3$ Hz, 1H), 5.53 (d, $J = 11.3$ Hz, 1H), 3.79 (s, 3H), 2.32–2.20 (m, 2H), 1.01 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz): $\delta = 163.7$, 160.6, 143.4, 138.4, 138.0, 130.1, 124.4, 123.6, 119.3, 118.7, 112.9, 112.8, 111.1, 55.7, 21.3, 14.3; IR (neat): $\nu = 3273$, 3179, 3070, 2999, 2964, 2932, 2873, 1640, 1596, 1523, 1492, 1464, 1434, 1309, 1261, 1217, 1190, 1158, 1047, 954, 863, 810, 776, 712, 689 cm^{-1}; MS (EI): *m*/*z* (%): 257 (60) $[M]^+$, 228 (9), 149 (100), 109 (91), 81 (68).

(2*Z*,4*Z*)-Heptadienoic acid [2-(3-hydroxyphenyl)-vinyl]-amide (44b): The reaction was performed as described above using amide **42** (38 mg, 0.305 mmol), CuTC (5 mg, 0.030 mmol), Rb_2CO_3 (42 mg, 0.183 mmol), and 3-(2-iodo-vinyl)-phenol **43b** (15 mg, 0.061 mmol). A standard extractive work-up followed by flash chromatography (hexanes/ethyl acetate 4:1)

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afforded compound **44b** (13 mg, 86 %) as a colorless syrup. ^{1}H NMR (CD_2Cl_2, 300 MHz): $\delta = 7.54-7.46$ (m, 2H), 7.31 (m, 1H), 7.07 (t, $J = 7.7$ Hz, 1H), 6.89–6.76 (m, 2H), 6.60 (d, $J = 7.7$ Hz, 1H), 6.03 (d, $J = 14.2$ Hz, 1H), 5.87 (q, $J = 7.7$ Hz, 1H), 5.76 (s, 1H), 5.61 (d, $J = 11.5$ Hz, 1H), 2.20 (m, 2H), 1.12 (t, $J = 6.5$ Hz, 3H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz): $\delta = 163.9$, 156.7, 143.4, 138.3, 138.0, 130.2, 124.2, 123.3, 119.0, 118.6, 114.1, 112.9, 112.2, 21.2, 14.1; IR (neat): $\nu = 3281$, 3074, 2967, 2933, 2873, 1666, 1640, 1591, 1526, 1492, 1262, 1217, 1159, 950, 869, 778, 689 cm^{-1}; MS (EI): *m*/*z* (%): 243 (58) $[M]^+$, 214 (8), 135 (79), 109 (100), 108 (10), 81 (63), 79 (16), 53 (17), 41 (13).

(10*E*)-11-Benzoylamino-undecenoic isopropyl ester (46): An oven-dried Schlenk flask was charged with benzoic acid amide (51 mg, 0.421 mmol), CuTC (16 mg, 0.084 mmol) and Cs_2CO_3 (138 mg, 0.421 mmol). Anhydrous NMP (1 mL) was added and the suspension formed was carefully degassed. Compound **45** (100 mg, 0.282 mmol) was added, the mixture was degassed again prior to heating to 90 °C for 4 h under argon. The red slurry was cooled to ambient temperature, diluted with Et_2O and washed with pH 7 buffer. The aqueous layer was extracted twice with Et_2O, the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (hexanes/ethyl acetate 10:1) to afford compound **46** (65 mg, 70 %) as a colorless syrup. ^{1}H NMR (CD_2Cl_2, 300 MHz): $\delta = 7.79$ (d, $J = 8.1$ Hz, 3H), 7.55–7.42 (m, 3H), 6.93 (dd, $J = 14.2$, 10.3 Hz, 1H), 5.32 (dd, $J = 14.2$ Hz, 7.1 Hz, 1H), 4.95 (sept, $J = 6.2$ Hz, 1H), 2.23 (t, $J = 7.2$ Hz, 2H), 2.06 (q, $J = 7.2$ Hz, 2H), 1.60–1.30 (m, 10H), 1.20 (d, $J = 6.2$ Hz, 6H), 0.92–0.87 (m, 2H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz): $\delta = 173.5$, 164.3, 134.4, 132.1, 129.0, 127.3, 123.1, 114.5, 67.5, 35.0, 30.3, 30.2, 29.7, 29.6, 29.4, 29.3, 25.4, 24.0, 22.0; IR (neat): $\nu = 3310$, 2197, 3066, 2927, 2854, 1731, 1677, 1640, 1579, 1527, 1489, 1374, 1322, 1259, 1190, 1109, 956, 707 cm^{-1}; MS (EI): *m*/*z* (%): 345 (4) $[M]^+$, 240 (14), 122 (29), 105 (100), 77 (22); HR-MS (ESI pos): ($C_{21}H_{31}NO_3$) calcd 345.2304; found 345.2301.

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