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Elaboration of Sterically Hindered δ-Lactones through Ring-Closing Metathesis: Application to the Synthesis of the C1−C27 Fragment of Hemicalide

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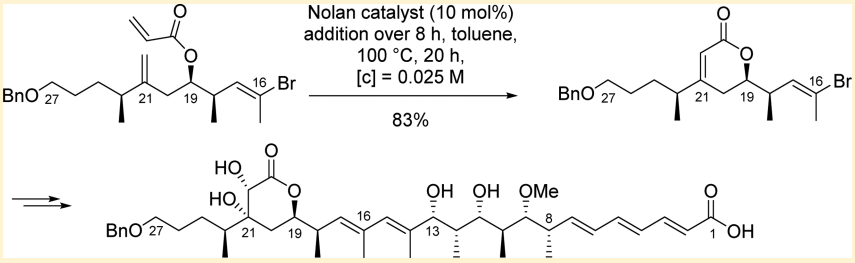
Supporting Information



ABSTRACT: The synthesis of the C1−C27 fragment of hemicalide, a marine metabolite displaying a unique potent antiproliferative activity, has been accomplished. The synthetic approach highlights a remarkably efficient ring-closing metathesis reaction catalyzed by Nolan ruthenium indenylidene complexes to elaborate the highly substituted δ-lactone framework.

INTRODUCTION

Marine organisms constitute an important source of structurally diverse and biologically active secondary metabolites. Several marine-derived agents are now approved, and when combined with the rich pipeline of compounds in clinical trials and preclinical evaluation, it can be assumed that the marine environment performed particularly well in yielding new medicines as well as pharmacological tools.[1] However, difficulties inherent to this type of drug, such as adequate sourcing of the agent and issues related to structural complexity still need to be overcome.

Hemicalide is a new complex polyketide that was recently isolated by French researchers of the CNRS-Pierre Fabre Laboratories joint unit in association with the Institut de Recherche pour le Développement (IRD), from the marine sponge *Hemimycale sp.* collected in deep water around the Torres Islands (Vanuatu).[2] This compound was reported to display high antiproliferative potency against a panel of human cancer cell lines at subnanomolar concentrations, by acting as a mitotic blocker. Additionally, preliminary studies indicated that hemicalide operates by a unique mechanism involving the destabilization of the α/β microtubule network. Hemicalide could be considered as a promising chemotherapeutic agent. Nevertheless, the scarcity of the natural source (less than 1 mg was isolated) could not provide the quantities of hemicalide required to support complementary pharmacological evaluation and full elucidation of the chemical structure. As a result, we rose to the challenge of developing a total synthesis of this structurally complex natural product (or stereoisomers thereof).

The planar structure of hemicalide **1** is characterized by a densely functionalized 46 carbon atom backbone (Figure 1). It is noteworthy that the configuration of the 21 stereocenters was initially undetermined. Recently, assignment of the relative configuration of C8−C13 hexad as well as C18−C24 δ-lactone subunit was achieved by comparison of the NMR spectroscopic data of hemicalide **1** with those of model compounds[3−5] and a convergent approach toward the C1−C25 fragment was performed (Figure 1).[6] Additionally, synthetic studies toward the C32−C46 segment of hemicalide allowed the assignment of the relative configuration of the C36−C42 subunit.[7]

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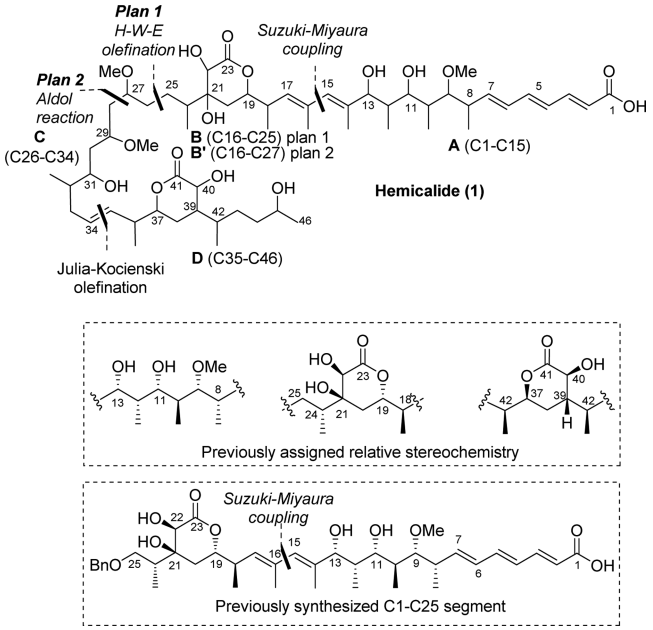
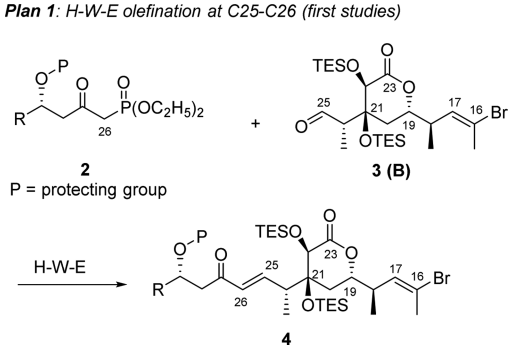


Figure 1. Structure of hemicalide **1** and previous studies.

Synthetic Considerations. As previously reported,[6,7] the original synthetic plan toward hemicalide **1** hinged upon disconnections at C15−C16, C25−C26 and C34−C35 and consequent elaboration of four subunits: **A** (C1−C15), **B** (C16−25), **C** (C26−C34) and **D** (C35−C46) with Suzuki−Miyaura cross-coupling and two olefination reactions [Horner−Wadsworth−Emmons (H−W−E) and Julia−Kocienski] as the key coupling events (Plan 1, Figure 1). However, difficulties were encountered in the carbon chain extension of fragment **B** at the C25 position, since H−W−E olefination involving aldehyde **3** (C16−C25 subunit) and various substituted β-ketophosphonates **2** did not afford the corresponding enones **4** in decent yields in the context of a total synthesis (Scheme 1).[8]

Scheme 1. H−W−E Olefination at C25−C26: First Studies (Plan 1)

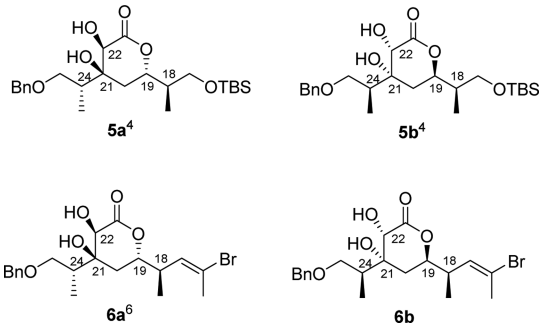


Faced with this hurdle, a second approach was devised based on the replacement of the H−W−E olefination at C25−C26 by an aldol reaction at C27−C28 (Plan 2, Figure 1). The present publication focuses on the synthesis of the C1−C27 fragment (**AB′** segment) of hemicalide **1** (or a stereoisomer) through a straightforward approach involving a challenging ring-closing metathesis (RCM) reaction to construct the highly sterically hindered α,β-dihydroxy δ-lactone framework **B′** (C16−C27).

RESULTS AND DISCUSSION

Assignment of the Stereocenters of δ-Lactone B or B′. The assignment of the relative stereochemistry of the central δ-lactone of hemicalide **1** proved to be critical. In our previous studies, NMR spectroscopic data comparisons of hemicalide **1** with those of model lactones C17−C25 (**5a** and **5b**) were achieved.[4] This work evidenced that diastereomers **5a,b** (with a *cis* relationship between the C19 and C24 centers) were closest to hemicalide **1** and lactone **5a** was finaly elected. However, in the course of the synthesis of C1−C25 fragment of hemicalide **1**, we observed that C16−C25 lactone **6a** did not closely match the natural product **1**.[6] Therefore, δ-lactone **6b** was synthesized in order to perform more accurate NMR comparisons (Scheme 2).

Scheme 2. Assignment of the Relative Stereochemistry of the δ-Lactone Framework 6



By analogy with our previous sequence to access δ-lactone **6a**, synthesis of δ-lactone **6b** started from (*R*)-(4-(benzyloxy)-3-methyl-2-methylenebutyl)trimethylsilane **7**,[4] readily prepared from (*S*)-Roche ester. Dias allylation reaction between allyl stannane derived from **7** and aldehyde (*R*)-**8**[9] delivered homoallyl alcohol **9** in a good yield (71%) and diastereoselectivity (*dr*: 90:10).[4,6,10] Subsequent two-steps sequence ozonolysis-acylation of C19 hydroxy group by means of bromoacetyl bromide led to ester **10**. This compound (**10**) was engaged in a SmI_2-induced intramolecular Reformatsky reaction, followed by dehydration ($SOCl_2$, Py) to afford α,β-unsaturated δ-lactone **11**, in a moderate 49% yield over two steps. Finally, a chemo- and diastereoselective *syn*-dihydroxylation promoted by potassion osmate afforded δ-lactone **6b** in 45% yield (Scheme 3). Noteworthy, in this sequence, both dehydration and dihydroxylation steps are much less efficient than previously reported in the case of 18,19-*anti* lactone **6a.**

With δ-lactones **6a**[6] and **6b** in hand, more accurate comparisons were possible (Scheme 2). The differences in the ^{1}H and ^{13}C NMR spectra are highlighted in Table 1. Comparison mainly focused on the most significant 19 and 22 positions, the chemical shift and multiplicities of H19 and H22 being particularly dependent on the orientation of the δ-lactone substituents. Thus, it appeared that lactone **6b**, with a *syn* relationship between C18, C19 and C24, and a *trans* orientation between C19 and C22, most closely matched the authentic natural product **1**. Concomitantly with our work, reassignment of the initially attributed C18−C19 relative stereochemistry was also disclosed by Paterson et al.[11]

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Scheme 3. Synthesis of δ-Lactone 6b

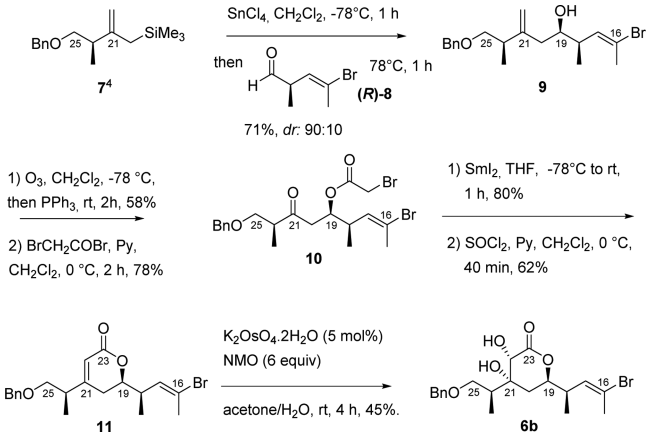


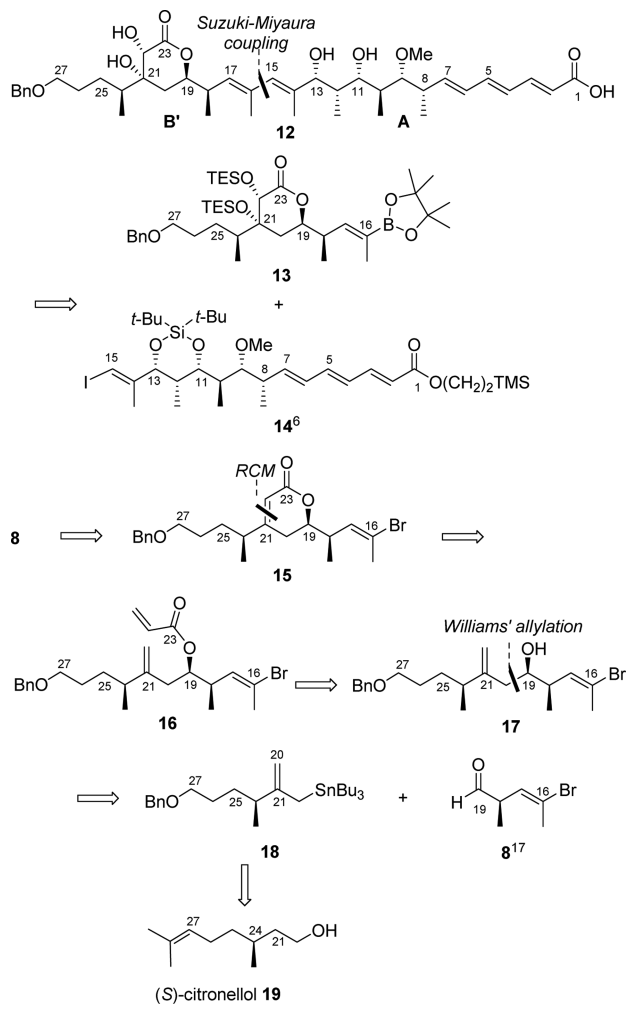
Table 1. Comparison of ^{1}H and ^{13}C NMR Data (Methanol-d_4, 500 MHz) for Hemicalide 1 and δ-Lactones 6a−b

	H−C19 δH, m, ^{3}J [Hz]	H−C22 δH, m, ^{3}J [Hz]	δC-19	δC-22
Hemicalide **1**	4.42, ddd, 11.5, 7.5, 3.5	4.27, s	82.8	72.5
δ-lactone **6a**	4.49, ddd, 10.7, 4.8, 4.3	4.19, s	81.7	73.2
δ-lactone **6b**	4.42, ddd, 11.3, 6.3, 4.1	4.24, s	81.5	73.2

Retrosynthetic Analysis. δ-Lactone frameworks are widely present in biologically active natural compounds[12] and RCM reaction has become one of the most powerful tools for their elaboration. In particular, the development of ruthenium alkylidene complexes bearing *N*-heterocyclic carbene ligands (NHC) (i.e., classical Grubbs' II and Hoveyda−Grubbs' II catalysts) has largely broadened the scope and the utility of this reaction.[13,14] However, to date, applications such as highly sterically demanding transformations still need to be improved by identifying more suitable catalysts with enhanced reactivity and stability, that would also be readily available. In this context, recent progresses in ruthenium olefin metathesis catalysts have brought about significant impacts in the synthesis of cyclic compounds containing tri- or tetrasubstituted olefin structures.[14b,c,15,16]

In accordance with the second strategy for the total synthesis of hemicalide **1** (Plan 2, Figure 1), we decided to develop a new route toward the δ-lactone moiety in the corresponding C1−C27 subunit **12** of hemicalide **1**. By analogy with our previous synthesis of the shorter C1−C25 segment,[6] a Suzuki−Miyaura coupling reaction between alkenyl iodide **14** (C1−C15 subunit) and alkenyl boronate **13** (C16−C27 subunit) would be used to create the C15−C16 bond. Alkenyl boronate **13** would be elaborated from the α,β-unsaturated δ-lactone **15** by chemo- and diastereoselective dihydroxylation of the C21−C22 double bond and borylation of the vinylic bromide at C16. The defining feature of our new strategy would be the construction of the highly substituted δ-lactone **15** by means of a RCM reaction of acrylate **16** bearing a hindered chain on the homoallylic double bond. To this aim, we hypothesized that the combination of a suitable catalyst with an optimized experimental procedure should permit an efficient elaboration of the δ-lactone subunit **15** (Scheme 4).

Scheme 4. Retrosynthetic Analysis of the C1−C27 Subunit 12



Acrylate **16** would be obtained from homoallylic alcohol **17** whose preparation was envisioned by an asymmetric Williams' allylation reaction[17,14c] of aldehyde **8**[9] with allylstannane **18**. The C24 stereocenter of **18** would originate from (*S*)-citronellol **19** as an inexpensive starting material.

Preliminary tests were performed in the RCM reaction of acrylate **20**, prepared from previously synthesized homoallyl alcohol **9**, by acylation of C19 hydroxy group. Lactone **11** was obtained in an encouraging, yet unoptimized, 58% yield when Grubbs II catalyst (**cat-2**) was slowly added to acrylate **20**, over 8 h, in refluxing dichloromethane (Scheme 5).

RCM Optimization Using a Model Acrylate. For the purpose of seeking effective catalyst and conditions, an extensive survey of the RCM was further performed using a model acrylate **24**, structurally related to the C16−C27 acrylate **16**. The synthesis of this model compound **24** started with the three-step conversion of (*S*)-citronellol **19** into known alcohol **21**.[18] The corresponding benzyl ether was formed and the terminal alkene was subjected to a Wacker-type oxidation[19] to provide methyl ketone **22**. The aldol **23** was then prepared as a mixture of diastereomers (*dr*: 50:50) by reaction between the lithium enolate derived from **22** and isobutyraldehyde. Subsequent acylation with acryloyl chloride and methylenation[20] reaction allowed the elaboration of

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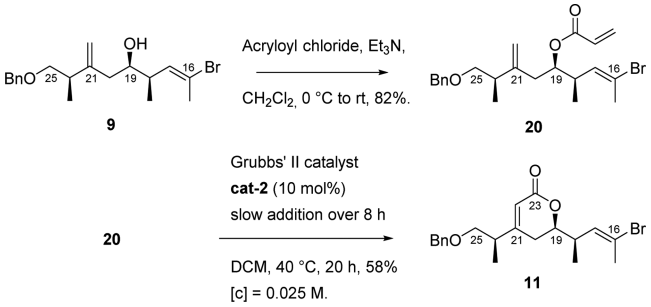
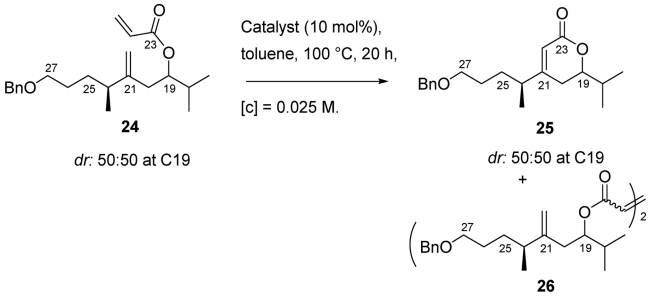
Scheme 5. Synthesis and RCM Reaction of C16−C25 Acrylate 20



Scheme 7. RCM Reaction of Model Acrylate 24



homoallyl acrylate **24**, a potential precursor of *δ*-lactone **25** by RCM (Scheme 6).

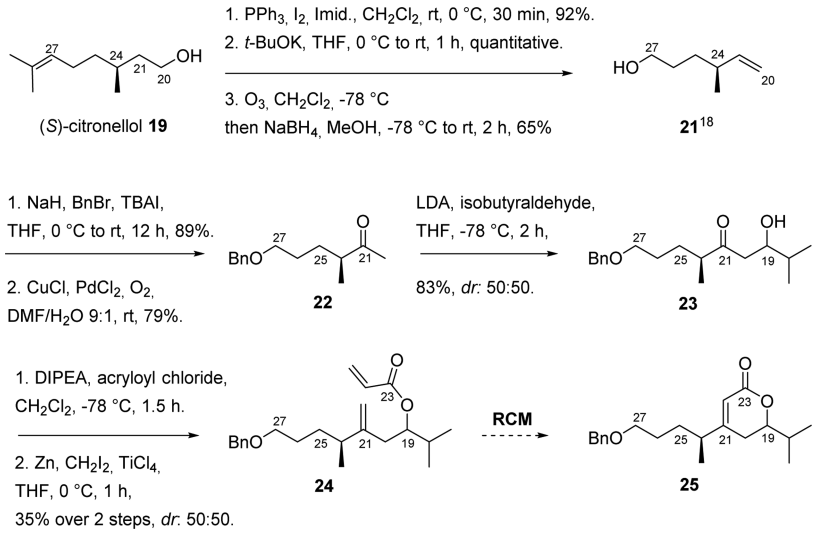
The study of RCM reaction of acrylate **24** into lactone **25** was initiated by using commercially available ruthenium-based catalysts, very commonly used in the olefin metathesis of more simple systems: Grubbs' I and II (**cat-1** and **cat-2**), and Hoveyda−Grubbs' II (**cat-3**) catalysts (Schemes 7 and 8).[14]

When acrylate **24** was subjected to catalysts **cat-1**−**2**−**3** (10 mol %) added in one-shot in toluene at 100 °C, the reaction was rather sluggish and did not reach completion after 20 h (Table 2, Entries 1, 3, 5). Best results were observed with **cat-3** (67% conversion): the expected lactone **25** was formed along with homodimer **26** as a minor side product (**24**/**25**/**26** 33:62:5, Table 2, Entry 5). A careful monitoring of the RCM reaction revealed a high catalytic activity at the beginning of the reaction which rapidly diminished as the reaction proceeded further. Given this fact, we envisioned that slow addition of the catalyst may sustain the catalyst activity all along the reaction. Thereby, a dropwise addition of a solution of catalysts **cat-1**−**2**−**3** to the reaction mixture over 8 h (Table 2, Entries 2, 4, 6) was performed, and this resulted in a significant optimization of the reaction when **cat-2** and **cat-3** were used as catalysts (Table 2, Entries 4, 6). Interestingly, the conversion reached 89% with **cat-3** (Table 2, Entry 6, **24**/**25**/**26** 11:80:9), and lactone **25** could be isolated in 67% yield (Scheme 7).[21]

Other catalysts were then screened while implementing the slow addition mode of the catalyst. Performing the reaction with bulky catalyst **cat-4**[22] (Table 2, Entries 7, 8) resulted in no improvement. We were next interested in catalyst **cat-5** reported by Schrödi et al., for which it was demonstrated that the removal of one *ortho* substituent onto the *N*-aryl ring of the NHC ligand, was beneficial for the RCM of hindered substrates.[23] However, no enhancement in conversion was observed (Table 2, Entries 9, 10). We also examined the activity of catalyst **cat-6**, a Hoveyda−Grubbs-type complex containing a trifluoroacetamido group, described by Mauduit et al. as a highly efficient precatalyst.[15a] However, its activity was found to be slightly lower than that of catalyst **cat-3** (Table 2, Entry 11). Interestingly, by using Plenio catalyst **cat-7**, a noncommercially available complex with mixed NHC ligands (one electron-rich, one electro-deficient),[15b] acrylate **24** displayed a conversion of 94% and the desired lactone **25** was isolated in 79% yield (Table 2, Entry 12). Finally, the activity of the phenylindenylidene catalyst **cat-8** was evaluated.[24] This complex, described by Nolan as more resistant to harsh reaction conditions than its benzylidene counterpart **cat-2**, turned out to be the most efficient catalyst: remarkably, the conversion was complete and *α*,*β*-unsaturated *δ*-lactone **25** was obtained in an excellent 85% yield (Table 2, Entry 13).

These results suggest that the nature of the catalyst and the addition mode are essential factors for this RCM reaction involving hindered substrate **24**. Moreover, this study has clearly demonstrated how challenging it is to anticipate the

Scheme 6. Synthesis of the Model Acrylate 24



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Scheme 8. RCM Catalysts

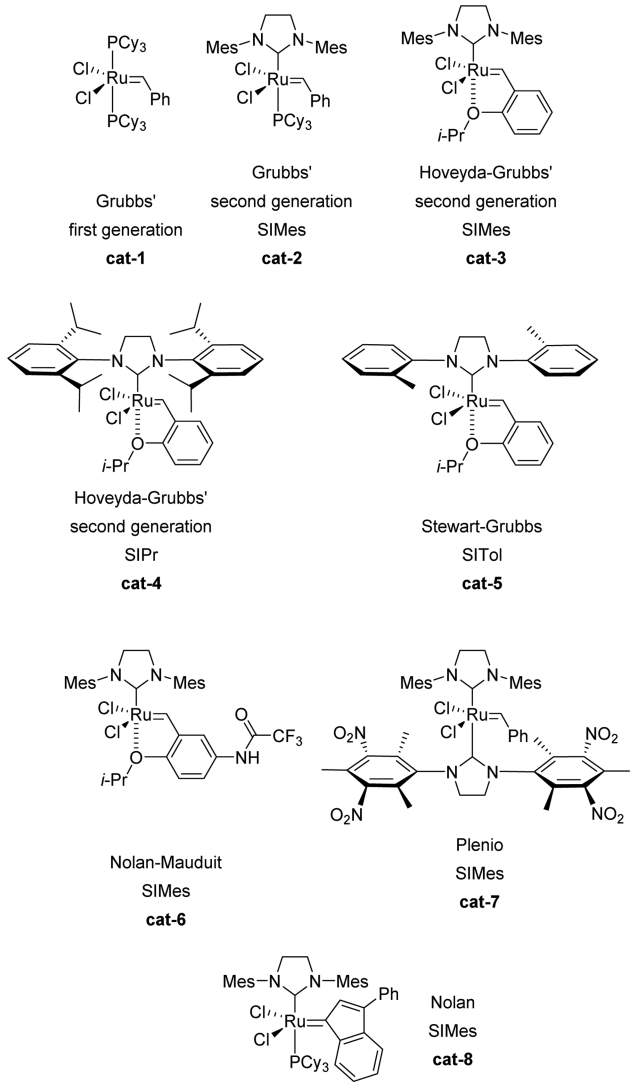

Table 2. Optimization of the RCM Reaction with Model Acrylate 24

entry	catalyst	addition mode	conversion **24**/**25**/**26**[a]	**25**: yield (%)[b]
1	**cat-1**	one-shot	5% 95:5:0	–
2	**cat-1**	slow addition	8% 92:7:1	–
3	**cat-2**	one-shot	30% 70:27:3	–
4	**cat-2**	slow addition	78% 22:71:7	–
5	**cat-3**	one-shot	67% 33:62:5	–
6	**cat-3**	slow addition	89% 11:80:9	67
7	**cat-4**	one-shot	69% 31:64:5	–
8	**cat-4**	slow addition	77% 23:71:6	–
9	**cat-5**	one-shot	52% 48:50:2	–
10	**cat-5**	slow addition	60% 40:57:3	–
11	**cat-6**	slow addition	71% 29:65:6	
12	**cat-7**	slow addition	94% 6:86:8	79
13	**cat-8**	slow addition	100% 0:93:7	85

[a]Ratio determined by ^{1}H NMR spectroscopy. [b]Isolated product.

activity of a catalyst toward a specific substrate. The optimized conditions defined above on model substrate **24**, i.e., dropwise addition of commercial Nolan catalyst **cat-8** (10 mol %) over 8 h, in toluene at 100 °C for 20 h, were selected for further RCM reaction in the synthesis of the C16−C27 δ-lactone **15** from acrylate **16** (Scheme 4).[25] However, it is interesting to note that the results obtained with classical Hoveyda−Grubbs and noncommercial Plenio catalysts **cat-3** and **cat-7**, demonstrate that they could also be valuable alternatives for the RCM reaction under consideration.

Synthesis of the C1−C27 Fragment of Hemicalide. The synthesis of lactone **15** commenced with the smooth transformation of (*S*)-citronellol **19** into triethylsilyl ether **27** by protection of the alcohol function and subsequent ozonolysis of the double bond (Scheme 9). Then, a five-step sequence without purification of the intermediates, involving protection of the primary alcohol by a benzyl group, Swern oxidation of the silyl ether, Pihko homologation (providing aldehyde **28**),[26] reduction and esterification allowed the formation of benzoate **29** in 64% yield. Displacement of the benzoate with $Bu_3SnAlEt_2$ mediated by palladium employing the Trost's conditions[27] quantitatively completed the synthesis of allylstannane **18**. Asymmetric allylation of aldehyde **8** was then achieved under Williams conditions,[17,14c] i.e., by transmetalation of allylstannane **18** with Corey's bromoborane complex **30** (prepared from BBr_3 and *bis*-tosylated (*R*,*R*)-1,2-diamino-1,2-diphenylethane) and subsequent reaction with aldehyde **8**[9] at −78 °C. This easily scalable reaction provided a mixture of epimers at C-19 (78%, *dr*: 88:12) in which homoallylic alcohol **17** was the major component. After purification, major diastereomer 18,19-*syn* **17** was isolated in 69% yield.[10] Esterification of **17** with acryloyl chloride easily delivered C16−C27 acrylate **16**, RCM precursor of the δ-lactone **15**. Through the optimized conditions determined previously (dropwise addition of the catalyst (10 mol %) over 8 h, in toluene at 100 °C), Hoveyda−Grubbs' second generation catalyst (**cat-3**) afforded lactone **15** in good yield (74%, Table 3, Entry 1). In accordance with the model series, Nolan's catalyst (**cat-8**) provided lactone **15** in an excellent 83% yield (Table 3, Entry 2), and it should be mentioned that similar proportions of homodimer **31** were formed during the RCM reaction (Scheme 10 and Table 3).

Subsequent chemo- and diastereoselective dihydroxylation of the C21−C22 double bond of **15** turned out to be more difficult than expected. Under the classical conditions used to access lactone **6a−b** ($K_2OsO_4{\cdot}2H_2O$ (5 mol %), NMO, acetone/H_2O),[6] diol **32** was isolated in a modest 47% yield along with degradation products resulting from oxidative cleavage of the hindered C16−C17 double bond and retro-aldol reactions. After an extensive screening, we were finally pleased to find that recourse to acidic conditions led to a significant improvement in yield. Hence, addition of an excess of citric acid[28] into the reaction medium, while adjusting the quantity of potassium osmate ($K_2OsO_4.2H_2O$) to 2 mol %, provided the expected pure *cis*-1,2-diol **32** in 70% yield. Finally, protection of the diol as a *bis*-triethylsilyl ether (formation of **33** in 96% yield)[29] followed by palladium-catalyzed borylation with *bis*-pinacolato-diboron **34**[30] delivered the trisubstituted (*E*)-alkenylboronate **13** in 66% yield (Scheme 11).

In summary, the synthesis of the C16−C27 fragment **13** has been achieved in 18% overall yield over 14 steps from (*S*)-citronellol **19**.

At this stage, a $Pd(PPh_3)_4$ catalyzed Suzuki−Miyaura coupling reaction was performed between alkenyl iodide (C1−C15 subunit) **14**[6] and alkenyl pinacol boronate **13**

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J. Org. Chem. 2016, 81, 12275−12290

Scheme 9. Synthesis of the α,β-Unsaturated δ-Lactone 15

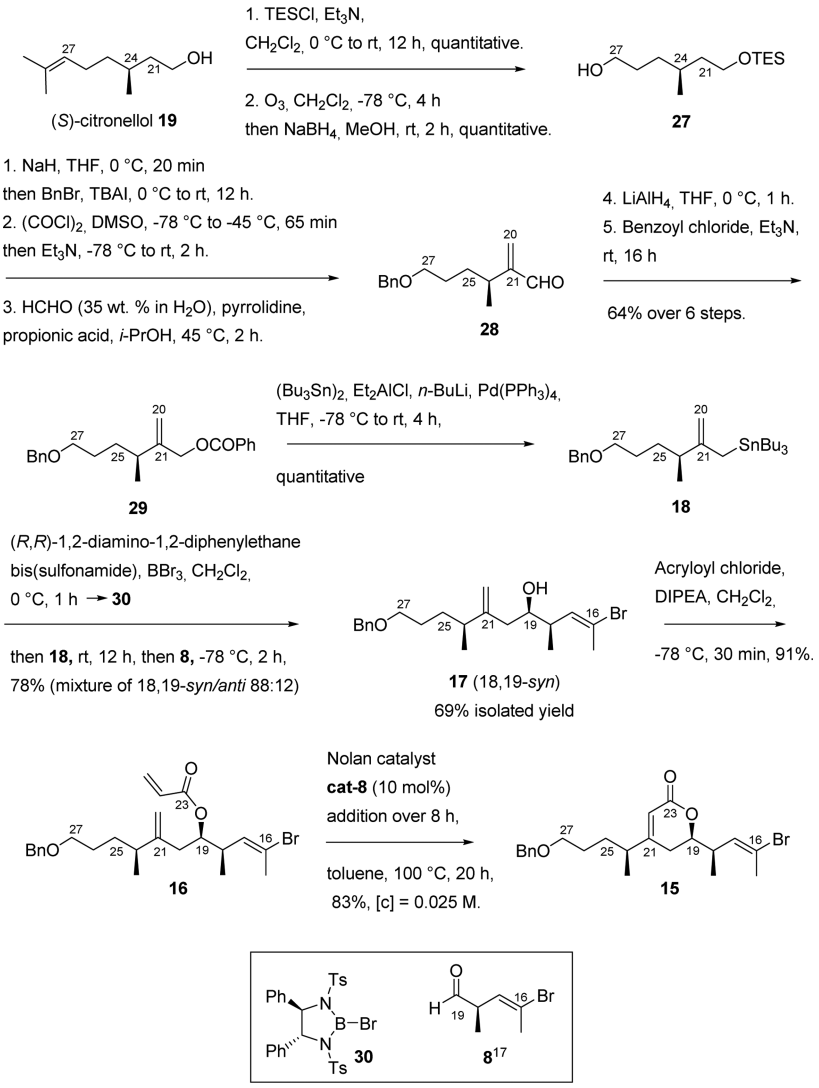
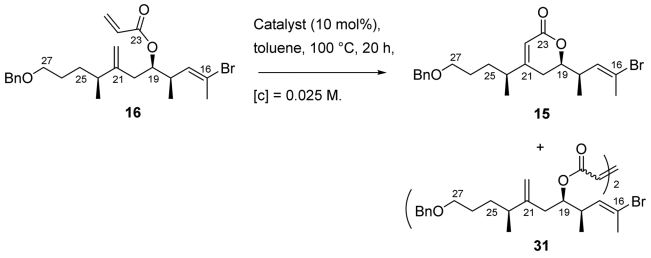


Table 3. Optimization of the RCM Reaction with Acrylate 16

entry	catalyst	addition mode	conversion 16/15/31[a]	15: yield (%)
1	**Cat-3**	slow addition	100% 0:90:10	74
2	**Cat-8**	slow addition	100% 0:93:7	83

[a]Ratio determined by ^{1}H NMR spectroscopy.

Scheme 10. RCM Reaction of Acrylate 16



(C16−C27 subunit), in the presence of aqueous TlOEt as the base.[31] Under these conditions, trisubstituted (*E*,*E*)-diene C1−C27 **35** was isolated in excellent yield (82%) The challenging final deprotection step was largely optimized, to afford the desired desilylated product **12** in 90% yield over two steps: the TES ethers and the 2-trimethylsilyl ester were first cleaved using tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) in DMF, and then the 1,3-diol at C11,C13 was deprotected by means of a buffered HF·Py solution. The synthesis of fragment **12**, which should constitute one of the two possible diastereomers of the C1−C27 subunit of hemicalide **1** was thus successfully accomplished (Scheme 12).

A comparison of the NMR spectroscopic data of hemicalide **1** with those of δ-lactone **32** and segment C1−C27 **12** was accomplished at this stage. More specifically, examination at significant C19 and C22 positions, revealed that both lactone frameworks, **32** and **12**, closely matched the authentic natural product **1** (Table 4).

Finally, with lactone **33** in hand, we focused our efforts on the validation of the key-aldol reaction at C27−C28 position, in order to establish the reliability of our second strategy. A first aldol reaction involving aldehyde **36** and a model boron enolate derived from methyl ketone **37**[32] delivered 1,5-*anti* aldol **38**[32,33] in unoptimized, however promising, yield and selectivity (80% yield, *dr*: up 80:20) (Scheme 13).

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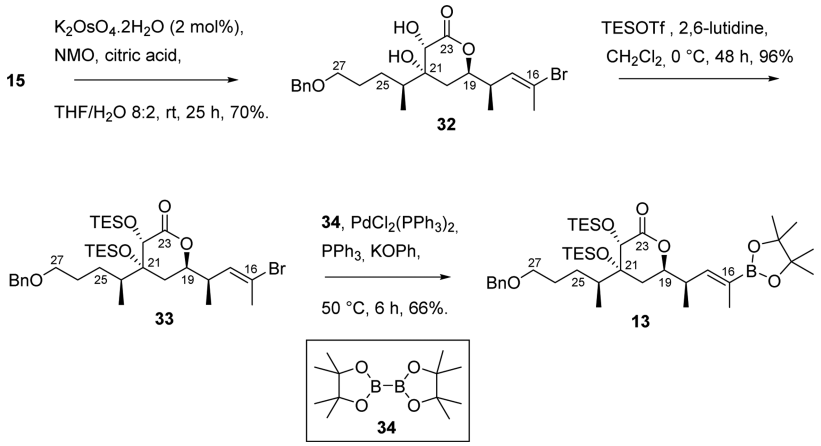
J. Org. Chem. 2016, 81, 12275−12290

Scheme 11. Synthesis of the C16−C27 Subunit 13



Scheme 12. Synthesis of the C1−C27 Subunit 12

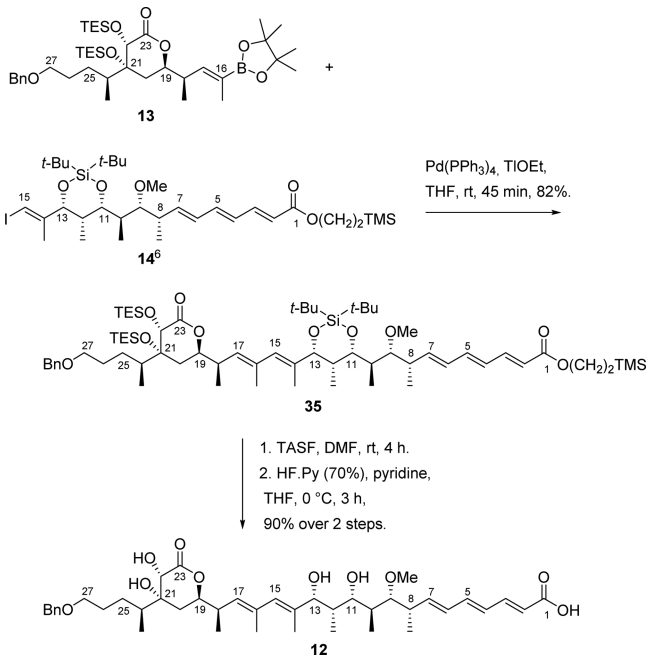


Table 4. Comparison of ^{1}H and ^{13}C NMR Data (Methanol-d_4, 500 MHz) for Hemicalide 1, δ-Lactone 32 and Subunit 12

	H−C19 δH, m, ^{3}J [Hz]	H−C22 δH, m, ^{3}J [Hz]	δC-19	δC-22
Hemicalide **1**	4.42, ddd, 11.5, 7.5, 3.5	4.27, s	82.8	72.5
δ-lactone **32**	4.42, ddd, 11.7, 6.7, 3.9	4.22, s	81.6	72.5
Subunit **12**	4.40, ddd, 11.0, 7.5, 3.5	4.23, s	82.7	72.4

CONCLUSION

In the present publication, we have expanded our investigations on the configurational assignment and synthesis of the marine product hemicalide. The synthesis of one of the two possible diastereomers of the C1−C27 subunit of this polyketide was achieved, featuring the efficient elaboration of a highly substituted α,β-unsaturated δ-lactone intermediate **15** by unprecedented RCM reaction of diene **16**. The optimized conditions, first established with a model compound, involving the slow addition of commercially available Nolan ruthenium-indenylidene catalyst (over 8 h) to the substrate in toluene (100 °C, 20 h) allowed the synthesis of the key α,β-unsaturated δ-lactone **15** in an excellent 83% yield. Besides, the feasibility of a boron-mediated aldol reaction to generate the C27−C28 bond was demonstrated. Moreover, this work further contributes to the assignment of the relative configuration of the central δ-lactone core of hemicalide. The total synthesis of hemicalide (or stereoisomer thereof) is currently underway in our laboratories.

EXPERIMENTAL SECTION

General Remarks. All reactions sensitive to moisture and/or air were carried out under argon atmosphere in dry, freshly distilled solvents under anhydrous conditions using oven-dried glassware, unless otherwise noted. THF and toluene were distilled over sodium/benzophenone system, DCM, DMSO and DMF were distilled over calcium hydride, MeOH and EtOH were distilled over magnesium turnings. Reactions were monitored by TLC (silica gel 60 F254plates) and visualization was accomplished with UV light (254 and 366 nm) and subsequent use of phosphomolybdic acid solution in EtOH (5%), $KMnO_4$ solution or vanillin/sulfuric acid solution in EtOH, followed by heating at 100−110 °C. Flash chromatography was performed with silica gel 60 (particle size 0.040−0.063 μm). Yield refers to chromatography and spectroscopically pure compounds, unless otherwise noted. ^{1}H NMR spectra were recorded at 300, 400, and 500 MHz. Chemical shifts are expressed in ppm, relative to the residual ^{1}H solvent signal ($CDCl_3$ δ = 7.26 ppm, CD_3OD δ = 3.31 ppm) as the internal reference. Coupling constants (J) are reported in hertz (Hz). The following abbreviations are used to designate the multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; quint. = quintet, sext. = sextet, sept. = septet, m = multiplet; br = broad. ^{1}H NMR assignments were confirmed by 2D COSY spectra. The given multiplicities reflect apparent signal patterns. . Diastereomer ratio (dr) was estimated by ^{1}H NMR spectroscopic analysis (300 or 400 MHz), unless otherwise noted. ^{13}C NMR spectra were recorded at 75 MHz, 100 and 125 MHz. Chemical shifts are given in ppm relative to the residual ^{13}C solvent signal ($CDCl_3$ δ = 77.16 ppm, CD_3OD δ = 49.00 ppm). ^{13}C NMR assignments were confirmed by 2D HSQC and HMBC spectra. Coupling constants (J) are given in Hz for all NMR spectroscopic data. IR spectra were recorded with a FT-IR spectrometer. High-resolution mass spectra (HRMS) were measured on a mass spectrometer equipped with a TOF system and an electrospray ionization (ESI) ion source.

One Shot Ring-Closing Metathesis, General Procedure (GP1). In an oven-dried round-bottom flask equipped with a magnetic stirring bar and a reflux condenser were placed acrylate

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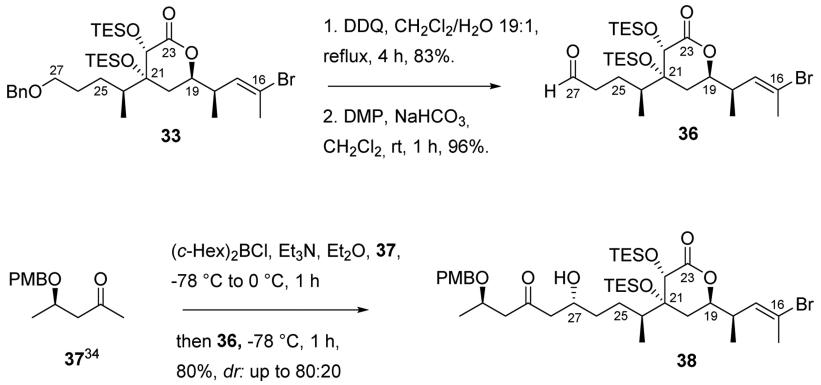
Scheme 13. Validation of the Aldol Reaction at the C27−C28 Position



(0.112 mmol) and catalyst **cat-X** (**X** = **1** to **8**) ($1.12.10^{-2}$ mmol, 10 mol %) in dry and degassed toluene (4.6 mL). The reaction mixture was heated to 100 °C for 20 h under argon, then stopped and solvent was evaporated.

Slow Addition Ring-Closing Metathesis, General Procedure (GP2). In an oven-dried round-bottom flask equipped with a magnetic stirring bar and a reflux condenser was placed acrylate (0.112 mmol) in dry and degassed toluene (2.3 mL). The reaction mixture was heated to 100 °C then catalyst **cat-X** (**X** = **1** to **8**) ($1.12.10^{-2}$ mmol, 10 mol %) diluted in dry and degassed toluene (2.3 mL) was slowly added over 8 h via syringe-pump. The reaction was stopped after 20 h and solvent was evaporated. Crude product was purified by flash chromatography on silica gel.

(3R,4S,6S)-4((R)-1-(Benzyloxy)propan-2-yl)-6-((R,E)-4-bromopent-3-en-2-yl)-3,4-dihydroxytetrahydro-2H-pyran-2-one ***(6a)***. Lactone **6a** was previously synthesized by our group:[6] $[\alpha]_D^{20}$ +12.7 (*c* 0.60, $CHCl_3$) IR (neat) 3432, 2971, 2926, 2860, 1733, 1655, 1452, 1384, 1228, 1106, 862, 741 cm^{-1}; ^1H NMR (500 MHz, MeOD) δ 7.39−7.24 (m, 5H), 5.73 (qd, *J* = 1.4, 10.1 Hz, 1H), 4.51 (d, *J* = 12.0 Hz, 1H), 4.49 (ddd, *J* = 4.3, 4.8, 10.7 Hz, 1H), 4.47 (d, *J* = 12.0 Hz, 1H), 4.19 (s, 1H), 3.53 (dd, *J* = 5.7, 9.8 Hz, 1H), 3.50 (dd, *J* = 5.0, 9.8 Hz, 1H), 2.61 (ddq, *J* = 4.3, 7.0, 10.1 Hz, 1H), 2.29 (m, 1H), 2.21 (d, *J* = 1.4 Hz, 3H), 1.89 (dd, *J* = 4.8, 14.2 Hz, 1H), 1.83 (dd, *J* = 10.7, 14.2 Hz, 1H), 1.08 (d, *J* = 7.0 Hz, 3H); 1.04 (d, *J* = 6.9 Hz, 3H);^{13}C NMR (125 MHz, MeOD) δ 176.4, 139.5, 133.5, 129.4 (2C), 129.0 (2C), 128.9, 122.4, 81.7, 75.5, 74.3, 73.3, 73.2, 40.2, 40.0, 33.9, 23.9, 17.0, 11.9; HRMS (ESI) calcd for $C_{20}H_{27}BrO_5Na^+$ $[(M + Na)^+]$ 449.0940, found 449.0944.

(4R,5R,8R,E)-9-(Benzyloxy)-2-bromo-4,8-dimethyl-7-methylene-non-2-en-5-ol ***(9)***. Tin(IV) chloride (0.11 mL, 1.0 mmol, 1.0 equiv) was slowly added to a cooled (−78 °C) solution of (*R*)-(4-(benzyloxy)-3-methyl-2-methylenebutyl)trimethylsilane **7** (see reference 4 for the preparation of the corresponding (*S*)-enantiomer) (0.26 g, 1.0 mmol, 1.0 equiv) in CH_2Cl_2 (2.2 mL). The mixture was stirred 30 min at −78 °C, then a solution of aldehyde **(*R*)-8** (0.185 g, 1.04 mmol, 1.04 equiv) in CH_2Cl_2 (0.8 mL) was added. The solution was stirred 1 h at −78 °C and quenched by addition of triethylamine (0.9 mL). The mixture was partitioned between CH_2Cl_2 and brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (pentane/diethyl ether 100:0 to 80:20) in order to yield homoallylic alcohol **9** (*dr*: 90:10) as a pale yellow oil (0.292 g, 71%): $[\alpha]_D^{20}$ +20.00 (*c* 0.14, $CHCl_3$); IR (neat) 3445, 3066, 2961, 2927, 2871, 1646, 1454, 1379, 1368, 1205, 1090, 1073, 1040, 1029, 999, 897, 867, 735, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36−7.28 (m, 5H), 5.73 (d, *J* = 10.4 Hz, 1H), 4.95 (bs, 2H), 4.52 (d, *J* = 12.9 Hz, 1H), 4.49 (d, *J* = 12.9 H, 1H), 3.54 (m, 1H), 3.45 (m, 1H), 3.40 (dd, *J* = 5.6, 8.9 Hz, 1H), 2.76 (*br*.s, 1H), 2.46 (m, 1H), 2.46 (m, 1H), 2.30 (*br*.d, *J* = 13,4 Hz, 1H), 2.25 (s, 3H), 1.98 (dd, *J* = 10.4, 13.4 Hz, 1H), 1.07 (d, *J* = 6.8 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.4, 137.9, 135.0, 128.5 (2C), 127.9 (2C), 127.8, 119.9, 112.7, 74.7, 73.3, 72.2, 41.9, 40.9, 38.8, 23.8, 17.9, 16.6 (CH_3); HRMS (ESI) calcd for $C_{19}H_{27}BrO_2Na^+$ $[(M + Na)^+]$ 389.1092, found 389.1088.

(4R,5R,8R,E)-9-(Benzyloxy)-2-bromo-4,8-dimethyl-7-methylene-non-2-en-5-yl (R)-2-methoxy-2-phenylacetate..[10a−c] Homoallyl alcohol **9** (54.8 mg, 0.15 mmol, 1.0 equiv) was dissolved in anhydrous DCM (2 mL) and (*R*)-methoxyphenylacetic acid (56.4 mg, 0.37 mmol, 2.5 equiv), DMAP (33 mg, 0.15 mmol, 1.0 equiv) and DCC (70 mg, 0.37 mmol, 2.5 equiv) were successively added. The mixture was stirred at rt for 30 min before addition of diethyl ether (10 mL).The crude mixture was filtered through a pad of Celite, which was rinsed with diethyl ether. The filtrate was concentrated in vacuo and the residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 90:10) to furnish corresponding (*R*)-MPA ester (50 mg, 65%) as a colorless oil: $[\alpha]_D^{20}$ −18.9 (*c* 0.23, $CHCl_3$); IR (neat) 3028, 2970, 2946, 1739, 1454, 1365, 1228, 1216, 1205, 1175, 1113, 1003, 899, 736, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44−7.27 (m, 10H), 5.37 (qd, *J* = 1.2, 10.4 Hz, 1H), 4.96 (m, 1H), 4.82 (*br*.s, 2H), 4.68 (s, 1H), 4.54 (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 3.47 (dd, *J* = 6.0, 9.6 Hz, 1H), 3.37 (s, 3H), 3.32 (dd, *J* = 7.6, 9.6 Hz, 1H), 2.48−2.42 (m, 2H), 2.32 (dd, *J* = 4.4, 14.8 Hz, 1H), 2.20 (dd, *J* = 8.8, 14.8 Hz, 1H), 1.97 (d, *J* = 1.2 Hz, 3H), 1.08 (d, *J* = 6.4 Hz, 3H), 0.71 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 147.5, 138.6, 136.4, 133.0, 128.8, 128.7 (2C), 128.4 (2C), 127.6 (2C), 127.5, 127.4 (2C), 120.7, 112.2, 82.7, 75.9, 74.4, 73.0, 57.4, 39.4, 38.1, 37.4, 23.4, 17.3, 15.4; HRMS (ESI) calcd for $C_{28}H_{35}BrNaO_4^+$ $[(M + Na)^+]$ 537.1616, found 537.1614.

(4R,5R,8R,E)-9-(Benzyloxy)-2-bromo-4,8-dimethyl-7-methylene-non-2-en-5-yl (S)-2-methoxy-2-phenylacetate..[10a−c] Homoallyl alcohol **9** (54.8 mg, 0.15 mmol, 1.0 equiv) was dissolved in anhydrous dichloromethane (2 mL) and (*R*)-methoxyphenylacetic acid (56.4 mg, 0.37 mmol, 2.5 equiv), DMAP (33 mg, 0.15 mmol, 1.0 equiv) and DCC (70 mg, 0.37 mmol, 2.5 equiv) were successively added. The mixture was stirred at rt for 30 min before addition of diethyl ether (10 mL).The crude mixture was filtered through a pad of Celite, which was rinsed with diethyl ether. The filtrate was concentrated in vacuo and the residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 90:10) to furnish corresponding (*S*)-MPA ester (49.0 mg, 63%) as a pale yellow oil: $[\alpha]_D^{20}$ +36.8 (*c* 0.24, $CHCl_3$); IR (neat) 3029, 2970, 2929, 1744, 1648, 1454, 1365, 1229, 1216, 1203, 1173, 1103, 1000, 903, 734, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41−7.27 (m, 10H), 5.63 (qd, *J* = 1.2, 10.4 Hz, 1H), 4.94 (m, 1H), 4.70 (s, 1H), 4.51 (s, 1H), 4.47 (d, *J* = 12.4 Hz, 1H), 4.46 (s, 1H), 4.43 (d, *J* = 12.0 Hz, 1H), 3.39 (s, 3H), 3.31 (dd, *J* = 6.0, 9.6 Hz, 1H), 3.18 (dd, *J* = 7.6, 9.6 Hz, 1H), 2.62 (m, 1H), 2.27−2.21 (m, 2H), 2.15 (d, *J* = 1.2 Hz, 3H), 2.08 (dd, *J* = 9.2, 15.2 Hz, 1H), 0.95 (d, *J* = 7.2 Hz, 3H),0.93 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 146.7, 138.7, 136.3, 133.1, 128.7, 128.6 (2C), 128.4 (2C), 127.6 (2C), 127.5, 127.4 (2C), 120.9, 112.0, 82.9, 75.9, 74.4, 73.0, 57.5, 39.0, 38.3, 37.4, 23.7, 17.3, 16.0; HRMS (ESI) calc for $C_{28}H_{35}BrNaO_4^+$ $[(M + Na)^+]$ 537.1616, found 537.1613.

(4R,5R,8S,E)-9-(Benzyloxy)-2-bromo-4,8-dimethyl-7-oxonon-2-en-5-yl 2-bromoacetate ***(10)***. A stream of ozone was bubbled into a

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magnetically stirred solution of alkene **9** (1.1 g, 3.0 mmol, 1 equiv) in CH_2Cl_2 (75 mL) at −78 °C for 20 min, until a light blue color appeared. The solution was vigorously flushed under argon at −78 °C and triphenylphosphine was added (1.2 g, 4.5 mmol, 1.5 equiv) and the reaction mixture was warned up and stirred at room temperature for 4 h. The solution was concentrated under reduced pressure. Flash chromatography on silica gel (pentane/ethyl acetate, 90:10) afforded corresponding aldol (642 mg, 58% yield), as a colorless oil: $[\alpha]_D^{20}$ +41.5 (*c* 0.857, $CHCl_3$); IR (neat) 3466, 3028, 2972, 2931, 2871, 1706, 1455, 1379, 1096, 752, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.39−7.27 (m, 5H), 5.64 (qd, *J* = 1.2, 10.3 Hz, 1H), 4.50 (d, *J* = 12.8 Hz, 1H), 4.47 (d, *J* = 12.8 Hz, 1H), 3.82 (ddd, *J* = 2.2, 7.4, 9.5 Hz, 1H), 3.60 (dd, *J* = 8,6, 9.1 Hz, 1H), 3.48 (dd, *J* = 5.2, 9.1 Hz, 1H), 3.16 (bs, 1H), 2.90 (dqd, *J* = 5.2, 7.1, 8.6 Hz, 1H), 2.74 (dd, *J* = 2.2, 17.5 Hz, 1H), 2.51 (dd, *J* = 9.5, 17.5 Hz, 1H), 2,42 (dqd, *J* = 6.9, 7.4, 10.3 Hz, 1H), 2,23 (d, *J* = 1.2 Hz, 3H), 1.06 (d, *J* = 7.1 Hz, 3H), 1.03 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 214.7, 137.8, 134.2, 128.6 (2C), 127.9, 127.8 (2C), 120.5, 73.5, 72.3, 71.6, 46.9, 46.7, 40.2, 23.8, 16.5, 13.3; HRMS (ESI) calc for: $C_{18}H_{25}BrNaO_3^+$ $[(M + Na)^+]$ 391.0879, found 391.0865.

To a solution of aldol (1.1 g, 3.0 mmol, 1.0 equiv) in anhydrous DCM (24 mL) at 0 °C was added pyridine (485 μL, 6.0 mmol, 2.0 equiv) followed by bromoacetyl bromide (392 μL, 4.5 mmol, 1.5 equiv). The reaction was stirred for 2 h at 0 °C and quenched with an aqueous sat. NH_4Clsolution. The mixture was extracted with DCM (×3), the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography over silica gel (pentane/ethyl acetate, 90:10) to provide desired ester **10** as a colorless oil (1.1 g, 78% yield): $[\alpha]_D^{20}$ +38.7 (*c* 0.857, $CHCl_3$); IR (neat) 3033, 2972, 2931, 2871, 1739, 1719, 1650, 1454, 1391, 1277, 1164, 1103, 989, 751, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) 7.38−7.27 (m, 5H), 5.64 (qd, *J* = 1.3, 10.3 Hz, 1H), 5.23 (quint, *J* = 6.0 Hz, 1H), 4.49 (d, *J* = 12.3 Hz, 1H), 4.46 (d, *J* = 12.3 Hz, 1H), 3.74 (s, 2H), 3.58 (dd, *J* = 8,3, 9.0 Hz, 1H), 3.47 (dd, *J* = 5.2, 9.0 Hz, 1H), 2.85 (dqd, *J* = 5.2, 7.1, 8.3 Hz, 1H), 2.81−2.75 (m, 3H), 2.22 (d, *J* = 1.3 Hz, 3H), 1.05 (d, *J* = 7.1 Hz, 3H), 0.97 (d, *J* = 6.9 Hz, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) 209.5, 166.6, 138.0, 132.5, 128.6 (2C), 127.9, 127.8 (2C), 121.8, 74.6, 73.5, 72.3, 46.9, 43.3, 37.6, 25.8, 23.9, 16.0, 13.2; HRMS (ESI) calc for: $C_{20}H_{26}Br_2NaO_4^+$ $[(M + Na)^+]$ 511.0090, found 511.0101.

*(R)-4-((R)-1-(Benzyloxy)propan-2-yl)-6-((R,E)-4-bromopent-3-en-2-yl)-5,6-dihydro-2H-pyran-2-one (**11**). Reformatsky Route.* In an oven-dried flask under argon was introduced a samarium diiodide solution (0.1 M in THF, 67 mL, 6.72 mmol, 3 equiv). The solution was cooled to −78 °C and bromoacetate **10** (1.1 g, 2.24 mmol, 1 equiv) diluted in THF (38 mL) was slowly added. After 15 min, the mixture was allowed to warm to room temperature and stirred for 45 min. The solution was quenched with an aqueous sat. solution of Rochelle's salt and extracted with Et_2O (×3). The organic extracts were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography over silica gel (ethyl acetate 100%) to furnish hydroxy lactone as a pale yellow oil (736 mg, 80%): IR (neat) 3455, 2967, 2928, 2876, 1730, 1650, 1455, 1382, 1251, 1215, 1098, 1060, 992, 752, 697, 668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.41−7.28 (m, 5H), 5.72 (qd, *J* = 1.2, 10.2 Hz, 1H), 4.56 (m, 1H), 4.55 (d, *J* = 12.1 Hz, 1H), 4.49 (d, *J* = 12.1 Hz, 1H), 4.25 (bs, 1H), 3.66 (dd, *J* = 4.0, 9.7 Hz, 1H), 3.46 (dd, *J* = 8.0, 9.7 Hz, 1H), 2.63 (dqd, *J* = 6.5, 6.9, 10.2 Hz, 1H), 2.58 (dd, *J* = 2.5, 17.4 Hz, 1H), 2.40 (d, *J* = 17.4 Hz, 1H), 2.26 (d, *J* = 1.2 Hz, 3H), 1.95 (m, 1H), 1.78 (td, *J* = 2.5, 13.4 Hz, 1H), 1.48 (dd, *J* = 12.0, 13.4 Hz, 1H) 1.10 (d, *J* = 6.9 Hz, 3H), 0.93 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 170.9, 136.9, 132.6, 128.8 (2C), 128.4, 128.0 (2C), 121.5, 79.0, 74.0, 72.7, 72.3, 41.5, 39.4, 39.2, 36.6, 24.0, 16.3, 12.5; HRMS (ESI) calc for: $C_{20}H_{27}BrNaO_4^+$ $[(M + Na)^+]$ 433.0985, found 433.0997.

Hydroxy lactone (736 mg, 1.79 mmol, 1 equiv) was dissolved in DCM (24 mL) and the solution was cooled to 0 °C. Pyridine (7.0 mL, 85.9 mmol, 48 equiv) and thionyl chloride (3.4 mL, 46.5 mmol, 26 equiv) were successively added. The mixture was stirred at 0 °C for 1 h. The solution was then carefully quenched with an aqueous sat. $NaHCO_3$ solution, extracted with DCM (×3), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography over silica gel (pentane/ethyl acetate 100:0 to 70:30) to furnish lactone **11** as a pale yellow oil (437 mg, 49% yield over two steps).

RCM Route. In an oven-dried round-bottom flask equipped with a magnetic stirring bar and a reflux condenser was placed acrylate **20** (0.112 mmol) in dry and degassed dichloromethane (2.3 mL). The reaction mixture was heated to 40 °C then Grubbs'second generation catalyst **cat-2** (9.5 mg, $1.12.10^{-2}$ mmol, 10 mol %) diluted in dry and degassed dichloromethane (2.3 mL) was slowly added over 8 h via syringe-pump. The reaction was stopped after 20 h and solvent was evaporated. Purification of the crude residue by flash chromatography on silica gel (cyclohexane/ethyl acetate, 90:10 to 80:20) afforded corresponding lactone **11** (26 mg, 58%) as a colorless oil. $[\alpha]_D^{20}$ +84.8 (*c* 1.43, $CHCl_3$); IR (neat) 3032, 2967, 2875, 1716, 1651, 1381, 1249, 1096, 1026, 869, 735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.25 (m, 5H), 5.84 (s, 1H), 5.65 (qd, *J* = 1.2, 10.4 Hz, 1H), 4.51 (d, *J* = 12.0 Hz, 1H), 4.47 (d, *J* = 12.0 Hz, 1H), 4.08 (ddd, *J* = 4.6, 7.1, 11.0 Hz, 1H), 3.46 (m, 2H), 2.65 (m, 2H), 2.28 (dd, *J* = 4.6, 12.4 Hz, 1H), 2.24 (d, *J* = 1.2 Hz, 3H), 2.23 (m, 1H), 1.11 (d, *J* = 7.0 Hz, 3H), 1.10 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 163.2, 137.9, 132.3, 128.6 (2C), 128.0 (2C), 127.9, 121.7, 115.7, 80.2, 73.4, 72.9, 40.4, 39.1, 29.7, 23.9, 16.4, 15.7; HRMS (ESI) calcd for $C_{20}H_{25}BrO_3Na^+$ $[(M + Na)^+]$ 415.0885, found 415.0891.

*(3S,4R,6R)-4((S)-1-(Benzyloxy)propan-2-yl)-6-((R,E)-4-bromopent-3-en-2-yl)-3,4-dihydroxytetrahydro-2H-pyran-2-one (**6b**).* α,β-Unsaturated lactone **11** (707 mg, 1.8 mmol, 1.0 equiv) was placed in an acetone/H_2O 1:1 solution (22 mL) at rt and potassium osmate (VI) dihydrate (34 mg, 0.09 mmol, 0.05 equiv) was added. After 10 min stirring, NMO (1.46 g, 10.8 mmol, 6.0 equiv) was added and the mixture was kept under very slight stirring until total consumption of the starting material. The dark brown solution was partitioned between ethyl acetate and brine, and extracted with AcOEt (×3). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (pentane/ethyl acetate 70:30) afforded diol **6b** (236 mg, 45%) as a colorless oil: $[\alpha]_D^{20}$ +11.0 (*c* 0.57, $CHCl_3$); IR (neat) 3432, 2971, 2926, 2860, 1733, 1655, 1452, 1384, 1228, 1106, 862, 741 cm^{-1}; ^1H NMR (500 MHz, MeOD) δ 7.36−7.25 (m, 5H), 5.72 (qd, *J* = 1.5, 10.4 Hz, 1H), 4.49 (s, 2H), 4.41 (ddd, *J* = 4.1, 6.3, 11.3 Hz, 1H), 4.24 (s, 1H), 3.56 (dd, *J* = 5.7, 9.8 Hz, 1H), 3.53 (dd, *J* = 5.0, 9.8 Hz, 1H), 2.67 (ddq, *J* = 6.3, 6.6, 10.4 Hz, 1H), 2.29 (ddd, *J* = 5.0, 5.7, 7.3 Hz, 1H), 2.20 (d, *J* = 1.5 Hz, 3H), 1.90 (dd, *J* = 4.1, 14.2 Hz, 1H), 1.83 (dd, *J* = 11.3, 14.2 Hz, 1H), 1.06 (d, *J* = 6.6 Hz, 3H), 1.04 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, MeOD) δ 176.3, 139.6, 133.9, 129.5 (2C), 129.0 (2C), 128.7, 122.5, 81.5, 75.4, 74.4, 73.4, 73.2, 40.5, 40.2, 33.4, 24.0, 16.1, 12.0; HRMS (ESI) calcd for $C_{20}H_{27}BrO_5Na^+$ $[(M + Na)^+]$ 449.0940, found 449.0944.

*(4R,5R,8R,E)-9-(Benzyloxy)-2-bromo-4,8-dimethyl-7-methylenenon-2-en-5-yl acrylate (**20**).* Homoallyl alcohol **9** (85.3 mg, 0.23 mmol, 1.0 equiv) and DCM (2.5 mL) were placed in a flame-dried round-bottom flask under argon. The reaction mixture was cooled to 0 °C, then were successively added triethylamine (47 μL, 0.35 mmol, 2.0 equiv) and acryloyl chloride (28 μL, 0.35 mmol, 1.5 equiv). The mixture was allowed to warm to rt and the reaction was monitored by thin layer chromatography. Upon completion, the mixture was partitioned between CH_2Cl_2 (×3) and an aqueous saturated NH_4Cl solution. The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 100:0 to 95:5) to afford title compound **20** (80 mg, 82%): $[\alpha]_D^{20}$ +34.32 (*c* 0.24, $CHCl_3$); IR (neat) 2963, 2928, 2855, 1722, 1637, 1454, 1404, 1294, 1268, 1189, 1084, 1046, 984, 899, 734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34−7.26 (m, 5H), 6.38 (dd, *J* = 1.2, 17.2 Hz, 1H), 6.09 (dd, *J* = 10,4, 17.2 Hz, 1H), 5.81 (dd, *J* = 1.2, 10.4 Hz, 1H)

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J. Org. Chem. 2016, 81, 12275−12290

5.71 (qd, J = 1.2, 10.4 Hz, 1H), 5.00 (m, 1H), 4.85 (s, 2H), 4.53 (d, J = 12.0 Hz, 1H), 4.50 (d, J = 12.0 Hz, 1H), 3.47 (dd, J = 6.0, 9.2 Hz, 1H), 3.32 (dd, J = 7.2, 9.2 Hz, 1H), 2.67 (m, 1H), 2.45 (ddq, J = 6.0, 6.8, 7.2 Hz, 1H), 2.37 (dd, J = 4.0, 14.8 Hz, 1H), 2.24 (dd, J = 8.8, 14.8 Hz, 1H), 2.19 (d, J = 1.2 Hz, 3H), 1.08 (d, J = 6.8 Hz, 3H), 1.01 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 147.7, 138.7, 133.3, 130.8, 128.6, 128.4 (2C), 127.6 (2C), 127.5, 120.8, 112.1, 75.7, 74.5, 73.0, 39.6, 38.3, 37.1, 23.7, 17.3, 16.1; HRMS (ESI) calcd for $C_{22}H_{29}O_3NaBr^+$ [(M + Na)$^+$] 443.1198, found 443.1182.

*(S)-4-Methylhex-5-en-1-ol (**21**).* (*S*)-citronellol **19** (8.0 g, 51.2 mmol, 1.0 equiv) was placed in DCM (250 mL), triphenylphosphine (16.8 g, 64.1 mmol, 1.25 equiv) and imidazole (7.68 g, 112.8 mmol, 2.2 equiv) were added at rt and stirring was maintained at this temperature until complete dissolution. The reaction mixture was then cooled to 0 °C and iodine (19.5 g, 76.4 mmol, 1.5 equiv) was added portionwise. Stirring was continued for an additional 30 min at 0 °C then, the reaction was quenched by an aqueous sat. $Na_2S_2O_3$ solution. The solution was extracted with DCM, the combined organic layers were washed with brine, dried over magnesium sulfate, filtered and the solvent was carefully removed under light reduced pressure (min. 200 mbar). The crude product was first triturated in pentane to remove triphenylphosphine oxide then purified by flash chromatography on silica gel (cyclohexane/ethyl acetate, 80:20) to yield corresponding iodide as a colorless liquid (12.5 g, 92%): $[\alpha]_D^{20}$ +10.1 (c 0.16, $CHCl_3$); IR (neat) 2962, 2913, 2870, 2853, 1449, 1377, 1219, 1179, 1106, 984, 826, 734 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.09 (th, J = 1.5, 7.1 Hz, 1H), 3.25 (ddd, J = 5.7, 9.4, 17.6 Hz, 1H), 3.17 (m, 1H), 1.98 (m, 2H), 1.87 (m, 1H), 1.69 (s, 3H), 1.66 (m, 1H), 1.61 (s, 3H, C-27′-CH_3), 1.55 (m, 1H), 1.34 (m, 1H), 1.18 (m, 1H), 0.89 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.6, 124.6, 41.1, 36.5, 33.7, 25.9, 25.5, 18.8, 17.8, 5.3. Spectroscopic data were consistent with those reported in the literature.[18a]

Potassium *tert*-butoxide (10.5 g, 93.9 mmol, 2.5 equiv) was added portionwise to a solution of iodide (10.0 g, 37.5 mmol, 1.0 equiv) in anhydrous THF (150 mL) at 0 °C. The mixture was stirred at rt for 1 h then quenched with an aqueous saturated NH_4Cl solution. The solution was extracted with diethyl ether (×3) and combined organic layers were washed with brine. The organic layers were dried over $MgSO_4$, filtered and the solvent was carefully removed under reduced pressure (min. 200 mbar). The crude product was directly used in the next step without further purification (quantitative yield): $[\alpha]_D^{20}$ +8.1 (c 0.15, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70 (ddd, J = 17.2, 10.3, 7.5 Hz, 1H), 5.09 (t, J = 7.2 Hz, 1H), 4.97−4.90 (m, 2H), 2.13−2.08 (m, 1H), 1.98−1.93 (m, 2H), 1.68 (s, 3H), 1.59 (s, 3H), 1.34−1.28 (m, 2H), 0.99 (d, J = 7.0 Hz, 3H). Spectroscopic data were consistent with those reported in the literature.[18b]

Citronellene (11.5 g, 83.1 mmol, 1.0 equiv) was dissolved in DCM (100 mL) and cooled to −78 °C. Ozone was bubbled through the solution and the reaction progress was closely monitored by TLC. Upon completion of starting material on TLC, the ozone flow was stopped and the reaction was purged with argon several times. This solution was slowly added to a suspension of $NaBH_4$ (8 g, 210 mmol, 2.5 equiv) in methanol (70 mL) at −78 °C. The mixture was allowed to warm to rt over 2 h with stirring. The reaction mixture was quenched by 1 N aqueous HCl at 0 °C. The aqueous layer was extracted with DCM, combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and carefully concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (pentane/diethyl ether, 70:30) to yield alcohol **21** as a colorless liquid (6.2 g, 65%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.69 (ddd, J = 7.6, 10.3, 17.2 Hz, 1H), 4.99−4.90 (m, 2H), 3.63 (dt, J = 4.4, 6.4 Hz, 2H), 2.13 (dquintd, J = 6.2, 6.8, 7.6 Hz, 1H), 1.61−1.51 (m, 2H), 1.38−1.30 (m, 2H), 1.00 (d, J = 6.8 Hz, 3H). Spectroscopic data were consistent with those reported in the literature.[18c]

*(S)-6-(Benzyloxy)-3-methylhexan-2-one (**22**).* NaH (6.5 g (60%), 162.9 mmol, 3.0 equiv) was suspended in THF (80 mL) and the mixture was cooled to 0 °C. Alcohol **21** (6.2 g, 54.2 mmol, 1.0 equiv) in THF (20 mL) was added dropwise and the solution was stirred for 20 min at 0 °C until gaz evolution ceased. Benzyl bromide (6.45 mL, 54.2 mmol, 1.0 equiv) was then slowly added, followed by TBAI (1.0 g, 2.7 mmol, 0.05 equiv). The reaction was warmed to rt and stirred overnight. The reaction was quenched at 0 °C by addition of ice cold water. After warming to rt, the aqueous layer was extracted (×3) with diethyl ether, the combined organic layers were washed with brine, dried over $MgSO_4$ then filtered and concentrated under reduced pressure. Purification by flash chromatography on silica gel (cyclohexane/ethyl acetate, 95:5) provided desired benzyl ether (9.85 g, 89%) as a colorless oil: $[\alpha]_D^{20}$ +8.1 (c 0.15, $CHCl_3$); IR (neat) 3066, 3030, 2938, 2853, 1640, 1496, 1454, 1361, 1099, 1028, 995, 909, 732, 696 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.27 (m, 5H), 5.69 (ddd, J = 7.7, 10.3, 17.6, Hz, 1H), 4.96 (dd, J = 1.2, 17.6 Hz, 1H), 4.92 (dd, J = 1.2, 9.9 Hz, 1H), 4.50 (s, 2H), 3.46 (t, J = 6.7 Hz, 2H), 2.12 (sept.$_{app}$, J = 6.6 Hz, 1H), 1.62 (m, 2H), 1.38 (m, 2H), 1.00 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7, 138.8, 128.5 (2C), 127.7 (2C), 127.6, 112.8, 73.0, 70.7, 37.8, 33.2, 27.7, 20.4; HRMS (ESI) calcd. for $C_{14}H_{20}ONa^+$ [(M + Na)$^+$] 227.1412; found 227.1418.

Alkene (1.0 g, 4.9 mmol, 1.0 equiv), $PdCl_2$ (173 mg, 0.975 mmol, 0.2 equiv) and CuCl (727 mg, 7.35 mmol, 1.5 equiv) were placed in a DMF/H_2O 9:1 solution (20 mL). The mixture was bubbled with oxygen for 20 min and stirred at rt for 15 h under an oxygen atmosphere. Reaction was stopped by addition of water and diethyl ether, stirred for 10 additional minutes and filtered on a pad of clarcel flo. The layers were separated and the aqueous layer was extracted (×3) with diethyl ether. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (cyclohexane/ethyl acetate, 90:10) afforded ketone **22** (850 mg, 79%) as a colorless oil: $[\alpha]_D^{20}$ +4.8 (c 0.23, $CHCl_3$); IR (neat) 3064, 2935, 2857, 1709, 1496, 1455, 1358, 1172, 1098, 1027, 953, 735, 696 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.27 (m, 5H), 4.49 (s, 2H), 3.46 (t, J = 6.2 Hz, 2H), 2.52 (sext, J = 6.9 Hz, 1H), 2.13 (s, 3H), 1.74 (m, 1H), 1.59 (m, 2H), 1.45 (m, 1H), 1.09 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.6, 138.5, 128.4 (2C), 127.7 (2C), 127.6, 73.0, 70.1, 46.9, 29.5, 28.1, 27.5, 16.3; HRMS (ESI) calcd. for $C_{14}H_{20}O_2Na^+$ [(M + Na)$^+$] 243.1361; found 243.1369.

*(4S)-1-(Benzyloxy)-7-hydroxy-4,8-dimethylnonan-5-one (**23**).* A freshly prepared LDA solution (2 mL, 0.51 mol·L^{-1}) was placed in a flame-dried round-bottom flask under argon at −78 °C and ketone **22** (150 mg, 0.68 mmol, 1 equiv) dissolved in THF (1 mL) was added dropwise. The reaction mixture was stirred 1 h at −78 °C then isobutyraldehyde (120 μL, 1.36 mmol, 2 equiv) was slowly added. Stirring was maintained 1 h at −78 °C and the reaction was quenched with an aqueous sat. NH_4Cl solution. The aqueous layer was extracted (×3) with diethyl ether and the organic layers were washed with brine, filtered, dried over $MgSO_4$, and solvent was removed in vacuo. Purification by flash chromatography over silica gel (cyclohexane/ethyl acetate, 95:5 to 70:30) provided aldol **23** as a 1:1 mixture of diastereoisomers (165 mg, 83%, colorless oil): IR (neat) 3477, 2960, 2934, 2872, 1702, 1455, 1365, 1205, 1098, 1028, 998, 917, 869, 735, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.27 (m, 5H), 4.51 (s, 2H), 3.80 (m, 1H), 3.48 (t, J = 6.2 Hz, 2H), 3.16 and 3.12 (d, J = 3.3 Hz, 1H), 2.68−2.46 (m, 3H), 1.79 (m, 1H), 1.68 (m, 1H), 1.61 (m, 2H), 1.47 (m, 1H), 1.11 (d, J = 6.8 Hz, 3H), 0.95 (d, J = 6.9 Hz, 3H), 0.93 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.4 and 216.3, 138.5, 128.4 (2C), 127.7 (2C), 127.6, 73.0, 72.4 and 72.2, 70.1, 46.8, 44.5 and 44.4, 33.1, 29.4, 27.5 and 27.4, 18.5, 17.8, 16.3; HRMS (ESI) calcd. for $C_{18}H_{28}O_3Na^+$ [(M + Na)$^+$] 315.1936; found 315.1929.

*(6S)-9-(Benzyloxy)-2,6-dimethyl-5-methylenenonan-3-yl acrylate (**24**).* Aldol **23** (810 mg, 2.77 mmol, 1 equiv) and DCM (30 mL) were placed in a flame-dried round-bottom flask under argon. The reaction mixture was cooled to −78 °C, then were successively added DIPEA (2.41 mL, 13.8 mmol, 5 equiv) and acryloyl chloride (450 μL, 5.5 4 mmol, 2 equiv). The reaction mixture was stirred for 1.5 h at −78 °C then quenched by addition of an aqueous sat.

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$NaHCO_3$ solution. The aqueous layer was extracted (×3) with DCM, combined organic layers were washed with brine and dried over $MgSO_4$. Subsequent filtration and evaporation of the volatiles afforded corresponding acrylate quantitatively. The product was engaged in the next step without further purification.

A slurry of Zn dust (3.26 g, 49.8 mmol, 18 equiv) in THF (47 mL) was submitted to a vigorous stirring and CH_2I_2 (2.22 mL, 27.6 mmol, 10 equiv) was added. After 30 min, the gray slurry was cooled to 0 °C and $TiCl_4$ (1.0 M in DCM, 3.6 mL, 3.6 mmol, 1.3 equiv) was added via syringe. The solution was stirred for 1 h at rt and acrylate (959 mg, 2.77 mmol, 1 equiv) diluted in THF (11.6 mL) was added dropwise via syringe. Stirring was maintained for 1 h at rt, then the reaction was diluted with diethyl ether and a 5% HCl solution (v/v). The solution was extracted (×3) with diethyl ether and the organic layer was successively washed with a saturated $NaHCO_3$ solution and brine and subsequently dried over $MgSO_4$, and solvent was removed in vacuo. The residue was purified by flash chromatography over silica gel (cyclohexane/ethyl acetate, 100:0 to 98:2) to afford pure acrylate **24** as a colorless oil (330 mg, 35% over two steps): IR (neat) 3067.0, 3031, 2962, 2938, 2872, 1718, 1637, 1455, 1404, 1368, 1294, 1270, 1194, 1101, 1046, 985, 895, 807, 734, 697, 675 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.27 (m, 5H), 6.36 (dd, J = 1.4, 17.6 Hz, 1H), 6.09 (dd, J = 10.3, 17.6 Hz, 1H), 5.78 and 5.77 (dd, J = 1.4, 10.3 Hz, 1H), 5.02 (m, 1H), 4.79 (s, 2H), 4.50 (s, 2H), 3.46 and 3.45 (t, J = 6.5 Hz, 2H), 2.31−2.20 (m, 2H), 2.14 (sept, J = 6.8 Hz, 1H), 1.90 (m, 1H), 1.64−1.29 (m, 4H), 1.02 (d, J = 6.8 Hz, 3H), 0.93 (2d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 150.3 and 150.1, 138.8, 130.2, 129.0, 128.4 (2C), 127.7 (2C), 127.5, 110.8, 76.9 and 76.8, 73.0 and 72.9, 70.7, 39.6 and 38.9, 36.5 and 35.8, 32.2 and 31.9, 31.7 and 31.6, 27.7 and 27.6, 20.1 and 19.7, 18.8, 17.4 and 17.3; HRMS (ESI) calcd. for $C_{22}H_{32}O_3Na^+$ [(M + Na)$^+$] 367.2249; found 367.2257.

*4-((S)-5-(Benzyloxy)pentan-2-yl)-6-isopropyl-5,6-dihydro-2H-pyran-2-one (**25**).* **GP1** on acrylate **24** (39 mg, 0.112 mmol) using Hoveyda Grubbs' second generation catalyst **cat-3** (7.0 mg, 0.0112 mmol, 10 mol %) and subsequent NMR of the crude mixture revealed a 33:62:5 ratio of products **24**/**25**/**26** or **GP2** on acrylate **24** (39 mg, 0.112 mmol) using Nolan ruthenium-indenylidene catalyst **cat-8** (10.6 mg, 0.0112 mmol, 10 mol %) and subsequent purification of the crude residue by flash chromatography on silica gel (cyclohexane/ethyl acetate, 90:10 to 80:20) afforded lactone **25** (30 mg, 85% yield) as a colorless oil along with homodimer **26** (5 mg, 7% yield). IR (neat) 3063, 3030, 2962, 2933, 2873, 1713, 1455, 1389, 1361, 1249, 1100, 1075, 1028, 868, 734, 697 cm^1; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39−7.25 (m, 5H), 5.78 (bs, 1H), 4.49 (s, 2H), 4.06 (m, 1H), 3.46 (t, J = 5.7 Hz, 2H), 2.42−2.07 (m, 3H), 1.94 (oct.$_{app}$, J = 6.7 Hz, 1H), 1.65−1.42 (m, 4H), 1.11 and 1.09 (d, J = 6.8 Hz, 3H), 1.03 (d, J = 6.8 Hz, 3H), 0.99 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 165.3 and 165.1, 138.5, 128.5 (2C), 127.7 (3C), 115.2 and 115.0, 82.3, 73.1 70.0, 40.3, 32.1, 31.1 and 30.7, 28.0 and 27.9, 27.6 and 27.5, 18.2, 18.1 and 17.9; HRMS (ESI) calcd. for $C_{20}H_{28}O_3Na^+$ [(M + Na)$^+$] 339.1936; found 339.1943.

*Bis-((6S)-9-(benzyloxy)-2,6-dimethyl-5-methylenenonan-3-yl) fumarate (**26**).* Homodimer **26** is obtained as a side product of the above-described RCM reaction following **GP2** (5 mg, 7% yield): IR (neat) 3019, 2964, 2932, 1716, 1277, 1215, 1116, 1027, 754, 714, 668 cm-^{1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34−7.27 (m, 10H), 6.79 and 6.78 (2s, 2H), 5.04 (2m, 2H), 4.79 and 4.77 (2s, 2H), 4.49 (s, 4H), 3.45 (t, J = 6.3 Hz, 4H), 2.24 (m, 4H), 2.14 (sept, J = 6.9 Hz, 2H), 1.87 (m, 2H), 1.55 (m, 4H), 1.47 (m, 2H), 1.29 (m, 2H), 1.00 (2d, J = 6.9 Hz, 6H), 0.93 (2d, J = 6.9 Hz, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8 (2C), 150.0 and 149.9 (2C), 138.7 (2C), 133.8 (2C), 128.4 (4C), 127.7 (4C), 127.6 (2C), 111.1 and 110.9 (2C), 78.0 (2C), 73.0 and 72.9 (2C), 70.6 (2C), 39.5 and 38.8 (2C), 36.4 and 35.9 (2C), 32.2 and 31.9 (2C), 31.6 and 31.5 (2C), 27.6 and 27.5 (2C), 20.0 and 19.5 (2C), 18.9 and 18.8 (2C), 17.4 and 17.3 (2C); HRMS (ESI) calcd. for $C_{42}H_{60}NaO_6^+$ [(M + Na)$^+$] 683.4282; found 683.4276.

*(S)-((3,7-Dimethyloct-6-en-1-yl)oxy)triethylsilane (**27**).* (*S*)-citronellol **19** (12.95 g, 83.0 mmol, 1 equiv) and CH_2Cl_2 (170 mL) were placed in a flame-dried round-bottom flash under argon. The reaction mixture was cooled to 0 °C, then triethylamine (12.8 mL, 91.3 mmol, 1.1 equiv) and triethylsilyl chloride (12.8 mL, 91.3 mmol, 1.1 equiv) were successively added. At the end of addition, the solution was warmed to room temperature, stirred overnight then quenched at 0 °C with an aqueous sat. $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (×3) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Purification on silica gel (cyclohexane/ethyl acetate, 90:10 deactivated with 5% Et_3N) afforded title silyl ether (22.4 g, quantitative) as a colorless oil: $[\alpha]_D^{20}$ +17.9 (*c* 0.73, $CHCl_3$); IR (neat) 2955, 2912, 2876, 1458, 1377, 1238, 1091, 1004, 893, 738, 725, 671 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.09 (t, J = 7.8 Hz, 1H), 3.70−3.57 (m, 2H), 1.97 (m, 2H), 1.68 (s, 3H), 1.62−1−49 (m, 2H), 1.60 (s, 3H), 1.40−1.27 (m, 2H), 1.21−1.11 (m, 1H), 0.96 (t, J = 7.8 Hz, 9H), 0.88 (d, J = 6.6 Hz, 3H), 0.60 (q, J = 7.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.2, 125.0, 61.3, 40.2, 37.4, 29.3, 25.8, 25.6, 19.8, 17.7, 6.9 (3C), 4.6 (3C).

A stream of ozone was bubbled into a magnetically stirred solution of silyl ether (83.0 mmol, 1 equiv) in CH_2Cl_2 (150 mL) at −78 °C for 4 h, until a light blue color appeared. The solution was vigorously flushed under argon at −78 °C and methanol (130 mL) was added. Finally, sodium borohydride was added portionwise (36.4 g, 830 mmol, 10 equiv) at the same temperature, then the reaction was allowed to stir at room temperature for 2 h. Upon completion, the reaction mixture was added to an aqueous sat. NH_4Cl solution at 0 °C, stirred for 2 h and filtered on Celite. The phases were separated and the aqueous layer was extracted (×3) with CH_2Cl_2, then the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude alcohol **27** was obtained in quantitative yield and directly used in the next step: $[\alpha]_D^{20}$ +3.0 (*c* 0.20, $CHCl_3$); IR (neat) 3351, 2935, 2876, 1458, 1414, 1379, 1239, 1091, 1005, 906, 727 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.70−3.59 (m, 4H), 1.66−1.49 (m, 4H), 1.43−1.29 (m, 3H), 1.23−1.15 (m, 1H), 0.95 (t, J = 8.0 Hz, 9H), 0.89 (d, J = 6.4 Hz, 3H), 0.59 (q, J = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 63.5, 61.2, 40.1, 33.2, 30.4, 29.5, 19.8, 6.9, 4.6; HRMS (ESI) calc for $C_{13}H_{30}NaO_2Si^+$ [(M + Na)$^+$] 269.1913, found 269.1922.

*(S)-6-(Benzyloxy)-3-methyl-2-methylenehexanal (**28**).* NaH (5.3 g (60%), 132.8 mmol, 1.6 equiv) was suspended in THF (60 mL) and the mixture was cooled to 0 °C. Alcohol **27** (83.0 mmol, 1.0 equiv) in THF (50 mL) was added dropwise and the reaction was stirred for 20 min at 0 °C. Benzyl bromide (15.8 mL, 132.8 mmol, 1.6 equiv) was slowly added, followed by TBAI (1.5 g, 4.15 mmol, 0.05 equiv). The reaction was warmed to room temperature and stirred overnight. Ice cold water was added and the reaction mixture was warmed to room temperature. The layers were separated and the aqueous layer was further extracted with diethyl ether (×3). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude benzyl ether, obtained as a colorless oil, was directly used in the next step without further purification: $[\alpha]_D^{20}$ −1.4 (*c* 0.58, $CHCl_3$); IR (neat) 3066, 2955; 2875, 1456, 1091, 1005, 906, 726, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43−7.22 (m, 5H), 4.51 (s, 2H), 3.66 (m, 2H), 3.46 (t, J = 6.8 Hz, 2H), 1.73−1.51 (m, 4H), 1.43−1.36 (m, 2H), 1.21 (m, 1H), 0.97 (t, J = 7.9 Hz, 9H), 0.90 (d, J = 6.4 Hz, 3H), 0.62 (q, J = 7.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 128.4 (2C), 127.7 (2C), 127.6, 73.0, 70.9, 61.2, 40.1, 33.6, 29.5, 27.3, 19.7, 6.9 (3C), 4.6 (3C); HRMS (ESI) calcd for $C_{20}H_{36}O_2SiNa^+$ [(M + Na)$^+$] 359.2382, found 359.2365.

A solution of oxalyl chloride (9.3 mL, 108 mmol, 1.3 equiv) in CH_2Cl_2 (220 mL) was cooled to −78 °C. DMSO (17.1 mL, 241 mmol, 2.9 equiv) was added dropwise and stirring was maintained at −78 °C, until gas evolution ceased (10 min). A solution of silyl ether (83.0 mmol, 1.0 equiv) in CH_2Cl_2 (55 mL) was slowly added and the mixture was stirred successively at −78 °C for 20 min then at −50 °C for 45 min at cooled again to −78 °C. Triethylamine (64 mL, 465 mmol, 5.6 equiv) was added dropwise and the mixture was

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J. Org. Chem. 2016, 81, 12275−12290

allowed to warm to room temperature over 2 h. The resulting cloudy white solution was diluted in diethyl ether and washed successively with an aqueous sat. NH_4Cl solution and water. The organic layer was dried over $MgSO_4$ and the solvent was removed in vacuo. The crude aldehyde was directly used in the next step without further purification: $[\alpha]_D^{20}$ −9.5 (*c* 0.4, $CHCl_3$); IR (neat) 2936, 2857, 1722, 1455, 1362, 1266, 1096, 733, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.75 (t, *J* = 2.4 Hz, 1H), 7.36−7.27 (m, 5H), 4.50 (s, 2H), 3.46 (t, *J* = 6.6 Hz, 2H), 2.41 (ddd, *J* = 2.4, 5.7, 16.2 Hz, 1H), 2.24 (ddd, *J* = 2.4, 7.8, 16.2 Hz, 1H), 2.07 (m, 1H), 1.73−1.54 (m, 2H), 1.46−1.26 (m, 2H), 0.97 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.2, 138.4, 128.4 (2C), 127.7 (2C), 127.6, 72.9, 70.4, 41.6, 33.1, 30.1, 27.2, 19.7; HRMS (ESI) calc for $C_{14}H_{20}O_2Na^+$ [(M + Na)$^+$] 243.1361, found 243.1351.

An aqueous formaldehyde solution (37% w/v, 7 mL, 91.3 mmol, 1.0 equiv) and previously prepared aldehyde (83 mmol, 1.0 equiv) were placed in isopropanol (7 mL, 91.3 mmol 1.1 equiv), then propionic acid (645 μL, 8.3 mmol, 0.1 equiv) and pyrrolidine (692 μL, 8.3 mmol, 0.1 equiv) were successively added. The reaction mixture was stirred at 45 °C for 2 h. An aqueous saturated $NaHCO_3$ solution was added, and the mixture was extracted with CH_2Cl_2 (×3). The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude aldehyde **28** was directly used in the next step without further purification: $[\alpha]_D^{20}$ +15.3 (*c* 0.30, $CHCl_3$); IR (neat) 3939, 2857, 1690, 1454, 1362, 1266, 1099, 946, 734, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.52 (s, 1H), 7.36−7.27 (m, 5H), 6.23 (s, 1H), 5.99 (s, 1H), 4.49 (s, 2H), 3.45 (m, 2H), 2.71 (sext, *J* = 6.8 Hz, 1H), 1.64−1.44 (m, 4H), 1.07 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.6, 155.2, 138.6, 133.4, 128.3 (2C), 127.6 (2C), 127.5, 72.9, 70.3, 32.0, 31.1, 27.5, 19.5; HRMS (ESI) calc for $C_{15}H_{20}O_2Na^+$ [(M + Na)$^+$] 255.1361, found 255.1359.

*(S)-6-(Benzyloxy)-3-methyl-2-methylenehexylbenzoate (**29**).* Aldehyde **28** (83 mmol, 1.0 equiv) in THF (40 mL) was added dropwise to a suspension of lithium aluminum hydride (1.66 g, 42 mmol, 0.5 equiv) in THF (100 mL) at 0 °C. The reaction mixture was stirred for 1 h, then quenched by successive addition of water (1.6 mL), 15% w/v sodium hydroxide solution in water (1.6 mL), and water (4.8 mL). Stirring was maintained until a white precipitate appears, then the solution is directly dried over $MgSO_4$, filtered and concentrated. The crude allylic alcohol was directly used in the next step without further purification: $[\alpha]_D^{20}$ +11.9 (*c* 0.32, $CHCl_3$); IR (neat) 3405, 2934, 2861, 1455, 1364, 1265, 1095, 897, 732, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38−7.28 (m, 5H), 5.05 (m, 1H), 4.89 (m, 1H), 4.50 (s, 2H), 4.08 (d, *J* = 4.8 Hz, 2H), 3.46 (t, *J* = 6.3 Hz, 2H), 2.19 (sext, *J* = 6.9 Hz, 1H), 1.67−1.36 (m, 4H), 1.06 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.8, 138.7, 128.5 (2C), 127.8 (2C), 127.7, 108.4, 73.0, 70.6, 64.8, 36.9, 32.2, 27.7, 20.3; HRMS (ESI) calc for $C_{15}H_{22}O_2Na^+$ [(M + Na)$^+$] 257.1517, found 257.1512.

Allylic alcohol (83 mmol, 1.0 equiv) and triethylamine (13 mL, 91.3 mmol, 1.1 equiv) were placed in a round-bottomed flask filled with DCM (150 mL) at 0 °C. Benzoyl chloride (10.8 mL, 91.3 mmol, 1.1 equiv) was added dropwise and the reaction mixture was warmed to room temperature and stirred overnight. An aqueous sat. NH_4Cl solution was added, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (×3). The combined organic layers were washed with water, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification on silica gel (cyclohexane/ethyl acetate, 95:5 to 90:10) afforded allyl benzoate **29** (18.0 g, 64% over 6 steps) as a colorless oil: $[\alpha]_D^{20}$ +5.9 (*c* 0.70, $CHCl_3$); IR (neat) 3066, 2939, 2860, 1717, 1453, 1271, 1110, 1097, 1027, 905, 727, 710, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (m, 2H), 7.57 (m, 1H), 7.46 (m, 2H), 7.41−7.27 (m, 5H), 5.19 (q, *J* = 1.5 Hz, 1H), 5.04 (s, 1H), 4.83 (s, 2H), 4.51 (s, 2H), 3.49 (t, *J* = 6.4 Hz, 2H), 2.32 (sext, *J* = 6.9 Hz, 1H), 1.74−1.58 (m, 3H), 1.52 (m, 1H), 1.16 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 148.3, 138.7, 133.0, 130.3, 129.7 (2C), 128.5 (2C), 128.4 (2C), 127.7 (2C), 127.6, 111.8, 73.0, 70.5, 66.2, 37.4, 32.1, 27.7, 20.1; HRMS (ESI) calc for $C_{22}H_{26}O_3Na^+$ [(M + Na)$^+$] 361.1780, found 361.1770.

*(S)-(6-(Benzyloxy)-3-methyl-2-methylenehexyl)tributylstannane (**18**).* $(Bu_3Sn)_2$ (14.6 mL, 26 mmol, 1.5 equiv) and THF (60 mL) were placed in a flame-dried round-bottom flask under argon. The mixture was cooled to 0 °C, and *n*-BuLi (2.0 M, 13 mL, 26 mmol, 1.5 equiv) was added dropwise via syringe-pump. The resulting clear pale yellow solution was stirred at 0 °C for 20 min and the reaction mixture was cooled to −78 °C. Et_2AlCl (31 mL, 26 mmol, 1.5 equiv) was added dropwise via syringe-pump and stirring was maintained at −78 °C for 1 h. A degassed solution of $Pd(PPh_3)_4$ (1.0 g, 0.86 mmol, 0.05 equiv) in THF (10 mL) and a solution of benzoate **29** (0.58 g, 1.34 mmol) in THF (20 mL) were successively added dropwise at −78 °C and the reaction mixture was warmed up to ambient temperature over 2 h. After cooling to 0 °C, quench was performed by dropwise addition of a solution of $NaHCO_3$. The resulting suspension was filtered through a pad of Celite and the layers were separated and the aqueous layer was extracted with Et_2O (×3). The organic solutions were dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography on deactivated silica gel (cyclohexane/Et_3N 95:5) provided allylstannane **18** in a quantitative yield along with unseparable tetrabutyl tin: ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.27 (m, 5H), 4.50 (m, 4H), 3.47 (t, *J* = 6.6 Hz, 2H), 1.93 (sext, *J* = 6.9 Hz, 1H), 1.78 (dd, *J* = 0.9, 13.8 Hz, 1H), 1.74 (dd, *J* = 0.9, 13.8 Hz, 1H), 1.67−1.38 (m, 10H), 1.36−1.25 (sext., *J* = 7.2 Hz, 6H), 1.03 (d, *J* = 6.9 Hz, 3H), 0.94 (t, *J* = 7.2 Hz, 9H), 0.86 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 138.8, 128.5 (2C), 127.7 (2C), 127.6, 103.7, 73.0, 70.9, 40.8, 32.5, 29.3 (3C), 27.9, 27.6 (3C), 19.8, 17.8, 13.9 (3C), 9.7 (3C); IR (neat) 2959, 2931, 2856, 1646, 1455, 1374, 1100, 908, 889, 732, 697 cm^{-1}.

*(4R,5R,8S,E)-11-(Benzyloxy)-2-bromo-4,8-dimethyl-7-methyleneundec-2-en-5-ol (**17**).* A 200 mL Schlenk flask was charged with (*R*,*R*)-1,2-*bis*-paratoluenesulfonyl-1,2-diphenylethane (4.4 g, 8.45 mmol, 1.3 equiv) and heated at 90 °C under vacuum for 12 h. The white solid was cooled to room temperature and CH_2Cl_2 (35 mL) was added under argon. The resultant solution was cooled to 0 °C and treated with fresh boron tribromide in CH_2Cl_2 (1.0 M in CH_2Cl_2, 8.45 mL, 8.45 mmol, 1.3 equiv). The resulting orange solution was stirred at 0 °C for 10 min, warmed to room temperature and stirred for 1 h. The solvent and HBr were carefully removed under reduced pressure, then, the resulting solid was dissolved in CH_2Cl_2 (20 mL), stirred for 10 min and concentrated under vacuum. This procedure was conducted with pH control of the aqueous phase, and repeated until pH value was adjusted to 7, in order to remove any trace of HBr The bromoborane complex **30**, obtained as a yellow solid, was then diluted again in CH_2Cl_2 (30 mL) under argon, cooled to 0 °C and a solution of the allylstannane **18** (4.95 g, 9.75 mmol, 1.5 equiv) in CH_2Cl_2 (~5 mL) was added. The yellow solution was stirred for 16 h at room temperature. After this time, the reaction was cooled to −78 °C and a solution of aldehyde (*R*)-**8** (1.15 g, 6.5 mmol, 1 equiv) in CH_2Cl_2 (~5 mL) was added. The reaction mixture was stirred at −78 °C for 1 h, and subsequently quenched with pH 7 buffer (10 mL). After warming to room temperature, the mixture was diluted with CH_2Cl_2. The organic phase was washed with saturated aqueous $NaHCO_3$, and the aqueous phase was extracted (×3) with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting solid was taken up with Et_2O and filtered to recover the sparingly soluble chiral auxiliary, i.e., *bis*-tosylated (*R*,*R*)-1,2-diamino-1,2-diphenylethane. The filtrate was concentrated in vacuo and the resulting residue was purified by flash chromatography over silica gel (cyclohexane/ethyl acetate, 90:10) to yield title compound as a 88:12 mixture of 18,19-*syn*/*anti* diastereomers (2.0 g, 78% yield) as a colorless oil. After a second purification by flash chromatography over silica gel (cyclohexane/ethyl acetate, 98:2 to 90:10), major diastereoisomer 18,19-*syn*-**17** was isolated (1.7 g, 69% yield): $[\alpha]_D^{20}$ +17.9 (*c* 0.73, $CHCl_3$); IR (neat) 3541, 2958, 2871, 1737, 1455, 1334, 1154, 1090, 735, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.28 (m, 5H), 5.74 (d, *J* = 9.2 Hz, 1H), 4.92 (s,

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1H), 4.86 (s, 1H), 4.50 (s, 2H), 3.47 (m, 3H), 2.41 (m, 1H), 2.30 (d, J = 14.0 Hz, 1H), 2.25 (s, 3H), 2.07 (m, 1H), 1.93 (dd, J = 10.4, 14.0 Hz, 1H), 1.63−1.48 (m, 3H), 1.46−1.33 (m, 1H), 1.06 (d, J = 6.4 Hz, 3H), 1.02 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.1, 138.7, 134.7, 128.5 (2C), 127.8 (2C), 127.6, 120.1, 111.1, 73.1, 72.3, 70.6, 40.9, 40.3, 39.6, 31.9, 27.9, 23.8, 20.6, 16.2; HRMS (ESI) calc for $C_{21}H_{31}BrO_2Na^+$ [(M + Na)$^+$] 417.1405, found 417.1404.

(R)-((4R,5R,8S,E)-11-(Benzyloxy)-2-bromo-4,8-dimethyl-7-methyleneundec-2-en-5-yl) 2-methoxy-2-phenylacetate.[10a−c] Homoallyl alcohol **17** (50 mg, 0.13 mmol, 1.0 equiv) was dissolved in anhydrous DCM (1 mL). and (*R*)-methoxyphenylacetic acid (53 mg, 0.32 mmol, 2.5 equiv), DMAP (16 mg, 0.13 mmol, 1.0 equiv) and DCC (65 mg, 0.32 mmol, 2.5 equiv) were successively added. The mixture was stirred at rt for 30 min before addition of diethyl ether (10 mL).The crude mixture was filtered through a pad of Celite, which was rinsed with diethyl ether. The filtrate was concentrated in vacuo and the residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate, 90:10) to furnish corresponding (*R*)-MPA ester (67 mg, 97% yield) as a colorless oil: $[\alpha]_D^{20}$ −17.3 (*c* 0.87, $CHCl_3$); IR (neat) 3031, 2929, 2856, 1748, 1647, 1455, 1361, 1175, 1112, 1003, 907, 732, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.27 (m, 10H), 5.40 (d, J = 10.4 Hz, 1H), 4.96 (m, 1H), 4.80 (s, 1H), 4.77 (s, 1H), 4.68 (s, 1H), 4.51 (s, 2H), 3.47 (t, J = 6.4 Hz, 2H), 3.38 (s, 3H), 2.45 (m, 1H), 2.27 (dd, J = 4.0, 15.2 Hz, 1H), 2.19−2.07 (m, 2H), 1.99 (s, 3H), 1.62−1.51 (m, 2H), 1.49−1.35 (m, 2H), 1.00 (d, J = 6.8 Hz, 3H), 0.72 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 149.7, 138.9, 136.6, 133.1, 128.9, 128.8 (2C), 128.5 (2C), 127.7 (2CH), 127.6, 127.5 (2CH), 120.7, 111.1, 82.8, 75.9, 73.1, 70.8, 57.5, 39.5, 38.3, 36.3, 31.9, 27.8, 23.4, 20.0, 15.5; HRMS (ESI) calc for $C_{30}H_{39}BrO_4Na^+$ [(M + Na)$^+$] 565.1929, found 565.1925.

(S)-((4R,5R,8S,E)-11-(Benzyloxy)-2-bromo-4,8-dimethyl-7-methyleneundec-2-en-5-yl) 2-methoxy-2-phenylacetate.[10a−c] Homoallyl alcohol **17** (50 mg, 0.13 mmol, 1.0 equiv) was dissolved in anhydrous DCM (1 mL). and (*S*)-methoxyphenylacetic acid (53 mg, 0.32 mmol, 2.5 equiv), DMAP (16 mg, 0.13 mmol, 1.0 equiv) and DCC (65 mg, 0.32 mmol, 2.5 equiv) were successively added. The mixture was stirred at rt for 30 min before addition of diethyl ether (10 mL).The crude mixture was filtered through a pad of Celite, which was rinsed with diethyl ether. The filtrate was concentrated in vacuo and the residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate, 90:10) to furnish corresponding (*S*)-MPA ester (65 mg, 94% yield) as colorless oil: $[\alpha]_D^{20}$ +34.0 (*c* 0.50, $CHCl_3$); IR (neat) 2929, 2857, 1746, 1650, 1455, 1362, 1265, 1175, 1104, 1002, 908, 731, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.26 (m, 10H), 5.65 (d, J = 10.4 Hz, 1H), 4.94 (ddd, J = 3.7, 6.2, 9.0 Hz, 1H), 4.70 (s, 1H), 4.51 (s, 1H), 4.49 (s, 2H), 4.42 (s, 1H), 3.43−3.38 (m, 2H), 3.40 (s, 3H), 2.62 (m, 1H), 2.20 (dd, J = 3.6, 15.2 Hz, 1H), 2.17 (s, 3H), 2.05 (dd, J = 9.0, 15.2 Hz, 1H), 1.92 (m, 1H), 1.45 (m, 2H), 1.28 (m, 2H), 0.94 (d, J = 7.2 Hz, 3H), 0.88 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 149.1, 139.0, 136.4, 133.3, 128.8, 128.6 (2C), 128.5 (2C), 127.7 (2C), 127.6, 127.5 (2C), 120.9, 110.9, 83.1, 76.1, 73.0, 70.7, 57.6, 39.1, 38.4, 36.3, 31.8, 27.6, 23.7, 19.9, 16.0; HRMS (ESI) calc for $C_{30}H_{39}BrO_4Na^+$ [(M + Na)$^+$] 565.1929, found 565.1901.

*(4R,5R,8S,E)-11-(Benzyloxy)-2-bromo-4,8-dimethyl-7-methyleneundec-2-en-5-yl acrylate (**16**).* Alcohol **17** (490 mg, 1.24 mmol, 1.0 equiv) and DCM (10 mL) were placed in a flame-dried round-bottom flask under argon. The reaction mixture was cooled to −78 °C, then were successively added DIPEA (1.1 mL, 6.20 mmol, 5.0 equiv) and acryloyl chloride (210 mL, 2.48 mmol, 2.0 equiv). The reaction mixture was stirred 30 min at −78 °C then quenched with an aqueous sat. $NaHCO_3$ solution. The aqueous layer was extracted (×3) with DCM and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Flash purification on silica gel (cyclohexane/ethyl acetate, 90:10) afforded title compound **16** (506 mg, 91% yield) as a yellow oil: $[\alpha]_D^{20}$ +37.5 (*c* 0.67, $CHCl_3$); IR (neat) 2924, 2853, 1723, 1637, 1455, 1405, 1267, 1191, 1102, 985, 736, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.27 (m, 5H), 6.36 (dd, J = 1.4, 17.1 Hz, 1H), 6.08 (dd, J = 10.2, 17.1 Hz, 1H), 5.80 (dd, J = 1.5, 10.2 Hz, 1H), 5.72 (dd, J = 1.2, 10.2 Hz, 1H), 5.00 (ddd, J = 4.2, 6.3, 9.0 Hz, 1H), 4.80 (s, 1H), 4.78 (s, 1H), 4.49 (s, 2H), 3.45 (t, J = 6.3 Hz, 2H), 2.66 (m, 1H), 2.31 (dd, J = 3.6, 14.7 Hz, 1H), 2.21 (m, 1H), 2.20 (d, J = 1.4 Hz, 3H), 2.11 (m, 1H), 1.62−1.51 (m, 2H), 1.50−1.33 (m, 2H), 1.01 (d, J = 6.9 Hz, 3H), 0.99 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 149.5, 138.7, 133.2, 130.7, 128.5, 128.3 (2C), 127.6 (2C), 127.4, 120.7, 110.9, 75.4, 72.8, 70.5, 39.4, 38.3, 35.8, 31.7, 27.5, 23.6, 19.9, 16.1; HRMS (ESI) calcd. for $C_{24}H_{33}O_3BrNa^+$ [(M + Na)$^+$] 471.1511; found 471.1512.

*(R)-4-((S)-5-(Benzyloxy)pentan-2-yl)-6-((R,E)-4-bromopent-3-en-2-yl)-5,6-dihydro-2H-pyran-2-one (**15**).* GP on acrylate **16** (50 mg, 0.112 mmol) using Nolan ruthenium-indenylidene catalyst **cat-8** (10.6 mg, 0.0112 mmol, 10 mol %) and subsequent purification of the crude residue by flash chromatography on silica gel (cyclohexane/ethyl acetate, 90:10 to 80:20) afforded lactone **15** (39 mg, 83% yield) along with homodimer **31** (6 mg, 6% yield). $[\alpha]_D^{20}$ +63.2 (*c* 0.56, $CHCl_3$); IR (neat) 2927, 2857, 1716, 1454, 1251, 1103, 908, 732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.26 (m, 5H), 5.78 (s, 1H), 5.70 (qd, J = 1.2, 10.4 Hz, 1H), 4.48 (s, 2H), 4.08 (td, J = 7.1, 8.4 Hz, 1H), 3.45 (t, J = 6.0 Hz, 2H), 2.68 (m, 1H), 2.31 (m, 1H), 2.25 (d, J = 1.2 Hz, 3H), 2.20 (m, 2H), 1.61−1.44 (m, 4H), 1.12 (d, J = 6.8 Hz, 3H), 1.09 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 165.1, 138.5, 132.4, 128.5 (2C), 127.7 (3C), 121.7, 115,1, 80.3, 73.2, 70.0, 40.3, 39.2, 30.7, 28.8, 27.6, 23.9, 18.8, 16.5; HRMS (ESI) calc for $C_{22}H_{29}O_3BrNa^+$ [(M + Na)$^+$] 443.1198, found 443.1196.

*Bis-((4R,5R,8S)-11-(Benzyloxy)-2-bromo-4,8-dimethyl-7-methyleneundec-2-en-5-yl) fumarate (**31**).* Homodimer **31** is obtained as a side-product of the above-described RCM reaction following GP2 procedure (6 mg, 6%): $[\alpha]_D^{20}$ +82.9 (*c* 0.33, $CHCl_3$); IR (neat) 2929, 2856, 1720, 1647, 1455, 1294, 1259, 1156, 1101, 1000, 909, 733 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.28 (m, 10H), 6.79 (s, 2H), 5.71 (qd, J = 1.5, 10.2 Hz, 2H), 5.01 (m, 2H), 4.81 (s, 2H), 4.77 (s, 2H), 4.49 (s, 4H), 3.45 (t, J = 6.6 Hz, 4H), 2.66 (m, 2H), 2.33 (m, 2H), 2.20 (d, J = 1.5 Hz, 6H), 2.23−2.15 (m, 2H), 2.09 (m, 2H), 1.61−1.46 (m, 4H), 1.46−1.34 (m, 4H), 1.01 (d, J = 6.8 Hz, 6H), 1.00 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5 (2C), 149.6 (2C), 138.8 (2C), 133.8 (2C), 133.2 (2C), 128.5 (4C), 127.7 (4C), 127.6 (2C), 121.1 (2C), 111.3 (2C), 76.7 (2C), 73.3 (2C), 70.6 (2C), 39.5 (2C), 38.3 (2C), 36.3 (2C), 32.0 (2C), 27.7 (2C), 23.8 (2C), 20.0 (2C), 16.1 (2C); HRMS calcd for $C_{46}H_{62}O_6Br_2Na^+$ [(M + Na)$^+$] 891.2811, found 891.2808.

*(3S,4R,6R)-4-((S)-5-(Benzyloxy)pentan-2-yl)-6-((R,E)-4-bromopent-3-en-2-yl)-3,4-dihydroxytetrahydro-2H-pyran-2-one (**32**).* To a solution of lactone **15** (500 mg, 1.19 mmol, 1.0 equiv) in a THF/water 8:2 solution (10 mL) at room temperature were successively added citric acid (860 mg, 2.37 mmol, 2.0 equiv), potassium osmate (VI) dihydrate (8 mg, 23.8 μmol, 0.02 equiv) and NMO (170 mg, 1.31 mmol, 1.1 equiv). The mixture was vigorously stirred for 25 h then quenched with a saturated aqueous $Na_2S_2O_3$ solution and extracted with AcOEt (×3). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (cyclohexane/ethyl acetate, 80:20 to 70:30) afforded **32** as a single diastereoisomer (379 mg, 70%) as a colorless oil: $[\alpha]_D^{20}$ −12.7 (*c* 0.30, $CHCl_3$); IR (neat) 3465, 2966, 2860, 1732, 1455, 1228, 1103, 1060, 737, 689 cm^{-1}; ^{1}H NMR (500 MHz, MeOD) δ 7.36−7.24 (m, 5H), 5.75 (qd, J = 1.5, 10.2 Hz, 1H), 5.48 (m, 2H), 4.49 (s, 2H), 4.42 (ddd, J = 3.9, 6.7, 11.7 Hz, 1H), 4.22 (s, 1H), 3.52 (dt, J = 1.2, 6.3 Hz, 2H), 2.72 (dquint, J = 6.7, 10.2 Hz, 1H), 2.27 (d, J = 1.5 Hz, 3H), 1.98 (m, dqd, J = 2.6, 6.9, 11.0 Hz, 1H), 1.87 (dd, J = 3.9, 14.3 Hz, 1H), 1.77 (m, 1H), 1.64 (dd, J = 11.7, 14.3 Hz, 1H), 1.60−1.48 (m, 2H), 1.10 (m, 1H), 1.09 (d, J = 6.7 Hz, 3H), 0.99 (d, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, MeOD) δ 176.7, 139.8, 133.9, 129.4 (2C), 128.9 (2C), 128.7, 122.4, 81.6, 76.3, 73.9, 72.5, 71.6, 40.6, 39.0, 31.4, 29.5, 29.4, 24.0, 16.1, 12.9; HRMS (ESI) calc for $C_{22}H_{31}O_5BrNa^+$ [(M + Na)$^+$] 477.1253, found 477.1255.

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*(3S,4R,6R)-4-((S)-5-(Benzyloxy)pentan-2-yl)-6-((R,E)-4-bromopent-3-en-2-yl)-3,4-bis-((triethylsilyl)oxy)tetrahydro-2H-pyran-2-one (**33**).* TESOTf (2.0 mL, 8.7 mmol, 9.0 equiv) and 2,6-lutidine (1.3 mL, 11.6 mmol, 12.0 equiv) were successively added to a stirred solution of diol **32** (440 mg, 0.97 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (3.0 mL) at 0 °C. The mixture was stirred for 48 h at room temperature then quenched with a saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2 (×3). The organic layers were combined, washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography on silica gel (pentane/ethyl acetate, 100:0 to 95:5) to yield the expected disilyl ether **33** (650 mg, 96% yield) as colorless oil: $[\alpha]_D^{20}$ −1.7 (*c* 0.54, $CHCl_3$); IR (neat) 2953, 2876, 1748, 1455, 1380, 1265, 1150, 1091, 1006, 829, 728 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.27 (m, 5H), 5.68 (qd, *J* = 1.4, 10.1 Hz, 1H), 4.51 (s, 2H), 4.38 (ddd, *J* = 3.4, 6.5, 11.6 Hz, 1H), 4.19 (s, 1H), 3.47 (t, *J* = 6.3 Hz, 2H), 2.62 (ddq, *J* = 6.5, 7.2, 9.8 Hz, 1H), 2.27 (d, *J* = 1.4 Hz, 3H), 2.01 (m, 1H), 1.79 (dd, *J* = 3.4, 13.9 Hz, 1H), 1.77 (m, 1H), 1.47 (m, 1H), 1.39 (dd, *J* = 11.6, 13.9 Hz, 1H), 1.38 (m, 2H), 1.07 (d, *J* = 7.2 Hz, 3H), 0.97 (t, *J* = 8.0 Hz, 9H), 0.93 (d, *J* = 6.9 Hz, 3H), 0.91 (t, *J* = 8.0 Hz, 9H), 0.75 (m, 6H), 0.64 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 138.6, 132.4, 128.5 (2C), 127.7 (3C), 121.6, 79.8, 79.7, 73.2, 73.1, 70.6, 39.4, 37.5, 31.7, 29.2, 28.7, 24.0, 16.5, 12.9, 7.4 (3C), 7.3 (3C), 6.7 (3C), 5.3 (3C); HRMS (ESI) calc for $C_{34}H_{59}BrO_5Si_2Na^+$ $[(M + Na)^+]$ 705.2982, found 707.2972.

*(3S,4R,6R)-4-((S)-5-(Benzyloxy)pentan-2-yl)-6-((R,Z)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-3-en-2-yl)-3,4-bis-((triethylsilyl)oxy)tetrahydro-2H-pyran-2-one (**13**).* To an oven-dried flask under argon were added disilyl ether **33** (100 mg, 146 μmol, 1.0 equiv), *bis*-(pinacolato)diboron 34 (82 mg, 322 μmol, 2.2 equiv), $PdCl_2(PPh_3)_2$ (26 mg, 37 μmol, 0.24 equiv), PPh_3 (19 mg, 72 μmol, 0.48 equiv), and KOPh (61 mg, 439 μmol, 3.0 equiv). The mixture was submitted to vacuum/argon cycles (×2) then dry toluene was added and the solution was heated to 50 °C for 6 h. After being cooled to room temperature, the mixture was diluted with water, extracted with AcOEt (×3), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was submitted to flash chromatography on silica gel (cyclohexane EtOAc: 100:0 to 90:10) to provide boronate **13** as a colorless oil (71 mg, 66% yield): $[\alpha]_D^{20}$ −6.9 (*c* 0.72, $CHCl_3$); IR (neat) 2955, 2877, 1747, 1457, 1370, 1143, 1099, 909, 831, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37−7.28 (m, 5H), 6.07 (qd, *J* = 1.7, 9.6 Hz, 1H), 4.50 (s, 2H), 4.37 (ddd, *J* = 3.5, 7.6, 11.6 Hz, 1H), 4.18 (s, 1H), 3.45 (t, *J* = 6.6 Hz, 2H), 2.76 (ddq, *J* = 6.8, 7.6, 9.6 Hz, 1H), 1.99 (m, 1H), 1.80 (dd, *J* = 3.5, 13.9 Hz, 1H), 1.74 (m, 1H), 1.71 (d, *J* = 1.7 Hz, 3H), 1.46 (m, 1H), 1.38 (dd, *J* = 11.6, 13.9 Hz, 1H), 1.27 (m, 2H), 1.27 (s, 6H), 1.26 (s, 6H), 1.08 (d, *J* = 6.8 Hz, 3H), 0.97 (t, *J* = 8.0 Hz, 9H), 0.91 (t, *J* = 8.0 Hz, 9H), 0.89 (d, *J* = 6.8 Hz, 3H), 0.73 (m, 6H), 0.63 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 145.7, 138.7, 128.5 (2C), 127.7 (3C), 127.7, 83.4 (2C), 80.3, 80.0, 73.3, 73.1, 70.7, 38.5, 37.6, 32.9, 29.1, 28.8, 25.1 (2C), 24.8 (2C), 16.4, 14.6, 12.9, 7.4 (3C), 7.3 (3C), 6.8 (3C), 5.4 (3C); HRMS (ESI) calcd for $C_{40}H_{71}BO_7Si_2Na^+$ $[(M + Na)^+]$ 753.4729, found 753.4739.

*2-(Trimethylsilyl)ethyl(2E,4E,6E,8S,9R,10R)-10-((4R,5S,6R)-6-((R,2E,4E)-6-((2R,4R,5S)-4-((S)-5-(benzyloxy)pentan-2-yl)-6-oxo-4,5-bis-((triethylsilyl)oxy)tetrahydro-2H-pyran-2-yl)-4-methylhepta-2,4-dien-2-yl)-2,2-di-tert-butyl-5-methyl-1,3,2-dioxasilinan-4-yl)-9-methoxy-8-methylundeca-2,4,6-trienoate (**35**).* Boronate **13** (40 mg, 55 μmol, 1.1 equiv) and vinyl iodide **14** (35 mg, 50 μmol, 1.0 equiv) were dissolved in a THF/water 3:1 solution (3.2 mL). The mixture was degassed by argon bubbling for 10 min then $Pd(PPh_3)_4$ (5.8 mg, 5 μmol, 0.1 equiv) was added. The mixture was stirred for 5 min, and TlOEt (5.3 μL, 7.5 μmol, 1.5 equiv) was added via syringe. The reaction was kept at room temperature for 45 min, and subsequently quenched with a saturated $NaHCO_3$ solution. The aqueous layer was extracted with AcOEt (×3), and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to furnish **35** as a colorless oil (49 mg, 82% yield): $[\alpha]_D^{20}$ +29.7 (*c* 0.32, $CHCl_3$); IR (neat) 2954; 2876, 1749, 1709, 1617, 1456, 1305, 1250, 1145, 1005, 826, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32−7.23 (m, 6H), 6.50 (dd, *J* = 10.8, 14.7 Hz, 1H), 6.21 (dd, *J* = 11.4, 14.7 Hz, 1H), 6.16 (dd, *J* = 10.8, 15.3 Hz, 1H), 6.05 (s, 1H), 5.93 (dd, *J* = 8.4, 15.3 Hz, 1H), 5.83 (d, *J* = 15.3 Hz, 1H), 5.02 (d, *J* = 9.6 Hz, 1H), 4.56 (s, 1H), 4.49 (s, 2H), 4.38 (ddd, *J* = 2.7, 7.2, 10.5 Hz, 1H), 4.27−4.17 (m, 4H), 3.48 (t, *J* = 6.3 Hz, 2H), 3.39 (s, 3H), 3.28 (dd, *J* = 1.5, 8.1 Hz, 1H), 2.74 (m, 1H), 2.66 (m, 1H), 2.02 (m, 2H), 1.91 (dd, *J* = 2.4, 13.6 Hz, 1H), 1.79 (m, 1H), 1.75 (s, 3H), 1.61 (s, 3H), 1.50−1.25 (m, 3H), 1.12−0.55 (m, 67H), 0.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 167.5, 144.6, 144.1, 141.1, 138.6, 135.2, 134.0, 129.7, 129.3, 128.5 (2C), 128.4, 127.7 (4C), 120.6, 86.1, 80.9, 80.8, 79.9, 78.3, 73.2, 73.1, 70.7, 62.6, 59.3, 40.6, 39.8, 38.1, 37.5, 35.9, 32.8, 29.2, 28.7, 28.2 (6C), 23.8, 21.0, 18.0, 17.9, 17.5, 16.9, 15.7, 12.9, 12.2, 7.4 (3C), 7.3 (3C), 6.8 (3C), 5.4 (3C), 4.8, −1.3 (3C); HRMS (ESI) calc for $C_{67}H_{118}O_{10}Si_4Na^+$ $[(M + Na)^+]$ 1217.7700, found 1217.7736.

*(2E,4E,6E,8S,9R,10S,11S,12S,13R,14E,16E,18R)-18-((2R,4R,5S)-4-((S)-5-(Benzyloxy)pentan-2-yl)-4,5-dihydroxy-6-oxotetrahydro-2H-pyran-2-yl)-11,13-dihydroxy-9-methoxy-8,10,12,14,16-pentamethylnonadeca-2,4,6,14,16-pentaenoic acid (**12**).* To a solution of ester **35** (16 mg, 13.4 μmol, 1.0 equiv) in dry DMF (520 μL) at 0 °C was added TASF (37 mg, 134 μmol, 10.0 equiv). The reaction was warmed to room temperature and stirred for 4 h. The mixture was diluted with AcOEt then quenched by addition of an aqueous sat. NH_4Cl solution. The aqueous phase was extracted with AcOEt (×3) then organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was immediately solubilized in THF (1.5 mL) at 0 °C and a stock solution of HF/pyridine was added (365 μL). The reaction was stirred to 0 °C for 3 h. The mixture was diluted with CH_2Cl_2 then quenched with an aqueous sat. NH_4Cl solution (2 mL). The aqueous phase was extracted with CH_2Cl_2 (×3), combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH: 96:4) to furnish **12** as a clear oil (10 mg, 90% yield): $[\alpha]_D^{20}$ +13.0 (*c* 0.10, $CHCl_3$); IR (neat) 3421, 2971, 2932, 2876, 1726, 1617, 1385, 1217, 1106, 1007, 756, 700 cm^{-1}; ^1H NMR (500 MHz, MeOD) δ 7.34−7.25 (m, 5H), 7.14 (dd, *J* = 11.5, 15.0 Hz, 1H), 6.49 (dd, *J* = 11.0, 15.0 Hz, 1H), 6.27 (dd, *J* = 11.5, 15.0 Hz, 1H), 6.17 (dd, *J* = 11.0, 15.0 Hz, 1H), 5.95 (s, 1H), 5.91 (dd, *J* = 7.0, 15.0 Hz, 1H), 5.89 (d, *J* = 15.0 Hz, 1H), 5.14 (d, *J* = 9.5 Hz, 1H), 4.49 (s, 2H), 4.40 (ddd, *J* = 3.5, 7.5, 11.0 Hz, 1H), 4.23 (s, 1H), 4.00 (d, *J* = 7.0 Hz, 1H), 3.58 (d, *J* = 8.5 Hz, 1H), 3.50 (m, 2H), 3.38 (s, 3H), 3.26 (dd, *J* = 5.0, 6.0 Hz, 1H), 2.78 (m, 1H), 2.53 (m, 1H), 2.02−1.92 (m, 3H), 1.80 (s, 3H), 1.79 (m, 1H), 1.67 (s, 3H), 1.56−1.25 (m, 3H), 1.11 (d, *J* = 6.5 Hz, 3H), 1.07 (d, *J* = 6.5 Hz, 3H), 1.06 (m, 2H), 0.94 (d, *J* = 6.5 Hz, 3H), 0.92 (d, *J* = 7.0 Hz, 3H), 0.84 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, MeOD) δ 176.9, 143.6, 143.3, 140.4, 139.8, 137.4, 135.3, 131.4, 131.2, 130.7, 130.3, 129.4 (2C), 128.9 (2C), 128.7, 126.0, 88.5, 82.7, 81.9, 76.3, 76.0, 74.0, 72.5, 71.6, 59.7, 41.4, 40.0, 39.2, 39.0, 38.4, 32.1, 29.6, 29.4, 17.9, 17.1, 16.9, 14.2, 13.2, 13.0, 7.4; HRMS (ESI) calc for $C_{42}H_{62}O_{10}Na^+$ $[(M + Na)^+]$ 749.4241, found 749.4244.

*(S)-4-((3S,4R,6R)-6-((R,E)-4-Bromopent-3-en-2-yl)-2-oxo-3,4-bis-((triethylsilyl)oxy)-tetrahydro-2H-pyran-4-yl)pentanal (**36**).* Disilyl ether **33** (200 mg, 0.29 mmol, 1 equiv) was dissolved in a CH_2Cl_2/H_2O 19:1 solution (4.2 mL). at room temperature and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone DDQ (266 mg, 1.16 mmol, 4 equiv) was added. The reaction mixture was refluxed for 4 h then quenched with an aqueous sat. Na_2CO_3 solution and an aqueous sat. $Na_2S_2O_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (×3), the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Flash purification on silica gel (pentane/ethyl acetate, 80:20) afforded corresponding alcohol as a colorless oil (144 mg, 83% yield): $[\alpha]_D^{20}$ −4.1 (*c* 0.47, $CHCl_3$), IR (neat) 2955, 2877, 1741, 1458, 1381, 1234, 1158, 905, 726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.66 (qd, *J* = 0.8, 10.4 Hz, 1H), 4.37 (ddd, *J* = 3.5, 6.5, 11.7 Hz, 1H), 4.20 (s, 1H), 3.66 (m, 2H), 2.61 (ddq, *J* = 6.5, 7.1, 10.4 Hz, 1H), 2.25 (d, *J*

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J. Org. Chem. 2016, 81, 12275−12290

= 0.8 Hz, 3H), 2.02 (m, 1H), 1.79 (dd, J = 3.5, 13.7 Hz, 1H), 1.73 (m, 1H), 1.44 (m, 1H), 1.40 (dd, J = 11.7, 13.7 Hz, 1H), 1.37 (m, 2H), 1.06 (d, J = 7.1 Hz, 3H), 0.99 (t, J = 8.0 Hz, 9H), 0.94 (d, J = 6.9 Hz, 3H), 0.91 (t, J = 8.0 Hz, 9H), 0.76 (m, 6H), 0.63 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 132.4, 121.6, 79.9, 79.8, 73.2, 63.4, 39.5, 37.4, 31.7, 31.6, 28.7, 24.0, 16.5, 13.0, 7.4 (3C), 7.3 (3C), 6.8 (3C), 5.4 (3C); HRMS (ESI) calc for $C_{27}H_{53}BrO_5Si_2Na^+$ [(M + Na)$^+$] 615.2513, found 615.2518.

Alcohol (75 mg, 0.13 mmol, 1 equiv) was dissolved in anhydrous CH_2Cl_2 (1 mL) and $NaHCO_3$ (33 mg, 0.39 mmol, 3 equiv) and Dess Martin's reagent (83 mg, 0.19 mmol, 1.5 equiv) were successively added. The mixture was stirred for 1 h at room temperature then quenched with an aqueous sat. $Na_2S_2O_3$ solution and extracted with CH_2Cl_2 (×3), the organic layers were combined, washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography on silica gel (pentane/ethyl acetate 98:2 to 95:5) to afford aldehyde **36** (72 mg, 96% yield) as a colorless oil: $[\alpha]_D^{20}$ +10.5 (c 0.33, $CHCl_3$); IR (neat) 2957, 2877, 1745, 1726, 1458, 1381, 1238, 1157, 907, 731 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.82 (s, 1H), 5.67 (qd, J = 1.2, 9.9 Hz, 1H), 4.36 (ddd, J = 3.6, 6.9, 11.7 Hz, 1H), 4.21 (s, 1H), 2.61 (m, 2H), 2.36 (m, 1H), 2.26 (d, J = 1.2 Hz, 3H), 2.01 (m, 1H), 1.80 (dd, J = 3.6, 13.7 Hz, 1H), 1.67 (m, 1H), 1.42 (dd, J = 11.7, 13.7 Hz, 1H), 1.22 (m, 1H), 1.08 (d, J = 6.9 Hz, 3H), 0.98 (t, J = 8.1 Hz, 9H), 0.92 (m, 3H), 0.91 (t, J = 7.9 Hz, 9H), 0.75 (m, 6H), 0.63 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.5, 172.4, 132.3, 121.7, 79.7, 73.2, 42.9, 39.6, 37.0, 31.9, 24.1, 24.0, 16.5, 12.9, 7.4 (3C), 7.2 (3C), 6.7 (3C), 5.3 (3C); HRMS: decomposition.

*(3S,4R,6R)-6-((R,E)-4-Bromopent-3-en-2-yl)-4-((2S,5R,9R)-5-hydroxy-9-((4-methoxybenzyl)oxy)-7-oxodecan-2-yl)-3,4-bis((triethylsilyl)oxy)tetrahydro-2H-pyran-2-one (**38**).* (c-Hex)$_2$BCl (1 M, 66 μL, 66 μmol, 1.95 equiv) was dissolved in Et_2O (0.5 mL) at −78 °C and triethylamine (12 μL, 85 μmol, 2.5 equiv) was added via syringe. A solution of methylketone **37** (27 mg, 68 μmol, 2 equiv) in Et_2O (0.5 mL) was added dropwise at −78 °C and the reaction warmed to 0 °C for 1 h. The mixture was cooled to −78 °C, and a solution of aldehyde **36** (20 mg, 34 μmol, 1 equiv) in Et_2O (0.5 mL) was added over 30 min by means of a syringe pump. The resulting mixture was stirred for 1 h at −78 °C, and quenched by dropwise addition of MeOH (1 mL) and pH 7 buffer solution (1 mL). The solution was extracted with Et_2O (×3) and the combined organic extracts were washed with brine and dried over $MgSO_4$. The solvents were removed in vacuo. The residue was purified by flash chromatography on silica gel (pentane/Et_2O 90:10 to 80:20) to afford alcohol **38** as a 80:20 mixture of 31,27 *anti/syn* diastereoisomers (17 mg, 80% yield), as a colorless oil: IR (neat): 3491, 2956, 2877, 1743, 1708, 1514, 1458, 1378, 1248, 1157, 1139, 1090, 907, 828, 730 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *major diastereoisomer* δ 7.21 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 8.4 Hz, 2H), 5.67 (*br*dd, J = 1.2, 10.0 Hz, 1H), 4.50 (d, J = 11.2 Hz, 1H), 4.37 (m, 1H), 4.35 (d J = 11.2 Hz, 1H), 4.21 (s, 1H), 4.03 (m, 1H), 3.97 (m, 1H), 3.79 (s, 3H), 3.04 (*br*s, 1H), 2.77 (dd, J = 7.6, 15.5 Hz, 1H), 2.62 (m, 2H), 2.53 (dd, J = 8.6, 17.7 Hz, 1H), 2.43 (dd, J = 4.8, 15.5 Hz, 1H), 2.25 (d, J = 1.2 Hz, 3H), 1.96 (m, 1H), 1.77 (dd, J = 3.4, 13.8 Hz, 1H), 1.54 (m, 1H), 1.38 (dd, J = 11.8, 13.8 Hz, 1H), 1.28 (m, 1H), 1.25 (m, 2H), 1.23 (d, J = 6.4 Hz, 3H), 1.07 (d, J = 7.2 Hz, 3H), 0.99 (t, J = 8.0 Hz, 9H), 0.90 (t, J = 8.0 Hz, 9H), 0.90 (d, J = 6.8 Hz, 3H), 0.76 (m, 6H), 0.63 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.7, 172.7, 159.4, 132.5, 130.4, 129.5 (2C), 121.5, 113.9 (2C), 79.9, 79.7, 73.2, 71.4, 70.7, 67.9, 55.4, 50.8, 50.7, 39.5, 37.4, 35.1, 31.8, 28.2, 24.0, 19.9, 16.6, 13.1, 7.4 (3C), 7.3 (3C), 6.8 (3C), 5.4 (3C); HRMS (ESI) calc for $C_{40}H_{69}BrO_8Si_2Na^+$ [(M + Na)$^+$] 835.3612, found 835.3607.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02208.

Experimental details as well as compound characterization data and copies of ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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