JOC The Journal of Organic Chemistry

Total Synthesis of Ripostatin B and Structure-Activity Relationship Studies on Ripostatin Analogs

Florian Glaus, Darija Dedic, Priyanka Tare, Valakunja Nagaraja, Liliana Rodrigues, Jose A. Ainsa, Jens Kunze, Gisbert Schneider, Ruben C. Hartkoorn, Stewart T. Cole, and Karl-Heinz Altmann

J. Org. Chem., **Just Accepted Manuscript** • Publication Date (Web): 15 Mar 2018

ACS Publications

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Total Synthesis of Ripostatin B and Structure-Activity Relationship Studies on Ripostatin Analogs

Florian Glaus,[‡] Darija Dedić,[‡] Priyanka Tare,[†] Valakunja Nagaraja,[†] Liliana Rodrigues,[&] José Antonio Aínsa,[∥] Jens Kunze,[‡] Gisbert Schneider,[‡] Ruben C. Hartkoorn,[§] Stewart T. Cole,[§] and Karl-Heinz Altmann,[‡,*]

ORCID-ID (KHA): https://orcid.org/0000-0002-0747-9734

[‡]ETH Zürich, Department of Chemistry and Applied Biosciences, Institute of Pharmaceutical Sciences, Zürich, Switzerland.

karl-heinz.altmann@pharma.ethz.ch

[§]École Polytechnique Fédérale de Lausanne, Global Health Institute, Lausanne, Switzerland

[†]Department of Microbiology and Cell Biology, Indian Institute of Science, Bangalore 560 012, India

[∥]Grupo de Genética de Micobacterias, Departamento de Microbiología, Medicina Preventiva y Salud Pública, Facultad de Medicina and BIFI, Universidad de Zaragoza, Zaragoza, Spain and CIBER Enfermedades Respiratorias (CIBERES), Madrid, Spain

[&]Fundación Agencia Aragonesa para la Investigación y el Desarrollo (ARAID), Zaragoza, Spain

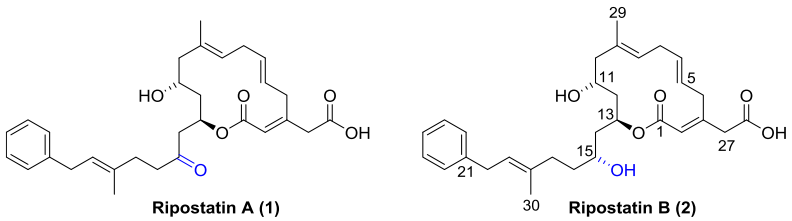
Abstract

Described is the total synthesis of the myxobacterial natural product ripostatin B and of a small number of analogs. Ripostatin B is a polyketide-derived 14-membered macrolide that acts as an inhibitor of bacterial RNA-polymerase, but is mechanistically distinct from rifamycin-derived RNA-polymerase inhibitors that are in use for tuberculosis treatment. The macrolactone ring of ripostatin B features two stereocenters and a synthetically challenging doubly skipped triene motif, with one of the double bonds being in conjugation with the ester carbonyl. Appended to the macrolactone core are an extended hydroxy-bearing phenylalkyl side chain at C13 and a carboxymethyl group at C3. The triene motif was established with high efficiency by ring-closing olefin metathesis, which proceeded in almost 80% yield. The side chain-bearing stereocenter α to the ester oxygen was formed in a Paterson aldol reaction between a methyl ketone and a β-chiral β-hydroxy aldehyde with excellent *syn* selectivity (dr >10:1). The total synthesis provided a blueprint for the synthesis of analogs with modifications in the C3 and C13 side chains. The C3-modified analogs showed good antibacterial activity against efflux-deficient *Escherichia coli* but, as ripostatin B, were inactive against *Mycobacterium tuberculosis*, in spite of significant *in vitro* inhibition of *M. tuberculosis* RNA-polymerase.

Introduction

In 1995, Höfle, Reichenbach and co-workers described the isolation of two antibacterial metabolites from the culture supernatant of *Sorangium cellulosum* (strain So ce377; obtained from a Kenyan soil sample in 1989).[1,2] The two compounds were named ripostatin A and B, respectively, which reflects their biological mechanism of action, the inhibition of **ri**bonucleic acid **po**lymerase (RNAP; *vide infra*). The isolation procedure delivered 30 mg of ripostatin per liter of extract, with ripostatin A being the major constituent (A/B *ca*. 25:1).[1]

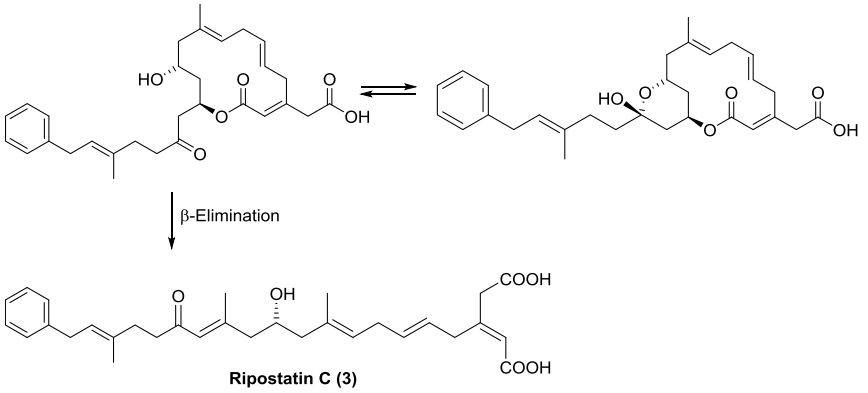
Ripostatins A (**1**) and B (**2**) are 14-membered polyketide-derived macrolides incorporating an unusual 1,4,7-triene-framework, an exocyclic carboxylic acid functionality and an apolar side chain terminating in a phenyl ring. The two compounds show a high degree of structural homology, differing only in the oxidation state at C15.



Ripostatin A (**1**) exists as an equilibrium mixture of a hemiacetal and a keto form (Scheme 1);[2] the latter can undergo elimination to the biologically inactive ripostatin C (**3**), a process that is triggered even by mildly basic conditions (36% elimination in methanolic buffer solution pH 8 at 40 °C within 1 hour). In contrast, ripostatin B (**2**) is significantly more stable, with saponification of the lactone functionality being observed only above pH 11.[2]

Ripostatins A (**1**) and B (**2**) were reported by the isolation group to be narrow spectrum antibiotics, with notable activity (minimum inhibitory concentrations (MICs) between 0.63 and 2.5 μg/mL) being observed only against *Staphylococcus aureus* and an *Escherichia coli* "mutant with altered outer membrane" (*E. coli* Tol C),[1] although the exact mutation in the *tolC* gene was not specified. In addition, ripostatin B (**2**), but not ripostatin A (**1**), also showed minor activity against yeasts and *fungi*.[1] Based on the differential activity of ripostatins against wild-type *E. coli* and a corresponding Tol C mutant the isolation group suggested that the lack of broad-based antibacterial activity of ripostatins was related to poor penetration through the bacterial cell wall rather than degradation of the compounds.

Scheme 1. Keto/hemiacetal equilibrium in ripostatin A (**1**) and elimination to ripostatin C (**3**).



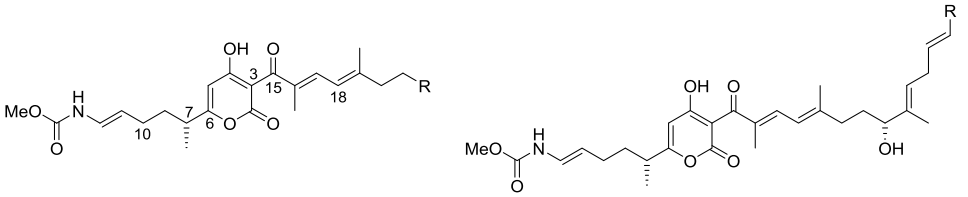
Both ripostatin A (**1**) and B (**2**) appear to exhibit low toxicity towards mouse fibroblasts, although it is not entirely clear how the numerical data provided in ref. 1 are to be interpreted.

At the mechanistic level, ripostatin A (**1**) was demonstrated by the isolation group to be a potent inhibitor of RNAP from *E. coli* with an IC_{50} of 0.1 μM.[1] At the same time, (eukaryotic) wheat germ RNA polymerase II was insensitive to the compound; the RNAP-inhibitory activity of ripostatin B (**2**) was not investigated in the context of the isolation work. Intriguingly, ripostatin-resistant *S. aureus* mutants showed no cross-resistance with rifampicin and *vice versa*, thus suggesting for the binding sites of the two compounds on RNAP to be distinctly different.

The lack of cross-resistance between ripostatin A (**1**) and rifampicin in *S. aureus* was subsequently confirmed for a whole series of mutant strains.[3] More recently, both ripostatins have also been demonstrated to inhibit the growth of the hypersensitive *E. coli* strain D21f2*tolC::*Tn*10* with MICs below 1 μg/mL,[4] thus confirming the earlier findings of the isolation group with the unspecified *E. coli* Tol C mutant strain. The *E. coli* strain D21f2*tolC::*Tn*10* harbors two primary defects in the outer membrane, a "deep rough" (rfa) mutation[5] that causes loss of heptose from the outer-membrane lipopolysaccharides and a Tn10 insertion mutation in the *tolC* gene,[6] which disrupts the Tol C protein that serves as an outer membrane channel for several efflux pumps. In combination, these defects lead to greatly enhanced susceptibility of the bacteria towards hydrophobic, but not hydrophilic, antibacterials.[5] The activity of ripostatins against *E. coli* D21f2*tolC::*Tn*10* re-enforces the hypothesis that the intrinsic activity of the compounds against bacterial RNAP would be

sufficient to elicit potent antibacterial effects, which, however, do not become manifest in most cases due to a lack of efficient intracellular accumulation.

In 2008, Ebright and co-coworkers discovered that ripostatin A (**1**) showed a high degree of cross-resistance with the myxopyronin[7]/corallopyronin[8,9] class of natural RNAP inhibitors, thus indicating that these antibiotics all shared the same binding site on RNAP, or at least bound to largely overlapping sites.[10]



Myxopyronin A: R = Me
Myxopyronin B: R = Et

Corallopyronin A: R = Me
Corallopyronin B: R = Et

Analysis of the myxopyronin-resistance substitution cluster suggested this binding site to be located in the RNAP switch region, which was subsequently confirmed by X-ray crystallography of myxopyronin A in complex with RNAP from *Thermus thermophilus*.[10] Binding of myxopyronin to the "switch region" of RNAP stabilizes a closed conformation of the enzyme, which prevents access of the dsDNA substrate to the active site cleft, and the same is likely to be true for ripostatin A (**1**). Importantly, this inhibition mode is fundamentally different from that of rifamycin-type inhibitors;[10,11] as a result, switch region binders exhibit very limited cross-resistance with rifampicin.[3,10]

While virtually no work on ripostatins as targets for total synthesis had been reported in the literature for more than 15 years after their discovery, with the notable exception of a paper by Kirschning in 2006,[12] three total syntheses of ripostatin B (**2**) were communicated simultaneously in 2012 by Christmann and co-workers,[13] Prusov and co-workers[14] and our own group.[15,16] While all these syntheses were based on ring-closure by ring-closing olefin metathesis (RCM), different approaches were pursued to prepare the requisite diene precursor, especially in the case of the Christmann synthesis.[13] More recently, the Prusov group has also reported the total synthesis of ripostatin A (**1**)[17] followed by a full paper on the synthesis of both ripostatins and a limited number of analogs for structure-activity relationship (SAR) studies.[4]

Our own interest in ripostatins as targets for total synthesis arose in the context of a broader program directed at the discovery of new natural product-based antimicrobials in

general, and of antimycobacterial agents in particular. As demonstrated by the clinical importance of several rifamycin derivatives for tuberculosis (TB) treatment, RNAP is a highly validated target for TB drugs. At the same time, it appears that the potential of bacterial RNAP as a drug target for TB is still underexplored, given the fact that there is only one structural class of RNAP inhibitors in clinical use.[18] While natural ripostatins are not suitable drug candidates *per se*, primarily due to their inability to cross the bacterial cell wall efficiently, this issue might be addressable by structural modifications. It was also not clear *a priori* if the lack of antibacterial activity of ripostatins would necessarily extend to *M. tuberculosis* (*Mtb*), given the unique nature of the mycobacterial cell wall.[19] In order to provide insight into the effects of ripostatins on the growth of *Mtb* and to establish the chemical basis for SAR studies, we embarked on the stereoselective total synthesis of ripostatin B (**2**) as the (chemically) more stable of the two ripostatin variants. At the time when this work was initiated, it could only be inferred that ripostatin B (**2**), like ripostatin A (**1**), was an inhibitor of the bacterial RNAP, as no experimental data on this question were available in the literature. In the meantime, work by Prusov and Ebright has shown that **1** and **2** inhibit RNAP from *E. coli* with similar potency, while **2** is *ca*. 10-fold more potent than **1** against the enzyme from *S. aureus*.[4]

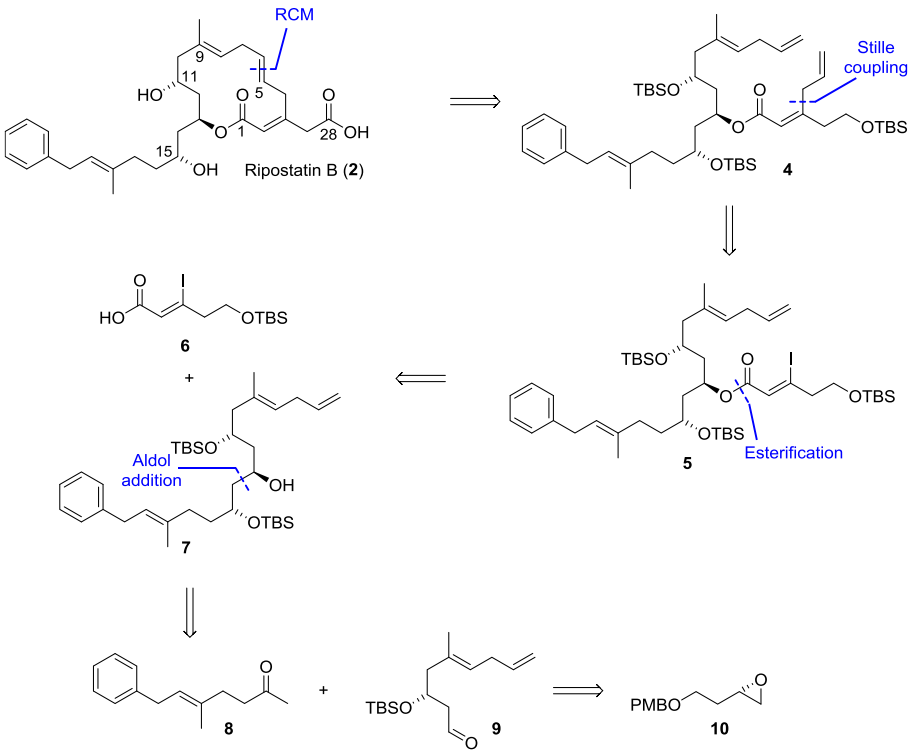
In this report, we present full details on the total synthesis of ripostatin B (**2**), the essential elements of which we have already reported in previous communications.[15,16] In addition, we describe the synthesis of a series of new ripostatin analogs and their (partial) assessment as inhibitors of RNAP from *Mtb*. While some of the compounds were found to inhibit this enzyme with sub-μM IC_{50}s, none of them (including the natural product **2**) showed any measurable antibacterial activity against the pathogen. Like natural ripostatins, several compounds showed significant activity against an efflux-impaired strain of *E. coli*, which has allowed to deduce an SAR for their intrinsic antibacterial potency.

Results and Discussion

One of the key structural characteristics of the ripostatins is the doubly skipped triene motif from C2 to C9, which we felt should be established only late in the synthesis under mild conditions, in order to minimize the risk for migration of the C5–C6 double bond into conjugation with the enoate system. A particularly suitable approach towards the construction of this critical structural motif thus appeared to be macrocyclic ring-closure by

ring-closing olefin metathesis (RCM), which is conducted under very mild conditions in the absence of acids or bases.[20] More specifically, the C5–C6 double bond was selected for disconnection, as this led to a precursor (**4**) with two unencumbered double bonds (Scheme 2).

Scheme 2. Retrosynthesis of ripostatin B (**2**).

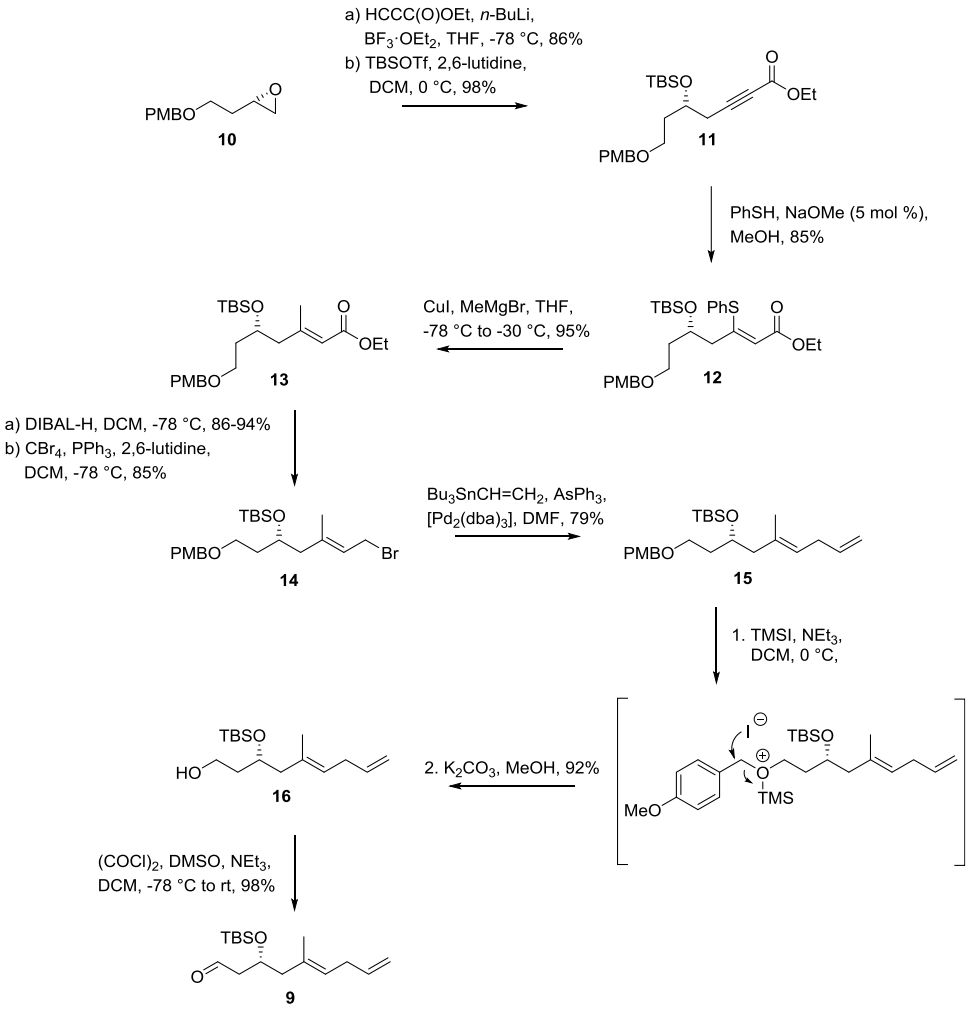


The RCM substrate **4** was envisioned to be accessed from vinyl iodide **5** by Stille coupling with allyltributylstannane. Vinyl iodide **5** can be further disconnected into acid **6** and the partially protected triol **7**. The latter was planned to be accessed through a stereoselective Paterson aldol reaction between methyl ketone **8** and protected β-hydroxy aldehyde **9**, followed by stereoselective *anti* 1,3-reduction of the resulting aldol product and protecting group manipulations. In contrast to most other methods, the Paterson aldol reaction is known to furnish reasonable levels of stereoselectivity also for reactions involving *methyl* ketones[21,22] and, thus, was considered the most promising approach for our system. It should also be noted that the particular order of steps projected for the assembly of **4** from **7** was chosen based on Kirschning's finding that dienoic acids derived from **6** were incompatible with various esterification protocols.[12] Finally, aldehyde **9** was projected to be

derived from chiral epoxide **10** by epoxide ring opening with an appropriate carbon nucleophile and subsequent elaboration of the diene moiety. Epoxide **10** was literature known and could be obtained in 4 straightforward steps from *D*-aspartic acid as the ultimate source of the C11 stereocenter.[23]

For building block **9**, the specific implementation of the strategy outlined above involved treatment of epoxide **10** with the anion of ethyl propiolate in the presence of $BF_3{\cdot}OEt_2$, followed by reaction of the ensuing secondary alcohol with TBSCl, to furnish TBS-ether **11** in 84% overall yield (Scheme 3).

Scheme 3. Synthesis of aldehyde **9**.



The subsequent stereoselective transformation of the triple bond in **11** into the required trisubstituted *E*-configured double bond was based on methodology that was originally developed by Kobayashi and Mukaiyama[24,25] and more recently has been applied to the

synthesis of a closely related variant of enoate **13** by Takamura and co-workers.[26] Thus, the treatment of **11** with thiophenol/NaOMe afforded a *ca*. 8:1 mixture of *Z* and *E* thioenol ethers, from which the desired *Z* isomer **12** could be isolated in yields of around 85% on small scale. On multigram scale, the isomers could not be separated in a single chromatographic run, but separation was performed at the stage of ester **13** or the corresponding alcohol. Reaction of **12** with dimethylcuprate[24,25] then provided enoate **13** in ≥95% yield as a single isomer. The reaction appeared to be very sensitive to the exact experimental conditions, such that the desired product was only obtained if the reaction mixture, after addition of **12** to the suspension of dimethylcuprate at −78 °C, was allowed to warm to −30 °C in the cooling bath over a period of 30 - 40 min. No conversion was observed upon slow warming to room temperature or if **12** was added at −40 °C or 0 °C.

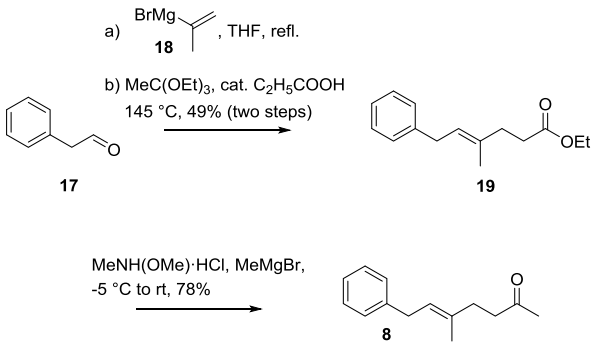
After reduction of ester **13** to the corresponding primary alcohol, the latter was treated with CBr_4 and PPh_3 in the presence of 2,6-lutidine[27] to effect formation of allylic bromide **14** (Scheme 3). The presence of 2,6-lutidine in this Appel-type reaction was crucial, in order to avoid decomposition (presumably caused by HBr). The 1,4-diene unit was then installed by Stille cross coupling[28] of **14** with tributylvinylstannane and $[Pd_2(dba)_3]/AsPh_3$ in DMF, which gave diene **15** in 79% yield. It should be noted that washing with brine was normally avoided during work-up of the bromination reaction, as this led to partial substitution of chlorine for bromine; for all practical purposes, however, the halogen exchange was inconsequential, as the use of mixtures of **14** and the corresponding allylic chloride afforded similar yields in the subsequent Stille reaction as pure **14**.

The final elaboration of **15** into aldehyde **9** then proved to be unexpectedly challenging. An initial attempt to remove the PMB-group by standard oxidative cleavage with DDQ only led to decomposition. This finding was not entirely surprising, as difficulties with the DDQ-mediated cleavage of a PMB-ether in the presence of a 1,4-diene moiety have been reported previously;[29] however, a range of other methods investigated also failed to deliver the desired primary alcohol. Thus, $BF_3{\cdot}OEt_2$/thiophenol[29] led to selective TBS deprotection, $BCl_3{\cdot}SMe_2$[30,31] and $SnCl_4$/thiophenol[32] both induced decomposition, and $AlMe_3$[33] left the molecule unchanged even at elevated temperature (40 °C). A combination of $MgBr_2{\cdot}OEt_2$ and SMe_2, which has been reported by Iwasaki and co-workers as a mild reagent for PMB-removal[34] afforded **15** in scale-dependent yields, i. e., 74% on a 13 mg scale, but only 50% (25% recovered starting material) on an 80 mg scale; thus, this method was also considered

unsuitable. Finally, we discovered that the PMB-group was most efficiently removed by treatment of **9** with TMSI[35] followed by cleavage of the ensuing TMS-ether with K_2CO_3 in MeOH (Scheme 3) which afforded primary alcohol **16** in 92% yield. The reaction likely proceeds via activation of the benzylic oxygen by TMS addition, followed by S_N2-type attack of iodide (Scheme 3). Oxidation of **16** under Swern conditions then completed the synthesis of building block **9**.

The synthesis of ketone **8**, comprising the C14–C24 unit of ripostatin B (**2**), departed from phenylacetaldehyde (**17**) (Scheme 4). The latter was elaborated into unsaturated γ,δ-unsaturated ester **19** in a known two-step sequence that involved addition of 2-propenylmagnesium bromide (**18**) and subsequent reaction of the resulting secondary alcohol with triethyl orthoacetate and Johnson-Claisen rearrangement.[36] Ester **19** was obtained in 49% overall yield.

Scheme 4. Synthesis of methyl ketone **8**.

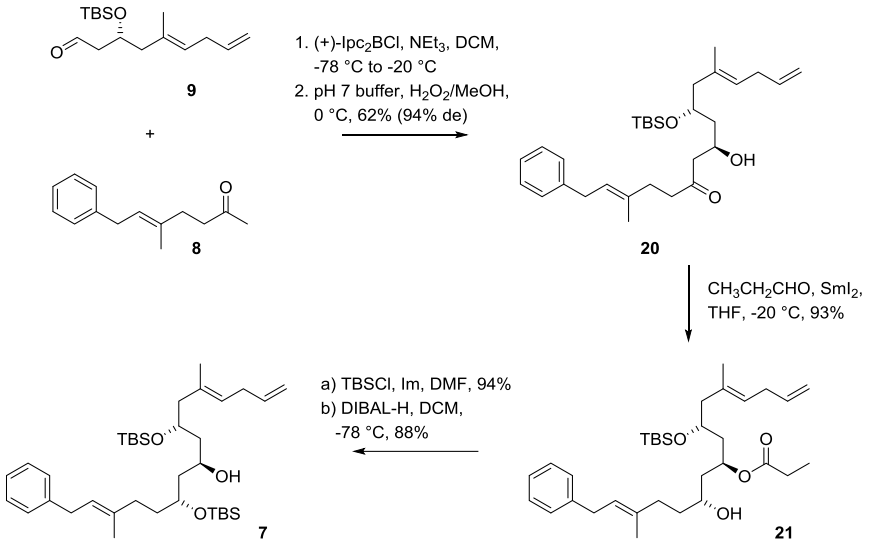


Following a procedure developed by Williams and co-workers,[37] **19** was then directly transformed into methyl ketone **8** in 78% yield with MeNH(OMe) and an excess of MeMgBr. A comparable yield was obtained if the intermediate Weinreb amide was isolated and reacted with MeMgBr in a separate step.

With methyl ketone **8** and aldehyde **9** in hand, we began our investigations into the feasibility of the critical Paterson aldol reaction.[21,22] As alluded to above, we considered this method to be best suited for our system, although it was not clear initially how the β-substituent on the aldehyde would affect the stereochemical outcome of the reaction. In the event, the aldol reaction between the (+)-Ipc_2BCl-derived Ipc_2B-enolate[22] of **8** and aldehyde

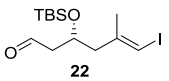
9 (Scheme 5) proceeded with high diastereoselectivity (>10:1 dr), to provide the desired aldol product **20** in 62% yield with a dr of 97:3 after chromatographic purification.

Scheme 5. Building block assembly. Aldol reaction between ketone **8** and aldehyde **9**.



The configuration of the newly formed stereocenter in **20** was verified explicitly at the stage of partly protected triol **7** (*vide infra*); direct Mosher analysis[38,39] of **20** was not feasible due to a pronounced tendency of the Mosher esters to undergo β-elimination.

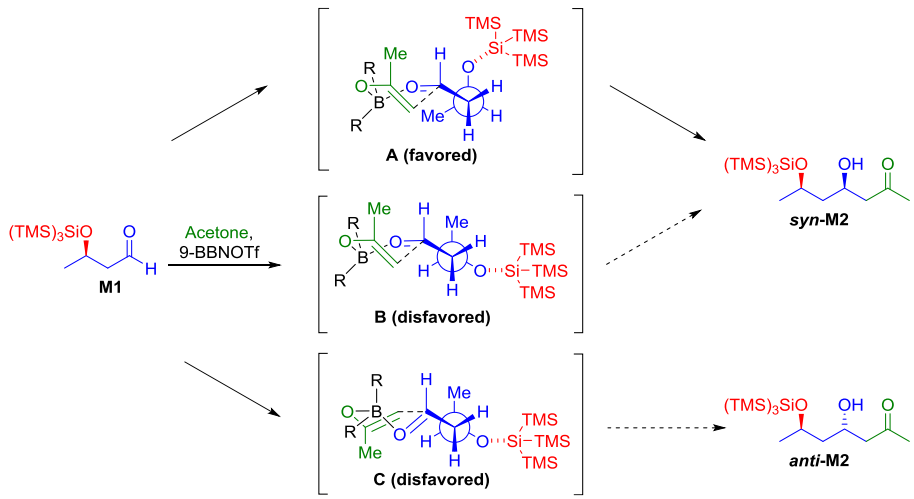
As Paterson aldol additions with methyl ketones, in the absence of additional elements of stereocontrol, typically proceed with selectivities of 50%-80% ee,[21,22] the high selectivity observed for the reaction between **9** and **8** with (+)-Ipc_2Cl as the Lewis acid clearly points to synergistic stereoinduction by the β-substituent of the aldehyde. This assumption is in line with results obtained by Prusov and Tang as part of their work on the synthesis of ripostatin A (**1**),[17] where they found the reaction of **8**, (-)-Ipc_2BCl and aldehyde **22**[4,17] to be completely non-selective.



In contrast, and in agreement with our own observations, formation of the enolborinate of **8** with (+)-Ipc_2BCl and subsequent reaction with **22** gave the corresponding aldol product with high diastereoselectivity (11-15:1 dr),[17] thus clearly indicating the matched nature of

the latter combination of reactants. 1,3-*Syn* induction has previously been reported for additions of methyl ketone-derived enolborinates to aldehydes bearing a silyloxy group at a β-stereocenter.[40,41] Notably, this phenomenon cannot be accounted for by the Evans 1,3-induction model, which predicts for a β-stereocenter of an aldehyde to favor formation of the 1,3-*anti* addition product.[42,43] Only recently, Yamamoto and co-workers have proposed a transition state model that explains the 1,3-*syn* induction in the addition of methyl ketone-derived enolborinates to chiral β-supersilyloxy aldehydes (Scheme 6):[44] DFT calculations for the addition of the enolborinate derived from acetone and 9-BBNOTf to aldehyde **M1** revealed a transition state such as **A** to be preferred, in spite of the C=O group being located *gauche* to both the methyl and the silyloxy group. Transition state **B**, in which gauche interactions are minimized, is about 1.5 kcal/mol higher in energy than **A**; this was suggested to be the result of steric interactions between the silyloxy moiety and the enolate CH_2.[44]

Scheme 6. Proposed transition state models for stereoinduction in the addition of the enolborinate derived from acetone and 9-BBN to β-silyloxy aldehyde **M1**.[44]

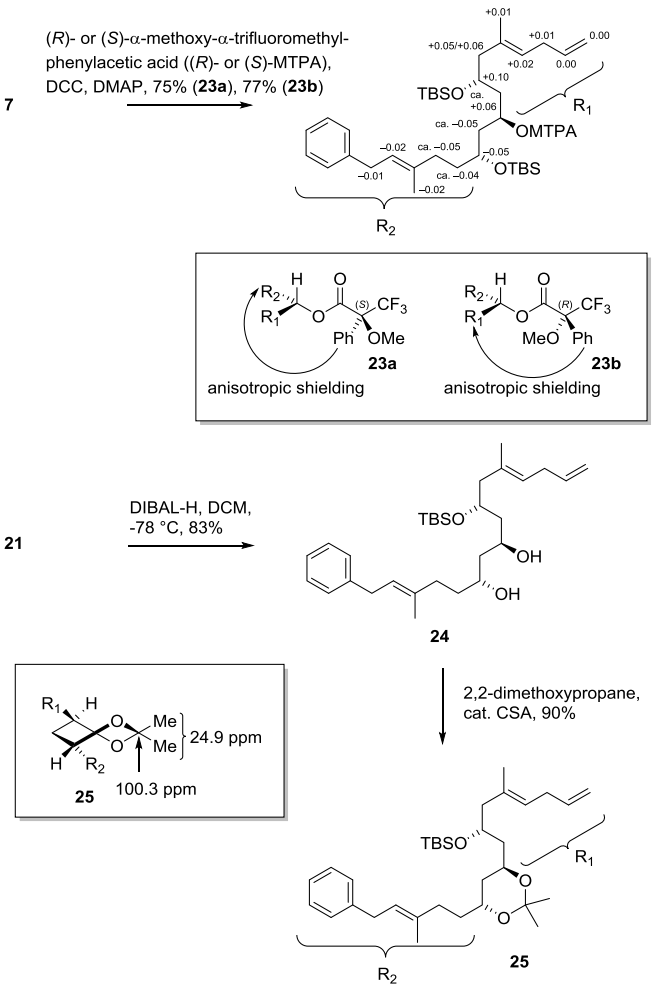


In analogy, the silyloxy group was proposed to interfere with the C=O group in the case of transition state **C** (Scheme 6), which was found to be the lowest energy transition state leading to *anti*-products (about 1 kcal/mol higher in energy than **A**).[44] Unfortunately, no calculations have been performed for aldehydes carrying sterically less demanding β-silyloxy groups (such as OTES, OTBS, OTIPS, OTBDPS). It appears likely, however, that the above considerations could also account for the 1,3-*syn* induction observed in the reaction of **9** and **22**, respectively, with the enolborinate of **8** obtained with (+)-Ipc_2Cl.

In order to establish the stereocenter at C15 (ripostatin numbering), aldol product **20** was submitted to an Evans-Tishchenko reduction (Scheme 5).[45] The reaction proceeded smoothly and furnished the desired hydroxy ester **21** in excellent yield (93%) and with high selectivity (>20:1 dr). Hydroxy ester **21** was then elaborated into bis-TBS-protected triol **7** by reaction with TBSCl and subsequent reduction of the ester moiety with DIBAL-H (Scheme 5); **7** was obtained in 82% yield from **21**.

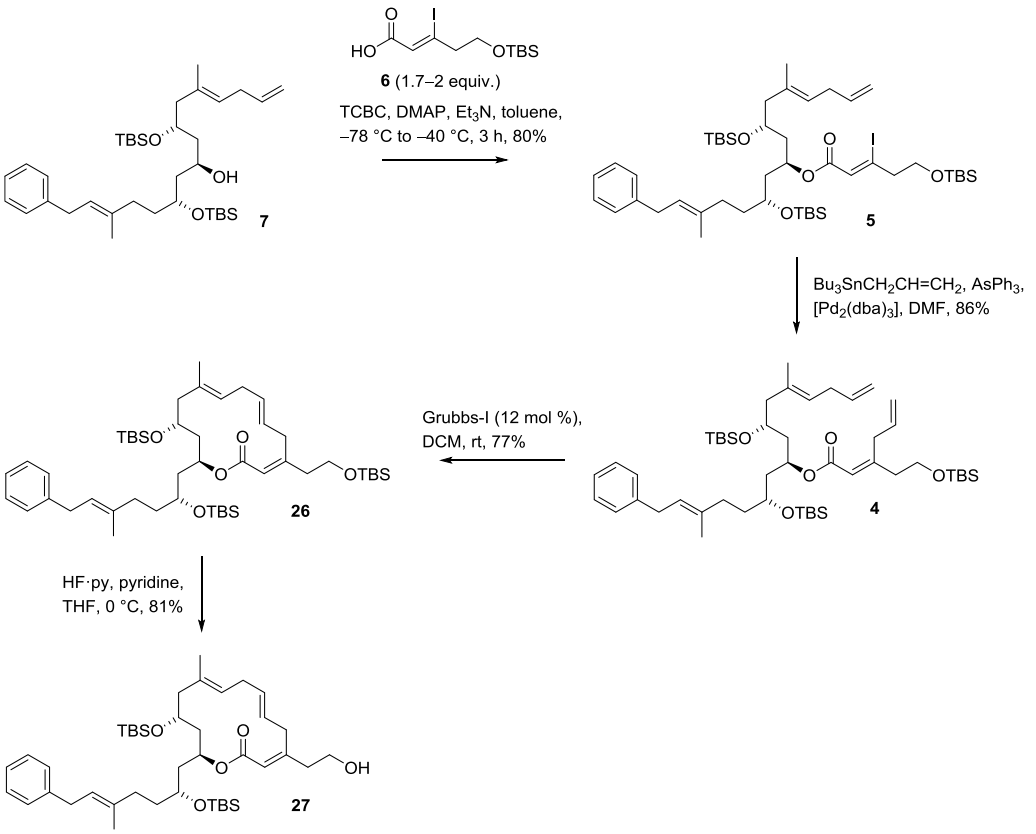
As alluded to above, the configuration of the C13 stereocenter was verified by Mosher ester analysis of **7** (Scheme 7).[38,39] Furthermore, removal of the ester moiety in **21** followed by ketalization with 2,2-dimethoxypropane furnished a ketal (**25**) suitable for stereochemical analysis according to Rychnovsky, which also allowed unambiguous assignment of the configuration of the stereocenter at C15 as *S*[46,47] (Scheme 7).

Scheme 7. Configurational assignment of the C13 and C15 stereocenters.



With **7** in hand, we turned our attention to its esterification with acid **6**,[48] which proved to be far more difficult than anticipated. A series of esterification methods were investigated, including the use of Mukaiyama's salt,[49] DCC (without and with DMAP),[50] PyBOP[51] or TBTU[52] as coupling agents, but none of these methods provided the desired ester in notable quantities. Appreciable amounts of ester **5** (Scheme 8) (< 30% yield) were obtained only upon preactivation of **6** with 2,4,6-trichlorobenzoyl chloride (TCBC) according to Yamaguchi and co-workers[53] und subsequent reaction of the mixed anhydride with **7**. Closer investigation of the reaction conditions revealed that immediate mixing of all components (**6**, **7**, TCBC, Et_3N, and DMAP), rather than pre-activating the carboxylic acid, led to a slight increase in yield to 35% (with *ca*. 20% of **7** recovered). Interestingly, the reaction proved to be very fast, reaching maximum conversion in less than 20 min at room temperature. This observation led us to speculate that the incomplete conversion was caused by decomposition of the anhydride intermediate and we started to investigate lower reaction temperatures.

Scheme 8. Completion of building block assembly and macrocyclization.



These experiments showed that mixing all components at −78 °C and then allowing the reaction mixture to warm to −20 °C, gave **5** in isolated yields of around 60% (with 20-25% of **7** recovered). Finally, we discovered that the temperature ideally had to be kept between −40 and −50 °C (after mixing the reactants at −78 °C). In this temperature regime, maximum conversion was reached within 2-3 h and the desired ester **5** could be isolated in 80% yield (Scheme 8); in addition, ca. 8% of alcohol **7** were also recovered.

Having established a reliable and high-yielding esterification protocol, the second 1,4-diene unit in **4** was installed in 86% yield by Stille coupling of **5** and tributylallylstannane (Scheme 8). The stage was thus set for the crucial ring-closure reaction. The efficiency of the RCM was initially assessed in a series of small-scale experiments (*ca*. 2 mg of **4**) with either Grubbs-II or Hoveyda-Grubbs-II catalyst,[20] where conversion was monitored by low-resolution ESI-MS; after concentration, the reaction products were further analyzed by TLC and, in some cases, also by ^{1}H-NMR spectroscopy. With both catalysts, rapid consumption of starting material was observed, regardless of solvent (DCM, 1,2-dichloroethane or toluene) and temperature (room temperature to 80 °C). Unfortunately, three close spots were usually observed on TLC (after concentration).

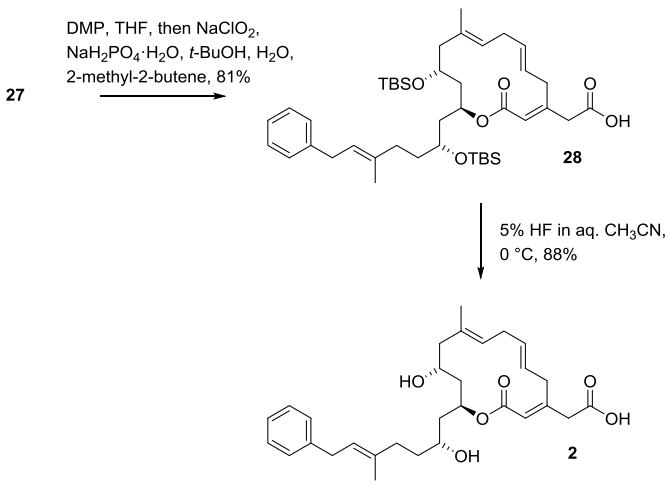
In light of the rapid reaction rates with the ruthenium-based second-generation catalysts, it appeared that the less reactive first-generation catalysts might still show practically useful conversion rates. In the event, the Grubbs-I catalyst gave reaction rates comparable to the ones observed for second-generation catalysts. At the same time, the reaction was cleaner, allowing isolation of macrocycle **26** in 77% yield as a single isomer (Scheme 8). The *E* configuration of the newly formed C5–C6 double bond was confirmed by ^{1}H-NMR spectroscopy (J = 14.8 Hz). Best results were obtained if the reaction was not allowed to reach completion, which could be achieved by using less than 15 mol-% of the catalyst. Otherwise, formation of side products was observed. Interestingly, and in contrast to the Grubbs-I catalyst, the Hoveyda-Grubbs-I catalyst left the starting material unaffected. Noteworthy, we noticed decomposition of initial batches of macrocycle **26** upon storage even at low temperature (about 50% decomposition within 72 hours at −20 °C), which we presumed was caused by ruthenium-derived by-products. Following a procedure developed by Georg and co-workers for the removal of such by-products,[54] the RCM reaction was thus quenched by the addition of DMSO (50 equivalents relative to the catalyst) and stirring was continued for at least 12 hours, then the reaction mixture was concentrated and purified by

silica gel chromatography. If this procedure was applied, **26** could be stored for 48 hours at −20 °C without loss in purity. Nonetheless, as a rule, **26** was usually directly subjected to TBS removal without storage.

Selective cleavage of the primary TBS-ether was best achieved with buffered HF·pyr (Scheme 8), which was superior to TASF (decomposition), AcOH/THF/H_2O 1:2:1 (slow reaction) or $NaIO_4$,[55] and delivered the desired primary alcohol **27** in 81% yield. While $NaIO_4$ allowed deprotection of the primary TBS-ether with good selectivity on a scale smaller than 10 mg of **26** (ca. 70% yield), extended reaction times were required even on slightly larger scale, which were also associated with over-deprotection (i. e. 50% yield on a 25 mg scale).

The final conversion of **27** into ripostatin B (**2**) in a first step required oxidation of the free hydroxy group to the corresponding carboxyl functionality (Scheme 9). In order to circumvent handling of the intermediate aldehyde, whose carbonyl group is part of a vinylogous malonate-type system and which we thus presumed to be highly labile, we initially focused on methods that should directly deliver acid **28**. Unfortunately, however, TEMPO/$PhIOAc_2$,[56] TPAP/NMO·H_2O[57] as well as PDC all led to decomposition of the starting material.

Scheme 9. Side chain oxidation and final deprotection.



In light of the failure of direct oxidation methods, we decided to investigate the feasibility of two-step protocols. These experiments revealed that the Dess-Martin periodinane (DMP)[58] afforded very clean oxidation of **27** to the intermediate aldehyde within 5 min, as demonstrated by conducting the reaction in an NMR tube (in THF-d_8). After aqueous work-

up (saturated aqueous $NaHCO_3$/saturated aqueous $Na_2S_2O_3$), however, numerous side products were visible on TLC and subsequent Pinnick oxidation[59,60] of this material furnished **28** in very low yields only. This finding confirmed our original suspicions about the labile nature of the aldehyde derived from **27** and led us to perform the final oxidation of the aldehyde without any work-up of the DMP oxidation by simply adding the necessary Pinnick reagents to the reaction mixture. Gratifyingly, conducting the reactions in this fashion enabled isolation of acid **28** in 81% yield (Scheme 9). Final cleavage of the secondary TBS-ethers was best accomplished with 5% HF in aqueous CH_3CN, furnishing ripostatin B (**2**) in 88% yield (Scheme 9). Other protocols, such as the use of HF·pyr, AcOH/THF/H_2O 3:1:1, or $NaIO_4$[55] gave distinctly less clean reactions.

A comparison of the NMR data for synthetic **2** with the published data for the natural product revealed certain deviations in a number of signals in both the ^{1}H- ($\Delta\delta > 0.1$ ppm for three protons) and the ^{13}C-NMR ($\Delta\delta > 0.5$ ppm for five carbons) spectra, especially for the C11–C15 region. However, our ^{1}H-NMR spectrum fully matched with the one that has been obtained for natural **2** by the group of Prusov,[14] as well as with the ones for synthetic **2** from both Prusov[14] and Christmann.[13] Furthermore, HPLC chromatograms of our synthetic **2** and natural ripostatin B were superimposable (experiments carried out in the group of Prof. Rolf Müller at the Helmholtz Institute for Pharmaceutical Research Saarbrücken, Germany, data not shown).

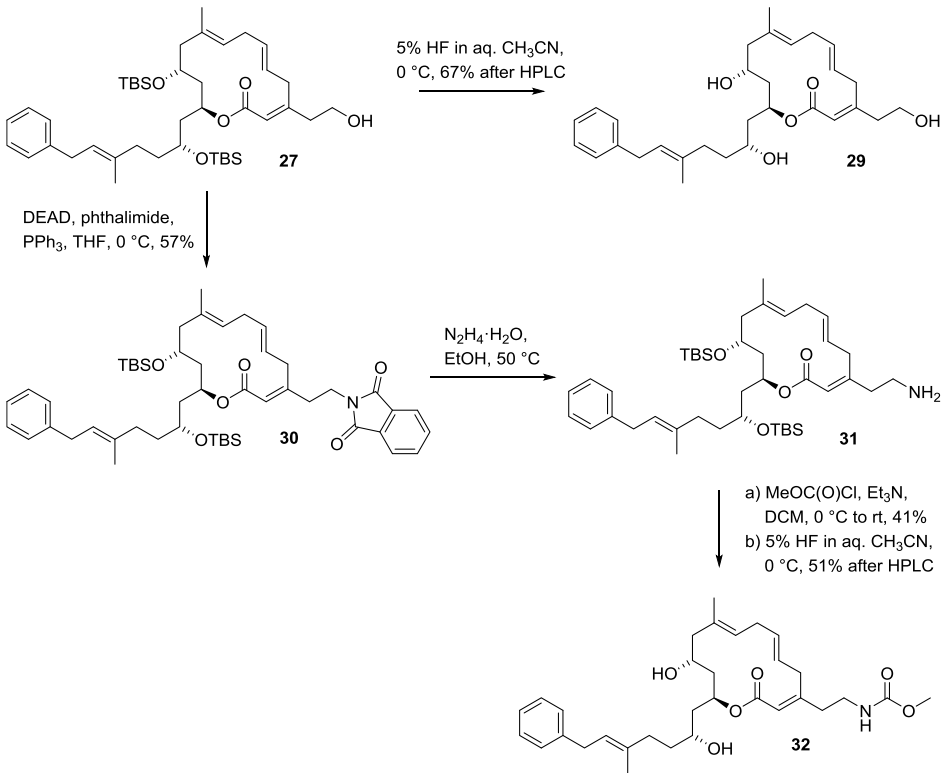
As alluded to in the Introduction, so far, specific SAR data for ripostatins are available only from the recent work of Prusov, Ebright and co-workers on a limited number of synthetic analogs.[17] While a few semisynthetic ripostatin derivatives were reported in the context of the original isolation work, no numerical data were provided for these compounds;[2] rather, the methyl ester of **2**, a C15-2-phenylbutyryloxy derivative of **2**, and the methyl ketal form of **1** were simply classified as "inactive", while the C15-epimer of **2** was stated to be equally active as natural **2**, without specifying which type of activity these conclusions related to. The investigations conducted by Prusov and Ebright suggest that the active form of ripostatin A (**1**) is the bicyclic hemiketal, based on the assessment of RNAP inhibition (for *E. coli* as well as *S. aureus* RNAP) and antibacterial activity against *E. coli* D21f2tolC and *S. aureus* ATCC 12600. Prusov and Ebright also prepared the C14-difluoro analogs of **2** and 15-*epi*-**2**, respectively, and found those two compounds to exhibit markedly different biological activity, with C14-difluoro-**2** being *ca*. 20-fold more potent than its C15-epimer. This finding

stands in contrast to the statement in the isolation paper about the similar activity of **2** and C15-*epi*-**2**. Finally, Prusov and Ebright found both natural ripostatins to be inactive against RNAP from *Mtb* (*vide infra*).

Our own work on ripostatin analogs has focused (a) on the replacement of the carboxylic acid group by other polar functionalities, as we speculated that the charge associated with this group at neutral pH might hamper cell wall and/or membrane penetration, an effect that has already been noted decades ago for rifamycin B;[61,62] and (b) on evaluating modifications of the C13-side chain that would reduce the overall lipophilicity of the corresponding analogs (relative to ripostatin B (**2**)), again hoping that this would improve cell wall penetration.

The first analog prepared in the context of these SAR evaluations was triol **29** (Scheme 10), as this was easily accessible from the bis-TBS-ether **27**. Thus, treatment of **27** with 5% HF in aqueous acetonitrile furnished analog **29** in 67% yield after HPLC purification (Scheme 10).

Scheme 10. Synthesis of C3-side chain-modified analogs.



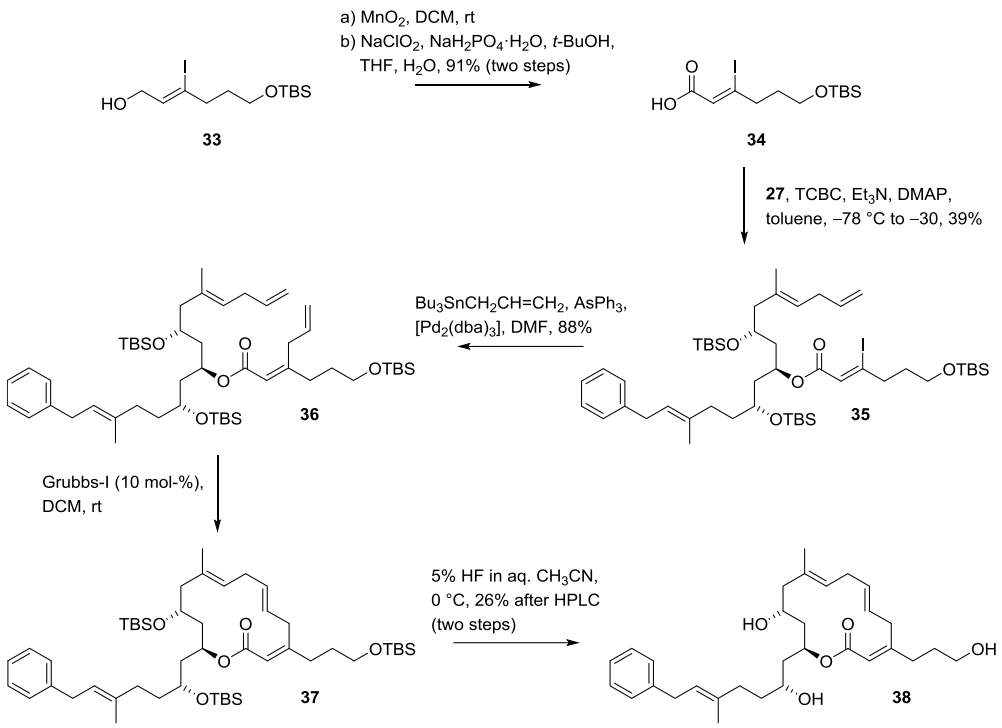
While not investigated, **29** should also have been accessible by global deprotection of tris-TBS-ether **26**, an approach that was later applied in the preparation of related analogs (*vide infra*).

Advanced intermediate **27** was also elaborated into analog **32**, bearing a C3-side chain terminating in a methyl carbamate moiety (Scheme 10). This analog had emerged as a plausible and attractive target from preliminary docking studies, based on the X-ray crystal structure of RNAP from *T. thermophilus*[10] with the bound natural product myxopyronin[7] using GOLD.[63] The docking suggested a binding mode of **2** where the carboxy group of the C3-side chain would overlap with the methylcarbamate moiety in bound myxopyronin, hence leading to the design of analog **32**.

Intermediate **27** was first converted into primary amine **31** by Mitsunobu reaction with phthalimide followed by treatment of the ensuing *N*-substituted phthalimide **30** with ethanolic hydrazine (Scheme 10). Treatment of crude **31** (*ca*. 80% pure) with methyl chloroformate in the presence of Et_3N followed by removal of the TBS-protecting groups under the previously established conditions then furnished analog **32** in 21% overall yield from **30** after HPLC purification.

As will be discussed below, analog **29** was found to be biologically more active than ripostatin B (**2**), which also led us to investigate homologated analog **38** with an extended C3-side chain, in order to assess the effect of side chain length on biological activity (Scheme 11). The synthesis of **38** followed the same overall route that we had established for the synthesis of ripostatin B (**2**), with homologated acid **34** substituting for **6** in the synthesis of the natural product. Acid **34** was obtained in 5 steps and 41% overall yield from 1-pentyn-5-ol *via* known propargylic alcohol **33**.[64]

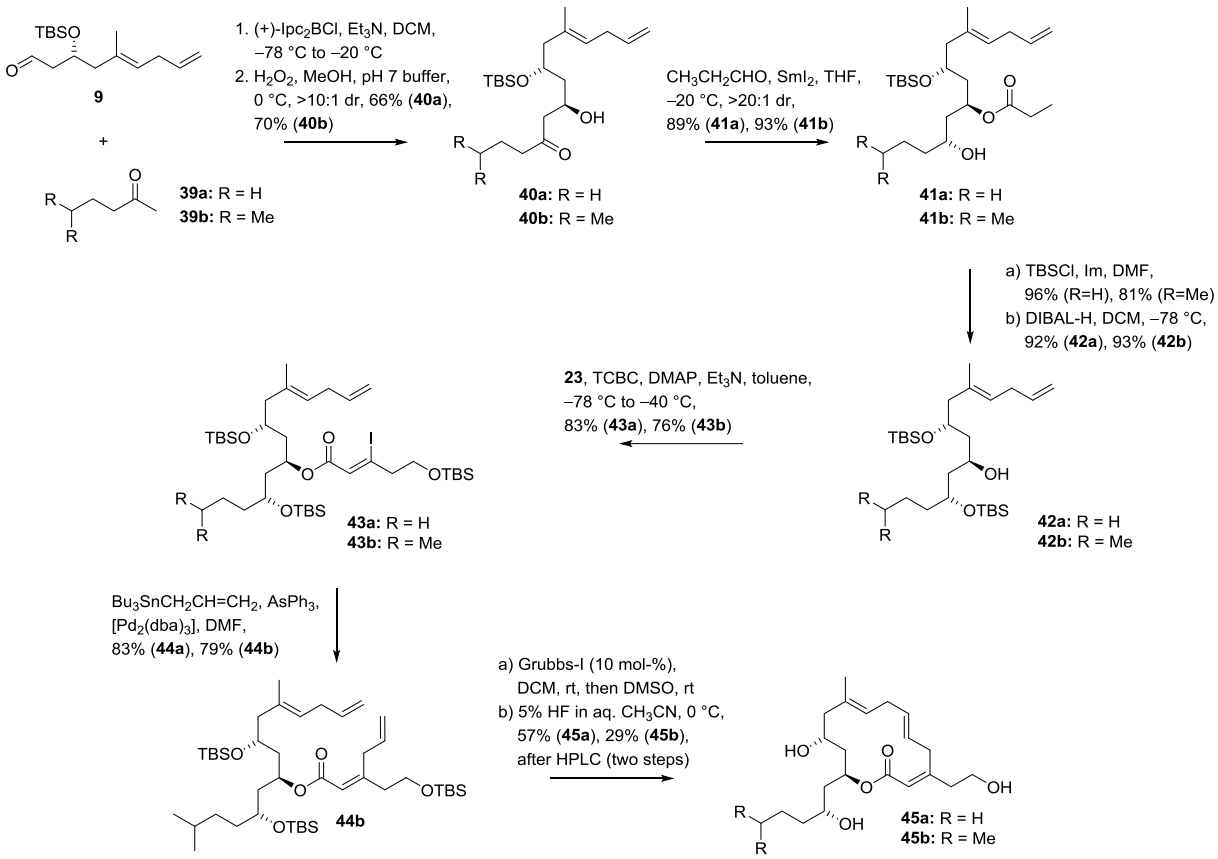
Scheme 11. Synthesis of C3-side chain-extended analog **38**.



Our strategy towards ripostatin B analogs with reduced lipophilicity entailed truncation of the phenyl-bearing C13-side chain to a hydroxy-substituted pentyl or isoheptyl substituent, respectively (analogs **45a** and **45b**; Scheme 12). In light of the sustained biological activity of **29**, analogs incorporating a hydroxyethyl group at C3, rather than the natural side chain were targeted for an initial evaluation.

The synthesis of analogs **45a** and **45b** was conceptually analogous to the total synthesis of ripostatin B (**2**), which served as an efficient blueprint for analog generation. Thus, the addition of the enolborinates derived from commercially available ketones **39a** or **39b** by reaction with (+)-Ipc_2BCl to aldehyde **9** (Scheme 3) afforded β-hydroxy ketones **40a** and **40b** in 66% and 70% yield, respectively, and with high diastereoselectivities (>10:1 dr) (Scheme 12). Of note, in both cases the excess ketone could be readily removed by rotary evaporation, allowing more straightforward purification than for hydroxy ketone **20** (leading to the natural product).

Scheme 12. Synthesis of ripostatin analogs with truncated C13-side chains.



The elaboration of **40a/b** into **42a/b** was uneventful for both series and so was the low-temperature Yamaguchi esterification, which afforded high yields of both **43a** and **43b** (83% and 76%, respectively). After Stille cross coupling, the RCM precursors **44a/b** were treated with Grubbs-I catalyst to effect macrocyclization. As discussed above, the reactions were not allowed to go to completion and a work-up protocol involving the addition of DMSO to the reaction mixture was applied in order to remove ruthenium by-products.[54] Separation of the macrocycle from unreacted starting material was not attempted, rather, after filtration through a plug of silica gel, the mixture was immediately submitted to global deprotection. After purification by preparative RP-HPLC, **45a** and **45b** were obtained in 29% and 57% yield, respectively, for the two-step sequence from **44a/b**.

In order to assess the intrinsic antibacterial activity of ripostatin analogs, all compounds were tested against *E. coli* JW5503-1 (originating from the Keio collection, and supplied by the Coli Genetic Stock Center, CGSC-11430), which (among other changes), lacks the Tol C efflux channel (*ΔtolC732::kan*).[65] As can be seen from the data summarized in Table 1,

analogs **29**, **32**, and **38**, harboring modified C3-side chains, are more potent against *E. coli* JW5503-1 than either the parent compound ripostatin B (**2**) or ripostatin A (**1**).

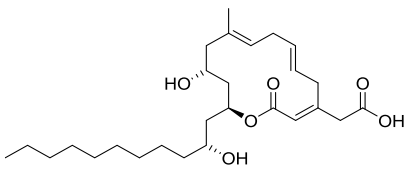
Table 1. Antibacterial activity of natural ripostatins and selected analogs against efflux-deficient *E. coli* JW5503-1.

Compound	*E. coli* JW5503-1 MIC (μg/mL)
Ripostatin B (2)	3.125 - 6.25
Ripostatin A (1)[a]	6.3 - 12.5
29	0.39 - 0.78
38	0.78 - 1.56
32	1.56 - 3.125
45a	>100
45b	50 - 100

[a]Ripostatin A (**1**) was a kind gift of Prof. Rolf Müller (Helmholtz Institute for Pharmaceutical Research (HIPS), Saarbrücken, Germany).

These data clearly suggest that the carboxylate group in ripostatin B (**2**) is not an essential requirement for intrinsic antibiotic activity. In contrast, truncated analogs **45a** and **45b** showed no meaningful activity (MICs >50 μg/mL), thus indicating that a hydrophobic tail of sufficient length is required for ripostatin-type analogs, in order to display antibacterial activity. In light of their poor (or non-existent) intrinsic antibiotic activity, truncated analogs **45a** and **45b** were not further investigated.

Interestingly, as we discovered only very recently, a natural product with a similar structure as ripostatin B (**2**) was reported already in 1988 by Singh *et al*.[66] This compound, named aerocavin (**46**), was isolated from a non-pigmented strain of *Chromobacterium violaceum* and it displays the same relative configuration as ripostatin B (**2**).



Aerocavin (46)

While the absolute configuration of **46** has not been secured, its specific rotation has the same sign as that of **2** ($[\alpha]_D^{22}$ = +25.1° (c 0.9 in MeOH) *vs*. $[\alpha]_D^{25}$ = +35.7 (c 1 in MeOH) for **2**[2]), which makes it very likely that the two compounds also have the same absolute

configuration. Aerocavin (**46**), whose C13-side chain has the same length as that of ripostatin B (**2**), has been reported to be moderately active against different strains of *S. aureus*, with MICs similar to those that have been obtained for ripostatin B (**2**) (3.1 - 6. 3 μg/mL). The compound was found to be inactive against wild-type *E. coli*.

As we were particularly interested in the potential of ripostatins to serve as lead structures for the development of new antitubercular agents, ripostatin B (**2**) and analog **29** were also assessed for activity against *Mtb*. Disappointingly, however, both **2** and **29** proved to be inactive against *Mtb* H37Rv or *Mycobacterium smegmatis* (MICs >100 μg/mL). These findings are in line with the data reported recently by Prusov and Ebright.[4] However, in contrast to Prusov and Ebright, who have reported both ripostatins to be inactive against RNAP from *Mtb*, we have found good activity of **2** and **29** against *Mtb* RNAP in a promoter non-specific transcription assay using calf thymus DNA as a template;[67] IC_{50} values were 2.8 μM for **2** and 0.44 μM for **29** *vs*. 0.1 μM for rifampicin. Using the same assay format, IC_{50} values obtained against *E. coli* RNAP were 0.2 μM for **2**, and 0.11 μM for rifampicin; the value for **2** is about one order of magnitude higher than the one reported recently by Prusov and Ebright (IC_{50} of **2** against *E. coli* RNAP of 0.018 μM).[4] It should be noted, however, that literature IC_{50} values for bacterial RNAP inhibition by ripostatins vary significantly, even if reported by the same laboratory. Thus, the IC_{50} value of **1** against *E. coli* RNAP reported in ref. 10 is 0.6 μM (i. e. >20-fold higher than in ref. 4). For *S. aureus* RNAP the IC_{50}s for **1** in ref. 4 and ref. 10 are 0.88 μM and 6 μM, respectively.

The reasons for the discrepancy between our own data for *Mtb* RNAP inhibition by ripostatin B (**2**) and those reported by Prusov and Ebright are unclear at this point but may be related to different assay set-ups. If so, the question arises which of the assays employed is the more relevant; while one might argue that the lack anti-*Mtb* activity of **2** indicates that the compound is a poor inhibitor of *Mtb* RNAP indeed, this conclusion is not inevitable. Obviously, the possible RNAP inhibitory activity of **2** could be obscured by poor penetration into *Mtb* (due to rapid efflux[68,69] or impaired influx[70] or both), as is the case for *E. coli*. We have tried to address this question by exposing *Mtb* H37Rv to ripostatin B (**2**) in the presence of sub-inhibitory concentrations (one fourth of their MIC) of the efflux inhibitors carbonyl cyanide *m*-chlorophenyl hydrazone (CCCP), chlorpromazine (CPZ) and phenylalanyl-arginine-β-naphthylamide (PAβN); in no case, however, could any antibacterial activity be observed (MIC >100 μg/mL). In contrast, an MIC of 12.5 μg/mL was obtained for inhibition of *E. coli*

(ATCC 25932) in the presence PAβN, a competitive inhibitor of the AcrAB-TolC system[71] (*vs*. MIC >100 μg/mL for wild-type *E. coli*). Interestingly, the addition of 0.01% sodium dodecyl sulfate (SDS), a known chemical penetration enhancer,[72] to the growth medium led to detectable (but still high) MIC values for ripostatin B (**2**) and analog **29** against *Mtb* H37Rv (MIC *ca*. 50 μg/mL), suggesting that limited cell wall permeability might at least partly contribute to the lack of antimycobacterial activity of ripostatin B (**2**) and related structures. Finally, preliminary stability experiments with analog **29** in Middlebrook 7H9 broth medium (used in this work for determination of *Mtb* susceptibility to ripostatins) have indicated that the complete lack of activity of the compound against *Mtb* H37Rv is not caused by massive degradation in the culture medium.

It remains to be investigated if compounds such as **29**, **32**, and **38**, which lack an ionizable group in the C3 side chain, exhibit more potent antibacterial activity than **2** against bacteria with intact efflux systems.

Conclusions

In conclusion, we have developed a successful total synthesis of the myxobacterial natural product ripostatin B (**2**), which provided the target molecule in 21 steps (longest linear sequence, starting from *D*-aspartic acid) and 3.6% overall yield. The molecule's Achilles heel, the doubly skipped C2–C9 triene motif, was installed at a late stage of the synthesis by ring-closing olefin metathesis with Grubbs-I catalyst, which afforded a cleaner reaction than second-generation catalysts and produced macrocycle **26** in 78% yield as the pure *E* isomer at C5–C6.

A major hurdle to overcome was the esterification of acid **6** with alcohol **7**, a reaction that failed to produce synthetically useful yields under a plethora of conditions examined. This problem could finally be solved by employing a low-temperature Yamaguchi protocol, which delivered ester **5** in 80% yield. Other key steps in the assembly of the RCM precursor were a Paterson aldol reaction to install the stereocenter at C13 and a reduction under Evans-Tishchenko conditions to set the stereocenter at C15.

The total synthesis provided a conceptual blueprint for the synthesis of an analog with an extended C3 side chain (**38**) and two ripostatin B variants with truncated C13-side chains. While analogs **29**, **32**, and **38** were active against the efflux-deficient *E. coli* strain JW5503-1, neither ripostatin B (**2**) nor **29**, as the most potent inhibitor of *E. coli* JW5503-1 showed any

activity against *Mtb* H37Rv. While the data available at this point may be interpreted such as to suggest that **2** lacks sufficient inhibitory activity again *Mtb* RNAP, this conclusion is still premature, as efflux phenomena in *Mtb* are highly complex[68,69] and most likely have not been fully addressed by our experiments. Testing of **29**, **32**, and **38** against other species of bacteria has not been performed yet.

We continue to work on new ripostatin analogs, in order to identify compounds whose intrinsic antibacterial activity, as displayed against efflux-deficient strains of *E. coli*, will also become manifest in bacteria with intact efflux systems. The results of these efforts will be reported in due course.

Experimental Section

General experimental methods. All non-aqueous reactions were performed under an argon atmosphere using flame-dried glassware and standard syringe/septa techniques.

CH_2Cl_2 (DCM), THF and Et_2O used for reactions were distilled under argon prior to use (DCM from CaH_2, THF and Et_2O from Na/benzophenone). All other absolute solvents were purchased as anhydrous grade from Fluka (puriss.; dried over molecular sieves; H_2O <0.005%) and used without further purification unless otherwise stated. Solvents for extractions, flash column chromatography (FC) and thin layer chromatography (TLC) were purchased as commercial grade and distilled prior to use. All other commercially available reagents were used without further purification unless otherwise stated. Reactions were magnetically stirred and monitored by TLC performed on Merck TLC aluminum sheets (silica gel 60 F254). Spots were visualized with UV light (λ = 254 nm) or through staining with $Ce_2(SO_4)_3$/phosphomolybdic acid/H_2SO_4 (CPS), vanillin/H_2SO_4/EtOH or $KMnO_4/K_2CO_3$. Chromatographic purification of products (FC) was performed using Fluka silica gel 60 for preparative column chromatography (particle size 40-63 µm).

Melting points were obtained in open capillary tubes using a Büchi melting point apparatus B-540 and are uncorrected.

^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$, CD_3OD or C_6D_6 on a Bruker AV-400 400 MHz or on a Bruker AV-500 500 MHz spectrometer at room temperature. Chemical shifts (δ) are reported in ppm and are referenced to chloroform (δ 7.26 ppm for ^{1}H, δ 77.16 ppm for ^{13}C), MeOH (δ 3.31 ppm for ^{1}H, δ 49.00 ppm for ^{13}C) or benzene (δ 7.16 ppm for ^{1}H, δ 128.06 ppm for ^{13}C). All ^{13}C-NMR spectra were measured with complete proton decoupling. Data for

NMR spectra are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal, *J* = coupling constant in Hz.

Infrared spectra (IR) were recorded on a Jasco FT/IR-6200 instrument. Resonance frequencies are given as wavenumbers in cm^{-1}.

Optical rotations were measured on a Jasco P-1020 polarimeter at the sodium D line with a 10 or 100 mm path length cell and are reported as follows: $[\alpha]_D^{24}$: (concentration (g/100 mL), and solvent).

High resolution mass spectra (HRMS) were recorded on a Bruker maXis ESI-Qq-TOF-MS or on a Waters Micromass AutoSpec Ultima EI-Sector-MS, respectively, by the ETH Zürich MS service (Louis Bertschi, Rolf Häfliger and Oswald Greter under the direction of Dr. Xiangyang Zhang).

For analytical **HPLC** the following combination of devices by VWR HITACHI was used: column oven L-2350, PDA detector L-2455, autosampler L-2200, pump L-2130. A reversed phase Waters Symmetry C18 column (3.5 µm, 4.6x100 mm) or chiral, normal phase Daicel Chiralpak AD-H (6 µm, 4.6x150 mm) were used. For preparative HPLC a device by Gilson equipped with a Waters SymmetryPrep C18 column (5 µm, 19x100 mm, room temperature) was used.

Ethyl (*R*)-5-hydroxy-7-((4-methoxybenzyl)oxy)hept-2-ynoate (E-1): To a solution of ethyl propiolate (5.1 mL, 49.5 mmol, 2.0 equiv.) in THF (200 mL) at –78 °C was added dropwise *n*-BuLi (1.6m in hexane, 29.4 mL, 47.0 mmol, 1.9 equiv.). The resulting yellow solution was stirred at –78 °C for 20 min, then a solution of epoxide **4** (5.15 g, 24.7 mmol, 1.0 equiv.) in THF (50 mL) was added at a rate such that that the internal temperature did not rise above −70 °C, followed by neat $BF_3{\cdot}OEt_2$ (7.6 mL, 61.8 mmol, 2.5 equiv.). After being stirred for 45 min at –78 °C, the orange solution was quenched by the addition of MeOH (30 mL). Sat. aq. $NaHCO_3$ (50 ml), water (50 mL) and EtOAc (150 mL) were next added (the pH should be >7). The phases were separated and the aqueous layer was extracted with EtOAc (3x100 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 2:1) afforded alcohol **E-1** (6.51 g, 21.2 mmol, 86%) as a yellow oil.

TLC: R_f = 0.30 (hexane/EtOAc 2:1, UV, CPS); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.26-7.21 (m, 2H), 6.90-6.85 (m, 2H), 4.45 (s, 2H), 4.20 (q, *J* = 7.1, 2H), 4.08-3.99 (m, 1H), 3.80 (s, 3H), 3.75-3.68

(m, 1H), 3.67-3.60 (m, 1H), 3.32 (d, *J* = 3.5, O*H*), 2.56 (dd, *J* = 17.2, 5.8, 1H), 2.49 (dd, *J* = 17.2, 6.6, 1H), 1.94-1.78 (m, 2H), 1.29 (t, *J* = 7.1, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 159.5, 153.7, 129.8, 129.5, 114.0, 85.8, 75.0, 73.2, 69.5, 68.4, 62.0, 55.4, 35.4, 27.3, 14.1; **IR** (thin film): ν 3454, 3010, 2980, 2938, 2910, 2864, 2837, 2234, 1705, 1612, 1513, 1464, 1366, 1301, 1244, 1173, 1070, 1032, 847; **HRMS** (ESI): calculated for $C_{17}H_{26}NO_5$ $[M+NH_4]^+$: 324.1805, found 324.1799; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: −1.0 (c 0.5 in $CHCl_3$).

TBS-ether 11: To a solution of alcohol **E-1** (6.49 g, 21.2 mmol, 1.0 equiv.) in DCM (150 mL) at 0 °C was added 2,6-lutidine (4.2 mL, 36.0 mmol, 1.7 equiv.) followed by TBSOTf (5.9 mL, 27.5 mmol, 1.3 equiv.). The pale yellow solution was stirred at 0 °C for 30 min. Water (50 mL) was added, the phases were separated and the aqueous layer was extracted with DCM (3x50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 10:1) afforded silylether **11** (8.78 g, 20.9 mmol, 98%) as a colorless oil.

TLC: R_f = 0.73 (hexane/EtOAc 2:1, UV, CPS); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.28-7.22 (m, 2H), 6.90-6.85 (m, 2H), 4.43 (d, *J* = 11.4, 1H), 4.38 (d, *J* = 11.4, 1H), 4.21 (q, *J* = 7.1, 2H), 4.09-4.00 (m, 1H), 3.81 (s, 3H), 3.52 (dd, *J* = 6.8, 5.6, 2H), 2.52 (dd, *J* = 17.2, 6.2, 1H), 2.47 (dd, *J* = 17.1, 5.7, 1H), 1.95-1.85 (m, 1H), 1.85-1.75 (m, 1H), 1.29 (t, *J* = 7.1, 3H), 0.88 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 159.3, 153.8, 130.6, 129.4, 113.9, 86.5, 74.8, 72.8, 67.6, 66.2, 61.9, 55.4, 37.1, 28.1, 25.9, 18.1, 14.2, −4.5, −4.7; **IR** (thin film): ν 2953, 2930, 2893, 2856, 2238, 1710, 1613, 1586, 1513, 1472, 1464, 1366, 1302, 1245, 1173 1092, 1072, 1035, 1005, 917; **HRMS** (ESI): calculated for $C_{23}H_{37}O_5Si$ $[M+H]^+$ 421.2405, found 421.2418; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: −13.4 (c 0.7 in $CHCl_3$).

Thioether 12: To a solution of alkyne **5** (8.78 g, 20.9 mmol, 1.0 equiv.) in MeOH (100 mL) was added thiophenol (2.4 mL, 23.0 mmol, 1.1 equiv.) and sodium methoxide (56.4 mg, 1.04 mmol, 0.05 equiv.). The reaction was stirred at room temperature for 14 h before being filtered through a plug of celite (eluting with EtOAc). The filtrate was concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 10:1) gave thioether **12** in quantitative yield as an about 8:1 mixture of (*Z*/*E*)-isomers. On small scale, it was possible to separate the isomers in a single chromatographic run, affording **(*Z*)-12** in yields of about 85%. Analytical data are for pure **(*Z*)-12**.

TLC: R_f = 0.36 (hexane/EtOAc 4:1, UV, CPS); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.52-7.48 (m, 2H), 7.38-7.28 (m, 3H), 7.24-7.18 (m, 2H), 6.90-6.85 (m, 2H), 5.90 (s, 1H), 4.28 (s, 2H), 4.27-4.14 (m, 2H), 3.81 (s, 3H), 3.77-3.69 (m, 1H), 3.22-3.12 (m, 2H), 2.40-2.28 (m, 2H), 1.66-1.56 (m, 1H), 1.52-1.42 (m, 1H), 1.30 (t, *J* = 7.1, 3H), 0.80 (s, 9H), –0.08 (s, 3H), –0.15 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 166.0, 159.3, 157.0, 135.8, 131.4, 130.7, 129.4, 129.3, 129.2, 115.5, 113.9, 72.6, 68.3, 66.2, 60.0, 55.4, 44.8, 37.1, 25.9, 18.1, 14.6, –4.5, –4.7; **IR** (thin film): ν 2952, 2928, 2894, 2855, 1701, 1613, 1582, 1513, 1472, 1463, 1440, 1389, 1366, 1331 1302, 1247, 1196, 1171, 1092, 1035, 1005, 921; **HRMS** (ESI): calculated for $C_{29}H_{46}NO_5SSi$ $[M+NH_4]^+$: 548.2860, found 548.2861; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: –11.4 (c 0.6 in $CHCl_3$).

Ester 13: To a brown-grey suspension CuI (7.83 g, 41.1 mmol, 1.93 equiv.) in THF (120 mL) at –78 °C was added dropwise MeMgBr (2.8m in Et_2O, 27.8 mL, 77.7 mmol, 3.7 equiv.) (the internal temperature increased to −65 °C). The grey suspension was immersed in an ice bath for about 5 min, giving a viscous green suspension. At –78 °C, a solution of thioether **12** (11.3 g, 21.3 mmol, 1.0 equiv.; mixture of the (*Z*)- and the (*E*)-isomer, *vide supra*) in THF (30 mL) was added drop-by-drop. The remaining dry ice was removed from the cooling bath and the yellow mixture was allowed to warm to –30 °C in the cooling bath over *ca.* 30-40 min. Sat. aq. NH_4Cl (130 mL), 25% aq. NH_3 solution (40 mL) and EtOAc (100 mL) were added, the phases were separated and the aqueous layer was extracted with EtOAc (3x100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered through a short plug of celite and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 10:1 → 7:3) afforded ester **13** (9.05 g, 20.7 mmol, 97%) as a yellow oil (contains *ca.* 6% of the undesired (*Z*)-isomer derived from the minor isomer of the thiophenol addition reaction). Note: If pure **(*Z*)-12** was employed, **(*E*)-13** was also obtained in quantitative yields (≥95%). Sometimes, a yellow instead of a green suspension was obtained upon addition of MeMgBr to the suspension of CuI and warming to 0 °C, leading to the same outcome.

TLC: R_f = 0.57 (hexane/EtOAc 4:1, UV, CPS); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.27-7.22 (m, 2H), 6.89-6.83 (m, 2H), 5.66 (q, *J* = 1.3, 1H), 4.44 (d, *J* = 11.5, 1H), 4.38 (d, *J* = 11.5, 1H), 4.14 (qd, *J* = 7.1, 1.6, 2H), 4.06-3.97 (m, 1H), 3.80 (s, 3H), 3.50 (t, *J* = 6.5, 2H), 2.29 (ddd, *J* = 13.0, 6.4, 1.0, 1H), 2.24 (ddd, *J* = 13.0, 6.2, 0.8, 1H), 2.16 (d, *J* = 1.3, 3H), 1.81-1.63 (m, 2H), 1.26 (t, *J* = 7.1, 3H), 0.85 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 166.7, 159.3,

156.6, 130.7, 129.4, 118.5, 113.9, 72.8, 68.1, 66.6, 59.6, 55.4, 49.4, 37.3, 26.0, 19.6, 18.2, 14.5, –4.4, –4.6; **IR** (thin film): ν 2952, 2929, 2856, 2362, 1714, 1646, 1613, 1587, 1513, 1472, 1463, 1442, 1366, 1302, 1247, 1221, 1172, 1148, 1094, 1037, 1005, 938; **HRMS** (ESI): calculated for $C_{24}H_{44}NO_5Si$ $[M+NH_4]^+$: 454.2983, found 454.2987; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: +1.0 (c 0.5 in $CHCl_3$).

(*R*,*E*)-5-((*t*-butyldimethylsilyl)oxy)-7-((4-methoxybenzyl)oxy)-3-methylhept-2-en-1-ol (E-2): To a solution of **13** (9.05 g, 20.7 mmol, 1.0 equiv.; mixture of (*E*/*Z*)-isomers, *vide supra*) in DCM (150 mL) was added dropwise DIBAL-H (1.2m in toluene, 37.1 mL, 44.6 mmol, 2.15 equiv.). The solution was stirred for at –78 °C for 30 min. Sat. aq. Rochelle salt (200 mL) was added and stirring was continued at room temperature until two clear phases formed (*ca.* 3 h). The phases were separated and the aqueous layer was extracted with DCM (4x100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 3:1 → 2:1 → 1:1) furnished allylic alcohol **E-2** (7.1 g, 18.0 mmol, 87%, pure (*E*)-isomer) as a pale yellow oil. Note: If pure **(*E*)-13** was employed, **(*E*)-E-2** was obtained in yields of between 86-94%.

TLC: R_f = 0.13 (hexane : EtOAc 4:1, UV, CPS); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.29-7.22 (m, 2H), 6.90-6.84 (m, 2H), 5.41 (tq, *J* = 6.8, 1.3, 1H), 4.43 (d, *J* = 11.5, 1H), 4.38 (d, *J* = 11.5, 1H), 4.15-4.09 (m, 2H), 3.99-3.91 (m, 1H), 3.80 (s, 3H), 3.51 (dd, *J* = 7.2, 6.0, 2H), 2.21 (dd, *J* = 13.3, 6.0, 1H), 2.13 (dd, *J* = 13.3, 6.9, 1H), 1.83-1.72 (m, 1H), 1.67 (m, 3H), 1.68-1.58 (m, 1H), 1.24 (t, *J* = 5.5, O*H*), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 159.3, 136.6, 130.8, 129.4, 126.7, 113.9, 72.8, 68.2, 66.9, 59.5, 55.4, 48.2, 37.0, 26.0, 18.2, 17.1, –4.2, –4.6; **IR** (thin film): ν 3387, 2952, 2928, 2855, 1613, 1586, 1512, 1472, 1463, 1442, 1361, 1302, 1247, 1173, 1089, 1036, 1004, 938; **HRMS** (ESI): calculated for $C_{22}H_{39}O_4Si$ $[M+H]^+$: 395.2612, found 395.2623; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: –7.3 (c 0.6 in $CHCl_3$).

Allylic bromide 14: To a solution of **E-2** (2.60 g, 6.59 mmol, 1.0 equiv.), 2,6-lutidine (1.2 mL, 10.6 mmol, 1.6 equiv.) and PPh_3 (3.80 g, 14.5 mmol, 2.2 equiv.) in DCM (130 mL) at −78 °C was added dropwise a solution of CBr_4 (4.81 g, 14.5 mmol, 2.2 equiv.) in DCM (5 mL). After 2 h, the reaction was carefully quenched with water (50 mL). The phases were separated and the aqueous layer was extracted with DCM (3x50 mL). The combined organic layers were dried over $MgSO_4$. (Note: Washing with brine leads to partial substitution of chloride for

bromide), filtered and concentrated under reduced pressure. The crude product was carefully adsorbed on silica gel and purified by flash chromatography (hexane/EtOAc 20:1). Allylic bromide **14** (2.55 g, 5.57 mmol, 85%) was obtained as a yellow oil.

TLC: R_f = 0.73 (hexane/EtOAc 4:1, UV, CPS); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.28-7.22 (m, 2H), 6.90-6.85 (m, 2H), 5.53 (tq, *J* = 8.5, 1.2, 1H), 4.43 (d, *J* = 11.4, 1H), 4.38 (d, *J* = 11.4, 1H), 4.02-3.92 (m, 3H), 3.81 (s, 3H), 3.50 (dd, *J* = 7.1, 6.3, 2H), 3.49 (d, *J* = 6.3, 1H), 2.24 (dd, *J* = 13.2, 6.0, 1H), 2.16 (dd, *J* = 13.2, 6.5, 1H), 1.80-1.70 (m, 1H), 1.73 (d, *J* = 1.3, 3H), 1.68-1.57 (m, 1H), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 159.3, 140.7, 130.8, 129.4, 123.5, 113.9, 72.7, 68.2, 66.7, 55.4, 48.1, 37.0, 29.3, 26.0, 18.2, 16.8. –4.2, –4.5; **IR** (thin film): ν 2952, 2928, 2855, 1654, 1613, 1586, 1512, 1472, 1463, 1442, 1360, 1302, 1247, 1201, 1172, 1092, 1036, 1005, 926, 834, 773; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: +3.6 (c 1.5 in $CHCl_3$).

Diene 15: To a solution of **14** (2.50 g, 5.46 mmol, 1.0 equiv.) and $AsPh_3$ (0.84 g, 2.73 mmol., 0.5 equiv.) in degassed DMF (argon was bubbled through the solution for 10 min) (30 mL) was added vinyltributylstannane (3.2 mL, 10.9 mmol, 2.0 equiv.) and $[Pd_2(dba)_3]$ (0.60 g, 0.66 mmol, 0.12 equiv.). A dark green solution was obtained that was stirred at room temperature for 75 h. The obtained black mixture was diluted with Et_2O (150 mL) and washed with water (3x50 mL). The combined washing phases were back-extracted with Et_2O (2x100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 50:1; two runs were required to remove all tin by-products) afforded diene **15** (1.75 g, 4.32 mmol, 79%) as a pale yellow oil.

TLC: R_f = 0.51 (hexane/EtOAc 9:1, UV, CPS); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.28-7.23 (m, 2H), 6.89-6.85 (m, 2H), 5.78 (ddt, *J* = 17.0, 10.1, 6.3, 1H), 5.17 (tm, *J* = 7.3, 1H), 5.04-4.97 (m, *J* = 17.1, 1H), 4.97-4.92 (m, *J* = 10.1, 1H), 4.44 (d, *J* = 11.6, 1H), 4.38 (d, *J* = 11.6, 1H), 3.98-3.89 (m, 1H), 3.80 (s, 3H), 3.51 (dd, *J* = 7.3, 6.3, 2H), 2.73 (t, *J* = 6.7, 2H), 2.21 (dd, *J* = 13.2, 6.1, 1H), 2.11 (dd, *J* = 13.2, 7.0, 1H), 1.84-1.72 (m, 1H), 1.67-1.56 (m, 1H), 1.61 (m, 3H), 0.87 (s, 9H), 0.03 (s, 6H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 159.2, 137.3, 133.4, 130.9, 129.4, 124.7, 114.5, 113.9, 72.7, 68.4, 67.1, 55.4, 48.5, 36.9, 32.5, 26.0, 18.2, 16.8, –4.2, –4.6; **IR** (thin film): ν 2953, 2928, 2855, 1613, 1513, 1472, 1463, 1442, 1361, 1302, 1247, 1172, 1090, 1038, 1005, 910; **HRMS** (ESI): calculated for $C_{24}H_{40}NaO_3Si$ $[M+Na]^+$: 427.2639, found 427.2657; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: –4.1 (c 1.0 in $CHCl_3$).

Primary alcohol 16: To a solution of **15** (2.47 g, 6.10 mmol, 1.0 equiv.) in DCM (45 mL) at 0 °C was added NEt_3 (4.2 mL, 30.5 mmol, 5.0 equiv.) followed by TMSI (3.5 mL, 24.4 mmol, 4.0 equiv.). The pale yellow solution was stirred at 0 °C for 1.5 h in the dark. Sat. aq. $NaHCO_3$ (50 mL) was added, the phases were separated and the aqueous layer was extracted with DCM (3x30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The brown-yellow residue was taken up in MeOH (45 mL) before K_2CO_3 (1.69 g, 12.2 mmol, 2.0 equiv.) was added. The resulting white mixture was stirred at room temperature for 5 min. Sat. aq. NH_4Cl (40 mL) and EtOAc (60 mL) were added, the phases were separated and the aqueous layer was extracted with EtOAc (4x30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 9:1) furnished alcohol **16** (1.60 g, 5.62 mmol, 92%) as a pale yellow oil.

TLC: R_f = 0.21 (hexane/EtOAc 9:1, UV (weak), CPS); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 5.78 (ddt, *J* = 17.0, 10.1, 6.3, 1H), 5.21 (tq, *J* = 7.3, 1.2, 1H), 5.03-4.96 (m, *J* = 17.0, 1H), 4.96-4.92 (m, *J* = 10.1, 1H), 4.09-4.01 (m, 1H), 3.90-3.80 (m, 1H), 3.75-3.65 (m, 1H), 2.74 (t, *J* = 6.7, 2H), 2.48-2.42 (m, OH), 2.30 (dd, *J* = 13.1, 5.3, 1H), 2.20 (dd, *J* = 13.3, 8.2, 1H) 1.87-1.77 (m, 1H), 1.62-1.53 (m, 1H), 1.61 (s, 3H), 0.89 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 137.1, 133.0, 125.1, 114.6, 70.6, 60.4, 47.6, 37.6, 32.4, 26.0, 18.1, 16.6, –4.3, –4.6; **IR** (thin film): ν 3368, 2954, 2928, 2888, 2857, 1638, 1472, 1463, 1430, 1361, 1253, 1091, 1057, 1029, 1005, 966, 938, 909, 878, 834, 772; **HRMS** (ESI): calculated for $C_{16}H_{33}O_2Si$ $[M+H]^+$: 285.2244, found 285.2238; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: –17.4 (c 1.0 in $CHCl_3$).

Aldehyde 9: To a solution of $(COCl)_2$ (0.71 mL, 8.43 mmol, 1.5 equiv.) in DCM (43 mL) at –78 °C was added dropwise a solution of DMSO (1.20 mL, 16.9 mmol, 3.0 equiv.) in DCM (15 mL). After 15 min, a solution of **16** (1.60 g, 5.62 mmol, 1.0 equiv.) in DCM (8 mL; the vial was rinsed twice with 3 mL) was added. The resulting white suspension was stirred at –78 °C for 1 h, then NEt_3 (3.1 mL, 22.5 mmol, 4.0 equiv.) was added dropwise. The cooling bath was removed and the now clear solution was allowed to warm to room temperature, giving again a suspension. Water (50 mL) and DCM (25 mL) were added, the phases were separated and the aqueous layer was extracted with DCM (3x30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash

chromatography (hexane/EtOAc 17:1) afforded aldehyde **9** (1.55 g, 5.49 mmol, 98%) as a colorless oil.

TLC: R_f = 0.47 (hexane/EtOAc 9:1, UV (weak), CPS); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 9.80 (dd, *J* = 2.8, 2.0, 1H), 5.77 (ddt, *J* = 17.0, 10.1, 6.3, 1H), 5.22 (tq, *J* = 7.3, 1.1, 1H), 5.04-4.97 (m, *J* = 17.2, 1H), 4.98-4.93 (m, *J* = 10.1, 1H), 4.36-4.29 (m, 1H), 2.74 (t, *J* = 6.7, 2H), 2.53 (ddd, *J* = 15.7, 4.8, 2.1, 1H), 2.47 (ddd, *J* =15.7, 6.6, 2.8, 1H), 2.31 (dd, *J* = 13.3, 5.5, 1H), 2.18 (dd, *J* = 13.3, 7.7, 1H), 1.64 (m, 3H), 0.87 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 202.4, 136.9, 132.6, 125.9, 114.7, 67.3, 50.6, 48.6, 32.5, 25.9, 18.1, 16.8, –4.3, –4.7; **IR** (thin film): ν 2955, 2929, 2897 2857, 1726, 1638, 1472, 1463, 1435, 1407, 1389, 1362, 1253, 1092, 1030, 1004, 939, 909, 835, 810, 774; **HRMS** (ESI): calculated for $C_{16}H_{30}NaO_2Si$ $[M+Na]^+$: 305.1907, found 305.1918; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: –8.6 (c 0.8 in $CHCl_3$).

Ester 19:[36] To magnesium turnings (0.31 g, 12.9 mmol, 1.35 equiv.) and a crystal of iodine in THF (2 mL) was added a solution of 2-bromoprop-1-ene (1.1 mL, 12.4 mmol, 1.3 equiv.) in THF (8 mL) at such a rate as to maintain reflux. After complete addition, the reaction was refluxed for another 15 min and then stirred for 2.5 h at room temperature. Then, the mixture was transferred by cannula to a solution of phenylacetaldehyde (**17**) (1.1 mL, 9.54 mmol, 1.0 equiv.) in THF (9 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h, then sat. aq. NH_4Cl (30 mL) and EtOAc (40 mL) were added. The phases were separated and the aqueous layer was extracted with EtOAc (2x40 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 2.67 g of the desired secondary alcohol, which was directly employed in the subsequent step.

To the crude alcohol in a round-bottomed flask equipped with a Claisen distillation head was added triethyl orthoacetate (15 mL, 82.3 mmol) followed by propanoic acid (0.22 mL, 4.11 mmol). The solution was heated to 145 °C for 3 h (until no more EtOH distilled over). Excess triethyl orthoacetate was removed carefully under reduced pressure (room temperature to 40 °C at $2\cdot10^{-2}$ mbar) and the resulting liquid was distilled at $2\cdot10^{-2}$ mbar (bp: 89-94 °C) to afford ester **19** (1.10 g, 4.73 mmol, 49% over two steps) as a colorless oil.

Bp.: 89-94 °C ($2\cdot10^{-2}$ mbar); **TLC**: R_f = 0.27 (hexane/EtOAc 20:1, UV, CPS); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.30-7.24 (m, 2H), 7.21-7.13 (m, 3H), 5.38 (tq, *J* = 7.4, 1.4, 1H), 4.10 (q, *J* = 7.2, 2H), 3.35 (d, *J* = 7.3, 2H), 2.47-2.41 (m, 2H), 2.39-2.33 (m, 2H), 1.73 (s, 3H), 1.22 (t, *J* = 7.2, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 173.5, 141.5, 134.7, 128.5, 128.4, 125.9, 124.0, 60.4, 34.8,

34.3, 33.3, 16.3, 14.4; **IR** (thin film): ν 3010, 2902, 2642, 2532, 1700, 1418, 1404, 1303, 1287, 1185, 935, 648; **HRMS** (ESI): calculated for $C_{15}H_{21}O_2$ $[M+H]^+$: 233.1536, found 233.1541.

Ketone 8: To a slurry of ester **19** (375 mg, 1.61 mmol, 1.0 equiv.) and *N*,*O*-dimethylhydroxylamine hydrochloride (197 mg, 2.02 mmol, 1.25 equiv.) in THF (15 mL) at –5 °C (ice/NaCl) was added dropwise MeMgBr (2.7m in Et_2O, 4.0 mL, 10.7 mmol, 6.6 equiv.). The mixture was stirred at –5 °C for 1.5 h and was then allowed to warm slowly in the cooling bath. The reaction was aged for 14 h at room temperature before sat. aqueous NH_4Cl (25 mL) and EtOAc (15 mL) were added carefully. The phases were separated and the aqueous layer was extracted with EtOAc (3x15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 8:2) furnished ketone **8** (256 mg, 1.26 mmol, 78%) as a yellow oil.

TLC: R_f = 0.60 (hexane/EtOAc 7:3, UV, $KMnO_4$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.31-7.24 (m, 2H), 7.21-7.13 (m, 3H), 5.35 (tq, *J* = 7,3, 1.3, 1H), 3.35 (d, *J* = 7.3, 2H), 2.59-2.53 (m, 2H), 2.35-2.27 (m, 2H), 2.13 (br s, 3H), 1.72 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 208.7, 141.5, 134.9, 128.5, 128.4, 125.9, 123.8, 42.4, 34.3, 33.6, 30.0, 16.4; **IR** (thin film): ν 3084, 3061, 3026, 2971, 2913, 2857, 1714, 1603, 1494, 1452, 1436, 1356, 1284, 1230, 1160, 1094, 1073, 1029, 930, 786; **HRMS** (EI): calculated for $C_{14}H_{18}O$ $[M]^+$: 202.1355, found 202.1351.

β-Hydroxy ketone 20: To a suspension of (+)-Ipc_2BCl (2.64 g, 8.23 mmol, 1.5 equiv.) in DCM (30 mL) at –78 °C was added NEt_3 (2.3 mL, 16.5 mmol, 3.0 equiv.) followed by a solution of methyl ketone **8** (1.66 g, 8.23 mmol, 1.5 equiv.) in DCM (8 mL; the vial was rinsed twice with 3 mL). The yellow solution was stirred at –78 °C for 3 h, during which time a white precipitate was formed. Aldehyde **9** (1.55 g, 5.49 mmol, 1.0 equiv.) in DCM (2 mL; the vial was rinsed twice with 0.5 mL) was added dropwise. The reaction (suspension) was stirred at –78 °C for 4 h and was then allowed to stand in the freezer (–20 °C) for 12 h. Phosphate buffer (pH 7; 30 mL) was added to the reaction, the phases were separated and the aqueous layer was extracted with DCM (3x30 mL). The combined organic layers were concentrated under reduced pressure and the residue was taken up in MeOH (35 mL) and pH 7 phosphate buffer (8 mL). The mixture was cooled to 0 °C, 30% aq. H_2O_2 was added (10 mL) and the suspension was stirred at 0 °C for 1.5 h before being poured into water (30 mL). DCM (30

mL) was added, the phases were separated and the aqueous layer was extracted with DCM (3x30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 7:1 → 5:1 → 4:1; two runs were required to obtain a pure product) afforded β-hydroxy ketone **20** (1.64 g, 3.39 mmol, 62%) as a colorless oil.

TLC: R_f = 0.23 (hexane/EtOAc 9:1, UV, CPS); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.31-7.24 (m, 2H), 7.21-7.13 (m, 3H), 5.77 (ddt, *J* = 17.2, 10.1, 6.3, 1H), 5.34 (tq, *J* = 7.3, 1.3, 1H), 5.19 (tq, 7.3, 1.1, 1H), 5.03-4.96 (m, *J* = 17.2, 1H), 4.98-4.92 (m, *J* = 10.1, 1H), 4.23-4.15 (m, 1H), 4.07-3.98 (m, 1H), 3.43 (d, *J* = 2.1, O*H*), 3.34 (d, *J* = 7.3, 2H), 2.74 (t, *J* = 6.7, 2H), 2.62-2.48 (m, 4H), 2.31 (t, *J* = 7.6, 2H), 2.24 (dd, *J* = 13.3, 5.5, 1H), 2.14 (dd, *J* = 13.3, 7.6, 1H), 1.72 (s, 3H), 1.62, (s, 3H), 1.60-1.49 (m, 2H), 0.89 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 210.7, 141.5, 137.1, 134.8, 132.9, 128.5, 128.4, 125.9, 125.2, 123.8, 114.5, 70.7, 66.7, 49.9, 48.5, 42.9, 42.4, 34.3, 33.3, 32.4, 26.0, 18.1, 16.7, 16.4, –4.0, –4.5; **IR** (thin film): ν 3527, 3084, 3064, 3027, 3003, 2927, 2856, 1708, 1495, 1452, 1254, 1075, 1030, 1004, 908, 835, 809, 774; **HRMS** (ESI): calculated for $C_{30}H_{49}O_3Si$ $[M+H]^+$: 485.3445, found 485.3447; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: –18.0 (c 1.1 in $CHCl_3$).

Ester 21: Preparation of SmI_2:[45] A brown slurry of samarium powder (0.38 g, 2.52 mmol, 0.75 equiv.) and I_2 (0.58 g, 2.28 mmol, 0.68 equiv.) in THF (23 mL) was heated to 80 °C for 30 min, giving a dark blue solution of SmI_2 (*ca.* 0.1m), which, after reaching room temperature, was used immediately.

To a solution of freshly distilled (over $CaCl_2$; bp. 51-54 °C; ambient pressure) propionaldehyde (1.45 mL, 20.2 mmol, 6.0 equiv.) in THF (15 mL) at –20 °C (cryostat) was added SmI_2 (12.9 mL of the above solution, 1.17 mmol, 0.35 equiv.). The solution turned yellow within 30 seconds. Hydoxy ketone **20** (1.63 g, 3.36 mmol, 1.0 equiv.) in THF (5 mL; the vial was rinsed twice with 1 mL) was then added slowly. The yellow solution was stirred at –20 °C for 1 h. Sat. aq. $NaHCO_3$ (20 mL) and EtOAc (20 mL) were added, the phases were separated and the aqueous layer was extracted with EtOAc (3x20 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 20:1 → 10:1) furnished ester **21** (1.68 g, 3.12 mmol, 93%) as a colorless oil.

TLC: R_f = 0.36 (hexane/EtOAc 9:1, UV, CPS); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.30-7.24 (m, 2H), 7.20-7.14 (m, 3H), 5.78 (ddt, *J* = 17.1, 10.1, 6.3, 1H), 5.36 (tq, *J* = 7.3, 1.3, 1H), 5.27-5.15 (m, 2H), 5.04-4.97 (m, *J* = 17.2, 1H), 4.97-4.92 (m, *J* = 10.1, 1H), 3.84-3.76 (m, 1H), 3.45-3.37 (m, 1H), 3.35 (d, *J* = 7.3, 2H), 3.07 (d, *J* = 3.7, O*H*), 2.74 (t, *J* = 6.7, 2H), 2.32 (q, *J* = 7.6, 2H), 2.25-2.12 (m, 3H), 2.12-2.01 (m, 1H), 1.83-1.74 (m, 1H), 1.72-1.44 (m, 5H), 1.71 (s, 3H), 1.60 (s, 3H), 1.15 (t, *J* = 7.6, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 175.7, 141.8, 137.2, 136.2, 133.1, 128.5, 128.4, 125.9, 125.2, 123.2, 114.5, 69.2, 68.1, 66.8, 47.7, 43.5, 42.7, 36.0, 35.4, 34.3, 32.6, 28.0, 26.0, 18.2, 16.8, 16.4, 9.5, –4.3, –4.4; **IR** (thin film): ν 3530, 3063, 3026, 2928, 2856, 2362, 2358, 1717, 1495, 1472, 1463, 1453, 1361, 1253, 1199, 1082, 1004, 908, 835, 808, 773; **HRMS** (ESI): calculated for $C_{33}H_{55}O_4Si$ $[M+H]^+$: 543.3864, found 543.3859; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: –10.0 (c 0.5 in $CHCl_3$).

(5*R*,7*S*,9*R*)-2,2,3,3,11,11,12,12-octamethyl-5-((*E*)-3-methyl-5-phenylpent-3-en-1-yl)-9-((*E*)-2-methylhexa-2,5-dien-1-yl)-4,10-dioxa-3,11-disilatridecan-7-yl propionate (E-3): To a solution of ester **21** (945 mg, 1.74 mmol, 1.0 equiv.) in DMF (2 mL) at room temperature was added imidazole (142 mg, 2.09 mmol, 1.2 equiv.) followed by TBSCl (315 mg, 2.09 mmol, 1.2 equiv.). The colorless solution was stirred at room temperature for 20 h, giving a yellow suspension. Sat. aq. $NaHCO_3$ (30 mL) and Et_2O (40 mL) were added, the phases were separated, the organic layer was washed with water (3x5 mL) and the combined washes were back-extracted with Et_2O (10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 50:1) afforded **E-3** (1.08 g, 1.64 mmol, 94%) as a colorless oil.

TLC: R_f = 0.52 (hexane/EtOAc 20:1, UV, CPS); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.30-7.24 (m, 2H), 7.20-7.14 (m, 3H), 5.78 (ddt, *J* = 17.2, 10.1, 6.3, 1H), 5.34 (tq, *J* = 7.3, 1.3, 1H), 5.19 (t, *J* = 7.2, 1H), 5.08-4.97 (m, 2H), 4.97-4.91 (m, *J* = 10.1, 1H), 3.83-3.75 (m, 1H), 3.74-3.65 (m, 1H), 3.35 (d, *J* = 7.3, 2H), 2.82-2.67 (m, 2H), 2.32-2.18 (m, 1H), 2.26 (q, *J* = 7.6, 2H), 2.10 (dd, *J* = 13.3, 7.3, 1H), 2.08-2.01 (m, 2H), 1.82-1.54 (m, 6H), 1.71 (m, 3H), 1.60 (m, 3H), 1.12 (t, *J* = 7.6, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.03 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H), 0.00 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 173.9, 141.8, 137.4, 136.4, 133.4, 128.5, 128.4, 125.9, 125.0, 123.1, 114.4, 69.5, 68.9, 68.3, 47.2, 43.3, 42.6, 36.5, 34.8, 34.4, 32.7, 28.1, 26.1, 26.0, 18.2, 16.8, 16.4, 9.4, –4.1, –4.3, –4.4, –4.5; **IR** (thin film): ν 3084, 3028, 2951, 2928, 2856, 1735, 1495, 1472, 1463, 1453, 1384, 1361, 1253, 1187, 1063, 1004, 938, 909, 834, 806, 773, 740; **HRMS**

(ESI): calculated for $C_{39}H_{69}O_4Si_2$ $[M+H]^+$: 657.4729, found 657.4729; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: −7.6 (c 0.6 in $CHCl_3$).

Alcohol 7: To a solution of ester **E-3** (1.08 g, 1.64 mmol, 1.0 equiv.) in DCM (16 mL) at −78 °C was added dropwise DIBAL-H (1.2m solution in toluene, 2.9 mL, 3.45 mmol, 2.1 equiv.). The colorless solution was stirred at −78 °C for 1 h. Sat. aq. Rochelle salt (40 mL) was added and stirring was continued at room temperature until two clear phases were obtained (*ca.* 1.5 h). The phases were separated and the aqueous layer was extracted with DCM (3x20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 25:1) furnished alcohol **7** (872 mg, 1.45 mmol, 88%) as a colorless oil.

TLC: R_f = 0.38 (hexane/EtOAc 20:1, UV, CPS); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.31-7.25 (m, 2H), 7.21-7.14 (m, 3H), 5.79 (ddt, *J* = 17.1, 10.1, 6.3, 1H), 5.34 (tq, *J* = 7.3, 1.3, 1H), 5.19 (tm, *J* = 7.2, 1H), 5.04-4.97 (m, *J* = 17.1, 1H), 4.97-4.92 (m, *J* = 10.1, 1H), 4.05-3.93 (m, 3H), 3.57 (d, *J* = 1.0, O*H*), 3.35 (d, *J* = 7.3, 2H), 2.74 (t, *J* = 6.7, 2H), 2.27 (dd, *J* = 13.2, 5.1, 1H), 2.15 (dd, *J* = 13.2, 7.7, 1H), 2.08-1.99 (m, 2H), 1.71 (s, 3H), 1.69-1.45 (m, 6H), 1.62 (s, 3H), 0.90 (s, 9H), 0.89 (s 9H), 0.10 (s, 3H), 0.10 (s, 6H), 0.08 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 141.8, 137.2, 136.3, 133.1, 128.5, 128.4, 125.8, 125.0, 123.1, 114.5, 71.3, 70.0, 67.0, 48.6, 44.3, 43.9, 36.0, 35.5, 34.3, 32.5, 26.1, 26.0, 18.2, 18.1, 16.8, 16.4, −3.8, −4.3, −4.4, −4.4; **IR** (thin film): ν 3526, 3084, 3064, 3028, 2952, 2928, 2856, 1495, 1472, 1463, 1453, 1382, 1362, 1254, 1076, 1030, 1004, 938, 909, 834, 808; **HRMS** (ESI): calculated for $C_{36}H_{65}O_3Si_2$ $[M+H]^+$: 601.4467, found 601.4458; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: −21.5 (c 0.6 in $CHCl_3$).

***R*-Mosher ester of 7 (23a)**: To alcohol **7** (12.0 mg, 20.0 µmol, 1.0 equiv.) in DCM (0.5 mL) at room temperature was added (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (11.7 mg, 49.9 µmol, 2.5 equiv.), DCC (12.4 mg, 59.9 µmol, 3.0 equiv.) and DMAP (0.7 mg, 6.0 µmol, 0.3 equiv.). The resulting white mixture was stirred at room temperature for 14 h. Sat. aq. $NaHCO_3$ (5 mL) and EtOAc (5 mL) were added, the phases were separated and the aqueous layer was extracted with EtOAc (3x5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (pentane/Et_2O 40:1 → 30:1) afforded Mosher ester **23a** (12.6 mg, 15.4 µmol, 77%) as a colorless oil.

The other diasteroisomer (**23b**) was prepared analogously (colorless oil, 12.3 mg, 15.1 µmol, 75%) using (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid as the reagent.

23a: **TLC**: R_f = 0.53 (hexane/EtOAc 20:1,UV, CPS); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.59-7.53 (m, 2H), 7.42-7.34 (m, 3H), 7.31-7.24 (m, 2H), 7.20-7.14 (m, 3H), 5.78 (ddt, *J* = 17.1, 10.1, 6.3, 1H), 5.33 (tq, *J* = 7.3, 1.3, 1H), 5.29-5.22 (m, 1H), 5.18 (tm, *J* = 7.2 1H), 5.04-4.97 (m, *J* = 17.1, 1H), 4.96-4.91 (m, *J* = 10.1, 1H), 3.78-3.70 (m 1H), 3.69-3.61 (m, 1H), 3.54 (m, 3H) 3.34 (d, *J* = 7.3, 2H), 2.80-2.66 (m, 2H), 2.22 (dd, *J* = 13.5, 4.5, 1H), 2.06 (dd, *J* = 13.5, 7.3, 1H), 2.04-1.96 (m, 2H), 1.87-1.65 (m, 4H), 1.70 (m, 3H), 1.62-1.49 (m, 2H), 1.58 (m, 3H), 0.89 (s, 9H), 0.84 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H), –0.06 (s, 3H), –0.07 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 166.0, 141.8, 137.3, 136.1, 133.1, 129.7, 128.6, 128.5, 128.4, 127.5, 127.5, 125.9, 125.2, 123.2, 114.5, 73.2, 69.0, 67.8, 55.5, 46.8, 42.8, 42.6, 36.5, 34.7, 34.3, 32.7, 26.1, 26.0, 18.2, 18.1, 16.9, 16.4, –4.1, –4.3, –4.5, –4.6 (not all carbons assigned); **IR** (thin film): ν 3028, 2952, 2928, 2856, 1743, 1472, 1463, 1452, 1253, 1186, 1168, 1105, 1080, 1015, 994, 937, 910, 834, 808, 774; **HRMS** (ESI): calculated for $C_{46}H_{71}F_3NaO_5Si_2$ $[M+Na]^+$: 839.4684, found 839.4675; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: +10.0 (c 0.4 in $CHCl_3$).

23b: **TLC**: R_f = 0.51 (hexane/EtOAc 20:1,UV, CPS); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.58-7.52 (m, 2H), 7.43-7.34 (m, 3H), 7.31-7.24 (m, 2H), 7.21-7.14 (m, 3H), 5.78 (ddt, *J* = 17.1, 10.1, 6.3, 1H), 5.30 (tq, *J* = 7.3, 1.3, 1H), 5.30-5.23 (m, 1H), 5.20 (tm, *J* = 7.2 1H), 5.04-4.97 (m, *J* = 17.1, 1H), 4.96-4.91 (m, *J* = 10.1, 1H), 3.87-3.79 (m 1H), 3.65-3.56 (m, 1H), 3.52 (m, 3H) 3.33 (d, *J* = 7.3, 2H), 2.82-2.66 (m, 2H), 2.27 (dd, *J* = 13.5, 4.5, 1H), 2.11 (dd, *J* = 13.5, 7.3, 1H), 2.02-1.84 (m, 3H), 1.83-1.65 (m, 3H), 1.68 (m, 3H), 1.59 (m, 3H), 1.56-1.48 (m, 2H), 0.89 (s, 9H), 0.86 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H), –0.01 (s, 3H), –0.03 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 166.0, 141.8, 137.3, 136.2, 133.1, 129.7, 128.6, 128.5, 128.4, 127.7, 125.9, 125.2, 123.1, 122.2, 114.5, 73.3, 68.9, 68.1, 55.3, 47.0, 42.7, 42.7, 36.7, 34.6, 34.3, 32.6, 26.1, 26.0, 18.2, 18.1, 16.8, 16.4, –4.1, –4.3, –4.5, –4.5 (not all carbons assigned); **IR** (thin film): ν 3029, 2952, 2928, 2857, 1744, 1472, 1463, 1452, 1388, 1362, 1253, 1185, 1168, 1105, 1081, 1015, 994, 964, 938, 909, 834, 806, 773; **HRMS** (ESI): calculated for $C_{46}H_{71}F_3NaO_5Si_2$ $[M+Na]^+$: 839.4684, found 839.4683; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: –14.7 (c 0.6 in $CHCl_3$).

Diol 24: To a solution of ester **21** (30.0 mg, 55.3 µmol, 1.0 equiv.) in DCM (0.7 mL) at –78 °C was added dropwise DIBAL-H (1.2m solution in toluene; 150 µL; 180 µmol, 3.25 equiv.). The

colorless solution was stirred at −78 °C for 1 h. Sat. aq. Rochelle salt (6 mL) and DCM (5 mL) were added and stirring was continued until two clear phases were obtained (*ca.* 1 h). The phases were separated and the aqueous layer was extracted with DCM (3x5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 9:1) afforded diol **24** (22.3 mg, 45.8 µmol, 83%) as a colorless oil.

TLC: R_f = 0.41 (hexane/EtOAc 4:1, UV, CPS); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.30-7.24 (m, 2H), 7.20-7.14 (m, 3H), 5.78 (ddt, *J* = 17.3, 10.1, 6.3, 1H), 5.38 (tq, *J* = 7.3, 1.3, 1H), 5.20 (t, *J* = 7.2, 1H), 5.04-4.96 (m, *J* = 17.1, 1H), 4.98-4.93 (m, *J* = 10.1, 1H), 4.16-4.00 (m, 2H), 3.95-3.85 (m, 1H), 3.75 (s, O*H*), 3.36 (d, *J* = 7.3, 2H), 3.05 (d, *J* = 4.1, O*H*), 2.74 (t, *J* = 6.7, 2H), 2.33 (dd, *J* = 13.0, 4.3, 1H), 2.25-2.02 (m, 3H), 1.73 (m, 3H), 1.69-1.49 (m, 6H), 1.61 (s, 3H), 0.90 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 141.8, 137.0, 136.4, 132.6, 128.5, 128.4, 125.8, 125.3, 123.2, 114.6, 72.7, 69.5, 68.9, 49.1, 43.1, 42.5, 36.1, 35.9, 34.4, 32.4, 26.0, 18.0, 16.7, 16.4, –3.7, –4.5; **IR** (thin film): ν 3395, 3028, 2928, 2856, 1638, 1603, 1495, 1472, 1463, 1453, 1432, 1383, 1361, 1254, 1084, 1030, 1004, 992, 908, 808, 740, 669; **HRMS** (ESI): calculated for $C_{30}H_{51}O_3Si$ $[M+H]^+$: 487.3602, found 487.3597; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: –20.9 (c 0.5 in $CHCl_3$).

Acetonide 25: To a solution of diol **24** (22.3 mg, 45.8 µmol, 1.0 equiv.) in 2,3-dimethoxypropane (0.65 mL) at room temperature was added camphorsulfonic acid (1.1 mg, 4.6 µmol, 10 mol-%). The colorless solution was stirred at room temperature for 1 h. Sat. aq. $NaHCO_3$ (5 mL) and EtOAc (5 mL) were added, the phases were separated and the aqueous layer was extracted with EtOAc (3x5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 100:1) provided acetonide **25** (21.8 mg, 41.4 µmol, 90%) as a colorless oil.

TLC: R_f = 0.64 (hexane/EtOAc 20:1, UV, CPS); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.31-7.24 (m, 2H), 7.21-7.14 (m, 3H), 5.79 (ddt, *J* = 17.1, 10.1, 6.3, 1H), 5.36 (tq, *J* = 7.3, 1.3, 1H), 5.19 (tq, *J* = 7.2, 1.2, 1H), 5.05-4.98 (m, *J* = 17.1, 1H), 4.97-4.92 (m, *J* = 10.1, 1H), 4.00-3.83 (m, 2H), 3.80-3.69 (m, 1H), 3.35 (d, *J* = 7.3, 2H), 2.74 (t, *J* = 6.7, 2H), 2.25-1.99 (m, 4H), 1.76-1.48 (m, 6H), 1.72 (m, 3H), 1.61 (m, 3H), 1.33 (s, 3H), 1.29 (s, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 141.8, 137.3, 135.8, 133.4, 128.5, 128.4, 125.9, 124.9,

123.4, 114.5, 100.3, 67.9, 66.2, 63.7, 47.9, 43.5, 39.2, 35.5, 34.4, 34.3, 32.6, 26.0, 24.9, 24.9, 18.2, 16.8, 16.3, –4.2, –4.4; **IR** (thin film): ν 3063, 2984, 2928, 2855, 1638, 1604, 1495, 1472, 1453, 1378, 1250, 1163, 1086, 1030, 1004, 966, 930, 908, 809; **HRMS** (ESI): calculated for $C_{33}H_{55}O_3Si$ $[M+H]^+$: 527.3915, found 527.3919; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: –22.4 (c 0.7 in $CHCl_3$).

Ester 5: To a solution of alcohol **7** (434 mg, 0.72 mmol, 1.0 equiv.), acid **6** (515 mg, 1.44 mmol, 2.0 equiv.) and NEt_3 (0.50 mL, 3.61 mmol, 5.0 equiv.) in toluene (6 mL) at –78 °C was added a solution of DMAP (221 mg, 1.81 mmol, 2.5 equiv.) in toluene (2 mL; an ultrasonic bath was used to achieve complete dissolution) followed by 2,4,6-trichlorobenzoyl chloride (0.34 mL, 2.17 mmol, 3.0 equiv.). Initially, a white solid was obtained. (The appearance of this precipitate was scale- and concentration-dependent). The remaining dry ice was removed from the cooling bath and the temperature was increased to about −70 °C by the addition of room-temperature acetone to the cooling bath, then the reaction was allowed to warm slowly. Above –60 °C the solid dispersed giving a white mixture, which turned yellow at temperatures above –50 °C. The temperature was kept between –40 °C and –50 °C for 2.5 h, then sat. aq. $NaHCO_3$ (35 mL) was added followed by EtOAc (20 mL). The phases were separated and the aqueous layer was extracted with EtOAc (3x20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (pentane/Et_2O 70:1 → 50:1 → 30:1) afforded ester **5** (545 mg, 0.58 mmol, 80%) as a colorless oil; in addition, unreacted alcohol **7** (35 mg, 0.06 mmol, 8%) was re-isolated.

TLC: R_f = 0.40 (hexane/EtOAc 20:1, UV, CPS); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.31-7.25 (m, 2H), 7.20-7.15 (m, 3H), 6.34 (t, *J* = 0.9, 1H), 5.79 (ddt, *J* = 17.1, 10.1, 6.3, 1H), 5.35 (tq, *J* = 7.3, 1.3, 1H), 5.20 (tm, *J* = 7.2, 1H), 5.15-5.07 (m, 1H), 5.05-4.97 (m, *J* = 17.2, 1H), 4.96-4.91 (m, *J* = 10.1, 1H), 3.88-3.81 (m, 1H), 3.78 (t, *J* = 6.1, 2H), 3.77-3.70 (m, 1H), 3.35 (d, *J* = 7.2, 2H), 2.87 (td, *J* = 6.1, 0.9, 2H), 2.81-2.66 (m, 2H), 2.26 (dd, *J* = 13.2, 4.5, 1H), 2.12 (dd, *J* = 13.2, 7.3, 1H), 2.09-2.01 (m, 2H), 1.88-1.79 (m, 1H), 1.79-1.67 (m, 3H), 1.71 (m, 3H), 1.61 (m, 3H), 1.61-1.54 (m, 2H), 0.88 (s, 9H), 0.88 (s, 9H), 0.87 (s, 9H), 0.06 (s, 6H), 0.03 (s, 3H), 0.03 (s, 3H), 0.03 (s, 3H), –0.02 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 163.8, 141.8, 137.4, 136.5, 133.4, 128.5, 128.4, 127.3, 125.8, 125.0, 123.0, 116.3, 114.4, 70.2, 68.8, 68.3, 61.5, 51.0, 47.1, 43.0, 42.5, 36.5, 34.8, 34.3, 32.7, 26.1, 26.1, 26.0, 18.4, 18.2, 16.8, 16.4, –4.1, –4.2, –4.3, –4.4, –5.1; **IR** (thin film): ν 3081, 3062, 3027, 2952, 2927, 2895, 2886, 2856, 1727, 1707, 1623, 1495, 1472,

1463, 1453, 1435, 1387, 1361, 1306, 1252, 1210, 1168, 1106, 1087, 1060, 1046, 1005, 994, 938, 909, 834, 808; **HRMS** (ESI): calculated for $C_{47}H_{84}IO_5Si_3$ $[M+H]^+$: 939.4666, found 939.4677; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: −5.9 (c 0.8 in $CHCl_3$).

Tetraene 4: Argon was bubbled through a solution of vinyl iodide **5** (540 mg, 0.57 mmol, 1.0 equiv.) and $AsPh_3$ (88.0 mg, 0.29 mmol, 0.5 equiv.) in DMF (5 mL) for 15 min. Allyltributylstannane (360 µL, 1.15 mmol, 2.0 equiv.) was added followed by $[Pd_2(dba)_3]$ (79.0 mg, 86.2 µmol, 15 mol-%). The resulting green solution was stirred at room temperature for 16 h before it was diluted with Et_2O (30 mL) and water (10 mL). The phases were separated, the organic layer was washed with water (3x10 mL) and the combined aqueous layers were back-extracted with Et_2O (20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (pentane/Et_2O 75:1 → 50:1; two chromatographic runs were necessary to obtain a pure product) afforded **4** (421.4 mg, 0.49 mmol, 86%) as a colorless oil.

TLC: R_f = 0.50 (hexane/EtOAc 20:1, UV, CPS); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.30-7.24 (m, 2H), 7.21-7.14 (m, 3H), 5.79 (ddt, *J* = 17.1, 10.1, 6.3, 1H), 5.78 (ddt, *J* = 17.2, 10.0, 6.3, 1H), 5.69 (s, 1H), 5.34 (tq, *J* = 7.3, 1.3, 1H), 5.19 (tm, *J* = 7.2, 1H), 5.12-4.97 (m, 4H), 4.96-4.91 (m, *J* = 10.1, 1H), 3.85-3.77 (m, 1H), 3.75-3.68 (m, 1H, hidden), 3.73 (t, *J* = 6.7, 2H), 3.48-3.37 (m, 2H), 3.35 (d, *J* = 7.2, 2H), 2.81-2.66 (m, 2H), 2.34 (td, *J* = 6.7, 1.0, 2H), 2.26 (dd, *J* = 13.2, 4.5, 1H), 2.10 (dd, *J* = 13.2, 7.3, 1H), 2.08-2.01 (m, 2H), 1.84-1.75 (m, 1H), 1.74-1.63 (m, 3H), 1.70 (s, 3H), 1.62-1.53 (m, 2H), 1.60 (s, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.87 (s, 9H), 0.05 (s, 6H), 0.02 (s, 3H), 0.02 (s, 3H), 0.02 (s, 3H), −0.01 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 165.6, 157.7, 141.8, 137.4, 136.5, 135.2, 133.5, 128.5, 128.4, 125.8, 124.9, 123.0, 117.9, 166.6, 114.4, 68.9, 68.8, 68.4, 61.6, 47.2, 43.4, 42.7, 41.0, 36.9, 36.6, 34.8, 34.3, 32.7, 26.1, 26.1, 26.1, 18.4, 18.2, 16.7, 16.4, −4.1, −4.3, −4.4, −5.2; **IR** (thin film): ν 3081, 3062, 3027, 2953, 2928, 2896, 2887, 2856, 1713, 1647, 1634, 1495, 1472, 1463, 1435, 1407, 1387 1370, 1361, 1252, 1184, 1146, 1092, 1059, 1030, 1005, 995, 937, 910, 857, 834, 807, 773, 738, 733, 697; **HRMS** (ESI): calculated for $C_{50}H_{88}NaO_5Si_3$ $[M+Na]^+$: 875.5832, found 875.5839; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: −2.6 (c 0.8 in $CHCl_3$).

Macrolactone 26: To a solution of **4** (50.1 mg, 58.6 µmol, 1.0 equiv.) in freshly distilled (from CaH_2) DCM (37 mL) at room temperature was added Grubbs-I catalyst (0.7 mL of a

stock solution of 5.8 mg catalyst in 2 mL DCM, *ca.* 4 mol-%) and the solution (the color turned from purple to orange within about 30 min) was stirred at room temperature. Additional catalyst was added after 2.5 h (0.7 mL of the stock solution) and after a total of 3.5 h (0.6 mL of the stock solution; *ca.* 12 mol-% in total). After a total of 4.5 h, DMSO (25 µL, 50 equiv. relative to the catalyst) was added to the solution and stirring was continued for 17 h. The reaction mixture was concentrated under reduced pressure and the crude product was purified by flash chromatography (hexane/EtOAc 60:1), affording macrocycle **26** (37.1 mg, 44.9 µmol, 77%) as a colorless oil. In addition, a small amount (*ca.* 5-10%; not exactly determined) unreacted **4** was re-isolated.

Note: If the reaction was allowed to go to completion, a lower yield was obtained due to the formation of side products. Macrolactone **26** was not stored but directly employed in the subsequent step.

TLC: R_f = 0.42 (hexane/EtOAc 20:1, UV, CPS); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.30-7.24 (m, 2H), 7.20-7.14 (m, 3H), 5.63 (m, 1H), 5.44-5.31 (m, 2H), 5.29-5.16 (m, 2H), 5.05-4.99 (m, 1H), 4.02 (dd, *J* = 12.7, 9.1, 1H), 3.91-3.83 (m, 1H), 3.78-3.68 (m, 1H), 3.75 (t, *J* = 6.6, 2H), 3.36 (d, *J* = 7.2, 2H), 2.61-2.34 (m, 3H), 2.36 (tm, *J* = 6.6, 2H), 2.28-2.21 (m, 2H), 2.17-1.99 (m, 2H), 1.94-1.85 (m, 2H), 1.70 (s, 3H), 1.68-1.54 (m, 3H), 1.48 (s, 3H), 1.39 (ddd, *J* = 15.4, 8.5, 2.5, 1H), 0.89 (s, 9H), 0.88 (s, 9H), 0.87 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H), 0.05 (s, 6H), 0.00 (s, 3H), −0.03 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 165.7, 158.3, 141.9, 136.7, 134.2, 129.0, 128.5, 128.4, 125.8, 125.7, 125.6, 122.8, 118.2, 69.9, 69.0, 67.4, 61.2, 49.8, 43.5, 40.4, 39.1, 36.9, 34.9, 34.6, 34.3, 31.1, 26.2, 26.1, 26.1, 18.4, 18.2, 18.1, 16.9, 16.4, −2.9, −3.7, −4.0, −4.6, −5.2, −5.2; **IR** (thin film): ν 3029, 3024, 2953, 2928, 2856, 1717, 1646, 1495, 1472, 1463, 1453, 1387, 1362, 1255, 1231, 1179, 1151, 1129, 1100, 1079, 1038, 1005, 965, 931, 909, 832, 809, 792, 772, 733. 727, 697; **HRMS** (ESI): calculated for $C_{48}H_{85}O_5Si_3$ $[M+H]^+$: 825.5699, found 825.5688; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: −1.4 (c 0.3 in $CHCl_3$).

Primary alcohol 27: To a solution of **26** (37.1 mg, 44.8 µmol, 1.0 equiv.) in THF (2.6 mL) and pyridine (0.8 mL) at 0 °C was added dropwise HF·py (70% HF in pyridine, 0.4 mL). The milky reaction mixture was stirred at 0 °C for 4 h (additional pyridine (0.1 mL) and HF·py (0.05 mL) were added after 2 h). The reaction mixture was then added dropwise to a stirring mixture of sat. aq. $NaHCO_3$ (10 mL) and EtOAc (5 mL) (after complete addition, the pH should be >7). The phases were separated and the aqueous layer was extracted with EtOAc (3x10 mL). The

combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 9:1 → 8:2) afforded primary alcohol **27** (25.7 mg, 36.1 µmol, 81%) as a colorless oil. In addition, a small amount of unreacted **26** (*ca.* 7%) was re-isolated.

TLC: R_f = 0.55 (hexane/EtOAc 7:3, UV, CPS); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.31-7.24 (m, 2H), 7.21-7.14 (m, 3H), 5.66 (m, 1H), 5.42 (ddd, *J* = 15.0, 8.7, 4.8, 1H), 5.36 (tq, *J* = 7.3, 1.3, 1H), 5.26 (t, *J* = 7.7, 1H), 5.25-5.17 (m, 1H), 5.10-5.02 (m, 1H), 4.04 (dd, *J* = 12.9, 8.7, 1H), 3.92-3.85 (m, 1H), 3.82-3.67 (m, 3H), 3.37 (d, *J* = 7.3, 2H), 2.64-2.40 (m, 3H), 2.41 (td, *J* = 6.4, 1.0, 2H), 2.30-2.20 (m, 2H), 2.17-1.99 (m, 2H), 1.97-1.86 (m, 2H), 1.76-1.53 (m, 3H), 1.71 (m, 3H), 1.49 (s, 3H), 1.42 (ddd, *J* = 15.4, 8.5, 2.5, 1H), 1.38-1.30 (br, O*H*), 0.88 (s, 9H), 0.87 (s, 9H), 0.11 (s, 3H), 0.11 (s, 3H), 0.01 (s, 3H), −0.02 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 165.6, 157.1, 141.8, 136.6, 134.4, 129.3, 128.5, 128.4, 125.8, 125.6, 125.4, 122.9, 119.1, 70.2, 69.0, 67.3, 60.1, 49.8, 43.5, 40.3, 39.2, 36.8, 34.6, 34.6, 34.3, 31.0, 26.2, 26.1, 18.2, 18.1, 16.8, 16.4, −2.8, −3.6, −4.0, −4.6; **IR** (thin film): ν 3443, 2950, 2928, 2855, 1716, 1642, 1472, 1462, 1453, 1362, 1254 1230, 1179, 1151, 1132, 1102, 1077, 1038, 1005, 965, 930, 833, 805, 772, 730, 697; **HRMS** (ESI): calculated for $C_{42}H_{70}NaO_5Si_2$ $[M+Na]^+$: 733.4654, found 733.4644; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: +3.7 (c 1.3 in $CHCl_3$).

Acid 28: To a solution of **27** (13.5 mg, 19.0 µmol, 1.0 equiv.) in THF (0.5 mL) at room temperature was added Dess-Martin periodinane (25.0 mg, 58.8 µmol, 3.1 equiv.). The reaction mixture was stirred at room temperature for 15 min before 2-methyl-2-butene (130 µL) and *t*-BuOH (0.45 mL) were added followed by a solution of $NaClO_2$ (6.5 mg, 71.9 µmol, 3.8 equiv.) and $NaH_2PO_4{\cdot}H_2O$ (12.6 mg, 91.5 µmol, 4.8 equiv.) in water (0.4 mL) (dropwise by Pasteur pipette). The mixture was stirred at room temperature for 20 min. Sat. aq. NH_4Cl (3 mL) and EtOAc (5 mL) were added, the phases were separated and the aqueous layer was extracted with EtOAc (4x5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 8:2 → 7:3; with 0.2% AcOH) afforded acid **28** (11.1 mg, 15.3 µmol, 81%) as a colorless oil. Residual AcOH was removed by azeotropic distillation with toluene.

Note: Attempted purification with DCM/MeOH/AcOH 94:6:0.1 or DCM/MeOH 94:6 did not afford a pure product.

TLC: R_f = 0.38 (DCM/MeOH 20:1, UV, CPS); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.30-7.24 (m, 2H), 7.20-7.14 (m, 3H), 5.73 (br s, 1H), 5.41 (ddd, *J* = 15.1, 8.7, 4.8, 1H), 5.35 (tq, *J* = 7.3, 1.3, 1H), 5.29-5.18 (m, 2H), 5.09-5.03 (m, 1H), 4.07 (dd, *J* = 13.3, 8.9, 1H), 3.91-3.84 (m, 1H), 3.74-3.66 (m, 1H), 3.36 (d, *J* = 7.2, 2H), 3.21 (dd, *J* = 15.2, 1.3, 1H), 3.14 (dd, *J* = 15.2, 0.8, 1H), 2.63-2.44 (m, 3H), 2.30-2.20 (m, 2H), 2.16-1.98 (m, 2H), 1.97-1.85 (m, 2H), 1.74-1.54 (m, 3H), 1.70 (s, 3H), 1.48 (s, 3H), 1.41 (ddd, *J* = 15.4, 8.5, 2.5, 1H), 0.88 (s, 9H), 0.87 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H), 0.01 (s, 3H), −0.02 (s, 3H) (COO*H* not assigned); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 174.6, 165.1, 151.7, 141.8, 136.6, 134.3, 129.7, 128.5, 128.4, 125.8, 125.5, 125.0, 122.9, 121.2, 70.5, 69.0, 67.3, 49.8, 44.8, 40.4, 39.2, 36.8, 34.6, 34.6, 34.3, 31.1, 26.2, 26.1, 18.2, 18.1, 16.8, 16.4, −2.9, −3.7, −4.0, −4.6; **IR** (thin film): ν 3028, 2954, 2927, 2856, 1715, 1648, 1495, 1472, 1463, 1370, 1256, 1181, 1152, 1102, 1077, 1037, 1005, 966, 933, 833, 805, 773; **HRMS** (ESI): calculated for $C_{42}H_{69}O_6Si_2$ $[M+H]^+$: 725.4627, found 725.4626; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: −7.2 (c 0.3 in MeOH).

Ripostatin B (2): A polypropylene tube was charged with **28** (5.8 mg, 8.0 µmol) and immersed in a cooling bath at about −10 °C (NaCl/ice). A precooled (*ca.* −10 °C) 5% (w/v) solution of HF in aq. acetonitrile (0.5 mL; prepared from 250 µL 48% aq. HF and 2.15 mL acetonitrile) was then added, resulting in slow dissolution of **28**). The reaction mixture was stirred at temperatures between 0 °C and −10 °C for 3 h (additional 0.25 mL of the stock solution were added after 2 h) before it was added to a stirring mixture of sat. aq. $NaHCO_3$ (7 mL) and EtOAc (3 mL) (after complete addition, the pH should be >7). The phases were separated and the aqueous layer was extracted with EtOAc (5x5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (DCM/MeOH 9:1 → 9:1 + 0.2% AcOH) afforded ripostatin B (**2**) (3.5 mg, 7.0 µmol, 88%) as a colorless oil. Residual AcOH was removed by azeotropic distillation with toluene.

TLC: R_f = 0.30 (DCM/MeOH 9:1, UV, CPS); **^{1}H-NMR** (500 MHz, MeOH-d_4): δ 7.25-7.21 (m, 2H), 7.17-7.10 (m, 3H), 5.72 (br s, 1H), 5.40-5.33 (m, 1H), 5.35 (tm, *J* = 7.3, 1H), 5.32-5.25 (m, 1H), 5.27 (t, *J* = 7.7, 1H), 5.19-5.14 (m, 1H), 4.00 (dd, *J* = 13.1, 8.8, 1H), 3.80-3.74 (m, 1H), 3.61-3.54 (m, 1H), 3.35 (d, *J* = 7.3, 2H), 3.16 (d, *J* = 14.8, 1H), 3.08 (dd, *J* = 14.8, 1H), 2.66-2.58 (m, 1H), 2.55 (dd, *J* = 13.0, 4.3, 1H), 2.49-2.42 (m, 1H), 2.30-2.15 (m, 3H), 2.14-2.01 (m, 2H), 1.96 (t, *J* = 11.7, 1H), 1.73 (s, 3H), 1.72-1.64 (m, 1H), 1.62-1.54 (m, 2H), 1.50 (s, 3H), 1.34

(ddd, *J* = 15.7, 9.0, 2.7, 1H); **^{13}C-NMR** (125 MHz, MeOH-d_4): δ 173.8, 167.0, 155.1, 142.9, 137.0, 135.5, 130.2, 129.4, 129.2, 126.7, 126.6, 126.3, 124.6, 121.0, 71.2, 68.7, 66.3, 51.0, 45.9, 41.1, 38.4, 37.8, 36.7, 35.4, 35.1, 31.9, 16.8, 16.3; **IR** (thin film): ν 3348, 3024, 2960, 2918, 2850, 1717, 1647, 1559, 1495, 1453, 1375, 1261, 1232, 1182, 1154, 1097, 1028, 967, 867, 800, 757, 751, 743; **HRMS** (ESI): calculated for $C_{30}H_{40}NaO_6$ $[M+Na]^+$: 519.2717, found 519.2716; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: +27.9 (c 0.3 in MeOH).

Analog 29: A polypropylene tube was charged with **27** (8.2 mg, 11.5 µmol) and immersed in a cooling bath at −10 °C bath (NaCl/ice). A 5% (w/v) solution of HF in aq. acetonitrile (125 µL 48% aq. HF in 1.08 mL acetonitrile; precooled to −10 °C) was added, the reaction was allowed to warm to 0 °C in the cooling bath and was stirred at that temperature for 2.5 h. The solution was then added dropwise to a stirring mixture of sat. aq. $NaHCO_3$ (10 mL) and EtOAc (5 mL) (after complete addition, the pH should be >7). The phases were separated and the aqueous layer was extracted with EtOAc (5x6 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was filtered through a pipette filled with silica gel (DCM/MeOH 95:5) and then purified by preparative HPLC (63% MeOH in water for 2 min, then gradient to 100% MeOH over the course of 11 min; R_t = 8.7 min), furnishing **29** (3.7 mg, 7.71 µmol, 67%) as a colorless oil.

Alternative conditions for the purification of **29** by preparative HPLC: 33% acetonitrile in water for 2 min, then gradient to 80% acetonitrile over the course of 18 min; R_t = 10.8 min.

TLC: R_f = 0.22 (DCM/MeOH 95:5, UV, CPS); **^{1}H-NMR** (500 MHz, CD_3OD): δ 7.26-7.20 (m, 2H), 7.18-7.10 (m, 3H), 5.66 (m, 1H), 5.41-5.33 (m, 2H), 5.30-5.22 (m, 2H), 5.19-5.13 (m, 1H), 3.98 (dd, *J* = 12.9, 8.9, 1H), 3.81-3.74 (m, 1H), 3.73-3.64 (m, 2H), 3.61-3.54 (m, 1H), 3.35 (d, *J* = 7.4, 2H), 2.67-2.59 (m, 1H), 2.50-2.42 (m, 2H), 2.39 (td, *J* = 6.7, 1.0, 2H), 2.27 (dd, *J* = 15.5, 3.9, 1H), 2.24-2.16 (m, 2H), 2.14-2.01 (m, 2H), 1.97 (t, *J* = 11.7, 1H), 1.73 (s, 3H), 1.72-1.64 (m, 1H), 1.62-1.55 (m, 2H), 1.50 (s, 3H), 1.34 (ddd, *J* = 15.6, 9.0, 2.7, 1H); **^{13}C-NMR** (125 MHz, CD_3OD): δ 167.4, 159.5, 142.9, 137.0, 135.4, 129.8, 129.3, 129.2, 126.9, 126. 7, 126.3, 124.5, 119.1, 71.0, 68.8, 66.3, 60.6, 51.0, 43.9, 41.1, 38.5, 37.8, 36.7, 35.3, 35.1, 31.9, 16.8, 16.3; **IR** (thin film): ν 3338, 2923, 2853, 1715, 1700, 1696, 1685, 1653, 1646, 1636, 1559, 1452, 1448, 1437, 1374, 1363, 1231, 1219, 1182, 1153, 1120, 1100, 1044, 996, 966, 854, 842, 750, 741, 728, 724; **HRMS** (ESI): calculated for $C_{30}H_{42}NaO_5$ $[M+Na]^+$: 505.2924, found 505.2944; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: +36.7 (c 0.2 in MeOH).

(3*E*,6*E*,9*E*,12*R*,14*S*)-4-(2-aminoethyl)-12-((*t*-butyldimethylsilyl)oxy)-14-((*R*,*E*)-2-((tert-butyldimethylsilyl)oxy)-5-methyl-7-phenylhept-5-en-1-yl)-10-methyl-oxacyclotetradeca-3,6,9-trien-2-one (E-4): To **27** (25.4 mg, 35.7 µmol, 1.0 equiv.), phthalimide (7.88 mg, 53.6 µmol, 1.5 equiv.) and triphenylphosphine (14.1 mg, 53.6 µmol, 1.5 equiv.) in THF (400 µL) at 0 °C was added diethyl azodicarboxylate (50 µL of a stock solution of 84 µL DEAD in 500 µL THF, 45.7 µmol, 1.3 equiv.). After stirring at 0 °C for 1 h, the reaction was diluted with water (5 mL) and EtOAc (10 mL). The phases were separated and the aqueous layer was extracted with EtOAc (3x5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 9:1) furnished phthalimide **30** (17.0 mg, 20.2 µmol, 57%) as a yellow oil.

A solution of **30** (13.0 mg, 15.5 µmol, 1.0 equiv.) and hydrazine hydrate (65 µL of a solution of 100 µL $N_2H_4{\cdot}H_2O$ (64% aq.) in 500 µL EtOH, 139 µmol, 9.0 equiv.) in EtOH (0.2 mL) was heated to 50 °C for 1 h, during which time a white precipitate formed. Sat. aq. $NaHCO_3$ (5 mL) and EtOAc (5 mL) were added, the phases were separated and the aqueous layer was extracted with EtOAc (4x5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was filtered through a plug of silica gel (DCM/MeOH 95:5), affording primary amine **31** (*ca.* 4 mg, *ca.* 80% pure) as a yellow oil.

To **31** (11.3 mg, 15.9 µmol, 1.0 equiv., *ca.* 80% pure) in DCM (100 µL) at 0 °C was added NEt_3 (80 µL of a stock solution of 22 µL NEt_3 in 380 µL DCM, 31.5 µmol, 2.0 equiv.) followed by methyl chloroformate (44 µL of a stock solution of methyl chloroformate (12 µL) in DCM (390 µL), 16.6 µmol, 1.05 equiv.). After 30 min, the cooling bath was removed and the reaction was stirred at room temperature. After 2 h, additional methyl chloroformate (22 µL of the above stock solution) and NEt_3 (40 µL of the above stock solution) were added. After additional 30 min, the reaction mixture was diluted by the addition of water (3 mL) and EtOAc (10 mL). The phases were separated and the aqueous layer was extracted with EtOAc (3x5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was filtered through a plug of silica gel (hexane/EtOAc 6:1), affording carbamate **E-4** (5 mg, 6.5 µmol, 41%) as a yellow oil.

TLC: R_f = 0.38 (hexane/EtOAc 5:1, UV, CPS); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.30-7.24 (m, 2H), 7.21-7.14 (m, 3H), 5.60 (br s, 1H), 5.46-5.32 (m, 2H), 5.26 (t, *J* = 7.8, 1H), 5.18 (ddd, *J* = 15.3, 8.6, 5.0, 1H), 5.09-5.01 (m, 1H), 4.67-4.56 (br, 1H), 4.02 (dd, *J* = 13.1, 8.7, 1H), 3.91-3.83 (m,

1H), 3.76-3.67 (m, 1H), 3.66 (s, 3H), 3.37-3.26 (m, 2H), 3.36 (d, *J* = 7.4, 2H), 2.64-2.44 (m, 2H), 2.44-2.19 (m, 5H), 2.19-1.99 (m, 2H), 1.99-1.84 (m, 2H), 1.75-1.54 (m, 3H), 1.70 (s, 3H), 1.48 (s, 3H), 1,41 (ddd, J = 15.5, 8.4, 2.6, 1H), 0.88 (s, 9H), 0.87 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H), 0.01 (s, 3H), −0.03 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 165.5, 157.3, 157.0, 141.8, 136.7, 134.4, 129.4, 128.5, 128.4, 125.8, 125.5, 125.4, 122.8, 118.8, 70.2, 69.0, 67.4, 52.3, 49.8, 40.4, 40.3, 39.2, 38.6, 36.9, 34.5, 34.4, 34.3, 31.0, 26.2, 26.1, 18.2, 18.1, 16.8, 16.4, −2.9, −3.6, −4.0, −4.6; **IR** (thin film): ν 3365, 2954, 2928, 2855, 1716, 1643, 1523, 1463, 1380, 1255, 1180, 1079, 1032, 1009, 962, 929, 834, 773 cm^{-1}; **HRMS** (ESI): calculated for $C_{44}H_{74}NO_6Si_2$ $[M+H]^+$: 768.5049, found 768.5044; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: −5.4 (c 0.3 in $CHCl_3$).

Analog 32: A polypropylene tube was charged with **E-4** (5.0 mg, 6.5 µmol) and immersed in an ice bath. A 5% solution of HF in aq. acetonitrile (0.9 mL; prepared from 0.25 mL 48% aq. HF and 2.15 mL acetonitrile), precooled to 0 °C, was added. The reaction was stirred at 0 °C for 3 h before it was added to a stirred mixture of sat. aq. $NaHCO_3$ (10 mL) and EtOAc (10 mL) (after complete addition, the pH should be >7). The phases were separated and the aqueous layer was extracted with EtOAc (3x10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was filtered through a plug of silica (DCM → DCM/MeOH 90:10) and was purified further by preparative HPLC (38% acetonitrile in water for 2 min, then gradient to 80% acetonitrile over the course of 18 min; R_t = 11.0 min), furnishing **32** (1.8 mg, 3.33 µmol, 51%) as a colorless oil.

TLC: R_f = 0.60 (DCM/MeOH 9:1, UV, CPS); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.32-7.24 (m, 2H), 7.21-7.13 (m, 3H), 5.62 (s, 1H), 5.42-5.32 (m, 2H), 5.28 (t, *J* = 7.6, 1H), 5.24-5.15 (m, 1H), 5.14-5.08 (m, 1H), 4.8-4.6 (br, 1H), 3.96 (dd, *J* = 13.0, 8.6, 1H), 3.86 (t, *J* = 9.5, 1H), 3.73-3.62 (m, 1H), 3.66 (s, 3H), 3.42-3.25 (m, 2H), 3.35 (d, *J* = 7.2, 2H), 2.90-2.60 (br, O*H*), 2.66-2.57 (m, 1H), 2.54-2.45 (m, 1H), 2.42 (dd, *J* = 13.0, 4.4, 1H), 2.38-2.32 (m, 2H), 2.28-2.14 (m, 3H), 2.14-2.06 (m, 1H), 2.02 (t, *J* = 11.6, 1H), 1.98-1.91 (m, 1H), 1.84 (dd, J = 14.3, 7.3, 1H) 1.73 (s, 3H), 1.67-1.54 (m, 3H), 1.49 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 165.7, 157.2, 157.0, 141.7, 136.2, 134.1, 129.1, 128.5, 128.4, 125.9, 125.6 (2 carbons according to HSQC) 123.6, 118.6, 70.9, 69.2, 65.8, 52.3, 49.8, 40.2, 39.7, 38.6, 37.5, 36.7, 35.9, 34.3 (2 signals carbons according to HSQC), 31.0, 16.6, 16.3; **IR** (thin film): ν 3353, 2924, 2852, 1703, 1646, 1523, 1495, 1454, 1377, 1260, 1230, 1181, 1153, 1081, 1021, 966, 854, 801, 753 cm^{-1}; **HRMS** (ESI): calculated for for $C_{32}H_{46}NO_6$ $[M+H]^+$: 540.3320, found 540.3317; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: +34.0 (c 0.2, $CHCl_3$).

Carboxylic acid 34: To a solution of **33** (0.30 g, 0.84 mmol, 1.0 equiv.) in DCM (9 mL) at 0 °C was added MnO_2 (1.46 g, 16.8 mmol, 20 equiv.) in one portion. After stirring at room temperature for 15 h, the black mixture was filtered through a plug of celite (eluting with Et_2O). The filtrate was concentrated under reduced pressure, giving an orange oil which was directly employed in the next step.

To a solution of the above crude aldehyde in *t*-BuOH (2.9 mL), THF (1 mL), 2-methyl-2-butene (1 mL) at room temperature was added a solution of $NaH_2PO_4{\cdot}H_2O$ (0.51 mg, 3.70 mmol, 4.4 equiv., 1.7 w/w aldehyde) and $NaClO_2$ (0.48 g, 4.23 mmol, 5.0 equiv.) in water (2.9 mL) by Pasteur pipette. The reaction mixture was vigorously stirred at room temperature for 1 h before sat. aq. NH_4Cl (6 mL) and DCM (10 mL) were added. The phases were separated and the aqueous layer was extracted with DCM (3x10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 3:1 with 0.1% AcOH) furnished acid **100** (283 mg, 0.76 mmol, 91%) as a white solid.

TLC: R_f = 0.49 (hexane/EtOAc 3:1, UV, CPS); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.43 (t, *J* = 1.0, 1H), 3.63 (t, *J* = 6.0, 2H), 2.84 (td, *J* = 7.4, 0.7, 2H), 1.86-1.77 (m, 2H), 0.90 (s, 9H), 0.05 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 169.0, 124.8, 124.6, 61.1, 45.0, 32.3, 26.1, 18.4, −5.2; **IR** (thin film): ν 3027, 2952, 2928, 2886, 2857, 1700, 1615, 1471, 1406, 1362, 1297, 1254, 1223, 1106, 1028, 1006, 970, 938, 834, 781 cm^{-1}; **HRMS** (ESI): calculated for $C_{12}H_{23}INaO_3Si$ $[M+Na]^+$: 393.0353, found 393.0353.

Ester 35: To a solution of alcohol **27** (36.1 mg, 60.1 µmol, 1.0 equiv.), acid **34** (44.5 mg, 0.12 mmol, 2.0 equiv.) and NEt_3 (42 µL, 0.30 mmol, 5.0 equiv.) in toluene (0.7 mL) at −78 °C was added DMAP (18.3 mg, 0.15 mmol, 2.5 equiv.) in one portion. After 5 min, 2,4,6-trichlorobenzoyl chloride (28 µL, 0.18 mmol, 3.0 equiv.) was added. A white suspension was obtained which was allowed to warm slowly to −40 °C in the cooling bath (remaining dry ice was removed from the cooling bath), giving a yellow suspension. The temperature was then kept between −30 °C and −40 °C for 2.5 h before sat. aq. $NaHCO_3$ (10 mL) and EtOAc (10 mL) were added to the mixture. The phases were separated and the aqueous layer was extracted with EtOAc (3x10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (pentane/Et_2O 40:1) afforded ester **35** (22.6 mg, 23.7 µmol, 39%) as a pale green oil.

TLC: R_f = 0.78 (hexane/EtOAc 20:1, UV, CPS); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.31-7.24 (m, 2H), 7.21-7.14 (m, 3H), 6.29 (t, *J* = 1.0, 1H), 5.79 (ddt, *J* = 17.1, 10.1, 6.4, 1H), 5.34 (tq, *J* = 7.4, 1.2, 1H), 5.20 (br t, *J* = 7.2, 1H), 5.15-5.06 (m, 1H), 5.01 (ddd, *J* = 17.1, 3.6, 1.7, 1H), 4.94 (ddd, *J* = 10.1, 3.3, 1.4, 1H), 3.89-3.79 (m, 1H), 3.79-3.70 (m, 1H), 3.61 (t, *J* = 6.0, 2H), 3.35 (d, *J* = 7.3, 2H), 2.81-2.65 (m, 4H), 2.25 (dd, *J* = 13.3, 4.5, 1H), 2.12 (dd, *J* = 13.3, 7.2, 1H), 2.09-2.01 (m, 2H), 1.89-1.66 (m, 6H), 1.70 (s, 3H), 1.61 (s, 3H), 1.62-1.55 (m, 2H), 0.90 (s, 9H), 0.88 (s, 9H), 0.87 (s, 9H), 0.05 (s, 6H), 0.03 (s, 3H), 0.02 (s, 6H), −0.01 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 163.9, 141.8, 137.4, 136.5, 133.4, 128.5, 128.4, 125.8, 125.6, 125.0, 123.0, 120.5, 114.4, 70.2, 68.8, 68.3, 61.1, 47.2, 44.5, 43.0, 42.4, 36.5, 34,8, 34.3, 32.7, 32.4, 26.1, 26.1, 18.4, 18.2, 16.8, 16.4, −4.1, −4.2, −4.3, −5.2. **IR** (thin film): ν 2954, 2951, 2927, 2856, 1728, 1620, 1495, 1472, 1463, 1388, 1361, 1255, 1191, 1166, 1105, 1061, 1005, 981, 835, 774 cm^{-1}; **HRMS** (ESI): calculated for $C_{48}H_{86}IO_5Si_3$ $[M+H]^+$: 953.4822, found 953.4806; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: −5.4 (c 1.0 in $CHCl_3$).

Tetraene 36: Argon was passed through a solution of ester **35** (22.6 mg, 23.7 µmol, 1.0 equiv.) and triphenylarsine (3.6 mg, 11.9 µmol, 0.5 equiv.) in DMF (0.5 mL) for 5 min. Allyltributylstannane (15 µL, 47.4 µmol, 2.0 equiv.) was added followed by $[Pd_2(dba)_3]$ (6.5 mg, 7.1 µmol, 30 mol-%). The resulting dark green solution was stirred at room temperature for 16 h. Water (10 mL) and Et_2O (10 mL) were added, the phases were separated and the organic layer was washed with water (3x10 mL). The combined aqueous layers were extracted with Et_2O (10 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 40:1 → 30:1) furnished tetraene **36** (18.0 mg, 20.7 µmol, 88%) as a pale green oil.

TLC: R_f = 0.30 (hexane/EtOAc 30:1, UV, CPS); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.32-7.23 (m, 2H), 7.21-7.13 (m, 3H), 5.86-5.71 (m, 2H), 5.66 (br s, 1H), 5.34 (t, *J* = 7.3, 1H), 5.19 (t, *J* = 6.7, 1H), 5.12-4.88 (m, 5H), 3.88-3.77 (m, 1H), 3.77-3.68 (m, 1H), 3.60 (t, *J* = 6.3, 2H), 3.47-3.38 (m, 2H), 3.35 (d, *J* = 7.2, 2H), 2.82-2.65 (m, 2H), 2.32-2.16 (m, 3H), 2.15-1.98 (m, 3H), 1.90-1.47 (m, 8H), 1.70 (s, 3H), 1.60 (s, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.86 (s, 9H), 0.05 (s, 6H), 0.02 (s, 3H), 0.02 (m, 6H), −0.01 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 165.8, 160.8, 141.8, 137.4, 136.5, 135.4, 133.5, 128.5, 128.4, 125.8, 124.9, 123.0, 116.5, 116.3, 114.4, 68.9, 68.7, 68.4, 62.5, 47.2, 43.4, 42.7, 36.8, 36.5, 34.8, 34.3, 34.3, 32.7, 30.8, 26.1, 26.1, 18.4, 18.2, 16.7,

16.4, −4.1, −4.3, −4.4, −5.2; **IR** (thin film): ν 2954, 2928, 2896, 2857, 1714, 1646, 1633, 1472, 1463, 1437, 1387, 1362, 1255, 1183, 1146, 1104, 1005, 939, 911, 835, 774 cm^{-1}; **HRMS** (ESI): calculated for $C_{51}H_{91}O_5Si_3$ $[M+H]^+$: 867.6169, found 867.6162; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: +0.33 (c 0.8 in $CHCl_3$).

Analog 38: To a solution of **36** (18.0 mg, 20.7 µmol, 1.0 equiv.) in DCM at room temperature was added Grubbs-I catalyst (1 mL of a stock solution of 3.4 mg catalyst in 2 mL DCM, 10 mol-%). The solution was stirred at room temperature for 45 min, during which time the color turned from purple to orange. DMSO was added before the reaction had reached completion) and stirring was continued for 20 h. Then, the solvent was removed under reduced pressure and the crude product was purified by flash chromatography (pentane/Et_2O 40:1), to afford macrolactone **37** (8.7 mg; not entirely pure) as a colorless oil. This material was directly used in the next step.

A polypropylene tube was charged with **37** (8.7 mg) and immersed in an ice bath. A solution of 5% HF in aq. acetonitrile (1.5 mL; prepared from 0.5 mL 48% aq. HF and 4.3 mL acetonitrile), precooled to 0 °C, was added. The reaction mixture was stirred at 0 °C for 2 h and was then transferred to a stirred mixture of sat. aq. $NaHCO_3$ (10 mL) and EtOAc (10 mL) (after complete addition, the pH should be >7). The phases were separated and the aqueous layer was extracted with EtOAc (3x10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (DCM → DCM/MeOH 95:5) followed by preparative HPLC (33% acetonitrile in water for 2 min, then gradient to 80% acetonitrile over the course of 18 min; R_t = 11.2 min) furnished **38** (2.7 mg, 5.44 µmol, 26% over two steps) as a colorless oil.

TLC: R_f = 0.25 (DCM/MeOH 95:5, UV, CPS); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.21-7.14 (m, 2H), 7.10-7.03 (m, 3H), 5.51 (s, 1H), 5.31-5.22 (m, 2H), 5.18 (t, *J* = 7.6, 1H), 5.11 (ddd, J = 15.1, 8.5, 5.0, 1H), 5.02-4.95 (m, 1H), 3.87 (dd, *J* = 13.0, 8.7, 1H), 3.80-3.72 (m, 1H), 3.60-3.51 (m, 1H), 3.55 (t, *J* = 6.3, 2H), 3.25 (d, *J* = 7.5, 2H), 3.0-2.6 (br, O*H*), 2.55-2.45 (m, 1H), 2.43-2.35 (m, 1H), 2.32 (dd, *J* = 13.1, 4.7, 1H), 2.19-2.04 (m, 5H), 2.03-1.95 (m, 1H), 1.92 (t, *J* = 11.7, 1H), 1.88-1.79 (m, 1H), 1.74 (ddd, *J* = 14.4, 9.3, 1.8, 1H), 1.67-1.57 (m, 2H), 1.62 (s, 3H), 1.56-1.42 (m, 3H), 1.39 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 166.1, 160.8, 141.7, 136.2, 133.9, 128.8, 128.5, 128.4, 125.9, 125.9, 125.7, 123.6, 116.7, 70.7, 69.2, 65.8, 62.2, 49.7, 39.8, 37.5, 36.7, 36.4, 35.9, 34.8, 34.3, 31.1, 30.2, 16.6, 16.3; **IR** (thin film): ν 3309, 2922, 2851, 1715, 1455,

1376, 1260, 1020, 965, 799, 743, 698 cm^{-1}; **HRMS** (ESI): calculated for $C_{31}H_{44}NaO_5$ $[M+Na]^+$: 519.3081, found 519.3079; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: +35.1 (c 0.1 in $CHCl_3$).

Ketone 40a: To (+)-Ipc_2BCl (281 mg, 0.88 mmol, 2.1 equiv.) in DCM (1.5 mL) at −78 °C was added NEt_3 (200 µL, 1.46 mmol, 3.5 equiv.) followed by 2-pentanone (89 µL, 0.84 mmol, 2.0 equiv.). The reaction mixture was stirred at −78 °C for 3 h, during which time a white precipitate formed. A solution of aldehyde **9** (118 mg, 0.42 mmol, 1.0 equiv.) in DCM (1 mL, the vial was rinsed twice with 0.5 mL DCM) was added dropwise. The reaction was stirred at −78 °C for 4 h and was then allowed to stand in a freezer (−20 °C) for 2 days. The mixture was diluted with pH 7 phosphate buffer (5 mL) and DCM (3 mL), the phases were separated and the aqueous layer was extracted with DCM (3x10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was suspended in MeOH (1.2 mL) and pH 7 phosphate buffer (0.3 mL) before 30% aq. H_2O_2 (0.4 mL) was added dropwise at 0 °C. The suspension was stirred at room temperature for 90 min and was then poured into water (20 mL). DCM was added, the phases were separated and the aqueous layer was extracted with DCM (3x10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 8:1) furnished β-hydroxy ketone **40a** (101 mg, 0.27 mmol, 66%, >10:1 dr) as a colorless oil.

TLC: R_f = 0.40 (hexane/EtOAc 8:1, CPS); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.77 (ddt, *J* = 17.1, 10.1, 6.3, 1H), 5.19 (tm, *J* = 7.2, 1H), 4.99 (ddd, *J* = 17.1, 3.6, 1.8, 1H), 4.94 (ddd, *J* = 10.1, 3.3, 1.5, 1H), 4.24-4.15 (m, 1H), 4.07-3.98 (m, 1H), 3.46 (d, *J* = 2.1, O*H*), 2.73 (t, *J* = 6.6, 2H), 2.57-2.51 (m, 2H), 2.40 (t, *J* = 7.3, 2H), 2.26 (dd, *J* = 13.3, 5.3, 1H), 2.14 (dd, *J* = 13.2, 7.6, 1H), 1.66-1.46 (m, 4H), 1.62 (s, 3H), 0.91 (t, *J* = 7.5, 3H), 0.88 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 211.3, 137.1, 132.9, 125.2, 114.5, 70.6, 66.7, 49.8, 48.5, 45.8, 42.9, 32.5, 26.0, 18.1, 17.2, 16.7, 13.8, −4.0, −4.5; **IR** (thin film): ν 3505, 2957, 2929, 2857, 1707, 1638, 1463, 1409, 1362, 1254, 1168, 1090, 1004, 908, 834, 808, 773, 736 cm^{-1}; **HRMS** (ESI): calculated for $C_{21}H_{40}NaO_3Si$ $[M+Na]^+$: 391.2639, found 391.2643; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: −22.1 (c 1.1, $CHCl_3$).

Ketone 40b: To (+)-Ipc_2BCl (128 mg, 0.40 mmol, 2.8 equiv.) in DCM (0.6 mL) at −78 °C was added NEt_3 (86 µL, 0.62 mmol, 4.4 equiv.) followed by 5-methyl-2-hexanone (40 µL, 0.28 mmol, 2.0 equiv.). The reaction was stirred at −78 °C for 3 h, during which time a white

precipitate formed. A solution of aldehyde **9** (40.0 mg, 0.14 mmol, 1.0 equiv.) in DCM (0.6 mL, the vial was rinsed twice with 0.4 mL) was added dropwise and the mixture was stirred at −78 °C for 4 h and then at −20 °C (cryostat) for 16 h. The reaction mixture was diluted with pH 7 phosphate buffer (5 mL) and DCM (3 mL), the phases were separated and the aqueous layer was extracted with DCM (3x10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was suspended in MeOH (1.2 mL) and pH 7 phosphate buffer (0.3 mL) before 30% aq. H_2O_2 (0.4 mL) was added dropwise at 0 °C. The suspension was stirred at room temperature for 90 min and was then poured into water (20 mL). DCM was added, the phases were separated and the aqueous layer was extracted with DCM (3x10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 9:1) afforded ketone **40b** (39.0 mg, 0.10 mmol, 70%, >10:1 dr) as a colorless oil.

TLC: R_f = 0.29 (hexane/EtOAc 9:1, CPS); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.78 (ddt, *J* = 17.2, 10.1, 6.3, 1H), 5.19 (tm, *J* = 7.3, 1H), 5.00 (ddd, *J* = 17.2, 3.6, 1.8, 1H), 4.95 (ddd, *J* = 10.1, 3.3, 1.4, 1H), 4.25-4.14 (m, 1H), 4.07-3.99 (m, 1H), 3.45 (d, *J* = 2.1, 1H, O*H*), 2.74 (t, *J* = 6.7, 2H), 2.59-2.52 (m, 2H), 2.42 (dd, *J* = 7.5, 6.7, 2H), 2.26 (dd, *J* = 13.2, 5.2, 1H), 2.15 (dd, *J* = 13.2, 7.5, 1H), 1.62 (s, 3H), 1.62-1.42 (m, 5H), 0.90-0.86 (6H), 0.89 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 211.6, 137.1, 132.9, 125.1, 114.5, 70.6, 66.7, 49.8, 48.4, 42.9, 41.9, 32.5, 32.4, 27.8, 26.0, 22.5, 18.1, 16.7, −4.0, −4.5; **IR** (thin film): ν 3512, 2955, 2929, 2857, 1706, 1472, 1410, 1386, 1368, 1254, 1075, 1005, 908, 835, 809, 772 cm^{-1}; **HRMS** (ESI): calculated for $C_{23}H_{44}NaO_3Si$ $[M+Na]^+$: 419.2952, found 419.2957; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: −21.7 (c 0.7 in $CHCl_3$).

Ester 41a: Preparation of SmI_2:[45]A brown mixture of samarium powder (41.2 mg, 0.27 mmol) and I_2 (62.6 mg, 0.25 mmol) in THF (3.5 mL) under argon was heated to 80 °C for 30 min, resulting in the formation of a dark blue solution of SmI_2 (*ca.* 0.08m). This solution was allowed to cool to room temperature and was then used immediately.

To a solution of propionaldehyde (118 µL, 1.64 mmol, 6.0 equiv.) in THF (2 mL) at −20 °C (cryostat) was added SmI_2 (1.4 mL of the above solution, 0.11 mmol, 0.4 equiv.), resulting in the formation of a yellow solution within about 30 seconds. To this solution was added dropwise a solution of **40a** (101 mg, 0.27 mmol, 1 equiv.) in THF (1 mL, the vial was rinsed

twice with 0.5 mL). The reaction mixture was stirred at −20 °C for 1 h. Sat. aq. $NaHCO_3$ (6 mL) and EtOAc were added, the phases were separated and the aqueous layer was extracted with EtOAc (3x10 mL). The combined organic layers were washed with brine (2 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 9:1) afforded ester **41a** (104 mg, 0.24 mmol, 89%, >20:1 dr) as a colorless oil.

TLC: R_f = 0.55 (hexane/EtOAc 8:1, CPS); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.78 (ddt, *J* = 17.1, 10.1, 6.3, 1H), 5.28-5.15 (m, 2H), 5.01 (ddd, *J* = 17.1, 3.6, 1.7, 1H), 4.95 (ddd, *J* = 10.1, 3.3, 1.5, 1H), 3.84-3.75 (m, 1H), 3.49-3.34 (m, 1H), 3.03 (d, *J* = 3.6, O*H*), 2.83-2.66 (m, 2H), 2.36 (dq, *J* = 7.8, 0.8, 2H), 2.22-2.09 (m, 2H), 1.79 (ddd, *J* = 14.1, 7.8, 5.3, 1H), 1.68 (ddd, *J* = 14.1, 6.7, 5.3, 1H), 1.60 (s, 3H), 1.56 (dd, *J* = 7.6, 5.4, 2H), 1.50-1.41 (m, 2H), 1.38-1.29 (m, 2H), 1.16 (t, *J* = 7.6, 3H), 0.90 (t, *J* = 7.0, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 175.7, 137.2, 133.1, 125.2, 114.5, 69.3, 68.1, 66.8, 47.7, 43.5, 42.7, 39.3, 32.6, 28.0, 26.0, 19.2, 18.2, 16.8, 14.2, 9.5, −4.3, −4.4; **IR** (thin film): ν 3524, 2956, 2929, 2857, 1718, 1638, 1463, 1434, 1362, 1254, 1196, 1080, 1026, 1004, 937, 908, 834, 807, 773, 741, 666 cm^{-1}; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: −15.7 (c 0.8 in $CHCl_3$); **HRMS** (ESI): calculated for $C_{24}H_{46}NaO_4Si$ $[M+Na]^+$: 449.3058, found 449.3059.

Ester 41b: Preparation of SmI_2:[45] A brown mixture of samarium powder (29.2 mg, 0.19 mmol) and I_2 (44.3 mg, 0.17 mmol) in THF (2.5 mL) under argon was heated to 80 °C for 30 min, resulting in the formation of a dark blue solution of SmI_2 (*ca*. 0.08m). This solution was allowed to cool to room temperature and was then used immediately.

To a solution of propionaldehyde (84 µL, 1.16 mmol, 6.0 equiv.) in THF (0.9 mL) at −20 °C (cryostat) was added SmI_2 (0.8 mL of the above solution, *ca*. 61 µmol, 0.3 equiv.), resulting in the formation of a yellow solution within about 30 seconds. To this solution was added dropwise a solution of **40b** (77.0 mg, 0.19 mmol, 1.0 equiv.) in THF (0.8 mL, the vial was rinsed twice with 0.3 mL). The reaction was stirred at −20 °C for 1 h. Sat. aq. $NaHCO_3$ (5 mL) and EtOAc (5 mL) were then added, the phases were separated and the aqueous layer was extracted with EtOAc (3x10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 8:1) furnished ester **41b** (82.1 mg, 0.18 mmol, 93%; >20:1 dr) as a colorless oil.

TLC: R_f = 0.49 (hexane/EtOAc 9:1, CPS); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.78 (ddt, *J* = 17.2, 10.1, 6.3, 1H), 5.29-5.14 (m, 2H), 5.00 (ddd, *J* = 17.1, 3.6, 1.7, 1H), 4.94 (ddd, *J* = 10.1, 3.4, 1.4, 1H), 3.86-3.74 (m, 1H), 3.43-3.29 (m, 1H), 3.05 (d, *J* = 3.5, 1H, O*H*), 2.74 (t, *J* = 6.6, 2H), 2.35 (qd, *J* = 7.7, 0.8, 2H), 2.22-2.09 (m, 2H), 1.79 (ddd, *J* = 14.1, 7.8, 5.3, 1H), 1.73-1.64 (m, 1H), 1.59 (s, 3H), 1.62-1.54 (m, 2H), 1.54-1.28 (m, 4H), 1.22-1.10 (m, 1H), 1.16 (t, *J* = 7.6, 3H), 0.89-0.85 (m, 6H), 0.87 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 175.7, 137.2, 133.1, 125.2, 114.5, 69.2, 68.1, 67.5, 47.7, 43.5, 42.7, 35.2, 35.0, 32.6, 28.3, 28.0, 26.0, 22.7, 22.7, 18.2, 16.8, 9.5, −4.3, −4.4; **IR** (thin film): ν 3524, 2954, 2938, 2857, 1717, 1463, 1384, 1366, 1253, 1193, 1081, 1005, 908, 835, 807, 773 cm^{-1}; **HRMS** (ESI): calculated for $C_{26}H_{51}O_4Si$ $[M+H]^+$: 455.3551, found 455.3551; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: −13.1 (c 0.7 in $CHCl_3$).

(5*R*,7*S*,9*R*)-2,2,3,3,11,11,12,12-octamethyl-5-((*E*)-2-methylhexa-2,5-dien-1-yl)-9-propyl-4,10-dioxa-3,11-disilatridecan-7-yl propionate (E-5a): To a solution of alcohol **41a** (91.2 mg, 0.21 mmol, 1.0 equiv.) in DMF (0.32 mL) at room temperature was added imidazole (18.3 mg, 0.27 mmol, 1.25 equiv.) followed by TBSCl (38.8 mg, 0.26 mmol, 1.2 equiv.). The colorless solution was stirred at room temperature for 2 days before sat. aq. NH_4Cl (6 mL) and EtOAc (6 mL) were added. The phases were separated, the organic phase was washed with brine (2x2 mL) and the combined aqueous phases were extracted with EtOAc (10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 40:1) furnished bis-TBS ether **E-5a** (111 mg, 0.21 mmol, 96%) as a colorless oil.

TLC: R_f = 0.68 (hexane/EtOAc 20:1, CPS); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.79 (ddt, *J* = 17.1, 10.1, 6.4, 1H), 5.19 (tm, *J* = 7.2, 1H), 5.08-4.99 (m, 1H), 5.01 (ddd, *J* = 17.1, 3.6, 1.7, 1H), 4.94 (ddd, *J* = 10.1, 3.4, 1.4, 1H), 3.83-3.75 (m, 1H), 3.72-3.63 (m, 1H), 2.83-2.65 (m, 2H), 2.29 (q, *J* = 7.6, 2H), 2.24 (dd, *J* = 13.3, 4.5, 1H), 2.10 (dd, *J* = 13.3, 7.2, 1H), 1.82-1.62 (m, 4H), 1.61 (s, 3H), 1.46-1.38 (m, 2H), 1.38-1.26 (m, 2H), 1.14 (t, *J* = 7.6, 3H), 0.89 (t, *J* = 7.3, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.03 (s, 3H), 0.02 (s, 6H), 0.00 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 173.9, 137.4, 133.4, 125.0, 114.4, 69.5, 68.9, 68.3, 47.2, 43.3, 42.6, 40.2, 32.7, 28.1, 26.1, 26.0, 18.2, 18.0, 16.8, 14.4, 9.5, −4.2, −4.4, −4.4, −4.5; **IR** (thin film): ν 2956, 2929, 2857, 1737, 1471, 1463, 1362, 1254, 1187, 1070, 1005, 957, 938, 908, 834, 807, 772 cm^{-1}; **HRMS** (ESI): calculated for $C_{30}H_{60}NaO_4Si_2$ $[M+Na]^+$: 563.3922, found 563.3918; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: −12.2 (c 0.8 in $CHCl_3$).

(5*R*,7*S*,9*R*)-5-isopentyl-2,2,3,3,11,11,12,12-octamethyl-9-((*E*)-2-methylhexa-2,5-dien-1-yl)-4,10-dioxa-3,11-disilatridecan-7-yl propionate (E-5b): To a solution of **41b** (76.7 mg, 0.17 mmol, 1.0 equiv.) in DCM (0.27 mL) at room temperature was added imidazole (14.4 mg, 0.21 mmol, 1.25 equiv.) followed by TBSCl (30.5 mg, 0.20 mmol, 1.2 equiv.). The resulting white suspension was stirred at room temperature. After 20 h, DMF (250 µL) was added. After 2 h more, additional imidazole (4.6 mg, 0.07 mmol, 0.4 equiv.) and TBSCl (10.0 mg, 0.07 mmol, 0.4 equiv.) were added and stirring was continued for 30 min. The reaction mixture was diluted with sat. aq. NH_4Cl (6 mL) and EtOAc (6 mL). The phases were separated, the organic layer was washed with brine (2x2 mL) and the combined aqueous layers were extracted with EtOAc (10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 60:1 → 40:1) afforded bis-TBS ether **E-5b** (78.1 mg, 0.14 mmol, 81%) as a colorless oil.

TLC: R_f = 0.85 (hexane/EtOAc 9:1, CPS); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.79 (ddt, *J* = 17.2, 10.1, 6.4, 1H), 5.19 (t, *J* = 7.2, 1H), 5.08-5.00 (m, 1H), 5.01 (ddd, *J* = 17.2, 3.5, 1.5, 1H), 4.94 (ddd, *J* = 10.1, 3.4, 1.8, 1H), 3.89-3.75 (m, 1H), 3.72-3.61 (m, 1H), 2.82-2.66 (m, 2H), 2.29 (q, *J* = 7.6, 2H), 2.28-2.20 (m, 1H), 2.11 (dd, *J* = 13.3, 7.3, 1H), 1.81-1.58 (m, 4H), 1.61 (s, 3H), 1.54-1.38 (m, 3H), 1.24-1.10 (m, 2H), 1.14 (t, *J* = 7.6, 3H), 0.89-0.86 (6H), 0.88 (s, 9H), 0.87 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H), 0.02 (s, 3H), 0.00 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 173.9, 137.4, 133.4, 125.0, 114.4, 69.6, 69.3, 68.3, 47.2, 43.3, 42.6, 35.8, 33.8, 32.7, 28.4, 28.1, 26.1, 26.0, 22.8, 22.8, 18.2, 16.7, 9.5, −4.1, −4.4, −4.4, −4.5; **IR** (thin film): v 2954, 2928, 2857, 1736, 1472, 1463, 1434, 1385, 1362, 1254, 1188, 1079, 1005, 938, 908, 834, 807 cm^{-1}; **HRMS** (ESI): calculated for $C_{32}H_{64}NaO_4Si_2$ $[M+Na]^+$: 591.4235, found 591.4235; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: −12.5 (c 0.7 in $CHCl_3$).

Alcohol 42a: To ester **E-5a** (110 mg, 0.20 mmol, 1.0 equiv.) in DCM (2 mL) at −78 °C was added DIBAL-H (1.2m solution in toluene, 360 µL, 0.43 mmol, 2.1 equiv.). The colorless solution was stirred at −78 °C for 1 h. Sat. aq. Rochelle salt (12 mL) and DCM (10 mL) were added and stirring was continued at room temperature until two clear phases were obtained (about 2 h). The phases were separated and the aqueous layer was extracted with DCM (3x15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated

under reduced pressure. Purification by flash chromatography (hexane/EtOAc 30:1) furnished alcohol **42a** (90.8 mg, 0.19 mmol, 92%) as a colorless oil.

TLC: R_f = 0.37 (hexane/EtOAc 25:1, CPS); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.78 (ddt, *J* = 17.1, 10.1, 6.3, 1H), 5.20 (t, *J* = 7.2, 1H), 5.01 (ddd, *J* = 17.1, 3.6, 1.8, 1H), 4.95 (ddd, *J* = 10.1, 3.4, 1.5, 1H), 4.05-3.90 (m, 3H), 3.59 (d, *J* = 1.1, O*H*), 2.74 (t, *J* = 6.6, 2H), 2.27 (dd, *J* = 13.1, 5.0, 1H), 2.15 (dd, *J* = 13.1, 7.6, 1H), 1.62 (s, 3H), 1.60-1.41 (m, 6H), 1.38-1.22 (m, 2H), 0.90 (t, *J* = 7.4, 3H), 0.89 (s, 9H), 0.89 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H), 0.09 (s, 3H), 0.07 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 137.2, 133.2, 125.0, 114.5, 71.2, 70.2, 67.0, 48.6, 44.4, 43.8, 39.8, 32.5, 26.1, 26.0, 18.7, 18.2, 18.1, 16.8, 14.5, −3.9, −4.3, −4.4, −4.5; **IR** (thin film): ν 3562, 2955, 2929, 2857, 1471, 1464, 1426, 1410, 1381, 1362, 1254, 1074, 1038, 1004, 908, 833, 807, 773 cm^{-1}; **HRMS** (ESI): calculated for $C_{27}H_{57}O_3Si_2$ $[M+H]^+$: 485.3841, found 485.3840; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: −20.5 (c 0.6 in $CHCl_3$).

Alcohol 42b: To ester **E-5b** (76.2 mg, 0.13 mmol, 1.0 equiv.) in DCM (1.3 mL) at −78 °C was added dropwise DIBAL-H (1.2m solution in toluene, 240 µL, 0.29 mmol, 2.2 equiv.). The colorless solution was stirred at −78 °C for 1 h. Sat. aq. Rochelle salt (6 mL) and DCM (3 mL) were added and stirring was continued at room temperature until two clear phases were obtained (about 2 h). The phases were separated and the aqueous layer was extracted with DCM (3x10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 50:1 → 40:1) furnished alcohol **42b** (64.2 mg, 0.13 mmol, 93%) as a colorless oil.

TLC: R_f = 0.61 (hexane/EtOAc 20:1, CPS); **^{1}H NMR** (400 MHz, $CDCl_3$) : δ 5.78 (ddt, *J* = 17.1, 10.1, 6.3, 1H), 5.20 (tm, *J* = 7.2, 1H), 5.01 (ddd, *J* = 17.1, 3.6, 1.8, 1H), 4.95 (ddd, *J* = 10.1, 3.4, 1.5, 1H), 4.06-3.88 (m, 3H), 3.58 (d, *J* = 1.1, 1H, O*H*), 2.74 (t, *J* = 6.7, 2H), 2.27 (dd, *J* = 13.1, 5.1, 1H), 2.15 (dd, *J* = 13.2, 7.7, 1H), 1.62 (s, 3H), 1.58-1.42 (m, 7H), 1.22-1.10 (m, 2H), 0.90 (s, 9H), 0.89 (s, 9H), 0.87 (d, *J* = 6.6, 3H), 0.87 (d, *J* = 6.7, 3H), 0.10 (s, 3H), 0.09 (s, 6H), 0.07 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 137.2, 133.1, 125.0, 114.5, 71.3, 70.5, 67.0, 48.6, 44.3, 43.8, 35.3, 34.5, 32.5, 28.4, 26.1, 26.0, 22.8, 22.7, 18.2, 18.1, 16.8, −3.9, −4.3, −4.4, −4.5; **IR** (thin film): ν 3524, 2954, 2929, 2857, 1472, 1463, 1410, 1385, 1362, 1254, 1078, 1004, 938, 909, 834, 808 cm^{-1}; **HRMS** (ESI): calculated for $C_{29}H_{61}O_3Si_2$ $[M+H]^+$: 513.4154, found 513.4152; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: −20.9 (c 0.7 in $CHCl_3$).

Ester 43a: To a solution of alcohol **42a** (89.3 mg, 0.18 mmol, 1.0 equiv.), acid **23** (131 mg, 0.37 mmol, 2.0 equiv.) and NEt_3 (128 µL, 0.92 mmol, 5.0 equiv.) in toluene (1.9 mL) at −78 °C was added DMAP (56.2 mg, 0.46 mmol, 2.5 equiv.) in one portion. After 5 min, 2,4,6-trichlorobenzoyl chloride (86 µL, 0.55 mmol, 3.0 equiv.) was added and the white suspension was allowed to warm slowly to −50 °C in the cooling bath (remaining dry ice was removed from the cooling bath and some room-temperature acetone was added), giving a yellow mixture. Then, the temperature was kept between −40 °C and −50 °C for 3 h before sat. aq. $NaHCO_3$ (5 mL) and EtOAc (5 mL) were added to the reaction. The phases were separated and the aqueous layer was extracted with EtOAc (3x10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 40:1) afforded ester **43a** (125.7 mg, 0.15 mmol, 83%) as a colorless oil.

TLC: R_f = 0.68 (hexane/EtOAc 40:1, UV, CPS); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.35 (br s, 1H), 5.79 (ddt, *J* = 17.1, 10.1, 6.4, 1H), 5.20 (t, *J* = 7.1, 1H), 5.15-5.06 (m, 1H), 5.01 (ddd, *J* = 17.1, 3.6, 1.7, 1H), 4.94 (ddd, *J* = 10.1, 3.3, 1.4, 1H), 3.88-3.77 (m, 1H), 3.79 (t, *J* = 6.1, 2H), 3.74-3.66 (m, 1H), 2.89 (t, *J* = 6.1, 2H), 2.82-2.66 (m, 2H), 2.26 (dd, *J* = 13.4, 4.5, 1H), 2.12 (dd, *J* = 13.3, 7.3, 1H), 1.88-1.64 (m, 4H), 1.61 (s, 3H), 1.47-1.38 (m, 2H), 1.38-1.24 (m, 2H), 0.89 (t, *J* = 7.5, 3H), 0.88 (s, 9H), 0.88 (s, 9H), 0.86 (s, 9H), 0,06 (s, 6H), 0.03 (s, 3H), 0.02 (s, 3H), 0.02 (s, 3H), −0.01 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 163.8, 137.4, 133.4, 127.3, 125.0, 116.2, 114.4, 70.2, 68.8, 68.3, 61.5, 51.1, 47.2, 43.0, 42.6, 40.2, 32.7, 26.1, 26.1, 26.0, 18.4, 18.2, 18.0, 16.8, 14.5, −4.1, −4.2, −4.3, −4.4, −5.1; **IR** (thin film): ν 2954, 2928, 2857, 1728, 1623, 1471, 1463, 1434, 1386, 1362, 1253, 1210, 1170, 1106, 1044, 1006, 959, 937, 909, 833, 772 cm^{-1}; **HRMS** (ESI): calculated for $C_{38}H_{76}IO_5Si_3$ $[M+H]^+$: 823.4040, found 823.4033; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: −7.9 (c 0.6 in $CHCl_3$).

Ester 43b: To a solution of alcohol **42b** (61.6 mg, 0.12 mmol, 1.0 equiv.), acid **23** (85.6 mg, 0.24 mmol, 2.0 equiv.) and NEt_3 (83 µL, 0.60 mmol, 5.0 equiv.) in toluene (1.3 mL) at −78 °C was added DMAP (36.7 mg, 0.30 mmol, 2.5 equiv.) in one portion. After 5 min, 2,4,6-trichlorobenzoyl chloride (56 µL, 0.36 mmol, 3.0 equiv.) was added. The white suspension was allowed to warm slowly to −50 °C in the cooling bath (remaining dry ice was removed from the bath and some room temperature acetone was added), giving a yellow mixture. Then, the temperature was kept between −40 °C and −50 °C for 3 h before sat. aq. $NaHCO_3$

(10 mL) and EtOAc (10 mL) were added. The phases were separated and the aqueous layer was extracted with EtOAc (3x10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (pentane/Et_2O 50:1 → 40:1 gradient) afforded ester **43b** (77.6 mg, 91.1 µmol, 76%) as a colorless oil.

TLC: R_f = 0.87 (hexane/EtOAc 20:1, UV, CPS); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.36 (br s, 1H), 5.79 (ddt, *J* = 17.1, 10.1, 6.4, 1H), 5.20 (t, *J* = 7.2, 1H), 5.15-5.07 (m, 1H), 5.01 (ddd, *J* = 17.1, 3.6, 1.7, 1H), 4.94 (ddd, *J* = 10.1, 3.3, 1.4, 1H), 3.90-3.80 (m, 1H), 3.79 (t, *J* = 6.1, 2H), 3.73-3.64 (m, 1H), 2.89 (t, *J* = 6.1, 2H), 2.82-2.65 (m, 2H), 2.26 (dd, *J* = 13.3, 4.4, 1H), 2.12 (dd, *J* = 13.3, 7.3, 1H), 1.90-1.64 (m, 4H), 1.61 (s, 3H), 1.52-1.38 (m, 3H), 1.23-1.11 (m, 2H), 0.89-0.86 (6H), 0.88 (s, 9H), 0.88 (s, 9H), 0.87 (s, 9H), 0.06 (s, 6H), 0.03 (s, 3H), 0.02 (s, 3H), 0.02 (s, 3H), −0.01 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 163.8, 137.4, 133.4, 127.3, 125.0, 116.1, 114.4, 70.3, 69.2, 68.3, 61.5, 51.1, 47.1, 43.0, 42.5, 35.8, 33.8, 32.7, 28.4, 26.1, 26.1, 26.0, 22.8, 18.4, 18.2, 16.8, −4.1, −4.2, −4.4, −5.1; **IR** (thin film): ν 2954, 2928, 2857, 1728, 1623, 1472, 1463, 1386, 1361, 1306, 1252, 1210, 1169, 1104, 1081, 1048, 1005, 909, 834, 807, 772 cm^{-1}; **HRMS** (ESI): calculated for $C_{40}H_{80}IO_5Si_3$ $[M+H]^+$: 851.4353, found 851.4341; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: −10.9 (c 0.8 in $CHCl_3$).

Triene 44a: Argon was passed through a solution of vinyl iodide **43a** (109.3 mg, 0.13 mmol, 1.0 equiv.) and triphenylarsine (20.3 mg, 66.3 µmol, 0.5 equiv.) in DMF (1.5 mL) for 5 min. Allyltributylstannane (82 µL, 0.26 mmol, 2.0 equiv.) was added followed by $[Pd_2(dba)_3]$ (24.3 mg, 26.6 µmol, 20 mol-%). The resulting dark green solution was stirred at room temperature for 18 h before Et_2O (10 mL) and water (10 mL) were added. The phases were separated, the organic layer was washed with water (3x10 mL) and the combined aqueous layers were extracted with Et_2O (10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (pentane/Et_2O 60:1 → 50:1) furnished **44a** (81.2 mg, 0.11 mmol, 83%) as a pale yellow oil.

TLC: R_f = 0.44 (hexane/EtOAc 95:5); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.85-5.72 (m, 2H), 5.70 (s, 1H), 5.19 (t, *J* = 6.8, 1H), 5.13-4.97 (m, 4H), 4.93 (ddd, J = 10.1, 3.4, 1.4, 1H), 3.85-3.77 (m, 1H), 3.73 (t, *J* = 6.7, 2H), 3.73-3.65 (m, 1H), 3.55-3.30 (m, 2H), 2.81-2.65 (m, 2H), 2.35 (td, *J* = 6.6, 0.7, 2H), 2.26 (dd, *J* = 13.2, 4.3, 1H), 2.10 (dd, *J* = 13.3, 7.4, 1H), 1.83-1.62 (m, 4H), 1.60

(s, 3H), 1.46-1.39 (m, 2H), 1.38-1.25 (m, 2H), 0.90-0.86 (3H, hidden), 0.89 (s, 9H), 0.87 (s, 9H), 0.87 (s, 9H), 0.05 (s, 6H), 0.02 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H), −0.01 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 165.6, 157.6, 137.4, 135.3, 133.5, 124.9, 118.0, 116.6, 114.4, 68.9, 68.8, 68.4, 61.6, 47.2, 43.4, 42.8, 41.0, 40.3, 36.9, 32.7, 26.1, 26.1, 18.4, 18.2, 18.0, 16.8, 14.5, −4.2, −4.3, −4.4, −5.2; **IR** (thin film): ν 2955, 2929, 2857, 2857, 1713, 1634, 1471, 1463, 1434, 1408, 1362, 1253, 1184, 1144, 1098, 1005, 937, 910, 833, 808, 772 cm^{-1}; **HRMS** (ESI): calculated for $C_{41}H_{81}O_5Si_3$ $[M+H]^+$: 737.5386, found 737.5376; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: −6.3 (c 0.7, $CHCl_3$).

Triene 44b: Argon was passed through a solution of ester **43b** (73.6 mg, 86.5 µmol, 1.0 equiv.) and triphenylarsine (13.2 mg, 43.2 µmol, 0.5 equiv.) in DMF (0.8 mL) for 5 min. Allyltributylstannane (54 µL, 0.17 mmol, 2.0 equiv.) was added followed by $[Pd_2(dba)_3]$ (23.8 mg, 25.9 µmol, 30 mol-%). The resulting dark green solution was stirred at room temperature for 16 h before it was diluted with Et_2O (10 mL) and water (10 mL). The phases were separated, the organic layer was washed with water (3x10 mL) and the combined aqueous layers were extracted with Et_2O (10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (pentane/Et_2O 50:1) afforded **44b** (52.3 mg, 68.3 µmol, 79%) as a colorless oil.

TLC: R_f = 0.72 (hexane/EtOAc 30:1, UV, CPS); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.79 (ddt, *J* = 17.1, 10.0, 6.3, 1H), 5.78 (ddt, *J* = 17.1, 10.0, 6.9, 1H), 5.70 (br s, 1H), 5.19 (t, *J* = 7.1, 1H), 5.09 (ddd, *J* = 17.1, 3.3, 1.8, 1H), 5.05-4.97 (m, 3H), 4.93 (ddd, *J* = 10.1, 3.4, 1.8, 1H), 3.87-3.77 (m, 1H), 3.73 (t, *J* = 6.7, 2H), 3.71-3.63 (m, 1H), 3.50-3.35 (m, 2H), 2.82-2.65 (m, 2H), 2.35 (td, *J* = 6.6, 0.7, 2H), 2.27 (dd, *J* = 13.2, 4.2, 1H), 2.10 (dd, *J* = 13.3, 7.4, 1H), 1.86-1.63 (m, 4H), 1.60 (s, 3H), 1.52-1.38 (m, 3H), 1.23-1.10 (m, 2H), 0.90-0.85 (6H), 0.89 (s, 9H), 0.88 (s, 9H), 0.86 (s, 9H), 0.05 (s, 6H), 0.02 (s, 3H), 0.01 (s, 6H), −0.02 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 165.6, 157.6, 137.4, 135.3, 133.5, 124.9, 118.0, 116.6, 114.4, 69.3, 68.9, 68.4, 61.6, 47.2, 43.4, 42.8, 41.0, 36.9, 35.8, 33.8, 32.7, 28.4, 26.1, 26.1, 26.1, 22.8, 18.4, 18.2, 16.7, −4.1, −4.3, −4.4, −4.4, −5.2; **IR** (thin film): ν 2954, 2928, 2857, 1713, 1634, 1472, 1463, 1435, 1407, 1386, 1362, 1253, 1184, 1145, 1092, 1055, 1005, 938, 911, 834, 809 cm^{-1}; **HRMS** (ESI): calculated for $C_{43}H_{85}O_5Si_3$ $[M+H]^+$: 765.5699, found 765.5688; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: −5.5 (c 0.5 in $CHCl_3$).

Analog 45a: To a solution of **44a** (23.8 mg, 32.3 µmol, 1.0 equiv.) in DCM (20 mL) at room temperature was added Grubbs-I catalyst (1 mL of a stock solution of 5.3 mg catalyst in 2 mL DCM, 10 mol-%). The reaction mixture was stirred at room temperature for 3.5 h (additional 0.3 mL of the catalyst stock solution were added after 90 min), during which time the color turned from purple to orange. DMSO (23 µL, 0.32 mmol, 10 equiv.) was added and stirring was continued for 14 h. (Note: The reaction was not allowed to reach completion; *ca.* 95% conversion). Then, the solvent was removed under reduced pressure and the crude was purified by flash chromatography (pentane/Et_2O 50:1), affording the tris-TBS-ether of **45a** as a colorless oil, which was used as such in the next step.

A polypropylene tube was charged with the above protected macrolactone and immersed in an ice bath. Acetonitrile (0.25 mL) was added followed by HF in aq. acetonitrile (a solution consisting of 0.38 mL 48% aq. HF and 3 mL acetonitrile). The reaction was stirred at 0 °C for 3.5 h before it was added dropwise to a stirred mixture of sat. aq. $NaHCO_3$ (25 mL) and EtOAc (10 mL). The phases were separated and the aqueous layer was extracted with EtOAc (5x10 mL). The combined organic layers were washed with brine (3 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (DCM/MeOH 97:3 → 95:5) followed by preparative HPLC (20% acetonitrile in water for 2 min, then gradient to 50% acetonitrile over the course of 23 min; R_t = 14.2 min) afforded **44a** (6.7 mg, 18.3 µmol, 57% over two steps) as a colorless oil.

TLC: R_f = 0.43 (DCM/MeOH 9:1); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 5.69 (s, 1H), 5.42-5.34 (m, 1H), 5.31-5.19 (m, 2H), 5.15-5.09 (m, 1H), 3.97 (dd, *J* = 13.2, 8.5, 1H), 3.92-3.84 (m, 1H), 3.83-3.74 (m, 2H), 3.72-3.64 (m, 1H), 2.67-2.58 (m, 1H), 2.54-2.42 (m, 2H), 2.42 (t, *J* = 6.3, 2H), 2.28-2.19 (m, 2H), 2.03 (t, *J* = 11.7, 1H), 1.95-1.80 (m, 2H), 1.59 (ddd, *J* = 15.9, 8.6, 2.8, 1H), 1.50 (s, 3H), 1.49-1.23 (m, 4H), 0.92 (t, *J* = 6.9, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 166.0, 157.4, 134.1, 129.0, 125.7, 125.6, 118.7, 71.0, 68.8, 65.6, 59.9, 49.7, 43.2, 40.8, 39.7, 37.4, 34.5, 31.0, 18.8, 16.6, 14.2; **IR** (thin film): v 3320, 2958, 2925, 2871, 2853, 1714, 1696, 1644, 1436, 1375, 1261, 1229, 1180, 1153, 1042, 965, 850, 800, 755 cm^{-1}; **HRMS** (ESI): calculated fo $C_{21}H_{34}NaO_5$ $[M+Na]^+$: 389.2302, found 389.2298; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: +37.6 (c 0.3 in $CHCl_3$).

Analog 45b: To a solution of **44b** (22.4 mg, 29.2 µmol, 1.0 equiv.) in DCM at room temperature was added Grubbs-I catalyst (1 mL of a stock solution of 4.8 mg catalyst in 2 mL DCM, 10 mol-%). The solution was stirred at room temperature for 30 min, during which

time the color turned from purple to orange. DMSO (21 µL, 0.29 mmol, 10 equiv.) was added. (Note: The reaction was not allowed to reach completion; *ca.* 90% conversion) and stirring was continued for 20 h before the solvent was removed under reduced pressure. Purification by flash chromatography (pentane/Et_2O 50:1) afforded the tris-TBS-ether of **45b** as a colorless oil, which was used as such in the next step.

A polypropylene tube was charged with the above protected macrolactone and placed in a NaCl/ice bath (about −10 °C). A 5% solution of HF in aq. acetonitrile (3.8 mL; prepared from 0.55 mL 48% aq. HF and 4.3 mL acetonitrile), precooled to −10 °C, was added. The reaction was allowed to warm to 0 °C and was stirred at that temperature for 2 h before it was added to a stirred mixture of sat. aq. $NaHCO_3$ (30 mL) and EtOAc (10 mL) (after complete addition, the pH should be >7). The phases were separated and the aqueous layer was extracted with EtOAc (5x10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (DCM/MeOH 98:2 → 95:5) followed by preparative HPLC (20% acetonitrile in water for 2 min, then gradient to 50% acetonitrile over the course of 23 min; R_t = 17.7 min) furnished analog **45b** (3.3 mg, 8.36 µmol, 29% over two steps) as a colorless oil.

TLC: R_f = 0.24 (DCM/MeOH 95:5, UV, CPS); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 5.67 (br s, 1H), 5.41-5.32 (m, 1H), 5.27 (t, *J* = 7.7, 1H), 5.26-5.17 (m, 1H), 5.12-5.06 (m, 1H), 3.95 (dd, *J* = 13.0, 8.4, 1H), 3.89-3.82 (m, 1H), 3.76 (t, *J* = 6.3, 2H), 3.66-3.57 (m, 1H), 3.4-3.0 (br, O*H*), 2.66-2.56 (m, 1H), 2.52-2.41 (m, 2H), 2.40 (t, *J* = 6.3, 2H), 2.24 (br d, *J* = 11.8, 1H), 2.20 (dd, *J* = 15.9, 3.8, 1H), 2.2-2.0 (br, O*H*), 2.01 (t, *J* = 11.8, 1H), 1.94-1.79 (m, 2H), 1.57 (ddd, *J* = 15.9, 8.6, 2.8, 1H), 1.55-1.40 (m, 3H), 1.49 (s, 3H), 1.34-1.22 (m, 1H), 1.22-1.12 (m, 1H), 0.87 (d, *J* = 6.6, 3H), 0.87 (d, *J* = 6.6, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 166.0, 157.3, 134.1, 129.0, 125.7, 125.6, 118.8, 71.0, 69.4, 65.7, 60.0, 49.7, 43.2, 39.7, 37.5, 36.5, 34.7, 34.5, 31.0, 28.2, 22.8, 22.7, 16.6; **IR** (thin film): ν 3343, 2927, 1715, 1647, 1437, 1366, 1229, 1180, 1154, 1041, 965, 853, 810, 785, 768, 757 cm^{-1}; **HRMS** (ESI): calculated for $C_{23}H_{38}NaO_5$ $[M+Na]^+$: 417.2611, found 417.2617; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$: +48.5 (c 0.2 in $CHCl_3$).

Acknowledgements

This work was supported by the European Community Framework Programme 7, More Medicines For Tuberculosis (MM4TB) grant agreement no. 260872 (FG, PT, VN, LR, JAA, RCH, STC, KHA). We are indebted to Dr. Bernhard Pfeiffer (ETH Zürich) for NMR support and to

Louis Bertschi from the ETHZ LOC MS-Service for HRMS spectra. We would also like thank Anthony Vocat for excellent technical assistance. We are particularly grateful to Dr. Evgeny Prusov, Helmholtz Institute for Infectious Research, Braunschweig, Germany, for sharing with us spectroscopic data for natural ripostatin B. We are also indebted to Prof. Rolf Müller, Helmholtz Insitute for Pharmaceutical Research, Saarbrücken, Germany, for providing us with a sample of natural ripostatin A.

Supporting Information

^{1}H- and ^{13}C-NMR spectra of compounds **E-1**, **11-13**, **E-2**, **14-16**, **9**, **19**, **8**, **20**, **21**, **E-3**, **7**, **23-25**, **5**, **4**, **26-28**, **2**, **29**, **E-4**, **32**, **34-36**, **38**, and **40a/b-45a/b**.

References

(1) Irschik, H.; Augustiniak, H.; Gerth, K.; Höfle, G.; Reichenbach, H. *J. Antibiot.* **1995**, *48*, 787–792.

(2) Augustiniak, H.; Irschik, H.; Reichenbach, H.; Höfle, G. *Liebigs Ann.* **1996**, 1657–1663.

(3) O'Neill, A.; Oliva, B.; Storey, C.; Hoyle, A.; Fishwick, C.; Chopra, I. *Antimicrob. Agents Ch.* **2000**, *44*, 3163–3166.

(4) Tang, W. F.; Liu, S.; Degen, D.; Ebright, R. H.; Prusov, E. V. *Chem. Eur. J.* **2014**, *20*, 12310–12319.

(5) Fralick, J. A.; Burns-Keliher, L. L. *J. Bacteriol.* **1994**, *176*, 6404–6406.

(6) For a review, see: Blair, J. M.; Piddock, L. J. *Curr. Opin. Microbiol.* **2009**, *12*, 512–519.

(7) Irschik, H.; Jansen, R.; Höfle, G.; Gerth, K.; Reichenbach, H. *J. Antibiot.* **1985**, *38*, 145–152.

(8) Irschik, H.; Gerth, K.; Höfle, G.; Kohl, W.; Reichenbach, H. *J. Antibiot.* **1983**, *36*, 1651–1658.

(9) Jansen, R.; Irschik, H.; Reichenbach, H.; Höfle, G. *Liebigs Ann. Chem.* **1985**, 822–836.

(10) Mukhopadhyay, J.; Das, K.; Ismail, S.; Koppstein, D.; Jang, M.; Hudson, B.; Sarafianos, S.; Tuske, S.; Patel, J.; Jansen, R.; Irschik, H.; Arnold, E.; Ebright, R. H. *Cell* **2008**, *135*, 295–307.

(11) Srivastava, A.; Talaue, M.; Liu, S.; Degen, D.; Ebright, R. Y.; Sineva, E.; Chakraborty, A.; Druzhinin, S. Y.; Chatterjee, S.; Mukhopadhyay, J.; Ebright, Y. W.; Zozula, A.; Shen, J.;

Sengupta, S.; Niedfeldt, R. R.; Xin, C.; Kaneko, T.; Irschik, H.; Jansen, R.; Donadio, S.; Connell, N.; Ebright, R. H. *Curr. Opin. Microbiol*. **2011**, *14*, 532–543.

(12) Kujat, C.; Bock, M.; Kirschning, A. *Synlett* **2006**, 419–422.

(13) Winter, P.; Hiller, W.; Christmann, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 3396–3400.

(14) Tang, W.; Prusov, E. V. *Angew. Chem. Int. Ed.* **2012**, *51*, 3401–3404.

(15) Glaus, F.; Altmann, K.-H. *Angew. Chem. Int. Ed.* **2012**, *51*, 3405–3409.

(16) Glaus, F.; Altmann, K.-H. *Chimia* **2013**, *67*, 227–230.

(17) Tang, W.; Prusov, E. V. *Org. Lett.* **2012**, *14*, 4690–4693.

(18) Anderson, R. J.; Groundwater, P. W.; Todd, A.; Worsley, A. J. in: *Antibacterial Agents: Chemistry, Mode of Action, Mechanisms of Resistance and Clinical Applications.* John Wiley & Sons, 2012, pp. 63–83.

(19) Alderwick, L. J.; Birch, H. L.; Mishra, A. K.; Eggeling, L.; Besra, G. S. *Biochem. Soc. Trans.* **2007**, *35,* 1325–1328.

(20) For a recent reviews on ring-closing metathesis see: Schmidt, B.; Hauke, S.; Krehl, S.; Kunz, O. *In Comprehensive Organic Synthesis*, 2nd ed.; Vol. 5; Elsevier: Amsterdam, **2014**, pp. 1400–1482.

(21) Paterson, I.; Goodman, J. M. *Tetrahedron Lett.* **1989**, *30*, 997–1000.

(22) Paterson, I.; Goodman, J. M.; Lister, M. A.; Schumann, R. C.; McClure, C. K.; Norcross, R. D. *Tetrahedron* **1990**, *46*, 4663–4684.

(23) Frick, J. A.; Klassen, J. B.; Bathe, A.; Abramson, J. M.; Rapoport, H. *Synthesis* **1992**, 621–623.

(24) Kobayashi, S.; Mukaiyama, T. *Chem. Lett.* **1974**, 1425–1428.

(25) Kobayashi, S.; Mukaiyama, T. *Chem. Lett.* **1974**, 705–708.

(26) Murata, T.; Sano, M.; Takamura, H.; Kadota, I.; Uemura, D. *J. Org. Chem.* **2009**, *74*, 4797–4803.

(27) Vicario, J. L.; Job, A.; Wolberg, M.; Müller, M.; Enders, D. *Org. Lett.* **2002**, *4*, 1023–1026.

(28) Hutchings, M.; Moffat, D.; Simpkins, N. S. *Synlett* **2001**, 661–663.

(29) Nicolaou, K. C.; Mitchell, H. J.; Suzuki, H.; Rodríguez, R. M.; Baudoin, O.; Fylaktakidou, K. C. *Angew. Chem. Int. Ed.* **1999**, *38*, 3334–3339.

(30) Burton, J. W.; Clark, J. S.; Derrer, S.; Stork, T. C.; Bendall, J. G.; Holmes, A. B. *J. Am. Chem. Soc.* **1997**, *119*, 7483–7498.

(31) Congreve, M. S.; Davison, E. C.; Fuhry, M. A. M.; Holmes, A. B.; Payne, A. N.; Robinson, R. A. *Synlett* **1993**, 663–664.

(32) Yu, W.; Su, M.; Gao, X.; Yang, Z.; Jin, Z. *Tetrahedron Lett.* **2000**, *41*, 4015–4017.

(33) Miyashita, M.; Hoshino, M.; Yoshikoshi, A. *J. Org. Chem.* **1991**, *56*, 6483–6485.

(34) Onoda, T.; Shirai, R.; Iwasaki, S. *Tetrahedron Lett.* **1997**, *38*, 1443–1446.

(35) Kadota, I.; Yamagami, Y.; Fujita, N.; Takamura, H. *Tetrahedron Lett.* **2009**, *50*, 4553–4553.

(36) Guthrie, A. E.; Semple, J. E.; Joullié, M. M. *J. Org. Chem.* **1982**, *47*, 2369–2376.

(37) Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U.-H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461–5464.

(38) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512–519.

(39) Hoye, T. R.; Jeffrey, C. S.; Shao, F. *Nat. Protoc.* **2007**, *2*, 2451–2458.

(40) Paterson, I.; Oballa, R. M.; Norcross, R. D. *Tetrahedron Lett.* **1996**, *37*, 8581–8584.

(41) Dieckmann, M.; Rudolph, S.; Lang, C.; Ahlbrecht, W.; Menche, D. *Synthesis* **2013**, *45*, 2305–2315.

(42) Evans, D. A.; Dart, M. J.; Duffy, J. L. *Tetrahedron Lett.* **1994**, *35*, 8541–8544.

(43) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322–4343.

(44) Brady, P. B.; Albert, B. J.; Akakura, M.; Yamamoto, H. *Chem. Sci.* **2013**, *4*, 3223–3231.

(45) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447–6449.

(46) Rychnovsky, S. D.; Rogers, B. N.; Richardson, T. I. *Acc. Chem. Res.* 1998, *31*, 9–17.

(47) Rychnovsky, S. D. Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945–948.

(48) Kanematsu, M.; Shindo, M.; Yoshida, M.; Shishido, K. *Synthesis* **2009**, *17*, 2893–2904.

(49) Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* **1976**, 49–50.

(50) Neises, B.; Steglich, W. *Angew. Chem. Int. Ed.* **1978**, *17*, 522–524.

(51) Frérot, E.; Coste, J.; Pantaloni, A.; Dufour, M.-N.; Jouin, P. *Tetrahedron* **1991**, *47*, 259–270.

(52) Twibanire, J. K.; Grindley, T. B. *Org. Lett.* **2011**, *13*, 2988–2991.

(53) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.

(54) Ahn, Y. M.; Yang, K.; Georg, G. I. *Org. Lett.* **2001**, *3*, 1411–1413.

(55) Li, J.; Menche, D. *Synthesis* **2009**, 1904–1908.

(56) De Mico, A.; Margarita, R.; Parlanti, L.; Piancatelli, G.; Vescovi, A. *J. Org. Chem.* **1997**, *62*, 6974–6977.

(57) Schmidt, A.-K. C.; Stark, C. B. W. *Org. Lett.* **2011**, *13*, 4164–4167.

(58) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156.

(59) Bal, B. S.; Childers, W. E.; Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091–2096.

(60) Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888–890.

(61) Sensi, P. *Rev. Infect. Dis.* **1983**, *5 Suppl. 3*, 402–406.

(62) Sensi, P.; Timbal, M. T. Maffii, G. *Experientia* **1960**, *16*, 412.

(63) Jones, G.; Willett, P.; Glen, R. C. *J. Mol. Biol.* **1995**, *245*, 43–53. Docking runs were performed with the GOLD Suite v.5.2.2 software and the poses were evaluated by the ChemPLP scoring function [GOLD]. The Molecular Operating Environment (MOE 2011.10) software (Chemical Computing Group, Montreal, Canada) function “wash” (de-protonation of strong acids and protonation of strong bases) was used to define the protonation state of the ligands for single conformations computed by Corina 3.46 (Molecular Networks, Erlangen, Germany).

(64) Marshall, J. A.; DeHoff, B. S. *J. Org. Chem*. **1986**, *51*, 863–872.

(65) The Coli Genetic Stock Center, Strain JW5503-1, http://cgsc.biology.yale.edu/Strain.php?ID=109711, accessed January 2018.

(66) Singh, P. D.; Liu, W.-C.; Gougoutas, J. Z.; Malley, M. F.; Porubcan, M. A.; Trejo, W. H.; Wells, J. S.; Sykes, R. B. *J. Antibiot.* **1988**, *41*, 446–453.

(67) Malshetty, V.; Kurthkoti, K.; China, A.; Mallick, B.; Yamunadevi, S.; Biak Sang, P.; Srinivasan, N.; Nagaraja, V.; Varshney, U. *Microbiol.* **2010**, *156*, 1565–1573.

(68) da Silva, P. E. A.; Von Groll, A.; Martin, A.; Palomino, J. C. *FEMS Immunol. Med. Microbiol.* **2011**, *63*, 1–9.

(69) De Rossi, E.; Aínsa, J. A.; Riccardi, G. *FEMS Microbiol Rev.* **2006**, *30*, 36–52.

(70) Jarlier, V.; Nikaido, H. *FEMS Microbiol. Lett.* **1994**, 123, 11–18.

(71) Lomovskaya, O.; Warren, M. S.; Lee, A.; Galazzo, J.; Fronko, R.; Lee, M.; Blais, J.; Cho, D.; Chamberland, S.; Renau, T.; Leger, R.; Hecker, S.; Watkins, W.; Hoshino, K.; Ishida, H.; Lee, V. J. *Antimicrob. Agents Ch.* **2001**, *45*, 105–116.

(72) Naik, S. P.; Samsonoff, W. A.; Ruck, R. E. *Diagn. Microbiol. Infect. Dis.* **1989**, *11*, 11–19.

Graphic for abstract