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Total Synthesis of Tiacumicin A. Total Synthesis, Relay Synthesis, and Degradation Studies of Fidaxomicin (Tiacumicin B, Lipiarmycin A3)

Hiromu Hattori,[†,‡] Elias Kaufmann,[†,‡] Hideki Miyatake-Ondozabal,[†] Regina Berg,[‡] Karl Gademann*[‡]

[‡]Department of Chemistry, University of Zurich, Winterthurerstrasse 190, CH-8057 Zurich, Switzerland
[†]Department of Chemistry, University of Basel, St. Johanns-Ring 19, CH-4056 Basel, Switzerland

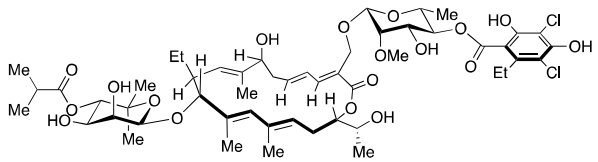
ABSTRACT: The commercial macrolide antibiotic fidaxomicin was synthesized in a highly convergent manner. Salient features of this synthesis include a β-selective noviosylation, a β-selective rhamnosylation, a ring closing metathesis, a Suzuki coupling and a vinylogous Mukaiyama aldol reaction. Careful choice of protecting groups and fine tuning of the glycosylation reactions led to the first total synthesis of fidaxomicin. In addition, a relay synthesis of fidaxomicin was established, which gives access to a conveniently protected intermediate from the natural material for derivatization. The first total synthesis of a related congener, tiacumicin A, is presented.

INTRODUCTION

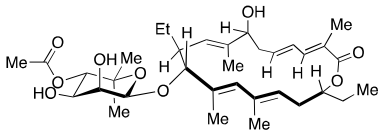
Fidaxomicin (**1**, Figure 1), also known as tiacumicin B and lipiarmycin A3, constitutes a macrolide antibiotic used for the treatment of *Clostridium difficile* infections (CDI),[1] which are considered responsible for a significant number of hospital-acquired infections, resulting in over 29'000 deaths each year in the USA.[2] While vancomycin and metronidazole are generally prescribed for this condition as first-line treatment,[3] the introduction of fidaxomicin (**1**) in the USA and the EU in 2011 presented a new therapeutic option.[4] Currently, it is recommended for the treatment of severe or moderate cases of CDI and lower recurrence rates than the standard vancomycin control have been reported.[5] Upon oral administration, fidaxomicin (**1**) shows selective bactericidal activity without being absorbed into the blood stream.[6] The mechanism of action includes binding to RNA polymerase[7] at a different binding site compared to other RNA polymerase inhibitors. Binding of fidaxomicin prevents formation of the RNA polymerase open complex and initiation of transcription.[8] For these reasons, fidaxomicin (**1**) presents a first-in-class drug with a validated mechanism of action. Interestingly, fidaxomicin (**1**) was also reported to be active against *Mycobacterium tuberculosis*, including drug resistant strains,[9] thus attracting further biological interest to this class of antibiotics.

Over the last four decades, over forty members of the tiacumicin family of natural products have been reported from several sources of bacteria.[10] The first isolation of fidaxomicin (**1**) from *Actinoplanes deccanensis* by Gruppo Lepetit scientists dates back to 1972.[11] The only structural element they could elucidate at that time however, was the dichlorohomoorsellinic acid fragment, probably due to the complex structure of the macrolide. In 1986, tiacumicins A, B and C were isolated from *Dactylosporangium aurantiacum*, as were the clostomicins from *Micromonospora echinospora,* and the relative configuration was elucidated.[12] At this point, it remained unclear if tiacumicin B, clostomicin B1, and lipiarmycin A3 shared an identical constitution and configuration. The complete structure of tiacumicin B was unambiguously established by X-ray crystallographic analysis in 2006.[13] Currently, lipiarmycin A3 and tiacumicin B (fidaxomicin, **1**) as well as clostomicin B1 have been established to be identical.[13] Further isolation of fidaxomicin derivatives was recently achieved in a biosynthetic study by Zhang and co-workers,[14] where the genes responsible for the biosynthesis were also investigated.

Figure 1. Fidaxomicin and Tiacumicin A



Fidaxomicin (**1**, Tiacumicin B, Lipiarmycin A3)



Tiacumicin A (**2**)

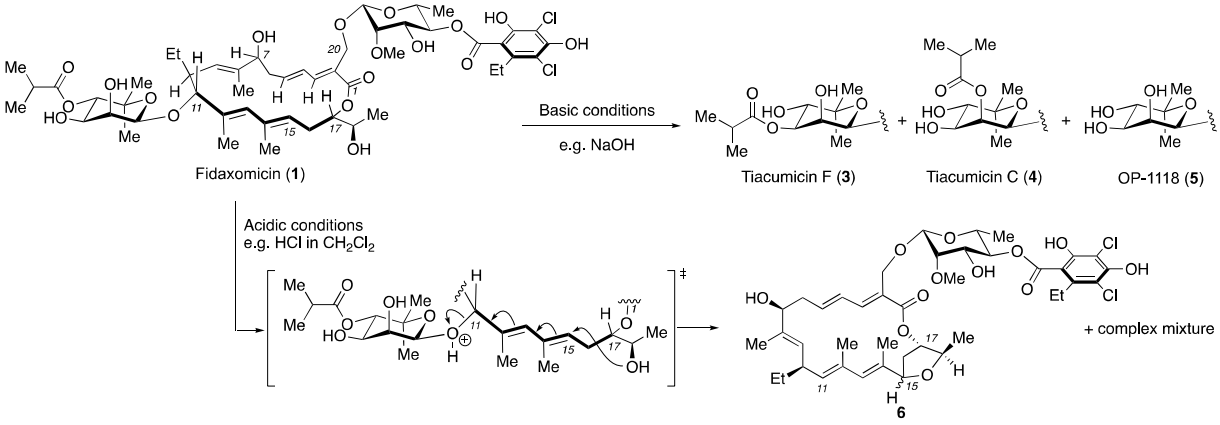
Concerning its molecular architecture, fidaxomicin (**1**) displays a number of remarkable features. The 18-membered macrocycle features five stereogenic centers and five double bonds arranged in two different diene moieties. Additionally, one of the two carbohydrate segments, 4-demethyl-D-noviose, is rarely found in natural products, rendering fidaxomicin (**1**) a unique antibiotic. Moreover, the two glycosidic linkages are arranged in β-fashion. Therefore, the major synthetic challenges for the synthesis of fidaxomicin (**1**) are associated with (1) the selective installation of the two glycosidic linkages (the *cis*–1,2 diol linkage, *cf.* the β-mannose problem)[15] between the macrocycle and the two carbohydrate segments as well as (2) convergent construction of the highly unsaturated macrocycle domains. Up to date, four synthetic studies of the 18-membered macrocycle of fidaxomicin (**1**) have been reported by Zhu,[16] Altmann,[17] Roulland[18] and our research group.[19] Furthermore, the synthesis of noviose,[20] rhamnose[21] and a resorcinol domain[22] have been reported. As is demonstrated in the synthesis of β-lactams or erythromycin derivatives,[23] we support the notion that both total chemical synthesis as well as semisynthesis can offer a pivotal platform for the discovery of new antibiotics. Consequently, we have published the first total synthesis of fidaxomicin (**1**, tiacumicin B, lipiarmycin A3) in a preliminary communication.[24] In this study, we report (1) on the second generation total synthesis of fidaxomicin (**1**) leading to a 72-fold increase in overall yield; (2) on a successful relay synthesis of the target, which enables the preparation of semisynthetic analogs from the natural material; (3) degradation studies of this drug under a variety of conditions and (4) document the first total synthesis of the related congener, tiacumicin A (**2**).

RESULTS AND DISCUSSION

Stability Analysis of Fidaxomicin (1). Although fidaxomicin (**1**) is a commercialized antibiotic, little about the chemical stability nor semisynthetic studies had been reported at the start of our synthetic endeavor.[25] Therefore, we decided to embark on evaluating the stability of fidaxomicin under a series of conditions. Specifically, we determined the pK_a of **1**, examined the sensitivity of **1** towards acidic conditions and basic conditions and identified the degradation products.

For determination of the pK_a value, an aqueous solution of NaOH (0.01 M) was added portionwise to a solution of fidaxomicin (**1**) in a MeOH/H_2O solvent mixture, as fidaxomicin is hardly soluble in pure water at neutral pH. The pH was determined after each addition of NaOH solution. The pK_a value of fidaxomicin in this MeOH/H_2O mixture was determined by identification of the titration's mid-point to be ${}^{s}_{w}pK_a = 6.6$. This is in accordance with the value given in the literature, ${}^{s}_{w}pK_a = 6.8$, in a solvent mixture 2-methoxyethanol/H_2O 4/1.[26] However, the pK_a value in pure H_2O, which was not experimentally determined due to the low solubility of fidaxomicin (**1**) in H_2O, is of higher interest for reasons of comparability. With the help of empirical parameters specific for phenols as acids, the corresponding value was calculated to be ${}^{w}_{w}pK_a = 5.6$.[27] The very high acidity of the dichlorohomoorsellinic acid group in fidaxomicin can be rationalized by the electron withdrawing effect of the ester substituent at *para*-position and the inductive effects by the chloro substituents at the *ortho*-positions.

Scheme 1. Stability Analysis of Fidaxomicin (1)



Next, we examined the sensitivity of **1** towards acidic conditions (Scheme 1). Treatment of **1** with hydrochloric acid under anhydrous conditions in dichloromethane led to a formation of tetrahydrofuran derivatives (*15R*)-**6** and its epimer.[28] This particular reaction was supposed to have occurred via an intramolecular oxy-S_N2' type attack of the hydroxy group at C18. Alternatively, when hydrochloric acid was added to fidaxomicin (**1**) in protic solvents such as MeOH, the corresponding methoxy-adducts were formed as methanol attacks the diene system instead of the hydroxy group at C18 (not shown). With only ten equivalents of HCl in MeOH at room temperature, fidaxomicin (**1**) slowly degraded. However, with 100 equivalents of HCl, nearly complete degradation was observed within four hours with the main degradation product resulting from nucleophilic attack of methanol (m/z = 863 for $[M+Na]^+$) and loss of the noviose segment. These results are consistent with the regulatory information for fidaxomicin, where fidaxomicin is reported chemically unstable outside of pH range from 4 to 8.[29]

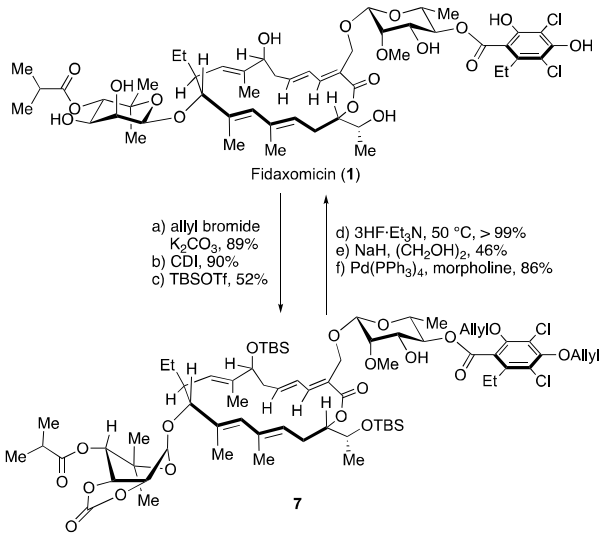
Next, the stability of fidaxomicin (**1**) was investigated under basic conditions. When **1** was treated with NaOH in MeOH and water, the isobutyrate group of noviose segment migrated from the C4'' to the C3'' position to provide tiacumicin F (**3**) and from the C4'' to the C2'' position to provide tiacumicin C (**4**). Under even stronger basic conditions or prolonged exposure to base, the isobutyrate was hydrolyzed to give alcohol **5**, which is the main metabolite of fidaxomicin, OP-1118.[4], [30] Therefore, the choice of cleavable protecting groups under

very mild and orthogonal conditions was critically important for the total synthesis of **1**.

To identify the optimal protecting groups for the sensitive groups in fidaxomicin (**1**), a series of protection and deprotection experiments was performed (Scheme 2). First, we protected the aromatic hydroxy groups on the resorcylate moiety as allyl ethers which could be cleaved under standard Pd catalysis conditions. Next, the 1,2-*syn*-diol on the noviose moiety was success protected as a cyclic carbonate using CDI (carbonyl diimidazole). At this point, the carbonate was the best protecting group for the diol, as it offered fast hydrolysis. Additionally, the electron withdrawing effect was expected to contribute to the β-selective glycosylation as it destabilizes the oxacarbenium ions and should therefore prevent the non-selective S_N1 process (*vide infra*). Other protecting groups, such as di-*tert*-butylsilylene or dimethylsilylene could not be implemented. Finally, the two remaining hydroxy groups on the macrocycle were protected as TBS ethers using TBSOTf and 2,6-lutidine, to provide protected fidaxomicin **7**. The C3 hydroxy group on the rhamnose fragment was not protected under these conditions, presumably due to steric reasons.

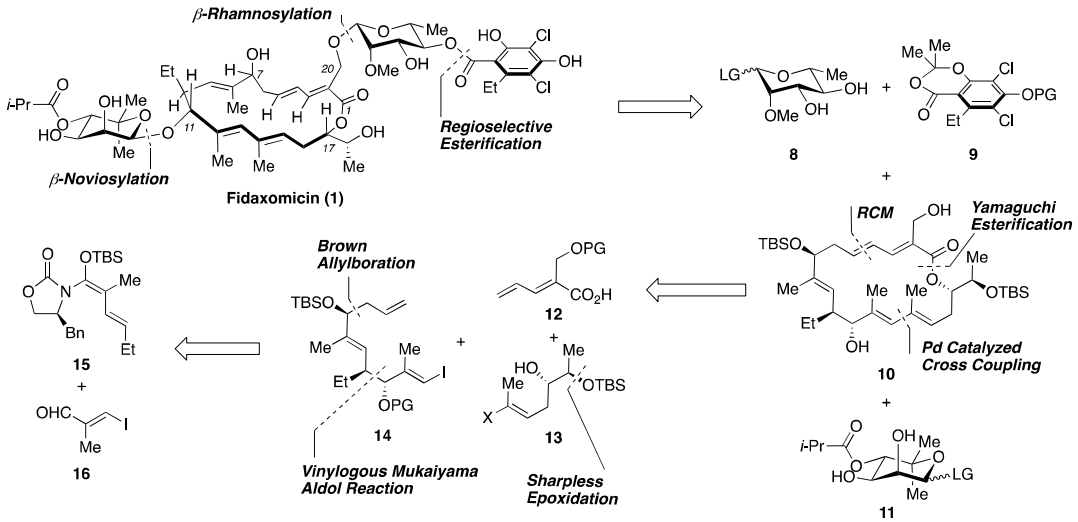
The deprotections were initiated by treatment with $3HF{\cdot}NEt_3$ at 50 °C to cleave the two TBS groups, which led to the clean formation of the corresponding alcohol. By the careful monitoring of the deprotection reactions, we observed the quick cleavage of C18 TBS ether at room temperature. However, the TBS group at C7 was found to be very stable reflecting the steric bulkiness of the surrounding environment, requiring harsher deprotection conditions. As it was expected, subsequent carbonate deprotection turned out to be troublesome due to the migration of the C4´´ ester group on the noviose segment: DBU, K_2CO_3, DMAP, or DABCO led to the formation of tiacumicin F (**3**), tiacumicin C (**4**) and **5.** Finally, the desired product was isolated by the treatment with Barton´s base[31] at room temperature in wet dichloromethane, although isobutyrate migration reactions could still not be completely suppressed. Further improvement for the selective hydrolysis was achieved by the treatment with NaH and ethylene glycol in dry tetrahydrofurane at 0 °C. Finally, the allyl groups were removed under Pd (0) catalysis to provide fidaxomicin (**1**).

Scheme 2. Semisynthetic Approach for the Selection of Protecting Groups[a]



[a]Reagents and conditions: a) allyl bromide, K_2CO_3, DMF, 45 °C, 3 h, 89%; b) CDI, Et_3N, CH_2Cl_2, rt, 24 h, 90%; c) TBSOTf, 2,6-lut., CH_2Cl_2, 0 °C to rt, 5 h, 52%; d) $3HF{\cdot}NEt_3$, THF, 50 °C, 2 d, > 99%; e) NaH, $(CH_2OH)_2$, THF, 0 °C, 15 min; RP-HPLC, 46%; f) $Pd(PPh_3)_4$, morpholine, THF, 0 °C, 30 min, 86%. DMF = *N,N*-dimethyl formamide, CDI = 1,1-carbonyldiimidazole, TBS = *tert*-butyldimethylsilyl, 2,6-lut. = 2,6-lutidine, THF = tetrahydrofuran.

Scheme 3. Retrosynthetic Analysis

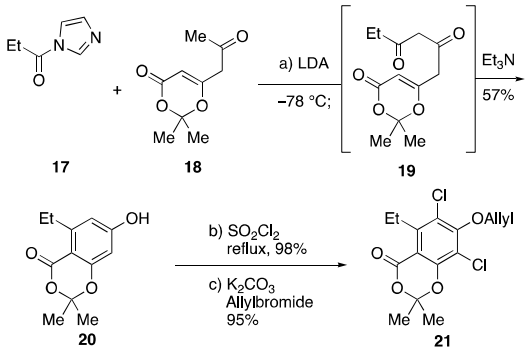


Retrosynthetic Analysis. Based on the preliminary stability assessment and the evaluation of protecting groups, we identified a retrosynthetic strategy outlined in Scheme 3. Cleavage of the two β-glycosidic bonds and the orsellinic ester bond would give the four segments **8**, **9**, **10** and **11**. The macrocycle **10** could be accessed via Yamaguchi esterification, Pd catalyzed Suzuki or Stille cross coupling and a ring closing metathesis from fragments **12**, **13** and **14**. Although Zhu and coworkers utilized extensive Evans aldol reactions,[16] we propose that a vinylogous Mukaiyama aldol reaction of the silyl ketene aminal **15** and the iodide **16** may offer a more efficient entry to the synthesis.

Rhamnose Segment Synthesis. The synthesis commenced with the preparation of the rhamnose segment. For the prepa-

ration of a protected resorcylate, we applied the biomimetic cascade reactions established by Barrett and co-workers (Scheme 4).[32] First, the known keto dioxinone **18**[33a] was treated with freshly prepared propionyl imidazole **17**[33c] to provide diketone **19**, which was then treated with excess Et_3N at room temperature to trigger a spontaneous cyclization and aromatization and provide phenol **20** in 57% yield. The obtained electron rich phenol **20** was treated with sulfuryl chloride to convert it to the dichloride, [34] which was then protected with allyl bromide to yield the acylation precursor **21** in 95% yield.

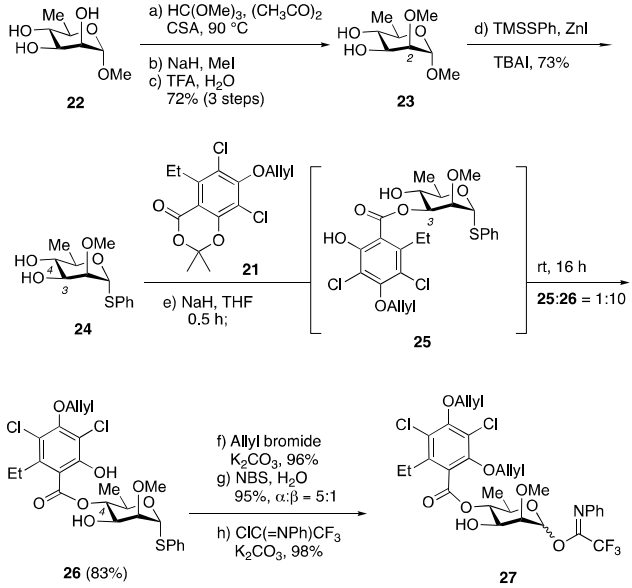
Scheme 4. Synthesis of Acylation Precursor 21[a]



[a]Reagents and conditions: a) LDA (4.2 equiv), ketone **18** (2.1 equiv), THF, −78 °C, 1.5 h; propionyl imidazole **17**, 2.5 h, −78 °C; Et_3N (excess), CH_2Cl_2, rt, 16 h, 57%; b) SO_2Cl_2, CH_2Cl_2, reflux, 1.5 h, 98%; c) allyl bromide, K_2CO_3, DMF, rt, 4 h, 95%. LDA = lithium diisopropylamide.

The next key steps towards the synthesis of rhamnoside segment were the selective introduction of the C2′ methyl group and C4′ ester on the unusual monosaccharide (Scheme 5). First, the two equatorial hydroxy groups at C3′ and C4′ of known **22**[35] was protected as the butane-2,3-diacetal. After methylation at the C2′ hydroxy group with MeI and the hydrolysis of the temporary acetal protecting group (72% over 3 steps), the resulting diol **23** was advanced to the thioglycoside **24** by the treatment with TMSSPh in the presence of ZnI_2. Next, we performed an acylation of diol **24** with the resorcylate **21**. Although the C4′ hydroxy group was expected to be less reactive than C3′,[36] we were very satisfied to obtain the desired C4′ acylated product **26** with an excellent regioselectivity ratio (10:1). Upon careful observation, we found that the acylation of the C3′ hydroxy group is indeed kinetically favored and this regioisomer was obtained as a single product after stirring for 30 min at room temperature (judged by ^1H NMR analysis). With longer reaction times, the aromatic ester migrates from C3′ to C4′ to give the desired regioisomer **26**. Subsequent protection of the aromatic hydroxy group with allyl bromide and oxidative hydrolysis of the thioglycoside by treatment with aqueous NBS resulted in the formation of hemiacetal in 95% yield. Considering the thermodynamic stability of the ester at C4′ and the steric bulkiness of the surrounding functionality, the remaining C3′ hydroxy group was not protected. Finally, the resulting hemiacetal was treated with *N*-phenyl trifluorochloroacetimidate[37] to afford acetimidate **27** suitable for glycosylation.

Scheme 5. Synthesis of Rhamnoside Donor 27[a]

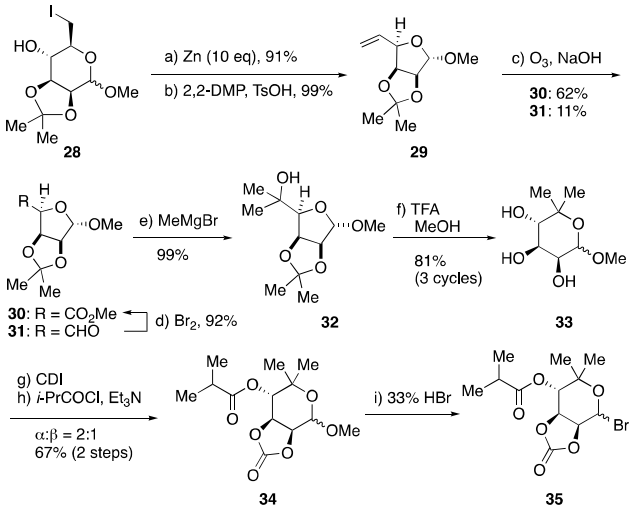


[a]Reagents and conditions: a) $HC(OMe)_3$, $(MeCO)_2$, CSA (6 mol%), MeOH, 90 °C (sealed tube), 24 h; b) NaH, MeI, THF, 0 °C to rt, 3.5 h; c) TFA, H_2O, CH_2Cl_2, rt, 1 h, 72% (3 steps); d) TBAI, ZnI, TMSSPh, $ClCH_2CH_2Cl$, 65 °C, 2.5 h, 73%; e) **21** (1.0 equiv) NaH (5 equiv), THF, 0 °C, 30 min; rt, 16 h, **25**:**26** = 1:10, **26**: 83%; f) allyl bromide, K_2CO_3, DMF, 50 °C, 3 h, 96%; g) NBS, acetone/H_2O 10:1, 0 °C to rt, 95%, α:β = 5:1; h) $ClC(=NPh)CF_3$, acetone, K_2CO_3, rt, 3 h, 98%. CSA = camphorsulfonic acid, NBS = *N*-bromosuccinimide, TBAI = tetrabutylammonium iodide, TFA = trifluoroacetic acid, TMS = trimethylsilyl.

Noviose Segment Synthesis. The key steps in the synthesis of the noviose fragment include the incorporation of the additional methyl group at the C5′ position and appropriate functionalization of the neighboring hydroxy group so that the β-selective glycosylation proceeds with reasonable selectivity. As was briefly mentioned above in the context of fidaxomicin (**1**) protections, we decided to use the carbonate group for the protection of the 1,2-*syn* alcohol. The synthesis of the noviosyl donor started with the ring contraction reaction of iodide **28**[38a] to provide furanoside **29**[38b] in 91% yield under modified Vasella conditions[39] (Scheme 6). Next, the terminal olefin **29** was directly oxidized to the corresponding methyl ester **30** by employing Marshall's ozonolysis protocol[40] in NaOMe solution. The major side product isolated was an aldehyde intermediate **31**, which was transformed into the desired ester **30** under mild oxidation with bromine (92%).[41] Subsequent introduction of the additional methyl group at the C5′′ position using the Grignard reagent and isomerization of the obtained tertiary alcohol **32** under acidic conditions gave access to pyranoside **33**. Unfortunately, the equilibrium between furanose **32** and pyranose **33** in TFA in MeOH turned out to be only 2:1 in favor of the desired pyranose. The minor furanoside product **32** could be converted to pyranoside **33** by resubjection to the same acidic conditions. After three cycles of acid treatment and separation, the desired pyranoside **33** was obtained in 81% overall yield as an anomeric mixture (α:β = 2:1). The introduction of the carbonate group using CDI, followed by the treatment with isobutyryl chloride, resulted in formation of the fully functionalized noviose **34** in 67% yield over two steps as a separable 2:1 mixture of anomers. Finally, the acetal **34** was converted to the desired glycosyl bromide donor **35** using HBr in acetic acid. It is worth noting that this

glycosyl bromide **35** was isolated as a mixture with glycosyl acetate, and it was sensitive to silica gel when it had been concentrated at room temperature. Therefore, two equivalents of glycosyl bromide **35** were prepared immediately before the noviosylation reaction and used immediately after aqueous workup and concentration at low temperature.

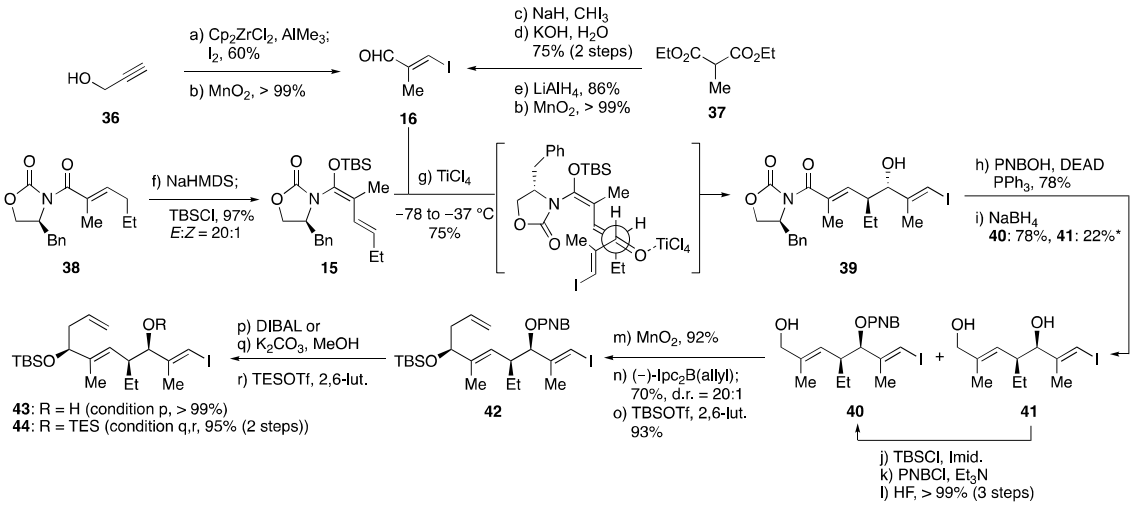
Scheme 6. Synthesis of Noviosyl Bromide 35[a]



[a]Reagents and conditions: a) Zn (10 equiv), NH_4Cl (0.4 equiv), MeOH, 60 °C, 91%; b) CSA (20 mol%), 2,2-DMP, MeOH, 55 °C, 18 h, 99%; c) O_3, NaOH in 2.5 M MeOH, CH_2Cl_2, −78 °C, **30**: 62%, **31**: 11%; d) Br_2, $NaHCO_3$, MeOH, H_2O, 40 °C, 92%; e) MeMgBr (2.4 equiv), Et_2O, 35 °C, 30 min, 99%; f) TFA (excess), MeOH, 100 °C (μw), 3 h, 81% (3 cycles), α:β = 2:1; g) CDI, $ClCH_2CH_2Cl$, reflux, 3 h; h) isobutyryl chloride, Et_3N, CH_2Cl_2, rt, 1 h, 67% (2 steps) α:β = 2:1; i) 33% HBr in AcOH, CH_2Cl_2, 0 °C to rt, 2 h. 2,2-DMP = 2,2-dimethoxypropane.

Synthesis of Vinyl Iodide via VMAR. Our initial efforts for macrocycle construction are depicted in Scheme 7. The synthesis of the macrocycle fragment began with the synthesis of silyl ketene aminal **15** from **38** through γ-deprotonation.[42] The other key component, aldehyde **16**, was synthesized either from propargyl alcohol **36** through methylzirconation or from diethyl methylmalonate **37** in four steps through a decarboxylative elimination.[43] Next, the key vinylogous Mukaiyama aldol reaction (VMAR) between **15** and the α,β-unsaturated aldehyde **16** was investigated. All the initial investigations to yield *syn*-aldol adduct using excess Lewis acid failed.[44] The reason for this can be ascribed to the combination of electron rich and bulky α,β-unsaturated aldehyde and sterically more demanding ethyl substituted silyl ketene aminal **15** compared to the standard methyl group. Actually, VMAR is quite sensitive to electronic and steric properties of the electrophiles and nucleophiles.[45] In our earlier investigation towards the synthesis of JBIR-02, for example, we failed to achieve a reaction with electron rich unsaturated aldehyde substrates.[46] As there are many more successful applications of *anti*-selective VMAR in polyketide natural product synthesis, we next investigated *anti*-selective VMAR,[47] expecting the hydroxy group to be invertible by Mitsunobu reaction (*vide infra*). After extensive experimentation, the best conditions to cleanly obtain the desired product were identified: $TiCl_4$ was slowly added to the aldehyde **16**, followed by syringe pump addition of aminal **15** at −78 °C over 20 min; then the reaction mixture was slowly warmed to –37 °C and stirred overnight at the same temperature for 18 h. The reaction mixture had to be kept at –37 °C to observe a reasonable reaction rate and selectivity. In addition, the purification of aminal **15** and aldehyde **16** had to be performed thoroughly as the contamination of TBSOH and water accelerated the reaction.[48] The obtained *anti*-**39** was then transformed into the *syn*-nitrobenzoate by employing the Mitsunobu protocol. Cleavage of the Evans auxiliary in the presence of *para*-nitrobenzoate was performed selectively under reductive conditions to provide primary alcohol **40**. (78%)[49] Although some overreaction led to the formation of diol **41** in 22% yield (based on ^{1}H NMR) as a mixture with nitrobenzyl alcohol, the material throughput of this reaction was improved by transforming the diol side product **41** into **40** by a three-step sequence. First, the primary hydroxy group was protected as TBS ether in the presence of the secondary hydroxy group. Second, the obtained TBS ether was transformed into the *para*-nitrobenzoate under standard esterification conditions and finally treated with HF in MeCN to provide the alcohol **40**. The obtained allylic alcohol **40** was oxidized with MnO_2 to provide the corresponding α,β-unsaturated aldehyde in 92% yield. At this stage, the absolute configuration of this α,β-unsaturated aldehyde was unambiguously confirmed by a single crystal X-ray analysis of its bromide derivative. Subsequent diastereoselective Brown allylation of aldehyde with (–)-allyl-diisopinocampheylborane[50] established the C7 hydroxy group and gave the alcohol in 70% yield. The separation of the desired product from isopinocampheol was difficult at this point, however, the pure TBS ether **42** was easily separable by silica gel column chromatography after TBS protection of the mixture. Subsequent deprotection of the nitrobenzoyl ester cleanly provided the desired alcohol **43**, which was re-protected as TES ether **44**.

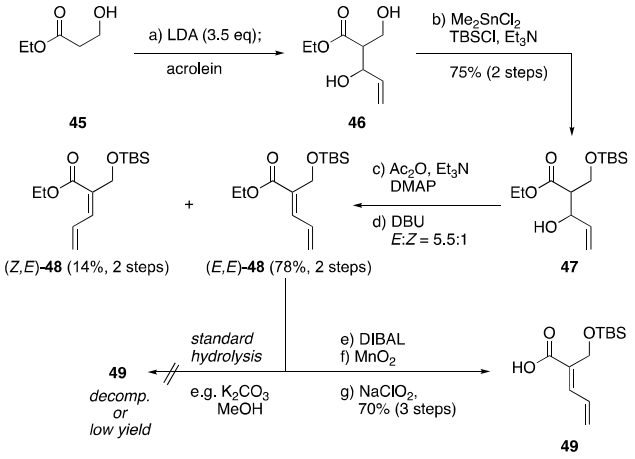
Scheme 7. Synthesis of Vinyl Iodide 43 and 44 via Vinylogous Mukaiyama Aldol Reaction (VMAR)[a]



[a]Reagents and conditions: a) Cp_2ZrCl_2, $AlMe_3$, CH_2Cl_2, rt, 12 h; I_2, 60%; b) MnO_2, CH_2Cl_2, > 99%; c) NaH, CHI_3, Et_2O, reflux; d) KOH, H_2O, EtOH, reflux, 75% (2 steps); e) $LiAlH_4$, Et_2O, 86%; g) NaHMDS, THF, −78 °C; TBSCl, *E*:*Z* = 20:1, 97%; g) **16** (2.0 equiv), $TiCl_4$ (1.0 equiv), CH_2Cl_2, −78 °C; **15** via syringe pump for 20 min; −78 to −37 °C; −37 °C, 18 h, **39**: 75%, d.r. > 50 :1, **38**: ca. 20%; h) PNBOH, DEAD, PPh_3, THF, 0 °C to rt, **40**: 78%, **41**: 22%; i) $NaBH_4$ (3.0 equiv), THF/H_2O, 0 to 15 °C, 3 h; j) TBSCl, imid., CH_2Cl_2, rt, 10 min; k) PNBCl, DIPEA, DMAP, CH_2Cl_2, rt, 6 h; l) 48% HF, MeCN, rt, 3 h, > 99% (3 steps); m) MnO_2, CH_2Cl_2, 92%; n) (−)-Ipc_2B(allyl) (1.5 equiv), Et_2O, −78 °C; *aq*. $NaBO_3{\cdot}4H_2O$, 70%, d.r. = 20:1; o) TBSOTf, 2,6-lut., CH_2Cl_2, 93%; p) DIBAL, PhMe, CH_2Cl_2, −40 °C, **43**: > 99%.; q) K_2CO_3, MeOH/H_2O; r) TESOTf, 2,6-lut., CH_2Cl_2, **44**: 95% (2 steps). Cp = cyclopentadienyl, DEAD = diethyl azodicarboxylate, NaHMDS = sodium bis(trimethylsilyl)amide, Ipc = isopinocampheyl, PNB = *para*-nitrobenzoyl, imid. = imidazole, DMAP = 4-dimethyl-aminopyridine, TES = triethylsilyl, DIBAL = diisobutylaluminum hydride.

Conjugated Ester Synthesis. The carboxylic acid fragment **49** was prepared from commercially available ethyl 3-hydroxypropanoate **45** (Scheme 8). First, the dianion of ester **45** was condensed with freshly distilled acrolein to furnish the corresponding aldol adduct **46**. The obtained crude mixture of diol **46** was directly treated with TBSCl and Et_3N in the presence of $SnMe_2Cl_2$[51] to give primary TBS ether **47**. Acetylation of the remaining secondary hydroxy group and the subsequent E1cB elimination using DBU as a base furnished the unsaturated ester (*E*)-**48** (*E*:*Z* 5.5:1).

[a]Scheme 8. Synthesis of α,β,γ,δ-Unsaturated Carboxylic Acid 49[a]

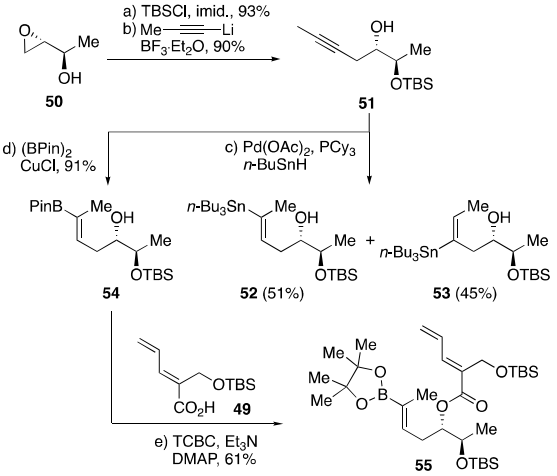


[a]Reagents and conditions: a) LDA (3.5 equiv), THF, −78 to −30 °C; acrolein (1.2 equiv), −78 to −10 °C; b) Me_2SnCl_2 (10 mol%), TBSCl, Et_3N, CH_2Cl_2, rt, 75 % (2 steps) d.r. = 3:2; c) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt; d) DBU, CH_2Cl_2, rt, *E*:*Z* = 5.5:1, (*E,E*)-**48**: 78%, (*Z,E*)-**48**: 14% (2 steps); e) DIBAL (2.5 equiv), CH_2Cl_2, −78 °C; −10 °C; f) MnO_2, CH_2Cl_2, rt; g) $NaClO_2$, KH_2PO_4, 2-methyl-2-butene, *t*-BuOH/H_2O 1:1, rt, 70% (3 steps). DBU = 1,8-diazabicycloun-dec-7-ene.

The following hydrolysis proved to be troublesome due to the formation of side products probably via spontaneous TBS deprotection and / or (hetero-) Diels Alder reactions. Fortunately, the desired carboxylic acid **49** was obtained by formal hydrolysis of the delicate substrate. It should also be noted that the ester **48** and carboxylic acid **49** were relatively unstable at room temperature. Therefore, it is recommended to store **48** in frozen benzene at –20 °C when it is kept for more than a day.

Synthesis of Coupling Partners 52 and 55. The coupling partners for iodide **44** were synthesized in three steps from the known epoxide **50**[52] (Scheme 9). First, the TBS ether was prepared from epoxy alcohol **50**, which was obtained through a kinetic resolution of 3-buten-2-ol through a Sharpless epoxidation.[52b] Regioselective alkylation with propynyllithium in the presence of $BF_3{\cdot}OEt_2$ provided the desired secondary alcohol **51**.[53] Pd-catalyzed hydrostannylation gave access to the stannane **52**, along with the undesired regio isomer **53**. Other approaches such as hydrozirconation[54] and stannylcupration[55] gave a complex mixture of products. Alternatively, the alcohol **51** was subjected to copper-catalyzed hydroboration using bis(pinacolato)diborane to provide boronic ester **54** as a single regioisomer using the protocol developed by Altmann and co-workers.[17] The obtained boronate **54** was further advanced to ester **55** by Yamaguchi esterification.

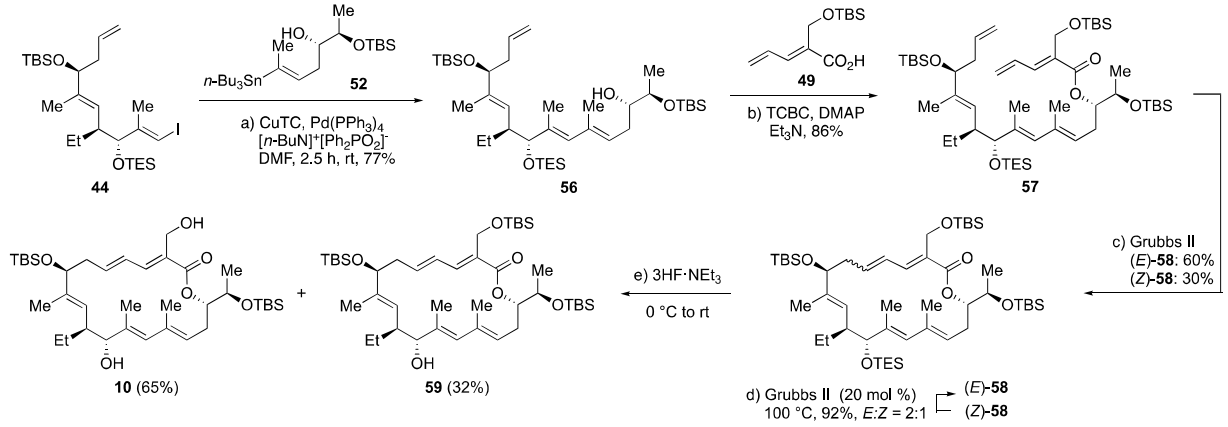
Scheme 9. Synthesis of Stannane 52 and Boronic Ester 55[a]



[a]Reagents and conditions: a) TBSCl, imid., CH_2Cl_2, 93%; b) propyne, *n*-BuLi, $BF_3{\cdot}OEt_2$, THF, −78 to 0 °C, 90%; c) $Pd(OAc)_2$ (5 mol%), PCy_3 (10 mol%), *n*-Bu_3SnH, *n*-hexane, **52**: 51%, **53**: 45%; d) B_2Pin_2 (1.1 equiv), CuCl (5 mol%), PPh_3 (6 mol%), KO*t*-Bu (20 mol%), THF, rt, 26 h, 91%; e) **49** (1.2 equiv) TCBC (1.25 equiv), DMAP, Et_3N, PhMe, 61%, Cy = cyclohexyl, Pin = pinacolato, TCBC = 2,4,6-trichlorobenzoyl chloride.

Synthesis of the Macrocycle 10. With the three key fragments in hand, the planned Pd-catalyzed cross coupling was explored (Scheme 10). The first approach employing a Stille coupling was found to be very challenging due to the steric hindrance of the methyl groups of stannane **52** and iodide **44**, resulting only in side product formation. To our delight, the desired coupled product **56** was obtained in 77% yield by applying the Pd/Cu-mediated cross coupling conditions reported by Fürstner and co-workers.[56] Interestingly, the alcohol at C11 needed to be protected as TES ether, otherwise the reaction did not proceed even under Fürstner´s conditions. Later, we also found that this reaction could be replaced by a TlOEt promoted Suzuki coupling between **44** and **54** (not shown). The use of TlOEt as a base was essential[57] to accelerate this reaction to reach the best results. Next, the obtained alcohol **56** was condensed with carboxylic acid **49** using the Yamaguchi protocol to give rise to polyene **57**. The obtained polyene **57** was cyclized using second generation Grubbs catalyst (15 mol%) to provide macrocycle **58**.[58] Interestingly, when this reaction was performed at room temperature, *Z* isomer was exclusively formed after 30 min (not shown), probably due to the conformational restriction during the cyclization. However, by heating this reaction mixture for an additional 18 hours at 100 °C, (*Z*)-**58** was partially converted to (*E*)-**58** to give a 2:1 mixture in favor of the *E* isomer. It is worth noting that this isomerization did not occur only with heat and, neither light-induced[59] nor Morita-Baylis-Hillman type isomerization provided complex mixtures. Alternatively, the cyclization was performed at 100 °C for 2 h to yield the same results.[16] Fortunately, the two isomers could be separated by silica gel column chromatography, which in turn allowed for recycling of the undesired *Z* isomer by subjecting it to the same metathesis conditions with the aim to convert it into the *E* isomer. Finally, the primary TBS and TES groups were cleaved using $3HF{\cdot}NEt_3$. As the TBS group at the C18 position was also sensitive under these conditions, the reaction was not allowed to proceed to complete conversion in order to avoid over-deprotection. The desired diol **10** was obtained in 65% yield along with the TES deprotected intermediate **59** in 32% yield. The latter could be further deprotected under the same conditions to afford diol **10**. With this, the synthesis of the protected fidaxomicin aglycon was completed with the appropriate hydroxy groups available for the subsequent glycosylation reactions.

Scheme 10. Synthesis of Macrocycle 10[a]

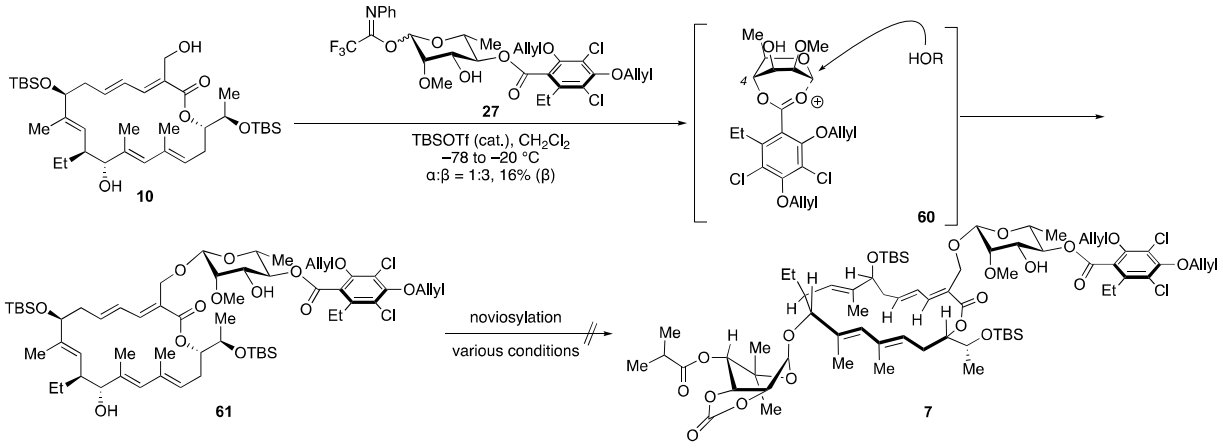


[a]Reagents and conditions: a) **52** (1.7 equiv), CuTC (3.0 equiv), $Pd(PPh_3)_4$ (70 mol%), $[n\text{-}Bu_4N]^+[Ph_2PO_2]^-$ (3.9 equiv), DMF, 2.5 h, rt, 77%; b) **49** (2.0 equiv), TCBC (1.95 equiv), DMAP, Et_3N, PhMe, rt, 1.5 h, 86%; c) Grubbs II (20 mol%), PhMe, 40 °C, 10 min; 100 °C, 18 h, *E*:*Z* = 2:1, (*E*)-**58**: 60%, (*Z*)-**58**: 30%; d) Grubbs II (20 mol%), PhMe, 100 °C, 18 h, 92%, *E*:*Z* = 2:1; e) $3HF{\cdot}NEt_3$, THF, MeCN, 0 °C to rt, 8 h, **10**: 65%, **59**: 32%. CuTC = Copper(I) 2-thiophenecarboxylate.

β-Selective Glycosylations. We were now poised to explore the final glycosylations (Scheme 11). We started exploration of the rhamnosylation[60] using model substrates with similar functional groups (see supporting information for screening results). Searching for the best reaction conditions, we found that using trifluoroacetimidate **27** and TBSOTf as an activator at cryogenic temperature[37] led to the best yield and diastereoselectivity.[61] Therefore, we applied these optimized conditions with the primary alcohol **10** and obtained the desired glycoside **61** in 19% yield with good selectivity (α:β = 1:3**)**.

The selectivity of this particular reaction is ascribed to the formation of oxocarbenium cation intermediate **60**, which was selectively attacked by the glycosyl acceptor **10** from the β-face.[62]

Scheme 11. Successful β-Selective Rhamnosylation and Failed β-Selective Noviosylation[a]

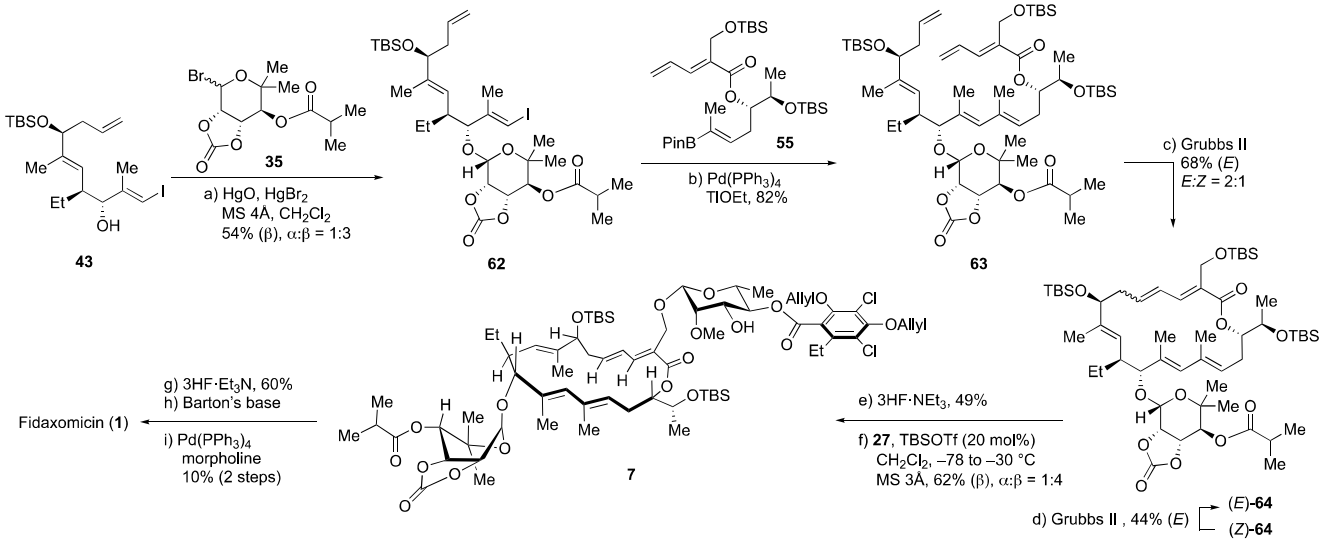


[a]Reagents and conditions: Imidate **27** (4.2 equiv), TBSOTf (20 mol%), CH_2Cl_2, MS 4Å, –78 to –20 °C, 2.5 h, α:β = 1:3, β-**61**: 16%.

Having succeeded with the rhamnosylation, we then explored noviosylation of **61**. Applying several glycosylation conditions, it was found that the reactivity of the glycosyl acceptor **61** was much lower than we had initially expected. All the attempts to obtain the desired glycoside **7** failed after screening various glycosyl donors and activation conditions, probably due to the following two reasons: (1) steric bulkiness of substituents close to the hydroxy group; and (2) rigidity of the macrocycle and an allylic strain of the double bond system. Additionally, the material supply for noviosylation hampered the investigation, as the previous rhamnosylation reaction only gave 16% of product. Therefore, we concluded not to investigate this strategy any further and established a new synthetic strategy. Based on the results obtained with **61**, we hypothesized that glycosylation might succeed if we employed a more flexible acceptor. Therefore, we decided to use alcohol **43** as a glycosyl acceptor, expecting it to offer increased conformational flexibility, good material availability and compatibility of the following reactions to the glycosylated product (e.g. Suzuki coupling and RCM).

β-Selective Noviosylation and Completion of the Total Synthesis. With this new strategy, β-selective noviosylation of alcohol **43** was screened under various reaction conditions. Although this transformation was still challenging owing to the sterically demanding nature of glycosyl acceptor **43**, we identified that the use of HgO in combination with $HgBr_2$ would lead to the smooth formation of the desired β-glycoside **62** (Scheme 12).

Scheme 12. Total Synthesis of Fidaxomicin (1)[a]



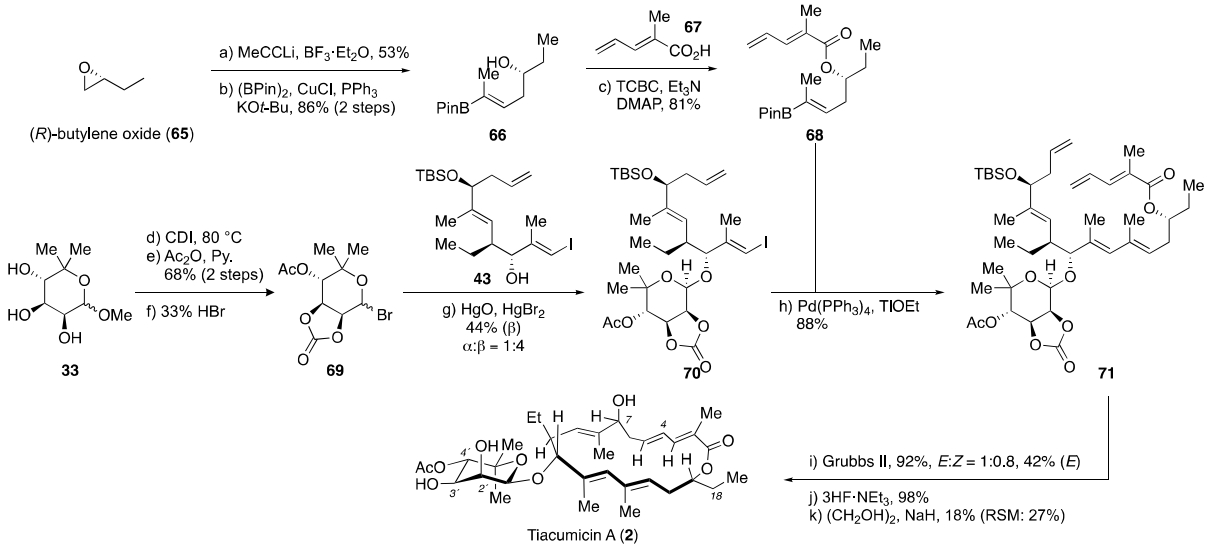
[a]Reagents and conditions: a) Bromide **35** (2.8 equiv), HgO (6.5 equiv), $HgBr_2$ (15 mol%), MS 4Å, CH_2Cl_2, 1 h, α:β = 1:3, β-**62**: 54%; b) **55** (1.5 equiv), $Pd(PPh_3)_4$ (20 mol%), TlOEt (1.6 equiv), THF/H_2O 3:1, 0 °C to rt, 30 min, 82%; c) Grubbs II (20 mol%), PhMe, 100 °C, 1 h, *E:Z* = 2:1, (*E*)-**64**: 68%; d) Grubbs II (20 mol%), PhMe, 100 °C, 11 h, (*E*)-**64**: 44%; e) 3HF·NEt_3, THF/MeCN 1:1, rt, 8 h, **7**: 49%, **64**: 40%; f) **27** (1.15 equiv), TBSOTf (20 mol%), CH_2Cl_2, MS 3Å, –78 to –30 °C, 1 h, α:β = 1:4, β-**7**: 62%; g) 3HF·NEt_3 (excess), THF, 50 °C, 24 h, 60%; h) Barton's

base, CH_2Cl_2, H_2O, rt, 3 h; i) $Pd(PPh_3)_4$ (10 mol%), morpholine (excess), THF, 0 °C, 30 min; RP-HPLC, 10% (2 steps). Barton`s base = 2-*tert*-butyl-1,1,3,3-tetramethylguanidine.

The configuration of the glycosidic bonding was determined by extensive ^{1}H and 2D NMR studies, which confirmed the selective formation of the desired β-anomer **62**. We assume the reaction proceeds *via* an S_N2-like mechanism under classical Helferich's conditions[63] to provide the desired anomer. The obtained β-glycoside was further transformed into the macrocycle in three steps. First, the iodide **62** was coupled with boronate **55** under the previously described Suzuki coupling conditions.[17] Next, the polyene **63** was cyclized to yield the desired macrocycle **64** as a mixture of *E* and *Z* isomers. Fortunately, in this case, both stereoisomers were separable using preparative thin layer chromatography (PTLC). After selective removal of the primary TBS group, the rhamnosylation reaction was performed. Gratifyingly, we confirmed the formation of fully protected fidaxomicin **7** with a diastereomeric ratio of 4:1 at the rhamnose linkage, thereby accomplishing a relay synthesis of fidaxomicin (**1**). The identity of a semisynthetic and a totally synthetic sample of **7** was confirmed by comparing the spectroscopic data of both (i.e. ^{1}H NMR, see detailed comparison results listed in supporting information). We further converted fully protected fidaxomicin **7** to synthetic **1** by employing the deprotection conditions investigated in the early stage of this synthetic program. TBS deprotection with $3HF{\cdot}NEt_3$, carbonate deprotection with Barton's base and allyl deprotection under palladium catalyzed conditions delivered the desired fully synthetic fidaxomicin (**1**). As the relay synthesis conditions presented in Scheme 2 were only identified after the successful total synthesis, we think that the yield of this transformation under the new conditions (e.g. NaH instead of Barton's base) should be much higher. ^{1}H NMR analysis confirmed the identity of synthetic and natural fidaxomicin (**1**).

Total Synthesis of Tiacumicin A (**2**). The synthesis of Tiacumicin A (**2**) started with the alkylation of commercially available epoxide **65** with propynyllithium (Scheme 13). Taking the volatility of the resulting secondary alcohol into account, it was immediately borylated to give boronate **66**. This boronate was further advanced to ester **68** via Yamaguchi esterification with known carboxylic acid **67**.[64] As tiacumicin A (**2**) contains an acetate instead of the isobutyrate on the noviose moiety, we prepared the corresponding glycosyl bromide **69** from the common intermediate **33** via acetylation with Ac_2O in THF. This bromide **69** was subsequently reacted with alcohol **43** and the desired β-glycoside **70** was obtained in 44% yield. The diastereoselectivity (1:4) was slightly better than in the corresponding reactions of fidaxomicin total synthesis (1:3) however, the yield was lower. Next, iodide **70** was coupled with the separately synthesized boronate **68** under Suzuki coupling conditions. Ring closing metathesis of the polyene **71** proceeded smoothly under the same conditions as for fidaxomicin. Although the separation of the stereoisomers turned out to be difficult by silica gel column chromatography, separation of the desired *E* isomer was achieved by HPLC on a chiral stationary phase (DAICEL, Chiralpack-IA column). The (*E*) isomer was then treated with $3HF{\cdot}NEt_3$ at 50 °C providing C7 alcohol. Finally, the carbonate group was cleaved to give tiacumicin A (**2**) together with another natural product, 4′-deacetyl tiacumicin (not shown).[14a] During hydrolysis, the prevention of transacylation was more difficult than in the case for fidaxomicin due to the smaller acetate group when compared to the isobutyrate. We separated all the isomers by reversed phase HPLC to provide four compounds. The spectroscopic data for tiacumicin A (**2**) was identical to the one reported for the natural sample,[14a] concluding the first total synthesis of this natural product. With these successful syntheses, we demonstrated the versatility of our synthetic strategy for the synthesis of tiacumicin class natural products. We are currently working on other members of this class of antibiotic natural products which have potential of increased clinical applications.

Scheme 13. Total Synthesis of Tiacumicin A (2)[a]



[a]Reagents and conditions: a) propyne, *t*-BuLi, $BF_3{\cdot}OEt_2$, THF, –78 °C to 0 °C, 2 h, 53%; b) B_2Pin_2, CuCl (5 mol%), PPh_3 (6 mol%), KO*t*-Bu (20 mol%), THF, 20 h, 86%; c) **67** (1.3 equiv), TCBC (1.3 equiv), Et_3N, DMAP, PhMe, 5 h, 81%; d) CDI, THF, 80 °C, 3.5 h; 6 N HCl, 2 h, rt; e) Ac_2O, Py., CH_2Cl_2, 68% (2 steps); f) 33% HBr in AcOH, CH_2Cl_2, 0 °C to rt; g) **69** (1.8 equiv), HgO, $HgBr_2$, MS 4Å, CH_2Cl_2, 44% (β), α:β = 1:4; h) **68** (1.7 equiv), $Pd(PPh_3)_4$, (10 mol%), TlOEt (1.5 equiv.), THF, H_2O, 88%; i) Grubbs II (20 mol%), PhMe, 100 °C, 92%, *E*:*Z* = 1:0.8; HPLC purification DAICEL, Chiralpack-IA, 42% (*E*); j) $3HF{\cdot}NEt_3$, THF, 50 °C, 98%; k) NaH, $(CH_2OH)_2$, CH_2Cl_2, 0 °C, Tiacumicin A: 18%, RSM: 27%. RSM = recovery of starting material.

Conclusion. A first total synthesis of the antibiotic natural product, fidaxomicin (**1**, tiacumicin B, lipiarmycin A3) was accomplished in a highly convergent manner. The developed protocol gives access to the conveniently protected 18-membered macrocycle in 15 steps from commercially available starting material. The macrocycle synthesis is highly convergent and high yielding. The modular strategy of the synthesis as well as the judicious design of the glycosyl donors and glycosylation point allowed β-selective rhamnosylation and β-selective noviosylation. Finally, removal of carefully chosen and validated protecting groups cumulated in the total synthesis of fidaxomicin (**1**). With this strategy, we are well equipped for the preparation of other tiacumicin class natural products, as exemplified by the preparation of tiacumicin A (**2**) reported herein. Further synthetic endeavors as well as the results from biological assays will be disclosed in due course.

EXPERIMENTAL SECTION

General Information, Materials and Equipment: Unless otherwise stated, all chemicals were of reagent grade and purchased from Sigma-Aldrich-Merck, Acros Organics, Honeywell, Fluorochem or Tront. Fidaxomicin was obtained by fermentation from *Actinoplanes deccanensis* (DSM 43806; ATCC 21983). Reactions were carried out under protecting gas (N_2 or Ar) in oven-dried (120 °C) glass equipment and monitored for completion by TLC or UHPLC-MS (ESI). Solvents for reactions were of analytical grade. Evaporation of solvents in vacuo was done with the rotary evaporator at 40 °C bath temperature and appropriate pressure. Thin layer chromatography (TLC): Merck TLC plates silica gel 60 F_{254} on glass plate with the indicated solvent system; the spots were visualized by UV light (254 nm), I_2, anisaldehyde, ninhydrin, ceric ammonium molybdate (CAM) or $KMnO_4$ stain. Preparative Thin layer chromatography (PTLC): Merck PTLC plates silica gel 60 F_{254} 0.5 mm on glass plate. For purification, ca. 5 -10 mg of sample was loaded on 20 x 10 cm plate and separated using indicated solvent. Flash Chromatography: Silica gel column chromatography was performed using silica gel 60 (230-400 Mesh) purchased from Sigma-Aldrich with solvent mixture indicated. Ultra high-performance liquid chromatography coupled to mass spectrometry (UHPLC-MS): Ultimate 3000 LC instrument (Thermo Fisher Scientific) coupled to a triple quadrupole Quantum Ultra EMR MS (Thermo Fisher Scientific) using a reversed-phase column (Kinetex® EVO C18; 1.7 µm; 100 Å, 50 x 2.1 mm; Phenomenex). The LC was equipped with a HPG-3400RS pump, a WPS-3000TRS autosampler, a TCC-3000RS column oven and a Vanquish DAD detector (all Thermo Fisher Scientific). The following solvents were applied: H_2O+0.1% HCO_2H (A), MeCN+0.1% HCO_2H (B). The MS was equipped with an H-ESI II ion source. The source temperature was 250 °C, the capillary temperature 270 °C and capillary voltage 3500 V, and datasets were acquired at resolution 0.7 on Q3 in centroid mode. High-performance liquid chromatography (HPLC): Prominence modular HPLC instrument (Shimadzu) coupled to a SPD-20A UV/Vis detector (Shimadzu) using a reversed-phase column (Gemini C18, 3 µm,10 Å, 150 mm x 4.6 mm; Phenomenex) for analytical HPLC and a reversed-phase column (Gemini, 10 µm, 110 Å, 150 mm x 10.0 mm) for preparative HPLC. The LC was equipped with a CBM-20A system controller, LC-20A solvent delivery unit, SIL-20A auto-sampler, CTO-20A column oven, and DGU-20A online degassing unit (all Shimadzu). The following solvents were used: H_2O+0.1% HCO_2H (A), MeCN + 0.1% HCO_2H (B). Specific optical rotation $[\alpha]_D^T$: Jasco P-2000 Polarimeter; measured at the indicated temperature T. Infrared spectra (IR): SpectrumTwo FT-IR Spectrometer (Perkin–Elmer) equipped with a Specac Golden GateTM ATR (attenuated total reflection) accessory; applied as neat samples or as films; $1/\lambda$ in cm^{-1}. Nuclear magnetic resonance spectra (NMR): ^1H NMR spectra were recorded in $CDCl_3$, CD_2Cl_2, acetone-d_6, CD_3OD or C_6D_6 at 298 K on the instruments Bruker AvanceNeo-600 (600 MHz with Cryo-TCI probe), AvanceII or III-500 (500 MHz with Cryo-BBO, TXI, BBI or BBO probe) or AvanceII-400 (400 MHz with QNP, BBO or BBFO probe); δ in ppm relative to solvent signals (δ = 7.26 ppm for $CDCl_3$, 5.32 ppm for CD_2Cl_2, 2.05 for acetone-d_6, 3.31 ppm for CD_3OD and 7.16 ppm for C_6D_6); *J* is given in Hz. ^{13}C NMR spectra were recorded in the indicated solvents and on the same instruments; δ in ppm relative to solvent signals (δ = 77.16 ppm for $CDCl_3$, 53.84 ppm for CD_2Cl_2, 49.00 ppm for CD_3OD and 128.06 ppm for C_6D_6); Data is reported as follow: chemical shift (δ, ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet or not resolved signal; br, broad signal), coupling constant(s) (*J*, Hz), integration. High-resolution electrospray ionization mass spectra (HRMS): QExactive (Thermo Fisher Scientific) with a heated ESI source connected to a Dionex Ultimate 3000 UHPLC system. Samples dissolved in MeOH at ca. 50 g mL^{-1}; injection of 1 µL on-flow with an auto-sampler (mobile phase: MeOH+0.1% HCO_2H or MeCN/H_2O 2:8 + 0.1% HCO_2H; flow rate: 120 µL/min); ion source parameters: spray voltage 3.0 kV, capillary temperature 320°, sheath gas rate: 5 l min^{-1}, s-lens RF level 55.0; full scan MS in alternating (+)/(–)-ESI mode; mass ranges 80–1200, 133–2000, or 200–3000 amu; resolution (full width half-maximum) 70'000; automatic gain control (AGC) target $3.00{\cdot}10^6$; maximum allowed ion transfer time (IT) 30 ms; mass calibration <2 ppm accuracy for m/z 130.06619–1621.96509 in (+)-ESI and for m/z 265.14790–1779.96528 in (–)-ESI with Pierce® ESI calibration solutions (Thermo Fisher Scientific); lock masses: ubiquitous erucamide (m/z 338.34174, (+)-ESI) and palmitic acid (m/z 255.23295, (–)-ESI).

Degradation Study of Fidaxomicin (1)

(2S,3S,4R,6R)-6-(((1S,4E,6E,9S,10E,12R,13E,15E,17R,19R)-12-ethyl-9-hydroxy-10,14,16,19-tetramethyl-3-oxo-2,18-dioxabicyclo[15.2.1]icosa-4,6,10,13,15-pentaen-4-yl)methoxy)-4-hydroxy-5-methoxy-2-methyltetrahydro-2H-pyran-3-yl 3,5-dichloro-2-ethyl-4,6-dihydroxybenzoate (6). To a solution of fidaxomicin (**1**, 34.2 mg, 32.3 µmol) in CH_2Cl_2 (dry, 2.0 mL) was added HCl solution (4.0 M in dioxane, 16 µL, 64.6 µmol, 2.0 equiv.) was added and stirred. After 60 min, HPLC-MS indicated full conversion of fidaxomicin (**1**). The reaction mixture was diluted with CH_2Cl_2 (10 mL) and brine (15 mL), and aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. Purification by preparative RP-HPLC (75% B, isocratic (Phenomenex Luna, C18(2), 100 Å, 250 mm x 21.2 mm, 5 µm). H_2O + 0.1% HCOOH (A) and MeCN + 0.1% HCOOH (B) were used for separation with the flow rate of 20 mL/min.) and concentration provided (*15R*)-**6** (t_R = 17.713 min; 17.2 mg, 66%) and (*15S*)-**6** (t_R = 20.859 min; 3.8 mg, 14.5%) as colourless solids. The structure was elucidated based on the ^1H and 2D NMR. The stereocenter at C15 was determined by NOESY experiment of both compounds. (*15R*)-**6** showed strong correlation between H15 and H19, but (*15S*)-**6** did not. Major isomer (*15R*)-**6**: R_f = 0.66 (acetone/pentane = 3/2); $[\alpha]_D^{25}$ = –71° (*c* 0.76, $CHCl_3$); ^1H NMR (500 MHz, acetone-d_6) δ 7.05 (d, *J* = 11.3 Hz, 1H, H3), 6.55 (dd, *J* = 15.1, 11.4 Hz, 1H, H4), 6.02 (dt, *J* = 14.8, 7.2

Hz, 1H, H5), 5.95 (s, 1H, H13), 5.37 (d, *J* = 10.4 Hz, 1H, H9), 5.13 (d, *J* = 9.2 Hz, 1H, H11), 5.10 (t, *J* = 9.8 Hz, 1H, H4'), 4.98 (d, *J* = 5.6 Hz, 1H, H17), 4.65 (s, 1H, H1'), 4.60 (d, *J* = 9.6 Hz, 1H, H15), 4.57 (d, *J* = 11.4 Hz, 1H, H20a), 4.42 (d, *J* = 11.4 Hz, 1H, H20b), 4.29 (s, 1H, H7), 4.23 (q, *J* = 6.6 Hz, 1H, H18), 3.81 (dd, *J* = 9.9, 3.4 Hz, 1H, H3'), 3.63 – 3.55 (m, 2H, H2', H5'), 3.52 (s, 3H, H7'), 3.23 (p, *J* = 7.6 Hz, 1H, H10), 3.01 (qd, *J* = 7.3, 2.1 Hz, 2H, H8'''), 2.62 (ddd, *J* = 15.5, 7.0, 3.3 Hz, 1H, H6a), 2.46 (ddt, *J* = 14.5, 9.0, 4.9 Hz, 2H, H6b, H16a), 2.13 (d, *J* = 14.1 Hz, 1H, H16b), 1.78 (s, 3H, H25), 1.68 (s, 3H, H24), 1.64 (s, 3H, H21), 1.42 (dt, *J* = 18.5, 7.0 Hz, 2H, H22), 1.30 (d, *J* = 6.2 Hz, 3H, H6'), 1.21 (dt, *J* = 7.4, 4.1 Hz, 6H, H19, H9'''), 0.89 (t, *J* = 7.3 Hz, 3H, H23); ^{13}C NMR (126 MHz, acetone-d_6) δ 169.7 (C1'''), 167.2 (C1), 156.2 (C3''' or 5'''), 154.5 (C3''' or 5'''), 145.8 (C3), 144.0 (C5), 142.7 (C7'''), 136.1 (C12 or 14), 133.6 (C11), 133.5 (C8), 131.2 (C12 or 14), 128.2 (C9), 127.6 (C4), 126.0 (C13), 125.1 (C2), 114.9 (C6'''), 110.2 (C2'''), 108.4 (C4'''), 101.6 (C1'), 82.2 (C15), 82.0 (C18), 81.8 (C2'), 80.4 (C17), 79.3 (C17), 77.7 (C4'), 73.0 (C7), 72.4 (C3'), 70.7 (C5'), 63.0 (C20), 61.8 (C7'), 40.2 (C10), 38.2 (C6), 35.6 (C16), 29.6 (C22), 26.4 (C8'''), 20.1 (C19), 18.8 (C24), 18.3 (C6'), 16.2 (C25), 15.3 (C21), 14.5 (C9'''), 12.4 (C23); IR (cm^{-1}) ν 2967, 2930, 2872, 1693, 1641, 1591, 1445, 1405, 1375, 1313, 1241, 1198, 1144, 1112, 1067, 1021, 985, 917, 871, 855, 798, 760, 735, 691. HRMS was measured as a mixture of (*15R*)-**6** and (*15S*)-**6:** HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{41}H_{54}Cl_2O_{12}Na$ 831.2885; Found 831.2893: Minor isomer (*15S*)-**6**: R_f = 0.66 (acetone/pentane = 3/2); $[\alpha]_D^{25}$ = –38° (*c* 0.26, $CHCl_3$); ^{1}H NMR (600 MHz, acetone-d_6) δ 7.39 (d, *J* = 11.3 Hz, 1H, H3), 6.68 (dd, *J* = 15.1, 11.4 Hz, 1H, H4), 6.19 (ddd, *J* = 14.8, 9.3, 5.1 Hz, 1H, H5), 6.12 (s, 1H, H13), 5.34 (d, *J* = 9.9 Hz, 1H, H9), 5.28 (d, *J* = 7.8 Hz, 1H, H11), 5.11 (t, *J* = 9.7 Hz, 1H, H4´), 5.10 (d, *J* = 4.0 Hz, 1H, H15), 5.00 (dd, *J* = 11.6, 3.9 Hz, 1H, H17), 4.70 (d, *J* = 0.9 Hz, 1H, H1´), 4.60 (d, *J* = 11.7 Hz, 1H, H20), 4.45 (d, *J* = 11.7 Hz, 1H, H20), 4.33 (s, 1H, H7), 4.07 (q, *J* = 6.6 Hz, 1H, H18), 3.82 (dd, *J* = 9.9, 3.4 Hz, 1H, H3´), 3.66 – 3.56 (m, 2H, H2´ H5´), 3.53 (s, 3H, H(OMe)), 3.21 (dq, *J* = 10.0, 7.3 Hz, 1H, H10), 3.01 (qd, *J* = 7.4, 4.6 Hz, 2H, H8´´´), 2.73 (d, *J* = 15.3 Hz, 1H, H6), 2.50 (ddd, *J* = 15.1, 9.3, 3.7 Hz, 1H, H6), 2.13 (ddd, *J* = 13.2, 11.7, 4.1 Hz, 1H, H16), 1.91 (s, 3H, H21), 1.75 (d, *J* = 1.5 Hz, 3H, H24), 1.72 – 1.68 (m, 1H, H16), 1.69 (s, 3H, H25), 1.42 (dt, *J* = 13.3, 7.2 Hz, 1H, H22), 1.38 – 1.31 (m, 1H, H22), 1.30 (d, *J* = 6.1 Hz, 3H, H6´), 1.22 (d, *J* = 6.6 Hz, 3H, H19), 1.21 (t, *J* = 7.5 Hz, 3H, H9´´´), 0.86 (t, *J* = 7.4 Hz, 3H, H23); ^{13}C NMR (151 MHz, acetone-d_6) δ 169.78 (C1´´´), 166.91 (C1), 156.38 (C3´´´), 154.85 (C5´´´), 146.97 (C3), 145.45 (C5), 142.74 (C7´´´), 136.27 (C11), 136.10 (C13), 134.81 (C8), 133.74 (C12), 133.28 (C14), 127.92 (C4), 127.28 (C9), 125.13 (C2), 115.04 (C6´´´), 109.74 (C2´´´), 108.36 (C4´´´), 101.75 (C1´), 81.85 (C5´), 80.91 (C15), 80.36 (C18), 77.63 (C4´), 77.35 (C17), 73.06 (C7), 72.42 (C3´), 70.79 (C2´), 63.11 (C20), 61.82 (C-OMe), 39.76 (C10), 36.79 (C6), 35.93 (C16), 30.64 (C22), 26.42 (C8´´´), 20.80 (C19), 18.64 (C24), 18.33 (C6´), 18.23 (C25), 14.82 (C21), 14.54 (C9´´´), 12.06 (C23); IR (cm^{-1}) ν 2969, 2932, 2873, 1698, 1638, 1590, 1449, 1367, 1311, 1240, 1198, 1167, 1142, 1110, 1088, 1063, 1023, 1003, 943, 902, 858, 884, 858, 799.

Protection of Fidaxomicin (1).

(2R,3R,6S)-6-(((3E,5E,8S,9E,11S,12R,13E,15E,18S)-12-(((2R,3S,4R,5S)-3,4-dihydroxy-5-(isobutyryloxy)-6,6-dimethyltetrahydro-2H-pyran-2-yl)oxy)-11-ethyl-8-hydroxy-18-((R)-1-hydroxyethyl)-9,13,15-trimethyl-2-oxooxacyclooctadeca-3,5,9,13,15-pentaen-3-yl)-methoxy)-4-hydroxy-5-methoxy-2-methyltetrahydro-2H-pyran-3-yl 2,4-bis(allyloxy)-3,5-dichloro-6-ethylbenzoate (Allyl protected fidaxomicin, 7a). To a solution of natural fidaxomicin (**1**) (400 mg, 0.38 mmol) in DMF (10 mL), K_2CO_3 (209 mg, 1.51 mmol, 4.0 equiv) was added. To the suspension, allyl bromide (82 µL, 0.95 mmol, 2.5 equiv) was added and the colourless reaction mixture was stirred at 45 °C for 3 h. The orange-red reaction mixture was quenched with sat. NH_4Cl and the mixture was extracted with AcOEt 3 times. The organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (acetone/pentane = 2/3) gave the allylated fidaxomicin **7a** (384 mg, 89%) as a colourless, amorphous solid; R_f = 0.2 (acetone/pentane = 2/3); $[\alpha]_D^{26}$ = –43.3° (*c* 0.58, $CHCl_3$); IR (cm^{-1}) ν 3472, 2976, 2934, 2878, 1701, 1642, 1382, 1247, 1067, 1024; ^{1}H NMR (400 MHz, acetone-d_6) δ 7.22 (d, *J* = 11.4 Hz, 1H), 6.62 (dd, *J* = 15.2, 11.5 Hz, 1H), 6.13 (dddt, *J* = 32.0, 17.2, 10.4, 5.8 Hz, 2H), 5.96 (ddd, *J* = 14.7, 9.6, 4.7 Hz, 1H), 5.83 (s, 1H), 5.62 (t, *J* = 8.2 Hz, 1H), 5.43 (ddq, *J* = 20.4, 17.2, 1.6 Hz, 2H), 5.33–5.23 (m, 2H), 5.21 (dt, *J* = 10.5, 1.6 Hz, 1H), 5.02 (t, *J* = 9.7 Hz, 1H), 4.99 (d, *J* = 10.1 Hz, 1H), 4.77 (d, *J* = 1.3 Hz, 1H), 4.76–4.69 (m, 1H), 4.64 (d, *J* = 0.8 Hz, 1H), 4.63–4.58 (m, 4H), 4.53 (ddt, *J* = 11.8, 5.8, 1.4 Hz, 1H), 4.40 (d, *J* = 11.5 Hz, 1H), 4.26 (br s, 1H), 4.02 (p, *J* = 6.4 Hz, 1H), 3.95 (dd, *J* = 3.4, 1.2 Hz, 1H), 3.75–3.66 (m, 3H), 3.59 (ddd, *J* = 3.1, 2.3, 1.3 Hz, 1H), 3.55 (dd, *J* = 3.6, 0.8 Hz, 1H), 3.52 (s, 3H), 2.94–2.59 (m, 6H), 2.56 (p, *J* = 7.0 Hz, 1H), 2.52–2.38 (m, 1H), 1.99–1.87 (m, 1H), 1.81 (d, *J* = 1.4 Hz, 3H), 1.73 (d, *J* = 1.4 Hz, 3H), 1.66 (dd, *J* = 1.4, 0.7 Hz, 3H), 1.33 (d, *J* = 6.1 Hz, 3H), 1.30–1.21 (m, 1H), 1.19–1.12 (m, 15H), 1.09 (d, *J* = 0.6 Hz, 3H), 0.82 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, acetone-d_6) δ 176.7, 167.8, 166.4, 153.8, 151.9, 145.2, 143.3, 139.9, 136.8, 136.8, 136.0, 134.1, 134.0, 133.7, 128.6, 128.1, 126.3, 125.9, 125.4, 123.9, 122.2, 118.7, 118.7, 101.8, 96.7, 93.2, 81.8, 78.2, 77.4, 77.4, 76.3, 75.6, 74.9, 73.7, 72.8, 72.7, 72.6, 72.3, 72.2, 70.7, 70.1, 70.0, 69.9, 69.6, 67.7, 67.5, 63.4, 61.7, 55.5, 55.4, 42.0, 37.2, 34.7, 32.0, 30.6, 28.7, 28.3, 26.5, 25.6, 20.7, 19.4, 19.1, 18.6, 18.3, 17.4, 15.2, 14.4, 13.8, 11.1; HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{58}H_{82}Cl_2O_{18}Na$ 1159.4770; Found 1159.4766. m.p. = 109–110 °C.

(2R,3R,6S)-6-(((3E,5E,8S,9E,11S,12R,13E,15E,18S)-11-ethyl-8-hydroxy-18-((R)-1-hydroxyethyl)-12-(((3aS,4R,7S,7aS)-7-(isobutyryloxy)-6,6-dimethyl-2-oxotetrahydro-4H-[1,3]dioxolo[4,5-c]pyran-4-yl)oxy)-9,13,15-trimethyl-2-oxooxacyclooctadeca-3,5,9,13,15-pentaen-3-yl)methoxy)-4-hydroxy-5-methoxy-2-methyltetrahydro-2H-pyran-3-yl 2,4-bis(allyloxy)-3,5-dichloro-6-ethylbenzoate (carbonate and allyl protected fidaxomicin, 7b). To a solution of allyl protected, semisynthetic fidaxomicin **7a** (130 mg, 0.11 mmol) in CH_2Cl_2 (5.0 mL) at room temperature, Et_3N (0.32 mL, 2.3 mmol, 21 equiv) and 1,1'-carbonyldiimidazole (28 mg, 0.17 mmol, 1.5 equiv) were added and the mixture was stirred for 24 h. Then it was quenched with sat. NH_4Cl (10 mL) and extracted with CH_2Cl_2 (1 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (Et_2O only) gave the desired carbonate and allyl protected fidaxomicin **7b** (120 mg, 90%). R_f = 0.85 (acetone/pentane = 2/3); $[\alpha]_D^{25}$ = –55.3° (*c* 0.02, MeOH); IR (cm^{-1}) ν 3485, 2976, 2935, 1813, 1738, 1701, 1247, 1066, 1023, 734; ^{1}H NMR (400 MHz, acetone-d_6) δ 7.19 (d, *J* = 11.4 Hz, 1H), 6.63 (dd, 14.4, 12.0 1H), 6.17 (ddt, *J* = 17.2, 10.4, 5.8 Hz, 1H), 6.09 (ddt, *J* = 17.1, 10.4, 5.8 Hz, 1H), 6.00–5.90 (m, 1H) 5.93 (s, 1H), 5.74 (d, *J* = 6.9 Hz, 1H), 5.61 (dd, *J* = 8.1, 8.1 Hz, 1H), 5.43 (ap ddq, *J* = 20.4, 17.2, 1.6 Hz, 1H), 5.31–5.23 (m, 2H), 5.21–5.16 (m, 2H), 5.18 (d, *J* = 3.2 Hz, 1H), 5.12–4.99 (m, 3H), 4.72–4.67 (m, 1H), 4.64 (s, 1H), 4.64–4.57 (m, 4H), 4.53 (dddd, *J* = 11.7, 5.8, 1.4, 1.4 Hz, 1H), 4.39 (d, *J* = 11.5 Hz, 1H), 4.29–4.24 (m, 1H), 4.07–4.00 (m, 2H), 3.86 (d, *J* = 10.1 Hz, 1H), 3.80 (d, *J* = 9.8 Hz, 1H), 3.75 (d, *J* = 4.2 Hz, 1H), 3.73–3.66 (m, 1H), 3.55 (d, *J* = 3.3 Hz, 1H), 3.55–3.50 (m, 1H), 3.52 (s, 3H), 2.92–2.62 (m, 6H), 2.50 (ddd, *J* = 14.7, 9.6, 4.4 Hz, 1H), 2.40 (ddd, *J* = 13.7, 8.3, 4.4 Hz, 1H), 1.96–1.90 (m, 1H), 1.89 (ap s, 3H), 1.79 (ap s, 3H), 1.68 (ap s, 3H), 1.33 (d, *J* = 6.2 Hz, 3H), 1.25–1.12 (m, 19H), 0.82 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, acetone-d_6) δ 176.0, 168.1, 166.5, 154.7, 153.9, 152.0, 145.1, 143.1, 140.0, 137.3, 136.0, 135.5, 134.7, 134.1, 134.1, 128.7, 128.4, 127.5, 126.0, 125.6, 123.8, 122.3, 118.8, 118.7, 101.9, 95.3, 93.0, 81.9, 78.5, 77.5, 76.4, 76.4, 75.4, 75.0, 73.3, 73.1, 72.9, 72.4, 70.7, 66.1, 63.5, 61.8, 42.8, 37.4, 34.6, 28.5, 28.4, 26.0, 25.6, 23.9, 20.4, 19.2, 19.0, 18.3, 17.4, 15.3, 14.4, 13.8, 11.2; HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{59}H_{80}Cl_2O_{19}Na$ 1185.4563; found: 1185.4558.

(2R,4S,5R)-6-(((3E,5E,8S,9E,11S,12R,13E,15E,18S)-8-((tert-butyldimethylsilyl)oxy)-18-((R)-1-((tert-butyldimethylsilyl)oxy)ethyl)-11-ethyl-12-(((4R,7S,7aR)-7-

(isobutyryloxy)-6,6-dimethyl-2-oxotetrahydro-4H-[1,3]dioxolo[4,5-c]pyran-4-yl)oxy)-9,13,15-trimethyl-2-oxooxacyclooctadeca-3,5,9,13,15-pentaen-3-yl)methoxy)-4-hydroxy-5-methoxy-2-methyltetrahydro-2H-pyran-3-yl 2,4-bis(allyloxy)-3,5-dichloro-6-ethylbenzoate (fully protected fidaxomicin, 7). To a solution of carbonate and allyl protected, semisynthetic fidaxomicin **7b** (23 mg, 18 µmol) in CH_2Cl_2 (0.5 mL) at 0 °C, 2,6-lutidine (20 µL, 0.18 mmol, 10 equiv) and TBSOTf (24 µL, 90 µmol, 5 equiv) were added. The solution was stirred at room temperature for 5 h. Then it was quenched with sat. NH_4Cl (5 mL) and extracted with AcOEt (3 x 3 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (Et_2O/pentane = 1/1) gave the fully protected fidaxomicin **7** (13 mg, 52%). R_f = 0.32 (AcOEt/cyclohexane = 1/4), 0.45 (Et_2O/pentane); $[\alpha]_D^{25}$ = –45.3° (*c* 0.6 MeOH); IR (cm^{-1}) ν 2928, 1819, 1741, 1703, 1249, 1069, 1018, 1003, 836; ^{1}H NMR (400 MHz, acetone-d_6) δ 7.19 (d, *J* = 11.5 Hz, 1H), 6.64–6.56 (m, 1H), 6.23–6.05 (m, 2H), 5.95 (s, 1H), 5.92 (ddd, *J* = 14.8, 10.3, 4.5 Hz 1H), 5.77 (d, *J* = 7.0 Hz, 1H), 5.55 (dd, *J* = 8.3, 8.3 Hz, 1H), 5.49–5.37 (m, 2H), 5.31–5.23 (m, 2H), 5.19 (d, *J* = 3.2 Hz, 1H), 5.17 (ap d, *J* = 11.0 Hz 1H), 5.12–5.05 (m, 2H), 5.03 (dd, *J* = 9.6, 9.6 Hz, 1H), 4.67–4.56 (m, 4H), 4.64 (s, 1H), 4.52 (dddd, *J* = 11.7, 5.9, 1.4, 1.4 Hz, 1H), 4.35 (d, *J* = 10.8 Hz, 1H), 4.36–4.34 (m, 1H), 4.27–4.20 (m, 1H), 3.90 (d, *J* = 10.1 Hz, 1H), 3.76 (d, *J* = 9.8 Hz, 1H), 3.69 (ddd, *J* = 9.7, 9.7, 3.3, Hz, 1H), 3.55 (d, *J* = 3.5 Hz, 1H), 3.54–3.47 (m, 1H) 3.52 (s, 3H), 2.92–2.76 (m, 3H), 2.75–2.63 (m, 3H), 2.40 (ddd, *J* = 14.8, 10.3, 4.5 Hz, 1H), 2.32 (ddd, *J* = 13.8, 7.6, 4.1 Hz, 1H), 2.02–1.94 (m, 1H), 1.91 (ap s, 3H), 1.87 (ap s, 3H), 1.71 (ap s, 3H), 1.34 (d, *J* = 6.2 Hz, 3H), 1.22–1.14 (m, 19H), 0.91 (s, 9H), 0.88 (s, 9H), 0.85 (t, *J* = 7.4 Hz, 3H), 0.09 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (101 MHz, acetone-d_6) δ 175.8, 167.9, 166.5, 154.7, 153.9, 152.0, 145.2, 142.9, 140.0, 136.7, 136.5, 136.0, 134.5, 134.2, 134.1, 128.7, 128.6, 127.8, 126.0, 125.4, 124.8, 122.3, 118.8, 118.7, 102.2, 95.1, 93.4, 81.8, 77.9, 77.5, 76.4, 76.4, 75.4, 75.0, 74.0, 73.2, 73.0, 72.4, 70.8, 69.2, 63.2, 61.7, 42.9, 38.1, 34.6, 28.8, 27.1, 26.3, 26.2, 26.0, 25.6, 24.1, 20.9, 19.2, 19.0, 18.8, 18.6, 18.4, 17.3, 15.2, 14.4, 13.9, 11.3, –4.1, –4.2, –4.8, –4.9; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{71}H_{108}Cl_2O_{19}Si_2Na$ 1413.6293; found: 1413.6254.

Deprotection of Semisynthetic Fidaxomicin (1)

Carbonate and allyl protected fidaxomicin (7b). To a solution of the fully protected, semisynthetic macrolide **7** (2.5 mg, 1.66 µmol) in THF (0.4 mL), 3HF·NEt_3 (100 µL, excess) was added dropwise. The solution was stirred for 26 h at 50 °C before it was quenched by the addition of sat. $NaHCO_3$ (2 mL, Caution! Gas evolution). The aqueous layer was extracted with AcOEt (4 x 2 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated. Purification by preparative TLC (acetone/pentane = 2/3) yielded the alcohol **7b** (2.0 mg, > 99%). Analytical data matched those reported above.

Allyl protected fidaxomicin (7a). To a solution of the carbonate and allyl protected semisynthetic **7b** (8 mg, 7 µmol) in THF (0.2 mL) at 0 °C, a solution of NaH in ethylene glycol (20 µL, 0.5 mg/mL, 60% oil dispersion) was added. The mixture was stirred vigorously for 15 minutes and quenched with sat. NH_4Cl (2 mL) and AcOEt (3 mL) was added. The layers were separated and the aqueous layer was extracted with AcOEt (2 x 3 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (AcOEt/PhMe = 2/3 - 1/1 - 3/2) gave starting material (**7b**, 1.0 mg, 13%) and the allyl ether **7a** as a mixture with minor side products, **3**, **4** and others. The impure **7a** was further purified by RP-HPLC (A: H_2O+0.1% HCOOH; Solvent B: MeCN+0.1% HCOOH; 1 mL/min; T = 20°C; B[%] (t_R [min])= 65 (0 to 3); 90 (15); 100 (16)). The impure allylated fidaxomicin was dissolved in MeCN (0.15 mL) and separated in portions (100 µL). The **7a** eluted at t_R = 14.0 minutes and the solvents were evaporated under reduced pressure to give pure **7a** (3.6 mg, 46%, 53% brsm) as an amorphous solid. Analytical data matched those reported above.

Fidaxomicin (1). To a solution of the pure semisynthetic allyl protected pure fidaxomicin **7a** (3.0 mg, 2.6 µmol) in THF (0.5 mL) at 0 °C, morpholine (0.5 µL in 10 µL THF) and $Pd(PPh_3)_4$ (0.3 mg, in 0.1 mL THF) were added and the reaction mixture was stirred at the same temperature for 30 minutes. The reaction mixture was diluted with AcOEt (2 mL) and quenched with sat. NH_4Cl (2 mL). The layers were separated and the aqueous layer was extracted with AcOEt (3 x 2 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (acetone/pentane = 2/3 - 1/1) yielded pure fidaxomicin **1** (2.4 mg, 86%). No migration of the isobutylate was observed under this mild reaction conditions; R_f = 0.44 (MeOH/CH_2Cl_2 1/10); $[\alpha]_D^{25}$ = –7.6° (*c* 0.96, MeOH); IR (cm^{-1}) ν 3452, 2974, 2933, 1703, 1643, 1584, 1370, 1312, 1242, 1199, 1146, 1068, 1024, 900; ^{1}H NMR (400 MHz, acetone-d_6) *δ* 7.24 (dd, *J* = 11.5, 0.8 Hz, 1H), 6.63 (dddd, *J* = 14.8, 11.6, 2.0, 1.0 Hz, 1H), 5.96 (ddd, *J* = 14.6, 9.3, 4.6 Hz, 1H), 5.83 (s, 1H), 5.71–5.54 (m, 1H), 5.22 (dt, *J* = 10.6, 1.5 Hz, 1H), 5.10 (t, *J* = 9.8 Hz, 1H), 5.00 (d, *J* = 10.1 Hz, 1H), 4.77 (d, *J* = 1.3 Hz, 1H), 4.75–4.71 (m, 1H), 4.68 (d, *J* = 0.8 Hz, 1H), 4.60 (d, *J* = 11.5 Hz, 1H), 4.42 (d, *J* = 11.5 Hz, 1H), 4.26 (s, 1), 4.05–3.99 (m, 1H), 3.95 (dd, *J* = 3.4, 1.2 Hz, 1H), 3.80 (dd, *J* = 9.9, 3.4 Hz, 1H), 3.75–3.73 (m, 1H), 3.73–3.70 (m, 1H), 3.65–3.60 (m, 1H,), 3.59 (d, *J* = 2.5 Hz, 1H), 3.52 (s, 3H), 3.01 (qd, *J* = 7.4, 2.0 Hz, 2H), 2.76 (dd, *J* = 14.4, 7.2 Hz, 1H), 2.72–2.67 (m, 1H), 2.67–2.60 (m, 1H), 2.56 (sept, *J* = 7.0 Hz, 1H), 2.53–2.46 (m, 1H), 2.46–2.38 (m, 1H), 1.93 (qdd, *J* = 10.5, 6.3, 1.9 Hz, 1H), 1.81 (d, *J* = 1.3 Hz, 3H), 1.73 (d, *J* = 1.5 Hz, 3H), 1.65 (dd, *J* = 1.4, 0.7 Hz, 3H), 1.31 (d, *J* = 6.2 Hz, 3H), 1.29–1.24 (m, 1H), 1.22 (t, *J* = 7.4 Hz, 3H), 1.18 (d, *J* = 6.3 Hz, 3H), 1.16–1.12 (m, 9H), 1.09 (s, 3H), 0.83 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, CD_3OD) *δ* 178.4, 169.7, 169.1, 154.6, 153.9, 146.2, 143.7, 141.9, 137.0, 137.0, 136.4, 134.6, 128.5, 126.9, 125.6, 124.6, 114.8, 112.7, 108.8, 102.2, 97.2, 94.3, 82.5, 78.6, 76.9, 75.9, 74.5, 73.5, 73.2, 72.8, 71.6, 70.6, 68.3, 63.9, 62.2, 42.5, 37.3, 35.4, 28.7, 28.4, 26.9, 26.4, 20.3, 19.5, 19.1, 18.7, 18.1, 17.5, 15.4, 14.5, 13.9, 11.3; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{52}H_{74}Cl_2O_{18}Na$ 1079.4144; found: 1079.4147. (see supporting information for the detailed assignment of fidaxomicin)

Total (*de novo*) Synthesis of Fidaxomicin (1)

5-Ethyl-7-hydroxy-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one (20). To a solution of DIPA (0.35 mL, 2.5 mmol, 4.2 equiv) in THF (25 mL) at –78 °C was added *n*-BuLi (1.6 m in hexane; 1.57 mL, 2.5 mmol, 4.2 equiv) slowly and it was stirred at 0 °C for 40 min before keto-dioxinone **18**[33a] (221 mg, 1.2 mmol, 2.0 equiv) in THF (1.5 mL) was added. The resulting orange reaction mixture was stirred for 100 min at –78 °C. Then propionyl imidazole **17**[33c] (74 mg, 0.6 mmol) dissolved in THF (1.1 mL) was added. After stirring the reaction mixture for 2.5 h at –78 °C, the reaction was quenched with sat. NH_4Cl (20 mL). The medium was adjusted to pH = 3 using aqueous HCl (1 M), extracted with AcOEt (3 x 50 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated. The yellow residue was dissolved in CH_2Cl_2 (15 mL) and Et_3N (2 mL, excess). After stirring for 16 h, the mixture was acidified to pH = 1 using aqueous HCl (1 M) and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (Et_2O/pentane = 1/2 to 2/1) afforded the isopropylidene-protected resorcylate **20** (76 mg, 57%) as a yellow crystalline solid; R_f = 0.45 (Et_2O/pentane = 1/2); m.p. = 138.0-140.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 6.54 (d, *J* = 2.4 Hz, 1H), 6.36 (d, *J* = 2.4 Hz, 1H), 3.05 (q, *J* = 7.4 Hz, 2H), 1.68 (s, 6H), 1.22 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.2, 161.8, 159.3, 152.1, 112.6, 105.1, 103.8, 101.7, 27.8, 25.5 (2C), 14.9; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_{15}O_4$ 223.0965; Found 223.0967; IR (cm^{-1}) ν 3224, 3000, 2955, 2870, 1688, 1608, 1499, 1442, 1294, 1213, 1154, 1048, 915, 840, 704.

6,8-Dichloro-5-ethyl-7-hydroxy-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one (20a). To a solution of resorcylate **20** (500 mg, 2.3 mmol) in CH_2Cl_2 (25 mL) at room temperature, sulfuryl chloride (0.43 mL, 5.3 mmol, 2.3 equiv) was added dropwise. The resulting yellow solution was heated to reflux for 1.5 h and subsequently the solvent was concentrated. The yellow residue was suspended in pentane (3 x 7 mL) and the supernatant was decanted off. The remaining solid was dried under HV to afford the dichloride **20a** (639 mg, 98%) as a beige solid; R_f = 0.25 (pentane/Et_2O = 3/1); m.p. = 172.5-173.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.47 (s, 1H), 3.30 (q, *J* = 7.4 Hz, 2H), 1.75 (s, 6H), 1.21 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6, 153.3, 152.9, 145.9, 116.5, 107.2, 106.3, 105.9, 25.6 (2C), 24.5, 13.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_{11}Cl_2O_4$ 289.0040; Found 289.0037; IR (cm^{-1}) ν 3287, 3001, 2974, 2950, 2881, 1716, 1584, 1561, 1437, 1280, 1192, 1044, 786, 621.

7-(Allyloxy)-6,8-dichloro-5-ethyl-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one (21). To a suspension of resorcylate **20a** (492 mg, 1.7 mmol) and K_2CO_3 (701 mg, 5.1 mmol, 3.0 equiv) in DMF (5.0 mL), allyl bromide (0.44 mL, 5.1 mmol, 3.0 equiv) was added and the reaction mixture was stirred at room temperature for 4 h. The reaction was quenched with H_2O (50 mL) and sat. $NaHCO_3$ (50 mL). The aqueous layer was extracted with Et_2O (3 x 50 mL), the organic layers washed with H_2O (50 mL) and brine (50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to afford the allyl-protected resorcylate **21** (534 mg, 95%) as a beige, crystalline compound; R_f = 0.74 (Et_2O/pentane = 1/3); m.p. = 93.5-94.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.15 (ddt, *J* = 17.1, 10.3, 6.0 Hz, 1H), 5.45 (ddd, *J* = 17.1, 1.4, 2.9 Hz, 1H), 5.32 (ddd, *J* = 10.3, 2.4, 1.1 Hz, 1H), 4.63 (dt, *J* = 6.0, 1.3 Hz, 2H), 3.30 (q, *J* = 7.4 Hz, 2H), 1.74 (s, 6H), 1.21 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5, 156.9, 152.7, 146.2, 132.5, 124.9, 119.3, 115.9, 109.9, 105.9, 74.6, 25.6 (2C), 24.5, 13.4; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{16}Cl_2O_4Na$ 353.0318; Found 353.0312; IR (cm^{-1}) ν 2990, 2943, 1733, 1573, 1380, 1277, 1231, 1204, 1112, 1047, 911, 787.

(2S,3S,4S,5S,6R)-2-methoxy-6-methyltetrahydro-2H-pyran-3,4,5-triol (22).[35] To a solution of Methyl 6-deoxy-6-iodo-α-mannopyranoside **22a** (3.59 g, 11.8 mmol) in MeOH (42 mL), DIPEA (6.19 mL, 35.4 mmol, 3.0 equiv) and $Pd(OH)_2$ (0.83 g, , 1.2 mmol, 20% Wt on activated carbon) were added. The dark turbid mixture was degassed with argon during 10 min, then hydrogen was bubbled through the suspension for 0.5 h, and the reaction mixture was subsequently stirred under a hydrogen atmosphere. The hydrogen atmosphere was exchanged by argon and the solution was filtered through Hyflo. The filtrate was concentrated and purified by column chromatography (MeOH/ CH_2Cl_2 = 1/10) to yield the rhamnoside **22** (2.19 g, quant.) as a colorless oil; The spectroscopic data were in good agreement with the literature.[35] ^{1}H NMR (400 MHz, CD_3OD) δ 4.56 (d, *J* = 1.7 Hz, 1H), 3.78 (dd, *J* = 3.5, 1.7 Hz, 1H), 3.61 (dd, *J* = 9.4, 3.5 Hz, 1H), 3.57-3.48 (m, 1H), 3.38 (pt, *J* = 9.5 Hz, 1H), 3.35 (s, 3H), 1.27 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (101 MHz, CD_3OD,) δ 102.8, 74.0 , 72.4, 72.2, 69.6, 55.1, 18.0.

(2R,3S,4S,5S,6S)-5,6-Dimethoxy-2-methyltetrahydro-2H-pyran-3,4-diol (23). To a solution of D-rhamnoside **22**[35] (494 mg, 2.8 mmol) in MeOH (28 mL), 2,3-butadione (0.29 mL, 3.3 mmol, 1.2 equiv), trimethyl orthoformate (1.17 mL, 10.6 mmol, 3.8 equiv) and 10-camphorsulfonic acid (41.1 mg, 0.16 mmol, 6 mol%) were added. The mixture was heated in a sealed tube to 90 °C for 24 h. Then the reaction mixture was neutralized with Et_3N and the solvent was removed under reduced pressure, yielding the protected intermediate **22b** which was used in the next step without further purification.

To the protected intermediate **22b** in THF (17 mL) at 0 °C, NaH (60 % dispersion in mineral oil, 223 mg, 5.6 mmol, 2.0 equiv) was added in portions. The mixture was allowed to warm to room temperature and was stirred for an additional 1 h. Then MeI (0.19 mL, 3.1 mmol, 1.1 equiv) was added dropwise and the mixture was stirred for 3.5 h at room temperature. The reaction was quenched with sat. NH_4Cl (20 mL), the solvent was removed under reduced pressure and the remaining aqueous suspension was diluted with H_2O (40 mL). The mixture was extracted with CH_2Cl_2 (3 x 50 mL) and the organic layers were washed with brine (30 mL), combined, dried over Na_2SO_4, filtered and concentrated. The methylated intermediate was used in the next step without further purification.

To a solution of methylated intermediate in CH_2Cl_2 (30 mL), a mixture of TFA/H_2O (9:1, 2.4 mL) was added. The reaction was stirred for 1 h while the mixture turned slightly yellow. The reaction was quenched with Et_3N (2.5 mL), and then PhMe (10 mL) was added. The solvent was removed under reduced pressure. Azeotropic removal of Et_3N was carried out twice with PhMe (5 mL). Purification by column chromatography (Et_2O) afforded the desired product **23** (356 mg, 72% over three steps) as a colorless oil; R_f = 0.18 (Et_2O); $[\alpha]_D^{25}$ = +40.2° (*c* 0.48, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.75 (d, *J* = 1.1 Hz, 1H), 3.72-3.65 (m, 1H), 3.59 (dq, *J* = 9.3, 6.2 Hz, 1H), 3.47 (s, 3H), 3.45 (dd, *J* = 3.9, 1.5 Hz, 1H), 3.37 (s, 3H), 3.38-3.32 (m, 1H) 2.50 (d, *J* = 2.7 Hz, 1H), 2.43 (d, *J* = 10.4 Hz, 1H), 1.31 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 97.2, 80.2, 74.0, 71.5, 67.5, 58.8, 54.8, 17.5; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_8H_{16}O_5Na$ 215.0890; Found 215.0889; IR (cm^{-1}) ν 3426, 2976, 2935, 2905, 2832, 1540, 1378, 1190, 1136, 1104 ,1046, 966, 836, 807.

(2R,3S,4S,5S,6R)-5-Methoxy-2-methyl-6-(phenylthio)tetrahydro-2H-pyran-3,4-diol (24). To a solution of pyrannoside **23** (240 mg, 1.3 mmol) in 1,2-dichloroethane (10 mL), tetrabutylammonium iodide (692 mg, 1.9 mmol, 1.45 equiv), ZnI (1.19 g, 3.8 mmol, 3.0 equiv) and trimethyl(phenylthio)silane (1.14 g, 6.2 mmol, 4.8 equiv) were added. The white turbid mixture was heated to 65 °C for 2.5 h. Then it was cooled to room temperature and a solution of TFA/H_2O (9:1, 3 mL) was added. After stirring for 30 min, PhMe (5 mL) was added and concentrated. The residue was treated with Et_2O (10 mL) and the biphasic mixture was stirred for 5 min. The etheral extract was decanted and the remaining oil was re-extracted twice in the same manner. The combined etheral extracts were concentrated and purified by column chromatography (Et_2O) to afford the title compound **24** (247 mg, 73%) as a yellowish oil; R_f = 0.3 (Et_2O); $[\alpha]_D^{25}$ = +184.4° (*c* 0.47, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.46 (m, 2H), 7.35-7.30 (m, 2H), 7.30-7.27 (m, 1H), 5.62 (ap s, 1H), 4.13 (dqd, *J* = 9.4, 6.2 Hz, 0.6, 1H), 3.77-3.70 (m, 2H), 3.48-3.43 (m, 1H), 3.46 (s, 3H), 2.41 (d, *J* = 10.0 Hz, 1H), 2.39 (d, *J* = 2.6 Hz, 1H), 1.32 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.4, 131.3 (2C), 129.1 (2C), 127.4, 84.0, 81.7, 74.3, 72.1, 68.9, 58.1, 17.4; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{18}O_4SNa$ 293.0818; Found 293.0817; IR (cm^{-1}) ν 3523, 3296, 2976, 2932, 2898, 2831, 1581, 1478, 1438, 1355, 1141, 1099, 1055, 1021, 839, 740, 690.

(2R,3S,4S,5S,6R)-4-Hydroxy-5-methoxy-2-methyl-6-(phenylthio)tetrahydro-2H-pyran-3-yl 4-(allyloxy)-3,5-dichloro-2-ethyl-6-hydroxybenzoate (26). To a solution of the rhamnose **24** (163 mg, 0.60 mmol) and the resorcylate **21** (200 mg, 0.60 mmol, 1.0 equiv) in THF (6.0 mL) at 0 °C, NaH (60% dispersion in mineral oil, 114 mg, 2.84 mmol, 4.7 equiv) was added in portions. The grey turbid mixture was stirred at room temperature for 16 h. The reaction was quenched with sat. NH_4Cl (10 mL) and the aqueous layer was extracted with Et_2O (3 x 10 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (TBME/cyclohexane = 1/3) afforded the desired ester **26** (272 mg, 83%) as pale yellow oil; R_f = 0.1 (Et_2O/pentane = 1/3); $[\alpha]_D^{25}$ = +138.4° (*c* 1.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.29 (s, 1H), 7.44-7.40 (m, 2H), 7.30-7.22 (m, 3H), 6.09 (ddt, *J* = 16.3, 10.3, 5.9 Hz, 2H), 5.60 (d, *J* = 0.7 Hz, 1H), 5.39 (ddd, *J* = 17.2, 3.0, 1.5 Hz, 1H), 5.24 (ddd, *J* = 10.3, 2.5, 1.1, 1H), 5.19 (dd, *J* = 9.8, 9.8, 1H), 4.54 (ddd, *J* = 5.9, 1.2, 1.2 Hz, 2H), 4.31 (dq, *J* = 9.8, 6.1 Hz, 1H), 3.96-3.87 (m, 1H), 3.78 (dd, *J* = 3.6, 1.3 Hz, 1H), 3.44 (s, 3H), 3.02-2.94 (m, 2H), 2.47 (d, *J* = 10.9 Hz, 1H), 1.23 (d, *J* = 6.3 Hz, 3H), 1.20 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 155.5, 155.4, 142.5, 133.9, 132.7, 131.2 (2C), 129.2 (2C), 127.7, 121.7, 119.1, 115.6, 112.4, 83.8, 81.6, 76.8, 74.3, 69.9, 66.9, 58.0, 26.0, 17.5, 14.0; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{25}H_{28}Cl_2O_7SNa$

565.0825; Found 565.0825; IR (cm^{-1}) ν 2980, 2936, 2878, 1737, 1664, 1583, 1549, 1392, 1311, 1222, 1099, 998, 840, 764, 742, 691.

(2R,3S,4S,5S,6R)-4-Hydroxy-5-methoxy-2-methyl-6-(phenylthio)tetrahydro-2H-pyran-3-yl 2,4-bis(allyloxy)-3,5-dichloro-6-ethylbenzoate (26a). To a suspension of the rhamnose **26** (90 mg, 0.17 mmol) and K_2CO_3 (69 mg, 0.50 mmol, 2.9 equiv) in DMF (2.0 mL), allyl bromide (22 µL, 0.25 mmol, 1.5 equiv) was added and the suspension was heated to 50 °C for 3 h. It was subsequently diluted with Et_2O (5 mL), quenched with aqueous sat. NH_4Cl (50 mL) and extracted with Et_2O (3 x 20 mL). The organic layers were washed with brine (40 mL), combined, dried over $MgSO_4$, filtered and concentrated to afford the allyl ether **26a** (93 mg, 96%) as a colorless oil; R_f = 0.3 (Et_2O/pentane = 1/3); $[\alpha]_D^{25}$ = +111.1° (*c* 0.54, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.36 (m, 2H), 7.26-7.17 (m, 3H), 6.07 (ddt, *J* = 17.3, 10.4, 5.9 Hz, 2H), 5.97 (ddt, *J* = 17.2, 10.3, 5.9, 1H) 5.57 (d, *J* = 1.2 Hz, 1H), 5.36 (ddd, *J* = 17.1, 1.5, 1.5 Hz, 1H), 5.30 (ddd, *J* = 17.1, 1.5, 1.5 Hz, 1H), 5.22 (ddd, *J* = 10.3, 2.6, 1.1 Hz, 1H), 5.17 (ddd, *J* = 10.3, 2.6, 1.1 Hz, 1H), 5.10 (dd, *J* = 9.7, 9.7 Hz, 1H), 4.52 (dddd, *J* = 11.6, 5.9, 1.4, 1.4 Hz, 1H) 4.48 (ddd, *J* = 5.9, 1.3, 1.3 Hz, 2H) 4.42 (dddd, *J* = 11.5, 6.0, 1.3, 1.3 Hz, 1H), 4.22 (dq, *J* = 9.8, 6.2 Hz, 1H), 3.85 (dd, *J* = 9.8, 3.6 Hz, 1H), 3.73 (dd, *J* =3.6, 1.4 Hz, 1H), 3.42 (s, 3H), 3.39 (q, *J* = 7.0 Hz, 2H) 2.83-2.66 (m, 2H), 1.25 (d, *J* = 6.2 Hz, 3H), 1.14 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5, 153.3, 151.1, 139.2, 134.1, 132.9, 132.9, 131.4 (2C), 129.3 (2C), 127.7, 127.3, 125.7, 121.7, 119.1, 113.0, 84.2, 81.9, 76.6, 75.9, 74.4, 70.2, 67.2, 58.3, 25.3, 17.6, 14.1; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{28}H_{32}Cl_2O_7SNa$ 605.1138; Found 605.1130; IR (cm^{-1}) ν 3548, 2978, 2936, 2883, 1736, 1570, 1402, 1314, 1246, 1099, 998, 929, 841, 742, 692.

(2R,3S,4S,5S)-4,6-dihydroxy-5-methoxy-2-methyltetrahydro-2H-pyran-3-yl 2,4-bis(allyloxy)-3,5-dichloro-6-ethylbenzoate (26b). To a solution of thioglycoside **26a** (17.5 mg, 0.03 mmol) in acetone (1.0 mL) and H_2O (0.1 mL) at 0 °C, NBS (5.9 mg, 0.03 mmol, 1.0 equiv) was added. The orange reaction mixture was stirred at 0 °C for 15 min then it was warmed to room temperature. The colorless solution was treated with NBS in the same manner until full consumption of the starting material was observed by TLC. The reaction was quenched with sat. $NaHCO_3$ (10 mL) extracted with CH_2Cl_2 (3 x 10 mL), dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (AcOEt/cyclohexane = 1/4 to 1/2) gave the desired pyranose **26b** (14.0 mg, 95%, α:β = 5:1) as a colourless oil of inseparable anomers; R_f = 0.18 (AcOEt/cyclohexane = 1/2); ^1H NMR (400 MHz, $CDCl_3$, major anomer) δ 6.15 (ddt, *J* = 16.4, 10.4, 5.9 Hz, 1H), 6.05 (ddt, *J* = 16.4, 10.4, 6.0 Hz, 1H), 5.44 (ddd, *J* = 17.1, 1.4, 1.4 Hz, 1H), 5.39 (ddd, *J* = 17.1, 1.4, 1.4 Hz, 1H), 5.35 (s, 1H), 5.32 (ddd, *J* = 10.3. 1.2, 1.2 Hz, 1H), 5.27 (ddd, *J* = 10.4, 1.3, 1.3 Hz, 1H), 5.09 (dd *J* = 9.8, 9.8 Hz, 1H), 4.60 (dddd, *J* = 11.5, 5.9, 1.3, 1.3 Hz, 1H), 4.57 (ddd, *J* = 6.0, 1.3, 1.3 Hz, 2H), 4.51 (dddd, *J* = 11.5, 6.1, 1.3, 1.3 Hz, 1H), 4.03 (dq, *J* = 9.8, 6.2 Hz, 1H) 3.99 (dd, *J* = 9.8, 3.7 Hz, 1H), 3.58 (dd, *J* = 3.6, 1.5 Hz, 1H), 3.53 (s, 3H), 2.89-2.73 (m, 2H), 1.30 (d, *J* = 6.2 Hz, 3H), 1.20 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$, major anomer) δ 166.6, 153.2, 151.1, 139.2, 132.9, 132.9, 127.4, 125.7, 121.7, 119.1, 119.0, 91.1, 80.7, 75.6, 75.9, 74.5, 69.3, 66.1, 59.2, 25.3, 17.8, 14.1; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{22}H_{28}Cl_2O_8Na$ 513.1053; Found 513.1052; IR (cm^{-1}) ν 3442, 2936, 1734, 1567, 1460, 1403, 1315, 1248, 1100, 1065, 1041, 995, 930, 798, 748.

(2R,3S,4S,5S,6R)-4-Hydroxy-5-methoxy-2-methyl-6-((E)-2,2,2-trifluoro-1-(phenylimino)ethoxy)tetrahydro-2H-pyran-3-yl 2,4-bis(allyloxy)-3,5-dichloro-6-ethylbenzoate (27). To a solution of rhamnose **26b** (4.5 mg, 0.01 mmol) in acetone (0.3 mL, technical grade) at 0 °C was added K_2CO_3 (5.0 mg, 0.4 mmol, 40 equiv) and ClC(=NPh)CF_3 (1.7 µL, 0.01 mmol, 1.0 equiv) in acetone (0.1 mL). Then the reaction mixture was stirred at room temperature for 3 h. The suspension was diluted with PhMe (1 mL), filtered and concentrated. Purification by preparative TLC (AcOEt/cyclohexane = 1/4) afforded the acetimidate **27** (6.0 mg, 98%) as a colorless oil; R_f = 0.5 (AcOEt/cyclohexane = 1/4); $[\alpha]_D^{25}$ = +20.2° (*c* 0.07, $CHCl_3$); ^1H NMR (400 MHz, acetone-d_6) δ 7.42-7.32 (m, 2H), 7.18-7.12 (m, 1H), 6.99-6.89 (m, 2H), 6.24 (br, 1H), 6.23-6.02 (m, 2H), 5.46 (ddd, *J* = 17.2, 1.6, 1.6 Hz, 1H), 5.40 (ddd, *J* = 17.2, 1.6, 1.6 Hz, 1H), 5.31-5.23 (m, 2H), 5.19 (dd *J* = 10.0, 10.0 Hz, 1H), 4.68-4.58 (m, 3H), 4.54 (dddd, *J* = 11.8, 5.7, 1.4, 1.4 Hz, 2H), 4.20 (d, *J* = 9.4, 1H), 4.04-3.88 (m, 2H), 3.83 (br, 1H), 3.50 (br, 3H), 2.92-2.75 (m, 2H), 1.35-1.26 (m, 3H), 1.17 (t, *J* = 7.4 Hz, 3H); HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{30}H_{32}Cl_2F_3NO_8Na$ 684.1349; Found 684.1348; IR (cm^{-1}) ν 3546, 2981, 2937, 1737, 1569, 1454, 1404, 1330, 1316, 1249, 1211, 1164, 1118, 1024, 2012, 975, 929, 777, 752, 695.

(3aS,4S,6R,6aS)-2,2-Dimethyl-6-vinyltetrahydrofuro[3,4-d][1,3]dioxol-4-ol (28a). To a solution of iodo-mannopyranoside **28** (4.42 g, 12.8 mmol) in MeOH (40 mL), zinc powder (8.40 g, 128.0 mmol, 10 equiv) was added and the grey suspension was heated to 60 °C. Solid NH_4Cl (150 mg, 2.8 mmol, 0.2 equiv) was added and it was stirred for 30 min. Then it was treated again with solid NH_4Cl (150 mg, 2.8 mmol, 0.2 equiv). After stirring for 90 min it was allowed to cool to room temperature. The grey suspension was filtered through Celite, washed with CH_2Cl_2 (3 x 20 mL) and the solvent was concentrated. Purification by column chromatography (Et_2O/pentane = 1/3) afforded the desired furanose **28a** (2.2 g, 91%) as a colorless oil which crystallized at –20 °C; The spectroscopic data matched those reported in the literature.[38a] R_f = 0.6 (Et_2O/pentane = 1/1); m.p. = 58.0-59.0 °C; $[\alpha]_D^{25}$ = –28.7° (*c* 0.54, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.99 (ddd, *J* = 17.6, 10.4, 7.4 Hz, 1H), 5.42 (ddd, *J* = 17.4, 1.6, 1.1 Hz, 1H), 5.41 (d, *J* = 2.3 Hz, 1H), 5.34 (ddd, *J* = 10.4, 1.6, 0.8 Hz, 1H), 4.73 (dd, *J* = 5.8, 3.7 Hz, 1H), 4.64 (d, *J* = 5.8 Hz, 1H), 4.62-4.59 (m, 1H), 2.69 (d, *J* = 2.3 Hz, 1H), 1.49-1.46 (m, 3H), 1.32 (d, *J* = 0.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.2, 119.3, 112.7, 101.1, 85.8, 81.6, 26.1, 24.9.

(3aS,4S,6R,6aS)-4-Methoxy-2,2-dimethyl-6-vinyltetrahydrofuro[3,4-d][1,3]dioxole (29). To a solution of furanose **28a (**1.00 g, 5.45 mmol) in MeOH (10 mL) and 2,2-dimethoxypropane (5 mL), 10-camphorsulfonic acid (250 mg, 1.1 mmol, 20 mol%) was added. The solution was heated to 55 °C for 18 h. Then, the dark solution was neutralized with Et_3N (solution turned bright yellow) and the solvents were carefully concentrated. The residue was treated with H_2O (100 mL) and aqueous layer extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Purification by Kugelrohr distillation afforded product **29** (1.08 g, 99%) as a colorless liquid; The spectroscopic data matched those reported in the literature.[38b] R_f = 0.6 (Et_2O/pentane = 1/3); b.p. = 130 °C (5.6 mbar); $[\alpha]_D^{25}$ = +24.3° (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.99 (ddd, *J* = 17.3, 10.1, 7.4 Hz, 1H), 5.42 (ddd, *J* = 17.4, 1.7, 1.1 Hz, 1H), 5.34 (ddd, *J* = 10.4, 1.5, 0.8 Hz, 1H), 4.91 (s, 1H), 4.68 (dd, *J* = 5.8, 3.7 Hz, 1H), 4.58 (d, *J* = 5.8 Hz, 1H), 4.39 (dd, *J* = 7.4, 3.7 Hz, 1H), 3.35 (s, 3H), 1.47 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.3, 119.1, 112.6, 107.2, 85.3, 81.5, 81.1, 54.7, 26.1, 24.9.

Methyl (3aR,4S,6S,6aS)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxole-4-carboxylate (30) and (3aS,4S,6S,6aS)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxole-4-carbaldehyde (31). To a solution of furanoside **29** (1.03 g, 5.14 mmol) in CH_2Cl_2 (20 mL) and methanolic NaOH (5.0 mL, 2.5 m) was cooled to –78 °C. Then ozone was bubbled through the solution. The solution turned orange and faded to yellow after a while, after 1 h it turned deep blue. After 8 h, again methanolic NaOH (5.0 mL, 2.5 m) was added (solution turns yellow and turbid again which faded again after 45 minutes). Additional methanolic NaOH (2.5 m) was added until full conversion to the ester (monitored by TLC). Then, N_2 was bubbled through the solution for 15 minutes before it was diluted with CH_2Cl_2 (50 mL) and H_2O (20 mL). The reaction mixture was allowed to warm to room temperature then sat. NH_4Cl (30 mL) was added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 50 mL). The organic layers were dried with MgSO4, filtered and concentrated. Purification by

column chromatography (Et_2O/pentane = 1/3 - 1/2) afforded the desired ester **30** (0.740 g, 62%) as a colourless fluid, aldehyde **31** (110 mg, 11%) and ozonide mixture (46 mg); **Aldehyde 31**: The spectroscopic data matched to those reported in the literature.[38c] R_f = 0.1 (Et_2O/pentane = 1/3); $[\alpha]_D^{25}$ = +44.5° (*c* 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (d, *J* = 1.2 Hz, 1H), 5.09 (s, 1H), 5.07 (dd, *J* = 5.9, 4.3 Hz, 1H), 4.61 (d, *J* = 5.8 Hz, 1H), 4.37 (d, *J* = 4.3 Hz, 1H), 3.36 (s, 3H), 1.43 (s, 3H), 1.29 (d, *J* = 0.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.9, 113.7, 108.0, 84.7, 84.1, 81.0, 55.2, 26.0, 24.7.; **Methylester 30**: R_f = 0.17 (Et_2O/pentane = 1/3); $[\alpha]_D^{25}$ = +23.5° (*c* 0.65, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.07 (s, 1H), 4.98 (dd, *J* = 5.8, 4.3 Hz, 1H), 4.60-4.55 (m, 2H), 3.81 (s, 3H), 3.35 (s, 3H), 1.42 (s, 3H), 1.31-1.27 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 113.4, 107.5, 84.0, 80.6, 79.5, 55.1, 52.2, 25.9, 25.1; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{10}H_{16}O_6Na$ 255.0839; Found 255.0840; IR (cm^{-1}) ν 2990, 2942, 2839, 1769, 1739, 1439, 1374, 1208, 1095, 1061, 967, 860, 775, 613.

Compound 30. To a solution of aldehyde **31** (795 mg, 3.9 mmol) in MeOH (24 mL) and water (4 mL) at room temperature was added solid $NaHCO_3$ (5.30 g, 63 mmol). To this suspension under vigorous stirring was added Br_2 (0.65 mL, 13 mmol, 3.25 equiv) and the mixture was heated to 40 °C. After stirring for 3 h again Br_2 (50 µL, 1.0 mmol, 0.25 equiv) was added and it was stirred for another 1 h. The reaction was quenched with sat. $Na_2S_2O_3$ (50 mL) and the reaction mixture was diluted with water (50 mL), and extracted with AcOEt (3 x 70 mL). The combined organic layers were washed with water (50 mL) and with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give desired ester **30** (0.840 g, 92%) as a colourless fluid.

2-((3aS,4S,6S,6aS)-6-Methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)propan-2-ol (32). To a solution of ester **30** (735 mg, 3.2 mmol) in Et_2O (28 mL), MeMgBr (3 M solution in Et_2O, 3.2 mL, 9.5 mmol, 2.4 equiv) was added dropwise at room temperature. Then it was heated to 35 °C for 30 min. The reaction was cooled to room temperature and carefully quenched with sat. NH_4Cl (10 mL). Then H_2O (30 mL) was added and the total was extracted with Et_2O (3 x 20 mL). The organic layers were dried over Na_2SO_4, filtered and concentrated. This gave the tertially alcohol **32** (721 mg, 99%) as a colorless oil; The spectroscopic data matched those reported for its enantiomer in the literature.[65] R_f = 0.4 (Et_2O/pentane = 1/1); $[\alpha]_D^{25}$ = +84.0° (*c* 1.15, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.01 (s, 1H), 4.86 (dd, *J* = 5.9, 3.4, Hz 1H), 4.58 (d, *J* = 5.9 Hz, 1H), 3.71 (d, *J* = 3.3 Hz, 1H), 3.56 (s, 1H), 3.35 (s, 3H), 1.52 (s, 3H), 1.40 (s, 3H), 1.36 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 112.8, 106.6, 85.2, 82.9, 80.7, 70.9, 54.5, 27.3, 27.3, 25.8, 24.2; IR (cm^{-1}) ν 3525, 2979, 2937, 1465, 1374, 1209, 1153, 1092, 1031, 964, 881, 854.

(3S,4S,5S)-6-Methoxy-2,2-dimethyltetrahydro-2H-pyran-3,4,5-triol (33). To a solution of furanoside **32** (210 mg, 0.90 mmol) in MeOH (2.0 mL), TFA (1.0 mL) was added. The colorless solution was heated in the microwave to 100 °C for 3 h. The reaction mixture was diluted with PhMe (10 mL), concentrated and the residue was submitted to column chromatography (CH_2Cl_2/MeOH = 20/1 to 10/1) to afford the desired pyranoside **33** and a mixture of acetonide deprotected furanoside **32a** with starting material **32**. The same protocol was applied twice to convert this mixture to the pyranoside **33**. In this way the desired pyranoside **33** (141 mg, 81%) was obtained as a mixture of two inseparable anomers; R_f = 0.28 (CH_2Cl_2/MeOH = 10/1); ^{1}H NMR (400 MHz, CD_3OD α:β 2:1) δ 4.57 (d, *J* = 1.5 Hz, 1H), 4.54 (d, *J* = 1.0 Hz, 0.5H), 3.85 (dd, *J* = 3.0, 1.0 Hz, 0.5H), 3.83-3.78 (m, 1H) 3.81 (s, 1H), 3.63 (d, *J* = 9.1 Hz, 1H), 3.57 (dd, *J* = 10.0, 3.1 Hz, 0.5H), 3.52 (d, *J* = 10.0 Hz, 0.5H), 3.45 (s, 1.5H), 3.37 (s, 3H), 1.29 (s, 1.5H), 1.28 (s, 6H), 1.18 (s, 1.5H); ^{13}C NMR (101 MHz, CD_3OD α:β 2:1) δ 104.1, 98.4 (0.5C), 79.0, 76.2 (0.5C), 74.8 (0.5C), 74.7, 72.8, 72.5 (0.5C), 71.9 (0.5C), 69.3, 56.9 (0.5C), 55.8, 29.2, 28.7 (0.5C), 22.7, 18.5 (0.5C); HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_8H_{16}O_5Na$ 215.0890; Found 215.0890; IR (cm^{-1}) ν 3377, 2981, 2925, 2361, 1673, 1445, 1369, 1193, 1135, 1065, 1037, 979, 803, 736.

(3aS,4S,7S,7aS)-4-Methoxy-6,6-dimethyl-2-oxotetrahydro-4H-[1,3]dioxolo[4,5-c]pyran-7-yl isobutyrate (34). To a solution of noviosde **33** (106 mg, 0.55 mmol) in 1,2-dichloroethane (5.0 mL), 1,1'-carbonyldiimidazole (98 mg, 0.61 mmol, 1.1 equiv) was added and the reaction mixture was stirred at reflux for 3 h. Then, 1,1'-carbonyldiimidazole was added in portions until TLC indicated full consumption of the starting material. The reaction was quenched with aqueous HCl (1 M, 10 mL), extracted with CH_2Cl_2 (3 x 10 mL), the organic layers were dried over $MgSO_4$, filtered and concentrated. Next, this residue was dissolved in CH_2Cl_2 (4.0 mL) and it was added Et_3N (0.39 mL, 2.8 mmol, 5.1 equiv) and isobutyryl chloride (0.17 mL, 1.65 mmol, 3.0 equiv). After stirring for 1 h at room temperature it was quenched with H_2O (10 mL) and HCl (1 M, 10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the organic layers washed with aqueous $NaHCO_3$ (20 mL), combined, dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (Et_2O/pentane = 1/2 to Et_2O) afforded the two anomers as white solids (α-**34**: 66 mg, 42%; β-**34**: 40 mg, 25%); α-**34**: R_f = 0.63 (Et_2O/pentane = 1/1); m.p. = 89.0-90.0 °C; $[\alpha]_D^{25}$ = +18.5° (*c* 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.06 (d, *J* = 7.6 Hz, 1H), 4.85 (d, *J* = 2.9 Hz, 1H), 4.72 (pt, *J* = 7.7 Hz, 1H), 4.62 (dd, *J* = 7.8, 2.9 Hz, 1H), 3.40 (s, 3H), 2.56 (qq, *J* = 7.0 Hz, 1H), 1.22 (s, 6H), 1.14 (d, *J* = 7.0 Hz, 3H), 1.14 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.6, 153.2, 97.3, 76.6, 75.4, 74.7, 72.0 56.1, 34.1, 26.9, 23.2, 19.0, 18.8; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{21}O_7$ 289.1282; Found 289.1281; IR (cm^{-1}) ν 2988, 1793, 1737, 1464, 1392, 1340, 1127, 1087, 1026, 969, 818; β-**34**: R_f = 0.3 (Et_2O/pentane = 1/1); m.p. = 134.0-137.0 °C; $[\alpha]_D^{25}$ = –101.9° (*c* 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.73-5.66 (m, 1H), 4.79-4.75 (m, 1H), 4.73-4.70 (m, 2H), 3.45 (s, 3H), 2.61-2.49 (qq, *J* = 7.0 Hz, 1H), 1.21 (s, 3H), 1.14 (d, *J* = 7.0 Hz, 3H), 1.14 (d, *J* = 7.0 Hz, 3H), 1.14 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.2, 153.9, 95.8, 75.7, 75.0, 72.3, 71.9, 56.2, 34.1, 28.7, 24.3, 19.1, 18.8; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{21}O_7$ 289.1282; Found 289.1281; IR (cm^{-1}) ν 2984, 1790, 1740, 1472, 1394, 1355, 1148, 1048, 962, 807, 774.

The experimental protocol for the synthesis of **35** is shown together with noviosylation with **43**. The synthesis of known aldehyde **16** from **36** and **37** is briefly described in supporting information.

(S,E)-4-Benzyl-3-(2-methylhex-2-enoyl)oxazolidin-2-one (38).[42] To a stirred solution of 2-methyl-2-hexenoic acid **38a** (0.70 g, 5.46 mmol, prepared by a Wittig reaction between butanal and Ethyl 2-(triphenylphosphoranylidene)propanoate and a subsequent hydrolysis) and Et_3N (2.46 mL, 17.50 mmol, 3.2 equiv) in THF (30 mL) at −40 °C, PivCl (0.85 mL, 6.83 mmol, 1.25 equiv) was added and the resulting white slurry was stirred at −40 °C for 1.5 h. Next, flame dried LiCl (0.32 g, 7.65 mmol, 1.4 equiv) and (*S*)-4-benzyloxazolidin-2-one (0.97 g, 5.46 mmol, 1.0 equiv) were added and the cooling bath was removed and the reaction mixture was allowed to stir for 15 h at room temperature. The reaction was quenched MeOH (5 mL) and sat. NH_4Cl (60 mL). The ensuing aqueous layer was extracted with Et_2O (2 x 60 mL) and the combined organic layers were washed sequentially with sat. $NaHCO_3$ (60 mL), brine (60 mL) and H_2O (60 mL). The resulting organic layer was then dried over Na_2SO_4, filtered and concentrated. Purification by column chromatography (AcOEt/pentane = 1/10 to 1/6) gave imide **38**[42] (1.25 g, 79%) as a white solid upon storage in the fridge; R_f = 0.73 (AcOEt/pentane = 1/2); m.p. = 40-41 °C; $[\alpha]_D^{25}$ = +66.1° (*c* 0.53, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.31-7.16 (m, 3H), 7.16-7.09 (m, 2H), 6.03 (tq, *J* = 7.3, 1.2 Hz, 1H), 4.64 (dddd, *J* = 9.2, 8.1, 5.6, 3.5 Hz, 1H), 4.17 (dd, *J* = 8.9, 8.0 Hz, 1H), 4.07 (dd, *J* = 8.9, 5.6 Hz, 1H), 3.27 (dd, *J* = 13.5, 3.5 Hz, 1H), 2.76 (dd, *J* = 13.5, 9.2 Hz, 1H), 2.24-1.96 (m, 2H), 1.84 (d, *J* = 1.2 Hz, 3H), 1.42 (h, *J* = 7.4 Hz, 2H), 0.89 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 172.1, 153.3, 140.3, 135.3, 130.8, 129.6 (2C), 129.0 (2C), 127.5, 66.5, 55.6, 37.7, 30.6, 21.9, 14.0, 13.7; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{21}NO_3Na$ 310.1414; Found 310.1415; IR (cm^{-1}) ν 2960, 2931, 2872, 1782, 1678, 1455, 1389, 1350, 1297, 1211, 1096, 1043, 902, 761, 704, 631.

(S)-4-Benzyl-3-((1E,3E)-1-((tert-butyldimethylsilyl)oxy)-2-methylhexa-1,3-dien-1-yl)oxazolidin-2-one (15). To a stirred solution

of imide **38**[42] (9.5 g, 33.1 mmol) in THF (220 mL) at −78 °C, NaHMDS (2 M in THF; 24.8 mL, 49.6 mmol, 1.5 equiv) was added and stirred for 2 h. A solution of TBSCl (9.0 g, 59.5 mmol, 1.8 equiv) in THF (75 mL) was then added dropwise and the resulting mixture was stirred at −78 °C for 2 h. The reaction was quenched with sat. NH_4Cl (300 mL) and the aqueous layer was extracted with Et_2O (2 x 350 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (Et_2O/pentane = 1/8) gave a mixture of silyl ketene aminal **15** and byproduct TBSOH. Azeotropic removal of TBSOH with PhMe (3 x 15 mL) provided silyl ketene aminal **15** (12.8 g, 97%) as a pale yellow oil; R_f = 0.38 (Et_2O/pentane = 1/4); $[\alpha]_D^{25}$ = −57.9° (*c* 1.52, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) *δ* 7.35-7.27 (m, 2H), 7.26-7.22 (m, 1H), 7.13 (br. d, *J* = 7.5 Hz, 2H), 6.14 (d, *J* = 15.6 Hz, 1H), 5.68 (dt, *J* = 15.5, 6.7 Hz, 1H), 4.30-4.21 (m, 2H), 4.13 (br. s, 1H), 3.16-3.06 (m, 1H), 2.72-2.56 (m, 1H), 2.28-2.01 (m, 2H), 1.82 (s, 3H), 1.03 (t, *J* = 7.5 Hz, 3H), 0.99 (s, 9H), 0.21 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) *δ* 155.3, 135.8, 134.0, 132.1, 129.1 (2C), 129.0 (2C), 127.2, 125.9, 116.4, 67.9, 56.4, 38.9, 26.5, 25.8 (3C), 18.2, 14.2, 12.5, −4.2, −4.8; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{23}H_{35}NO_3SiNa$ 424.2278; Found 424.2281; IR (cm^{-1}) ν 2958, 2930, 2859, 1766, 1653, 1628, 1396, 1376, 1295, 1254, 1165, 1079, 1034, 997, 841, 784, 632.

(S)-4-Benzyl-3-((2E,4S,5S,6E)-4-ethyl-5-hydroxy-7-iodo-2,6-dimethylhepta-2,6-dienoyl)oxazolidin-2-one (39). To a solution of aldehyde **16** (7.58 mmol, 2.0 equiv) in CH_2Cl_2 (ca. 14 g of solution) at –78 °C, $TiCl_4$ (1 M, 3.79 mL, 3.79 mmol, 1.0 equiv) was slowly added and the resulting mixture was stirred for 20 mins at the same temperature to give an orange precipitate. A silyl ketene aminal **15** (1522 mg, 3.79 mmol) in CH_2Cl_2 (4 mL) was then added dropwise at –78 °C using syringe pump over 20 min and stirred for 20 min. The resulting solution was then gradually warmed to –45 °C over 30 min and then stirred at –37 °C for 18 h (until the starting material consumed). During the course of the reaction, the color of the solution turned into orange-red from brown and the mixture was quenched with the mixture of sat. Rochelle solution (15 mL) and sat. $NaHCO_3$ (15 mL). The mixture was stirred for 30 min at room temperature and the resulting organic phase was separated. The remaining aqueous layer was extracted with Et_2O (2 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. Purification by column chromatography (AcOEt/cyclohexane = 1/5 - 1/4 - 1/3) gave desired alcohol **39** (1.39 g, 75%) as a pale yellow oil; R_f = 0.40 (AcOEt/pentane = 1/2); $[\alpha]_D^{25}$ = +9.3° (*c* 0.59, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) *δ* 7.36-7.25 (m, 3H), 7.21-7.12 (m, 2H), 6.25-6.24 (m, 1H), 5.67 (dq, *J* = 10.4, 1.4 Hz, 1H), 4.83 (tdd, *J* = 8.6, 6.7, 3.5 Hz, 1H), 4.33 (t, *J* = 8.8 Hz, 1H), 4.19 (dd, *J* = 9.0, 6.7 Hz, 1H), 3.89 (d, *J* = 9.0 Hz, 1H), 3.46 (br. s, 1H), 3.25 (dd, *J* = 13.7, 3.5 Hz, 1H), 2.94 (dd, *J* = 13.6, 8.6 Hz, 1H), 2.58 (tdd, *J* = 10.5, 9.1, 3.5 Hz, 1H), 1.99 (d, *J* = 1.5 Hz, 3H), 1.87 (d, *J* = 1.1 Hz, 3H), 1.43-1.30 (m, 1H), 1.16-1.01 (m, 1H), 0.86 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) *δ* 171.3, 154.4, 147.6, 140.4, 134.8, 134.2, 129.7 (2C), 129.1 (2C), 127.6, 80.5, 79.7, 66.4, 55.1, 45.9, 37.4, 24.0, 19.1, 14.3, 12.1; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{26}INO_4Na$ 506.0799; Found 506.0800; IR (cm^{-1}) ν 3495, 2961, 2929, 2872, 1766, 1682, 1454, 1392, 1352, 1292, 1213, 1095, 1044, 911, 734, 704, 632.

(1E,3R,4S,5E)-7-((S)-4-Benzyl-2-oxooxazolidin-3-yl)-4-ethyl-1-iodo-2,6-dimethyl-7-oxohepta-1,5-dien-3-yl 4-nitrobenzoate (39a). To a solution of secondary alcohol **39** (400 mg, 0.83 mmol) in THF (25 mL) at 0 °C, PPh_3 (434 mg, 1.66 mmol, 2.0 equiv), *p*-nitrobenzoic acid (282 mg, 1.66 mmol, 2.0 equiv) and DEAD (40% in PhMe; 1.53 mL, 1.66 mmol, 2.0 equiv) were added and stirred for 4.5 h. The reaction mixture was concentrated and the residue was purified by column chromatography (AcOEt/pentane = 1/10, 1/5, 1/3) to give benzoyl ester **39a** (410 mg, 78%) as a colourless foam; R_f = 0.42 (AcOEt/pentane = 1/4); $[\alpha]_D^{25}$ = +4.6° (*c* 1.60, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) *δ* 8.30 (d, *J* = 8.9 Hz, 2H), 8.23 (d, *J* = 8.9 Hz, 2H), 7.37-7.25 (m, 3H), 7.23-7.17 (m, 2H), 6.48-6.44 (m, 1H), 5.61 (dq, *J* = 10.4, 1.2 Hz, 1H), 5.52 (d, *J* = 7.4 Hz, 1H), 4.74-4.63 (m, 1H), 4.26 (t, *J* = 8.8 Hz, 1H), 4.17 (dd, *J* = 9.0, 4.9 Hz, 1H), 3.32 (dd, *J* = 13.6, 3.4 Hz, 1H), 2.90-2.84 (m, 1H), 2.88 (dd, *J* = 13.5, 9.2 Hz, 1H), 1.94 (d, *J* = 1.5 Hz, 3H), 1.91 (d, *J* = 1.2 Hz, 3H), 1.76-1.67 (m, 1H), 1.43-1.30 (m, 1H), 0.95 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) *δ* 171.3, 163.7, 152.8, 150.8, 143.8, 135.4, 135.2, 135.1, 134.5, 131.0 (2C), 129.6 (2C), 129.1 (2C), 127.6, 123.8 (2C), 82.6, 80.7, 66.6, 55.4, 42.7, 37.5, 24.2, 21.2, 14.5, 11.6; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{28}H_{29}IN_2O_7Na$ 655.0912; Found 655.0918; IR (cm^{-1}) ν 2964, 2930, 2875, 1784, 1724, 1681, 1607, 1526, 1348, 1267, 1212, 1099, 1013, 872, 718, 703.

(1E,3R,4S,5E)-4-Ethyl-7-hydroxy-1-iodo-2,6-dimethylhepta-1,5-dien-3-yl 4-nitrobenzoate (40). and ***(2E,4S,5R,6E)-4-ethyl-7-iodo-2,6-dimethylhepta-2,6-diene-1,5-diol (41).*** To a stirred solution of amide **39a** (white solid, 5.3 g, 8.38 mmol) in THF (110 mL) at 0 °C, $NaBH_4$ (970 mg, 25.1 mmol, 3.0 equiv) in water (35 mL) at 0 °C was added and stirred at 15 °C in the water bath. The reaction was monitored carefully by TLC (Et_2O/pentane = 1/3) and it was quenched with sat. NH_4Cl (100 mL) and the organic layer was separated. The aqueous layer was extracted with Et_2O (2 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated. Purification by column chromatography (Et_2O/pentane = 1/6 - 1/4 - 1/3 - 1/1.5 (product) - 1/1(diol and *p*-nitrobezyl alcohol) - 2/1) gave the desired *p*-nitrobenzoate **40** as a yellowish oil (3.02 g, 78%) and a diol **41*** as a solid (0.94 g, obtained as a mixture with *p*-nitrobezyl alcohol, 22% based on the yield of product in the next 3 steps); **Nitrobenzoate 40**: $[\alpha]_D^{25}$ = −8.2° (*c* 0.53, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) *δ* 8.31 (d, *J* = 8.8 Hz, 2H), 8.21 (d, *J* = 8.9 Hz, 2H), 6.38-6.37 (m, 1H), 5.42 (d, *J* = 8.5 Hz, 1H), 5.08 (dq, *J* = 10.4, 1.2 Hz, 1H), 4.03 (s, 2H), 2.77 (tdd, *J* = 10.2, 8.6, 3.3 Hz, 1H), 1.84 (d, *J* = 1.2 Hz, 3H), 1.71 (d, *J* = 1.4 Hz, 3H), 1.70-1.63 (m, 1H), 1.34-1.23 (m, 1H), 0.86 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) *δ* 163.8, 150.8, 144.6, 138.6, 135.5, 130.9 (2C), 124.1, 123.8 (2C), 81.9, 81.7, 68.6, 41.9, 24.3, 20.7, 14.5, 11.5; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{22}INO_5Na$ 482.0435; Found 482.0437; IR (cm^{-1}) ν 3399, 2962, 2930, 1723, 1674, 1607, 1527, 1457, 1409, 1347, 1270, 1101, 1014, 951, 874, 839, 783, 720. **Diol 41**: R_f = 0.30 (Et_2O/pentane = 1/1); ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.4 Hz)*, 7.54 (d, *J* = 8.4 Hz, 6H)*, 6.19 (s, 1H), 5.07 (d, *J* = 10.3 Hz, 1H), 4.84 (s)*, 4.04 (d, *J* = 7.4 Hz, 1H), 4.01 (s, 2H), 2.48 – 2.38 (m, 1H), 1.76 (s, 3H), 1.76 – 1.71 (m, 1H), 1.68 (s, 3H), 1.32 – 1.13 (m, 1H), 0.84 (t, *J* = 7.4 Hz, 3H). **p*-nitrobenzyl alcohol.

(1E,3R,4S,5E)-7-((tert-butyldimethylsilyl)oxy)-4-ethyl-1-iodo-2,6-dimethylhepta-1,5-dien-3-ol (41a). To a solution of diol **41** (940 mg, as a mixture with *p*-nitrobezyl alcohol, estimated ca. 1.8 mmol based on the previous reaction) in CH_2Cl_2 (35 mL) at 0 °C, imidazol (350 mg, 5.15 mmol, 1.7 equiv) and TBSCl (690 mg, 4.6 mmol, 1.5 equiv) was added and stirred for 20 min at the same temperature. Full conversion was confirmed by TLC after 10 min. The reaction was quenched with sat. NH_4Cl (25 mL) and organic layer was separated. The aqueous layer was extracted with Et_2O (3 x 20 mL) and the combined organic layer was washed with brine (25 mL), dried over Na_2SO_4, filtered and concentrated. Purification by column chromatography (Et_2O/pentane = 1/20 (*p*-NO_2BnOTBS) - 1/10 (product)) gave a desired secondary alcohol **41a** (808 mg, 63% based on initial 940 mg, 22% from **39a**) as a yellow oil; R_f = 0.30 (Et_2O/pentane = 1/10); $[\alpha]_D^{25}$ = +18.7° (*c* 1.11, $CHCl_3$); IR (cm^{-1}) ν 3380, 2956, 2930, 2858, 1254, 1076, 838, 777; ^1H NMR (400 MHz, $CDCl_3$) δ 6.17 (p, *J* = 1.1 Hz, 1H), 5.06 (dq, *J* = 10.3, 1.5 Hz, 1H), 4.01 (d, *J* = 7.5 Hz, 1H), 4.00 - 3.98 (m, 2H), 2.42 (tdd, *J* = 10.3, 7.4, 3.2 Hz, 1H), 1.75 (d, *J* = 1.1 Hz, 3H), 1.75 - 1.64 (m, 1H), 1.59 (d, *J* = 1.4 Hz, 3H), 1.25 - 1.11 (m, 1H), 0.90 (s, 9H), 0.82 (t, *J* = 7.4 Hz, 3H), 0.04 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.3, 137.0, 123.8, 79.9, 79.1, 68.2, 43.3, 26.1, 24.0, 20.3, 18.5, 14.2, 11.7, –5.1; HRMS (ESI-Orbitrap) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{33}IO_2SiNa$ 447.1187; Found 447.1189.

(1E,3R,4S,5E)-7-((tert-butyldimethylsilyl)oxy)-4-ethyl-1-iodo-2,6-dimethylhepta-1,5-dien-3-yl 4-nitrobenzoate (41b). To a solution of

alcohol **41a** (808 mg, 1.9 mmol) in CH_2Cl_2 (20.0 mL) at 0 °C, DIPEA (1.1 mL, 6.65 mmol, 3.5 equiv), PNBCl (1060 mg, 5.7 mmol, 3.0 equiv) and DMAP (115 mg, 0.95 mmol, 0.5 equiv) were added and stirred for 5 h at room temperature. The reaction mixture was added DIPEA (550 µL, 3.3 mmol, 1.5 equiv) and PNBCl (530 mg, 2.8 mmol, 1.5 equiv) and stirred further 30 min. No starting material detected by TLC at this point and the reaction was quenched with sat. NH_4Cl (20 mL) and the organic phase was separated. The resulting aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL) and the combined organic layers were washed with sat. $NaHCO_3$ (20 mL, to remove excess *p*-nitrobenzoic acid) and brine (20 mL), dried over Na_2SO_4, filtered, and concentrated to provide *p*-nitrobenzoate **41b**, which was used in the next reaction without purification (1090 mg). For analytical purpose, the crude product could be purified by column chromatography (Et_2O/pentane = 1/50 - 1/30 - 1/20) to give pure *p*-nitrobenzoate **41b**; R_f = 0.4 (Et_2O/pentane = 1/20); $[\alpha]_D^{24}$ = –12.6° (*c* 1.26, $CHCl_3$); IR (cm^{-1}) ν 2956, 2930, 2957, 1728, 1530, 1268, 1113; ^1H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 8.8 Hz, 2H), 8.20 (d, *J* = 8.8 Hz, 2H), 6.36 (s, 1H), 5.42 (d, *J* = 8.3 Hz, 1H), 5.10 (dd, *J* = 10.4, 1.5 Hz, 1H), 4.00 (s, 2H), 2.77 (tdd, *J* = 10.0, 8.3, 3.3 Hz, 1H), 1.84 (d, *J* = 1.2 Hz, 3H), 1.71 - 1.61 (m, 1H), 1.62 (d, *J* = 1.4 Hz, 3H), 1.33 - 1.20 (m, 1H), 0.88 (s, 9H), 0.85 (t, *J* = 7.4 Hz, 3H), 0.04 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.7, 150.8, 144.5, 138.1, 135.6, 130.9, 123.7, 121.9, 81.9, 81.7, 67.8, 41.8, 26.0, 24.5, 20.8, 18.5, 14.2, 11.4, –5.1, –5.1. HRMS (ESI-Orbitrap) m/z: $[M + Na]^+$ Calcd for $C_{24}H_{36}INO_5SiNa$ 596.1300; Found 596.1303.

Compound 40. To the solution of TBS ether **41b** (1.1 g, 1.9 mmol) in MeCN (30 mL, glass vial) at room temperature, HF (aq. 48%, 1.6 mL, 39 mmol, 16 equiv) was added and stirred at the same temperature for 3 h. The reaction was quenched carefully with sat. $NaHCO_3$ (caution! Gas evolution) at 0 °C and the aqueous layer was extracted with Et_2O (3 x 50 mL). Combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated. Purification by column chromatography (Et_2O/pentane = 1/4 - 1/3) gave desired primary alcohol **40** (0.9 g, > 99% over 3 steps) as a pale, yellow oil.

(1E,3R,4S,5E)-4-Ethyl-1-iodo-2,6-dimethyl-7-oxohepta-1,5-dien-3-yl 4-nitrobenzoate (40a). To a stirred solution of primary alcohol **40** (0.80 g, 1.74 mmol) in CH_2Cl_2 (115 mL), oven-dried activated MnO_2 (1.82 g, 20.90 mmol, 12 equiv) was added at room temperature and stirred for 18 h. The reaction mixture was filtered through a pad of Celite and washed with additional CH_2Cl_2 (50 mL). The filtrate was concentrated to give aldehyde **40a** (0.79 g, 99%) as a yellow solid upon storage in the fridge. This material was used in the following step without further purification; R_f = 0.26 (AcOEt/pentane = 1/9); m.p. = 92.5-92.8 °C; $[\alpha]_D^{25}$ = –1.7° (*c* 0.27, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) *δ* 9.43 (s, 1H), 8.32 (d, *J* = 8.9 Hz, 2H), 8.21 (d, *J* = 8.9 Hz, 2H), 6.51-6.50 (m, 1H), 6.13 (dq, *J* = 10.4, 1.2 Hz, 1H), 5.58 (d, *J* = 8.3 Hz, 1H), 3.10 (tdd, *J* = 10.1, 8.3, 3.4 Hz, 1H), 1.84 (d, *J* = 1.2 Hz, 3H), 1.81 (d, *J* = 1.4 Hz, 3H), 1.83-1.77 (m, 1H), 1.51-1.39 (m, 1H), 0.89 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) *δ* 194.8, 163.6, 150.9 (2C), 143.7, 141.8, 135.1, 130.9 (2C), 123.9 (2C), 83.2, 80.5, 43.2, 24.1, 20.5, 11.5, 10.1; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{20}INO_5Na$ 480.0278; Found 480.0281; IR (cm^{-1}) ν 3112, 3059, 2961, 2921, 2857, 1721, 1675, 1645, 1607, 1525, 1457, 1409, 1349, 1266, 1203, 1103, 1036, 1016, 951, 875, 839, 784, 721.

(1E,3R,4S,5E,7S)-4-Ethyl-7-hydroxy-1-iodo-2,6-dimethyldeca-1,5,9-trien-3-yl 4-nitrobenzoate (40b). To a stirred solution of aldehyde **40a** (190 mg, 0.42 mmol) in Et_2O (16 mL) at –78 °C, freshly prepared (–)-Ipc_2B(allyl) (0.19 M in Et_2O; 3.28 mL, 0.62 mmol, 1.5 equiv) was added dropwise and stirring was continued for 1.5 h at –78 °C. The reaction was quenched with $NaBO_3{\cdot}4H_2O$ (1.5 g) in H_2O (30 mL) and additional Et_2O (35 mL) was added. The resulting mixture was warmed to room temperature and stirred further for 30 min. The aqueous layer was extracted with Et_2O (2 x 25 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (Et_2O/pentane = 1/8 to 1/5) gave the secondary alcohol **40b** (145 mg, 70%, d.r = 20:1) as a colourless oil. At this point, the separation of isopinocampheol from the desired **40b** was difficult in large scale. Therefore, the material was used in the next TBS protection after removal of the undesired diastereomer. The yield over two steps were comparable to the yield described here; R_f = 0.31 (Et_2O/pentane = 3/7); $[\alpha]_D^{25}$ = –17.4° (*c* 0.73, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) *δ* 8.30 (d, *J* = 8.9 Hz, 2H), 8.21 (d, *J* = 8.9 Hz, 2H), 6.40-6.38 (m, 1H), 5.72 (ddt, *J* = 17.4, 10.3, 7.1 Hz, 1H), 5.43 (d, *J* = 8.8 Hz, 1H), 5.21-4.99 (m, 3H), 4.06 (t, *J* = 6.7 Hz, 1H), 2.83-2.65 (m, 1H), 2.42-2.16 (m, 2H), 1.83 (d, *J* = 1.2 Hz, 3H), 1.67 (d, *J* = 1.4 Hz, 3H), 1.66-1.63 (m, 1H), 1.30-1.21 (m, 1H), 0.85 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) *δ* 163.8, 150.8, 144.5, 140.2, 135.5, 134.3, 130.9 (2C), 124.1, 123.8 (2C), 118.4, 82.3, 81.9, 75.7, 41.8, 40.0, 24.4, 20.4, 13.2, 11.5; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{26}INO_5Na$ 522.0748; Found 522.0751; IR (cm^{-1}) ν 3551, 2961, 2929, 2873, 1725, 1608, 1528, 1455, 1347, 1267, 1101, 1014, 912, 873, 783, 720, 634.

(1E,3R,4S,5E,7S)-7-((tert-Butyldimethylsilyl)oxy)-4-ethyl-1-iodo-2,6-dimethyldeca-1,5,9-trien-3-yl 4-nitrobenzoate (42). To a solution of alcohol **40b** (30 mg, 0.06 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C, 2,6-lutidine (15 µL, 0.13 mmol, 2.0 equiv) and TBSOTf (17 µL, 0.07 mmol, 1.1 equiv) were added and the resulting mixture was stirred for 1 h at room temperature. The reaction was quenched with sat. NH_4Cl (10 mL) and the ensuing aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (Et_2O/pentane = 1/30) gave silyl-ether **42** (34.2 mg, 93%) as a colourless oil; R_f = 0.54 (Et_2O/pentane = 1/19); $[\alpha]_D^{25}$ = –2.8° (*c* 0.50, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) *δ* 8.30 (d, *J* = 9.0 Hz, 2H), 8.20 (d, *J* = 9.0 Hz, 2H), 6.47-6.38 (m, 1H), 5.70 (ddt, *J* = 17.2, 10.2, 7.1 Hz, 1H), 5.45 (d, *J* = 8.6 Hz, 1H), 5.10-4.93 (m, 3H), 4.00 (t, *J* = 6.4 Hz, 1H), 2.82-2.65 (m, 1H), 2.33-2.17 (m, 2H), 1.84 (d, *J* = 1.1 Hz, 3H), 1.70-1.62 (m, 1H), 1.63 (d, *J* = 1.4 Hz, 3H), 1.30-1.21 (m, 1H), 0.88 (s, 9H), 0.84 (t, *J* = 7.4 Hz, 3H), 0.01 (s, 3H), –0.02 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 163.8, 150.8, 144.4, 141.0, 135.7, 135.3, 130.9 (2C), 123.8 (2C), 123.2, 116.7, 82.8, 81.8, 77.5, 41.7, 41.6, 26.0 (3C), 24.7, 20.4, 18.3, 12.7, 11.3, –4.3, –4.7; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{27}H_{40}INO_5SiNa$ 636.1613; Found 636.1608; IR (cm^{-1}) ν 2942, 2930, 2857, 1727, 1608, 1529, 1463, 1346, 1266, 1099, 1089, 1014, 914, 836, 778, 719, 632.

(1E,3R,4S,5E,7S)-7-((tert-butyldimethylsilyl)oxy)-4-ethyl-1-iodo-2,6-dimethyldeca-1,5,9-trien-3-ol (43). To a solution of benzoyl ester **42** (155 mg, 0.25 mmol) in CH_2Cl_2 (5.0 mL) at –78 °C, DIBAL (1.2 M in PhMe, 450 µL, 0.54 mmol, 2.2 equiv) was added, and the reaction mixture was stirred for 30 min at the same temperature. Then it was warmed to –40 °C and stirred for additional 30 min. The reaction mixture was first treated with AcOEt (0.5 mL) and then with aqueous sat. Rochelle salt (5.0 mL) and stirred vigorously at room temperature for 2 h. The organic layer was separated and the aqueous layer was extracted with Et_2O (2 x 10 mL). The organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography (Et_2O/pentane = 1/25 to 1/20 to 1/15) gave alcohol **43 (**119 mg, > 99%) as a colorless oil; R_f = 0.50 (Et_2O/pentane = 1/9); $[\alpha]_D^{25}$ = +20.8° (*c* 0.54, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 6.24-6.19 (m, 2H), 5.72 (ddt, *J* = 17.3, 10.2, 7.1 Hz, 1H), 5.02 (d, *J* = 17.1 Hz, 1H), 4.99 (d, *J* = 9.8 Hz, 1H), 4.05-3.98 (m, 2H), 3.99 (d, *J* = 6.1 Hz, 1H), 2.42 (tdd, *J* = 10.0, 7.6, 3.2 Hz, 1H), 2.30-2.17 (m, 2H), 1.75 (d, *J* = 1.2 Hz, 3H), 1.73 (s, 1H), 1.59 (d, *J* = 1.5 Hz, 3H), 1.17 (ddd, *J* = 13.4, 9.8, 7.4 Hz, 1H), 0.88 (s, 9H), 0.82 (t, *J* = 7.5 Hz, 3H), 0.02 (s, 3H), –0.01 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.4, 139.9, 135.6, 124.8, 116.6, 78.0, 79.6, 77.7, 43.2, 41.7, 26.0 (3C), 24.3, 19.9, 18.3, 12.6, 11.5, –4.3, –4.7; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{20}H_{37}IO_2SiNa$ 487.1500; Found 487.1499; IR (cm^{-1}) ν 3389, 3076, 2956, 2930, 2857, 1640, 1615, 1463, 1387, 1254, 1076, 1005, 913, 836, 776, 673.

(5S,8S,9R,E)-5-Allyl-8,11,11-triethyl-9-((E)-1-iodoprop-1-en-2-yl)-2,2,3,3,6-pentamethyl-4,10-dioxa-3,11-disilatridec-6-ene (44). To a solution of nitrobenzoyl ester **42** (380 mg, 0.62 mmol) in MeOH (15 mL) and THF (5 mL) at 0 °C, K_2CO_3 (94 mg, 0.68 mmol, 1.1 equiv) in H_2O (1.5 mL) was added and stirring continued for 30 min at room temperature. The reaction was quenched with sat. $NaHCO_3$ (30 mL) and the resulting aqueous layer was extracted with Et_2O (2 x 35 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to give a residue, which was used in the following step without further purification.

To a stirred solution of intermediate **43** (crude, 0.62 mmol) in CH_2Cl_2 (12 mL) at 0 °C, 2,6-lutidine (0.14 mL, 1.24 mmol, 2.0 equiv) and TESOTf (0.17 mL, 0.74 mmol, 1.2 equiv) were added and the resulting mixture was stirred for 15 min at room temperature. The reaction was quenched with sat. NH_4Cl (30 mL) and the ensuing aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. Purification by column chromatography (Et_2O/pentane = 1/99) gave silyl ether **44** (340 mg, 95% over two steps) as a colourless oil; R_f = 0.67 (Et_2O/pentane = 1/99); $[\alpha]_D^{25}$ = +30.6° (*c* 0.32, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 6.11-6.05 (m, 1H), 5.72 (ddt, *J* = 17.2, 10.1, 7.1 Hz, 1H), 5.05-4.94 (m, 2H), 4.93-4.85 (m, 1H), 3.95 (t, *J* = 6.2 Hz, 1H), 3.91 (d, *J* = 8.3 Hz, 1H), 2.35 (dtd, *J* = 10.0, 8.4, 3.2 Hz, 1H), 2.30-2.15 (m, 2H), 1.85-1.75 (m, 1H), 1.70 (d, *J* = 1.1 Hz, 3H), 1.56 (d, *J* = 1.4 Hz, 3H), 1.12-1.01 (m, 1H), 0.93 (t, *J* = 7.9 Hz, 9H), 0.88 (s, 9H), 0.82-0.75 (t, *J* = 8.1 Hz, 3H), 0.56 (q, *J* = 7.9 Hz, 6H), 0.01 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.2, 139.3, 135.9, 125.0, 116.4, 81.0, 79.0, 77.9, 44.2, 42.1, 26.0 (3C), 24.8, 19.5, 18.4, 12.6, 11.5, 7.0 (3C), 4.9 (3C), −4.16, −4.72; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{51}IO_2Si_2Na$ 601.2364; Found 601.2362; IR (cm^{-1}) ν 2955, 2878, 1628, 1461, 1414, 1377, 1251, 1068, 1004, 912, 835, 775, 739, 669.

Ethyl 2-(((tert-butyldimethylsilyl)oxy)methyl)-3-hydroxypent-4-enoate (47). To a stirred solution of freshly prepared LDA (12 mmol, 3.5 equiv) in THF (35 mL) at −78 °C, hydroxyl-ester **45** (400 mg, 3.4 mmol) in THF (5 mL) was added dropwise and stirred for 1.5 h. Acrolein (0.34 mL, 5.08 mmol, 1.5 equiv) in THF (4 mL) was then added dropwise and stirred further for 1.5 h. The reaction was quenched with sat. NH_4Cl (60 mL) and the resulting aqueous layer was extracted with Et_2O (2 x 50 mL) and AcOEt (2 x 50 mL, Et_2O was not enough polar to extract diol **46**). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to give diol **46** (591 mg) as a yellow oil, which was used in the following step without further purification.

To a stirred solution of diol **46** (3.4 mmol), Et_3N (0.86 mL, 6.10 mmol, 1.8 equiv), and Me_2SnCl_2 (154 mg, 0.68 mmol, 20 mol%) in CH_2Cl_2 (25 mL) at room temperature, TBSCl (920 mg, 6.10 mmol, 1.8 equiv) was added and stirred for 6 h. The reaction was quenched with sat. NH_4Cl (50 mL) and the resulting aqueous layer was extracted with CH_2Cl_2 (2 x 40 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (Et_2O/pentane = 1/10 to 3/7) gave secondary alcohol **47** (733 mg, 75% over two steps, *d.r* = 3:2) as a yellow oil; R_f = 0.14 (Et_2O/pentane = 1/9); ^1H NMR (500 MHz, $CDCl_3$) δ 5.89 (ddd, *J* = 10.5, 5.8, 2.2 Hz, 0.4H) 5.86 (ddd, *J* = 10.5, 5.8, 2.2 Hz, 0.6H), 5.35 (q, *J* = 1.6 Hz, 0.6H), 5.31 (q, *J* = 1.6 Hz, 0.4H), 5.22-5.14 (m, 1H), 4.53 (tt, *J* = 5.8, 1.3 Hz, 0.6H), 4.46 (tt, *J* = 5.3, 1.2 Hz, 0.4H), 4.16 (q, *J* = 7.1 Hz, 1.2H), 4.16 (qd, *J* = 7.1, 0.7 Hz, 0.8H), 3.98 (d, *J* = 6.0 Hz, 1H), 3.92 (dd, *J* = 10.0, 6.5 Hz, 0.4H), 3.89 (dd, *J* = 10.0, 6.1 Hz, 0.6H), 3.27 (br. s, 1H), 2.74 (q, *J* = 5.7 Hz, 0.4 H), 2.70 (q, *J* = 6.0 Hz, 0.6H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.88 (s, 5.4H), 0.87 (s, 3.6H), 0.07 (s, 1.8H), 0.06 (s, 1.8H), 0.04 (s, 1.2H), 0.04 (s, 1.2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.0, 172.2, 138.0, 137.9, 116.4, 116.3, 72.9, 71.4, 62.1, 62.0, 60.9, 60.8, 52.9, 52.8, 25.9 (3C), 18.3, 18.2, 14.4, −5.49, −5.50 (as a mixture of diastereoisomers); HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{28}O_4SiNa$ 311.1649; Found 311.1653; IR (cm^{-1}) ν 3484, 2955, 2932, 2887, 2858, 1733, 1470, 1379, 1256, 1185, 1108, 1031, 925, 894, 838, 778.

(E)-Ethyl 2-((tert-butyldimethylsilyloxy)methyl)penta-2,4-dienoate (48). To a stirred solution of alcohol **47** (550 mg, 1.91 mmol) in CH_2Cl_2 (30 mL) at room temperature, triethylamine (0.54 mL, 3.81 mmol, 2.0 equiv), DMAP (23.5 mg, 0.19 mmol, 10 mol%) and Ac_2O (0.36 mL, 3.81 mmol, 2.0 equiv) were added and stirred for 2.5 h. The reaction was quenched with sat. $NaHCO_3$ (60 mL) and the ensuing aqueous layer was extracted with CH_2Cl_2 (100 mL). The organic layer was then washed with sat. NH_4Cl (60 mL), dried over $MgSO_4$, filtered and concentrated to give acetate **47a** (655 mg) as a yellow oil. This material was used in the following step without further purification.

To a stirred solution of acetate **47a** (1.91 mmol) in CH_2Cl_2 (30 mL) at room temperature, DBU (2.28 mL, 15.30 mmol, 8 equiv) was added and stirred for 18 h. The reaction was quenched with sat. NH_4Cl (120 mL) and the ensuing aqueous layer was extracted with CH_2Cl_2 (150 mL). The organic layer was then washed with sat. $NaHCO_3$ (120 mL), dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (Et_2O/pentane = 1/10) gave (*E*,*E*)-dienoate **48** (401 mg, 78% over two steps) as a yellow oil and (*Z*, *E*)-dienoate **48** (72 mg, 14% over two steps) as a yellow oil. The product **48** should be stored at –20 °C in a flozen benzene. The decomspotion of the compound was observed within 1 month at 4 °C; **(*E*,*E*)-Dienoate 48**: R_f = 0.36 (Et_2O/pentane = 1/19); ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 11.4 Hz, 1H), 6.88 (ddd, *J* = 16.8, 11.4, 10.0 Hz, 1H), 5.66-5.56 (m, 1H), 5.51 (dd, *J* = 10.0, 1.1 Hz, 1H), 4.50 (s, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.5, 141.5, 132.3, 131.3, 125.8, 60.8, 57.7, 26.0 (3C), 18.5, 14.5, −5.1 (2C); HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{26}O_3SiNa$ 293.1543; Found 293.1547; IR (cm^{-1}) ν 2943, 2932, 2858, 1711, 1635, 1595, 1469, 1378, 1248, 1179, 1074, 1003, 920, 838, 778; **(*Z*, *E*)-Dienoate 48**: R_f = 0.43 (Et_2O/pentane = 1/19); ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (ddd, *J* = 16.9, 11.3, 10.0 Hz, 1H), 6.73-6.67 (m, 1H), 5.52-5.43 (m, 1H), 5.45-5.37 (m, 1H), 4.38 (br. d, *J* = 1.0 Hz, 2H), 4.24 (q, *J* = 7.1 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 3H), 0.93 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 138.2, 133.5, 130.5, 124.2, 62.9, 60.5, 26.0 (3C), 18.5, 14.4, −5.2 (2C); HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{26}O_3SiNa$ 293.1543; Found 293.1545; IR (cm^{-1}) ν 2943, 2931, 2894, 2858, 1718, 1638, 1594, 1467, 1388, 1378, 1318, 1253, 1215, 1181, 1129, 1072, 1002, 925, 838, 776, 679, 632.

(E)-2-((tert-Butyldimethylsilyloxy)methyl)penta-2,4-dienoic acid (49). To a stirred solution of (*E*,*E*)-dienoate **49** (300 mg, 1.11 mmol) in CH_2Cl_2 (10 mL) at −78 °C, DIBAL (1 M in CH_2Cl_2; 2.77 mL, 2.77 mmol, 2.5 equiv) was added dropwise and stirring continued for 1.5 h at −10 °C. The reaction was quenched with sat. NH_4Cl (30 mL) and the resulting aqueous layer was extracted with Et_2O (2 x 30 mL). HCl (1 M; 10 mL) was added to the aqueous layer and re-extracted with Et_2O (20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to give the corresponding primary alcohol **48a**. This material was used in the following step without further purification.

To a stirred solution of crude primary alcohol **48a** (1.11 mmol) in CH_2Cl_2 (20 mL), oven-dried activated MnO_2 (1.45 g, 16.60 mmol, 15 equiv) was added and stirred for 18 h at room temperature. The reaction mixture was filtered through a pad of Celite and washed with additional CH_2Cl_2 (30 mL). The filtrate was concentrated to give aldehyde **48b** (251 mg) as a yellow liquid. This material was used in the following step without further purification.

To a stirred solution of crude aldehyde **48b** (251 mg) in *t*-BuOH (25 mL) and H_2O (25 mL) at 0 °C, $NaClO_2$ (627 mg, 5.55 mmol, 5 eq), KH_2PO_4 (906 mg, 6.66 mmol, 6 eq) and 2-methyl-2-butene (2.8 mL, 33.3 mmol, 30 eq) were added and stirring continued for 1 h at 10 °C. The reaction was slowly warmed to room temperature and further stirred for 3.5 h. H_2O (35 mL) was then added and the aqueous layer

was extracted with Et_2O (3 x 40 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. Purification by column chromatography (Et_2O/pentane = 1/6 to 1/5) gave carboxylic acid **49** (188 mg, 70% over three steps) as an off-white solid. This compound should be used in the next reaction within few days due to the side product formation probably via spontaneous TBS deprotection and / or (hetero) Diels Alder reactions; R_f = 0.19 (Et_2O/pentane = 3/7); m.p. = 56.5-57.0 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 11.30 (br. s, 1H), 7.35 (d, J = 11.5 Hz, 1H), 6.86 (ddd, J = 16.8, 11.5, 10.0 Hz, 1H), 5.75-5.64 (m, 1H), 5.61-5.57 (m, 1H), 4.53 (s, 2H), 0.90 (s, 9H), 0.11 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 143.4, 131.8, 129.7, 127.4, 57.8, 26.0 (3C), 18.5, −5.2 (2C); HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{12}H_{22}O_3SiNa$ 265.1230; Found 265.1233; IR (cm^{-1}) ν 2939, 2928, 2895, 2856, 1672, 1431, 1344, 1253, 1062, 998, 926, 836, 775, 677, 666.

***tert*-Butyldimethyl((*R*)-1-((*S*)-oxiran-2-yl)ethoxy)silane (50).**[52b, 52c] To a stirred solution of secondary alcohol **50a**[52a] (250 mg, 2.84 mmol) in CH_2Cl_2 (10 mL) at 0 °C, imidazole (429 mg, 6.24 mmol, 2.2 equiv) and TBSCl (0.74 mL, 4.26 mmol, 1.5 equiv) were added and the resulting mixture was stirred at room temperature for 2 h. The reaction was quenched with sat. NH_4Cl (25 mL) and the resulting aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. Purification by column chromatography (Et_2O/pentane = 1/99 to 1/19) gave silyl-ether **50** (535 mg, 93%) as a colourless oil; The spectroscopic data matched those reported in the literature.[52] R_f = 0.22 (Et_2O/pentane = 1/99); $[\alpha]_D^{25}$ = −20.7° (*c* 0.35, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 3.72 (qd, J = 6.3, 4.4 Hz, 1H), 2.85 (td, J = 4.1, 2.6 Hz, 1H), 2.70 (dd, J = 5.4, 3.9 Hz, 1H), 2.65 (dd, J = 5.4, 2.6 Hz, 1H), 1.23 (d, J = 6.3 Hz, 3H), 0.87 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 67.8, 55.8, 44.9, 25.9 (3C), 21.0, 18.3, −4.6, −4.7; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{10}H_{22}O_2SiNa$ 225.1281; Found 225.1278; IR (cm^{-1}) ν 2956, 2931, 2888, 2858, 1472, 1373, 1252, 1167, 1107, 995, 957, 899, 832, 775, 739, 666, 628.

***(2R,3S)*-2-((tert-Butyldimethylsilyl)oxy)hept-5-yn-3-ol (50a).** To a stirred solution of *n*-BuLi (1.6 M in hexane; 0.74 mL, 1.19 mmol, 3.0 equiv) in THF (2.5 mL) at −78 °C, propyne gas was bubbled through the reaction mixture using a balloon for 1 h. A milky white slurry was formed at which point, epoxide **50** (80 mg, 0.40 mmol) in THF (0.5 mL) was added dropwise followed by $BF_3{\cdot}Et_2O$ (0.05 mL, 0.42 mmol, 1.05 equiv). The stirring was continued at −30 °C for 30 min, and then at 0 °C for 1.5 h. The reaction was quenched with sat. NH_4Cl (15 mL) and the resulting aqueous layer was extracted with Et_2O (2 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (Et_2O/pentane = 1/9) afforded alkyne **50a** (85 mg, 90%) as a colourless oil; R_f = 0.55 (Et_2O/pentane = 1/4); $[\alpha]_D^{25}$ = −30.1° (*c* 0.40, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 3.84 (qd, J = 6.2, 4.8 Hz, 1H), 3.57 (ddd, J = 6.9, 5.8, 4.8 Hz, 1H), 2.44-2.24 (m, 2H), 2.16 (br. s, 1H), 1.79 (t, J = 2.6 Hz, 3H), 1.13 (d, J = 6.2 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 78.0, 75.4, 74.2, 70.4, 25.9 (3C), 23.0, 18.2, 18.1, 3.7, −4.3, −4.8; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{26}O_2SiNa$ 265.1594; Found 265.1592; IR (cm^{-1}) ν 3455, 2941, 2930, 2858, 1463, 1372, 1253, 1136, 1085, 1006, 975, 908, 833, 775, 667, 629.

***(2R,3S,E)*-2-(tert-Butyldimethylsilyloxy)-6-(tributylstannyl)hept-5-en-3-ol (52) and regioisomer (53).** Tricyclohexylphosphine (60 mg, 0.21 mmol, 10 mol%) was added to $Pd(OAc)_2$ (23 mg, 0.10 mmol, 5 mol%) in hexane (25 mL) and stirred for 20 min at room temperature until the solids were dissolved. Alkyne **28** (500 mg, 2.06 mmol) in hexane (7 mL) was then added slowly followed by dropwise addition of Bu_3SnH (2.22 mL, 8.24 mmol, 4.0 equiv) over 3 min. The ensuing dark-orange solution was stirred for additional 20 min. The reaction mixture was concentrated and column chromatography (oven-dried SiO_2, neutralized with Et_3N/pentane 1/9 prior to use, Et_2O/pentane = 0/1 to 1/9) gave vinyl stannane **52** (554 mg, 51%) as a pale yellow oil. The regioisomer **53** was isolated (494 mg, 45%) as a pale yellow oil; **Vinyl stannane 52**: R_f = 0.30 (Et_2O/pentane = 1/20); $[\alpha]_D^{25}$ = −11.3° (*c* 0.33, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.56 (tq, J = 6.9, 1.9 Hz, 1H), 3.79 (qd, J = 6.2, 3.9 Hz, 1H), 3.66-3.53 (m, 1H), 2.34-2.25 (m, 2H), 2.14 (d, J = 2.9 Hz, 1H), 1.93-1.76 (m, 3H), 1.55-1.41 (m, 6H), 1.38-1.21 (m, 6H), 1.11 (d, J = 6.2 Hz, 3H), 0.91-0.85 (m, 15 H), 0.90 (s, 9H), 0.07 (s, 2 x 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.5, 136.1, 75.2, 70.9, 31.2, 29.3 (3C), 27.5 (3C), 26.0 (3C), 19.5, 18.2, 17.3, 13.9 (3C), 9.3 (3C), −4.3, −4.7; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{25}H_{54}O_2SiSnNa$ 557.2811; Found 557.2806; IR (cm^{-1}) ν 3581, 2956, 2927, 2856, 1462, 1378, 1336, 1253, 1188, 1141, 1077, 1004, 975, 939, 834, 775, 667; **Regioisomer 53**: R_f = 0.50 (Et_2O/pentane = 1/20); $[\alpha]_D^{25}$ = −9.7° (*c* 0.33, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.93-5.71 (m, 1H), 3.75 (qd, J = 6.2, 4.4 Hz, 1H), 3.46-3.36 (m, 1H), 2.47 (dd, J = 13.5, 10.7 Hz, 1H), 2.39-2.30 (m, 1H), 1.96 (d, J = 2.6 Hz, 1H), 1.76-1.71 (m, 3H), 1.53-1.41 (m, 6H), 1.38-1.23 (m, 6H), 1.15 (d, J = 6.2 Hz, 3H), 0.91-0.85 (m, 15 H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.8, 137.7, 75.5, 71.6, 35.6, 29.3 (3C), 27.6 (3C), 26.0 (3C), 18.6, 18.2, 14.9, 13.8 (3C), 10.0 (3C), −4.2, −4.7; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{25}H_{54}O_2SiSnNa$ 557.2811; Found 557.2803; IR (cm^{-1}) ν 3578, 2955, 2927, 2856, 1462, 1377, 1337, 1254, 1198, 1143, 1084, 1004, 835, 776, 669.

***(2R,3S,Z)*-2-((tert-butyldimethylsilyl)oxy)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hept-5-en-3-ol (54).**[17] To a 10 mL two necked flask, CuCl (2 mg, 0.02 mmol, 5 mol%), PPh_3 (6,5 mg, 0,025 mmol, 6 mol%) and KO*t*-Bu (9.3 mg, 0.083 mmol, 20 mol%) were added, suspended in THF (2.0 mL) and stirred at room temperature for 0.5 h forming a brown to black solution. A solution of B_2pin_2 (115 mg, 0.453 mmol, 1.1 equiv) in dry THF (2 mL) was added and the reaction mixture was stirred for additional 10 min. Next, the reaction mixture was cooled to 0 °C and a solution of alkyne **51** (100 mg, 0.412 mmol) in MeOH (33.4 µL, 0.824 mmol, 2.0 equiv) and THF (1.5 mL) was added. The reaction was warmed to room temperature and stirred for 16 h. The reaction mixture was filtered through Celite with Et_2O and the filtrate was concentrated. Purification by column chromatography (Et_2O/pentane = 1/8 - 1/6 - 1/4, Caution! The boronate can decompose on the silica gel. Perform chromatography as quick as possible.) provided the desired boronic ester **54** (140 mg, 91%) as a colourless oil; R_f = 0.35 (Et_2O/pentane = 1/4); $[\alpha]_D^{25}$ = –13.2° (*c* 0.62, $CHCl_3$); 1H NMR (500 MHz, $CDCl_3$) δ 6.37 (tq, J = 6.7, 1.5 Hz, 1H), 3.77 (qd, J = 6.2, 3.8 Hz, 1H), 3.64-3.59 (m, 1H), 2.26 (ap d, J = 10.0 Hz, 1H), 2.24 (ap d, J = 10.0 Hz, 1H), 2.12 (d, J = 3.5 Hz, 1H), 1.69 (s, 3H), 1.24 (s, 12H), 1.09 (d, J = 6.3 Hz, 3H), 0.87 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.1, 128.3, 83.3 (2C), 74.9, 71.2, 31.7, 25.9 (3C), 24.9 (4C), 18.2, 17.5, 14.3, −4.3, −4.7; HMBC (δ_H: 1.69 ppm, δ_C: 128.3 ppm); ^{11}B NMR (128 MHz, $CDCl_3$) δ 29.9; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{39}BO_4SiNa$ 393.2603; Found 393.2604; IR (cm^{-1}) ν 3479, 2977, 2956, 2931, 2888, 2858, 1633, 1463, 1369, 1310, 1254, 1214, 1143, 1083, 975, 833, 775, 667.

***(2R,3S,Z)*-2-((tert-butyldimethylsilyl)oxy)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hept-5-en-3-yl (*E*)-2-(((tert-butyldimethylsilyl)oxy)methyl)penta-2,4-dienoate (55).** To a stirred solution of carboxylic acid **49** (40 mg, 0.17 mmol, 1.2 equiv) in PhH (1.5 mL) at room temperature, Et_3N (49 µL, 0.35 mmol, 2.0 equiv) and 2,4,6-trichlorobenzoyl chloride (29 µL, 0.18 mmol, 1.25 equiv) were added and stirred for 1.5 h. To this mixture, alcohol **54** (51 mg, 0.14 mmol) and DMAP (17 mg, 0.14 mmol, 0.8 equiv) in PhH (1.5 mL) were added and stirred for 7 h at room temperature. The reaction was quenched with sat. NH_4Cl (10 mL) and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with aqueous sat. $NaHCO_3$ (15 mL) and brine (15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by silica gel chromatography (Et_2O/pentane = 1/40 to 1/30 to 1/20) gave the desired ester **55** (50 mg, 61%) as a colorless oil; R_f = 0.40 (Et_2O/pentane = 1/12); $[\alpha]_D^{25}$ = –43.5° (*c* 1.08, $CHCl_3$); ^1H

NMR (500 MHz, $CDCl_3$) δ 7.20 (d, *J* = 11.4 Hz, 1H), 6.92 (ddd, *J* = 16.9, 11.5, 10.0 Hz, 1H), 6.33 (ddt, *J* = 7.1, 5.3, 1.8 Hz, 1H), 5.56 (ddd, *J* = 16.9, 1.8, 0.8 Hz, 1H), 5.48 (dd, *J* = 10.0, 1.8 Hz, 1H), 4.88 (dt, *J* = 7.9, 4.6 Hz, 1H), 4.49 (d, *J* = 1.5 Hz, 2H), 3.97 (qd, *J* = 6.3, 4.0 Hz, 1H), 2.58-2.44 (m, 2H), 1.69 (s, 3H), 1.22 (s, 12H), 1.15 (d, *J* = 6.4 Hz, 3H), 0.87 (s, 9H), 0.87 (s, 9H), 0.06 (s, 6H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.9, 141.6, 141.4, 132.6, 131.3, 129.3, 125.6, 83.2 (2C), 77.8, 69.4, 57.9, 28.6, 26.0 (3C), 25.9 (3C), 24.92 (2C), 24.89 (2C), 20.1, 18.5, 18.1, 14.2, −4.30, −4.7, −5.1 (2C); HMBC (δ_H: 1.69 ppm, δ_C: 129.3 ppm); ^{11}B NMR (128 MHz, $CDCl_3$) δ 29.6; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{31}H_{59}BO_6Si_2Na$ 617.3835; Found 617.3839; IR (cm^{-1}) ν 2930, 2887, 2858, 1706, 1634, 1370, 1305, 1370, 1145, 1072, 834, 775, 668.

(5R,6S,8E,10E,12R,13S,14E,16S)-16-Allyl-13-ethyl-2,2,3,3,5,9,11,15,18,18,19,19-dodecamethyl-12-((triethylsilyl)oxy)-4,17-dioxa-3,18-disilaicosa-8,10,14-trien-6-ol (56). A degassed solution of vinyl stannane **52** (266 mg, 0.50 mmol, 1.7 equiv) and vinyl iodide **44** (165 mg, 0.29 mmol) in DMF (10 mL) was added to a flask containing $[Ph_2PO_2]^-[NBu_4]^+$ (pre-dried with heat gun, 520 mg, 1.13 mmol, 3.9 equiv) at room temperature. After stirring for 5 min, CuTC (163 mg, 0.86 mmol, 3.0 equiv) was introduced followed by $Pd(PPh_3)_4$ (231 mg, 0.20 mmol, 70 mol%). The resulting brown-black mixture was stirred for 1 h at room temperature. The reaction was quenched with H_2O (60 mL) and the resulting aqueous layer was extracted with Et_2O (2 x 35 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. Purification by column chromatography (Et_2O/pentane = 1/99 - 1/50 - 1/15 - 1/8) afforded diene **56** (152 mg, 77%) as a pale yellow oil; R_f = 0.35 (Et_2O/pentane = 1/24); $[\alpha]_D^{25}$ = +11.7° (*c* 0.27, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 5.78-5.67 (m, 1H), 5.72 (s, 1H), 5.31-5.27 (m, 1H), 5.00-4.93 (m, 3H), 3.95 (t, *J* = 6.3 Hz, 1H), 3.85-3.75 (m, 1H), 3.75 (d, *J* = 8.1 Hz, 1H), 3.62-3.52 (m, 1H), 2.45-2.31 (m, 1H), 2.30-2.14 (m, 4H), 2.13 (br. s, 1H), 1.87-1.74 (m, 1H), 1.73 (s, 3H), 1.67 (d, *J* = 1.2 Hz, 3H), 1.56 (d, *J* = 1.4 Hz, 3H), 1.13-1.09 (m, 1H), 1.11 (d, *J* = 6.3 Hz, 3H), 0.94 (t, *J* = 7.9 Hz, 9H), 0.89 (s, 9H), 0.86 (s, 9H), 0.79 (t, *J* = 7.4 Hz, 3H), 0.58 (q, *J* = 8.0 Hz, 6H), 0.07 (s, 3H), 0.06 (s, 3H), −0.01 (s, 3H), −0.06 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 138.1, 137.1, 136.1, 134.8, 130.6, 126.0, 125.5, 116.2, 82.9, 78.0, 75.3, 71.0, 44.1, 42.2, 31.3, 26.0 (6C), 24.8, 18.3, 18.2, 17.4, 17.3, 13.6, 12.6, 11.6, 7.1 (3C), 5.1 (3C), −4.3, −4.5, −4.7, −4.9; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{39}H_{78}O_4Si_3Na$ 717.5100; Found 717.5098; IR (cm^{-1}) ν 3583, 2955, 2944, 2878, 1642, 1462, 1384, 1253, 1072, 1006, 911, 835, 776, 742, 670.

(E)-(5R,6S,8E,10E,12R,13S,14E,16S)-16-Allyl-13-ethyl-2,2,3,3,5,9,11,15,18,18,19,19-dodecamethyl-12-((triethylsilyl)oxy)-4,17-dioxa-3,18-disilaicosa-8,10,14-trien-6-yl 2-(((tert-butyldimethylsilyl)oxy)methyl)penta-2,4-dienoate (57). To a stirred solution of carboxylic acid **49** (101 mg, 0.42 mmol, 1.9 equiv) in PhMe (4 mL) at room temperature, Et_3N (0.15 mL, 1.04 mmol, 2.5 equiv) and 2,4,6-trichlorobenzoyl chloride (64 µL, 0.409 mmol, 1.95 equiv) were added and stirred for 1 h, forming white suspension. To a solution of alcohol **56** (145 mg, 0.21 mmol) and DMAP (76 mg, 0.63 mmol, 1.5 equiv) in PhMe (2.5 mL), suspension was added dropwise and the mixture was stirred for 1.5 h at room temperature. The reaction was quenched with sat. NH_4Cl (25 mL) and the resulting aqueous layer was extracted with Et_2O (2 x 25 mL). The combined organic layers were washed with sat. $NaHCO_3$ (40 mL), dried over Na_2SO_4, filtered and concentrated. Purification by column chromatography (Et_2O/pentane = 1/99) afforded polyene **57** (165 mg, 86%) as a colourless oil; R_f = 0.13 (Et_2O/pentane = 1/99); $[\alpha]_D^{25}$ = −21.0° (*c* 0.56, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.20 (d, *J* = 11.4 Hz, 1H), 6.92 (ddd, *J* = 16.9, 11.4, 10.0 Hz, 1H), 5.77-5.67 (m, 1H), 5.66 (s, 1H), 5.55 (dd, *J* = 16.9 Hz, 1.1, 1H), 5.49 (dd, *J* = 10.1, 1.5 Hz, 1H), 5.23 (t, *J* = 7.2 Hz, 1H), 5.02-4.90 (m, 3H), 4.91-4.84 (m, 1H), 4.51 (d, *J* = 12.2 Hz, 1H), 4.47 (d, *J* = 12.2 Hz, 1H), 4.02-3.88 (m, 2H), 3.72 (d, *J* = 7.9 Hz, 1H), 2.44 (t, *J* = 7.0 Hz, 2H), 2.40-2.30 (m, 1H), 2.26-2.13 (m, 2H), 1.83-1.73 (m, 1H), 1.70 (s, 3H), 1.60 (d, *J* = 1.3 Hz, 3H), 1.54 (d, *J* = 1.3 Hz, 3H), 1.16 (d, *J* = 6.3 Hz, 3H), 1.12-1.02 (m, 1H), 0.91 (t, *J* = 7.9 Hz, 9H), 0.88 (s, 9H), 0.88 (s, 9H), 0.86 (s, 9H), 0.78 (t, *J* = 7.4 Hz, 3H), 0.55 (q, *J* = 7.7 Hz, 6H), 0.07 (s, 2 x 3H), 0.03 (s, 2 x 3H), −0.02 (s, 3H), −0.07 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) *δ* 166.8, 141.5, 138.1, 137.0, 136.1, 134.6, 132.5, 131.3, 130.4, 126.1, 125.5, 124.9, 116.2, 82.7, 78.0, 77.9, 69.4, 57.9, 44.0, 42.2, 28.4, 26.0 (3C), 25.98 (3C), 25.9 (3C), 24.7, 19.9, 18.5, 18.3, 18.2, 17.4, 13.5, 12.6, 11.6, 7.1 (3C), 5.1 (3C), −4.3, −4.5, −4.7, −4.9, −5.11, −5.14; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{51}H_{98}O_6Si_4Na$ 941.6333; Found 941.6332; IR (cm^{-1}) ν 2955, 2944, 2881, 2870, 1709, 1463, 1378, 1252, 1149, 1071, 1007, 906, 836, 776, 670, 632.

(3E,5E,8S,9E,11S,12R,13E,15E,18S)-8-((tert-Butyldimethylsilyl)oxy)-18-((R)-1-((tert-butyldimethylsilyl)oxy)ethyl)-3-(((tert-butyldimethylsilyl)oxy)methyl)-11-ethyl-9,13,15-trimethyl-12-((triethylsilyl)oxy)oxacyclooctadeca-3,5,9,13,15-pentaen-2-one (58). To a stirred degassed solution of olefin **57** (90 mg, 0.10 mmol) in PhMe (22 mL), second generation Grubbs catalyst (12.7 mg, 15 mol%) was added and the resulting mixture was stirred at 40 °C (µw) for 10 min (full conversion, *E*/*Z* = 2/3). The reaction was then heated at 100 °C for 18 h (*E*/*Z* = 2/1). The solvent was removed by evaporation under reduced pressure and the residue was purified by column chromatography (Et_2O/pentane = 1/99) to give macrocycle (*E*)-**58** (52 mg, 60%) and (*Z*)-**58** (26.4 mg, 30%). *Z*-isomer was resubmitted to aforementioned isomerization conditions to give both macrocycles in *E*/*Z* = 2/1; R_f = 0.67 (Et_2O/pentane = 1/49); $[\alpha]_D^{25}$ = +27.2° (*c* 0.35, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.01 (d, *J* = 11.5 Hz, 1H), 6.58-6.41 (m, 1H), 5.79-5.70 (m, 1H), 5.70 (s, 1H), 5.38 (t, *J* = 8.2 Hz, 1H), 5.13 (dt, *J* = 10.5, 1.6 Hz, 1H), 4.73-4.62 (m, 1H), 4.46 (d, *J* = 12.1 Hz, 1H), 4.37 (d, *J* = 12.0 Hz, 1H), 4.17 (br. s, 1H), 4.11-4.01 (m, 1H), 3.76 (d, *J* = 9.4 Hz, 1H), 2.75-2.66 (m, 1H), 2.60-2.45 (m, 2H), 2.35 (ddd, *J* = 13.9, 9.0, 4.4 Hz, 1H), 2.27 (ddd, *J* = 14.6, 9.8, 4.2 Hz, 1H), 1.95-1.84 (m, 1H), 1.73 (d, *J* = 1.4 Hz, 3H), 1.67 (s, 3H), 1.56 (s, 3H), 1.24-1.16 (m, 1H), 1.14 (d, *J* = 6.1 Hz, 3H), 0.94 (t, *J* = 7.9 Hz, 9H), 0.88 (s, 9H), 0.87 (s, 9H), 0.87 (s, 9H), 0.81 (t, *J* = 7.4 Hz, 3H), 0.59 (q, *J* = 7.9 Hz, 6H), 0.07 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.02 (s, 3H), 0.00 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) *δ* 167.7, 143.0, 140.9, 136.5, 135.9, 134.5, 132.4, 127.8, 127.5, 124.9, 124.7, 83.8, 77.0, 73.2, 68.1, 57.7, 43.6, 37.3, 27.2, 26.1 (3C), 25.94 (3C), 25.92 (3C), 25.8, 21.0, 18.5, 18.3, 18.1, 17.2, 15.0, 12.7, 10.9, 7.2 (3C), 5.2 (3C), −4.1, −4.7, −4.91, −4.95, −5.1, −5.2; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{49}H_{94}O_6Si_4Na$ 913.6020; Found 913.6015; IR (cm^{-1}) ν 2955, 2943, 2858, 1706, 1645, 1463, 1377, 1252, 1071, 1006, 900, 837, 777, 680, 632.

Isomerization of (Z)-58 to (E)-58. To a solution of (*Z*)-**58** (30 mg, 34 µmol) in degassed PhMe (7.5 mL, microwave sealed tube), second generation Grubbs catalyst (4.33 mg, 15 mol%) was added and the resulting mixture was stirred at 100 °C for 16 h. The solvent was evaporated and ^{1}H NMR showed the formation of desired *E* isomer (*E*:*Z* = ca. 2:1). The residue was purified by column chromatography (Et_2O/pentane = 1/100) to give the desired (*E*)-**58** (13 mg, 43%, very pure ample) and (5.5 mg, 18%, acceptable purity for next reaction), and (*Z*)-**58** (7 mg, 23%, very pure sample) and (2 mg, 7%, acceptable purity). Total yield: 92%.

(3E,5E,8S,9E,11S,12R,13E,15E,18S)-8-((tert-Butyldimethylsilyl)oxy)-18-((R)-1-((tert-butyldimethylsilyl)oxy)ethyl)-11-ethyl-12-hydroxy-3-(hydroxymethyl)-9,13,15-trimethyloxacyclooctadeca-3,5,9,13,15-pentaen-2-one (10). To a stirred solution of protected macrocycle (*E*)-**58** (25 mg, 0.03 mmol) in THF/MeCN (1:1, 5 mL) at 0 °C, $3HF{\cdot}NEt_3$ (0.15 mL, 0.84 mmol, excess) was added dropwise and stirring was continued for 8 h at room temperature. The reaction was quenched with sat. $NaHCO_3$ (15 mL) and the resulting aqueous layer was extracted with Et_2O (2 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (Et_2O/pentane = 1/5 to 1/3) afforded diol **10**

(12 mg, 65%) as a colourless oil, and primary alcohol **59** (7 mg, 32%) as a colourless oil; **Diol 10**: R_f = 0.50 (Et_2O/pentane = 2/3); $[\alpha]_D^{25}$ = +17.2° (*c* 0.48, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 6.97 (d, *J* = 11.6 Hz, 1H), 6.34 (ddd, *J* = 14.8, 11.6, 1.5 Hz, 1H), 5.87 (s, 1H), 5.79 (ddd, *J* = 14.7, 10.1, 4.5 Hz, 1H), 5.48-5.37 (m, 1H), 5.13 (dt, *J* = 10.6, 1.6 Hz, 1H), 4.63 (ddd, *J* = 7.5, 5.2, 4.3 Hz, 1H), 4.39 (d, *J* = 12.7 Hz, 1H), 4.32 (d, *J* = 12.6 Hz, 1H), 4.22-4.13 (m, 2H), 3.82 (d, *J* = 9.6 Hz, 1H), 2.83 (dt, *J* = 14.3, 8.2 Hz, 1H), 2.66-2.44 (m, 3H, include 1 x OH), 2.38-2.15 (m, 2H), 1.99-1.90 (m, 1H), 1.80 (d, *J* = 1.3 Hz, 3H), 1.79 (s, 3H), 1.61 (s, 3H), 1.23-1.19 (m, 1H), 1.15 (d, *J* = 6.3 Hz, 3H), 0.88 (s, 9H), 0.86 (s, 9H), 0.84 (t, *J* = 7.2 Hz, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) *δ* 168.7, 142.3, 141.6, 136.5, 136.1, 134.9, 133.1, 127.4, 127.1, 126.6, 124.8, 83.2, 77.6, 73.2, 68.1, 57.6, 42.7, 37.6, 26.4, 25.9 (3C), 25.88 (3C) 25.8, 20.7, 18.4, 18.1, 17.1, 15.1, 12.7, 11.0, −4.3, −4.6, −4.91, −4.93; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{37}H_{66}O_6Si_2Na$ 685.4290; Found 685.4292; IR (cm^{-1}) ν 3424, 2954, 2930, 2857, 1688, 1643, 1462, 1443, 1377, 1297, 1254, 1205, 1146, 1107, 1070, 1007, 973, 938, 900, 837, 775, 676; **Secondary alcohol 59**: R_f = 0.46 (Et_2O/pentane = 1/4); $[\alpha]_D^{25}$ = −5.3° (*c* 0.38, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 6.95 (d, *J* = 11.4 Hz, 1H), 6.69-6.37 (m, 1H), 5.86 (s, 1H), 5.71 (ddd, *J* = 14.8, 10.0, 4.6 Hz, 1H), 5.42 (t, *J* = 8.2 Hz, 1H), 5.12 (dt, *J* = 10.3, 1.4 Hz, 1H), 4.64 (ddd, *J* = 7.4, 5.2, 4.1 Hz, 1H), 4.45 (d, *J* = 11.9 Hz, 1H), 4.35 (d, *J* = 12.0 Hz, 1H), 4.17 (br. s, 1H), 4.15-4.09 (m, 1H), 3.81 (d, *J* = 9.7 Hz, 1H), 2.79 (dt, *J* = 15.8, 8.1 Hz, 1H), 2.59-2.47 (m, 2H), 2.33-2.22 (m, 2H), 1.98-1.90 (m, 1H), 1.80 (d, *J* = 1.3 Hz, 3H), 1.78 (s, 3H), 1.60 (s, 3H), 1.23-1.18 (m, 1H), 1.15 (d, *J* = 6.2 Hz, 3H), 0.88 (s, 18H), 0.86 (s, 9H), 0.84 (t, *J* = 7.1 Hz, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) *δ* 168.0, 142.4, 140.1, 136.5, 135.9, 135.0, 133.2, 128.3, 127.9, 126.8, 124.8, 83.3, 77.0, 73.2, 68.4, 57.7, 42.8, 37.6, 26.7, 26.1 (3C), 26.0 (3C), 25.9 (3C), 25.8, 20.8, 18.5, 18.4, 18.1, 17.1, 15.1, 12.7, 11.0, −4.2, −4.5, −4.9, −5.0, −5.1, −5.2; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{43}H_{80}O_6Si_3Na$ 799.5155; Found 799.5144; IR (cm^{-1}) ν 3500, 2954, 2930, 2857, 1703, 1644, 1463, 1376, 1252, 1203, 1146, 1103, 1072, 1006, 938, 900, 837, 776.

(2S,3S,4R,6R)-6-(((3E,5E,8S,9E,11S,12R,13E,15E,18S)-8-((tert-butyldimethylsilyl)oxy)-18-((R)-1-((tert-butyldimethylsilyl)oxy)ethyl)-11-ethyl-12-hydroxy-9,13,15-trimethyl-2-oxooxacyclooctadeca-3,5,9,13,15-pentaen-3-yl)methoxy)-4-hydroxy-5-methoxy-2-methyltetrahydro-2H-pyran-3-yl 2,4-bis(allyloxy)-3,5-dichloro-6-ethylbenzoate (61). A mixture of primary alcohol **10** (3.2 mg, 4.83 µmol) and acetimidate **27** (3.2 mg, 4.83 µmol, 1.0 equiv) in PhMe (1 mL) was co-evaporated and dried. Next, the residue obtained was dissolved in CH_2Cl_2 (0.4 mL) and MS 4Å was added. The white suspension was stirred for 0.5 h at room temperature before it was cooled to –78 °C. To this mixture was added TBSOTf (a 50 µL CH_2Cl_2 stock solution, 0.48 µmol, 10 mol%) dropwise and the reaction mixture was stirred at –78 °C for 2 h before it was warmed to –50 °C and stirred for 1h. No conversion was observed. Additional amount of TBSOTf (a 50 µL CH_2Cl_2 stock solution, 0.48 µmol, 10 mol%) was added dropwise and the reaction mixture was slowly warmed to –20 °C. The reaction was quenched with diluted Et_3N in CH_2Cl_2 (2 mL), filtered and evaporated. ^{1}H NMR showed anomeric ratio to be β:α = 3/1. Purification by column chromatography (PhMe/AcOEt = 12/1) provided desired glycoside as a mixture with impurities. The obtained residue was further purified by preparative thin layer chromatography (PhMe/AcOEt = 8/1) to provide desired rather pure β-rhamnoside **61** (0.9 mg, 16%).

Although the relatively good site selectivity observed, the separation between diol **10** and desired β-**61** was difficult on the silica gel column chromatography. As we obtained bis-glycosylated side product (confirmed by HRMS and NMRs, not shown) with the extra equivalence of glycosyl donor **27**, exactly 1.0 eq of **27** had to be used. Although the desired β-**61** could also be synthesized under the similar condition using glycosyl sulfoxide prepared from **26**, however, the reproducibility and product yield was similarly low and the product was always contaminated with unknown aromatic side products: Conditions: glycosyl sulfoxide (4.0 equiv), Tf_2O (2.5 equiv), 2,6-di-*tert*-butyl-4-methylpyridine (5.0 equiv), Et_2O, MS 4Å, –90 to –80 °C, 2 h; primary alcohol **10**, –90 to –80 °C, 2.5 h, β:α = 2/1, β-**61**: 10-20%; R_f = β-**61**: 0.55, α-**61**: 0.4 (AcOEt/cyclohexane = 1:4); ^{1}H NMR (500 MHz, acetone-d_6) δ 7.17 (d, *J* = 11.5 Hz, 1H), 6.58 (dd, *J* = 14.4, 12.2 Hz, 1H), 6.17 (ddt, *J* = 17.7, 11.8, 6.4 Hz, 1H), 6.08 (ddd, *J* = 16.3, 11.2, 5.3 Hz, 1H), 5.92 (ddd, *J* = 15.0, 10.2, 4.4 Hz, 1H), 5.46 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.46 (s, 1H), 5.41 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.28 (d, *J* = 10.4 Hz, 1H), 5.25 (d, *J* = 10.4 Hz, 1H), 5.20 (d, *J* = 10.6 Hz, 1H), 5.03 (t, *J* = 9.7 Hz, 1H), 4.62 (m, 6H), 4.57 (d, *J* = 11.1 Hz, 1H), 4.52 (dd, *J* = 11.8, 5.8 Hz, 1H), 4.35 (d, *J* = 11.1 Hz, 1H), 4.34 (s, 1H), 4.29 – 4.20 (m, 1H), 3.91 (d, *J* = 10.0 Hz, 1H), 3.74 (s, 1H), 3.73 – 3.66 (m, 2H), 3.55 (d, *J* = 3.4 Hz, 1fH), 3.52 (s, 3H), 3.51 – 3.45 (m, 1H), 2.70 (d, *J* = 14.7 Hz, 1H), 2.52 (d, *J* = 8.7 Hz, 1H), 2.38 (ddd, *J* = 14.7, 10.4, 4.4 Hz, 1H), 2.30 (dd, *J* = 14.0, 7.7 Hz, 1H), 1.84 (s, 3H), 1.83 (s, 3H), 1.68 (s, 3H), 1.34 (d, *J* = 6.2 Hz, 3H), 1.17 (s, 3H), 1.16 – 1.15 (m, 7H), 0.91 (d, *J* = 2.7 Hz, 9H), 0.88 (s, 9H), 0.86 – 0.82 (m, 3H), 0.08 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H), 0.03 (s, 3H); HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{59}H_{92}Cl_2O_{13}Si_2Na$ 1157.53512; Found 1157.5343. Optical rotation, IR and ^{13}C NMR were not recorded.

(3aS,4R,7S,7aS)-4-(((1E,3R,4S,5E,7S)-7-((tert-Butyldimethylsilyl)oxy)-4-ethyl-1-iodo-2,6-dimethyldeca-1,5,9-trien-3-yl)oxy)-6,6-dimethyl-2-oxotetrahydro-4H-[1,3]dioxolo[4,5-c]pyran-7-yl isobutyrate (62). To a solution of pyranose **34** (40 mg, 0.14 mmol, 1.6 equiv) in CH_2Cl_2 (1.0 mL) under dark was added 33% HBr in AcOH (1.0 mL) at 0 °C and the resulting colorless, slightly orange solution was stirred at room temperature under dark for 2 h before it was cooled to 0 °C, diluted with CH_2Cl_2 (3 mL) and quenched with ice water (5 mL). Layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 mL) and combined organic layers were washed with sat. $NaHCO_3$ (10 mL). The separated organic layer was dried over Na_2SO_4, filtered and concentrated in cold water bath to provide desired glycosyl bromide **35** as a brown oil. Additional amount of pyranose **34** (30 mg, 0.11 mmol, 1.2 equiv) was subjected to the same condition to prepare additional amount of glycosyl bromide **35** and combined, and used in the next glycosylation (total 2.8 eq glycosyl bromide was used as a starting material. The glycosyl bromide **35** was isolated as a mixture with glycosyl acetate).

A solution of alcohol **43** (41 mg, 86.7 µmol) in PhH (1.5 mL) was concentrated and dried before use. Next, this was dissolved in CH_2Cl_2 (1.0 mL) and MS 3A (powder, 100 mg) was added and stirred for 90 minutes, before HgO (124 mg, 0.56 mmol, 6.5 equiv) and $HgBr_2$ (4.5 mg, 13 µmol, 0.15 equiv) were added and the orange suspension was stirred for 30 minutes. Then the glycosyl bromide in CH_2Cl_2 (0.5 mL) was added dropwise for 20 min and stirred for 50 min. Then it was diluted with $CHCl_3$ (5 mL) and quenched with $NaHCO_3$ (3 mL). Organic layer was separated and filtered over silica gel pad. The filtrate was washed with $NaHCO_3$ (15 mL), organic layer dried over Na_2SO_4, filtered and concentrated under reduced pressure. ^{1}H NMR showed anomeric ratio to be β:α = 3:1. Purification by column chromatography (AcOEt/cyclohexane = 1/15 - 1/10 - 1/8) gave alcohol starting material **43**, α-**62** and pure β-**62** (33.6 mg, 54%); β-**62**: R_f = 0.38 (AcOEt/cyclohexane = 1/4); $[\alpha]_D^{25}$ = –23.1° (*c* 0.22, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22 (d, *J* = 0.9 Hz, 1H), 5.79 (ap dd, 1H) 5.75-5.62 (m, 1H), 5.03-4.97 (m, 3H), 4.86 (d, *J* = 10.5 Hz, 1H), 4.79-4.76 (m, 2H), 3.94 (dd, *J* = 6.1, 6.1 Hz, 1H), 3.82 (d, *J* = 9.3 Hz, 1H), 2.62 (hept, *J* = 7.0 Hz, 1H), 2.58-2.48 (m, 1H), 2.27-2.14 (m, 2H), 1.92-1.78 (m, 1H), 1.78 (d, *J* = 0.9, 3H), 1.57 (d, *J* = 1.2, 3H), 1.21 (d, *J* = 6.9, 6H), 1.16 (s, 3H), 1.14 (s, 3H), 0.87 (s, 9H) 0.81 (t, *J* = 7.4, 3H), 0.01 (s, 3H), −0.03 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.2, 153.8, 147.6, 140.0, 135.6, 123.6, 116.5, 95.3, 89.8, 81.6, 75.7, 75.1, 72.1, 71.8, 42.6, 42.0, 34.1, 28.0, 26.0 (3C), 25.6, 28.8, 24.3, 19.8, 19.1, 18.8, 18.3, 12.8, 11.2, −4.2, −4.7; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{32}H_{53}IO_8SiNa$ 743.2447; Found 743.2445; IR (cm^{-1}) ν 2954, 2929, 2856, 1818, 1749, 1468, 1389, 1253, 1145, 1091, 1074, 1034, 915,

837, 775; α-**62**: R_f = 0.56 (AcOEt/cyclohexane = 1/4); $[\alpha]_D^{25}$ = +31.6° (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.23 (d, *J* = 1.0 Hz, 1H), 5.70 (dddd, *J* = 17.2, 10.2, 7.1, 7.1 Hz, 1H), 5.13 (d, *J* = 8.3 Hz, 1H), 5.04-4.98 (m, 2H), 4.90 (ap d, *J* = 10.5 Hz, 1H), 4.78 (dd, *J* = 8.3, 8.3 Hz, 1H), 4.78 (d, *J* = 5.2 Hz, 1H), 4.66 (dd, *J* = 8.4, 5.2 Hz, 1H), 4.06 (d, *J* = 9.2 Hz, 1H), 3.95 (dd, *J* = 6.1, 6.1 Hz, 1H), 2.63 (hept, *J* = 7.0 Hz, 1H), 2.53-2.45 (m, 1H), 2.27-2.15 (m, 2H), 1.85-1.76 (m, 1H), 1.67 (d, *J* = 1.1 Hz, 3H), 1.57 (d, *J* = 1.3 Hz, 3H), 1.25 (s, 3H), 1.24 (s, 3H), 1.21 (d, *J* = 1.3 Hz, 3H), 1.20 (d, *J* = 1.3 Hz, 3H), 1.18-1.10 (m, 1H), 0.88 (s, 9H), 0.80 (t, *J* = 7.4 Hz, 3H), 0.01 (s, 3H), –0.02 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.5, 153.2, 145.4, 139.8, 135.5, 123.7, 116.4, 91.8, 83.9, 82.3, 77.5, 76.6, 75.6, 74.8, 72.0, 41.9, 41.5, 33.9, 25.9 (3C), 25.8, 25.0, 23.8, 18.9, 18.7, 18.7, 18.2, 12.5, 10.9, –4.28, –4.85; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{32}H_{53}IO_8SiNa$ 743.2447; Found 743.2451; IR (cm^{-1}) ν 2954, 2931, 2858, 1831, 1748, 1468, 1389, 1253, 1138, 1080, 1037, 914, 837, 777.

(5R,6S,8E,10E,12R,13S,14E,16S)-16-allyl-13-ethyl-12-(((3aS,4R,7S,7aS)-7-(isobutyryloxy)-6,6-dimethyl-2-oxotetrahydro-4H-[1,3]dioxolo[4,5-c]pyran-4-yl)oxy)-2,2,3,3,5,9,11,15,18,18,19,19-dodecamethyl-4,17-dioxa-3,18-disilaicosa-8,10,14-trien-6-yl (E)-2-(((tert-butyldimethylsilyl)oxy)methyl)penta-2,4-dienoate (63). To a solution of iodide **62** (16.5 mg, 23 μmol) and boronate **55** (22.5 mg, 34 μmol, 1.7 equiv) in degassed THF (600 μL) and degassed H_2O (150 μL) at 0 °C, $Pd(PPh_3)_4$ (5.4 mg, 20 mol%) was added and stirred for 5 min. Then the stock solution of TlOEt* (45 μL, ca. 4.5 mg, 18 μmol, 1.6 equiv) was added dropwise for 2 min at room temperature. After stirring for 30 min at the same temperature, the reaction mixture was diluted with Et_2O (5 mL) and quenched with brine (5 mL) and aqueous sat. NH_4Cl (5 mL). The aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (Et_2O/pentane = 1/6 to 1/4) gave polyene **63** (20 mg, 82%) as a colorless oil. *A water stock solution of TlOEt was prepared as follows: To a vial under Ar, TlOEt (12.0 mg) and degassed H_2O (120 μL) were added and stirred until all the residue completely dissolved. Later it was found that the dropwise addition of TlOEt into the reaction mixture over 10-15 min at room temperature gives the better yield using different substrate; R_f = 0.43 (AcOEt/cyclohexane = 1/4); $[\alpha]_D^{25}$ = –48.5° (*c* 0.57, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (d, *J* = 11.4 Hz, 1H), 6.92 (ddd, *J* = 16.9, 11.4, 9.9 Hz, 1H), 5.85-5.79 (m, 1H), 5.74 (s, 1H), 5.69 (ddt, *J* = 17.2, 10.1, 7.2 Hz, 1H), 5.56 (dd, *J* = 16.8, 1.0 Hz, 1H), 5.50 (dd, *J* = 10.1, 1.7 Hz, 1H), 5.32 (t, *J* = 7.3 Hz, 1H), 5.03 (d, *J* = 1.7 Hz, 1H), 4.97 (dd, *J* = 17.2, 2.2 Hz, 1H), 4.93-4.92 (m, 1H), 4.92 (dd, *J* = 19.2, 2.2 Hz, 1H), 4.89-4.81 (m, 1H), 4.76 (d, *J* = 1.2 Hz, 1H), 4.75 (d, *J* = 1.9 Hz, 1H), 4.51 (d, *J* = 12.2 Hz, 1H), 4.47 (d, *J* = 12.2 Hz, 1H), 3.98-3.90 (m, 2H), 3.66 (d, *J* = 8.9 Hz, 1H), 2.65-2.56 (m, 1H), 2.56-2.37 (m, 3H), 2.18 (t, *J* = 6.9 Hz, 2H), 1.86-1.77 (m, 1H), 1.74 (d, *J* = 1.3 Hz, 3H), 1.71 (d, *J* = 1.2 Hz, 3H), 1.62-1.56 (m, 1H), 1.56 (d, *J* = 1.3 Hz, 3H), 1.21 (s, 3H), 1.20 (s, 3H), 1.16 (s, 3H), 1.15 (d, *J* = 5.0 Hz, 3H), 1.12 (s, 3H), 0.88 (s, 9H), 0.88 (s, 9H), 0.85 (s, 9H), 0.80 (t, *J* = 7.4 Hz, 3H), 0.07 (s, 3H), 0.07 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H), –0.03 (s, 3H), –0.09 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.2, 166.8, 153.9, 141.5, 138.8, 135.8, 134.3, 133.8, 133.6, 132.5, 131.3, 126.5, 125.7, 124.8, 116.3, 94.1, 92.1, 78.1, 77.7, 75.8, 74.9, 72.3, 72.0, 69.5, 57.9, 42.3, 42.0, 34.1, 28.4, 28.2, 26.1 (3C), 26.0 (3C), 25.9 (3C), 24.7, 24.3, 20.0, 19.1, 18.8, 18.5, 18.3, 18.1, 17.2, 13.8, 12.7, 11.3, –4.3, –4.5, –4.7, –4.9, –5.10, –5.12; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{57}H_{100}O_{12}Si_3Na$ 1083.6415; Found 1083.6417; IR (cm^{-1}) ν 2954, 2929, 2856, 1818, 1747, 1468, 1254, 1146, 1091, 1035, 837, 777, 668.

(3aS,4R,7S,7aS)-4-(((2S,4E,6E,8R,9S,10E,12S,14E,16E)-12-((tert-butyldimethylsilyl)oxy)-2-((R)-1-((tert-butyldimethylsilyl)oxy)ethyl)-17-(((tert-butyldimethylsilyl)oxy)methyl)-9-ethyl-5,7,11-trimethyl-18-oxooxacyclooctadeca-4,6,10,14,16-pentaen-8-yl)oxy)-6,6-dimethyl-2-oxotetrahydro-4H-[1,3]dioxolo[4,5-c]pyran-7-yl isobutyrate (64). To an alkene **63** (11.7 mg, 11 μmol) in PhMe (2.0 mL), second generation Grubbs catalyst (1.05 mg, 2.2 μmol, 20 mol%) was added and the resulting mixture was stirred at 100 °C in a preheated oil bath for 3 h. The reaction mixture was filtered through Celite or a pad of silica gel and resulting filtrate was concentrated. Crude ^{1}H NMR showed *E*/*Z* = ca. 2/1. Purification by short silica gel column chromatography (Et_2O/pentane = 1/4) followed by preparative TLC (Et_2O/pentane = 1/4, ca. 5 mg sample was loaded on 0.5 mm, 20 cm x 20 cm preparative TLC plate from Merck and 4 times elevation was needed for a good separation) gave desired (*E*)-macrocycle **64** (7.8 mg, 68%) and (*Z*)-macrocycle **64** as a mixture; (*E*)-**64**: R_f = 0.20 (Et_2O/pentane = 1/4); $[\alpha]_D^{25}$ = –42.5° (*c* 0.41, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.97 (d, *J* = 11.5 Hz, 1H), 6.48 (ddd, *J* = 14.8, 11.4, 1.4 Hz, 1H), 5.85-5.80 (m, 2H), 5.71 (ddd, *J* = 14.8, 10.0, 4.5 Hz, 1H), 5.44 (t, *J* = 8.3 Hz, 1H), 5.11 – 5.03 (m, 2H), 4.80-4.74 (m, 2H), 4.68-4.62 (m, 1H), 4.45 (d, *J* = 12.0 Hz, 1H), 4.35 (d, *J* = 12.0 Hz, 1H), 4.16 (br, 1H), 4.10 (p, *J* = 6.1 Hz, 1H), 3.67 (d, *J* = 9.8 Hz, 1H), 2.82-2.72 (m, 1H), 2.69-2.62 (m, 1H), 2.66-2.58 (m, 1H), 2.55 (dt, *J* = 15.0, 2.4 Hz, 1H), 2.32-2.22 (m, 2H), 1.89 (dt, *J* = 7.4, 4.5 Hz, 1H), 1.83 (s, 3H), 1.76 (s, 3H), 1.60 (m, 1H), 1.59 (s, 3H), 1.22-1.20 (m, 9H), 1.14 (d, *J* = 6.2 Hz, 3H), 1.13 (s, 3H), 0.88 (s, 18H), 0.85 (s, 9H), 0.82 (t, *J* = 7.4 Hz, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H), 0.02 (s, 3H), –0.02 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.3, 167.9, 154.0, 142.6, 140.4, 135.8, 135.4, 133.1, 128.2, 127.8, 126.9, 125.7, 124.0, 93.6, 93.1, 77.1, 75.7, 75.0, 73.2, 72.4, 72.1, 68.4, 57.6, 42.0, 37.5, 34.1, 28.4, 26.9, 26.1 (3C), 26.0 (3C), 25.9 (3C), 25.4, 24.2, 20.8, 19.1, 18.8, 18.5, 18.3, 18.1, 17.0, 15.1, 13.4, 10.9, –4.1, –4.5, –4.9, –5.0, –5.1, –5.2; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{55}H_{96}O_{12}Si_3Na$ 1055.6102; Found 1055.6104; IR (cm-1) ν 2930, 2857, 1820, 1751, 1703, 1645, 1465, 1252, 1145, 1072, 1004, 838, 776.

Isomerization of (Z)-64 to (E)-64. To a degassed solution of (*Z*)-**64** (7.9 mg, 7.5 μmol) in PhMe (1.5 mL), second generation Grubbs catalyst (1.3 mg, 1.5 μmol, 20 mol%) was added using Schlenk technique and the resulting mixture was heated to 100 °C in a pre-heated oil bath for 11 h. After cooling to room temperature, the reaction mixture was diluted with Et_2O (3.0 mL) and H_2O (3.0 mL). The organic layer was separated and the resulting aqueous layer was extracted by Et_2O (2 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. ^{1}H NMR analysis revealed the desired product formation as a 2:1 (*E*/*Z*) mixture at C4-C5 olefin. Purification by preparative TLC (Et_2O/pentane = 1/4, 3 times elevation) gave desired (*E*)-**64** (3.5 mg, 44%) as a colorless oil.

(3aS,4R,7S,7aS)-4-(((2S,4E,6E,8R,9S,10E,12S,14E,16E)-12-((tert-butyldimethylsilyl)oxy)-2-((R)-1-((tert-butyldimethylsilyl)oxy)ethyl)-9-ethyl-17-(hydroxymethyl)-5,7,11-trimethyl-18-oxooxacyclooctadeca-4,6,10,14,16-pentaen-8-yl)oxy)-6,6-dimethyl-2-oxotetrahydro-4H-[1,3]dioxolo[4,5-c]pyran-7-yl isobutyrate (64a). To a solution of macrolide **64** (8.0 mg, 8 μmol) in THF/MeCN 1:1 (1.0 mL) at 0 °C, $3HF{\cdot}NEt_3$ (50 μL, 0.31 mmol, excess) was added dropwise. The reaction mixture was stirred at room temperature for 8 h, then it was quenched with aqueous sat. $NaHCO_3$ (5 mL), extracted with CH_2Cl_2 (3 x 2 mL), dried over $MgSO_4$, filtered and concentrated. Purification by preparative TLC (AcOEt/cyclohexane = 1/4) afforded the alcohol **64a** (3.5 mg, 49%) as a colorless oil and recovered starting material **64** (2.5 mg, 40%) which was subjected to the same reaction conditions to obtain **64a**. As is mentioned above, the TBS deprotection had to be stopped before reaching full conversion due to the competing TBS cleavage at C18 position; The alcohol was used in the next steps without characterization. R_f = 0.24 (AcOEt/cyclohexane = 1/4).

(2R,4S,5R)-6-(((3E,5E,8S,9E,11S,12R,13E,15E,18S)-8-((tert-butyldimethylsilyl)oxy)-18-((R)-1-((tert-butyldimethylsilyl)oxy)ethyl)-11-ethyl-12-(((4R,7S,7aR)-7-(isobutyryloxy)-6,6-dimethyl-2-oxotetrahydro-4H-[1,3]dioxolo[4,5-c]pyran-4-yl)oxy)-9,13,15-trimethyl-2-oxooxacyclooctadeca-3,5,9,13,15-pentaen-3-yl)methoxy)-4-hydroxy-5-methoxy-2-

methyltetrahydro-2H-pyran-3-yl 2,4-bis(allyloxy)-3,5-dichloro-6-ethylbenzoate (Fully protected fidaxomicin, 7). To a solution of alcohol **64a** (2.8 mg, 4 µmol) and acetimidate **27** (3.0 mg, 3 µmol, 1.15 equiv) in CH_2Cl_2 (0.3 mL) molecular sieves 4Å (30 mg) was added and the white suspension was stirred for 30 min. Then, it was cooled to –78 °C and TBSOTf (0.15 µL, 20 mol%) in CH_2Cl_2 (50 µL) was added dropwise. The reaction mixture was then warmed to –50 °C and subsequently warmed to –30 °C within 1 h. The reaction mixture was diluted with CH_2Cl_2 (1 mL), quenched with a drop of Et_3N, filtered through cotton and concentrated. The anomeric ratio was determined to be α:β = 1:4 by ^{1}H NMR of this crude mixture. Purification by preparative TLC (AcOEt/cyclohexane = 1/4) afforded the desired β-rhamnoside **7** (β-**7**: 3.3 mg, 62%) as a mixture with a tiny amount of inseparable impurity; β-**7**: R_f = 0.32 (AcOEt/cyclohexane = 1/4); ^{1}H NMR (400 MHz, acetone-d_6,) δ 7.19 (d, *J* = 11.5 Hz, 1H), 6.64-6.56 (m, 1H), 6.23-6.05 (m, 2H), 5.95 (s, 1H), 5.92 (ddd, *J* = 14.8, 10.3, 4.5 Hz 1H), 5.77 (d, *J* = 7.0 Hz, 1H), 5.55 (dd, *J* = 8.3, 8.3 Hz, 1H), 5.49-5.37 (m, 2H), 5.31-5.23 (m, 2H), 5.19 (d, *J* = 3.2 Hz, 1H), 5.17 (ap d, *J* = 11.0 Hz 1H), 5.12-5.05 (m, 2H), 5.03 (dd, *J* = 9.6, 9.6 Hz, 1H), 4.67-4.56 (m, 4H), 4.64 (s, 1H), 4.52 (dddd, *J* = 11.7, 5.9, 1.4, 1.4 Hz, 1H), 4.35 (d, *J* = 10.8 Hz, 1H), 4.36-4.34 (m, 1H), 4.27-4.20 (m, 1H), 3.90 (d, *J* = 10.1 Hz, 1H), 3.76 (d, *J* = 9.8 Hz, 1H), 3.69 (ddd, *J* = 9.7, 9.7, 3.3, Hz, 1H), 3.55 (d, *J* = 3.5 Hz, 1H), 3.54-3.47 (m, 1H) 3.52 (s, 3H), 2.92-2.76 (m, 3H), 2.75-2.63 (m, 3H), 2.40 (ddd, *J* = 14.8, 10.3, 4.5 Hz, 1H), 2.32 (ddd, *J* = 13.8, 7.6, 4.1 Hz, 1H), 2.02-1.94 (m, 1H), 1.91 (ap s, 3H), 1.87 (ap s, 3H), 1.71 (ap s, 3H), 1.34 (d, *J* = 6.2 Hz, 3H), 1.22-1.14 (m, 19H), 0.91 (s, 9H), 0.88 (s, 9H), 0.85 (t, *J* = 7.4 Hz, 3H), 0.09 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H), 0.04 (s, 3H); HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{71}H_{108}Cl_2O_{19}Si_2Na$ 1413.6293; Found 1413.6276. HRMS (ESI-TOF) m/z: $[M + NH_4]^+$ Calcd for $C_{71}H_{112}Cl_2O_{19}Si_2N$ 1408.6739; Found 1408.6725. (See supporting information for the comparison of ^{1}H NMR experiments between semisynthetic and totally synthetic sample.)

Carbonate and allyl protected fidaxomicin (7b). To a solution of the totally synthetic macrolide **7** (3.0 mg, 2.15 µmol) in THF (0.5 mL), $3HF{\cdot}NEt_3$ (50 µL, excess) was added dropwise. The solution was stirred for 48 h at 50 °C before it was quenched by the addition of sat. $NaHCO_3$ (3 mL, Caution! Gas evolution). The aqueous layer was extracted with AcOEt (4 x 2 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated. Purification by preparative TLC (acetone/pentane = 2/3) yielded the alcohol **7b** (21.5 mg, 60%). Analytical data matched those reported above. ^{1}H NMR (400 MHz, acetone-d_6) δ 7.19 (d, *J* = 11.4 Hz, 1H), 6.62 (dd, *J* = 15.1, 11.4 Hz, 1H), 6.22 – 6.11 (m, 1H), 6.13 – 6.03 (m, 1H), 6.01 – 5.90 (m, 1H), 5.93 (s, 1H), 5.74 (d, *J* = 6.9 Hz, 1H), 5.61 (t, *J* = 8.2 Hz, 1H), 5.46 (dq, *J* = 16.9, 1.5 Hz, 1H), 5.45 – 5.36 (m, 1H), 5.33 – 5.25 (m, 1H), 5.29 – 5.21 (m, 1H), 5.18 (dt, *J* = 10.3, 1.5 Hz, 1H), 5.18 (d, *J* = 3.1 Hz, 1H), 5.11 (dd, *J* = 8.7, 3.2 Hz, 1H), 5.05 (dd, *J* = 9.2, 6.4 Hz, 1H), 5.03 (t, *J* = 9.7 Hz, 1H), 4.74 – 4.66 (m, 1H), 4.65 (s, 1H), 4.63 – 4.58 (m, 3H), 4.59 (m, 1H), 4.57 – 4.47 (m, 1H), 4.39 (d, *J* = 11.4 Hz, 1H), 4.26 (s, 1H), 4.08 – 3.98 (m, 2H), 3.83 – 3.76 (m, 2H), 3.75 – 3.65 (m, 1H), 3.61 – 3.55 (m, 1H), 3.52 (s, 3H), 3.54 – 3.49 (m, 1H), 2.87 (dd, *J* = 13.5, 7.5 Hz, 3H), 2.75 (t, *J* = 8.2 Hz, 3H), 2.72 – 2.64 (m, 2H), 2.50 (ddd, *J* = 14.8, 9.5, 4.4 Hz, 1H), 2.40 (ddd, *J* = 13.7, 8.3, 4.3 Hz, 1H), 1.89 (d, *J* = 1.3 Hz, 3H), 1.79 (d, *J* = 1.4 Hz, 3H), 1.68 (s, 3H), 1.33 (d, *J* = 6.2 Hz, 3H), 1.23 – 1.13 (m, 16H), 0.82 (t, *J* = 7.4 Hz, 3H); HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{59}H_{80}Cl_2O_{19}Na$ 1185.4563; found: 1185.4570.

Fidaxomicin (1). To a solution of the totally synthetic carbonate **7b** (0.9 mg, 0.8 µmol) in CH_2Cl_2 (0.2 mL), a drop of Barton's base (ca. mg) and a drop of H_2O (ca. 13 mg) were added. The mixture was stirred vigorously for 1.5 h before it was diluted with AcOEt (2.0 mL) and quenched with sat. NH_4Cl (2 mL). The layers were separated and the aqueous layer was extracted with AcOEt (3 x 2 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated. Purification by preparative TLC (MeOH/PhMe = 1/5) gave the allylether **7a** (0.4 mg) with minor impurities; To a solution of the fully protected fidaxomicin **7a** (crude, 0.4 mg) in THF (0.2 mL) at 0 °C, morpholine (0.3 µL, 3.6 mmol) in CH_2Cl_2 (10 µL) and $Pd(PPh_3)_4$ (0.14 mg, 10 mol%) were added and the reaction mixture was stirred at this temperature for 20 minutes. The reaction was quenched with sat. NH_4Cl (2 mL), extracted with AcOEt (4 x 2 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Purification by preparative TLC (MeOH/CH_2Cl_2 = 1/10) yielded *totally synthetic* fidaxomicin (0.4 mg) as a colourless oil with minor impurities. The compound was further purified by RP-HPLC (A: H_2O+0.1% HCOOH; Solvent B: MeCN+0.1% HCOOH; 1 mL/min; T = 20°C; B[%] (t_R [min])= 50 (0 to 3); 65 (15); 100 (16)). The impure fidaxomicin was dissolved in MeCN (0.15 mL) and separated in portions (3 x 50 µL). Fidaxomicin (**1**) eluted at t_R = 12.3 minutes and the solvents were evaporated under a constant stream of nitrogen yielding fidaxomicin contaminated with formate (ca. 0.1 mg 10% over 2 steps, calculated from a UV-standard curve of an authentic sample of fidaxomicin by linear regression analysis); ^{1}H NMR (600 MHz equipped with cryoplatform, CD_3OD, containing $HCOO^-$ from final RP-HPLC purification) *δ* 8.55 (s, $HCOO^-$), 7.23 (d, *J* = 11.5 Hz, 1H), 6.60 (dd, *J* = 14.9, 11.8 Hz, 1H), 5.95 (ddd, *J* = 14.7, 9.5, 4.8 Hz, 1H), 5.83 (s, 1H), 5.57 (ap t, *J* = 8.2 Hz, 1H), 5.14 (ap d, *J* = 10.7, 1H), 5.13 (dd, *J* = 9.7 Hz, 1H), 5.02 (d, *J* = 10.2 Hz, 1H), 4.74–4.70 (m, 1H), 4.71 (s, 1H), 4.64 (s, 1H), 4.61 (d, *J* = 11.6 Hz, 1H), 4.44 (d, *J* = 11.6 Hz, 1H), 4.22 (ap s, 1H), 4.02 (p, *J* = 6.3 Hz, 1H), 3.92 (dd, *J* = 3.2, 1.2 Hz, 1H), 3.75 (ddd, *J* = 13.9, 10.2, 3.3 Hz, 1H) 3.71 (d, *J* = 9.7 Hz 1H), 3.58–3.52 (m, 2H) 3.54 (s, 3H), 3.15–3.06 (m, 1H), 3.04–2.95 (m, 1H), 2.76–2.66 (m, 3H), 2.60 (hept, *J* = 7.0 Hz, 1H), 2.49 (ddd, *J* = 14.9, 9.5, 4.4 Hz, 1H), 2.43 (ddd, *J* = 13.8, 8.8, 4.5 Hz, 1H), 2.05–1.98 (m, 1H), 1.82 (d, *J* = 1.3 Hz, 3H), 1.76 (ap s, 3H), 1.66 (ap s, 3H), 1.32–1.27 (m, 4H), 1.22–1.15 (m, 12H), 1.15 (s, 3H), 1.13 (s, 3H), 0.88 (t, *J* = 7.4 Hz, 3H); HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{52}H_{74}Cl_2O_{18}Na$ 1079.4144; found: 1079.4151. (The observed overall yield (10%) for these transformations can be explained by difficulties in the purification of the final synthetic product on a small scale (compare with semisynthetic approach). This low value is also partially explained by the impurity of **7** contaminated after the rhamnosylation reaction, which was difficult to remove by simple column chromatographic purification. Although the purity of semisynthetic sample **7** is much higher than that of fully synthetic **7**, we concluded synthetic **7** is pure enough for further transformations. The contaminant of **7** was successfully removed after RP-HPLC at the end of synthesis. The identity of the synthetic compound was confirmed by co-injection of synthetic and authentic material on RP-HPLC and ^{1}H NMR analysis. The retention time of both compounds was identical for both compounds and co-injection showed only single peak. However, the ^{1}H NMR spectrum of synthetic **1** did not match completely to those of natural **1** (at most 0.2 ppm difference observed, especially around the resorcylate segment (ethyl group) and rhamnose segment (C4´ hydrogen atom and C6´ hydrogen atoms)) probably due to the formate salt formation (see pKa experiment). Therefore, identity of the compounds was confirmed in ^{1}H NMR by mixing equimolar amounts of synthetic **1** and natural **1**, the ^{1}H NMR spectrum clearly showed a single set of peaks. See supporting information for the detailed comparison in ^{1}H NMR experiments between natural **1** and totally synthetic **1**.)

Total Synthesis of Tiacumicin A (2)

(3aS,4S,7S,7aS)-4-methoxy-6,6-dimethyl-2-oxotetrahydro-4H-[1,3]dioxolo[4,5-c]pyran-7-yl acetate (α-33b) and (3aS,4R,7S,7aS)-4-methoxy-6,6-dimethyl-2-oxotetrahydro-4H-[1,3]dioxolo[4,5-c]pyran-7-yl acetate (β-33b). To a solution of triol **33** (200 mg, 1.04 mmol) in THF (30 mL) at 50 °C was added 1,1-carbodiimidazol (590 mg, 3.64 mmol, 3.5 equiv, addition of ca. 100 mg every 30 min) was added portion wise over 3.5 h. Then 6N HCl (3.0 mL) was added and stirred for 2 h at room temperature, during which time UV active side product at low R_f value (checked by TLC: AcOEt/cyclohexane 1/1) have disappeared and two non-UV active desired products at

high R_f left. Then it was extracted with AcOEt three times, washed with brine, dried over Na_2SO_4, filtered and concentrated. The obtained carbonate **33a** was used in the next reaction without further purification.

To a solution of carbonate **33a** (crude, 1.04 mmol) in CH_2Cl_2 (5 mL) at room temperature was added Ac_2O (2 mL, 20 equiv) and pyridine (2 mL, 25 equiv) and stirred at room temperature for 5 h. The reaction was quenched with water (40 mL), extracted with CH_2Cl_2 (3 x 10mL). The combined organic layers were added 1N HCl (50 mL) and the resulting aqueous phase was extracted again (50 mL, 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. Purification by silica gel column chromatography (AcOEt/cyclohexane = 1/5 - 1/4 - 1/3 - 1/2) gave desired α and β glycoside **33b** as a separable isomer (total 190 mg, 70% over 2 steps); **β-33b**: R_f = 0.45 (AcOEt/PhMe = 1/3); IR (cm^{-1}) ν 2983, 1806, 1745, 1223, 1171, 1042; $[\alpha]_D^{26}$ = –91.6° (*c* 1.10, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.81 – 5.72 (m, 1H), 4.83 (d, *J* = 1.9 Hz, 1H), 4.81 – 4.75 (m, 2H), 3.52 (s, 3H), 2.14 (s, 3H), 1.28 (s, 3H), 1.20 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 153.9, 95.8, 75.7, 75.0, 72.6, 71.9, 56.2, 28.9, 24.2, 21.0; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for Calcd for $C_{11}H_{16}O_7Na$ 283.07882; Found 283.0793; **α-33b**: R_f = 0.6 (AcOEt/PhMe = 1/3); $[\alpha]_D^{26}$ = +21.6° (*c* 0.82, $CHCl_3$); IR (cm^{-1}) ν 2987, 1827, 1809, 1748, 1223, 1082, 1035; ^1H NMR (400 MHz, $CDCl_3$) δ 5.11 (d, *J* = 7.7 Hz, 1H), 4.91 (d, *J* = 3.0 Hz, 1H), 4.78 (t, *J* = 7.7 Hz, 1H), 4.68 (dd, *J* = 7.8, 3.0 Hz, 1H), 3.46 (s, 3H), 2.13 (s, 3H), 1.28 (d, *J* = 2.6 Hz, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 169.6, 153.2, 97.3, 76.7, 75.4, 74.7, 72.4, 56.1, 26.7, 23.1, 20.9; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{11}H_{16}O_7Na$ 283.0788; Found 283.0790.

(R)-hept-5-yn-3-ol (65a). To a stirred solution of propyne (ca. 3% in heptane 63 mL, 31.9 mmol, 3.5 equiv) in 120 mL of THF at –78 °C was added *n*-BuLi (1.6 M, 11.5 mL, 18.2 mmol, 2.0 equiv) and stirred at –78 °C. The reaction mixture was heated up to –30 °C and continued to stirred for 15 min and cooled again to –78 °C. Commercially available optically active epoxide **65** (800 µL, 9.1 mmol, 99% ee) was added drop wise followed by $BF_3{\cdot}OEt_2$ (1210 µL, 9.56 mmol, 1.05 equiv). Stirring was continued at –78 °C for 10 min and heated up to –10 °C gradually over 2 h. Reaction was quenched with sat. NH_4Cl (50 mL) and stirred for 15 min. Organic layer was separated and the resulting aqueous layer was extracted with Et_2O 2 times. Combined organic layer was washed with brine, dried over Na_2SO_4, filtered and evaporated slowly up to 100 mbar at 40 °C gave heptane solution of alcohol. Purification by silica gel chromatography (Et_2O/pentane = 0/10 - 1/9 - 1/7.5 - 1/5) gave alcohol **65a** (540 mg, 53%) as a color less liquid; R_f = 0.25 (Et_2O/pentane = 1/6); $[\alpha]_D^{25}$ = –12.3° (*c* 1.34, $CHCl_3$); IR (cm^{-1}) ν 3369 (br), 2964, 2922, 1461, 1103, 1019, 976; ^1H NMR (400 MHz, $CDCl_3$) δ 3.68 – 3.55 (m, 1H), 2.42 – 2.33 (m, 1H), 2.29 – 2.17 (m, 1H), 1.93 (d, *J* = 4.2 Hz, 1H), 1.80 (t, *J* = 2.6 Hz, 1H), 1.59 – 1.47 (m, *J* = 7.5 Hz, 2H), 0.95 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 78.5, 75.4, 71.7, 29.2, 27.4, 10.1, 3.7; HRMS (APCI-TOF) m/z: $[M + H]^+$ Calcd for $C_7H_{13}O$ 113.0961; Found 113.0971.

(R,Z)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hept-5-en-3-ol (66). A suspension of CuCl (11 mg, 0.11 mmol, 5 mol%), PPh_3 (35 mg, 0.13 mmol, 6 mol%) and KO*t*-Bu (50 mg, 0.45 mmol, 20 mol%) in THF (1.5 mL) was stirred at room temperature for 30 min forming a brown solution. A solution of B_2Pin_2 (620 mg, 2.45 mmol, 1.1 equiv) in THF (2 mL) was added and the reaction mixture and stirred for further 10 min forming a black solution. The reaction mixture was cooled to 0 °C and a solution of alkyne **65a** (235 mg, 2.09 mmol) in THF (1.0 mL) were added. The reaction was warmed to room temperature and stirred for 16 h. Then MeOH (180 µL, 4.46 mmol, 2.0 equiv) was added and continued stirring for more 10 h. The reaction mixture was filtered through Celite and washed with Et_2O. Purification by flash column chromatography (Et_2O/pentane = 1/6 - 1/5 -1/3) yielded the product boronic ester **66** (432 mg, 86%) as a colorless oil; R_f = 0.34 (Et_2O/pentane = 1/4); $[\alpha]_D^{25}$ = –11.0° (*c* 0.316, $CHCl_3$); IR (cm^{-1}) ν 3409 (br), 2977, 2931, 1370, 1301, 1138; ^1H NMR (400 MHz, $CDCl_3$) δ 6.35 (tt, *J* = 7.2, 1.6 Hz, 1H), 3.69 – 3.58 (m, 1H), 2.32 (t, *J* = 6.8 Hz, 2H), 1.71 (s, 3H), 1.57 – 1.41 (m, 2H), 1.26 (d, *J* = 1.6 Hz, 12H), 0.96 (td, *J* = 7.4, 1.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.7, 82.4, 71.8, 35.5, 28.9, 24.0, 13.4, 9.2; ^{11}B NMR (128 MHz, $CDCl_3$) δ 30.4; HMBC (δ_H: 1.71 ppm, δ_C: 129.6 ppm); HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{25}BO_3Na$ 263.1789; Found 263.1787.

(R,Z)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hept-5-en-3-yl (E)-2-methylpenta-2,4-dienoate (68). To a stirred solution of the known carboxylic acid **67**[64] (76 mg, 0.68 mmol, 1.3 equiv, see supporting information for the synthesis of **67**) in PhMe (6 mL), Et_3N (210 µL, 1.46 mmol, 2.8 equiv) and 2,4,6-trihlorobenzoyl chloride (110 µL, 0.68 mmol, 1.3 equiv) was added successively and stirred at room temperature for 1.5 h. To the reaction mixture, PhMe (5 mL) solution of alcohol **66** (125 mg, 0.52 mmol, 1.0 equiv) and DMAP (83 mg, 0.68 mmol, 1.3 equiv) was added and continued to stir for 5 h. Reaction was quested with sat. NH_4Cl and aqueous layer was extracted with Et_2O, washed with brine. Organic phase was dried over Na_2SO_4, filtered, and concentrated under the reduced pressure. Purification by silica gel chromatography (Et_2O/pentane = 1/30 - 1/20) gave desired ester **68** (140 mg, 81%) as a color less oil; R_f = 0.30 (Et_2O/pentane = 1/20); $[\alpha]_D^{25}$ = –13.3° (*c* 1.47, $CHCl_3$); IR (cm^{-1}) ν 2976, 2934, 1706, 1370, 1306, 1247, 1143, 1100; ^1H NMR (500 MHz, $CDCl_3$) δ 7.13 (d, *J* = 11.3 Hz, 1H), 6.64 (ddd, *J* = 16.8, 11.4, 10.1 Hz, 1H), 6.28 (td, *J* = 7.2, 1.8 Hz, 1H), 5.54 (d, *J* = 17.3 Hz, 1H), 5.42 (d, *J* = 10.1 Hz, 1H), 4.96 - 4.87 (m, 1H), 2.46 (ddd, *J* = 7.0, 5.8, 1.0 Hz, 1H), 2.44 - 2.35 (m, 1H), 1.93 (d, *J* = 1.4 Hz, 3H), 1.69 (s, 3H), 1.68 - 1.55 (m, 2H), 1.24 (s, 12H), 0.90 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.1, 140.4, 138.1, 132.4, 128.6, 124.0, 83.3, 75.2, 32.9, 26.7, 24.9, 24.9, 14.3, 12.9, 9.8; ^{11}B NMR (128 MHz, $CDCl_3$) δ 29.9; HMBC (δ_H: 1.69 ppm, δ_C: 129.7 ppm); HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{31}BO_4Na$ 357.2208; Found 357.2215.

(3aS,4R,7S,7aS)-4-(((1E,3R,4S,5E,7S)-7-((tert-butyldimethylsilyl)oxy)-4-ethyl-1-iodo-2,6-dimethyldeca-1,5,9-trien-3-yl)oxy)-6,6-dimethyl-2-oxotetrahydro-4H-[1,3]dioxolo[4,5-c]pyran-7-yl acetate (70). To a solution of methyl novioside **33c** (124 mg, 0.476 mmol, 1.8 equiv) in CH_2Cl_2 (4.0 mL) under dark at 0 °C was added HBr (33% in AcOH, 2 mL). The colorless, slightly orange solution was warmed up to room temperature and stirred for 100 min then AcBr (a drop) was added and stirred further 1 h. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and quenched with ice water (4 mL). Layers were separated and the aqueous layer was re-extracted using CH_2Cl_2 (5 mL). Obtained organic layer was washed with sat. $NaHCO_3$ and dried over $MgSO_4$, filtered and concentrated under reduced pressure without heating (water bath) giving glycosyl bromide **69** as a rather dark oil. An alcohol **43** (122 mg, 0.263 mmol) solution in PhH was azeotroped and dried before use. It was then dissolved in CH_2Cl_2 (1.5 mL) and MS 3Å (powder, 240 mg) was added. After stirring for 100 minutes, HgO (450 mg, 2.1 mmol, 8 equiv) and $HgBr_2$ (8 mg, 0.026 mmol, 10 mol%) were added and the orange suspension was stirred for 0.5 h. Then the glycosyl bromide 69 in CH_2Cl_2 (3.0 mL) was slowly added over 25 min and stirred for overnight. After the reaction mixture was diluted with $CHCl_3$, it was filtered through Celite. Organic layer was separated and extracted with $CHCl_3$/$NaHCO_3$/sat. Rochelle and $Na_2S_2O_3$ solution. Then organic layer was dried over Na_2SO_4, and concentrated under reduced pressure after addition of 1 drop of Et_3N. Purification by column chromatography (AcOEt/cyclohexane = 1/15 (sm) - 1/10 - 1/6 - 1/4 (β-anomer) then 1/1 (acetylated sugar recovery)) gave alcohol starting material, acetylated sugar, and desired β-glycoside **70** (80.3 mg, 44%); R_f = 0.60 (Et_2O/pentane = 1/1); IR (cm^{-1}) ν 2931, 1813, 1223, 1167, 1093, 1073, 1043, 1007, 836, 775; $[\alpha]_D^{25}$ = –33.0° (*c* 0.58, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 6.22 (d, *J* = 1.2 Hz, 1H), 5.80 - 5.74 (m, 1H), 5.70 (ddt, *J* = 17.3, 10.2, 7.1 Hz, 1H), 5.03 - 4.99 (m, 2H), 4.99 - 4.97 (m, 3H), 4.87 (dt, *J* = 10.6, 1.3 Hz, 1H), 4.80 - 4.75 (m, 2H), 3.95 (t, *J* = 6.1 Hz, 1H), 3.84 (d, *J* = 9.1 Hz, 1H), 2.50 (qd, *J* = 9.6, 3.1 Hz, 1H), 2.21 (tdd, *J* = 7.0, 5.6, 1.3 Hz, 2H), 2.14 (s, 3H), 1.84 (ddd, *J* = 13.2, 7.6, 3.1 Hz, 1H), 1.78 (d, *J* = 1.1 Hz, 3H), 1.57 (d, *J* = 1.4 Hz, 3H), 1.17 (s, 3H), 1.14 (s, 3H), 1.14 - 1.10 (m, 1H), 0.88 (s, 9H), 0.81 (t, *J* = 7.4 Hz, 3H),

0.01 (s, 3H), –0.02 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 153.7, 147.5, 140.1, 135.6, 123.7, 116.6, 95.2, 89.5, 81.6, 77.4, 75.6, 75.1, 72.1, 72.1, 42.7, 42.0, 28.0, 26.0, 24.7, 24.2, 21.0, 19.9, 18.3, 12.8, 11.3, –4.2, –4.7; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{30}H_{49}IO_8SiNa$ 715.2134; Found 715.2139.

(3R,5E,7E,9R,10S,11E,13S)-9-(((3aS,4R,7S,7aS)-7-acetoxy-6,6-dimethyl-2-oxotetrahydro-4H-[1,3]dioxolo[4,5-c]pyran-4-yl)oxy)-13-((tert-butyldimethylsilyl)oxy)-10-ethyl-6,8,12-trimethylhexadeca-5,7,11,15-tetraen-3-yl (E)-2-methylpenta-2,4-dienoate (71). To an iodide **70** (25.9 mg, 63 µmol) and bronate **68** (22 mg, 64 µmol, 1.7 equiv) in dry THF (1.0 mL) and degassed water (200 µL) at 0 °C, $Pd(PPh_3)_4$ (4.0 mg, 3.7 mmol, 10 mol%) was added. Next, the stock solution of TlOEt* (ca. 140 µL solution, 56 µmol, 1.5 equiv) was added dropwise for 1 min (better to add TlOEt slowly, preferably over ca. 10 min.). Reaction was monitored by TLC. After stirring for 20 min at room temperature, the reaction mixture was diluted with Et_2O (2 mL), AcOEt (2 mL), sat. NH_4Cl (2 mL) and water (1 mL). The aqueous layer was extracted with AcOEt (2 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated. Purification by silica gel column chromatography (Et_2O/pentane = 1/6 - 1/4 - 1/2) gave desired alkene **71** (25.5 mg, 88%) as an oil. *TlOEt stock solution; To TlOEt (41.8 mg, a clear colourless to bit brown liquid) in a HPLC vial tube under Ar was added degassed water (400 µL) and it was dissolved prior to use; R_f = 0.70 (Et_2O/pentane = 1/1); IR (cm^{-1}) ν 2930, 2857, 1815, 1706, 1251, 1172, 1095, 1005, 837; $[\alpha]_D^{25}$ = –64.6° (*c* 0.105, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (dd, *J* = 11.3, 1.4 Hz, 1H), 6.65 (ddd, *J* = 16.8, 11.3, 10.1 Hz, 1H), 5.87 - 5.79 (m, 1H), 5.77 (s, 1H), 5.76 - 5.63 (m, 1H), 5.55 (d, *J* = 16.8 Hz, 1H), 5.44 (d, *J* = 10.8 Hz, 1H), 5.33 (t, *J* = 7.4 Hz, 1H), 5.04 (dd, *J* = 2.5, 1.3 Hz, 1H), 4.97 (ddd, *J* = 17.2, 2.5, 1.2 Hz, 1H), 4.94 (ddt, *J* = 10.2, 2.3, 1.1 Hz, 2H), 4.89 (dt, *J* = 12.4, 6.4 Hz, 1H), 4.79 - 4.74 (m, 2H), 3.93 (t, *J* = 6.1 Hz, 1H), 3.68 (d, *J* = 9.0 Hz, 1H), 2.52 (qd, *J* = 9.5, 3.2 Hz, 1H), 2.45 - 2.31 (m, 2H), 2.20 - 2.16 (m, 2H), 2.12 (s, 3H), 1.94 (d, *J* = 1.4 Hz, 3H), 1.88 - 1.77 (m, 1H), 1.74 (dd, *J* = 6.5, 1.3 Hz, 6H), 1.67 - 1.59 (m, 3H), 1.57 (d, *J* = 1.3 Hz, 3H), 1.25 (s, 3H), 1.17 (s, 3H), 1.12 (s, 3H), 0.90 (t, *J* = 7.4 Hz, 3H), 0.85 (s, 9H), 0.81 (t, *J* = 7.4 Hz, 3H), –0.03 (s, 3H), –0.08 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.1, 168.1, 153.9, 138.9, 138.2, 135.8, 134.6, 134.1, 133.5, 132.4, 128.6, 125.8, 124.7, 124.1, 116.3, 94.2, 92.0, 77.6, 75.7, 75.6, 74.9, 72.3, 42.5, 42.0, 32.5, 28.1, 26.6, 26.0, 24.7, 24.3, 21.0, 18.3, 17.3, 13.9, 12.9, 12.8, 11.4, 9.9, –4.5, –4.9; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{43}H_{68}O_{10}SiNa$ 795.4474; Found 795.4473.

(3aS,4R,7S,7aS)-4-(((2R,4E,6E,8R,9S,10E,12S,14E,16E)-12-((tert-butyldimethylsilyl)oxy)-2,9-diethyl-5,7,11,17-tetramethyl-18-oxooxacyclooctadeca-4,6,10,14,16-pentaen-8-yl)oxy)-6,6-dimethyl-2-oxotetrahydro-4H-[1,3]dioxolo[4,5-c]pyran-7-yl acetate (71a). To an alkene **71** (4.0 mg, 9.5 µmol) in PhMe (1.0 mL), second generation Grubbs catalyst (0.86 mg, 1.0 µmol, 20 mol%) was added at 0 °C and the resulting mixture was stirred at 100 °C in a preheated oil bath for 90 min. The reaction mixture was diluted with Et_2O (3 mL) and brine (5 mL) and separated. Organic layer was dried over Na_2SO_4, filtered and concentrated. Purification by silica gel column chromatography (Et_2O/pentane = 1/3) gave desired macrocycle as a mixture of *E* and *Z* isomer (*E*:*Z* = 1:0.8 determined by ^{1}H NMR). Further purification by HPLC with DAICEL Chiral-IA (Eluant: *n*-hexane/IPA = 99/1) gave desired (*E*)-macrocycle **71a** (1.6 mg, 42%); R_f = 0.3 (Et_2O/pentane = 1/1); IR (cm^{-1}) ν 2958, 2930, 1815, 1701, 1371, 1253, 1224, 1167, 1097, 1044; $[\alpha]_D^{25}$ = +49.8° (*c* 0.32, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.01 (d, *J* = 11.4 Hz, 1H), 6.25 (dd, *J* = 15.1, 11.3 Hz, 1H), 5.83 (m, 1H), 5.78 (s, 1H), 5.71 (ddd, *J* = 14.6, 9.0, 5.0 Hz, 1H), 5.48 (d, *J* = 8.0 Hz, 1H), 5.16 (d, *J* = 10.4 Hz, 1H), 5.09 (s, 1H), 4.86 (td, *J* = 6.9, 3.3 Hz, 1H), 4.78 (dd, *J* = 4.4, 1.6 Hz, 2H), 4.19 (br, 1H), 3.72 (d, *J* = 9.8 Hz, 1H), 2.67 (qd, *J* = 11.4, 10.0, 3.2 Hz, 2H), 2.57 (m, 1H), 2.52 (m, 1H), 2.38 - 2.19 (m, 2H), 2.13 (s, 3H), 1.85 (m, 1H), 1.85 (s, 3H), 1.81 (s, 3H), 1.84 - 1.62 (m, 2H), 1.64 (s, 3H), 1.57 (s, 3H), 1.23 (s, 3H), 1.15 (s, 3H), 0.95 (t, *J* = 7.5 Hz, 3H), 0.87 (s, 9H), 0.83 (t, *J* = 7.4 Hz, 3H), 0.03 (s, 3H), –0.01 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 169.0, 153.9, 140.5, 138.7, 135.6, 135.2, 134.9, 134.0, 127.9, 124.9, 124.3, 123.6, 94.2, 92.7, 77.4, 75.7, 74.9, 74.6, 73.0, 72.4, 41.6, 37.1, 31.3, 30.5, 29.9, 28.2, 26.2, 25.9, 25.5, 24.2, 21.0, 18.3, 17.0, 14.8, 13.0, 12.2, 10.7, 10.4, –4.9, –5.0; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{41}H_{64}O_{10}SiNa$ 767.4161; Found 767.4163.

(3aS,4R,7S,7aS)-4-(((2R,4E,6E,8R,9S,10E,12S,14E,16E)-2,9-diethyl-12-hydroxy-5,7,11,17-tetramethyl-18-oxooxacyclooctadeca-4,6,10,14,16-pentaen-8-yl)oxy)-6,6-dimethyl-2-oxotetrahydro-4H-[1,3]dioxolo[4,5-c]pyran-7-yl acetate (71b). To a TBS ether **71a** (5.2 mg, 7.0 µmol) in THF (0.65 mL) in a glass sealed tube (PP tube is recommended), $3HF{\cdot}NEt_3$ (0.35 mL, 2.05 mmol, excess) was added and stirred at room temperature for 2 h and at 50 °C for 24 h. The reaction mixture was diluted with AcOEt (1 mL) and carefully quenched with sat. $NaHCO_3$ (caution! Gas evolution.). The aqueous layer was further diluted with water (10 mL) and extracted with AcOEt (3 x 10 mL), dried over Na_2SO_4, filtered and concentrated. Purification by column chromatography (AcOEt/cyclohexane = 1/3 - 2/3) gave desired alcohol **71b** as a white solid (4.3 mg, 98%); R_f = 0.35 (AcOEt/cyclohexane = 2/3), R_f = 0.6 (Et_2O only); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.96 (d, *J* = 11.3 Hz, 1H), 6.39 (ddd, *J* = 15.0, 11.3, 1.6 Hz, 1H), 5.84 - 5.80 (m, 2H), 5.64 (td, *J* = 10.4, 5.2 Hz, 1H), 5.45 (t, *J* = 8.1 Hz, 1H), 5.07 (s, 1H), 4.99 (d, *J* = 10.5 Hz, 1H), 4.82 – 4.74 (m, 3H), 4.23 (s, 1H), 3.72 (d, *J* = 9.8 Hz, 1H), 2.73 - 2.66 (m, 2H), 2.48 - 2.32 (m, 3H), 2.13 (s, 3H), 1.90 (m, 1H), 1.88 (s, 3H), 1.85 (s, 3H), 1.80 (m, 1H), 1.74 (s, 3H), 1.69 (m, 1H), 1.66 (s, 3H), 1.50 (m, 1H), 1.26 (m, 1H), 1.20 (s, 3H), 1.14 (s, 3H), 0.95 (t, *J* = 7.5 Hz, 3H), 0.85 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.2, 169.0, 153.9, 139.0, 136.6, 136.3, 135.3, 135.1, 133.7, 129.8, 126.8, 126.2, 123.0, 94.4, 92.7, 75.7, 75.1, 74.9, 72.7, 72.4, 42.1, 36.6, 31.8, 29.9, 28.1, 26.8, 25.4, 24.2, 21.0, 17.2, 15.2, 13.4, 12.5, 11.0, 10.1; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{35}H_{50}O_{10}Na$ 653.3296; Found 653.3292.

Tiacumicin A (2). To the solution of carbonate protected tiacumicin A (**71b**) (10.2 mg, 16.2 µmol) in THF (2000 µL) and ethylene glycol (100 µL), a stock solution (25 µL, prepared from 1.5 mg NaH in 1.5 mL ethylene glycol) was added at 0 °C and the reaction mixture was stirred for 10 min at the same temperature. Then, stock solution (10 µL) was added and stirred for 30 min resulting in slightly yellowish solution and the reaction mixture was first diluted with AcOEt (2 mL) and water (2 mL). The aqueous layer was extracted with AcOEt (3 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. UPLC MS analysis showed desired molecule ion as a Na^+ adduct. Purification of crude mixture with reversed phase HPLC *without formic acid* lead to the isolation of desired tiacumicin A (**2**) as a slow eluting entity (t_R = 26 min, 1.80 mg, 18.4%) on the RP-HPLC (A: H_2O; Solvent B: MeCN; 20 mL/min; T = 20 °C; B[%] (t_R [min])=35 (0 to 0.5); 70 (30); 90 (35), Phenomenox Gemini column 5 µm NX-C18 110, 250 x 21.2 mm). This hydrolysis also led to the isolation of dacetyl tiacumicin A (t_R = 18 min, 0.91 mg, 10.0%), 2`-acetylated product ($t_R$ = 23 min, 0.33 mg, 3.5%), 3`-acetylated product (t_R = 24 min, 0.72 mg, 7.4%) and recovery of starting material (t_R = 36 min, 2.76 mg, 27%); Tiacumicin A (**1**) R_f = 0.15 (Et_2O only); IR (cm^{-1}) ν 3484, 2969, 2928, 1735, 1700, 1643, 1369, 1249, 1166, 1046, 1006, 899, 802, 752; $[\alpha]_D^{25}$ = +59.0° (*c* 0.205, $CHCl_3$) [lit.[12a] $[\alpha]_D^{25}$ = +128.2º (*c* 1.19, MeOH)]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00 (d, *J* = 11.3 Hz, 1H), 6.40 (dd, *J* = 14.7, 11.8 Hz, 1H), 5.75 (s, 1H), 5.65 (ddd, *J* = 14.8, 10.2, 4.5 Hz, 1H), 5.46 (t, *J* = 8.3 Hz, 1H), 5.01 (d, *J* = 10.0 Hz, 1H), 4.83 (p, *J* = 6.2 Hz, 1H), 4.67 (s, 1H), 4.24 (s, 1H), 4.01 (s, 1H), 3.66 (d, *J* = 9.3 Hz, 1H), 2.77 – 2.67 (m, 3H), 2.52 (ddd, *J* = 13.8, 9.0, 4.3 Hz, 1H), 2.50 – 2.38 (m, 3H), 2.31 (dt, *J* = 13.7, 6.5 Hz, 1H), 2.11 (s, 3H), 1.89 (s, 4H), 1.84 (dd, *J* = 14.1, 7.0 Hz, 1H), 1.80 (s, 4H), 1.69 (s, 3H), 1.65 (s, 3H), 1.33 – 1.24 (m, 1H), 1.18 (s, 3H), 1.11 (s, 3H), 0.96 (t, *J* = 7.5 Hz, 3H), 0.86 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.22, 168.80, 139.11, 136.63, 136.33, 135.46, 134.39, 134.26, 129.75, 126.14, 125.80, 122.83, 94.89, 92.76, 75.28, 74.91, 73.52, 72.64, 71.67, 70.24, 41.34, 36.61, 31.50, 28.20, 26.60, 26.19, 21.22, 18.41, 17.23, 15.07, 13.43, 12.41, 11.00, 10.17; HRMS (ESI-Orbitrap) m/z: $[M + Na]^+$ Calcd for $C_{34}H_{52}O_9Na$ 627.3504; Found

627.3504. See supporting information for the comparison of ^{1}H and ^{13}C NMR experiments between natural and totally synthetic tiacumicin A. Although the results obtained was reproducible (same experiment was repeated 3 times with 10 - 12 mg of starting material), the migration of the acyl group was not avoided. To get the best yield, the reaction should be stopped before full consumption of the starting material.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
pKa determination experiments, degradation study and characterization data (including ^{1}H, ^{13}C and 2D NMR spectra) of products **6**, **7**, **7a**, **7b**, **1**, **20**, **20a**, **21**, **22**, **23**, **24**, **25**, **26**, **26a**, **26b**, **27**, **28a**, **29**, **30**, **31**, **32**, **33**, **α,β-34**, **38**, **15**, **39**, **39a**, **40**, **41**, **41a**, **41b**, **40a**, **40b**, **42**, **43**, **44**, **47**, **48**, **49**, **50**, **50a**, **52**, **53**, **54**, **54**, **55**, **55**, **56**, **57**, **58**, **59**, **10, β-61**, **α,β-62**, **63**, **64**, **33b**, **65a**, **66**, **37**, **68**, **70**, **71**, **71a**, **71b and 2** (PDF)

Corresponding Author

* E-mail: karl.gademann@uzh.ch

Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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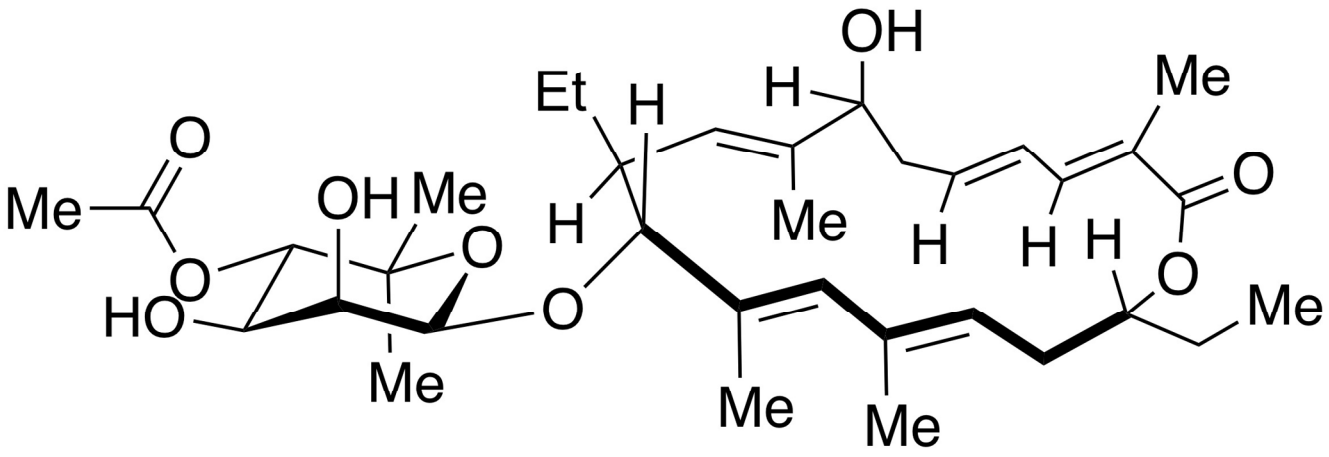
TOC Graphic



Tiacumicin A