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A Bidirectional Approach to the Synthesis of Polypropionates: Synthesis of C1−C13 Fragment of Zincophorin and Related Isomers

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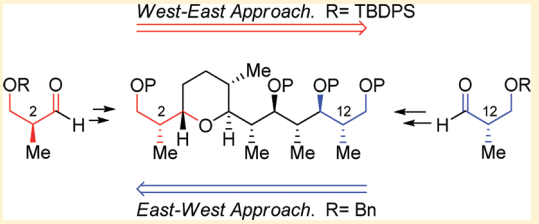
Supporting Information

ABSTRACT: The structure−activity study of a bioactive natural product containing polypropionate subunits requires that its stereoisomers also be evaluated. Therefore, a general approach to synthesize these motifs is necessary. We describe herein the synthesis of the C1−C13 polypropionate subunit of zincophorin and isomers thereof using a two-reaction sequence: an aldol reaction using a mixture of tetrasubstituted enoxysilanes and a hydrogen-transfer reaction, both under Lewis acid control. Selection of the appropriate Lewis acid dictates the stereochemical outcome of these reactions. From a tactical standpoint, this study shows how a polypropionate sequence can be read and constructed in two directions, either the east−west or the west−east approaches. The choice of the optimal route is influenced by the number of complexation sites that can interfere in the aldol step under bidentate Lewis acid control.



INTRODUCTION

For decades, ionophores have been of great interest for both their biological properties and their architectural complexity.[1] Their capacity to affect ion-exchange processes of monovalent (Na^+, K^+) or divalent cations (Ca^{2+}, Zn^{2+}, Mg^{2+}, etc.) across cell membranes by forming lipophilic complexes explains their antifungal and antibiotic activities.[2] Recently, some polyketide members of this family such as zincophorin **1**, narasin **3**, and salinomycin **4** (Figure 1) have drawn increased attention after the discovery of their potential anticancer activity.[3,4] Zincophorin **1** was isolated from *Streptomyces griseus* and has demonstrated a strong activity against Gram-positive bacteria and *Clostridium welchii*.[5] Its methyl ester **2** (Figure 1) was reported to have strong inhibitory properties against influenza WSN virus and reduced host cell toxicity compared to the free acid.[6] Narasin **3** has recently been identified as an inhibitor of the NF-κB signaling pathway.[7] Constitutive activity of NF-κB signaling in tumor cells is involved in cellular proliferation, blocking apoptosis, promotion of angiogenesis, and metastasis.[8] Although the mechanism of action of salinomycin **4** is not well understood, it has demonstrated a unique activity against cancer stem cells (CSCs).[9] It has been shown that these cells play a critical role in the growth of some tumors. CSCs are also resistant to chemotherapy and radiation, justifying the interest of the biomedical community to identify and develop novel molecules that would target them.[10,11]

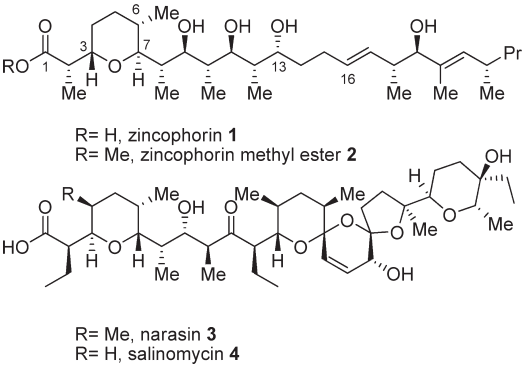


Figure 1. Representative polyketide ionophores.

These polyketides are natural products which have been biosynthesized by various organisms in response to environmental stress. The biological activities described above are unlikely correlated with their natural functions that have been selected through evolution. These molecules could therefore be considered as "chemical leads" that could be optimized for their potency, selectivity, and "druglike" properties. From a medicinal

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chemistry standpoint, pharmacophores will need to be identified. This could be done notably by deleting or inverting the stereocenters present to evaluate the impact of these changes on the biological profiles and conformation of parent molecules.[12,13] The selection of a strategy to synthesize a molecule such as zincophorin should therefore take into account the flexibility needed to also prepare some of its epimers while allowing the synthesis of the 8,9-*anti*-9,10-*anti*-10,11-*anti*-11,12-*anti* (C8−C12) polypropionate motif known for its synthetic challenge.

Many groups have been inspired by the stereochemical complexity and challenges associated with the synthesis of these chains of consecutive carbon centers bearing methyl and hydroxyl substituents.[14] As a consequence, a number of approaches to the stereoselective synthesis of polypropionates have been described in the last decades.[15−22] These contributions have advanced considerably our collective knowledge in organic chemistry. Our group has been interested, during this period, in developing a general substrate-controlled strategy for the synthesis of polypropionates,[23] avoiding some of the mismatched scenarios noted in reagent-controlled strategies involving chiral substrates.

In the present study, we aim to synthesize the C1−C13 portion of zincophorin (Figure 1). Stereocenters bearing a hydroxyl moiety at C3 will be created using a Mukaiyama aldol reaction on a β-hydroxy-α-methyl aldehyde (Figure 2). The methyl substituent at C2 will originate from a stereocontrolled hydrogen-transfer reaction to a carbon-centered free radical as illustrated in Figure 2.

These reactions are remarkable in three aspects. First, our previous results indicated that the stereospecifity of both reactions depends uniquely on 1,2-induction with no opposing 1,3-induction observed. Second, diastereoselectivity in both reactions depends on the choice of Lewis acid used. Third, the enoxysilanes used in the aldol step are a mixture of stereoisomers (*Z* and *E*). Since a free radical is formed at the carbon α to the ester in the second step of the reaction sequence, there is no need to control the stereochemistry of the C2 precursors in the aldol step. Consequently, stereodefined tetrasubstituted enoxysilanes do not need to be made, thus removing a significant roadblock from a practical standpoint.

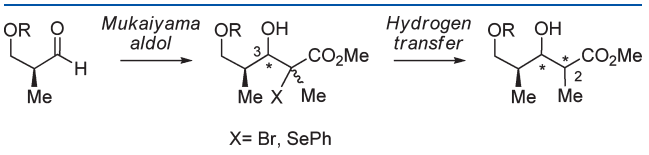

Figure 2. General strategy to the synthesis of polypropionates.

The polypropionate motifs can be constructed in two different directions. In the case of zincophorin, the C5−C13 sequence could be elaborated from the C6 stereocenter with introduction of the other chiral centers using the series of reactions described before. This is referred to as the west−east approach. Alternatively, the synthesis can start with the C12 stereocenter (e.g., from C12 to C1) and is termed the east−west approach. From a tactical standpoint, these two approaches may provide different challenges that would need to be considered prior to synthesis. In order to make such decisions easier in the future, both directions will be evaluated in this study in the context of the C1−C13 zincophorin fragment synthesis. Finally, as stated before, our approach should also allow for the preparation of various isomers in a predictable and controlled fashion.

This study emphasizes the need to control the number of complexing sites in planning the aldol step while also demonstrating long distance disturbances in the course of a hydrogen-transfer step. More importantly, it illustrates how, depending on the stereochemistry sought after, any polypropionate chain can be stereoselectively constructed by identifying the nature of the Lewis acid needed in each reaction sequence to induce the desired stereocenters.

RESULTS AND DISCUSSION

During the past decade, our group studied the synthesis of polypropionate motifs using a highly selective tandem reaction sequence consisting of a Mukaiyama aldol reaction combined with a radical reduction, as illustrated in Figure 3. The aldolization reaction is performed using a mixture of tetrasubstituted ketene silylated acetals (KSA) bearing a heteroatom (X = Br, SePh). Depending on the nature of the Lewis acid (monodentate or bidentate), we can expect to generate either a 3,4-*syn* or *anti* relationship. A monodentate Lewis acid ($BF_3 \cdot OEt_2$) will lead to a 3,4-*syn* relationship through a Felkin−Anh transition state,

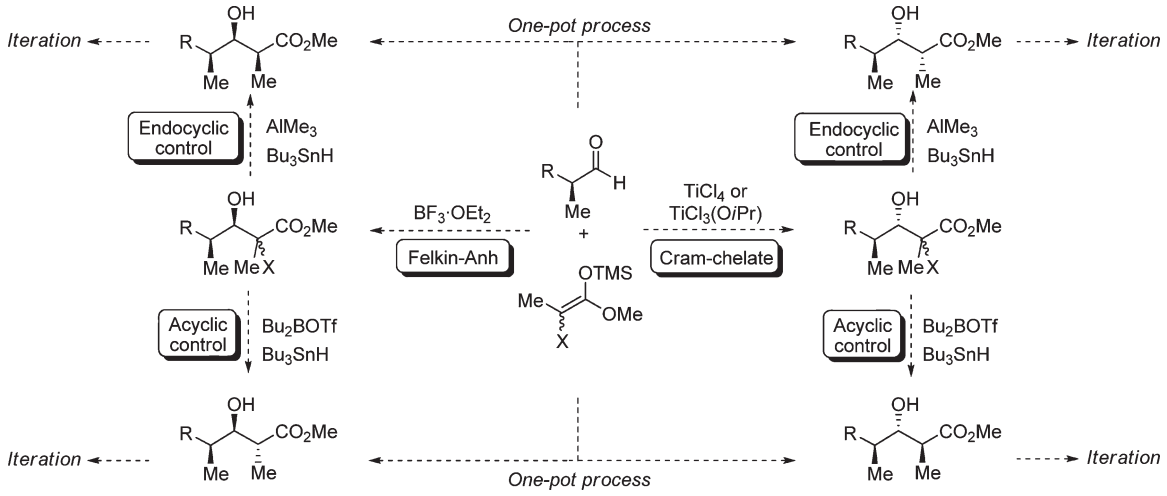

Figure 3. Mukaiyama and free-radical hydrogen-transfer approach to polypropionate formation.

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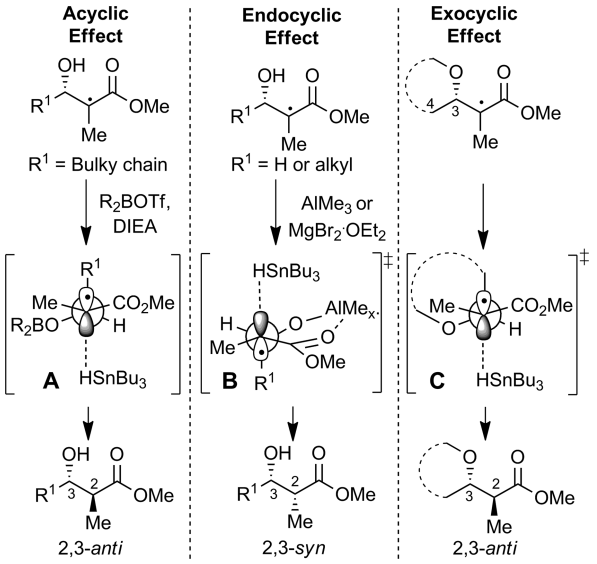
Scheme 1. Radical Reduction Strategies



while a bidentate Lewis acid ($TiCl_4$ or $TiCl_3OiPr$) will lead to a 3,4-*anti* relationship through a Cram chelate transition state. In both cases, a mixture of stereoisomers at C2 was obtained.

Our group and others have shown that some radical processes on acyclic substrates can be domesticated.[24] We demonstrated that hydrogen-transfer reactions on carbon-centered free radicals, flanked on one side by an ester and on the other by a stereogenic center bearing an electronegative group such as a hydroxyl, are controlled through the use of Lewis acids.[25] The 2,3-*anti* relationship (Figure 3) is achieved by reacting the tertiary halide aldol products with Bu_2BOTf or Et_2BOTf. First, a borinate intermediate is formed at C3 which eliminates hydrogen bonding between the parent hydroxyl and ester. Transition state **A**, illustrated in Scheme 1, rationalizes predominance for the 2,3-*anti* product in the hydrogen-transfer reaction, termed the "acyclic effect". Minimization of allylic-1,3 strain and dipole−dipole effects are critical factors resulting in the lower energy of this transition state. The 2,3-*syn* relationship is generated when the radical precursors are first complexed with a bidentate Lewis acid (e.g., $MgBr_2 \cdot OEt_2$ or $AlMe_3$) followed by hydrogen transfer. The resulting "endocyclic effect", the radical being embedded in a temporary ring, favors transition state **B**, leading predominantly to the 2,3-*syn* product. Given that polypropionates are a continuing sequence of hydroxyl and methyl groups, our set of reactions was repeated using the resulting β-benzyloxy-α-methyl aldehydes (Figure 3) derived from the propionate motifs as described in Figure 2. Recently, this strategy led to the synthesis of all possible 16 stereopentads starting from a single stereocenter in the starting material.[23e] Fifteen out of the 16 hydrogen-transfer reactions demonstrated both high stereocontrol and yield.[23d] In one case, we had to take advantage of the "exocyclic effect" in order to obtain a high *anti* ratio (C2−C3). The presence of a cycle α to the carbon-centered radical generally led to higher *anti* stereoselectivity (Scheme 1, transition state **C**).[25b,e]

In the context of the Mukaiyama reaction, the presence of two stereogenic centers at C2 and C3 of the starting aldehyde is known to be a potential complicating factor in aldol reactions due to opposing 1,2- and 1,3-inductions.[26] Indeed, 2,3-*syn* relative disubstituted aldehydes (in Felkin−Anh controlled aldols) and

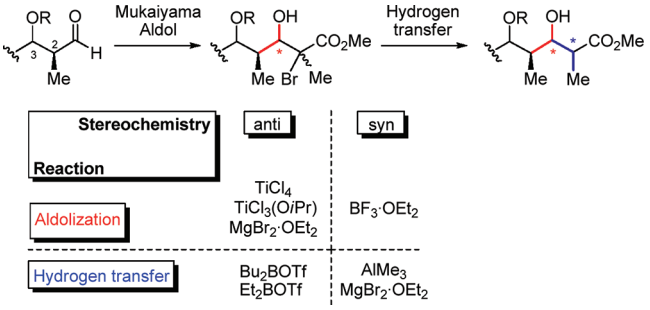


Figure 4. Stereochemistry as a function of Lewis acids.

2,3-*anti* relative disubstituted aldehydes (Cram chelate controlled aldols) are often problematic, leading to poor diastereoselectivities. Nevertheless, such complications were not detected in our aldolizations.[23b−d]

Figure 4 summarizes our previous results and can be used for the planning of any synthesis. Depending on the relative stereochemistry sought after in each reaction, a Lewis acid is suggested to create each stereocenter in a stepwise process. Armed with this tool, the synthesis of zincophorin was initiated.

Zincophorin's architectural complexity has elicited considerable synthetic interest. Four total syntheses were completed by Danishefsky,[27] Cossy,[28] Myashita,[29] and Leighton,[22c] while syntheses of various fragments were provided by Hsung,[30] Marshall,[20a] Roush,[18b,d] Burke,[31] Holzapfel,[32] Kallmerten,[33] and our group.[34]

A first retrosynthetic disconnection of zincophorin **1** was envisioned at the C16−C17 olefin. A Julia−Kocienski coupling[35] would occur between the aldehyde **5** and a sulfobenzotetrazole bearing the C17−C25 fragment. The aldehyde **5** could in turn be obtained from a carbon−carbon bond-forming reaction at C12−C13, the primary alcohol **6** serving as precursor. The 3,7-*trans* trisubstituted tetrahydropyran could be constructed stepwise by first reacting our brominated tetrasubstituted enoxysilane **7a** with aldehyde **8** (precursor of a six-membered oxonium) using slightly modified Evans conditions[36] that should lead to a C3−C7 *trans*-selective stereochemistry and tertiary bromides at C2. Interestingly, we recognized that the C2−C3 *anti* stereochemistry could also be accessed from a radical reaction. The resulting mixture of C2 tertiary bromides could then be reduced by a hydrogen-transfer reaction taking advantage of the exocyclic effect, illustrated in Scheme 1, which allows for a high C2−C3 *anti* ratio. Finally, aldehyde **8** could originate from a chain extension starting from the generic stereoheptad **9** bearing the requisite polypropionate sequence sought after. Synthon **9** could be conceptually envisioned in two directions as illustrated in Scheme 2. The sequence could be "read" from east−west starting from C12, the starting stereogenic center. Creation of the stereogenic center at C11 would necessitate a stepwise *anti* aldol followed by an *anti* hydrogen transfer at C10 to create the first propionate unit. Repeating the sequence will then require an *anti* aldol to generate C9, an *anti* hydrogen transfer (C8), followed by a *syn* aldol (C7) and an *anti* hydrogen transfer (C6). Lewis acids needed to achieve this sequence of reactions and the corresponding stereochemistry can be decrypted using Figure 4. The tetrahydropyran would then be constructed to create the stereogenic center at C2, as previously described (vide supra).

Similarly, the west−east approach can be considered starting from the stereogenic center at C6. In this case, as illustrated in Scheme 2, three *anti* aldol reactions will be needed, along with a

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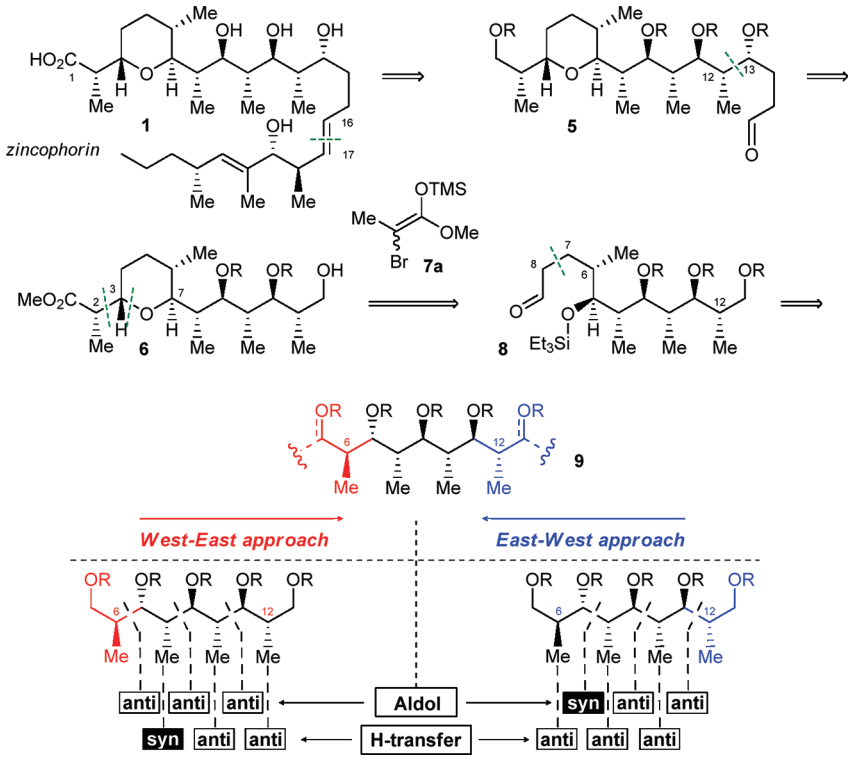
Scheme 2. Retrosynthetic Analysis of Zincophorin and of Its Polypropionate Chain



first hydrogen transfer to establish a *syn* relationship (C5−C6) followed by two *anti* hydrogen transfers. In this direction, construction of the tetrahydropyran ring will be completed earlier in the synthesis.

Are both reaction sequences equivalent? As stated before, the west−east approach would require an *anti* aldol to create the hydroxyl at C11 in the third iteration. This requires the formation of a Cram chelate intermediate in the presence of many benzyl ethers which show a high affinity for titanium Lewis acids. The east−west approach, however, suggests the use of a *syn* aldol in the third iteration, thus requiring a simple monodentate activation of the carbonyl. The sequence of hydrogen-transfer reactions only differs slightly. In the west−east approach, a *syn* hydrogen transfer is needed in the first iteration that will involve a chelated intermediate. The next iterations require *anti* selective hydrogen transfers. Both reaction sequences were studied. We also planned to vary the stereoisomers (C9−C12) using the west−east approach, their stereocontrolled synthesis having been proven difficult.

East−West Approach. Our first approach to the synthesis of the C1−C13 fragment of zincophorin is illustrated in Scheme 3. The aldehyde **11** derived from the (*S*)-Roche ester was used as a starting material. This stereocenter will become C12 (using the zincophorin numbering) of the final product, and from it eight other stereogenic centers will be generated.

Aldehyde **10** was first reacted with bromoenoxysilanes **7a** in the presence of $TiCl_4$ at −78 °C, as depicted in Figure 3. Resulting tertiary bromides **S1a** and **S1b** were then treated with dibutylboron triflate at −78 °C in the presence of DIEA prior to the hydrogen-transfer step. This was followed by addition of tributyltin hydride and Et_3B to the reaction mixture. The free-radical chain is simply initiated by air injection with a syringe. A one-pot procedure was also developed where a mixture of phenylselenated enoxysilanes **7b** was used with Et_2BOTf as the sole Lewis acid for both steps.[23e] The 2,3-*anti*-3,4-*anti* propionate **11** was obtained in excellent yield, and high diastereoselectivity was noted for both steps (>20:1). The C3 alcohol of **11** was then protected as a benzyl ether (**S2**) and the ester converted to aldehyde as in **12** (88% over three steps).

Stereopentad **13** was the next target. The 3,4-*anti* relative stereochemistry (C9−C10 in **1**) required use of a bidentate Lewis acid ($TiCl_4$) in the aldol step (**S4a**, **S4b**) while dibutylboron triflate can be used for the hydrogen-transfer step to obtain a 2,3-*anti* relative stereochemistry (C8−C9 in **1**). Stereopentad **13** was obtained in a 76% yield from **12** with excellent diastereoselectivity. As stated before, aldehydes bearing α and β substituents are known to induce, in certain cases, opposing stereochemistry in many aldol reactions, leading to poor diastereoselectivities. Considering product **12**, the 2,3-*anti* relative stereochemistry could cause mismatch scenarios under chelation control (1,2- and 1,3- opposing inductions). However, we obtained a greater than 20:1 ratio (3,4-*anti* versus 3,4-*syn*; as measured by ^1H NMR on crude reaction mixtures) in the aldol step, testifying to the synthetic usefulness of our sterically encumbered tetrasubstituted enoxysilanes **7**, 1,2-induction being the dominant paradigm in our reactions. These results are impressive considering the known difficulties of inducing the *anti,anti* motif in polypropionates.

A second iteration of our reaction sequence was then carried out to synthesize stereoheptad **15** (Scheme 3). First, free-alcohol **13** was protected as a benzyl ether (**S5**) and the ester converted in two steps to aldehyde **14** (72% overall yield). The 3,4-*syn* relative stereochemistry (C7−C8 in **1**) of **S7** now required a Mukaiyama reaction under control of a monodentate Lewis acid

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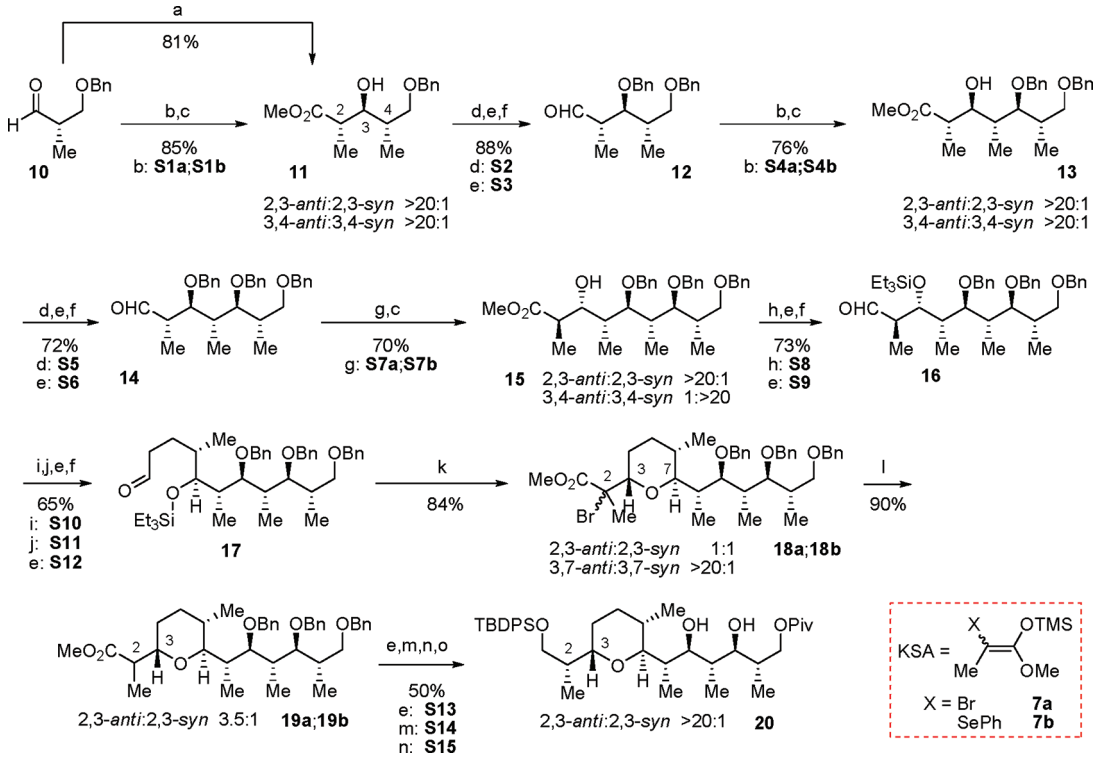
Scheme 3. East−West Synthesis of C1−C13 Fragment 20 of Zincophorin[a]



[a] Key: (a) Et_2BOTf, **7b**, CH_2Cl_2, −78 °C then Bu_3SnH, BEt_3, air, CH_2Cl_2, −78 °C; (b) $TiCl_4$, **7a**, CH_2Cl_2, 78 °C; (c) Bu_2BOTf, DIEA, CH_2Cl_2, −78 °C then Bu_3SnH, BEt_3, air, CH_2Cl_2, −78 °C; (d) BnOC═NHCCl$_3$, TfOH, *c*-Hex/CH_2Cl_2, 0 °C; (e) DIBAL-H, CH_2Cl_2, −40 °C; (f) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C then NEt_3, −78 °C; (g) $BF_3\cdot OEt_2$, **7a**, CH_2Cl_2, −78 °C; (h) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; (i) $(EtO)_2POCH_2CO_2Et$, DBU, LiCl, MeCN, 0 °C; (j) H_2, Pd−C, pyridine, MeOH, rt; (k) $BiBr_3$, **7a**, CH_2Cl_2/MeCN, −78 °C; (l) Ph_3SnH, BEt_3, air, toluene, −78 °C; (m) TBDPSCl, imidazole, CH_2Cl_2, rt; (n) $Pd(OH)_2$, H_2, THF, rt; (o) PivCl, NEt_3, CH_2Cl_2, rt.

such as $BF_3\cdot OEt_2$ (Figure 4). The 2,3-*anti* relative stereochemistry (C6−C7 in **1**) requires once again a hydrogen-transfer reaction under acyclic control as previously described (i.e., Bu_2BOTf). The stereoheptad **15** was obtained in a 70% yield from aldehyde **14** with excellent diastereoselectivities for both steps (>20:1). With the C5−C13 fragment in hand, we considered the synthesis of the C3−C7 *trans* tetrahydropyran. The secondary alcohol of **15** was first protected with a triethylsilyl group (TES; **S8**), and the ester reduced to aldehyde **16** (73% over three steps). Chain extension was performed by a Horner−Wadsworth−Emmons olefination (**S10**) followed by a chemoselective hydrogenation of the olefin in presence of benzyl groups (**S11**).[37]

The resulting ester was reduced to aldehyde **17** (65% overall yield from **16**) which was reacted with bromoenoxysilanes **7a** in the presence of $BiBr_3$ as suggested in the Evans protocol,[36] with slight modifications (Scheme 3). The cyclization took place in a 3,7-*trans* stereoselective manner with a 1:1 ratio of C2 epimeric tertiary bromides **18a** and **18b** obtained in excellent yield (84%). The hydrogen-transfer reaction was then performed on **18** to give in excellent yield the expected C2−C3 *anti* product **19a**, but with a disappointing isomeric ratio of 3.5:1. This result was very intriguing to us, having in the past achieved many radical reductions with an adjacent tetrahydropyran or tetrahydrofuran flanking the carbon-centered radical with excellent *anti*-selective ratios.[25,34,38] Nevertheless, the 2,3-*anti* diastereoisomer was easily separated by flash chromatography after reduction of the ester to the corresponding alcohol (**S13**) and further elaboration of fragment C1−C13.

This result provided one more reason to evaluate the other approach (i.e., west−east) described before. The planned second synthesis dictates that the tetrahydropyran ring be built earlier, thus shedding light on the impact of a shorter side chain at C7 of the tetrahydropyran on the reduction of the tertiary bromides at C2.

West−East Approach. Alternatively, the C1−C13 fragment **21** could originate through two successive iterations of our reaction sequence on aldehydes **22** and **23** (Scheme 4). These successive iterations would install the all-*anti* core of zincophorin (C8−C12) that was previously proven very challenging to synthesize (vide infra). The aldehyde **23** bearing the requisite 3,7-*trans* tetrahydropyran could be obtained from a cycloetherification process on aldehyde **24** as previously described (Scheme 3). Finally, the latter would come from an extension of propionate motif **25** (C5−C9).

Synthesis of the substituted tetrahydropyran ring is depicted in Scheme 5.[39] The first propionate unit **27** targeted has a 3,4-*syn* relative stereochemistry (C7−C8 of **1**). This was achieved through a Mukaiyama aldol reaction on aldehyde **26** with enoxysilane **7a** under $BF_3\cdot OEt_2$ control (Figure 4). A Felkin−Anh transition state had to be favored; therefore, the presence of a large protecting group on the primary hydroxyl (TBDPS) was needed to increase the diastereoselectivity of this reaction (ratio of 11:1 favoring the 3,4-*syn* relative isomer **S16**). The 2,3-*anti*

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stereochemistry (C6−C7 of **1**) was secured by an *anti*-selective hydrogen-transfer reaction as described before. This sequence was also developed as a one-pot reaction using phenylselenated enoxysilanes **7b**.[23e] A similar sequence of reactions was followed in order to successively convert propionate motif **27** to aldehyde **28** (through **S17** and **S18**; 84% over three steps) and then to aldehyde **29** (56% over four steps). The latter was subjected to cycloetherification to form stereoselectively the 3,7-*trans* tetrahydropyran tertiary bromides **30a** and **30b** as a C2 epimeric mixture, in good yield. These bromides were then reduced under radical conditions. The C2−C3 *anti* product **31** was obtained in good yield and ratio (12:1). The major product (2,3-*anti*) **31a** obtained was identical (^{1}H, ^{13}C NMR and $[\alpha]_D$) to the one reported by Cossy et al.[28c] Interestingly, the 2,3-*anti* ratio observed for **31** is significantly improved as compared to its extended analogue **19** (12:1 versus 3.5:1; Scheme 3). This result might point to long distance disturbance of the acyclic substituted side-chain attached at C7, a hypothesis currently being evaluated in a separate study.

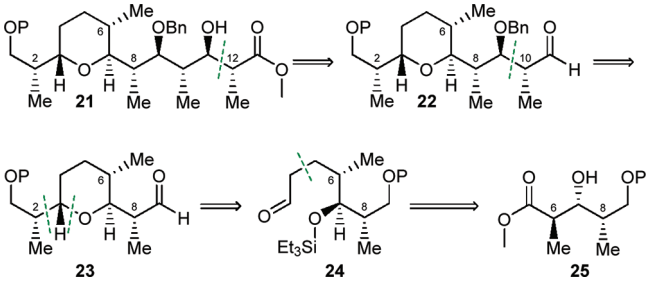
Ester **31** was reduced to the corresponding primary alcohol **S22** and the 2,3-*anti* isomer easily separated by chromatography (Scheme 5). The alcohol at C1 was protected by a benzyl group (**S23**) followed by TBDPS group deprotection (**S24**) and subsequent oxidation of the resulting primary alcohol to aldehyde **32** (68% overall yield from **31**).

We were then ready to synthesize subsequent propionate units following the west to east direction. Interestingly, Cossy et al.[28] used a similar aldehyde and various chiral reagents or approaches (chiral boron enolates; crotyl titanate and allenyl zinc), in their remarkable study.[25c] They were hoping to overcome the opposing inductions of substituents at C7 and C8, in the context of the nucleophilic additions on their aldehyde at C9. The diastereoselectivities observed were modest (4:1 at most) or nonexistent in spite of the demonstrated usefulness of these well-crafted chiral reagents toward polypropionate synthesis. In the case of our substrate-controlled approach, the desired *anti* relative stereochemistry at C8−C9 of **1** required formation of a Cram chelate bicyclic intermediate between the carbonyl of the aldehyde (C9) and the tetrahydropyran oxygen. In addition, we sought to stereoselectively prepare the four possible isomers at C9 and C10 to test the versatility of our approach.

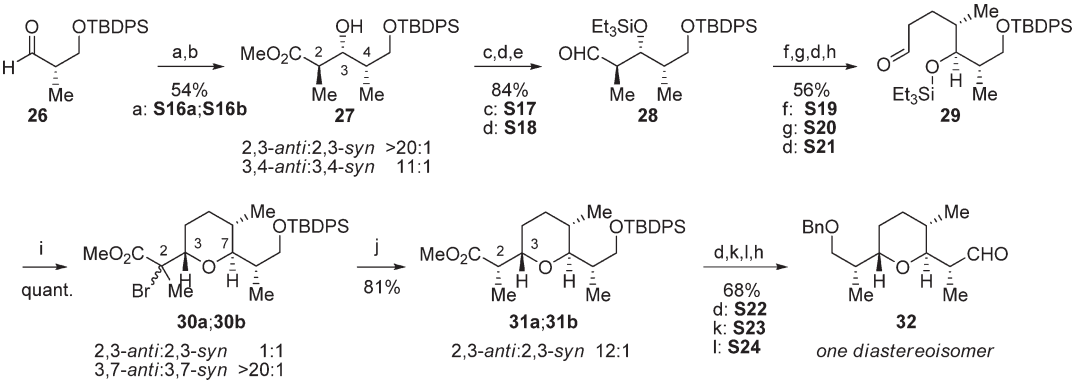
Different Lewis acids were screened for the Mukaiyama aldol reaction (Table 1). Monodentate Lewis acid, such as $BF_3\cdot OEt_2$ (entry 1), led to very good ratios favoring the 8,9-*syn* adduct **34** with an excellent yield. $TiCl_4$, a bidentate Lewis acid, was inefficient to promote a diastereoselective Cram chelate aldol reaction using either 1.3 equiv (entry 2) or 2.5 equiv (entry 3) although good yields of aldol products were recovered. Switching from $TiCl_4$ to 1.3 equiv of $TiCl_3$(O*i*Pr) led to a reversal of the diastereoselectivity toward Felkin−Anh adducts (entry 4). However, 8,9-*anti* Cram chelate adducts **33** were obtained selectively by increasing the amount of Lewis acid to 2.5 equiv (entry 5). As well, we obtained good selectivity toward the 8,9-*anti* products **34** using $MgBr_2\cdot OEt_2$, albeit with a lower yield (entry 6).

These results are interesting in many aspects. We demonstrated for the first time, the feasibility of our approach to successfully achieve an aldolization step in presence of a coordinating functionality embedded in a ring (tetrahydropyran). Increased rigidity of the corresponding Cram chelate intermediate could potentially increase the energy of the transition states. However, we were pleased to note high ratios and good yield. The second point of interest is the importance of the stoichiometry of $TiCl_3$(O*i*Pr) to obtain a high 8,9-*anti* ratio. We did observe a similar requirement in our recent study on the synthesis of stereopentads and suggested that an "ate" complex was involved. Our rationale was based on NMR studies and Gau's previous reports on titanium complexes where he ranked the affinity of various ligands to titanium (*i*PrO$^-$ > Cl$^-$ > THF >

Scheme 4. Retrosynthetic Analysis of West−East Modified Approach



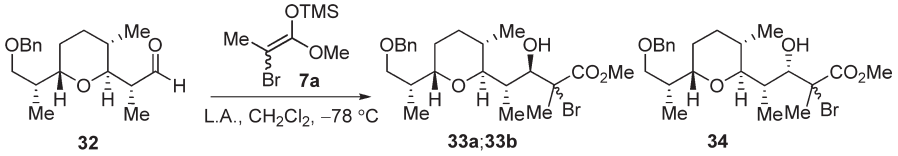
Scheme 5. Synthesis of Tetrahydropyran Fragment 32[a]



[a] Key: (a) $BF_3\cdot OEt_2$, **7a**, CH_2Cl_2, −78 °C; (b) Bu_2BOTf, DIEA, CH_2Cl_2, −78 °C then Bu_3SnH, BEt_3, air, CH_2Cl_2, −78 °C; (c) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; (d) DIBAL-H, CH_2Cl_2, −40 °C; *separation*; (e) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C then NEt_3, −78 °C; (f) $Ph_3PC(H)=CO_2Me$, toluene, reflux; (g) H_2, Pd−C, pyridine, EtOAc, rt; (h) DMP, $NaHCO_3$, CH_2Cl_2, rt; (i) $BiBr_3$, **7a**, CH_2Cl_2/MeCN, −78 °C; (j) Ph_3SnH, BEt_3, air, toluene, −78 °C; (k) BnOC=NHCCl$_3$, TfOH, c-Hex/CH_2Cl_2, 0 °C; (l) TBAF, THF, 0 °C to rt.

dx.doi.org/10.1021/jo2013884 |*J. Org. Chem.* 2011, 76, 7654–7676

Table 1. Iterative Mukaiyama aldolization on aldehyde 32



entry	Lewis acid	(equiv)	yield[c] (%)	selectivity[d] 33:34
1	$BF_3 \cdot OEt_2$[a]	(1.5)	quant[e]	1:>20
2	$TiCl_4$[b]	(1.3)	89	1:1
3	$TiCl_4$[b]	(2.5)	82	6:1
4	$TiCl_3(OiPr)$[b]	(1.3)	77	1:3
5	$TiCl_3(OiPr)$[b]	(2.5)	71	>20:1
6	$MgBr_2.OEt_2$[b]	(5.0)	53	>20:1

[a] Reactions were conducted with 2.0 equiv of enoxysilane **7a** followed by the Lewis acid in CH_2Cl_2 (0.1 M) at −78 °C for 2 h. [b] Aldehydes were precomplexed with the Lewis acid followed by the addition of 2.0 equiv of enoxysilane **7a** in CH_2Cl_2 (0.1 M) at −78 °C for 2 h. [c] Isolated yields over two steps: oxidation then aldol reaction. [d] 8,9-*anti*/8,9-*syn*. Product ratios were determined by ^{1}H NMR analysis of the crude reaction mixture. [e] NMR-based yield since the products could not be separated from the *C*-silylated ester.

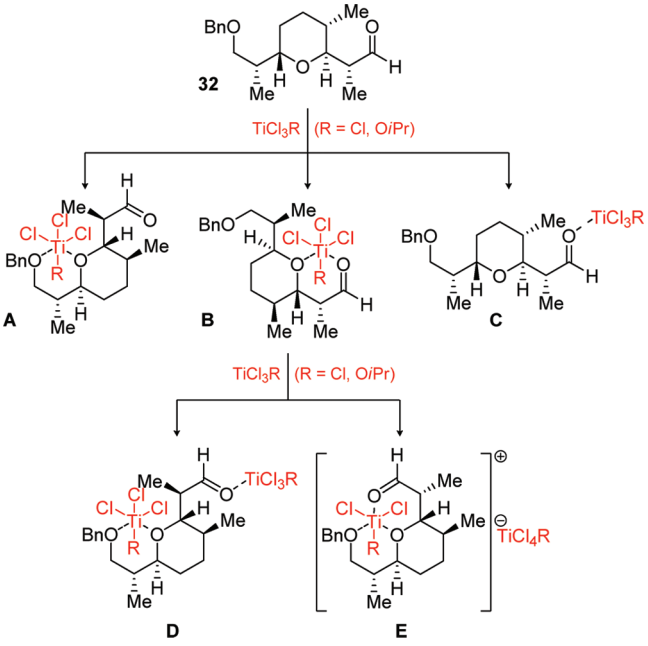
Et_2O > PhCHO > RCO_2Me).[40] Our ^{13}C NMR studies showed, as well, that in presence of an excess of $TiCl_3(OiPr)$, two benzyl ethers and the aldehyde of an acyclic polypropionate were involved in a three-point chelation complex.[23a] The results of entry 5 (Table 1) suggest that a similar complex is at work.

As illustrated in Scheme 6, one could suggest that complex **A** would be significantly populated, both the oxygen of the benzyl ether and that of the substituted tetrahydropyran being better ligands to titanium. This is, however, a nonreactive complex where the carbonyl is not activated by the Lewis acid. A priori, applying the Curtin−Hammet principle, this should be of little consequence, the equilibrium allowing for **B** to be involved in a Cram chelate transition state. Yet, poor ratios were obtained (entry 4; Table 1). This is therefore suggestive that an unidentified monodentate complex such as **C** or **D** be present and also involved in a Felkin−Anh addition. Similarly, this suggests that both transition states leading to 8,9-*anti* and 8,9-*syn* products (**33** and **34**, respectively) are close in energy.

This scenario may be altered by formation of a thermodynamically preferred complex in which the oxygens of the benzyl ether, the tetrahydropyran and the aldehyde are implicated. In order to accommodate three ligands, a chloride has been displaced creating a cationic species stabilized by its counterion, as in the "ate" complex **E** which would also have a slow rate of equilibrium compared to the other possible complexes depicted before. Once the rigid three-point chelate is formed, the stereochemical outcome of the aldol reaction will be controlled by 1,2-induction due to the steric hindrance of enoxysilane **7a**. Interestingly, this "ate" complex may not be obtained if another oxygen, such as an additional benzyl ether, was present in the molecule. This hypothesis will be tested in a further iteration of this approach (vide infra).

Zincophorin possesses a C8−C9 *anti* and a C9−C10 *anti* relative stereochemistry. The major Cram chelate adducts **33a** and **33b** were thus reduced under an acyclic stereocontrol. Excellent yield and 2,3-*anti* diastereoselectivity (**35**) were indeed observed using these conditions (entry 1, Table 2). Other isomers of the C1−C11 fragment of zincophorin were also prepared, attesting to the flexibility of our approach. From Cram chelate adducts **33**, the complementary C9−C10 *syn* product

Scheme 6



36 was efficiently obtained by using a bidentate Lewis acid ($MgBr_2 \cdot OEt_2$) in the hydrogen-transfer step (entry 2, Table 2). The C8−C9 *syn* isomer (Felkin−Anh adduct **34**) achieved as the result of the Mukaiyama reaction in the presence of $BF_3 \cdot OEt_2$ (entry 1, Table 1), was submitted to the same hydrogen-transfer reactions to give, respectively, the C9−C10 *anti* product **37** (entry 3; Table 2) and *syn* **38** (entry 4; Table 2) with excellent diastereoselectivity in both cases.

In order to converge to a C1−C11 fragment of Miyashita's total synthesis, the resulting propionate **35** was debenzylated to intermediate **S25** (Scheme 7) and reprotected by a TIPS group (**S26**), prior to the reduction to the corresponding diol **39**. Diol **39** was found identical to that reported by Miyashita (^{1}H NMR, ^{13}C NMR and $[\alpha]_D$).[29]

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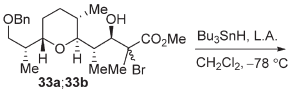
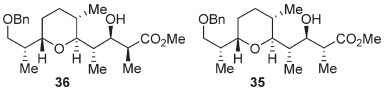
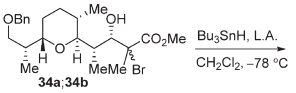
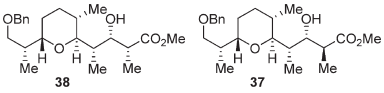
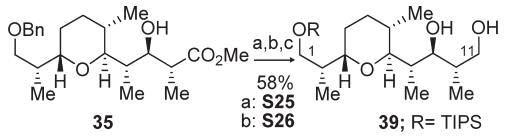
Table 2. Stereoselective Hydrogen Transfer Reactions on C1−C11 Aldol Adducts 33 and 34

Entry	Substrate	Conditions[a]	Products		Yield[b]	Selectivity[c]
						
	33a;33b		**36**	**35**		
1	**33a;33b**	A		**35**	77	1 : >20
2	**33a;33b**	B	**36**		83	>20 : 1
						
	34a;34b		**38**	**37**		
3	**34a;34b**	A		**37**	68	1 : >20
4	**34a;34b**	B	**38**		59	>20 : 1

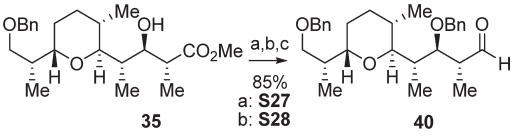
[a] Conditions A: Substrates (0.1 M) were pretreated with *i*-Pr_2NEt (1.5 equiv) and Bu_2BOTf (1.5 equiv) at −78 °C for 1 h. Addition of Bu_3SnH (1.5 equiv) was followed by Et_3B (0.2 equiv) and air (injections of Et_3B and air were repeated every 30 min until the reaction was complete by TLC). Conditions B: Substrates (0.1 M) were pretreated with $AlMe_3$ (3.0 equiv) for 1 h at −78 °C. Addition of Bu_3SnH (1.5 equiv) was followed by Et_3B (0.2 equiv) and air (injections of Et_3B and air were repeated every 30 min until the reaction was complete by TLC). [b] Isolated yields. [c] 9,10-*syn*/9,10-*anti*. Product ratios were determined by ^1H NMR analysis of the crude reaction mixture.

Scheme 7[a]



[a] Key: (a) Pd−C, H_2, MeOH, rt; (b) TIPSOTf, 2,6-lutidine, CH_2Cl_2, rt; (c) DIBAL-H, CH_2Cl_2, −40 °C.

Scheme 8. Synthesis of Aldehyde 40[a]



[a] Key: (a) BnOC═$NHCCl_3$, TfOH, 0 °C; (b) DIBAL-H, CH_2Cl_2, −40 °C; (c) Dess−Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt.

A final iteration (west−east approach) was then considered using aldehyde **40** as a starting material (Scheme 8). The ester **35** was first protected with a benzyl group (**S27**) before being transformed to the corresponding aldehyde **40** (85% over three steps).

The structure of the natural product (Scheme 1) dictated that a C10−C11 *anti* aldol and a C11−C12 *anti* hydrogen transfer be performed. To test the robustness and limitations of our approach, we also planned to synthesize the corresponding three other isomers C1−C13 (Table 3).

Felkin−Anh adduct **42** (C10−C11 *syn*) was efficiently obtained using $BF_3 \cdot OEt_2$ (entry 1, Table 3). The diastereoselective synthesis of the C10−C11 *anti* adducts **41** was, however, problematic. The first Lewis acid used, $MgBr_2 \cdot OEt_2$, was inefficient in promoting the reaction (entry 2). Titanium-based Lewis acids (entries 3−5) gave good yields of coupling adducts, albeit with no significant diastereoselectivities as opposed to our previous results. Only a large excess of $TiCl_4$ (entry 6) led, in a poor yield, to a 5:1 ratio of the desired isomer **41**. After separation, both the C10−C11 *anti*-**41** and *syn*-**42** isomers were submitted to the hydrogen-transfer step (Table 4).

Acyclic-controlled reduction (*anti* hydrogen transfer) of Cram chelate adducts **41** gave the C11−C12 *anti* product **43** with excellent diastereoselectivity (entry 1). The complementary C11−C12 *syn* product **44** was also obtained diastereoselectively using the endocyclic effect (*syn* hydrogen transfer) by inducing formation of the cyclic complex with $AlMe_3$ (entry 2). The C10−C11 *syn* aldol isomer **42** (Felkin−Anh adduct) was reduced stereoselectively, as well (entries 3 and 4). Proofs of structure were provided for compounds **43**−**45** by hydrogenolysis of the benzyl groups and cyclization to their corresponding lactone (**47**, **48**, and **49**, respectively). As illustrated in Scheme 9, the relative stereochemistry of the two newly created stereogenic centers was determined by ^1H NMR analysis using both coupling constants and NOE studies.

As predicted, the presence of additional oxygen in **40** (as compared to **32**) has provided another potential chelation site to titanium that could explain the low ratios noted (entries 5 and 6, Table 3). Formation of the "ate" complex described before (Scheme 6) was not favored. Both reaction pathways (Felkin−Anh and Cram−chelate) are now at play, resulting in a poor ratio for the aldol reaction. We reasoned that removing or blocking one of the chelation sites of **40** may solve the problem. Therefore, our synthesis was modified to replace the benzyl group on the C1-primary alcohol of **35** by a bulky silyl group (TBDPS; 55% over four steps), as illustrated in Scheme 10. The Mukaiyama aldol reactions were then performed on the corresponding aldehyde **50** and the results reported in Table 5. Once again, $BF_3 \cdot OEt_2$, as a monodentate Lewis acid, gave an excellent ratio and yield, favoring the C11−C12 *syn* isomer **52**. We were also pleased to note that adding 4 equiv of $TiCl_3(OiPr)$ provided high ratios of the C11−C12 *anti* product **51** in excellent yield (entry 2). These results support our three-point chelation "ate" complex with $TiCl_3(OiPr)$ described herein. Furthermore, in the context of the synthesis of polyketide-like molecules, they highlight *the necessity during the aldol step to limit the number of potential chelation sites to meet the "ate" complex requirement (three ligands at most)*.

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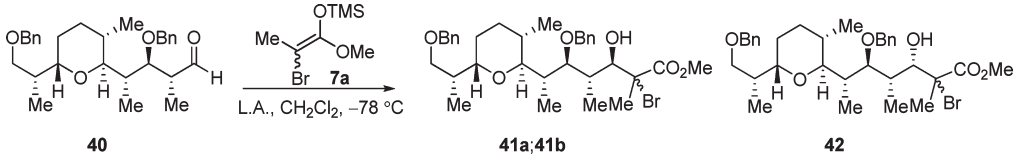
Table 3. Iterative Mukaiyama Aldolization on Aldehyde 40

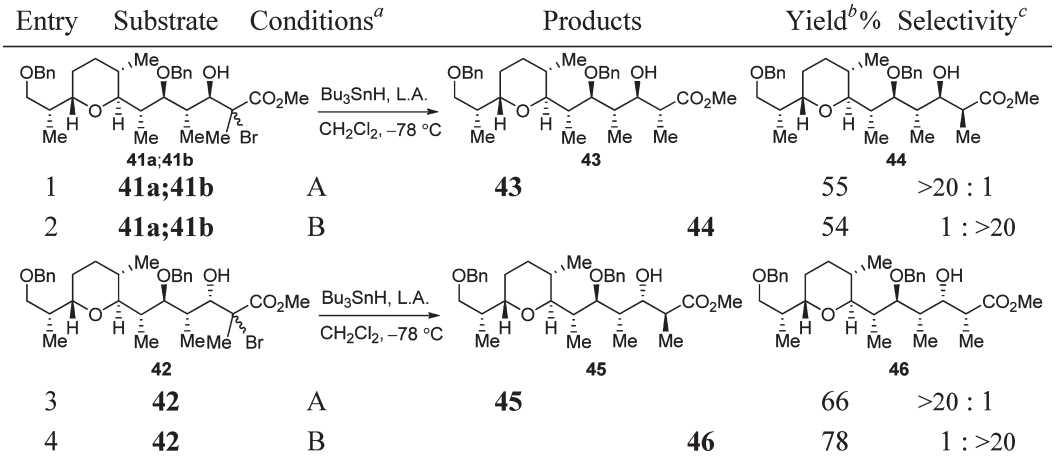


40 41a;41b 42

entry	Lewis acid	(equiv)	yield[c] (%)	selectivity[d] 41:42
1	$BF_3 \cdot OEt_2$[a]	(1.5)	68	1:>20
2	$MgBr_2 \cdot OEt_2$[b]	(5.0)	10	ND
3	$TiCl_3(OiPr)$[b]	(2.5)	62	1:1
4	$TiCl_3(OiPr)$[b]	(4.0)	72	1:1
5	$TiCl_4$[b]	(2.5)	77	2:1
6	$TiCl_4$[b]	(4.0)	32[e]	5:1

[a] Reactions were conducted with 2.0 equiv of enoxysilane **7a** followed by the Lewis acid in CH_2Cl_2 (0.1 M) at −78 °C for 2 h. [b] Aldehydes were precomplexed with the Lewis acid at −78 °C, followed by the addition of 2.0 equiv of enoxysilane **7a** in CH_2Cl_2 (0.1 M) at −78 °C for 2 h. [c] Isolated yields over two steps: oxidation then aldolization. [d] 10,11-*anti*/10,11-*syn*. Product ratios were determined by ^{1}H NMR analysis of the crude reaction mixture. [e] Secondary debenzylation product observed.

Table 4. Stereoselective Hydrogen-Transfer Reactions on C1−C13 Aldol Adducts



[a] Conditions A: Substrates (0.1 M) were pretreated with *i*-Pr_2NEt (1.5 equiv) and Bu_2BOTf (1.5 equiv) at −78 °C for 1 h. Addition of Bu_3SnH (1.5 equiv) was followed by Et_3B (0.2 equiv) and air (injections of Et_3B and air were repeated every 30 min until the reaction was complete by TLC). Conditions B: Substrates (0.1 M) were pretreated with $AlMe_3$ (3.0 equiv) for 1 h at −78 °C. Addition of Bu_3SnH (1.5 equiv) was followed by Et_3B (0.2 equiv) and air (injections of Et_3B and air were repeated every 30 min until the reaction was complete by TLC). [b] Isolated yields. [c] 11,12-*anti*/11,12-*syn*. Product ratios were determined by ^{1}H NMR analysis of the crude reaction mixture.

CONCLUSION

The present study provides evidence that it is possible using a substrate-based approach to synthesize complex polyketide molecules, fragments, and isomers thereof as illustrated herein in the case of zincophorin. We demonstrated that a bidirectional approach to these syntheses can be considered. Central to our approach is the optimization of two Lewis acid controlled reactions: a Mukaiyama aldol reaction and a free-radical-based hydrogen transfer. These processes allow creation of each stereocenter with high levels of 1,2-induction. Synthetic planning of targets and analogues thereof are highly simplified, rendering it accessible to organic and medicinal chemists interested in deciphering the origin of the biological activities of this family of natural products.

We reported a long distance disturbance during the course of one free-radical reduction (exocyclic control) at C2. It is likely to originate from the polysubstituted chain attached at C7, a surprising result to us. The three-dimensional structures of the acyclic polypropionate may be at the source of this disturbance, a hypothesis that will be verified in a separate study. Nevertheless, in all other examples, these hydrogen-transfer reactions were shown to be extremely reliable in terms of diastereocontrol and yield.

Finally, our study also suggests the presence of tricyclic "ate" complexes and their role in Cram chelate controlled Mukaiyama aldolizations in the synthesis of the C1−C13 fragment of zincophorin. In addition, it emphasizes the importance of a protecting group strategy (chelating versus nonchelating) considering their potential impact during the course of *anti* aldolizations using titanium-based Lewis acids. In this context, exceeding two ether-like sites of chelation is more likely to be troublesome. Considering that polyketide synthesis could be envisioned in a bidirectional

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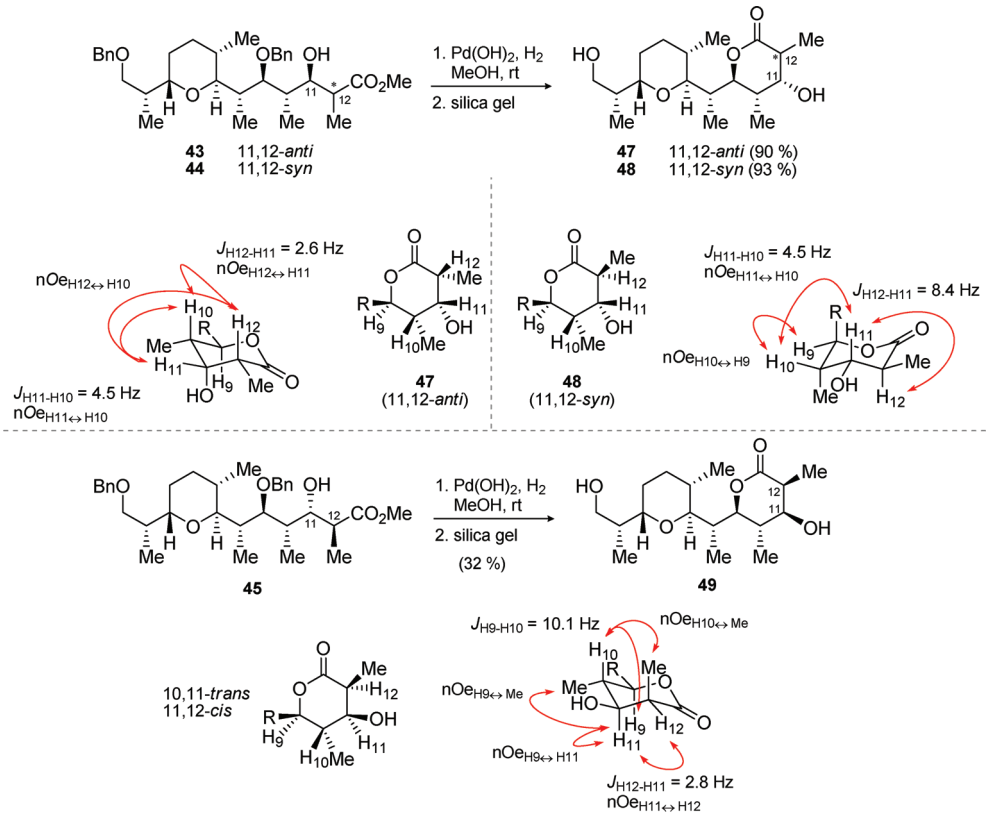
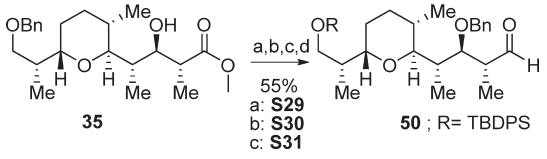
Scheme 9. Proof of Structure for Compounds 43, 44 and 45



Scheme 10. Synthesis of Aldehyde 50[a]



[a] Key: (a) (i) H_2, Pd−C, MeOH, rt; (ii) TBDPSCl, NEt_3, DMAP, CH_2Cl_2; (b) BnOC═NHCCl$_3$, TfOH, c-Hex/CH_2Cl_2, 0 °C; (c) DIBAL-H, CH_2Cl_2, −40 °C; (d) Dess−Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt.

fashion, these mechanistic insights are extremely valuable to help design the most efficient route of synthesis.

EXPERIMENTAL SECTION

General Comments. Silylated enol ethers **7a** (X = Br) and **7b** (X = SePh) were prepared according to the procedure already described by our group.[23a] Experimental methods and physical characterization of products **S1a**, **S1b**, and **11**[23b] and products **S2**, **S3**, **12**, **S4a**, **S4b**, and **13**[23e] have already been reported by our group. All procedures requiring anhydrous conditions were carried out under a positive argon atmosphere in oven-dried glassware. All solvents were purified by standard methods. ^{1}H (400 or 500 MHz) and ^{13}C spectra (100 or 125 MHz) were referenced to residual solvent peaks, and ratios of products were measured from crude ^{1}H spectra. Optical rotations were measured at room temperature from the sodium D line (589 nm) using a cell of 1 mL measuring 1 dm in length. Infrared spectra were recorded on a FTIR spectrophotometer on a NaCl support. Mass spectra were recorded either through electrospray ionization (ESI) or electron impact (EI) on an instrument operating at 70 eV, and FAB mass spectra were recorded with or without ionization.

General Experimental Method for Mukaiyama Aldol Reaction: Felkin−Anh Control (A1). To a cold (−78 °C) solution of aldehyde **14** (8.50 g) in dry CH_2Cl_2 (0.1 M, 179 mL) were added successively silylated enol ether **7a** (3 equiv, 9.9 mL) and $BF_3 \cdot OEt_2$ (1.5 equiv, 3.4 mL), followed by stirring for 1 h at −78 °C. The reaction mixture was treated with a saturated aqueous solution of NH_4Cl, followed by separation of the organic phase at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3×), and the combined organic fractions were dried ($MgSO_4$), filtered, and concentrated in vacuo to a pale yellow oil. The crude product yielded an inseparable mixture of 3,4-*syn* bromide adducts **S7a** and **S7b** in a >20:1 ratio of products 3,4-*syn*/3,4-*anti* which was used without further purification.

(−)-(3*R*,4*R*,5*R*,6*S*,7*S*,8*S*)-Methyl 5,7,9-tris(benzyloxy)-2-bromo-3-hydroxy-2,4,6,8-tetramethylnonanoate (S7a, S7b): R_f = 0.23 (hexanes/EtOAc, 80:20); formula $C_{35}H_{45}BrO_6$; MW 641.63 g/mol; $[\alpha]_D$ −27.1 (*c* 0.35, $CHCl_3$); IR (neat) ν_{max} 3461, 2876, 1730, 1453, 1252, 735 cm^{-1}; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 139.0, 138.7, 138.0, 128.5, 128.27, 128.24, 127.78, 127.75, 127.50, 127.40, 127.34, 87.9, 84.1, 74.8, 74.4, 74.1, 73.0, 72.6, 53.1, 37.3, 36.9, 36.4, 24.7, 16.3, 14.8, 13.6 ppm; MS (ESI) *m*/*z* 663.2 (M + Na$^+$, 30), 583.2 (100); HRMS calcd for $C_{35}H_{45}BrO_6Na$ [M + Na$^+$] 663.2297, found 663.2308 (1.6 ppm).

General Experimental Method for Mukaiyama Aldol Reaction: Cram Chelate Control (A2). To a cold (−78 °C) solution of aldehyde **32** (213 mg) in dry CH_2Cl_2 (0.1 M, 7 mL) was added a 1 M solution of $TiCl_3(OiPr)$ in CH_2Cl_2 (2.5 equiv, 1.75 mL), followed by stirring for 5 min at −78 °C. To the mixture was added silylated enol ether **7a** (3 equiv, 0.39 mL), followed by stirring for 1 h at −78 °C. The reaction mixture was treated with the addition of a saturated aqueous

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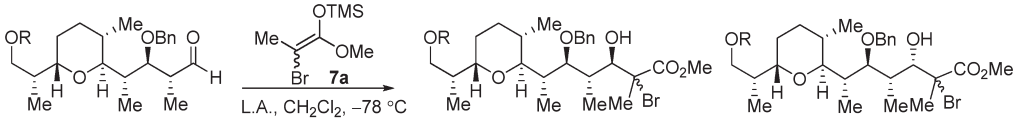
Table 5. Iterative Mukaiyama Aldolization on Aldehyde 50



50 R = TBDPS **51** **52**

entry	Lewis acid	equiv	product	yield[c] (%)	selectivity[d] **51**:**52**
1	$BF_3 \cdot OEt_2$[a]	1.5	**52**	quant	1:>20
2	$TiCl_3(OiPr)$[b]	4.0	**51**	93	>20:1

[a] Reaction was conducted with 2.0 equiv of enoxysilane **7a** followed by the Lewis acid in CH_2Cl_2 (0.1 M) at −78 °C for 2 h. [b] Aldehyde was precomplexed with the Lewis acid at −78 °C followed by the addition of 2.0 equiv of enoxysilane **7a** in CH_2Cl_2 (0.1 M) at −78 °C for 2 h. [c] Isolated yields over two steps: oxidation then aldolization. [d] 10,11-*anti*/10,11-*syn*. Product ratios were determined by ^1H NMR analysis of the crude reaction mixture.

solution of NH_4Cl into the mixture followed by separation of the organic phase at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3×), and the combined organic fractions were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (hexanes/EtOAc, 85:15) to give a ∼1: 1 mixture of bromide adducts **33a** and **33b** as a pale yellow oil (271 mg, yield =71% over two steps) in a >20:1 ratio of products 3,4-*anti* (**33a**,**b**):3,4-*syn* (**34**). The purified mixture of bromide adducts was found to be contaminated by unreactive *C*-silylated product from enol ether **7a**.

(±)-(3*R*,4*S*)-Methyl 4-((2*S*,3*S*,6*S*)-6-((*R*)-1-(Benzyloxy)propan-2-yl)-3-methyltetrahydro-2*H*-pyran-2-yl)-2-bromo-3-hydroxy-2-methylpentanoate (33a and 33b). **33a**: R_f = 0.40 (hexanes/EtOAc, 85:15); formula $C_{23}H_{35}BrO_5$; MW 471.43 g/mol; IR (neat) ν_{max} 3407, 2952, 2927, 2856, 1738, 1453, 1378, 1258, 1117, 1097, 1039, 1019, 962, 915, 738, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39−7.26 (m, 5H), 4.58 (d, J = 12.4 Hz, 1H), 4.55 (d, J = 12.4 Hz, 1H), 4.25 (d, J = 8.3 Hz, 1H), 3.75 (s, 3H), 3.71 (dd, J = 1.7 Hz, 9.9 Hz, 1H), 3.63 (dd, J = 4.4 Hz, 9.1 Hz, 1H), 3.65−3.59 (m, 1H), 3.57−3.51 (m, 1H), 3.35 (dd, J = 6.7 Hz, 9.1 Hz, 1H), 2.41−2.31 (m, 1H), 1.86 (s, 3H), 1.84−1.75 (m, 1H), 1.73−1.61 (m, 2H), 1.33−1.21 (m, 3H), 0.89 (d, J = 6.8 Hz, 3H), 0.79 (d, J = 6.4 Hz, 3H), 0.75 (d, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 138.7, 128.4, 127.5, 127.5, 75.5, 75.4, 75.3, 73.9, 73.1, 69.4, 52.9, 37.4, 31.8, 31.4, 30.9, 27.7, 26.2, 21.8, 17.7, 14.8 ppm; MS (ESI) m/z 149.1 (11), 233.2 (22), 263.0 (100), 283.2 (15), 345.1 (12), 373.2 (9), 471.2 (^{79}Br; M + H^+, 34); HRMS calcd for $C_{23}H_{36}O_5{}^{79}Br$ [M + H^+] 471.17409, found 471.1741 (0.1 ppm). **33b**: R_f = 0.31 (hexanes/EtOAc, 85:15); formula $C_{23}H_{35}BrO_5$; MW 471.43 g/mol; IR (neat) ν_{max} 3405, 3029, 2952, 2930, 2860, 1741, 1453, 1379, 1253, 1098, 1070, 1017, 963, 739, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36−7.26 (m, 5H), 4.57 (d, J = 4.4 Hz, 1H), 4.53 (d, J = 12.2 Hz, 1H), 4.50 (d, J = 12.2 Hz, 1H), 4.14−4.10 (m, 1H), 3.81−3.78 (m, 1H), 3.76 (s, 3H), 3.71−3.66 (m, 1H), 3.56 (dd, J = 4.7 Hz, 9.1 Hz, 1H), 3.37 (dd, J = 6.0 Hz, 9.1 Hz, 1H), 2.38−2.26 (m, 1H), 2.17 (ddq, J = 1.7 Hz, 5.4 Hz, 7.1 Hz, 1H), 1.94 (s, 3H), 1.73−1.64 (m, 3H), 1.63−1.54 (m, 1H), 1.30−1.20 (m, 1H), 1.06 (d, J = 7.2 Hz, 3H), 0.87 (d, J = 6.9 Hz, 3H), 0.85 (d, J = 6.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 138.4, 128.3, 127.7, 127.5, 78.1, 76.2, 75.7, 74.3, 73.1, 65.9, 53.1, 36.7, 32.1, 31.5, 27.4, 26.1, 25.1, 18.0, 14.8, 12.7 ppm; MS (ESI) m/z 413.2 (8), 471.2 (^{79}Br; M + H^+, 20), 493.2 (^{79}Br; M + Na^+, 100), 495.2 (^{81}Br; M + Na^+, 99); HRMS calcd for $C_{23}H_{36}O_5{}^{79}Br$ [M + H^+] 471.1741, found 471.1739 (−0.3 ppm); calcd for $C_{23}H_{35}O_5{}^{79}BrNa$ [M + Na^+] 493.1560, found 493.1555 (−1.1 ppm).

General Experimental Method for Radical Reduction: Exocyclic Effect Control (A3). To a cold (−78 °C) solution of a mixture of bromides **18a** and **18b** (0.99 g) in dry toluene (0.1 M, 14 mL) were added successively Ph_3SnH (2 equiv, 0.72 mL), a 1 M solution of BEt_3 in CH_2Cl_2 (0.2 equiv, 280 μL), and air (syringe). The reaction mixture was maintained at −78 °C as supplementary addition of BEt_3 solution (0.2 equiv, 280 μL) and air was realized each 30 min, until the reaction was judged complete by TLC (3−4 h). The reaction was treated with the addition of 1,4-dinitrobenzene (0.2 equiv, 47 mg) and stirring of the mixture for 15 min at −78 °C. Once at room temperature, the reaction was concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (hexanes/EtOAc, 90:10) to give an inseparable mixture of reduced product **19a** and **19b** as a pale yellow oil (0.813 g, yield = 92%) in a 3.5:1 ratio of products 2,3-*anti* (**19a**)/2,3-*syn* (**19b**).

(+)-Methyl 2-((2*S*,5*S*,6*S*)-5-methyl-6-((2*S*,3*S*,4*S*,5*S*,6*S*)-3,5,7-tris(benzyloxy)-4,6-dimethylheptan-2-yl)tetrahydro-2*H*-pyran-2-yl)propanoate (19a, 19b): R_f = 0.27 (hexanes/EtOAc, 85:15); formula $C_{40}H_{54}O_6$; MW 630.85 g/mol; $[\alpha]_D$ +28.6 (c 0.39, $CHCl_3$); IR (neat) ν_{max} 2949, 1737, 1455, 1376, 966, 734, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37−7.19 (m, 15$H_{19a,19b}$), 4.72−4.37 (m, 6$H_{19a,19b}$), 3.90−3.83 (m, 1H_{19a}), 3.82−3.75 (m, 1H_{19b}), 3.68 (dd, J = 9.2 Hz, 4.4 Hz, 1H_{19a}), 3.64 (s, 3H_{19b}), 3.61 (s, 3H_{19a}), 3.59−3.50 (m, 2H_{19a}, 3H_{19b}), 3.46−3.38 (m, 2$H_{19a,19b}$), 2.88−2.79 (m, 1H_{19b}), 2.73−2.64 (m, 1H_{19a}), 2.34−2.04 (m, 3$H_{19a,19b}$), 1.76−1.38 (m, 4$H_{19a,19b}$), 1.29−1.18 (m, 1$H_{19a,19b}$), 1.14 (d, J = 6.8 Hz, 3H_{19b}), 1.10 (d, J = 7.0 Hz, 3H_{19b}), 1.08−0.99 (m, 9H_{19a}, 3H_{19b}), 0.96 (d, J = 7.1 Hz, 3H_{19b}), 0.92 (d, J = 7.0 Hz, 3H_{19a}), 0.75 (d, J = 6.6 Hz, 3H_{19a}), 0.72 (d, J = 6.3 Hz, 3H_{19b}) ppm; ^{13}C NMR [19a] (100 MHz, $CDCl_3$) δ 176.0, 139.7, 139.5, 138.8, 128.3, 128.13, 128.07, 127.5, 127.3, 127.04, 126.99, 84.1, 83.5, 77.7, 73.3, 73.2, 73.0, 72.7, 72.5, 51.5, 43.2, 37.7, 37.2, 36.3, 29.3, 26.2, 24.2, 18.2, 16.7, 15.2, 13.9, 11.8 ppm; MS (ESI) m/z 631.4 (M + H^+, 25), 415.3 (80), 325.2 (35), 185.1 (100); HRMS calcd for $C_{40}H_{56}O_6$ [M + H^+] 631.3999, found 631.3974 (3.9 ppm). Anal. Calcd for $C_{40}H_{54}O_6$: C, 76.16; H, 8.63. Found: C, 76.50; H, 8.63.

General Experimental Method for Radical Reduction: Acyclic Stereoselection Control (A4). To a cold (−78 °C) solution of a mixture of bromides **S7a** and **S7b** (4.30 g) in dry CH_2Cl_2 (0.1 M, 67 mL) were added successively DIEA (1.5 equiv, 1.75 mL) and a 1 M solution of Bu_2BOTf in CH_2Cl_2 (1.3 equiv, 8.70 mL) followed by stirring for 1.5 h at −78 °C. The mixture was then successively treated with Bu_3SnH (2 equiv, 3.60 mL), a 1 M solution of BEt_3 in CH_2Cl_2 (0.2 equiv, 1.35 mL), and air (syringe). Supplementary addition of BEt_3 solution (0.2 equiv, 1.35 mL) and air was realized each 30 min until reaction was judged completed by TLC (3−4 h). The reaction was treated with the addition of 1,4-dinitrobenzene (0.2 equiv, 227 mg) and stirring of the mixture for 15 min at −78 °C before being treated by a saturated aqueous solution of NH_4Cl. The organic phase was separated at room temperature, and the aqueous layer was extracted with Et_2O (3×). Combined organic fractions were washed (2×) with a saturated aqueous solution of KF and brine before being dried ($MgSO_4$). The

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filtrate was concentrated to a residue which was solubilized in MeOH and cooled to 0 °C before being treated by a 35% w/w of H_2O_2 in water (3 equiv, 1.77 mL). The solution was stirred for 2 h at 0 °C and then treated with addition of water before extraction with Et_2O (3×). Combined organic fractions were washed with a saturated brine solution, then dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (hexanes/EtOAc, 85:15) to give 2,3-*anti* product **15** (3.09 g, yield = 82%) in a >20:1 ratio of product 2,3-*anti*/2,3-*syn* as a pale yellow oil.

(−)-(2*R*,3*R*,4*R*,5*R*,6*S*,7*S*,8*S*)-Methyl 5,7,9-tris(benzyloxy)-3-hydroxy-2,4,6,8-tetramethylnonanoate (15): R_f = 0.25 (hexanes/EtOAc, 75:25); formula $C_{35}H_{46}O_6$; MW 562.74 g/mol; $[\alpha]_D$ −41.7 (*c* 0.23, $CHCl_3$); IR (neat) ν_{max} 3494, 3030, 2969, 1737, 1455 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34−7.20 (m, 15H), 4.67 (d, *J* = 10.9 Hz, 1H), 4.58 (d, *J* = 11.4 Hz, 1H), 4.53 (d, *J* = 10.4 Hz, 1H), 4.48 (d, *J* = 7.4 Hz, 1H), 4.44 (s, 2H), 4.18 (d, *J* = 10.1 Hz, 1H), 3.80 (d, *J* = 0.8 Hz, 1H), 3.71 (s, 3H), 3.70−3.67 (m, 1H), 3.60−3.49 (m, 3H), 2.61−2.51 (m, 1H), 2.44−2.35 (m, 1H), 2.20−2.09 (m, 1H), 2.01−1.91 (m, 1H), 1.09 (d, *J* = 7.0 Hz, 3H), 1.07 (d, *J* = 7.0 Hz, 3H), 1.05 (d, *J* = 7.0 Hz, 3H), 0.96 (d, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 138.8, 138.7, 137.7, 128.4, 128.3, 127.8, 127.6, 127.5, 127.41, 127.37, 86.7, 83.6, 74.7, 73.9, 73.0, 72.9, 72.6, 51.8, 43.6, 37.5, 36.9, 34.2, 16.3, 14.3, 13.6, 11.8 ppm; MS (FAB) *m*/*z* 563.2 (M + H^+, 24), 181.1 (100), 154.0 (35); HRMS calcd for $C_{31}H_{40}O_4Na$ [M + Na^+] 499.2824, found 499.2824 (0.7 ppm). Anal. Calcd for $C_{35}H_{46}O_6$: C, 74.70; H, 8.24. Found: C, 74.74; H, 7.92.

General Experimental Method for Radical Reduction: Endocyclic Effect Control with $MgBr_2 \cdot OEt_2$ (A5). To a cold (0 °C) solution of a mixture of bromides **33a** and **33b** (14.1 mg) in dry CH_2Cl_2 (0.1 M, 300 μL) was added $MgBr_2 \cdot OEt_2$ (3 equiv, 23 mg). The reaction mixture was stirred at 0 °C for 1 h and then cooled to −78 °C before successive additions of Bu_3SnH (2 equiv, 16 μL), a 1 M solution of BEt_3 in CH_2Cl_2 (0.2 equiv, 6 μL), and air (syringe). Supplementary addition of BEt_3 solution (0.2 equiv, 6 μL) and air was realized each 30 min until the reaction was judged completed by TLC (3−4 h). The reaction was treated with the addition of 1,4-dinitrobenzene (0.2 equiv, 1 mg) and stirring of the mixture for 15 min at −78 °C before being treated by a saturated aqueous solution of NH_4Cl. The organic phase was separated at room temperature, and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated in vacuo to a pale yellow oil. The crude product was purified by flash chromatography on silica gel (hexanes/EtOAc, 90:10) to give product **36** (9.8 mg, yield =83%) in a >20:1 ratio of product 2,3-*syn* (**36**): 2,3-*anti* (**35**) as a pale yellow oil.

(±)-(2*S*,3*R*,4*S*)-Methyl 4-((2*S*,3*S*,6*S*)-6-((*R*)-1-(benzyloxy)-propan-2-yl)-3-methyltetrahydro-2*H*-pyran-2-yl)-3-hydroxy-2-methylpentanoate (36): R_f = 0.27 (hexanes/EtOAc, 85:15); formula $C_{23}H_{36}O_5$; MW 392.53 g/mol; IR (neat) ν_{max} 3452, 2930, 2859, 1736, 1456, 1379, 1246, 1201, 1072, 1017, 962, 913, 735, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37−7.25 (m, 5H), 4.53 (d, *J* = 12.1 Hz, 1H), 4.49 (d, *J* = 12.1 Hz, 1H), 3.84−3.78 (m, 1H), 3.78−3.72 (m, 2H), 3.68−3.63 (m, 1H), 3.65 (s, 3H), 3.61 (dd, *J* = 3.6 Hz, 9.0 Hz, 1H), 3.37 (dd, *J* = 6.8 Hz, 8.8 Hz, 1H), 2.70 (dq, *J* = 7.0 Hz, 7.0 Hz, 1H), 2.45−2.35 (m, 1H), 1.75−1.65 (m, 3H), 1.65−1.52 (m, 2H), 1.32−1.21 (m, 1H), 1.26 (d, *J* = 7.0 Hz, 3H), 0.98 (d, *J* = 7.1 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.76 (d, *J* = 6.5 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 138.6, 128.3, 127.5, 127.4, 75.8, 75.4, 75.0, 73.6, 73.2, 51.5, 43.3, 35.4, 31.8, 31.6, 27.2, 26.1, 17.6, 14.9, 12.6, 10.6 ppm; MS (ESI) *m*/*z* 393.3 (M + H^+, 100); HRMS calcd for $C_{23}H_{37}O_5$ [M + H^+] 393.2636, found 393.2624 (−3.0 ppm).

General Experimental Method for Radical Reduction: Endocyclic Effect Control with $AlMe_3$ (A6). To a cold (−78 °C) solution of a mixture of bromide **41a** and **41b** (21.1 mg) in dry CH_2Cl_2 (0.1 M, 340 μL) was added a 2 M solution of $AlMe_3$ in hexanes (2.5 equiv, 52 μL). The reaction mixture was stirred at −78 °C for 1 h before successive additions of Bu_3SnH (2 equiv, 18 μL), a 1 M solution of BEt_3 in CH_2Cl_2 (0.2 equiv, 7 μL), and air (syringe). Supplementary addition of BEt_3 solution (0.2 equiv, 7 μL) and air was realized each 30 min until the reaction was judged completed by TLC (3−4 h). The reaction was treated with the addition of 1,4-dinitrobenzene (0.2 equiv, 1 mg) and stirring of the mixture for 15 min at −78 °C. The mixture was treated first with the dropwise addition of MeOH at −78 °C until gas evolution ceased, followed by a saturated aqueous solution of potassium sodium tartrate (Rochelle's salt). The mixture was stirred overnight at room temperature followed by separation of the organic phase. The organic phase was separated at room temperature, and the aqueous layer was extracted with Et_2O (3×). The combined organic fractions were washed with a saturated aqueous solution of KF. The combined organic fractions were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (hexanes/EtOAc, 85:15) to give product **44** as a pale yellow oil (10.1 mg, yield = 55%) in a >20:1 ratio of products 2,3-*syn* (**44**)/2,3-*anti* (**43**).

(±)-(2*S*,3*R*,4*S*,5*S*,6*S*)-Methyl 5-(benzyloxy)-6-((2*S*,3*S*,6*S*)-6-((*R*)-1-(benzyloxy)propan-2-yl)-3-methyltetrahydro-2*H*-pyran-2-yl)-3-hydroxy-2,4-dimethylheptanoate (44): R_f = 0.18 (hexanes/EtOAc, 85:15); formula $C_{33}H_{48}O_6$; MW 540.73 g/mol; IR (neat) ν_{max} 3515, 3029, 2952, 2927, 1735, 1495, 1455, 1379, 1201, 1092, 1066, 1025, 969, 735, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35−7.23 (m, 10H), 4.63 (d, *J* = 11.3 Hz, 1H), 4.58 (d, *J* = 11.3 Hz, 1H), 4.48−4.43 (m, 2H), 4.09 (dd, *J* = 2.9 Hz, 9.3 Hz, 1H), 3.70 (s, 3H), 3.63 (dd, *J* = 3.7 Hz, 8.7 Hz, 1H), 3.56−3.50 (m, 2H), 3.48 (dd, *J* = 4.9 Hz, 6.4 Hz, 2H), 3.36 (dd, *J* = 7.1 Hz, 8.6 Hz, 1H), 2.63 (dq, *J* = 2.8 Hz, 7.0 Hz, 1H), 2.25−2.15 (m, 1H), 2.09−2.00 (m, 1H), 1.99−1.90 (m, 1H), 1.79−1.47 (m, 5H), 1.16 (d, *J* = 7.1 Hz, 3H), 0.99 (d, *J* = 7.0 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 7.1 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.2, 138.8, 138.3, 128.4, 128.2, 127.6, 127.6, 127.5, 127.3, 86.4, 76.6, 74.1, 74.0, 73.1, 72.9, 72.4, 51.8, 42.1, 37.9, 35.6, 29.8, 27.8, 26.8, 26.6, 24.7, 18.4, 15.8, 14.0, 11.9, 9.0 ppm; MS (ESI) *m*/*z* 541.4 (M + H^+, 12), 563.3 (M + Na^+, 100), 653.4 (10); HRMS calcd for $C_{33}H_{49}O_6$ [M + H^+] 541.3524, found 541.3517 (−1.2 ppm); calcd for $C_{33}H_{48}O_6Na$ [M + Na^+] 563.3343, found 563.3340 (−0.5 ppm).

General Experimental Method for Protection of Alcohol with Benzyl Ether (A7). To a cold (0 °C) solution of alcohol **13** (10.16 g) in *c*-Hex/CH_2Cl_2 (2: 1, 0.1 M, 245 mL) were added successively 2,2,2-benzyltrichloroacetimidate (1.5 equiv, 6.83 mL) and TfOH (0.1 equiv, 0.22 mL), followed by overnight stirring at 0 °C. The reaction mixture was treated with NEt_3 (0.15 equiv, 0.40 mL) and then concentrated in vacuo. The crude product was dissolved in hexanes and filtered onto a pad of Celite. The filtrate was concentrated and purified by flash chromatography on silica gel (hexanes/EtOAc, 85:15) to give product **S5** as a colorless oil (10.01 g, yield = 81%).

(+)-(2*S*,3*S*,4*S*,5*S*,6*S*)-Methyl 3,5,7-tris(benzyloxy)-2,4,6-trimethylheptanoate (S5): R_f = 0.25 (hexanes/EtOAc, 85:15); formula $C_{32}H_{40}O_5$; MW 504.66 g/mol; $[\alpha]_D$ +12.2 (*c* 0.45, $CHCl_3$); IR (neat) ν_{max} 3087, 3063, 3029, 2879, 1735, 1454 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.13 (m, 15H), 4.65 (d, *J* = 11.3 Hz, 1H), 4.54 (s, 2H), 4.47 (d, *J* = 11.3 Hz, 1H), 4.44 (d, *J* = 1.6 Hz, 2H), 3.86 (t, *J* = 5.3 Hz, 1H), 3.62 (s, 3H), 3.62−3.59 (m, 1H), 3.55 (dd, *J* = 10.5 Hz, 4.7 Hz, 1H), 3.42 (dd, *J* = 9.1 Hz, 7.0 Hz, 1H), 2.98 (dq, *J* = 6.9 Hz, 6.9 Hz, 1H), 2.28−2.18 (m, 1H), 2.18−2.09 (m, 1H), 1.16 (d, *J* = 7.1 Hz, 3H), 1.07 (d, *J* = 7.0 Hz, 3H), 0.97 (d, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 139.0, 138.77, 138.73, 128.3, 128.2, 127.6, 127.46, 127.41, 127.35, 127.29, 83.4, 83.0, 73.5, 73.0, 72.5, 51.5, 42.4, 37.5, 36.4, 16.2, 13.8, 13.0 ppm; MS (ESI) *m*/*z* 519.3 (M + H^+, 100), 541.2 (M + Na^+, 55), 181.1 (100); HRMS calcd for $C_{33}H_{43}O_5$ [M + H^+] 519.3111, found 519.3095 (−1.8 ppm).

General Experimental Method for Protection of Alcohol with Trialkylsilyl Trifluoromethanesulfonate Reagents (A8). To a cold (0 °C) solution of alcohol **15** (2.25 g) in dry CH_2Cl_2 (0.1 M, 40 mL) were added successively 2,6-lutidine (1.2 equiv, 0.56 mL) and TESOTf (1.1 equiv, 1.00 mL). The reaction mixture was stirred for 1.5 h at 0 °C or until alcohol was completely consumed as verified by TLC. The reaction mixture was then treated with a saturated aqueous solution of NH_4Cl followed by separation of the organic phase at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3×), and the combined organic fractions were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (hexanes/EtOAc, 95:5) to give the desired protected alcohol **S8** as a colorless oil (2.74 g, quantitative yield).

(+)-(2*R*,3*R*,4*S*,5*S*,6*S*,7*S*,8*S*)-Methyl 5,7,9-tris(benzyloxy)-2,4,6,8-tetramethyl-3-(triethylsilyloxy)nonanoate (S8): R_f = 0.19 (hexanes/EtOAc, 90:10); formula $C_{41}H_{60}O_6Si$; MW 677.00 g/mol; $[\alpha]_D$ +18.2 (*c* 0.22, $CHCl_3$); IR (neat) ν_{max} 2954, 2877, 1738, 1455, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39−7.22 (m, 15H), 4.74 (d, *J* = 3.9 Hz, 1H), 4.71 (d, *J* = 4.0 Hz, 1H), 4.60 (d, *J* = 21.0 Hz, 1H), 4.57 (d, *J* = 21.0 Hz, 1H), 4.50 (d, *J* = 12.0 Hz, 1H), 4.46 (d, *J* = 12.0 Hz, 1H), 4.23 (dd, *J* = 7.4 Hz, 1.7 Hz, 1H), 3.72 (dd, *J* = 9.2 Hz, 5.0 Hz, 1H), 3.61−3.54 (m, 1H), 3.56 (s, 3H), 3.46−3.39 (m, 2H), 2.61−2.51 (m, 1H), 2.37−2.27 (m, 1H), 2.27−2.15 (m, 1H), 2.03−1.92 (m, 1H), 1.10 (d, *J* = 4.7 Hz, 3H), 1.08 (d, *J* = 5.0 Hz, 3H), 0.92−0.86 (m, 12H), 0.84 (d, *J* = 7.0 Hz, 3H), 0.64−0.47 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 139.4, 139.3, 138.7, 128.3, 128.2, 128.1, 127.5, 127.4, 127.12, 127.06, 127.0, 126.6, 84.9, 83.5, 74.1, 73.40, 73.36, 73.0, 72.3, 51.3, 45.8, 39.3, 37.3, 36.3, 16.5, 15.9, 13.7, 11.7, 7.0, 5.6 ppm; MS (ESI) *m*/*z* 699.4 (M + Na^+, 100), 591.3 (10), 435.2 (12); HRMS calcd for $C_{41}H_{60}O_6NaSi$ [M + Na^+] 699.4057, found 699.4059 (0.3 ppm). Anal. Calcd for $C_{41}H_{60}O_6Si$: C, 72.74; H, 8.93. Found: C, 72.72; H, 8.83.

General Experimental Method for Reduction of Ester to Primary Alcohol with DIBAL-H (A9). To a cold (−40 °C) solution of ester **S5** (1.67 g) in dry CH_2Cl_2 (0.1 M, 33 mL) was added a 1.0 M solution of DIBAL-H in hexanes (3 equiv, 9.9 mL). The mixture was stirred for 1 h at −40 °C or until ester was completely consumed as verified by TLC. The reaction mixture was treated first with the dropwise addition of MeOH at −40 °C until gas evolution ceased, followed by a saturated potassium sodium tartrate solution (Rochelle's salt). The mixture was stirred for 1 h at room temperature (or until clarification of phases) followed by separation of the organic phase. The aqueous layer was extracted with Et_2O (3×), and the combined organic fractions were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (hexanes/EtOAc, 75:25) to give the desired primary alcohol **S6** as a colorless oil (1.46 g, yield = 93%).

(−)-(2*R*,3*R*,4*R*,5*S*,6*S*)-3,5,7-Tris(benzyloxy)-2,4,6-trimethylheptan-1-ol (S6): R_f = 0.19 (hexanes/EtOAc, 75:25); formula $C_{31}H_{40}O_4$; MW 476.65 g/mol; $[\alpha]_D$ −10.0 (*c* 0.39, $CHCl_3$); IR (neat) ν_{max} 3451, 3063, 3030, 1495, 1455 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.24 (m, 15H), 4.65 (d, *J* = 11.1 Hz, 1H), 4.55 (d, *J* = 1.5 Hz, 2H), 4.48 (d, *J* = 10.4 Hz, 1H), 4.47 (s, 2H), 3.81 (ddd, *J* = 11.1 Hz, 4.8 Hz, 3.3 Hz, 1H), 3.64−3.58 (m, 2H), 3.57−3.46 (m, 3H), 2.86 (dd, *J* = 6.7 Hz, 4.8 Hz, 1H), 2.36−2.26 (m, 1H), 2.25−2.14 (m, 1H), 2.06−1.96 (m, 1H), 1.11 (d, *J* = 7.0 Hz, 3H), 1.07 (d, *J* = 6.2 Hz, 3H), 1.05 (d, *J* = 6.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 138.7, 138.1, 129.0, 128.4, 128.29, 128.26, 127.8, 127.7, 127.5, 127.41, 127.35, 86.1, 83.6, 73.9, 73.6, 73.1, 72.4, 66.0, 38.2, 36.6, 36.4, 16.5, 16.1, 13.7 ppm; MS (ESI) *m*/*z* 499.2 (M + Na^+, 100), 477.2 (M + H^+, 30), 369.2 (10); HRMS calcd for $C_{31}H_{40}O_4Na$ [M + Na^+] 499.2824, found 499.2828 (0.7 ppm). Anal. Calcd for $C_{31}H_{40}O_4$: C, 78.11; H, 8.46. Found: C, 78.27; H, 8.55.

General Experimental Method for Swern Oxidation of Primary Alcohols (A10). To a cold (−78 °C) solution of oxalyl chloride (1.3 equiv, 1.52 mL) in dry CH_2Cl_2 (0.1 M, 138 mL) was added dropwise anhydrous DMSO (2.2 equiv, 2.16 mL), and the mixture was stirred for 10 min at −78 °C. A solution of the alcohol **S6** (6.58 g) in dry CH_2Cl_2 (0.2 M, 69 mL) was cannulated into the reaction flask, and the mixture was allowed to stir for an additional 30 min at −78 °C before addition of dry NEt_3 (5 equiv, 9.62 mL). The mixture was then stirred for 1 h at −78 °C and quenched by the addition of a saturated aqueous solution of NH_4Cl followed by separation of organic phase at room temperature. The aqueous layer was extracted with Et_2O (3×), and the combined organic fractions were washed with a saturated brine solution and then dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (hexanes/EtOAc, 85:15) to give the desired aldehyde **14** as a colorless oil (5.89 g, yield = 90%).

(+)-(2*S*,3*S*,4*S*,5*S*,6*S*)-3,5,7-Tris(benzyloxy)-2,4,6-trimethylheptanal (14): R_f = 0.32 (hexanes/EtOAc, 80:20); formula $C_{31}H_{38}O_4$; MW 474.63 g/mol; $[\alpha]_D$ +10.2 (*c* 0.38, $CHCl_3$); IR (neat) ν_{max} 3030, 1720, 1454, 736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.79 (d, *J* = 2.7 Hz, 1H), 7.40−7.22 (m, 15H), 4.62−4.38 (m, 6H), 3.84 (dd, *J* = 5.4 Hz, 3.3 Hz, 1H), 3.59 (dd, *J* = 9.0 Hz, 4.5 Hz, 1H), 3.47 (ddd, *J* = 7.4 Hz, 7.0 Hz, 1.6 Hz, 2H), 2.81−2.71 (m, 1H), 2.38−2.24 (m, 1H), 2.21−2.07 (m, 1H), 1.10 (d, *J* = 3.9 Hz, 3H), 1.08 (d, *J* = 3.8 Hz, 3H), 0.99 (d, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.2, 138.7, 138.6, 138.3, 128.9, 128.4, 128.3, 127.5, 127.4, 83.6, 82.1, 74.2, 73.1, 72.4, 72.3, 48.3, 37.6, 36.5, 15.9, 13.4, 12.5 ppm; MS (ESI) *m*/*z* 497.2 (M + Na^+, 100), 345.2 (60), 237.1 (30). Anal. Calcd for $C_{31}H_{38}O_4$: C, 78.45; H, 8.07. Found: C, 78.48; H, 8.28.

General Experimental Method for Oxidation of Primary Alcohol with Dess−Martin Periodinane (A11). To a solution of alcohol **S21** (1.96 g) in dry CH_2Cl_2 (0.1 M, 37 mL) were added successively $NaHCO_3$ (10 equiv, 3.11 g) and Dess−Martin periodinane (1.5 equiv, 2.35 g). The mixture was stirred for 1 h at room temperature and then concentrated. Product was digested from white solid residue in hexanes and filtered onto a pad of Celite. The filtrate was concentrated in vacuo and purified by flash chromatography on silica gel (hexanes/EtOAc, 85:15) to give the desired aldehyde **29** as a colorless oil (1.70 g, yield = 87%).

(−)-(4*R*,5*S*,6*S*)-7-(*tert*-Butyldiphenylsilyloxy)-4,6-dimethyl-5-(triethylsilyloxy)heptanal (29): R_f = 0.65 (hexanes/EtOAc, 85:15); formula $C_{31}H_{50}O_3Si_2$; MW 526.90 g/mol; $[\alpha]_D$ −0.5 (*c* 0.98, $CHCl_3$); IR (neat) ν_{max} 3017, 2957, 2934, 2877, 2714, 1727, 1436, 1427, 1387, 1239, 1109, 1054, 1008, 823, 738, 703, 613 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.72 (dd, *J* = 1.7 Hz, 1.7 Hz, 1H), 7.68−7.62 (m, 4H), 7.45−7.35 (m, 6H), 3.70 (dd, *J* = 3.0 Hz, 6.0 Hz, 1H), 3.53 (dd, *J* = 7.5 Hz, 9.9 Hz, 1H), 3.42 (dd, *J* = 6.0 Hz, 10.0 Hz, 1H), 2.50−2.41 (m, 1H), 2.37−2.28 (m, 1H), 1.90−1.75 (m, 2H), 1.58−1.50 (m, 1H), 1.39−1.23 (m, 2H), 1.06 (s, 9H), 0.92 (t, *J* = 7.9 Hz, 9H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H), 0.62−0.53 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.8, 135.6, 133.83, 133.79, 129.6, 127.6, 75.8, 66.9, 42.2, 38.3, 37.3, 26.8, 24.9, 19.2, 16.2, 11.3, 7.1, 5.4 ppm; MS (ESI) *m*/*z* 139.1 (38), 239.1 (12), 285.2 (26), 317.2 (40), 395.2 (100), 435.2 (8), 527.3 (M + H^+, 30), 549.3 (M + Na^+, 24), 581.3 (61); HRMS calcd for $C_{31}H_{51}O_3Si_2$ [M + H^+] 527.3371, found 527.3376 (0.9 ppm); calcd for $C_{31}H_{50}O_3Si_2Na$ [M + Na^+] 549.3191, found 549.3194 (0.6 ppm).

General Experimental Method for Hydrogenolysis with Palladium (A12). To a solution of α,β-unsaturated ester **S10** (1.40 g) in MeOH (0.1 M, 19.5 mL) at room temperature was added 10 wt % Pd on activated carbon (0.1 equiv, 208 mg). Inert gas atmosphere was purged by three cycles of vacuum/H_2 gas, and the reaction mixture was stirred until the reaction was judged completed by TLC. The mixture was then filtered onto a pad of Celite and washed with hexanes. The filtrate was concentrated in vacuo and purified by flash chromatography on silica gel (hexanes/EtOAc, 85:15) to give the desired product **S11** as a colorless oil (1.36 g, yield = 97%).

(+)-(4*S*,5*S*,6*S*,7*S*,8*S*,9*S*,10*S*)-Ethyl 7,9,11-tris(benzyloxy)-4,6,8,10-tetramethyl-5-(triethylsilyloxy)undecanoate (S11): R_f = 0.23 (hexanes/EtOAc, 90:10); formula $C_{44}H_{66}O_6Si$; MW 719.08 g/mol; $[\alpha]_D$ +25.0 (*c* 0.12, $CHCl_3$); IR (neat) ν_{max} 2957, 2875, 1734, 1455, 1090 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34−7.20 (m, 15H), 4.71 (d, *J* = 8.8 Hz, 1H), 4.68 (d, *J* = 8.4 Hz, 1H), 4.57 (d, *J* = 3.2 Hz, 1H), 4.54 (d, *J* = 3.4 Hz, 1H), 4.49 (d, *J* = 11.9 Hz, 1H), 4.45 (d, *J* = 11.9 Hz, 1H), 4.07 (q, *J* = 7.1 Hz, 2H), 3.79 (dd, *J* = 4.7 Hz, 2.6 Hz, 1H), 3.70 (dd, *J* = 9.2 Hz, 4.7 Hz, 1H), 3.57 (dd, *J* = 7.9 Hz, 3.3 Hz, 1H), 3.45−3.38 (m, 2H), 2.34−2.06 (m, 4H), 2.01−1.88 (m, 1H), 1.76−1.64 (m, 1H), 1.54−1.42 (m, 1H), 1.30−1.16 (m, 1H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.09 (d, *J* = 7.0 Hz, 3H), 1.06 (d, *J* = 7.2 Hz, 3H), 0.93−0.86 (m, 12H), 0.72 (d, *J* = 6.8 Hz, 3H), 0.55 (q, *J* = 8.1 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 139.4, 139.3, 138.8, 128.3, 128.21, 128.16, 128.07, 127.5, 127.3, 127.1, 126.9, 126.7, 85.1, 83.5, 75.9, 73.3, 73.2, 73.0, 72.4, 60.1, 39.0, 38.7, 37.4, 36.3, 32.5, 27.4, 16.5, 15.7, 15.3, 14.2, 12.7, 7.1, 5.6 ppm; MS (ESI) *m*/*z* 627.3 (M + H^+ − TES + Na^+, 100), 605.3 (M + H^+ − TES, 18), 437.2 (100), 283.1 (50); HRMS calcd for $C_{38}H_{52}O_6Na$ [M + H^+ − TES + Na^+] 627.3662, found 627.3670 (1.3 ppm). Anal. Calcd for $C_{44}H_{64}O_6Si$: C, 73.49; H, 9.25. Found: C, 73.62; H, 9.01.

General Experimental Method for Cycloetherification Reaction (A13). To a cold (−78 °C) solution of aldehyde **17** (3.44 g) in dry CH_2Cl_2 (0.1 M, 51 mL) was added dropwise a solution of $BiBr_3$ (1 equiv, 2.29 g) in dry MeCN (0.5 M, 10.2 mL), followed by silylated enol ether **7a** (1.5 equiv, 1.41 mL). The mixture was stirred for 1.5 h at −78 °C or until aldehyde was completely consumed as verified by TLC. The reaction mixture was treated with the addition of a saturated aqueous solution of NH_4Cl into the mixture at −40 °C followed by separation of the organic phase at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3×), and the combined organic fractions were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (hexanes/EtOAc, 90:10) to give a mixture of bromide adducts **18a** and **18b** in a ∼1:1 ratio as a pale yellow oil (2.96 g, yield = 82%).

(+)-Methyl 2-Bromo-2-((2*S*,5*S*,6*S*)-5-methyl-6-((2*S*,3*S*,4*S*,5*S*,6*S*)-3,5,7-tris(benzyloxy)-4,6-dimethylheptan-2-yl)tetrahydro-2*H*-pyran-2-yl)propanoate (18a, 18b). 18a: R_f = 0.38 (hexanes/EtOAc, 85:15); formula $C_{40}H_{53}BrO_6$; MW 709.75 g/mol; $[\alpha]_D$ +19.0 (*c* 0.20, $CHCl_3$); IR (neat) ν_{max} 2960, 2873, 1741, 1453, 1377, 1262, 966, 735, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.20 (m, 15H), 4.65 (d, *J* = 11.8 Hz, 1H), 4.63 (d, *J* = 11.5 Hz, 1H), 4.52 (d, *J* = 25.6 Hz, 1H), 4.49 (d, *J* = 25.9 Hz, 1H), 4.45 (d, *J* = 2.44 Hz, 2H), 4.15 (dd, *J* = 11.0 Hz, 2.8 Hz, 1H), 3.75 (s, 3H), 3.67−3.60 (m, 2H), 3.60−3.54 (m, 1H), 3.44−3.32 (m, 2H), 2.30−2.06 (m, 3H), 1.94−1.60 (m, 4H), 1.84 (s, 3H), 1.41−1.32 (m, 1H), 1.04 (d, *J* = 7.0 Hz, 3H), 1.00 (d, *J* = 7.2 Hz, 3H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.79 (d, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 139.32, 139.26, 138.8, 128.3, 128.2, 128.1, 127.3, 127.19, 127.16, 127.08, 84.2, 83.4, 80.2, 73.6, 73.5, 73.2, 73.0, 72.6, 62.0, 52.9, 37.8, 36.5, 36.3, 27.4, 25.7, 22.4, 20.6, 17.8, 16.7, 15.3, 11.9 ppm; MS (FAB) *m*/*z* 709.3 (M + H^+, 20), 307.0 (20), 264.9 (80), 181.1 (90), 154.0 (100), 136.0 (75); HRMS calcd for $C_{40}H_{54}BrO_6$ [M + H^+] 709.3103, found 709.3069 (4.8 ppm). Anal. Calcd for $C_{40}H_{53}BrO_6$: C, 67.69; H, 7.53. Found: C, 68.05; H, 7.71. **18b**: R_f = 0.32 (hexanes/EtOAc, 85:15); formula $C_{40}H_{53}BrO_6$; MW 709.75 g/mol; $[\alpha]_D$ +19.0 (*c* 0.20, $CHCl_3$); IR (neat) ν_{max} 2959, 2873, 1739, 1453, 1264, 735, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37−7.23 (m, 15H), 4.69 (d, *J* = 11.5 Hz, 1H), 4.64 (d, *J* = 11.7 Hz, 1H), 4.54 (d, *J* = 11.5 Hz, 1H), 4.48 (d, *J* = 11.7 Hz, 1H), 4.47 (d, *J* = 12.0 Hz, 1H), 4.43 (d, *J* = 12.0 Hz, 1H), 3.95 (dd, *J* = 10.9 Hz, 3.2 Hz, 1H), 3.77 (s, 3H), 3.71 (dd, *J* = 7.5 Hz, 4.8 Hz, 1H), 3.66 (dd, *J* = 9.0 Hz, 4.0 Hz, 1H), 3.62−3.57 (m, 1H), 3.52−3.47 (m, 1H), 3.42 (dd, *J* = 9.1 Hz, 7.3 Hz, 1H), 2.38−2.08 (m, 3H), 1.98−1.88 (m, 1H), 1.83 (s, 3H), 1.81−1.62 (m, 2H), 1.47−1.32 (m, 2H), 1.053 (d, *J* = 6.9 Hz, 3H), 1.049 (d, *J* = 6.9 Hz, 3H), 1.02 (d, *J* = 7.2 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 139.3, 139.2, 138.8, 128.3, 128.2, 128.1, 127.5, 127.32, 127.28, 127.24, 127.14, 127.08, 84.0, 83.4, 80.1, 74.0, 73.3, 73.2, 73.0, 72.7, 65.8, 53.2, 38.0, 36.3, 36.2, 27.4, 25.3, 24.0, 21.7, 18.0, 16.7, 14.8, 12.7 ppm; MS (ESI) *m*/*z* 731.1 (M + Na^+, 100), 651.3 (50); HRMS calcd for $C_{40}H_{52}O_6$ [M − HBr] 628.3777, found 628.3763 (2.1 ppm). Anal. Calcd for $C_{40}H_{53}BrO_6$: C, 67.69; H, 7.53. Found: C, 67.98; H, 7.49.

(+)-(2*S*,3*S*,4*S*,5*S*,6*S*,7*S*,8*S*)-5,7,9-Tris(benzyloxy)-2,4,6,8-tetramethyl-3-(triethylsilyloxy)nonan-1-ol (S9). Primary alcohol **S9** as a colorless oil (6.95 g, quantitative yield) was obtained from ester **S8** (6.97 g) according to general procedure **A9**: R_f = 0.25 (hexanes/EtOAc, 80:20); formula $C_{40}H_{60}O_5Si$; MW 648.99 g/mol; $[\alpha]_D$ +36.4 (*c* 0.22; $CHCl_3$); IR (neat) ν_{max} 3466, 2957, 2876, 1455 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.20 (m, 15H), 4.69 (d, *J* = 10.8 Hz, 1H), 4.58−4.48 (m, 3H), 4.45 (s, 2H), 4.15 (s, 1H), 3.89 (d, *J* = 9.7 Hz, 1H), 3.73−3.60 (m, 3H), 3.60−3.47 (m, 3H), 2.41−2.30 (m, 1H), 2.21−2.09 (m, 1H), 2.00−1.90 (m, 1H), 1.90−1.77 (m, 1H), 2.61−2.51 (m, 1H), 2.37−2.27 (m, 1H), 2.27−2.15 (m, 1H), 1.10 (d, *J* = 4.7 Hz, 3H), 1.08 (d, *J* = 5.0 Hz, 3H), 0.92−0.86 (m, 12H), 0.84 (d, *J* = 7.0 Hz, 3H), 0.64−0.47 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.4, 138.9, 138.5, 129.2, 128.6, 128.5, 128.4, 128.3, 127.9, 127.8, 127.7, 127.6, 127.3, 126.9, 85.0, 83.7, 77.4, 75.3, 73.7, 73.3, 73.2, 72.4, 65.8, 41.3, 38.7, 37.8, 36.5, 16.5, 14.8, 13.3, 13.2, 7.2, 5.6, 5.5 ppm; MS (ESI) *m*/*z* 649.4 (M + H^+, 55), 541.3 (30), 433.3 (50), 301.2 (70), 203.1 (100); HRMS calcd for $C_{40}H_{60}O_5NaSi$ [M + Na^+] 671.4108, found 671.4095 (1.9 ppm). Anal. Calcd for $C_{40}H_{60}O_5Si$: C, 74.03; H, 9.32. Found: C, 74.17; H, 9.62.

(+)-(2*R*,3*R*,4*S*,5*S*,6*S*,7*S*,8*S*)-5,7,9-Tris(benzyloxy)-2,4,6,8-tetramethyl-3-(triethylsilyloxy)nonanal (16). Aldehyde **16** as a colorless oil (6.28 g, quantitative yield) was obtained from primary alcohol **S9** (6.17 g) according to general procedure **A10**: R_f = 0.39 (hexanes/EtOAc, 85:15); formula $C_{40}H_{58}O_5Si$; MW 646.97 g/mol; $[\alpha]_D$ +16.9 (*c* 0.13, $CHCl_3$); IR (neat) ν_{max} 2959, 2876, 1726, 1455 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.61 (d, *J* = 2.3 Hz, 1H), 7.35−7.20 (m, 15H), 4.74 (d, *J* = 11.7 Hz, 1H), 4.68 (d, *J* = 11.8 Hz, 1H), 4.59 (d, *J* = 11.8 Hz, 1H), 4.53 (d, *J* = 11.7 Hz, 1H), 4.49 (s, 1H), 4.48 (s, 1H), 4.16 (dd, *J* = 5.8 Hz, 3.0 Hz, 1H), 3.70 (dd, *J* = 9.2 Hz, 5.0 Hz, 1H), 3.56 (dd, *J* = 8.2 Hz, 3.3 Hz, 1H), 3.48 (dd, *J* = 8.2 Hz, 3.1 Hz, 1H), 3.44 (dd, *J* = 9.1 Hz, 7.4 Hz, 1H), 2.50−2.40 (m, 1H), 2.40−2.28 (m, 1H), 2.28−2.12 (m, 1H), 2.06−1.94 (m, 1H), 1.10 (d, *J* = 7.0 Hz, 3H), 1.08 (d, *J* = 7.3 Hz, 3H), 0.92 (d, *J* = 7.0 Hz, 3H), 0.88 (t, *J* = 7.9 Hz, 9H), 0.82 (d, *J* = 7.0 Hz, 3H), 0.53 (q, *J* = 8.0 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.2, 139.2, 139.0, 138.7, 128.27, 128.26, 128.1, 127.5, 127.4, 127.3, 127.0, 126.7, 84.7, 83.6, 74.3, 73.5, 73.2, 73.1, 72.3, 52.0, 40.5, 37.5, 36.4, 16.4, 15.6, 12.4, 11.2, 7.0, 5.5 ppm; MS (FAB) *m*/*z* 647.4 (M + H^+, 15), 201.1 (50), 181.1 (100); HRMS calcd for $C_{40}H_{58}O_5NaSi$ [M + Na^+] 669.3951, found 669.3962 (1.6 ppm). Anal. Calcd for $C_{40}H_{58}O_5Si$: C, 74.26; H, 9.04. Found: C, 74.49; H, 9.31.

(+)-(4*S*,5*S*,6*S*,7*S*,8*S*,9*S*,10*S*,*E*)-Ethyl 7,9,11-Tris(benzyloxy)-4,6,8,10-tetramethyl-5-(triethylsilyloxy)undec-2-enoate (S10). To a cold (0 °C) solution of vacuum-dried LiCl (5.6 equiv, 2.23 g) in MeCN (1 M, 53 mL) under argon gas were added successively triethyl phosphonoacetate (1.3 equiv, 2.42 mL) and DBU (1.25 equiv, 1.76 mL) before the solution was stirred for 30 min at room temperature. The mixture was then cooled to 0 °C before being treated dropwise with a solution of aldehyde **16** (1 equiv, 6.08 g) in MeCN (0.2 M, 47 mL). The reaction was stirred for 4 h at 0 °C before being treated with a saturated aqueous solution of NH_4Cl and separation of the organic phase at room temperature. The aqueous layer was extracted with Et_2O (3×), and the combined organic fractions were washed with a saturated brine solution and then dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (hexanes/EtOAc, 90:10) to give the desired (*E*)-α,β-unsaturated ester **S10** (6.07 g, yield = 90%): R_f = 0.22 (hexanes/EtOAc, 90:10); formula $C_{44}H_{64}O_6Si$; MW 717.06 g/mol; $[\alpha]_D$ +6.0 (*c* 0.15, $CHCl_3$); IR (neat) ν_{max} 2960, 2876,

1718, 1455 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.23 (m, 15H), 6.95 (dd, J = 8.3 Hz, 15.8 Hz, 1H), 5.70 (dd, J = 1.1 Hz, 15.8 Hz, 1H), 4.68 (d, J = 11.9 Hz, 1H), 4.67 (d, J = 11.7 Hz, 1H), 4.54 (d, J = 11.9 Hz, 1H), 4.53 (d, J = 11.7 Hz, 1H), 4.49 (d, J = 11.9 Hz, 1H), 4.45 (d, J = 11.9 Hz, 1H), 4.16 (q, J = 7.1 Hz, 2H), 3.89 (dd, J = 3.2 Hz, 5.2 Hz, 1H), 3.69 (dd, J = 4.7 Hz, 9.2 Hz, 1H), 3.56 (dd, J = 3.7 Hz, 7.7 Hz, 1H), 3.46−3.38 (m, 2H), 2.43−2.33 (m, 1H), 2.34−2.24 (m, 1H), 2.24−2.13 (m, 1H), 1.97−1.87 (m, 1H), 1.26 (t, J = 7.1 Hz, 3H), 1.08 (d, J = 7.0 Hz, 3H), 1.06 (d, J = 7.3 Hz, 3H), 1.92−1.86 (m, 15H), 0.85 (d, J = 6.9 Hz, 3H), 0.58−0.51 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 152.1, 139.3, 139.2, 138.8, 128.3, 128.2, 128.1, 127.5, 127.4, 127.1, 127.0, 127.0, 126.8, 121.0, 84.7, 83.5, 75.9, 73.4, 73.2, 73.0, 72.4, 60.0, 42.6, 40.3, 37.4, 36.4, 16.56, 16.50, 15.5, 14.3, 12.3, 7.1, 5.7 ppm; MS (FAB) m/z 717.1 ($M + H^+$, 38), 501.2 (25), 271.1 (100), 181.1 (90); HRMS calcd for $C_{44}H_{64}O_6NaSi$ [$M + Na^+$] 739.4370, found 739.4351 (2.6 ppm). Anal. Calcd for $C_{44}H_{64}O_6Si$: C, 73.70; H, 9.00. Found: C, 73.87; H, 9.06.

(+)-(4*S*,5*S*,6*S*,7*S*,8*S*,9*S*,10*S*)-7,9,11-Tris(benzyloxy)-4,6,8,10-tetramethyl-5-(triethylsilyloxy)undecan-1-ol (S12). Primary alcohol **S12** as a colorless oil (7.55 g, quantitative yield) was obtained from ester **S11** (7.98 g) according to general procedure **A9**: R_f = 0.30 (hexanes/EtOAc, 75:25); formula $C_{42}H_{64}O_5Si$; MW 677.04 g/mol; $[\alpha]_D$ +23.6 (c 0.33, $CHCl_3$); IR (neat) ν_{max} 3431, 2956, 2912, 2875, 1455, 1090, 1066, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34−7.22 (m, 15H), 4.73 (d, J = 11.8 Hz, 1H), 4.70 (d, J = 11.3 Hz, 1H), 4.56 (d, J = 12.8 Hz, 1H), 4.53 (d, J = 11.5 Hz, 1H), 4.50 (d, J = 12.0 Hz, 1H), 4.46 (d, J = 12.0 Hz, 1H), 3.82 (dd, J = 4.3 Hz, 2.7 Hz, 1H), 3.72 (dd, J = 9.2 Hz, 4.7 Hz, 1H), 3.59 (dd, J = 8.0 Hz, 3.3 Hz, 1H), 3.47−3.35 (m, 4H), 2.38−2.26 (m, 1H), 2.26−2.14 (m, 1H), 2.02−1.90 (m, 1H), 1.54−1.38 (m, 2H), 1.38−1.22 (m, 2H), 1.10 (d, J = 7.2 Hz, 3H), 1.08 (d, J = 7.7 Hz, 3H), 0.95−0.88 (m, 14H), 0.75 (d, J = 6.8 Hz, 3H), 0.56 (q, J = 7.5 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.5, 139.3, 138.8, 128.3, 128.2, 128.1, 127.5, 127.4, 127.2, 126.9, 126.7, 85.3, 83.6, 77.2, 75.8, 73.3, 73.1, 72.4, 63.2, 39.3, 38.6, 37.4, 36.4, 30.8, 28.2, 16.6, 15.8, 15.4, 12.8, 7.1, 5.7 ppm; MS (FAB) m/z 677.3 ($M + H^+$, 10), 231.2 (28), 201.2 (27), 181.2 (100); HRMS calcd for $C_{36}H_{50}O_5Na$ [$M + H^+ - TES + Na^+$] 585.3556, found 585.3564 (1.4 ppm). Anal. Calcd for $C_{42}H_{64}O_5Si$: C, 74.51; H, 9.53; found: C, 74.27; H, 9.71.

(+)-(4*S*,5*S*,6*S*,7*S*,8*S*,9*S*,10*S*)-7,9,11-Tris(benzyloxy)-4,6,8,10-tetramethyl-5-(triethylsilyloxy)undecanal (17). Aldehyde **17** as a colorless oil (602 mg, yield = 92%) was obtained from primary alcohol **S12** (660 mg) according to general procedure **A10**: R_f = 0.33 (hexanes/EtOAc, 85:15); formula $C_{42}H_{62}O_5Si$; MW 675.02 g/mol; $[\alpha]_D$ +26.9 (c 0.23, $CHCl_3$); IR (neat) ν_{max} 3030, 2716, 1726, 1455, 734, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.51 (t, J = 1.6 Hz, 1H), 7.40−7.20 (m, 15H), 4.73 (d, J = 11.5 Hz, 1H), 4.72 (d, J = 11.9 Hz, 1H), 4.59 (d, J = 11.9 Hz, 1H), 4.52 (d, J = 11.4 Hz, 1H), 4.50 (d, J = 12.0 Hz, 1H), 4.46 (d, J = 12.1 Hz, 1H), 3.80 (dd, J = 2.4 Hz, 4.4 Hz, 1H), 3.72 (dd, J = 5.0 Hz, 9.2 Hz, 1H), 3.57 (dd, J = 3.2 Hz, 8.2 Hz, 1H), 3.44 (dd, J = 7.6 Hz, 9.1 Hz, 1H), 3.40 (dd, J = 3.1 Hz, 9.0 Hz, 1H), 2.41−2.25 (m, 1H), 2.25−2.10 (m, 3H), 2.00−1.89 (m, 1H), 1.62−1.51 (m, 1H), 1.51−1.40 (m, 1H), 1.13−1.06 (m, 6H), 0.95−0.86 (m, 12H), 0.71 (d, J = 6.9 Hz, 3H), 0.55 (q, J = 8.0 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.9, 139.4, 139.2, 138.8, 128.3, 128.2, 128.1, 127.5, 127.4, 127.22, 127.15, 126.9, 126.6, 85.6, 83.6, 75.5, 73.4, 73.3, 73.1, 72.3, 42.1, 39.0, 38.9, 37.3, 36.4, 24.4, 16.5, 15.7, 15.6, 12.8, 7.1, 5.6 ppm; MS (ESI) m/z 675.4 ($M + H^+$, 100), 435.2 (30), 343.2 (32), 229.1 (27); HRMS calcd for $C_{42}H_{62}O_5NaSi$ [$M + Na^+$] 697.4264, found 697.4270 (0.8 ppm). Anal. Calcd for $C_{42}H_{62}O_5Si$: C, 74.73; H, 9.26. Found: C, 74.49; H, 9.31.

(+)-(*R*)-2-((2*S*,5*S*,6*S*)-5-Methyl-6-((2*S*,3*S*,4*S*,5*S*,6*S*)-3,5,7-tris(benzyloxy)-4,6-dimethyl heptan-2-yl)tetrahydro-2*H*-pyran-2-yl)propan-1-ol (S13a) and (*S*)-2-((2*S*,5*S*,6*S*)-5-Methyl-6-((2*S*,3*S*,4*S*,5*S*,6*S*)-3,5,7-tris(benzyloxy)-4,6-dimethylheptan-2-yl)-tetrahydro-2*H*-pyran-2-yl)propan-1-ol (S13b). A separable mixture of their corresponding primary alcohol 2,3-*anti* (**S13a**) and 2,3-*syn* (**S13b**) as a colorless oil (0.304 g, yield = 70% for **S13a**) was obtained from a mixture of esters **19a** and **19b** (0.454 g) according to general procedure **A9**. **S13a**: R_f = 0.22 (hexanes/EtOAc, 75:25); formula $C_{39}H_{54}O_5$; MW 602.84 g/mol; $[\alpha]_D$ +5.9 (c 0.17, $CHCl_3$); IR (neat) ν_{max} 3468, 2961, 1455, 1378, 734, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.20 (m, 15H), 4.68 (d, J = 11.7 Hz, 1H), 4.62 (d, J = 2.3 Hz, 2H), 4.50 (d, J = 11.7 Hz, 1H), 4.45 (d, J = 2.6 Hz, 2H), 3.67 (dd, J = 9.1 Hz, 4.1 Hz, 1H), 3.61 (dd, J = 6.1 Hz, 3.8 Hz, 1H), 3.59 (dd, J = 5.1 Hz, 3.8 Hz, 1H), 3.54−3.45 (m, 4H), 3.42 (dd, J = 9.1 Hz, 7.4 Hz, 1H), 3.10 (bs, 1H), 2.34−2.25 (m, 1H), 2.25−2.06 (m, 2H), 1.97−1.84 (m, 1H), 1.88−1.67 (m, 1H), 1.68−1.47 (m, 3H), 1.35−1.22 (m, 1H), 1.06 (d, J = 7.0 Hz, 3H), 1.03 (d, J = 7.0 Hz, 3H), 1.02 (d, J = 7.1 Hz, 3H), 0.81 (d, J = 6.7 Hz, 3H), 0.76 (d, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.4, 139.2, 138.8, 128.3, 128.2, 128.1, 127.5, 127.33, 127.26, 127.16, 127.09, 84.3, 83.1, 77.2, 77.0, 73.4, 73.1, 73.0, 72.6, 68.0, 37.9, 36.8, 36.3, 36.29, 29.9, 26.3, 25.7, 18.4, 16.7, 14.3, 13.9, 12.5 ppm; MS (ESI) m/z 625.3 ($M + Na^+$, 100), 603.3 ($M + H^+$, 10), 437.1 (20); HRMS calcd for $C_{39}H_{54}O_5Na$ [$M + Na^+$] 625.3869, found 625.3887 (2.9 ppm). Anal. Calcd for $C_{39}H_{54}O_5$: C, 77.70; H, 9.03. Found: C, 77.36; H, 9.26. **S13b**: R_f = 0.16 (hexanes/EtOAc, 75:25); formula $C_{39}H_{54}O_5$; MW 602.84 g/mol; IR (neat) ν_{max} 3457, 3029, 1495, 1455, 1378, 1090, 734, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40−7.20 (m, 15H), 4.65 (d, J = 11.6 Hz, 1H), 4.58 (s, 2H), 4.50 (d, J = 11.6 Hz, 1H), 4.45 (d, J = 3.1 Hz, 2H), 3.72−3.48 (m, 7H), 3.42 (dd, J = 9.0 Hz, 7.5 Hz, 1H), 2.51 (t, J = 5.3 Hz, 1H), 2.34−2.20 (m, 2H), 2.20−2.08 (m, 1H), 1.94−1.77 (m, 2H), 1.77−1.65 (m, 2H), 1.45−1.27 (m, 2H), 1.06 (d, J = 6.9 Hz, 3H), 1.03 (d, J = 7.2 Hz, 3H), 1.00 (d, J = 7.0 Hz, 3H), 0.92 (d, J = 7.0 Hz, 3H), 0.85 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3, 139.2, 138.8, 128.3, 128.2, 128.1, 127.5, 127.3, 127.2, 127.12, 127.07, 83.6, 83.4, 78.2, 77.2, 73.8, 73.3, 73.0, 72.6, 66.3, 38.0, 37.5, 36.3, 36.1, 28.7, 26.0, 23.0, 18.2, 16.6, 14.4, 12.5, 12.3 ppm; MS (ESI) m/z 625.3 ($M + Na^+$, 100), 603.4 ($M + H^+$, 80), 495.3 (20); HRMS calcd for $C_{39}H_{55}O_5$ [$M + H^+$] 603.4050, found 603.4038 (1.9 ppm).

(+)-*tert*-Butyl((*R*)-2-((2*S*,5*S*,6*S*)-5-methyl-6-((2*S*,3*S*,4*S*,5*S*,6*S*)-3,5,7-tris(benzyloxy)-4,6-dimethylheptan-2-yl)tetrahydro-2*H*-pyran-2-yl)propoxy)diphenylsilane (S14). Product **S14** was obtained from a cold (0 °C) solution of primary alcohol **S13a** (0.70 g) in dry CH_2Cl_2 (0.2 M, 5.8 mL) to which were successively added imidazole (2.2 equiv, 0.17 g) and TBDPSCl (2.2 equiv, 0.66 g) before the mixture was stirred overnight at room temperature. The reaction mixture was then treated with the addition of a saturated aqueous solution of NH_4Cl into the mixture followed by solvent evaporation in vacuo. The residue was extracted with Et_2O (3×), and the combined organic fractions were dried ($MgSO_4$), filtered, and concentrated in vacuo to a colorless oil used as crude without further purification: R_f = 0.25 (hexanes/EtOAc, 90:10); formula $C_{55}H_{72}O_5Si$; MW 841.24 g/mol; $[\alpha]_D$ +27.7 (c 0.13, $CHCl_3$); IR (neat) ν_{max} 2857, 1455, 1091, 735, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70−7.62 (4H), 7.43−7.33 (m, 10H), 7.32−7.16 (m, 11H), 4.71 (d, J = 11.9 Hz, 1H), 4.51 (d, J = 11.9 Hz, 1H), 4.48 (d, J = 10.6 Hz, 1H), 4.47 (d, J = 11.9 Hz, 1H), 4.44 (d, J = 11.7 Hz, 1H), 4.38 (d, J = 11.6 Hz, 1H), 3.76−3.66 (m, 4H), 3.64 (dd, J = 4.0 Hz, 9.5 Hz, 1H), 3.55 (dd, J = 3.4 Hz, 7.5 Hz, 1H), 3.48−3.42 (m, 1H), 3.39 (dd, J = 3.8 Hz, 7.9 Hz, 1H), 2.26−2.09 (m, 4H), 2.00−1.90 (m, 1H), 1.67−1.48 (m, 4H), 1.08 (d, J = 6.9 Hz, 3H), 1.05 (s, 9H), 0.93 (d, J = 7.2 Hz, 3H), 0.92 (d, J = 7.0 Hz, 3H), 0.88 (d, J = 6.9 Hz, 3H), 0.65 (d, J = 6.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.5, 138.8, 135.7, 133.9, 129.4, 128.3, 128.0, 127.6, 127.51, 127.47, 127.3, 126.91, 126.88, 126.80, 84.9, 83.6, 76.4, 73.7, 73.3, 73.0, 72.5, 71.6, 65.7, 37.6, 37.3, 36.4, 36.3, 30.3, 30.2, 26.9, 24.7, 19.3, 18.1, 16.8, 16.2, 13.4, 11.5 ppm; MS (ESI) m/z 841.5 ($M + H^+$, 5), 359.3 (100), 341.3 (97); HRMS calcd for $C_{55}H_{73}O_5Si$ [$M + H^+$] 841.5227, found 841.5212 (−1.0 ppm).

(+)-(2*S*,3*S*,4*S*,5*S*,6*S*)-6-((2*S*,3*S*,6*S*)-6-((*R*)-1-(*tert*-Butyldiphenylsilyloxy)propan-2-yl)-3-methyltetrahydro-2*H*-pyran-2-yl)-2,4-dimethylheptane-1,3,5-triol (S15). Product **S15** as a colorless

oil (0.50 g, yield = 92%) was obtained from benzyl ether product **S14** (0.80 g) according to general procedure **A12** in THF (0.1 M, 9.5 mL) with $Pd(OH)_2$ 20 wt % on activated carbon. The crude product was purified by flash chromatography on silica gel (hexanes/EtOAc, 65:35): R_f = 0.28 (hexanes/EtOAc, 65:35); formula $C_{34}H_{54}O_5Si$; MW 570.88 g/mol; $[\alpha]_D$ +62.1 (*c* 0.14, $CHCl_3$); IR (neat) ν_{max} 3380, 2859, 1459, 1428, 1383, 823, 739, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67−7.63 (m, 2H), 7.61−7.57 (m, 2H), 7.44−7.34 (m, 6H), 5.65 (s, 1H), 4.56 (d, *J* = 8.2 Hz, 1H), 4.16−4.09 (m, 1H), 3.92 (dd, *J* = 10.0 Hz, 3.0 Hz, 1H), 3.77 (dt, *J* = 10.9 Hz, 2.4 Hz, 1H), 3.62 (dd, *J* = 10.1 Hz, 2.8 Hz, 1H), 3.60 (dd, *J* = 10.5 Hz, 1.9 Hz, 1H), 3.53 (dd, *J* = 8.5 Hz, 2.4 Hz, 1H), 3.48−3.38 (m, 2H), 3.10 (dd, *J* = 8.4 Hz, 2.1 Hz, 1H), 2.18−2.07 (m, 1H), 2.06−1.97 (m, 1H), 1.82−1.54 (m, 7H), 1.11 (d, *J* = 7.1 Hz, 3H), 1.10 (d, *J* = 7.1 Hz, 3H), 1.05 (s, 9H), 0.86 (d, *J* = 7.1 Hz, 3H), 0.79 (d, *J* = 6.5 Hz, 3H), 0.65 (d, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7, 135.55, 133.65, 129.6, 127.63, 127.59, 83.8, 82.5, 76.2, 73.0, 65.1, 64.4, 39.3, 35.5, 33.8, 33.5, 31.6, 27.07, 27.00, 25.6, 19.5, 17.8, 15.5, 14.1, 13.3, 11.3 ppm; MS (ESI) *m*/*z* 593.3 (M + Na^+, 98), 571.3 (M + H^+, 100), 493.3 (20), 365.1 (20); HRMS calcd for $C_{34}H_{55}O_5Si$ [M + H^+] 571.3819, found 571.3814 (0.8 ppm).

(+)-(2*S*,3*S*,4*S*,5*S*,6*S*)-6-((2*S*,3*S*,6*S*)-6-((*R*)-1-(*tert*-Butyldiphenylsilyloxy)propan-2-yl)-3-methyltetrahydro-2*H*-pyran-2-yl)-3,5-dihydroxy-2,4-dimethylheptyl Pivalate (20). Product **20** as a colorless oil (0.501 g, yield = 90%) was obtained from a cold (0 °C) solution of primary alcohol **S15** (0.485 g) in dry CH_2Cl_2 (0.1 M, 8.5 mL) to which were successively added pyridine (5 equiv, 0.34 mL) and PivCl (2.5 equiv, 0.26 mL) before the mixture was stirred overnight at room temperature. The reaction mixture was then treated with the addition of a saturated $NaHCO_3$ solution into the mixture followed by solvent evaporation in vacuo. The residue was extracted with Et_2O (3×), and the combined organic fractions were washed with a saturated brine solution and then dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (hexanes/EtOAc, 85:15): R_f = 0.19 (hexanes/EtOAc, 85:15); formula $C_{39}H_{62}O_6Si$; MW 654.99 g/mol; $[\alpha]_D$ +22.5 (*c* 0.12, $CHCl_3$); IR (neat) ν_{max} 3393, 2963, 2932, 1726, 1159, 1112, 1072, 1007, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67−7.63 (m, 2H), 7.62−7.58 (m, 2H), 7.41−7.33 (m, 6H), 4.50 (bs, 1H), 4.21 (dd, *J* = 10.8 Hz, 5.2 Hz, 1H), 4.10−4.03 (m, 1H), 3.93 (dd, *J* = 10.0 Hz, 3.1 Hz, 1H), 3.66 (dd, *J* = 10.8 Hz, 8.3 Hz, 1H), 3.63−3.57 (m, 2H), 3.46−3.38 (m, 2H), 2.19−2.08 (m, 1H), 2.07−1.96 (m, 2H), 1.74−1.45 (m, 7H), 1.17 (s, 9H), 1.09 (d, *J* = 7.1 Hz, 3H), 1.05 (s, 9H), 1.02 (d, *J* = 6.9 Hz, 3H), 0.83 (d, *J* = 6.9 Hz, 3H), 0.77 (d, *J* = 6.5 Hz, 3H), 0.73 (d, *J* = 6.7 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.7, 135.8, 135.6, 133.9, 133.7, 129.5, 127.61, 127.55, 83.8, 79.9, 77.2, 76.3, 73.1, 65.2, 38.9, 38.7, 34.8, 33.7, 33.5, 31.6, 27.2, 27.06, 26.99, 25.6, 19.4, 17.8, 15.6, 13.9, 13.2, 11.3 ppm; MS (ESI) *m*/*z* 677.4 (M + Na^+, 100), 655.4 (M + H^+, 25), 381.3 (30); HRMS calcd for $C_{39}H_{63}O_6Si$ [M + Na^+] 655.4394, found 655.4377 (2.6 ppm). Anal. Calcd for $C_{39}H_{62}O_6Si$: C, 71.52; H, 9.54. Found: C, 71.57; H, 9.73.

(−)-(2*S*,3*R*,4*S*)-Methyl 5-(*tert*-Butyldiphenylsilyloxy)-2,4-dimethyl-3-(triethylsilyloxy)pentanoate (S17). Product **S17** as a colorless oil (7.81 g, yield = 89%) was obtained from alcohol **27** (6.88 g) following general procedure **A8**: R_f = 0.42 (hexanes/EtOAc, 90:10); formula $C_{30}H_{48}O_4Si_2$; MW 528.87 g/mol; $[\alpha]_D$ −12.4 (*c* 0.5, $CHCl_3$); IR (neat) ν_{max} 3072, 3050, 2955, 2878, 1741, 1460, 1429, 1381, 1242, 1194, 1174, 1111, 823, 807, 739, 704, 614 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.72−7.65 (m, 4H), 7.47−7.36 (m, 6H), 4.19 (dd, *J* = 2.0 Hz, 8.6 Hz, 1H), 3.67 (s, 3H), 3.59 (dd, *J* = 7.7 Hz, 10.0 Hz, 1H), 3.45 (dd, *J* = 6.5 Hz, 10.0 Hz, 1H), 2.71−2.63 (m, 1H), 1.85−1.75 (m, 1H), 1.10 (s, 9H), 1.07 (d, *J* = 7.1 Hz, 3H), 0.91 (t, *J* = 8.0 Hz, 9H), 0.81 (d, *J* = 6.8 Hz, 3H), 0.62−0.48 (m, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.1, 135.6, 135.6, 133.81, 133.76, 129.6, 129.5, 127.6, 73.3, 66.5, 51.4, 45.0, 37.9, 26.8, 19.2, 14.2, 9.6, 6.9, 5.2 ppm; MS (ESI) *m*/*z* 273.2 (28), 451.3 (18), 529.3 (M + H^+, 100), 628.4 (6); HRMS calcd for $C_{30}H_{49}O_4Si_2$ [M + H^+] 529.3164, found 529.3180 (3.0 ppm).

(+)-(2*R*,3*S*,4*S*)-5-(*tert*-Butyldiphenylsilyloxy)-2,4-dimethyl-3-(triethylsilyloxy)pentan-1-ol (S18). Primary alcohol **S18** as a colorless oil (1.25 g, yield = 87%) was obtained from ester **S17** (1.51 g) following general procedure **A9**: R_f = 0.40 (hexanes/EtOAc, 85:15); formula $C_{29}H_{48}O_3Si_2$; MW 500.86 g/mol; $[\alpha]_D$ +4.2 (*c* 0.44, $CHCl_3$); IR (neat) ν_{max} 3411, 3071, 2957, 2934, 2877, 1590, 1463, 1427, 1387, 1240, 1109, 1030, 1008, 823, 802, 738, 703, 613 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70−7.63 (m, 4H), 7.47−7.36 (m, 6H), 3.91−3.87 (m, 1H), 3.60 (d, *J* = 4.6 Hz, 2H), 3.56 (dd, *J* = 7.4 Hz, 10.2 Hz, 1H), 3.49 (dd, *J* = 6.0 Hz, 10.2 Hz, 1H), 2.59−5.53 (bs, 1H), 1.90−1.78 (m, 2H), 1.08 (s, 9H), 0.98−0.93 (m, 12H), 0.88 (d, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 133.7, 133.6, 129.6, 127.6, 77.2, 66.3, 66.2, 39.7, 38.6, 26.8, 19.2, 15.3, 11.5, 7.0, 5.2 ppm; MS (ESI) *m*/*z* 192.7 (27), 229.1 (36), 291.2 (100), 345.2 (85), 423.3 (59), 501.3 (M + H^+, 61), 600.4 (32); HRMS calcd for $C_{29}H_{49}O_3Si_2$ [M + H^+] 501.3215, found 501.3214 (−0.1 ppm).

(±)-(2*S*,3*R*,4*S*)-5-(*tert*-Butyldiphenylsilyloxy)-2,4-dimethyl-3-(triethylsilyloxy)pentanal (28). Aldehyde **28** as a colorless oil (1.43 g, quantitative yield) was obtained from primary alcohol **S18** (1.35 g) according to general procedure **A10**: R_f = 0.83 (hexanes/EtOAc, 85:15); formula $C_{29}H_{46}O_3Si_2$; MW 498.84 g/mol; IR (neat) ν_{max} 3072, 3051, 2957, 2936, 2878, 2710, 2361, 1889, 1728, 1590, 1463, 1427, 1389, 1363, 1240, 1187, 1110, 1046, 1009, 972, 941, 912, 829, 801, 739, 704, 614 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.81 (d, *J* = 2.6 Hz, 1H), 7.74−7.67 (m, 4H), 7.49−7.39 (m, 6H), 4.22 (dd, *J* = 3.4 Hz, 6.4 Hz, 1H), 3.63 (dd, *J* = 7.4 Hz, 10.2 Hz, 1H), 3.55 (dd, *J* = 5.8 Hz, 10.2 Hz, 1H), 2.68−2.61 (m, 1H), 1.92−1.83 (m, 1H), 1.15 (s, 9H), 1.10 (d, *J* = 7.0 Hz, 3H), 0.99 (t, *J* = 8.0 Hz, 9H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.69−0.61 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.1, 135.59, 135.58, 133.6, 129.7, 129.6, 127.64, 127.63, 73.8, 65.9, 50.6, 39.5, 26.9, 19.2, 11.5, 11.0, 6.9, 5.3 ppm; MS (ESI) *m*/*z* 171.1 (79), 189.1 (22), 289.2 (100), 349.2 (37), 381.2 (50), 437.3 (19), 481.3 (14), 521.3 (M + Na^+, 55), 553.3 (76), 598.4 (15); HRMS calcd for $C_{29}H_{46}O_3NaSi_2$ [M + Na^+] 521.2878, found 521.2890 (2.4 ppm).

(−)-(4*R*,5*S*,6*S*,*E*)-Methyl 7-(*tert*-Butyldiphenylsilyloxy)-4,6-dimethyl-5-(triethylsilyloxy)hept-2-enoate (S19). To a solution of aldehyde **28** (2.44 g) in toluene (0.1 M, 49 mL) was added methyl (triphenylphosphoranylidene)acetate (1.5 equiv, 2.46 g), and the reaction mixture was heated to reflux overnight. The mixture was cooled to room temperature and then concentrated in vacuo. The solid yellow residue was digested in hexanes and filtered onto a pad of Celite, leading to a filtrate which was concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (hexanes/EtOAc, 95:5) to give (*E*)-α,β-unsaturated ester **S19** as a colorless oil (2.23 g, yield = 82%): R_f = 0.53 (hexanes/EtOAc, 90:10); formula $C_{32}H_{50}O_4Si_2$; MW 554.91 g/mol; $[\alpha]_D$ −8.3 (*c* 0.40, $CHCl_3$); IR (neat) ν_{max} 3071, 2957, 2878, 1726, 1657, 1590, 1462, 1429, 1386, 1271, 1240, 1190, 1153, 1110, 1009, 823, 801, 738, 704, 613 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.67−7.63 (m, 4H), 7.46−7.35 (m, 6H), 7.01 (dd, *J* = 8.3 Hz, 15.8 Hz, 1H), 5.75 (dd, *J* = 1.0 Hz, 15.8 Hz, 1H), 3.84 (dd, *J* = 3.5 Hz, 5.8 Hz, 1H), 3.72 (s, 3H), 3.54 (dd, *J* = 7.1 Hz, 10.1 Hz, 1H), 3.43 (dd, *J* = 6.0 Hz, 10.1 Hz, 1H), 2.51−2.41 (m, 1H), 1.80−1.71 (m, 1H), 1.06 (s, 9H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.92 (t, *J* = 7.9 Hz, 9H), 0.83 (d, *J* = 6.8 Hz, 3H), 0.62−0.53 (m, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 152.6, 135.6, 135.6, 133.8, 133.8, 129.6, 129.6, 127.6, 120.6, 75.5, 66.4, 51.3, 41.4, 39.2, 26.9, 19.2, 16.7, 11.3, 7.0, 5.4 ppm; MS (ESI) *m*/*z* 229.1 (4), 345.2 (14), 477.3 (100), 555.3 (M + H^+, 21), 654.4 (6); HRMS calcd for $C_{32}H_{51}O_4Si$ [M + H^+] 555.3320, found 555.3327 (+1.1 ppm).

(−)-(4*R*,5*S*,6*S*)-Methyl 7-(*tert*-Butyldiphenylsilyloxy)-4,6-dimethyl-5-(triethylsilyloxy)heptanoate (S20). Product **S20** as a colorless oil was obtained from α,β-unsaturated ester **S19** (1.00 g) according to general procedure **A12** in EtOAc (0.1 M, 18 mL). The

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filtrate was concentrated in vacuo and used as crude without further purification: R_f = 0.51 (hexanes/EtOAc, 90:10); formula $C_{32}H_{52}O_4Si_2$; MW 556.92 g/mol; $[\alpha]_D$ −0.5 (c 0.66, $CHCl_3$); IR (neat) ν_{max} 3071, 2956, 2934, 2877, 1742, 1462, 1429, 1386, 1242, 1171, 1110, 823, 739, 703, 612 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.76−7.69 (m, 4H), 7.48−7.38 (m, 6H), 3.79 (dd, J = 2.9 Hz, 5.9 Hz, 1H), 3.68 (s, 3H), 3.60 (dd, J = 7.5 Hz, 9.9 Hz, 1H), 3.49 (dd, J = 6.0 Hz, 9.9 Hz, 1H), 2.47−2.38 (m, 1H), 2.33−2.24 (m, 1H), 2.00−1.82 (m, 2H), 1.67−1.58 (m, 1H), 1.47−1.37 (m, 1H), 1.12 (s, 9H), 0.99 (t, J = 8.0 Hz, 9H), 0.92 (d, J = 6.8 Hz, 3H), 0.88 (d, J = 6.8 Hz, 3H), 0.69−0.59 (m, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 135.5, 133.8, 133.8, 129.5, 127.5, 75.6, 66.9, 51.3, 38.1, 37.3, 32.3, 27.9, 26.8, 19.1, 15.9, 11.3, 7.0, 5.4 ppm; MS (ESI) m/z 169.1 (93), 288.3 (12), 347.2 (82), 425.3 (70), 479.3 (7), 557.3 (M + H^+, 100), 656.5 (10); HRMS calcd for $C_{32}H_{53}O_4Si_2$ [M + H^+] 557.3477, found 557.3487 (1.6 ppm).

(−)-(4*R*,5*S*,6*S*)-7-(*tert*-Butyldiphenylsilyloxy)-4,6-dimethyl-5-(triethylsilyloxy)heptan-1-ol (S21). Primary alcohol **S21** as a colorless oil (1.98 g, yield = 83% over two steps) was obtained from ester **S20** (2.51 g) according to general procedure **A9**: R_f = 0.33 (hexanes/EtOAc, 85:15); formula $C_{31}H_{52}O_3Si_2$; MW 528.91 g/mol; $[\alpha]_D$ −0.8 (c 0.48, $CHCl_3$); IR (neat) ν_{max} 3341, 3072, 3050, 2957, 2934, 2876, 1590, 1463, 1428, 1386, 1239, 1188, 1109, 1155, 1009, 970, 824, 738, 703, 612 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.71−7.63 (m, 4H), 7.46−7.34 (m, 6H), 3.71 (dd, J = 2.2 Hz, 5.3 Hz, 1H), 3.65−3.52 (m, 3H), 3.43 (dd, J = 5.9 Hz, 9.8 Hz, 1H), 1.88−1.78 (m, 1H), 1.71−1.61 (m, 1H), 1.61−1.41 (m, 2H), 1.36−1.28 (bs, 1H), 1.08 (s, 9H), 0.94 (t, J = 7.9 Hz, 9H), 0.88 (d, J = 6.1 Hz, 3H), 0.83 (d, J = 6.8 Hz, 3H), 0.63−0.55 (m, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.6, 133.9, 129.5, 127.6, 75.9, 67.1, 63.4, 38.0, 37.7, 30.9, 28.8, 26.8, 19.2, 16.1, 11.2, 7.1, 5.4 ppm; MS (ESI) m/z 141.1 (16), 192.7 (12), 241.2 (14), 288.3 (11), 319.2 (99), 397.3 (100), 415.3 (6), 529.4 (M + H^+, 59), 582.5 (7), 628.5 (26); HRMS calcd for $C_{31}H_{52}O_3Si_2$ [M + H^+] 529.3528, found 529.3529 (0.2 ppm).

(+)-Methyl 2-Bromo-2-((2*S*,5*S*,6*S*)-6-((*S*)-1-(*tert*-butyldiphenylsilyloxy)propan-2-yl)-5-methyltetrahydro-2*H*-pyran-2-yl)-propanoate (30a, 30b). A mixture of bromide adducts **30a** and **30b** in a ~1:1 ratio as a pale yellow oil (1.98 g, quantitative yield) was obtained from aldehyde **29** (1.69 g) according to general procedure **A13**. A quantitative yield was calculated due to contamination with *C*-silylated product from enol ether **7a**. **30a**: R_f = 0.43 (hexanes/EtOAc, 90:10); formula $C_{29}H_{41}BrO_4Si$; MW 561.62 g/mol; $[\alpha]_D$ +4.49 (c 0.54, $CHCl_3$); IR (neat) ν_{max} 3070, 2956, 2932, 2860, 1744, 1589, 1458, 1429, 1378, 1263, 1200, 1142, 1110, 1044, 1005, 859, 823, 804, 740, 704, 613 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.67−7.62 (m, 4H), 7.46−7.36 (m, 6H), 4.08 (dd, J = 3.2 Hz, 10.2 Hz, 1H), 3.76 (s, 3H), 3.55 (dd, J = 4.6 Hz, 10.1 Hz, 1H), 3.50 (dd, J = 4.9 Hz, 10.2 Hz, 1H), 3.46 (d, J = 9.2 Hz, 1H), 2.17−2.07 (m, 1H), 1.91 (s, 3H), 1.89−1.81 (m, 1H), 1.80−1.71 (m, 3H), 1.48−1.41 (m, 1H), 1.06 (d, J = 7.2 Hz, 3H), 1.04 (s, 9H), 0.96 (d, J = 6.6 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 135.6, 135.6, 133.6, 129.6, 127.6, 81.4, 73.6, 66.4, 62.2, 53.0, 34.8, 26.9, 26.8, 24.7, 22.5, 19.6, 19.3, 18.2, 13.5 ppm; MS (ESI) m/z 225.1 (11), 305.1 (10), 395.2 (7), 485.2 (15), 561.2 (^{79}Br; M + H^+, 100), 563.2 (^{81}Br; M + H^+, 99), 662.3 (6); HRMS calcd for $C_{29}H_{42}O_4{}^{79}BrSi$ [M + H^+] 561.2030, found 561.2037 (1.2 ppm). **30b**: R_f = 0.33 (hexanes/EtOAc, 90:10); formula $C_{29}H_{41}BrO_4Si$; MW 561.62 g/mol; IR (neat) ν_{max} 3071, 2956, 2933, 2860, 1740, 1590, 1452, 1429, 1379, 1265, 1190, 1159, 1111, 1055, 1034, 908, 861, 829, 704, 614 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.68−7.62 (m, 4H), 7.46−7.35 (m, 6H), 3.89 (dd, J = 2.2 Hz, 11.0 Hz, 1H), 3.78 (s, 3H), 3.61−3.51 (m, 3H), 2.22−2.13 (m, 1H), 1.90−1.84 (bs, 1H), 1.87 (s, 3H), 1.82−1.65 (m, 3H), 1.47−1.29 (m, 2H), 1.11 (d, J = 7.0 Hz, 3H), 1.10 (d, J = 6.4 Hz, 3H), 1.05 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 135.60, 135.56, 133.59, 133.57, 129.6, 127.6, 81.3, 74.0, 66.6, 65.6, 53.2, 34.7, 26.9, 26.8, 24.3, 24.0, 20.7, 19.3, 18.3, 14.0 ppm; MS (ESI) m/z 161.1 (18), 305.1 (9), 395.2 (11), 485.2 (10), 561.2 (^{79}Br; M + H^+, 100), 563.2 (^{81}Br; M + H^+, 98), 660.3 (6); HRMS calcd for $C_{29}H_{42}O_4{}^{79}BrSi$ [M + H^+] 561.2030, found 561.2040 (1.7 ppm).

(+)-(*S*)-Methyl 2-((2*S*,5*S*,6*S*)-6-((*S*)-1-(*tert*-Butyldiphenylsilyloxy)propan-2-yl)-5-methyltetrahydro-2*H*-pyran-2-yl)propanoate (31). Product **31** as a pale yellow oil (15.7 mg, yield = 81%) was obtained from a mixture of bromides **30a** and **30b** (22.5 mg) according to general procedure **A3** in a 12:1 ratio of products 2,3-*anti* (**31**)/2,3-*syn*: R_f = 0.44 (hexanes/EtOAc, 90:10); formula $C_{29}H_{42}O_4Si$; MW 482.73 g/mol; $[\alpha]_D$ +34.9 (c 0.46, $CHCl_3$); IR (neat) ν_{max} 3071, 2952, 2931, 2857, 1740, 1460, 1429, 1379, 1361, 1267, 1194, 1167, 1110, 1967, 824, 740, 704, 612 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.68−7.62 (m, 4H), 7.43−7.34 (m, 6H), 3.75 (td, J = 4.9 Hz, 9.9 Hz, 1H), 3.55 (dd, J = 4.2 Hz, 9.9 Hz, 1H), 3.52−3.44 (m, 2H), 3.33 (s, 3H), 3.29 (dd, J = 5.9 Hz, 5.9 Hz, 1H), 2.78 (qd, J = 7.1 Hz, 9.9 Hz, 1H), 2.04−1.95 (m, 1H), 1.70−1.49 (m, 5H), 1.30−1.21 (m, 1H), 1.04 (s, 9H), 1.01 (d, J = 6.9 Hz, 3H), 0.97 (d, J = 6.7 Hz, 3H), 0.90 (d, J = 6.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.2, 135.9, 134.4, 134.3, 129.8, 127.9, 78.5, 73.9, 67.8, 67.8, 51.6, 42.2, 36.5, 30.2, 27.2, 26.5, 24.5, 19.6, 18.3, 14.3, 11.5 ppm; MS (ESI) m/z 405.2 (46), 483.3 (M + H^+, 100); HRMS calcd for $C_{29}H_{43}O_4Si$ [M + H^+] 483.2925, found 483.2937 (2.5 ppm).

(+)-(*R*)-2-((2*S*,5*S*,6*S*)-6-((*S*)-1-(*tert*-Butyldiphenylsilyloxy)-propan-2-yl)-5-methyltetrahydro-2*H*-pyran-2-yl)propan-1-ol (S22). Primary alcohol **S22** as a colorless oil (1.40 g, yield = 81%) was obtained from ester **31** (1.83 g) according to general procedure **A9**: R_f = 0.30 (hexanes/EtOAc, 75:25); formula $C_{28}H_{42}O_3Si$; MW 454.72 g/mol; $[\alpha]_D$ +19.4 (c 0.34, $CHCl_3$); IR (neat) ν_{max} 3453, 3071, 2958, 2859, 1590, 1462, 1428, 1190, 1110, 1024, 823, 801, 740, 704, 614 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62−7.68 (m, 4H), 7.46−7.35 (m, 6H), 3.64−3.58 (m, 3H), 3.51 (dd, J = 5.4 Hz, 10.1 Hz, 1H), 3.49−3.44 (m, 1H), 3.43 (dd, J = 4.5 Hz, 7.2 Hz, 1H), 2.93 (dd, J = 4.4 Hz, 7.2 Hz, 1H), 2.13−2.02 (m, 1H), 1.95−1.83 (m, 1H), 1.78−1.47 (m, 4H), 1.39−1.29 (m, 1H), 1.05 (s, 9H), 0.99 (d, J = 6.9 Hz, 3H), 0.97 (d, J = 6.8 Hz, 3H), 0.84 (d, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 133.7, 129.6, 127.6, 78.3, 75.9, 67.5, 66.5, 37.9, 35.3, 28.8, 26.8, 25.6, 25.0, 19.3, 18.3, 13.8, 12.4 ppm; MS (EI) m/z 55.0 (13), 69.1 (17), 95.1 (19), 135.0 (28), 163.1 (35), 183.0 (34), 199.0 (100), 229 (21), 269.0 (7), 289.0 (9), 319.1 (40), 379.1 (6), 397.1 (17); HRMS calcd for $C_{24}H_{33}O_3Si$ [M − *t*-Bu] 397.2199, found 397.2210 (−2.8 ppm). Anal. Calcd for $C_{28}H_{42}O_3Si$: C, 73.96; H, 9.31. Found: C, 73.92; H, 9.44.

(+)-((*S*)-2-((2*S*,3*S*,6*S*)-6-((*R*)-1-(Benzyloxy)propan-2-yl)-3-methyltetrahydro-2*H*-pyran-2-yl)propoxy)(*tert*-butyl)diphenylsilane (S23). Protected benzyl ether product **S23** as a colorless oil (1.47 g, yield = 90%) was obtained from alcohol **S22** (1.36 g) according to general procedure **A7**: R_f = 0.40 (hexanes/EtOAc, 90:10); formula $C_{35}H_{48}O_3Si$; MW 544.84 g/mol; $[\alpha]_D$ +25.8 (c 0.33, $CHCl_3$); IR (neat) ν_{max} 3069, 2858, 1685, 1589, 1459, 1428, 1110, 1023, 824, 739, 703, 613 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69−7.63 (m, 4H), 7.42−7.33 (m, 6H), 7.32−7.27 (m, 2H), 7.26−7.22 (m, 3H), 4.37 (d, J = 12.1 Hz, 1H), 4.33 (d, J = 12.0 Hz, 1H), 3.66 (dd, J = 6.0 Hz, 9.9 Hz, 1H), 3.54 (dd, J = 6.5 Hz, 9.8 Hz, 1H), 3.51 (dd, J = 4.7 Hz, 8.4 Hz, 2H), 3.39−3.34 (m, 2H), 2.18−2.09 (m, 1H), 2.04−1.92 (m, 1H), 1.69−1.52 (m, 1H), 1.35−1.25 (m, 1H), 1.05 (s, 9H), 0.92 (d, J = 6.8 Hz, 3H), 0.91 (d, J = 6.9 Hz, 3H), 0.89 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 135.59, 135.56, 134.1, 133.9, 129.5, 128.2, 127.6, 127.4, 127.2, 76.6, 73.0, 72.8, 72.5, 67.0, 36.1, 34.3, 30.1, 26.9, 26.6, 24.8, 19.3, 18.1, 14.2, 11.1 ppm; MS (ESI) m/z 159.0 (7), 239.1 (8), 288.2 (20), 299.2 (9), 545.3 (100), 567.3 (51), 590.4 (6), 632.4 (9), 652.4 (21); HRMS calcd for $C_{35}H_{49}O_3Si$ [M + H^+] 545.3445, found 545.3438 (−1.3 ppm); calcd for $C_{35}H_{48}O_3SiNa$ [M + Na^+] 567.3265, found 567.3257 (−1.4 ppm). Anal. Calcd for $C_{35}H_{48}O_3Si$: C, 77.16; H, 8.88. Found: C, 77.08; H, 8.90.

(+)-(*S*)-2-((2*S*,3*S*,6*S*)-6-((*R*)-1-(Benzyloxy)propan-2-yl)-3-methyltetrahydro-2*H*-pyran-2-yl)propan-1-ol (S24). To a cold (0 °C) solution of product **S23** (1.63 g) in dry THF (0.1 M, 30 mL) was

added dropwise a 1 M solution of TBAF in THF (1.2 equiv, 3.6 mL), followed by overnight stirring at room temperature. The reaction mixture was treated with the addition of a saturated aqueous solution of NH_4Cl and then concentrated in vacuo. The product was extracted with Et_2O (3×), and the combined organic fractions were washed with a saturated brine solution and then dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (hexanes/EtOAc, 75:25) to give the desired primary alcohol **S24** as a colorless oil (0.84 g, yield = 91%): R_f = 0.22 (hexanes/EtOAc, 75:25); formula $C_{19}H_{30}O_3$; MW 306.44 g/mol; $[\alpha]_D$ +64.0 (*c* 0.25, $CHCl_3$); IR (neat) ν_{max} 3441, 2961, 1456, 1233, 1075, 1020, 967, 737, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37−7.26 (m, 5H), 4.56 (d, *J* = 12.1 Hz, 1H), 4.50 (d, *J* = 12.1 Hz, 1H), 3.63 (dd, *J* = 3.6 Hz, 8.5 Hz, 1H), 3.64−3.61 (m, 1H), 3.60 (dd, *J* = 3.6 Hz, 6.8 Hz, 1H), 3.55 (dd, *J* = 5.6 Hz, 10.7 Hz, 1H), 3.41 (dd, *J* = 2.9 Hz, 9.4 Hz, 1H), 3.35 (dd, *J* = 6.9 Hz, 9.1 Hz, 1H), 2.40−2.30 (m, 1H), 1.88−1.78 (m, 1H), 1.71−1.65 (m, 2H), 1.60−1.52 (m, 2H), 1.33−1.21 (m, 1H), 0.95 (d, *J* = 7.1 Hz, 3H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.81 (d, *J* = 6.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 128.3, 127.7, 127.4, 78.6, 74.6, 73.2, 72.8, 67.5, 35.4, 32.0, 31.7, 27.1, 25.8, 17.7, 14.8, 9.4 ppm; MS (EI) *m*/*z* 41.0 (8), 55.0 (12), 81.1 (14), 91.0 (100), 121.1 (18), 139.1 (17), 157.1 (35), 200.1 (8), 247.1 (16), 288.2 (2), 306.2 ($M + H^+$, 2); HRMS calcd for $C_{19}H_{30}O_3$ [$M + H^+$] 306.2195, found 306.2190 (1.8 ppm). Anal. Calcd for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 74.17; H, 9.82.

(+)-(*R*)-2-((2*S*,3*S*,6*S*)-6-((*R*)-1-(Benzyloxy)propan-2-yl)-3-methyltetrahydro-2*H*-pyran-2-yl)propanal (32). Aldehyde **32** as a colorless oil (0.57 g, yield = 94%) was obtained from primary alcohol **S24** (0.61 g) according to general procedure **A10**: R_f = 0.28 (hexanes/EtOAc, 85:15); formula $C_{19}H_{28}O_3$; MW 304.42 g/mol; $[\alpha]_D$ +21.9 (*c* 1.2, $CHCl_3$); IR (neat) ν_{max} 2927, 2856, 1725, 1456, 1376, 1092, 1020, 738, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.54 (d, *J* = 1.2 Hz, 1H), 7.36−7.24 (m, 5H), 4.49 (s, 2H), 3.75 (dd, *J* = 4.4 Hz, 8.1 Hz, 1H), 3.52 (dd, *J* = 3.5 Hz, 9.1 Hz, 1H), 3.53−3.46 (m, 1H), 3.24 (dd, *J* = 7.5 Hz, 9.0 Hz, 1H), 2.57 (ddq, *J* = 1.2 Hz, 4.4 Hz, 6.9 Hz, 1H), 2.32−2.19 (m, 1H), 1.73−1.55 (m, 4H), 1.43−1.29 (m, 1H), 1.10 (d, *J* = 7.0 Hz, 3H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.7, 138.7, 128.3, 127.6, 127.4, 75.1, 74.0, 73.1, 72.5, 47.7, 33.1, 31.1, 26.5, 25.1, 17.8, 14.4, 7.1 ppm; MS (ESI) *m*/*z* 141.1 (3), 195.1 (6), 247.2 (12), 303.2 (34), 305.2 ($M + H^+$, 35), 321.2 (52), 327.2 ($M + Na^+$, 38), 359.2 (78), 375.2 (13), 389.2 (4), 557.3 (16), 573.3 (59), 647.4 (42), 663.3 (100), 679.3 (70); HRMS calcd for $C_{19}H_{28}O_3Na$ [$M + Na^+$] 327.1931, found 327.1925 (−3.5 ppm).

(±)-(3*S*,4*S*)-Methyl 4-((2*S*,3*S*,6*S*)-6-((*R*)-1-(Benzyloxy)propan-2-yl)-3-methyltetrahydro-2*H*-pyran-2-yl)-2-bromo-3-hydroxy-2-methylpentanoate (34). Bromide product **34** as a pale yellow oil (72 mg, quantitative yield) was obtained from aldehyde **32** (43 mg) according to general procedure **A1** in a >20:1 ratio of products 3,4-*syn* (**34**)/3,4-*anti* (**33**). The purified bromide product **34** was found to be contaminated by unreactive *C*-silylated product from enol ether **7a**: R_f = 0.29 (hexanes/EtOAc, 85:15); formula $C_{23}H_{35}BrO_5$; MW 471.43 g/mol; IR (neat) ν_{max} 3464, 2951, 2930, 2859, 1737, 1453, 1378, 1313, 1261, 1100, 1051, 1016, 967, 919, 738, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40−7.24 (m, 5H), 4.58 (d, *J* = 12.2 Hz, 1H), 4.55 (d, *J* = 12.2 Hz, 1H), 4.35 (s, 1H), 3.80 (s, 3H), 3.66 (ddd, *J* = 3.2 Hz, 4.7 Hz, 10.4 Hz, 1H), 3.61 (dd, *J* = 3.3 Hz, 9.1 Hz, 1H), 3.42 (dd, *J* = 6.8 Hz, 9.0 Hz, 1H), 3.33 (dd, *J* = 3.1 Hz, 9.1 Hz, 2H), 2.37−2.27 (m, 1H), 1.95 (s, 3H), 1.93−1.87 (m, 1H), 1.74−1.51 (m, 4H), 1.33−1.18 (m, 1H), 0.94 (d, *J* = 6.7 Hz, 3H), 0.93 (d, *J* = 6.9 Hz, 3H), 0.80 (d, *J* = 6.4 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 138.7, 128.3, 127.7, 127.4, 82.2, 79.5, 74.4, 73.3, 72.8, 65.8, 53.0, 35.0, 32.3, 30.9, 26.7, 25.5, 23.9, 17.5, 14.7, 6.6 ppm; MS (ESI) *m*/*z* 185.2 (55), 233.2 (78), 283.2 (87), 345.1 (32), 363.1 (13), 453.2 (8), 471.2 (^{79}Br; $M + H^+$, 100), 570.3 (7); HRMS calcd for $C_{23}H_{36}O_5{}^{79}Br$ [$M + H^+$] 471.1741, found 471.1739 (−0.3 ppm).

(±)-(2*R*,3*R*,4*S*)-Methyl 4-((2*S*,3*S*,6*S*)-6-((*R*)-1-(Benzyloxy)propan-2-yl)-3-methyltetrahydro-2*H*-pyran-2-yl)-3-hydroxy-2-methylpentanoate (35). Product **35** as a pale yellow oil (0.48 g, yield = 77%) was obtained from a mixture of bromides **33a** and **33b** (0.75 g) according to general procedure **A4** in a >20:1 ratio of products 2,3-*anti* (**35**)/2,3-*syn* (**36**): R_f = 0.24 (hexanes/EtOAc, 85:15); formula $C_{23}H_{36}O_5$; MW 392.53 g/mol; IR (neat) ν_{max} 3463, 3030, 2950, 2931, 2859, 1740, 1457, 1379, 1362, 1272, 1249, 1196, 1169, 1097, 1071, 1016, 985, 737, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41−7.25 (m, 5H), 4.63 (d, *J* = 11.9 Hz, 1H), 4.54 (d, *J* = 11.9 Hz, 1H), 3.78−3.65 (m, 4H), 3.72 (s, 3H), 3.63 (dd, *J* = 1.7 Hz, 10.2 Hz, 1H), 3.43 (dd, *J* = 7.1 Hz, 9.0 Hz, 1H), 2.83−2.76 (m, 1H), 2.46−2.36 (m, 1H), 1.92−1.84 (m, 1H), 1.78−1.54 (m, 4H), 1.33−1.22 (m, 1H), 1.13 (d, *J* = 7.0 Hz, 3H), 1.07 (d, *J* = 7.1 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.81 (d, *J* = 6.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.1, 138.8, 128.2, 127.6, 127.2, 77.6, 75.3, 74.6, 73.2, 72.9, 51.4, 43.7, 34.3, 31.7, 31.6, 26.9, 25.8, 17.7, 14.7, 14.6, 10.8 ppm; MS (ESI) *m*/*z* 185.1 (100), 235.2 (47), 267.2 (22), 325.2 (38), 393.3 ($M + H^+$, 42); HRMS calcd for $C_{23}H_{37}O_5$ [$M + H^+$] 393.2636, found 393.2634 (−0.4 ppm).

(±)-(2*S*,3*S*,4*S*)-Methyl 4-((2*S*,3*S*,6*S*)-6-((*R*)-1-(Benzyloxy)propan-2-yl)-3-methyltetrahydro-2*H*-pyran-2-yl)-3-hydroxy-2-methylpentanoate (37). Product **37** as a pale yellow oil (7.2 mg, yield = 68%) was obtained from bromide **34** (12.7 mg) according to general procedure **A4** in a >20:1 ratio of products 2,3-*anti* (**37**)/2,3-*syn* (**38**): R_f = 0.18 (hexanes/EtOAc, 85:15); formula $C_{23}H_{36}O_5$; MW 392.53 g/mol; IR (neat) ν_{max} 3462, 2930, 2859, 1738, 1540, 1457, 1347, 1249, 1195, 1170, 1071, 1044, 1016, 965, 908, 736, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37−7.26 (m, 5H), 4.53 (d, *J* = 11.8 Hz, 1H), 4.49 (d, *J* = 11.8 Hz, 1H), 3.96−3.91 (m, 2H), 3.72 (s, 3H), 3.68 (dt, *J* = 10.3 Hz, 3.7 Hz, 1H), 3.55 (dd, *J* = 3.2 Hz, 9.0 Hz, 1H), 3.43 (dd, *J* = 2.4 Hz, 9.4 Hz, 1H), 3.42−3.38 (m, 1H), 2.63 (dq, *J* = 9.6 Hz, 7.1 Hz, 1H), 2.37−2.28 (m, 1H), 1.87−1.80 (m, 1H), 1.71−1.66 (m, 2H), 1.66−1.59 (m, 1H), 1.59−1.52 (m, 1H), 1.34−1.22 (m, 1H), 1.07 (d, *J* = 7.0 Hz, 3H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.90 (d, *J* = 7.1 Hz, 3H), 0.81 (d, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 138.8, 128.9, 128.2, 127.8, 127.4, 81.8, 78.2, 74.5, 73.2, 72.4, 51.7, 43.5, 33.6, 31.8, 30.3, 26.9, 25.6, 17.6, 14.9, 14.1, 4.7 ppm; MS (ESI) *m*/*z* 393.3 ($M + H^+$, 100); HRMS calcd for $C_{23}H_{37}O_5$ [$M + H^+$] 393.2636, found 393.2623 (−3.1 ppm).

(±)-(2*R*,3*S*,4*S*)-Methyl 4-((2*S*,3*S*,6*S*)-6-((*R*)-1-(Benzyloxy)propan-2-yl)-3-methyltetrahydro-2*H*-pyran-2-yl)-3-hydroxy-2-methylpentanoate (38). Product **38** as a pale yellow oil (6.3 mg, yield = 59%) was obtained from bromide **34** (12.7 mg) according to general procedure **A5** in a >20:1 ratio of products 2,3-*syn* (**38**)/2,3-*anti* (**37**): R_f = 0.25 (hexanes/EtOAc, 85:15); formula $C_{23}H_{36}O_5$; MW 392.53 g/mol; IR (neat) ν_{max} 3470, 2955, 2927, 2871, 1736, 1456, 1433, 1360, 1314, 1232, 1197, 1160, 1117, 1074 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37−7.26 (m, 5H), 4.56 (d, *J* = 11.9 Hz, 1H), 4.50 (d, *J* = 11.9 Hz, 1H), 3.85−3.79 (m, 2H), 3.73−3.67 (m, 1H), 3.66 (s, 3H), 3.58 (dd, *J* = 3.1 Hz, 9.0 Hz, 1H), 3.44−3.38 (m, 2H), 2.65 (dq, *J* = 9.2 Hz, 6.8 Hz, 1H), 2.39−2.30 (m, 1H), 1.72−1.62 (m, 3H), 1.62−1.50 (m, 2H), 1.31−1.21 (m, 1H), 1.28 (d, *J* = 6.9 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.91 (d, *J* = 7.1 Hz, 3H), 0.76 (d, *J* = 6.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 136.9, 128.3, 127.7, 127.4, 81.5, 76.6, 74.6, 73.3, 72.5, 51.5, 43.8, 43.1, 35.7, 31.7, 29.7, 26.9, 25.7, 17.5, 14.8,5.2 ppm; MS (ESI) *m*/*z* 393.3 ($M + H^+$, 100); HRMS calcd for $C_{23}H_{37}O_5$ [$M + H^+$] 393.2636, found 393.2626 (−2.6 ppm).

(±)-(2*R*,3*R*,4*S*)-Methyl 3-Hydroxy-4-((2*S*,3*S*,6*S*)-6-((*R*)-1-hydroxypropan-2-yl)-3-methyltetrahydro-2*H*-pyran-2-yl)-2-methylpentanoate (S25). Product **S25** as a colorless oil was obtained from benzyl ether **35** (90 mg) according to general procedure **A12**. The crude product was used as crude without further purification: R_f = 0.05 (hexanes/EtOAc, 85:15); formula $C_{16}H_{30}O_5$; MW 302.41 g/mol; ^1H NMR (500 MHz, $CDCl_3$) δ 3.85−3.76 (m, 2H), 3.69 (s, 3H), 3.64

(dd, J = 1.5 Hz, 9.9 Hz, 1H), 3.59−3.53 (m, 2H), 3.44 (dd, J = 6.2 Hz, 10.5 Hz, 1H), 3.12 (sl, 1H), 2.75 (dq, J = 7.0 Hz, 7.0 Hz, 1H), 2.28−2.17 (m, 1H), 1.85−1.76 (m, 1H), 1.73−1.64 (m, 2H), 1.64−1.52 (m, 2H), 1.29−1.18 (m, 1H), 1.15 (d, J = 7.0 Hz, 3H), 0.97 (d, J = 7.1 Hz, 3H), 0.85 (d, J = 6.8 Hz, 3H), 0.76 (d, J = 6.4 Hz, 3H) ppm.

(±)-(2*R*,3*R*,4*S*)-Methyl 3-Hydroxy-2-methyl-4-((2*S*,3*S*,6*S*)-3-methyl-6-((*R*)-1-(triisopropylsilyloxy)propan-2-yl)tetrahydro-2*H*-pyran-2-yl)pentanoate (S26). Product **S26** as a colorless oil (96 mg, yield = 77% over two steps) was obtained from crude alcohol **S25** according to general procedure **A8** with TIPSOTf (1.1 equiv, 68 μL): R_f = 0.21 (hexanes/EtOAc, 95:5); formula $C_{25}H_{50}O_5Si$; MW 458.75 g/mol; IR (neat) ν_{max} 3521, 2942, 2866, 1742, 1719, 1461, 1381, 1250, 1196, 1170, 1095, 1068, 1013, 883, 838, 777, 682, 660 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.86−3.79 (m, 2H), 3.74 (dd, J = 3.1 Hz, 9.6 Hz, 1H), 3.67 (s, 3H), 3.65−3.54 (m, 2H), 3.43 (d, J = 9.4 Hz, 1H), 2.65 (dq, J = 7.0 Hz, 7.1 Hz, 1H), 2.24−2.15 (m, 1H), 1.82−1.74 (m, 1H), 1.71−1.65 (m, 2H), 1.65−1.51 (m, 2H), 1.28−1.18 (m, 1H), 1.13 (d, J = 7.1 Hz, 3H), 1.10−1.06 (m, 3H), 1.06−1.02 (m, 18H), 0.98 (d, J = 7.1 Hz, 3H), 0.89 (d, J = 6.8 Hz, 3H), 0.77 (d, J = 6.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.4, 76.7, 75.1, 73.3, 64.7, 51.5, 43.2, 35.4, 33.3, 31.7, 27.4, 25.9, 18.01, 17.98, 17.8, 14.8, 14.1, 11.9, 10.6 ppm; MS (ESI) m/z 459.4 (M + H$^+$, 100); HRMS calcd for $C_{25}H_{51}O_5Si$ [M + H$^+$] 459.3500, found 459.3503 (0.5 ppm).

(±)-(2*S*,3*S*,4*S*)-2-Methyl-4-((2*S*,3*S*,6*S*)-3-methyl-6-((*R*)-1-(triisopropylsilyloxy)propan-2-yl)tetrahydro-2*H*-pyran-2-yl)pentane-1,3-diol (39)[29]. Primary alcohol **39** as a colorless oil (69 mg, yield = 76%) was obtained from ester **S26** (96 mg) according to general procedure **A9**: R_f = 0.23 (hexanes/EtOAc, 85:15); formula $C_{24}H_{50}O_4Si$; MW 430.74 g/mol; IR (neat) ν_{max} 3416, 2959, 2940, 2866, 1461, 1382, 1235, 1096, 1074, 1012, 883, 836, 775, 682 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.29 (d, J = 7.9 Hz, 1H), 3.90 (ddd, J = 3.7 Hz, 3.7 Hz, 9.3 Hz, 1H), 3.80 (dd, J = 4.4 Hz, 9.6 Hz, 1H), 3.75 (dd, J = 3.1 Hz, 9.6 Hz, 1H), 3.73−3.62 (m, 4H), 3.43 (ddd, J = 3.2 Hz, 9.2 Hz, 9.1 Hz, 1H), 2.24−2.14 (m, 1H), 1.97−1.90 (m, 1H), 1.90−1.81 (m, 1H), 1.72−1.61 (m, 3H), 1.61−1.53 (m, 1H), 1.30−1.16 (m, 1H), 1.13−1.06 (m, 3H), 1.08 (d, J = 7.2 Hz, 3H), 1.06−1.02 (m, 18H), 0.91 (d, J = 6.9 Hz, 3H), 0.80 (d, J = 6.5 Hz, 3H), 0.76 (d, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 83.2, 76.1, 73.4, 68.9, 65.1, 38.0, 34.0, 33.7, 31.8, 27.0, 25.9, 18.03, 17.99, 17.9, 14.2, 13.7, 11.9, 11.3 ppm; MS (ESI) m/z 159.1 (67), 244.3 (83), 288.3 (32), 339.1 (27), 431.4 (M + H$^+$, 100), 663.5 (66); HRMS calcd for $C_{24}H_{51}O_4Si$ [M + H$^+$] 431.3551, found 431.3553 (0.3 ppm).

(±)-(2*R*,3*R*,4*S*)-Methyl 3-(Benzyloxy)-4-((2*S*,3*S*,6*S*)-6-((*R*)-1-(benzyloxy)propan-2-yl)-3-methyltetrahydro-2*H*-pyran-2-yl)-2-methylpentanoate (S27). Protected benzyl ether product **S27** as a colorless oil (227 mg, yield = 92%) was obtained from alcohol **35** (200 mg) according to general procedure **A7**: R_f = 0.24 (hexanes/EtOAc, 90:10); formula $C_{30}H_{42}O_5$; MW 482.65 g/mol; IR (neat) ν_{max} 3064, 3030, 2949, 2929, 1737, 1496, 1455, 1379, 1359, 1205, 1094, 1069, 1026, 966, 736, 696 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.22 (m, 10H), 4.53 (s, 2H), 4.48 (d, J = 12.0 Hz, 1H), 4.44 (d, J = 12.0 Hz, 1H), 3.79 (dd, J = 5.3 Hz, 7.1 Hz, 1H), 3.68−3.64 (m, 1H), 3.66 (s, 3H), 3.57 (dd, J = 3.9 Hz, 7.6 Hz, 2H), 3.35 (dd, J = 7.2 Hz, 8.8 Hz, 1H), 2.91 (dq, J = 5.4 Hz, 7.1 Hz, 1H), 2.19−2.05 (m, 2H), 1.75−1.53 (m, 4H), 1.36−1.26 (m, 1H), 1.19 (d, J = 7.1 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H), 0.89 (d, J = 7.1 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 138.8, 128.20, 128.15, 127.5, 127.3, 127.2, 82.7, 75.6, 73.1, 73.0, 72.8, 72.6, 51.5, 41.6, 36.2, 34.4, 30.3, 26.8, 25.0, 18.3, 14.2, 12.1, 10.1 ppm; MS (ESI) m/z 185.1 (100), 235.2 (33), 267.2 (40), 325.2 (28), 375.3 (37), 451.3 (5), 483.3 (M + H$^+$, 22), 573.4 (8); HRMS calcd for $C_{30}H_{43}O_5$ [M + H$^+$] 483.3105, found 483.3099 (−1.3 ppm).

(±)-(2*S*,3*S*,4*S*)-3-(Benzyloxy)-4-((2*S*,3*S*,6*S*)-6-((*R*)-1-(benzyloxy)propan-2-yl)-3-methyltetrahydro-2*H*-pyran-2-yl)-2-methylpentan-1-ol (S28). Primary alcohol **S28** as a colorless oil (220 mg, yield = 95%) was obtained from ester **S27** (246 mg) according to general procedure **A9**: R_f = 0.33 (hexanes/EtOAc, 80:20); formula $C_{29}H_{42}O_4$; MW 454.64 g/mol; IR (neat) ν_{max} 3440, 3063, 3030, 2962, 2927, 2876, 1495, 1455, 1379, 1207, 1093, 1070, 1025, 966, 909, 735, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.23 (m, 10H), 4.63 (d, J = 11.0 Hz, 1H), 4.52 (d, J = 11.0 Hz, 1H), 4.48 (d, J = 11.9 Hz, 1H), 4.45 (d, J = 11.9 Hz, 1H), 3.83 (dt, J = 10.8 Hz, 3.7 Hz, 1H), 3.68 (dd, J = 3.6 Hz, 8.8 Hz, 1H), 3.59−3.52 (m, 2H), 3.50 (dd, J = 4.3 Hz, 7.2 Hz, 1H), 3.41 (dd, J = 3.9 Hz, 7.2 Hz, 1H), 3.34 (dd, J = 7.5 Hz, 8.5 Hz, 1H), 2.88 (dd, J = 4.3 Hz, 7.1 Hz, 1H), 2.20−2.12 (m, 1H), 2.12−2.03 (m, 1H), 1.96−1.87 (m, 1H), 1.75−1.53 (m, 4H), 1.35−1.23 (m, 1H), 1.11 (d, J = 7.1 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H), 0.92 (d, J = 7.0 Hz, 3H), 0.89 (d, J = 6.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.7, 138.3, 128.4, 128.3, 127.7, 127.6, 127.5, 127.4, 87.0, 76.4, 74.8, 73.2, 73.1, 72.6, 65.3, 37.0, 36.3, 35.2, 30.0, 26.7, 24.9, 18.4, 16.3, 14.1, 11.0 ppm; MS (ESI) m/z 347.3 (6), 455.3 (M + H$^+$, 100), 456.3 (30), 545.4 (20); HRMS calcd for $C_{29}H_{43}O_4$ [M + H$^+$] 455.3156, found 455.3153 (−0.6 ppm).

(+)-(2*R*,3*R*,4*S*)-3-(Benzyloxy)-4-((2*S*,3*S*,6*S*)-6-((*R*)-1-(benzyloxy)propan-2-yl)-3-methyltetrahydro-2*H*-pyran-2-yl)-2-methylpentanal (40). Aldehyde **40** as a colorless oil was obtained from primary alcohol **S28** (105 mg) according to general procedure **A11**: R_f = 0.65 (hexanes/EtOAc, 80:20); formula $C_{29}H_{40}O_4$; MW 452.63 g/mol; $[\alpha]_D$ +31.0 (c 1.6, $CHCl_3$); IR (neat) ν_{max} 3030, 2955, 2925, 2854, 1724, 1456, 1379, 1263, 1094, 1070, 1020, 965, 802, 736, 697, 645 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.79 (d, J = 1.8 Hz, 1H), 7.34−7.25 (m, 10H), 4.53−4.48 (m, 2H), 4.48−4.42 (m, 2H), 3.69 (dd, J = 3.0 Hz, 7.7 Hz, 1H), 3.62−3.55 (m, 2H), 3.52 (dd, J = 3.2 Hz, 8.3 Hz, 1H), 3.33 (dd, J = 7.2 Hz, 8.7 Hz, 1H), 2.73 (ddq, J = 2.0 Hz, 2.7 Hz, 6.9 Hz, 1H), 2.21−2.12 (m, 1H), 2.12−2.06 (m, 1H), 1.68−1.57 (m, 3H), 1.33−1.21 (m, 2H), 1.14 (d, J = 7.0 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H), 0.84 (d, J = 6.5 Hz, 3H), 0.82 (d, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.4, 138.7, 138.4, 128.28, 128.25, 127.6, 127.42, 127.38, 127.2, 82.3, 75.6, 73.2, 73.1, 72.9, 72.5, 48.5, 36.7, 33.8, 30.6, 27.0, 25.3, 18.2, 14.3, 10.8, 9.8 ppm; MS (ES-TOF) m/z 237.2 (8), 327.2 (8), 342.3 (24), 345.2 (31), 415.2 (53), 431.2 (57), 453.3 (M + H$^+$, 10), 475.3 (M + Na$^+$, 100), 491.3 (81), 492.3 (30), 507.3 (26), 521.8 (8), 683.4 (5); HRMS calcd for $C_{29}H_{40}O_4Na$ [M + Na$^+$] 475.2824, found 475.2828 (0.8 ppm).

(±)-(3*R*,4*S*,5*S*,6*S*)-Methyl 5-(Benzyloxy)-6-((2*S*,3*S*,6*S*)-6-((*R*)-1-(benzyloxy)propan-2-yl)-3-methyltetrahydro-2*H*-pyran-2-yl)-2-bromo-3-hydroxy-2,4-dimethylheptanoate (41a, 41b). A ∼1:1 mixture of bromide adducts **41a** and **41b** as a pale yellow oil (45.6 mg, yield = 32% over two steps) was obtained from aldehyde **40** (104 mg) according to general procedure **A2** in a 5:1 ratio of products 3,4-*anti* (**41a**,**b**)/3,4-*syn* (**42**) with 1 M solution of $TiCl_4$ in CH_2Cl_2 (4 equiv, 0.92 mL). Purified mixture of bromide adducts was found to be contaminated by unreactive *C*-silylated product from enol ether **7a**. **41a**: R_f = 0.40 (hexanes/EtOAc, 85:15); formula $C_{33}H_{47}BrO_6$; MW 619.63 g/mol; IR (neat) ν_{max} 3561, 3030, 2952, 2928, 2860, 1738, 1453, 1379, 1307, 1260, 1093, 1068, 1027, 967, 913, 736, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.24 (m, 10H), 4.60−4.53 (m, 2H), 4.49 (d, J = 12.2 Hz, 1H), 4.45 (d, J = 12.1 Hz, 1H), 4.37 (d, J = 9.6 Hz, 1H), 3.78 (s, 3H), 3.65 (dd, J = 2.9 Hz, 8.6 Hz, 2H), 3.62−3.57 (m, 2H), 3.36 (dd, J = 7.3 Hz, 8.4 Hz, 1H), 3.05 (sl, 1H), 2.19−1.99 (m, 3H), 1.87 (s, 3H), 1.74−1.54 (m, 4H), 1.33−1.21 (m, 1H), 0.96 (d, J = 7.0 Hz, 3H), 0.91 (d, J = 6.8 Hz, 3H), 0.83 (d, J = 6.2 Hz, 3H), 0.82 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 138.85, 138.84, 128.3, 128.2, 127.5, 127.34, 127.29, 127.26, 84.0, 77.2, 75.6, 75.2, 73.2, 73.14, 73.12, 73.11, 68.9, 52.8, 38.6, 37.8, 34.2, 30.4, 27.2, 25.3, 21.0, 18.4, 14.2, 10.8 ppm; MS (ESI) m/z 247.2 (5), 345.2 (9), 431.3 (7), 449.3 (61), 491.2 (6), 539.3 (11), 619.3 (^{79}Br; M + H$^+$, 100); HRMS calcd for $C_{33}H_{48}O_6{}^{79}Br$ [M + H$^+$] 619.2629, found 619.2620 (−1.5 ppm).

(±)-(3*S*,4*S*,5*S*,6*S*)-Methyl 5-(Benzyloxy)-6-((2*S*,3*S*,6*S*)-6-((*R*)-1-(benzyloxy)propan-2-yl)-3-methyltetrahydro-2*H*-pyran-2-yl)-2-bromo-3-hydroxy-2,4-dimethylheptanoate (42). Bromide

adduct **42** as a pale yellow oil (16.9 mg, yield = 68% over two steps) was obtained from aldehyde **40** (18.1 mg) according to general procedure **A1** in a >20:1 ratio of products 3,4-*syn* (**42**)/3,4-*anti* (**41a,b**). The purified product was found to be contaminated by unreactive *C*-silylated product from enol ether **7a**: R_f = 0.44 (hexanes/EtOAc, 85:15); formula $C_{33}H_{47}BrO_6$; MW 619.63 g/mol; IR (neat) ν_{max} 3454, 3030, 2950, 2928, 1737, 1454, 1380, 1260, 1085, 735, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34−7.24 (m, 10H), 4.65 (d, J = 10.9 Hz, 1H), 4.52 (d, J = 10.9 Hz, 1H), 4.48 (s, 2H), 4.46 (dd, J = 1.2 Hz, 1.7 Hz, 1H), 3.78 (s, 3H), 3.73 (d, J = 2.0 Hz, 1H), 3.67 (dd, J = 3.5 Hz, 8.7 Hz, 1H), 3.60−3.56 (m, 1H), 3.56 (dd, J = 2.8 Hz, 8.7 Hz, 1H), 3.36 (dd, J = 2.5 Hz, 8.7 Hz, 1H), 3.34 (dd, J = 7.3 Hz, 8.5 Hz, 1H), 2.10−2.01 (m, 2H), 1.99−1.92 (m, 1H), 1.95 (s, 3H), 1.78−1.70 (m, 1H), 1.70−1.66 (m, 1H), 1.66−1.60 (m, 2H), 1.31−1.23 (m, 1H), 1.12 (d, J = 7.1 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H), 0.87 (d, J = 6.5 Hz, 3H), 0.87 (d, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 138.6, 138.0, 128.5, 128.2, 127.7, 127.53, 127.49, 127.39, 88.4, 75.9, 75.6, 74.4, 73.20, 73.17, 72.9, 66.4, 53.1, 37.2, 35.9, 35.4, 30.0, 27.1, 25.3, 24.8, 18.5, 14.1, 13.9, 10.2 ppm; MS (ESI) m/z 329.1 (12), 619.3 (^{79}Br; M + H^+, 98), 621.3 (^{81}Br; M + H^+, 94), 636.3 (94), 641.2 (^{79}Br; M + Na^+, 100), 643.2 (^{81}Br; M + Na^+, 95), 644.2 (36), 718.4 (89); HRMS calcd for $C_{33}H_{48}O_6{}^{79}Br$ [M + H^+] 619.2629, found 619.2637 (1.4 ppm); calcd for $C_{33}H_{47}O_6{}^{79}BrNa$ [M + Na^+] 641.2448, found 641.2458 (1.5 ppm).

(±)-(2*R*,3*R*,4*S*,5*S*,6*S*)-Methyl 5-(Benzyloxy)-6-((2*S*,3*S*,6*S*)-6-((*R*)-1-(benzyloxy)propan-2-yl)-3-methyltetrahydro-2*H*-pyran-2-yl)-3-hydroxy-2,4-dimethylheptanoate (43). Product **43** as a pale yellow oil (9.9 mg, yield = 54%) was obtained from a mixture of bromide **41a** and **41b** (21.1 mg) according to general procedure **A4** in a >20:1 ratio of products 2,3-*anti* (**43**)/2,3-*syn* (**44**): R_f = 0.24 (hexanes/EtOAc, 85:15); formula $C_{33}H_{48}O_6$; MW 540.73 g/mol; IR (neat) ν_{max} 3500, 3030, 2952, 2928, 2879, 1738, 1540, 1496, 1456, 1378, 1360, 1198, 1170, 1095, 1067, 1025, 966, 736, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34−7.23 (m, 10H), 4.59 (d, J = 10.8 Hz, 1H), 4.55 (d, J = 10.8 Hz, 1H), 4.51 (d, J = 12.3 Hz, 1H), 4.48 (d, J = 12.3 Hz, 1H), 3.71 (sl, 1H), 3.70−3.67 (m, 1H), 3.67 (s, 3H), 3.65 (dd, J = 3.6 Hz, 8.8 Hz, 1H), 3.53 (dd, J = 4.7 Hz, 7.3 Hz, 2H), 3.49 (dd, J = 4.3 Hz, 7.1 Hz, 1H), 3.35 (dd, J = 7.2 Hz, 8.7 Hz, 1H), 2.79 (dq, J = 3.5 Hz, 7.1 Hz, 1H), 2.21 (ddq, J = 4.7 Hz, 6.9 Hz, 7.0 Hz, 1H), 2.09−2.01 (m, 2H), 1.78−1.70 (m, 1H), 1.70−1.61 (m, 1H), 1.61−1.51 (m, 2H), 1.34−1.25 (m, 1H), 1.26 (d, J = 7.1 Hz, 3H), 0.96 (d, J = 7.0 Hz, 3H), 0.95 (d, J = 7.1 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H), 0.89 (d, J = 6.7 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.1, 138.8, 138.6, 128.3, 128.2, 127.60, 127.56, 127.43, 127.37, 85.9, 76.7, 76.5, 74.0, 73.1, 73.0, 72.4, 51.6, 42.1, 39.2, 37.5, 35.5, 29.8, 26.7, 24.8, 18.4, 15.9, 15.0, 14.1, 11.8 ppm; MS (ESI) m/z 433.3 (13), 541.4 (M + H^+, 100); HRMS calcd for $C_{33}H_{49}O_6$ [M + H^+] 541.3524, found 541.3513 (−1.9 ppm).

(±)-(2*S*,3*S*,4*S*,5*S*,6*S*)-Methyl 5-(Benzyloxy)-6-((2*S*,3*S*,6*S*)-6-((*R*)-1-(benzyloxy)propan-2-yl)-3-methyltetrahydro-2*H*-pyran-2-yl)-3-hydroxy-2,4-dimethylheptanoate (45). Product **45** as a pale yellow oil (17 mg, yield = 78%) was obtained from bromide **42** (25 mg) according to general procedure **A4** in a >20:1 ratio of products 2,3-*anti* (**45**)/2,3-*syn* (**46**): R_f = 0.20 (hexanes/EtOAc, 85:15); formula $C_{33}H_{48}O_6$; MW 540.73 g/mol; IR (neat) ν_{max} 3481, 2951, 2925, 1739, 1455, 1378, 1196, 1172, 1096, 1069 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37−7.24 (m, 10H), 4.62 (d, J = 10.8 Hz, 1H), 4.57 (d, J = 10.9 Hz, 1H), 4.54 (d, J = 12.2 Hz, 1H), 4.51 (d, J = 12.1 Hz, 1H), 4.15 (d, J = 10.0 Hz, 1H), 4.01 (s, 1H), 3.75−3.71 (m, 1H), 3.74 (s, 3H), 3.61 (dt, J = 9.5, 4.7 Hz, 1H), 3.55 (t, J = 10.0 Hz, 2H), 3.35 (t, J = 8.1 Hz, 1H), 2.62 (dq, J = 9.8, 7.0 Hz, 1H), 2.19−2.09 (m, 2H), 1.91 (q, J = 7.2 Hz, 1H), 1.74−1.61 (m, 4H), 1.32−1.22 (m, 1H), 1.13 (d, J = 7.1 Hz, 3H), 1.08 (d, J = 7.0 Hz, 3H), 0.94 (d, J = 6.7 Hz, 3H), 0.865 (d, J = 7.0 Hz, 3H), 0.864 (d, J = 6.1 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.8, 138.7, 138.0, 128.5, 128.4, 127.83, 127.75, 127.6, 127.5, 87.5, 76.1, 75.7, 73.54, 73.49, 73.47, 72.8, 52.0, 43.7, 37.7, 34.5, 33.9, 30.7, 27.4, 25.6, 18.6, 14.5, 13.8, 12.0, 10.4 ppm; MS (ESI) m/z 338.3 (11), 541.4 (M + H^+, 26), 550.6 (30), 563.3 (M + Na^+, 100), 653.4 (17); HRMS calcd for $C_{33}H_{49}O_6$ [M + H^+] 541.3524, found 541.3518 (−1.0 ppm); calcd for $C_{33}H_{48}O_6Na$ [M + Na^+] 563.3343, found 563.3350 (1.2 ppm).

(±)-(2*R*,3*S*,4*S*,5*S*,6*S*)-Methyl 5-(Benzyloxy)-6-((2*S*,3*S*,6*S*)-6-((*R*)-1-(benzyloxy)propan-2-yl)-3-methyltetrahydro-2*H*-pyran-2-yl)-3-hydroxy-2,4-dimethylheptanoate (46). Product **46** as a pale yellow oil (15 mg, yield = 66%) was obtained from bromide **42** (25 mg) according to general procedure **A6** in a >20: 1 ratio of products 2,3-*syn* (**46**)/2,3-*anti* (**45**): R_f = 0.25 (hexanes/EtOAc, 85:15); formula $C_{33}H_{48}O_6$; MW 540.73 g/mol; IR (neat) ν_{max} 3473, 2927, 2874, 1735, 1455, 1380, 1349, 1272, 1193, 1085, 1052 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33−7.21 (m, 10H), 4.60 (d, J = 10.8 Hz, 1H), 4.53 (d, J = 10.9 Hz, 1H), 4.50 (d, J = 9.7 Hz, 1H), 4.48 (d, J = 9.7 Hz, 1H), 4.04−3.98 (m, 2H), 3.71 (dd, J = 8.6, 3.3 Hz, 1H), 3.66 (s, 3H), 3.56 (dt, J = 9.4, 4.8 Hz, 1H), 3.49 (ddd, J = 19.1, 9.3, 1.7 Hz, 2H), 3.30 (dd, J = 8.4, 7.9 Hz, 1H), 2.66−2.58 (m, 1H), 2.16−2.03 (m, 2H), 1.79−1.56 (m, 6H), 1.27 (d, J = 6.8 Hz, 3H), 1.14 (d, J = 7.2 Hz, 3H), 0.91 (d, J = 6.7 Hz, 3H), 0.83 (d, J = 6.4 Hz, 3H), 0.79 (d, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.8, 138.7, 138.0, 128.5, 128.4, 127.83, 127.75, 127.6, 127.5, 87.5, 76.1, 75.7, 73.54, 73.49, 73.47, 72.8, 52.0, 43.7, 37.7, 34.5, 33.9, 30.7, 27.4, 25.6, 18.6, 14.5, 13.8, 12.0, 10.4 ppm; MS (ESI) m/z 360.3 (7), 541.4 (M + H^+, 5), 563.3 (M + Na^+, 100), 577.3 (13), 653.4 (6); HRMS calcd for $C_{33}H_{49}O_6$ [M + H^+] 541.3524, found 541.3515 (−1.6 ppm); calcd for $C_{33}H_{48}O_6Na$ [M + Na^+] 563.3343, found 563.3349 (1.1 ppm).

(±)-(3*R*,4*R*,5*S*,6*S*)-4-Hydroxy-6-((*R*)-1-((2*S*,3*S*,6*S*)-6-((*R*)-1-Hydroxypropan-2-yl)-3-methyltetrahydro-2*H*-pyran-2-yl)-ethyl)-3,5-dimethyltetrahydro-2*H*-pyran-2-one (47). Product **47** as a colorless oil (5.6 mg, yield = 90%) was obtained from product **43** (10.3 mg) according to general procedure **A12** with 20 wt % $Pd(OH)_2$ on activated carbon (3.5 equiv, 35 mg) in MeOH (0.1 M, 190 μL). The crude product was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 95:5): R_f = 0.16 (CH_2Cl/MeOH, 95:5); formula $C_{18}H_{32}O_5$; MW 328.44 g/mol; IR (neat) ν_{max} 3400, 2932, 1711, 1460, 1380, 1206, 1121, 1082, 1014, 971, 912, 732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.38 (dd, J = 5.2 Hz, 9.7 Hz, 1H), 3.85 (t, J = 2.1 Hz, 1H), 3.75 (dd, J = 6.0 Hz, 10.9 Hz, 1H), 3.60 (dd, J = 4.6 Hz, 7.1 Hz, 1H), 3.54 (dt, J = 9.5 Hz, 4.7 Hz, 1H), 3.44 (dd, J = 5.2 Hz, 10.9 Hz, 1H), 2.61 (dq, J = 2.5 Hz, 7.1 Hz, 1H), 2.17−2.03 (m, 3H), 1.75−1.57 (m, 4H), 1.37−1.29 (m, 1H), 1.31 (d, J = 7.1 Hz, 3H), 1.11 (d, J = 6.8 Hz, 3H), 1.08 (d, J = 7.0 Hz, 3H), 0.91 (d, J = 6.5 Hz, 3H), 0.82 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 83.5, 76.3, 75.3, 74.0, 67.8, 41.9, 37.6, 36.5, 35.7, 30.5, 26.5, 25.6, 18.2, 15.5, 14.0, 12.6, 10.9 ppm; MS (ESI) m/z 329.2 (M + H^+, 100), 657.5 (6); HRMS calcd for $C_{18}H_{33}O_5$ [M + H^+] 329.2323, found 329.2315 (−2.3 ppm).

(±)-(3*S*,4*R*,5*S*,6*S*)-4-Hydroxy-6-((*R*)-1-((2*S*,3*S*,6*S*)-6-((*R*)-1-hydroxypropan-2-yl)-3-methyltetrahydro-2*H*-pyran-2-yl)-ethyl)-3,5-dimethyltetrahydro-2*H*-pyran-2-one (48). Product **48** as a colorless oil (5.7 mg, yield = 96%) was obtained from product **44** (9.7 mg) according to general procedure **A12** with 20 wt % $Pd(OH)_2$ on activated carbon (3.5 equiv, 34 mg) in MeOH (0.1 M, 180 μL). The crude product was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 95:5): R_f = 0.14 (CH_2Cl_2:MeOH, 95:5); formula $C_{18}H_{32}O_5$; MW 328.44 g/mol; IR (neat) ν_{max} 3394, 2930, 2883, 1707, 1460, 1384, 1304, 1204, 1133, 1082, 1055, 1017, 985, 910, 733 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.24 (dd, J = 4.1 Hz, 8.9 Hz, 1H), 3.92 (dd, J = 3.8 Hz, 10.9 Hz, 1H), 3.83 (dd, J = 4.5 Hz, 8.4 Hz, 1H), 3.58 (dd, J = 3.1 Hz, 8.7 Hz, 1H), 3.54−3.48 (m, 1H), 3.35 (dd, J = 6.6 Hz, 10.9 Hz, 1H), 2.55 (dq, J = 7.2 Hz, 7.2 Hz, 1H), 2.30−2.23 (m, 1H), 2.20−2.11 (m, 1H), 2.00−1.89 (m, 1H), 1.73−1.56 (m, 4H), 1.36 (d, J = 7.1 Hz, 3H), 1.34−1.23 (m, 1H), 1.13 (d, J = 7.0 Hz, 3H), 0.97 (d, J = 6.9 Hz, 3H), 0.88 (d, J = 6.8 Hz, 3H), 0.81 (d, J = 6.4 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8, 83.1, 75.3, 74.0, 71.0, 66.5, 40.6, 37.9, 35.1, 33.7, 31.2, 27.2, 25.8, 17.6, 14.4, 14.2, 12.3, 9.9 ppm; MS (ESI) m/z

329.2 (M + H^+, 20), 351.2 (M + Na^+, 100), 679.4 (30); HRMS calcd for $C_{18}H_{33}O_5$ [M + H^+] 329.2323, found 329.2317 (−1.6 ppm); calcd for $C_{18}H_{32}O_5Na$ [M + Na^+] 351.2142, found 351.2135 (−1.9 ppm).

(±)-(3*S*,4*S*,5*S*,6*S*)-4-Hydroxy-6-((*R*)-1-((2*S*,3*S*,6*S*)-6-((*R*)-1-hydroxypropan-2-yl)-3-methyltetrahydro-2*H*-pyran-2-yl)-ethyl)-3,5-dimethyltetrahydro-2*H*-pyran-2-one (49). Product **49** as a colorless oil (3.6 mg, yield = 32%) was obtained from product **45** (18.7 mg) according to general procedure **A12** with 20 wt % $Pd(OH)_2$ on activated carbon (1.5 equiv, 35 mg) in MeOH (0.05 M, 800 μL). The crude product was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 95:5): R_f = 0.36 (CH_2Cl_2/MeOH, 95:5); formula $C_{18}H_{32}O_5$; MW 328.44 g/mol; IR (neat) ν_{max} 3414, 2927, 2878, 2858, 1725, 1459, 1380, 1206 cm^{-1}; ^1H NMR (500 MHz, CD_2Cl_2) δ 3.84 (dd, *J* = 10.1, 4.5 Hz, 1H), 3.76 (dd, *J* = 9.7, 1.2 Hz, 1H), 3.75−3.71 (m, 1H), 3.71 (s, 1H), 3.61 (dd, *J* = 2.8, 0.9 Hz, 1H), 3.57 (dd, *J* = 11.0, 8.5 Hz, 1H), 3.50 (dd, *J* = 11.0, 4.8 Hz, 1H), 3.45 (s, 1H), 2.64 (qd, *J* = 6.8, 3.0 Hz, 1H), 2.44−2.34 (m, 1H), 2.30 (td, *J* = 14.1, 6.9 Hz, 1H), 2.09−2.01 (m, 1H), 1.81−1.58 (m, 4H), 1.38−1.30 (m, 1H), 1.25 (d, *J* = 6.8 Hz, 3H), 1.12 (d, *J* = 7.1 Hz, 3H), 1.06 (d, *J* = 7.1 Hz, 3H), 0.88 (d, *J* = 6.4 Hz, 3H), 0.74 (d, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 85.0, 79.0, 76.7, 73.8, 69.6, 39.2, 39.1, 35.5, 32.0, 31.9, 27.5, 26.6, 18.4, 17.3, 13.6, 11.8, 10.9 ppm; MS (ESI) *m*/*z* 329.2 (M + H^+, 19), 351.2 (M + Na^+, 100), 383.2 (7), 550.6 (20), 679.4 (23); HRMS calcd for $C_{18}H_{33}O_5$ [M + H^+] 329.2323, found 329.2319 (−1.2 ppm); calcd for $C_{18}H_{32}O_5Na$ [M + Na^+] 351.2142, found 351.2140 (−0.5 ppm).

(±)-(2*R*,3*R*,4*S*)-Methyl 4-((2*S*,3*S*,6*S*)-6-((*R*)-1-(*tert*-Butyldiphenylsilyloxy)propan-2-yl)-3-methyltetrahydro-2*H*-pyran-2-yl)-3-hydroxy-2-methylpentanoate (S29). Product **35** (200 mg) was deprotected according to general procedure **A12**. The crude product was dissolved in dry CH_2Cl_2 (0.1 M, 5.1 mL) and cooled to 0 °C before being successively treated with TBDPSCl (1.1 equiv, 146 μL), Et_3N (1.3 equiv, 92 μL), and DMAP (0.2 equiv, 13 mg). The mixture was stirred overnight at 0 °C before being treated with the addition of a saturated aqueous solution of NH_4Cl followed by separation of the organic phase at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3×), and the combined organic fractions were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (hexanes/EtOAc, 90:10) to give product **S29** as a colorless oil (257 mg, yield = 93% over two steps): R_f = 0.47 (hexanes/EtOAc, 85:15); formula $C_{32}H_{48}O_5Si$; MW 540.81 g/mol; IR (neat) ν_{max} 3474, 3071, 2957, 2931, 2857, 1739, 1717, 1460, 1429, 1382, 1361, 1196, 1171, 1112, 1011, 822, 740, 704, 610 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70−7.64 (m, 4H), 7.43−7.33 (m, 6H), 3.92−3.86 (m, 1H), 3.86 (dd, *J* = 4.8 Hz, 9.9 Hz, 1H), 3.72 (dd, *J* = 3.2 Hz, 9.9 Hz, 1H), 3.55−3.50 (m, 1H), 3.52 (s, 3H), 3.48 (dt, *J* = 6.4 Hz, 9.3 Hz, 1H), 3.12 (d, *J* = 9.4 Hz, 1H), 2.57 (dq, *J* = 7.0 Hz, 7.0 Hz, 1H), 2.27−2.16 (m, 1H), 1.76−1.65 (m, 3H), 1.65−1.53 (m, 2H), 1.29−1.15 (m, 1H), 1.05 (s, 9H), 1.01 (d, *J* = 7.1 Hz, 3H), 0.95 (d, *J* = 7.1 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.77 (d, *J* = 6.4 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.4, 135.71, 135.70, 134.17, 134.09, 129.42, 129.36, 127.5, 77.2, 76.2, 75.0, 73.4, 65.4, 51.4, 42.7, 36.2, 33.4, 31.6, 27.5, 26.94, 26.92, 26.90, 25.9, 19.4 ppm; MS (ESI) *m*/*z* 161.1 (5), 189.2 (10), 217.2 (15), 249.2 (66), 385.2 (49), 463.3 (11), 541.3 (M + H^+, 100), 543.3 (37); HRMS calcd for $C_{32}H_{49}O_5Si$ [M + H^+] 541.3344, found 541.3333 (−2.0 ppm).

(±)-(2*R*,3*R*,4*S*)-Methyl 3-(Benzyloxy)-4-((2*S*,3*S*,6*S*)-6-((*R*)-1-(*tert*-butyldiphenylsilyloxy)propan-2-yl)-3-methyltetrahydro-2*H*-pyran-2-yl)-2-methylpentanoate (S30). Protected product **S30** as a colorless oil (yield = 78%) was obtained from alcohol **S29** (254 mg) according to general procedure **A7**: R_f = 0.57 (hexanes/EtOAc, 85:15); formula $C_{39}H_{54}O_5Si$; MW 630.93 g/mol; IR (neat) ν_{max} 3069, 2952, 2930, 2858, 1737, 1460, 1429, 1384, 1205, 1110, 1091, 1028, 1013, 823, 738, 703, 615 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.63−7.67 (m, 4H), 7.46−7.36 (m, 6H), 7.28−7.21 (m, 3H), 7.18−7.14 (m, 2H), 4.37 (d, *J* = 11.6 Hz, 1H), 4.20 (d, *J* = 11.6 Hz, 1H), 3.81−3.77 (m, 1H), 3.77 (dd, *J* = 5.0 Hz, 9.6 Hz, 1H), 3.71 (dd, *J* = 4.5 Hz, 8.0 Hz, 1H), 3.65 (s, 3H), 3.59 (dd, *J* = 3.8 Hz, 9.6 Hz, 1H), 3.53 (dd, *J* = 3.6 Hz, 7.6 Hz, 1H), 2.87 (dq, *J* = 4.9 Hz, 7.0 Hz, 1H), 2.14−2.06 (m, 1H), 2.06−1.97 (m, 1H), 1.75−1.67 (m, 1H), 1.67−1.55 (m, 3H), 1.34−1.25 (m 1H), 1.16 (d, *J* = 7.1 Hz, 3H), 1.09 (s, 9H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 6.5 Hz, 3H), 0.86 (d, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0, 138.8, 135.75, 135.69, 134.04, 134.03, 129.44, 129.42, 128.0, 127.54, 127.53, 127.03, 126.97, 82.2, 75.4, 72.2, 71.8, 65.6, 51.4, 41.3, 36.4, 35.7, 30.3, 27.0, 26.9, 24.8, 19.4, 18.3, 13.6, 12.0, 9.9 ppm; MS (ESI) *m*/*z* 631.4 (M + H^+, 66), 653.4 (M + Na^+, 100), 654.4 (33), 690.5 (5); HRMS calcd for $C_{39}H_{55}O_5Si$ [M + H^+] 631.3813; found 631.3819 (0.9 ppm); calcd for $C_{39}H_{54}O_5SiNa$ [M + Na^+] 653.3633; found 653.3640 (1.1 ppm).

(±)-(2*S*,3*S*,4*S*)-3-(Benzyloxy)-4-((2*S*,3*S*,6*S*)-6-((*R*)-1-(*tert*-butyldiphenylsilyloxy)propan-2-yl)-3-methyltetrahydro-2*H*-pyran-2-yl)-2-methylpentan-1-ol (S31). Primary alcohol **S31** as a colorless oil (173 mg, yield = 82%) was obtained from ester **S30** (221 mg) according to general procedure **A9**: R_f = 0.18 (hexanes/EtOAc, 85:15); formula $C_{38}H_{54}O_4Si$; MW 602.92 g/mol; IR (neat) ν_{max} 3442, 3069, 2959, 2929, 2859, 1460, 1428, 1385, 1110, 1092, 1028, 966, 823, 738, 703, 615 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.74−7.68 (m, 4H), 7.47−7.37 (m, 6H), 7.34−7.25 (m, 3H), 7.25−7.21 (m, 2H), 4.45 (d, *J* = 11.2 Hz, 1H), 4.42 (d, *J* = 11.2 Hz, 1H), 3.85 (dd, *J* = 1.8 Hz, 10.8 Hz, 1H), 3.79−3.74 (m, 2H), 3.73 (dt, *J* = 3.9 Hz, 9.5 Hz, 1H), 3.58−3.50 (m, 1H), 3.47 (dd, *J* = 3.4 Hz, 7.8 Hz, 1H), 3.35 (dd, *J* = 3.1 Hz, 8.0 Hz, 1H), 2.93−2.85 (bs, 1H), 2.13 (ddq, *J* = 3.9 Hz, 7.1 Hz, 7.0 Hz, 1H), 2.06−1.96 (m, 1H), 1.91−1.84 (m, 1H), 1.77−1.56 (m, 4H), 1.34−1.24 (m, 1H), 1.08 (s, 9H), 1.06 (d, *J* = 7.1 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.91 (d, *J* = 7.5 Hz, 3H), 0.90 (d, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.3, 135.69, 135.66, 133.90, 133.83, 129.52, 129.46, 128.3, 127.55, 127.51, 127.3, 86.7, 76.0, 74.9, 71.9, 65.7, 64.8, 37.4, 36.4, 36.1, 30.2, 26.94, 26.88, 24.8, 19.3, 18.4, 16.3, 13.5, 10.7 ppm; MS (ESI) *m*/*z* 307.1 (6), 525.3 (21), 603.4 (M + H^+, 100), 693.4 (5); HRMS calcd for $C_{38}H_{55}O_4Si$ [M + H^+] 603.3864, found 603.3861 (−0.5 ppm).

(2*R*,3*R*,4*S*)-3-(Benzyloxy)-4-((2*S*,3*S*,6*S*)-6-((*R*)-1-(*tert*-butyldiphenylsilyloxy)propan-2-yl)-3-methyltetrahydro-2*H*-pyran-2-yl)-2-methylpentanal (50). Aldehyde **50** as a colorless oil was obtained from primary alcohol **S31** (20 mg) according to general procedure **A11**. The crude product was used without further purification: R_f = 0.55 (hexanes/EtOAc, 85:15); formula $C_{38}H_{52}O_4Si$; MW 600.90 g/mol; ^1H NMR (500 MHz, $CDCl_3$) δ 9.68 (d, *J* = 1.4 Hz, 1H), 7.75−7.61 (m, 4H), 7.47−7.33 (m, 6H), 7.32−7.19 (m, 3H), 7.19−7.08 (m, 2H), 4.24 (d, *J* = 11.6 Hz, 1H), 4.15 (d, *J* = 11.6 Hz, 1H), 3.81−3.75 (m, 1H), 3.72 (dd, *J* = 9.5, 5.2 Hz, 1H), 3.59 (dd, *J* = 9.5, 3.5 Hz, 1H), 3.54 (dd, *J* = 8.2, 2.6 Hz, 1H), 3.44 (dd, *J* = 8.6, 2.4 Hz, 1H), 2.61 (q, *J* = 6.7 Hz, 1H), 2.11−1.96 (m, 2H), 1.78−1.68 (m, 1H), 1.68−1.56 (m, 3H), 1.55−1.48 (m, 1H), 1.05 (s, 9H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.81 (d, *J* = 6.3 Hz, 3H), 0.78 (d, *J* = 7.1 Hz, 3H) ppm.

(±)-(3*R*,4*S*,5*S*,6*S*)-Methyl 5-(Benzyloxy)-2-bromo-6-((2*S*,3*S*,6*S*)-6-((*R*)-1-(*tert*-butyldiphenylsilyloxy)propan-2-yl)-3-methyltetrahydro-2*H*-pyran-2-yl)-3-hydroxy-2,4-dimethylheptanoate (51). Bromide adduct **51** as a pale yellow oil (23.7 mg, yield = 93% over two steps) was obtained from aldehyde **50** (19.9 mg) according to general procedure **A2** in a >20:1 ratio of products 3,4-*anti* (**51**)/3,4-*syn* (**52**): R_f = 0.31 (hexanes/EtOAc, 85:15); formula $C_{42}H_{59}BrO_6Si$; MW 767.90 g/mol; IR (neat) ν_{max} 3558, 2953, 2929, 2857, 1745, 1728, 1428, 1384, 1259, 1112, 1063 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.69−7.63 (m, 4H), 7.44−7.33 (m, 6H), 7.29−7.23 (m, 3H), 7.19−7.14 (m, 2H), 4.41 (d, *J* = 11.4 Hz, 1H), 4.37 (d, *J* = 11.3 Hz, 1H), 4.05 (dd, *J* = 8.4, 4.9 Hz, 1H), 3.75 (s, 3H), 3.75−3.68 (m, 2H), 3.58 (dd, *J* = 9.6, 4.0 Hz, 1H), 3.51 (dd, *J* = 7.7, 3.8 Hz, 1H), 3.42 (d,

J = 4.9 Hz, 1H), 3.36 (dd, J = 8.0, 3.5 Hz, 1H), 2.19−2.07 (m, 2H), 1.98−1.89 (m, 1H), 1.91 (s, 3H), 1.75−1.53 (m, 4H), 1.31−1.21 (m, 1H), 1.03 (s, 9H), 0.97 (d, J = 7.6 Hz, 3H), 0.96 (d, J = 7.4 Hz, 3H), 0.89 (d, J = 6.9 Hz, 3H), 0.84 (d, J = 6.6 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 138.4, 135.93, 135.89, 134.2, 134.1, 129.7, 129.6, 128.5, 127.74, 127.68, 127.66, 127.5, 86.4, 77.8, 76.1, 74.1, 71.8, 65.82, 65.77, 53.3, 39.5, 38.2, 36.9, 30.1, 27.14, 27.06, 25.9, 24.8, 19.5, 18.6, 17.6, 13.5, 11.5 ppm; MS (ESI) m/z 251.1 (42), 360.3 (42), 408.3 (24), 550.6 (22), 619.3 (100), 709.4 (95), 789.3 (^{79}Br; M + Na^+, 80), 791.3 (^{81}Br; M + Na^+, 80); HRMS calcd for $C_{42}H_{60}O_6Si^{79}Br$ [M + H^+] 767.3337, found 767.3329 (−1.1 ppm); calcd for $C_{42}H_{59}O_6Si^{79}BrNa$ [M + Na^+] 789.3156, found 789.3153 (−0.5 ppm).

(±)-(3*S*,4*S*,5*S*,6*S*)-Methyl 5-(Benzyloxy)-2-bromo-6-((2*S*,3*S*,6*S*)-6-((*R*)-1-(*tert*-butyldiphenylsilyloxy)propan-2-yl)-3-methyltetrahydro-2*H*-pyran-2-yl)-3-hydroxy-2,4-dimethylheptanoate (52). Bromide product **52** as a pale yellow oil (17.6 mg, yield = 82% over two steps) was obtained from aldehyde **50** (16.8 mg) according to general procedure **A1** in a >20:1 ratio of products 3,4-*syn* (**52**)/3,4-*anti* (**51**): R_f = 0.30 (hexanes/EtOAc, 90:10); formula $C_{42}H_{59}BrO_6Si$; MW 767.90 g/mol; IR (neat) ν_{max} 3455, 3069, 2954, 2930, 2859, 1737, 1458, 1429, 1385, 1259, 1109, 1087, 911, 738, 703 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68−7.62 (m, 4H), 7.43−7.38 (m, 2H), 7.38−7.33 (m, 4H), 7.30−7.24 (m, 3H), 7.19−7.15 (m, 2H), 4.44 (d, J = 11.0 Hz, 1H), 4.42 (s, 1H), 4.35 (d, J = 10.9 Hz, 1H), 3.79 (d, J = 1.3 Hz, 1H), 3.78 (s, 3H), 3.74−3.66 (m, 3H), 3.49 (dd, J = 2.0 Hz, 9.0 Hz, 1H), 3.22 (dd, J = 1.3 Hz, 9.4 Hz, 1H), 2.03−1.94 (m, 2H), 1.93 (s, 3H), 1.92−1.84 (m, 1H), 1.74−1.65 (m, 2H), 1.65−1.58 (m, 2H), 1.28−1.19 (m, 1H), 1.03 (s, 9H), 0.99 (d, J = 7.1 Hz, 3H), 0.91 (d, J = 6.8 Hz, 3H), 0.84 (d, J = 7.0 Hz, 3H), 0.83 (d, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 138.0, 135.71, 135.66, 133.87, 133.86, 129.56, 129.49, 128.4, 127.68, 127.58, 127.53, 127.4, 88.6, 75.8, 75.6, 74.4, 72.2, 66.3, 65.8, 53.1, 37.4, 36.7, 35.7, 30.1, 27.3, 26.9, 25.3, 24.8, 19.3, 18.5, 14.0, 13.6, 10.1 ppm; MS (ESI) m/z 144.0 (16), 193.7 (12), 592.3 (5), 767.3 (M + H^+, 70), 789.3 (M + Na^+, 59), 791.3 (67), 868.4 (100), 886.4 (12); HRMS calcd for $C_{42}H_{60}O_6Si^{79}Br$ [M + H^+] 767.3337, found 767.3345 (1.0 ppm); calcd for $C_{42}H_{59}O_6Si^{79}BrNa$ [M + Na^+] 789.3156, found 789.3167 (1.3 ppm).

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H and ^{13}C spectra for compounds **14**−**20**, **28**−**38**, **40**−**52**, **S5**, **S6**, **S10**−**S15**, **S17**−**S24**, and **S27**−**S31**. This material is available free of charge via the Internet at http://pubs.acs.org.

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