Stereodivergent Synthesis of the C1–C9 Tetrahydropyran Subunit of Zincophorin and Isomers Thereof

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Received 13 October 2011

Abstract: Zincophorin C1–C9 fragment and seven tetrahydropyran analogues were prepared diastereoselectively by sequential iodoetherification and radical hydrogen-transfer reactions. Stereoselective formation of 3,7-*trans* or 3,7-*cis* rings was rationalized through minimization of allylic-1,3 strain in chair-like transition states. Subsequent hydrogen-transfer provided 7,8-*anti* or 7,8-*syn* isomers under acyclic stereocontrol or endocyclic control respectively. The latter approach relies on the formation of a [4.4.0] bicyclic complexes resulting from the chelation of the oxygen of the tetrahydropyran ring and the ester by a bidentate Lewis acid.

Key words: ionophore, iodoetherification, radical reduction, Lewis acid, substituted tetrahydropyrans

The need to identify novel lead molecules and mechanisms of action to control infections or resistant cancers is still acutely present. Several complex natural products of the polyketide family, such as zincophorin (**1**)[1] and salinomycin (**2**),[2] are highly interesting in this regard (Figure 1). Zincophorin (**1**) is an antibiotic, while salinomycin (**2**) has been recently shown to kill selectively cancer stem cells in vitro and in vivo.[3] Significant differences of gene expression were noted when cancerous cells were treated with this molecule as compared to other antiproliferative agents (e.g., paclitaxel). The complexity of these molecules, however, limits their drug potential. Little is known about the structural features of these polyketides responsible for their biological activities, a crucial information that could lead to the development of simplified analogues with improved biological and pharmacological properties. To identify these pharmacophores, a QSAR study[4] will be conducted where stereogenic centers will be removed or their relative stereochemistry altered.

Numerous compounds of the polyketide family are ionophores[2] owing to their ability to bind inorganic cations and form lipophilic complexes that facilitate ion transport across cell membrane. Zincophorin (**1**), for instance, forms preferentially complexes with zinc cation, the carboxyl functionality at C1 and the secondary alcohols at C11 and C13 acting as ligands.[5] These functionalities are oriented in space by the tetrahydropyran ring on one side and a complex network of steric interactions between the polypropionate substituents side chain on the other.[1a,b] Is chelation to a cation the real mechanism of action? Are these induced conformations (pre- or post-complexation) optimal for their biological activity? We hope to answer these questions by synthesizing zincophorin (**1**) and related analogues in the context of our QSAR study. The development of a strategy to generate efficiently and selectively a library of C1–C9 subunits of **1** was therefore considered. Keeping the configuration at C2 constant,[6] 16 isomers of the C1–C9 fragment are possible. We report herein the synthesis of eight of them, as illustrated in Figure 2.

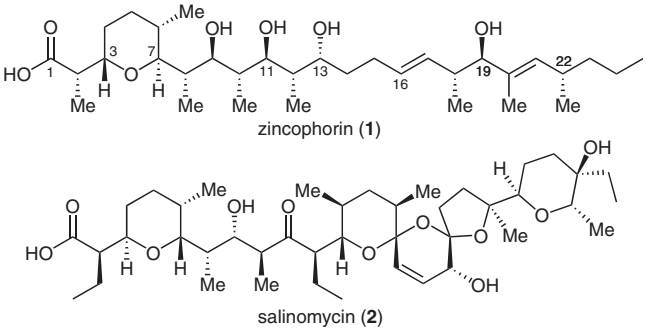


Figure 1 Structure of zincophorin (**1**) and salinomycin (**2**)

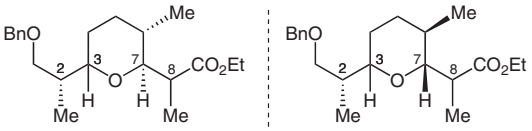
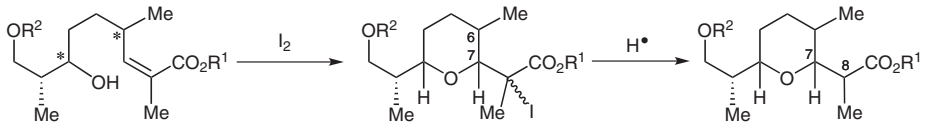


Figure 2 Structure of tetrahydropyran isomers **3a**–**6b**[6]

Inspired by a methodology previously developed by our group to access tetrahydrofuran,[7] we envisioned that the targeted substituted tetrahydropyran (Figure 2) could be generated by an intramolecular iodoetherification coupled to a radical reduction (Scheme 1). An electron-poor trisubstituted olefin, adjacent to a stereogenic center, will

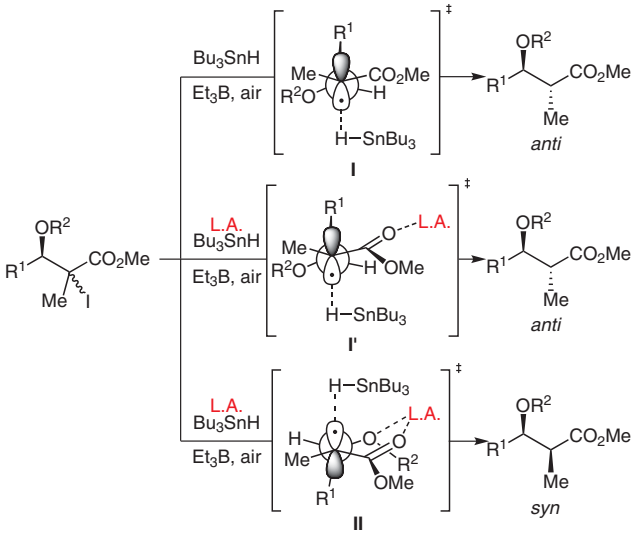
SYNTHESIS 2012, 44, 474–488
Advanced online publication: 16.01.2012
DOI: 10.1055/s-0031-1289661; Art ID: M97511SS



Scheme 1 Methodology to access trisubstituted tetrahydropyrans

be used to control the relative C6–C7 stereochemistry in the iodoetherification step.

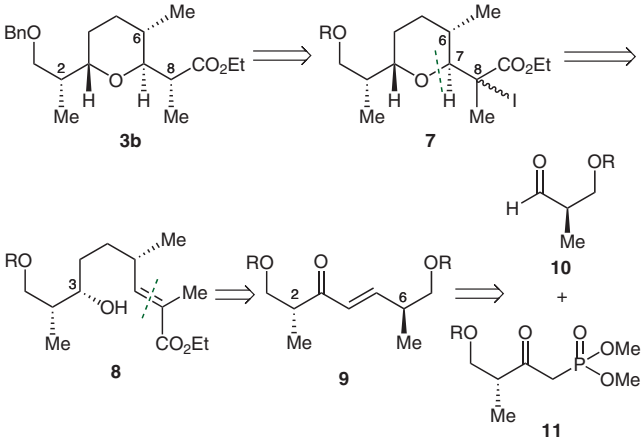
Hydrogen-transfer reaction of the resulting tertiary iodides will then be performed in order to control the stereochemistry at C8. We and others[8–10] have discovered that acyclic carbon-centered radicals could react stereoselectively in hydrogen-transfer reactions. Our group has demonstrated the efficiency of the reduction of a carbon-centered free radical flanked on one side by an ester and on the other, by a stereogenic center bearing an oxygen in order to access the *anti*-isomer (acyclic stereocontrol).[7b,c,11] Such stereocontrol, obtained in other series of molecules, was rationalized from the minimizations of allylic-1,3 strain and intramolecular dipole–dipole effect to favor transition state **I** (Scheme 2).[12]



Scheme 2 Transition states for radical reduction on substituted tetrahydropyrans

As importantly, we demonstrated that adding a bidentate Lewis acid to the reaction mixture leads to the opposite *syn*-isomer (i.e., endocyclic control) through a bicyclic transition state **II** (Scheme 2).[13] These bidentate complexes have to display a slow equilibration rate to avoid an erosion of diastereoselectivity resulting from competitive pathways (i.e., monodentate activation of the ester as in **I′** or uncomplexed substrate as in **I**). Indeed, no kinetic preferences favoring either the bidentate or the monodentate complexes in hydrogen-transfer reactions have been observed in previous studies,[14] thus the need to pre-organize stable bidentate complexes in order to achieve *syn*-diastereoselectivity. In the present study, we planned to form [4.4.0] bicyclic bidentate complexes from functionalized tetrahydropyrans. Steric effects induced by the ring substituents in these complexes may raise their energy of formation and influence the diastereoselectivity of the reduction, a hypothesis tested herein.

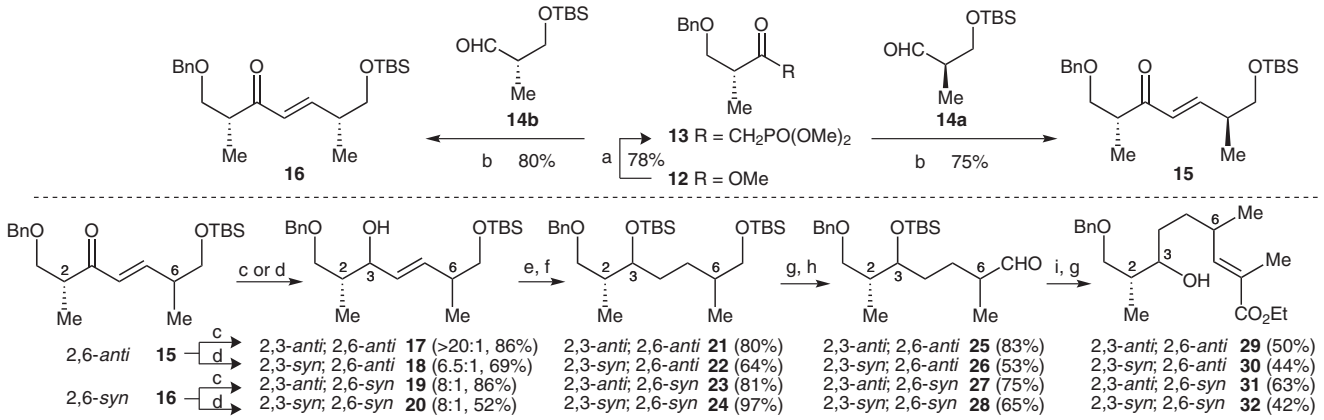
We embarked on the synthesis of zincophorin C1–C9 fragments as exemplified by the retrosynthesis of tetrahydropyran **3b** (Scheme 3). As previously discussed, a radical reduction under endocyclic control (Scheme 2, TS **II**) would generate the latter from tertiary iodide **7**. Construction of the tetrahydropyran ring will be achieved using a kinetically-controlled iodoetherification reaction on trisubstituted α,β-unsaturated olefin **8**, leading to a C6–C7 *trans* relationship.



Scheme 3 Retrosynthetic analysis of tetrahydropyran ring **3b**

The hydroxy group at C3 of **8** would in turn originate from a stereocontrolled reduction of α,β-unsaturated ketone **9** using the Corey–Bakshi–Shibata (CBS) oxazaborolidine.[15] These enones would be obtained from a Horner–Wadsworth–Emmons (HWE) coupling between aldehyde **10** and β-ketophosphonate **11**, both derived from (*R*)-Roche ester.

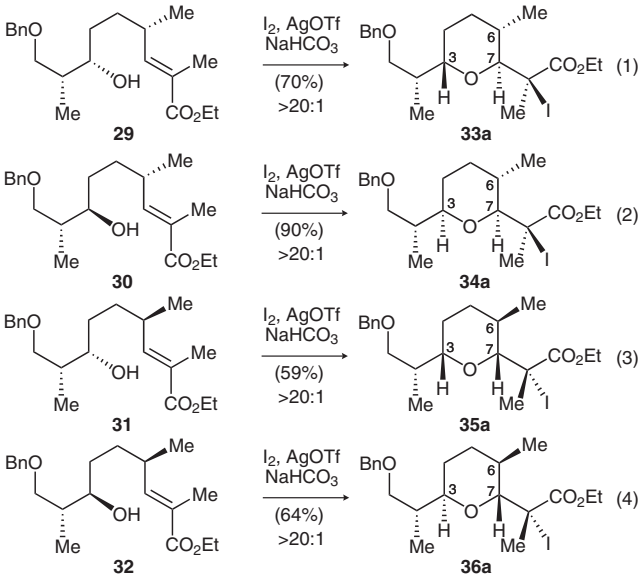
The stereodivergent synthesis of all diastereoisomers at C3 and C6 illustrated in Figure 2 began with the preparation of the β-ketophosphonate **13** from the benzylated (*R*)-Roche ester **12** (Scheme 4). Compound **13** was reacted with the OTBS protected aldehyde **14a** and **14b** derivatives of the (*R*)- and (*S*)-Roche esters (using hydrated LiOH as a base)[16] to give the α,β-unsaturated ketones **15** (2,6-*anti*) and **16** (2,6-*syn*), respectively, in good yields. Enones **15** and **16** were then reduced diastereoselectively with chiral oxazaborolidine reagents to give the 2,3-*anti* (**17** and **19**) and 2,3-*syn* (**18** and **20**) allylic alcohols with good to excellent diastereoselectivities. Only few examples of such reductions have been reported in the literature.[17] The four allylic alcohols **17**–**20** were then reduced



Scheme 4 Synthesis of trisubstituted olefins **29**–**32**. *Reagents and conditions*: (a) $MePO(OMe)_2$, *n*-BuLi, THF, –78 °C; (b) $LiOH·H_2O$, THF, r.t.; (c) (*S*)-2-Me-CBS-oxazaborolidine, $THF·BH_3$, THF, –40 °C; (d) (*R*)-2-Me-CBS-oxazaborolidine, $THF·BH_3$, THF, –40 °C; (e) H_2, Pd/C, pyridine, MeOH, r.t.; (f) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; (g) HF·pyridine, THF, 0 °C; (h) DMP, $NaHCO_3$, CH_2Cl_2, r.t.; (i) $Ph_3P(Me)CO_2Et$, toluene, reflux.

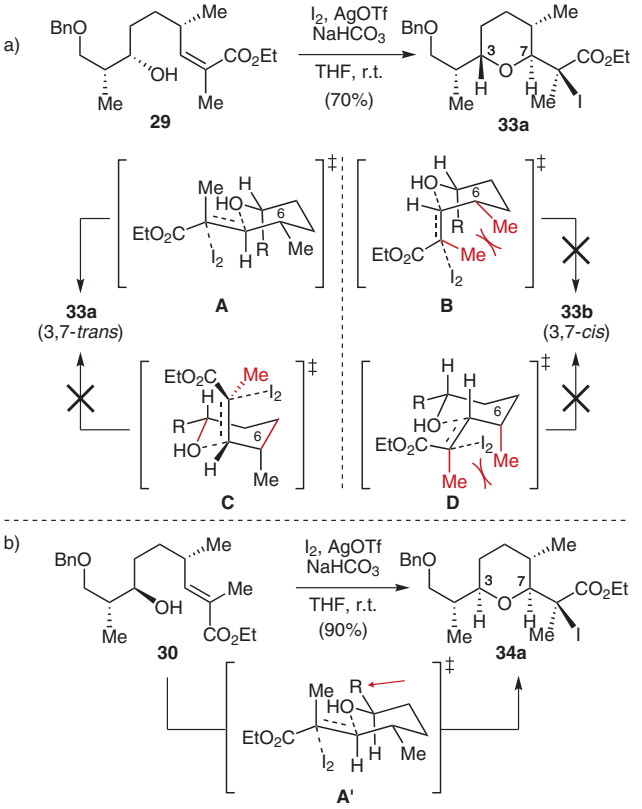
by hydrogenation using Pd/C in the presence of pyridine[18] and a TBS protecting group was installed on the secondary alcohol to give products **21**–**24**. The primary silyloxy groups were then selectively cleaved with HF·pyridine and the corresponding alcohols oxidized to aldehydes **25**–**28** using Dess–Martin periodinane. Olefination of each aldehyde provided trisubstituted α,β-unsaturated esters in good yields. Removal of the TBS protecting groups from the secondary alcohols completed the synthetic sequence to access precursors **29**–**32** for the subsequent key iodoetherification reaction.

Iodoetherification of substituted olefins **29**–**32** was then studied under reaction conditions reported to provide kinetic products (I_2, AgOTf, and $NaHCO_3$ in THF at r.t.).[7a,b,19] As shown in Scheme 5, all substrates reacted diastereoselectively to give 6,7-*trans* relative stereochemistry. The 3,7-*trans* products were generated from the cyclization of **29** and **32** (Scheme 5, equations 1 and 4), whereas 3,7-*cis* products were obtained from **30** and **31** (Scheme 5, equations 2 and 3) in good to excellent yields.



Scheme 5 Iodoetherification of substrates **29**–**32**

Iodocyclization reaction, which involves activation of a double bond by iodine followed by an intramolecular nucleophilic attack, have been extensively studied in the context of the synthesis of various heterocycles including carbamates,[19a,20] carbonates,[21] lactones,[22] and cyclic ethers (furans and pyrans).[7a,23] Under kinetic control, the outcome of these reactions has been rationalized by mechanisms taking into account steric and stereoelectronic effects[23,24] (e.g., *endo*-alkoxy effect) generated in the cy-



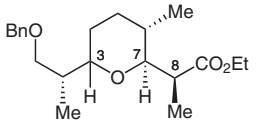
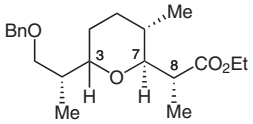
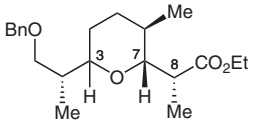
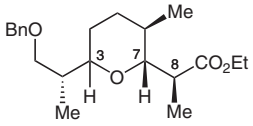
Scheme 6 Possible transition states for iodoetherification of **29** and **30**

clic transition states by substituents proximal to the olefin. The reacting intermediate has been suggested to be either an iodonium ion or a π-complex, between the double bond and the iodine. Plausible six-membered-ring chair-like transition states leading to isomers of **33a** are depicted in Scheme 6 (part a).

The presence of a terminal trisubstituted olefin induces strong steric interactions (allylic-1,3 strain; depicted in red in Scheme 6, part a) with the substituent at C6 in **B** and **D**, which should therefore be prohibitively high in energy.[25] Conversely, transition state **C** should be disfavored because of interactions between the methyl group of the olefin and the ring. Minimization of both allylic 1,3-strain and steric effects leads therefore to transition state **A**. Inverting the configuration at C3 led to the 3,7-*cis* product **34a** obtained from **30** (TS **A′**, Scheme 6, part b). The resulting transition state **A′** differ from **A** by having the R substituent in an equatorial position. It is tempting to suggest that transition state **A** is higher in energy than **A′**, which would lead to a faster cyclization rate of **30** as compared to **29**. In order to test this hypothesis, we combined together an equal amount of **29** and **30**. Half of the necessary amount of I_2 and AgOTf were then added to initiate the iodoetherification following a competitive scenario. Interestingly, both **29** and **30** were consumed equally, suggesting similar reaction rates. This lack of apparent reaction rate difference could point to an early transition state. The forming bond being longer in such instance, steric effects induced by the axial substituent are expected to decrease, a hypothesis that would need to be verified by theoretical calculations.

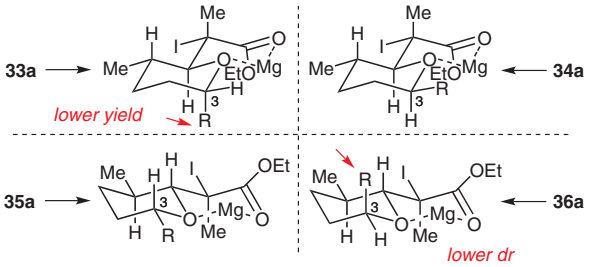
Hydrogen-transfer reactions were then performed on radical precursors **33a**–**36a** (Table 1). Under an acyclic stereocontrol, a 7,8-*anti* relative stereochemistry was observed at –78 °C using Bu_3SnH and Et_3B as radical chain initiator (condition **A**: entries 1, 3, 5, and 7). In the presence of $MgBr_2{\cdot}OEt_2$, a bidentate Lewis acid (condition **B**), an inversion of configuration at C8 was observed as expected (see Scheme 2, TS **II**). An excellent ratio for 7,8-*syn* products was noted (entries 2, 4, and 6). The structural assignment for ester **3b**, which displays the same configuration as zincophorin tetrahydropyran fragment, was confirmed by reduction to the corresponding known alcohol.[1c] Reduced stereoselectivity was, however, noted when the radical precursor **36a** was reacted in the presence of $MgBr_2{\cdot}OEt_2$ (entry 8), and a lower yield in the case of **33a**

Table 1 Radical Reduction of Substrates **33a**–**36a**

Entry	Substrate	Conditions[a]	Products	Ratio[b]	Yield (%)[c]
			7,8-*anti*:7,8-*syn*		
	3,7-*trans* (**33a**) 3,7-*cis* (**34a**)	A or B →	 7,8-*anti* 3,7-*trans* **3a** 3,7-*cis* **4a**	+  7,8-*syn* 3,7-*trans* **3b** 3,7-*cis* **4b**	
1	3,7-*trans* (**33a**)	A	**3a/3b**	>20:1	62
2	3,7-*trans* (**33a**)	B	**3a/3b**	1:>20	40
3	3,7-*cis* (**34a**)	A	**4a/4b**	>20:1	96
4	3,7-*cis* (**34a**)	B	**4a/4b**	1:>20	79
	3,7-*cis* (**35a**) 3,7-*trans* (**36a**)	A or B →	 7,8-*anti* 3,7-*cis* **5a** 3,7-*trans* **6a**	+  7,8-*syn* 3,7-*cis* **5b** 3,7-*trans* **6b**	
5	3,7-*cis* (**35a**)	A	**5a/5b**	>20:1	76
6	3,7-*cis* (**35a**)	B	**5a/5b**	1:>20	71
7	3,7-*trans* (**36a**)	A	**6a/6b**	>20:1	82
8	3,7-*trans* (**36a**)	B	**6a/6b**	1:6.4	79

[a] Conditions A: Substrate in toluene (0.1 M) at –78 °C was treated with Bu_3SnH (1.5 equiv) followed by Et_3B (0.2 equiv) and air. Conditions B: Substrate in CH_2Cl_2 (0.1 M) was pretreated with $MgBr_2{\cdot}OEt_2$ (3 equiv) for 1 h at 0 °C. Mixture cooled to –78 °C before successive addition of Bu_3SnH (1.5 equiv), Et_3B (0.2 equiv), and air.
[b] Product ratios determined by ^1H NMR analysis of the crude reaction mixture.
[c] Yields of isolated products.

(entry 2). As discussed before, a pre-organization of bicyclic bidentate intermediates, prior to the homolytic cleavage of the carbon–iodine bond, is important to avoid competitive *anti*-selective monodentate activation pathways (Scheme 2).[14] The *trans*-decalin-like bidentate complex originating from complexation of **33a** (or **36a**) with $MgBr_2{\cdot}OEt_2$ exhibits indeed an axial substituent (i.e., R) at C3 as seen in Scheme 7. It is likely that their energy of formation would be increased because of these additional steric interactions.[26]



Scheme 7 Bidentate complexes of **33a**–**36a** with $MgBr_2{\cdot}OEt_2$[26]

This analysis points to the importance of considering the structure of bidentate complexes to predict the stereochemical outcome in reactions involving chelated intermediates such as the ones depicted herein. The presence of an axial substituent in a [4.4.0] bicyclic complex could be at the origin of reduced ratio or yield.

In conclusion, iodine-mediated cyclization of γ-methyl α,β-unsaturated esters proceeds with excellent diastereocontrol to yield exclusively 6,7-*trans* products bearing a tertiary iodide. These intermediates then undergo diastereoselective radical reductions, either under acyclic stereocontrol or endocyclic control, to generate respectively the 7,8-*anti* or 7,8-*syn* isomers. Results obtained using this methodology improve the understanding of radical processes involving bidentate Lewis acids complexed to trisubstituted tetrahydropyrans. Moreover, the efficacy of these radical reductions to access selectively both configurations α to the tetrahydropyran ring was demonstrated in the preparation of zincophorin C1–C9 fragment and isomers thereof from which analogues will be derived in the context of a QSAR study.

All reactions requiring anhydrous conditions were conducted under a positive argon atmosphere in oven-dried glassware using standard syringe techniques (exception should be noted that free-radical based reactions were conducted under N_2). All solvents were purified by standard methods. Flash chromatography was performed on silica gel (0.040–0.063 mm) using compressed air pressure. Analytical TLC was carried out on precoated (0.25 mm) aluminum-backed silica gel plates. ^1H (400 or 500 MHz) and ^{13}C spectra (100 or 125 MHz) were referenced to residual solvents peak and ratios of products were measured from crude ^1H spectra. IR spectra were recorded on a FTIR spectrophotometer on a NaCl support. Mass spectra were recorded through electrospray ionization (ESI) on an instrument operating at 70 eV.

Deprotection of TBS Group with HF·Pyridine; General Procedure (A1)

To a cold (0 °C) solution of TBS protected alcohol (1 equiv) in anhyd THF (0.1 M) was added dropwise a solution of HF·pyridine (1 mL per mmol of substrate), followed by stirring at 0 °C and monitoring of the reaction mixture by TLC until complete consumption of starting material. The reaction mixture was then treated slowly with sat. aq $NaHCO_3$ (5 mL per mmol of substrate) followed by separation of the organic phase at r.t. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL per mmol of substrate) 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, 80:20) to give the desired alcohol product.

Radical Reduction – Acyclic Stereocontrol; General Procedure (A2)

To a cold (–78 °C) solution of iodide (1 equiv) in anhyd toluene (0.1 M) was added successively Bu_3SnH (1.5 equiv), a 1 M solution of Et_3B in CH_2Cl_2 (0.2 equiv), and air (syringe). Supplementary additions of Et_3B solution (0.2 equiv) and air were realized each 30 min, until reaction was judged complete by TLC (eluent: hexanes–EtOAc, 90:10; 3–4 h). The reaction mixture was treated with 1,3-dinitrobenzene (0.2 equiv) and stirred for 15 min at –78 °C. Once at r.t., the mixture was concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (hexanes–EtOAc, 90:10) to give the reduced product.

Radical Reduction – Endocyclic Control; General Procedure (A3)

To a cold (0 °C) solution of iodide (1 equiv) in anhyd CH_2Cl_2 (0.1 M) was added $MgBr_2{\cdot}OEt_2$ (3 equiv). The reaction mixture was stirred at 0 °C for 1 h and then cooled to –78 °C before successive additions of Bu_3SnH (1.5 equiv), a 1 M solution of Et_3B in CH_2Cl_2 (0.2 equiv), and air (syringe). Supplementary additions of Et_3B solution (0.2 equiv) and air were realized each 30 min until reaction was judged completed by TLC (eluent: hexanes–EtOAc, 90:10; 3–4 h). The reaction mixture was treated with 1,3-dinitrobenzene (0.2 equiv), stirred for 15 min at –78 °C before treating with sat. aq NH_4Cl (5 mL per mmol of substrate). The organic phase was separated at r.t. and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL per mmol of substrate). 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 the reduced product.

Dimethyl (–)-(*R*)-4-(Benzyloxy)-3-methyl-2-oxobutylphosphonate (13)

To a cold (–78 °C) solution of dimethyl methylphosphonate (15.3 mL, 143 mmol, 4 equiv) in anhyd THF (0.5 M, 310 mL) was added dropwise a 2.5 M solution of *n*-BuLi in hexanes (3.5 equiv, 125 mmol, 50 mL). The mixture was stirred for 1 h at –78 °C before slow addition of a solution of benzyl ester **12**[12c] (7.43 g, 35.7 mmol) in THF (1 M, 36 mL), followed by stirring for 15 min at –78 °C. The reaction mixture was then treated with sat. aq NH_4Cl (175 mL) followed by separation of the organic phase at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL) 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 (EtOAc); colorless oil; yield: 8.36 g (78%); R_f = 0.33 (EtOAc–MeOH, 95:5); $[\alpha]_D^{25}$ –48.9 (*c* 1.7, $CDCl_3$).

IR (neat): 3468, 2957, 2858, 1713, 1455, 1367, 1253, 1186, 1031, 877, 842, 743, 700 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.24 (m, 5 H), 4.48 (d, *J* = 12.5 Hz, 1 H), 4.46 (d, *J* = 12.9 Hz, 1 H), 3.75 (dd, *J* = 7.6, 11.2 Hz, 6 H), 3.61–3.51 (m, 2 H), 3.30 (dd, *J* = 14.1, 22.5 Hz, 1 H), 3.18–3.09 (m, 2 H), 1.10 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.9 (*J* = 6.3 Hz), 137.3, 127.8, 127.1, 127.0, 72.6, 71.6, 52.3 (*J* = 1.7 Hz), 52.2 (*J* = 6.7 Hz), 46.5, 40.8, 39.5, 12.4.

MS (ESI): *m*/*z* (%) = 193.1 (46), 301.1 (M + H^+, 100), 400.2 (17), 601.2 (18).

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{22}O_{15}P$ [M + H^+]: 301.1199; found: 301.1202 (0.8 ppm).

(–)-(2*R*,6*S*,*E*)-1-(Benzyloxy)-7-(*tert*-butyldimethylsilyloxy)-2,6-dimethylhept-4-en-3-one (15)

To a cold (0 °C) solution of **13** (2.02 g, 6.7 mmol, 1.05 equiv) in anhyd THF (0.15 M, 45 mL) was added LiOH·H_2O (0.28 g, 6.7 mmol, 1.05 equiv). The mixture was stirred for 10 min at 0 °C before slow addition of aldehyde **14a**[19b] (1.29 g, 6.4 mmol) in THF (1 M, 6.4 mL), followed by stirring for 18 h allowing warming to r.t. The reaction mixture was then treated with sat. aq NH_4Cl (30 mL) followed by separation of the organic phase at r.t. The aqueous layer was extracted with EtOAc (3 × 20 mL) and the combined organic fractions were dried ($MgSO_4$), filtered, and concentrated in vacuo. Crude product was purified by flash chromatography on silica gel (hexanes–EtOAc, 90:10) to give the desired 2,6-*anti*-enone **15**; colorless oil; yield: 1.81 g (75%); R_f = 0.51 (hexanes–EtOAc, 80:20); $[\alpha]_D^{25}$ –17.0 (*c* 1.0, $CDCl_3$).

IR (neat): 2956, 2931, 2857, 1695, 1669, 1627, 1457, 1363, 1255, 1201, 1099, 839, 777, 738, 698 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.25 (m, 5 H), 6.86 (dd, *J* = 7.1, 15.9 Hz, 1 H), 6.19 (dd, *J* = 1.3, 15.9 Hz, 1 H), 4.52 (d, *J* = 12.1 Hz, 1 H), 4.47 (d, *J* = 12.1 Hz, 1 H), 3.70 (dd, *J* = 7.1, 9.2 Hz, 1 H), 3.54 (dd, *J* = 6.4, 9.8 Hz, 1 H), 3.52 (dd, *J* = 6.4, 9.8 Hz, 1 H), 3.45 (dd, *J* = 6.1, 9.2 Hz, 1 H), 3.14 (hept, *J* = 7.0 Hz, 1 H), 2.50 (hept, *J* = 6.7 Hz, 1 H), 1.11 (d, *J* = 7.1 Hz, 3 H), 1.05 (d, *J* = 6.8 Hz, 3 H), 0.88 (s, 9 H), 0.033 (s, 3 H), 0.031 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.2, 149.9, 138.1, 128.6, 128.2, 127.5, 126.8, 73.2, 72.1, 66.9, 44.0, 39.3, 25.8, 18.2, 15.5, 14.1, –3.6, –5.5.

MS (ESI): *m*/*z* (%) = 137.1 (12), 245.2 (6), 269.2 (11), 287.2 (7), 377.3 (M + H^+, 100), 401.3 (21).

HRMS (ESI): *m*/*z* calcd for $C_{22}H_{37}O_3Si$ [M + H^+]: 377.2506; found: 377.2519 (3.2 ppm).

(+)-(2*R*,6*R*,*E*)-1-(Benzyloxy)-7-(*tert*-butyldimethylsilyloxy)-2,6-dimethylhept-4-en-3-one (16)

To a cold (0 °C) solution of **13** (5.2 g, 17.3 mmol, 1.05 equiv) in anhyd THF (0.15 M, 116 mL) was added LiOH·H_2O (0.73 g, 17.4 mmol, 1.05 equiv). The mixture was stirred for 10 min at 0 °C before slow addition of aldehyde **14b**[27] (3.34 g, 16.5 mmol) in THF (1 M, 16.5 mL), followed by stirring for 18 h allowing warming to r.t. The reaction mixture was then treated with sat. aq NH_4Cl (75 mL) followed by separation of the organic phase at r.t. The aqueous layer was extracted with EtOAc (3 × 60 mL) 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 the desired 2,6-*syn*-enone **16**; colorless oil; yield: 4.97 g (80%); R_f = 0.38 (hexanes–EtOAc, 90:10); $[\alpha]_D^{25}$ +29.2 (*c* 0.12, $CDCl_3$).

IR (neat): 2956, 2930, 2857, 1695, 1671, 1628, 1457, 1363, 1254, 1098, 838, 776, 697 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.25 (m, 5 H), 6.85 (dd, *J* = 15.9, 7.2 Hz, 1 H), 6.19 (dd, *J* = 15.9, 0.9 Hz, 1 H), 4.51 (d, *J* = 12.1 Hz, 1 H), 4.47 (d, *J* = 12.1 Hz, 1 H), 3.70 (dd, *J* = 9.1, 7.3 Hz, 1 H), 3.53 (dd, *J* = 6.3, 4.3 Hz, 2 H), 3.45 (dd, *J* = 9.1, 6.1 Hz, 1 H), 3.15 (hept, *J* = 7.0 Hz, 1 H), 2.50 (hept, *J* = 6.5 Hz, 1 H), 1.11 (d, *J* = 7.0 Hz, 3 H), 1.05 (d, *J* = 6.8 Hz, 3 H), 0.88 (s, 9 H), 0.03 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 202.5, 150.2, 138.4, 128.9, 128.5, 127.72, 127.70, 73.4, 72.3, 67.1, 44.1, 39.6, 26.0, 18.4, 15.8, 14.3, –5.24, –5.25.

MS (ESI): *m*/*z* (%) = 137.1 (8), 217.2 (7), 269.2 (10), 377.3 (M + H^+, 100).

HRMS (ESI): *m*/*z* calcd for $C_{22}H_{37}O_3Si$ [M + H^+]: 377.2506; found: 377.2518 (3.0 ppm).

(–)-(2*R*,3*S*,6*S*,*E*)-1-(Benzyloxy)-7-(*tert*-butyldimethylsilyloxy)-2,6-dimethylhept-4-en-3-ol (17)

To a cold (–40 °C) solution of **15** (1.19 g, 3.15 mmol) in anhyd THF (0.1 M, 31 mL) was added dropwise a 1 M solution of (*S*)-2-Me-CBS oxazaborolidine in toluene (3.30 mL, 3.30 mmol, 1.05 equiv), followed by stirring for 1 h at –40 °C. The reaction mixture was then treated with a 1 M solution of THF·BH_3 in THF (7.9 mL, 7.9 mmol, 2.5 equiv), followed by stirring for 1 h at –40 °C or until enone was completely consumed as verified by TLC (eluent: hexanes–EtOAc, 80:20). The reaction mixture was then treated with sat. aq NH_4Cl (15 mL) followed by separation of the organic phase at r.t. The aqueous layer was extracted with EtOAc (3 × 10 mL) and combined organic fractions were dried ($MgSO_4$), filtered, and concentrated in vacuo. ^{1}H NMR analysis indicated a >20:1 ratio of product 2,3-*anti* (**17**): 2,3-*syn* (**18**). The crude product was purified by flash chromatography on silica gel (hexanes–EtOAc, 85:15); colorless oil; yield: 1.02 g (86%); R_f = 0.38 (hexanes–EtOAc, 80:20); $[\alpha]_D^{25}$ –22.9 (*c* 1.3, $CDCl_3$).

IR (neat): 3446, 2957, 2930, 2887, 2857, 1459, 1387, 1363, 1254, 1092, 1025, 1009, 973, 838, 777, 739, 697, 667 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.26 (m, 5 H), 5.57 (dd, *J* = 7.2, 15.5 Hz, 1 H), 5.46 (ddd, *J* = 0.8, 7.2, 15.5 Hz, 1 H), 4.55 (d, *J* = 12.1 Hz, 1 H), 4.53 (d, *J* = 12.1 Hz, 1 H), 3.96 (dt, *J* = 3.1, 7.3 Hz, 1 H), 3.60 (dd, *J* = 4.4, 9.2 Hz, 1 H), 3.49 (dd, *J* = 6.2, 9.8 Hz, 1 H), 3.47 (dd, *J* = 7.5, 9.2 Hz, 1 H), 3.39 (dd, *J* = 7.0, 9.8 Hz, 1 H), 3.25 (d, *J* = 3.1 Hz, 1 H), 2.33 (hept, *J* = 6.7 Hz, 1 H), 1.89 (dh, *J* = 4.4, 7.1 Hz, 1 H), 1.00 (d, *J* = 6.8 Hz, 3 H), 0.89 (s, 9 H), 0.87 (d, *J* = 7.0 Hz, 3 H), 0.034 (s, 3 H), 0.031 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.8, 135.4, 131.0, 128.4, 127.7, 127.6, 77.6, 74.8, 73.4, 68.0, 39.1, 38.7, 25.9, 18.3 16.6, 13.8, –5.33, –5.36.

MS (ESI): *m*/*z* (%) = 211.1 (17), 229.2 (100), 361.3 (M – H_2O + H^+, 71), 757.5 (22).

HRMS (ESI): *m*/*z* calcd for $C_{22}H_{37}O_2Si$ [M – H_2O + H^+]: 361.2557; found: 361.2565 (2.1 ppm).

(–)-(2*R*,3*R*,6*S*,*E*)-1-(Benzyloxy)-7-(*tert*-butyldimethylsilyloxy)-2,6-dimethylhept-4-en-3-ol (18)

Product **18** was prepared from **15** (1.32 g, 3.50 mmol) following the procedure used to prepare **17** using a 1 M solution of (*R*)-2-Me-CBS oxazaborolidine in toluene. ^{1}H NMR analysis indicated a 1:6.5 ratio of product 2,3-*anti* (**17**):2,3-*syn* (**18**). The crude product, obtained as a separable mixture of diastereoisomers, was purified by flash chromatography on silica gel (hexanes–EtOAc, 85:15); colorless oil; yield: 915 mg (69%); R_f = 0.42 (hexanes–EtOAc, 80:20); $[\alpha]_D^{25}$ –8.5 (*c* 1.0, $CDCl_3$).

IR (neat): 3441, 2957, 2930, 2886, 2857, 1459, 1387, 1362, 1253, 1090, 1025, 1009, 972, 838, 777, 735, 697, 667 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.26 (m, 5 H), 5.61 (ddd, *J* = 0.9, 6.9, 15.6 Hz, 1 H), 5.50 (ddd, *J* = 0.9, 6.2, 15.6 Hz, 1 H), 4.53 (d, *J* = 12.3 Hz, 1 H), 4.51 (d, *J* = 12.4 Hz, 1 H), 4.18 (dd, *J* = 5.7, 9.1 Hz, 1 H), 3.54–3.48 (m, 2 H), 3.47 (dd, *J* = 4.9, 9.1 Hz, 1 H), 3.38 (dd, *J* = 7.2, 9.7 Hz, 1 H), 2.76 (d, *J* = 5.6 Hz, 1 H), 2.34 (hept, *J* = 6.7 Hz, 1 H), 2.09–2.00 (m, 1 H), 0.99 (d, *J* = 6.7 Hz, 3 H), 0.89 (d, *J* = 7.0 Hz, 3 H), 0.88 (s, 9 H), 0.04 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.0, 134.5, 129.7, 128.4, 127.7, 127.6, 75.3, 73.8, 73.4, 68.0, 39.1, 38.6, 25.9, 18.3, 16.6, 11.9, –5.32, –5.33.

MS (ESI): *m*/*z* (%) = 211.1 (16), 229.2 (100), 361.3 (M – H_2O + H^+, 67), 757.5 (13).

HRMS (ESI): *m*/*z* calcd for $C_{22}H_{37}O_2Si$ [M – H_2O + H^+]: 361.2557; found: 361.2563 (1.6 ppm).

(–)-(2*R*,3*S*,6*R*,*E*)-1-(Benzyloxy)-7-(*tert*-butyldimethylsilyloxy)-2,6-dimethylhept-4-en-3-ol (19)

Product **19** was prepared from **16** (2.19 g, 5.80 mmol) following the procedure used to prepare **17** using a 1 M solution of (*S*)-2-Me-CBS oxazaborolidine in toluene. ^{1}H NMR analysis indicated an 8:1 ratio of product 2,3-*anti* (**19**):2,3-*syn* (**20**). The crude product, obtained as a separable mixture of diastereoisomers, was purified by flash chromatography on silica gel (hexanes–EtOAc, 85:15); colorless oil; yield: 1.89 g (86%); R_f = 0.27 (hexanes–EtOAc, 85:15); $[\alpha]_D^{25}$ –0.1 (*c* 3.6, $CDCl_3$).

IR (neat): 3424, 2956, 2930, 2856, 1455, 1362, 1254, 1089, 837, 776, 738, 699 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.25 (m, 5 H), 5.61 (dd, *J* = 15.5, 6.9 Hz, 1 H), 5.47 (ddd, *J* = 15.6, 7.2, 1.0 Hz, 1 H), 4.53 (d, *J* = 12.5 Hz, 1 H), 4.51 (d, *J* = 12.7 Hz, 1 H), 3.97 (dt, *J* = 3.1, 7.3 Hz, 1 H), 3.59 (dd, *J* = 9.2, 4.4 Hz, 1 H), 3.52 (dd, *J* = 9.7, 5.9 Hz, 1 H), 3.47 (dd, *J* = 9.2, 7.4 Hz, 1 H), 3.39 (dd, *J* = 9.7, 7.2 Hz, 1 H), 3.17 (d, *J* = 3.2 Hz, 1 H), 2.34 (hept, *J* = 6.8 Hz, 1 H), 1.89 (dh, *J* = 4.5, 7.2 Hz, 1 H), 1.00 (d, *J* = 6.7 Hz, 3 H), 0.89 (s, 9 H), 0.87 (d, *J* = 7.0 Hz, 3 H), 0.03 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 135.4, 131.0, 128.6, 127.9, 127.8, 77.7, 75.0, 73.6, 68.1, 39.1, 38.9, 26.1, 16.7, 13.9, –5.2.

MS (ESI): *m*/*z* (%) = 167.1 (83), 229.2 (100), 287.2 (6), 361.3 (M – H_2O + H^+, 75), 377.3 (18), 413.2 (8), 757.5 (29).

HRMS (ESI): *m*/*z* calcd for $C_{22}H_{37}O_2Si$ [M – H_2O + H^+]: 361.2557; found: 361.2567 (2.6 ppm).

(+)-(2*R*,3*R*,6*R*,*E*)-1-(Benzyloxy)-7-(*tert*-butyldimethylsilyloxy)-2,6-dimethylhept-4-en-3-ol (20)

Product **20** was prepared from **16** (1.17 g, 3.1 mmol) following the procedure used to prepare **17** using a 1 M solution of (*R*)-2-Me-CBS oxazaborolidine in toluene. ^{1}H NMR analysis indicated a 1:8 ratio of product 2,3-*anti* (**19**):2,3-*syn* (**20**). The crude product, obtained as a separable mixture of diastereoisomers, was purified by flash chromatography on silica gel (hexanes–EtOAc, 85:15); colorless oil; yield: 0.91 g (52%); R_f = 0.47 (hexanes–EtOAc, 85:15); $[\alpha]_D^{25}$ +1.7 (*c* 4.4, $CDCl_3$).

IR (neat): 3450, 2956, 2930, 2857, 1458, 1363, 1090, 972, 838, 776, 736, 697, 667 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.26 (m, 5 H), 5.59 (dd, *J* = 15.6, 7.1 Hz, 1 H), 5.50 (dd, *J* = 15.6, 6.1 Hz, 1 H), 4.51 (d, *J* = 12.2 Hz, 1 H), 4.49 (d, *J* = 12.2 Hz, 1 H), 4.18 (dd, *J* = 8.9, 5.5 Hz, 1 H), 3.54–3.49 (m, 2 H), 3.47 (dd, *J* = 9.2, 5.3 Hz, 1 H), 3.39 (dd, *J* = 9.7, 7.1 Hz, 1 H), 2.80 (d, *J* = 5.5 Hz, 1 H), 2.33 (hept, *J* = 6.7 Hz, 1 H), 2.10–2.00 (m, 1 H), 1.00 (d, *J* = 6.8 Hz, 3 H), 0.89 (s, 9 H), 0.89 (d, *J* = 7.0 Hz, 3 H), 0.04 (s, 3 H), 0.03 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.1, 134.8, 129.9, 128.6, 127.9, 127.8, 75.5, 74.0, 73.6, 68.2, 39.4, 38.8, 26.1, 18.5, 16.8, 12.1, –5.1, –5.2.

MS (ESI): *m*/*z* (%) = 211.1 (14), 229.2 (100), 361.3 (M – H_2O + H^+, 69), 377.3 (10), 757.5 (7).

HRMS (ESI): *m*/*z* calcd for $C_{22}H_{37}O_2Si$ [M – H_2O + H^+]: 361.2557; found: 361.2561 (1.1 ppm).

(–)-(2*R*,3*S*,6*S*)-1-(Benzyloxy)-7-(*tert*-butyldimethylsilyloxy)-2,6-dimethylheptan-3-ol (S1); Typical Procedure

To a solution of allylic alcohol **17** (1.40 g, 3.7 mmol) in MeOH (0.1 M, 37 mL) at r.t. was added pyridine (0.30 mL, 1 equiv), followed by 10 wt% Pd/C (0.98 g, 0.92 mmol, 0.25 equiv). Inert gas atmosphere was purged by 3 cycles of vacuum/H_2 gas before stirring the reaction mixture for 2 h or until reaction was judged complete by TLC (eluent: hexanes–EtOAc, 85:15). The mixture was then filtered onto a pad of Celite and washed with hexanes (3 × 15 mL). The filtrate was concentrated in vacuo and purified by flash chromatography on silica gel (hexanes–EtOAc, 85:15); colorless oil; yield: 1.15 g (82%); R_f = 0.25 (hexanes–EtOAc, 85:15); $[\alpha]_D^{25}$ –16.5 (*c* 1.5, $CDCl_3$).

IR (neat): 3434, 2955, 2931, 2857, 1459, 1363, 1253, 1094, 837, 776, 737, 697 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.24 (m, 5 H), 4.53 (d, *J* = 12.2 Hz, 1 H), 4.51 (d, *J* = 12.2 Hz, 1 H), 3.61 (dd, *J* = 4.2, 9.2 Hz, 1 H), 3.54–3.43 (m, 3 H), 3.37 (dd, *J* = 6.8, 9.5 Hz, 1 H), 3.27 (d, *J* = 3.7 Hz, 1 H), 1.89–1.80 (m, 1 H), 1.62–1.53 (m, 1 H), 1.53–1.41 (m, 3 H), 1.32–1.22 (m, 1 H), 0.91 (d, *J* = 6.8 Hz, 3 H), 0.90–0.86 (m, 3 H), 0.89 (s, 9 H), 0.03 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 137.8, 128.4, 127.7, 127.6, 76.2, 75.0, 73.5, 68.5, 38.3, 35.8, 32.3, 28.9, 26.0, 18.4, 16.7, 14.0, –5.34, –5.35.

MS (ESI): *m*/*z* (%) = 381.3 (M + H^+, 100)

HRMS (ESI): *m*/*z* calcd for $C_{22}H_{41}O_3Si$ [M + H^+]: 381.2819; found: 381.2830 (2.8 ppm).

(+)-(2*R*,3*R*,6*S*)-1-(Benzyloxy)-7-(*tert*-butyldimethylsilyloxy)-2,6-dimethylheptan-3-ol (S2)

Product **S2** was prepared from **18** (1.17 g, 3.1 mmol) following the typical procedure used to prepare **S1**; colorless oil; yield: 1.02 g (87%); R_f = 0.26 (hexanes–EtOAc, 90:10); $[\alpha]_D^{25}$ +182.9 (*c* 0.24, $CDCl_3$).

IR (neat): 3463, 2954, 2931, 2857, 1458, 1363, 1253, 1094, 838, 776, 737, 697, 667 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.26 (m, 5 H), 4.53 (d, *J* = 12.1 Hz, 1 H), 4.50 (d, *J* = 12.1 Hz, 1 H), 3.74 (t, *J* = 5.8 Hz, 1 H), 3.53 (d, *J* = 5.4 Hz, 2 H), 3.47 (dd, *J* = 9.8, 5.6 Hz, 1 H), 3.37 (dd, *J* = 9.8, 6.4 Hz, 1 H), 2.55 (br s, 1 H), 1.93–1.85 (m, 1 H), 1.66–1.51 (m, 2 H), 1.51–1.40 (m, 2 H), 1.12–1.02 (m, 1 H), 0.94 (d, *J* = 7.1 Hz, 3 H), 0.90 (s, 9 H), 0.89 (d, *J* = 7.0 Hz, 3 H), 0.04 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.2, 128.6, 127.8, 127.7, 75.0, 74.5, 73.5, 68.4, 37.8, 36.0, 31.5, 29.9, 26.1, 18.5, 16.9, 10.7, –5.2.

MS (ESI): *m*/*z* (%) = 381.3 (M + H^+, 100), 403.3 (M + Na^+, 81), 440.4 (6), 783.5 (10).

HRMS (ESI): *m*/*z* calcd for $C_{22}H_{41}O_3Si$ [M + H^+]: 381.2819; found: 381.2818 (–0.4 ppm); *m*/*z* calcd for $C_{22}H_{40}O_3Si$ + Na [M + Na^+]: 403.2639; found: 403.2640 (0.2 ppm).

(+)-(2*R*,3*S*,6*R*)-1-(Benzyloxy)-7-(*tert*-butyldimethylsilyloxy)-2,6-dimethylheptan-3-ol (S3)

Product **S3** was prepared from **19** (0.98 g, 2.6 mmol) following the typical procedure used to prepare **S1**; colorless oil; yield: 0.91 g (92%); R_f = 0.18 (hexanes–EtOAc, 90:10); $[\alpha]_D^{25}$ +24.9 (*c* 0.55, $CDCl_3$).

IR (neat): 3435, 2954, 2930, 2857, 1742, 1456, 1363, 1253, 1093, 838, 776, 738, 698 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.27 (m, 5 H), 4.53 (d, *J* = 12.2 Hz, 1 H), 4.51 (d, *J* = 12.0 Hz, 1 H), 3.61 (dd, *J* = 9.2, 4.3 Hz, 1 H), 3.54–3.44 (m, 3 H), 3.36 (dd, *J* = 9.8, 6.4 Hz, 1 H), 3.26 (d, *J* = 3.9 Hz, 1 H), 1.85 (dh, *J* = 7.0, 4.4 Hz, 1 H), 1.62–1.53 (m,

3 H), 1.38 (ddd, *J* = 13.6, 10.8, 2.1 Hz, 1 H), 1.19–1.08 (m, 1 H), 0.92 (d, *J* = 7.0 Hz, 3 H), 0.89 (s, 9 H), 0.89 (d, *J* = 6.2 Hz, 3 H), 0.03 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.9, 128.6, 127.9, 127.8, 76.6, 75.2, 73.6, 68.4, 38.2, 36.1, 32.4, 28.9, 26.1, 18.5, 17.1, 14.2, –5.2.

MS (ESI): *m*/*z* (%) = 167.1 (6), 381.3 (M + H$^+$, 100).

HRMS (ESI): *m*/*z* calcd for $C_{22}H_{41}O_3Si$ [M + H$^+$]: 381.2819; found: 381.2825 (1.5 ppm).

(+)-(2*R*,3*R*,6*R*)-1-(Benzyloxy)-7-(*tert*-butyldimethylsilyloxy)-2,6-dimethylheptan-3-ol (S4)

Product **S4** was prepared from **20** (0.84 g, 2.2 mmol) following the typical procedure used to prepare **S1**; colorless oil; yield: 835 mg (99%); R_f = 0.23 (hexanes–EtOAc, 85:15); $[\alpha]_D^{25}$ +6.7 (*c* 1.1, $CDCl_3$).

IR (neat): 3454, 2954, 2931, 2857, 1460, 1363, 1253, 1094, 838, 776, 737, 698, 667 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.26 (m, 5 H), 4.53 (d, *J* = 12.1 Hz, 1 H), 4.50 (d, *J* = 12.0 Hz, 1 H), 3.76–3.70 (m, 1 H), 3.53 (d, *J* = 5.4 Hz, 2 H), 3.45 (dd, *J* = 9.7, 5.9 Hz, 1 H), 3.39 (dd, *J* = 9.7, 6.4 Hz, 1 H), 1.89 (ddd, *J* = 12.4, 5.5, 2.1 Hz, 1 H), 1.64–1.54 (m, 2 H), 1.54–1.46 (m, 1 H), 1.44–1.33 (m, 2 H), 1.30–1.19 (m, 1 H), 0.93 (d, *J* = 7.1 Hz, 3 H), 0.89 (s, 9 H), 0.88 (d, *J* = 6.9 Hz, 3 H), 0.03 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.5, 128.6, 127.82, 127.75, 75.0, 74.4, 73.6, 68.5, 38.1, 36.0, 31.7, 30.0, 26.1, 18.6, 17.0, 10.9, –5.2.

MS (ESI): *m*/*z* (%) = 381.3 (M + H$^+$, 100).

HRMS (ESI): *m*/*z* calcd for $C_{22}H_{41}O_3Si$ [M + H$^+$]: 381.2819; found: 381.2829 (2.5 ppm).

(+)-(5*S*,8*S*)-5-[(*R*)-1-(Benzyloxy)propan-2-yl]-2,2,3,3,8,11,11,12,12-nonamethyl-4,10-dioxa-3,11-disiladodecane (21); Typical Procedure

To a cold (0 °C) solution of alcohol **S1** (564 mg, 1.5 mmol) in anhyd CH_2Cl_2 (0.1 M, 15 mL) was added successively 2,6-lutidine (0.35 mL, 3.0 mmol, 2.05 equiv) and TBSOTf (0.51 mL, 2.2 mmol, 1.5 equiv). 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 sat. aq $NaHCO_3$ (10 mL) followed by separation of the organic phase at r.t. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) 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); colorless oil; yield: 0.72 g (98%); R_f = 0.49 (hexanes–EtOAc, 95:5); $[\alpha]_D^{25}$ +1.1 (*c* 1.8, $CDCl_3$).

IR (neat): 2955, 2930, 2857, 1463, 1254, 1095, 836, 774 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.29 (m, 5 H), 4.52 (d, *J* = 12.1 Hz, 1 H), 4.48 (d, *J* = 12.1 Hz, 1 H), 3.66 (dd, *J* = 10.2, 5.2 Hz, 1 H), 3.47 (dd, *J* = 5.7, 9.1 Hz, 1 H), 3.43 (dd, *J* = 5.9, 9.7 Hz, 1 H), 3.35 (dd, *J* = 6.6, 9.7 Hz, 1 H), 3.28 (dd, *J* = 7.2, 9.0 Hz, 1 H), 1.96 (hept, *J* = 6.4 Hz, 1 H), 1.55–1.49 (m, 1 H), 1.49–1.36 (m, 2 H), 1.36–1.23 (m, 1 H), 1.16–1.06 (m, 1 H), 0.92 (d, *J* = 6.9 Hz, 3 H), 0.89 (s, 9 H), 0.87 (s, 9 H), 0.85 (d, *J* = 6.7 Hz, 3 H), 0.03 (s, 9 H), 0.02 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.9, 128.3, 127.5, 127.4, 73.8, 73.0, 72.8, 68.6, 38.7, 36.1, 30.4, 28.6, 25.98, 25.95, 18.4, 18.1, 16.6, 13.1, –4.3, –4.6, –5.3.

MS (ESI): *m*/*z* (%) = 363.3 (15), 495.4 (M + H$^+$, 100).

HRMS (ESI): *m*/*z* calcd for $C_{28}H_{55}O_3Si_2$ [M + H$^+$]: 495.3684; found: 495.3691 (1.4 ppm).

(–)-(5*R*,8*S*)-5-[(*R*)-1-(Benzyloxy)propan-2-yl]-2,2,3,3,8,11,11,12,12-nonamethyl-4,10-dioxa-3,11-disiladodecane (22)

Product **22** was prepared from **S2** (1.14 g, 3.0 mmol) following the typical procedure used to prepare **21**; colorless oil; yield: 1.08 g (73%); R_f = 0.70 (hexanes–EtOAc, 90:10); $[\alpha]_D^{25}$ –0.2 (*c* 5.6, $CDCl_3$).

IR (neat): 3031, 2955, 2931, 2887, 2857, 1469, 1387, 1362, 1253, 1097, 1050, 837, 774 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.26 (m, 5 H), 4.52 (d, *J* = 12.0 Hz, 1 H), 4.46 (d, *J* = 12.0 Hz, 1 H), 3.75 (dt, *J* = 2.9, 6.4 Hz, 1 H), 3.48 (dd, *J* = 8.9, 6.6 Hz, 1 H), 3.43 (dd, *J* = 9.8, 5.8 Hz, 1 H), 3.37 (dd, *J* = 9.7, 6.4 Hz, 1 H), 3.27 (dd, *J* = 8.8, 7.0 Hz, 1 H), 1.91 (dh, *J* = 3.0, 6.8 Hz, 1 H), 1.58–1.49 (m, 2 H), 1.46–1.32 (m, 2 H), 1.02–0.95 (m, 1 H), 0.93–0.90 (m, 3 H), 0.91 (s, 9 H), 0.90–0.87 (m, 3 H), 0.89 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 6 H), 0.03 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.9, 128.4, 127.7, 127.5, 73.4, 73.1, 72.8, 68.4, 37.7, 36.1, 32.0, 29.3, 26.13, 26.10, 18.5, 18.3, 16.9, 11.1, –3.9, –4.6, –5.19, –5.20.

MS (ESI): *m*/*z* (%) = 363.3 (10), 381.3 (5), 495.4 (M + H$^+$, 100), 512.4 (17), 517.3 (M + Na$^+$, 13).

HRMS (ESI): *m*/*z* calcd for $C_{28}H_{55}O_3Si_2$ [M + H$^+$]: 495.3684; found: 495.3674 (–2.0 ppm); *m*/*z* calcd for $C_{28}H_{54}O_3Si_2$ + Na [M + Na$^+$]: 517.3504; found: 517.3496 (–1.5 ppm).

(+)-(5*S*,8*R*)-5-[(*R*)-1-(Benzyloxy)propan-2-yl]-2,2,3,3,8,11,11,12,12-nonamethyl-4,10-dioxa-3,11-disiladodecane (23)

Product **23** was prepared from **S3** (0.83 g, 2.2 mmol) following the typical procedure used to prepare **21**; colorless oil; yield: 0.95 g (88%); R_f = 0.47 (hexanes–EtOAc, 95:5); $[\alpha]_D^{25}$ +5.7 (*c* 1.0, $CDCl_3$).

IR (neat): 2955, 2930, 2857, 1463, 1253, 1093, 836, 774 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.25 (m, 5 H), 4.52 (d, *J* = 12.1 Hz, 1 H), 4.47 (d, *J* = 12.1 Hz, 1 H), 3.67 (dd, *J* = 10.3, 5.2 Hz, 1 H), 3.50 (dd, *J* = 9.2, 5.6 Hz, 1 H), 3.44 (dd, *J* = 9.7, 5.5 Hz, 1 H), 3.37 (ddd, *J* = 9.8, 6.2, 3.3 Hz, 1 H), 3.30 (dd, *J* = 9.1, 7.1 Hz, 1 H), 1.95 (hept, *J* = 6.7 Hz, 1 H), 1.57–1.33 (m, 4 H), 1.12–1.00 (m, 1 H), 0.91 (d, *J* = 6.9 Hz, 3 H), 0.90 (s, 9 H), 0.89 (s, 9 H), 0.87 (d, *J* = 6.6 Hz, 3 H), 0.05 (s, 3 H), 0.044 (s, 6 H), 0.038 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 139.0, 128.4, 127.6, 127.5, 74.0, 73.1, 72.9, 68.4, 38.6, 36.3, 30.8, 28.7, 26.13, 26.10, 18.5, 18.3, 17.1, 13.5, –4.1, –4.5, –5.19, –5.20.

MS (ESI): *m*/*z* (%) = 167.1 (14), 363.3 (15), 495.4 (M + H$^+$, 100), 496.4 (27).

HRMS (ESI): *m*/*z* calcd for $C_{28}H_{55}O_3Si_2$ [M + H$^+$]: 495.3684; found: 495.3687 (0.6 ppm).

(+)-(5*R*,8*R*)-5-[(*R*)-1-(Benzyloxy)propan-2-yl]-2,2,3,3,8,11,11,12,12-nonamethyl-4,10-dioxa-3,11-disiladodecane (24)

Product **24** was prepared from **S4** (1.11 g, 2.9 mmol) following the typical procedure used to prepare **21**; colorless oil; yield: 1.41 g (98%); R_f = 0.48 (hexanes–EtOAc, 95:5); $[\alpha]_D^{25}$ +1.5 (*c* 1.1, CH_2Cl_2).

IR (neat): 2955, 2930, 2887, 2857, 1362, 1253, 1097, 1049, 836, 774 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.27 (m, 5 H), 4.52 (d, *J* = 12.0 Hz, 1 H), 4.45 (d, *J* = 12.0 Hz, 1 H), 3.72 (dt, *J* = 2.9, 6.3 Hz, 1 H), 3.48 (dd, *J* = 8.8, 6.6 Hz, 1 H), 3.43 (dd, *J* = 9.7, 5.8 Hz, 1 H), 3.36 (dd, *J* = 9.7, 6.4 Hz, 1 H), 3.26 (dd, *J* = 8.6, 7.3 Hz, 1 H), 1.89 (dh, *J* = 6.8, 2.9 Hz, 1 H), 1.58–1.47 (m, 1 H), 1.47–1.39 (m, 2 H), 1.37–1.28 (m, 1 H), 1.11–0.98 (m, 1 H), 0.89 (s, 9 H), 0.88 (d,

J = 6.9 Hz, 3 H), 0.87 (s, 9 H), 0.86 (d, J = 6.8 Hz, 3 H), 0.03 (s, 9 H), 0.02 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.9, 128.4, 127.7, 127.5, 73.3, 73.10, 73.05, 68.3, 37.9, 36.2, 32.0, 29.4, 26.1, 18.5, 18.3, 17.0, 11.3, –3.9, –4.5, –5.2.

MS (ESI): m/z (%) = 363.3 (16), 495.4 (M + H$^+$, 100), 496.4 (29).

HRMS (ESI): m/z calcd for $C_{28}H_{55}O_3Si_2$ [M + H$^+$]: 495.3684; found: 495.3689 (0.9 ppm).

(–)-(2*S*,5*S*,6*R*)-7-(Benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-2,6-dimethylheptan-1-ol (S5)

Primary alcohol **S5** was obtained from bis-TBS product **21** (503 mg, 1.0 mmol) following general procedure **A1**; colorless oil; yield: 0.33 g (85%); R_f = 0.29 (hexanes–EtOAc, 80:20); $[\alpha]_D^{25}$ –3.0 (c 1.3, $CDCl_3$).

IR (neat): 3372, 2954, 2929, 2857, 1460, 1363, 1253, 1074, 1044, 943, 836, 774, 735, 697, 669 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.26 (m, 5 H), 4.51 (d, J = 12.1 Hz, 1 H), 4.45 (d, J = 12.1 Hz, 1 H), 3.68 (dd, J = 10.5, 5.0 Hz, 1 H), 3.52–3.44 (m, 2 H), 3.44–3.38 (m, 1 H), 3.27 (dd, J = 6.7, 9.1 Hz, 1 H), 1.98 (hept, J = 6.1 Hz, 1 H), 1.53–1.33 (m, 3 H), 1.31–1.24 (m, 1 H), 1.22–1.10 (m, 1 H), 0.91 (d, J = 6.9 Hz, 3 H), 0.90 (d, J = 6.7 Hz, 3 H), 0.87 (s, 9 H), 0.04 (s, 3 H), 0.03 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.8, 128.3, 127.5, 127.4, 73.7, 73.0, 72.7, 68.3, 38.5, 36.0, 30.4, 28.4, 25.9, 18.1, 16.6, 13.2, –4.3, –4.6.

MS (ESI): m/z (%) = 141.1 (12), 233.2 (10), 249.2 (90), 381.3 (M + H$^+$, 100).

HRMS (ESI): m/z calcd for $C_{22}H_{41}O_3Si$ [M + H$^+$]: 381.2819; found: 381.2824 (1.2 ppm).

(–)-(2*S*,5*R*,6*R*)-7-(Benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-2,6-dimethylheptan-1-ol (S6)

Primary alcohol **S6** was obtained from bis-TBS product **22** (1.08 g, 2.2 mmol) following general procedure **A1**; colorless oil; yield: 0.44 g (53%); R_f = 0.09 (hexanes–EtOAc, 90:10); $[\alpha]_D^{25}$ –3.2 (c 1.1, $CDCl_3$).

IR (neat): 3359, 2954, 2930, 2857, 1460, 1362, 1252, 1102, 1047, 836, 774 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.26 (m, 5 H), 4.51 (d, J = 12.0 Hz, 1 H), 4.45 (d, J = 12.0 Hz, 1 H), 3.75 (dt, J = 3.0, 6.8 Hz, 1 H), 3.51–3.44 (m, 1 H), 3.46 (dd, J = 8.8, 6.9 Hz, 1 H), 3.40 (t, J = 8.2 Hz, 1 H), 3.26 (dd, J = 8.8, 6.8 Hz, 1 H), 1.89 (dh, J = 3.1, 6.8 Hz, 1 H), 1.60–1.50 (m, 2 H), 1.45–1.32 (m, 2 H), 1.29–1.22 (m, 1 H), 1.07–0.97 (m, 1 H), 0.91 (d, J = 6.7 Hz, 3 H), 0.87 (s, 9 H), 0.87 (d, J = 6.6 Hz, 3 H), 0.04 (s, 3 H), 0.02 (s, 3 H). One signal was missing (OH) presumably due to proton exchange in $CDCl_3$.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.9, 128.5, 127.8, 127.6, 73.3, 73.2, 72.7, 68.5, 44.9, 37.6, 36.1, 32.0, 29.2, 26.1, 18.3, 16.7, 11.1, –3.9, –4.5.

MS (ESI): m/z (%) = 249.2 (35), 338.3 (5), 381.3 (M + H$^+$, 100), 403.3 (M + Na$^+$, 70).

HRMS (ESI): m/z calcd for $C_{22}H_{41}O_3Si$ [M + H$^+$]: 381.2819; found: 381.2814 (–1.3 ppm); m/z calcd for $C_{22}H_{40}O_3Si$ + Na [M + Na$^+$]: 403.2639; found: 403.2637 (–0.6 ppm).

(+)-(2*R*,5*S*,6*R*)-7-(Benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-2,6-dimethylheptan-1-ol (S7)

Primary alcohol **S7** was obtained from bis-TBS product **23** (837 mg, 1.7 mmol) following general procedure **A1**; colorless oil; yield: 519 mg (81%); R_f = 0.24 (hexanes–EtOAc, 85:15); $[\alpha]_D^{25}$ +7.3 (c 1.0, $CDCl_3$).

IR (neat): 3368, 2954, 2930, 2857, 1459, 1363, 1253, 1075, 1043, 836, 774, 735, 697 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.26 (m, 5 H), 4.51 (d, J = 12.1 Hz, 1 H), 4.45 (d, J = 12.1 Hz, 1 H), 3.67 (dd, J = 10.1, 5.3 Hz, 1 H), 3.53–3.45 (m, 2 H), 3.40 (dd, J = 10.4, 6.6 Hz, 1 H), 3.28 (dd, J = 9.2, 6.8 Hz, 1 H), 1.98 (hept, J = 6.6 Hz, 1 H), 1.61–1.52 (m, 1 H), 1.50–1.41 (m, 2 H), 1.41–1.30 (m, 1 H), 1.18–1.08 (m, 1 H), 0.92 (d, J = 6.1 Hz, 3 H), 0.90 (d, J = 6.6 Hz, 3 H), 0.88 (s, 9 H), 0.04 (s, 3 H), 0.03 (s, 3 H). One signal missing (OH) presumably due to proton exchange in $CDCl_3$.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.9, 128.4, 127.7, 127.6, 73.9, 73.1, 72.7, 68.3, 38.5, 36.1, 30.4, 28.5, 26.1, 18.3, 16.9, 13.5, –4.1, –4.5.

MS (ESI): m/z (%) = 167.1 (60), 249.2 (73), 381.3 (M + H$^+$, 100), 547.4 (25).

HRMS (ESI): m/z calcd for $C_{22}H_{41}O_3Si$ [M + H$^+$]: 381.2819; found: 381.2824 (1.1 ppm).

(–)-(2*R*,5*R*,6*R*)-7-(Benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-2,6-dimethylheptan-1-ol (S8)

Primary alcohol **S8** was obtained from bis-TBS product **24** (387 mg, 0.78 mmol) following general procedure **A1**. Colorless oil; yield: 213 mg (72%); R_f = 0.32 (hexanes–EtOAc, 80:20); $[\alpha]_D^{25}$ –1.6 (c 0.9, CH_2Cl_2).

IR (neat): 3369, 2954, 2928, 2856, 1459, 1377, 1252, 1100, 1044, 835, 773, 735, 697 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.27 (m, 5 H), 4.52 (d, J = 12.0 Hz, 1 H), 4.45 (d, J = 12.0 Hz, 1 H), 3.73 (dt, J = 3.1, 6.3 Hz, 1 H), 3.53–3.48 (m, 1 H), 3.47 (dd, J = 8.8, 6.6 Hz, 1 H), 3.44–3.37 (m, 1 H), 3.26 (dd, J = 8.8, 6.9 Hz, 1 H), 1.89 (dh, J = 3.1, 6.8 Hz, 1 H), 1.62–1.52 (m, 1 H), 1.48–1.41 (m, 2 H), 1.39–1.30 (m, 1 H), 1.28 (t, J = 5.7 Hz, 1 H), 1.16–1.08 (m, 1 H), 0.91 (d, J = 6.7 Hz, 3 H), 0.88 (d, J = 6.1 Hz, 3 H), 0.87 (s, 9 H), 0.04 (s, 3 H), 0.02 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.8, 128.4, 127.7, 127.6, 77.3, 73.2, 72.9, 68.3, 37.9, 36.1, 31.8, 29.2, 26.1, 18.3, 16.8, 11.4, –3.9, –4.5.

MS (ESI): m/z (%) = 141.1 (20), 249.2 (69), 381.3 (M + H$^+$, 100).

HRMS (ESI): m/z calcd for $C_{22}H_{41}O_3Si$ [M + H$^+$]: 381.2819; found: 381.2823 (1.0 ppm).

(+)-(2*S*,5*S*,6*R*)-7-(Benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-2,6-dimethylheptanal (25); Typical Procedure

To a solution of alcohol **S5** (377 mg, 0.99 mmol) in anhyd CH_2Cl_2 (0.1 M, 10 mL) was added successively $NaHCO_3$ (0.83 g, 9.9 mmol, 10 equiv) and Dess–Martin periodinane (0.63 g, 1.5 mmol, 1.5 equiv). The mixture was stirred for 30 min at r.t. and then concentrated. The product was digested from white solid residue in hexanes (3 × 10 mL) 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); colorless oil; yield: 366 mg (98%); R_f = 0.58 (hexanes–EtOAc, 80:20); $[\alpha]_D^{25}$ +5.8 (c 1.3, $CDCl_3$).

IR (neat): 2956, 2856, 1727, 1459, 1254, 1074, 836 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.58 (d, J = 2.0 Hz, 1 H), 7.38–7.26 (m, 5 H), 4.51 (d, J = 12.0 Hz, 1 H), 4.44 (d, J = 12.1 Hz, 1 H), 3.74–3.68 (m, 1 H), 3.43 (dd, J = 9.2, 6.2 Hz, 1 H), 3.28 (dd, J = 9.2, 6.5 Hz, 1 H), 2.33–2.23 (m, 1 H), 1.98 (hept, J = 6.5 Hz, 1 H), 1.78–1.63 (m, 1 H), 1.52–1.34 (m, 3 H), 1.07 (d, J = 7.0 Hz, 3 H), 0.90 (d, J = 6.9 Hz, 3 H), 0.88 (s, 9 H), 0.04 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.3, 138.8, 128.4, 127.63, 127.59, 73.1, 72.7, 46.5, 38.7, 30.0, 26.2, 26.0, 18.2, 13.4, 12.9, –4.2, –4.4.

MS (ESI): *m/z* (%) = 401.2 (M + Na^+, 100).

HRMS (ESI): *m/z* calcd for $C_{22}H_{38}O_3Si$ + Na [M + Na^+]: 401.2482; found: 401.2474.

(+)-(2*S*,5*R*,6*R*)-7-(Benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-2,6-dimethylheptanal (26)

Aldehyde **26** was obtained from alcohol **S6** (398 mg, 1.0 mmol) following the typical procedure used to prepare **25**; colorless oil; yield: 387 mg (98%); R_f = 0.41 (hexanes–EtOAc, 90:10); $[\alpha]_D^{25}$ +5.2 (*c* 1.5, CH_2Cl_2).

IR (neat): 2956, 2930, 2856, 1726, 1461, 1361, 1252, 1100, 1049 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.58 (d, *J* = 1.9 Hz, 1 H), 7.37–7.26 (m, 5 H), 4.51 (d, *J* = 12.0 Hz, 1 H), 4.45 (d, *J* = 12.0 Hz, 1 H), 3.76 (dt, *J* = 3.3, 6.3 Hz, 1 H), 3.46 (dd, *J* = 8.9, 6.7 Hz, 1 H), 3.26 (dd, *J* = 8.9, 6.7 Hz, 1 H), 2.29 (dh, *J* = 1.8, 6.9 Hz, 1 H), 1.93–1.84 (m, 1 H), 1.79–1.68 (m, 1 H), 1.51 (ddd, *J* = 17.9, 11.5, 5.6 Hz, 1 H), 1.40 (ddd, *J* = 13.1, 11.1, 5.5 Hz, 1 H), 1.34–1.23 (m, 1 H), 1.09 (d, *J* = 7.0 Hz, 3 H), 0.88 (d, *J* = 7.5 Hz, 3 H), 0.87 (s, 9 H), 0.04 (s, 3 H), 0.03 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.1, 138.8, 128.5, 127.7, 127.6, 73.2, 73.0, 72.5, 46.5, 38.0, 31.8, 26.8, 26.1, 18.3, 13.5, 11.5, –4.0, –4.5.

MS (ESI): *m/z* (%) = 247.2 (25), 379.3 (M + H^+, 12), 401.2 (M + H^+, 81), 433.3 (100).

HRMS (ESI): *m/z* calcd for $C_{22}H_{39}O_3Si$ [M + H^+]: 379.2663; found: 379.2662 (–0.2 ppm); *m/z* calcd for $C_{22}H_{38}O_3Si$ + Na [M + Na^+]: 401.2482; found: 401.2483 (0.1 ppm).

(2*R*,5*S*,6*R*)-7-(Benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-2,6-dimethylheptanal (27)

Aldehyde **27** was obtained from alcohol **S7** (434 mg, 1.1 mmol) following the typical procedure used to prepare **25**; colorless oil; yield: 402 mg (93%); R_f = 0.48 (hexanes–EtOAc, 90:10).

IR (neat): 2956, 2931, 2857, 1726, 1459, 1363, 1254, 1074, 836, 774, 736, 698 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.58 (d, *J* = 1.9 Hz, 1 H), 7.37–7.26 (m, 5 H), 4.51 (d, *J* = 12.1 Hz, 1 H), 4.44 (d, *J* = 12.1 Hz, 1 H), 3.71 (q, *J* = 5.1 Hz, 1 H), 3.44 (dd, *J* = 9.2, 6.1 Hz, 1 H), 3.29 (dd, *J* = 9.1, 6.6 Hz, 1 H), 2.29 (dh, *J* = 1.7, 6.7 Hz, 1 H), 1.98 (hept, *J* = 6.5 Hz, 1 H), 1.83–1.73 (m, 1 H), 1.45–1.34 (m, 3 H), 1.07 (d, *J* = 7.1 Hz, 3 H), 0.90 (d, *J* = 7.0 Hz, 3 H), 0.88 (s, 9 H), 0.042 (s, 3 H), 0.037 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.3, 138.8, 128.5, 127.63, 127.59, 73.2, 73.1, 72.7, 46.6, 38.7, 30.2, 26.2, 26.0, 18.2, 13.6, 13.0, –4.2, –4.4.

MS (ESI): *m/z* (%) = 155.1 (19), 233.2 (25), 247.2 (55), 263.2 (44), 379.3 (M + H^+, 43), 395.3 (100).

HRMS (ESI): *m/z* calcd for $C_{22}H_{39}O_3Si$ [M + H^+]: 379.2663; found: 379.2672 (2.3 ppm).

(2*R*,5*R*,6*R*)-7-(Benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-2,6-dimethylheptanal (28)

Aldehyde **28** was obtained from alcohol **S8** (293 mg, 0.77 mmol) following the typical procedure used to prepare **25**; colorless oil; yield: 262 mg (90%); R_f = 0.41 (hexanes–EtOAc, 90:10).

IR (neat): 2956, 2931, 2857, 1727, 1459, 1363, 1253, 1100, 1048, 836, 774, 736, 697 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.60 (d, *J* = 1.8 Hz, 1 H), 7.38–7.26 (m, 5 H), 4.52 (d, *J* = 12.0 Hz, 1 H), 4.45 (d, *J* = 12.0 Hz, 1 H), 3.76 (dt, *J* = 3.4, 6.1 Hz, 1 H), 3.47 (dd, *J* = 8.8, 6.7 Hz, 1 H), 3.26 (dd, *J* = 8.8, 6.7 Hz, 1 H), 2.30 (dh, *J* = 1.5, 6.9 Hz, 1 H), 1.90 (dh, *J* = 3.2, 6.8 Hz, 1 H), 1.69–1.59 (m, 1 H), 1.53–1.35 (m, 3 H), 1.08 (d, *J* = 7.0 Hz, 3 H), 0.89 (d, *J* = 6.8 Hz, 3 H), 0.88 (s, 9 H), 0.04 (s, 3 H), 0.03 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.1, 138.7, 128.4, 127.7, 127.6, 73.2, 72.9, 72.5, 46.5, 38.1, 31.8, 26.9, 26.0, 18.3, 13.6, 11.5, –4.0, –4.5.

MS (ESI): *m/z* (%) = 155.1 (25), 233.2 (37), 247.2 (100), 263.2 (35), 351.3 (15), 379.3 (M + H^+, 44), 395.3 (75).

HRMS (ESI): *m/z* calcd for $C_{22}H_{39}O_3Si$ [M + H^+]: 379.2663; found: 379.2671 (2.1 ppm).

Ethyl (+)-(4*S*,7*S*,8*R*,*E*)-9-(Benzyloxy)-7-(*tert*-butyldimethylsilyloxy)-2,4,8-trimethylnon-2-enoate (S9); Typical Procedure

To a solution of aldehyde **25** (280 mg, 0.74 mmol) in toluene (0.1 M, 7.4 mL) at r.t. was added (carbethoxyethylidene)triphenylphosphorane (0.40 g, 1.1 mmol, 1.5 equiv), followed by stirring and warming to reflux for 18 h. The mixture was then cooled and concentrated. The product was digested from dark yellow 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, 95:5); pale yellow oil; yield: 244 mg (72%); R_f = 0.70 (hexanes–EtOAc, 90:10); $[\alpha]_D^{25}$ +10.9 (*c* 1.1, $CDCl_3$).

IR (neat): 2957, 2932, 2857, 1711, 1649, 1458, 1366, 1255, 1198, 1097, 941, 836, 774, 719, 698 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.26 (m, 5 H), 6.55 (dd, *J* = 1.4, 10.1 Hz, 1 H), 4.52 (d, *J* = 12.1 Hz, 1 H), 4.47 (d, *J* = 12.1 Hz, 1 H), 4.20 (q, *J* = 7.1 Hz, 2 H), 3.67 (dd, *J* = 5.4, 9.7 Hz, 1 H), 3.48 (dd, *J* = 5.6, 9.1 Hz, 1 H), 3.30 (dd, *J* = 6.8, 9.1 Hz, 1 H), 2.49–2.40 (m, 1 H), 2.00–1.91 (m, 1 H), 1.85 (d, *J* = 1.4 Hz, 3 H), 1.52–1.33 (m, 4 H), 1.31 (t, *J* = 7.1 Hz, 3 H), 1.02 (d, *J* = 6.7 Hz, 3 H), 0.93 (d, *J* = 7.0 Hz, 3 H), 0.90 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.3, 147.8, 138.7, 128.2, 127.4, 127.3, 126.4, 73.3, 72.9, 72.6, 60.3, 45.0, 38.4, 33.5, 31.8, 30.8, 25.9, 20.0, 18.1, 14.3, 13.2, 12.5, –4.3, –4.7.

MS (ESI): *m/z* (%) = 223.2 (8), 331.2 (29), 463.3 (M + H^+, 100).

HRMS (ESI): *m/z* calcd for $C_{27}H_{47}O_4Si$ [M + H^+]: 463.3238; found: 463.3225 (–2.9 ppm).

Ethyl (–)-(4*S*,7*R*,8*R*,*E*)-9-(Benzyloxy)-7-(*tert*-butyldimethylsilyloxy)-2,4,8-trimethylnon-2-enoate (S10)

Product **S10** was prepared from **26** (393 mg, 1.0 mmol) following the typical procedure used to prepare **S9**; pale yellow oil; yield: 290 mg (60%); R_f = 0.53 (hexanes–EtOAc, 95:5); $[\alpha]_D^{25}$ –1.4 (*c* 0.3, $CDCl_3$).

IR (neat): 2956, 2930, 2856, 1712, 1457, 1364, 1253, 1100, 1044, 836, 774, 749, 697 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.25 (m, 5 H), 6.51 (dd, *J* = 10.1, 1.2 Hz, 1 H), 4.50 (d, *J* = 12.0 Hz, 1 H), 4.44 (d, *J* = 12.0 Hz, 1 H), 4.18 (dq, *J* = 1.8, 7.1 Hz, 2 H), 3.75–3.69 (m, 1 H), 3.44 (dd, *J* = 8.8, 6.8 Hz, 1 H), 3.24 (dd, *J* = 8.8, 6.8 Hz, 1 H), 2.47–2.38 (m, 1 H), 1.88–1.81 (m, 1 H), 1.82 (d, *J* = 1.2 Hz, 3 H), 1.47–1.37 (m, 1 H), 1.36–1.24 (m, 3 H), 1.29 (t, *J* = 7.1 Hz, 3 H), 0.99 (d, *J* = 6.7 Hz, 3 H), 0.86 (s, 9 H), 0.85 (d, *J* = 7.1 Hz, 3 H), 0.01 (s, 3 H), 0.00 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.5, 147.8, 138.9, 128.5, 127.7, 127.6, 126.7, 73.2, 73.2, 72.5, 60.5, 44.9, 37.9, 33.4, 32.9, 32.3, 26.1, 20.1, 18.3, 14.5, 12.7, 11.2, –4.0, –4.5.

MS (ESI): *m/z* (%) = 463.3 (M + H^+, 100), 480.3 (61), 485.3 (M + Na^+, 51).

HRMS (ESI): *m/z* calcd for $C_{27}H_{47}O_4Si$ [M + H^+]: 463.3238; found: 463.3234 (–0.8 ppm); *m/z* calcd for $C_{27}H_{46}O_4Si$ + Na [M + Na^+]: 485.3058; found: 485.3051 (–1.4 ppm).

Ethyl (–)-(4*R*,7*S*,8*R*,*E*)-9-(Benzyloxy)-7-(*tert*-butyldimethylsilyloxy)-2,4,8-trimethylnon-2-enoate (S11)

Product **S11** was prepared from **27** (387 mg, 1.0 mmol) following the typical procedure used to prepare **S9**. Pale yellow oil; yield: 369 mg (78%); R_f = 0.30 (hexanes–EtOAc, 95:5); $[\alpha]_D^{25}$ –6.2 (*c* 1.0, CH_2Cl_2).

IR (neat): 2957, 2931, 2857, 1711, 1457, 1366, 1254, 1198, 1098, 836, 774 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.26 (m, 5 H), 6.52 (dd, *J* = 10.0, 1.2 Hz, 1 H), 4.50 (d, *J* = 12.1 Hz, 1 H), 4.44 (d, *J* = 12.1 Hz, 1 H), 4.18 (dq, *J* = 1.1, 7.1 Hz, 2 H), 3.65 (q, *J* = 5.0 Hz, 1 H), 3.45 (dd, *J* = 9.2, 5.8 Hz, 1 H), 3.27 (dd, *J* = 9.1, 6.8 Hz, 1 H), 2.47–2.36 (m, 1 H), 1.94 (hept, *J* = 6.1 Hz, 1 H), 1.82 (s, 3 H), 1.45–1.32 (m, 4 H), 1.29 (t, *J* = 7.1 Hz, 3 H), 0.99 (d, *J* = 6.6 Hz, 3 H), 0.89 (d, *J* = 7.0 Hz, 3 H), 0.87 (s, 9 H), 0.03 (s, 3 H), 0.02 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5, 148.0, 138.9, 128.4, 127.6, 127.5, 126.6, 73.5, 73.1, 72.7, 60.5, 38.6, 33.5, 32.2, 30.9, 26.0, 20.2, 18.2, 14.4, 13.3, 12.7, –4.2, –4.5.

MS (ESI): *m*/*z* (%) = 145.1 (5), 191.1 (12), 223.2 (9), 331.2 (32), 463.3 ($M + H^+$, 3).

HRMS (ESI): *m*/*z* calcd for $C_{27}H_{47}O_4Si$ [$M + H^+$]: 463.3238; found: 463.3243 (1.0 ppm).

Ethyl (–)-(4*R*,7*R*,8*R*,*E*)-9-(Benzyloxy)-7-(*tert*-butyldimethylsilyloxy)-2,4,8-trimethylnon-2-enoate (S12)

Product **S12** was prepared from **28** (268 mg, 0.71 mmol) following the typical procedure used to prepare **S9**; pale yellow oil; yield: 177 mg (54%); R_f = 0.34 (hexanes–EtOAc, 95:5); $[\alpha]_D^{25}$ –15.5 (*c* 1.2, CH_2Cl_2).

IR (neat): 2956, 2931, 2857, 1711, 1458, 1365, 1255, 1198, 1099, 1046, 836, 774, 749 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.27 (m, 5 H), 6.52 (dd, *J* = 10.1, 1.1 Hz, 1 H), 4.51 (d, *J* = 11.9 Hz, 1 H), 4.45 (d, *J* = 11.9 Hz, 1 H), 4.19 (dq, *J* = 1.0, 7.0 Hz, 2 H), 3.73 (dt, *J* = 3.3, 6.2 Hz, 1 H), 3.45 (dd, *J* = 8.8, 6.9 Hz, 1 H), 3.25 (dd, *J* = 8.8, 6.7 Hz, 1 H), 2.49–2.37 (m, 1 H), 1.86 (dh, *J* = 3.1, 6.8 Hz, 1 H), 1.82 (d, *J* = 1.1 Hz, 3 H), 1.44–1.33 (m, 3 H), 1.30 (t, *J* = 7.1 Hz, 3 H), 1.28–1.21 (m, 1 H), 0.98 (d, *J* = 6.7 Hz, 3 H), 0.87 (s, 9 H), 0.85 (d, *J* = 7.0 Hz, 3 H), 0.02 (s, 3 H), 0.01 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5, 147.8, 138.8, 128.4, 127.7, 127.6, 126.7, 73.1, 72.3, 60.5, 37.7, 33.4, 33.0, 32.4, 26.1, 20.3, 18.3, 14.4, 12.7, 11.2, –4.0, –4.6.

MS (ESI): *m*/*z* (%) = 191.1 (5), 223.2 (12), 233.2 (9), 331.2 (35), 463.3 ($M + H^+$, 100).

HRMS (ESI): *m*/*z* calcd for $C_{27}H_{47}O_4Si$ [$M + H^+$]: 463.3238; found: 463.3240 (0.4 ppm).

Ethyl (–)-(4*S*,7*S*,8*R*,*E*)-9-(Benzyloxy)-7-hydroxy-2,4,8-trimethylnon-2-enoate (29)

Primary alcohol **29** was obtained from TBS-protected alcohol **S9** (483 mg, 1.0 mmol) following general procedure **A1**; colorless oil; yield: 254 mg (70%); R_f = 0.21 (hexanes–EtOAc, 80:20); $[\alpha]_D^{25}$ –6.1 (*c* 0.8, $CDCl_3$).

IR (neat): 3501, 3030, 2960, 2930, 2868, 1708, 1649, 1454, 1367, 1259, 1193, 1098, 1029, 991, 749, 699 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.26 (m, 5 H), 6.54 (dd, *J* = 1.2, 10.1 Hz, 1 H), 4.54 (d, *J* = 12.1 Hz, 1 H), 4.52 (d, *J* = 12.1 Hz, 1 H), 4.18 (q, *J* = 7.1 Hz, 2 H), 3.60 (dd, *J* = 4.0, 9.2 Hz, 1 H), 3.53–3.44 (m, 1 H), 3.45 (dd, *J* = 7.6, 9.2 Hz, 1 H), 3.38 (d, *J* = 3.7 Hz, 1 H), 2.54–2.42 (m, 1 H), 1.89–1.77 (m, 1 H), 1.83 (d, *J* = 1.2 Hz, 3 H), 1.70–1.60 (m, 1 H), 1.53–1.40 (m, 1 H), 1.40–1.31 (m, 2 H), 1.29 (t, *J* = 7.1 Hz, 3 H), 1.01 (d, *J* = 6.7 Hz, 3 H), 0.89 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5, 147.9, 137.6, 128.5, 127.8, 127.6, 126.4, 76.4, 75.2, 73.5, 60.4, 38.2, 33.5, 32.8, 32.6, 20.0, 14.3, 14.0, 12.6.

MS (ESI): *m*/*z* (%) = 223.2 (6), 285.2 (8), 331.2 (13), 349.2 ($M + H^+$, 100).

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{33}O_4$ [$M + H^+$]: 349.2373; found: 349.2366 (–2.1 ppm).

Ethyl (+)-(4*S*,7*R*,8*R*,*E*)-9-(Benzyloxy)-7-hydroxy-2,4,8-trimethylnon-2-enoate (30)

Primary alcohol **30** was obtained from TBS-protected alcohol **S10** (394 mg, 0.85 mmol) following general procedure **A1**; colorless oil; yield: 219 mg (74%); R_f = 0.41 (hexanes–EtOAc, 70:30); $[\alpha]_D^{25}$ +180 (*c* 0.7, $CDCl_3$).

IR (neat): 3505, 2960, 2932, 2868, 1707, 1649, 1454, 1367, 1257, 1194, 1099, 747, 699 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.27 (m, 5 H), 6.54 (dd, *J* = 10.1, 1.2 Hz, 1 H), 4.52 (d, *J* = 12.0 Hz, 1 H), 4.49 (d, *J* = 12.0 Hz, 1 H), 4.18 (q, *J* = 7.1 Hz, 2 H), 3.72 (dt, *J* = 4.3, 7.9 Hz, 1 H), 3.54–3.48 (m, 2 H), 2.54 (d, *J* = 4.6 Hz, 1 H), 2.57–2.45 (m, 1 H), 1.90–1.84 (m, 1 H), 1.83 (d, *J* = 1.3 Hz, 3 H), 1.55–1.46 (m, 1 H), 1.46–1.37 (m, 2 H), 1.37–1.31 (m, 1 H), 1.29 (t, *J* = 7.1 Hz, 3 H), 1.01 (d, *J* = 6.7 Hz, 3 H), 0.91 (d, *J* = 7.1 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.6, 147.8, 138.1, 128.6, 127.9, 127.7, 126.7, 74.9, 74.2, 73.6, 60.6, 38.0, 33.5, 33.3, 31.8, 20.3, 14.5, 12.7, 10.9.

MS (ESI): *m*/*z* (%) = 223.2 (5), 331.2 (11), 349.2 ($M + H^+$, 100), 371.2 ($M + Na^+$, 82), 408.3 (5), 719.4 (7).

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{33}O_4$ [$M + H^+$]: 349.2373; found: 349.2369 (–1.3 ppm); *m*/*z* calcd for $C_{21}H_{32}O_4$ + Na [$M + Na^+$]: 371.2193; found: 371.2190 (–0.7 ppm).

Ethyl (–)-(4*R*,7*S*,8*R*,*E*)-9-(Benzyloxy)-7-hydroxy-2,4,8-trimethylnon-2-enoate (31)

Primary alcohol **31** was obtained TBS-protected alcohol **S11** (677 mg, 1.5 mmol) following general procedure **A1**; colorless oil; yield: 413 mg (81%); R_f = 0.25 (hexanes–EtOAc, 80:20); $[\alpha]_D^{25}$ –33.4 (*c* 1.0, CH_2Cl_2).

IR (neat): 3493, 2960, 2931, 2868, 1707, 1648, 1454, 1367, 1258, 1098, 749, 699 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.27 (m, 5 H), 6.54 (dd, *J* = 10.1, 1.1 Hz, 1 H), 4.53 (d, *J* = 13.3 Hz, 1 H), 4.49 (d, *J* = 12.1 Hz, 1 H), 4.18 (q, *J* = 7.1 Hz, 2 H), 3.60 (dd, *J* = 9.2, 4.0 Hz, 1 H), 3.55–3.45 (m, 1 H), 3.45 (dd, *J* = 9.0, 7.9 Hz, 1 H), 3.40 (d, *J* = 3.6 Hz, 1 H), 2.56–2.44 (m, 1 H), 1.88–1.78 (m, 1 H), 1.83 (d, *J* = 1.0 Hz, 3 H), 1.54–1.41 (m, 3 H), 1.39–1.31 (m, 1 H), 1.29 (t, *J* = 7.1 Hz, 3 H), 1.01 (d, *J* = 6.6 Hz, 3 H), 0.86 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.6, 147.9, 137.9, 128.6, 128.0, 127.8, 126.7, 76.2, 75.4, 73.7, 60.5, 38.4, 33.4, 32.9, 32.5, 20.4, 14.5, 14.2, 12.8.

MS (ESI): *m*/*z* (%) = 195.1 (7), 303.2 (11), 331.2 (16), 349.2 ($M + H^+$, 100).

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{33}O_4$ [$M + H^+$]: 349.2373; found: 349.2382 (2.4 ppm).

Ethyl (–)-(4*R*,7*R*,8*R*,*E*)-9-(Benzyloxy)-7-hydroxy-2,4,8-trimethylnon-2-enoate (32)

Primary alcohol **32** was obtained from TBS-protected alcohol **S12** (139 mg, 0.30 mmol) following general procedure **A1**; colorless oil; yield: 80.5 mg (77%); R_f = 0.24 (hexanes–EtOAc, 80:20); $[\alpha]_D^{25}$ –10.6 (*c* 1.5, CH_2Cl_2).

IR (neat): 3488, 2959, 2928, 2855, 1706, 1639, 1453, 1365, 1255, 1189, 1097, 747, 697 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.27 (m, 5 H), 6.53 (dd, *J* = 10.1, 1.1 Hz, 1 H), 4.53 (d, *J* = 12.0 Hz, 1 H), 4.49 (d, *J* = 12.0 Hz, 1 H), 4.18 (q, *J* = 7.1 Hz, 2 H), 3.71 (ddd, *J* = 8.4, 6.5, 4.1 Hz, 1 H), 3.54–3.48 (m, 2 H), 2.58 (d, *J* = 4.5 Hz, 1 H), 2.54–2.43 (m, 1 H), 1.90–1.81 (m, 1 H), 1.83 (d, *J* = 1.1 Hz, 3 H), 1.68–1.60 (m, 1 H), 1.45–1.35 (m, 1 H), 1.34–1.24 (m, 2 H), 1.29 (t, *J* = 7.1 Hz, 3 H), 1.01 (d, *J* = 6.7 Hz, 3 H), 0.91 (d, *J* = 7.1 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.6, 147.9, 138.1, 128.6, 127.9, 127.8, 126.7, 74.9, 74.5, 73.6, 60.6, 38.0, 33.8, 33.6, 32.1, 20.3, 14.5, 12.8, 10.8.

MS (ESI): *m*/*z* (%) = 223.2 (12), 285.2 (7), 331.2 (18), 349.2 (M + H^+, 100), 363.3 (5).

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{33}O_4$ [M + H^+]: 349.2373; found: 349.2385 (3.2 ppm).

Ethyl (+)-(*S*)-2-{(2*S*,3*S*,6*S*)-6-[(*R*)-1-(Benzyloxy)propan-2-yl]-3-methyltetrahydro-2*H*-pyran-2-yl}-2-iodopropanoate (33a); Typical Procedure

To a solution of alcohol **29** (174 mg, 0.50 mmol) in anhyd THF (0.1 M, 5 mL) at r.t. was added successively $NaHCO_3$ (0.17 g, 2.0 mmol, 4 equiv), I_2 (0.76 g, 3.0 mmol, 6 equiv), and AgOTf (0.26 g, 1.0 mmol, 2 equiv) in a flask protected from light. Stirring is maintained for 1.5 h or until reaction was judged complete by TLC (eluent: hexanes–EtOAc, 90:10). The reaction mixture was diluted with EtOAc (10 mL), treated with brine (5 mL) and sat. aq $Na_2S_2O_3$ (5 mL), followed by separation of the organic phase at r.t. The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic fractions were dried ($MgSO_4$), filtered, and concentrated in vacuo. ^1H NMR analysis indicated a >20: 1 ratio of product 3,7-*trans*:3,7-*cis*. The crude product was purified by flash chromatography on silica gel (hexanes–EtOAc, 90:10) yielding an inseparable ~5:1 mixture of iodides; pale yellow oil; yield: 0.33 g (70%); R_f = 0.23 (hexanes–EtOAc, 90:10); $[\alpha]_D^{25}$ +30.7 (*c* 1.2, $CDCl_3$).

IR (neat): 3030, 2960, 2933, 2860, 1730, 1453, 1377, 1248, 1098, 1052, 737, 698 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.24 (m, 5 H), 4.52 (d, *J* = 12.0 Hz, 1 H), 4.48 (d, *J* = 12.0 Hz, 1 H), 4.27–4.03 (m, 2 H), 3.68 (d, *J* = 6.4 Hz, 1 H), 3.66 (ddd, *J* = 9.2, 6.7, 5.3 Hz, 1 H), 3.57 (dd, *J* = 3.6, 8.9 Hz, 1 H), 3.26 (dd, *J* = 7.4, 8.9 Hz, 1 H), 2.10 (s, 3 H), 1.75–1.41 (m, 6 H), 1.28 (t, *J* = 7.1 Hz, 3 H), 1.11 (d, *J* = 6.9 Hz, 3 H), 0.92 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.0, 138.8, 128.2, 127.5, 127.3, 80.2, 75.0, 73.1, 72.4, 61.9, 47.4, 35.7, 31.6, 28.5, 27.3, 23.9, 20.5, 13.9, 13.7.

MS (ESI): *m*/*z* (%) = 347.2 (14), 475.1 (M + H^+, 100), 492.2 (22).

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{32}IO_4$ [M + H^+]: 475.1340; found: 475.1342 (0.4 ppm).

Ethyl (+)-(*S*)-2-{(2*S*,3*S*,6*R*)-6-[(*R*)-1-(Benzyloxy)propan-2-yl]-3-methyltetrahydro-2*H*-pyran-2-yl}-2-iodopropanoate (34a)

Product **34a** was prepared from alcohol **30** (229 mg, 0.66 mmol) following the typical procedure used to prepare **33a**. ^1H NMR analysis indicated a >20:1 ratio of product 3,7-*trans*:3,7-*cis*. The crude product was purified by flash chromatography on silica gel (hexanes–EtOAc, 90:10) yielding an inseparable ~12:1 mixture of iodides; pale yellow oil; yield: 281 mg (90%); R_f = 0.59 (hexanes–EtOAc, 85:15); $[\alpha]_D^{25}$ +6.5 (*c* 1.7, $CDCl_3$).

IR (neat): 2977, 2930, 2853, 1733, 1454, 1380, 1249, 1082, 1025, 737, 698 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.26 (m, 5 H), 4.48 (d, *J* = 12.1 Hz, 1 H), 4.45 (d, *J* = 12.1 Hz, 1 H), 4.23 (dq, *J* = 10.9, 7.1 Hz, 1 H), 4.07 (dq, *J* = 10.8, 7.1 Hz, 1 H), 3.43–3.36 (m, 1 H), 3.388 (d, *J* = 9.1 Hz, 1 H), 3.392 (dd, *J* = 9.2, 5.8 Hz, 1 H), 3.26 (dd, *J* = 9.1, 6.3 Hz, 1 H), 2.05 (s, 3 H), 1.80–1.70 (m, 2 H), 1.69–1.59 (m, 1 H), 1.55–1.49 (m, 1 H), 1.46–1.34 (m, 2 H), 1.27 (t, *J* = 7.1 Hz, 3 H), 1.14 (d, *J* = 6.7 Hz, 3 H), 0.91 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.3, 138.8, 128.5, 127.63, 127.60, 86.3, 79.1, 73.2, 73.1, 61.9, 44.9, 38.9, 35.2, 33.7, 29.2, 27.0, 20.1, 13.9, 12.5.

MS (ESI): *m*/*z* (%) = 369.2 (4), 475.1 (M + H^+, 14), 497.1 (M + Na^+, 100), 498.1 (19).

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{32}IO_4$ [M + H^+]: 475.1340; found: 475.1341 (0.3 ppm); *m*/*z* calcd for $C_{21}H_{31}IO_4$ + Na [M + Na^+]: 497.1159; found: 497.1155 (–0.8 ppm).

Ethyl (–)-(*R*)-2-{(2*R*,3*R*,6*S*)-6-[(*R*)-1-(Benzyloxy)propan-2-yl]-3-methyltetrahydro-2*H*-pyran-2-yl)-2-iodopropanoate (35a)

Product **35a** was prepared from alcohol **31** (126 mg, 0.36 mmol) following the typical procedure used to prepare **33a**. ^1H NMR analysis indicated a >20:1 ratio of product 3,7-*trans*:3,7-*cis*. The crude product was purified by flash chromatography on silica gel (hexanes–EtOAc, 90:10); pale yellow oil; yield: 101 mg (59%); R_f = 0.38 (hexanes–EtOAc, 90:10); $[\alpha]_D^{25}$ –3.5 (*c* 0.7, $CDCl_3$).

IR (neat): 2929, 2849, 1732, 1453, 1378, 1249, 1189, 1074, 1025, 736, 697 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.29 (m, 5 H), 4.48 (d, *J* = 12.4 Hz, 1 H), 4.45 (d, *J* = 12.2 Hz, 1 H), 4.24–4.16 (m, 1 H), 4.12–4.02 (m, 1 H), 3.50 (dd, *J* = 9.1, 4.9 Hz, 1 H), 3.37 (d, *J* = 9.3 Hz, 1 H), 3.28–3.20 (m, 1 H), 3.22 (dd, *J* = 8.8, 7.6 Hz, 1 H), 2.04 (s, 3 H), 1.88–1.74 (m, 2 H), 1.70–1.58 (m, 1 H), 1.40–1.29 (m, 3 H), 1.26 (t, *J* = 7.1 Hz, 3 H), 1.14 (d, *J* = 6.8 Hz, 3 H), 0.90 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.3, 138.9, 128.5, 127.6, 127.5, 86.4, 80.1, 73.2, 72.5, 61.9, 44.9, 39.0, 35.2, 33.7, 28.9, 27.0, 20.1, 13.9, 13.7.

MS (ESI): *m*/*z* (%) = 475.1 (M + H^+, 100), 476.1 (22), 489.2 (10).

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{32}IO_4$ [M + H^+]: 475.1340; found: 475.1351 (2.3 ppm).

Ethyl (–)-(*R*)-2-{(2*R*,3*R*,6*R*)-6-[(*R*)-1-(Benzyloxy)propan-2-yl)-3-methyltetrahydro-2*H*-pyran-2-yl)-2-iodopropanoate (36a)

Product **36a** was prepared from alcohol **32** (72 mg, 0.21 mmol) following the typical procedure used to prepare **33a**. ^1H NMR analysis indicated a >20:1 ratio of product 3,7-*trans*:3,7-*cis*. The crude product was purified by flash chromatography on silica gel (hexanes–EtOAc, 90:10) yielding an inseparable ~4:1 mixture of iodides; pale yellow oil; yield: 63 mg (64%); R_f = 0.42 (hexanes–EtOAc, 90:10); $[\alpha]_D^{25}$ –4.2 (*c* 0.6, $CDCl_3$).

IR (neat): 2953, 2922, 2855, 1718, 1453, 1359, 1246, 1092, 1049, 1013, 721, 697 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.26 (m, 5 H), 4.51 (d, *J* = 11.9 Hz, 1 H), 4.42 (d, *J* = 11.9 Hz, 1 H), 4.29–4.20 (m, 1 H), 4.20–4.13 (m, 1 H), 3.77 (d, *J* = 5.6 Hz, 1 H), 3.72 (dt, *J* = 4.2, 7.4 Hz, 1 H), 3.36 (dd, *J* = 9.1, 5.7 Hz, 1 H), 3.27 (dd, *J* = 9.1, 5.8 Hz, 1 H), 2.17 (s, 3 H), 1.99–1.90 (m, 1 H), 1.87–1.66 (m, 2 H), 1.65–1.57 (m, 1 H), 1.55–1.45 (m, 2 H), 1.30 (t, *J* = 7.1 Hz, 3 H), 1.13 (d, *J* = 6.9 Hz, 3 H), 0.96 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3, 138.7, 128.5, 127.7, 127.6, 80.8, 75.3, 73.3, 73.1, 62.1, 47.6, 36.5, 30.9, 28.8, 27.7, 24.2, 20.9, 14.0, 13.5.

MS (ESI): *m*/*z* (%) = 347.2 (7), 475.1 (M + H^+, 100), 476.1 (23), 489.2 (5).

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{32}IO_4$ [M + H$^+$]: 475.1340; found: 475.1344 (1.0 ppm).

Ethyl (+)-(*S*)-2-{(2*S*,3*S*,6*S*)-6-[(*R*)-1-(Benzyloxy)propan-2-yl]-3-methyltetrahydro-2*H*-pyran-2-yl}propanoate (3a)

Product **3a** was obtained from iodide product **33a** (39 mg, 0.08 mmol) following general procedure **A2**. ^{1}H NMR analysis of crude product indicated a >20:1 ratio of product 7,8-*anti* (**3a**):7,8-*syn* (**3b**); colorless oil; yield: 17.8 mg (62%); R_f = 0.29 (hexanes–EtOAc, 90:10); $[\alpha]_D^{25}$ +43.9 (*c* 1.5, $CDCl_3$).

IR (neat): 3030, 2969, 2933, 2860, 1735, 1552, 1455, 1376, 1338, 1267, 1251, 1208, 1172, 1110, 1047, 1028, 737, 698 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.23 (m, 5 H), 4.52 (d, *J* = 12.4 Hz, 1 H), 4.50 (d, *J* = 12.7 Hz, 1 H), 4.14–4.02 (m, 2 H), 3.64 (dd, *J* = 4.3, 9.1 Hz, 1 H), 3.56 (dd, *J* = 8.3, 3.6 Hz, 1 H), 3.54 (dt, *J* = 3.6, 7.4 Hz, 1 H), 3.17 (t, *J* = 8.8 Hz, 1 H), 2.96 (dq, *J* = 6.9, 8.4 Hz, 1 H), 2.03–1.94 (m, 1 H), 1.79–1.63 (m, 2 H), 1.62–1.52 (m, 1 H), 1.50–1.42 (m, 1 H), 1.42–1.34 (m, 1 H), 1.22 (t, *J* = 7.1 Hz, 3 H), 1.09 (d, *J* = 6.9 Hz, 3 H), 1.05 (d, *J* = 6.9 Hz, 3 H), 0.92 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.7, 138.9, 128.3, 127.5, 127.3, 79.8, 73.0, 72.8, 72.7, 60.2, 40.9, 36.7, 28.3, 25.4, 23.5, 18.4, 14.4, 14.2, 13.8.

MS (ESI): *m*/*z* (%) = 349.2 (M + H$^+$, 100).

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{33}O_4$ [M + H$^+$]: 349.2373; found: 349.2363 (–2.9 ppm).

Ethyl (–)-(*S*)-2-{(2*S*,3*S*,6*R*)-6-[(*R*)-1-(Benzyloxy)propan-2-yl]-3-methyltetrahydro-2*H*-pyran-2-yl}propanoate (4a)

Product **4a** was obtained from iodide product **34a** (23 mg, 0.05 mmol) following general procedure **A2**. ^{1}H NMR analysis of crude product indicated a >20:1 ratio of product 7,8-*anti* (**4a**):7,8-*syn* (**4b**); colorless oil; yield: 16 mg (96%); R_f = 0.16 (hexanes–EtOAc, 95:5); $[\alpha]_D^{25}$ –5.0 (*c* 0.2, $CDCl_3$).

IR (neat): 2973, 2933, 2852, 1736, 1456, 1376, 1248, 1182, 1091, 1059, 736, 698 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.27 (m, 5 H), 4.51 (d, *J* = 12.1 Hz, 1 H), 4.48 (d, *J* = 12.1 Hz, 1 H), 4.18–4.06 (m, 2 H), 3.50 (dd, *J* = 8.9, 6.9 Hz, 1 H), 3.35 (ddd, *J* = 13.3, 4.7, 3.6 Hz, 1 H), 3.32 (dd, *J* = 9.0, 6.1 Hz, 1 H), 3.06 (dd, *J* = 9.9, 2.5 Hz, 1 H), 2.72 (dq, *J* = 2.5, 7.0 Hz, 1 H), 1.84–1.73 (m, 2 H), 1.64–1.55 (m, 2 H), 1.47–1.40 (m, 1 H), 1.40–1.32 (m, 1 H), 1.25 (t, *J* = 7.1 Hz, 3 H), 1.18 (d, *J* = 7.1 Hz, 3 H), 0.91 (d, *J* = 6.9 Hz, 3 H), 0.84 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.9, 139.0, 128.5, 127.7, 127.6, 85.5, 78.1, 73.23, 73.19, 60.1, 42.2, 38.8, 33.4, 33.1, 29.0, 17.6, 14.5, 13.9, 12.1.

MS (ESI): *m*/*z* (%) = 349.2 (M + H$^+$, 100), 350.2 (22), 366.3 (8), 371.2 (M + Na$^+$, 93), 372.2 (20).

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{33}O_4$ [M + H$^+$]: 349.2373; found: 349.2372 (–0.5 ppm); *m*/*z* calcd for $C_{21}H_{32}O_4$ + Na [M + Na$^+$]: 371.2193; found: 371.2192 (–0.3 ppm).

Ethyl (+)-(*R*)-2-{(2*R*,3*R*,6*S*)-6-[(*R*)-1-(Benzyloxy)propan-2-yl]-3-methyltetrahydro-2*H*-pyran-2-yl}propanoate (5a)

Product **5a** was obtained from iodide product **35a** (21 mg, 0.04 mmol) following general procedure **A2**. ^{1}H NMR analysis of crude product indicated a >20:1 ratio of product 7,8-*anti* (**5a**):7,8-*syn* (**5b**); colorless oil; yield: 12 mg (76%); R_f = 0.38 (hexanes–EtOAc, 95:5); $[\alpha]_D^{25}$ +2.1 (*c* 1.1, $CDCl_3$).

IR (neat): 2958, 2926, 2852, 1734, 1456, 1376, 1248, 1200, 1181, 1085, 910, 736, 650 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.24 (m, 5 H), 4.50 (d, *J* = 12.1 Hz, 1 H), 4.47 (d, *J* = 12.3 Hz, 1 H), 4.16–4.06 (m, 2 H), 3.54 (dd, *J* = 9.0, 4.8 Hz, 1 H), 3.40 (dd, *J* = 9.1, 6.7 Hz, 1 H), 3.19 (ddd, *J* = 10.9, 7.1, 1.9 Hz, 1 H), 3.07 (dd, *J* = 9.9, 2.7 Hz, 1 H), 2.72 (dq, *J* = 2.6, 6.9 Hz, 1 H), 1.91–1.81 (m, 1 H), 1.78 (ddd, *J* = 13.0, 6.8, 3.4 Hz, 1 H), 1.65–1.49 (m, 1 H), 1.31–1.20 (m, 3 H), 1.24 (t, *J* = 7.1 Hz, 3 H), 1.18 (d, *J* = 7.1 Hz, 3 H), 0.93 (d, *J* = 6.9 Hz, 3 H), 0.83 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.9, 139.1, 128.4, 127.6, 127.5, 85.5, 79.3, 73.1, 72.6, 60.1, 42.2, 39.0, 33.4, 33.0, 28.7, 17.6, 14.5, 13.74, 13.69.

MS (ESI): *m*/*z* (%) = 349.2 (M + H$^+$, 20), 371.2 (M + Na$^+$, 100), 372.2 (20).

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{33}O_4$ [M + H$^+$]: 349.2373; found: 349.2365 (–2.3 ppm); *m*/*z* calcd for $C_{21}H_{32}O_4$ + Na [M + Na$^+$]: 371.2193; found: 371.2180 (–3.5 ppm).

Ethyl (–)-(*R*)-2-{(2*R*,3*R*,6*R*)-6-[(*R*)-1-(Benzyloxy)propan-2-yl]-3-methyltetrahydro-2*H*-pyran-2-yl)propanoate (6a)

Product **6a** was obtained from iodide product **36a** (32 mg, 0.07 mmol) following general procedure **A2**. ^{1}H NMR analysis of crude product indicated a >20:1 ratio of product 7,8-*anti* (**6a**):7,8-*syn* (**6b**); colorless oil; yield: 19 mg (82%); R_f = 0.25 (hexanes–EtOAc, 95:5); $[\alpha]_D^{25}$ –10.6 (*c* 0.3, $CDCl_3$).

IR (neat): 2970, 2931, 2859, 1735, 1455, 1378, 1266, 1250, 1206, 1174 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.27 (m, 5 H), 4.51 (d, *J* = 12.1 Hz, 1 H), 4.44 (d, *J* = 12.1 Hz, 1 H), 4.17–4.04 (m, 2 H), 3.61 (ddd, *J* = 9.3, 6.5, 3.0 Hz, 1 H), 3.54 (dd, *J* = 9.1, 2.8 Hz, 1 H), 3.41 (dd, *J* = 9.1, 4.6 Hz, 1 H), 3.28 (dd, *J* = 9.1, 7.1 Hz, 1 H), 3.02 (dq, *J* = 9.0, 6.9 Hz, 1 H), 1.91–1.82 (m, 1 H), 1.79–1.72 (m, 1 H), 1.72–1.66 (m, 1 H), 1.65–1.56 (m, 1 H), 1.44–1.35 (m, 2 H), 1.24 (t, *J* = 7.2 Hz, 3 H), 1.11 (d, *J* = 6.9 Hz, 3 H), 1.08 (d, *J* = 6.9 Hz, 3 H), 0.99 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.0, 138.9, 128.4, 127.7, 127.6, 80.1, 73.3, 73.2, 72.7, 60.3, 41.1, 37.6, 27.9, 25.4, 23.7, 18.6, 14.7, 14.4, 13.3.

MS (ESI): *m*/*z* (%) = 349.2 (M + H$^+$, 35), 371.2 (M + Na$^+$, 100), 372.2 (24).

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{33}O_4$ [M + H$^+$]: 349.2373; found: 349.2380 (1.8 ppm); *m*/*z* calcd for $C_{21}H_{32}O_4$ + Na [M + Na$^+$]: 371.2193; found: 371.2199 (1.6 ppm).

Ethyl (+)-(*R*)-2-{(2*S*,3*S*,6*S*)-6-[(*R*)-1-(Benzyloxy)propan-2-yl]-3-methyltetrahydro-2*H*-pyran-2-yl}propanoate (3b)

Product **3b** was obtained from iodide product **33a** (52 mg, 0.11 mmol) following general procedure **A3**. ^{1}H NMR analysis of crude product indicated a >20:1 ratio of product 7,8-*syn* (**3b**):7,8-*anti* (**3a**); colorless oil; yield: 15.1 mg (40%); R_f = 0.35 (hexanes–EtOAc, 90:10); $[\alpha]_D^{25}$ +16.7 (*c* 1.5, $CDCl_3$).

IR (neat): 3030, 2957, 2930, 2860, 1731, 1553, 1456, 1375, 1249, 1181, 1150, 1100, 1073, 1046, 735, 698 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.24 (m, 5 H), 4.51 (d, *J* = 12.3 Hz, 1 H), 4.49 (d, *J* = 12.8 Hz, 1 H), 4.20–4.03 (m, 2 H), 3.65 (dd, *J* = 5.2, 7.4 Hz, 1 H), 3.55 (dd, *J* = 3.9, 8.9 Hz, 1 H), 3.45 (ddd, *J* = 4.1, 7.4, 8.5 Hz, 1 H), 3.36 (dd, *J* = 6.9, 8.9 Hz, 1 H), 2.89 (hept, *J* = 7.0 Hz, 1 H), 2.10–2.00 (m, 1 H), 1.78–1.70 (m, 1 H), 1.65–1.46 (m, 3 H), 1.43–1.34 (m, 1 H), 1.25 (t, *J* = 7.1 Hz, 3 H), 1.15 (d, *J* = 7.0 Hz, 3 H), 0.99 (d, *J* = 6.8 Hz, 3 H), 0.93 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.3, 138.8, 128.3, 127.5, 127.3, 78.2, 73.1, 72.4, 72.3, 60.3, 40.6, 35.8, 30.4, 25.9, 24.1, 18.1, 14.2, 13.9, 11.9.

MS (ESI): *m/z* (%) = 303.2 (5), 349.2 (M + H^+, 100).

HRMS (ESI): *m/z* calcd for $C_{21}H_{33}O_4$ [M + H^+]: 349.2373; found: 349.2364 (–2.6 ppm).

Ethyl (+)-(*R*)-2-{(2*S*,3*S*,6*R*)-6-[(*R*)-1-(Benzyloxy)propan-2-yl)-3-methyltetrahydro-2*H*-pyran-2-yl)propanoate (4b)

Product **4b** was obtained from iodide product **34a** (23 mg, 0.05 mmol) following general procedure **A3**. ^{1}H NMR analysis of crude product indicated a >20:1 ratio of product 7,8-*syn* (**4b**):7,8-*anti* (**4a**); colorless oil; yield: 13 mg (79%); R_f = 0.26 (hexanes–EtOAc, 95:5); $[\alpha]_D^{25}$ +27 (*c* 0.3, $CDCl_3$).

IR (neat): 2927, 2853, 1739, 1455, 1200, 1090, 1025, 736, 698 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.27 (m, 5 H), 4.48 (d, *J* = 12.1 Hz, 1 H), 4.43 (d, *J* = 12.0 Hz, 1 H), 4.14–4.04 (m, 2 H), 3.44 (dd, *J* = 9.9, 3.2 Hz, 1 H), 3.41 (dd, *J* = 9.1, 6.1 Hz, 1 H), 3.32–3.29 (m, 1 H), 3.28 (dd, *J* = 9.0, 6.4 Hz, 1 H), 2.64 (dq, *J* = 3.2, 7.1 Hz, 1 H), 1.83–1.71 (m, 2 H), 1.51–1.31 (m, 4 H), 1.23 (t, *J* = 7.2 Hz, 3 H), 1.10 (d, *J* = 7.1 Hz, 3 H), 0.91 (d, *J* = 6.9 Hz, 3 H), 0.81 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.2, 138.9, 128.5, 127.7, 127.5, 83.6, 78.4, 73.3, 73.2, 60.4, 41.7, 38.8, 33.1, 32.2, 29.3, 17.2, 14.5, 12.4, 9.0.

MS (ESI): *m/z* (%) = 227.0 (12), 349.2 (M + H^+, 30), 371.2 (M + Na^+, 100), 372.2 (23).

HRMS (ESI): *m/z* calcd for $C_{21}H_{33}O_4$ [M + H^+]: 349.2373; found: 349.2381 (2.2 ppm); calcd for $C_{21}H_{32}O_4$ + Na [M + Na^+]: 371.2193; found: 371.2201 (2.1 ppm).

Ethyl (–)-(*S*)-2-{(2*R*,3*R*,6*S*)-6-[(*R*)-1-(Benzyloxy)propan-2-yl]-3-methyltetrahydro-2*H*-pyran-2-yl)propanoate (5b)

Product **5b** was obtained from iodide product **35a** (21 mg, 0.04 mmol) following general procedure **A3**. ^{1}H NMR analysis of crude product indicated a >20:1 ratio of product 7,8-*syn* (**5b**):7,8-*anti* (**5a**); colorless oil; yield: 11 mg (71%); R_f = 0.36 (hexanes–EtOAc, 90:10); $[\alpha]_D^{25}$ –71 (*c* 0.2, $CDCl_3$).

IR (neat): 2958, 1919, 2850, 1739, 1455, 1378, 1249, 1200, 1089, 1073, 1027 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.26 (m, 5 H), 4.47 (d, *J* = 12.8 Hz, 1 H), 4.44 (d, *J* = 12.3 Hz, 1 H), 4.08 (q, *J* = 7.1 Hz, 2 H), 3.55 (dd, *J* = 9.1, 4.7 Hz, 1 H), 3.42 (dd, *J* = 9.9, 3.3 Hz, 1 H), 3.26 (dd, *J* = 9.1, 7.3 Hz, 1 H), 3.17–3.10 (m, 1 H), 2.63 (dq, *J* = 3.3, 7.0 Hz, 1 H), 1.85–1.76 (m, 1 H), 1.64–1.56 (m, 2 H), 1.33–1.16 (m, 3 H), 1.21 (t, *J* = 7.1 Hz, 3 H), 1.10 (d, *J* = 7.1 Hz, 3 H), 0.91 (d, *J* = 6.9 Hz, 3 H), 0.81 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.2, 139.1, 128.4, 127.6, 127.5, 83.7, 79.5, 73.1, 72.7, 60.4, 41.7, 39.0, 33.1, 32.2, 29.2, 17.2, 14.5, 13.9, 9.1.

MS (ESI): *m/z* (%) = 171.1 (5), 349.2 (M + H^+, 12), 371.2 (M + Na^+, 100), 397.2 (18).

HRMS (ESI): *m/z* calcd for $C_{21}H_{33}O_4$ [M + H^+]: 349.2373; found: 349.2370 (–1.1 ppm); *m/z* calcd for $C_{21}H_{32}O_4$ + Na [M + Na^+]: 371.2193; found: 371.2191 (–0.5 ppm).

Ethyl (–)-(*S*)-2-{(2*R*,3*R*,6*R*)-6-[(*R*)-1-(Benzyloxy)propan-2-yl)-3-methyltetrahydro-2*H*-pyran-2-yl)propanoate (6b)

Product **6b** was obtained from iodide product **36a** (35 mg, 0.07 mmol) following general procedure **A3**. ^{1}H NMR analysis of crude product indicated a 6.4:1 ratio of product 7,8-*syn* (**6b**):7,8-*anti* (**6a**), which could be separated by flash chromatography on silica gel (hexanes–EtOAc, 95:5); colorless oil; yield: 23 mg (79%); R_f = 0.31 (hexanes–EtOAc, 95:5); $[\alpha]_D^{25}$ –5.3 (*c* 0.3, $CDCl_3$).

IR (neat): 2959, 2924, 2853, 1732, 1455, 1376, 1260, 1179, 1093, 1028 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.39–7.27 (m, 5 H), 4.50 (d, *J* = 11.9 Hz, 1 H), 4.44 (d, *J* = 11.9 Hz, 1 H), 4.20–4.04 (m, 2 H), 3.61 (dd, *J* = 7.8, 4.6 Hz, 1 H), 3.52 (dt, *J* = 2.9, 7.6 Hz, 1 H), 3.44 (dd, *J* = 9.0, 6.1 Hz, 1 H), 3.30 (dd, *J* = 9.1, 5.7 Hz, 1 H), 2.94 (hept, *J* = 7.3 Hz, 1 H), 1.97 (dt, *J* = 12.5, 6.3 Hz, 1 H), 1.76 (dt, *J* = 11.6, 6.4 Hz, 1 H), 1.67 (dd, *J* = 17.8, 9.6 Hz, 1 H), 1.59–1.49 (m, 1 H), 1.45–1.36 (m, 2 H), 1.25 (t, *J* = 7.1 Hz, 3 H), 1.16 (d, *J* = 6.9 Hz, 3 H), 1.01 (d, *J* = 6.9 Hz, 3 H), 0.97 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.5, 138.7, 128.5, 127.7, 127.6, 78.5, 73.3, 73.1, 72.0, 60.5, 40.7, 36.4, 30.3, 26.1, 24.4, 18.3, 14.3, 13.0, 12.4.

MS (ESI): *m/z* (%) = 338.3 (12), 349.2 (M + H^+, 19), 371.2 (M + Na^+, 100).

HRMS (ESI): *m/z* calcd for $C_{21}H_{33}O_4$ [M + H^+]: 349.2373; found: 349.2373 (–0.1 ppm); *m/z* calcd for $C_{21}H_{32}O_4$ +Na [M + Na^+]: 371.2193; found: 371.2191 (–0.4 ppm).

Supporting Information

Supporting Information for this article is available online at http://www.thieme-connect.com/ ejournals/toc/synthesis.

Acknowledgment

The authors wish to express their gratitude to the Natural Sciences and Engineering Research Council of Canada (NSERC) and to the Fonds Québécois de la Recherche sur la Nature et les Technologies (FQRNT) for their financial support. Fellowship support from NSERC PGS D and FQRNT B2 (F.G.) is also gratefully acknowledged.

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