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A Study of Exocyclic Radical Reductions of Polysubstituted Tetrahydropyrans

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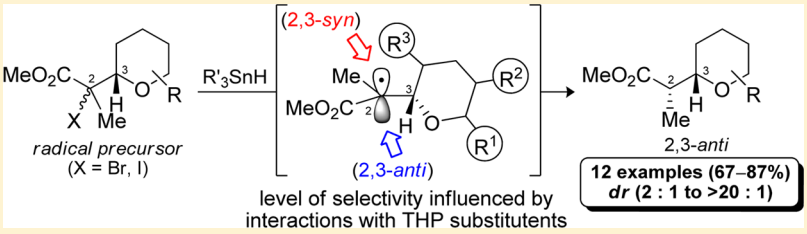
Supporting Information



ABSTRACT: Exocyclic radical reductions were thoroughly investigated in the context of the synthesis of polysubstituted tetrahydropyrans, which are found in numerous macrolides. The radical precursors studied herein were generated by tandem cycloetherification and iodoetherification reactions or, alternatively, by semicyclic acetals substitutions. DFT calculations (BHandHLYP/TZVP) performed at the transition-state level for the hydrogen radical delivery are in good accordance with the experimental data and enabled the identification of important conformational factors that govern the selectivities obtained. This study demonstrates that both the preferred reactive conformation of the radical and steric interactions with the incoming hydride have to be considered in order to fully rationalize the levels of diastereoselection generated in acyclic free-radical processes.

INTRODUCTION

Biologically relevant ionophores,[1] such as zincophorin (**1a**),[2] salinomycin (**1b**), and narasin (**1c**),[3] have attracted the attention of many groups interested in their synthesis and biological evaluation.[4] These molecules feature complex polypropionate motifs and substituted tetrahydropyranyl (THP) fragments for which different synthetic strategies were developed (Figure 1).[5]

One of the original aspects of the stereoselective strategies that our group has developed is the use of hydrogen transfers to acyclic carbon-centered free radical intermediates. These reactions allowed us to generate most of the stereogenic centers bearing a secondary methyl group present in ionophores.[6] As a requirement for the reaction to be stereoselective, the radical must be flanked on one side by an ester and, on the other, by a stereogenic center bearing an electron-withdrawing group (i.e., alkoxy groups in the context of polypropionate synthesis). We were particularly interested in the high 2,3-*anti* selectivities reached when performing the hydrogen-transfer reactions on substrates embedding the vicinal C3−O bond within a ring (THP or THF). The enhancement of selectivity obtained with these systems was referred as the *exocyclic effect* (**I**, Scheme 1).[7] The complementary 2,3-*syn* isomer was achieved by performing the radical reduction in presence of a bidentate Lewis acid (**II**).[6a]

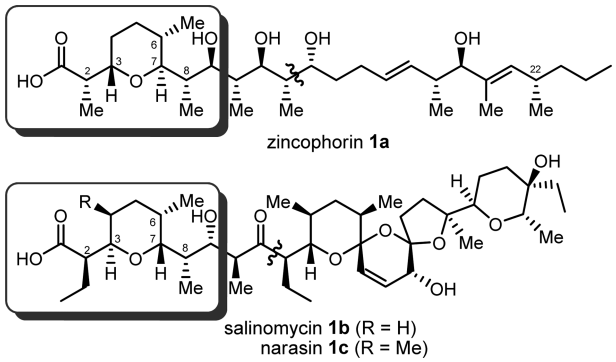


Figure 1. Structure of zincophorin (**1a**), salinomycin (**1b**), and narasin (**1c**).

Their common radical precursors at C2 (X = Br, I) are obtained efficiently by the addition of enoxysilanes **2** to acetals or from an aldehyde by cycloetherification[8] (**III** or **IV**, Scheme 1).[6c,d] Alternatively, C4-methyl-substituted cyclic precursors were

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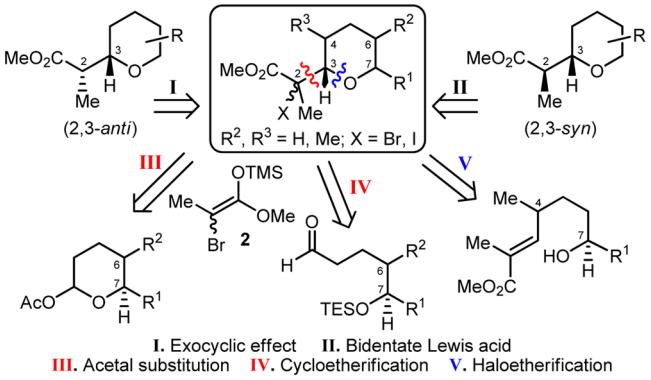
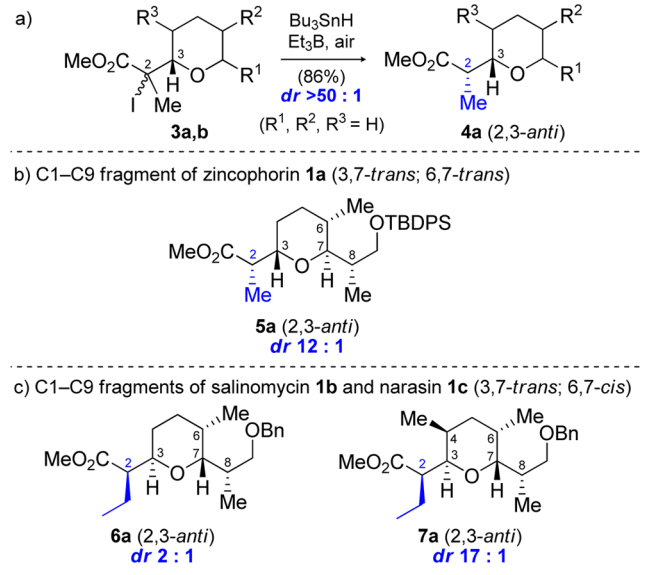
Scheme 1. Strategies To Generate Polysubstituted THP Bearing a Radical Precursor at C2 for Exocyclic Hydrogen-Transfer Reactions



accessed by diastereoselective iodoetherification of α,β-unsaturated olefins (**V**).[6e]

Excellent diastereoselectivities were routinely observed, as exemplified by the reduction of tertiary halides **3a,b** (Scheme 2a).[7a,b] In the course of our synthetic efforts toward ionophores

Scheme 2. Exocyclic Radical Reductions of C1−C9 Fragments of Zincophorin (5a), Salinomycin (6a), and Narasin (7a).[9]



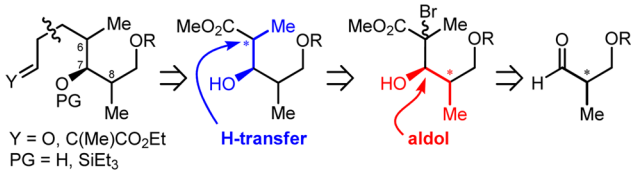
(**1a−c**), however, we observed that certain THP substitution patterns had a dramatic impact on the stereochemical outcome of the radical reduction at C2. A somewhat lower 2,3-*anti* selectivity was obtained for the hydrogen transfer leading to the C1−C9 zincophorin fragment **5a** (Scheme 2b),[6d] while a significant loss of 2,3-*anti* selectivity was noted with the corresponding fragment leading to salinomycin **6a** (Scheme 2c). The presence of an additional methyl group at C4 on the latter scaffold led to the recovery of the 2,3-*anti* selectivity, which enabled the stereoselective formation of the C1−C9 fragment of narasin **7a** (Scheme 2c).[6c]

The impact of these different THP substitutions on the outcome of exocyclic radical reductions was challenging to rationalize. We first postulated that the various substituents on the THP (i.e., at C3, C4, C6, and C7)[9] could, in certain cases, favor positioning of the C2-chain bearing the carbon-centered free radical in the axial conformation, an orientation that was demonstrated experimentally in rigidified systems to provide low selectivities.[10] Alternatively, destabilizing interactions between cyclic substituents and the incoming hydride in the anti- and syn-predictive transition states (TS) could also influence the difference in energy and, thus, the level of selectivity under kinetic control. To further investigate these hypotheses, we embarked on the synthesis of several THP precursors bearing different substitution patterns to evaluate their impact on the outcome of the exocyclic reduction. A transition state DFT analysis (BHandHLYP/TZVP) was also initiated to better rationalize the stereochemical outcome of free-radical reduction on polysubstituted THP precursors.

RESULTS AND DISCUSSION

Synthesis of the Radical Precursors. Radical precursors that would lead to isomers of the C1−C9 fragment of zincophorin (**1a**) were first synthesized.[6c−e] These tertiary halides could be obtained from a corresponding propionate sequence, which were generated using a sequential strategy involving Mukaiyama aldol and hydrogen-transfer reactions from a β-hydroxy-α-methyl aldehyde.[11] The stereochemical outcome of the acyclic radical reaction step was controlled by the nature of the Lewis acids, as illustrated in Scheme 3. Various THP analogues with different substitutions at C7 were also synthesized by varying the nature of the starting aldehyde (R^1).

Scheme 3. Lewis Acid-Controlled Synthesis of Acyclic Propionates



Stereochemistry / Reaction	*anti*	*syn*
Aldolization	$TiCl_4$ $TiCl_3(O\textit{i}Pr)$ $MgBr_2{\cdot}OEt_2$	$BF_3{\cdot}OEt_2$
Hydrogen transfer	Bu_2BOTf Et_2BOTf	$AlMe_3$ $MgBr_2{\cdot}OEt_2$

A representative example for the synthesis of THP radical precursors **14a,b**, corresponding to the C6-isomer of zincophorin **1a**, is presented in Scheme 4.[9] β-Silyloxy aldehyde **8** was first reacted with enoxysilane **2** in the presence of $BF_3{\cdot}OEt_2$ at −78 °C to afford the 7,8-*syn* relationship selectively.[6d] A mixture of tertiary bromides **9a,b** was then submitted to the hydrogen-transfer reaction in the presence of $AlMe_3$ to take advantage of the *endocyclic* stereocontrol,[6a] which provided the 6,7-*syn* isomer **10**. The radical reaction was initiated with Et_3B at −78 °C.[12] The secondary alcohol **10** was then protected by a TES group before reduction of the ester and oxidation of the resulting alcohol to aldehyde **11**. A Wittig olefination using the appropriate triphenylphosphoranylidene was then realized to provide the α,β-unsaturated ester. The olefin was hydrogenated and the ester transformed to the corresponding aldehyde **12**. The tetrahydropyran was prepared using enoxysilane **2** and Evans' procedure[8] with $BiBr_3$, yielding a mixture of C2 tertiary bromides **13a,b** with a 3,7-*trans* stereochemistry selectively. Tertiary bromides **14a,b** were obtained after cleavage of TBDPS on the

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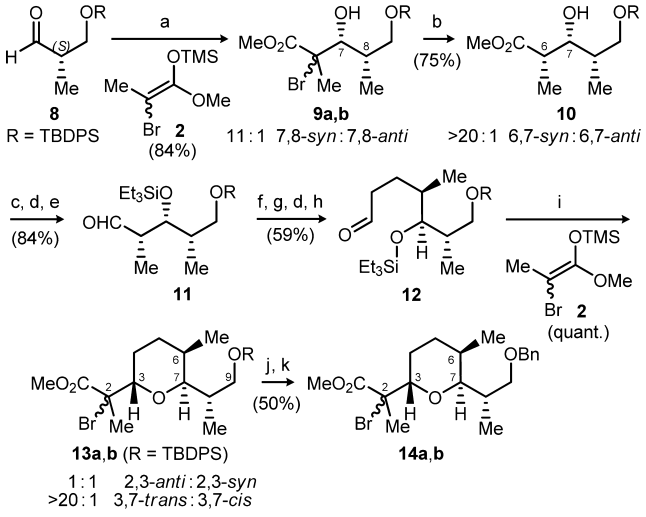
Scheme 4. Synthesis of Radical Precursors 14a,b as the C6-Epimer of Zincophorin C1−C9 Fragment[a]



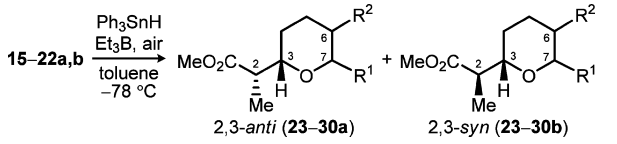
[a]Reactions and conditions: (a) $BF_3{\cdot}OEt_2$, **2**, CH_2Cl_2, −78 °C; (b) $AlMe_3$, CH_2Cl_2, −78 °C then Bu_3SnH, Et_3B, air, CH_2Cl_2, −78 °C; (c) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; (d) DIBAL-H, CH_2Cl_2, −40 °C; (e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C; (f) $Ph_3PC(H)$=CO_2Me, toluene, reflux; (g) H_2, Pd/C, EtOAc, rt; (h) DMP, $NaHCO_3$, CH_2Cl_2, rt; (i) $BiBr_3$, **2**, CH_2Cl_2/MeCN, −78 °C; (j) HF·py, THF, 0 °C; (k) BnOC=$NHCCl_3$, TfOH, *c*-Hex/CH_2Cl_2, 0 °C.

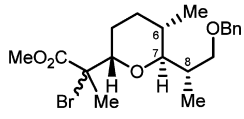
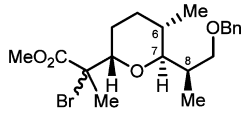
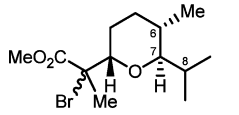
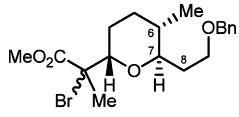
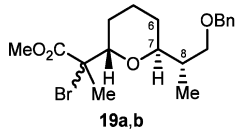
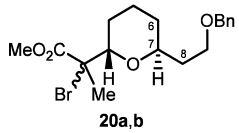
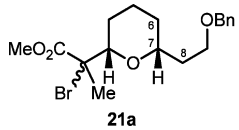
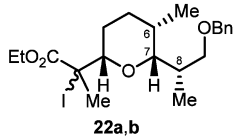
oxygen at C9 with HF·pyridine and protection by a benzyl group. As mentioned previously, other analogues were prepared using a similar reaction sequence starting either from (*R*)-Roche ester, isobutyraldehyde, or *β*-hydroxyaldehyde. Detailed schemes for the syntheses of the different radical precursors studied are provided in the Experimental Section.

Reductions of Radical Precursors Analogues of the C1−C9 Subunit of Zincophorin. Radical precursors **15**−**22a,b** were first examined (Table 1). Radical reductions were performed at −78 °C in toluene in the presence of Ph_3SnH using Et_3B as the radical chain initiator. Benzyloxy-protected precursor **15a,b** provided a marginal increase in 2,3-*anti* selectivity, as compared to the corresponding silyl-protected THP **5a** (entry 1, Table 1 and Scheme 2b). Inversion of the configuration at C8 (entry 2) and removal of the C9-benzyloxy group (entry 3) or of the C8-methyl group (entry 4) did not significantly influence the observed 2,3-*anti* selectivity. Substrates without the C6-methyl group also provided comparable levels of selectivity (entries 5 and 6). The high induction obtained with 3,7-*cis* substrates **21a** and **22a,b** is, however, noteworthy (entries 7 and 8) and indicates that the 3,7-stereochemical relation has an impact on the levels of inductions in exocyclic reductions (entry 1 vs 8).

THP precursors bearing a 6,7-*cis* relationship were found to undergo radical reduction with markedly lower anti-inductions (Table 2). Indeed, a considerable loss of diastereoselectivity was first observed with 6,7-*cis* THPs fragments **31a,b** (entry 1). The epimer at C8 of the latter (**14a,b**, entry 2) and fragment **32a,b** lacking the C9-benzyloxy group (entry 3), furnished comparable modest selectivities, while THP analogue **33a,b** lacking a methyl group at C8 (entry 4) led to a significant increase in 2,3-*anti* product selectivity. It is notable from these experimental results that structural modifications at C6 and C8 influence greatly the levels of diastereoselectivity, while being distant to the reacting carbon-centered free radical at C2.

Table 1. Radical Reductions of THP Analogues 15−22a,b



Entry	Substrate[a]	*dr*[b] (anti : syn)	Yield[c] (%)
1	 **15a,b**	15 : 1 (**23a** : **23b**)	81
2	 **16a,b**	16 : 1 (**24a** : **24b**)	79
3	 **17a,b**	17 : 1 (**25a** : **25b**)	76
4	 **18a,b**	17 : 1 (**26a** : **26b**)	70
5	 **19a,b**	12 : 1 (**27a** : **27b**)	75
6	 **20a,b**	14 : 1 (**28a** : **28b**)	82
7	 **21a**	>20 : 1 (**29a** : **29b**)	83[d]
8	 **22a,b**	>20 : 1 (**30a** : **30b**)	87

[a]See the Experimental Section for details on the synthesis of radical precursors. [b]Product ratios were determined by ^1H NMR analysis of the crude reaction mixture. [c]Yields of isolated products. [d]The yield reported was obtained with Bu_3SnH, which provided the same selectivity as Ph_3SnH.

DFT CALCULATIONS FOR THE REDUCTION OF THP RADICAL PRECURSORS

Description of the Computational Method. Geometry optimizations of modeled compounds were realized using standard gradient techniques and tight SCF convergence as implemented in Gaussian 09[13] with the BHandHLYP functional,[14] which was demonstrated[15] to be well suited for radical

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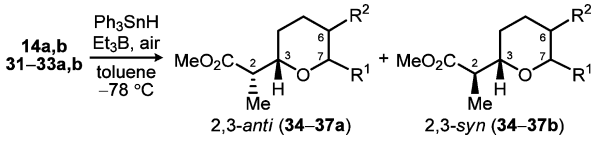
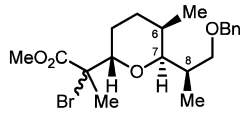
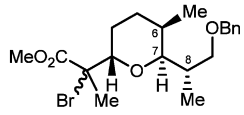
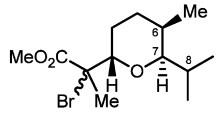
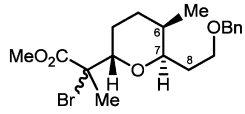
Table 2. Radical Reductions of 6,7-*cis*-THP Analogues 14a,b and 31−33a,b



Entry	Substrate[a]	*dr*[b] (anti : syn)	Yield[c] (%)
1[d]	 **31a,b**	2 : 1 **(34a : 34b)**	83
2	 **14a,b**	5 : 1 **(35a : 35b)**	68
3	 **32a,b**	5 : 1 **(36a : 36b)**	67
4	 **33a,b**	15 : 1 **(37a : 37b)**	85

[a]See the Experimental Section for details on the synthesis of radical precursors. [b]Product ratios were determined by ^{1}H NMR analysis of the crude reaction mixture. [c]Yields of isolated products. [d]The enantiomer is depicted for clarity.

systems.[16] Transition-state calculations were performed with Me_3SnH, which was demonstrated to provide selectivities comparable to other hydrides.[10] The effective core potential LANL2DZ (Hay and Wadt)[17] supplemented with a single set of *d*-type polarization functions was used for tin ($d(\zeta)_{Sn}$ = 0.20),[16b,d,18] in combination with the valence triple-ζ TZVP basis set[19] for all other atoms. The difference in Gibbs free energies of activation ($\Delta\Delta G^{\ddagger}$) was calculated for each reaction between the lowest energy anti- and syn-predictive TS after consideration of all conformers, and the ratio of products was calculated from eq 1. Gibbs free energies in solution were determined from geometry optimizations using the IEFPCM implicit solvation model.[20] More details concerning the computational method used are provided in the Experimental Section and in the Supporting Information.

$$\Delta\Delta G^{\ddagger} = RT \ln \frac{[2,3\text{-}anti]}{[2,3\text{-}syn]} \quad (1)$$

DFT Study of Radical Intermediates Conformers. A previously reported DFT study (BHandHLYP/TZVP level) by our group demonstrated that the experimental diastereoselectivity observed for the reduction of carbon-centered radicals, vicinal to an ester and a stereogenic center bearing an alkoxy group, correlated with the difference in Gibbs free energy between TS **A** and TS **B** (Figure 2).[10] Minimization of pseudo allylic-1,3 strain and optimal dipole minimization between the alkoxy group and the ester were proposed to explain why anti-

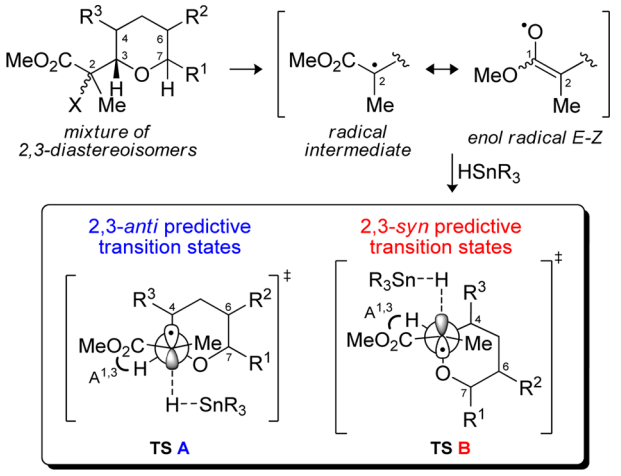


Figure 2. Proposed transition states for the reduction of radical intermediates.[21]

predictive TS **A** was preferred among the other possible transitions states (Figure 2).[21] When the C3−O alkoxy group is embedded in an exocycle, higher 2,3-*anti* selectivities are observed, unless the radical-bearing chain is oriented in the axial position.[10]

Previous in silico evaluation for unsubstituted THP radical intermediates suggested that Curtin−Hammett conditions[22] were met for the hydrogen radical delivery in these simple systems.[10] In order to ensure that the more substituted THP systems presented herein were also reduced under kinetic conditions, the radical intermediates were examined, as depicted in Figure 3 for **17c** (generated from **17a,b**). A significant energy

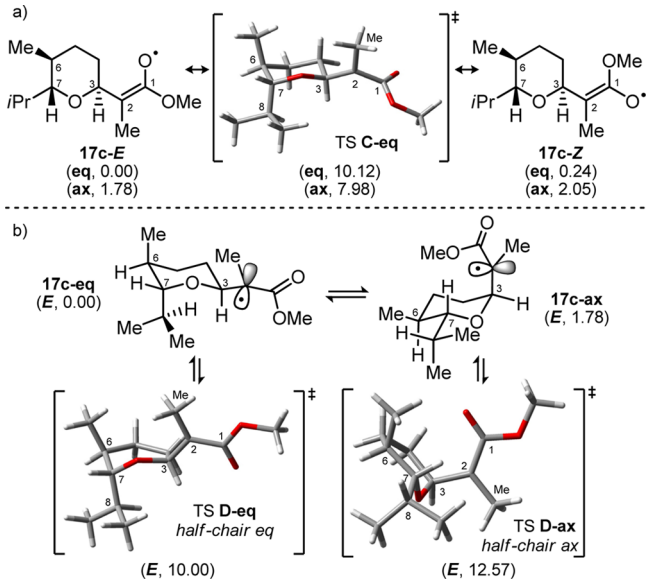


Figure 3. Energy barriers of radical intermediates for *E*−*Z* isomerization and chair ring-flip (depicted for **17c**).

barrier was noted for the isomerization between *E* and *Z* configuration of the enol radical resulting from radical delocalization in the vicinal ester (TS **C**) and another corresponding to the THP ring-flip through half-chair conformers (TS **D**). These two energy barriers are markedly lower than TS **A** and **B** located for the hydrogen radical delivery (Table 3). It is noteworthy that all the possible rotamers of the C7−C8

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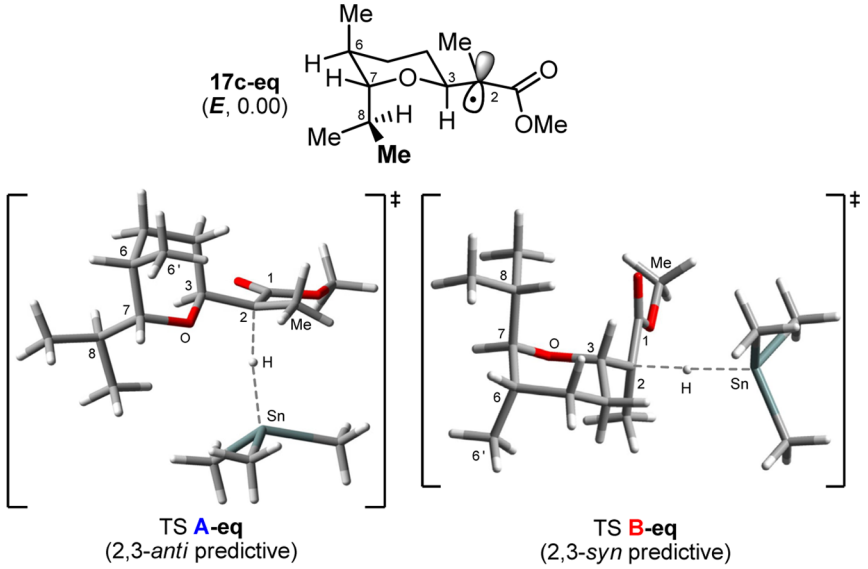
Table 3. Relative Gibbs Free Energies (kcal mol^{-1}) in Toluene of Radical Intermediates and TS Hydrogen Delivery Relative to Their Respective Lowest Radical GS

Entry (Substrate)[a]		GS and Energy Barriers			TS for Hydrogen Radical Delivery		Predicted Ratio at –78 °C (*anti* : *syn*)
		GS	TS **C**	TS **D**	TS **A** (*anti*)	TS **B** (*syn*)	
1	eq	0.00	10.12	10.00	18.29	19.03	6.7 : 1
2	ax	1.78	7.98	12.57	20.48	20.15	
3	eq	0.00	10.16	9.16	18.37	19.33	5.5 : 1
4	ax	0.74	6.62	10.37[b]	19.29	19.02	
5	eq	0.00	10.04	–[c]	17.61	18.66	15.4 : 1
6	eq	0.00	10.02	7.53	19.68	21.60	>140 : 1
7	ax	3.29	9.48	8.11	22.36	22.28	

[a]Numbering of atoms was attributed according to that of ionophores **1a–c**. [b]The value reported corresponds to the electronic energy maximum determined by the unrestricted dihedral scan in vacuum. [c]No axial chair conformer was located for **38c**.



conditions at –78°C	ΔΔG‡ (2,3-*anti* **25a** : 2,3-*syn* **25b**)	
	experimental	calculated
vacuum	–	**1.10** (17.1 : 1)
toluene	**1.10** (17 : 1)	**0.74** (6.7 : 1)
DCM	**0.43** (3 : 1)	**0.22** (1.8 : 1)

Figure 4. Transition states of hydrogen delivery to 6,7-*trans* THP radical intermediate **17c**. Gibbs free energies (kcal mol^{-1}) are reported relative to the energy of **17c**.

bond and chair conformations were considered in these calculations.[23]

The relative Gibbs free energies of modeled compounds for the GS radical conformers and for hydrogen radical delivery at the TS are represented in Table 3. The isomerization barrier

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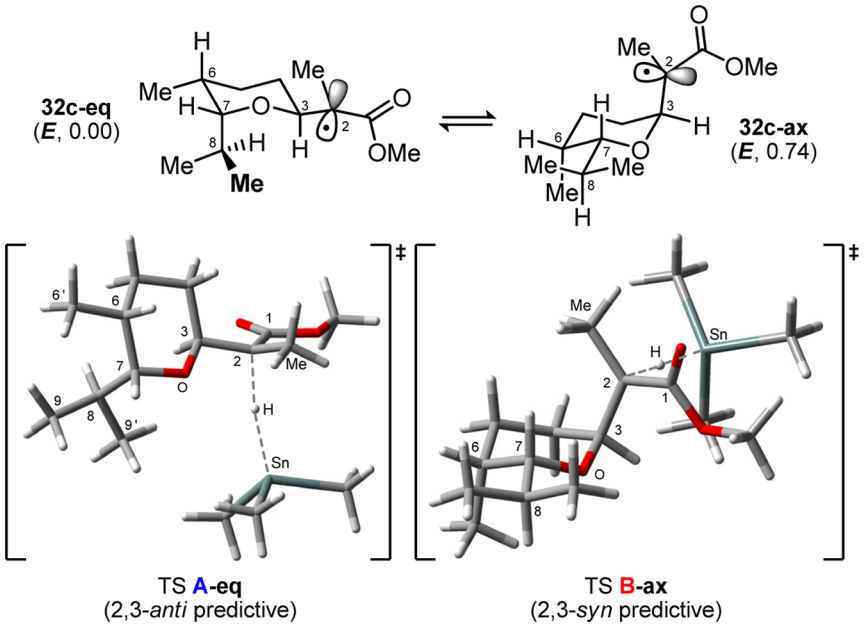

conditions at −78°C	ΔΔG‡ (2,3-*anti* **36a** : 2,3-*syn* **36b**)	
	experimental	calculated
vacuum	–	**0.68** (5.8 : 1)
toluene	**0.62** (5 : 1)	**0.66** (5.5 : 1)
DCM	**−0.27** (1 : 2)	**−0.18** (1 : 1.6)

Figure 5. Transition states of hydrogen delivery to 6,7-*cis* THP radical intermediate **32c**. Gibbs free energies (kcal mol^{-1}) are reported relative to the energy of **32c**.

between the two possible enols (TS **C**) was found to vary between 6 and 10 kcal mol^{-1}, well under the TS energy measured for the different transition states located in this study (Table 3, entries 1−7). The appropriate transition state corresponding to the interconversion between the two chair conformations of 3,7-*trans* THPs through half-chair conformers (TS **D**) was first established by an unrestricted scan of all dihedral angles of the two chair conformer (bearing the C3-chain either equatorial or axial). Each energy maximum identified was then further examined by TS analysis using the QST3 method implemented in Gaussian. The Gibbs free energies are reported for the lowest energy half-chair (*E* or *Z*) involved in the interconversion of the chair conformers (eq or ax) to their corresponding twist-boats, as confirmed by the evaluation of the imaginary frequency. The energy barriers of chair ring-flip (TS **D**) and enol radical isomerization (TS **C**) were determined to also be significantly lower than the energies for hydrogen radical delivery (Figure 3 and Table 3, entries 1−4, 6, and 7), therefore allowing for the consideration of all ground-state conformations in the transition-state analysis. For substrate **38c** (3,7-*cis*), it was not possible to determine the energy of the half-chair barrier (entry 5, Table 3). Indeed, the 1,3-diaxial interactions between the substituents at C3 and C7 present in the chair conformer when oriented axial are likely prohibitively high in energy. This could suggest that this THP radical intermediate may only react in the chair conformer with an equatorial radical chain at C3.

Reductions of 6,7-*trans*- versus 6,7-*cis*-Substituted THP. The origin of the decreased 2,3-*anti* selectivity (17:1 vs 5:1) for the reduction of 6,7-*trans* **17c** and 6,7-*cis* substrates **32c** (respectively generated from radical precursors **17a,b** and **32a,b**) was investigated by examining their lowest energy anti-predictive and syn-predictive transition states. TS **A** and **B** of **17c** (6,7-*trans*) both displayed an equatorial orientation of the C3-chain bearing the radical (Figure 4). The calculated $\Delta\Delta G^{\ddagger}$ of 1.10 kcal mol^{-1} predicted formation of 2,3-*anti* product **25a** with high selectivity in vacuum. The 6,7-*cis* THP **32c** was likewise calculated to undergo radical reduction with C3-chain bearing the radical in the equatorial orientation for TS **A** (Figure 5), but the lowest syn-predictive TS **B** was determined to bear the C3-chain in an axial orientation. For the calculated $\Delta\Delta G^{\ddagger}$ in vacuum, toluene and DCM are in good accordance with the observed diastereoselectivity. The *syn*-pentane interaction (C6′−C6−C7−C8−C9) probably destabilizes TS **A-eq**, thus reducing the gap with syn-predictive TS **B-ax** in 6,7-*cis* THP systems.

It is of interest that DFT calculations considering solvent effects correctly modeled the decrease in anti-selectivity that was observed experimentally in DCM (3:1, Figure 4). This decrease in selectivity in more polar media is likely the result of less favorable stabilization in TS **A** from the antiperiplanar dipole orientation of the ester group relative to the C3-alkoxy group. The solvent correction in toluene provided a calculated $\Delta\Delta G^{\ddagger}$ value that is not as consistent with the observed ratio for this particular substrate.

Reductions of 3,7-*trans*- versus 3,7-*cis*-Substituted THP. In the different 3,7-*trans* systems analyzed (**17c** and **32c**), the C7-substituent was oriented in the trajectory of the incoming hydride for anti-predictive TS **A** (Figures 4 and 5). This unfavorable interaction is not present in less substituted THP systems, which are reduced with significantly higher selectivities, such as **3c** generated from **3a,b** (Scheme 2a). Similarly, this interaction could also be partially alleviated in 3,7-*cis* radical intermediate **38c** (corresponding to the C7−*i*Pr analogue generated from **22a,b**) that was determined in silico to preferably react through equatorial TS (**A** and **B**, Figure 6). The

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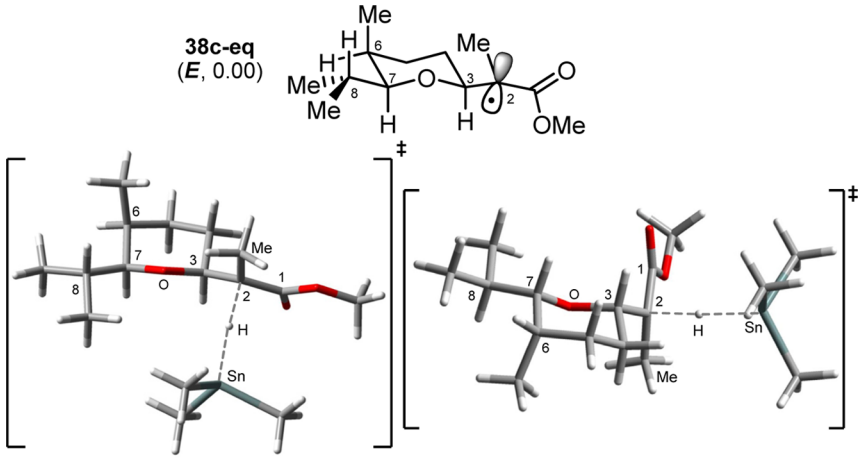

conditions at −78°C	ΔΔG‡ (2,3-*anti* **30a** : 2,3-*syn* **30b**)	
	experimental*	calculated
vacuum	–	**1.04** (14.6 : 1)
toluene	**>1.16** (>20 : 1)	**1.06** (15.4 : 1)

* product selectivity reported correspond to precursor **22a**,**b**

Figure 6. Transition states of hydrogen delivery to 3,7-*cis* THP radical intermediate **38c**. Gibbs free energies (kcal mol^{-1}) are reported relative to the energy of **38c**.

greater $\Delta\Delta G^{\ddagger}$ calculated between these TS correctly predicts the observed experimental selectivities. As discussed previously, the calculated interconversion barrier between the chair conformers of the radical intermediates are significantly lower than the activation energy required for hydrogen radical delivery, allowing access to the axial conformations at the transition state level.

Reductions of *β*-Methyl-Substituted THP Systems. Reductions of the 6,7-*trans* radical precursors **40a** generated from a stereoselective iodoetherification reaction were previously demonstrated to provide product **41a** selectively[6e] and were further examined in silico using C7−*i*Pr analogue **39c** (Figure 7). The substitution pattern of this THP substrate corresponds to the C1−C9 fragment of zincophorin **1a**, where the radical reduction occurs at C8 in comparison with substrate **17c** bearing the reacting center at C2 (Figure 4). As determined for the other 6,7-*trans* substrates, the lowest anti-predictive TS **A** was calculated to prefer an equatorial orientation of the C3 radical-bearing chain. The most striking difference is observed, however, in the syn-predictive TS **B**; the equatorial methyl group at C6 in substrate **39c** presenting a severe steric clash with the incoming hydride. This interaction is potentially raising the activation energy required to reach the syn-predictive TS, and as a consequence, the resulting larger $\Delta\Delta G^{\ddagger}$ gap calculated allows for high anti-selectivity. A decreased $\Delta\Delta G^{\ddagger}$ of 1.54 kcal mol^{-1} was calculated in THF, although this energy gap is sufficient to account for the observed exclusive formation of the 7,8-*anti* product.

It is noteworthy that the computational analysis presented herein demonstrates the importance of considering both the minor- and major-predicting TS to rationalize trends in selectivity. In the case of 3,7-*cis* substrate **38c** (Figure 6), the reduced destabilizing interaction in the anti-predictive TS **A** allows to explain the increase in $\Delta\Delta G^{\ddagger}$ and corresponding 2,3-*anti* selectivity. Conversely, destabilizing interaction in syn-predictive TS **B** noted for 6,7-*trans* substrate **39c** also furnishes higher 7,8-*anti* selectivity (Figure 7).

CONCLUSION

In the context of the reductions of radical intermediates bearing a vicinal polysubstituted THP, it was observed that certain substitution patterns influence significantly the observed selectivities. The analysis of transition states by DFT calculations for 6,7-*cis* and 6,7-*trans* THP intermediates allowed to identify unfavorable interactions between the axial chain at C7 with the incoming hydride. Moreover, important steric interactions between the C6 and C7 alkyl chains could destabilize significantly TS conformers with an equatorial chain bearing the radical, which in turn would reduce the energy gap between anti- and syn-predictive TS. This work led to the elaboration of a highly predictive model that takes into account the relative energy of radical intermediates in combination with potential interactions at the transition state. The analysis in silico of experimental diastereoselectivities provided substantial insight to further improve our collective knowledge of the reactivity of radicals in stereocontrolled processes.

EXPERIMENTAL SECTION

General Comments. The experimental procedure and physical characterization of silylated enol ether **2** and product **10** have already been described by our group.[6a] All procedures requiring anhydrous conditions were carried out under a positive argon atmosphere in oven-dried glassware using standard syringe techniques (exception should be noted that free-radical reactions were conducted under nitrogen). All solvents were purified by standard methods. Flash chromatography was performed on silica gel (0.040−0.063 mm) using compressed air pressure. Analytical thin-layer chromatography (TLC) was carried out on aluminum-precoated (0.25 mm) silica gel plates. ^{1}H (400 or 500 MHz) and ^{13}C spectra (100 or 125 MHz) were referenced to residual solvents peak for $CHCl_3$ (7.26 ppm for ^{1}H NMR, 77.16 ppm for ^{13}C NMR), and ratios of products were measured from crude ^{1}H spectra. Multiplets were assigned with s (singlet), bs (broad singlet), app s

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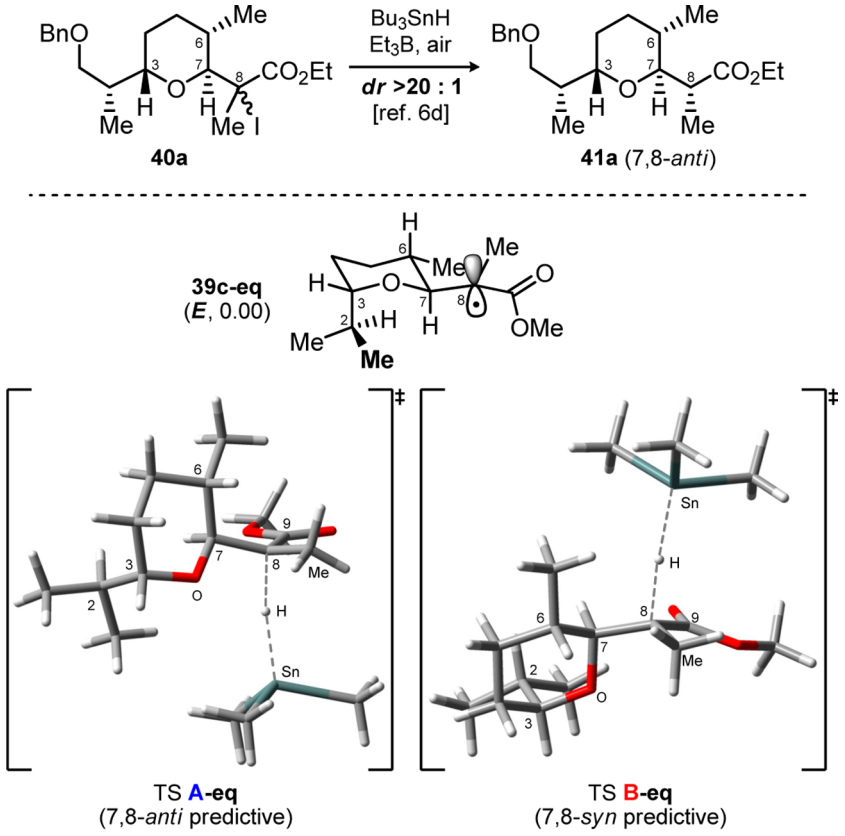

conditions at −78°C	ΔΔG‡ (7,8-*anti* **41a** : 7,8-*syn* **41b**)	
	experimental*	calculated
vacuum	–	**2.02** (>180 : 1)
toluene	**>1.16** (>20 : 1)	**1.92** (>140 : 1)
THF	**>1.16** (>20 : 1)	**1.54** (>50 : 1)

* product selectivity reported corresponds to precursor **40a**

Figure 7. Transition states of hydrogen delivery to 6,7-*trans* THP radical intermediate **39c**. Gibbs free energies (kcal mol^{-1}) are reported relative to the energy of **39c**.

(apparent singlet), d (doublet), app d (apparent doublet), t (triplet), app t (apparent triplet), q (quartet), sept (septet) and m (multiplet). 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 through electrospray ionization (ESI) coupled to an ion trap (IT) on an instrument operating at 70 eV.

Computational Method for the Conformational Analysis of Radical Intermediates. All geometry optimizations were performed using standard gradient techniques and tight SCF convergence in Gaussian 09[13] with the BHandHLYP exchange-correlation (XC) functional[14] using restricted (RBHandHLYP) and unrestricted (UBHandHLYP) methods for closed- and open-shell systems, respectively.[24] It was previously demonstrated[15] that BHandHLYP functional performed better for radical systems than other XC functionals,[16] disparity often associated with inadequate treatment of the exchange terms.[25] The effective core potential of Hay and Wadt[17] LANL2DZ supplemented with a single set of d-type polarization functions was used for tin (d(ζ)Sn = 0.20)[16b,d,18] together with the valence triple-ζ TZVP basis set[19] for all other atoms. Ground state (GS) radicals were evaluated by unconstrained optimization of all possible rotating bonds including both *E*- and *Z*-enol radical conformations. Staggered transition states (TS) for hydrogen radical delivery using Me_3SnH (anti- and syn-predictive TS) were considered for each conformation of methyl ester radical intermediates. Unscaled harmonic frequency calculations at the appropriate temperature were performed for each optimized structure to characterize it as an energy minimum or a TS structure and to calculate Gibbs free energies (ΔG). To calculate Gibbs free energies in solution, geometry optimizations and harmonic frequency calculations were performed with the IEFPCM model[20] and the UFF atomic radii for either toluene or dichloromethane. Wiberg bond indices[26] were calculated using the natural bonding orbitals[27] as implemented in Gaussian 09.[13] The stereochemistry of the radical precursor at C2 was demonstrated experimentally to be unrelated to the stereochemical outcome of radical reduction reaction.[6a−d] It was thus reasonable to consider the same radical intermediates for both halide isomers at the C2 position at the transition state.

General Experimental Method for Radical Reduction: Exocyclic Effect Control (A1). To a cold (−78 °C) solution of a mixture of bromides (1 equiv) in dry toluene (0.1 M) were added successively Ph_3SnH (2 equiv), a 1 M solution of Et_3B in CH_2Cl_2 (0.2 equiv), and air (syringe). The reaction mixture was maintained at −78 °C as supplementary addition of Et_3B solution (0.2 equiv) and air was realized each 30 min, until reaction was judged complete by TLC (3−4 h). The reaction mixture was treated with the addition of 1,4-dinitrobenzene (0.2 equiv), followed by stirring of the mixture for 15 min at −78 °C. Once at room temperature, reaction was concentrated in vacuo. The two diastereoisomers were separated by flash chromatography on silica gel.

General Experimental Method for Hydrogenolysis with Palladium (A2). To a solution of α,β-unsaturated ester or benzyl-protected alcohol (1 equiv) in EtOAc (0.1 M) at room temperature was added 10 wt % Pd on activated carbon (0.1 equiv). Inert gas atmosphere was purged by three cycles of vacuum/H_2 gas, and the reaction mixture

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was stirred until the reaction was judged complete 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.

General Experimental Method for Protection of Alcohol with Trialkylsilyl Trifluoromethanesulfonate Reagents (A3). To a cold (0 °C) solution of alcohol (1 equiv) in dry CH_2Cl_2 (0.1 M) were added successively 2,6-lutidine (1.2 equiv) and TESOTf (1.1 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 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 mixture was purified by flash chromatography on silica gel.

General Experimental Method for Reduction of Ester to Primary Alcohol with DIBAL-H (A4). To a cold (−40 °C) solution of ester (1 equiv) in dry CH_2Cl_2 (0.1 M) was added a 1.0 M solution of DIBAL-H in hexanes (3 equiv). The mixture was stirred for 1 h at −40 °C or until the 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 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 mixture was purified by flash chromatography on silica gel.

General Experimental Method for Oxidation of Primary Alcohol with Dess−Martin Periodinane (A5). To a solution of alcohol (1 equiv) in dry CH_2Cl_2 (0.1 M) were added successively $NaHCO_3$ (10 equiv) and Dess−Martin periodinane (1.5 equiv). The reaction mixture was stirred for 1 h at room temperature and then concentrated. The resulting white solid residue was digested in hexanes and filtered onto a pad of Celite. The filtrate was then concentrated in vacuo and purified by flash chromatography on silica gel.

General Experimental Method for Wittig Olefination of Aldehyde (A6). To a solution of aldehyde (1 equiv) in dry toluene (0.1 M) was added methyl (triphenylphosphoranylidene)acetate (1.5 equiv), and the resulting solution 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 that was concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel.

General Experimental Method for Cycloetherification Reaction with $BiBr_3$ (A7). To a cold (−78 °C) solution of aldehyde (1 equiv) in dry CH_2Cl_2 (0.1 M) was added dropwise a solution of $BiBr_3$ (1 equiv) in dry MeCN (0.5 M), followed by silylated enol ether **2** (1.5 equiv). 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 a saturated aqueous solution of NH_4Cl at −40 °C, followed by separation of the organic phase at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3×) and combined organic fractions were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel.

General Experimental Method for Lactonization (A8). To a stirred solution of crude ester (1 equiv) in benzene (0.1 M) was added *p*-TSOH (1 equiv), and the reaction was heated to reflux for 1 h. The mixture was cooled to room temperature, followed by filtration onto a pad of silica and washing with Et_2O. The filtrate was concentrated in vacuo, and the crude mixture was purified by flash chromatography on silica gel.

General Experimental Method for Reduction of Lactone to Protected Lactol (A9). To a cold (−40 °C) solution of lactone (1 equiv) in dry CH_2Cl_2 (0.1 M) was added dropwise a 1.0 M solution of DIBAL-H in toluene (1.2 equiv). The mixture was stirred for 1.5 h at −40 °C or until starting material was completely consumed, as verified by TLC. To the reaction mixture were then added successively pyridine (4.0 equiv), DMAP (1.2 equiv) and acetic anhydride (5 equiv). The reaction mixture was then stirred overnight at room temperature before treatment with a saturated aqueous solution of NH_4Cl and concentration in vacuo. The aqueous layer was extracted with Et_2O (3×), and the combined organic fractions were washed with a saturated brine solution, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel.

General Experimental Method for Preparation of Tertiary Bromides from Protected Lactol (A10). To a cold (−78 °C) solution of protected lactol (1 equiv) in dry CH_2Cl_2 (0.1 M) was added silylated enol ether **2** (2.8 equiv). The mixture was stirred for 2 min at −78 °C, followed by dropwise addition of a 1.0 M solution of $SnCl_4$ in CH_2Cl_2 (1.5 equiv) and stirring for 1.5 h at −78 °C. 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 mixture was purified by flash chromatography on silica gel.

General Experimental Method for Swern Oxidation (A11). To a cold (−78 °C) solution of oxalyl chloride (1.2 equiv) in dry CH_2Cl_2 (0.1 M) was added dropwise anhydrous DMSO (2.4 equiv), and the mixture was stirred for 10 min at −78 °C. A solution of the alcohol (1 equiv) in dry CH_2Cl_2 (0.5 M) 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 Et_3N (5 equiv). The mixture was stirred 1 h at −78 °C and then treated with 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, dried ($MgSO_4$), filtered, and concentrated in vacuo to afford aldehyde as a colorless oil.

General Experimental Method for Mukaiyama Aldol Reaction: Felkin−Anh Control (A12). To a cold (−78 °C) solution of aldehyde (1 equiv) in dry CH_2Cl_2 (0.1 M) were added successively silylated enol ether **2** (2 equiv) and $BF_3{\cdot}OEt_2$ (1.5 equiv). The reaction mixture was stirred for 1 h at −78 °C before treatment with a saturated aqueous solution of NH_4Cl and separation of the organic phase at room temperature. The aqueous layer was extracted with EtOAc (3×), and the combined organic fractions were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel.

General Experimental Method for Radical Reduction: Acyclic Stereoselection Control (A13). To a cold (−78 °C) solution of a mixture of bromides (1 equiv) in dry CH_2Cl_2 (0.1 M) were added successively DIEA (1.5 equiv) and a 1 M solution of Bu_2BOTf in CH_2Cl_2 (1.3 equiv), followed by stirring for 1.5 h at −78 °C. The mixture was then successively treated with Bu_3SnH (2 equiv), a 1 M solution of Et_3B in CH_2Cl_2 (0.2 equiv), and air (syringe). Supplementary addition of Et_3B solution (0.2 equiv) 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) 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×). The combined organic fractions were washed (2×) with a saturated aqueous solution of KF and brine before being dried ($MgSO_4$). The filtrate was concentrated to a residue which was solubilized in MeOH (0.1 M) and cooled to 0 °C before being treated by a 35% w/w of H_2O_2 in water (3 equiv). The solution was stirred for 2 h at 0 °C and then treated with addition of water before extraction with Et_2O (3×). The combined organic fractions were washed with a saturated brine solution and then dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel.

General Experimental Method for Parikh−Doering Oxidation of Primary Alcohols (A14). To a cold (0 °C) solution of alcohol (1 equiv) in dry CH_2Cl_2 (0.1 M) were added successively DMSO (7 equiv), DIEA (5 equiv), and $SO_3{\cdot}$py complex (3 equiv). The reaction mixture was stirred for 15 min at 0 °C or until alcohol was completely consumed, as verified by TLC before treatment with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted with Et_2O (3×), and the combined organic fractions were washed with a saturated

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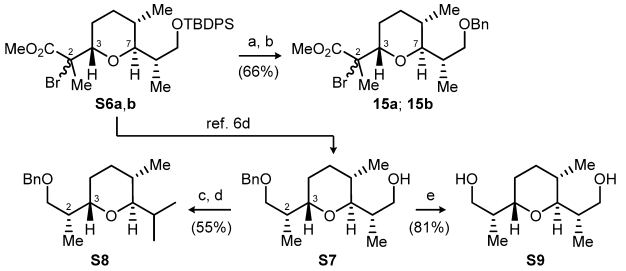
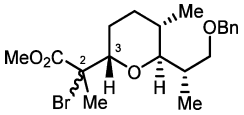
aqueous solution of NH_4Cl, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel.



Reactions and conditions: a) HF·py, THF, 0 °C. b) BnOC=NHCCl$_3$, TfOH, *c*-Hex/CH$_2$Cl$_2$, 0 °C. c) MsCl, pyridine, CH$_2$Cl$_2$, 0 °C. d) LiAlH$_4$, Et$_2$O, 0 °C. e) H$_2$, Pd/C, EtOAc, rt.

(±)-Methyl 2-((2*S*,5*S*,6*S*)-6-((*S*)-1-(Benzyloxy)propan-2-yl)-5-methyltetrahydro-2*H*-pyran-2-yl)-2-bromopropanoate (15a, 15b).

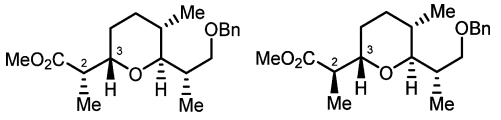


To a cold (0 °C) solution of a mixture of product **S6a**,**b**[6d] (537 mg) in dry THF (0.1 M, 9.6 mL) was added dropwise a solution of HF·pyridine (ca. 70% HF, 1 mL per mmol of substrate, 0.95 mL). The reaction mixture was stirred overnight at 0 °C and then treated slowly with a saturated aqueous solution of $NaHCO_3$, 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 mixture was purified by flash chromatography on silica gel (hexanes/EtOAc, 80:20) to afford an inseparable mixture of bromide adducts as a colorless oil. To a cold (0 °C) solution of crude product in solvent mixture of cyclohexane and CH_2Cl_2 (2:1, 0.1 M, 9.6 mL) were added successively 2,2,2-benzyltrichloroacetimidate (1.3 equiv, 230 μL) and TfOH (0.1 equiv, 8 μL). The reaction mixture was stirred overnight at 0 °C before treatment with Et_3N (0.15 equiv, 20 μL) and then concentration in vacuo. The crude mixture was dissolved in hexanes and filtered onto a pad of Celite, followed by concentration in vacuo of the filtrate. ^{1}H NMR spectroscopic analysis of the unpurified product indicated a pair of 2,3-diastereomers in a ~1:1 ratio of products **15a**:**15b**. The two diastereoisomers were separated by flash chromatography on silica gel (hexanes/EtOAc, 90:10) to afford product **15a** and **15b** as colorless oils (261 mg, yield = 66% over two steps).

15a: R_f = 0.46 (toluene/EtOAc, 98:2); formula $C_{20}H_{29}BrO_4$; MW 413.35 g/mol; IR (neat) ν_{max} 2955, 2932, 2868, 1742, 1452, 1377, 1263, 1202, 1143, 1097, 1047, 984, 858, 737, 697 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.25 (m, 5H), 4.50 (d, J = 12.1 Hz, 1H), 4.43 (d, J = 12.1 Hz, 1H), 4.13 (dd, J = 3.8 Hz, 10.8 Hz, 1H), 3.76 (s, 3H), 3.38 (dd, J = 2.7 Hz, 8.5 Hz, 1H), 3.35 (dd, J = 5.4 Hz, 9.2 Hz, 1H), 3.28 (dd, J = 5.5 Hz, 9.2 Hz, 1H), 2.27−2.18 (m, 1H), 1.90 (s, 3H), 1.90−1.67 (m, 4H), 1.51−1.43 (m, 1H), 1.03 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 6.7 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 138.6, 128.3, 127.44, 127.41, 81.2, 73.9, 73.3, 73.0, 62.1, 53.0, 33.3, 27.3, 25.2, 22.5, 19.8, 18.3, 13.4 ppm; MS (ESI-IT) m/z 305.1 (8), 413.1 (M + H$^+$, 100), 503.2 (7); HRMS calcd for $C_{20}H_{30}O_4Br$ [M + H$^+$] 413.1322, found 413.1319 (−0.7 ppm).

15b: R_f = 0.40 (toluene/EtOAc, 98:2); formula $C_{20}H_{29}BrO_4$; MW 413.35 g/mol; IR (neat) ν_{max} 2954, 2932, 2868, 1739, 1452, 1378, 1264, 1204, 1110, 1055, 988, 736, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.25 (m, 5H), 4.51 (d, J = 12.1 Hz, 1H), 4.45 (d, J = 12.1 Hz, 1H), 3.93 (dd, J = 3.0 Hz, 11.3 Hz, 1H), 3.77 (s, 3H), 3.45 (dd, J = 1.4 Hz, 9.2 Hz, 1H), 3.40 (dd, J = 5.1 Hz, 9.3 Hz, 1H), 3.32 (dd, J = 5.4 Hz, 9.3 Hz, 1H), 2.34−2.24 (m, 1H), 1.92−1.81 (m, 2H), 1.86 (s, 3H), 1.78−1.66 (m, 1H), 1.49−1.35 (m, 2H), 1.08 (d, J = 6.9 Hz, 3H), 1.07 (d, J = 6.7 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 138.6, 128.3, 127.44, 127.37, 81.4, 74.3, 73.6, 73.1, 65.6, 53.2, 33.2, 27.3, 24.6, 24.0, 20.9, 18.3, 14.1 ppm; MS (ESI-IT) m/z 305.1 (15), 413.1 (M + H$^+$, 100), 468.0 (44); HRMS calcd for $C_{20}H_{30}O_4Br$ [M + H$^+$] 413.1322, found 413.1326 (0.9 ppm).

(±)-(*S*)-Methyl 2-((2*S*,5*S*,6*S*)-6-((*S*)-1-(Benzyloxy)propan-2-yl)-5-methyltetrahydro-2*H*-pyran-2-yl)propanoate (23a) and (±)-(*R*)-Methyl 2-((2*S*,5*S*,6*S*)-6-((*S*)-1-(Benzyloxy)propan-2-yl)-5-methyltetrahydro-2*H*-pyran-2-yl)propanoate (23b).



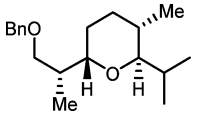
23a (2,3-*anti*) **23b** (2,3-*syn*)

Products **23a** and **23b** (33 mg, yield = 81%) were obtained as pale yellow oils from a mixture of bromides **15a**; **15b** (50 mg) following general procedure **A1** and purification by flash chromatography on silica gel (hexanes/EtOAc 85:15). ^{1}H NMR spectroscopic analysis of the unpurified product indicated a pair of diastereomers in a 15:1 ratio of products 2,3-*anti* (**23a**):2,3-*syn* (**23b**).

23a: R_f = 0.22 (hexanes/EtOAc, 90:10); formula $C_{20}H_{30}O_4$; MW 334.45 g/mol; IR (neat) ν_{max} 2949, 2929, 2858, 1739, 1456, 1436, 1377, 1362, 1269, 1256, 1197, 1074, 1099, 1074 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.24 (m, 5H), 4.53 (d, J = 12.1 Hz, 1H), 4.47 (d, J = 12.1 Hz, 1H), 3.86 (dt, J = 8.8 Hz, 4.1 Hz, 1H), 3.57 (s, 3H), 3.40 (dd, J = 4.6 Hz, 9.1 Hz, 1H), 3.33 (dd, J = 4.0 Hz, 7.9 Hz, 1H), 3.23 (app t, J = 8.9 Hz, 1H), 2.95 (dq, J = 10.4 Hz, 6.9 Hz, 1H), 2.13−2.04 (m, 1H), 1.72−1.55 (m, 4H), 1.34−1.22 (m, 1H), 1.06 (d, J = 6.9 Hz, 3H), 0.95 (d, J = 6.8 Hz, 3H), 0.88 (d, J = 6.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.7, 138.8, 128.3, 127.44, 127.35, 77.7, 74.5, 74.1, 73.0, 51.4, 40.9, 34.2, 30.7, 26.7, 24.6, 17.8, 14.3, 10.7 ppm; MS (ESI-IT) m/z 171 (70), 227.2 (100), 303.2 (33), 352.9 (25), 517.1 (10), 687.1 (24); HRMS calcd for $C_{20}H_{31}O_4$ [M + H$^+$] 335.2217, found 335.2216 (−0.2 ppm).

23b: R_f = 0.28 (hexanes/EtOAc, 90:10); formula $C_{20}H_{30}O_4$; MW 334.45 g/mol; IR (neat) ν_{max} 2930, 2859, 1737, 1456, 1377, 1255, 1195, 1168, 1111, 1049, 1021, 737, 697 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.26 (m, 5H), 4.51 (d, J = 11.9 Hz, 1H), 4.44 (d, J = 11.9 Hz, 1H), 3.84 (ddd, J = 2.9 Hz, 5.1 Hz, 10.1 Hz, 1H), 3.67 (s, 3H), 3.52 (dd, J = 7.7 Hz, 8.7 Hz, 1H), 3.32 (dd, J = 6.2 Hz, 8.9 Hz, 1H), 3.27 (dd, J = 3.4 Hz, 8.6 Hz, 1H), 3.01 (dq, J = 10.3 Hz, 6.8 Hz, 1H), 2.16−2.07 (m, 1H), 1.76−1.67 (m, 1H), 1.67−1.58 (m, 2H), 1.50−1.43 (m, 1H), 1.42−1.32 (m, 1H), 1.19 (d, J = 6.8 Hz, 3H), 0.90 (d, J = 6.9 Hz, 3H), 0.86 (d, J = 6.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.9, 138.6, 128.3, 127.6, 127.45, 75.3, 73.6, 73.4, 73.0, 51.6, 40.0, 34.0, 31.0, 27.4, 27.0, 17.7, 14.0, 10.3 ppm; MS (ESI-IT) m/z 227.2 (12), 335.2 (M + H$^+$, 100); HRMS calcd for $C_{20}H_{31}O_4$ [M + H$^+$] 335.2217, found 335.2206 (−3.4 ppm).

(±)-(2*R*,3*S*,6*S*)-6-((*R*)-1-(Benzyloxy)propan-2-yl)-2-isopropyl-3-methyltetrahydro-2*H*-pyran (S8).



To a cold (0 °C) solution of alcohol **S7**[6d] (9.2 mg) in dry CH_2Cl_2 (0.1 M, 300 μL) were added successively Et_3N (3.0 equiv, 14 μL) and MsCl (1.2 equiv, 3 μL). The reaction mixture was stirred for 3 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 Et_2O (3×), and the combined organic fractions were dried ($MgSO_4$), filtered, and concentrated in vacuo to yield the mesylated product as a colorless oil which was used as crude without further purification. To a cold (0 °C) solution of crude mesylate in dry Et_2O (0.1 M, 300 μL) was added a 1.0 M solution of $LiAlH_4$ in THF (1.1 equiv, 33 μL). The mixture was stirred for 3 days at 0 °C or until mesylate 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 Et_2O (3×), and combined organic fractions were dried ($MgSO_4$), filtered, and concentrated in vacuo. Product **S8** (4.9 mg, 56% over two steps) was

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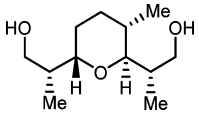
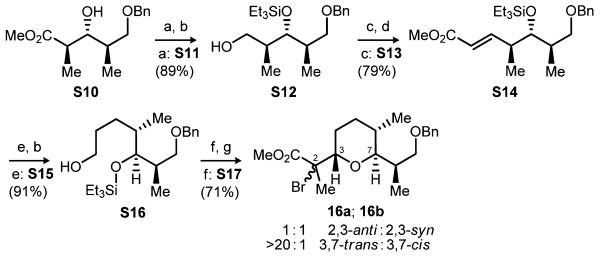
obtained as a colorless oil after purification by flash chromatography on silica gel (hexanes/EtOAc 95:5): R_f = 0.35 (hexanes/EtOAc, 80:20); formula $C_{19}H_{30}O_2$; MW 290.44 g/mol; IR (neat) ν_{max} 3062, 3030, 2957, 2928, 2872, 1456, 1363, 1096, 735 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36−7.26 (m, 5H), 4.52 (d, J = 12.0 Hz, 1H), 4.48 (d, J = 12.0 Hz, 1H), 3.64 (dd, J = 3.8 Hz, 9.0 Hz, 1H), 3.48 (ddd, J = 4.4 Hz, 6.4 Hz, 9.4 Hz, 1H), 3.34 (dd, J = 7.6 Hz, 8.9 Hz, 1H), 2.97 (app t, J = 5.8 Hz, 1H), 2.13−2.04 (m, 1H), 2.05−1.94 (m, 1H), 1.70−1.62 (m, 2H), 1.62−1.55 (m, 1H), 1.54−1.47 (m, 1H), 1.37−1.28 (m, 1H), 0.95 (d, J = 6.2 Hz, 3H), 0.94 (d, J = 6.7 Hz, 3H), 0.87 (d, J = 6.7 Hz, 3H), 0.85 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 128.3, 127.6, 127.3, 82.0, 73.1, 72.6, 72.5, 35.5, 29.7, 27.6, 26.3, 24.4, 20.29, 18.4, 16.9, 14.1 ppm; MS (ESI-IT) m/z 291.2 (M + H^+, 35), 313.2 (M + Na^+, 100), 360.3 (16), 371.2 (8); HRMS calcd for $C_{19}H_{31}O_2$ [M + H^+] 291.2319, found 291.2313 (−1.9 ppm); calcd for $C_{19}H_{30}O_2Na$ [M + Na^+] 313.2138, found 313.2134 (−1.1 ppm).

(±)-(2*S*,2′*R*)-2,2′-((2*S*,3*S*,6*S*)-3-Methyltetrahydro-2*H*-pyran-2,6-diyl)dipropan-1-ol (S9).

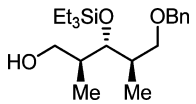


Product **S9** (56 mg, yield =81%) was obtained as a white solid from primary alcohol **S7**[6d] (98 mg) following general procedure **A2** and purification by flash chromatography on silica gel (EtOAc). Structural assignment of compound **S9** was confirmed by X-ray analysis (cf. Supporting Information, part III, X-ray): R_f = 0.38 (EtOAc); formula $C_{12}H_{24}O_3$; MW 216.32 g/mol; IR (neat) ν_{max} 3366, 2928, 2876, 1459, 1379, 1233, 1079, 1017 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.69−3.64 (m, 3H), 3.63−3.59 (m, 2H), 3.53 (dd, J = 3.7 Hz, 8.4 Hz, 1H), 2.53 (s, 2H), 2.30−2.19 (m, 1H), 2.03−1.93 (m, 1H), 1.74−1.61 (m, 4H), 1.39−1.29 (m, 1H), 0.96 (d, J = 7.0 Hz, 3H), 0.90 (d, J = 6.6 Hz, 3H), 0.86 (d, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 77.6, 76.7, 67.1, 66.3, 35.8, 34.4, 31.5, 27.2, 26.3, 18.1, 14.5, 10.1 ppm; MS (ESI-IT) m/z 217.2 (9, M + H^+), 239.2 (100), 455.3 (17); HRMS calcd for $C_{12}H_{25}O_3$ [M + H^+] 217.1798, found 217.1803 (2.1 ppm); calcd for $C_{12}H_{24}O_3Na$ [M + Na^+] 239.1618, found 239.1622 (1.7 ppm).



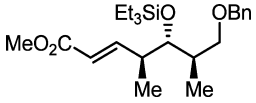
Reactions and conditions: a) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C. b) DIBAL-H, CH_2Cl_2, −40 °C. c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C. d) $Ph_3PC(H)=CO_2Me$, toluene, reflux. e) H_2, Pd/C, EtOAc, rt. f) DMP, $NaHCO_3$, CH_2Cl_2, rt. g) $BiBr_3$, **2**, CH_2Cl_2/MeCN, −78 °C.

(±)-(2*R*,3*R*,4*S*)-5-(Benzyloxy)-2,4-dimethyl-3-(triethylsilyloxy)pentan-1-ol (S12).



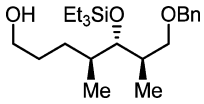
Product **S11** was obtained as a pale yellow oil from **S10**[6d] (505 mg) following general procedure **A3** and was used as crude without further purification. Product **S12** (595 mg, yield = 89% over two steps) was obtained as a colorless oil from crude ester **S11** following general procedure **A4** and purification by flash chromatography on silica gel (hexanes/EtOAc 85:15): R_f = 0.17 (hexanes/EtOAc, 90:10); formula $C_{20}H_{36}O_3Si$; MW 352.58 g/mol; IR (neat) ν_{max} 3428, 3030, 2956, 2877, 1456, 1094, 1009, 735 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37−7.27 (m, 5H), 4.53 (d, J = 12.0 Hz, 1H), 4.49 (d, J = 12.0 Hz, 1H), 3.74−3.68 (m, 2H), 3.59 (dt, J = 11.0 Hz, 5.6 Hz, 1H), 3.52 (dd, J = 5.4 Hz, 9.1 Hz, 1H), 3.36 (dd, J = 6.8 Hz, 9.1 Hz, 1H), 2.75 (t, J = 5.6 Hz, 1H), 2.13−2.04 (m, 1H), 1.91−1.82 (m, 1H), 1.00 (d, J = 7.0 Hz, 6H), 0.96 (t, J = 7.9 Hz, 9H), 0.64 (q, J = 7.8 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 128.5, 127.8, 127.7, 79.7, 73.3, 72.8, 66.0, 39.0, 36.9, 16.2, 14.4, 7.2, 5.5 ppm; MS (ESI-IT) m/z 353.2 (100), 375.2 (65); HRMS calcd for $C_{20}H_{37}O_3Si$ [M + H]$^+$ 353.2506, found 353.2499 (−2.0 ppm); calcd for $C_{20}H_{36}O_3SiNa$ [M + H]$^+$ 375.2326, found 375.2317 (−2.5 ppm).

(±)-(4*R*,5*R*,6*S*,*E*)-Methyl 7-(Benzyloxy)-4,6-dimethyl-5-(triethylsilyloxy)hept-2-enoate (S14).



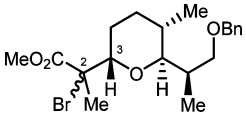
Aldehyde **S13** was obtained as a pale yellow oil from alcohol **S12** (1.11 g) following general procedure **A5** and was used as crude without further purification. Product **S14** (1.01 g, yield = 79% over two steps) was obtained as a colorless oil from crude aldehyde **S13** following general procedure **A6** and purification by flash chromatography on silica gel (hexanes/EtOAc 90:10): R_f = 0.32 (hexanes/EtOAc, 90:10); formula $C_{23}H_{38}O_4Si$; MW 406.63 g/mol; IR (neat) ν_{max} 3030, 2957, 2910, 2877, 1726, 1271, 735 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39−7.29 (m, 5H), 7.06 (dd, J = 8.5 Hz, 15.8 Hz, 1H), 5.80 (dd, J = 1.0 Hz, 15.8 Hz, 1H), 4.53 (d, J = 12.0 Hz, 1H), 4.47 (d, J = 12.0 Hz, 1H), 3.74 (s, 3H), 3.64 (dd, J = 3.8 Hz, 6.3 Hz, 1H), 3.51 (dd, J = 4.9 Hz, 9.1 Hz, 1H), 3.36 (dd, J = 6.7 Hz, 9.1 Hz, 1H), 2.60−2.52 (m, 1H), 1.97−1.88 (m, 1H), 1.09 (d, J = 6.9 Hz, 3H), 0.97 (t, J = 6.8 Hz, 9H), 0.95 (d, J = 6.6 Hz, 3H), 0.62 (q, J = 7.9 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 152.2, 138.8, 128.4, 127.7, 127.6, 120.6, 77.9, 73.2, 72.5, 51.5, 40.5, 38.4, 17.7, 14.8, 7.2, 5.5 ppm; MS (ESI-IT) m/z 279.1 (13), 407.3 (M + H^+, 100), 429.2 (78), 707.3 (5); HRMS calcd for $C_{23}H_{39}O_4Si$ [M + H^+] 407.2612, found 407.2605 (−1.8 ppm).

(±)-(4*R*,5*R*,6*S*)-7-(Benzyloxy)-4,6-dimethyl-5-(triethylsilyloxy)heptan-1-ol (S16).



Product **S15** was obtained as a colorless oil from α,β-unsaturated ester **S14** (376 mg) following general procedure **A2** and was used as crude without further purification. Primary alcohol **S16** (318 mg, yield = 91% over two steps) was obtained as a colorless oil from crude ester **S15** following general procedure **A4** and purification by flash chromatography on silica gel (hexanes/EtOAc 75:25): R_f = 0.21 (hexanes/EtOAc, 80:20); formula $C_{22}H_{40}O_3Si$; MW 380.64 g/mol; IR (neat) ν_{max} 3365, 3030, 2956, 2912, 2876, 1456, 1098, 1058, 1008, 735 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36−7.27 (m, 5H), 4.52 (d, J = 12.0 Hz, 1H), 4.49 (d, J = 12.0 Hz, 1H), 3.66−3.62 (m, 2H), 3.60 (dd, J = 4.1 Hz, 9.0 Hz, 1H), 3.45 (dd, J = 4.5 Hz, 5.7 Hz, 1H), 3.32 (dd, J = 7.8 Hz, 9.0 Hz, 1H), 2.01−1.91 (m, 1H), 1.73−1.40 (m, 4H), 1.15−1.05 (m, 1H), 1.00 (d, J = 6.9 Hz, 3H), 0.96 (t, J = 7.9 Hz, 9H), 0.93 (d, J = 6.8 Hz, 3H), 0.60 (q, J = 7.9 Hz, 6H) ppm. *OH signal missing possibly due to exchange in* $CDCl_3$; ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0, 128.5, 127.8, 127.6, 79.7, 73.3, 73.1, 63.6, 37.3, 36.9, 31.2, 27.7, 17.1, 16.0, 7.4, 5.7 ppm; MS (ESI-IT) m/z 381.3 (M + H^+, 90), 382.3 (26), 383.3 (5), 403.3 (M + Na^+, 100), 404.3 (30), 405.3 (5); HRMS calcd for $C_{22}H_{41}O_3Si$ [M + H^+] 381.2825, found 381.2810 (−2.6 ppm); calcd for $C_{22}H_{40}O_3SiNa$ [M + Na^+] 403.2639, found 403.2629 (−2.5 ppm).

(±)-Methyl 2-((2*R*,5*R*,6*R*)-6-((*S*)-1-(Benzyloxy)propan-2-yl)-5-methyltetrahydro-2*H*-pyran-2-yl)-2-bromopropanoate (16a, 16b).



Aldehyde **S17** was obtained as a colorless oil from alcohol **S16** (197 mg) following general procedure **A5** and was used as crude without further purification. Products **16a** and **16b** (152 mg, yield = 71% over two steps) were obtained as colorless oils from crude aldehyde **S17** following general procedure **A7** and purification by flash chromatography on silica gel (hexanes/EtOAc 90:10). ^1H NMR spectroscopic analysis of the unpurified product indicated a pair of 2,3-diastereomers in a ∼1:1 ratio of products **16a**:**16b**.

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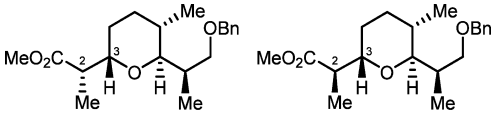
16a: R_f = 0.50 (hexanes/EtOAc, 85:15); formula $C_{20}H_{29}BrO_4$; MW 413.35 g/mol; IR (neat) ν_{max} 2961, 2868, 1742, 1452, 1262, 1095, 1047, 737 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37−7.25 (m, 5H), 4.54 (d, J = 12.0 Hz, 1H), 4.50 (d, J = 12.1 Hz, 1H), 4.14 (dd, J = 4.3 Hz, 10.4 Hz, 1H), 3.74 (s, 3H), 3.61 (dd, J = 3.3 Hz, 9.0 Hz, 1H), 3.33 (d, J = 10.3 Hz, 1H), 3.28 (dd, J = 7.5 Hz, 9.0 Hz, 1H), 2.40−2.30 (m, 1H), 1.90 (s, 3H), 1.89−1.80 (m, 2H), 1.80−1.70 (m, 2H), 1.56−1.48 (m, 1H), 1.12 (d, J = 7.0 Hz, 3H), 0.96 (d, J = 6.7 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 139.1, 128.5, 127.7, 127.6, 81.4, 73.5, 73.4, 72.6, 62.4, 53.2, 32.7, 26.6, 24.3, 22.7, 19.7, 18.6, 15.0 ppm; MS (ESI-IT) m/z 413.1 ($M + H^+$, 100), 416.1 (31), 430.2 (57), 435.1 ($M + Na^+$, 85), 437.1 (82), 438.1 (25); HRMS calcd for $C_{20}H_{30}BrO_4$ [$M + H^+$] 413.1327, found 413.1311 (−2.7 ppm); calcd for $C_{20}H_{29}BrO_4Na$ [$M + Na^+$] 435.1141, found 435.1132 (−2.2 ppm).

16b: R_f = 0.40 (hexanes/EtOAc, 85:15); formula $C_{20}H_{29}BrO_4$; MW 413.35 g/mol; IR (neat) ν_{max} 2865, 1739, 1452, 1264, 1112, 1055, 736 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36−7.23 (m, 5H), 4.57 (d, J = 12.1 Hz, 1H), 4.54 (d, J = 12.1 Hz, 1H), 4.01 (dd, J = 2.8 Hz, 11.6 Hz, 1H), 3.83 (dd, J = 3.2 Hz, 9.1 Hz, 1H), 3.78 (s, 3H), 3.41−3.35 (m, 2H), 2.43−2.33 (m, 1H), 1.89−1.78 (m, 2H), 1.86 (s, 3H), 1.74−1.63 (m, 1H), 1.51−1.44 (m, 1H), 1.38−1.32 (m, 1H), 1.14 (d, J = 6.9 Hz, 3H), 0.98 (d, J = 6.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 139.1, 128.5, 127.9, 127.6, 81.3, 74.0, 73.5, 72.8, 65.2, 53.4, 32.7, 26.5, 24.1, 23.7, 20.7, 18.6, 15.1 ppm; MS (ESI-IT) m/z 413.1 ($M + H^+$, 100), 416.1 (30), 417.1 (3), 432.2 (46), 435.1 ($M + Na^+$, 92), 438.1 (29), 439.1 (2); HRMS calcd for $C_{20}H_{30}BrO_4$ [$M + H^+$] 413.1327, found 413.1315 (−1.8 ppm); calcd for $C_{20}H_{29}BrO_4Na$ [$M + Na^+$] 435.1141, found 435.1134 (−1.7 ppm).

(±)-(*R*)-Methyl 2-((2*R*,5*R*,6*R*)-6-((*S*)-1-(Benzyloxy)propan-2-yl)-5-methyltetrahydro-2*H*-pyran-2-yl)propanoate (24a) and (±)-(*S*)-Methyl 2-((2*R*,5*R*,6*R*)-6-((*S*)-1-(Benzyloxy)propan-2-yl)-5-methyltetrahydro-2*H*-pyran-2-yl)propanoate (24b).

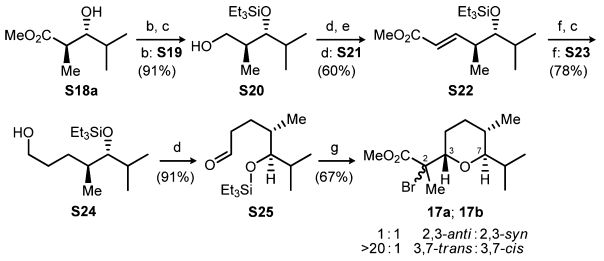


24a (2,3-*anti*) **24b** (2,3-*syn*)

Product **24a** and **24b** (23 mg, yield = 79%) were obtained as colorless oils from a mixture of bromides **16a,b** (36 mg) following general procedure **A1** and purification by flash chromatography on silica gel (hexanes/EtOAc 85:15). ^1H NMR spectroscopic analysis of the unpurified product indicated a pair of diastereomers in a 16:1 ratio of products 2,3-*anti* (**24a**):2,3-*syn* (**24b**).

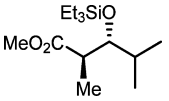
24a: R_f = 0.32 (hexanes/EtOAc, 85:15); formula $C_{20}H_{30}O_4$; MW 334.45 g/mol; IR (neat) ν_{max} 2930, 2859, 1739, 1456, 1376, 1168, 1098, 737 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38−7.25 (m, 5H), 4.53 (d, J = 12.0 Hz, 1H), 4.50 (d, J = 12.0 Hz, 1H), 3.83 (dt, J = 10.0 Hz, 5.4 Hz, 1H), 3.68 (s, 3H), 3.66 (dd, J = 4.2 Hz, 9.3 Hz, 1H), 3.30−3.24 (m, 2H), 2.79 (dq, J = 9.5 Hz, 7.0 Hz, 1H), 2.30−2.21 (m, 1H), 1.80−1.65 (m, 2H), 1.60−1.54 (m, 2H), 1.37−1.30 (m, 1H), 1.08 (d, J = 7.0 Hz, 3H), 1.01 (d, J = 6.7 Hz, 3H), 0.96 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 139.2, 128.5, 127.7, 127.5, 80.1, 73.5, 73.3, 72.1, 51.8, 42.9, 33.6, 29.6, 26.1, 24.2, 18.5, 15.7, 14.2 ppm; MS (ESI-IT) m/z 335.2 (100), 336.2 (14), 352.2 (4), 357.2 (45), 358.2 (11); HRMS calcd for $C_{20}H_{31}O_4$ [$M + H^+$] 335.2222, found 335.2212 (−1.3 ppm); calcd for $C_{20}H_{30}O_4Na$ [$M + Na^+$] 357.2036, found 357.2029 (−2.2 ppm).

24b: R_f = 0.38 (hexanes/EtOAc, 85:15); formula $C_{20}H_{30}O_4$; MW 334.45 g/mol; IR (neat) ν_{max} 2931, 1737, 1455, 1108, 1049 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38−7.25 (m, 5H), 4.53 (d, J = 12.3 Hz, 1H), 4.51 (d, J = 12.2 Hz, 1H), 3.78 (dt, J = 9.1 Hz, 5.4 Hz, 1H), 3.70−3.65 (m, 1H), 3.67 (s, 3H), 3.30 (dd, J = 8.1 Hz, 9.1 Hz, 1H), 3.14 (t, J = 6.0 Hz, 1H), 2.80−2.73 (m, 1H), 2.32−2.24 (m, 1H), 1.80−1.65 (m, 2H), 1.55−1.49 (m, 2H), 1.42−1.33 (m, 1H), 1.19 (d, J = 6.9 Hz, 3H), 1.03 (d, J = 6.8 Hz, 3H), 1.00 (d, J = 6.7 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 139.0, 128.5, 127.7, 127.6, 80.0, 73.3, 72.6, 72.1, 51.8, 42.5, 33.6, 29.5, 26.3, 25.6, 18.5, 16.0, 13.8 ppm; MS (ESI-IT) m/z 335.2 ($M + H^+$, 100), 336.2 (14), 352.2 (5), 357.2 ($M + Na^+$, 35), 358.2 (9); HRMS calcd for $C_{20}H_{31}O_4$ [$M + H^+$] 335.2222, found 335.2212 (−1.3 ppm); calcd for $C_{20}H_{30}O_4Na$ [$M + Na^+$] 357.2036, found 357.2028 (−2.3 ppm).



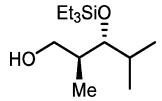
Reactions and conditions: a) Bu_2BOTf, DIEA, CH_2Cl_2, −78 °C then Bu_3SnH, Et_3B, air, CH_2Cl_2, −78 °C. b) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C. c) DIBAL-H, CH_2Cl_2, −40 °C. d) SO_3·py, DMSO, DIEA, CH_2Cl_2, 0 °C. e) $Ph_3PC(H)=CO_2Me$, toluene, reflux. f) H_2, Pd/C, EtOAc, rt. g) $BiBr_3$, **2**, CH_2Cl_2/MeCN, −78 °C.

(±)-(2*R*,3*R*)-Methyl 2,4-Dimethyl-3-(triethylsilyloxy)-pentanoate (S19).



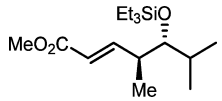
Product **S19** (326 mg, yield = 95%) was obtained as a pale yellow oil from alcohol **S18a**[28] (0.25 g) following general procedure **A3** and purification by flash chromatography on silica gel (hexanes/EtOAc 90:10): R_f = 0.56 (hexanes/EtOAc, 80:20); formula $C_{14}H_{30}O_3Si$; MW 274.47 g/mol; IR (neat) ν_{max} 2957, 2912, 2879, 1742, 1461, 1058, 786 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.81 (dd, J = 3.9 Hz, 7.5 Hz, 1H), 3.69 (s, 3H), 2.64 (dq, J = 7.2 Hz, 7.2 Hz, 1H), 1.79 (dsept, J = 4.0 Hz, 6.8 Hz, 1H), 1.10 (d, J = 7.1 Hz, 3H), 0.97 (t, J = 8.0 Hz, 9H), 0.92 (d, J = 6.9 Hz, 3H), 0.87 (d, J = 6.8 Hz, 3H), 0.61 (q, J = 7.9 Hz, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.2, 78.7, 51.6, 45.3, 30.5, 20.1, 16.3, 13.5, 7.1, 5.5 ppm; MS (ESI-IT) m/z 143.1 (65), 243.2 (13), 275.2 ($M + H^+$, 100); HRMS calcd for $C_{14}H_{31}O_3Si$ [$M + H^+$] 275.2037, found 275.2034 (−1.3 ppm).

(±)-(2*S*,3*R*)-2,4-Dimethyl-3-(triethylsilyloxy)pentan-1-ol (S20).



Product **S20** (233 mg, yield =96%) was obtained as a colorless oil from ester **S19** (268 mg) following general procedure **A4** and purification by flash chromatography on silica gel (hexanes/EtOAc 80:20): R_f = 0.38 (hexanes/EtOAc, 80:20); formula $C_{13}H_{30}O_2Si$; MW 246.46 g/mol; IR (neat) ν_{max} 3369, 2958, 2912, 2878, 1462, 1054, 736 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.73 (dd, J = 3.8 Hz, 10.9 Hz, 1H), 3.59 (dd, J = 5.6 Hz, 10.9 Hz, 1H), 3.45 (t, J = 5.1 Hz, 1H), 2.75 (bs, 1H), 1.90−1.78 (m, 2H), 1.01 (d, J = 8.0 Hz, 3H), 1.00 (t, J = 8.1 Hz, 9H), 0.94 (d, J = 6.8 Hz, 6H), 0.68 (q, J = 7.9 Hz, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 83.4, 66.2, 37.1, 33.0, 19.3, 18.6, 16.5, 7.2, 5.5 ppm; MS (ESI-IT) m/z 229.2 (34), 247.2 ($M + H^+$, 10), 361.3 (100), 363.3 (15); HRMS calcd for $C_{13}H_{31}O_2Si$ [$M + H^+$] 247.2088, found 247.2088 (0.04 ppm).

(±)-(4*S*,5*R*,*E*)-Methyl 4,6-Dimethyl-5-(triethylsilyloxy)hept-2-enoate (S22).



Aldehyde **S21** was obtained as a pale yellow oil from alcohol **S20** (219 mg) following general procedure **A11** and was used as crude without further purification. Product **S22** (155 mg, yield = 60% over two steps) was obtained as a colorless oil from crude aldehyde **S21** following general procedure **A6** and purification by flash chromatography on silica gel (hexanes/EtOAc 85:15): R_f = 0.51 (hexanes/EtOAc, 80:20); formula $C_{16}H_{32}O_3Si$; MW 300.51 g/mol; IR (neat) ν_{max} 2958, 2913, 2878, 1724, 1657, 1272, 736 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.05 (dd, J = 8.4 Hz, 15.8 Hz, 1H), 5.80 (d, J = 15.8 Hz, 1H), 3.73 (s, 3H), 3.36 (app t, J = 4.9 Hz, 1H), 2.56−2.47 (m, 1H), 1.75−1.65 (m, 1H), 1.05 (d, J = 6.9 Hz, 3H), 0.97 (t, J = 7.9 Hz, 9H), 0.88 (d, J = 6.8 Hz, 3H), 0.86 (d, J = 6.9 Hz, 3H), 0.62 (q, J = 8.0 Hz, 6H) ppm; ^{13}C NMR (125

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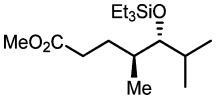
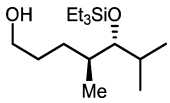
MHz, $CDCl_3$) δ 167.4, 152.8, 120.5, 81.4, 51.5, 40.9, 32.4, 19.9, 18.2, 17.6, 7.3, 5.7 ppm; MS (ESI-IT) m/z 169.1 (29), 209.1 (100), 301.2 (10), 323.2 (M + Na^+, 47); HRMS calcd for $C_{16}H_{32}O_3NaSi$ [M + Na^+] 323.2013, found 323.2015 (0.8 ppm).

(±)-(4*S*,5*R*)-Methyl 4,6-Dimethyl-5-(triethylsilyloxy)-heptanoate (S23).



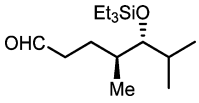
Product **S23** was obtained as a colorless oil from α,β-unsaturated ester **S22** (1.06 g) following general procedure **A2** and was used as crude without further purification: R_f = 0.51 (hexanes/EtOAc, 80:20); formula $C_{16}H_{34}O_3Si$; MW 302.53 g/mol; IR (neat) ν_{max} 2957, 2913, 2878, 1743, 1461, 1172, 1052, 737 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.68 (s, 3H), 3.24 (app t, J = 5.0 Hz, 1H), 2.41 (ddd, J = 5.5 Hz, 9.8 Hz, 15.4 Hz, 1H), 2.26 (ddd, J = 6.9 Hz, 9.5 Hz, 15.8 Hz, 1H), 1.90 (dddd, J = 3.5 Hz, 6.9 Hz, 10.1 Hz, 13.4 Hz, 1H), 1.78 (dq, J = 13.4 Hz, 6.7 Hz, 1H), 1.64–1.57 (m, 1H), 1.46–1.35 (m, 1H), 0.98 (t, J = 7.9 Hz, 9H), 0.90 (d, J = 6.7 Hz, 3H), 0.895 (d, J = 6.8 Hz, 3H), 0.887 (d, J = 6.6 Hz, 3H), 0.64 (q, J = 7.9 Hz, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.7, 82.4, 51.7, 36.5, 32.6, 31.4, 27.1, 20.6, 18.4, 16.9, 7.4, 5.8 ppm; MS (ESI-IT) m/z 171.1 (10), 211.1 (27), 303.2 (M + H^+, 98), 325.2 (M + Na^+, 100); HRMS calcd for $C_{16}H_{35}O_3Si$ [M + H^+] 303.2350, found 303.2339 (−3.6 ppm); calcd for $C_{16}H_{34}O_3NaSi$ [M + Na^+] 325.2175, found 325.2159 (−3.2 ppm).

(±)-(4*S*,5*R*)-4,6-Dimethyl-5-(triethylsilyloxy)heptan-1-ol (S24).



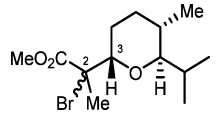
Primary alcohol **S24** (0.76 g, yield = 78% over two steps) was obtained as a colorless oil from crude ester **S23** (1.07 g) following general procedure **A4** and purification by flash chromatography on silica gel (CH_2Cl_2/Et_2O, 95:5): R_f = 0.18 (CH_2Cl_2/Et_2O, 95:5); formula $C_{15}H_{34}O_2Si$; MW 274.51 g/mol; IR (neat) ν_{max} 3332, 2957, 2913, 2877, 1462, 1056, 1009, 736 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.65–3.62 (m, 2H), 3.23 (app t, J = 4.9 Hz, 1H), 1.80–1.64 (m, 3H), 1.61–1.54 (m, 2H), 1.51–1.42 (m, 1H), 1.12–1.04 (m, 1H), 0.97 (t, J = 8.0 Hz, 9H), 0.89 (d, J = 6.7 Hz, 3H), 0.88 (d, J = 6.7 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H), 0.62 (q, J = 8.0 Hz, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 82.5, 63.6, 37.2, 31.19, 31.18, 28.2, 20.9, 18.1, 17.0, 7.4, 5.8 ppm; MS (ESI-IT) m/z 143.1 (60), 183.1 (100), 261.1 (11), 297.2 (M + Na^+, 11), 343.3 (8), 421.2 (8); HRMS calcd for $C_{15}H_{34}O_2NaSi$ [M + Na^+] 297.2226, found 297.2229 (2.9 ppm).

(±)-(4*S*,5*R*)-4,6-Dimethyl-5-(triethylsilyloxy)heptanal (S25).



Product **S25** (0.66 g, yield = 91%) was obtained as a pale yellow oil from alcohol **S24** (0.73 g) following general procedure **A14** and purification by flash chromatography on silica gel (hexanes/EtOAc 85:15): R_f = 0.56 (hexanes/EtOAc, 80:20); formula $C_{15}H_{32}O_2Si$; MW 272.50 g/mol; IR (neat) ν_{max} 2958, 2912, 2878, 2714, 1728, 1101, 1054, 1009, 736 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.79 (app t, J = 1.8 Hz, 1H), 3.25 (app t, J = 5.0 Hz, 1H), 2.51 (dddd, J = 1.6 Hz, 5.6 Hz, 9.6 Hz, 15.3 Hz, 1H), 2.41–2.34 (m, 1H), 1.92 (dddd, J = 13.4 Hz, 9.8 Hz, 6.5 Hz, 3.5 Hz, 1H), 1.79 (dq, J = 13.4 Hz, 6.7 Hz, 1H), 1.65–1.57 (m, 1H), 1.44–1.35 (m, 1H), 0.99 (t, J = 7.9 Hz, 9H), 0.905 (d, J = 6.5 Hz, 3H), 0.903 (d, J = 6.7 Hz, 3H), 0.89 (d, J = 6.2 Hz, 3H), 0.64 (q, J = 7.9 Hz, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.2, 82.4, 42.5, 36.5, 31.5, 24.3, 20.6, 18.2, 17.1, 7.4, 5.8 ppm; MS (ESI-IT) m/z 157.1 (30), 271.2 (M − H^+, 76), 403.3 (100), 778.6 (5); HRMS calcd for $C_{15}H_{31}O_2Si$ [M − H^+] 271.2088, found 271.2088 (−0.04 ppm).

(±)-Methyl 2-Bromo-2-((2*S*,5*S*,6*R*)-6-isopropyl-5-methyltetrahydro-2*H*-pyran-2-yl)propanoate (17a, 17b).

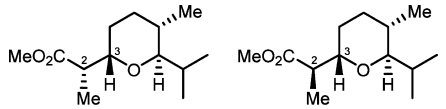


Products **17a** and **17b** (481 mg, yield = 67%) were obtained as pale yellow oils from aldehyde **S25** (643 mg) following general procedure **A7** and purification by flash chromatography on silica gel (hexanes/EtOAc 90:10). ^1H NMR spectroscopic analysis of the unpurified product indicated a pair of 2,3-diastereomers in a ~1:1 ratio of products **17a**:**17b**.

17a: R_f = 0.43 (hexanes/EtOAc, 90:10); formula $C_{13}H_{23}BrO_3$; MW 307.22 g/mol; IR (neat) ν_{max} 2959, 2872, 1745, 1449, 1262, 1048 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.11 (dd, J = 4.0 Hz, 10.6 Hz, 1H), 3.79 (s, 3H), 3.04 (d, J = 9.9 Hz, 1H), 2.19–2.09 (m, 1H), 1.93 (s, 3H), 1.89–1.82 (m, 2H), 1.80–1.68 (m, 2H), 1.52–1.48 (m, 1H), 1.10 (d, J = 7.0 Hz, 3H), 0.90 (d, J = 6.5 Hz, 3H), 0.84 (d, J = 6.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 86.0, 73.5, 62.5, 53.2, 27.0, 26.9, 24.5, 22.7, 20.1, 19.8, 19.3, 18.7 ppm; MS (ESI-IT) m/z 209.2 (5), 307.1 (M + H^+, 19), 329.1 (M + Na^+, 100), 637.2 (25); HRMS calcd for $C_{13}H_{24}BrO_3$ [M + H^+] 307.0903, found 307.0914 (3.4 ppm); calcd for $C_{13}H_{23}BrNaO_3$ [M + Na^+] 329.0728, found 329.0734 (3.4 ppm).

17b: R_f = 0.56 (hexanes/EtOAc, 90:10); formula $C_{13}H_{23}BrO_3$; MW 307.22 g/mol; IR (neat) ν_{max} 2957, 2872, 1741, 1450, 1265, 1058 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.91 (dd, J = 2.9 Hz, 11.5 Hz, 1H), 3.78 (s, 3H), 3.12 (d, J = 10.3 Hz, 1H), 2.21–2.11 (m, 1H), 1.87 (s, 3H), 1.86–1.80 (m, 2H), 1.70 (ddd, J = 4.4 Hz, 12.6 Hz, 24.7 Hz, 1H), 1.48–1.43 (m, 1H), 1.34 (ddd, J = 3.2 Hz, 6.7 Hz, 12.7 Hz, 1H), 1.12 (d, J = 7.0 Hz, 3H), 1.01 (d, J = 6.5 Hz, 3H), 0.85 (d, J = 6.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 85.7, 74.1, 65.8, 53.4, 27.0, 26.9, 24.3, 24.2, 20.9, 20.1, 19.6, 18.8 ppm; MS (ESI-IT) m/z 209.2 (11), 307.1 (M + H^+, 60), 329.1 (M + Na^+, 100), 332.1 (94), 637.2 (54); HRMS calcd for $C_{13}H_{24}BrO_3$ [M + H^+] 307.0903, found 307.0912 (2.9 ppm); calcd for $C_{13}H_{23}BrNaO_3$ [M + Na^+] 329.0728, found 329.0733 (3.0 ppm).

(±)-(*S*)-Methyl 2-((2*S*,5*S*,6*R*)-6-Isopropyl-5-methyltetrahydro-2*H*-pyran-2-yl)propanoate (25a) and (±)-(*R*)-Methyl 2-((2*S*,5*S*,6*R*)-6-Isopropyl-5-methyltetrahydro-2*H*-pyran-2-yl) propanoate (25b).



25a (2,3-*anti*) **25b** (2,3-*syn*)

Products **25a** and **25b** (58 mg, yield = 76%) were obtained as pale yellow oils from a mixture of bromides **17a** and **17b** (103 mg) following general procedure **A1** and purification by flash chromatography on silica gel (hexanes/EtOAc 90:10). ^1H NMR spectroscopic analysis of the unpurified product indicated a pair of diastereomers in a 17:1 ratio of products 2,3-*anti* (**25a**):2,3-*syn* (**25b**). The reaction performed on a mixture of bromides **17a** and **17b** (15 mg) according to general procedure **A1** with Ph_3SnH in CH_2Cl_2 led to the formation of product 2,3-*anti* (**25a**) and 2,3-*syn* (**25b**) in a 3:1 ratio of products (11 mg, yield = 98%) as verified by ^1H NMR analysis of the crude mixture.

25a: R_f = 0.25 (hexanes/EtOAc, 90:10); formula $C_{13}H_{24}O_3$; MW 228.33 g/mol; IR (neat) ν_{max} 2955, 2933, 2875, 1740 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.84 (dt, J = 10.2 Hz, 5.3 Hz, 1H), 3.70 (s, 3H), 3.09 (app t, J = 5.9 Hz, 1H), 2.85 (dq, J = 9.7 Hz, 6.9 Hz, 1H), 1.99 (qd, J = 6.7 Hz, 13.3 Hz, 1H), 1.72–1.54 (m, 4H), 1.36–1.30 (m, 1H), 1.09 (d, J = 7.0 Hz, 3H), 0.96 (d, J = 6.6 Hz, 3H), 0.861 (d, J = 6.7 Hz, 3H), 0.858 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.1, 82.2, 73.7, 51.8, 42.7, 30.1, 27.9, 26.5, 24.4, 20.2, 18.4, 16.6, 14.3 ppm; MS (ESI-IT) m/z 229.2 (M + H^+, 12), 251.2 (M + Na^+, 100), 252.2 (14); HRMS calcd for $C_{13}H_{25}O_3$ [M + H^+] 229.1798, found 229.1794 (−2.1 ppm); calcd for $C_{13}H_{24}NaO_3$ [M + Na^+] 251.1618, found 251.1613 (−1.7 ppm).

25b: R_f = 0.29 (hexanes/EtOAc, 90:10); formula $C_{13}H_{24}O_3$; MW 228.33 g/mol; IR (neat) ν_{max} 2927, 2861, 1733, 1461, 1277, 1123, 1072 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.80 (dt, J = 9.4 Hz, 5.3 Hz, 1H), 3.69 (s, 3H), 2.95 (app t, J = 5.9 Hz, 1H), 2.83 (dq, J = 9.2 Hz, 6.9 Hz,

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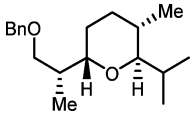
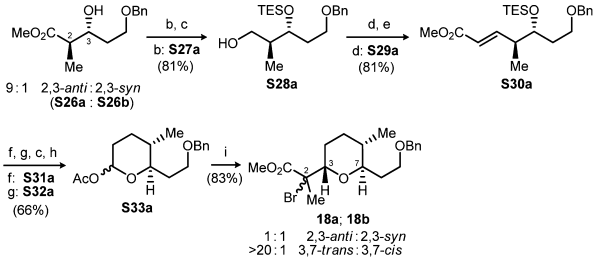
1H), 2.02 (dq, J = 13.3 Hz, 6.6 Hz, 1H), 1.74−1.47 (m, 4H), 1.46−1.30 (m, 1H), 1.24 (d, J = 6.9 Hz, 3H), 0.96 (d, J = 6.7 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H), 0.90 (d, J = 6.7 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.0, 82.0, 72.8, 51.8, 42.2, 30.1, 27.9, 26.7, 26.2, 20.6, 18.4, 16.7, 13.9 ppm; MS (ESI-IT) m/z 118.1 (62), 141.0 (20), 251.2 (28), 338.3 (45), 360.3 (54), 391.3 (25), 413.3 (100); HRMS calcd for $C_{13}H_{24}NaO_3$ [M + Na^+] 251.1618, found 251.1615 (−1.2 ppm).

(±)-(2*R*,3*S*,6*S*)-6-((*R*)-1-(Benzyloxy)propan-2-yl)-2-isopropyl-3-methyltetrahydro-2*H*-pyran (S8).

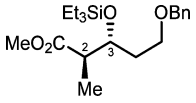


Primary alcohol was obtained as a colorless oil from ester **25a** (10 mg) following general procedure **A4** and was used as crude without further purification. To a cold (0 °C) solution of crude alcohol in dry CH_2Cl_2 (0.1 M, 435 μL) were added successively a 60% w/w dispersion of NaH in mineral oil (1.3 equiv, 2 mg) and benzyl bromide (1.5 equiv, 8 μL). The reaction mixture was stirred for 1 h at 0 °C followed by stirring for 18 h at room temperature. 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 Et_2O (3×), and combined organic fractions were dried ($MgSO_4$), filtered, and concentrated in vacuo. Product **S8** (8.8 mg, 69% over two steps) was obtained as a colorless oil after purification by flash chromatography on silica gel (hexanes/EtOAc 90:10). ^{1}H and ^{13}C NMR chemical shift were identical to those previously reported for product **S8** synthesized from **S7**[6d] (vide supra).



Reactions and conditions: a) Bu_2BOTf, DIEA, CH_2Cl_2, −78 °C then Bu_3SnH, Et_3B, air, CH_2Cl_2, −78 °C. b) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C. c) DIBAL-H, CH_2Cl_2, −40 °C. d) SO_3·py, DMSO, DIEA, CH_2Cl_2, 0 °C. e) $Ph_3PC(H)=CO_2Me$, toluene, reflux. f) H_2, Pd/C, EtOAc, rt. g) *p*-TsOH, benzene, reflux. h) Ac_2O, pyridine, DMAP, CH_2Cl_2, −40 °C to rt. i) $SnCl_4$, **2**, CH_2Cl_2, −78 °C.

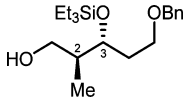
(±)-(2*R*,3*R*)-Methyl 5-(Benzyloxy)-2-methyl-3-(triethylsilyloxy)pentanoate (S27a).



An inseparable mixture of product 2,3-*anti* (**S27a**):2,3-*syn* (**S27b**) was obtained as a pale yellow oil from an inseparable 9:1 mixture (1.97 g) of alcohol 2,3-*anti* (**S26a**) and 2,3-*syn* (**S26b**)[10] following general procedure **A3**. Crude product as a mixture was used without further purification. ^{1}H NMR spectroscopic analysis of the unpurified product indicated a pair of diastereomers in a 9:1 ratio of products 2,3-*anti* (**S27a**); 2,3-*syn* (**S27b**).

S27a: R_f = 0.66 (hexanes/EtOAc, 70:30); formula $C_{20}H_{34}O_4Si$; MW 366.56 g/mol IR (neat) ν_{max} 2853, 2878, 1740, 1440, 1108, 734 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.25 (m, 5H), 4.50 (d, J = 12.0 Hz, 1H), 4.47 (d, J = 12.1 Hz, 1H), 4.15 (dt, J = 5.7 Hz, 5.7 Hz, 1H), 3.65 (s, 3H), 3.56 (app t, J = 6.6 Hz, 2H), 2.65 (dq, J = 6.9 Hz, 6.9 Hz, 1H), 1.77 (q, J = 6.4 Hz, 2H), 1.12 (d, J = 7.1 Hz, 3H), 0.93 (t, J = 7.9 Hz, 9H), 0.58 (q, J = 7.9 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 138.7, 128.5, 127.8, 127.7, 73.1, 71.0, 66.8, 51.7, 46.2, 33.6, 12.1, 7.1, 5.2 ppm; MS (ESI-IT) m/z 259.2 (11), 335.2 (51), 367.2 (M + H^+, 100), 481.3 (15); HRMS calcd for $C_{20}H_{35}O_4Si$ [M + H^+] 367.2299, found 367.2302 (0.6 ppm).

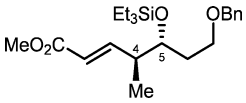
(±)-(2*S*,3*R*)-5-(Benzyloxy)-2-methyl-3-(triethylsilyloxy)-pentan-1-ol (S28a).



An inseparable mixture of product 2,3-*anti* (**S28a**):2,3-*syn* (**S28b**) was obtained as a colorless oil (2.32 g, yield = 81% over two steps) from an inseparable 9:1 mixture (2.37 g) of product 2,3-*anti* (**S27a**):2,3-*syn* (**S27b**) following general procedure **A4** and purification by flash chromatography on silica gel (hexanes/EtOAc 70:30). ^{1}H NMR spectroscopic analysis of the unpurified product indicated a pair of diastereomers in a 9:1 ratio of products 2,3-*anti* (**S28a**):2,3-*syn* (**S28b**).

S28a: R_f = 0.38 (hexanes/EtOAc, 70:30); formula $C_{19}H_{34}O_3Si$; MW 338.56 g/mol; IR (neat) ν_{max} 3435, 2956, 2877, 1100, 1012, 734 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.27 (m, 5H), 4.51 (d, J = 11.9 Hz, 1H), 4.47 (d, J = 11.9 Hz, 1H), 3.91 (dd, J = 5.7 Hz, 10.4 Hz, 1H), 3.74 (dd, J = 3.8 Hz, 11.0 Hz, 1H), 3.53 (app t, J = 6.6 Hz, 3H), 2.62 (bs, 1H), 1.90−1.84 (m, 1H), 1.78−1.71 (m, 1H), 0.99 (d, J = 7.0 Hz, 3H), 0.96 (t, J = 7.9 Hz, 9H), 0.62 (q, J = 7.8 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 128.6, 127.9, 127.8, 74.6, 73.3, 67.0, 65.8, 39.3, 35.0, 14.3, 7.1, 5.2 ppm; MS (ESI-IT) m/z 339.2 (M + H^+, 100), 438.3 (11), 453.3 (34); HRMS calcd for $C_{19}H_{35}O_3Si$ [M + H^+] 339.2350, found 339.2357 (2.0 ppm).

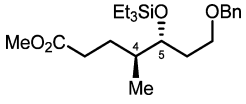
(±)-(4*S*,5*R*,*E*)-Methyl 7-(Benzyloxy)-4-methyl-5-(triethylsilyloxy)hept-2-enoate (S30a).



An inseparable mixture of aldehyde 2,3-*anti* (**S29a**):2,3-*syn* (**S29b**) was obtained as a pale yellow oil from an inseparable 9:1 mixture (1.01 g) of product 2,3-*anti* (**S28a**):2,3-*syn* (**S28b**) following general procedure **A11** and was used as crude without further purification. An inseparable mixture of product 4,5-*anti* (**S30a**); 4,5-*syn* (**S30b**) was obtained as a colorless oil (0.947 g, yield = 81% over two steps) from an inseparable mixture of aldehyde following general procedure **A6** and purification by flash chromatography on silica gel (hexanes/EtOAc 80:20). ^{1}H NMR spectroscopic analysis of the unpurified product indicated a pair of diastereomers in a 9:1 ratio of products 4,5-*anti* (**S30a**):4,5-*syn* (**S30b**).

S30a: R_f = 0.43 (hexanes/EtOAc, 80:20); formula $C_{22}H_{36}O_4Si$; MW 392.60 g/mol; IR (neat) ν_{max} 2955, 2873, 1725, 1274, 1103, 1011, 734 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.23 (m, 5H), 6.95 (dd, J = 7.8 Hz, 15.8 Hz, 1H), 5.80 (dd, J = 1.2 Hz, 15.8 Hz, 1H), 4.50 (d, J = 11.9 Hz, 1H), 4.45 (d, J = 11.9 Hz, 1H), 3.87 (td, J = 4.8 Hz, 7.3 Hz, 1H), 3.73 (s, 3H), 3.50 (app t, J = 6.5 Hz, 2H), 2.48−2.42 (m, 1H), 1.73−1.65 (m, 2H), 1.06 (d, J = 6.9 Hz, 3H), 0.95 (t, J = 7.9 Hz, 9H), 0.59 (q, J = 7.9 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 151.4, 138.6, 128.6, 127.9, 127.8, 121.3, 73.2, 72.4, 67.1, 51.6, 42.7, 34.4, 14.9, 7.2, 5.3 ppm; MS (ESI-IT) m/z 169.1 (6), 229.1 (16), 261.1 (16), 393.2 (M + H^+, 100), 492.4 (8), 507.3 (11); HRMS calcd for $C_{22}H_{37}O_4Si$ [M + H^+] 393.2456, found 393.2468 (3.0 ppm).

(±)-(4*S*,5*R*)-Methyl 7-(Benzyloxy)-4-methyl-5-(triethylsilyloxy)heptanoate (S31a).



An inseparable mixture of product 4,5-*anti* (**S31a**):4,5-*syn* (**S31b**) was obtained as a colorless oil (0.86 g, yield = 83%) from an inseparable 9:1 mixture (1.03 g) of product 4,5-*anti* (**S30a**):4,5-*syn* (**S30b**) following general procedure **A2** to which was added pyridine[29] (1.5 equiv, 0.26 mL) before the gas atmosphere was changed to H_2. ^{1}H NMR spectroscopic analysis of the unpurified product indicated a pair of diastereomers in a 9:1 ratio of products 4,5-*anti* (**S31a**):4,5-*syn* (**S31b**).

S31a: R_f = 0.43 (hexanes/EtOAc, 80:20); formula $C_{22}H_{38}O_4Si$; MW 394.62 g/mol; IR (neat) ν_{max} 2955, 2877, 1741, 1456, 1240, 1101, 1010, 735 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.22 (m, 5H), 4.51 (d, J = 11.8 Hz, 1H), 4.47 (d, J = 11.8 Hz, 1H), 3.76 (dt, J = 8.3 Hz, 3.3 Hz, 1H), 3.66 (s, 3H), 3.54 (app t, J = 6.2 Hz, 2H), 2.42−2.33 (m, 1H),

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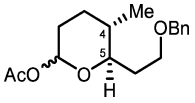
2.31−2.22 (m, 1H), 1.73−1.62 (m, 3H), 1.60−1.48 (m, 1H), 1.44−1.37 (m, 1H), 0.94 (t, J = 7.9 Hz, 9H), 0.88 (d, J = 6.7 Hz, 3H), 0.57 (q, J = 7.9 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 138.8, 128.6, 127.9, 127.7, 73.2, 72.8, 67.7, 51.8, 38.7, 32.5, 28.1, 14.2, 7.2, 5.3 ppm; MS (ESI-IT) m/z 141.1 (16), 213.1 (9), 231.1 (18), 263.2 (100), 363.2 (6), 395.3 (M + H$^+$, 16); HRMS calcd for $C_{22}H_{39}O_4Si$ [M + H$^+$] 395.2612, found 395.2610 (−0.5 ppm).

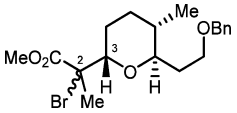
(±)-(5*S*,6*R*)-6-(2-(Benzyloxy)ethyl)-5-methyltetrahydro-2*H*-pyran-2-yl acetate (S33a).



An inseparable mixture of lactone 4,5-*anti* (**S32a**):4,5-*syn* (**S32b**) was obtained as a colorless oil from an inseparable 9:1 mixture (453 mg) of product 4,5-*anti* (**S31a**):4,5-*syn* (**S31b**) following general procedure **A8**. An inseparable mixture of product 4,5-*anti* (**S33a,b**):4,5-*syn* (**S33c,d**) (156 mg, yield = 79% over three steps) was obtained as a colorless oil from an inseparable mixture of crude lactone 4,5-*anti* (**S32a**):4,5-*syn* (**S32b**) following general procedure **A9** and purification by flash chromatography on silica gel (hexanes/EtOAc 95:5). ^{1}H NMR spectroscopic analysis of the unpurified product indicated a pair of diastereomers in a 9:1 ratio of products 4,5-*anti* (**S33a,b**):4,5-*syn* (**S33c,d**).

S33a: R_f = 0.21 (hexanes/Acetone, 95:5); formula $C_{17}H_{24}O_4$; MW 292.37 g/mol; IR (neat) ν_{max} 3068, 3032, 2956, 2930, 2866, 1746, 1456, 1221, 951, 737 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.27 (m, 5H), 6.13 (bs, 1H), 4.52 (d, J = 11.8 Hz, 1H), 4.50 (d, J = 12.1 Hz, 1H), 3.65−3.56 (m, 3H), 2.06−1.99 (m, 1H), 2.05 (s, 3H), 1.85−1.74 (m, 2H), 1.66−1.59 (m, 2H), 1.56−1.45 (m, 2H), 0.91 (d, J = 6.0 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 139.0, 128.6, 127.74, 127.65, 92.3, 73.9, 73.3, 67.0, 34.9, 33.3, 29.3, 27.0, 21.5, 18.2 ppm; MS (ESI-IT) m/z 233.2 (38), 273.2 (9), 310.2 (M + NH_4^+, 11), 315.2 (M + Na$^+$, 100), 392.3 (4), 607.3 (13); HRMS calcd for $C_{17}H_{28}O_4N$ [M + NH_4^+] 310.2013, found 310.2011 (−0.5 ppm); calcd for $C_{17}H_{24}NaO_4$ [M + Na$^+$] 315.1572, found 315.1564 (−0.8 ppm).

(±)-Methyl 2-((2*S*,5*S*,6*R*)-6-(2-(Benzyloxy)ethyl)-5-methyltetrahydro-2*H*-pyran-2-yl)-2-bromopropanoate (18a; 18b).

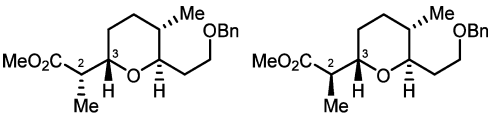


Products **18a** and **18b** (120 mg, yield = 83%) were obtained as pale yellow oils from an inseparable mixture (106 mg) of product 4,5-*anti* (**S33a,b**):4,5-*syn* (**S33c,d**) following general procedure **A10** and purification by flash chromatography on silica gel (hexanes/EtOAc 80:20). ^{1}H NMR spectroscopic analysis of the unpurified product indicated a pair of 2,3-diastereomers in a ∼1:1 ratio of products **18a**:**18b**.

18a: R_f = 0.36 (hexanes/EtOAc, 80:20); formula $C_{19}H_{27}BrO_4$; MW 399.32 g/mol; IR (neat) ν_{max} 3056, 3030, 2953, 2867, 1738, 1452, 1267, 1113, 1058, 738 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.27 (m, 5H), 4.56 (d, J = 11.9 Hz, 1H), 4.52 (d, J = 11.9 Hz, 1H), 3.97 (dd, J = 2.8 Hz, 11.5 Hz, 1H), 3.86 (dd, J = 1.8 Hz, 9.9 Hz, 1H), 3.78 (s, 3H), 3.66−3.61 (m, 1H), 2.29−2.21 (m, 1H), 1.95−1.87 (m, 1H), 1.86 (s, 3H), 1.75−1.67 (m, 2H), 1.64−1.57 (m, 1H), 1.53−1.46 (m, 1H), 1.42−1.35 (m, 1H), 1.13 (d, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 138.8, 128.6, 128.0, 127.8, 75.6, 73.8, 73.4, 67.6, 65.5, 53.4, 31.6, 30.7, 24.8, 23.9, 21.4, 18.6 ppm; MS (ESI-IT) m/z 399.1 (M + H$^+$, 30), 423.1 (M + Na$^+$, 100); HRMS calcd for $C_{19}H_{28}BrO_4$ [M + H$^+$] 399.1165, found 399.1162 (−1.0 ppm); calcd for $C_{19}H_{27}BrNaO_4$ [M + Na$^+$] 423.0990, found 423.0979 (−1.5 ppm).

18b: R_f = 0.41 (hexanes/EtOAc, 80:20); formula $C_{19}H_{27}BrO_4$; MW 399.32 g/mol; IR (neat) ν_{max} 2953, 2867, 1742, 1451, 1264, 1096, 1049, 738 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.27 (m, 5H), 4.52 (d, J = 12.0 Hz, 1H), 4.49 (d, J = 12.0 Hz, 1H), 4.16 (dd, J = 3.0 Hz, 11.5 Hz, 1H), 3.77−3.72 (m, 1H), 3.73 (s, 3H), 3.55−3.47 (m, 2H), 2.21−2.12 (m, 1H), 1.95−1.88 (m, 1H), 1.89 (s, 3H), 1.82−1.77 (m, 1H), 1.74−1.68 (m, 2H), 1.61−1.52 (m, 2H), 1.10 (d, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 138.7, 128.6, 127.83, 127.77, 76.9, 73.3, 73.2, 67.5, 61.7, 53.2, 31.7, 30.8, 25.0, 22.3, 20.0, 18.6 ppm; MS (ESI-IT) m/z 338.3 (7), 399.1 (M + H$^+$, 100), 421.1 (M + Na$^+$, 96), 458.2 (9); HRMS calcd for $C_{19}H_{28}BrO_4$ [M + H$^+$] 399.1165, found 399.1166 (0.2 ppm); calcd for $C_{19}H_{27}BrNaO_4$ [M + Na$^+$] 421.0990, found 421.0987 (0.4 ppm).

(±)-(*S*)-Methyl 2-((2*S*,5*S*,6*R*)-6-(2-(Benzyloxy)ethyl)-5-methyltetrahydro-2*H*-pyran-2-yl)propanoate (26a) and (±)-(*R*)-Methyl 2-((2*S*,5*S*,6*R*)-6-(2-(Benzyloxy)ethyl)-5-methyltetrahydro-2*H*-pyran-2-yl)propanoate (26b).

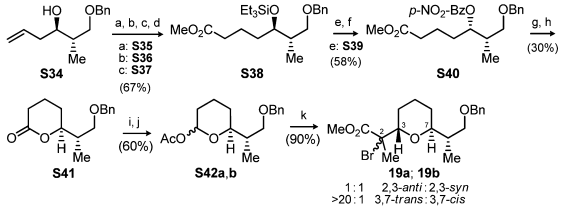


26a (2,3-*anti*) **26b** (2,3-*syn*)

Products **26a** and **26b** (28 mg, yield = 70%) were obtained as pale yellow oils from a mixture of bromides **18a** and **18b** (50 mg) following general procedure **A1** and purification by flash chromatography on silica gel (hexanes/EtOAc 80:20). ^{1}H NMR spectroscopic analysis of the unpurified product indicated a pair of diastereomers in a 17:1 ratio of products 2,3-*anti* (**26a**):2,3-*syn* (**26b**).

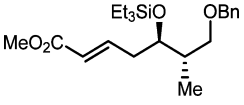
26a: R_f = 0.26 (hexanes/EtOAc, 80:20); formula $C_{19}H_{28}O_4$; MW 320.42 g/mol; IR (neat) ν_{max} 3026, 2950, 2935, 2868, 1738, 1456, 1196, 1092, 738 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.26 (m, 5H), 4.53 (d, J = 11.9 Hz, 1H), 4.50 (d, J = 11.9 Hz, 1H), 3.85 (td, J = 4.9 Hz, 10.0 Hz, 1H), 3.62 (s, 3H), 3.57−3.45 (m, 3H), 2.86 (dq, J = 10.0 Hz, 6.9 Hz, 1H), 1.92−1.80 (m, 2H), 1.73−1.56 (m, 3H), 1.49−1.42 (m, 1H), 1.36−1.29 (m, 1H), 1.08 (d, J = 6.9 Hz, 3H), 0.98 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 138.9, 128.6, 127.9, 127.7, 74.8, 73.7, 73.3, 67.9, 51.7, 42.3, 33.8, 33.0, 26.4, 24.6, 18.5, 14.2 ppm; MS (ESI-IT) m/z 321.2 (M + H$^+$, 100), 343.2 (M + Na$^+$, 22), 380.3 (8); HRMS calcd for $C_{19}H_{29}O_4$ [M + H$^+$] 321.2060, found 321.2058 (−0.8 ppm); calcd for $C_{19}H_{28}NaO_4$ [M + Na$^+$] 343.1885, found 343.1881 (0.3 ppm).

26b: R_f = 0.31 (hexanes/EtOAc, 80:20); formula $C_{19}H_{28}O_4$; MW 320.42 g/mol; IR (neat) ν_{max} 3062, 3030, 2950, 2932, 2861, 1736, 1455, 1112, 1048, 738 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.27 (m, 5H), 4.53 (d, J = 11.8 Hz, 1H), 4.49 (d, J = 11.9 Hz, 1H), 3.84 (td, J = 4.2 Hz, 9.0 Hz, 1H), 3.68 (s, 3H), 3.65−3.56 (m, 2H), 3.39−3.33 (m, 1H), 2.92 (dq, J = 9.6 Hz, 6.9 Hz, 1H), 1.98−1.89 (m, 1H), 1.81−1.72 (m, 1H), 1.72−1.63 (m, 2H), 1.54−1.35 (m, 3H), 1.20 (d, J = 6.9 Hz, 3H), 0.95 (d, J = 6.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 138.8, 128.6, 128.0, 127.8, 73.5, 73.3, 73.2, 67.3, 51.9, 41.1, 34.3, 33.3, 27.0, 26.6, 18.4, 14.1 ppm; MS (ESI-IT) m/z 321.2 (M + H$^+$, 47), 343.2 (M + Na$^+$, 100); HRMS calcd for $C_{19}H_{29}O_4$ [M + H$^+$] 321.2060, found 321.2056 (−1.4 ppm); calcd for $C_{19}H_{28}NaO_4$ [M + Na$^+$] 343.1885, found 343.1872 (−2.2 ppm).



Reactions and conditions: a) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C. b) OsO_4, 2,6-lutidine, $NaIO_4$, 1,4-dioxane/H_2O (3 : 1), rt. c) $Ph_3PC(H)=CO_2Me$, toluene, reflux. d) H_2, Pd/C, EtOAc, rt. e) $BF_3{\cdot}OEt_2$, MeCN, 0 °C. f) *p*-$NO_2C_6H_4COOH$, DEAD, PPh_3, THF, 25 °C. g) MeONa, MeOH, 0 °C. h) *p*-TsOH, benzene, reflux. i) DIBAL-H, CH_2Cl_2, −40 °C. j) Ac_2O, pyridine, DMAP, CH_2Cl_2, −40 °C to rt. k) $SnCl_4$, **2**, CH_2Cl_2, −78 °C.

(±)-(5*R*,6*S*,*E*)-Methyl 7-(Benzyloxy)-6-methyl-5-(triethylsilyloxy)hept-2-enoate (S37).



Product **35** as a pale yellow oil was obtained from alcohol **S34**[30] (1.33 g) following general procedure **A3** and was used as crude without further purification. To a solution at room temperature of crude product in a solvent mixture of 1,4-dioxane and H_2O (3:1, 0.1 M, 60 mL) were added successively 2,6-lutidine (2 equiv, 1.40 mL), OsO_4 (0.2 equiv, 0.74 mL), and $NaIO_4$ (4 equiv, 5.17 g). The reaction mixture was stirred for 1.5 h at

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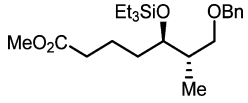
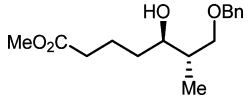
room temperature before filtration onto a pad of Celite and washing with Et_2O. The filtrate was then treated with a saturated aqueous solution of $Na_2S_2O_3$, followed by stirring overnight at room temperature before separation of the organic phase. The aqueous layer was extracted with Et_2O (3×), and combined organic fractions were dried ($MgSO_4$), filtered, and concentrated in vacuo. Product **S37** (1.64 g, yield =78% over three steps) was obtained as a colorless oil from crude aldehyde **S36** following general procedure **A6** and purification by flash chromatography on silica gel (hexanes/EtOAc 80:20): R_f = 0.44 (hexanes/EtOAc, 80:20); formula $C_{22}H_{36}O_4Si$; MW 392.60 g/mol; IR (neat) ν_{max} 3065, 3027, 2954, 2877, 1726, 1657, 1456, 1269, 1078 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37−7.25 (m, 5H), 7.01 (td, J = 7.4 Hz, 15.4 Hz, 1H), 5.84 (d, J = 15.7 Hz, 1H), 4.51 (d, J = 12.1 Hz, 1H), 4.45 (d, J = 12.1 Hz, 1H), 3.86 (dd, J = 5.5 Hz, 11.1 Hz, 1H), 3.73 (s, 3H), 3.44 (dd, J = 6.1 Hz, 9.2 Hz, 1H), 3.34 (dd, J = 6.2 Hz, 9.2 Hz, 1H), 2.34−2.32 (m, 2H), 1.95 (hept, J = 6.3 Hz, 1H), 0.94 (t, J = 7.9 Hz, 9H), 0.92 (d, J = 6.9 Hz, 3H), 0.58 (q, J = 7.9 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 146.9, 138.8, 128.5, 127.72, 127.70, 123.0, 73.2, 72.8, 72.4, 51.6, 39.4, 36.8, 13.1, 7.2, 5.2 ppm; MS (ESI-IT) m/z 193.1 (52), 393.2 (M + H^+, 100), 507.3 (10); HRMS calcd for $C_{22}H_{37}O_4Si$ [M + H^+] 393.2456, found 393.2450 (−1.4 ppm).

(±)-(5*R*,6*S*)-Methyl 7-(Benzyloxy)-6-methyl-5-(triethylsilyloxy)heptanoate (S38).



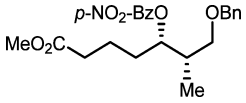
Product **S38** (1.41 g, yield = 86%) was obtained as a colorless oil from α,β-unsaturated ester **S37** (1.63 g) following general procedure **A2** and purification by flash chromatography on silica gel (hexanes/EtOAc 80:20): R_f = 0.44 (hexanes/EtOAc, 80:20); formula $C_{22}H_{38}O_4Si$; MW 394.62 g/mol; IR (neat) ν_{max} 3065, 3030, 2954, 2911, 2876, 1741, 1456, 1242, 1089 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37−7.29 (m, 5H), 4.52 (d, J = 12.1 Hz, 1H), 4.47 (d, J = 12.1 Hz, 1H), 3.76 (td, J = 4.7 Hz, 6.8 Hz, 1H), 3.68 (s, 3H), 3.46 (dd, J = 6.0 Hz, 9.2 Hz, 1H), 3.31 (dd, J = 6.7 Hz, 9.1 Hz, 1H), 2.31 (dt, J = 1.9 Hz, 7.6 Hz, 2H), 1.99 (hept, J = 6.3 Hz, 1H), 1.80−1.71 (m, 1H), 1.68−1.59 (m, 1H), 1.48−1.35 (m, 2H), 0.97 (t, J = 7.9 Hz, 9H), 0.93 (d, J = 6.9 Hz, 3H), 0.61 (q, J = 7.9 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 139.0, 128.5, 127.7, 127.6, 73.4, 73.2, 72.9, 51.7, 39.1, 34.5, 32.6, 21.1, 13.0, 7.2, 5.4 ppm; MS (ESI-IT) m/z 192.6 (21), 263.2 (79), 303.2 (75), 395.3 (M + H^+, 76), 417.2 (M + Na^+, 100), 433.2 (5), 590.9 (8); HRMS calcd for $C_{22}H_{39}O_4Si$ [M + H^+] 395.2612, found 395.2614 (0.3 ppm); calcd for $C_{22}H_{38}NaO_4Si$ [M + Na^+] 417.2432, found 417.2433 (0.3 ppm).

(±)-(5*R*,6*S*)-Methyl 7-(Benzyloxy)-5-hydroxy-6-methylheptanoate (S39).



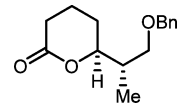
To a cold (0 °C) solution of ester **S38** (50 mg) in dry MeCN (0.1 M, 1.30 mL) was added $BF_3{\cdot}OEt_2$ (2 equiv, 28 μL), followed by stirring at 0 °C for 1 h. The reaction mixture was treated with solid $NaHCO_3$, filtered onto a pad of Celite, and washed with Et_2O and the filtrate concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel (hexanes/EtOAc, 80:20 to 70:30) to afford product **S39** as a colorless oil (29 mg, yield = 80%): R_f = 0.16 (hexanes/EtOAc 60:40); formula $C_{16}H_{24}O_4$; MW 280.36 g/mol; IR (neat) ν_{max} 3486, 3062, 3030, 2952, 2872, 1737, 1454, 1097, 739 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38−7.30 (m, 5H), 4.55 (d, J = 11.9 Hz, 1H), 4.52 (d, J = 12.1 Hz, 1H), 3.68 (s, 3H), 3.63 (dd, J = 4.1 Hz, 9.2 Hz, 1H), 3.55 (ddd, J = 3.4 Hz, 7.7 Hz, 11.2 Hz, 1H), 3.48 (dd, J = 7.6 Hz, 9.1 Hz, 1H), 3.41 (d, J = 3.7 Hz, 1H), 2.37 (t, J = 7.5 Hz, 2H), 1.91−1.82 (m, 2H), 1.78−1.69 (m, 1H), 1.60−1.53 (m, 1H), 1.45 (dddd, J = 5.0 Hz, 8.8 Hz, 10.0 Hz, 13.7 Hz, 1H), 0.92 (d, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 137.9, 128.7, 128.0, 127.9, 76.0, 75.5, 73.7, 51.7, 38.4, 34.4, 34.2, 21.0, 14.2 ppm; MS (ESI-IT) m/z 201.1 (100), 213.1 (61), 231.1 (48), 244.3 (13), 281.2 (M + H^+, 9), 535.9 (7), 591.5 (13); HRMS calcd for $C_{16}H_{25}O_4$ [M + H^+] 281.1747, found 281.1789 (0.5 ppm).

(±)-(2*S*,3*S*)-1-(Benzyloxy)-7-methoxy-2-methyl-7-oxoheptan-3-yl 4-nitrobenzoate (S40).



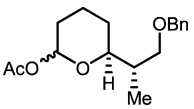
To a solution at room temperature of alcohol **S39** (0.26 g) in dry THF (0.1 M, 9.30 mL) were added successively p-nitrobenzoic acid (2 equiv, 310 mg), PPh_3 (2 equiv, 486 mg), and DEAD (2 equiv, 292 μL). The reaction mixture was stirred overnight at room temperature before concentration in vacuo. The crude mixture was purified by flash chromatography on silica gel (hexanes/EtOAc, 80:20 to 65:35) to afford product **S40** as a pale yellow oil (287 mg, yield = 72%): R_f = 0.53 (hexanes/EtOAc, 50:50); formula $C_{23}H_{27}O_7N$; MW 429.46 g/mol; IR (neat) ν_{max} 3111, 3060, 3030, 2952, 2866, 1729, 1529, 1348, 1276, 1102, 721 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, J = 8.8 Hz, 2H), 8.16 (d, J = 8.8 Hz, 2H), 7.29−7.22 (m, 5H), 5.40 (td, J = 3.9 Hz, 8.0 Hz, 1H), 4.47 (d, J = 11.7 Hz, 1H), 4.45 (d, J = 11.8 Hz, 1H), 3.67 (s, 3H), 3.40 (dd, J = 1.9 Hz, 6.3 Hz, 2H), 2.37 (t, J = 6.8 Hz, 2H), 2.17 (dh, J = 4.0 Hz, 6.9 Hz, 1H), 1.87−1.78 (m, 1H), 1.76−1.65 (m, 3H), 1.08 (d, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 164.5, 150.6, 138.4, 136.1, 130.9, 128.5, 127.9, 127.7, 123.7, 76.1, 73.4, 72.5, 51.8, 37.3, 33.8, 31.4, 21.3, 11.9 ppm; MS (ESI-IT) m/z 263.2 (7), 452.2 (M + Na^+, 100); HRMS calcd for $C_{23}H_{28}O_7N$ [M + H^+] 430.1860, found 430.1851 (−2.1 ppm); calcd for $C_{23}H_{27}NaO_7N$ [M + Na^+] 452.1685, found 452.1673 (−1.6 ppm).

(±)-(*S*)-6-((*S*)-1-(Benzyloxy)propan-2-yl)tetrahydro-2*H*-pyran-2-one (S41).



To a cold (0 °C) solution of product **S40** (0.27 g, 0.63 mmol) in dry MeOH (0.1 M, 6.0 mL) was added a freshly prepared 1 M solution of MeONa in MeOH (1.1 equiv, 0.69 mL), followed by stirring overnight at 0 °C. The reaction mixture was treated with solid NH_4Cl and filtered onto a pad of silica (hexanes/EtOAc, 50:50) and the filtrate concentrated in vacuo. Product **S41** as a colorless oil (45 mg, yield = 30% over two steps) was obtained from crude product following general procedure **A8** and purification by flash chromatography on silica gel (hexanes/EtOAc 70:30 to 50:50): R_f = 0.36 (hexanes/EtOAc, 50:50); formula $C_{15}H_{20}O_3$; MW 248.32 g/mol; IR (neat) ν_{max} 3061, 3030, 2941, 2870, 1731, 1453, 1240, 1102 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36−7.27 (m, 5H), 4.53 (d, J = 11.9 Hz, 1H), 4.48 (d, J = 11.8 Hz, 1H), 4.48 (dt, J = 3.4 Hz, 11.6 Hz, 1H), 3.54 (dd, J = 7.7 Hz, 9.1 Hz, 1H), 3.42 (dd, J = 5.3 Hz, 9.2 Hz, 1H), 2.60 (ddd, J = 5.0 Hz, 7.1 Hz, 17.8 Hz, 1H), 2.42 (ddd, J = 7.4 Hz, 9.1 Hz, 17.6 Hz, 1H), 2.02−1.78 (m, 4H), 1.66 (dtd, J = 6.3 Hz, 11.8 Hz, 13.7 Hz, 1H), 1.00 (d, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 138.5, 128.6, 127.9, 127.8, 80.7, 73.5, 71.9, 38.4, 29.8, 25.6, 18.9, 11.4 ppm; MS (ESI-IT) m/z 249.1 (M + H^+, 5), 271.1 (M + Na^+, 100); HRMS calcd for $C_{15}H_{21}O_3$ [M + H^+] 249.1485, found 249.1488 (1.1 ppm); calcd for $C_{15}H_{20}NaO_3$ [M + Na^+] 271.1310, found 271.1309 (1.5 ppm).

(±)-(*S*)-6-((*S*)-1-(Benzyloxy)propan-2-yl)tetrahydro-2*H*-pyran-2-yl acetate (S42a,b).



An inseparable 4:1 mixture of product **S42a,b** (38 mg, yield = 60% over two steps, based on recovery of starting material) was obtained as a pale yellow oil from lactone **S41** (64 mg) following general procedure **A9** and purification by flash chromatography on silica gel (hexanes/EtOAc 70:30): R_f = 0.39 (hexanes/EtOAc, 70:30); formula $C_{17}H_{24}O_4$; MW 292.37 g/mol; IR (neat) ν_{max} 3063, 3030, 2944, 2863, 1750, 1455, 1236, 1101, 1035, 738 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38−7.29 (m, $5H_a$+$5H_b$), 6.14 (bs, $1H_b$), 5.64 (dd, J = 2.2 Hz, 9.8 Hz, $1H_a$), 4.54 (d, J = 12.0 Hz, $1H_a$), 4.52 (d, J = 11.9 Hz, $1H_b$), 4.49 (d, J = 12.0 Hz, $1H_a$), 4.48 (d, J = 12.0 Hz, $1H_b$), 3.98 (td, J = 3.4 Hz, 11.2 Hz, $1H_b$), 3.62 (ddd, J =

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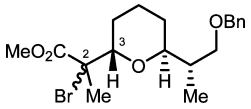
1.9 Hz, 4.9 Hz, 11.4 Hz, 1H$_a$), 3.50 (dd, J = 6.4 Hz, 9.1 Hz, 1H$_a$), 3.46 (dd, J = 7.4 Hz, 9.0 Hz, 1H$_b$), 3.38 (dd, J = 5.9 Hz, 9.1 Hz, 1H$_a$), 3.34 (dd, J = 5.9 Hz, 9.0 Hz, 1H$_b$), 2.12 (s, 3H$_a$), 2.05 (s, 3H$_b$), 1.95−1.78 (m, 2H$_a$+3H$_b$), 1.73−1.68 (m, 1H$_a$), 1.65−1.41 (m, 3H$_a$+3H$_b$), 1.35 (ddd, J = 4.1 Hz, 12.9 Hz, 24.7 Hz, 1H$_a$), 1.29−1.20 (m, 1H$_b$), 1.01 (d, J = 6.9 Hz, 3H$_a$), 0.94 (d, J = 6.9 Hz, 3H$_b$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1$_b$, 169.5$_a$, 138.80$_b$, 138.77$_a$, 128.4$_{a+b}$, 127.7$_{a+b}$, 127.59$_a$, 127.56$_b$, 95.4$_a$, 92.8$_b$, 78.0$_a$, 73.3$_a$, 73.2$_b$, 72.53$_a$, 72.48$_b$, 71.0$_b$, 38.5$_a$, 38.2$_b$, 30.2$_a$, 28.8$_b$, 27.7$_b$, 27.5$_a$, 22.1$_a$, 21.45$_a$, 21.37$_b$, 18.2$_b$, 12.5$_a$, 11.7$_b$ ppm; MS (ESI-IT) m/z 172.9 (9), 255.1 (13), 273.1 (33), 315.2 (M + Na$^+$, 100); HRMS calcd for $C_{17}H_{24}NaO_4$ [M + Na$^+$] 315.1572, found 315.1564 (−0.8 ppm).

(±)-Methyl 2-((2*S*,6*S*)-6-((*S*)-1-(Benzyloxy)propan-2-yl)-tetrahydro-2*H*-pyran-2-yl)-2-bromopropanoate (19a, 19b).

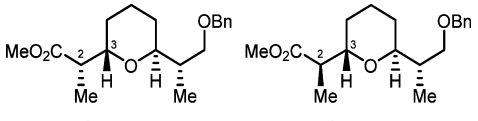


Products **19a** and **19b** (43 mg, yield = 90%) were obtained as pale yellow oils from a mixture of product **S42a,b** (35 mg) following general procedure **A10** and purification by flash chromatography on silica gel (hexanes/EtOAc 80:20 to 70:30). ^{1}H NMR spectroscopic analysis of the unpurified product indicated a pair of 2,3-diastereomers in a ∼1:1 ratio of products **19a**:**19b**.

19a: R_f = 0.24 (hexanes/EtOAc, 80:20); formula $C_{19}H_{27}BrO_4$; MW 399.32 g/mol; IR (neat) ν_{max} 3063, 3029, 2950, 2866, 1742, 1450, 1261, 1098, 738 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.30 (m, 5H), 4.50 (d, J = 12.0 Hz, 1H), 4.46 (d, J = 12.1 Hz, 1H), 4.15 (dd, J = 2.6 Hz, 11.4 Hz, 1H), 3.79 (s, 3H), 3.71 (ddd, J = 2.4 Hz, 4.5 Hz, 7.5 Hz, 1H), 3.36 (dd, J = 5.0 Hz, 9.3 Hz, 1H), 3.30 (dd, J = 5.3 Hz, 9.3 Hz, 1H), 2.31−2.23 (m, 1H), 2.02 (ddd, J = 2.9 Hz, 5.1 Hz, 9.5 Hz, 1H), 1.89 (s, 3H), 1.75−1.60 (m, 4H), 1.48 (dq, J = 4.6 Hz, 11.7 Hz, 1H), 0.99 (d, J = 6.7 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 138.6, 128.4, 127.6, 127.5, 76.9, 73.9, 73.3, 73.2, 61.9, 53.1, 32.8, 26.1, 25.0, 22.5, 18.6, 14.4 ppm; MS (ESI-IT) m/z 399.1 (M + H$^+$, 6), 421.1 (M + Na$^+$, 100); HRMS calcd for $C_{19}H_{28}BrO_4$ [M + H$^+$] 399.1165, found 399.1159 (−1.6 ppm); calcd for $C_{19}H_{27}NaBrO_4$ [M + Na$^+$] 421.0985, found 421.0977 (−1.8 ppm).

19b: R_f = 0.18 (hexanes/EtOAc, 80:20); formula $C_{19}H_{27}BrO_4$; MW 399.32 g/mol; IR (neat) ν_{max} 3062, 3026, 2949, 2865, 1738, 1450, 1263, 1110, 1054, 738 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.29 (m, 5H), 4.51 (d, J = 12.1 Hz, 1H), 4.47 (d, J = 12.1 Hz, 1H), 3.96 (dd, J = 2.5 Hz, 11.1 Hz, 1H), 3.82−3.78 (m, 1H), 3.80 (s, 3H), 3.39 (dd, J = 5.0 Hz, 9.3 Hz, 1H), 3.32 (dd, J = 5.3 Hz, 9.3 Hz, 1H), 2.34 (ddd, J = 5.2 Hz, 10.5 Hz, 11.8 Hz, 1H), 1.87 (s, 3H), 1.76−1.66 (m, 4H), 1.62−1.57 (m, 1H), 1.53−1.44 (m, 1H), 1.13 (d, J = 6.7 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 138.6, 128.5, 127.6, 127.5, 77.4, 74.3, 73.5, 73.2, 65.5, 53.4, 32.5, 26.4, 26.0, 24.1, 18.5, 14.7 ppm; MS (ESI-IT) m/z 229.1 (6), 321.2 (7), 399.1 (M + H$^+$, 100); HRMS calcd for $C_{19}H_{28}BrO_4$ [M + H$^+$] 399.1165, found 399.1173 (2.0 ppm).

(±)-(*S*)-Methyl 2-((2*S*,6*S*)-6-((*S*)-1-(Benzyloxy)propan-2-yl)-tetrahydro-2*H*-pyran-2-yl) propanoate (27a) and (±)-(*R*)-Methyl 2-((2*S*,6*S*)-6-((*S*)-1-(Benzyloxy)propan-2-yl) tetrahydro-2*H*-pyran-2-yl)propanoate (27b).

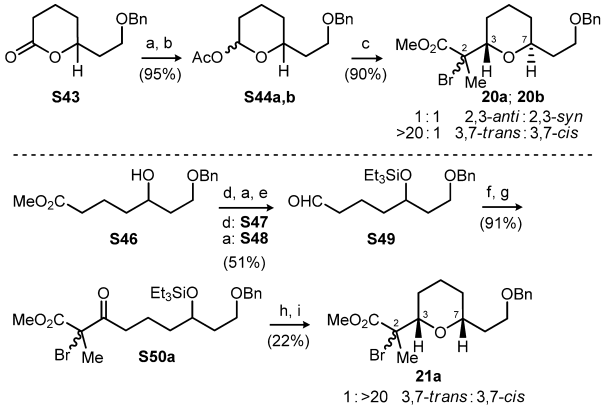


27a (2,3-*anti*) **27b** (2,3-*syn*)

Products **27a** and product **27b** (72 mg, yield = 75%) were obtained as pale yellow oils from a mixture of bromides **19a** and **19b** (120 mg) following general procedure **A1** and purification by flash chromatography on silica gel (hexanes/EtOAc 70:30). ^{1}H NMR spectroscopic analysis of the unpurified product indicated a pair of diastereomers in a 12:1 ratio of products 2,3-*anti* (**27a**):2,3-*syn* (**27b**).

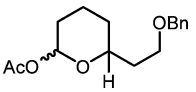
27a: R_f = 0.46 (hexanes/EtOAc, 70:30); formula $C_{19}H_{28}O_4$; MW 320.42 g/mol; IR (neat) ν_{max} 3063, 3029, 2944, 2935, 2864, 1738, 1455, 1108, 1039, 737 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.29 (m, 5H), 4.52 (d, J = 12.1 Hz, 1H), 4.46 (d, J = 12.1 Hz, 1H), 3.84 (ddd, J = 4.5 Hz, 5.2 Hz, 9.9 Hz, 1H), 3.67 (s, 3H), 3.63 (dt, J = 3.2 Hz, 7.6 Hz, 1H), 3.40 (dd, J = 4.8 Hz, 9.2 Hz, 1H), 3.28 (dd, J = 6.4 Hz, 9.2 Hz, 1H), 2.86 (qd, J = 6.9 Hz, 10.0 Hz, 1H), 2.04−1.96 (m, 1H), 1.73−1.56 (m, 4H), 1.55−1.43 (m, 2H), 1.09 (d, J = 6.9 Hz, 3H), 0.98 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 138.8, 128.4, 127.58, 127.56, 74.0, 73.7, 73.4, 73.2, 51.6, 42.6, 36.1, 27.7, 26.6, 18.6, 14.1, 13.5 ppm; MS (ESI-IT) m/z 289.2 (6), 321.2 (M + H$^+$, 100); HRMS calcd for $C_{19}H_{29}O_4$ [M + H$^+$] 321.2060, found 321.2066 (1.8 ppm).

27b: R_f = 0.54 (hexanes/EtOAc, 70:30); formula $C_{19}H_{28}O_4$; MW 320.42 g/mol; IR (neat) ν_{max} 3062, 3030, 2963, 2938, 2861, 1736, 1454, 1039, 737 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.30 (m, 5H), 4.52 (d, J = 12.0 Hz, 1H), 4.46 (d, J = 12.0 Hz, 1H), 3.85 (dt, J = 8.3 Hz, 3.8 Hz, 1H), 3.69 (s, 3H), 3.55 (ddd, J = 3.4 Hz, 6.7 Hz, 9.5 Hz, 1H), 3.46 (dd, J = 6.2 Hz, 9.1 Hz, 1H), 3.33 (dd, J = 5.7 Hz, 9.1 Hz, 1H), 2.95 (qd, J = 6.9 Hz, 9.6 Hz, 1H), 1.96 (hept, J = 6.4 Hz, 1H), 1.70−1.63 (m, 3H), 1.55−1.47 (m, 2H), 1.44−1.36 (m, 1H), 1.22 (d, J = 6.9 Hz, 3H), 1.00 (d, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 138.8, 128.6, 127.81, 127.74, 73.5, 73.4, 73.1, 71.8, 51.8, 41.3, 37.0, 28.13, 28.07, 19.0, 14.1, 13.0 ppm; MS (ESI-IT) m/z 321.2 (M + H$^+$, 10), 343.2 (M + Na$^+$, 100); HRMS calcd for $C_{19}H_{29}O_4$ [M + H$^+$] 321.2060, found 321.2066 (1.6 ppm); calcd for $C_{19}H_{28}NaO_4$ [M + Na$^+$] 343.1880, found 343.1885 (1.5 ppm).



Reactions and conditions: a) DIBAL-H, CH_2Cl_2, −40 °C. b) Ac_2O, pyridine, DMAP, CH_2Cl_2, −40 °C to rt. c) $SnCl_4$, **2**, CH_2Cl_2, −78 °C. d) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C. e) SO_3·py, DMSO, DIEA, CH_2Cl_2, 0 °C. f) $MgBr_2$·OEt_2, **2**, CH_2Cl_2, −40 °C. g) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C to rt. h) $BiBr_3$, CH_2Cl_2/MeCN, −78 °C. i) Et_3SiH, CH_2Cl_2, −78 °C.

(±)-6-(2-(Benzyloxy)ethyl)tetrahydro-2*H*-pyran-2-yl acetate (S44a, S44b).



Product **S44a** and **S44b** (593 mg, yield = 95%) were obtained as pale yellow oils from lactone **S43**[31] (525 mg) following general procedure **A9** and purification by flash chromatography on silica gel (hexanes/EtOAc 80:20 to 70:30). ^{1}H NMR spectroscopic analysis of the unpurified product indicated a pair of diastereomers in a 2:1 ratio of products **S44a**:**S44b**.

S44a: R_f = 0.52 (hexanes/EtOAc, 70:30); formula $C_{16}H_{22}O_4$; MW 278.34 g/mol; IR (neat) ν_{max} 3063, 3030, 2945, 2863, 1751, 1234, 1038 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39−7.28 (m, 5H), 5.67 (dd, J = 2.3 Hz, 9.7 Hz, 1H), 4.54 (d, J = 11.9 Hz, 1H), 4.50 (d, J = 11.9 Hz, 1H), 3.77−3.71 (m, 1H), 3.65−3.54 (m, 2H), 2.12 (s, 3H), 1.95−1.85 (m, 2H), 1.85−1.77 (m, 2H), 1.64−1.56 (m, 2H), 1.54−1.43 (m, 1H), 1.32−1.21 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 138.5, 128.3, 127.6, 127.4, 94.8, 74.2, 73.0, 66.5, 36.0, 30.3, 29.9, 21.6, 21.2 ppm; MS (ESI-IT) m/z 219.1 (42), 273.1 (24), 301.1 (M + Na$^+$, 100), 378.3 (7), 477.3 (10); HRMS calcd for $C_{16}H_{22}NaO_4$ [M + Na$^+$] 301.1410, found 301.1419 (2.8 ppm).

S44b: R_f = 0.44 (hexanes/EtOAc, 70:30); formula $C_{16}H_{22}O_4$; MW 278.34 g/mol; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.26 (m, 5H), 6.13 (app s, 1H), 4.50 (d, J = 11.8 Hz, 1H), 4.48 (d, J = 12.0 Hz, 1H), 4.00 (dt, J = 5.6 Hz, 11.4 Hz, 1H), 3.60−3.50 (m, 2H), 2.05 (s, 3H), 1.87−1.77 (m, 1H), 1.77−1.62 (m, 6H), 1.41−1.31 (m, 1H) ppm.

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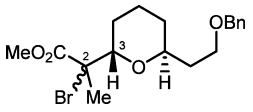
(±)-Methyl 2-((2*S*,6*S*)-6-(2-(Benzyloxy)ethyl)tetrahydro-2*H*-pyran-2-yl)-2-bromopropanoate (20a, 20b).

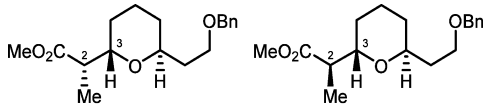


Products **20a** and **20b** (744 mg, yield = 90%) were obtained as pale yellow oils from a mixture of product **S44a,b** (597 mg) following general procedure **A10** and purification by flash chromatography on silica gel (hexanes/EtOAc 85:15). ^{1}H NMR spectroscopic analysis of the unpurified product indicated a pair of 2,3-diastereomers in a ~1:1 ratio of products **20a**:**20b**.

20a: R_f = 0.54 (hexanes/EtOAc, 80:20); formula $C_{18}H_{25}BrO_4$; MW 385.29 g/mol; IR (neat) ν_{max} 3062, 3029, 3001, 2945, 2861, 1742, 1263, 1097, 1046 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.26 (m, 5H), 4.50 (d, J = 11.6 Hz, 1H), 4.48 (d, J = 12.2 Hz, 1H), 4.14 (dd, J = 2.2 Hz, 11.5 Hz, 2H), 3.70 (s, 3H), 3.53−3.45 (m, 2H), 2.22−2.12 (m, 1H), 2.05−1.98 (m, 1H), 1.83 (s, 3H), 1.79−1.61 (m, 4H), 1.47−1.34 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 138.5, 128.4, 127.53, 127.52, 73.09, 73.05, 71.2, 67.2, 61.3, 52.9, 30.4, 28.4, 25.2, 22.0, 18.5 ppm; MS (ESI-IT) m/z 385.1 (M + H$^+$, 100); HRMS calcd for $C_{18}H_{26}BrO_4$ [M + H $^+$] 385.1009, found 385.1005 (−0.9 ppm).

20b: R_f = 0.46 (hexanes/EtOAc, 80:20); formula $C_{18}H_{25}BrO_4$; MW 385.29 g/mol; IR (neat) ν_{max} 3062, 3031, 2946, 2866, 1738, 1267, 1112, 1053 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.26 (m, 5H), 4.50 (d, J = 11.6 Hz, 1H), 4.48 (d, J = 12.2 Hz, 1H), 4.14 (dd, J = 2.2 Hz, 11.5 Hz, 2H), 3.70 (s, 3H), 3.53−3.45 (m, 2H), 2.22−2.12 (m, 1H), 2.05−1.98 (m, 1H), 1.83 (s, 3H), 1.79−1.61 (m, 4H), 1.47−1.34 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 138.4, 128.2, 127.5, 127.3, 73.5, 73.0, 70.7, 67.1, 64.8, 53.0, 30.1, 28.0, 26.4, 23.5, 18.2 ppm; MS (ESI-IT) m/z 385.1 (M + H$^+$, 100); HRMS calcd for $C_{18}H_{26}BrO_4$ [M + H$^+$] 385.1009, found 385.1003 (−1.6 ppm).

(±)-(*S*)-Methyl 2-((2*S*,6*S*)-6-(2-(Benzyloxy)ethyl)tetrahydro-2*H*-pyran-2-yl)propanoate (28a) and (±)-(*R*)-Methyl 2-((2*S*,6*S*)-6-(2-(Benzyloxy)ethyl)tetrahydro-2*H*-pyran-2-yl)propanoate (28b).



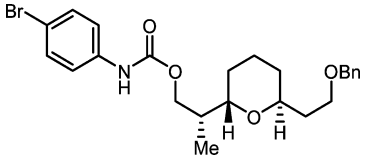
28a (2,3-*anti*) **28b** (2,3-*syn*)

Products **28a** and product **28b** (80 mg, yield = 82%) were obtained as pale yellow oils from a mixture of bromides **20a** and **20b** (122 mg) following general procedure **A1** and purification by flash chromatography on silica gel (hexanes/EtOAc 80:20 to 70:30). ^{1}H NMR spectroscopic analysis of the unpurified product indicated a pair of diastereomers in a 14:1 ratio of products 2,3-*anti* (**28a**):2,3-*syn* (**28b**).

28a: R_f = 0.13 (hexanes/EtOAc, 80:20); formula $C_{18}H_{26}O_4$; MW 306.40 g/mol; IR (neat) ν_{max} 3056, 3029, 2942, 2860, 1738, 1203, 1162, 1102, 1040 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.26 (m, 5H), 4.51 (d, J = 12.0 Hz, 1H), 4.48 (d, J = 11.9 Hz, 1H), 4.00 (dq, J = 9.3 Hz, 4.5 Hz, 1H), 3.77 (ddd, J = 3.4 Hz, 8.1 Hz, 9.8 Hz, 1H), 3.63 (s, 3H), 3.56−3.45 (m, 2H), 2.70 (dq, J = 9.4 Hz, 7.0 Hz, 1H), 2.10−2.01 (m, 1H), 1.76−1.66 (m, 2H), 1.66−1.58 (m, 3H), 1.40−1.32 (m, 2H), 1.07 (d, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 138.6, 128.3, 127.6, 127.4, 73.1, 72.7, 69.2, 67.3, 51.5, 43.6, 32.5, 29.6, 27.2, 18.3, 13.7 ppm; MS (ESI-IT) m/z 307.2 (M + H$^+$, 37), 329.2 (M + Na$^+$, 100), 635.4 (8); HRMS calcd for $C_{18}H_{27}O_4$ [M + H$^+$] 307.1904, found 307.1909 (1.7 ppm); calcd for $C_{18}H_{26}NaO_4$ [M + Na$^+$] 329.1723, found 329.1730 (1.9 ppm).

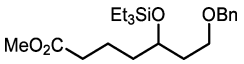
28b: R_f = 0.22 (hexanes/EtOAc, 80:20); formula $C_{18}H_{26}O_4$; MW 306.40 g/mol; IR (neat) ν_{max} 3063, 3030, 2940, 2864, 1736, 1455, 1258, 1201, 1166, 1106, 1038, 738 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.26 (m, 5H), 4.51 (d, J = 11.9 Hz, 1H), 4.48 (d, J = 12.0 Hz, 1H), 3.82 (ddd, J = 3.5 Hz, 7.2 Hz, 12.5 Hz, 2H), 3.66 (s, 3H), 3.61−3.50 (m, 2H), 2.80 (dq, J = 6.9 Hz, 8.6 Hz, 1H), 1.95 (dq, J = 5.3 Hz, 10.2 Hz, 1H), 1.73−1.59 (m, 5H), 1.41−1.30 (m, 2H), 1.17 (d, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.6, 138.4, 128.3, 127.7, 127.5, 73.1, 72.4, 68.0, 66.9, 51.6, 42.0, 33.6, 30.1, 28.1, 18.6, 13.5 ppm; MS (ESI-IT) m/z 307.2 (M + H$^+$, 36), 329.2 (M + Na$^+$, 100), 635.4 (4); HRMS calcd for $C_{18}H_{27}O_4$ [M + H$^+$] 307.1904, found 307.1901 (−0.9 ppm); calcd for $C_{18}H_{26}NaO_4$ [M + Na$^+$] 329.1723, found 329.1720 (−0.9 ppm).

(±)-(*R*)-2-((2*S*,6*S*)-6-(2-(Benzyloxy)ethyl)tetrahydro-2*H*-pyran-2-yl)propyl (4-Bromophenyl)carbamate (S45).



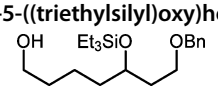
A primary alcohol as a colorless oil was obtained from ester **28a** (48 mg) following general procedure **A4**. To a cold (0 °C) solution of crude alcohol in dry CH_2Cl_2 (0.1 M, 1.0 mL) were added successively Et_3N (1.1 equiv, 14 μL) and *p*-bromophenyl isocyanate (1.1 equiv, 21 mg). The reaction mixture was stirred for 3 h at 0 °C before the reaction mixture was treated with a saturated aqueous solution of $NaHCO_3$ followed by separation of the organic phase at room temperature. The aqueous layer was extracted with EtOAc (3×), and combined organic fractions were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel (hexanes/EtOAc, 90:10 to 80:20) to afford product **S45** as a white solid (48 mg, yield = 64% over two steps), for which structural assignment was confirmed by X-ray analysis (cf. Supporting Information, part III, X-ray): R_f = 0.19 (hexanes/EtOAc, 80:20); formula $C_{24}H_{30}BrNO_4$; MW 476.40 g/mol; IR (neat) ν_{max} 3304, 3068, 2937, 2855, 1726, 1708, 1594, 1530, 1400, 1307, 1220, 1077, 1042, 824, 733 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41−7.20 (m, 9H), 6.76 (s, 1H), 4.53 (d, J = 11.8 Hz, 1H), 4.46 (d, J = 11.8 Hz, 1H), 4.28 (dd, J = 4.2 Hz, 10.5 Hz, 1H), 4.10 (dd, J = 6.1 Hz, 10.5 Hz, 1H), 3.97−3.91 (m, 1H), 3.62 (ddd, J = 6.0 Hz, 8.2 Hz, 8.9 Hz, 1H), 3.57−3.49 (m, 2H), 2.21−2.11 (m, 1H), 1.96 (tdd, J = 5.5 Hz, 9.5 Hz, 14.6 Hz, 1H), 1.72−1.60 (m, 5H), 1.52−1.44 (m, 1H), 1.38−1.30 (m, 1H), 0.92 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 138.4, 137.2, 131.9, 128.3, 127.7, 127.5, 120.1, 115.6, 73.0, 72.8, 68.2, 67.7, 67.0, 34.5, 33.6, 30.3, 27.2, 18.6, 14.1 ppm; MS (ESI-IT) m/z 476.1 (M + H$^+$, 49), 498.1 (M + Na$^+$, 100), 975.3 (20); HRMS calcd for $C_{24}H_{31}O_4NBr$ [M + H$^+$] 476.1431, found 476.1434 (0.6 ppm); calcd for $C_{24}H_{30}NaO_4NBr$ [M + Na$^+$] 498.1250, found 498.1254 (0.7 ppm).

(±)-Methyl 7-(Benzyloxy)-5-((triethylsilyl)oxy)heptanoate (S47).



Product **S47** was obtained as a pale yellow oil from alcohol **S46**[31] (1.50 g) following general procedure **A3** and was used as crude without further purification. A small quantity (~100 mg) of crude product **S47** was purified by flash chromatography on silica gel (hexanes/EtOAc, 90:10 to 80:20) for characterization: R_f = 0.58 (hexanes/EtOAc, 80:20); formula $C_{21}H_{36}O_4Si$; MW 380.59 g/mol; IR (neat) ν_{max} 3086, 3068, 3030, 2953, 2913, 2876, 1741, 1456, 1241, 1163, 1100, 1009, 738 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.26 (m, 5H), 4.51 (d, J = 11.9 Hz, 1H), 4.46 (d, J = 11.9 Hz, 1H), 3.86 (tt, J = 5.6 Hz, 5.7 Hz, 1H), 3.66 (s, 3H), 3.58−3.49 (m, 2H), 2.30 (t, J = 7.5 Hz, 2H), 1.82−1.72 (m, 2H), 1.72−1.60 (m, 2H), 1.51−1.43 (m, 2H), 0.95 (t, J = 7.9 Hz, 9H), 0.59 (q, J = 7.9 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 138.5, 128.3, 127.6, 127.5, 72.9, 69.0, 67.0, 51.4, 36.96, 36.87, 34.1, 20.6, 6.9, 5.0 ppm; MS (ESI-IT) m/z 141.1 (65), 171.1 (22), 187.1 (42), 199.1 (75), 217.1 (100), 249.1 (79); HRMS calcd for $C_{21}H_{37}O_4Si$ [M + H$^+$] 381.2456, found 381.2450 (−1.4 ppm).

(±)-7-(Benzyloxy)-5-((triethylsilyl)oxy)heptan-1-ol (S48).



Product **S48** was obtained as a colorless oil from crude ester **S47** following general procedure **A4** and was used as crude without further purification. A small quantity (~100 mg) of crude product **S48** was purified by flash chromatography on silica gel (hexanes/EtOAc, 80:20) for characterization: R_f = 0.30 (hexanes/EtOAc, 80:20); formula

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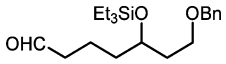
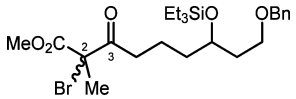
$C_{20}H_{36}O_3Si$; MW 352.58 g/mol; IR (neat) ν_{max} 3392, 3056, 3031, 2950, 2914, 2875, 1456, 1414, 1371, 1238, 1100, 1060, 1008, 734 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37−7.27 (m, 5H), 4.51 (d, J = 11.9 Hz, 1H), 4.46 (d, J = 11.9 Hz, 1H), 3.85 (tt, J = 5.6 Hz, 5.8 Hz, 1H), 3.63 (dd, J = 6.2 Hz, 11.3 Hz, 2H), 3.58−3.50 (m, 2H), 1.82−1.68 (m, 2H), 1.59−1.51 (m, 1H), 1.51−1.44 (m, 2H), 1.44−1.35 (m, 2H), 1.26−1.20 (m, 1H), 0.95 (t, J = 7.9 Hz, 9H), 0.59 (q, J = 7.9 Hz, 6H) ppm; *OH signal missing possibly due to exchange in* $CDCl_3$; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 128.3, 127.6, 127.5, 72.9, 69.4, 67.1, 62.8, 37.3, 37.0, 32.8, 21.3, 6.9, 5.0 ppm; MS (ESI-IT) m/z 221.2 (26), 239.2 (23), 353.3 (M + H^+, 100), 467.3 (17); HRMS calcd for $C_{20}H_{37}O_3Si$ [M + H^+] 353.2506, found 353.2505 (−0.4 ppm).

(±)-7-(Benzyloxy)-5-((triethylsilyl)oxy)heptanal (S49).



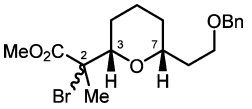
Product **S49** (1.10 g, yield = 51% over three steps) was obtained as a pale yellow oil from crude alcohol **S48** (0.73 g) following general procedure **A14** and purification by flash chromatography on silica gel (hexanes/EtOAc 95:5 to 85:15): R_f = 0.50 (hexanes/EtOAc, 60:40); formula $C_{20}H_{34}O_3Si$; MW 350.57 g/mol; IR (neat) ν_{max} 3064, 3031, 2953, 2913, 2876, 2717, 1726, 1456, 1413, 1375, 1239, 1101, 1008, 738 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.75 (t, J = 1.5 Hz, 1H), 7.37−7.26 (m, 5H), 4.51 (d, J = 11.9 Hz, 1H), 4.46 (d, J = 11.9 Hz, 1H), 3.87 (tt, J = 5.7 Hz, 5.8 Hz, 1H), 3.58−3.49 (m, 2H), 2.41 (dt, J = 1.4 Hz, 7.3 Hz, 2H), 1.81−1.72 (m, 2H), 1.73−1.60 (m, 2H), 1.53−1.40 (m, 2H), 0.95 (t, J = 7.9 Hz, 9H), 0.59 (q, J = 7.9 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.8, 138.7, 128.6, 127.9, 127.8, 73.2, 69.3, 67.2, 44.2, 37.3, 37.1, 18.0, 7.2, 5.3 ppm; MS (ESI-IT) m/z 127.1 (40), 217.1 (48), 235.1 (37), 259.2 (10), 349.2 (M − H^+, 100), 363.2 (13); HRMS calcd for $C_{20}H_{33}O_3Si$ [M − H^+] 349.2204, found 349.2199 (1.6 ppm).

(±)-Methyl 9-(Benzyloxy)-2-bromo-2-methyl-3-oxo-7-((triethylsilyl)oxy)nonanoate (S50a).



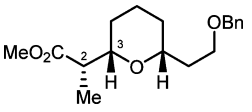
To a cold (−40 °C) solution of aldehyde **S49** (400 mg) in dry CH_2Cl_2 (0.1 M, 11.5 mL) were added successively silylated enol ether **2** (2.5 equiv, 526 μL) and $MgBr_2{\cdot}OEt_2$ (7.0 equiv, 2.06 g). The reaction mixture was stirred for 1 h at −40 °C before treatment with a saturated aqueous solution of NH_4Cl and separation of the organic phase at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3×), and combined organic fractions were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel (hexanes/EtOAc, 85:15) to afford an inseparable mixture of bromide adducts as a colorless oil. Product **S50a** (535 mg, 91%) was obtained as a pale yellow oil from the mixture of bromide adducts following general procedure **A5** and purification by flash chromatography on silica gel (hexanes/EtOAc 95:5). ^1H NMR spectroscopic analysis of the unpurified product indicated the sole formation (>20:1) of one diastereoisomer product (**S50a**): R_f = 0.35 (hexanes/EtOAc, 80:20); formula $C_{24}H_{39}O_5BrSi$; MW 515.55 g/mol; IR (neat) ν_{max} 3064, 3030, 2953, 2913, 2876, 1753, 1728, 1453, 1375, 1245, 1118, 1009, 739 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37−7.27 (m, 5H), 4.51 (d, J = 11.9 Hz, 1H), 4.46 (d, J = 11.9 Hz, 1H), 3.87 (tt, J = 5.8 Hz, 5.9 Hz, 1H), 3.80 (s, 3H), 3.58−3.49 (m, 2H), 2.89−2.78 (m, 1H), 2.75−2.64 (m, 1H), 1.98 (s, 3H), 1.82−1.62 (m, 4H), 1.52−1.39 (m, 2H), 0.95 (t, J = 7.9 Hz, 9H), 0.59 (q, J = 7.8 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.5, 168.9, 138.5, 128.3, 127.6, 127.5, 73.0, 69.2, 67.0, 62.5, 53.8, 38.1, 37.0, 36.6, 25.5, 20.2, 6.9, 5.0 ppm; MS (ESI-IT) m/z 181.1 (9), 383.1 (16), 423.1 (100), 515.2 (M + H^+, 5), 517.2 (5), 537.2 (M + Na^+, 20), 539.2 (20), 825.2 (16); HRMS calcd for $C_{24}H_{40}O_5BrSi$ [M + H^+] 515.1823, found 515.1830 (1.3 ppm); calcd for $C_{24}H_{39}O_5BrNaSi$ [M + Na^+] 537.1642, found 537.1653 (2.0 ppm).

(±)-Methyl 2-((2*S*,6*R*)-6-(2-(Benzyloxy)ethyl)tetrahydro-2*H*-pyran-2-yl)-2-bromopropanoate (21a).



To a cold (−78 °C) solution of ketone **S50a** (98 mg) in dry CH_2Cl_2 (0.1 M, 1.9 mL) was added dropwise a solution of $BiBr_3$ (1 equiv, 87 mg) in dry MeCN (0.5 M, 0.4 mL), followed by Et_3SiH (2.0 equiv, 62 μL). The mixture was stirred for 0.5 h at −78 °C, followed by warming to room temperature and stirring for 18 h. The reaction mixture was treated with a saturated aqueous solution of NH_4Cl followed by separation of the organic phase. The aqueous layer was extracted with CH_2Cl_2 (3×), and combined organic fractions were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel (hexanes/EtOAc 95:5 to 80:20) to yield product **21a** as a pale yellow oil (16 mg, 22%). ^1H NMR spectroscopic analysis of the unpurified product indicated the sole formation (>20:1) of one diastereoisomer product (**21a**): R_f = 0.38 (hexanes/EtOAc, 80:20); formula $C_{18}H_{25}O_4Br$; MW 385.29 g/mol; IR (neat) ν_{max} 3030, 2943, 2860, 1743, 1449, 1264, 1098, 1055, 738 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37−7.26 (m, 5H), 4.47 (d, J = 12.3 Hz, 1H), 4.45 (d, J = 12.3 Hz, 1H), 3.93 (dd, J = 1.5 Hz, 11.3 Hz, 1H), 3.71 (s, 3H), 3.56−3.49 (m, 1H), 3.47 (t, J = 6.4 Hz, 2H), 2.00 (app d, J = 12.7 Hz, 1H), 1.96−1.89 (m, 1H), 1.82 (s, 3H), 1.74−1.66 (m, 2H), 1.62−1.53 (m, 2H), 1.33 (dq, J = 3.9 Hz, 12.7 Hz, 1H), 1.19 (dq, J = 4.2 Hz, 13.3 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 138.5, 128.4, 127.6, 127.5, 81.1, 77.2, 75.7, 73.1, 66.8, 60.3, 36.3, 31.4, 24.8, 23.4, 22.1 ppm; MS (ESI-IT) m/z 385.1 (M + H^+, 13), 387.1 (13), 407.1 (M + Na+, 100), 409.1 (97); HRMS calcd for $C_{18}H_{26}O_4Br$ [M + H^+] 385.1009, found 385.1009 (0.07 ppm); calcd for $C_{18}H_{25}O_4BrNa$ [M + Na^+] 407.0828, found 407.0829 (0.02 ppm).

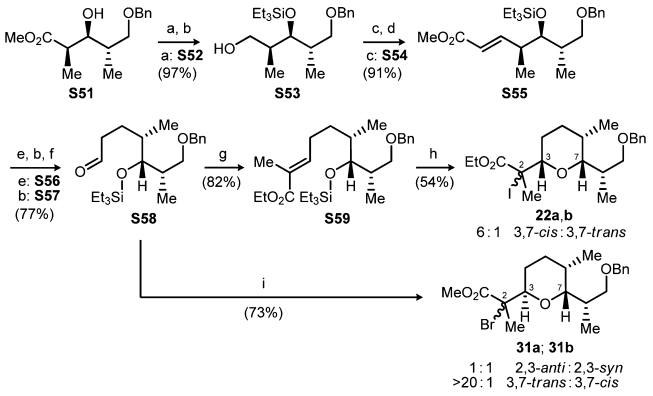
(±)-(*S*)-Methyl 2-((2*S*,6*R*)-6-(2-(Benzyloxy)ethyl)tetrahydro-2*H*-pyran-2-yl)propanoate (29a).



29a (2,3-*anti*)

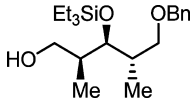
Product **29a** (80 mg, yield = 83%) was obtained as a yellow oil from bromide **21a** (121 mg) following to general procedure **A1** with Bu_3SnH instead of Ph_3SnH and purification by flash chromatography on silica gel (hexanes/EtOAc 95:5). ^1H NMR spectroscopic analysis of the unpurified product indicated the sole formation (>20:1) of 2,3-*anti* product (**29a**): R_f = 0.32 (hexanes/EtOAc, 80:20); formula $C_{18}H_{26}O_4$; MW 306.40 g/mol; IR (neat) ν_{max} 3026, 2941, 2857, 1739, 1456, 1360, 1198, 1090, 738 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39−7.24 (m, 5H), 4.50 (d, J = 11.9 Hz, 1H), 4.45 (d, J = 11.9 Hz, 1H), 3.62 (s, 3H), 3.52 (t, J = 6.5 Hz, 2H), 3.45 (ddd, J = 1.7 Hz, 8.9 Hz, 10.9 Hz, 2H), 2.50 (dq, J = 14.2, 7.1 Hz, 1H), 1.89−1.81 (m, 1H), 1.75−1.64 (m, 3H), 1.57−1.45 (m, 2H), 1.27−1.12 (m, 2H), 1.09 (d, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 138.6, 128.3, 127.6, 127.5, 79.5, 75.0, 73.1, 67.0, 51.4, 45.8, 36.5, 31.5, 28.3, 23.4, 13.1 ppm; MS (ESI-IT) m/z 307.2 (M + H+, 14), 329.2 (M + Na^+, 100); HRMS calcd for $C_{18}H_{27}O_4$ [M + H^+] 307.1904, found 307.1898 (−2.0 ppm); calcd for $C_{18}H_{26}O_4Na$ [M + Na^+] 329.1723, found 329.1714 (−2.8 ppm).

dx.doi.org/10.1021/jo400721e | J. Org. Chem. 2013, 78, 6075−6103



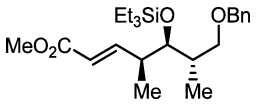
Reactions and conditions: a) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C. b) DIBAL-H, CH_2Cl_2, −40 °C. c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C. d) $Ph_3PC(H)=CO_2Me$, toluene, reflux. e) H_2, Pd/C, EtOAc, rt. f) DMP, $NaHCO_3$, CH_2Cl_2, rt. g) $Ph_3PC(Me)=CO_2Et$, CH_2Cl_2, rt. h) I_2, MeCN, rt then AgOTf, MeCN, rt. i) $BiBr_3$, **2**, CH_2Cl_2/MeCN, −78 °C.

(−)-(2*S*,3*R*,4*S*)-5-(Benzyloxy)-2,4-dimethyl-3-(triethylsilyloxy)pentan-1-ol (S53).



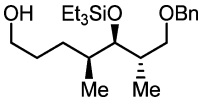
Product **S52** was obtained as a pale yellow oil from alcohol **S40**[6a] (509 mg) following general procedure **A3** and was used as crude without further purification. Product **S53** (656 mg, yield = 97% over two steps) was obtained as a colorless oil from crude ester **S52** following general procedure **A4** and purification by flash chromatography on silica gel (hexanes/EtOAc 90:10): R_f = 0.20 (hexanes/EtOAc, 90:10); $[\alpha]^{25}_D$ −7.4 (*c* 1.2, $CHCl_3$); formula $C_{20}H_{36}O_3Si$; MW 352.58 g/mol; IR (neat) ν_{max} 3412, 3031, 2957, 1456 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36−7.26 (m, 5H), 4.52 (d, *J* = 11.9 Hz, 1H), 4.48 (d, *J* = 12.0 Hz, 1H), 3.74 (dd, *J* = 3.2 Hz, 6.3 Hz, 1H), 3.59−3.54 (m, 2H), 3.50 (dd, *J* = 5.6 Hz, 10.5 Hz, 1H), 3.33 (dd, *J* = 6.9 Hz, 9.0 Hz, 1H), 2.07−1.97 (m, 1H), 1.93−1.83 (m, 1H), 0.97 (d, *J* = 7.0 Hz, 3H), 0.95 (t, *J* = 7.9 Hz, 9H), 0.86 (d, *J* = 6.8 Hz, 3H), 0.60 (q, *J* = 7.9 Hz, 6H) ppm; *OH signal missing possibly due to exchange in CDCl*$_3$; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 128.4, 127.7, 127.6, 75.2, 73.2, 73.0, 66.2, 38.9, 37.6, 15.2, 11.6, 7.1, 5.4 ppm; MS (ESI-IT) *m*/*z* 261.1 (M − TES+Na^+, 100), 239.1 (65); HRMS calcd for $C_{14}H_{22}O_3Na$ [M + TES+Na^+] 261.1467, found 261.1467 (−1.0 ppm).

(−)-(4*S*,5*R*,6*S*,*E*)-Methyl 7-(Benzyloxy)-4,6-dimethyl-5-(triethylsilyloxy)hept-2-enoate (S55).



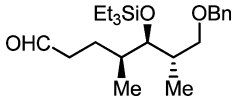
Aldehyde **S54** was obtained as a pale yellow oil from alcohol **S53** (1.00 g) following general procedure **A11** and was used as crude without further purification. Product **S55** (1.05 g, yield = 91% over two steps) was obtained as a colorless oil from crude aldehyde **S54** following general procedure **A6** and purification by flash chromatography on silica gel (hexanes/EtOAc 90:10): R_f = 0.39 (hexanes/EtOAc, 90:10); $[\alpha]^{25}_D$ −16.8 (*c* 1.2, $CHCl_3$); formula $C_{23}H_{38}O_4Si$; MW 406.63 g/mol; IR (neat) ν_{max} 3031, 2956, 2877, 1726, 1456, 1097, 1011, 735 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35−7.25 (m, 5H), 6.96 (dd, *J* = 7.9 Hz, 15.8 Hz, 1H), 5.80 (dd, *J* = 1.2 Hz, 15.8 Hz, 1H), 4.48 (d, *J* = 12.0 Hz, 1H), 4.45 (d, *J* = 12.1 Hz, 1H), 3.73 (s, 3H), 3.62 (t, *J* = 5.4 Hz, 1H), 3.51 (dd, *J* = 4.8 Hz, 9.1 Hz, 1H), 3.30 (dd, *J* = 7.2 Hz, 9.1 Hz, 1H), 2.59−2.49 (m, 1H), 1.97−1.88 (m, 1H), 1.03 (d, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 7.0 Hz, 3H), 0.93 (t, *J* = 7.9 Hz, 9H), 0.58 (q, *J* = 7.9 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 153.1, 138.8, 128.5, 127.7, 127.6, 120.5, 77.6, 73.2, 72.3, 51.7, 40.7, 38.2, 15.2, 14.6, 7.3, 5.5 ppm; MS (ESI-IT) *m*/*z* 293.2 (33), 315.2 (100), 407.3 (M + H^+, 15), 429.3 (M + Na^+, 60), 585.4 (23); HRMS calcd for $C_{23}H_{39}O_4Si$ [M + H]$^+$ 407.2618, found 407.2633 (3.8 ppm).

(−)-(4*S*,5*R*,6*S*)-7-(Benzyloxy)-4,6-dimethyl-5-(triethylsilyloxy)heptan-1-ol (S57).



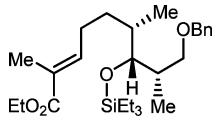
Product **S56** was obtained as a colorless oil from *α*,*β*-unsaturated ester **S55** (860 mg) following general procedure **A2** and was used as crude without further purification. Primary alcohol **S57** (702 mg, yield = 88% over two steps) was obtained as a colorless oil from crude ester **S56** following general procedure **A4** and purification by flash chromatography on silica gel (hexanes/EtOAc 80:20): R_f = 0.25 (hexanes/EtOAc, 80:20); $[\alpha]^{25}_D$ −13.8 (*c* 1.1, $CHCl_3$); formula $C_{22}H_{40}O_3Si$; MW 380.64 g/mol; IR (neat) ν_{max} 3357, 2956, 2876, 1456, 1100, 1062, 1009, 735 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35−7.26 (m, 5H), 4.51 (d, *J* = 12.0 Hz, 1H), 4.46 (d, *J* = 12.1 Hz, 1H), 3.61 (app t, *J* = 6.3 Hz, 1H), 3.55 (dd, *J* = 4.4 Hz, 8.9 Hz, 1H), 3.47 (dd, *J* = 3.4 Hz, 6.5 Hz, 1H), 3.29 (dd, *J* = 7.3 Hz, 9.0 Hz, 1H), 1.97−1.90 (m, 1H), 1.64−1.56 (m, 1H), 1.54−1.47 (m, 1H), 1.46−1.37 (m, 2H), 1.31−1.25 (m, 1H), 1.24−1.14 (m, 1H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.94 (t, *J* = 6.9 Hz, 9H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.58 (q, *J* = 7.9 Hz, 6H) ppm; *OH signal missing possibly due to exchange in CDCl*$_3$; ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0, 128.5, 127.8, 127.6, 78.4, 73.3, 73.2, 63.3, 37.8, 36.2, 31.1, 30.5, 15.6, 14.3, 7.4, 5.7 ppm; MS (ESI-IT) *m*/*z* 403.3 (M + Na^+, 72), 289.2 (100); HRMS calcd for $C_{22}H_{40}O_3NaSi$ [M + Na]$^+$ 403.2644, found 403.2648 (0.9 ppm).

(±)-(4*S*,5*R*,6*S*)-7-(Benzyloxy)-4,6-dimethyl-5-(triethylsilyloxy)heptanal (S58).



Aldehyde **S58** (500 mg, yield = 88%) was obtained as a colorless oil from alcohol **S57** (573 mg) following general procedure **A5** and purification by flash chromatography on silica gel (hexanes/EtOAc 85:15): R_f = 0.38 (hexanes/EtOAc, 85:15); formula $C_{22}H_{38}O_3Si$; MW 378.62 g/mol; IR (neat) ν_{max} 3056, 2958, 2877, 1726, 1455, 1095, 1068, 734 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.77 (t, *J* = 1.8 Hz, 1H), 7.36−7.26 (m, 5H), 4.53 (d, *J* = 12.0 Hz, 1H), 4.48 (d, *J* = 12.0 Hz, 1H), 3.55 (dd, *J* = 4.6 Hz, 8.9 Hz, 1H), 3.54 (dd, *J* = 2.9 Hz, 6.3 Hz, 1H), 3.34 (dd, *J* = 7.1 Hz, 9.0 Hz, 1H), 2.52−2.26 (m, 2H), 1.99−1.90 (m, 1H), 1.77−1.70 (m, 1H), 1.64−1.56 (m, 1H), 1.54−1.46 (m, 1H), 0.97 (d, *J* = 7.3 Hz, 3H), 0.96 (t, *J* = 7.9 Hz, 9H), 0.87 (d, *J* = 6.7 Hz, 3H), 0.61 (q, *J* = 7.9 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.9, 138.9, 128.5, 127.8, 127.7, 77.9, 73.3, 73.1, 42.5, 38.0, 36.0, 27.0, 15.3, 13.9, 7.4, 5.7 ppm.

(±)-(6*S*,7*R*,8*S*,*E*)-Ethyl 9-(Benzyloxy)-2,6,8-trimethyl-7-(triethylsilyloxy)non-2-enoate (S59).



To a solution of crude aldehyde **S58** (37 mg) in dry CH_2Cl_2 (0.1 M, 1.05 mL) was added ethyl 2-(triphenylphosphoranylidene)propanoate (1.5 equiv, 57 mg), and the resulting solution was heated to reflux overnight. The mixture was cooled to room temperature and then concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel (hexanes/EtOAc, 90:10) to afford (*E*)-*α*,*β*-unsaturated ester **S59** as a colorless oil (40 mg, yield =82% over two steps): R_f = 0.42 (hexanes/EtOAc, 80:20); formula $C_{27}H_{46}O_4Si$; MW 462.73 g/mol; IR (neat) ν_{max} 3030, 2958, 2877, 1712, 1456, 1267, 1098, 737 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37−7.27 (m, 5H), 6.75 (dt, *J* = 1.1 Hz, 7.5 Hz, 1H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.48 (d, *J* = 12.0 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.56 (dd, *J* = 4.2 Hz, 8.9 Hz, 1H), 3.52 (dd, *J* = 3.1 Hz, 6.7 Hz, 1H), 3.33 (dd, *J* = 7.5 Hz, 8.8 Hz, 1H), 2.26−2.10 (m, 2H), 1.98−1.89 (m, 1H), 1.84 (s, 3H), 1.66−1.58 (m, 1H), 1.55−1.49 (m, 1H), 1.35−1.28 (m, 1H), 1.31 (t, *J* = 7.1 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.96 (t, *J* = 7.9 Hz, 9H), 0.88 (d, *J* = 6.8 Hz, 3H), 0.59 (q, *J* = 7.9 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 142.5, 139.0, 128.5, 128.0, 127.8, 127.6, 78.0, 73.3, 73.2, 60.6, 38.0, 36.3, 33.4, 27.1, 15.5, 14.5, 14.1, 12.6, 7.4, 5.8 ppm; MS (ESI-IT) *m*/*z* 193.8 (3), 285.2 (3), 331.2 (10), 349.2

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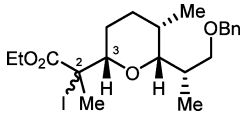
(24), 371.2 (50), 448.3 (17), 463.3 (M + H$^+$, 56), 485.3 (M + Na$^+$, 100), 499.3 (6), 562.4 (20); HRMS calcd for $C_{27}H_{47}O_4Si$ [M + H$^+$] 463.3238, found 463.3234 (−1.0 ppm); calcd for $C_{27}H_{46}NaO_4Si$ [M + Na$^+$] 485.3063, found 485.3051 (−1.4 ppm).

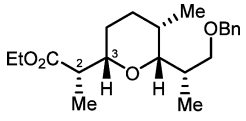
(±)-Ethyl 2-((2*S*,5*S*,6*R*)-6-((*S*)-1-(Benzyloxy)propan-2-yl)-5-methyltetrahydro-2*H*-pyran-2-yl)-2-iodopropanoate (22a,b).



To a solution at room temperature of product **S59** (40 mg) in dry MeCN (0.1 M, 0.86 mL) was added I_2 (2.9 equiv, 66 mg). The reaction mixture was stirred for 5 h at room temperature before addition of AgOTf (1.4 equiv, 33 mg) and stirring overnight at room temperature. The reaction mixture was diluted with EtOAc and then treated with a saturated aqueous solution of $Na_2S_2O_3$. The resulting mixture was stirred for 1 h at room temperature before 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. ^{1}H NMR spectroscopic analysis of the unpurified product indicated a pair of diastereomers in a 6:1 mixture of 3,7-*cis* (**22a**,**b**):3,7-*trans* products. The two diastereoisomers were separated by flash chromatography on silica gel (hexanes/EtOAc, 95:5) to afford an inseparable mixture of 2,3-iodides **22a**,**b** as a colorless oil (22 mg, yield = 54%).

22a: R_f = 0.25 (hexanes/EtOAc, 80:20); formula $C_{21}H_{31}IO_4$; MW 474.37 g/mol; IR (neat) ν_{max} 3062, 3026, 2964, 2857, 1732, 1453, 1253, 1094, 1055, 736 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.26 (m, 5H), 4.49 (d, J = 12.0 Hz, 1H), 4.45 (d, J = 12.0 Hz, 1H), 4.21 (dq, J = 10.7 Hz, 7.1 Hz, 1H), 4.05 (dq, J = 10.7 Hz, 7.1 Hz, 1H), 3.88 (dd, J = 2.0 Hz, 11.6 Hz, 1H), 3.55 (dd, J = 3.2 Hz, 8.8 Hz, 1H), 3.22−3.16 (m, 2H), 2.05 (s, 3H), 1.98−1.93 (m, 1H), 1.86−1.75 (m, 3H), 1.74−1.67 (m, 1H), 1.66−1.56 (m, 1H), 1.26 (t, J = 7.1 Hz, 3H), 0.92 (d, J = 6.7 Hz, 3H), 0.91 (d, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 139.1, 128.5, 127.65, 127.59, 82.8, 82.3, 73.3, 73.2, 62.0, 42.6, 35.9, 31.5, 27.7, 24.9, 21.2, 14.0, 13.3, 11.5 ppm; MS (ESI-IT) m/z 365.2 (5), 387.2 (10), 403.2 (16), 442.3 (14), 475.1 (M + H$^+$, 67), 497.1 (M + Na$^+$, 100), 536.2 (4), 749.4 (5); HRMS calcd for $C_{21}H_{32}IO_4$ [M + H$^+$] 475.1334, found 475.1334 (−1.2 ppm); calcd for $C_{21}H_{31}INaO_4$ [M + Na$^+$] 497.1151, found 497.1151 (−1.7 ppm).

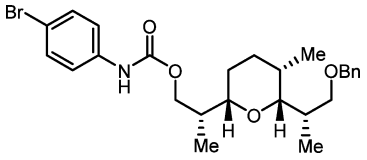
(±)-(*S*)-Ethyl 2-((2*S*,5*S*,6*R*)-6-((*S*)-1-(Benzyloxy)propan-2-yl)-5-methyltetrahydro-2*H*-pyran-2-yl)propanoate (30a).



30a (2,3-*anti*)

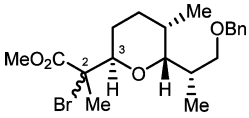
Product **30a** (13 mg, yield = 87%) was obtained as a colorless oil from a mixture of iodides **22a**,**b** (20 mg) following general procedure **A1** and purification by flash chromatography on silica gel (hexanes/EtOAc 70:30). ^{1}H NMR spectroscopic analysis of the unpurified product indicated exclusively (>20:1) product 2,3-*anti* (**30a**): R_f = 0.15 (hexanes/EtOAc, 80:20); formula $C_{21}H_{32}O_4$; MW 348.48 g/mol; IR (neat) ν_{max} 3062, 3026, 2970, 2856, 1735, 1454, 1176, 1067, 736 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.25 (m, 5H), 4.50 (d, J = 12.1 Hz, 1H), 4.47 (d, J = 12.0 Hz, 1H), 4.14−4.04 (m, 2H), 3.62 (dd, J = 3.2 Hz, 8.9 Hz, 1H), 3.46 (ddd, J = 3.5 Hz, 8.9 Hz, 12.1 Hz, 1H), 3.31 (dd, J = 7.7 Hz, 8.6 Hz, 1H), 3.16 (dd, J = 1.9 Hz, 10.2 Hz, 1H), 2.53−2.45 (m, 1H), 1.87−1.76 (m, 2H), 1.75−1.69 (m, 2H), 1.52−1.36 (m, 2H), 1.25 (t, J = 7.1 Hz, 3H), 1.10 (d, J = 7.1 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H), 0.92 (d, J = 6.7 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 139.4, 128.5, 127.7, 127.5, 81.5, 80.3, 73.32, 73.29, 60.4, 46.1, 36.0, 31.3, 28.1, 23.4, 14.6, 13.4, 13.3, 11.5 ppm; MS (ESI-IT) m/z 349.2 (M + H$^+$, 45), 371.2 (M + Na$^+$, 100), 372.2 (22), 448.3 (6); HRMS calcd for $C_{21}H_{33}O_4$ [M + H$^+$] 349.2366, found 349.2366 (−2.0 ppm); calcd for $C_{21}H_{32}NaO_4$ [M + Na$^+$] 371.2182, found 371.2182 (−2.8 ppm).

(±)-(*R*)-2-((2*S*,5*S*,6*R*)-6-((*S*)-1-(Benzyloxy)propan-2-yl)-5-methyltetrahydro-2*H*-pyran-2-yl)propyl 4-bromophenylcarbamate (S60).



Primary alcohol as a colorless oil was obtained from ester **30a** (13 mg) following general procedure **A4**. To a cold (0 °C) solution of crude alcohol in dry CH_2Cl_2 (0.1 M, 0.4 mL) were added successively Et_3N (1.1 equiv, 6 μL) and *p*-bromophenyl isocyanate (1.1 equiv, 8 mg). The reaction mixture was stirred for 3 h at 0 °C before the reaction mixture was treated with a saturated aqueous solution of $NaHCO_3$ and separation of the organic phase at room temperature. The aqueous layer was extracted with EtOAc (3×), and the combined organic fractions were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel (hexanes/EtOAc, 90:10) to afford product **S60** as a white solid (14 mg, yield = 76% over two steps), for which structural assignment was confirmed by X-ray analysis (cf. Supporting Information, part III, X-ray): R_f = 0.53 (hexanes/EtOAc, 80:20); formula $C_{26}H_{34}BrNO_4$; MW 504.46 g/mol; IR (neat) ν_{max} 3319, 2965, 2926, 2855, 1707, 1595, 1532, 1491, 1399, 1307, 1221, 1075, 1059, 825, 735, 697 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43−7.21 (m, 9H), 6.52 (bs, 1H), 4.51 (d, J = 12.0 Hz, 1H), 4.47 (d, J = 12.0 Hz, 1H), 4.31 (dd, J = 4.0 Hz, 10.4 Hz, 1H), 4.17 (dd, J = 6.4 Hz, 10.4 Hz, 1H), 3.62 (dd, J = 2.8 Hz, 8.7 Hz, 1H), 3.49 (dd, J = 6.4 Hz, 8.6 Hz, 1H), 3.22 (dd, J = 1.3 Hz, 10.2 Hz, 1H), 3.16 (dd, J = 7.5 Hz, 13.9 Hz, 1H), 1.93−1.85 (m, 1H), 1.84−1.76 (m, 2H), 1.76−1.69 (m, 2H), 1.48−1.42 (m, 2H), 0.97 (d, J = 7.0 Hz, 3H), 0.94 (d, J = 7.2 Hz, 3H), 0.93 (d, J = 7.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 139.4, 137.4, 132.2, 128.5, 127.6, 127.5, 120.3, 115.9, 81.2, 79.7, 73.3, 73.1, 67.6, 38.8, 36.3, 31.5, 28.1, 24.1, 13.8, 13.5, 11.5 ppm; MS (ESI-IT) m/z 360.3 (7), 504.2 (15, M + H$^+$), 528.2 (100), 865.5 (8), 1031.3 (24); HRMS calcd for $C_{26}H_{35}BrNO_4$ [M + H$^+$] 504.1544, found 504.1734 (−2.0 ppm); calcd for $C_{26}H_{34}BrNO_4Na$ [M + Na$^+$] 526.1563, found 526.1550 (−2.5 ppm).

(±)-Methyl 2-((2*R*,5*S*,6*R*)-6-((*S*)-1-(Benzyloxy)propan-2-yl)-5-methyltetrahydro-2*H*-pyran-2-yl)-2-bromopropanoate (31a, 31b).



Products **31a** and **31b** (32 mg, yield = 73%) were obtained as pale yellow oils from aldehyde **S58** (40 mg) following general procedure **A7** and purification by flash chromatography on silica gel (hexanes/EtOAc 95:5 to 90:10). ^{1}H NMR spectroscopic analysis of the unpurified product indicated a pair of 2,3-diastereomers in a ~1:1 ratio of products **31a**:**31b**.

31a: R_f = 0.56 (hexanes/EtOAc, 90:10); formula $C_{20}H_{29}BrO_4$; MW 413.35 g/mol; IR (neat) ν_{max} 2953, 2861, 1736, 1455 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39−7.26 (m, 5H), 4.55 (d, J = 11.9 Hz, 1H), 4.45 (d, J = 11.9 Hz, 1H), 4.33 (dd, J = 4.8 Hz, 10.4 Hz, 1H), 3.78 (s, 3H), 3.67 (dd, J = 3.7 Hz, 9.9 Hz, 1H), 3.53 (dd, J = 3.1 Hz, 8.7 Hz, 1H), 3.41 (dd, J = 6.3 Hz, 8.7 Hz, 1H), 2.10−2.02 (m, 1H), 1.97−1.89 (m, 2H), 1.91 (s, 3H), 1.88−1.76 (m, 2H), 1.36−1.26 (m, 1H), 0.95 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 139.1, 128.5, 127.8, 127.6, 77.1, 75.3, 73.2, 72.5, 62.9, 53.3, 35.1, 29.0, 27.9, 23.1, 20.5, 15.7, 14.2 ppm; MS (ESI-IT) m/z 413.1 (M + H$^+$, 87), 416.1 (22), 432.2 (23), 435.1 (M + Na$^+$, 100), 438.1 (25); HRMS calcd for $C_{20}H_{30}BrO_4$ [M + H$^+$] 413.1327, found 413.1324 (0.4 ppm); calcd for $C_{20}H_{29}O_4BrNa$ [M + Na$^+$] 435.1141, found 435.1142 (0.08 ppm).

31b: R_f = 0.46 (hexanes/EtOAc, 90:10); formula $C_{20}H_{29}BrO_4$; MW 413.35 g/mol; IR (neat) ν_{max} 2928, 2867, 1736, 1455, 1165, 741 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39−7.26 (m, 5H), 4.57 (d, J = 11.9 Hz, 1H), 4.52 (d, J = 12.0 Hz, 1H), 4.13 (dd, J = 4.5 Hz, 10.6 Hz, 1H), 3.76 (s, 3H), 3.74−3.70 (m, 2H), 3.51 (dd, J = 7.2 Hz, 8.9 Hz, 1H), 2.09−

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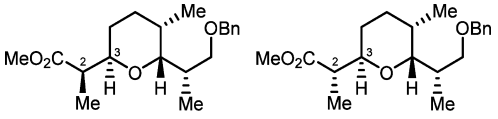
1.92 (m, 3H), 1.86 (s, 3H), 1.78−1.69 (m, 1H), 1.67−1.60 (m, 1H), 1.37−1.26 (m, 1H), 0.99 (d, J = 6.7 Hz, 3H), 0.96 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 139.1, 128.5, 127.8, 127.6, 77.4, 76.2, 73.3, 73.0, 66.1, 53.4, 34.5, 30.2, 27.6, 24.5, 22.8, 16.5, 14.7; MS (ESI-IT) m/z 413.1 (98), 415.1 (100), 427.1 (27), 430.2 (10), 432.2 (11), 435.1 (58), 438.1 (16); HRMS calcd for $C_{20}H_{30}BrO_4$ [M + H$^+$] 413.1327, found 413.1313 (−2.3 ppm); calcd for $C_{20}H_{29}O_4BrNa$ [M + Na$^+$] 435.1141, found 435.1136 (−1.1 ppm).

(±)-(*R*)-Methyl 2-((2*R*,5*S*,6*R*)-6-((*S*)-1-(Benzyloxy)propan-2-yl)-5-methyltetrahydro-2*H*-pyran-2-yl)propanoate (34a) and (±)-(*S*)-Methyl 2-((2*R*,5*S*,6*R*)-6-((*S*)-1-(Benzyloxy)propan-2-yl)-5-methyltetrahydro-2*H*-pyran-2-yl)propanoate (34b).

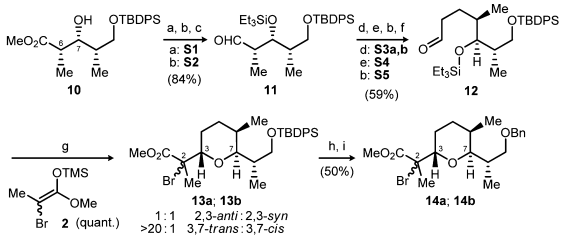


34a (2,3-*anti*) **34b** (2,3-*syn*)

Products **34a** and **34b** (20 mg, yield = 83%) were obtained as colorless oils from a mixture of bromides **31a** and **31b** (30 mg) following general procedure **A1** and purification by flash chromatography on silica gel (hexanes/EtOAc 95:5 to 85:15). ^{1}H NMR spectroscopic analysis of the unpurified product indicated a pair of diastereomers in a 2:1 ratio of products 2,3-*anti* (**34a**):2,3-*syn* (**34b**).

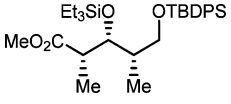
34a: R_f = 0.48 (hexanes/EtOAc, 85:15); formula $C_{20}H_{30}O_4$; MW 334.45 g/mol; IR (neat) ν_{max} 2953, 2870, 1739, 1455, 1165, 741 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.23 (m, 5H), 4.52 (d, J = 12.1 Hz, 1H), 4.48 (d, J = 12.1 Hz, 1H), 3.96 (dd, J = 5.8 Hz, 10.9 Hz, 1H), 3.62 (dd, J = 3.4 Hz, 8.9 Hz, 1H), 3.56 (s, 3H), 3.39 (dd, J = 2.3 Hz, 10.0 Hz, 1H), 3.15−3.05 (m, 2H), 1.98−1.89 (m, 1H), 1.89−1.81 (m, 2H), 1.80−1.72 (m, 1H), 1.48 (ddd, J = 3.6 Hz, 7.2 Hz, 13.3 Hz, 1H), 1.44−1.38 (m, 1H), 1.07 (d, J = 6.9 Hz, 3H), 0.98 (d, J = 6.9 Hz, 3H), 0.93 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 139.2, 128.5, 127.7 127.5, 75.7, 74.3, 73.7, 73.3, 51.6, 39.9, 36.0, 28.4, 26.2, 19.7, 15.0, 13.4, 11.5 ppm; MS (ESI-IT) m/z 335.2 (M + H$^+$, 30), 357.2 (M + Na$^+$, 100), 359.2 (13); HRMS calcd for $C_{20}H_{31}O_4$ [M + H$^+$] 335.2222, found 335.2210 (−2.1 ppm); calcd for $C_{20}H_{30}O_4Na$ [M + Na$^+$] 357.2036, found 357.2033 (−0.9 ppm).

34b: R_f = 0.54 (hexanes/EtOAc, 85:15); formula $C_{20}H_{30}O_4$; MW 334.45 g/mol; IR (neat) ν_{max} 2938, 1737, 1455, 1165, 1043, 737 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.26 (m, 5H), 4.51 (d, J = 11.9 Hz, 1H), 4.46 (d, J = 11.9 Hz, 1H), 3.90 (dd, J = 5.5 Hz, 10.8 Hz, 1H), 3.67 (s, 3H), 3.55 (dq, J = 4.4 Hz, 8.6 Hz, 2H), 3.36 (dd, J = 2.3 Hz, 10.1 Hz, 1H), 3.17−3.10 (m, 1H), 2.00−1.86 (m, 2H), 1.86−1.75 (m, 2H), 1.52−1.46 (m, 1H), 1.24−1.18 (m, 1H), 1.19 (d, J = 6.8 Hz, 3H), 0.97 (d, J = 6.9 Hz, 3H), 0.95 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 139.0, 128.5, 127.8, 127.6, 75.0, 73.3, 72.6, 72.4, 51.9, 39.3, 36.2, 28.2, 26.6, 21.9, 14.5, 13.5, 11.3 ppm; MS (ESI-IT) m/z 335.2 (M + H$^+$, 100), 357.2 (M + Na$^+$, 77); HRMS calcd for $C_{20}H_{31}O_4$ [M + H$^+$] 335.2222, found 335.2210 (−2.1 ppm); calcd for $C_{20}H_{30}O_4Na$ [M + Na$^+$] 357.2036, found 357.2027 (−2.6 ppm).



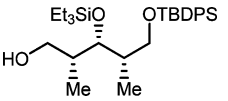
Reactions and conditions: a) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C. b) DIBAL-H, CH_2Cl_2, −40 °C. c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C. d) $Ph_3PC(H)=CO_2Me$, toluene, reflux. e) H_2, Pd/C, EtOAc, rt. f) DMP, $NaHCO_3$, CH_2Cl_2, rt. g) $BiBr_3$, **2**, CH_2Cl_2/MeCN, −78 °C. h) HF•py, THF, 0 °C. i) BnOC=NHCCl$_3$, TfOH, *c*-Hex/CH_2Cl_2, 0 °C.

(±)-(2*S*,3*R*,4*S*)-Methyl 5-(*tert*-butyldiphenylsilyloxy)-2,4-dimethyl-3-(triethylsilyloxy)pentanoate (S1).



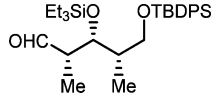
To a cold (0 °C) solution of alcohol **10**[6a] (6.89 g) in dry CH_2Cl_2 (0.1 M, 166 mL) were added successively 2,6-lutidine (1.2 equiv, 2.3 mL) and TESOTf (1.1 equiv, 4.1 mL). The reaction mixture was stirred for 1.5 h at 0 °C or until alcohol was completely consumed, as verified by TLC (hexanes/EtOAc, 85:15). 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 combined organic fractions were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel (hexanes/EtOAc, 95:5) to afford protected alcohol **S1** as a colorless oil (8.00 g, yield = 91%): R_f = 0.75 (hexanes/EtOAc, 85:15); formula $C_{30}H_{48}O_4Si_2$; MW 528.87 g/mol; IR (neat) ν_{max} 3071, 3050, 2955, 2878, 1739, 1590, 1461, 1429, 1388, 1363, 1246, 1195, 1140, 1110, 1057, 1010, 941, 822, 739, 704, 614 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68−7.62 (m, 4H), 7.46−7.34 (m, 6H), 4.19 (dd, J = 4.0 Hz, 6.4 Hz, 1H), 3.66 (s, 3H), 3.54 (dd, J = 7.0 Hz, 10.1 Hz, 1H), 3.44 (dd, J = 5.9 Hz, 10.1 Hz, 1H), 2.69−2.59 (m, 1H), 1.76−1.67 (m, 1H), 1.15 (d, J = 7.0 Hz, 3H), 1.06 (s, 9H), 0.93 (t, J = 7.9 Hz, 9H), 0.86 (d, J = 6.9 Hz, 3H), 0.61−0.54 (m, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.7, 135.61, 135.58, 133.8, 133.7, 129.6, 129.5, 127.59, 127.58, 73.7, 66.3, 51.5, 44.1, 40.1, 26.8, 19.2, 13.0, 11.5, 7.0, 5.3 ppm; MS (ESI-IT) m/z 273.2 (51), 451.3 (32), 529.3 (M + H$^+$, 100); HRMS calcd for $C_{30}H_{49}O_4Si_2$ [M + H$^+$] 529.3164, found 529.3168 (0.7 ppm).

(±)-(2*R*,3*S*,4*S*)-5-(*tert*-Butyldiphenylsilyloxy)-2,4-dimethyl-3-(triethylsilyloxy)pentan-1-ol (S2).



To a cold (−40 °C) solution of ester **S1** (1.51 g) in dry CH_2Cl_2 (0.1 M, 29 mL) was added a 1.0 M solution of DIBAL-H in hexanes (3 equiv, 8.6 mL). The mixture was stirred for 1 h at −40 °C or until ester was completely consumed, as verified by TLC (hexanes/EtOAc, 85:15). 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 mixture was purified by flash chromatography on silica gel (hexanes/EtOAc, 85:15) to afford primary alcohol **S2** as a colorless oil (1.32 g, yield = 92%): R_f = 0.43 (hexanes/EtOAc, 85:15); formula $C_{29}H_{48}O_3Si_2$; MW 500.86 g/mol; IR (neat) ν_{max} 3382, 3071, 3050, 2957, 2934, 2877, 1590, 1463, 1427, 1388, 1239, 1109, 1030, 968, 912, 823, 738, 703, 613 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72−7.64 (m, 4H), 7.47−7.36 (m, 6H), 4.03−3.99 (m, 1H), 3.71−3.65 (m, 1H), 3.56−3.43 (m, 3H), 2.39 (bs, 1H), 2.03−1.93 (m, 1H), 1.93−1.83 (m, 1H), 1.08 (s, 9H), 0.96 (t, J = 7.9 Hz, 9H), 0.92 (d, J = 6.9 Hz, 3H), 0.84 (d, J = 7.0 Hz, 3H), 0.67−0.58 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 135.8, 134.02, 133.99, 129.9, 127.9, 74.7, 67.0, 66.6, 40.5, 37.8, 27.1, 19.4, 13.2, 12.5, 7.2, 5.4 ppm; MS (ESI-IT) m/z 227.2 (19), 291.2 (63), 351.2 (26), 423.3 (29), 501.3 (M + H$^+$, 100), 600.4 (19); HRMS calcd for $C_{29}H_{49}O_3Si_2$ [M + H$^+$] 501.3215, found 501.3226 (2.2 ppm).

(±)-(2*S*,3*R*,4*S*)-5-(*tert*-Butyldiphenylsilyloxy)-2,4-dimethyl-3-(triethylsilyloxy)pentanal (11).



To a cold (−78 °C) solution of oxalyl chloride (1.2 equiv, 0.26 mL) in dry CH_2Cl_2 (0.1 M, 25 mL) was added dropwise anhydrous DMSO (2.4 equiv, 0.43 mL), and the mixture was stirred for 10 min at −78 °C. A solution of the alcohol **S2** (6.58 g) in dry CH_2Cl_2 (0.5 M, 5 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 Et_3N (5 equiv, 1.75 mL). The mixture was stirred 1 h at −78 °C and then treated with a saturated aqueous solution of NH_4Cl followed by separation of organic phase at room temperature. The aqueous layer was extracted with Et_2O

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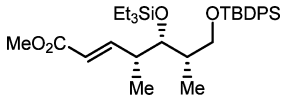
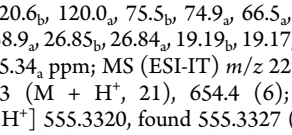
(3×), and combined organic fractions were washed with a saturated brine solution, dried ($MgSO_4$), filtered, and concentrated in vacuo to afford aldehyde **11** as a colorless oil (1.26 g, quantitative yield) which was used as crude without further purification: R_f = 0.72 (hexanes/EtOAc, 85:15); formula $C_{29}H_{46}O_3Si_2$; MW 498.84 g/mol; IR (neat) ν_{max} 3071, 3050, 2957, 2878, 2706, 1890, 1725, 1590, 1463, 1427, 1390, 1363, 1240, 1187, 1109, 1109, 965, 942, 909, 821, 734, 709, 614 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.87 (d, J = 1.0 Hz, 1H), 7.76−7.69 (m, 4H), 7.50−7.40 (m, 6H), 4.40 (app t, J = 4.6 Hz, 1H), 3.65 (dd, J = 7.0 Hz, 10.2 Hz, 1H), 3.54 (dd, J = 5.6 Hz, 10.2 Hz, 1H), 2.64−2.57 (m, 1H), 1.91−1.81 (m, 1H), 1.14 (m, 9H), 1.11 (d, J = 7.0 Hz, 3H), 1.01 (t, J = 8.0 Hz, 9H), 0.92 (d, J = 6.9 Hz, 3H), 0.70−0.63 (m, 6H) ppm; MS (ESI-IT) m/z 111.1 (100), 171.1 (33), 243.2 (19), 289.2 (42), 349.2 (14), 381.2 (77), 437.3 (19), 481.3 (13), 521.3 (M + Na^+, 48), 598.4 (15), 629.4 (26); HRMS calcd for $C_{29}H_{46}O_3NaSi_2$ [M + Na^+] 521.2878, found 521.2880 (0.4 ppm).

(±)-(4*R*,5*S*,6*S*,*E*)-Methyl 7-(*tert*-Butyldiphenylsilyloxy)-4,6-dimethyl-5-(triethylsilyloxy)hept-2-enoate (S3a,b).



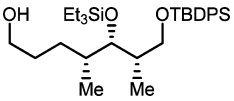
To a solution of aldehyde **11** (2.44 g) in dry toluene (0.1 M, 49 mL) was added methyl (triphenylphosphoranylidene)acetate (1.5 equiv, 2.46 g), and the resulting solution was heated to reflux overnight. The mixture was cooled to room temperature and then concentrated in vacuo. The solid yellow residue was digested in hexanes and filtered onto a pad of Celite, leading to a filtrate which was concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel (hexanes/EtOAc, 95:5) to afford an inseparable 10:1 mixture of (*E*):(*Z*) α,β-unsaturated ester **S3a,b** as a colorless oil (2.23 g, yield = 82%): R_f = 0.55 (hexanes/EtOAc, 90:10); formula $C_{32}H_{50}O_4Si_2$; MW 554.91 g/mol; IR (neat) ν_{max} 2957, 2877, 1726, 1656, 1461, 1429, 1387, 1334, 1270, 1236, 1109, 1009, 824, 803, 736, 703, 613 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.69−7.62 (m, $4H_a$ + $4H_b$), 7.46−7.35 (m, $6H_a$+$6H_b$), 7.02 (dd, J = 8.4 Hz, 15.7 Hz, $1H_b$), 7.00 (dd, J = 7.9 Hz, 15.8 Hz, $1H_a$), 5.81 (dd, J = 1.1 Hz, 15.8 Hz, $1H_a$), 5.76 (dd, J = 0.9 Hz, 15.8 Hz, $1H_b$), 3.90 (dd, J = 2.7 Hz, 6.6 Hz, $1H_a$), 3.85 (dd, J = 3.5 Hz, 5.8 Hz, $1H_b$), 3.76 (s, $3H_a$), 3.72 (s, $3H_b$), 3.53 (dd, J = 7.9 Hz, 10.0 Hz, $1H_a$+$1H_b$), 3.44 (dd, J = 5.9 Hz, 10.1 Hz, $1H_b$), 3.41 (dd, J = 5.9 Hz, 10.1 Hz, $1H_a$), 2.57−2.47 (m, $1H_a$), 2.50−2.42 (m, $1H_b$), 1.81−1.76 (m, $1H_b$), 1.76−1.69 (m, $1H_a$), 1.07 (s, $9H_a$+$9H_b$), 1.06 (d, J = 7.0 Hz, $3H_a$), 1.02 (d, J = 6.9 Hz, $3H_b$), 0.95 (t, J = 7.9 Hz, $9H_a$+$9H_b$), 0.83 (d, J = 6.8 Hz, $3H_b$), 0.76 (d, J = 6.8 Hz, $3H_a$), 0.65−0.55 (m, $6H_a$), 0.56−0.49 (m, $6H_b$) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0_{a+b}, 152.6_b, 152.4_a, 135.59_a, 135.58_b, 135.57_b, 135.55_a, 133.83_b, 133.82_a, 133.67_b, 133.66_a, 129.59_a, 129.58_b, 129.56_b, 129.55_a, 127.59_b, 127.58_a, 120.6_b, 120.0_a, 75.5_b, 74.9_a, 66.5_a, 66.4_b, 51.4_a, 51.3_b, 41.6_a, 41.4_b, 39.2_b, 38.9_a, 26.85_b, 26.84_a, 19.19_b, 19.17_a, 16.7_b, 15.8_a, 11.3_b, 10.8_a, 7.0_{a+b}, 5.36_b, 5.34_a ppm; MS (ESI-IT) m/z 229.1 (4), 345.2 (14), 477.3 (100), 555.3 (M + H^+, 21), 654.4 (6); HRMS calcd for $C_{32}H_{51}O_4Si_2$ [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 (S4).



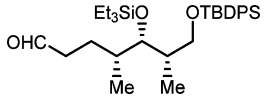
To a solution of α,β-unsaturated ester **S3a,b** (1.00 g) in EtOAc (0.1 M, 10 mL) at room temperature was added 10 wt % Pd on activated carbon (0.1 equiv, 192 mg). The inert gas atmosphere was purged by three cycles of vacuum/H_2 gas before the reaction mixture was stirred until the reaction was judged complete by TLC (hexanes/EtOAc, 90:10). 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 afford product **S4** as a colorless oil (1.02 g, quantitative yield): R_f = 0.45 (hexanes/EtOAc, 90:10); formula $C_{32}H_{52}O_4Si_2$; MW 556.92 g/mol; IR (neat) ν_{max} 3072, 2956, 2877, 1742, 1462, 1429, 1387, 1241, 1171, 1109, 823, 739, 703, 613 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.76−7.68 (m, 4H), 7.49−7.38 (m, 6H), 3.77 (dd, J = 3.7 Hz, 5.0 Hz, 1H), 3.70 (s, 3H), 3.59 (dd, J = 7.1 Hz, 10.0 Hz, 1H), 3.49 (dd, J = 6.0 Hz, 10.0 Hz, 1H), 2.46−2.37 (m, 1H), 2.37−2.26 (m, 1H), 1.92−1.82 (m, 2H), 1.69−1.59 (m, 1H), 1.52−1.42 (m, 1H), 1.12 (s, 9H), 0.99 (t, J = 8.0 Hz, 9H), 0.91 (d, J = 6.7 Hz, 3H), 0.90 (d, J = 6.8 Hz, 3H), 0.69−0.59 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 135.53, 135.52, 133.76, 133.73, 129.49, 129.48, 127.53, 127.52, 75.7, 66.8, 51.3, 38.5, 37.1, 32.2, 28.8, 26.8, 19.1, 15.1, 11.8, 7.1, 5.4 ppm; MS (ESI-IT) m/z 169.1 (100), 347.2 (81), 425.3 (73), 557.3 (M + H^+, 38), 656.5 (6); HRMS calcd for $C_{32}H_{53}O_4Si_2$ [M + H^+] 557.3477, found 557.3485 (1.4 ppm).

(±)-(4*R*,5*S*,6*S*)-7-(*tert*-Butyldiphenylsilyloxy)-4,6-dimethyl-5-(triethylsilyloxy)heptan-1-ol (S5).



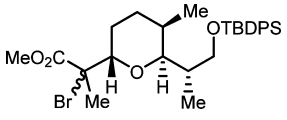
Primary alcohol **S5** as a colorless oil (1.98 g, yield = 83%) was obtained from ester **S4** (2.51 g) following general procedure **A4** and purification by flash chromatography on silica gel (hexanes/EtOAc 85:15): R_f = 0.38 (hexanes/EtOAc, 85:15); formula $C_{31}H_{52}O_3Si_2$; MW 528.91 g/mol; IR (neat) ν_{max} 3339, 3071, 3050, 2956, 2936, 2876, 2361, 2341, 1590, 1463, 1427, 1387, 1239, 1188, 1109, 1059, 1009, 968, 832, 738, 703, 613 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.71−7.64 (m, 4H), 7.46−7.36 (m, 6H), 3.73−3.69 (m, 1H), 3.65−3.59 (m, 2H), 3.56 (dd, J = 7.2 Hz, 9.6 Hz, 1H), 3.45 (dd, J = 6.1 Hz, 9.7 Hz, 1H), 1.87−1.78 (m, 1H), 1.69−1.54 (m, 2H), 1.54−1.44 (m, 2H), 1.39−1.27 (bs, 1H), 1.08 (s, 9H), 0.95 (t, J = 7.9 Hz, 9H), 0.88 (d, J = 7.0 Hz, 3H), 0.86 (d, J = 6.8 Hz, 3H), 0.64−0.56 (m, 6H) ppm; *OH signal missing possibly due to exchange in CDCl*$_3$; ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.59, 135.58, 133.89, 133.88, 129.52, 129.51, 127.55, 127.54, 75.9, 67.0, 63.4, 38.5, 37.4, 30.8, 29.5, 26.9, 19.2, 15.5, 12.0, 7.1, 5.5 ppm; MS (ESI-IT) m/z 192.7 (16), 288.3 (55), 319.2 (84), 397.3 (100), 529.4 (M + H^+, 26), 608.4 (7), 628.5 (17); HRMS calcd for $C_{31}H_{53}O_3Si_2$ [M + H^+] 529.3528, found 529.3526 (−0.4 ppm).

(±)-(4*R*,5*S*,6*S*)-7-(*tert*-Butyldiphenylsilyloxy)-4,6-dimethyl-5-(triethylsilyloxy)heptanal (12).



To a solution of alcohol **S5** (1.97 g) in dry CH_2Cl_2 (0.1 M, 37 mL) were added successively $NaHCO_3$ (10 equiv, 3.08 g) and Dess−Martin periodinane (1.5 equiv, 2.33 g). The reaction mixture was stirred for 1 h at room temperature and then concentrated. The resulting white solid residue was digested in hexanes and filtered onto a pad of Celite. The filtrate was then concentrated in vacuo and purified by flash chromatography on silica gel (hexanes/EtOAc, 90:10) to afford aldehyde **12** as a colorless oil (1.68 g, yield = 87%): R_f = 0.74 (hexanes/EtOAc, 85:15); formula $C_{31}H_{50}O_3Si_2$; MW 526.90 g/mol; IR (neat) ν_{max} 3071, 3050, 2957, 2934, 2877, 2714, 1727, 1590, 1464, 1427, 1388, 1363, 1240, 1189, 1109, 1057, 1009, 970, 823, 739, 704, 613 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.76 (dd, J = 1.8 Hz, 3.4 Hz, 1H), 7.69−7.63 (m, 4H), 7.46−7.35 (m, 6H), 3.75−3.71 (m, 1H), 3.53 (dd, J = 7.3 Hz, 9.9 Hz, 1H), 3.44 (dd, J = 5.8 Hz, 9.9 Hz, 1H), 2.50−2.41 (m, 1H), 2.41−2.32 (m, 1H), 1.84−1.75 (m, 2H), 1.64−1.54 (m, 1H), 1.44−1.34 (m, 1H), 1.07 (s, 9H), 0.94 (t, J = 8.0 Hz, 9H), 0.86 (d, J = 6.8 Hz, 3H), 0.85 (d, J = 6.8 Hz, 3H), 0.63−0.54 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.7, 135.60, 135.57, 133.80, 133.79, 129.57, 129.56, 127.58, 127.57, 75.7, 66.8, 42.2, 38.5, 37.3, 26.9, 25.7, 19.2, 15.2, 12.0, 7.1, 5.4 ppm; MS (ESI-IT) m/z 111.1 (100), 171.1 (38), 245.1 (36), 289.2 (47), 359.2 (22), 381.2 (95), 439.2 (29), 521.3 (51), 553.3 (54), 581.3 (18); HRMS calcd for $C_{31}H_{51}O_3Si_2$ [M + H^+] 527.3371, found 527.3373 (0.3 ppm); calcd for $C_{31}H_{50}O_3Si_2Na$ [M + Na^+] 549.3191, found 549.3192 (0.3 ppm).

(±)-Methyl 2-Bromo-2-((2*S*,5*R*,6*S*)-6-((*S*)-1-(*tert*-butyldiphenylsilyloxy)propan-2-yl)-5-methyltetrahydro-2*H*-pyran-2-yl)propanoate (13a, 13b).



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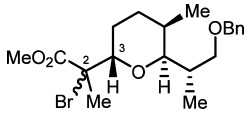
To a cold (−78 °C) solution of aldehyde **12** (1.69 g) in dry CH_2Cl_2 (0.1 M, 32 mL) was added dropwise a solution of $BiBr_3$ (1 equiv, 1.44 g) in dry MeCN (0.5 M, 6.4 mL), followed by silylated enol ether **2** (1.5 equiv, 0.89 mL). The mixture was stirred for 1.5 h at −78 °C or until aldehyde was completely consumed, as verified by TLC (hexanes/EtOAc, 90:10). The reaction mixture was treated with a saturated aqueous solution of NH_4Cl 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. ^1H NMR spectroscopic analysis of the unpurified product indicated exclusive (>20:1) formation of 3,7-trans products as a pair of 2,3-diastereomers in a ∼1:1 ratio of products **13a**:**13b**. The two diastereoisomers were separated by flash chromatography on silica gel (hexanes/EtOAc, 90:10) to afford product **23a** and **23b** as pale yellow oils. Product yield was not calculated due to contamination with C-silylated product from enol ether **2**.

13a: R_f = 0.47 (hexanes/EtOAc, 90:10); formula $C_{29}H_{41}BrO_4Si$; MW 561.62 g/mol; IR (neat) ν_{max} 3071, 2957, 2933, 2860, 1743, 1590, 1453, 1429, 1381, 1263, 1191, 1263, 1110, 1049, 823, 704, 615 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.66−7.63 (m, 4H), 7.45−7.35 (m, 6H), 4.30 (dd, J = 4.1 Hz, 10.3 Hz, 1H), 3.80−3.74 (m, 2H), 3.73 (s, 3H), 3.59 (dd, J = 4.4 Hz, 9.9 Hz, 1H), 3.44 (dd, J = 5.8 Hz, 9.9 Hz, 1H), 1.99−1.79 (m, 3H), 1.92 (s, 3H), 1.73−1.63 (m, 1H), 1.40−1.29 (m, 1H), 1.07 (d, J = 6.9 Hz, 3H), 1.05 (s, 9H), 0.82 (d, J = 6.6 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 135.57, 135.56, 133.77, 133.69, 129.57, 129.56, 127.60, 127.59, 76.2, 75.9, 66.0, 62.6, 53.0, 36.9, 30.6, 27.7, 26.8, 23.0, 22.0, 19.3, 16.3, 14.7 ppm; MS (ESI-IT) m/z 147.1 (14), 207.1 (32), 225.1 (39), 305.1 (62), 395.2 (23), 481.3 (14), 563.2 (100), 660.3 (9); HRMS calcd for $C_{29}H_{42}O_4BrSi$ [M + H^+] 561.2030, found 561.2036 (1.0 ppm).

13b: R_f = 0.40 (hexanes/EtOAc, 90:10); formula $C_{29}H_{41}BrO_4Si$; MW 561.62 g/mol; IR (neat) ν_{max} 3071, 2956, 2933, 2860, 1739, 1453, 1429, 1381, 1263, 1111, 823, 739, 704, 614 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.67−7.64 (m, 4H), 7.45−7.35 (m, 6H), 4.05 (dd, J = 4.3 Hz, 10.2 Hz, 1H), 3.80 (dd, J = 4.1 Hz, 8.3 Hz, 1H), 3.75 (s, 3H), 3.65 (dd, J = 4.1 Hz, 10.0 Hz, 1H), 3.49 (dd, J = 6.2 Hz, 10.0 Hz, 1H), 1.97−1.77 (m, 3H), 1.87 (s, 3H), 1.75−1.61 (m, 2H), 1.37−1.27 (m, 1H), 1.16 (d, J = 6.7 Hz, 3H), 1.06 (s, 9H), 0.81 (d, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 135.64, 135.61, 133.79, 133.74, 129.55, 129.54, 127.59, 127.58, 77.0, 76.0, 66.3, 65.8, 53.2, 36.5, 31.2, 27.5, 26.9, 24.8, 23.9, 19.3, 16.7, 15.1 ppm; MS (ESI-IT) m/z 229.1 (14), 305.1 (51), 395.2 (28), 563.2 (100), 662.3 (11); HRMS calcd for $C_{29}H_{42}O_4BrSi$ [M + H^+] 561.2030, found 561.2036 (1.1 ppm).

(±)-Methyl 2-((2*S*,5*R*,6*S*)-6-((*S*)-1-(Benzyloxy)propan-2-yl)-5-methyltetrahydro-2*H*-pyran-2-yl)-2-bromopropanoate (14a, 14b).

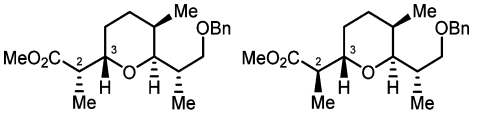


To a cold (0 °C) solution of a mixture of products **13a** and **13b** (652 mg) in dry THF (0.1 M, 12 mL) was added dropwise a solution of HF·pyridine (ca. 70% HF, 1 mL per mmol of substrate, 1.2 mL). The reaction mixture was stirred overnight at 0 °C and then treated slowly with a saturated aqueous solution of $NaHCO_3$, 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 mixture was purified by flash chromatography on silica gel (hexanes/EtOAc, 80:20) to afford an inseparable mixture of bromide adducts as a colorless oil (248 mg, yield = 66% over two steps). To a cold (0 °C) solution of crude product (165 mg) in solvent mixture of cyclohexane and CH_2Cl_2 (2:1, 0.1 M, 5.1 mL) were added successively 2,2,2-benzyltrichloroacetimidate (1.3 equiv, 130 μL) and TfOH (0.1 equiv, 5 μL). The reaction mixture was stirred overnight at 0 °C before treatment with Et_3N (0.15 equiv, 11 μL) and then concentration in vacuo. The crude mixture was dissolved in hexanes and filtered onto a pad of Celite, followed by concentration in vacuo of the filtrate. ^1H NMR spectroscopic analysis of the unpurified product indicated a pair of 2,3-diastereomers in a ∼1:1 ratio of products **14a**:**14b**. The two diastereoisomers were separated by flash chromatography on silica gel (hexanes/EtOAc, 90:10) to afford product **14a** and **14b** as colorless oils (0.24 g, yield = 50%).

14a: R_f = 0.39 (toluene/EtOAc, 98:2); formula $C_{20}H_{29}BrO_4$; MW 413.35 g/mol; IR (neat) ν_{max} 2955, 2933, 2869, 1742, 1452, 1378, 1263, 1097, 1049, 736, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37−7.25 (m, 5H), 4.48 (d, J = 12.1 Hz, 1H), 4.44 (d, J = 12.1 Hz, 1H), 4.30 (dd, J = 4.0 Hz, 10.6 Hz, 1H), 3.75 (s, 3H), 3.72 (dd, J = 4.3 Hz, 7.7 Hz, 1H), 3.39 (dd, J = 4.8 Hz, 9.2 Hz, 1H), 3.25 (dd, J = 6.2 Hz, 9.1 Hz, 1H), 2.02−1.84 (m, 4H), 1.89 (s, 3H), 1.72−1.62 (m, 1H), 1.46−1.35 (m, 1H), 1.07 (d, J = 6.8 Hz, 3H), 0.93 (d, J = 6.7 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 138.6, 128.3, 127.5, 127.4, 76.3, 76.2, 73.08, 73.05, 62.4, 53.0, 35.1, 31.0, 27.8, 22.8, 22.3, 16.4, 15.2 ppm; MS (ESI-IT) m/z 305.1 (21), 413.1 (M + H^+, 100), 503.2 (6); HRMS calcd for $C_{20}H_{30}O_4Br$ [M + H^+] 413.1322, found 413.1319 (−0.8 ppm).

14b: R_f = 0.32 (toluene/EtOAc, 98:2); formula $C_{20}H_{29}BrO_4$; MW 413.35 g/mol; IR (neat) ν_{max} 2954, 2933, 2873, 1739, 1665, 1452, 1379, 1306, 1263, 1089, 1054, 1024, 972, 827, 798, 737, 698, 649 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36−7.25 (m, 5H), 4.50 (d, J = 12.1 Hz, 1H), 4.46 (d, J = 12.1 Hz, 1H), 4.07 (dd, J = 4.5 Hz, 10.2 Hz, 1H), 3.79 (dd, J = 4.7 Hz, 8.2 Hz, 1H), 3.76 (s, 3H), 3.48 (dd, J = 4.4 Hz, 9.2 Hz, 1H), 3.30 (dd, J = 6.5 Hz, 9.2 Hz, 1H), 2.07−2.00 (m, 1H), 2.00−1.91 (m, 1H), 1.89−1.81 (m, 1H), 1.86 (s, 3H), 1.74−1.62 (m, 2H), 1.45−1.33 (m, 1H), 1.15 (d, J = 6.8 Hz, 3H), 0.93 (d, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 138.6, 128.3, 127.5, 127.4, 77.2, 76.2, 73.3, 73.1, 65.8, 53.2, 34.7, 31.5, 27.5, 24.8, 24.0, 16.8, 15.6 ppm; MS (ESI-IT) m/z 305.1 (35), 337.1 (5), 413.1 (M + H^+, 100), 468.0 (98); HRMS calcd for $C_{20}H_{30}O_4Br$ [M + H^+] 413.1322, found 413.1327 (1.3 ppm).

(±)-(*S*)-Methyl 2-((2*S*,5*R*,6*S*)-6-((*S*)-1-(Benzyloxy)propan-2-yl)-5-methyltetrahydro-2*H*-pyran-2-yl)propanoate (35a) and (±)-(*R*)-Methyl 2-((2*S*,5*R*,6*S*)-6-((*S*)-1-(Benzyloxy)propan-2-yl)-5-methyltetrahydro-2*H*-pyran-2-yl)propanoate (35b).



35a (2,3-*anti*) **35b** (2,3-*anti*)

To a cold (−78 °C) solution of a mixture of bromides **14a** and **14b** (69 mg) in dry toluene (0.1 M, 1.6 mL) were added successively Ph_3SnH (2 equiv, 114 mg), a 1 M solution of Et_3B in CH_2Cl_2 (0.2 equiv, 32 μL), and air (syringe). The reaction mixture was maintained at −78 °C as supplementary addition of Et_3B solution (0.2 equiv, 32 μL) and air were realized each 30 min, until reaction was judged complete by TLC (3−4 h, hexanes/EtOAc, 90:10). The reaction mixture was treated with the addition of 1,4-dinitrobenzene (0.2 equiv, 5 mg), followed by stirring of the mixture for 15 min at −78 °C. Once at room temperature, the reaction was concentrated in vacuo. ^1H NMR spectroscopic analysis of the unpurified product indicated a pair of diastereomers in a 5:1 ratio of products 2,3-*anti* (**35a**):2,3-*syn* (**35b**). The two diastereoisomers were separated by flash chromatography on silica gel (hexanes/EtOAc, 90:10) to afford product **35a** and **35b** as pale yellow oils (37 mg, yield = 68%).

35a: R_f = 0.29 (hexanes/EtOAc, 90:10); formula $C_{20}H_{30}O_4$; MW 334.45 g/mol; IR (neat) ν_{max} 2946, 2864, 1739, 1456, 1363, 1269, 1256, 1212, 1162, 1086, 1053, 1021, 967, 909, 852, 828, 738, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37−7.25 (m, 5H), 4.49 (d, J = 12.2 Hz, 1H), 4.45 (d, J = 12.2 Hz, 1H), 3.99 (dd, J = 6.1 Hz, 10.7 Hz, 1H), 3.68 (s, 3H), 3.49 (dd, J = 2.3 Hz, 9.5 Hz, 1H), 3.37 (dd, J = 4.1 Hz, 9.2 Hz, 1H), 3.24 (dd, J = 6.4 Hz, 9.2 Hz, 1H), 3.11 (dq, J = 11.0 Hz, 6.8 Hz, 1H), 1.97−1.87 (m, 1H), 1.85−1.68 (m, 3H), 1.46−1.35 (m, 2H), 1.07 (d, J = 6.9 Hz, 3H), 0.96 (d, J = 6.6 Hz, 3H), 0.95 (d, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 138.6, 128.3, 127.44, 127.41, 75.5, 74.6, 73.1, 72.2, 51.5, 39.8, 35.6, 28.9, 26.2, 19.7, 14.89, 14.83, 11.9 ppm; MS (ESI-IT) m/z 227.2 (44), 335.2 (M + H^+, 100); HRMS calcd for $C_{20}H_{31}O_4$ [M + H^+] 335.2217, found 335.2215 (−0.7 ppm).

35b: R_f = 0.37 (hexanes/EtOAc, 90:10); formula $C_{20}H_{30}O_4$; MW 334.45 g/mol; IR (neat) ν_{max} 2938, 2867, 1736, 1455, 1376, 1254, 1194,

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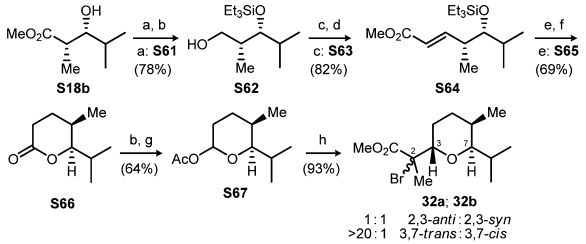
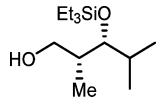
1163, 1107, 1046, 967, 902, 856, 738, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37−7.25 (m, 5H), 4.49 (d, J = 12.2 Hz, 1H), 4.45 (d, J = 12.2 Hz, 1H), 3.90 (dd, J = 5.5 Hz, 10.6 Hz, 1H), 3.66 (s, 3H), 3.38 (dd, J = 3.9 Hz, 9.2 Hz, 1H), 3.32 (dd, J = 3.0 Hz, 9.1 Hz, 1H), 3.30 (dd, J = 5.5 Hz, 9.2 Hz, 1H), 3.12 (dq, J = 10.8 Hz, 6.8 Hz, 1H), 1.99−1.89 (m, 1H), 1.88−1.72 (m, 3H), 1.43 (dq, J = 13.1 Hz, 3.5 Hz, 1H), 1.22 (d, J = 6.8 Hz, 3H), 1.21−1.15 (m, 1H), 1.10 (d, J = 6.7 Hz, 3H), 0.96 (d, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 138.5, 128.3, 127.51, 127.47, 74.8, 73.8, 73.1, 72.0, 51.6, 39.2, 35.8, 28.8, 26.5, 21.9, 15.4, 14.5, 11.9 ppm; MS (ESI-IT) m/z 227.2 (45), 335.2 (M + H^+, 100), 434.3 (19); HRMS calcd for $C_{20}H_{31}O_4$ [M + H^+] 335.2217, found 335.2215 (−0.7 ppm).



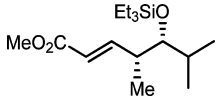
Reactions and conditions: a) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C. b) DIBAL-H, CH_2Cl_2, −40 °C. c) SO_3·py, DMSO, DIEA, CH_2Cl_2, 0 °C. d) $Ph_3PC(H)=CO_2Me$, toluene, reflux. e) H_2, Pd/C, EtOAc, rt. f) *p*-TsOH, benzene, reflux. g) Ac_2O, pyridine, DMAP, CH_2Cl_2, −40 °C to rt. h) $SnCl_4$, **2**, CH_2Cl_2, −78 °C.

(±)-(2*R*,3*R*)-2,4-Dimethyl-3-(triethylsilyloxy)pentan-1-ol (S62).



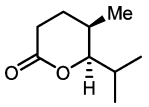
Product **S61** was obtained as a pale yellow oil from alcohol **S18b**[32] (0.32 g) following general procedure **A3** and was used as crude without further purification. Product **S62** (385 mg, yield = 78% over two steps) was obtained as a colorless oil from ester **S61** (549 mg) following general procedure **A4** and purification by flash chromatography on silica gel (hexanes/EtOAc 80:20): R_f = 0.34 (hexanes/EtOAc, 80:20); formula $C_{13}H_{30}O_2Si$; MW 246.46 g/mol; IR (neat) ν_{max} 3336, 2958, 2912, 2878, 1101, 1051, 1028 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.62 (ddd, J = 4.8 Hz, 7.8 Hz, 10.4 Hz, 1H), 3.52 (dd, J = 3.1 Hz, 6.1 Hz, 1H), 3.48 (dd, J = 5.7 Hz, 10.5 Hz, 1H), 1.90 (dh, J = 3.0 Hz, 7.0 Hz, 1H), 1.83 (app t, J = 5.2 Hz, 1H), 1.78 (ddd, J = 6.8 Hz, 13.4 Hz, 20.1 Hz, 1H), 0.98 (t, J = 7.9 Hz, 9H), 0.94 (d, J = 6.7 Hz, 3H), 0.90 (d, J = 6.9 Hz, 3H), 0.86 (d, J = 7.0 Hz, 3H), 0.63 (q, J = 7.9 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 79.0, 66.5, 39.3, 31.7, 20.3, 19.3, 11.7, 7.2, 5.6 ppm; MS (ESI-IT) m/z 155.1 (100), 195.1 (17), 247.2 (M + H^+, 13), 269.2 (M + Na^+, 99), 360.3 (13), 421.2 (8), 638.6 (9); HRMS calcd for $C_{13}H_{31}O_2Si$ [M + H^+] 247.2088, found 247.2090 (0.7 ppm); calcd for $C_{13}H_{30}NaO_2Si$ [M + Na^+] 269.1907, found 269.1911 (1.4 ppm).

(±)-(4*R*,5*R*,*E*)-Methyl 4,6-Dimethyl-5-(triethylsilyloxy)hept-2-enoate (S64).



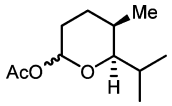
Aldehyde **S63** was obtained as a pale yellow oil from alcohol **S62** (0.38 g) following general procedure **A14** and was used as crude without further purification. Product **S64** (0.46 g, yield = 82% over two steps) was obtained as a colorless oil from crude aldehyde **S63** following general procedure **A6** and purification by flash chromatography on silica gel (hexanes/EtOAc 90:10): R_f = 0.55 (hexanes/EtOAc, 80:20); formula $C_{16}H_{32}O_3Si$; MW 300.51 g/mol; IR (neat) ν_{max} 2958, 2913, 2878, 1728, 1460, 1270, 1176, 1058, 1012, 735 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.98 (dd, J = 8.1 Hz, 15.8 Hz, 1H), 5.82 (dd, J = 0.9 Hz, 15.8 Hz, 1H), 3.75 (s, 3H), 3.41 (dd, J = 4.8 Hz, 5.5 Hz, 1H), 2.50 (h, J = 6.7 Hz, 1H), 1.76−1.66 (m, 1H), 1.07 (d, J = 6.8 Hz, 3H), 0.98 (t, J = 7.9 Hz, 9H), 0.91 (d, J = 6.9 Hz, 3H), 0.87 (d, J = 6.7 Hz, 3H), 0.63 (q, J = 7.9 Hz, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4, 153.3, 120.1, 80.8, 51.7, 41.2, 32.1, 20.4, 17.4, 15.3, 7.3, 5.7 ppm; MS (ESI-IT) m/z 169.1 (53), 209.1 (18), 301.2 (M + H^+, 14), 323.2 (M + Na^+, 100), 338.3 (15), 360.3 (10), 441.3 (6); HRMS calcd for $C_{16}H_{33}O_3Si$ [M + H^+] 301.2193, found 301.2198 (1.5 ppm); calcd for $C_{16}H_{32}O_3NaSi$ [M + Na^+] 323.2013, found 323.2019 (1.8 ppm).

(±)-(5*R*,6*R*)-6-Isopropyl-5-methyltetrahydro-2*H*-pyran-2-one (S66).



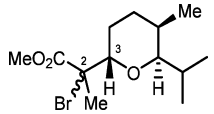
Product **S65** was obtained as a colorless oil from α,β-unsaturated ester **S64** (0.345 g) following general procedure **A2** and was used as crude without further purification. Product **S66**[33] (0.12 g, yield = 69% over two steps) was obtained as a colorless oil from crude ester **S65** following general procedure **A8** and purification by flash chromatography on silica gel (hexanes/EtOAc, 75:25): R_f = 0.16 (hexanes/EtOAc, 80:20); formula $C_9H_{16}O_2$; MW 156.22 g/mol; IR (neat) ν_{max} 2965, 2877, 1738, 1244, 1063, 986 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.82 (dd, J = 2.4 Hz, 10.0 Hz, 1H), 2.54 (dd, J = 6.3 Hz, 8.6 Hz, 2H), 2.23−2.16 (m, 1H), 2.11−2.02 (m, 1H), 1.93−1.82 (m, 1H), 1.73−1.65 (m, 1H), 1.10 (d, J = 6.4 Hz, 3H), 0.97 (d, J = 7.1 Hz, 3H), 0.91 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 88.6, 30.0, 27.1, 26.9, 26.4, 20.0, 18.3, 11.7 ppm; MS (ESI-IT) m/z 157.1 (M + H^+, 95), 179.1 (M + Na^+, 100), 241.1 (5), 335.2 (24), 360.3 (12); HRMS calcd for $C_9H_{17}O_2$ [M + H^+] 157.1223, found 157.1223 (0.03 ppm); calcd for $C_9H_{16}NaO_2$ [M + Na^+] 179.1043, found 179.1043 (0.3 ppm).

(±)-(5*R*,6*R*)-6-Isopropyl-5-methyltetrahydro-2*H*-pyran-2-yl Acetate (S67).



Product **S67** (0.10 g, yield = 64% over two steps) was obtained as a pale yellow oil from lactone **S66** (0.12 g) following general procedure **A9** and purification by flash chromatography on silica gel (hexanes/EtOAc 85:15): R_f = 0.49 (hexanes/EtOAc, 80:20); formula $C_{11}H_{20}O_3$; MW 200.27 g/mol; IR (neat) ν_{max} 2961, 2875, 1754, 1233, 1043, 989 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.59 (dd, J = 2.6 Hz, 9.4 Hz, 1H), 3.09 (dd, J = 2.0 Hz, 9.9 Hz, 1H), 2.12 (s, 3H), 1.86−1.80 (m, 1H), 1.79−1.67 (m, 4H), 1.63−1.59 (m, 1H), 1.00 (d, J = 6.5 Hz, 3H), 0.98 (d, J = 7.0 Hz, 3H), 0.84 (d, J = 6.7 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6, 96.0, 85.6, 29.9, 27.7, 25.3, 21.5, 20.2, 18.3, 11.5 ppm; MS (ESI-IT) m/z 141.1 (58), 181.1 (21), 223.1 (M + Na^+, 100), 281.2 (6), 321.2 (7), 423.3 (11); HRMS calcd for $C_{11}H_{20}NaO_3$ [M + Na^+] 223.1305, found 223.1299 (−2.6 ppm).

(±)-Methyl 2-Bromo-2-((2*S*,5*R*,6*R*)-6-isopropyl-5-methyltetrahydro-2*H*-pyran-2-yl) propanoate (32a, 32b).



Product **32a** and **32b** (0.25 g, yield = 93%) were obtained as pale yellow oils from product **S67** (0.18 g) following general procedure **A10** and purification by flash chromatography on silica gel (hexanes/EtOAc 85:15). ^1H NMR spectroscopic analysis of the unpurified product indicated a pair of 2,3-diastereomers in a ~1:1 ratio of products **32a**:**32b**.

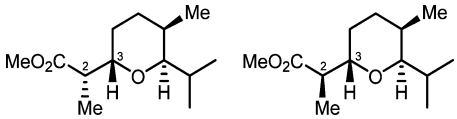
32a: R_f = 0.57 (hexanes/EtOAc, 80:20); formula $C_{13}H_{23}BrO_3$; MW 307.22 g/mol; IR (neat) ν_{max} 2957, 2873, 1742, 1263, 1052 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.29 (dd, J = 4.3 Hz, 10.1 Hz, 1H), 3.79 (s, 3H), 3.33 (dd, J = 3.5 Hz, 9.3 Hz, 1H), 2.01−1.82 (m, 3H), 1.92 (s, 3H), 1.79−1.70 (m, 2H), 1.39−1.30 (m, 1H), 0.92 (d, J = 6.5 Hz, 3H), 0.91 (d, J = 6.5 Hz, 3H), 0.82 (d, J = 6.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 80.5, 76.2, 63.0, 53.1, 30.0, 28.7, 27.6, 23.4, 21.3, 20.2, 19.5, 16.0 ppm; MS (ESI-IT) m/z 201.1 (38), 233.2 (88), 307.1 (M + H^+, 100); HRMS calcd for $C_{13}H_{24}BrO_3$ [M + H^+] 307.0903, found 307.0908 (1.6 ppm).

32b: R_f = 0.52 (hexanes/EtOAc, 80:20); formula $C_{13}H_{23}BrO_3$; MW 307.22 g/mol; IR (neat) ν_{max} 2957, 2873, 1742, 1263, 1051 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.05 (dd, J = 4.3 Hz, 10.6 Hz, 1H), 3.78 (s, 3H), 3.43 (dd, J = 4.0 Hz, 9.5 Hz, 1H), 2.01−1.82 (m, 3H), 1.88 (s, 3H), 1.79−1.70 (m, 1H), 1.65 (qd, J = 4.3 Hz, 13.2 Hz, 1H), 1.39−1.29 (m,

dx.doi.org/10.1021/jo400721e | J. Org. Chem. 2013, 78, 6075−6103

1H), 1.02 (d, J = 6.6 Hz, 3H), 0.93 (d, J = 7.0 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 80.6, 76.9, 65.8, 53.1, 30.9, 28.1, 27.3, 25.0, 23.4, 20.5, 20.0, 16.8, ppm; MS (ESI-IT) m/z 209.2 (17), 233.2 (7), 307.1 (M + H$^+$, 100), 391.3 (11); HRMS calcd for $C_{13}H_{24}BrO_3$ [M + H$^+$] 307.0903, found 307.0912 (2.7 ppm).

(±)-(*S*)-Methyl 2-((2*S*,5*R*,6*R*)-6-Isopropyl-5-methyltetrahydro-2*H*-pyran-2-yl)propanoate (36a) and (±)-(*R*)-Methyl 2-((2*S*,5*R*,6*R*)-6-Isopropyl-5-methyltetrahydro-2*H*-pyran-2-yl)propanoate (36b).

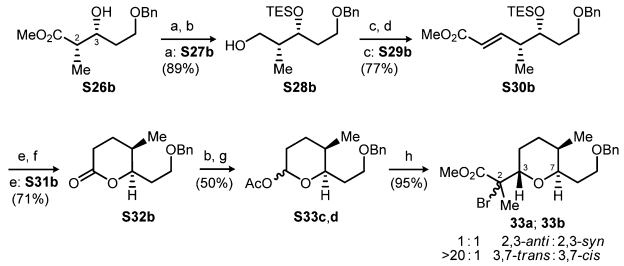


36a (2,3-*anti*) **36b** (2,3-*syn*)

Products **36a** and **36b** (26 mg, yield = 67%) were obtained as pale yellow oils from a mixture of bromides **32a** and **32b** (53 mg) following general procedure **A1** and purification by flash chromatography on silica gel (hexanes/EtOAc 90:10). ^{1}H NMR spectroscopic analysis of the unpurified product indicated a pair of diastereomers in a 5:1 ratio of products 2,3-*anti* (**36a**):2,3-*syn* (**36b**). The reaction performed on a mixture of bromides **32a** and **32b** (20 mg) according to general procedure **A1** with Ph_3SnH in CH_2Cl_2 led to the formation of product 2,3-*anti* (**36a**) and 2,3-*syn* (**36b**) in a 1:2 ratio of products (15 mg, quantitative yield) as verified by ^{1}H NMR analysis of the crude mixture.

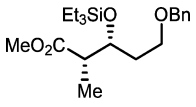
36a: R_f = 0.25 (hexanes/EtOAc, 90:10); formula $C_{13}H_{24}O_3$; MW 228.33 g/mol; IR (neat) ν_{max} 2952, 28.74, 1742, 1464, 1164, 1054 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.99 (dd, J = 5.7 Hz, 10.9 Hz, 1H), 3.69 (s, 3H), 3.21 (dd, J = 2.5 Hz, 9.7 Hz, 1H), 3.15 (dq, J = 11.0 Hz, 6.9 Hz, 1H), 1.97−1.88 (m, 1H), 1.88−1.82 (m, 1H), 1.80−1.72 (m, 1H), 1.60−1.54 (m, 1H), 1.47 (ddd, J = 13.4 Hz, 7.3 Hz, 3.6 Hz, 1H), 1.43−1.37 (m, 1H), 1.09 (d, J = 6.9 Hz, 3H), 0.95 (d, J = 7.0 Hz, 3H), 0.85 (d, J = 6.5 Hz, 3H), 0.81 (d, J = 6.7 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 78.3, 75.7, 51.7, 40.0, 30.1, 28.6, 26.4, 20.2, 19.7, 18.4, 15.1, 11.5 ppm; MS (ESI-IT) m/z 229.2 (M + H$^+$, 14), 251.2 (M + Na$^+$, 100), 479.3 (10); HRMS calcd for $C_{13}H_{25}O_3$ [M + H$^+$] 229.1798, found 229.1794 (−2.0 ppm); calcd for $C_{13}H_{24}NaO_3$ [M + Na$^+$] 251.1618, found 251.1613 (−1.8 ppm).

36b: R_f = 0.33 (hexanes/EtOAc, 90:10); formula $C_{13}H_{24}O_3$; MW 228.33 g/mol; IR (neat) ν_{max} 2942, 2870, 1738, 1454, 1166, 1043 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.91 (dd, J = 5.2 Hz, 10.9 Hz, 1H), 3.69 (s, 3H), 3.13 (dq, J = 10.7 Hz, 6.9 Hz, 1H), 2.98 (dd, J = 2.1 Hz, 9.6 Hz, 1H), 1.99−1.92 (m, 1H), 1.90−1.83 (m, 1H), 1.68−1.58 (m, 1H), 1.50−1.45 (m, 1H), 1.28−1.27 (m, 1H), 1.24 (d, J = 6.8 Hz, 3H), 1.23−1.18 (m, 1H), 1.00 (d, J = 6.5 Hz, 3H), 0.97 (d, J = 7.0 Hz, 3H), 0.83 (d, J = 6.7 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.1, 77.9, 75.0, 51.8, 39.4, 30.3, 28.7, 26.8, 22.1, 20.7, 18.5, 14.7, 11.6 ppm; MS (ESI-IT) m/z 251.2 (M + Na$^+$, 70), 360.3 (100), 408.3 (19), 697.7 (13); HRMS calcd for $C_{13}H_{24}NaO_3$ [M + Na$^+$] 251.1618, found 251.1619 (0.3 ppm).



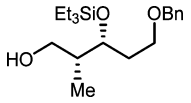
Reactions and conditions: a) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C. b) DIBAL-H, CH_2Cl_2, −40 °C. c) SO_3·py, DMSO, DIEA, CH_2Cl_2, 0 °C. d) $Ph_3PC(H)=CO_2Me$, toluene, reflux. e) H_2, Pd/C, EtOAc, rt. f) *p*-TsOH, benzene, reflux. g) Ac_2O, pyridine, DMAP, CH_2Cl_2, −40 °C to rt. h) $SnCl_4$, **2**, CH_2Cl_2, −78 °C.

(±)-(2*S*,3*R*)-Methyl 5-(Benzyloxy)-2-methyl-3-(triethylsilyloxy)pentanoate (S27b).



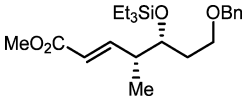
Product **S27b** was obtained as a pale yellow oil from alcohol **S26b**[34] (1.54 g) following general procedure **A3** and was used as crude without further purification: R_f = 0.66 (hexanes/EtOAc, 70:30); formula $C_{20}H_{34}O_4Si$; MW 366.56 g/mol; IR (neat) ν_{max} 2953, 2877, 1738, 1457, 1098, 738 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.23 (m, 5H), 4.51 (d, J = 11.9 Hz, 1H), 4.47 (d, J = 11.9 Hz, 1H), 4.20 (dd, J = 5.7 Hz, 11.2 Hz, 1H), 3.66 (s, 3H), 3.52 (app t, J = 6.5 Hz, 2H), 2.55 (dq, J = 4.8 Hz, 7.0 Hz, 1H), 1.87−1.75 (m, 2H), 1.13 (d, J = 7.0 Hz, 3H), 0.93 (t, J = 7.9 Hz, 9H), 0.57 (q, J = 7.9 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 138.7, 128.6, 127.9, 127.7, 73.2, 71.0, 67.0, 51.7, 45.4, 35.3, 11.6, 7.1, 5.3 ppm; MS (ESI-IT) m/z 259.2 (39), 335.2 (33), 367.2 (M + H$^+$, 100), 466.3 (6); HRMS calcd for $C_{20}H_{35}O_4Si$ [M + H$^+$] 367.2299, found 367.2307 (2.1 ppm).

(±)-(2*R*,3*R*)-5-(Benzyloxy)-2-methyl-3-(triethylsilyloxy)-pentan-1-ol (S28b).



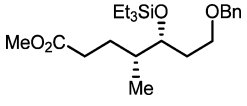
Product **S28b** (1.83 g, yield = 89% over two steps) was obtained as a colorless oil from ester **S27b** following general procedure **A4** and purification by flash chromatography on silica gel (hexanes/EtOAc 70:30): R_f = 0.36 (hexanes/EtOAc, 70:30); formula $C_{19}H_{34}O_3Si$; MW 338.56 g/mol; IR (neat) ν_{max} 3442, 2953, 2879, 1096, 1012, 736 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.24 (m, 5H), 4.51 (d, J = 11.9 Hz, 1H), 4.47 (d, J = 11.9 Hz, 1H), 3.91 (dd, J = 5.7 Hz, 10.4 Hz, 1H), 3.74 (dd, J = 3.8 Hz, 11.0 Hz, 1H), 3.53 (app t, J = 6.6 Hz, 3H), 2.62 (bs, 1H), 1.87 (q, J = 6.5 Hz, 2H), 1.79−1.70 (m, 1H), 0.99 (d, J = 7.0 Hz, 3H), 0.96 (t, J = 7.9 Hz, 9H), 0.62 (q, J = 7.8 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 128.6, 127.9, 127.8, 73.4, 73.3, 67.4, 66.2, 40.2, 32.5, 12.7, 7.1, 5.2 ppm; MS (ESI-IT) m/z 339.2 (M + H$^+$, 100), 438.3 (16), 453.3 (22); HRMS calcd for $C_{19}H_{35}O_3Si$ [M + H$^+$] 339.2350, found 339.2348 (−0.5 ppm).

(±)-(4*R*,5*R*,*E*)-Methyl 7-(Benzyloxy)-4-methyl-5-(triethylsilyloxy)hept-2-enoate (S30b).



Aldehyde **S29b** was obtained as a pale yellow oil from alcohol **S28b** (1.09 g) following general procedure **A14** and was used as crude without further purification. Product **S30b** (0.95 g, yield = 77% over two steps) was obtained as a pale yellow oil from crude aldehyde **S29b** following general procedure **A6** and purification by flash chromatography on silica gel (hexanes/EtOAc 80:20): R_f = 0.42 (hexanes/EtOAc, 80:20); formula $C_{22}H_{36}O_4Si$; MW 392.60 g/mol; IR (neat) ν_{max} 2953, 2880, 1726, 1274, 1098, 1012, 733 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.26 (m, 5H), 7.05 (dd, J = 7.1 Hz, 15.9 Hz, 1H), 5.81 (dd, J = 1.4 Hz, 15.9 Hz, 1H), 4.50 (d, J = 11.9 Hz, 1H), 4.46 (d, J = 11.9 Hz, 1H), 3.85 (td, J = 4.2 Hz, 8.3 Hz, 1H), 3.73 (s, 3H), 3.53−3.50 (m, 2H), 2.50−2.43 (m, 1H), 1.79−1.73 (m, 1H), 1.66−1.58 (m, 1H), 1.03 (d, J = 6.9 Hz, 3H), 0.94 (t, J = 7.9 Hz, 9H), 0.59 (q, J = 7.9 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 151.8, 138.6, 128.6, 127.9, 127.8, 121.0, 73.2, 72.7, 67.1, 51.6, 42.6, 34.1, 14.5, 7.2, 5.3 ppm; MS (ESI-IT) m/z 169.1 (7), 229.1 (6), 261.1 (14), 361.2 (5), 393.2 (M + H$^+$, 100), 492.4 (8), 507.3 (12); HRMS calcd for $C_{22}H_{37}O_4Si$ [M + H$^+$] 393.2456, found 393.2469 (3.5 ppm).

(±)-(4*R*,5*R*)-Methyl 7-(Benzyloxy)-4-methyl-5-(triethylsilyloxy)heptanoate (S31b).



Product **S31b** (0.906 g, yield = 90%) was obtained as a colorless oil from α,β-unsaturated ester **S30b** (1.01 g) following general procedure **A2** to which was added pyridine[29] (1.5 equiv, 315 μL) before the gas atmosphere was changed to H_2: R_f = 0.42 (hexanes/EtOAc, 80:20); formula $C_{22}H_{38}O_4Si$; MW 394.62 g/mol; IR (neat) ν_{max} 2955, 2877, 1740, 1457, 1240, 1093, 909, 735 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.26 (m, 5H), 4.52 (d, J = 11.9 Hz, 1H), 4.48 (d, J = 11.9 Hz, 1H), 3.77 (td, J = 3.9 Hz, 7.9 Hz, 1H), 3.67 (s, 3H), 3.53 (app t, J = 6.4 Hz, 2H), 2.39 (ddd, J = 5.7 Hz, 9.9 Hz, 15.6 Hz, 1H), 2.29 (ddd, J = 6.5 Hz,

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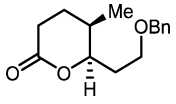
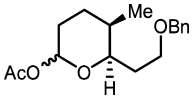
9.6 Hz, 15.7 Hz, 1H), 1.94−1.84 (m, 1H), 1.81−1.64 (m, 2H), 1.57−1.49 (m, 1H), 1.47−1.37 (m, 1H), 0.94 (t, J = 7.9 Hz, 9H), 0.84 (d, J = 6.8 Hz, 3H), 0.57 (q, J = 7.9 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 138.8, 128.5, 127.9, 127.7, 73.2, 73.1, 67.7, 51.7, 38.5, 33.3, 32.8, 27.5, 14.8, 7.2, 5.4 ppm; MS (ESI-IT) m/z 155.1 (9), 213.1 (5), 231.1 (10), 263.2 (100), 395.3 (M + H$^+$, 24); HRMS calcd for $C_{22}H_{39}O_4Si$ [M + H$^+$] 395.2612, found 395.2615 (0.6 ppm).

(±)-(5*R*,6*R*)-6-(2-(Benzyloxy)ethyl)-5-methyltetrahydro-2*H*-pyran-2-one (S32b).



To a cold (0 °C) solution of ester **S31b** (1.11 g) in dry MeCN (0.1 M, 28.0 mL) was added $BF_3{\cdot}OEt_2$ (2 equiv, 713 μL), followed by stirring for 1 h at 0 °C. The reaction mixture was then treated with a saturated aqueous solution of NH_4Cl. 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 mixture was purified by flash chromatography on silica gel (hexanes/EtOAc, 90:10 to 50:50) to afford lactone **S32b** as a pale yellow oil (0.698 g, yield =79%): R_f = 0.26 (hexanes/EtOAc, 80:20); formula $C_{15}H_{20}O_3$; MW 248.32 g/mol; IR (neat) ν_{max} 3030, 2961, 2877, 1734, 1455, 1365, 1241, 1205, 1109, 1078, 742, 700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39−7.29 (m, 5H), 4.57 (dt, J = 3.2 Hz, 9.6 Hz, 1H), 4.55 (d, J = 11.7 Hz, 1H), 4.51 (d, J = 11.8 Hz, 1H), 3.72−3.64 (m, 2H), 2.56 (app t, J = 7.2 Hz, 2H), 2.10−2.03 (m, 2H), 2.00−1.91 (m, 1H), 1.87−1.81 (m, 1H), 1.72−1.65 (m, 1H), 0.99 (d, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 138.4, 128.7, 128.0, 127.9, 79.7, 73.5, 66.4, 32.8, 29.7, 27.0, 26.3, 12.9 ppm; MS (ESI-IT) m/z 141.1 (72), 231.1 (8), 249.1 (M + H$^+$, 100), 317.2 (7), 497.3 (60), 695.3 (6); HRMS calcd for $C_{15}H_{21}O_3$ [M + H$^+$] 249.1485, found 249.1483 (−1.0 ppm).

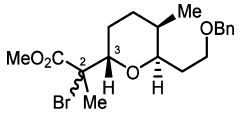
(±)-(5*R*,6*R*)-6-(2-(Benzyloxy)ethyl)-5-methyltetrahydro-2*H*-pyran-2-yl acetate (S33c, S33d).



An inseparable mixture of product **S33c,d** (0.41 g, yield = 50%) was obtained as a pale yellow oil from lactone **S32b** (2.51 g) following general procedure **A9** and purification by flash chromatography on silica gel (hexanes/EtOAc 80:20). ^{1}H NMR spectroscopic analysis of the unpurified product indicated a pair of diastereomers in a 10:1 ratio of products **S33c**:**S33d**.

S33c,d: R_f = 0.44 (hexanes/EtOAc, 80:20); formula $C_{17}H_{24}O_4$; MW 292.37 g/mol; IR (neat) ν_{max} 2956, 2864, 1749, 1366, 1235, 1036 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.27 (m, 5H$_c$+5H$_d$), 6.09 (d, J = 3.3 Hz, 1H$_d$), 5.68 (dd, J = 2.9 Hz, 8.7 Hz, 1H$_c$), 4.54 (d, J = 11.9 Hz, 1H$_c$), 4.52 (d, J = 12.1 Hz, 1H$_d$), 4.49 (d, J = 12.2 Hz, 1H$_d$), 4.50 (d, J = 11.9 Hz, 1H$_c$), 4.16 (ddd, J = 2.8 Hz, 3.5 Hz, 9.6 Hz, 1H$_d$), 3.84 (ddd, J = 2.6 Hz, 3.8 Hz, 9.4 Hz, 1H$_c$), 3.65−3.60 (m, 1H$_d$), 3.60−3.57 (m, 2H$_c$), 3.56−3.54 (m, 1H$_d$), 2.12 (s, 3H$_c$), 2.06 (s, 3H$_d$), 1.94−1.85 (m, 1H$_d$), 1.93−1.84 (m, 1H$_c$), 1.83−1.78 (m, 1H$_c$+1H$_d$), 1.75−1.62 (m, 5H$_c$+5H$_d$), 0.99 (d, J = 6.9 Hz, 3H$_c$), 0.87 (d, J = 6.5 Hz, 3H$_d$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2$_d$, 169.6$_c$, 138.9$_d$, 138.8$_c$, 128.6$_{c+d}$, 127.9$_{c+d}$, 127.8$_{c+d}$, 95.60$_c$, 95.13$_d$, 79.7$_d$, 76.2$_c$, 73.4$_c$, 69.8$_d$, 67.3$_c$, 67.0$_d$, 34.7$_d$, 33.3$_c$, 31.3$_d$, 30.5$_d$, 30.4$_c$, 29.1$_c$, 25.6$_c$, 23.6$_d$, 21.5$_c$, 17.3$_d$, 12.2$_c$, 11.4$_d$ ppm; MS (ESI-IT) m/z 233.2 (9), 315.2 (M + Na$^+$, 100), 607.3 (7); HRMS calcd for $C_{17}H_{24}NaO_4$ [M + Na$^+$] 315.1567, found 315.1569 (0.8 ppm).

(±)-Methyl 2-((2*S*,5*R*,6*R*)-6-(2-(Benzyloxy)ethyl)-5-methyltetrahydro-2*H*-pyran-2-yl)-2-bromopropanoate (33a; 33b).

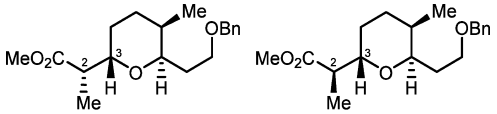


Products **33a** and **33b** (0.53 g, yield = 95%) were obtained as pale yellow oils from a mixture of product **S33c,d** (0.41 g) following general procedure **A10** and purification by flash chromatography on silica gel (hexanes/EtOAc, 80:20). ^{1}H NMR spectroscopic analysis of the unpurified product indicated a pair of 2,3-diastereomers in a ∼1:1 ratio of products **33a**:**33b**.

33a: R_f = 0.36 (hexanes/EtOAc, 80:20); formula $C_{19}H_{27}BrO_4$; MW 399.32 g/mol; IR (neat) ν_{max} 3063, 3030, 2956, 2870, 1742, 1452, 1263, 1101 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.27 (m, 5H), 4.53 (d, J = 12.2 Hz, 1H), 4.51 (d, J = 12.2 Hz, 1H), 4.10 (dd, J = 2.2 Hz, 11.2 Hz, 1H), 3.98 (ddd, J = 2.6 Hz, 5.2 Hz, 11.7 Hz, 1H), 3.70 (s, 3H), 3.58 (ddd, J = 4.5 Hz, 8.1 Hz, 8.7 Hz, 1H), 3.50 (dt, J = 9.0 Hz, 7.5 Hz, 1H), 2.09−2.01 (m, 2H), 1.96−1.90 (m, 1H), 1.86 (s, 3H), 1.69−1.64 (m, 1H), 1.70−1.58 (m, 1H), 1.52−1.38 (m, 2H), 0.84 (d, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 138.9, 128.6, 127.8, 127.7, 76.0, 73.3, 72.5, 67.5, 61.7, 53.1, 33.6, 26.8, 26.0, 24.8, 22.5, 17.7 ppm; MS (ESI-IT) m/z 160.1 (6), 291.1 (6), 399.1 (M + H$^+$, 100), 416.1 (9); HRMS calcd for $C_{19}H_{28}BrO_4$ [M + H$^+$] 399.1165, found 399.1156 (−2.4 ppm).

33b: R_f = 0.31 (hexanes/EtOAc, 80:20); formula $C_{19}H_{27}BrO_4$; MW 399.32 g/mol; IR (neat) ν_{max} 3056, 3030, 2953, 2870, 1738, 1452, 1266, 1113, 1087 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.27 (m, 5H), 4.57 (d, J = 12.0 Hz, 1H), 4.54 (d, J = 12.0 Hz, 1H), 4.08 (ddd, J = 3.0 Hz, 5.0 Hz, 12.0 Hz, 1H), 3.94 (dd, J = 2.0 Hz, 10.8 Hz, 1H), 3.78 (s, 3H), 3.75 (dt, J = 4.5 Hz, 9.0 Hz, 1H), 3.66 (dt, J = 9.1 Hz, 7.7 Hz, 1H), 2.14−2.04 (m, 1H), 2.01−1.92 (m, 1H), 1.84 (s, 3H), 1.68−1.54 (m, 3H), 1.50−1.38 (m, 2H), 0.84 (d, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 138.8, 128.6, 128.0, 127.8, 75.7, 73.5, 73.1, 67.6, 65.0, 53.4, 33.4, 27.1, 26.7, 24.7, 23.8, 17.7 ppm; MS (ESI-IT) m/z 160.1 (5), 291.1 (9), 399.1 (M + H$^+$, 100), 401.1 (98), 402.1 (18); HRMS calcd for $C_{19}H_{28}BrO_4$ [M + H$^+$] 399.1165, found 399.1160 (−1.4 ppm).

(±)-(*S*)-Methyl 2-((2*S*,5*R*,6*R*)-6-(2-(Benzyloxy)ethyl)-5-methyltetrahydro-2*H*-pyran-2-yl)propanoate (37a) and (±)-(*R*)-Methyl 2-((2*S*,5*R*,6*R*)-6-(2-(Benzyloxy)ethyl)-5-methyltetrahydro-2*H*-pyran-2-yl)propanoate (37b).



37a (2,3-*anti*) **37b** (2,3-*syn*)

Products **37a** and **37b** (35 mg, yield = 85%) were obtained as pale yellow oils from a mixture of bromides **33a** and **33b** (52 mg) following general procedure **A1** and purification by flash chromatography on silica gel (hexanes/EtOAc 80:20). ^{1}H NMR spectroscopic analysis of the unpurified product indicated a pair of diastereomers in a 15:1 ratio of products 2,3-*anti* (**37a**):2,3-*syn* (**37b**).

37a: R_f = 0.25 (hexanes/EtOAc, 80:20); formula $C_{19}H_{28}O_4$; MW 320.42 g/mol IR (neat) ν_{max} 3062, 3030, 2950, 2872, 1738, 1456, 1201, 1089 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.27 (m, 5H), 4.54 (d, J = 12.1 Hz, 1H), 4.52 (d, J = 12.0 Hz, 1H), 3.96 (ddd, J = 3.5 Hz, 4.6 Hz, 11.8 Hz, 1H), 3.68−3.58 (m, 2H), 3.64 (s, 3H), 3.52 (dt, J = 9.1 Hz, 7.5 Hz, 1H), 2.52 (dq, J = 8.9 Hz, 7.0 Hz, 1H), 2.10−2.00 (m, 1H), 1.99−1.89 (m, 1H), 1.76 (ddd, J = 3.5 Hz, 6.7 Hz, 12.8 Hz, 1H), 1.65−1.55 (m, 2H), 1.44−1.34 (m, 1H), 1.31−1.21 (m, 1H), 1.10 (d, J = 7.0 Hz, 3H), 0.83 (d, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 138.8, 128.4, 127.7, 127.5, 74.3, 73.3, 70.9, 67.4, 51.5, 45.4, 33.1, 28.2, 26.6, 25.3, 17.1, 13.5 ppm; MS (ESI-IT) m/z 213.1 (6), 289.2 (9), 321.2 (M + H$^+$, 100); HRMS calcd for $C_{19}H_{29}O_4$ [M + H$^+$] 321.2060, found 321.2054 (−1.8 ppm).

37b: R_f = 0.31 (hexanes/EtOAc, 80:20); formula $C_{19}H_{28}O_4$; MW 320.42 g/mol IR (neat) ν_{max} 3062, 3030, 2951, 2873, 1737, 1455, 1258, 1199, 1093 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.28 (m, 5H), 4.54 (d, J = 11.8 Hz, 1H), 4.52 (d, J = 12.2 Hz, 1H), 3.93 (ddd, J = 3.8 Hz, 4.2 Hz, 11.6 Hz, 1H), 3.69−1.65 (m, 1H), 3.67 (s, 3H), 3.62−3.54 (m, 2H), 2.55 (dq, J = 7.0 Hz, 7.0 Hz, 1H), 2.09−1.99 (m, 1H), 1.93−1.86 (m, 1H), 1.66−1.60 (m, 3H), 1.45−1.27 (m, 2H), 1.17 (d, J = 7.0 Hz, 3H), 0.84 (d, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.6, 138.7, 128.6, 128.0, 127.8, 74.0, 73.5, 70.4, 67.6, 51.8, 44.8, 33.2, 28.8, 26.9, 26.0, 16.9, 13.5 ppm; MS (ESI-IT) m/z 213.1 (9), 289.2 (18), 321.2 (M + H$^+$, 100); HRMS calcd for $C_{19}H_{29}O_4$ [M + H$^+$] 321.2060, found 321.2057 (−1.1 ppm).

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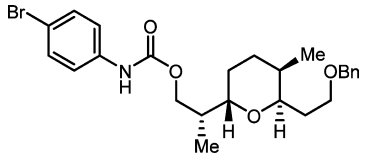
(±)-(*R*)-2-((2*S*,5*R*,6*R*)-6-(2-(Benzyloxy)ethyl)-5-methyltetrahydro-2*H*-pyran-2-yl)propyl 4-bromophenylcarbamate (S68).



Primary alcohol as a colorless oil was obtained from ester **37a** (34 mg) following general procedure **A4**. To a cold (0 °C) solution of crude alcohol in dry CH_2Cl_2 (0.1 M, 1.1 mL) were added successively Et_3N (1.1 equiv, 16 μL) and *p*-bromophenyl isocyanate (1.1 equiv, 23 mg). The reaction mixture was stirred for 3 h at 0 °C before the reaction mixture was treated with a saturated aqueous solution of $NaHCO_3$ followed by separation of the organic phase at room temperature. The aqueous layer was extracted with EtOAc (3×), and the combined organic fractions were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel (hexanes/EtOAc, 90:10) to afford product **S68** as a white solid (46 mg, yield = 90% over two steps), for which structural assignment was confirmed by X-ray analysis (cf. Supporting Information, part III, X-ray): R_f = 0.26 (hexanes/EtOAc, 80:20); formula $C_{25}H_{32}BrNO_4$; MW 490.43 g/mol; IR (neat) ν_{max} 3312, 2954, 2872, 1732, 1707, 1595, 1533, 1399, 1308, 1220, 1077, 1047, 824, 736, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34−7.13 (m, 9H), 6.60 (bs, 1H), 4.45 (d, *J* = 11.7 Hz, 1H), 4.39 (d, *J* = 11.8 Hz, 1H), 4.20 (dd, *J* = 4.0 Hz, 10.5 Hz, 1H), 4.04 (dd, *J* = 6.0 Hz, 10.5 Hz, 1H), 3.84 (ddd, *J* = 3.5 Hz, 4.3 Hz, 11.5 Hz, 1H), 3.58−3.52 (m, 1H), 3.52−3.46 (m, 1H), 3.35−3.28 (m, 1H), 1.99−1.90 (m, 1H), 1.87−1.79 (m, 2H), 1.69−1.63 (m, 1H), 1.61−1.52 (m, 2H), 1.35−1.21 (m, 2H), 0.87 (d, *J* = 6.9 Hz, 3H), 0.77 (d, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 138.6, 137.4, 132.2, 128.6, 128.0, 127.8, 120.2, 115.9, 74.0, 73.4, 70.0, 67.7, 67.6, 37.6, 33.3, 28.3, 27.0, 25.8, 17.1, 14.0 ppm; MS (ESI-IT) *m*/*z* 203.0 (10), 412.2 (10), 490.2 (100, M + H^+), 512.1 (68, M + Na^+), 530.1 (20), 574.1 (13); HRMS calcd for $C_{25}H_{33}BrNO_4$ [M + H^+] 490.1587, found 490.1589 (0.3 ppm); calcd for $C_{25}H_{32}BrNO_4Na$ [M + Na^+] 512.1407, found 512.1410 (0.5 ppm).

■ ASSOCIATED CONTENT

Supporting Information

NMR spectra (^1H and ^{13}C) of radical precursors (**13**−**22a,b**, **31**−**33a,b**) and reduced products (**23**−**30a,b**, **34**−**37a,b**). Cartesian coordinates (GS and TS) of radical intermediates for **17a,b**, **32a,b**, **38**−**39a,b**,. X-ray crystallographic structural proof for reduced products **25a** (**S9**), **28a** (**S45**), **30a** (**S60**) and **37a** (**S68**). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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