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Synthetic Studies towards Pectenotoxin-2: Synthesis of the Nonanomeric 10-*epi*-ABCDE Ring Segment by Kinetic Spiroketalization

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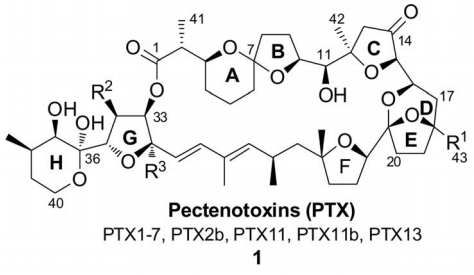
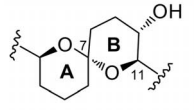
The synthesis of the nonanomeric 10-*epi*-ABCDE ring system of pectenotoxin-2 has been achieved by using a kinetic spiroketalization reaction. The synthesis of the spiroketalization precursor was achieved through a cross-metathesis/hydrogenation sequence. The formation of the *epi*-C10 isomer resulted from an unexpected anti-Felkin selective addition of organometallic nucleophiles to the advanced CDE ring precursor. This addition reaction was investigated with differently protected α,β-dioxygenated model aldehydes, which displayed similar anti-Felkin selectivities with organometallic nucleophiles.

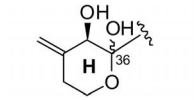
Introduction

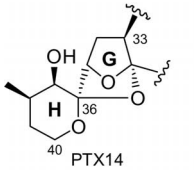
In 1985, Yasumoto and co-workers reported the isolation and characterization of a family of polyether macrolactones, the pectenotoxins (PTXs).[1] The pectenotoxin family has since grown to comprise over 20 structurally related compounds (Figure 1). Originally isolated from scallops (*Patinopecten yessoensis*),[1a] the actual producers of PTXs are *Dinophysis* dinoflagellates, which are found in coastal areas worldwide.[2]

The complex structure of the PTXs consist of a closed macrolactone containing a spiroketal ring unit, three differently substituted tetrahydrofurans, a bicyclic acetal ring system, a cyclic hemiketal, and two sites of unsaturation in the form of carbon–carbon double bonds. The main structural differences between the PTXs are the oxidation state of C43 and the configuration of the C7 spiroketal center. More recently, open-chained analogues, PTX seco acids (PTXsa),[3] and analogues containing variations at the GH ring system have also been isolated and characterized. However, the most commonly found PTX in algae is PTX2, which is reported to be produced by many different dinoflagellate species of the genera *Dinophysis* and is found in various parts of the world.[4] In tests with mice, PTX2 was found to be one of the most toxic PTXs. It is a potent cytotoxin against a variety of lung, colon, and breast cancer cell lines.[2b,5] The main target of PTX2 in cells is the actin cytoskeleton, and the recently determined X-ray crystal structure of PTX2 bound to G-actin reveals a shallow binding site and stresses the importance of the stereochemistry of the macrolactone ring, including the nonanomeric configuration present in the AB ring spiroketal.[6] Synthetic access to the pectenotoxins bearing the full natural configura-









	R^1	R^2	R^3	C7
PTX1 (**1a**)	CH_2OH	H	H	*R*
PTX2 (**1b**)	CH_3	H	H	*R*
PTX2b (**1c**)	CH_3	H	H	*S*
PTX2c (**1d**)	CH_3	H	H	*S*
PTX3 (**1e**)	CHO	H	H	*R*
PTX4 (**1f**)	CH_2OH	H	H	*S*
PTX5 (**1g**)	Structure not determined			
PTX6 (**1h**)	COOH	H	H	*R*
PTX7 (**1i**)	COOH	H	H	*S*
PTX8 (**1j**)	CH_2OH	H	H	*S*
PTX9 (**1k**)	COOH	H	H	*S*
PTX10 (**1l**)	Structure not determined			
PTX11 (**1m**)	CH_3	OH	H	*R*
PTX11b (**1n**)	CH_3	OH	H	*S*
PTX11c (**1o**)	CH_3	OH	H	*S*
36S-PTX12 (**1p**)	CH_3	H	H	*R*
36R-PTX12 (**1q**)	CH_3	H	H	*R*
PTX13 (**1r**)	CH_3	H	OH	*R*
PTX14 (**1s**)	CH_3	H	-	*R*

Figure 1. Structures of the pectenotoxins. Biosynthesis products (white); products produced by metabolism of shellfish (light grey); artificial products formed by acid catalysis (dark grey).

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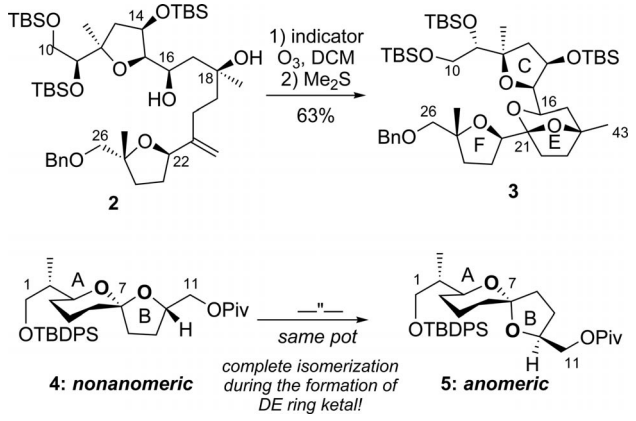
tion, including the nonanomeric *R* configuration at the C7 spiro carbon, is therefore an important, but challenging, objective in marine natural product synthesis.[7,8]

Herein, we outline our progress towards the synthesis of the nonanomeric ABCDE ring segment of PTX2. Although the goal of the nonanomeric spiroketal was indeed reached in these studies, the work also revealed a surprising anti-Felkin selectivity in a key addition reaction to C10 aldehyde.

Results and Discussion

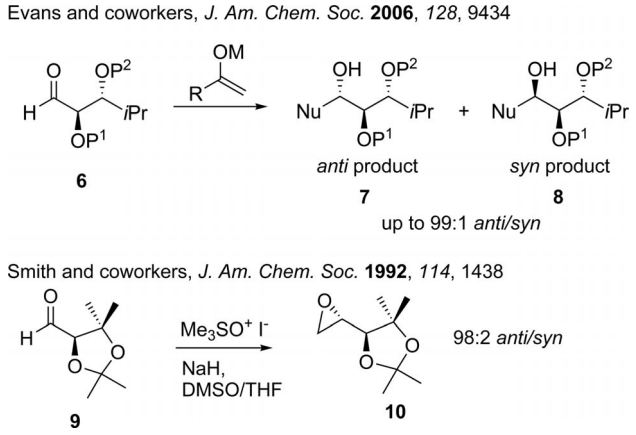
Strategy

We had previously reported that our otherwise robust method of constructing the CDE or the CDEF ring systems by final ozonolysis-triggered ketalization (Scheme 1) would not be applicable to substrates bearing the fragile nonanomeric spiroketal system.[9] This result indicated that our initially envisioned ABC + F → ABCDEF strategy would not work, and we would therefore need to postpone the construction of the nonanomeric spiroketal until after the cyclization of the DE ring ketal system.



Scheme 1. Synthesis of the CDEF ring fragment of PTX2 and the key strategic experiment.[9]

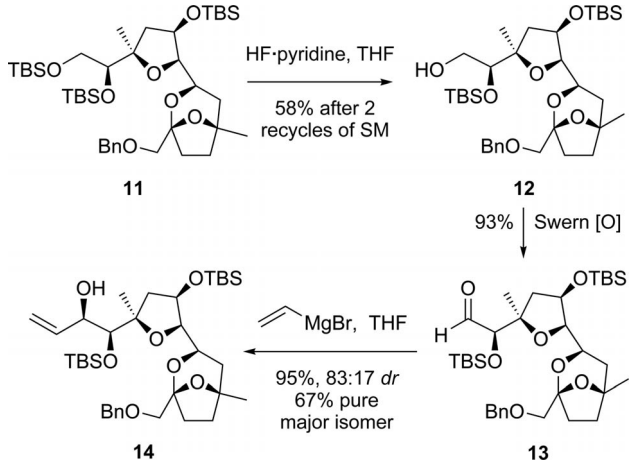
As such, our first task was to outline conditions that would facilitate the union of the A ring and the CDE(F) ring systems into a viable precursor for kinetic spiroketalization. Given the high sensitivity of the spiroketalization precursors (we sought precursors that would allow the kinetic spiroketalization to take place under very mild conditions), the route would most likely have to be devised with no protection at the C10 hydroxy group. Nucleophilic addition of a vinylmetal species to the CDE aldehyde **13** was expected to afford the desired *anti* product **14** in a Felkin-selective manner. We were encouraged by the reports of Evans on nucleophilic additions to α,β-bis(alkoxy) aldehydes that were, typically, highly Felkin-selective, especially with *anti*-α,β-bis(alkoxy) substituents (Scheme 2).[10] Although **13** cannot be readily classified as either *anti* or *syn* bis(alkoxy) aldehyde (the C12 stereocenter is a tertiary center), Smith and co-workers had also obtained high Felkin-selectivities in a Corey–Chaykovsky reaction of an α,β-bis-(alkoxy) aldehyde bearing a tertiary β-carbon.[11]



Scheme 2. Selectivities in nucleophilic addition reactions to α,β-bis-(alkoxy) aldehydes.

Synthesis of the *epi*-C10 ABCDE Ring System of PTX2

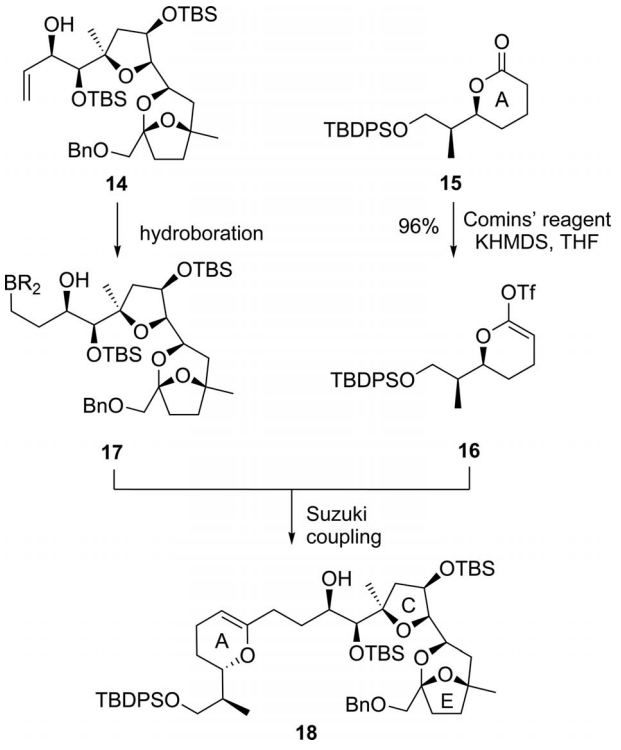
We initiated our study with the fully protected CDE ring fragment **11** (Scheme 3). Selective deprotection at C10 was possible in HF·pyridine, albeit in modest yield. The desired aldehyde **13** was readily obtained by Swern oxidation and was immediately engaged in the reaction with vinylmagnesium bromide. This reaction gave the desired allylic alcohol **14** in 83:17 diastereoselectivity. The stereochemistry of this product (*syn*, as shown in Scheme 3) was not confirmed at this juncture, because it was decided that decisive confirmation would become available upon final conversion into the ABCDE ring system of PTX2.



Scheme 3. Synthesis of allylic alcohol **14** from the fully protected CDE ring system **11**.

Our initial idea was to couple the A and the CDE fragments using a Suzuki–Miyaura coupling (Scheme 4). To this end, the previously prepared A ring lactone **15**[12] was readily converted into the corresponding ketene acetal triflate using Comins' reagent. The hydroboration of the all-

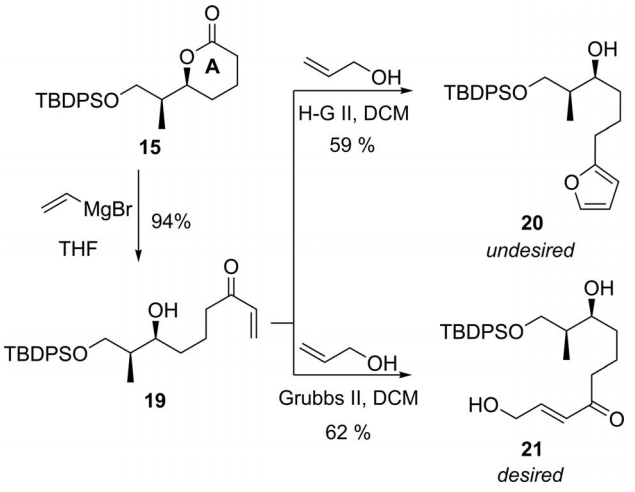
ylic alcohol **14**, however, turned out to be highly problematic. Extensive screening of different reagents (9-borabicyclo[3.3.1]nonane (9-BBN),[13] catecholborane,[14] thexylborane,[15] $BH_3{\cdot}SMe_2$[16]) was unsuccessful, resulting in either recovered starting material together with decomposition products or in a large number of products, none of which resembled the desired organoboron compounds.



Scheme 4. Attempts at Suzuki coupling were thwarted by the hydroboration step.

Cross-metathesis (CM) was then explored as an alternative mild method for linking the A and the CDE subunits.[17] To this end, the A ring lactone **15** was converted into the corresponding vinyl ketone **19** in excellent yield with vinylmagnesium bromide (Scheme 5). Initially, the CM reaction was explored with simple allyl alcohol as the model compound. Interestingly, the use of Hoveyda–Grubbs catalyst **22** led to the formation of the corresponding furan **20** instead of the desired enone **21** (Scheme 5). This result was ascribed to the Lewis acidic nature of the Hoveyda–Grubbs catalyst.[18] Attempts at buffering the reaction mixture with pyridine, 2,6-lutidine, or $NaHCO_3$ did not help; however, the use of the Grubbs 2nd generation catalyst **23** (Figure 2) did indeed provide the desired allyl alcohol in acceptable yield (Scheme 5) and the reaction also worked with a more complex model compound (Scheme 6).

In the real system, the cross metathesis between **14** and **19** was also successful with the Grubbs 2nd generation catalyst **23**, affording **26** in 48–55% yields (plus 36–45% recovered **14**) (Table 1, entry 1). In an attempt to improve the yields, the use of Hoveyda–Grubbs 2nd generation catalyst was examined because it was believed that the formation of the furan would not be a problem with this system. Although initial results were encouraging (entry 2) the CM protocol was not reproducible, and the undesired diene **27** was formed as the major product. Diene **27** turned out to be very unstable and attempts at partial hydrogenation of the C8–C9 double bond only led to decomposition. The formation of **27** could be avoided by the use of pyridine buffer, but the yields did not improve.



Scheme 5. Cross-metathesis: model studies with allyl alcohol.

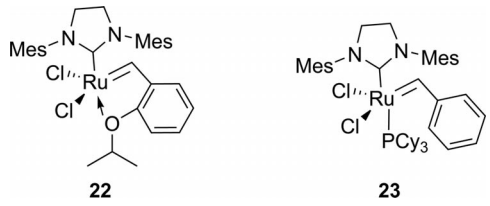
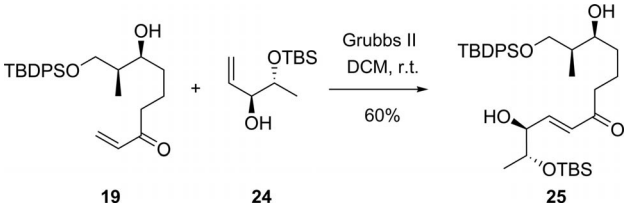


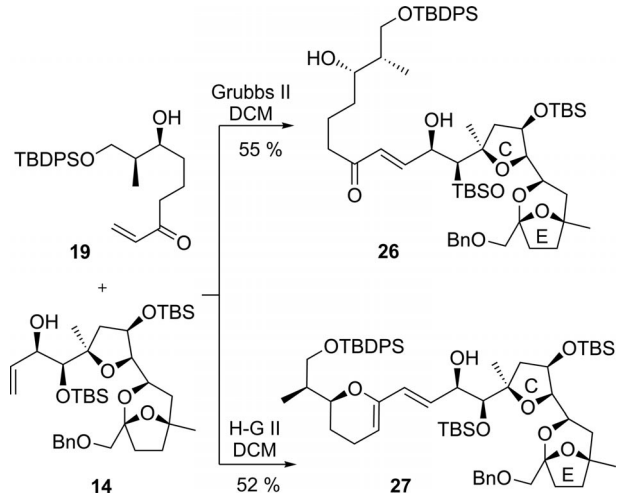
Figure 2. Hoveyda–Grubbs 2nd generation (**22**) and Grubbs 2nd generation (**23**) catalysts.



Scheme 6. Successful cross-metathesis with a more complex model compound **24**.

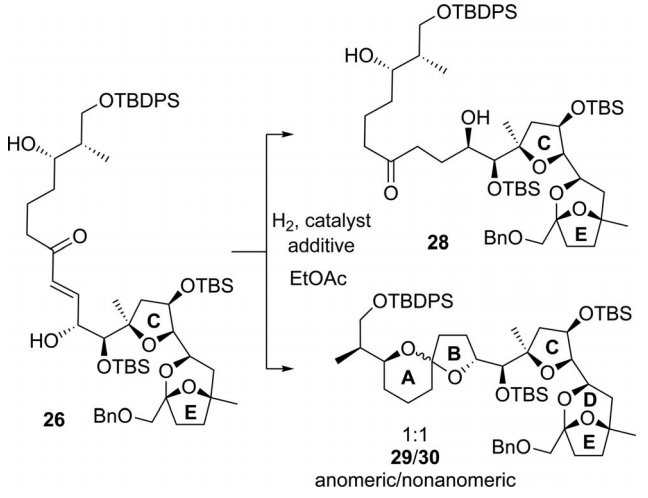
The selective hydrogenation of the C8–C9 double bond was then examined as a prelude to the key spiroketalization experiment (Table 2). With Wilkinson's catalyst, the hydrogenation proceeded smoothly, however, during the course of the reaction, the product underwent premature spiroketalization to afford a 1:1 mixture of anomeric and nonanomeric spiroketals **29** and **30**. Although buffering the reaction mixture with 2,6-lutidine did not help (entry 2), the use of pyridine-buffered Pd/C nicely solved the problem, giving **28** as the sole product in nearly quantitative yield (entry 4). Without pyridine, the premature spiroketalization to form **29** and **30** again took place (entry 3).

Table 1. Cross-metathesis approach to linkage of the A and CDE ring systems.



Entry	Catalyst	Product (% yield)
1	Grubbs 2nd gen. cat.	**26** (48–55)
2	Hoveyda-Grubbs 2nd gen. cat.	**26** (50)
3	Hoveyda-Grubbs 2nd gen. cat.	**27** (52)
4	Hoveyda-Grubbs 2nd gen. cat. + pyridine	**26** (48)

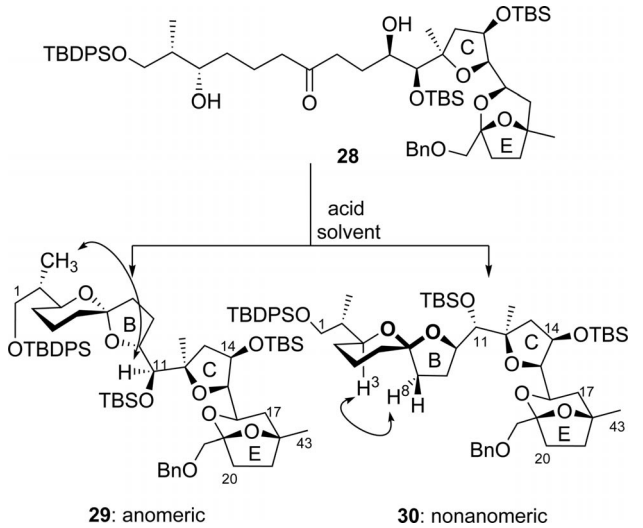
Table 2. Hydrogenation screens for enone **26**.



Entry	Catalyst	Additive	Product (% conversion)
1	Wilkinson	–	**29** and **30** (100)
2	Wilkinson	2,6-lutidine	no reaction
3	Pd/C	–	**29** and **30** (100)
4	Pd/C	pyridine	**28** (100)

With precursor **28** in hand, the final controlled spiroketalization was investigated (Table 3), using both anhydrous conditions (CH_2Cl_2/$ClCH_2COOH$)[12] as well as our more recently developed aqueous conditions [tetrahydrofuran (THF)/H_2O].[19] Surprisingly, the nonaqueous conditions afforded better selectivities towards the nonanomeric spiroketal, giving a 3:1 mixture of **30**/**29** (entry 1). In contrast, the aqueous conditions gave a 1:1 mixture of **29** and **30**. The stereochemistry at the newly formed spiro center was readily confirmed: the nonanomeric spiroketal **29** displayed a characteristic NOESY cross-peak between the C3 and C8 protons[12] as well as a characteristic downfield ^{13}C NMR shift at the spiroketal carbon C7 (δ = 105.8 ppm, the corresponding shift for C7 of **30** is δ = 108.0 ppm). Furthermore, when the 1:1 mixture of **29** and **30** was treated with pyridinium *p*-toluenesulfonate (PPTS) for 5 h, a 3:1 mixture of the spiroketals favoring the anomeric spiroketal **29** was obtained, confirming that **29** is the thermodynamically favored product.

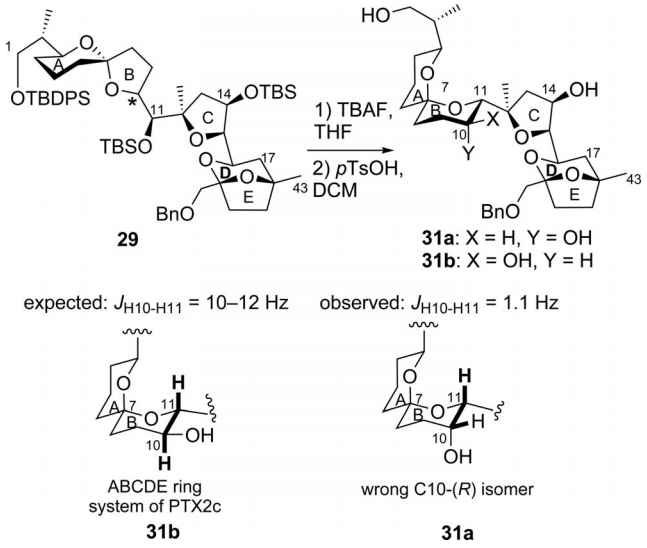
Table 3. Kinetic spiroketalizations to form the ABCDE ring fragment and key NOESY cross-peaks detected in the AB ring system.[20]



Entry	Acid	Solvent	Time	29:30 (% conversion)
1	$ClCH_2COOH$	CH_2Cl_2	0.5 h	1:3 (100)
2	Cl_3CCOOH	4:1 THF/H_2O	4 h	1:1 (100)
3	$ClCH_2COOH$	4:1 THF/H_2O	20 h	1:1 (20)

The stereochemistry at C10, however, could not be fully confirmed by NOE experiments. We therefore decided to convert the [6,5]-spiroketal system of the product into the corresponding [6,6]-spiroketal system. This was readily achieved by deprotection of the silyl protecting groups with tetrabutylammonium fluoride (TBAF), followed by treatment with *p*-toluenesulfonic acid (*p*TsOH) to afford the desired [6,6]-spiroketal **31a** (Scheme 7). The observed coupling constant between the C10-H and C11-H was 1.1 Hz (Scheme 7). To our dismay, this experiment confirmed that the stereochemistry at C10 was (*R*), not (*S*) as expected from a Felkin–Anh or Cornforth-controlled addition (cf. Scheme 2).

Because in the final synthesis we would have to differentiate between the C11 and C14 hydroxy groups, we decided to try an alternative protective group at C11 in an attempt



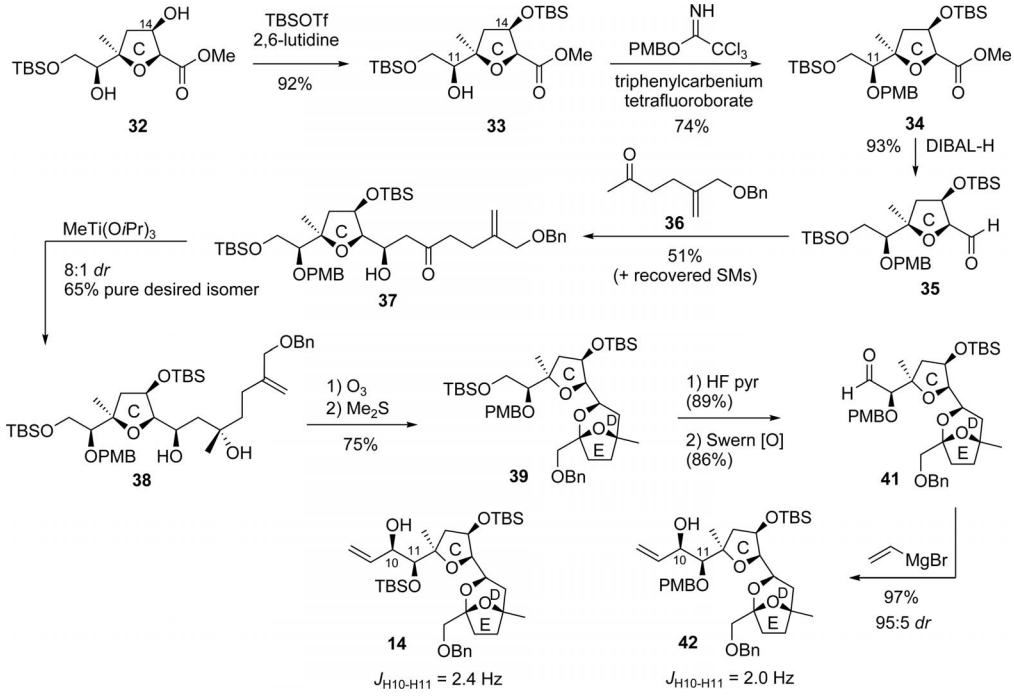
Scheme 7. Confirmation of the stereochemistry at C10.

to reverse the selectivity (Scheme 8). We found that selective protection of the 14-OH group in **32**[9] could readily be achieved with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) in 2,6-lutidine. *p*-Methoxybenzyl (PMB) protection of **33** under acidic conditions led to ester **34**, which was then carried through our CDE ring synthesis sequence,[9] affording the fully protected CDE ring **39** system in a four-step sequence. Desilylation of the primary silyl group of **39** proceeded more cleanly than the corresponding reaction with **11** (Scheme 3) and Swern oxidation of the resulting alcohol **40** (not shown) provided the desired aldehyde **41**. Addition of vinylmagnesium bromide to **41** afforded the desired allylic alcohol **42** in 95:5 selectivity. The C10–C11 coupling constant of **42** (J = 2.0 Hz) was nearly identical to that of **14** (J = 2.4 Hz) (Scheme 8).

Although the observed anti-Felkin selectivity with the α-[(*p*-methoxybenzyl)oxy] aldehyde **41** could, in retrospect, be explained by the intervention of chelation control in the nucleophilic addition,[21] this explanation could not be so readily applied to the corresponding α-silyloxy compound **11**, which gave the same selectivity. To allow us to test the selectivities more rapidly as well as to allow the stereochemistry of the newly formed stereocenter to be checked in a more straightforward manner, a set of model studies with simpler α,β-dioxygenated aldehydes bearing a tertiary protected C-O system was carried out (Table 4).

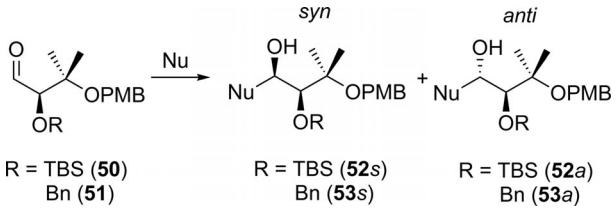
Synthesis of the model compounds began with epoxidation of commercially available acrylate **43**. Acid-catalyzed opening of the epoxide **44** with *p*-methoxybenzyl alcohol gave the desired partially protected diol **45** with perfect selectivity, but low yield. Protection of the free hydroxy moiety with either a silyl group or a benzyl group yielded esters **46** and **47**, which were then reduced with $LiAlH_4$ to primary alcohols and oxidized with Dess–Martin periodinane to form the aldehyde model compounds (±)-**50** and (±)-**51** (Scheme 9).

Test reactions with the prepared model compounds were performed with a variety of nucleophiles under different reaction conditions (Table 4). The results of the reactions showed varying degrees of *syn* selectivity in each case. The stereochemistries of the products were verified by forming



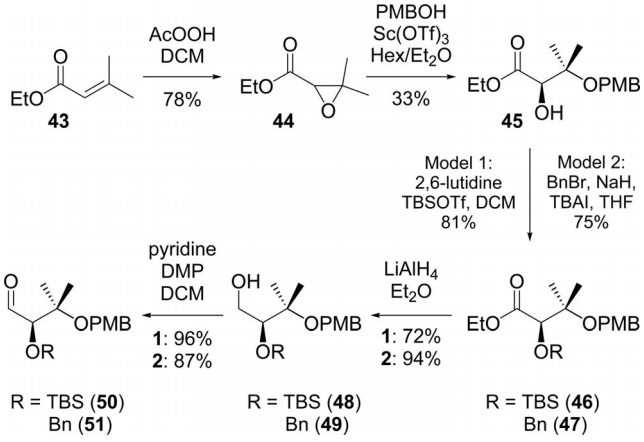
Scheme 8. Synthesis of the PMB protected CDE fragment and the $J_{H10–H11}$ coupling constants of **14** and **42**.

Table 4. Diastereoselectivities of nucleophilic additions to model compounds (±)-**50** and (±)-**51**.



Entry	Model	Nucleophile	Solvent	Temperature [°C]	Time [h]	Additive	*syn*/*anti*[b]
1	**50**	MeMgBr	THF	–78 to –30	1	–	2.0:1
2	**50**	MeMgBr	THF	–78 to 0	5.5	$BF_3{\cdot}Et_2O$	2.1:1
3	**50**	VinylMgBr	THF	–78 to 0	5.5	–	1.6:1
4	**51**	MeLi[a]	THF	–78 to –30	1	–	4.7:1
5	**51**	MeMgBr	THF	–78 to –30	1	–	3.6:1
6	**51**	VinylMgBr	THF	–78 to 0	5.5	–	4.1:1
7	**51**	MeMgBr	CH_2Cl_2	–78 to 0	2	–	22:1
8	**51**	MeMgBr	toluene	–78 to 0	2	–	11:1
9	**51**	MeMgBr	MeCN	–78 to 0	2	–	6.2:1

[a] In reactions with MeLi and **50**, significant migration of the silyl group was observed. [b] The diastereoselectivities were determined by ^{1}H NMR analysis of the crude reaction mixtures obtained after workup (aq. NH_4Cl). All reactions proceeded to >95% conversion.



Scheme 9. Preparation of model compounds (±)-**50** and (±)-**51**.

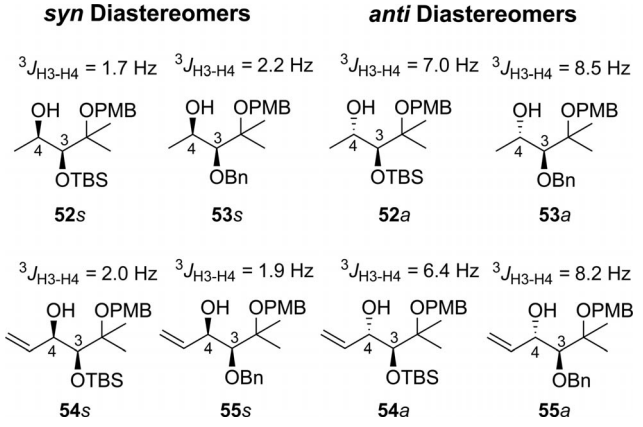


Figure 3. Coupling constants of the acyclic addition products (cf. Scheme 8).

the cyclic PMP acetals (see the Supporting Information for details). Additionally, a very clear trend for ^{1}H coupling constants for the *syn* and *anti* diastereomers could be observed (Figure 3), allowing the stereochemistry of **42** to be assigned by analogy.

Although higher *syn* selectivities were observed with the test substrate **51** where the α-substituent was a benzyloxy group, the silyl protected analogues **50** also displayed *syn* selectivity, confirming the patterns observed with the attempted Felkin-selective additions at C10 with the fully armed CDE ring systems **13** and **42**.

The unexpected breakdown of Felkin and Cornforth selectivities with the aldehydes studied herein cannot be readily reconciled with any of the known models. Chelation with the β-oxy substituent would be expected to afford the Felkin product. Although chelation to the α-substituent would indeed afford the anti-Felkin product,[21] α-silyloxy aldehydes that are generally poor substrates for chelation control also displayed anti-Felkin selectivity when the β-carbon was heavily substituted (two carbon chains and an alkoxy substituent). Although several models could be conceivably presented that account for these observations, at present we simply wish to issue a cautionary note that the usual Felkin/Cornforth selectivities appear to break down with these heavily substituted substrates.

Conclusions

A combination of cross-metathesis and hydrogenation can be used to afford complex spiroketalization precursors for kinetic spiroketalization reactions. Additionally, we have demonstrated that the kinetic spiroketalization protocol developed for the AB ring spiroketal system of the pectenotoxins, also works in more complex settings, such as the synthesis of the nonanomeric 10-*epi*-ABCDE ring system

of the pectenotoxins. The unexpected anti-Felkin selective addition of organometallic nucleophiles to the advanced CDE ring precursor was investigated with differently protected α,β-dioxygenated model aldehydes, which displayed similar anti-Felkin selectivities with organometallic nucleophiles. We are investigating the generality of this observation and the results will be published in due course.

Experimental Section

General Methods: All reactions were carried out under an argon atmosphere in flame-dried glassware, unless otherwise noted. When needed, nonaqueous reagents were transferred under argon by using syringe or cannula techniques and dried prior to use. THF, Et_2O, and CH_2Cl_2 were obtained by passing deoxygenated solvents through activated alumina columns (MBraun SPS-800 Series solvent purification system). Et_3N and iPr_2NH were distilled from Na. Allyl alcohol and DMSO were distilled from CaH_2. $TiCl_4$ was fractionally distilled. TBSOTf was prepared with Corey's procedure.[22] DMP was prepared with Ireland's procedure.[23] Other solvents and reagents were used as obtained from the supplier, unless otherwise noted. Analytical TLC was performed using Merck silica gel F254 (230–400 mesh) plates and analyzed by UV light or by staining upon heating with anisaldehyde solution (2.8 mL anisaldehyde, 2 mL concd. H_2SO_4, 1.2 mL concd. CH_3COOH, 100 mL EtOH), vanillin solution (6 g vanillin, 5 mL concd. H_2SO_4, 3 mL glacial acetic acid, 250 mL EtOH), or $KMnO_4$ solution (1 g $KMnO_4$, 6.7 g K_2CO_3, 1.7 mL 1 M NaOH, 100 mL H_2O). For silica gel chromatography, the flash chromatography technique was used, with Merck silica gel 60 (230–400 mesh) and p.a. grade solvents unless otherwise noted.

^1H and ^{13}C NMR spectra were recorded in either [D_6]acetone, $CDCl_3$, CD_3CN, or C_6D_6 with Bruker Avance 500, 400 or 250 spectrometers. The chemical shifts are reported in ppm relative to $CHCl_3$ (δ = 7.26 ppm), CHD_2CN (δ = 1.94 ppm) or C_6D_5H (δ = 7.16 ppm) for ^1H NMR spectroscopy. For the ^{13}C NMR spectra, the residual [D_6]acetone (δ = 29.84 ppm), $CDCl_3$ (δ = 77.0 ppm), CD_3CN (δ = 118.26 ppm) or C_6D_6 (δ = 128.06 ppm) were used as internal standards. The enantiomeric excess (*ee*) of the products were determined by HPLC analysis by comparison to the corresponding racemic samples (Waters 501 pump and Waters 486 detector). Melting points (m.p.) were determined in open capillaries using a Gallenkamp melting point apparatus. IR spectra were recorded with a Perkin–Elmer Spectrum One FTIR spectrometer. Optical rotations were obtained with a Perkin–Elmer 343 polarimeter. High-resolution mass spectrometric data were measured using MicroMass LCT Premier Spectrometer. Some of the high-resolution mass spectrometric data was obtained by the University of Oulu with a Micromass LCT spectrometer. Elemental analyses were recorded with a Perkin–Elmer 2400 CHN instrument by the Elemental Analytical Services of the Department of Chemistry.

(*S*)-2-((2*R*,4*R*,5*R*)-5-{(1*S*,3*R*,5*S*)-1-[(Benzyloxy)methyl]-5-methyl-2,8-dioxabicyclo[3.2.1]octan-3-yl}-4-[(*tert*-butyldimethylsilyl)oxy]-2-methyltetrahydrofuran-2-yl)-2-[(*tert*-butyldimethylsilyl)oxy]-ethanol (12): To a solution of **11**[9a] (2.0 g, 2.66 mmol, 100 mol-%) in THF (8.0 mL), was added HF·pyridine (70% HF, 2.08 mL, 1.6 g, 80.0 mmol, 3000 mol-%) at room temp. The reaction mixture was stirred at room temp. for 1.5 h before satd. aq. $NaHCO_3$ (50 mL) was added dropwise. The mixture was allowed to stir for 10 min, and then the layers were separated. The organic layer was washed with satd. aq. $NaHCO_3$ (2 × 50 mL). The combined aqueous layers were extracted with Et_2O (2 × 50 mL) and the combined organic extracts were dried with Na_2SO_4 and concentrated. Purification of the residue by flash chromatography (initially 10% EtOAc/hexanes, finally MeOH) afforded the desired product **12** as light-yellow viscous oil (0.76 g, 45%). Other collected fractions contained the starting material **11** (0.64 g) and a mixture of diol (2*S*,3*R*,5*R*)-2-{(1*S*,3*R*,5*S*)-1-[(benzyloxy)methyl]-5-methyl-2,8-dioxabicyclo-(3.2.1)octan-3-yl}-5-{(*S*)-1-[(*tert*-butyldimethylsilyl)oxy]-2-hydroxyethyl}-5-methyltetrahydrofuran-3-ol and triol (*S*)-1-((2*R*,4*R*,5*S*)-5-((1*S*,3*R*,5*S*)-1-[(benzyloxy)methyl]-5-methyl-2,8-dioxabicyclo[3.2.1]octan-3-yl)-4-hydroxy-2-methyltetrahydrofuran-2-yl)ethane-1,2-diol (0.26 g). After a second reaction with the recycled starting material, the desired product **12** was obtained in 58% combined yield (0.98 g). R_f = 0.49 (30% EtOAc/hexanes). $[\alpha]_D$ = –12.2 (*c* = 1.00, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3514, 2955, 2930, 2885, 2857, 1472, 1463, 1254, 1120, 1110, 1067 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.25 (m, 5 H), 4.61 (dd^{AB}, $|J_{AB}|$ = 12.3 Hz, $\Delta\nu$ = 29.5 Hz, 2 H), 4.29 (dd, *J* = 4.4, 3.0 Hz, 1 H), 4.15 (ddd, *J* = 11.5, 8.0, 3.7 Hz, 1 H), 3.82 (dd, *J* = 8.0, 3.9 Hz, 1 H), 3.77 (dd, *J* = 10.6, 8.0 Hz, 1 H), 3.60 (dd, *J* = 8.2, 2.9 Hz, 1 H), 3.51 (dd^{AB}, $|J_{AB}|$ = 10.7 Hz, $\Delta\nu$ = 22.0 Hz, 2 H), 3.56–3.50 (m, 1 H), 2.94 (s, 1 H), 2.19 (dt, *J* = 13.2, 4.2 Hz, 1 H), 2.08–1.95 (m, 2 H), 1.92–1.83 (m, 2 H), 1.74–1.64 (m, 2 H), 1.51 (dd, *J* = 13.1, 3.9 Hz, 1 H), 1.37 (s, 3 H), 1.17 (s, 3 H), 0.90 (s, 9 H), 0.87 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H), 0.05 (s, 3 H), –0.02 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.5, 128.4, 127.9, 127.6, 106.4, 85.7, 85.2, 81.0, 76.2, 73.8, 71.92, 71.87, 66.1, 64.7, 48.0, 40.7, 34.2, 31.8, 26.3, 26.1, 25.9, 20.5, 18.1 (2H), –3.8, –4.4, –4.5, –5.0 ppm. HRMS (ESI^+): calcd. for $C_{34}H_{60}O_7NaSi_2$ 659.3775; found 659.3775 (Δ = 0.2 ppm).

(*R*)-2-((2*R*,4*R*,5*R*)-5-{(1*S*,3*R*,5*S*)-1-[(Benzyloxy)methyl]-5-methyl-2,8-dioxabicyclo[3.2.1]octan-3-yl}-4-[(*tert*-butyldimethylsilyl)oxy]-2-methyltetrahydrofuran-2-yl}-2-[(*tert*-butyldimethylsilyl)oxy]acetaldehyde (13): To a solution of oxalyl chloride (21 μL, 30 mg, 0.24 mmol, 120 mol-%) in CH_2Cl_2 (1.5 mL), was added DMSO (36 μL, 40 mg, 0.5 mmol, 250 mol-%) at –50 °C. After stirring for 8 min, a solution of alcohol **12** (0.13 g, 0.2 mmol, 100 mol-%) in CH_2Cl_2 (2.5 mL) was added. The resulting mixture was stirred for 45 min, keeping the temperature below –30 °C. Triethylamine (0.13 mL, 91 mg, 0.90 mmol, 450 mol-%) was then added dropwise and stirring was continued at –30 °C for an additional 10 min and then the mixture was warmed to room temp. H_2O (5 mL) was added and the separated aqueous phase was extracted with CH_2Cl_2 (5 mL). The combined organic extracts were washed with brine (10 mL), dried with Na_2SO_4 and concentrated. Purification of the residue by flash chromatography (10% EtOAc/hexanes) afforded the desired product **13** as light-yellow oil (0.12 g, 93%). R_f = 0.70 (30% EtOAc/hexanes). $[\alpha]_D$ = –64.9 (*c* = 1.00, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 2954, 2930, 2857, 1736, 1255, 1105 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.80 (s, 1 H), 7.34–7.27 (m, 5 H), 4.62 (dd^{AB}, J_{AB} = 12.3 Hz, $\Delta\nu$ = 30.9 Hz, 2 H), 4.33 (dd, *J* = 4.6, 2.9 Hz, 1 H), 4.25 (s, 1 H), 4.18 (ddd, *J* = 11.0, 8.2, 4.1 Hz, 1 H), 3.65 (dd, *J* = 8.2, 2.8 Hz, 1 H), 3.52 (dd^{AB}, J_{AB} = 10.6 Hz, $\Delta\nu$ = 21.3 Hz, 2 H), 2.19 (dt, *J* = 13.1, 4.7 Hz, 1 H), 2.17 (d, *J* = 14.0 Hz, 1 H), 2.01 (ddd, *J* = 13.6, 9.2, 4.8 Hz, 1 H), 1.93–1.89 (m, 1 H), 1.85 (dd, *J* = 14.0, 5.0 Hz, 1 H), 1.76–1.57 (m, 4 H), 1.39 (s, 3 H), 1.13 (s, 3 H), 0.901 (s, 9 H), 0.900 (s, 9 H), 0.11 (s, 3 H), 0.05 (s, 3 H), 0.01 (s, 3 H), –0.0002 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.3, 138.5, 128.4, 127.9, 127.6, 106.4, 85.8, 84.1, 82.9, 81.1, 73.8, 72.1, 72.0, 66.4, 47.0, 40.7, 34.3, 31.9, 26.3, 26.1, 26.0, 22.8, 18.5, 18.1, –3.8, –4.4, –4.9, –5.0 ppm. HRMS (ESI^+): calcd. for $C_{34}H_{58}O_7NaSi_2$ 657.3619; found 657.3605 (Δ = 2.1 ppm).

(1*S*,2*R*)-1-((2*R*,4*R*,5*R*)-5-((1*S*,3*R*,5*S*)-1-[(Benzyloxy)methyl]-5-methyl-2,8-dioxabicyclo[3.2.1]octan-3-yl)-4-[(*tert*-butyldimethylsilyl)oxy]-2-methyltetrahydrofuran-2-yl)-1-[(*tert*-butyldimethylsilyl)oxy]but-3-en-2-ol (14): To a solution of aldehyde **13** (0.10 g, 0.16 mmol, 100 mol-%) in THF (3.5 mL), was added vinylmagnesium bromide (1 M in THF, 0.64 mL, 0.64 mmol, 400 mol-%) at –78 °C. The reaction mixture was stirred at –78 °C for 25 min and then quenched with satd. aq. NH_4Cl (4 mL). The reaction mixture was warmed to room temp. and H_2O (4 mL) was added to dissolve the precipitate. The separated organic layer was dried with Na_2SO_4 and concentrated. Purification of the residue by flash chromatography (initially 5% EtOAc/hexanes, then 7%, and finally 10% EtOAc/hexanes) afforded the major product **14** as a light-yellow oil (71 mg, 67%). A mixture containing the major and the minor diastereomers in 1:2 ratio (30 mg) was also isolated. R_f = 0.55 (30% EtOAc/hexanes). $[\alpha]_D$ = –1.9 (*c* = 1.00, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3497, 2954, 2929, 2857, 1254, 1100 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.27 (m, 5 H), 5.95 (ddd, *J* = 17.3, 10.6, 4.3 Hz, 1 H), 5.31 (dd, *J* = 17.2, 1.9 Hz, 1 H), 5.13 (dd, *J* = 10.6, 1.9 Hz, 1 H), 4.62 (dd^{AB}, $|J_{AB}|$ = 12.4 Hz, $\Delta\nu$ = 30.7 Hz, 2 H,), 4.38 (ddd, *J* = 9.1, 4.3, 2.2 Hz, 1 H), 4.29 (dd, *J* = 4.1, 3.1 Hz, 1 H), 4.14 (ddd, *J* = 11.4, 8.0, 3.7 Hz, 1 H), 3.82 (d, *J* = 2.4 Hz, 1 H), 3.56 (dd, *J* = 8.2, 2.9 Hz, 1 H), 3.52 (dd^{AB}, $|J_{AB}|$ = 10.5 Hz, $\Delta\nu$ = 22.5 Hz, 2 H), 2.91 (d, *J* = 9.1 Hz, 1 H), 2.20 (dt, *J* = 13.0, 4.1 Hz, 1 H), 2.02–1.95 (m, 2 H), 1.90–1.85 (m, 1 H), 1.84 (dd, *J* = 13.7, 5.3 Hz, 1 H), 1.75–1.65 (m, 2 H), 1.59–1.56 (m, 1 H), 1.39 (s, 3 H), 1.23 (s, 3 H), 0.902 (s, 9 H), 0.896 (s, 9 H), 0.10 (s, 3 H), 0.07 (s, 3 H), 0.05 (s, 3 H), –0.02 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.8, 138.5, 128.4, 127.9, 127.6, 114.1, 106.4, 84.8, 84.6, 81.1, 79.2, 73.8, 72.3, 72.1, 72.0, 66.2, 48.9, 40.8, 34.3, 31.8, 26.3, 26.12, 26.06, 22.3, 18.4, 18.1, –3.4, –4.0, –4.3, –5.0 ppm. HRMS (ESI^+): calcd. for $C_{36}H_{62}O_7NaSi_2$ 685.3932; found 685.328 (Δ = 0.6 ppm).

(7*S*,8*S*)-9-[(*tert*-Butyldiphenylsilyl)oxy]-7-hydroxy-8-methylnon-1-en-3-one (19): To a solution of **15**[12] (0.11 g, 0.27 mmol, 100 mol-%) in THF (3.0 mL), was added vinylmagnesium bromide (1 M in THF, 0.33 mL, 0.33 mmol, 120 mol-%) at –78 °C. The reaction mixture was stirred at –78 °C for 30 min and then quenched with satd. aq. NH_4Cl (3 mL). The reaction mixture was warmed to room temp. and H_2O (3 mL) was added to dissolve the precipitate. The separated organic layer was washed with brine (3 mL), dried with Na_2SO_4, and concentrated. Purification of the residue by flash chromatography (20% EtOAc/hexanes) afforded the desired product **19** as a light-yellow oil (0.11 g, 94%). R_f = 0.29 (30% EtOAc/Hexanes). $[\alpha]_D$ = 0.6 (*c* = 1.00, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3503, 2959, 2931, 2858, 1681, 1428, 1112 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.68–7.65 (m, 4 H), 7.46–7.37 (m, 6 H), 6.36 (dd, *J* = 17.7, 10.5 Hz, 1 H), 6.23 (dd, *J* = 17.7, 1.2 Hz, 1 H), 5.82 (dd, *J* = 10.5, 1.2 Hz, 1 H), 3.86 (m, 1 H), 3.75 (dd, *J* = 10.1, 4.2 Hz, 1 H), 3.66 (dd, *J* = 10.1, 6.0 Hz, 1 H), 2.84 (d, *J* = 4.0 Hz, 1 H), 2.63 (dt, *J* = 7.3, 2.3 Hz, 2 H), 1.85–1.65 (m, 3 H), 1.57–1.37 (m, 2 H), 1.06 (s, 9 H), 0.90 (d, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.7, 133.2, 133.1, 130.0, 129.95, 128.2, 127.92, 127.86, 74.0, 68.7, 39.6, 39.3, 33.7, 27.0, 20.8, 19.3, 10.4 ppm. HRMS (ESI^+): calcd. for $C_{26}H_{36}O_3NaSi$ 447.2331; found 447.2333 (Δ = 0.3 ppm).

(5*S*,6*R*,13*S*,14*S*,*E*)-5-((2*R*,4*R*,5*R*)-5-((1*S*,3*R*,5*S*)-1-[(Benzyloxy)methyl]-5-methyl-2,8-dioxabicyclo[3.2.1]octan-3-yl)-4-[(*tert*-butyldimethylsilyl)oxy]-2-methyltetrahydrofuran-2-yl)-6,13-dihydroxy-2,2,3,3,14,18,18-heptamethyl-17,17-diphenyl-4,16-dioxa-3,17-disilanonadec-7-en-9-one (26): To a solution of ketone **19** (0.15 g, 0.34 mmol, 150 mol-%) and alcohol **14** (0.15 g, 0.23 mmol, 100 mol-%) in CH_2Cl_2 (7 mL), was added Grubbs 2nd generation catalyst (9.8 mg, 0.012 mmol, 5 mol-%). The reaction mixture was warmed to reflux and stirred for 17 h. Solvent was evaporated and the residue was purified by flash chromatography (30% MTBE/hexanes, 50 μL Et_3N in 500 mL eluent) to give keto diol **26** as a tanned oil (0.12 g, 52%). R_f = 0.27 (30% EtOAc/hexanes). $[\alpha]_D$ = –7.9 (*c* = 1.00, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3480, 2955, 2931, 2858, 1694, 1472, 1255, 1111 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.68–7.65 (m, 4 H), 7.46–7.37 (m, 6 H), 7.33–7.32 (m, 5 H), 6.96 (dd, *J* = 15.9, 3.5 Hz, 1 H), 6.41 (dd, *J* = 15.8, 2.2 Hz, 1 H), 4.61 (dd^{AB}, J_{AB} = 12.3 Hz, $\Delta\nu$ = 28.4 Hz, 2 H), 4.55–4.51 (m, 1 H), 4.29 (dd, *J* = 4.4, 2.9 Hz, 1 H), 4.13 (ddd, *J* = 11.4, 8.0, 3.7 Hz, 1 H), 3.93 (d, *J* = 3.2 Hz, 1 H), 3.87–3.84 (m, 1 H), 3.74 (dd, *J* = 10.4, 4.2 Hz, 1 H), 3.66 (dd, *J* = 10.1, 5.9 Hz, 1 H), 3.56 (dd, *J* = 8.2, 2.8 Hz, 1 H), 3.51 (dd^{AB}, J_{AB} = 10.7 Hz, $\Delta\nu$ = 21.6 Hz, 2 H), 3.25 (d, *J* = 8.5 Hz, 1 H), 2.84 (d, *J* = 3.9 Hz, 1 H), 2.58 (dt, *J* = 7.5, 1.6 Hz, 2 H), 2.18 (dt, *J* = 13.0, 4.2 Hz, 1 H), 2.02–1.64 (m, 8 H), 1.86 (dd, *J* = 13.9, 5.2 Hz, 1 H), 1.55 (dd, *J* = 13.1, 3.9 Hz, 1 H), 1.52–1.44 (m, 2 H), 1.39 (s, 3 H), 1.05 (s, 9 H), 1.05 (s, 3 H), 0.91 (obscured d, 3 H), 0.906 (s, 9 H), 0.895 (s, 9 H), 0.11 (s, 3 H), 0.05 (s, 3 H), 0.04 (s, 3 H), –0.01 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.1, 148.4, 138.5, 135.7, 133.2, 133.1, 130.1, 130.0, 129.9, 128.5, 128.4, 128.2, 127.92, 127.89, 126.6, 106.4, 85.0, 84.9, 81.1, 78.5, 74.7, 73.8, 72.0, 71.97, 71.94, 68.8, 66.0, 48.9, 41.0, 40.8, 39.3, 34.2, 33.9, 31.9, 27.0, 26.3, 26.05, 26.01, 22.3, 20.8, 19.3, 18.3, 18.1, 10.3, –3.6, –4.0, –4.3, –5.1 ppm. HRMS (ESI^+): calcd. for $C_{60}H_{94}O_{10}NaSi_3$ 1081.6053; found 1081.6072 (Δ = 6.3 ppm).

(5*S*,6*R*,13*S*,14*S*)-5-((2*R*,4*R*,5*R*)-5-((1*S*,3*R*,5*S*)-1-[(Benzyloxy)methyl]-5-methyl-2,8-dioxabicyclo[3.2.1]octan-3-yl)-4-[(*tert*-butyldimethylsilyl)oxy]-2-methyltetrahydrofuran-2-yl)-6,13-dihydroxy-2,2,3,3,14,18,18-heptamethyl-17,17-diphenyl-4,16-dioxa-3,17-disilanonadecan-9-one (28): To a solution of ketone **26** (56 mg, 0.053 mmol, 100 mol-%) and pyridine (6.3 μL, 6.3 mg, 0.078 mmol, 150 mol-%) in EtOAc (5 mL), was added Pd on charcoal (11.2 mg of 5% Pd catalyst, 0.005 mmol, 10 mol-%) under argon flow. The reaction flask was repeatedly evacuated and flushed with H_2. The suspension was vigorously stirred under a H_2 atmosphere for 4 h and then filtered through Celite. The filter pad was washed with EtOAc (2 × 5 mL) and the combined filtrates were concentrated. Purification of the residue by flash chromatography (30% EtOAc/hexanes, 50 μL Et_3N in 500 mL eluent) afforded the desired product **28** as a colorless oil (53 mg, 94%). R_f = 0.25 (30% EtOAc/hexanes). $[\alpha]_D$ = –5.9 (*c* = 1.00, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3502, 2954, 2930, 2857, 1713, 1472, 1254, 1111 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.68–7.65 (m, 4 H), 7.46–7.28 (m, 11 H), 4.62 (dd^{AB}, $|J_{AB}|$ = 12.4 Hz, $\Delta\nu$ = 31.1 Hz, 2 H,), 4.29 (dd, *J* = 4.2, 3.1 Hz, 1 H), 4.14 (ddd, *J* = 12.0, 7.4, 4.0 Hz, 1 H), 3.85–3.82 (m, 1 H), 3.76–3.62 (m, 4 H), 3.59–3.55 (m, 1 H), 3.52 (dd^{AB}, $|J_{AB}|$ = 10.6 Hz, $\Delta\nu$ = 22.7 Hz, 2 H,), 2.84 (d, *J* = 3.8 Hz, 1 H), 2.65 (ddd, *J* = 15.9, 8.3, 6.5 Hz, 1 H), 2.57 (d, *J* = 8.4 Hz, 1 H), 2.51–2.42 (m, 3 H), 2.19 (dt, *J* = 13.0, 4.0 Hz, 1 H), 2.02–1.42 (m, 14 H), 1.39 (s, 3 H), 1.06 (s, 9 H), 1.05 (s, 3 H), 0.91 (s, 9 H), 0.90 (s, 9 H), 0.89 (obscured d, 3 H), 0.131 (s, 3 H), 0.129 (s, 3 H), 0.04 (s, 3 H), –0.02 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.9, 138.5, 135.8, 135.7, 133.2, 133.1, 130.0, 129.9, 128.4, 127.9, 127.89, 127.85, 127.6, 106.4, 84.4, 84.3, 81.1, 79.2, 74.0, 73.8, 72.1, 71.9, 70.8, 68.8, 66.2, 48.5, 43.0, 40.8, 39.8, 39.3, 34.2, 33.9, 31.8, 30.1, 27.0, 26.3, 26.2, 26.1, 22.0, 20.6, 19.3, 18.5, 18.1, 10.4, –3.69, –3.73, –4.4, –5.0 ppm. HRMS (ESI^+): calcd. for $C_{60}H_{96}O_{10}NaSi_3$ 1083.6209; found 1083.6238 (Δ = 9.6 ppm).

((*S*)-((2*R*,4*R*,5*R*)-5-((1*S*,3*R*,5*S*)-1-[(Benzyloxy)methyl]-5-methyl-2,8-dioxabicyclo[3.2.1]octan-3-yl)-4-[(*tert*-butyldimethylsilyl)oxy]-2-methyltetrahydrofuran-2-yl)((2*R*,5*S*,7*S*)-7-((*S*)-1-[(*tert*-butyldiphenylsilyl)oxy]propan-2-yl)-1,6-dioxaspiro[4.5]decan-2-yl)methoxy)(*tert*-butyl)dimethylsilane (30): To a solution of ketone **28**

(53 mg, 0.049 mmol, 100 mol-%) in CH_2Cl_2 (3.5 mL) was added chloroacetic acid (2.3 mg, 0.024 mol-%, 50 mol-%) at room temp. The reaction mixture was stirred at room temp. for 1 h and then diluted with CH_2Cl_2 (5 mL) and quenched with satd. aq. $NaHCO_3$ (5 mL). The separated organic layer was dried with Na_2SO_4 and concentrated. Purification of the residue by flash chromatography (10% EtOAc/hexanes, 50 μL Et_3N in 250 mL eluent) afforded the nonanomeric isomer **30** as a colorless oil (15 mg, 29%) and a mixture of the nonanomeric and anomeric isomer **29** (35 mg, combined total yield 98%). For **30**: R_f = 0.38 (15% EtOAc/hexanes). $[\alpha]_D$ = –13.2 (c = 0.50, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 2953, 2929, 2856, 1472, 1106 cm^{-1}. ^1H NMR (400 MHz, C_6D_6): δ = 7.82–7.78 (m, 4 H, TBDPS), 7.36–7.19 (m, 10 H, TBDPS, Bn), 7.11–7.07 (m, 1 H, TBDPS), 4.54 (dd^{AB}, $|J_{AB}|$ = 12.3 Hz, $\Delta\nu$ = 23.9 Hz, 2 H, Bn), 4.40–4.34 (m, 2 H, 16-H, 10-H), 4.22 (dd, J = 4.7, 2.8 Hz, 1 H, 14-H), 3.88 (d, J = 8.2 Hz, 1 H, 11-H), 3.85 (dd, J = 9.7, 7.3 Hz, 1 H, 1-H), 3.80 (s, 2 H, 22-H), 3.62 (dd, J = 11.1, 2.9 Hz, 1 H, 15-H), 3.60 (dd, J = 9.7, 6.0 Hz, 1 H, 1-H), 3.58–3.56 (m, 1 H, 3-H), 2.41 (dt, J = 13.2, 4.5 Hz, 1 H, 20-H_a), 2.32 (d, J = 13.9 Hz, 1 H, 13-H_a), 2.23–1.96 (m, 5 H, 6-H_a, 8-H_a, 9-H, 20-H_b), 1.86 (app t, J = 10.5 Hz, 1 H, 17-H_{ax}), 1.82–1.49 (m, 11 H, 2-H, 4-H, 5-H, 6-H_b, 8-H_b, 13-H_b, 17-H_{eq}, 19-H), 1.29 (s, 3 H, 43-H), 1.24 (s, 3 H, 42-H), 1.19 (s, 9 H, TBDPS), 1.10 (s, 9 H, 14-OSi-tBu), 1.04 (s, 9 H, 11-OSi-tBu), 1.00 (d, J = 6.8 Hz, 3 H, 41-H), 0.48 (s, 3 H, 14-OSi-Me_a), 0.37 (s, 3 H, 14-OSi-Me_b), 0.13 (s, 3 H, 11-OSi-Me_a), 0.12 (s, 3 H, 11-OSi-Me_b) ppm. ^{13}C NMR (100 MHz, CD_3CN): δ = 139.6, 136.4, 136.3, 134.80, 134.76, 130.6, 130.7, 129.2, 128.8, 128.75, 128.72, 128.4, 108.0, 107.0, 85.9, 84.6, 81.8, 81.4, 80.2, 74.0, 73.5, 72.94, 72.88, 67.2, 66.6, 49.2, 41.6, 41.3, 35.6, 34.7, 33.7, 32.5, 29.3, 28.9, 27.2, 26.7, 26.41, 26.37, 23.0, 21.8, 19.8, 19.3, 18.6, 11.6, –2.7, –4.1, –4.2, –4.9 ppm. HRMS (ESI^+): calcd. for $C_{60}H_{94}O_9NaSi_3$ 1065.6103; found 1065.6095 (Δ = 0.8 ppm).

Equilibration Experiment

((*S*)-((2*R*,4*R*,5*R*)-5-((1*S*,3*R*,5*S*)-1-[(Benzyloxy)methyl]-5-methyl-2,8-dioxabicyclo[3.2.1]octan-3-yl)-4-[(*tert*-butyldimethylsilyl)oxy]-2-methyltetrahydrofuran-2-yl)((2*R*,5*R*,7*S*)-7-((*S*)-1-[(*tert*-butyldiphenylsilyl)oxy]propan-2-yl)-1,6-dioxaspiro[4.5]decan-2-yl)methoxy)(*tert*-butyl)dimethylsilane (29): To a solution of a 1:1 mixture of spiroketals **29** and **30** (40 mg, 0.038 mmol, 100 mol-%) in CH_2Cl_2 (2.0 mL), was added PPTS (1.9 mg, 0.0075 mmol, 20 mol-%) at room temp. After 4 h, a second portion of PPTS (9.5 mg, 0.038 mmol, 100 mol-%) was added. Stirring was continued at room temp. for 2 h, then the reaction mixture was diluted with CH_2Cl_2 (5 mL) and quenched by addition of satd. aq. $NaHCO_3$ (4 mL). The layers were separated and the organic layer was dried with Na_2SO_4 and concentrated. Purification of the residue by flash chromatography (10% EtOAc/hexanes, 25 μL Et_3N in 125 mL eluent) afforded the anomeric isomer **29** as a colorless oil (26.5 mg, 67%). For **29**: R_f = 0.34 (15% EtOAc/hexanes). $[\alpha]_D$ = 0.6 (c = 0.50, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 2953, 2929, 2856, 1472, 1110 cm^{-1}. ^1H NMR (400 MHz, C_6D_6): δ = 7.85–7.79 (m, 4 H, Si-Ph), 7.36–7.18 (m, 10 H, Si-Ph, Bn), 7.10–7.06 (m, 1 H, Si-Ph), 4.54 (dd^{AB}, $|J_{AB}|$ = 12.3 Hz, $\Delta\nu$ = 26.4 Hz, 2 H, Bn), 4.35 (ddd, J = 11.5, 8.0, 3.7 Hz, 1 H, 16-H), 4.20 (dd, J = 5.0, 3.2 Hz, 1 H, 14-H), 3.96–3.86 (m, 3 H, 1-H_a, 3-H, 10-H), 3.81 (d, J = 7.8 Hz, 1 H, 11-H), 3.79 (s, 2 H, 22-H), 3.69 (dd, J = 9.9, 7.0 Hz, 1 H, 1-H_b), 3.64 (dd, J = 8.2, 3.1 Hz, 1 H, 15-H), 2.37 (dt, J = 13.1, 4.3 Hz, 1 H, 20-H), 2.37–2.28 (m, 1 H, 9-H_a), 2.28 (d, J = 14.1 Hz, 1 H, 13-H_a), 2.17 (ddd, J = 13.7, 9.2, 4.8 Hz, 1 H, 20-H_a), 1.99–1.83 (m, 5 H, 2-H, 6-H_a, 8-H_a, 9-H_b, 17-H_{ax}), 1.74–1.38 (m, 9 H, 4-H_a, 5-H, 6-H_b, 8-H_b, 13-H_b, 17-H_{eq}, 19-H), 1.35 (d, J = 6.8 Hz, 3 H, 41-H), 1.30 (s, 3 H, 43-H), 1.22 (s, 9 H, 1O-Si-tBu), 1.15 (s, 3 H, 42-H), 1.09 (s, 9 H, 11-OSi-tBu), 1.07 (s, 9 H, 14-OSi-tBu), 1.04 (d, J = 6.8 Hz, 1 H, 4-H_b), 0.43 (s, 3 H, 11-OSi-Me_a), 0.36 (s, 3 H, 11-OSi-Me_b), 0.14 (s, 6 H, 14-OSi-Me_2) ppm. ^{13}C NMR (100 MHz, CD_3CN): δ = 139.5, 136.42, 136.37, 136.36, 134.8, 130.7, 130.6, 129.2, 128.74, 128.66, 128.62, 128.4, 107.0, 105.8, 85.7, 84.7, 84.6, 83.0, 81.5, 74.0, 73.4, 72.9, 72.7, 67.5, 66.6, 49.7, 42.1, 41.4, 40.4, 34.8, 34.7, 32.5, 28.5, 28.0, 27.3, 26.52, 26.47, 26.41, 21.1, 21.0, 19.8, 19.2, 18.6, 15.1, –2.7, –3.9, –4.4, –4.7 ppm. HRMS (ESI^+): calcd. for $C_{60}H_{94}O_9NaSi_3$ 1065.6103; found 1065.6104 (Δ = 0.1 ppm).

(2*S*,3*R*,6*S*,8*S*)-2-((2*R*,4*R*,5*S*)-5-((1*S*,3*R*,5*S*)-1-[(Benzyloxy)methyl]-5-methyl-2,8-dioxabicyclo[3.2.1]octan-3-yl)-4-hydroxy-2-methyltetrahydrofuran-2-yl)-8-[(*S*)-1-hydroxypropan-2-yl]-1,7-dioxaspiro[5.5]undecan-3-ol (31a): To a solution of spiroketal **29** (6.0 mg, 0.006 mmol, 100 mol-%) in THF (0.5 mL), was added TBAF (1 M in THF, 56 μL, 0.06 mmol, 1000 mol-%) at room temp. The reaction mixture was stirred at room temp. for 24 h and then diluted with Et_2O (4 mL). The orange oil that separated from the solution was separated from the solution, and the solvent was evaporated. The crude product was dissolved in CH_2Cl_2 (1 mL) and pTsOH (0.5 mg, 0.003 mmol, 50 mol-%) was added. The reaction mixture was stirred at room temp. for 19 h then diluted with CH_2Cl_2 (4 mL) and satd. aq. $NaHCO_3$ (2 mL) was added. The layers were separated and the organic layer was dried with Na_2SO_4 and concentrated. Purification of the residue by flash chromatography (90% EtOAc/hexanes) afforded the [6,6]-spiroketal product **31** as a colorless oil (2.8 mg, 86%). R_f = 0.26 (90% EtOAc/hexanes). $[\alpha]_D$ = 1.7 (c = 0.23, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3401, 2918, 2850, 1454, 1099 cm^{-1}. ^1H NMR (400 MHz, CD_3CN): δ = 7.36–7.28 (m, 5 H, Bn), 4.56 (s, 2 H, Bn), 4.19 (d, J = 10.7 Hz, 1 H, 14-OH), 4.19–4.14 (m, 1 H, 16-H), 4.03–3.99 (m, 1 H, 14-H), 3.81–3.78 (m, 1 H, 10-H), 3.74 (ddd, J = 11.6, 5.1, 2.2 Hz, 1 H, 3-H), 3.56–3.53 (m, 1 H, 1-H_a), 3.51 (d, J = 1.1 Hz, 1 H, 11-H), 3.47 (s, 2 H, 22-H), 3.42 (dd, J = 7.9, 2.4 Hz, 1 H, 15-H), 3.39–3.33 (m, 1 H, 1-H_b), 2.77 (d, J = 6.4 Hz, 1 H, 10-OH), 2.66 (dd, J = 6.5, 4.9 Hz, 1 H, 1-OH), 2.49 (d, J = 14.5 Hz, 1 H, 13-H_a), 2.12–2.07 (m, 2 H, 8-H_a, 20-H_a), 2.01–1.96 (m, 2 H, 4-H_{eq}, 9-H_a), 1.87–1.75 (m, 4 H, 5-H_a, 13-H_b, 19-H_a, 20-H_b), 1.70–1.51 (m, 8 H, 2-H, 5-H_b, 6-H_a, 8-H_b, 9-H_b, 17-H, 19-H_b), 1.47 (dd, J = 13.9, 5.1 Hz, 1 H, 6-H_b), 1.38 (ddd, J = 14.0, 4.5, 2.3 Hz, 1 H, 4-H_{ax}), 1.29 (s, 3 H, 43-H), 1.20 (s, 3 H, 42-H), 0.91 (d, J = 6.9 Hz, 3 H, 41-H) ppm. HRMS (ESI^+): calcd. for $C_{32}H_{48}O_9Na$ 599.3196; found 599.3219 (Δ = 3.8 ppm).

(2*S*,3*R*,5*R*)-Methyl 3-[(*tert*-Butyldimethylsilyl)oxy]-5-{(*S*)-2-[(*tert*-butyldimethylsilyl)oxy]-1-hydroxyethyl}-5-methyltetrahydrofuran-2-carboxylate (33): To a solution of (2*S*,3*R*,5*R*)-methyl 5-{(*S*)-2-[(*tert*-butyldimethylsilyl)oxy]-1-hydroxyethyl}-3-hydroxy-5-methyltetrahydrofuran-2-carboxylate (0.10 g, 0.3 mmol, 100 mol-%) in CH_2Cl_2 (2 mL) at –78 °C, was added dropwise over a period of 30 min, a solution of 2,6-lutidine (70 μL, 0.6 mmol, 200 mol-%) and TBSOTf (76 μL, 0.33 mmol, 110 mol-%) in CH_2Cl_2 (2 mL). The reaction was stirred at –78 °C for 25 min and then quenched by addition of MeOH (1 mL). The solution was warmed to room temp. then washed with H_2O (2 mL) and brine (2 mL), dried with Na_2SO_4, and concentrated. Purification of the residue by flash chromatography (10% EtOAc/hexanes) afforded the desired product **34** as a colorless viscous oil (0.12 g, 92%). R_f = 0.73 (50% EtOAc/hexanes). $[\alpha]_D$ = +17.7 (c = 1.00, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3451, 2954, 2931, 2858, 2886, 1770, 1737, 1473, 1463, 1256, 1100, 838, 778 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.72 (q, J = 6.0 Hz, 1 H), 4.50 (d, J = 6.0 Hz, 1 H), 3.81 (t, J = 3.6 Hz, 1 H), 3.79 (dd, J = 13.2, 3.6 Hz, 1 H), 3.69 (dt, J = 13.2, 3.5 Hz, 1 H), 3.72 (s, 3 H), 2.42 (dd, J = 13.3, 5.6 Hz, 1 H), 1.84 (dd, J = 13.3, 6.3 Hz, 1 H), 1.23 (s, 3 H), 0.89 (s, 9 H), 0.86 (s, 9 H), 0.08 (s, 3 H), 0.073 (s, 3 H), 0.071 (s, 3 H), 0.05 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.8, 87.1, 80.2, 75.9, 74.7, 63.8, 52.0,

41.2, 26.0, 25.7, 24.0, 18.4, 18.0, –4.8, –5.2, –5.3, –5.4 ppm. HRMS (ESI^+): calcd. for $C_{21}H_{44}O_6NaSi_3$ 471.2574; found 471.2553 (Δ = 4.5 ppm).

(2*S*,3*R*,5*R*)-Methyl 3-[(*tert*-Butyldimethylsilyl)oxy]-5-{(S)-2-[(*tert*-butyldimethylsilyl)oxy]-1-[(4-methoxybenzyl)oxy]ethyl}-5-methyltetrahydrofuran-2-carboxylate (34): To a solution of compound **33** (1.4 g, 3.3 mmol, 100 mol-%) in CH_2Cl_2 (15 mL) at 0 °C, were added *p*-methoxybenzyl trichloroacetimidate (1.73 mL, 8.3 mmol, 250 mol-%) and triphenylcarbenium tetrafluoroborate (0.11 g, 0.33 mmol, 10 mol-%). The reaction mixture was warmed to room temp. and stirred for 2.5 h, then H_2O (10 mL) was added and the layers were separated. The organic phase was washed with brine (10 mL), dried with Na_2SO_4, and concentrated. Purification of the residue by flash chromatography (10% MTBE/hexanes) afforded the desired product **34** as a colorless oil (1.40 g, 74%). R_f = 0.44 (20% EtOAc/hexanes). $[\alpha]_D$ = –5.3 (*c* = 1.00, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 2953, 2931, 2857, 2886, 1770, 1737, 1614, 1514, 1250, 1105, 837, 777 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.26 (m, 2 H), 6.88–6.84 (m, 2 H), 4.95 (d, *J* = 11.2 Hz, 1 H), 4.64 (ddd, *J* = 5.7, 5.0, 3.0 Hz, 1 H), 4.58 (d, *J* = 11.2 Hz, 1 H), 4.56 (d, *J* = 4.9 Hz, 1 H), 4.18 (dd, *J* = 10.5, 1.5 Hz, 1 H), 3.89 (dd, *J* = 7.6, 1.5 Hz, 1 H), 3.84–3.81 (m, 1 H), 3.80 (s, 3 H), 3.72 (s, 3 H), 2.30 (dd, *J* = 13.5, 3.0 Hz, 1 H), 1.87 (dd, *J* = 13.5, 5.8 Hz, 1 H), 1.18 (s, 3 H), 0.92 (s, 9 H), 0.87 (s, 9 H), 0.11 (s, 3 H), 0.09 (s, 3 H), 0.05 (s, 3 H), 0.04 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.2, 159.0, 132.1, 129.6, 129.1, 128.1, 113.7, 85.8, 84.9, 82.5, 74.6, 73.8, 64.7, 55.4, 51.7, 45.6, 26.1, 25.8, 22.3, 18.3, 18.0, –4.5, –5.23, –5.25, –5.3 ppm. HRMS (ESI^+): calcd. for $C_{29}H_{52}O_7NaSi_2$ 591.3149; found 591.3138 (Δ = 1.9 ppm).

(2*S*,3*R*,5*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-5-{(*S*)-2-[(*tert*-butyldimethylsilyl)oxy]-1-[(4-methoxybenzyl)oxy]ethyl}-5-methyltetrahydrofuran-2-carbaldehyde (35): To a solution of compound **34** (1.34 g, 2.4 mmol, 100 mol-%) in CH_2Cl_2 (25 mL) at –90 °C, was added, dropwise, DIBAL-H (1 M in toluene, 2.6 mL, 2.6 mmol, 110 mol-%). The reaction mixture was stirred at –90 °C for 20 min and then quenched by addition of MeOH (15 mL). The solution was warmed to room temp. then satd. aq. Rochelle salt (20 mL) was added and the reaction mixture was stirred for an additional 45 min. The layers were separated and the aqueous phase was extracted with EtOAc (20 mL). The combined organic extracts were washed with brine (20 mL), dried with Na_2SO_4 and concentrated. Purification of the residue by flash chromatography (15% MTBE/hexanes) afforded aldehyde **35** as a light-yellow oil (1.19 g, 93%). R_f = 0.58 (30% EtOAc/hexanes). $[\alpha]_D$ = –25.6 (*c* = 1.00, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 2954, 2930, 2857, 2885, 1737, 1514, 1250, 1076, 837, 777 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.61 (d, *J* = 2.6 Hz, 1 H), 7.29–7.27 (m, 2 H), 6.88–6.86 (m, 2 H), 4.92 (d, *J* = 11.2 Hz, 1 H), 4.72 (ddd, *J* = 5.8, 5.1, 2.8 Hz, 1 H), 4.57 (d, *J* = 11.2 Hz, 1 H), 4.21 (dd, *J* = 5.0, 2.6 Hz, 1 H), 4.16 (dt, *J* = 9.3, 4.8 Hz, 1 H), 3.85–3.81 (m, 2 H), 3.80 (s, 3 H), 2.35 (dd, *J* = 13.7, 2.8 Hz, 1 H), 1.88 (dd, *J* = 13.6, 5.8 Hz, 1 H), 1.20 (s, 3 H), 0.92 (s, 9 H), 0.86 (s, 9 H), 0.10 (s, 3 H), 0.09 (s, 3 H), 0.04 (s, 3 H), 0.03 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.4, 159.1, 131.7, 129.6, 129.2, 128.1, 113.8, 86.7, 86.5, 85.2, 76.2, 73.7, 64.7, 55.4, 46.0, 26.0, 25.8, 22.5, 18.3, 18.1, –4.5, –5.19, –5.22, –5.3 ppm. HRMS (ESI^+): calcd. for $C_{28}H_{50}O_6NaSi_2$ 561.3044; found 561.3055 (Δ = 2.0 ppm).

(*R*)-6-[(Benzyloxy)methyl]-1-((2*R*,3*R*,5*R*)-3-[(*tert*-butyldimethylsilyl)oxy]-5-{(*S*)-2-[(*tert*-butyldimethylsilyl)oxy]-1-[(4-methoxybenzyl)oxy]ethyl}-5-methyltetrahydrofuran-2-yl)-1-hydroxyhept-6-en-3-one (37): A stock solution of LDA (0.5 M) was prepared as follows: To a solution of diisopropylamine (0.49 mL, 3.8 mmol, 210 mol-%) in THF (5.3 mL), was added *n*BuLi (2.5 M in hexanes, 1.43 mL, 3.6 mmol, 200 mol-%) at 0 °C, and the reaction mixture was stirred at 0 °C for 5 min. A portion of the LDA solution (0.5 M, 4.05 mL, 2.0 mmol, 110 mol-%) was transferred by using a syringe to a solution of 5-[(benzyloxy)methyl]hex-5-en-2-one (**36**;[9b] 0.4 g, 1.8 mmol, 100 mol-%) in THF (10 mL) at –78 °C. After 10 min, a solution of aldehyde **35** (1.14 g, 2.1 mmol, 115 mol-%) in THF (10 mL) was added by cannula into the reaction mixture. Stirring was continued at –78 °C for 10 min then satd. aq. NH_4Cl (10 mL) was added. The reaction mixture was warmed to room temp. and then diluted with H_2O (20 mL). The layers were separated and the organic phase was washed with brine (20 mL), dried with Na_2SO_4, and concentrated. Purification of the residue by flash chromatography (initially 10% EtOAc/hexanes, finally 15% EtOAc/hexanes) afforded ketone **37** as a light-yellow oil (0.72 g, 51%). The reaction did not go to completion and small amounts of both starting materials were recovered. R_f = 0.42 (30% EtOAc/hexanes). $[\alpha]_D$ = –1.0 (*c* = 1.00, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3503, 2954, 2930, 2885, 1708, 1514, 1250, 1103, 1070, 836, 776 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.29 (m, 5 H), 7.28–7.25 (m, 2 H), 6.88–6.84 (m, 2 H), 5.07 (dd, *J* = 2.0, 0.9 Hz, 1 H), 4.90 (t, *J* = 0.7 Hz, 1 H), 4.86 (d, *J* = 11.2 Hz, 1 H), 4.55 (d, *J* = 11.3 Hz, 1 H), 4.52–4.48 (m, 1 H), 4.49 (s, 2 H), 4.27 (td, *J* = 8.8, 2.2 Hz, 1 H), 3.99–3.96 (m, 1 H), 3.96 (s, 2 H), 3.79 (s, 3 H), 3.72 (dd, *J* = 10.9, 7.1 Hz, 1 H), 3.68 (dd, *J* = 8.1, 4.5 Hz, 1 H), 3.57 (dd, *J* = 7.1, 1.8 Hz, 1 H), 3.23 (br. s, 1 H), 2.83 (dd, *J* = 17.1, 2.5 Hz, 1 H), 2.66–2.59 (m, 3 H), 2.38 (t, *J* = 7.4 Hz, 2 H), 2.16 (dd, *J* = 13.5, 3.7 Hz, 1 H), 1.84 (dd, *J* = 13.5, 5.9 Hz, 1 H), 1.10 (s, 3 H), 0.90 (s, 9 H), 0.896 (s, 9 H), 0.10 (s, 3 H), 0.08 (s, 3 H), 0.05 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.0, 159.1, 144.9, 138.4, 131.8, 129.2, 128.5, 127.9, 127.7, 113.8, 112.2, 85.8, 83.5, 82.8, 73.62, 73.58, 73.3, 72.1, 66.8, 64.8, 55.4, 46.5, 45.5, 41.7, 26.8, 26.1, 26.0, 22.4, 18.3, 18.2, –4.3, –5.1, –5.17, –5.21 ppm. HRMS (ESI^+): calcd. for $C_{42}H_{68}O_8NaSi_2$ 779.4350; found 779.4353 (Δ = 0.4 ppm).

(1*R*,3*S*)-6-[(Benzyloxy)methyl]-1-((2*R*,3*R*,5*R*)-3-[(*tert*-butyldimethylsilyl)oxy]-5-{(*S*)-2-[(*tert*-butyldimethylsilyl)oxy]-1-[(4-methoxybenzyl)oxy]ethyl}-5-methyltetrahydrofuran-2-yl)-3-methylhept-6-ene-1,3-diol (38): A stock triisopropoxymethyltitanium solution (0.5 M) was prepared as follows: To gently cooled (ca. 5 °C), neat titanium(IV) isopropoxide (4.46 mL, 15 mmol, 2586 mol-%) was added, dropwise, titanium tetrachloride (0.54 mL, 5 mmol, 862 mol-%). The mixture was warmed to room temp. and stirred for 5 min. Et_2O (22.5 mL) was added and stirring was continued at room temp. for 30 min. The reaction mixture was cooled to 0 °C and MeLi (1.6 M in Et_2O, 12.5 mL, 20 mmol, 3448 mol-%) was added. The reaction mixture was stirred at 0 °C for 1 h, then a portion of the triisopropoxymethyltitanium solution (0.5 M, 17.4 mL, 8.7 mmol, 1500 mol-%) was transferred by using a syringe into a –78 °C solution of ketone **37** (0.44 g, 0.58 mmol, 100 mol-%) in Et_2O (13 mL). The reaction mixture was stirred at –78 °C for 10 min and then the dry-ice bath was changed into an ice-bath. Stirring was continued at 0 °C for a further 10 min then the reaction mixture was diluted with Et_2O (10 mL) and 2 M HCl (10 mL) was added dropwise. The layers were separated and the organic phase was washed with 2 M HCl (10 mL) and brine (10 mL), dried with Na_2SO_4, and concentrated. Purification of the residue by flash chromatography (10% EtOAc/hexanes) afforded diol **38** as a colorless oil (0.29 g, 65%). R_f = 0.24 (30% EtOAc/hexanes). $[\alpha]_D$ = –9.7 (*c* = 1.00, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3436, 2953, 2930, 2885, 2856, 1249, 1103, 1070, 836, 776 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.28 (m, 5 H), 7.28–7.24 (m, 2 H), 6.88–6.84 (m, 2 H), 5.07 (s, 1 H), 4.97 (s, 1 H), 4.85 (d, *J* = 11.3 Hz, 1 H), 4.62–4.57 (m, 1 H), 4.57 (d, *J* = 11.4 Hz, 1 H), 4.50 (s, 2 H), 4.22 (ddd, *J* = 10.2, 7.5, 2.6 Hz, 1 H), 3.98 (dd, *J* = 10.8, 1.8 Hz, 1 H), 3.98 (s, 2 H),

3.79 (s, 3 H), 3.73 (dd, J = 10.8, 7.0 Hz, 1 H), 3.64 (dd, J = 7.7, 5.0 Hz, 1 H), 3.52 (dd, J = 7.0, 1.8 Hz, 1 H), 2.23 (ddd, J = 15.1, 11.7, 4.0 Hz, 1 H), 2.14 (dd, J = 11.6, 4.8 Hz, 1 H), 2.08 (dd, J = 13.3, 5.1 Hz, 1 H), 1.91 (dd, J = 13.3, 6.3 Hz, 1 H), 1.87–1.81 (m, 2 H), 1.72 (dd, J = 14.6, 10.6 Hz, 1 H), 1.68 (dt, J = 6.3, 5.0 Hz, 1 H), 1.21 (s, 3 H), 1.11 (s, 3 H), 0.91 (s, 9 H), 0.90 (s, 9 H), 0.13 (s, 3 H), 0.10 (s, 3 H), 0.06 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.1, 146.5, 138.6, 131.6, 129.3, 128.5, 127.79, 127.65, 113.8, 111.2, 86.0, 83.3, 82.6, 74.4, 73.7, 73.3, 72.7, 72.1, 68.8, 64.7, 55.4, 45.2, 44.1, 39.0, 28.1, 27.9, 26.1, 25.9, 22.4, 18.3, 18.0, –4.1, –5.1, –5.21, –5.23 ppm. HRMS (ESI$^+$): calcd. for $C_{43}H_{72}O_8NaSi_2$ 795.4663; found 795.4668 (Δ = 0.6 ppm).

((*S*)-2-((2*R*,4*R*,5*R*)-5-((1*S*,3*R*,5*S*)-1-[(Benzyloxy)methyl]-5-methyl-2,8-dioxabicyclo[3.2.1]octan-3-yl)-4-[(*tert*-butyldimethylsilyl)oxy]-2-methyltetrahydrofuran-2-yl)-2-((4-methoxybenzyl)oxy)-ethoxy)(*tert*-butyl)dimethylsilane (39): A three-necked flask was charged with diol **38** (0.29 g, 0.38 mmol, 100 mol-%) in CH_2Cl_2 (5 mL) and cooled to –78 °C. Ozone was bubbled through the reaction mixture for 30 s or until a blue color emerged. Oxygen was then allowed to pass through the mixture for 3 min. Dimethyl sulfide (0.55 mL, 7.5 mmol, 2000 mol-%) was added and the reaction mixture was warmed to room temp. and stirred for 3 h. Concentration and purification of the residue by flash chromatography (initially 7% EtOAc/hexanes, finally 10% EtOAc/hexanes) afforded the desired product **39** as a colorless oil (0.19 g, 75%). R_f = 0.45 (30% EtOAc/hexanes). $[\alpha]_D$ = –6.2 (c = 1.00, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 2954, 2930, 2884, 2857, 1515, 1250, 1103, 1072, 836, 776 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.30 (m, 5 H), 7.29–7.25 (m, 2 H), 6.88–6.84 (m, 2 H), 4.92 (d, J = 11.2 Hz, 1 H), 4.62 (dd^{AB}, $|J_{AB}|$ = 12.3 Hz, $\Delta\nu$ = 33.5 Hz, 2 H), 4.52 (d, J = 11.2 Hz, 1 H), 4.29 (dd, J = 4.2, 3.2 Hz, 1 H), 4.14 (td, J = 9.5, 3.9 Hz, 1 H), 4.07 (dd, J = 10.6, 0.9 Hz, 1 H), 3.80 (s, 3 H), 3.75 (dd, J = 10.7, 7.6 Hz, 1 H), 3.69 (dd, J = 7.5, 0.8 Hz, 1 H), 3.62 (dd, J = 8.0, 3.1 Hz, 1 H), 3.53 (dd^{AB}, $|J_{AB}|$ = 10.7 Hz, $\Delta\nu$ = 21.4 Hz, 2 H), 2.24 (d, J = 14.0 Hz, 1 H), 2.21 (td, J = 13.1, 4.3 Hz, 1 H), 2.01 (ddd, J = 13.5, 9.0, 4.7 Hz, 1 H), 1.86 (ddd, J = 12.4, 8.9, 3.9 Hz, 1 H), 1.77–1.65 (m, 3 H), 1.60 (dd, J = 13.1, 4.0 Hz, 1 H), 1.39 (s, 3 H), 1.09 (s, 3 H), 0.92 (s, 9 H), 0.90 (s, 9 H), 0.08 (s, 3 H), 0.07 (s, 3 H), 0.04 (s, 3 H), –0.02 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0, 138.5, 132.1, 129.0, 128.4, 127.9, 127.6, 113.7, 106.4, 86.2, 85.2, 83.2, 81.1, 73.8, 73.5, 72.5, 71.9, 66.8, 65.4, 55.4, 46.5, 40.7, 34.4, 31.8, 26.3, 26.14, 26.11, 21.9, 18.4, 18.1, –4.3, –5.02, –5.05, –5.2 ppm. HRMS (ESI$^+$): calcd. for $C_{42}H_{68}O_8NaSi_2$ 779.4350; found 779.4341 (Δ = 1.2 ppm).

(*S*)-2-((2*R*,4*R*,5*R*)-5-((1*S*,3*R*,5*S*)-1-[(Benzyloxy)methyl]-5-methyl-2,8-dioxabicyclo[3.2.1]octan-3-yl)-4-[(*tert*-butyldimethylsilyl)oxy]-2-methyltetrahydrofuran-2-yl)-2-[(4-methoxybenzyl)oxy]ethanol (40): To a solution of compound **39** (0.12 g, 0.16 mmol, 100 mol-%) in THF (5.0 mL) was added, dropwise, HF·pyridine (70% HF, 0.20 mL, 0.22 g, 7.8 mmol, 5000 mol-%) at room temp. The reaction mixture was stirred at room temp. for 30 min then satd. aq. $NaHCO_3$ (5 mL) was added dropwise. The layers were separated and the organic layer was washed with satd. aq. $NaHCO_3$ (5 mL), dried with Na_2SO_4, and concentrated. Purification of the residue by flash chromatography (40% EtOAc/hexanes) afforded alcohol **40** as a colorless oil (90 mg, 89%). R_f = 0.10 (30% EtOAc/hexanes). $[\alpha]_D$ = +0.7 (c = 1.00, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3513, 2953, 2929, 2883, 2857, 1514, 1249, 1100, 1066, 834 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.26 (m, 5 H), 7.25–7.22 (m, 2 H), 6.89–6.85 (m, 2 H), 4.62 (dd^{AB}, $|J_{AB}|$ = 12.3 Hz, $\Delta\nu$ = 30.1 Hz, 2 H), 4.56 (dd^{AB}, $|J_{AB}|$ = 11.2 Hz, $\Delta\nu$ = 24.1 Hz, 2 H), 4.33 (dd, J = 4.4, 3.1 Hz, 1 H), 4.14 (ddd, J = 11.5, 7.9, 3.7 Hz, 1 H), 3.83 (dd, J = 11.3, 7.1 Hz, 1 H), 3.80 (s, 3 H), 3.71 (dd, J = 11.0, 4.0 Hz, 1 H), 3.65 (dd, J = 6.4, 4.7 Hz, 1 H), 3.63 (dd, J = 8.1, 2.9 Hz, 1 H), 3.52 (dd^{AB}, $|J_{AB}|$ = 10.7 Hz, $\Delta\nu$ = 20.7 Hz, 2 H), 2.67 (br. s, 1 H), 2.20 (td, J = 12.9, 4.2 Hz, 1 H), 2.15 (d, J = 14.1 Hz, 1 H), 1.99 (ddd, J = 13.5, 9.1, 4.7 Hz, 1 H), 1.88 (dd, J = 14.0, 5.2 Hz, 1 H), 1.88–1.84 (m, 1 H), 1.74–1.66 (m, 2 H), 1.54 (dd, J = 13.1, 3.9 Hz, 1 H), 1.37 (s, 3 H), 1.20 (s, 3 H), 0.90 (s, 9 H), 0.03 (s, 3 H), –0.01 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3, 138.4, 130.8, 129.2, 128.4, 127.9, 127.6, 114.0, 106.4, 85.2, 85.0, 82.8, 81.0, 73.8, 72.8, 72.2, 71.9, 66.3, 61.6, 55.4, 46.9, 40.7, 34.2, 31.8, 26.3, 26.1, 21.7, 18.1, –4.4, –5.0 ppm. HRMS (ESI$^+$): calcd. for $C_{36}H_{54}O_8NaSi$ 665.3486; found 665.3482 (Δ = 0.6 ppm).

(*R*)-2-((2*R*,4*R*,5*R*)-5-((1*S*,3*R*,5*S*)-1-[(Benzyloxy)methyl]-5-methyl-2,8-dioxabicyclo[3.2.1]octan-3-yl)-4-[(*tert*-butyldimethylsilyl)oxy]-2-methyltetrahydrofuran-2-yl)-2-[(4-methoxybenzyl)oxy]acetaldehyde (41): To a solution of oxalyl chloride (12.5 μL, 0.14 mmol, 120 mol-%) in CH_2Cl_2 (0.6 mL), was added DMSO (21 μL, 0.3 mmol, 250 mol-%) at –50 °C. After stirring for 5 min, a solution of alcohol **40** (77 mg, 0.12 mmol, 100 mol-%) in CH_2Cl_2 (1.2 mL) was added. The resulting mixture was stirred for 20 min keeping the temperature below –40 °C, then triethylamine (75 μL, 0.54 mmol, 450 mol-%) was added dropwise. The reaction mixture was warmed to room temp. and stirred for 10 min. H_2O (3 mL) was added and the separated organic phase was washed with brine (5 mL), dried with Na_2SO_4, and concentrated. Purification of the residue by flash chromatography (10% EtOAc/hexanes) afforded the desired product **41** as a colorless oil (66 mg, 86%). R_f = 0.38 (30% EtOAc/hexanes). $[\alpha]_D$ = –29.5 (c = 1.00, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 2954, 2930, 2882, 2857, 1733, 1515, 1250, 1109, 1066, 834 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.84 (d, J = 1.1 Hz, 1 H), 7.34–7.29 (m, 5 H), 7.29–7.26 (m, 2 H), 6.89–6.85 (m, 2 H), 4.67 (d, J = 10.9 Hz, 1 H), 4.62 (dd^{AB}, $|J_{AB}|$ = 12.3, $\Delta\nu$ = 31.4 Hz, 2 H), 4.35 (dd, J = 4.4, 3.1 Hz, 1 H), 4.31 (d, J = 10.9 Hz, 1 H), 4.18 (ddd, J = 10.9, 8.2, 4.1 Hz, 1 H), 4.10 (d, J = 1.0 Hz, 1 H), 3.80 (s, 3 H), 3.69 (dd, J = 8.2, 2.9 Hz, 1 H), 3.53 (dd^{AB}, $|J_{AB}|$ = 10.7, $\Delta\nu$ = 19.6 Hz, 2 H,), 2.24 (d, J = 14.0 Hz, 1 H), 2.22 (td, J = 13.3, 4.4 Hz, 1 H), 2.02 (ddd, J = 13.6, 9.2, 4.5 Hz, 1 H), 1.91 (ddd, J = 12.5, 9.0, 3.8 Hz, 1 H), 1.84 (dd, J = 14.1, 4.8 Hz, 1 H), 1.74 (dd, J = 13.3, 5.7 Hz, 1 H), 1.67 (d, J = 11.4 Hz, 1 H), 1.61 (dd, J = 13.1, 4.2 Hz, 1 H), 1.39 (s, 3 H), 1.20 (s, 3 H), 0.90 (s, 9 H), 0.04 (s, 3 H), 0.01 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.4, 159.5, 138.4, 130.1, 129.6, 128.4, 127.9, 127.6, 113.9, 106.4, 87.9, 86.1, 83.5, 81.1, 73.8, 72.5, 72.3, 72.0, 66.5, 55.4, 46.6, 40.7, 34.2, 31.8, 26.3, 26.1, 23.2, 18.1, –4.4, –5.0 ppm. HRMS (ESI$^+$): calcd. for $C_{36}H_{52}O_8NaSi$ 663.3329; found 663.3334 (Δ = 0.8 ppm).

(1*S*,2*R*)-1-((2*R*,4*R*,5*R*)-5-((1*S*,3*R*,5*S*)-1-[(Benzyloxy)methyl]-5-methyl-2,8-dioxabicyclo[3.2.1]octan-3-yl)-4-[(*tert*-butyldimethylsilyl)oxy]-2-methyltetrahydrofuran-2-yl)-1-[(4-methoxybenzyl)oxy]-but-3-en-2-ol (42): To a solution of aldehyde **41** (38 mg, 0.06 mmol, 100 mol-%) in THF (1.2 mL), was added vinylmagnesium bromide (1 M in THF, 0.18 mL, 0.18 mmol, 300 mol-%) at –78 °C. The reaction mixture was stirred at –78 °C for 20 min and then quenched with satd. aq. NH_4Cl (0.5 mL). The reaction mixture was warmed to room temp., H_2O (1 mL) was added to dissolve the precipitate, and the layers were separated. The organic phase was dried with Na_2SO_4 and concentrated. Purification of the residue by flash chromatography (20% EtOAc/hexanes) afforded allylic alcohol **42** as a colorless oil (38 mg, 97%, ca. 20:1 *dr*). R_f = 0.42 (40% EtOAc/hexanes). $[\alpha]_D$ = +5.2 (c = 1.00, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3523, 2954, 2930, 2883, 2857, 1515, 1250, 1102, 1072 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.26 (m, 5 H), 7.25–7.22 (m, 2 H), 6.89–6.86 (m, 2 H), 6.02 (ddd, J = 17.2, 10.6, 4.5 Hz, 1 H), 5.36 (dt, J = 17.2, 1.8 Hz, 1 H), 5.14 (dt, J = 10.6, 1.8 Hz, 1 H), 4.62 (dd^{AB}, $|J_{AB}|$ = 12.3 Hz, $\Delta\nu$ = 31.2 Hz, 2 H), 4.58 (dd^{AB}, $|J_{AB}|$ =

10.9, $\Delta\nu$ = 36.3 Hz, 2 H), 4.50 (br. s, 1 H), 4.33 (dd, J = 4.2, 3.2 Hz, 1 H), 4.12 (ddd, J = 11.4, 7.9, 3.7 Hz, 1 H), 3.80 (s, 3 H), 3.68 (d, J = 2.0 Hz, 1 H), 3.63 (dd, J = 8.1, 2.9 Hz, 1 H), 3.53 (dd^{AB}, $|J_{AB}|$ = 10.7 Hz, $\Delta\nu$ = 20.3 Hz, 2 H,), 2.87 (d, J = 5.4 Hz, 1 H), 2.21 (td, J = 13.2, 4.3 Hz, 1 H), 2.12 (d, J = 13.9 Hz, 1 H), 2.00 (ddd, J = 13.6, 9.1, 4.8 Hz, 1 H), 1.90–1.84 (m, 1 H), 1.85 (dd, J = 13.8, 5.0 Hz, 1 H), 1.75–1.67 (m, 2 H), 1.59 (dd, J = 13.2, 4.0 Hz, 1 H), 1.38 (s, 3 H), 1.25 (s, 3 H), 0.90 (s, 9 H), 0.04 (s, 3 H), –0.004 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.4, 141.6, 138.5, 130.5, 129.3, 128.4, 127.9, 127.6, 113.9, 113.7, 106.4, 85.0, 84.8, 84.4, 81.1, 74.6, 73.8, 72.3, 72.0, 70.3, 66.5, 55.4, 47.1, 40.8, 34.3, 31.8, 26.3, 26.1, 22.9, 18.1, –4.3, –5.1 ppm. HRMS (ESI^+): calcd. for $C_{38}H_{56}O_8NaSi$ 691.3642; found 691.3638 (Δ = 0.6 ppm).

General Method for Nucleophilic Addition with Aldehydes 50 or 51: To a stirred solution of aldehyde **50** or **51** (50 mg) in solvent (2 mL) at –78 °C, was added an excess of the organometallic reagent (150–200 mol-%). After the addition was complete, the reaction mixture was warmed slowly to the indicated temperature. The reactions were quenched by addition of satd. aq. NH_4Cl (2 mL) and the organic phase was separated. The aqueous phase was extracted with Et_2O (2 × 2 mL) and the combined organic layers were washed with brine (2 mL), dried with Na_2SO_4, and concentrated in vacuo. The residue was analyzed by ^{1}H NMR spectroscopy. If necessary, the isomers were separated by chromatography and converted into the corresponding PMP acetals (see the Supporting Information for details).

Supporting Information (see footnote on the first page of this article): Experimental details for the interconversion of **29** and **30**, syntheses of **16** as well as model compounds **50** and **51**, details on the assignment of relative stereochemistry, and copies of ^{1}H and ^{13}C NMR spectra of new compounds.

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