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Mechanistic and Computational Studies of Exocyclic Stereocontrol in the Synthesis of Bryostatin-like *cis*-2,6-Disubstituted-4-Alkylidene Tetrahydropyrans by Prins Cyclization

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Abstract

The Prins cyclization of *syn*- β -hydroxy allylsilanes and aldehydes gives *cis*-2,6-disubstituted 4-alkylidene tetrahydropyrans as sole products in excellent yields regardless of the aldehyde (R'') or *syn*- β -hydroxy allylsilane substituent (R') used. By reversing the R'' and R' groups, complementary exocyclic stereocontrol can be achieved. When the *anti*- β -hydroxy allylsilanes are used, the Prins cyclization gives predominantly *cis*-2,6-disubstituted 4-alkylidene tetrahydropyrans, now with the opposite olefin geometry in excellent yield. The proposed reaction mechanism and the observed stereoselectivity for these processes are supported by DFT calculations.

Introduction

Bryostatin 1 is a marine-derived macrolactone that has justifiably attracted considerable interest due to its novel structure and its initially observed antitumor activity.^{1,2} It has since been found to exhibit activity in animal models of cognitive dysfunction pertinent to treatments for Alzheimer's disease³ and in first-in-class strategies aimed at the eradication of HIV/AIDS⁴. Over 25 years ago, we initiated the first studies aimed at identifying the structural features of the bryostatin family of natural products (Figure 1) that contribute to their novel biological activities.⁵ Anticipating then the challenges that would attend a practical synthesis of the natural product as well as the potential need for better leads, the purpose of our program was to use structure-based pharmacophoric hypotheses to design simpler but potentially superior functional analogs that could be synthetically accessed in a step economical fashion.⁶ In 1998, we reported the first of these designed molecules which proved to be comparable to bryostatin 1 in binding affinity to protein kinase C (PKC), a putative target mediating its activity.⁷ Subsequently, second generation analogs were prepared that were more potent than bryostatin 1 itself in binding to PKC.⁸ The syntheses of these analogs were approximately 40–50 steps shorter than the reported syntheses of the natural bryostatins at the time,⁹ illustrating an advantage of this function-oriented synthesis

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DEDICATION: This article is dedicated to the memory of Professor Robert E. Ireland whose inspiration continues.

Supporting Information Available.

¹H and ¹³C NMR spectra of all new compounds. Additional details on computations, including coordinate and energies for computed structures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

strategy.¹⁰ Subsequently, over 100 designed analogs have been prepared in our studies with 35 exhibiting PKC affinities in the low nanomolar to picomolar range, i.e., comparable to or better than bryostatin 1.^{2b} Our lead, designed analogs exhibit potent functional activity in cellular studies related to Alzheimer's disease,^{3c} HIV/AIDS eradication,¹¹ and cancer cell apoptosis¹² and in animal models of cancer involving suppression of MYC-oncogene induced lymphoma.¹³ Further underscoring the potential value of these designed agents, patient accrual in a recent bryostatin lymphoma clinical trial was terminated early "given the more potent bryostatin analogs in development"¹⁴ in our laboratory.

One of our earlier bryostatin pharmacophore hypotheses was that the lactone carbonyl, C19 hydroxyl and C26 hydroxyl groups contact the protein target (PKC) and thus influence binding affinity and that the A- and B-rings serve to control the correct spatial array of these pharmacophoric contacts.⁵ This analysis suggests that simplifications could be made in the A- and B-rings of bryostatin without significantly changing affinity and it thus opens this approach up to synthesis-informed design of A- and B-ring simplified systems. Toward this end, in the design of our first generation analogs, we took the liberty of removing all unnecessary A- and B-ring appendages and replaced the C14 carbon of the B-ring pyran with an oxygen atom to allow for macrocycle formation through a then unexplored macrotransacetalization in which an oxo-carbenium ion intermediate is trapped by a nucleophilic C14 hydroxyl group to form a B-ring dioxane (Figure 2). This strategy allowed step economical access to analogs with bryostatin-like potency.^{7,8,15} Recognizing that the nucleophilic oxygen in this strategy could be replaced by a nucleophilic C14 carbon of a C13–C14 alkene, we next explored whether a Prins-driven macrocyclization could be used in place of our macrotransacetalization to access macrocycles now with a pyranyl B-ring.¹⁶ The Marko Group reported impressive early examples of an *intermolecular* allyl silane driven Prins reaction (a.k.a. silyl modified Sakurai reaction) for pyran synthesis¹⁷ and this *intermolecular* process was later used effectively in the Keck Group approach to bryostatin analogs.¹⁸ This intermolecular process has also been creatively deployed in syntheses of other natural systems.^{9e,9g,19} Our own work provided the first investigation of whether this process could be used *intramolecularly* to form macrocycles incorporating pyran rings. This novel Prins-driven macrocyclization strategy proved highly effective and was used in the preparation of bryostatin analogs (bryologs)^{11,20} and bryostatin 9.^{9f} Concurrent studies from several laboratories provided additional and impressive examples of the utility of this Prins-driven macrocyclization in accessing a wide range of natural products with pyranyl subunits.²¹

In the course of the above studies it became apparent that while much impressive effort has gone into studies on various aspects of the Prins reaction,²² little is known about its use in controlling exocyclic alkylidene stereochemistry. This synthetic problem is encountered in exocyclic unsaturated esters associated with the B- and C-rings of natural bryostatins, some bryostatin analogs and other natural products such as exiguolide (Figure 1). The bryostatin B-ring problem is especially challenging as the atoms flanking the C13 exocyclic alkene are virtually identical, thus providing no steric or electronic bias to control alkene geometry. Indeed direct olefination of a C13 carbonyl of a pyranone proceeds with no selectivity.²⁰ Current approaches to this problem preset the alkene geometry before formation of the pyran ring²³ or use reagent controlled strategies to set the geometry after pyran formation.²⁴ A third general approach to this problem is to set alkene geometry during the course of pyran formation,²⁵ a result that could be realized, for example, if the stereogenic center of an allylic silane²⁶ were to control alkene geometry during a silyl-terminated Prins cyclization (Figure 3). More specifically, if the silyl-terminated Prins cyclization were to proceed by capture of a *trans*-oxocarbenium ion exclusively through either an *anti*-S_E' or *syn*-S_E' process,²⁷ then control of the exocyclic double bond would be achieved. If these pathways compete or if both *cis*- and *trans*-oxocarbenium ions participate, mixtures of *E*- and *Z*-

alkenes would be obtained. We report herein synthetic, mechanistic and computational studies on this unexplored strategy.

Results and Discussion

To evaluate this concept, we prepared the *syn*- and *anti*- β -hydroxy allylsilanes **9–12** through a conventional but scalable route as given in Scheme 1. Epoxidation of **1** with *m*-CPBA²⁸ followed by treatment with allyl cuprate gave racemic hydroxyl silane **3**.²⁹ Alcohol **3** was protected with TBSCl and then treated with O₃ followed by Me₂S to give aldehyde **4** in 85% yield in 2 steps. Introduction of an α -methylene group with formaldehyde³⁰ followed by reduction gave alcohol **6**, which was converted to the allylic bromide **8** by mesylation, bromide displacement and deprotection. Allylic zinc bromide was generated in situ from allylic bromide **8** and zinc powder and then reacted individually with four different aldehydes to provide after protection *syn*- and *anti*-diastereomers **9–12**. These allylations proceeded with little stereoselectivity as desired because both diastereomers were required in this study. The aldehydes were selected on the basis of anticipated synthetic situations involving this process and include conjugated and non-conjugated aldehydes as well as straight chain and branched chain aldehydes. The diastereomers **9–12** were separated using silica gel chromatography. The stereochemistry of *syn*- and *anti*-**12** was determined by ¹H NMR and by transformation to the cyclic derivatives as shown in Scheme 2. For the determination of the stereochemistry of **12**, the mixture of diastereomers of 1,5-diol **13** was separated using silica gel chromatography to give **13a** and **13b**. Individual tosylation of **13a** and **13b** proceeded with a 1,2-silicon shift to give tetrahydrofurans **14a** and **14b**, respectively. The stereochemistry of each compound was confirmed by NOE experiments, indicating that **14a** has a *cis* configuration and **14b** has a *trans* configuration. This indicates that **13a** has the *syn*-configuration and **13b** has the *anti*-configuration. Finally, to confirm the stereochemistry of **12**, **13a** and **13b** were converted to *syn*-**12** and *anti*-**12**, respectively. The relative stereochemistry of the other β -hydroxy allylsilanes **9–11** was determined by comparison of their ¹H NMR spectra with that of **12**.

Our initial studies focused on the Prins cyclization of the *syn*- β -hydroxy allylsilanes. Prins cyclization reaction using *syn*-**9** and propionaldehyde proceeded smoothly with TMSOTf in Et₂O at –78 °C to give within 1 h **15a** as the sole product in excellent yield (Table 1, entry 1). No other diastereomers were detected. The *cis*-disposition of the C2 and C6 substituents and the *E* geometry of the exocyclic alkene in **15a** were established by NOE experiments (Figure 4). The results for several additional examples are provided in Table 1. Branched (entries 2 and 3), sterically encumbered (entry 3), aryl conjugated (entry 4) and styryl conjugated (entry 5) aldehydes behaved similarly upon reaction with *syn*-**9**, providing exclusively *cis*-pyran products **15b–e** with a single exocyclic geometry in high yields and with high selectivities. Even pivalaldehyde reacted smoothly albeit somewhat less rapidly to give the cyclized product (entry 3).

We next examined the effect of variations in the substituents of the *syn*- β -hydroxy allylsilanes with a fixed aldehyde, 3-phenylpropionaldehyde (Table 2). Normal alkyl (*syn*-**10**), branched (*syn*-**11**), and aryl (*syn*-**12**) substituted systems, each reacted to give the cyclized products in high yields and with high selectivities. The comparative results of Tables 1 and 2 show that one can form either **15a**, **b**, and **d** or **16a**, **b**, and **d** in a highly selective fashion. This strategy thus allows for the highly selective synthesis of *cis*-2,6-disubstituted pyrans with either an *E*- or *Z*-exocyclic alkene by the judicious selection of starting materials.

Our focus turned next to the Prins cyclization using *anti*- β -hydroxy allylsilanes. As before, the Prins cyclization reaction using *anti*-**9** and propionaldehyde with TMSOTf at –78 °C

was examined first (Table 3, entry 1). The reaction proceeded smoothly and in high yield but now gave two diastereomers in a 16:84 ratio favoring **16a** over **15a**. The lower diastereoselectivity obtained with the *anti* substrate relative to the *syn* substrate in this process could arise from epimerization of the product under the reaction conditions. However, the possibility of epimerization was discounted by two experiments. When product **16a** was treated with TMSOTf, no isomerization was observed. Moreover, when the reaction was monitored by ^1H NMR at 10, 30, and 60 min, the product ratio remained constant. The results obtained with other aldehydes are provided in Table 3. In general, the reactions proceeded in very good to high yields for all aldehydes. The reactions were somewhat slower for *anti*-**9** and branched aldehydes (entries 2 and 3) than for *syn*-**9** with the same aldehydes. All reactions provided **16** as main product with **15** as minor product, i.e., the stereochemical complement of the selectivity observed when *syn*-**9** was used (Table 1). When pivalaldehyde was used, the selectivity of olefin geometry was increased (entry 3). Higher selectivity was also observed when aromatic aldehyde and conjugated aldehyde were used (entries 4 and 5). When benzaldehyde was used, only one diastereomer (**16d**) was obtained.

We next examined the effect of variations in the substituents of the *anti*- β -hydroxy allylsilanes with a common aldehyde (Table 4). The ethyl and cyclohexyl substituted β -hydroxy allylsilanes reacted in good yields but with moderate selectivities (Table 4, entries 1 and 2) while the phenyl substituted system gave better selectivity but a lower yield (entry 3). In all cases, only the *cis*-2,6-disubstituted products are obtained. However, in contrast to the reactions using *syn*- β -hydroxy allylsilanes, the yields and selectivities for the reaction of *anti*- β -hydroxy allylsilanes are more sensitive to coreactant aldehydes and substituents.

To probe the mechanism of this reaction and the origin of observed stereoselectivity, density functional theory (DFT) calculations were carried out for model *syn*- β -hydroxy allylsilane **I** (Figure 5) and its *anti*- β -hydroxy allylsilane analogue (Figure 6b, R=R'=Me). It was found that cyclization and loss of the silyl group occur in separate steps, although the barriers for these steps are predicted to be small. In the first step, there are two possible cyclization modes (*anti* and *syn*; *syn* is defined here as the silicon group being oriented toward the forming C–C bond in the transition state structure) that take advantage of hyperconjugation between the C–Si σ -bond and the C=C π -bond. The transition state structures for cyclization, *anti*-TS1 and *syn*-TS1 are quite early (not surprising, given the exothermicity/exergonicity of the cyclizations), with the motion associated with their imaginary frequencies corresponding primarily to rotation around the internal O–C σ -bond. This rotation brings the C=C and C=O π -bonds into proximity, and their coupling occurs without an additional barrier (note that chair-like structures are encountered along these reaction coordinates once the initial conformational change is complete).³¹ Interconversion of **III** and **IV** is associated with a comparatively large barrier (through a transition state structure for which β -silyl stabilization is lost), suggesting that stereochemical scrambling at this stage is unlikely. The loss of the silyl group in the second step, modeled here using an attacking solvent molecule (dimethyl ether for simplicity) is also predicted to be facile, but the inherent preference for an *anti* silyl group is maintained in the corresponding transition state structures (*anti*- and *syn*-TS2) and the minima preceding them (Figure 5, bottom).

Given these results, it appears that the stereoselectivity of the Prins cyclization is determined by the energy difference between the transition state structures for cyclization (*anti*-TS1 and *syn*-TS1), although the preference for an *anti* silyl group is maintained throughout the reaction. For the *syn*- β -hydroxy allylsilane model **I**, the predicted difference in energy between *anti*-TS1 and *syn*-TS1 is 1.6 kcal mol⁻¹, favoring the transition state structure leading to the experimentally observed product. When the analogous *anti*- β -hydroxy allylsilane model with MeCHO (Figure 6b, R=R'=R''=Me) is used, the predicted energy

difference between the *anti* and *syn* transition state structures for cyclization is only 0.5 kcal mol⁻¹, which is consistent with the observation of decreased selectivity for *anti*- β -hydroxy allylsilane reactants.

The selectivity for these Prins cyclizations can be rationalized through a combination of simple steric and electronic effects. For *syn*- β -hydroxy allylsilanes (Figure 6a), cyclization occurs through chair-like structures in which the alkyl substituent occupies an equatorial position. Secondly, the SiR₃ group aligns itself perpendicular to the C=C π -bond to maximize the incipient β -silyl stabilization. The *anti* arrangement is preferred, which places the alkyl group α to the silyl on the side of the molecule where the new σ -bond forms. The situation is the same for *anti*- β -hydroxy allylsilanes (Figure 6b), except that the α -alkyl group now resides on the side of the molecule away from the forming bond. This environment is more sterically crowded, resulting in a diminution of the preferences for an *anti* silyl group: with C α H₂ rather than C α H(CH₃) the preference for *anti* is predicted to be 2.5 kcal mol⁻¹ which is reduced upon replacing one or the other hydrogen with a methyl group. Truncation of the *anti* and *syn* cyclization transition state structures for the system with C α H₂ to Ph(CH₃)₂SiCH₂vinyl groups and recalculation of their energies (without optimization of their geometries) indicated that the preference for the *anti* arrangement is almost entirely localized to this structural unit (i.e., the *anti* preference for the truncated system the *anti* preference for the full system). It appears that in order to reduce steric clashes in the *syn* transition state structure, the Si-C α -C β =C dihedral angle deviates from the 90° (this dihedral angle is predicted to be 91° in the *anti* transition state structure, but -67° in the *syn* transition state structure), leading to a reduction in hyperconjugation between the C-Si σ -bond and the C=C π -bond. This diminished interaction is manifested in a slight reduction of the Si-C α bond length (by 0.1 Å), a slight elongation of the C α -C β bond length (by 0.05 Å) and an opening of the Si-C α -C β angle (by 3°).³²

Conclusion

In conclusion, we have shown that the silyl-terminated Prins cyclization can be used to control both endocyclic and exocyclic stereochemistry, thus providing selective access to *cis*-2,6-disubstituted tetrahydropyrans with either a *Z*- or *E*-4-alkylidene group. The influence of the relative stereochemistry of silicon and oxygen-bearing chiral centers of the β -hydroxy allylsilanes on the product geometry in Prins cyclization has been established experimentally and supported computationally. When the *syn*- β -hydroxy allylsilanes were used, the Prins cyclization gave *cis*-2,6-disubstituted 4-alkylidene tetrahydropyrans as the sole products in excellent yields. The olefin geometry is set with high selectivity regardless of the aldehydes and the substituents of the *syn*- β -hydroxy allylsilanes used. When the *anti*- β -hydroxy allylsilanes were used, the Prins cyclization gave predominantly *cis*-2,6-disubstituted 4-alkylidene tetrahydropyrans, now with the opposite olefin geometry in excellent yield. The proposed reaction mechanism and the observed stereoselectivity for this reaction are consistent with results from the DFT calculations. This strategy can provide stereoselectively both *E* and *Z* *cis*-2,6-disubstituted 4-alkylidene tetrahydropyrans as required to access natural bryostatins and their structural and functional analogs as well as other pyranyl targets.

Experimental Section

General procedures

All reactions were run under a N₂ atmosphere in flame or oven dried glassware. Reactions were stirred using Teflon-coated magnetic stirrer bars. Reactions were monitored using thin layer silica gel chromatography (TLC) using 0.25 mm silica gel 60F plates with fluorescent indicator. Plates were visualized by treatment with UV, acidic *p*-anisaldehyde stain, KMnO₄

stain with gentle heating. Products were purified by silica gel (230–400 mesh) column chromatography using the solvent systems indicated. When necessary, solvents and reagents were purified before use. THF was distilled from sodium benzophenone ketyl under N₂. CH₂Cl₂, Et₂O and toluene were passed through an alumina drying column using N₂ pressure. Et₃N was distilled from CaH₂ under N₂. All other reagents were purchased from commercial supplies and were used as received without additional purification. NMR spectra were measured on magnetic resonance spectrometers (¹H at 500, 400 MHz, ¹³C at 125, 100 MHz), as noted. ¹H chemical shifts are reported relative to the residual solvent peak (chloroform = 7.26 ppm; benzene = 7.15 ppm) as follows: chemical shift (δ), (multiplicity (s = singlet, d = doublet, t = triplet, br = broad), coupling constant(s) in Hz, integration). ¹³C chemical shifts are reported relative to the residual deuterated solvent ¹³C signals (CDCl₃ = 77.1, C₆D₆ = 128.0 ppm). Infrared spectra were recorded on a Fourier transform spectrometer (FTIR) and are reported in wavenumbers (cm⁻¹). High resolution mass spectra were recorded on a hybrid quadrupole time-of-flight (Q-Tof) LC/MS instrument.

2

²⁸ ¹H NMR (400 MHz, CDCl₃): δ = 7.59–7.53 (m, 2H), 7.41–7.33 (m, 3H), 2.93 (t, *J* = 5.6 Hz, 1H), 2.56 (dd, *J* = 5.6, 4.0 Hz, 1H), 2.39 (dd, *J* = 5.2, 4.0 Hz, 1H), 0.36 (s, 3H), 0.31 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ = 136.0, 134.0, 129.6, 128.0, 44.7, 43.6, –5.2, –5.5. IR (thin film): 3047, 2959, 1428, 1315, 1250, 1232, 1117 cm⁻¹.

3

²⁹ ¹H NMR (400 MHz, CDCl₃): δ = 7.56–7.50 (m, 2H), 7.39–7.34 (m, 3H), 5.90–5.78 (m, 1H), 5.08–5.02 (m, 1H), 5.01–4.95 (m, 1H), 3.79 (ddd, *J* = 10.8, 6.0, 4.4 Hz, 1H), 3.69 (ddd, *J* = 10.8, 7.2, 5.2 Hz, 1H), 2.36–2.27 (m, 1H), 2.22–2.10 (m, 1H), 1.42 (dd, *J* = 6.0, 5.2 Hz, 1H), 1.29–1.21 (m, 1H), 0.35 (s, 6H). ¹³C NMR (100 MHz, CDCl₃): δ = 139.5, 138.0, 133.9, 129.2, 127.9, 115.5, 63.8, 32.3, 30.2, –3.6, –3.8. IR (thin film): 3369, 3070, 2956, 2903, 1638, 1427, 1250, 1156, 1111 cm⁻¹.

4

To a solution of **3** (4.65 g, 21.1 mmol) in DMF (50 mL) was added TBSCl (3.80 g, 25.1 mmol) and imidazole (3.44 g, 50.6 mmol). The mixture was stirred at rt for 1 h and diluted with water and Et₂O. The separated aqueous phase was extracted with Et₂O, and the combined organic solutions were washed with brine, dried with Na₂SO₄ and concentrated *in vacuo* to give crude TBS ether, which was used in the next step without further purification. The crude TBS ether was dissolved in CH₂Cl₂ (100 mL). The solution was cooled to –78°C and treated with ozone until the solution turned light blue. The reaction was quenched at –78°C with dimethyl sulfide (3.10 mL, 42.2 mmol), warmed to rt, stirred for 12 h, and concentrated *in vacuo*. The residual oil was purified by column chromatography (silica gel, 0%→10% EtOAc/pentane) to give **4** (6.05 g, 85% yield in 2 steps) as a colorless oil. *R*_f (pentane/EtOAc 10/1) = 0.63. ¹H NMR (400 MHz, CDCl₃): δ = 9.68 (dd, *J* = 3.2, 1.2 Hz, 1H), 7.53–7.46 (m, 2H), 7.40–7.32 (m, 3H), 3.76 (dd, *J* = 10.0, 4.0 Hz, 1H), 3.58 (dd, *J* = 10.0, 8.0 Hz, 1H), 2.43 (ddd, *J* = 16.8, 10.4, 3.2 Hz, 1H), 2.33 (ddd, *J* = 16.8, 4.0, 1.2 Hz, 1H), 1.82–1.74 (m, 1H), 0.86 (s, 9H), 0.34 (s, 3H), 0.33 (s, 3H), –0.01 (s, 3H), –0.01 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ = 203.5, 137.1, 133.9, 129.4, 128.0, 63.8, 42.4, 26.0, 25.4, 18.3, –3.9, –4.2, –5.50, –5.52. IR (thin film): 3070, 2955, 2857, 2712, 1725, 1471, 1428, 1253, 1094 cm⁻¹. HRMS (ESI+, *m/z*): Calculated for C₁₈H₃₂NaO₂Si₂ [(M+Na)]⁺, 359.1833; found, 359.1833.

5

To a mixture of aqueous formaldehyde solution (37% formaldehyde in water, 1.45 mL, 17.9 mmol) and **4** (6.0 g, 17.9 mmol) in *i*-PrOH (4 mL) were added propionic acid (132 mg, 1.79 mmol) and pyrrolidine (127 mg, 1.79 mmol). The reaction mixture was stirred at 45 °C for 3 h. The reaction was quenched with sat. NaHCO₃ aq. and then extracted with CH₂Cl₂. The combined extracts were washed with brine, dried with Na₂SO₄, and concentrated *in vacuo*. The residual oil was purified by column chromatography (silica gel, 0% → 5% EtOAc/pentane) to give **5** (4.40 g, 70% yield) as a colorless oil. R_f (pentane/EtOAc 10/1) = 0.68. ¹H NMR (400 MHz, C₆D₆): δ = 9.21 (s, 1H), 7.50–7.44 (m, 2H), 7.24–7.12 (m, 3H), 5.85 (s, 1H), 5.38 (s, 1H), 3.77 (dd, *J* = 10.0, 7.6 Hz, 1H), 3.72 (dd, *J* = 10.0, 4.8 Hz, 1H), 2.93 (dd, *J* = 7.2, 4.8 Hz, 1H), 0.89 (s, 9H), 0.29 (s, 3H), 0.27 (s, 3H), –0.06 (s, 3H), –0.07 (s, 3H). ¹³C NMR (100 MHz, C₆D₆): δ = 193.6, 150.8, 137.2, 134.4, 132.1, 129.4, 128.0, 63.8, 31.0, 26.1, 18.4, –3.0, –4.1, –5.39, –5.43. IR (thin film): 3071, 2955, 2857, 1693, 1612, 1471, 1253, 1087 cm^{–1}. HRMS (ESI+, *m/z*): Calculated for C₁₉H₃₂NaO₂Si₂ [(M+Na)]⁺, 371.1833; found, 371.1834.

6

5 (4.40 g, 12.6 mmol) was dissolved in toluene (100 mL). The solution was cooled to –78 °C and DIBAL in toluene (1.0 M, 25.2 mL) was added dropwise. The mixture was stirred at –78 °C for 3 h. After the reaction was quenched with MeOH, sat. Rochelle's salt solution was introduced and the heterogeneous reaction mixture was allowed to rt for 2 h. The separated aqueous phase was extracted with EtOAc, and the combined organic solutions were washed with brine, dried with Na₂SO₄, and concentrated. The residual oil was purified by column chromatography (silica gel, 10% → 20% EtOAc/pentane) to give **6** (4.06 g, 92% yield) as a colorless oil. R_f (pentane/EtOAc 10/1) = 0.18. ¹H NMR (400 MHz, C₆D₆): δ = 7.49–7.43 (m, 2H), 7.21–7.15 (m, 3H), 5.10 (td, *J* = 2.8, 0.8 Hz, 1H), 4.81 (d, *J* = 0.8 Hz, 1H), 3.89–3.78 (m, 4H), 2.06 (dd, *J* = 8.4, 5.2 Hz, 1H), 1.81 (t, *J* = 6.0 Hz, 1H), 0.93 (s, 9H), 0.32 (s, 3H), 0.29 (s, 3H), 0.00 (s, 3H), –0.01 (s, 3H). ¹³C NMR (100 MHz, C₆D₆): δ = 149.7, 138.0, 134.2, 129.4, 128.0, 109.3, 67.4, 65.3, 37.0, 26.1, 18.5, –3.4, –3.8, –5.39, –5.42. IR (thin film): 3367, 3070, 2955, 2856, 1643, 1471, 1253, 1084 cm^{–1}. HRMS (ESI+, *m/z*): Calculated for C₁₉H₃₄NaO₂Si₂ [(M+Na)]⁺, 373.1990; found, 373.1992.

7

To a solution of **6** (4.06 g, 11.6 mmol) and Et₃N (3.51 g, 34.8 mmol) in CH₂Cl₂ (100 mL) was added MsCl (1.98 g, 17.4 mmol) at 0 °C. The mixture was stirred at rt for 2 h and then water was added. The separated aqueous phase was extracted with CH₂Cl₂, and the combined organic solutions were washed with brine, dried with Na₂SO₄ and concentrated *in vacuo* to give crude mesylate, which was used in the next step without further purification. To a solution of crude mesylate in THF (100 mL) was added LiBr (3.03 g, 34.8 mmol) at rt. The mixture was stirred at 60 °C for 2 h. After reaction was cooled to rt and diluted with Et₂O and H₂O. The separated aqueous phase was extracted with Et₂O, and the combined organic solutions were washed with brine, dried with Na₂SO₄, and concentrated. The residual oil was purified by column chromatography (silica gel, 0% → 5% EtOAc/pentane) to give **7** (4.55 g, 95% yield in 2 steps) as a colorless oil. R_f (pentane/EtOAc 10/1) = 0.88. ¹H NMR (400 MHz, C₆D₆): δ = 7.48–7.42 (m, 2H), 7.21–7.15 (m, 3H), 4.96 (d, *J* = 0.8 Hz, 1H), 4.85 (d, *J* = 0.8 Hz, 1H), 3.86 (d, *J* = 6.0 Hz, 2H), 3.55 (dd, *J* = 10.0, 0.8 Hz, 1H), 3.39 (dd, *J* = 10.0, 0.8 Hz, 1H), 2.23 (t, *J* = 6.0 Hz, 1H), 0.95 (s, 9H), 0.33 (s, 3H), 0.32 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H). ¹³C NMR (100 MHz, C₆D₆): δ = 146.5, 138.0, 134.2, 129.4, 128.0, 114.0, 65.7, 39.9, 37.1, 26.1, 18.5, –3.3, –3.6, –5.38, –5.42. IR (thin film): 3070, 2955, 2857, 1627, 1471, 1254, 1208, 1084 cm^{–1}. HRMS (ESI+, *m/z*): Calculated for C₁₉H₃₃BrNaOSi₂ [(M+Na)]⁺, 435.1146; found, 435.1146.

8

To a solution of **7** (2.20 g, 5.34 mmol) in MeOH (50 mL) was added PPTS (134 mg, 0.534 mmol) at rt. The mixture was stirred at rt for 12 h. The reaction was quenched with sat. NaHCO_3 aq. and then diluted with Et_2O and H_2O . The separated aqueous phase was extracted with Et_2O , and the combined organic solutions were washed with brine, dried with Na_2SO_4 , and concentrated. The residual oil was purified by column chromatography (silica gel, 10% $\rightarrow$ 15% EtOAc /pentane) to give **8** (1.54 g, 97% yield) as a colorless oil. R_f (pentane/ EtOAc 10/1) = 0.19. ^1H NMR (400 MHz, C_6D_6): δ = 7.38–7.31 (m, 2H), 7.21–7.12 (m, 3H), 4.92 (t, J = 0.8 Hz, 1H), 4.66 (s, 1H), 3.72–3.62 (m, 2H), 3.49 (dd, J = 10.0, 0.8 Hz, 1H), 3.31 (dd, J = 10.0, 0.8 Hz, 1H), 2.18 (dd, J = 8.4, 6.0 Hz, 1H), 1.25 (brs, 1H), 0.17 (s, 3H), 0.16 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6): δ = 145.3, 137.2, 134.2, 129.5, 128.1, 113.9, 63.5, 39.6, 38.1, –4.1, –4.3. IR (thin film): 3401, 3069, 2957, 2878, 1626, 1427, 1250, 1209, 1112, 1048 cm^{-1} . HRMS (ESI+, m/z): Calculated for $\text{C}_{13}\text{H}_{19}\text{BrNaOSi}[(\text{M}+\text{Na})]^+$, 321.0281; found, 321.0276.

General procedure for β -hydroxy allylsilanes

A mixture of **8** (500 mg, 1.67 mmol), zinc powder (120 mg, 1.84 mmol), and aldehyde (1.84 mmol) in THF–sat. NH_4Cl aq. (9.6 mL–1.6 mL) was stirred for 2 h. After dilution with Et_2O , the separated aqueous phase was extracted with Et_2O , and the combined organic solutions were dried with Na_2SO_4 and concentrated to give crude 1,5-diol. To a solution of crude 1,5-diol in DMF (8 mL) was added TBDPSCl (477 mg, 1.67 mmol) and imidazole (227 mg, 3.34 mmol). The mixture was stirred at rt for 1 h and diluted with Et_2O and H_2O . The separated aqueous phase was extracted with Et_2O , and the combined organic solutions were washed with brine, dried with Na_2SO_4 and concentrated *in vacuo*. The residue was purified by chromatography with EtOAc –pentane to give *syn*- and *anti*- β -hydroxy allylsilane, respectively.

syn-9

A colorless oil. Yield: 405 mg, 41% (in 2 steps). R_f (pentane/ EtOAc 10/1) = 0.56. ^1H NMR (500 MHz, C_6D_6): δ = 7.79–7.73 (m, 4H), 7.30–7.26 (m, 2H), 7.25–7.06 (m, 14H), 5.02 (s, 1H), 4.84 (s, 1H), 4.03 (t, J = 10.5 Hz, 1H), 4.01–3.95 (m, 1H), 3.94 (dd, J = 10.5, 4.0 Hz, 1H), 3.00–2.93 (m, 2H), 2.76 (ddd, J = 14.0, 10.0, 6.5 Hz, 1H), 2.19 (dd, J = 10.5, 4.0 Hz, 1H), 2.05 (dd, J = 13.5, 10.0 Hz, 1H), 1.98–1.87 (m, 2H), 1.73–1.64 (m, 1H), 1.17 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6): δ = 146.2, 143.0, 137.1, 136.02, 135.93, 134.1, 133.63, 133.60, 130.03, 130.02, 129.4, 128.9, 128.6, 128.12, 128.09, 128.0, 125.9, 111.9, 67.3, 65.4, 48.0, 39.3, 39.2, 32.8, 27.0, 19.4, –4.2, –4.8. IR (thin film): 3474, 3071, 2931, 2858, 1632, 1427, 1250, 1112, 1070 cm^{-1} . HRMS (ESI+, m/z): Calculated for $\text{C}_{38}\text{H}_{48}\text{NaO}_2\text{Si}_2[(\text{M}+\text{Na})]^+$, 615.3085; found, 615.3079.

anti-9

A colorless oil. Yield: 346 mg, 35% (in 2 steps). R_f (pentane/ EtOAc 10/1) = 0.51. ^1H NMR (400 MHz, C_6D_6): δ = 7.80–7.70 (m, 4H), 7.31–7.26 (m, 2H), 7.24–7.04 (m, 14H), 4.93 (s, 1H), 4.76 (s, 1H), 4.02–3.94 (m, 2H), 3.92–3.83 (m, 1H), 3.34 (s, 1H), 2.91 (ddd, J = 13.6, 9.6, 5.2 Hz, 1H), 2.75 (ddd, J = 13.6, 9.6, 6.8 Hz, 1H), 2.59–2.51 (m, 1H), 2.12 (dd, J = 13.2, 2.8 Hz, 1H), 1.93 (dd, J = 13.2, 9.6 Hz, 1H), 1.90–1.79 (m, 1H), 1.75–1.63 (m, 1H), 1.17 (s, 9H), 0.13 (s, 3H), 0.10 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6): δ = 147.9, 142.9, 137.1, 136.03, 135.96, 134.2, 133.5, 133.4, 130.1, 130.0, 129.4, 128.9, 128.6, 128.10, 128.06, 128.0, 125.9, 110.7, 72.6, 66.1, 48.2, 41.4, 39.7, 32.4, 26.9, 19.3, –4.0, –5.0. IR (thin film): 3459, 3070, 2931, 2858, 1632, 1427, 1250, 1112, 1071 cm^{-1} . HRMS (ESI+, m/z): Calculated for $\text{C}_{38}\text{H}_{48}\text{NaO}_2\text{Si}_2[(\text{M}+\text{Na})]^+$, 615.3085; found, 615.3082.

syn-10

A colorless oil. Yield: 327 mg, 38% (in 2 steps). R_f (pentane/EtOAc 10/1) = 0.56. ^1H NMR (500 MHz, C_6D_6): δ = 7.79–7.74 (m, 4H), 7.31–7.27 (m, 2H), 7.25–7.08 (m, 9H), 5.03 (s, 1H), 4.84 (s, 1H), 4.04 (t, J = 10.5 Hz, 1H), 3.96 (dd, J = 10.5, 4.0 Hz, 1H), 3.91–3.84 (m, 1H), 2.88 (brs, 1H), 2.23 (dd, J = 10.5, 4.0 Hz, 1H), 2.04 (dd, J = 13.5, 10.0 Hz, 1H), 1.98–1.92 (m, 1H), 1.69–1.58 (m, 1H), 1.50–1.39 (m, 1H), 1.17 (s, 9H), 1.06 (t, J = 7.5 Hz, 3H), 0.14 (s, 3H), 0.11 (s, 3H). ^{13}C NMR (125 MHz, C_6D_6): δ = 146.4, 137.2, 136.0, 135.9, 134.1, 133.7, 133.6, 130.01, 129.99, 129.4, 128.10, 128.07, 128.0, 111.8, 69.3, 65.4, 47.8, 39.4, 30.2, 26.9, 19.4, 10.7, –4.2, –4.8. IR (thin film): 3483, 3071, 2959, 2858, 1631, 1427, 1249, 1112, 1069 cm^{-1} . HRMS (ESI+, m/z): Calculated for $\text{C}_{32}\text{H}_{44}\text{NaO}_2\text{Si}_2$ [(M+Na)] $^+$, 539.2772; found, 539.2761.

anti-10

A colorless oil. Yield: 302 mg, 35% (in 2 steps). R_f (pentane/EtOAc 10/1) = 0.50. ^1H NMR (400 MHz, C_6D_6): δ = 7.82–7.71 (m, 4H), 7.33–7.28 (m, 2H), 7.26–7.09 (m, 9H), 4.99 (s, 1H), 4.79 (s, 1H), 4.01 (t, J = 10.4 Hz, 1H), 3.97 (dd, J = 10.0, 4.8 Hz, 1H), 3.85–3.77 (m, 1H), 3.16 (d, J = 2.4 Hz, 1H), 2.56 (dd, J = 10.0, 4.8 Hz, 1H), 2.17 (dd, J = 13.2, 3.2 Hz, 1H), 1.94 (dd, J = 13.2, 9.6 Hz, 1H), 1.63–1.42 (m, 2H), 1.17 (s, 9H), 1.01 (t, J = 7.6 Hz, 3H), 0.15 (s, 3H), 0.13 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6): δ = 148.1, 137.2, 136.02, 135.96, 134.2, 133.5, 133.4, 130.03, 129.97, 129.4, 128.1, 128.0, 127.9, 110.5, 74.7, 66.0, 47.7, 41.4, 30.7, 26.9, 19.3, 10.4, –3.9, –4.9. IR (thin film): 3466, 3071, 2959, 2859, 1631, 1428, 1250, 1186, 1112, 1064 cm^{-1} . HRMS (ESI+, m/z): Calculated for $\text{C}_{32}\text{H}_{44}\text{NaO}_2\text{Si}_2$ [(M+Na)] $^+$, 539.2772; found, 539.2772.

syn-11

A colorless oil. Yield: 314 mg, 33% (in 2 steps). R_f (pentane/EtOAc 10/1) = 0.58. ^1H NMR (500 MHz, C_6D_6): δ = 7.80–7.75 (m, 4H), 7.33–7.29 (m, 2H), 7.25–7.19 (m, 6H), 7.18–7.09 (m, 3H), 5.06 (s, 1H), 4.86 (s, 1H), 4.05 (t, J = 10.5 Hz, 1H), 3.97 (dd, J = 10.5, 4.0 Hz, 1H), 3.79–3.73 (m, 1H), 2.83 (d, J = 2.0 Hz, 1H), 2.24 (dd, J = 10.5, 4.0 Hz, 1H), 2.19–2.12 (m, 1H), 2.09 (dd, J = 13.0, 10.5 Hz, 1H), 1.99 (d, J = 12.5 Hz, 1H), 1.82–1.60 (m, 4H), 1.48–1.39 (m, 1H), 1.30–1.09 (m, 14H), 0.16 (s, 3H), 0.13 (s, 3H). ^{13}C NMR (125 MHz, C_6D_6): δ = 146.7, 137.2, 136.05, 135.95, 134.1, 133.70, 133.67, 130.01, 129.99, 129.4, 128.12, 128.08, 128.0, 111.8, 71.6, 65.4, 45.2, 43.8, 39.1, 29.6, 29.1, 27.1, 27.0, 26.8, 26.7, 19.4, –4.2, –4.7. IR (thin film): 3488, 3071, 2929, 2856, 1632, 1428, 1250, 1112, 1064 cm^{-1} . HRMS (ESI+, m/z): Calculated for $\text{C}_{36}\text{H}_{50}\text{NaO}_2\text{Si}_2$ [(M+Na)] $^+$, 593.3242; found, 593.3234.

anti-11

A colorless oil. Yield: 286 mg, 30% (in 2 steps). R_f (pentane/EtOAc 10/1) = 0.57. ^1H NMR (500 MHz, C_6D_6): δ = 7.83–7.77 (m, 2H), 7.76–7.71 (m, 2H), 7.33–7.29 (m, 2H), 7.26–7.08 (m, 9H), 5.04 (s, 1H), 4.82 (s, 1H), 4.03 (t, J = 10.5 Hz, 1H), 3.99 (dd, J = 10.5, 5.0 Hz, 1H), 3.74–3.69 (m, 1H), 3.28 (d, J = 2.5 Hz, 1H), 2.62 (dd, J = 10.5, 4.5 Hz, 1H), 2.25 (dd, J = 13.0, 2.0 Hz, 1H), 2.09–2.03 (m, 1H), 1.99 (dd, J = 13.0, 10.0 Hz, 1H), 1.81–1.67 (m, 3H), 1.66–1.60 (m, 1H), 1.47–1.38 (m, 1H), 1.26–1.10 (m, 14H), 0.16 (s, 3H), 0.14 (s, 3H). ^{13}C NMR (125 MHz, C_6D_6): δ = 148.7, 137.2, 136.06, 135.98, 134.2, 133.5, 133.4, 130.05, 129.98, 129.4, 128.1, 128.1, 128.0, 110.6, 77.6, 66.0, 44.8, 44.2, 41.6, 29.6, 28.5, 27.1, 26.9, 26.8, 26.7, 19.3, –3.9, –4.9. IR (thin film): 3465, 3071, 2928, 2856, 1630, 1427, 1249, 1187, 1112, 1064 cm^{-1} . HRMS (ESI+, m/z): Calculated for $\text{C}_{36}\text{H}_{50}\text{NaO}_2\text{Si}_2$ [(M+Na)] $^+$, 593.3242; found, 593.3228.

syn-12

A colorless oil. Yield: 377 mg, 40% (in 2 steps). R_f (pentane/EtOAc 10/1) = 0.60. ^1H NMR (500 MHz, C_6D_6): δ = 7.82–7.77 (m, 4H), 7.51–7.47 (m, 2H), 7.30–7.08 (m, 14H), 5.12–5.07 (m, 1H), 5.06 (s, 1H), 4.88 (s, 1H), 4.09 (t, J = 10.5 Hz, 1H), 4.01 (dd, J = 10.5, 4.5 Hz, 1H), 3.30 (d, J = 2.0 Hz, 1H), 2.38–2.22 (m, 3H), 1.18 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H). ^{13}C NMR (125 MHz, C_6D_6): δ = 145.9, 145.0, 137.1, 136.06, 135.98, 134.1, 133.64, 133.61, 130.07, 130.05, 129.5, 128.4, 128.13, 128.11, 128.0, 127.1, 126.1, 112.6, 70.5, 65.2, 50.5, 39.3, 27.0, 19.4, –4.2, –4.6. IR (thin film): 3467, 3071, 2956, 2859, 1632, 1250, 1195, 1112, 1061 cm^{-1} . HRMS (ESI+, m/z): Calculated for $\text{C}_{36}\text{H}_{44}\text{NaO}_2\text{Si}_2$ [(M+Na)]⁺, 587.2772; found, 587.2758.

anti-12

A colorless oil. Yield: 348 mg, 37% (in 2 steps). R_f (pentane/EtOAc 10/1) = 0.50. ^1H NMR (500 MHz, C_6D_6): δ = 7.82–7.78 (m, 2H), 7.77–7.73 (m, 2H), 7.50–7.46 (m, 2H), 7.30–7.07 (m, 14H), 5.08–5.02 (m, 2H), 4.83 (s, 1H), 4.04 (t, J = 10.5 Hz, 1H), 4.01 (dd, J = 10.5, 5.0 Hz, 1H), 3.66 (d, J = 2.5 Hz, 1H), 2.61 (dd, J = 10.5, 4.5 Hz, 1H), 2.51 (dd, J = 13.5, 3.0 Hz, 1H), 2.28 (dd, J = 14.0, 10.0 Hz, 1H), 1.18 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H). ^{13}C NMR (125 MHz, C_6D_6): δ = 147.5, 145.3, 137.0, 136.04, 136.00, 134.2, 133.5, 133.4, 130.1, 130.0, 129.4, 128.4, 128.1, 128.1, 128.0, 127.2, 126.0, 111.2, 75.8, 66.1, 50.5, 41.5, 26.9, 19.3, –3.9, –5.0. IR (thin film): 3443, 3070, 2956, 2858, 1630, 1427, 1250, 1194, 1112, 1065 cm^{-1} . HRMS (ESI+, m/z): Calculated for $\text{C}_{36}\text{H}_{44}\text{NaO}_2\text{Si}_2$ [(M+Na)]⁺, 587.2772; found, 587.2765.

13a and 13b

A mixture of **8** (50.0 mg, 0.167 mmol), zinc powder (12.0 mg, 0.184 mmol), and benzaldehyde (19.7 mg, 0.184 mmol) in THF–sat. NH_4Cl aq. (1 mL–0.1 mL) was stirred for 2 h. After dilution with Et_2O , the separated aqueous phase was extracted with Et_2O , and the combined organic solutions were dried with Na_2SO_4 and concentrated. The residual oil was purified by column chromatography (silica gel, 0%→20% EtOAc/pentane) to give **13a** (21.8 mg, 40% yield) and **13b** (19.1 mg, 35% yield), respectively.

13a

A colorless oil. R_f (pentane/EtOAc 5/1) = 0.45. ^1H NMR (500 MHz, C_6D_6): δ = 7.39–7.34 (m, 4H), 7.22–7.14 (m, 5H), 7.12–7.07 (m, 1H), 5.02 (s, 1H), 4.93 (dd, J = 10.5, 3.0 Hz, 1H), 4.77 (s, 1H), 3.70–3.58 (m, 3H), 2.50 (brs, 1H), 2.29 (dd, J = 14.0, 11.0 Hz, 1H), 2.18–2.09 (m, 2H), 0.16 (s, 6H). ^{13}C NMR (125 MHz, C_6D_6): δ = 145.4, 145.1, 137.3, 134.2, 129.5, 128.5, 128.1, 127.2, 126.0, 112.9, 70.6, 63.2, 50.1, 38.8, –4.2, –4.8. IR (thin film): 3351, 3069, 2954, 1633, 1427, 1249, 1112, 1058 cm^{-1} . HRMS (ESI+, m/z): Calculated for $\text{C}_{20}\text{H}_{26}\text{NaO}_2\text{Si}$ [(M+Na)]⁺, 349.1594; found, 349.1601.

13b

A colorless oil. R_f (pentane/EtOAc 5/1) = 0.44. ^1H NMR (500 MHz, C_6D_6): δ = 7.40–7.34 (m, 4H), 7.21–7.13 (m, 5H), 7.12–7.06 (m, 1H), 4.97 (s, 1H), 4.84 (dd, J = 9.5, 3.5 Hz, 1H), 4.75 (s, 1H), 3.68 (br, s), 3.63 (d, J = 8.5 Hz, 2H), 2.39 (dd, J = 13.0, 3.5 Hz, 1H), 2.36 (d, J = 8.5 Hz, 1H), 2.16 (dd, J = 13.0, 9.5 Hz, 1H), 2.03 (brs, 1H), 0.16 (s, 3H), 0.15 (s, 3H). ^{13}C NMR (125 MHz, C_6D_6): δ = 147.4, 145.3, 137.2, 134.3, 129.5, 128.5, 128.1, 127.3, 126.0, 110.9, 76.6, 64.0, 50.2, 41.7, –4.0, –5.1. IR (thin film): 3338, 3069, 2954, 1631, 1427, 1249, 1112, 1060 cm^{-1} . HRMS (ESI+, m/z): Calculated for $\text{C}_{20}\text{H}_{26}\text{NaO}_2\text{Si}$ [(M+Na)]⁺, 349.1594; found, 349.1604.

14a

To a solution of **13a** (16.0 mg, 0.0491 mmol) and Et₃N (50.0 mg, 0.491 mmol) in CH₂Cl₂ (0.5 mL) was added TsCl (14.0 mg, 0.0737 mmol) at rt. The mixture was stirred at rt for 17 h and water was added. The separated aqueous phase was extracted with CH₂Cl₂, and the combined organic solutions were washed with brine, dried with Na₂SO₄ and concentrated *in vacuo*. The residue was purified by chromatography (silica gel, 10% CH₂Cl₂/pentane) to give **14a** (7.1 mg, 47% yield) as a colorless oil. *R*_f(pentane/CH₂Cl₂ 10/1) = 0.49. ¹H NMR (500 MHz, CDCl₃): δ = 7.61–7.56 (m, 2H), 7.37–7.23 (m, 8H), 4.94–4.91 (m, 1H), 4.86–4.83 (m, 1H), 4.81 (dd, *J* = 10.0, 5.5 Hz, 1H), 4.52–4.46 (m, 1H), 2.92 (dd, *J* = 15.5, 5.5 Hz, 1H), 2.50–2.42 (m, 1H), 1.34 (dd, *J* = 15.0, 4.0 Hz, 1H), 1.24 (dd, *J* = 15.0, 9.5 Hz, 1H), 0.40 (s, 3H), 0.39 (s, 3H). ¹³C NMR (125 MHz, CDCl₃): δ = 154.4, 142.3, 139.8, 133.8, 128.8, 128.3, 127.8, 127.3, 125.8, 103.9, 79.4, 79.2, 41.7, 22.9, –1.6, –2.0. IR (thin film): 3069, 2955, 2922, 2853, 1665, 1427, 1247, 1112, 1086 cm^{–1}. HRMS (ESI+, *m/z*): Calculated for C₂₀H₂₄NaOSi [(M+Na)]⁺, 331.1489; found, 331.1486.

14b

To a solution of **13b** (8.6 mg, 0.0263 mmol) and Et₃N (27.0 mg, 0.263 mmol) in CH₂Cl₂ (0.5 mL) was added TsCl (7.5 mg, 0.0395 mmol) at rt. The mixture was stirred at rt for 17 h and water was added. The separated aqueous phase was extracted with CH₂Cl₂, and the combined organic solutions were washed with brine, dried with Na₂SO₄ and concentrated *in vacuo*. The residue was purified by chromatography (silica gel, 10% CH₂Cl₂/pentane) to give **14b** (5.6 mg, 69% yield) as a colorless oil. *R*_f(pentane/CH₂Cl₂ 10/1) = 0.45. ¹H NMR (500 MHz, CDCl₃): δ = 7.60–7.56 (m, 2H), 7.37–7.22 (m, 8H), 5.04 (t, *J* = 7.0 Hz, 1H), 4.92 (dd, *J* = 4.0, 2.0 Hz, 1H), 4.83 (dd, *J* = 4.0, 2.0 Hz, 1H), 4.70–4.65 (m, 1H), 3.04–2.97 (m, 1H), 2.64–2.58 (m, 1H), 1.27 (dd, *J* = 15.0, 9.5 Hz, 1H), 1.23 (dd, *J* = 15.0, 5.0 Hz, 1H), 0.41 (s, 3H), 0.38 (s, 3H). ¹³C NMR (125 MHz, CDCl₃): δ = 154.1, 143.0, 139.7, 133.8, 128.9, 128.3, 127.8, 127.2, 125.8, 104.3, 78.4, 77.6, 40.6, 23.4, –1.6, –2.2. IR (thin film): 3068, 2954, 2922, 2853, 1667, 1427, 1246, 1112, 1056 cm^{–1}. HRMS (ESI+, *m/z*): Calculated for C₂₀H₂₄NaOSi [(M+Na)]⁺, 331.1489; found, 331.1491.

syn-12

To a solution of **14a** (8.5 mg, 0.0261 mmol) in DMF (0.5 mL) was added TBDPSCl (8.9 mg, 0.0313 mmol) and imidazole (4.4 mg, 0.0653 mmol). The mixture was stirred at rt for 1 h and diluted with water and Et₂O. The separated aqueous phase was extracted with Et₂O, and the combined organic solutions were washed with brine, dried with Na₂SO₄ and concentrated *in vacuo*. The residue was purified by chromatography (silica gel, 0%→2% EtOAc/pentane) to give **syn-12** (12.0 mg, 82% yield) as a colorless oil.

anti-12

To a solution of **14b** (7.0 mg, 0.0215 mmol) in DMF (0.5 mL) was added TBDPSCl (9.2 mg, 0.0258 mmol) and imidazole (3.7 mg, 0.0538 mmol). The mixture was stirred at rt for 1 h and diluted with water and Et₂O. The separated aqueous phase was extracted with Et₂O, and the combined organic solutions were washed with brine, dried with Na₂SO₄ and concentrated *in vacuo*. The residue was purified by chromatography (silica gel, 0%→2% EtOAc/pentane) to give **anti-12** (9.7 mg, 80% yield) as a colorless oil.

General procedure for TMSOTf promoted cyclization of β-hydroxy allylsilanes

To a solution of β-hydroxy allylsilane (0.030 mmol) in Et₂O (1.0 mL), aldehyde (0.060 mmol) was added and the mixture was cooled to –78 °C. TMSOTf (8.1 μL, 0.045 mmol) was added and the mixture was stirred until the starting material completely disappeared (monitored by TLC). The reaction was quenched with sat. NaHCO₃ aq. and then aqueous

layer was extracted with Et₂O. The combined organic layer was dried with Na₂SO₄ and concentrated *in vacuo*. The residue was purified by chromatography with EtOAc–pentane to give cyclized product.

15a

A colorless oil. Yield: 14.3 mg, 96% (from *syn-9*); 14.0 mg, 94%, 82:18 dr (from *anti-10*). R_f (pentane/EtOAc 10/1) = 0.88. ¹H NMR (500 MHz, CDCl₃): δ = 7.69–7.65 (m, 4H), 7.44–7.33 (m, 6H), 7.30–7.25 (m, 2H), 7.21–7.15 (m, 3H), 5.37 (t, *J* = 6.5 Hz, 1H), 4.23 (dd, *J* = 12.5, 6.5 Hz, 1H), 4.19 (dd, *J* = 12.5, 6.5 Hz, 1H), 3.21–3.14 (m, 1H), 2.96–2.89 (m, 1H), 2.80 (ddd, *J* = 13.5, 9.5, 5.5 Hz, 1H), 2.69 (dt, *J* = 13.5, 9.0 Hz, 1H), 2.21 (d, *J* = 13.5 Hz, 1H), 2.05 (d, *J* = 13.0 Hz, 1H), 1.94 (t, *J* = 12.0 Hz, 1H), 1.90–1.81 (m, 1H), 1.74–1.65 (m, 1H), 1.56–1.46 (m, 2H), 1.44–1.33 (m, 1H), 1.03 (s, 9H), 0.94 (t, *J* = 7.0 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃): δ = 142.4, 137.0, 135.71, 135.69, 134.00, 133.96, 129.6, 128.6, 128.4, 127.70, 127.68, 125.8, 122.6, 78.9, 77.0, 60.1, 42.2, 37.9, 34.9, 31.8, 29.4, 26.9, 19.2, 10.4. IR (thin film): 3070, 3027, 2931, 2857, 1671, 1603, 1589, 1428, 1111, 1069 cm^{−1}. HRMS (ESI+, *m/z*): Calculated for C₃₃H₄₂NaO₂Si [(M+Na)]⁺, 521.2846; found, 521.2834.

15b

A colorless oil. Yield: 15.4 mg, 93% (from *syn-9*); 15.7 mg, 95%, 79:21 dr (from *anti-11*). R_f (pentane/EtOAc 10/1) = 0.89. ¹H NMR (500 MHz, CDCl₃): δ = 7.70–7.65 (m, 4H), 7.44–7.33 (m, 6H), 7.31–7.24 (m, 2H), 7.21–7.16 (m, 3H), 5.37 (t, *J* = 6.5 Hz, 1H), 4.22 (dd, *J* = 12.5, 6.5 Hz, 1H), 4.19 (dd, *J* = 12.5, 6.5 Hz, 1H), 3.17–3.10 (m, 1H), 2.83–2.65 (m, 3H), 2.27 (d, *J* = 13.5 Hz, 1H), 2.03 (d, *J* = 13.0 Hz, 2H), 1.96–1.80 (m, 2H), 1.78–1.61 (m, 4H), 1.60–1.46 (m, 2H), 1.26–1.08 (m, 4H), 1.03 (s, 9H), 1.02–0.85 (m, 2H). ¹³C NMR (125 MHz, CDCl₃): δ = 142.4, 137.3, 135.7, 134.0, 129.6, 128.7, 128.3, 127.7, 125.7, 122.7, 81.7, 76.8, 60.0, 43.3, 42.4, 38.0, 32.2, 31.8, 29.3, 29.0, 26.9, 26.7, 26.2, 26.1, 19.2. IR (thin film): 3070, 3026, 2929, 2855, 1671, 1603, 1589, 1428, 1111, 1059 cm^{−1}. HRMS (ESI+, *m/z*): Calculated for C₃₇H₄₈NaO₂Si [(M+Na)]⁺, 575.3316; found, 575.3316.

15c

A colorless oil. Yield: 14.2 mg, 90% (from *syn-9*). R_f (pentane/EtOAc 10/1) = 0.90. ¹H NMR (500 MHz, CDCl₃): δ = 7.71–7.65 (m, 4H), 7.44–7.33 (m, 6H), 7.31–7.25 (m, 2H), 7.21–7.16 (m, 3H), 5.38 (t, *J* = 6.5 Hz, 1H), 4.22 (dd, *J* = 12.5, 6.5 Hz, 1H), 4.19 (dd, *J* = 12.5, 6.5 Hz, 1H), 3.19–3.12 (m, 1H), 2.80 (ddd, *J* = 14.0, 9.0, 5.0 Hz, 1H), 2.72–2.64 (m, 2H), 2.20 (d, *J* = 13.0 Hz, 1H), 2.05 (d, *J* = 13.0 Hz, 1H), 1.92–1.77 (m, 2H), 1.73–1.64 (m, 1H), 1.52 (t, *J* = 12.5 Hz, 1H), 1.03 (s, 9H), 0.86 (s, 9H). ¹³C NMR (125 MHz, CDCl₃): δ = 142.6, 137.9, 135.7, 134.0, 129.6, 128.7, 128.3, 127.7, 125.7, 122.5, 84.7, 76.8, 60.0, 42.4, 38.1, 34.4, 31.8, 29.1, 26.9, 26.1, 19.2. IR (thin film): 3070, 2953, 2858, 1671, 1608, 1589, 1428, 1361, 1111, 1062 cm^{−1}. HRMS (ESI+, *m/z*): Calculated for C₃₅H₄₆NaO₂Si [(M+Na)]⁺, 549.3159; found, 549.3154.

15d

A colorless oil. Yield: 15.1 mg, 92% (from *syn-9*); 12.9 mg, 79%, 92:8 dr (from *anti-12*). R_f (pentane/EtOAc 10/1) = 0.88. ¹H NMR (500 MHz, CDCl₃): δ = 7.70–7.65 (m, 4H), 7.42–7.14 (m, 16H), 5.48 (t, *J* = 6.5 Hz, 1H), 4.28 (dd, *J* = 12.5, 6.5 Hz, 1H), 4.22 (dd, *J* = 12.5, 6.5 Hz, 1H), 4.11 (dd, *J* = 11.5, 2.0 Hz, 1H), 3.44–3.38 (m, 1H), 2.82 (ddd, *J* = 13.5, 9.0, 5.5 Hz, 1H), 2.77–2.69 (m, 1H), 2.48 (d, *J* = 13.5 Hz, 1H), 2.16 (d, *J* = 13.0 Hz, 1H), 2.08 (t, *J* = 12.0 Hz, 1H), 2.00–1.91 (m, 1H), 1.89–1.76 (m, 2H), 1.04 (s, 9H). ¹³C NMR (125 MHz, CDCl₃): δ = 142.6, 142.3, 136.5, 135.71, 135.67, 133.93, 133.85, 129.7, 128.6, 128.4, 128.3, 127.7, 127.5, 125.9, 125.8, 123.4, 79.0, 77.5, 60.1, 41.7, 37.9, 36.8, 31.7, 26.9, 19.2. IR (thin

film): 3069, 3027, 2931, 2857, 1671, 1603, 1428, 1111, 1058 cm^{-1} . HRMS (ESI+, m/z): Calculated for $\text{C}_{37}\text{H}_{42}\text{NaO}_2\text{Si}[(\text{M}+\text{Na})]^+$, 569.2846; found, 569.2839.

15e

A colorless oil. Yield: 16.3 mg, 95% (from *syn-9*). R_f (pentane/EtOAc 10/1) = 0.90. ^1H NMR (500 MHz, CDCl_3): δ = 7.71–7.66 (m, 4H), 7.44–7.16 (m, 16H), 6.53 (d, J = 16.0 Hz, 1H), 6.18 (dd, J = 16.0, 5.5 Hz, 1H), 5.45 (t, J = 6.5 Hz, 1H), 4.28 (dd, J = 12.5, 6.5 Hz, 1H), 4.27 (dd, J = 12.5, 6.5 Hz, 1H), 4.22 (dd, J = 12.5, 6.0 Hz, 1H), 3.76–3.70 (m, 1H), 3.36–3.29 (m, 1H), 2.82 (ddd, J = 13.5, 9.0, 5.5 Hz, 1H), 2.77–2.68 (m, 1H), 2.35 (d, J = 13.5 Hz, 1H), 2.13 (d, J = 13.0 Hz, 1H), 2.05–1.89 (m, 2H), 1.82–1.71 (m, 2H), 1.04 (s, 9H). ^{13}C NMR (125 MHz, CDCl_3): δ = 142.2, 136.9, 136.1, 135.73, 135.70, 133.94, 133.86, 130.3, 130.1, 129.7, 128.6, 128.4, 127.74, 127.72, 127.65, 126.5, 125.8, 123.4, 77.7, 77.3, 60.1, 41.7, 37.8, 35.2, 31.8, 26.9, 19.2. IR (thin film): 3069, 3026, 2931, 2857, 1672, 1601, 1589, 1428, 1111, 1057 cm^{-1} . HRMS (ESI+, m/z): Calculated for $\text{C}_{39}\text{H}_{44}\text{NaO}_2\text{Si}[(\text{M}+\text{Na})]^+$, 595.3003; found, 595.2994.

16a

A colorless oil. Yield: 14.3 mg, 96% (from *syn-10*); 14.2 mg, 95%, 84:16 dr (from *anti-9*). R_f (pentane/EtOAc 10/1) = 0.90. ^1H NMR (500 MHz, CDCl_3): δ = 7.69–7.64 (m, 4H), 7.43–7.30 (m, 6H), 7.29–7.24 (m, 2H), 7.19–7.14 (m, 3H), 5.39 (t, J = 6.5 Hz, 1H), 4.21 (dd, J = 12.5, 6.5 Hz, 1H), 4.17 (dd, J = 12.5, 6.5 Hz), 3.15–3.08 (m, 1H), 3.06–2.99 (m, 1H), 2.76 (ddd, J = 13.5, 9.5, 5.5 Hz, 1H), 2.65 (dt, J = 14.0, 8.5 Hz, 1H), 2.15 (d, J = 13.5 Hz, 1H), 2.11 (d, J = 13.0 Hz, 1H), 1.90 (t, J = 12.5 Hz, 1H), 1.85–1.75 (m, 1H), 1.64–1.43 (m, 4H), 1.03 (s, 9H), 1.00 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, CDCl_3): δ = 142.3, 136.9, 135.7, 134.0, 129.7, 128.6, 128.4, 127.69, 127.67, 125.8, 122.6, 79.8, 76.2, 60.1, 41.8, 38.0, 35.2, 31.8, 29.4, 26.9, 19.2, 10.3. IR (thin film): 3070, 3026, 2931, 2857, 1670, 1603, 1589, 1428, 1111 cm^{-1} . HRMS (ESI+, m/z): Calculated for $\text{C}_{33}\text{H}_{42}\text{NaO}_2\text{Si}[(\text{M}+\text{Na})]^+$, 521.2846; found, 521.2844.

16b

A colorless oil. Yield: 15.7 mg, 95% (from *syn-11*); 15.7 mg, 95%, 84:16 dr (from *anti-9*). R_f (pentane/EtOAc 10/1) = 0.89. ^1H NMR (500 MHz, CDCl_3): δ = 7.69–7.64 (m, 4H), 7.43–7.24 (m, 8H), 7.20–7.15 (m, 3H), 5.39 (t, J = 6.5 Hz, 1H), 4.20 (dd, J = 12.5, 7.0 Hz, 1H), 4.17 (dd, J = 12.5, 6.5 Hz, 1H), 3.02–2.95 (m, 1H), 2.92 (ddd, J = 11.0, 7.5, 2.0 Hz, 1H), 2.76 (ddd, J = 14.0, 8.5, 4.5 Hz, 1H), 2.66 (dt, J = 14.0, 8.0 Hz, 1H), 2.19–2.06 (m, 3H), 1.89 (t, J = 11.5 Hz, 1H), 1.84–1.63 (m, 5H), 1.62–1.49 (m, 2H), 1.45–1.34 (m, 1H), 1.32–1.12 (m, 3H), 1.08–0.96 (m, 11H). ^{13}C NMR (125 MHz, CDCl_3): δ = 142.4, 137.2, 135.7, 134.0, 129.6, 128.7, 128.4, 127.68, 127.66, 125.7, 122.7, 82.5, 76.0, 60.1, 43.3, 39.4, 38.1, 35.4, 31.8, 29.5, 28.9, 26.9, 26.7, 26.3, 26.1, 19.2. IR (thin film): 3070, 3026, 2928, 2855, 1671, 1603, 1589, 1428, 1111, 1058 cm^{-1} . HRMS (ESI+, m/z): Calculated for $\text{C}_{37}\text{H}_{48}\text{NaO}_2\text{Si}[(\text{M}+\text{Na})]^+$, 575.3316; found, 575.3303.

16c

A colorless oil. Yield: 12.6 mg, 80%, 92:8 dr (from *anti-9*). R_f (pentane/EtOAc 10/1) = 0.90. ^1H NMR (500 MHz, CDCl_3): δ = 7.70–7.64 (m, 4H), 7.43–7.30 (m, 6H), 7.29–7.24 (m, 2H), 7.21–7.14 (m, 3H), 5.39 (t, J = 6.5 Hz, 1H), 4.23–4.14 (m, 2H), 3.03–2.96 (m, 1H), 2.85 (dd, J = 11.5, 2.0 Hz, 1H), 2.76 (ddd, J = 14.0, 9.0, 5.0 Hz, 1H), 2.64 (dt, J = 14.0, 8.5 Hz, 1H), 2.11 (d, J = 13.5 Hz, 1H), 2.06 (d, J = 13.5 Hz, 1H), 1.94 (t, J = 12.0 Hz, 1H), 1.80–1.71 (m, 1H), 1.62–1.54 (m, 1H), 1.49 (t, J = 12.0 Hz, 1H), 1.02 (s, 9H), 0.94 (s, 9H). ^{13}C NMR (125 MHz, CDCl_3): δ = 142.6, 137.8, 135.7, 134.01, 134.00, 129.6, 128.6, 128.3, 127.69, 127.66, 125.7, 122.6, 85.6, 76.0, 60.2, 38.2, 36.3, 35.3, 34.3, 31.8, 26.9, 26.1,

19.2. IR (thin film): 3070, 2954, 2858, 1671, 1603, 1589, 1428, 1361, 1111, 1061 cm^{-1} . HRMS (ESI+, m/z): Calculated for $\text{C}_{35}\text{H}_{46}\text{NaO}_2\text{Si}$ [(M+Na)]⁺, 549.3159; found, 549.3148.

16d

A colorless oil. Yield: 15.2 mg, 93% (from *syn*-**12**); 14.6 mg, 89% (from *anti*-**9**). R_f (pentane/EtOAc 10/1) = 0.88. ^1H NMR (500 MHz, CDCl_3): δ = 7.71–7.66 (m, 4H), 7.45–7.33 (m, 10H), 7.35–7.23 (m, 3H), 7.20–7.14 (m, 3H), 5.49 (t, J = 6.5 Hz, 1H), 4.30 (dd, J = 11.5, 2.5 Hz, 1H), 4.28–4.19 (m, 2H), 3.28–3.20 (m, 1H), 2.78 (ddd, J = 13.5, 9.0, 5.0 Hz, 1H), 2.68 (ddd, J = 13.5, 9.0, 7.0 Hz, 1H), 2.36 (d, J = 13.5 Hz, 1H), 2.28–2.17 (m, 2H), 1.94–1.84 (m, 1H), 1.75–1.63 (m, 2H), 1.05 (s, 9H). ^{13}C NMR (125 MHz, CDCl_3): δ = 142.7, 142.3, 136.5, 135.71, 135.70, 134.0, 133.9, 129.7, 128.6, 128.4, 127.73, 127.71, 127.4, 125.82, 125.79, 123.3, 79.8, 76.7, 60.1, 43.9, 38.0, 34.8, 31.7, 26.9, 19.2. IR (thin film): 3069, 3027, 2930, 2856, 1673, 1603, 1589, 1427, 1111, 1056 cm^{-1} . HRMS (ESI+, m/z): Calculated for $\text{C}_{37}\text{H}_{42}\text{NaO}_2\text{Si}$ [(M+Na)]⁺, 569.2846; found, 569.2838.

16e

A colorless oil. Yield: 16.1 mg, 94%, 94:6 dr (from *anti*-**9**). R_f (pentane/EtOAc 10/1) = 0.90. ^1H NMR (500 MHz, CDCl_3): δ = 7.71–7.66 (m, 4H), 7.45–7.14 (m, 16H), 6.63 (d, J = 16.0 Hz, 1H), 6.26 (dd, J = 16.0, 6.0 Hz, 1H), 5.46 (t, J = 6.5 Hz, 1H), 4.27–4.17 (m, 2H), 3.95–3.89 (m, 1H), 3.19–3.12 (m, 1H), 2.77 (ddd, J = 13.5, 9.0, 5.0 Hz, 1H), 2.67 (ddd, J = 14.0, 9.0, 7.5 Hz, 1H), 2.26–2.10 (m, 3H), 1.92–1.82 (m, 1H), 1.71–1.64 (m, 1H), 1.61 (t, J = 12.5 Hz, 1H), 1.04 (s, 9H). ^{13}C NMR (125 MHz, CDCl_3): δ = 142.2, 136.9, 136.1, 135.7, 133.93, 133.89, 130.3, 130.2, 129.7, 128.6, 128.4, 127.72, 127.66, 126.6, 125.8, 123.4, 78.6, 76.5, 60.1, 42.1, 37.9, 34.8, 31.8, 26.9, 19.2. IR (thin film): 3069, 3026, 2931, 2857, 1672, 1601, 1589, 1428, 1111, 1056 cm^{-1} . HRMS (ESI+, m/z): Calculated for $\text{C}_{39}\text{H}_{44}\text{NaO}_2\text{Si}$ [(M+Na)]⁺, 595.3003; found, 595.3001.

Computational methods

All structures were optimized with the B3LYP/6-31G(d) model chemistry^{33,34} using Gaussian 09.³⁵ Frequency calculations were used to characterize stationary points as minima or transition states along with Intrinsic Reaction Coordinate (IRC) calculations³⁶ to connect transition state structures to their respective minima. Single point energies were calculated for the B3LYP/6-31G(d) geometries at multiple model chemistries including CAM-B3LYP/6-31+G(d,p)³⁷, M06-2X/6-31+G(d,p)³⁸ and B3LYP/6-31+G(d,p). Single point solvent calculations were carried out using the SMD solvent model³⁹ with diethyl ether. Figures were generated using Ball & Stick.⁴⁰ Coordinates for all optimized structures, as well as energies computed with the various methods listed above, can be found in the Supporting Information.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Bryostatins and Exiguolide, examples of *E*- and *Z*-alkylidene-*cis*-2,6-disubstituted pyrans.

A) Macro-trans-acetalization **B) Prins-driven Macrocyclization**

Figure 2.
Ring-forming macrocyclizations.

A) Endo-cyclic stereocontrol **B) Endo- and Exo-cyclic stereocontrol**

Figure 3.
Silyl-terminated Prins cyclizations for endo-cyclic and endo- and exo-cyclic stereocontrol.

Figure 4.
Relative stereochemistry of **15a**.

Figure 5. Mechanism for the Prins cyclization with *syn*-β-hydroxy allylsilane proposed on the basis of computational results. Relative energies shown were computed with B3LYP/6-31+G(d,p)//B3LYP/6-31G(d).

Figure 6.
Model for rationalizing observed selectivity.

Scheme 1. The synthetic route to β -hydroxy allylsilanes **9–12**.

Scheme 2. Assignment of relative stereochemistry of β -hydroxy allylsilane **12**.

Table 1

Prins cyclization of *syn*-β-hydroxy allylsilane **9** with representative aldehydes.

<p> $\text{15: R}^1 = \text{TBDPSOCH}_2, \text{R}^2 = \text{H}$ $\text{16: R}^1 = \text{H}, \text{R}^2 = \text{TBDPSOCH}_2$ </p>				
Entry	R	time (h)	product	yield (%)
1	Et	1	15a	96
2	<i>c</i> -Hex	1	15b	93
3	<i>t</i> -Bu	4	15c	90
4	Ph	1	15d	92
5		1	15e	95

^aProduct ratios were determined by ¹H NMR.

Table 2

Substituents effects in the Prins cyclization of *syn*-β-hydroxy allylsilanes **10–12** with 3-phenyl-propionaldehyde.

Entry	allylsilane	R	time (h)	product	yield (%)	16:15 ^a
1	<i>syn</i> - 10	Et	1	16a	96	>95:5
2	<i>syn</i> - 11	<i>c</i> -Hex	1	16b	95	>95:5
3	<i>syn</i> - 12	Ph	1	16d	93	>95:5

^aProduct ratios were determined by ¹H NMR.

Table 3
Prins cyclization using *anti*-β-hydroxy allylsilanes **9** with representative aldehydes.

<div><p>15: R¹ = TBDPCH₂, R² = H 16: R¹ = H, R² = TBDPCH₂</p></div>					
Entry	R	time (h)	product	yield (%) ^a	15:16 ^b
1	Et	1	15a, 16a	95	16:84
2	<i>n</i> -Hex	1.5	15b, 16b	95	16:84
3	<i>t</i> -Bu	8	15c, 16c	80	8:92
4	Ph	1	16d	89	5:>95
5		1	15e, 16e	94	6:94

^aCombined isolated yield.

^bProduct ratios were determined by ¹H NMR.

Table 4

Substituents effects in the Prins cyclization of *anti*-β-hydroxy allylsilanes **10–12** with 3-phenyl-propionaldehyde.

16: R¹ = TBDPSOCH₂, R² = H
15: R¹ = H, R² = TBDPSOCH₂

Entry	allylsilane	R	time (h)	product	yield (%) ^a	16:15 ^b
1	<i>anti</i> - 10	Et	1	15a, 16a	94	18:82
2	<i>anti</i> - 11	<i>c</i> -Hex	3	15b, 16b	95	21:79
3	<i>anti</i> - 12	Ph	8	15d, 16d	79	8:92

^aCombined isolated yield.

^bProduct ratios were determined by ¹H NMR.