From Carbohydrates to the Discovery of Pronounced Heteroatomic Effects on Anionically Accelerated [3,3]-Sigmatropic Rearrangements

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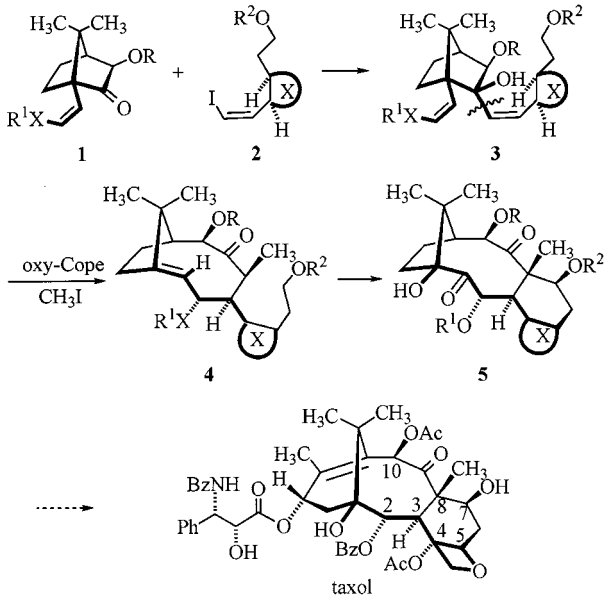
The (*Z*)-(iodovinyl)oxetane **12** was prepared from D-glucose and the acyclic analog **18** was obtained from D-mannitol. Following the generation of their lithium derivatives by halogen–metal exchange, coupling to the enantiopure vinyl-substituted norbornanones **20**, **23**, and **29** proceeded exclusively via *endo* attack to deliver the targeted *exo*-carbinols. The anionic oxy-Cope rearrangements of **21** and **24** were seen to differ appreciably in rate. While the sulfur derivative **24** experiences [3,3] sigmatropy with a half-life of less than a minute at –78 °C, its oxygen analogue **21** proved unreactive below –20 °C under entirely comparable conditions. This phenomenon is critically examined in a synthetic context involving **26** and **30**, where the heavily functionalized acyclic side chain involved previously is supplanted by an oxetane assembly. In the sulfur example, isomerization occurs very rapidly as before with 100% transfer of chirality. The kinetic response of vinyl ether **26** now proved to be entirely comparable. However, the pathway followed in this instance was intramolecular nucleophilic attack by the "naked" alkoxide at the less substituted C–O bond of the oxetane with ring cleavage and formation of alcohol **28**. The global findings provide a glimpse of the subtle way in which [3,3]-sigmatropic transpositions can be modulated by heteroatomic substitution.

Introduction

Over the past several years we have been concerned with the development of a convergent enantioselective approach to several of the more important taxane diterpenoids. Our recent successful focus on the de novo synthesis of natural (+)-taxusin[1] has demonstrated that the methodology is genuinely useful for elaborating this family of complex tricyclic systems. As an important extension of this study, we initiated a complementary investigation aimed at producing synthetic Taxol® in the laboratory. The requirements imposed on our protocol are twofold: The western sector should arise from a bicyclic ketone of type **1** readily derived from D-camphor, and the eastern half should stem from a (*Z*)-vinyl iodide such as **2** where X represents one of several possible preoxetane assemblies (Scheme 1).

In the broadest possible context, it is desirable to have rapid access to quantities of enantiopure samples of **1** with X being an oxygen or sulfur atom. This goal had previously been realized for the OPMP[2] and SPh derivatives.[4] The (*Z*)-configuration of the bridgehead-linked double bond in **1** is critical since it ultimately dictates the absolute configuration at C-2 (taxane numbering). In a similar way, the (*Z*)-geometry in **2** directly controls the α-orientation of the hydrogen atom at C-3.

If our synthetic agenda is ultimately to be viewed as economically feasible, the use of inexpensive carbohydrates as precursors to **2** was seen as meriting serious consideration. This tactic mandates that X should be either an intact oxetane ring or a functional group array having the intrinsic capacity for being crafted rapidly into an oxetane. Both options have been evaluated herein.[5]



Scheme 1. Generalized synthetic plan

In the context of this research, we also came to recognize that the relative rates of oxy-anionic Cope rearrangement of **3** into **4** are highly dependent on the nature of X.[6] Rapid acceleration is seen when R′X is thiophenyl. In contrast, an alkoxy substituent at this position exerts a modestly decelerative influence. These kinetic inequities will be shown to result in the adoption of different reaction pathways under circumstances where structural features allow this distinction to be made. Ultimately, the structural features resident in **4** are expected to be conducive to proper installation of absolute configuration at C-7 and C-8 in **5**.

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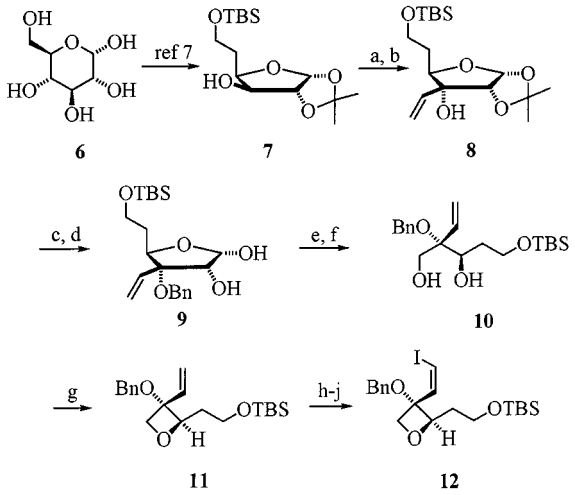
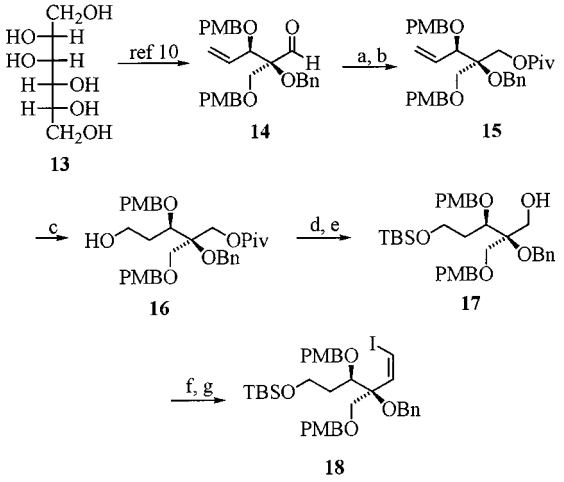


Scheme 2. Synthesis of enantiopure vinyl iodide **12**; reagents and conditions: a) Dess−Martin periodinane; b) CH_2=CHMgBr (79% for 2 steps); c) NaH, BnBr, $(n\text{Bu})_4N^+I^-$; d) $TiCl_4$, CH_2Cl_2, −78 °C (78% for 2 steps); e) Dess−Martin periodinane; f) $NaBH_4$, MeOH (76% for 2 steps); g) $KN(SiMe_3)_2$; $PhNTf_2$, −78 °C (74%); h) OsO_4, NMO; i) $NaIO_4$, pH 7 buffer; j) Ph_3P=CHI (69% for 3 steps)



Scheme 3. Synthesis of enantiopure vinyl iodide **18**; reagents and conditions: a) $LiAlH_4$; b) PivCl, DMAP (81% for 2 steps); c) 9-BBN; H_2O_2, NaOH 96%); d) TBSCL, imid; e) Dibal-H, −78 °C (76% for 2 steps); f) Swern (96%); g) Ph_3P=CHI (85%)

Results and Discussion

From Carbohydrates to (*Z*)-Vinyl Iodides

The allure of introducing an oxetane ring directly from the point of convergency could not be resisted, as no added steps would be required to craft this strained heterocyclic unit. Consequently, our initial experiments were designed to transform D-glucose (**6**) into **12** (Scheme 2). The five-step conversion of **6** to the furanose carbinol **7** has been described previously.[7] Application of the conventional periodinane oxidation conditions[8] to **7** afforded the ketone, the addition of vinylmagnesium bromide to which gave rise to **8**. Our expectation was that the steric shielding provided by the acetonide on the α-surface of **8** would direct nucleophilic entry from the β-direction. That this pathway had indeed been followed was confirmed by NOE studies. Subsequent to the *O*-benzylation of **8**, it proved an easy matter to effect deacetalization with titanium tetrachloride in CH_2Cl_2 at −78 °C.

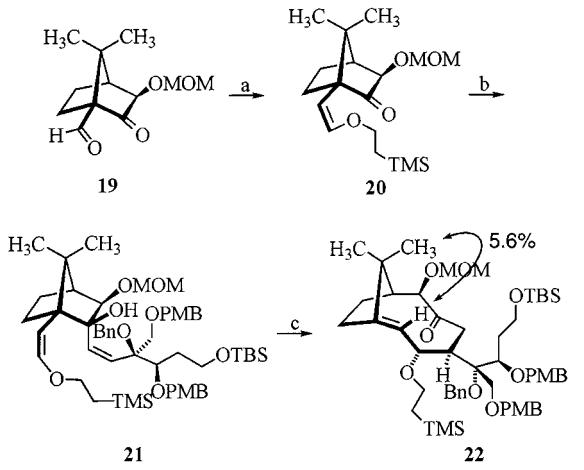
The time had now arrived to excise C-2 from **9** with concomitant cleavage of the tetrahydrofuran ring. This transformation was most conveniently achieved by initial oxidation to the aldehydo formate level with the Dess−Martin periodinane,[8] followed by direct reduction to diol **10** with sodium tetrahydroborate. This two-step sequence proceeded with an overall efficiency of 77%. The availability of **10** allowed for activation of the primary hydroxy group as the triflate and to engage the flanking secondary hydroxy group into neighboring-group participation. The conversion of **11** was accomplished in 73% yield by means of a single laboratory maneuver, and set the stage for oxidative cleavage of the vinyl substituent to the carboxaldehyde by traditional means. Wittig condensation of this intermediate with (iodomethylene)triphenylphosphorane[9] produced the homologated (*Z*)-vinyl iodide **12**.

In a companion series of reactions, D-mannitol (**13**) was chemically modified to deliver aldehyde **14** via a previously devised sequence[10] (Scheme 3). Subsequent to hydride reduction and pivaloylation in order to deliver **15**, the β-hydroxyethyl side chain was installed by hydroboration. Next, the terminal hydroxy group in **16** was silylated in advance of Dibal-H reduction so as to produce **17**. At this juncture, Swern oxidation and the predescribed Wittig condensation were the only steps required to produce the targeted **18**.

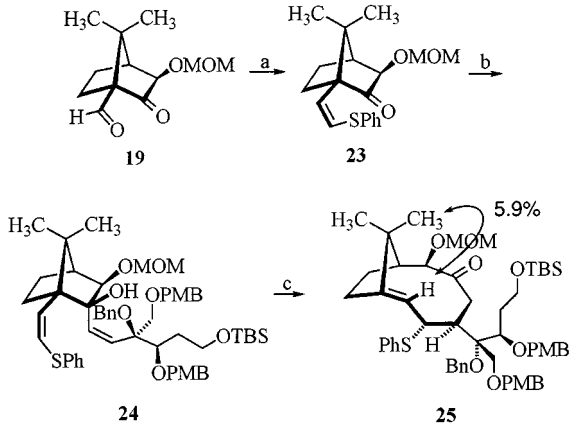
With the acquisition of both **12** and **18**, two nucleophilic building blocks were now available to serve as coupling reagents to norbornanones having the generic structural features given by **1**.

Evaluation of the Oxy-Anionic Cope Rearrangements − The Acyclic Side Chain

The chemoselective homologation of **19**[11] with triphenyl(trimethylsilylethoxymethylene)phosphorane[12] proceeded smoothly in ether at 0 °C to give predominantly **20** [(*Z*)/(*E*) = 3:1]. Once the isomerically pure vinyl ether was in hand, coupling to **18** was undertaken (Scheme 4). Since the significant steric shielding on the *exo* surface of **20** strongly favors *endo*-nucleophilic attack, the vinylorganometallic reagent generated with *n*-butyllithium gave rise to **21** in 80% yield. Subsequent conversion of this norbornanol to its alkoxide with potassium hexamethyldisilazide and 18-crown-6 in THF at 0 °C resulted in complete conversion into **22** within 5 min. The isomeric ketone nature of this product was immediately recognized on the basis of the infrared and mass spectra. Its detailed stereochemistry, anticipated on the basis of the adoption of an *endo*-chair transition state[13] was deduced on the strength of its ^{1}H- and ^{13}C-NMR features and selected NOE experiments. Attention is called to the fact that the **21** → **22** rearrangement did not occur at a useful rate until the reaction temperature reached ca. 0 °C, and therefore proceeds more slowly than related systems that carry only a simple bridgehead vinyl



Scheme 4. Rearrangement of **21**; reagents and conditions: a) $Ph_3P{=}CHOCH_2CH_2SiMe_3$, diethyl ether, 0 °C; (*E*)/(*Z*) = 1:3 (44%); b) **18**, *n*BuLi, diethyl ether, −78 °C → −40 °C (80%); c) KHMDS, 18-crown-6, THF, 0 °C; NH_4Cl, H_2O (70%)

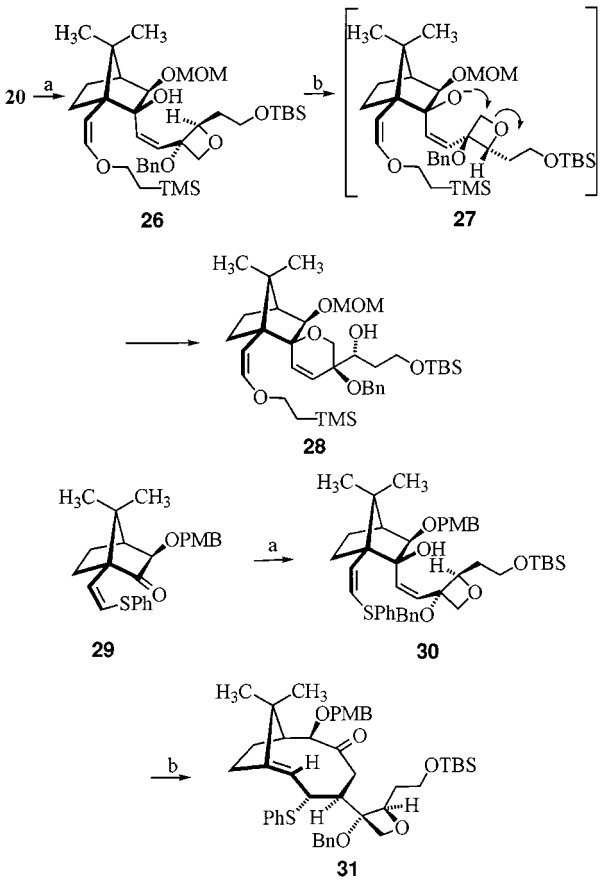


Scheme 5. Rearrangement of **24**; reagents and conditions: a) $Ph_3P{=}CHSPh$, THF, 20 °C, (*E*)/(*Z*) = 1:3 (84%); b) **18**, *n*BuLi, diethyl ether, −78 °C → −40 °C (71%); c) KHMDS, 18-crown-6, THF, −78 °C; NH_4Cl, H_2O (85%)

substituent. In such cases, rearrangement is complete within 45 min at −78 °C.[10a]

In contrast, the Wittig olefination of **19** with triphenyl(-phenylthiomethylene)phosphorane[14] provided **23**, which served as a useful precursor to **24** (Scheme 5). When this carbinol was brought into anionic oxy-Cope rearrangement under entirely parallel conditions, the conversion into **25** was noted to be complete within 5 min at −78 °C! Total stereocontrol was likewise realized in this example.

In the time intervening since the discovery of this phenomenon, alkoxy and alkylthio substituent effects on the anionic oxy-Cope rearrangement have been evaluated by means of hybrid density functional theory.[15] When such functionality is positioned either at C-4 or C-6 of a 3-hydroxy-1,5-hexadiene, two divergent effects are seen. A CH_3O substituent decelerates the reaction and favors operation of a concerted mechanism. This effect arises from higher stabilization of the alkene in the reactant than the transition state. When the group involved is CH_3S, bond dissociation energies point to significant acceleration with adoption of a stepwise cleavage pathway. Thus, theory correlates well with experimental observation. Beyond this, kinetic studies on simple structural analogs of **3** are now available.[16] Thiophenoxy groups were found to lower the activation engergy by 3−4 kcal/mol, such that k_S/k_O ranged from 6600 to 15700 depending on the geometry of the substituted double bond.



Scheme 6. Contrasting isomerization behavior of **26** and **30**; reagents and conditions: a) **12**, *n*BuLi, diethyl ether, −110 °C (83% for **20**, 80% for **29**); b) $KN(SiMe_3)_2$, 18-crown-6, THF; for **26**, −78 °C → −10 °C (76%); for **30**, −78 °C (78%)

Our original findings provided us with an opportunity to probe their synthetic potential in the context of Scheme 6. In this instance, **26** and **30**, available from the known ketones **20** and **29**, respectively, were noted to rearrange at qualitatively the same rate. This kinetic profile was clearly different than that exhibited by **21** and **24**. However, while **30** continued to adhere to a [3,3]-sigmatropic isomerization pathway, **26** reacted by an alternative route involving intramolecular S_N2 attack by the potassium alkoxide at the oxetane ring as in **27** to give **28**. In this case, therefore, a direct comparison of the rates of disappearance of the two *exo*-norbornanols is not warranted. What is clear, however, is the fact that the anionic oxy-Cope rearrangement of **26** is sufficiently slow to allow the oxetane fragmentation to operate. The sulfur analog **30** exhibits no detectable tendency to proceed in this direction.

Conclusions

The effects brought on by a *p*-anisyloxy and a phenylthio substituent positioned at C-6 of structurally related 3-ox-

ido-1,5-hexadienes have been elucidated in the context of a program of taxane synthesis. Whereas the oxygen-containing group proved to have a modest decelerating effect on the anionic oxy-Cope rearrangement, the sulfur-containing substituent promoted remarkable *added* acceleration to this sigmatropic process. This highly divergent response provides the first unambiguous glimpse of the subtle way in which structural rearrangements of this type can be modulated. From the practical vantage point, it is now clear that the matching of an oxy-Cope pathway with proper use of sulfur-containing groups holds considerable synthetic promise. The conversion of **30** into **31** is exemplary. In certain cases exemplified by **26**, failure to take advantage of this kinetic acceleration can result in rerouting of the planned reaction as a consequence of the accompanying deceleration of the sigmatropic event.

Experimental Section

General Remarks: Melting points are uncorrected. The column-chromatographic separations were performed with Woelm silica gel (230−400 mesh). Solvents were reagent grade and in most cases dried prior to use. The purity of all compounds was shown to be > 95% by TLC and high-field ^{1}H and ^{13}C NMR. The high-resolution and fast-atom-bombardment spectra were recorded at The Ohio State University Campus Chemical Instrumentation Center. Elemental analyses were performed at Atlantic Microlab, Inc., Norcross, GA, USA.

6-*O*-(*tert*-Butyldimethylsilyl)-5-deoxy-1,2-*O*-isopropylidene-3-*C*-vinyl-α-D-*ribo*-hexafuranose (8): A solution of **7**[7] (957 mg, 3.01 mmol) in CH_2Cl_2 (20 mL) was treated with the Dess−Martin periodinane (2.5 g, 5.9 mmol), stirred for 3 h at room temperature, diluted with diethyl ether, and filtered. The filtrate was concentrated and the residue was purified by flash column chromatography (elution with 6:1 hexanes/ethyl acetate) to provide the ketone as a pale yellow oil. This oil was redissolved in diethyl ether (16 mL), cooled to −78 °C, treated with vinylmagnesium bromide (1.0 M in THF, 7.5 mmol), and stirred for 20 min at that temperature. At the end of this time, the reaction mixture was quenched with saturated NH_4Cl solution and extracted with diethyl ether. The combined organic layers were dried ($MgSO_4$) and concentrated. Flash chromatography of the residue on silica gel (elution with 15:1 hexanes/ethyl acetate) afforded **8** (0.815 g, 79% for 2 steps) as a colorless oil. − IR (neat): $\tilde{\nu}$ = 3538, 1477, 1378, 1253 cm^{-1}. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.77 (d, *J* = 3.8 Hz, 1 H), 5.76 (dd, *J* = 17.4, 10.9 Hz, 1 H), 5.51 (dd, *J* = 17.4, 1.7 Hz, 1 H), 5.31 (dd, *J* = 10.9, 1.7 Hz, 1 H), 4.24 (d, *J* = 3.8 Hz, 1 H), 4.03 (t, *J* = 6.5 Hz, 1 H), 3.80−3.65 (m, 2 H), 3.23 (s, 1 H), 1.80−1.62 (m, 2 H), 1.60 (s, 3 H), 1.40 (s, 3 H), 0.89 (s, 9 H), 0.06 (s, 6 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.1, 116.1, 112.5, 103.5, 83.6, 79.9, 79.2, 60.3, 31.6, 26.4, 25.98, 18.3, −5.5. − HRMS (EI): calcd. for $C_{17}H_{32}O_5Si$ [M$^+$ − H] 343.1941, found 343.1932.

***O*-Benzylation of 8:** A stirred solution of **8** (815 mg, 2.37 mmol) in THF (5 mL) and DMF (5 mL) was treated with sodium hydride (0.58 g, 24.2 mmol) and stirred for 1 h at 0 °C, at which point benzyl bromide (0.86 g, 5.03 mmol) and tetra-*n*-butylammonium iodide (10 mg) were introduced. The reaction mixture was stirred at 0 °C for 20 min, allowed to warm to room temperature, and stirred for an additional 50 min. The product was extracted with diethyl ether, dried ($MgSO_4$), concentrated, and chromatographed on silica gel (elution with 40:1 hexanes/ethyl acetate) to provide the *O*-benzyl derivative (0.99 g, 96%) as a white crystalline solid, m.p. 50−51 °C. − IR (neat): $\tilde{\nu}$ = 1462, 1384, 1255 cm^{-1}. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40−7.24 (m, 5 H), 5.82 (d, *J* = 3.5 Hz, 1 H), 5.76 (dd, *J* = 17.9, 11.3 Hz, 1 H), 5.45 (d, *J* = 11.3 Hz, 1 H), 5.27 (d, *J* = 17.9 Hz, 1 H), 4.68 (d, *J* = 11.3 Hz, 1 H), 4.61 (d, *J* = 3.5 Hz, 1 H), 4.58 (d, *J* = 11.3 Hz, 1 H), 4.27 (dd, *J* = 9.5, 3.6 Hz, 1 H), 3.89−3.66 (m, 2 H), 1.89−1.81 (m, 1 H), 1.80−1.59 (m, 1 H), 1.59 (s, 3 H), 1.38 (s, 3 H), 0.88 (s, 9 H), 0.04 (s, 6 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.7, 135.2, 128.0, 127.2, 127.1, 118.0, 112.4, 104.2, 85.1, 81.1, 78.2, 66.9, 60.2, 32.4, 26.7, 26.6, 25.9, 18.2, −5.4. − HRMS (EI): calcd. for $C_{24}H_{38}O_5Si$ [M$^+$ − H] 419.2255, found 419.2242. − $[\alpha]_D^{22}$ = +66.0 (*c* = 2.7, $CHCl_3$). − $C_{24}H_{38}O_5Si$ (438.632): calcd. C 66.32, H 8.82; found C 66.29, H 8.84.

(2*S*,3*R*)-2-(Benzyloxy)-5-(*tert*-butyldimethylsiloxy)-2-vinyl-1,3-pentanediol (10): To a cold (−78 °C) solution of titanium tetrachloride (1.0 M in CH_2Cl_2, 17 mmol) in CH_2Cl_2 (40 mL) was added a solution of the above compound (1.225 g, 2.82 mmol) in CH_2Cl_2 via syringe. The resulting dark purple solution was immediately poured into cold (0 °C) saturated $NaHCO_3$ solution, diluted with diethyl ether, and stirred at room temperature for about 12 h. The organic phase was separated, dried ($MgSO_4$), and concentrated. Flash chromatography of the residue on silica gel (elution with 6:1 hexanes/ethyl acetate) furnished the lactol (0.708 g) as a colorless oil. After flushing of the column with ethyl acetate, concentrating, and reprotecting with TBSCl following the usual procedure, there was isolated an additional 0.146 g of desired product (total yield, 81%). This material was used directly. − A stirred solution of the lactol (158 mg, 0.401 mol) in CH_2Cl_2 (5 mL) was treated with the periodinane (0.46 g, 1.08 mmol), stirred for 20 min, diluted with diethyl ether, and filtered. The filtrate was concentrated and the remaining oil was purified by flash chromatography on silica gel (elution with 10:1 hexanes/ethyl acetate) to give the aldehyde (0.123 g) as a pale yellow oil. The aldehyde was dissolved in methanol (2 mL), cooled to 0 °C, and sodium tetrahydroborate (0.06 g, 1.58 mmol) was added portionwise. After 30 min at 0 °C, water was introduced, the solvent was evaporated and the residue was partitioned between water and diethyl ether. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried ($MgSO_4$) and concentrated to leave a residue that was purified by flash chromatography (elution with 10:1 hexanes/ethyl acetate) to give **10** (111 mg, 76% for 2 steps) as a white solid, m.p. 59−61 °C. − IR (neat): $\tilde{\nu}$ = 3480, 1471, 1254 cm^{-1}. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41−7.20 (m, 5 H), 5.77 (dd, *J* = 17.7, 11.3 Hz, 1 H), 5.41 (dd, *J* = 11.3, 1.3 Hz, 1 H), 5.36 (dd, *J* = 17.7, 1.3 Hz, 1 H), 4.58 (s, 2 H), 4.09−4.02 (m, 2 H), 3.95−3.79 (m, 3 H), 3.65−3.50 (br s, 1 H), 3.08−2.75 (br m, 1 H), 1.90−1.82 (m, 1 H), 1.77−1.64 (m, 1 H), 0.89 (s, 9 H), 0.07 (s, 6 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.9, 135.4, 128.3, 127.4, 118.4, 80.7, 75.1, 64.6, 62.6, 62.2, 33.4, 25.8, 18.1, −5.5. − MS (FAB): calcd. for $C_{20}H_{34}O_4Si$ [M$^+$ + H] 367.22, found 367.22. − $[\alpha]_D^{22}$ = +20.6 (*c* = 0.85, $CHCl_3$). − $C_{20}H_{34}O_4Si$ (370.556): calcd. C 65.53, H 9.36; found C 65.42, H 9.37.

{2-[(2*R*,3*S*)-3-(Benzyloxy)-3-vinyl-2-oxetanyl]ethoxy}-*tert*-butyldimethylsilane (11): Potassium hexamethyldisilazide (1 mL of 0.5 M in toluene, 0.5 mmol) was added to a solution of **10** (82 mg, 0.22 mmol) in THF (3.7 mL) at −78 °C and stirred for 30 min. The reaction mixture was treated with *N*-phenyltriflimide (180 mg, 0.504 mmol) in THF (2 mL) via cannula, allowed to stir for 30 min at −78 °C, quenched with saturated $NaHCO_3$ solution, and extracted with diethyl ether. The combined organic layers were dried

($MgSO_4$) and concentrated, and pure **11** was isolated as a colorless oil (57 mg, 74%) following flash chromatography on silica gel (elution with 60:1 hexanes/ether). − IR ($CHCl_3$): $\tilde{\nu}$ = 1468, 1256, 1162 cm^{-1}. − ^1H NMR (300 MHz, C_6D_6): δ = 7.39−7.26 (m, 5 H), 6.02 (dd, *J* = 17.6, 11.0 Hz, 1 H), 5.54 (dd, *J* = 11.0, 1.1 Hz, 1 H), 5.48 (dd, *J* = 17.6, 1.1 Hz, 1 H), 4.97 (t, *J* = 6.9 Hz, 1 H), 4.63 (d, *J* = 6.8 Hz, 1 H), 4.55 (d, *J* = 6.8 Hz, 1 H), 4.45 (d, *J* = 11.4 Hz, 1 H), 4.33 (d, *J* = 11.4 Hz, 1 H), 3.69−3.62 (m, 2 H), 1.85−1.78 (m, 2 H), 0.89 (s, 9 H), 0.48 (s, 6 H). − ^{13}C NMR (75 MHz, C_6D_6): δ = 138.9, 135.3, 128.5, 128.3, 127.7 (2 C), 118.1, 87.2, 82.1, 74.5, 66.4, 58.9, 36.3, 26.1, 18.5, −5.3. − MS (FAB): calcd. for $C_{20}H_{32}O_3Si$ [M^+ + H] 349.22, found 349.22. − $[\alpha]_D^{22}$ = +66.9 (*c* = 0.9, $CHCl_3$). − $C_{20}H_{32}O_3Si$ (352.540): calcd. C 68.92, H 9.26; found C 69.02, H 9.32.

[2-{(2*R*,3*S*)-3-(Benzyloxy)-3-[(*Z*)-2-iodovinyl]-2-oxetanyl}ethoxy]-*tert*-butyldimethylsilane (12): To a stirred solution of **11** (230 mg, 0.661 mmmol) in THF (6 mL) and H_2O (1.2 mL) was sequentially added an osmium tetroxide solution (0.17 M in THF, 0.13 mmol), *N*-methylmorpholine *N*-oxide (150 mg, 1.28 mmol), and H_2O (1.2 mL). The resulting brown black solution was stirred for about 12 h, treated with buffer (pH = 7) and sodium periodate (350 mg, 1.64 mmol). After an additional 1.5 h, a 20% Na_2SO_4 solution was introduced and stirring was maintained for 10 h prior to extraction with diethyl ether and drying. A solution of (iodomethyl)triphenylphosphonium iodide (765 mg, 1.90 mmol) in THF (7 mL) to which sodium hexamethyldisilazide (1.0 M in THF, 1.44 mmol) had been introduced was stirred for 5 min, cooled to −78 °C, treated with the aldehyde generated above, dissolved in THF (1 mL) via cannula and stirred at −78 °C for 10 min. The reaction mixture was quenched with water, extracted with diethyl ether, dried ($MgSO_4$), and concentrated. Flash chromatography of the residue on silica gel (elution with 30:1 hexanes/ethyl acetate) provided **12** (216 mg, 69% for 3 steps) as a pale yellow oil. − ^1H NMR (300 MHz, C_6D_6): δ = 7.36 (d, *J* = 7.2 Hz, 2 H), 7.20−7.07 (m, 3 H), 6.44 (d, *J* = 8.4 Hz, 1 H), 6.27 (d, *J* = 8.4 Hz, 1 H), 5.11 (dd, *J* = 8.6, 5.0 Hz, 1 H), 4.76 (d, *J* = 7.0 Hz, 1 H), 4.67 (d, *J* = 7.0 Hz, 1 H), 4.24 (d, *J* = 11.1 Hz, 1 H), 4.15 (d, *J* = 11.1 Hz, 1 H), 3.69 (t, *J* = 6.7 Hz, 1 H), 1.88−1.80 (m, 2 H), 0.94 (s, 9 H), 0.04 (s, 6 H). − ^{13}C NMR (75 MHz, C_6D_6): δ = 137.9, 136.5, 128.4, 128.0, 127.7, 87.7, 85.6, 81.3, 77.9, 66.5, 58.8, 35.9, 25.9, 18.3, −5.4. − HRMS (EI): calcd. for $C_{20}H_{31}IO_3Si$ [M^+] 475.1124, found 475.1183.

(2*S*,3*R*)-2-(Benzyloxy)-3-[(*p*-methoxybenzyl)oxy]-2-{[(*p*-methoxybenzyl)oxy]methyl}-4-penten-1-yl Pivalate (15): Lithium aluminum hydride (14 mg, 0.37 mmol) was added to a solution of aldehyde **14**[10] (140 mg, 0.290 mmol) in diethyl ether (5 mL) and stirred for 30 min, quenched with water, and extracted with diethyl ether. The combined ethereal layers were washed with water, dried ($MgSO_4$), and concentrated. The residue was dissolved in CH_2Cl_2 (2 mL), and treated with 4-(dimethylamino)pyridine (200 mg, 1.64 mmol) and trimethylacetyl chloride (150 mg, 1.24 mmol). The resulting solution was stirred for 5 h, quenched with saturated $NaHCO_3$ solution, and extracted with diethyl ether. The combined extracts were washed with water and dried ($MgSO_4$). After concentration, the residue was purified by chromatography on silica gel (elution with 1:4 ethyl acetate/hexanes) to provide **15** as a colorless oil (133 mg, 81%). − IR (neat): $\tilde{\nu}$ = 1729, 1613, 1248, 1096 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$): δ = 7.34−7.32 (m, 4 H), 7.30−7.20 (m, 5 H), 6.91−6.87 (m, 4 H), 6.05−5.93 (m, 1 H), 5.42−5.30 (m, 2 H), 4.85 (d, *J* = 11.3 Hz, 1 H), 4.71 (d, *J* = 3.4 Hz, 1 H), 4.68 (d, *J* = 4.3 Hz, 1 H), 4.62 (d, *J* = 11.3 Hz, 1 H), 4.43 (s, 2 H), 4.40 (d, *J* = 12.3 Hz, 1 H), 4.31 (d, *J* = 11.3 Hz, 1 H), 4.22 (d, *J* = 7.7 Hz, 1 H), 3.82 (s, 6 H), 3.66 (d, *J* = 9.6 Hz, 1 H), 3.53 (d, *J* = 9.6 Hz, 1 H), 1.20 (s, 9 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.9, 159.1, 159.0, 139.3, 134.0, 130.4, 130.2, 129.2 (2 C), 129.1 (2 C), 128.0 (2 C), 127.3 (2 C), 127.0, 119.6, 113.7 (4 C), 81.7, 79.6, 72.9, 70.6, 68.8, 66.2, 62.3, 55.1, 38.8, 27.1 (3 C). − HRMS (EI): calcd. for $C_{34}H_{42}O_7$ [M^+] 562.2930, found 562.2927. − $[\alpha]_D^{20}$ = −18.1 (*c* = 0.70, $CHCl_3$).

(2*S*,3*R*)-2-(Benzyloxy)-5-hydroxy-3-[(*p*-methoxybenzyl)oxy]-2-{[(*p*-methoxybenzyl)oxy]methyl}-1-pentyl Pivalate (16): A solution of 9-BBN in THF (32 mL of 0.5 M, 16 mmol) was added to a solution of **15** (4.56 g, 8.44 mmol) in THF (100 mL) under N_2. The resulting solution was stirred for 15 h, treated successively with a sodium hydroxide solution (20 mL of 3 M, 60 mmol) and hydrogen peroxide (12 mL of 30%, 180 mmol), stirred for an additional hour, and extracted with diethyl ether. The combined extracts were washed with water, dried ($MgSO_4$), and concentrated to leave an oil which was chromatographed on silica gel (elution with 2:3 ethyl acetate/hexanes) to afford **16** as a colorless oil (4.50 g, 96%). − IR (neat): $\tilde{\nu}$ = 3454, 1729, 1612, 1173 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$): δ = 7.33−7.21 (m, 9 H), 6.90 (d, *J* = 8.1 Hz, 4 H), 4.76 (d, *J* = 11.1 Hz, 1 H), 4.67 (d, *J* = 11.1 Hz, 1 H), 4.58, (s, 2 H), 4.50 (s, 2 H), 4.46 (s, 2 H), 4.05 (dd, *J* = 8.5, 4.0 Hz, 1 H), 3.80, (s, 6 H), 3.78−3.62 (m, 4 H), 2.35−1.97 (br, 1 H), 2.13−2.03 (m, 1 H), 1.94−1.80 (m, 1 H), 1.20 (s, 9 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.9, 159.2, 159.1, 138.8, 130.4, 129.7, 129.4 (4 C), 128.1 (2 C), 127.4 (2 C), 127.2, 113.7 (4 C), 80.5, 78.3, 73.7, 73.0, 68.6, 66.1, 62.6, 60.2, 55.1 (2 C), 38.8, 32.7, 27.1 (3 C). − HRMS (EI): calcd. for $C_{26}H_{35}O_7$ [M^+ − PMB] 459.2357, found 459.2370. − [a]$_D^{20}$ = −6.0 (*c* = 0.72, $CHCl_3$).

(2*S*,3*R*)-2-(Benzyloxy)-5-(*tert*-butyldimethylsiloxy)-3-[(*p*-methoxybenzyl)oxy]-2-{[(methoxybenzyl)oxy]methyl}-1-pentanol (17): A mixture of **16** (4.58 g, 7.90 mmol), *tert*-butyldimethylsilyl chloride (1.50 g, 9.95 mmol), and imidazole (900 mg, 13.2 mmol) in DMF (50 mL) was stirred for 1 h, quenched with saturated $NaHCO_3$ solution, and extracted with diethyl ether. The combined extracts were washed with water, dried ($MgSO_4$), and concentrated. Flash chromatography of the residue on silica gel (elution with 1:9 ethyl acetate/hexanes) gave an oil which was dissolved in CH_2Cl_2 (100 mL), treated with a solution of DIBAL-H in hexane (13 mL of 1.0 M, 13.0 mmol) at −78 °C under N_2, stirred at that temperature for 1 h, treated with a saturated NH_4Cl solution, warmed to room temp., and extracted with diethyl ether. The combined extracts were washed with water, dried ($MgSO_4$), and concentrated. Purification of the crude product by chromatography on silica gel (elution with 1:4 ethyl acetate/hexanes) gave **17** as a colorless oil (3.64 g, 76% over two steps). − IR (neat): $\tilde{\nu}$ = 3470, 1514, 1248, 1090 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$): δ = 7.37−7.19 (m, 9 H), 6.89−6.84 (m, 4 H), 4.76 (d, *J* = 11.4 Hz, 1 H), 4.68 (d, *J* = 11.4 Hz, 1 H), 4.60 (d, *J* = 10.9 Hz, 1 H), 4.65 (d, *J* = 10.9 Hz, 1 H), 4.48 (s, 2 H), 4.21 (dd, *J* = 9.3, 2.7 Hz, 1 H), 3.91−3.82 (m, 2 H), 3.81 (s, 6 H), 3.80−3.66 (m, 4 H), 2.76 (dd, *J* = 6.8, 5.4 Hz, 1 H), 2.09−1.98 (m, 1 H), 1.83−1.72 (m, 1 H), 0.91 (s, 9 H), 0.062 (s, 3 H), 0.056 (s, 3 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.2, 139.3, 130.7, 130.0, 129.3 (3 C), 128.2 (2 C), 127.4 (2 C), 127.2, 113.8 (2 C), 79.7, 76.9, 74.2, 73.1, 71.0, 65.6, 63.2, 60.0, 55.2, 33.5, 25.9 (3 C), 18.2, −5.3, −5.4. − HRMS (EI): calcd. for $C_{35}H_{50}O_7Si$ [M^+] 610.3326, found 610.3298. − [a]$_D^{20}$ = −0.44 (*c* = 0.32, $CHCl_3$).

{[(3*R*,4*S*,5*Z*)-4-(Benzyloxy)-6-iodo-3-[(*p*-methoxybenzyl)oxy]-4-{[(*p*-methoxybenzyl)oxy]methyl}-5-hexenyl]oxy}-*tert*-butyldimethylsilane (18): Neat oxalyl chloride (1.80 g, 14.18 mmol) was added to a solution of DMSO (1.20 g, 15.38 mmol) in CH_2Cl_2 (100 mL) at −78 °C under N_2 and stirred at that temperature for 20 min prior to

the addition of **17** (3.46 g, 5.67 mmol) in the same solvent (10 mL). The reaction mixture was stirred at −78 ° C for 30 min, treated with triethylamine (30 mL, 0.216 mol), stirred for additional 30 min, warmed to 0 °C, maintained at that temperature for 10 min, quenched with water, and extracted with diethyl ether. The combined extracts were washed with water, dried ($MgSO_4$), and concentrated. Chromatography of the residue on silica gel (elution with 1:4 ethyl acetate/hexanes) gave the oily aldehyde (3.33 g, 96%). − IR (neat). − $\tilde{\nu}$ = 1736, 1514, 1249, 1094 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$): δ = 9.76 (s, 1 H), 7.39−7.16 (m, 9 H), 6.88−6.83 (m, 4 H), 4.76 (d, *J* = 12.8 Hz, 1 H), 4.72 (d, *J* = 12.8 Hz, 1 H), 4.59 (d, *J* = 11.0 Hz, 1 H), 4.48 (d, *J* = 11.0 Hz, 1 H), 4.47 (d, *J* = 11.8 Hz, 1 H), 4.43 (d, *J* = 11.8 Hz, 1 H), 4.16 (dd, *J* = 8.7, 3.5 Hz, 1 H), 3.85 (d, *J* = 10.5 Hz, 1 H), 3.80 (s, 6 H), 3.79−3.67 (m, 3 H), 2.08−1.99 (m, 1 H), 1.81−1.70 (m, 1 H), 0.90 (s, 9 H), 0.41 (s, 3 H), 0.38 (s, 3 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.9, 159.3, 159.2, 138.9, 130.4, 129.6, 129.4 (2 C), 129.3 (2 C), 128.2 (2 C), 127.4, 127.35, 113.8 (2 C), 113.7 (2 C), 86.4, 73.7, 73.2, 69.1, 67.8, 59.8, 55.2, 33.7, 25.9 (3 C), 18.2, −5.31, −5.35. − HRMS (EI): calcd. for $C_{35}H_{48}O_7Si$ [M^+] 608.3169, found 608.3161. − $[\alpha]_D^{20}$ = +1.1 (*c* = 0.28, $CHCl_3$). − A solution of sodium bis(trimethylsilyl)amide in THF (8.0 mL of 1.0 M, 8.0 mmol) was added to a suspension of (iodomethyl)triphenylphosphonium iodide (4.50 g, 8.49 mmol) in THF (40 mL) under N_2. After 2 min, the reddish mixture was cooled to −78 °C, stirred at this temperature for 5 min, and treated with a solution of the above aldehyde (3.20 g, 5.26 mmol) in THF (10 mL). The mixture was stirred at −78 °C for 1 h, quenched with saturated NH_4Cl solution, and extracted with diethyl ether. The combined extracts were washed with water, dried ($MgSO_4$), and concentrated. Chromatography of the residue on silica gel (elution with 1:9 ethyl acetate/hexanes) gave **18** as a heavy oil (3.28 g, 85%). − IR (neat): $\tilde{\nu}$ = 1513, 1091 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$): δ = 7.46−7.20 (m, 9 H), 6.87−6.83 (m, 4 H), 6.74 (d, *J* = 8.9 Hz, 1 H), 6.64 (d, *J* = 8.9 Hz, 1 H), 4.74−4.58 (m, 4 H), 4.43 (s, 2 H), 4.31 (dd, *J* = 9.6, 2.6 Hz, 1 H), 3.90 (d, *J* = 10.3 Hz, 1 H), 3.83−3.80 (m, 1 H), 3.80 (s, 6 H), 3.69 (d, *J* = 7.8 Hz, 1 H), 3.66 (d, *J* = 7.8 Hz, 1 H), 1.97−1.92 (m, 1 H), 1.72−1.62 (m, 1 H), 0.90 (s, 9 H), 0.04 (s, 6 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.2, 159.0, 139.7, 138.8, 131.3, 130.1, 129.5 (2 C), 129.3 (2 C), 128.0 (2 C), 127.5 (2 C), 126.9, 113.7 (2 C), 113.6 (2 C), 83.3, 80.2, 78.1, 74.3, 72.9, 71.0, 66.5, 60.2, 55.2 (2 C), 34.6, 26.0 (3 C), 18.3, −5.2, −5.3. − MS (FAB): calcd. for $C_{36}H_{49}IO_6Si$ [M^+] 732.23, found 732.18. − $[\alpha]_D^{20}$ = −11.3 (*c* = 0.29, $CHCl_3$).

(1*S*,3*R*,4*S*)-3-(Methoxymethoxy)-7,7-dimethyl-1-{(*Z*)-2-[2-(trimethylsilyl)ethoxy]vinyl}bicyclo[2.2.1]heptan-2-one (20): A solution of potassium bis(trimethylsilyl)amide (6.0 mL of 0.5 M, 3.0 mmol) in toluene was added to a suspension of the phosphonium salt[12] (1.40 g, 3.26 mmol) in diethyl ether (10 mL) at 0 °C under N_2. After 5 min of stirring, a solution of **19**[11] (360 mg, 1.59 mmol) in diethyl ether (4 mL) was introduced via a syringe. The mixture was stirred at 0 °C for 30 min, quenched with a saturated NH_4Cl solution, and extracted with diethyl ether. The combined ethereal layers were washed with water, dried ($MgSO_4$), and concentrated. Flash chromatography of the residue on silica gel (elution with 1:9 ethyl acetate/hexanes) gave a colorless oily (*E*)/(*Z*) mixture (1:3) (240 mg, 44%) (NMR analysis). A further separation gave the pure (*Z*) product **20**. − IR (neat): $\tilde{\nu}$ = 1757, 1092, 1040 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$): δ = 6.19 (d, *J* = 7.1 Hz, 1 H), 4.83 (d, *J* = 6.6 Hz, 1 H), 4.71 (d, *J* = 6.6 Hz, 1 H), 4.21 (d, *J* = 7.1 Hz, 1 H), 3.78−3.72 (m, 2 H), 3.67 (s, 1 H), 3.38 (s, 3 H), 2.51−2.42 (m, 1 H), 2.06−1.96 (m, 2 H), 1.72−1.62 (m, 1 H), 1.42−1.34 (m, 1 H), 1.01 (s, 3 H), 0.99 (t, *J* = 7.4 Hz, 2 H), 0.96 (s, 3 H), 0.00 (s, 9 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 215.3, 149.0, 97.3, 96.7, 81.4, 70.1, 60.9, 55.5, 48.7, 47.8, 25.7, 25.4, 21.3, 20.9, 18.4, −1.5. − HRMS (EI): calcd. for $C_{18}H_{32}O_4Si$ [M^+] 340.2070, found 340.2047. − $[\alpha]_D^{20}$ = +58.9 (*c* = 0.30, $CHCl_3$).

(1*S*,2*S*,3*R*,4*S*)-2-{(1*Z*,3*S*,4*R*)-3-(Benzyloxy)-6-(*tert*-butyldimethylsiloxy)-4-[(*p*-methoxybenzyl)oxy]-3-[{(*p*-methoxybenzyl)oxy}methyl]1-hexenyl}-3-(methoxymethoxy)-7,7-dimethyl-1-{(*Z*)-2-[2-trimethylsilyl)ethoxy]vinyl}bicyclo[2.2.1]heptan-2-ol (21): A solution of *n*-butyllithium (0.16 mL of 1.6 M, 0.26 mmol) in hexanes was added to a solution of **18** (190 mg, 0.26 mmol) in diethyl ether (6 mL) at −78 °C under N_2. The resulting solution was stirred for 1 min prior to the introduction of **20** (67 mg, 0.197 mmol) in diethyl ether (2 mL). The reaction mixture was maintained at −78 °C for 30 min, warmed to 0 °C, quenched with saturated NH_4Cl solution, and extracted with diethyl ether. The combined ethereal layers were washed with water, dried ($MgSO_4$), and concentrated. Purification of the residue by chromatography on silica gel (elution with 1:9 ethyl acetate/hexanes) gave **21** as a colorless oil (148 mg, 80%). − IR (neat): $\tilde{\nu}$ = 3345, 1250, 1083 cm^{-1}. − ^1H NMR (300 MHz, C_6D_6): δ = 7.53 (d, *J* = 8.4 Hz, 2 H), 7.34 (d, *J* = 8.6 Hz, 2 H), 7.20−7.17 (m, 4 H), 7.10−7.06 (m, 1 H), 6.85 (d, *J* = 8.6 Hz, 2 H), 6.76 (d, *J* = 8.6 Hz, 2 H), 5.84−5.63 (m, 3 H), 5.00 (d, *J* = 10.6 Hz, 1 H), 4.90−4.71 (m, 5 H), 4.66 (d, *J* = 6.4 Hz, 1 H), 4.31 (s, 2 H), 4.23 (d, *J* = 7.2 Hz, 1 H), 4.17 (d, *J* = 6.7 Hz, 2 H), 3.89−3.78 (m, 2 H), 3.76 (s, 1 H), 3.62−3.49 (m, 2 H), 3.31 (s, 3 H), 3.30−3.27 (m, 1 H), 3.28 (s, 3 H), 3.27 (s, 3 H), 2.45−2.30 (m, 2 H), 2.03−1.75 (m, 4 H), 1.73 (s, 3 H), 1.03 (s, 3 H), 0.96 (s, 9 H), 0.95 (s, 1 H), 0.88 (t, *J* = 8.4 Hz, 2 H), 0.07 (s, 3 H), 0.06 (s, 3 H), −0.09 (s, 9 H). − ^{13}C NMR (75 MHz, C_6D_6): δ = 160.2, 147.4, 142.6, 139.1, 132.0, 131.0, 130.0, 129.7, 128.9, 126.8, 114.5, 114.4, 102.8, 97.0, 90.1, 84.9, 83.9, 75.5, 74.9, 73.3, 72.6, 70.1, 67.7, 61.0, 60.0, 55.6, 55.2, 55.1, 52.4, 50.8, 35.2, 28.4, 26.6, 25.9, 23.4, 23.3, 19.0, 18.9, −1.1, −4.7, −4.8. − MS (FAB): calcd. for $C_{54}H_{82}O_{10}Si_2$ [M^+] 946.54, found 946.47. − $[\alpha]_D^{20}$ = −60.1 (*c* = 0.25, C_6H_6).

(1*S*,2*R*,5*R*,6*R*,7*E*)-5-{(1*S*,2*R*)-1-(Benzyloxy)-4-(*tert*-butyldimethylsiloxy)-2-[(*p*-methoxybenzyl)oxy]-1-[{(*p*-methoxybenzyl)oxy}methyl]butyl}-2-(methoxymethoxy)-11,11-dimethyl-6-[2-(trimethylsilyl)ethoxy]bicyclo[6.2.1]undec-7-en-3-one (22): A solution of potassium bis(trimethylsilyl)amide (0.20 mL of 0.5 M, 0.10 mmol) in toluene was added to a solution of **21** (30 mg, 0.03 mmol) and 18-crown-6 (200 mg, 0.763 mmol) in THF at 0 °C under N_2. After stirring for 5 min, the reaction mixture was quenched with saturated NH_4Cl solution and extracted with diethyl ether. The combined ethereal layers were washed with water, dried ($MgSO_4$), and concentrated. Chromatography of the residue on silica gel (elution with 1:9 ethyl acetate/hexanes) gave **22** a colorless oil (21 mg, 70%). − IR (neat): $\tilde{\nu}$ = 1694 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$): δ = 7.33−7.21 (m, 9 H), 6.87−6.82 (m, 4 H), 5.12 (dd, *J* = 2.2, 1.3 Hz, 1 H), 4.82 (d, *J* = 11.6 Hz, 1 H), 4.77 (d, *J* = 11.6 Hz, 1 H), 4.64−4.38 (m, 8 H), 4.02 (dd, *J* = 8.3, 3.1 Hz, 1 H), 3.84 (d, *J* = 5.6 Hz, 1 H), 3.81 (s, 3 H), 3.80 (s, 3 H), 3.77−3.50 (m, 7 H), 3.44−3.35 (m, 1 H), 3.20 (s, 3 H), 3.09−3.00 (m, 1 H), 2.80−2.68 (m, 1 H), 2.15−1.75 (series of m, 8 H), 1.37 (s, 3 H), 1.07 (s, 3 H), 0.88 (s, 1 H), 0.87 (s, 9 H), 0.85−0.77 (m, 2 H), 0.02 (m, 2 H), 0.00 (s, 3 H), −0.10 (s, 6 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.7, 159.2, 158.9, 145.5, 140.1, 131.3, 130.1, 129.4, 129.1, 128.0, 127.0, 126.7, 124.7, 113.7, 113.6, 96.5, 89.1, 81.8, 77.7, 76.0, 73.7, 73.2, 71.7, 65.8, 64.9, 60.7, 55.7, 55.2, 54.0, 48.4, 46.3, 39.0, 34.3, 26.6, 26.0, 24.3, 23.8, 22.4, 18.5, −1.5, −5.3. − MS (FAB): calcd. for $C_{54}H_{82}O_{10}Si_2$ [M^+] 946.54, found 946.48. − $[\alpha]_D^{20}$ = −35.8 (*c* = 0.12, $CHCl_3$).

(1*S*,3*R*,4*S*)-3-(Methoxymethoxy)-7,7-dimethyl-1-[(*Z*)-2-(phenylthio)vinyl]bicyclo[2.2.1]heptan-2-one (23): To a suspension of the phosphonium salt[15] (2.61 g, 6.21 mmol) in THF (35 mL) was added a solution of potassium bis(trimethylsilyl)amide (12.4 mL of 0.5 M, 6.2 mmol) in toluene at 0 °C. The resulting mixture was stirred at 0 °C for 30 min prior to the introduction of a solution of aldehyde **19** (1.17 g, 5.18 mmol) in THF (10 mL). The reaction mixture was maintained at room temperature for 2 h, quenched with saturated NH_4Cl solution, and diluted with hexanes. The organic layer was separated, washed with water (2 × 50 mL), dried ($MgSO_4$), and concentrated. Chromatography of the residue on silica gel (elution with 1:9 ethyl acetate/hexanes) gave an (*E*)/(*Z*) mixture (1:3, NMR analysis) as an oil (1.37 g, 84%). A further separation of this mixture gave pure **23** as a colorless solid, m.p. 70−71 °C. − IR (neat): $\tilde{\nu}$ = 1755, 1586 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$): δ = 7.38−7.18 (m, 5 H), 6.57 (d, *J* = 10.6 Hz, 1 H), 5.68 (d, *J* = 10.6 Hz, 1 H), 4.58 (d, *J* = 6.6 Hz, 1 H), 4.72 (d, *J* = 6.6 Hz, 1 H), 3.75 (s, 1 H), 3.41 (s, 3 H), 2.37−2.27 (m, 1 H), 2.17−2.03 (m, 3 H), 1.54−1.45 (m, 1 H), 1.12 (s, 3 H), 1.04 (s, 3 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 213.3, 136.5, 129.7, 129.2, 128.9, 126.5, 124.0, 96.6, 81.1, 62.7, 55.5, 49.0, 47.8, 25.4, 25.3, 21.3, 20.7. − HRMS (EI): calcd. for $C_{19}H_{24}O_3S$ [M^+] 332.1446, found 332.1448. − $[\alpha]_D^{20}$ = −68.3 (*c* = 1.26, $CHCl_3$).

(1*S*,2*S*,3*R*,4*S*)-2-{(1*Z*,3*S*,4*R*)-3-(Benzyloxy)-6-(*tert*-butyldimethylsiloxy)-4-[(*p*-methoxybenzyl)oxy]-3-[{(*p*-methoxybenzyl)oxy}methyl]1-hexenyl}-3-(methoxymethoxy)-7,7-dimethyl-1-[(*Z*)-2-(phenylthio)vinyl]bicyclo[2.2.1]heptan-2-ol (24): A solution of *n*-butyllithium of hexanes (0.14 mL of 1.6 M, 0.22 mmol) was added to a solution of **18** (175 mg, 0.24 mmol) in dry ether (6 mL) at −78 °C under N_2. The resulting solution was stirred for 1 min prior to the addition of a solution of **23** (66 mg, 0.20 mmol) in diethyl ether (2 mL). The stirred reaction mixture was maintained at −78 °C for 1 h, warmed to −40 °C, quenched with saturated NH_4Cl solution, brought to room temperature, dried ($MgSO_4$), and extracted with diethyl ether. The combined extracts were washed with water, dried ($MgSO_4$), and concentrated. Purification of the residue by chromatography on silica gel (elution with 1:9 ethyl acetate/hexanes) gave **24** as a colorless oil (122 mg, 71%). − IR (neat): $\tilde{\nu}$ = 3322, 1612 cm^{-1}. − ^1H NMR (300 MHz, C_6D_6): δ = 7.54 (d, *J* = 6.9 Hz, 2 H), 7.38 (d, *J* = 8.4 Hz, 2 H), 7.30 (d, *J* = 7.3 Hz, 2 H), 7.22 (d, *J* = 8.7 Hz, 2 H), 7.14−7.01 (m, 5 H), 6.98−6.87 (m, 3 H), 6.79 (d, *J* = 7.0 Hz, 2 H), 6.13 (s, 1 H), 6.01 (d, *J* = 10.8 Hz, 1 H), 5.78 (d, *J* = 14.0 Hz, 1 H), 5.68 (d, *J* = 14.0 Hz, 1 H), 5.51 (d, *J* = 10.8 Hz, 1 H), 5.06 (d, *J* = 10.3 Hz, 1 H), 4.93−4.75 (m, 5 H), 4.74 (d, *J* = 6.5 Hz, 1 H), 4.32 (s, 2 H), 4.22 (d, *J* = 10.0 Hz, 1 H), 4.14 (d, *J* = 10.0 Hz, 1 H), 3.90−3.81 (m, 1 H), 3.79 (s, 1 H), 3.70−3.60 (m, 1 H), 3.35 (s, 3 H), 3.32 (s, 3 H), 3.29 (s, 3 H), 2.42−2.32 (m, 1 H), 2.30−2.15 (m, 1 H), 2.13−1.97 (m, 1 H), 1.92 (d, *J* = 5.9 Hz, 1 H), 1.90−1.79 (m, 1 H), 1.75 (s, 3 H), 1.74−1.65 (m, 1 H), 0.98 (s, 9 H), 0.90 (s, 3 H), 0.059 (s, 3 H), 0.056 (s, 3 H). − ^{13}C NMR (75 MHz, C_6D_6): δ = 160.2, 141.8, 139.0, 138.6, 132.1, 130.9, 130.2, 129.9, 129.5, 129.4, 129.0, 128.9, 127.5, 126.3, 125.9, 114.53, 114.46, 96.8, 89.7, 85.4, 83.8, 74.9, 74.5, 73.3, 72.6, 68.0, 62.5, 60.6, 55.6, 55.2, 55.1, 53.0, 51.0, 35.1, 27.9, 26.5, 25.7, 23.1, 23.0, 18.8, −4.8, −4.9. − MS (FAB): calcd. for $C_{55}H_{74}O_4SSi$ [M^+] 938.48, found 938.54. − $[\alpha]_D^{22}$ = −177.5 (*c* = 0.24, $CHCl_3$).

(1*S*,2*R*,4*S*,5*S*,6*R*,7*E*)-5-{(1*S*,2*R*)-1-(Benzyloxy)-4-(*tert*-butyldimethylsiloxy)-2-[(*p*-methoxybenzyl)oxy]-1-[{(*p*-methoxybenzyl)oxy}methyl]butyl}-2-(methoxymethoxy)-11,11-dimethyl-6-(phenylthio)bicyclo[6.2.1]undec-7-en-3-one (25): Potassium bis(trimethylsilyl)amide solution in toluene (1.8 mL of 0.5 M, 0.90 mmol) was added to a solution of **24** (270 mg, 0.287 mmol) and 18-crown-6 (410 mg, 1.56 mmol) in THF (30 mL) at −78 °C under N_2. The reaction mixture was stirred for 10 min prior to the addition of a solution of methyl iodide (1.8 g, 12.7 mmol) in THF (5 mL), stirred at the same temperature for 4.5 h, quenched with water, warmed to room temperature, and extracted with diethyl ether. The combined extracts were washed with water, dried ($MgSO_4$), and concentrated. Chromatography of the residue on silica gel (elution with 1:5 ethyl acetate/hexanes) gave **25** as a colorless oil (240 mg, 88%). − IR (neat): $\tilde{\nu}$ = 1712, 1514, 1249 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 7.0 Hz, 2 H), 7.32−7.23 (m, 5 H), 7.17 (d, *J* = 3.8, 1 H), 7.12−7.08 (m, 1 H), 6.84 (d, *J* = 8.5 Hz, 4 H), 5.21 (d, *J* = 5.8 Hz, 1 H), 5.08 (d, *J* = 11.1 Hz, 1 H), 4.93 (d, *J* = 11.1 Hz, 1 H), 4.73−4.66 (m, 3 H), 4.59−4.48 (m, 4 H), 4.44−4.37 (m, 2 H), 4.10 (s, 1 H), 4.04−3.95 (m, 1 H), 3.88 (d, *J* = 9.8, 1 H), 3.81 (s, 3 H), 3.80 (s, 3 H), 3.79 (s, 3 H), 3.77−3.63 (m, 3 H), 3.35 (s, 3 H), 3.30−2.95 (m, 1 H), 2.69 (d, *J* = 3.0 Hz, 1 H), 2.33−2.25 (m, 1 H), 2.16−1.98 (m, 4 H), 1.63−1.51 (m, 2 H), 1.24 (d, *J* = 7.4 Hz, 3 H), 1.12 (s, 3 H), 0.91 (s, 3 H), 0.87 (s, 9 H), 0.01 (s, 6 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.4, 159.0, 158.7, 149.7, 140.5, 137.3, 131.8, 130.6, 129.1, 128.7, 128.4, 128.3, 127.9, 127.8, 126.7, 125.2, 122.0, 113.6, 113.5, 95.0, 86.1, 84.4, 75.9, 73.7, 72.5, 71.2, 67.4, 60.7, 55.6, 55.2, 54.9, 54.3, 46.8, 46.5, 44.8, 33.5, 27.0, 26.3, 25.9, 24.3, 20.0, 18.1, −5.3, −5.4. − MS (FAB): calcd. for $C_{56}H_{76}O_4SSi$ [M^+] 952.50, found 952.54. − $[\alpha]_D^{22}$ = −83.1 (*c* = 0.38, $CHCl_3$).

(1*S*,2*S*,3*R*,4*S*)-2-{(*Z*)-2-[(2*R*,3*S*)-3-(Benzyloxy)-2-[2-(*tert*-butyldimethylsiloxy)ethyl]-3-oxetanyl]vinyl}-3-(methoxymethoxy)-7,7-dimethyl-1-{(*Z*)-2-[2-(trimethylsilyl)ethoxy]vinyl}bicyclo[2.2.1]heptan-2-ol (26): A solution of **12** (110 mg, 0.232 mmol) in diethyl ether (2.0 mL) at −110 °C was treated with *tert*-butyllithium (1.7 M in toluene, 262 μL, 0.446 mmol), followed by a solution of **20** (60.7 mg, 0.178 mmol) in diethyl ether (0.2 mL). After 30 min, the reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic phases were dried and concentrated to leave a residue which was chromatographed on silica gel (elution with 6:1 hexanes/ethyl acetate) to give **26** as a colorless oil (70 mg, 57%, 83% based on recovered **20**, 19.1 mg, 31%). − IR (neat): $\tilde{\nu}$ = 3466, 1660, 1462, 1388, 1368 cm^{-1}. − ^1H NMR (300 MHz, C_6D_6): δ = 7.32 (d, *J* = 17.2 Hz, 2 H), 7.16−7.02 (m, 3 H), 5.98 (d, *J* = 12.8 Hz, 1 H), 5.84 (d, *J* = 7.3 Hz, 1 H), 5.46 (d, *J* = 12.8 Hz, 1 H), 5.08 (br d, *J* = 10.2 Hz, 1 H), 4.78 (d, *J* = 7.1 Hz, 1 H), 4.63 (d, *J* = 7.3 Hz, 1 H), 4.56 (d, *J* = 7.1 Hz, 1 H), 4.45 (d, *J* = 6.6 Hz, 1 H), 4.44 (d, *J* = 12.3 Hz, 1 H), 4.36 (d, *J* = 12.3 Hz, 1 H), 4.26 (s, 1 H), 4.16 (d, *J* = 6.6 Hz, 1 H), 3.88−3.78 (m, 2 H), 3.59−3.49 (m, 2 H), 3.41 (s, 1 H), 3.06 (s, 3 H), 2.44−2.31 (m, 2 H), 2.10−1.98 (m, 2 H), 1.95 (d, *J* = 5.1 Hz, 1 H), 1.79−1.70 (m, 1 H), 1.58 (s, 3 H), 1.05−0.83 (m, 3 H), 0.99 (s, 3 H), 0.94 (s, 9 H), 0.44 (s, 6 H), −0.09 (s, 9 H). − ^{13}C NMR (75 MHz, C_6D_6): δ = 147.4, 142.9, 138.8, 128.2 (2 C), 127.1, 126.6 (2 C), 124.0, 101.5, 97.4, 90.4, 87.6, 84.1, 80.7, 79.7, 69.6, 65.5, 59.3, 58.6, 55.1, 51.6, 49.5, 37.1, 27.7, 25.9 (3 C), 25.0, 22.9, 22.6, 18.4, 18.2, −1.7 (3 C), −5.50, −5.52. − MS (FAB): calcd. for $C_{38}H_{64}O_7Si_2$ [M^+] 668.42, found 668.44. − $[\alpha]_D^{24}$ = −96.6 (*c* = 0.304, $CHCl_3$).

(α*R*,1*S*,2*S*,3*R*,4*S*,5′*S*)-5′-(Benzyloxy)-α-[2-(*tert*-butyldimethylsiloxy)ethyl]-5′,6′-dihydro-3-(methoxymethoxy)-7,7-dimethyl-1-{(*Z*)-2-[2-(trimethylsilyl)ethoxy]vinyl}spiro[bicyclo[2.2.1]heptane-2,2′-[2*H*]pyran]-5′-methanol (28): To a solution of **26** (22 mg, 0.032 mmol) and 18-crown-6 (18.6 mg, 0.070 mmol) in dry THF (2.0 mL) at −78 °C was added potassium hexamethyldisilazide (0.5 M in toluene, 160 μL, 0.08 mmol). After being stirred for 10 min at −78 °C, the reaction mixture was warmed to −10 °C during 30 min, quenched with cold methanol (0.1 mL), diluted with brine,

and extracted with ethyl acetate. The combined extracts were dried and concentrated to leave a residue that was chromatographed on silica gel (elution with 10:1 hexanes/ethyl acetate) to afford **28** (17 mg, 76%) as a colorless oil. − IR (neat): $\tilde{\nu}$ = 3492, 1661, 1462, 1389 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$): δ = 7.34−7.21 (m, 5 H), 6.36 (d, *J* = 10.7 Hz, 1 H), 5.88 (dd, *J* = 7.1, 0.6 Hz, 1 H), 5.81 (d, *J* = 10.7 Hz, 1 H), 4.72 (s, 2 H), 4.71 (d, *J* = 6.6 Hz, 1 H), 4.62 (d, *J* = 6.6 Hz, 1 H), 4.43 (d, *J* = 7.1 Hz, 1 H), 4.14 (d, *J* = 12.7 Hz, 1 H), 4.06 (d, *J* = 12.7 Hz, 1 H), 3.80−3.73 (m, 2 H), 3.68−3.58 (m, 2 H), 3.59 (dd, *J* = 9.8, 2.2 Hz, 1 H), 3.51 (s, 1 H), 3.38 (s, 3 H), 2.86 (d, *J* = 4.4 Hz, 1 H), 2.05−1.99 (m, 2 H), 1.83−1.58 (m, 4 H), 1.58 (s, 1 H), 1.36 (s, 3 H), 1.07−0.82 (m, 2 H), 0.88 (s, 9 H), 0.84 (s, 3 H), 0.44 (s, 3 H), 0.42 (s, 3 H), −0.34 (s, 9 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.7, 140.2, 138.3, 128.2 (2 C), 127.3 (2 C), 127.0, 124.0, 102.7, 97.0, 90.7, 84.2, 73.8, 73.0, 69.7, 68.6, 67.0, 61.1, 58.0, 55.7, 51.2, 48.8, 33.9, 27.5, 25.9 (3 C), 24.5, 22.4, 22.1, 18.4, 18.3, −1.5 (3 C), −5.4 (2 C). − MS (FAB): calcd. for $C_{38}H_{64}O_7Si_2$ [M^+] 668.42, found 668.36. − $[\alpha]_D^{24}$ = −16.8 (*c* = 0.66, $CHCl_3$).

(1*S*,2*S*,3*R*,4*S*)-2-{(*Z*)-2-[(2*R*,3*S*)-3-(Benzyloxy)-2-{2-(*tert*-butyldimethylsiloxy)ethyl}-3-oxetanyl]vinyl}-3-[(*p*-methoxybenzyl)oxy]-7,7-dimethyl-1-[(*Z*)-2-phenylthio)vinyl]bicyclo[2.2.1]heptan-2-ol (30): A solution of **12** (110 mg, 0.232 mmol) in diethyl ether (2.0 mL) at −110 °C was treated with *tert*-butyllithium (1.7 M in toluene, 250 μL, 0.42 mol), followed by a solution of **29**[10b] (73 mg, 0.18 mmol) in diethyl ether (0.2 mL). After 30 min, the reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic phases were dried and concentrated to leave a residue that was chromatographed on silica gel (elution with 6:1 hexanes/ethyl acetate) to afford **30** (108 mg, 80%) as a colorless oil. − IR (neat): $\tilde{\nu}$ = 3446, 1514, 1249 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$): δ = 7.38−7.14 (series of m, 12 H), 6.83−6.79 (m, 2 H), 6.06 (d, *J* = 12.8 Hz, 1 H), 5.99 (d, *J* = 10.9 Hz, 1 H), 5.81 (d, *J* = 12.8 Hz, 1 H), 5.76 (d, *J* = 10.9 Hz, 1 H), 4.88 (dd, *J* = 9.6, 3.9 Hz, 1 H), 4.77 (d, *J* = 7.1 Hz, 1 H), 4.60 (d, *J* = 7.1 Hz, 1 H), 4.59 (d, *J* = 12.2 Hz, 1 H), 4.49 (d, *J* = 11.2 Hz, 1 H), 4.44 (d, *J* = 11.2 Hz, 1 H), 4.38 (d, *J* = 12.2 Hz, 1 H), 4.21 (s, 1 H), 3.79 (s, 3 H), 3.80−3.66 (m, 2 H), 3.41 (s, 1 H), 2.11−1.85 (series of m, 6 H), 1.36 (s, 3 H), 1.26−1.00 (m, 1 H), 0.86 (s, 9 H), 0.85 (s, 3 H), 0.03 (s, 6 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.0, 142.0, 138.3, 137.0, 130.4, 129.0 (2 C), 128.97 (2 C), 128.9 (2 C), 128.1 (2 C), 127.2, 127.0, 126.7, 126.6 (2 C), 126.3, 124.5, 113.7 (2 C) 90.7, 87.7, 84.6, 80.5, 79.8, 72.4, 65.9, 61.2, 58.9, 55.2, 52.3, 48.0, 36.6, 26.9, 25.9 (3 C), 24.7, 22.7, 22.2, 18.3, −5.4 (2 C). − MS (FAB): calcd. for $C_{45}H_{60}O_6Si_2$ [M^+ + H] 757.39, found 757.29. − $[\alpha]_D^{24}$ = −122.4 (*c* = 0.58, $CHCl_3$).

(1*S*,2*R*,5*S*,6*R*,7*E*)-5-{(2*R*,3*S*)-3-(Benzyloxy)-2-[2-(*tert*-butyldimethylsiloxy)ethyl]-3-oxetanyl}-2-[(*p*-methoxybenzyl)oxy]-11,11-dimethyl-6-(phenylthio)bicyclo[6.2.1]undec-7-one (31): To a solution of **30** (25 mg, 0.033 mmol) and 18-crown-6 (19 mg, 0.073 mmol) in dry THF (2.0 mL) at −78 °C was added KHMDS (0.5 M in toluene, 165 μL, 0.08 mmol). After being stirred for 15 min, the reaction mixture was quenched with water and extracted with ethyl acetate. The combined extracts were dried and concentrated to leave a residue that was chromatographed on silica gel (elution with 10:1 hexanes/ethyl acetate) to give **31** (19 mg, 78%) as a colorless oil. − IR (neat): $\tilde{\nu}$ = 1695, 1612, 1514, 1463 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$): δ = 7.41−7.09 (m, 12 H), 6.85−6.80 (m, 2 H), 5.61 (br d, *J* = 5.5 Hz, 1 H), 5.02 (dd, *J* = 10.2, 3.4 Hz, 1 H), 4.88 (d, *J* = 11.6 Hz, 1 H), 4.79−4.64 (m, 2 H), 4.62 (d, *J* = 7.6 Hz, 1 H), 4.39 (d, *J* = 11.7 Hz, 1 H), 4.33 (d, *J* = 11.7 Hz, 1 H), 4.16 (br s, 1 H), 3.77 (s, 3 H), 3.79−3.60 (m, 4 H), 3.46−3.27 (m, 2 H), 2.20−1.84 (series of m, 6 H), 1.75−1.53 (m, 1 H), 1.44 (s, 3 H), 1.04 (s, 3 H), 0.85 (s, 9 H), 0.01 (s, 3 H), −0.01 (s, 3 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 211.9, 159.2, 149.3, 138.7, 137.8, 129.9, 128.9 (2 C), 128.6 (2 C), 128.4 (2 C), 128.2, 127.4 (2 C), 127.1 (2 C), 125.5, 122.9, 113.8 (2 C), 91.1, 86.4, 85.4, 74.6, 72.4, 65.3, 58.8, 55.2, 53.4, 47.3, 47.0, 43.4, 37.5, 36.3, 26.7, 25.9 (3 C), 25.3, 23.7, 22.3, 18.3, −5.4 (2 C). − MS (FAB): calcd. for $C_{45}H_{60}O_6SSi$ [M^+] 756.39, found 756.38. − $[\alpha]_D^{24}$ = −108.6 (*c* = 0.21, $CHCl_3$).

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[1] [1a] L. A. Paquette, M. Zhao, *J. Am. Chem. Soc.* **1998**, *120*, 5203−5212. − [1b] L. A. Paquette, H.-L. Wang, Z. Su, M. Zhao, *J. Am. Chem. Soc.* **1998**, *120*, 5213−5225.
[2] L. A. Paquette, M. Zhao, F. Montgomery, Q. Zeng, T.-Z. Wang, S. Elmore, K. Combrink, H.-L. Wang, S. Bailey, Z. Su, *Pure Appl. Chem.* **1998**, *70*, 1449−1457.
[3] L. A. Paquette, S. K. Huber, R. C. Thompson, *J. Org. Chem.* **1993**, *58*, 6874−6882.
[4] J. N. Johnston, H.-C. Tsui, L. A. Paquette, *J. Org. Chem.* **1998**, *63*, 129−136.
[5] L. A. Paquette, T.-L. Shih, Q. Zeng, J. E. Hofferberth, *Tetrahedron Lett.* **1999**, *40*, 3519−3522.
[6] L. A. Paquette, H.-L. Wang, Q. Zeng, T.-L. Shih, *J. Org. Chem.* **1998**, *63*, 6432−6433.
[7] H.-C. Tsui, L. A. Paquette, *J. Org. Chem.* **1998**, *63*, 9968−9977.
[8] [8a] D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155−4156. − [8b] R. E. Ireland, L. B. Liu, *J. Org. Chem.* **1993**, *58*, 2899.
[9] G. Stork, K. Zhao, *Tetrahedron Lett.* **1989**, *30*, 2173−2174.
[10] [10a] L. A. Paquette, F. J. Montgomery, T.-Z. Wang, *J. Org. Chem.* **1995**, *60*, 7857−7864. − [10b] L. A. Paquette, Q. Zeng, H.-C. Tsui, J. N. Johnston, *J. Org. Chem.* **1998**, *63*, 8491−8509.
[11] S. W. Elmore, L. A. Paquette, *J. Org. Chem.* **1995**, *60*, 889−902.
[12] K. Schönauer, E. Zbiral, *Tetrahedron Lett.* **1983**, *24*, 573−576.
[13] L. A. Paquette, N. A. Pegg, D. Toops, G. D. Maynard, R. D. Rogers, *J. Am. Chem. Soc.* **1990**, *112*, 277−283.
[14] [14a] J. P. Marino, T. Kaneko, *Tetrahedron Lett.* **1973**, 3975−3978. − [14b] I. Vlattas, A. O. Lee, *Tetrahedron Lett.* **1974**, 4451−4454. − [14c] R. Muthukrishnan, M. Schlosser, *Helv. Chim. Acta* **1976**, *59*, 13−20.
[15] F. Haeffner, K. N. Houk, Y. R. Reddy, L. A. Paquette, *J. Am. Chem. Soc.* **1999**, *121*, 11880−11884.
[16] L. A. Paquette, Y. R. Reddy, F. Haeffner, K. N. Houk, *J. Am. Chem. Soc.* **2000**, *122*, 740−741.

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