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Studies of the Synthesis of Providencin: Construction and Assembly of Two Major Subunits

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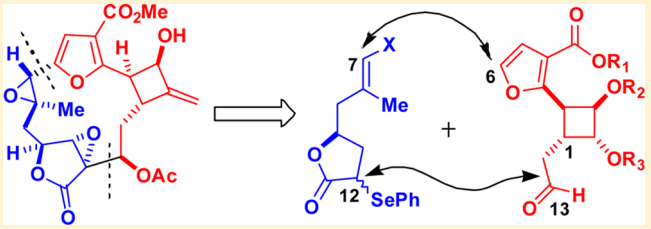
Supporting Information

ABSTRACT: The "northern" sector of the cembranoid diterpene providencin containing a tetrasubstituted cyclobutane was synthesized from the bis(acetonide) of D-glucose using dicyclopentadienylzirconium(0)-mediated oxygen abstraction from a furanose. Oxidative scission of the vinyl substituent of this cyclobutane gave an aldehyde, which was reacted with an alkynylstannane to provide an allenol. Cyclization of the derived allenone with silver nitrate led to a cyclobutylfuran comprising the northern subunit of providencin. The "southern" sector of the cembranoid skeleton containing a trisubstituted iodoalkene attached to an α-phenylselenyl-γ-lactone was synthesized from (*R*)-glycidol. Negishi carbometalation−iodination established the (*E*)-iodoalkene, and addition of the lithio dianion of phenylselenoacetic acid to a tosylate generated the substituted lactone. The two sectors were joined via stannylation of the furan of the northern component followed by Stille cross-coupling of the furylstannane with the iodoalkene of the southern subunit. Linkage of the two segments was also made at C12−C13 of providencin using intermolecular aldol condensation of the enolate from the selenyl lactone of the southern portion with an acetaldehyde appendage on the cyclobutane of the northern sector. Closure of the providencin macrocycle from these conjoined subunits was unsuccessful.



INTRODUCTION

The gorgonian octocorals *Pseudopterogorgia kallos* and *Pseudopterogorgia bipinnata* have proven to be rich sources of novel diterpenes, including many that bear the structural signature of a cembranoid origin.[1] A subset of this family comprises the furanocembranoids, exemplified by the kallolides (e.g., **1**)[2] and the bipinnatins (e.g., **2**),[3] where the common structural motif is a 14-membered macrocycle containing a 2,3,5-trisubstituted furan and a butenolide or epoxidized butenolide (Figure 1). Unique among this group is providencin (**3**), isolated by Rodriguez from *P. kallos* (Bielschowski) collected near Old Providence Island in the southwestern Caribbean sea.[4] The gross structure and relative configuration of providencin were secured through a combination of NMR experiments and X-ray crystallographic analysis, which revealed that the molecule contains a tetrasubstituted cyclobutane embedded in a bicyclo[12.2.0]hexadecane scaffold. These studies exposed important conformational details of the macrocyclic ring in providencin but did not establish its absolute configuration.

Although providencin displays only modest in vitro bioactivity,[4] its novel position within the cembranoid family has prompted several groups to attempt its synthesis. An intriguing approach to the cyclobutanol portion of providencin was conceived by Pattenden on the basis of its proposed biogenesis, in which a photochemically initiated Norrish type-II hydrogen abstraction at C2 of bipinnatin E (**2**) generates biradical **4**, which then closes to **3** (Scheme 1).[5] This concept was tested in a model substrate but gave a cyclobutanol in low yield.

A different approach to the furanylcyclobutane substructure of **3** based on a [2 + 2] ketene acetal cycloaddition to fumarate has been disclosed by Wood,[6] but the most extensive studies of a providencin synthesis have been conducted by Mulzer, who developed two methods for closing the macrocycle of **3** from a precyclization substrate containing both a trisubstituted furan and a modified cyclobutanol.[7] These noteworthy accomplishments notwithstanding, a completed synthesis of **3** has thus far remained elusive.

RESULTS AND DISCUSSION

Our initial strategy for the synthesis of providencin envisioned the formation of the macrocycle from aldehyde **5**, which would house reacting termini at C12 and C13 suitable for an asymmetric Nozaki−Hiyama−Kishi reaction (Scheme 2).[8] The acquisition of precyclization candidate **5** was programmed from two components, specifically, a "northern" sector **6** comprising the furanylcyclobutane moiety of **3** with appendages at C1 of the cyclobutane and C8 of the furan for fusion to a "southern" segment containing a suitably functionalized butenolide. Since the absolute configuration of providencin is unknown, an arbitrary choice was made that would construct the tetrasubstituted cyclobutane of **6** asymmetrically using an

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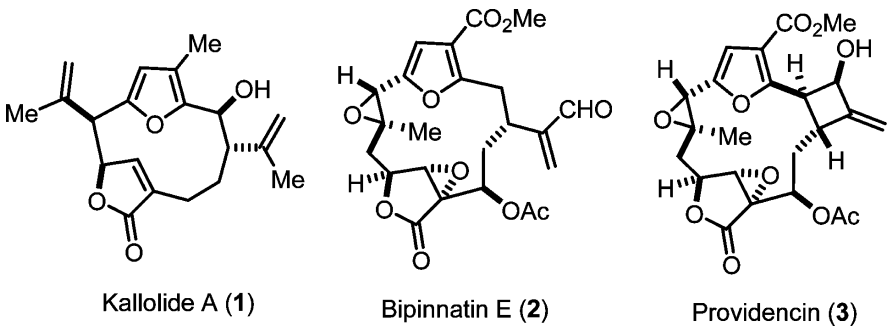
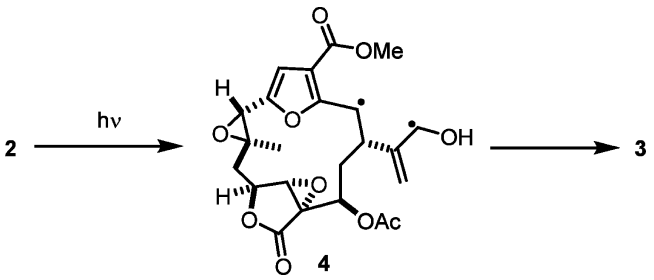


Figure 1. Cembranoid diterpenes from *Pseudopterogorgia kallos* and *Pseudopterogorgia bipinnata*.

Scheme 1. Pattenden's Proposed Biogenesis of Providencin



inexpensive material derived from the chiral pool, specifically, a bis(acetonide) of D-glucose, **7**.[9]

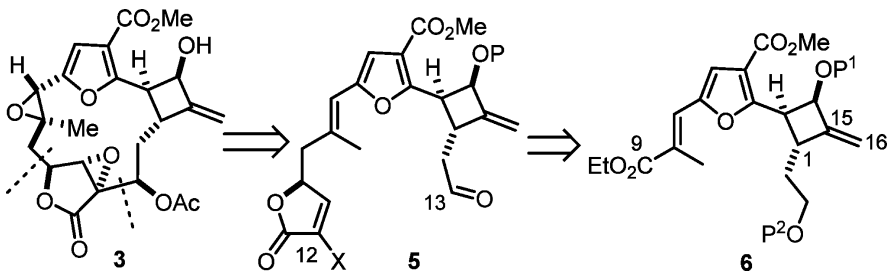
Our published sequence from **7** to the cyclobutane portion of **6**[10] is summarized in Scheme 3 and features oxygen abstraction from tetrahydrofuran **8** by dicyclopentadienylzirconium(0). This method was first reported by Taguchi[11] and was applied subsequently by Paquette to an enantioselective synthesis of cyclobutanols.[12] The presumed mechanism of the transformation from **8** to cyclobutane **9** is shown in Scheme 4, where the observed retention of configuration is rationalized in terms of conformationally favored alkylzirconium complex **10** over the alternative complex **11**.

Subsequent steps advanced **9** to furanylcyclobutanone **12**, a potential entry point to the C1−C9 segment of providencin, but problems that emerged in the course of this sequence made the route untenable. In particular, attempts at selective hydrolysis or hydride reduction of the methyl and ethyl esters in **12** resulted in no chemical differentiation of these functions, and although continuation of the synthesis could be envisioned with a different phosphonate for the Horner−Wadsworth−Emmons olefination of the C7 aldehyde, the aldehyde itself proved to be a difficult compound to handle. Furthermore, the C7−C8 double bond generated by olefination of the keto aldehyde precursor to **12** was produced as a mixture of *E* and *Z* isomers that was inseparable by chromatography. The coup de grace for this approach was the discovery that the cyclobutanone of **12** could not be reacted with any of the conventional methylenating agents to install the C15−C16 exomethylene unit of providencin. This last problem was thought to be due to steric hindrance by the three substituents surrounding the ketone of **12**, but later success with methylenation of a related cyclobutanone (vide infra) suggests a different explanation.

The difficulties encountered with diester **12** prompted us to revise our route to the macrocycle of **3** by relocating the point of sector assembly to C6 of the furan in a simplified northern subunit **13** (Scheme 5). Stille coupling with a haloalkene[13] (e.g., **14**) or a metal-mediated C−H activation of the furan[14] was envisioned for this step. The previously programmed C12−C13 union of the northern and southern segments would be retained, but we now favored an aldol-type coupling of lactone **14** with aldehyde **13** for this connection.

The new route to the northern portion of **3** began at cyclobutane **15** and set a goal that would build the disubstituted furan of **13** from an aldehyde obtained from oxidative cleavage of the vinyl substituent of **15**. Before the oxidative scission was attempted, however, a decision was made to replace both the *p*-methoxybenzyl and *tert*-butyldimethylsilyl ethers of **15** with more robust alcohol protection that could withstand the reaction conditions planned for later stages of the synthesis, particularly those envisioned for assembling the core structure of **3**. First, the *p*-methoxybenzyl ether of **15** was cleaved with 2,3-dichloro-4,5-dicyanobenzoquinone under neutral conditions[15] to yield primary alcohol **16**, and the latter was exposed to ethanol containing *p*-toluenesulfonic acid to provide diol **17** (Scheme 6). Acylation of **17** with trimethylacetyl chloride afforded pivalate **18**, and the remaining secondary alcohol was acetylated with acetic anhydride in the presence of DMAP to furnish diester **19**. Oxidative cleavage of the vinyl group in **19** with catalytic osmium tetroxide and excess sodium periodate[16] led cleanly to aldehyde **20**. Treatment of **20** with known alkynyl bromide **21**[17] in the presence of stannous chloride and

Scheme 2. Retrosynthetic Dissection of the Cyclobutylfuran "Northern" Sector of Providencin



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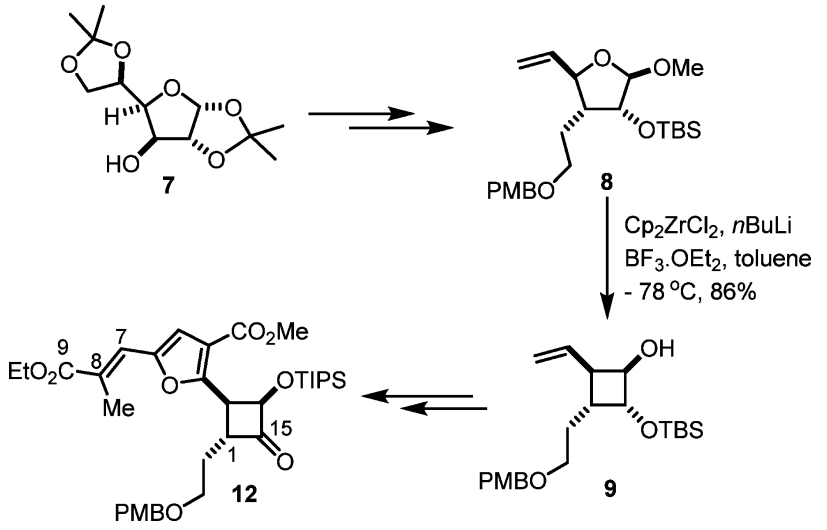
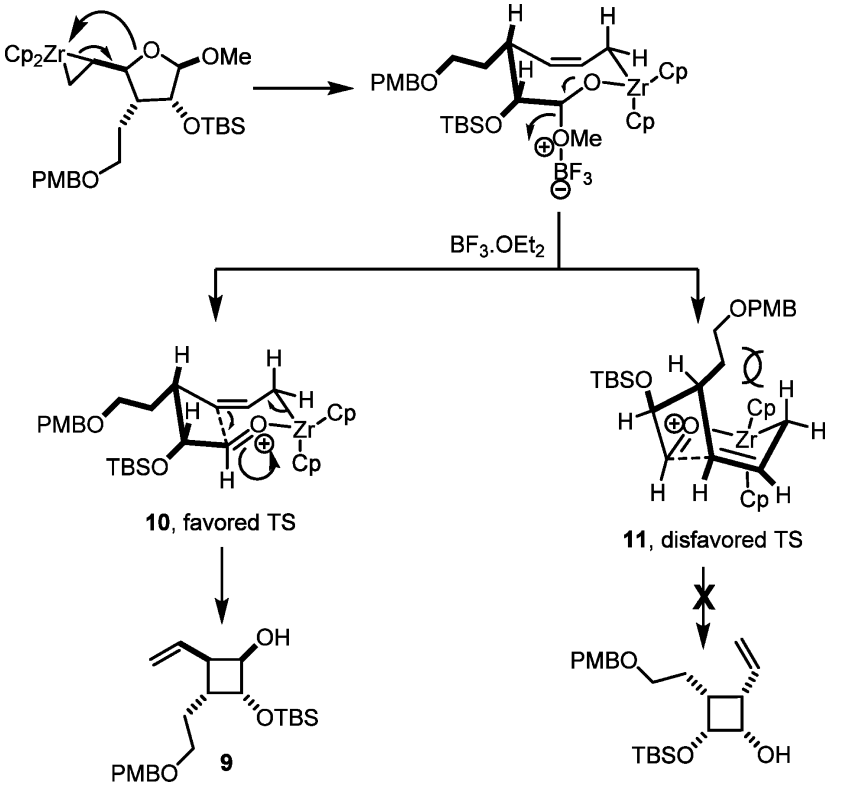
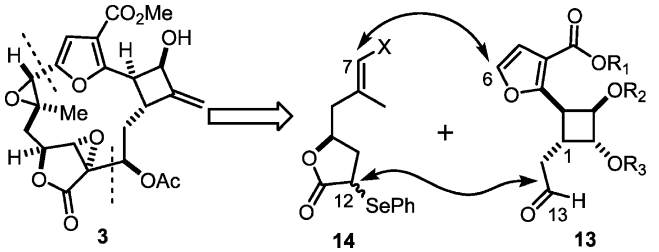
Scheme 3. First-Generation Synthesis of the Cyclobutylfuran Subunit of Providencin



Scheme 4. Mechanism for the Formation of 9 from Tetrahydrofuran 8



Scheme 5. Retrosynthetic Analysis of the Second-Generation Approach to Providencin



sodium iodide[18] produced allenic alcohol **22** as a single stereoisomer together with a small amount (17% yield) of an easily separable isomeric alkynyl alcohol. Although the configuration of the hydroxyl group in **22** was inconsequential for our purpose, Mosher ester analysis[19] of this alcohol established that it had the *S* orientation, indicating that attack by the organostannane formed from **21** had taken place at the *si* face of the carbonyl group of **20**. Oxidation of **22** with Dess–Martin periodinane yielded ketone **23**, which upon exposure to conditions described by Marshall[20] involving silver nitrate on silica in a mixture of dichloromethane and hexanes gave furan **24**. Selective methanolysis of the acetate in diester **24** led to alcohol **25**, and subsequent oxidation with Ley's reagent under

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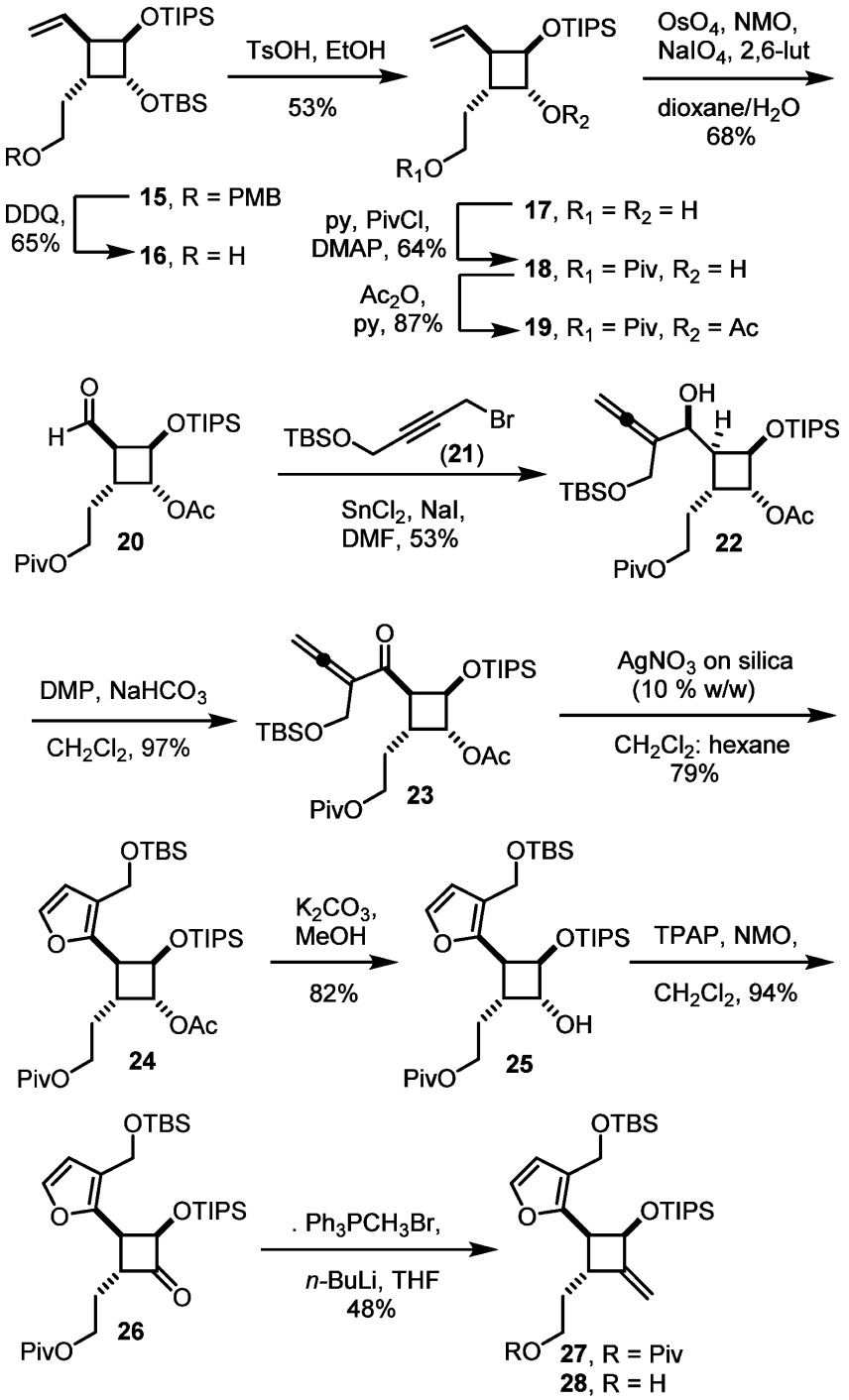
Scheme 6. Second-Generation Route to the Cyclobutylfuran Sector of Providencin



catalytic conditions[21] afforded cyclobutanone **26**. In contrast to cyclobutanone **12**, Wittig olefination of **26** led successfully to exomethylene-functionalized cyclobutane **27**, albeit in modest yield; alkene **27** was accompanied by a minor quantity (15% yield) of primary alcohol **28** resulting from base-induced cleavage of the pivalate. The failure of **12** to undergo methylenation must now be attributed to substituents on the furan rather than those on the cyclobutanone.[22]

Synthesis of the southern component of **3** for linkage to **27** was based on a route published by Pattenden and commenced from (*R*)-glycidol (**29**).[23] This epoxide was reacted with lithiotrimethylacetylene to give **30**, which was treated with methanolic potassium carbonate to afford diol **31**[24] (Scheme 7). Negishi carbometalation−iodination[25] of alkyne **31** led to (*E*)-iodoalkene **32** with only a trace of its regioisomer. The primary alcohol of diol **32** underwent selective tosylation to provide **33**, from which two routes to the southern sector were pursued. First, **33** was reacted with the lithio anion of ethoxyacetylene, and the resultant alkyne was treated with acidic ethanol to furnish γ-lactone **34**. However, mono-α-selenylation of this lactone proceeded in low yield, and **35** was accompanied by an equal quantity of the α,α′-diselenide. A more efficient one-pot pathway from **33** to **35** was discovered when tosylate **33** was reacted with the dilithio dianion of

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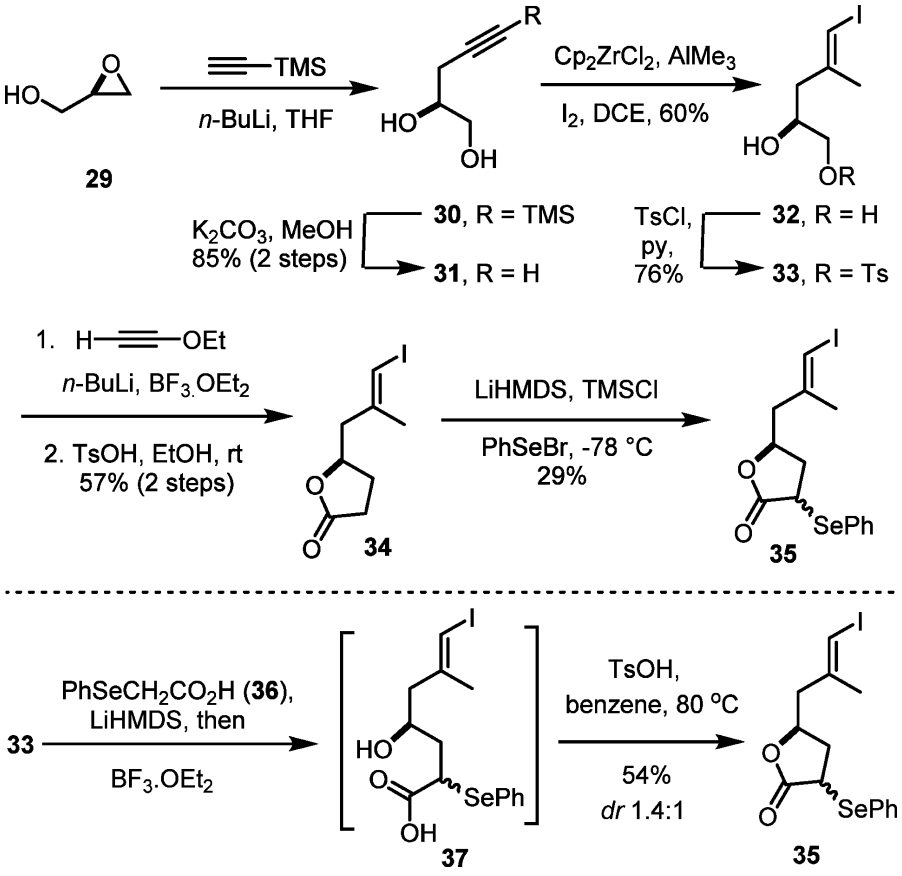
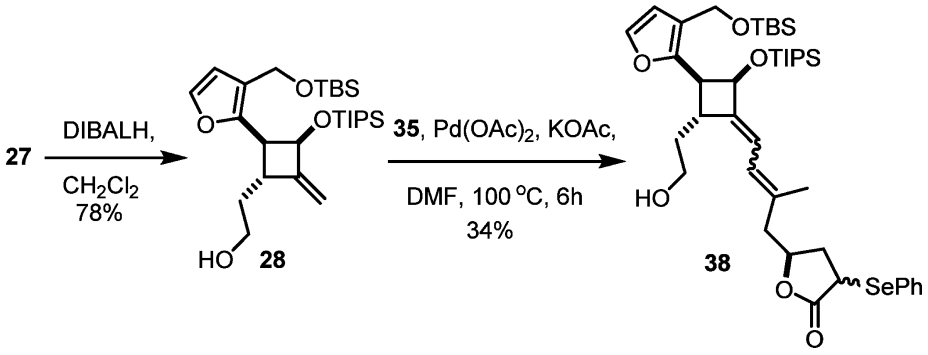
Scheme 7. Synthesis of the Butenolide Segment of Providencin



Scheme 8. Heck Reaction of Iodoalkene 35 with 28



phenylselenoacetic acid (**36**)[26] and the resultant hydroxy acid **37** was lactonized in situ with *p*-toluenesulfonic acid in hot benzene. This gave α-phenylselenyl lactone **35** as the sole product, formed as a 1.4:1 mixture of stereoisomers at the selenyl substituent.

The blueprint drafted for uniting the two subunits of providencin was designed initially around a C−H activation protocol published by Fagnou, who showed that substitution at C5 of a furan can be achieved by a catalytic palladium(II) species, which can lead to efficient coupling with aryl halides.[27] However, treatment of furan **27** and iodoalkene **35** with palladium(II) acetate in a biphasic medium at 60 °C or in *N*,*N*-dimethylacetamide at 100 °C under the conditions described by Fagnou resulted in extensive decomposition of the starting materials with no evidence for formation of a coupled product. The same outcome was observed when alcohol **28**, prepared by reduction of pivalate **27** with diisobutylaluminum hydride, was tested as a coupling partner with **35**. Doucet has published reaction conditions slightly different from those of Fagnou for C−H activation of furans and has shown that C5 arylation of a 2,3-disubstituted furan can be achieved in high yield by his method.[28] In the event, application of Doucet's palladium(II) acetate-catalyzed furan arylation to pivalate **27** and **35** in the presence of potassium acetate failed to produce a coupled product, but when alcohol **28** was invested in this process, a reaction took place to give conjugated diene **38** as a mixture of (*E*,*E*) and (*E*,*Z*) stereoisomers (Scheme 8). This result implies that a Heck reaction[29] of **35** with the exomethylene function of **28** takes precedence over palladium-catalyzed C−H activation of the furan.

The failure of these furan C−H activation procedures to promote the desired *intermolecular* coupling of our two

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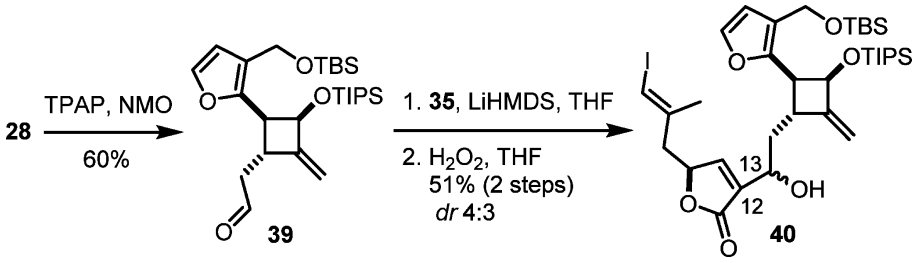
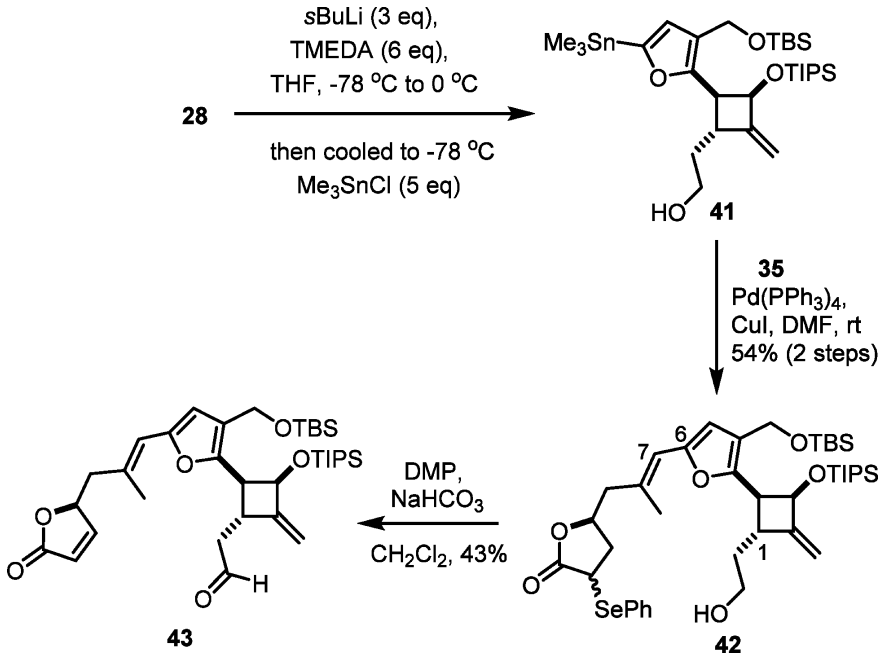
Scheme 9. Linkage of the Cyclobutylfuran and Butenolide Subunits of Providencin at C12−C13



Scheme 10. Fusion of the Cyclobutylfuran and Butenolide Subunits of Providencin at C6−C7



providencin subunits left open the possibility that *intramolecular* furan C−H activation, where driving force could accrue from formation of the natural macrocycle, would be more successful. This idea shifted our focus toward initial C12−C13 fusion of the northern and southern sectors, and oxidation of alcohol **28** to aldehyde **39** with Ley's reagent was the first step in this direction (Scheme 9). The lithium enolate of **35**, generated at low temperature, was reacted with **39**, and the product was treated in situ with 30% H_2O_2 to promote subsequent selenoxide formation and elimination.[23] Butenolide **40** was produced from this coupling as a 4:3 mixture of hydroxyl configurations at C13; however, attempts to close the macrocycle from **40** using furan C−H activation methods described above led only to decomposition of the substrate with no evidence for ring formation.

The foregoing results convinced us that *prefunctionalization* at the furan C5 position would be needed if the northern and southern sectors of **3** were to be merged at this locus. Pattenden showed in his synthesis of bis(deoxy)lophotoxin that this could be accomplished through site-selective stannylation of a furan and that subsequent macrocyclization could be achieved, though in very low yield, via intramolecular Stille coupling from a substrate resembling **40**.[23] Encouraging precedent for this plan also existed in Trauner's synthesis of (−)-bipinnatin J, where a C5-stannylated 2,3-disubstituted furan underwent efficient intermolecular Stille coupling with an iodoalkene that can be viewed as a surrogate for **35**.[30] Following these examples, stannylation of furan **28** was investigated under a variety of conditions, and these studies revealed that initial lithiation of **28** could be accomplished only with *sec*-butyllithium in the presence of TMEDA. Reaction of the intermediate C5 lithiofuran with trimethyltin chloride at low temperature provided unstable stannane **41**, which was reacted directly with **35** in the presence of catalytic tetrakis(triphenylphosphine)palladium(0) and copper(I) iodide (Scheme 10). The coupled product **42** was obtained from this sequence in acceptable yield based on furan **28**. In principle, access to our macrocyclic target from **42** required only a C12−C13 connection along lines demonstrated in the intermolecular enolate condensation of **35** with aldehyde **39**. Unfortunately, oxidation of the primary alcohol of **42** to an aldehyde for this step was accompanied in all cases by concomitant oxidation and elimination of the phenylselenyl substituent, leading to butenolide **43** as the sole product. This outcome effectively removed any prospect for macrocyclization from **42** and leaves in doubt a viable route to the core structure of providencin along lines developed here.

■ CONCLUSION

Two subunits of the cembranoid diterpene providencin have been prepared, including a sector that houses the heavily substituted cyclobutylfuran component. The two subunits were linked at C6 of the furan via Stille cross-coupling of a

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stannylated furan with a trisubstituted iodoalkene representing the "southern" sector of the molecule, and a second connection between these fragments was made at the C12−C13 bond of providencin via an intermolecular aldol condensation of an α-phenylselenyl-γ-lactone with an aldehyde. Combination of these fusion modes to complete the macrocyclic core of providencin was not successful.

EXPERIMENTAL SECTION

General Techniques. All of the reactions requiring anhydrous conditions were conducted in flame-dried glass apparatus under an atmosphere of argon. THF, Et_2O, CH_2Cl_2, DMF, benzene, and acetonitrile were dried by passage through an activated alumina column under argon. DMSO was distilled from CaH_2 at 15 mmHg and stored over activated 4 Å molecular sieves. Anhydrous MeOH was freshly distilled from calcium hydride. Preparative chromatographic separations were performed on silica gel (35−75 μm); reactions were followed by TLC analysis using silica plates with fluorescent indicator (254 nm) and visualized with a UV lamp or phosphomolybdic acid. Commercially available reagents were purchased and used as received unless stated otherwise. Optical rotations were measured with a polarimeter using a 1 mL capacity cell with 1 dm path length. Infrared spectra were recorded using thin films supported on KBr discs or dispersed in KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded in Fourier transform mode at the specified field strength on either a 300, 400, or 700 MHz spectrometer. Spectra were obtained on $CDCl_3$ solutions in 5 mm diameter tubes, and chemical shifts are quoted in parts per million relative to the residual signals of chloroform (δ_H = 7.26 ppm, δ_C = 77.0 ppm). Multiplicities in the ^{1}H NMR spectra are described as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad; coupling constants are reported in hertz. High-resolution mass spectrometry (HRMS) was performed using a quadrupole mass analyzer, and the data are reported with ion mass/charge (m/z) ratios as values in atomic mass units.

2-((1*R*,2*R*,3*R*,4*R*)-2-(*tert*-Butyldimethylsilyloxy)-3-(triisopropylsilyloxy)-4-vinylcyclobutyl)ethanol (16). To a stirred solution of **15** (44.0 mg, 0.08 mmol) in CH_2Cl_2 (1.0 mL) and pH 7 buffer (0.05 mL) at 0 °C was added DDQ (22.0 mg, 0.096 mmol). The solution was stirred at 0 °C for 1 h, after which the mixture was diluted with pH 7 buffer (50.0 μL). The aqueous layer was separated and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extract was dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude residue was purified by silica gel chromatography (6:94 ethyl acetate/hexanes) to yield **16** (22.0 mg, 65%) as a pale-yellow oil. R_f 0.43 (9:1 hexanes/ethyl acetate); $[\alpha]_D^{22}$ −39.5 (*c* 1.0, $CHCl_3$); IR (neat) 3330, 2943, 2863, 1478 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.08 (s, 3H), 0.09 (s, 3H), 0.90 (s, 9H), 1.06 (m, 21H), 1.59−1.68 (m, 1H), 1.86−1.95 (m, 1H), 2.10−2.19 (m, 1H), 2.65 (t, *J* = 8.3 Hz, 1H), 3.63−3.74 (m, 2H), 4.22 (dd, *J* = 6.9, 8.3 Hz, 1H), 4.31 (dd, *J* = 6.3, 7.5 Hz, 1H), 5.05 (dd, *J* = 6.3, 7.5 Hz, 1H), 5.05 (dd, *J* = 9.5, 10.2 Hz, 2H), 6.01 (ddd, *J* = 8.8, 10.2, 17.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.7, −4.6, 12.1 (3C), 18.0 (6C), 25.9 (3C), 29.7, 32.4, 38.4, 45.1, 61.3, 75.1, 75.6, 115.6, 138.1; CI-HRMS m/z calcd for $C_{23}H_{48}O_3Si_2$ $[M]^+$ 428.3164, found 428.3145.

(1*R*,2*R*,3*R*,4*R*)-2-(2-Hydroxyethyl)-4-(triisopropylsilyloxy)-3-vinylcyclobutanol (17). To an EtOH (absolute) solution (0.3 mL) of **16** (24.0 mg, 0.056 mmol) was added *p*-toluenesulfonic acid (1.0 mg, 0.0056 mmol) at room temperature, and the mixture was stirred for 4 h. When TLC showed that all the starting material had been consumed, the reaction was quenched with satd aqueous $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc (3 × 5 mL), and the combined organic extract was dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude oil was purified by silica gel chromatography (6:4 hexanes/ethyl acetate) to afford **17** (9.0 mg, 53%) as a colorless oil. R_f 0.28 (6:4 hexanes/ethyl acetate); $[\alpha]_D^{22}$ −29.0 (*c* 0.40, $CHCl_3$); IR (neat) 3302, 2920, 2868, 1455, 1154 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (m, 21H), 1.68−1.75 (m, 1H), 1.93−2.03 (m, 1H), 2.25−2.32 (m, 1H), 2.65 (dt, *J* = 2.8, 7.9 Hz, 1H), 3.14 (bs, 2OH), 3.63 (ddd, *J* = 7.8, 11.7, 17.5 Hz, 1H), 3.76−3.83 (m, 1H), 4.26 (t, *J* = 7.7 Hz, 2H), 5.00−5.08 (m, 2H), 6.00 (ddd, *J* = 8.6, 10.3, 17.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.9 (3C), 17.9 (6C), 32.3, 39.6, 45.7, 62.1, 74.6, 75.3, 115.3, 137.8; EI-HRMS m/z calcd for $C_{17}H_{35}O_3Si$ $[M]^+$ 315.2356, found 315.2328.

2-((1*R*,2*R*,3*R*,4*R*)-2-Hydroxy-3-(triisopropylsilyloxy)-4-vinylcyclobutyl)ethyl Pivalate (18). To a CH_2Cl_2 solution (0.8 mL) of **17** (27 mg, 0.085 mmol) at 0 °C were added pyridine (13.8 μL, 0.171 mmol), trimethylacetyl chloride (13.6 μL, 0.11 mmol), and DMAP (1.04 mg, 0.085 mmol). The mixture was allowed to warm to room temperature and stirred for 18 h, after which the reaction was quenched by addition of a satd aqueous $NaHCO_3$ solution (10 mL). The separated aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic extract was washed with saturated $CuSO_4$ solution, dried (Na_2SO_4), filtered, and concentrated. The crude residue was purified by silica gel chromatography (7:93 ethyl acetate/hexanes) to give **18** (22 mg, 64%) as a colorless oil. R_f 0.66 (8:2 hexanes/ethyl acetate); $[\alpha]_D^{25}$ −86.3 (*c* 1.0, $CHCl_3$); IR (neat) 3470, 2941, 2859, 1731 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (s, 21H), 1.21 (s, 9H), 1.63−1.73 (m, 1H), 1.96−2.06 (m, 1H), 2.08 (d, *J* = 2.0 Hz, OH), 2.16−2.23 (m, 1H), 2.67−2.72 (m, 1H), 4.06−4.20 (m, 2H), 4.23−4.31 (m, 2H), 5.00−5.08 (m, 2H), 5.98 (ddd, *J* = 8.3, 10.1, 17.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.9 (3C), 17.8 (6C), 27.2 (3C), 28.1, 36.8, 38.7, 44.9, 63.2, 75.1, 75.3, 115.5, 137.4, 178.7; CI-HRMS m/z calcd for $C_{22}H_{42}O_4Si$ $[M + H]^+$ 399.2930, found 399.2943.

2-((1*R*,2*R*,3*R*,4*R*)-2-Acetoxy-3-(triisopropylsilyloxy)-4-vinylcyclobutyl)ethyl Pivalate (19). To a CH_2Cl_2 solution (0.5 mL) of **18** (22 mg, 0.055 mmol) at 0 °C were slowly added pyridine (13.4 μL, 0.165 mmol), acetic anhydride (15.6 μL, 0.165 mmol), and DMAP (0.65 mg, 0.085 mmol). The mixture was allowed to warm to room temperature and stirred for 1 h, and the reaction was quenched by addition of satd aqueous $NaHCO_3$ solution (5 mL). The separated aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic extract was washed with satd $CuSO_4$ solution, dried (Na_2SO_4), filtered, and concentrated. The crude mixture was purified by silica gel chromatography (5:95 ethyl acetate/hexanes) to afford **19** (21 mg, 87%) as a colorless oil. R_f 0.51 (9:1 hexanes/ethyl acetate); $[\alpha]_D^{25}$ −77.5 (*c* 1.0, $CHCl_3$); IR (neat) 2945, 2870, 1751, 1729, 1462 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (s, 21H), 1.19 (s, 9H), 1.58−1.62 (m, 1H), 1.73−1.83 (m, 1H), 2.08 (s, 3H), 2.38 (m, 1H), 2.81 (t, *J* = 8.5 Hz, 1H), 4.05 (t, *J* = 6.6 Hz, 2H), 4.48 (dd, *J* = 6.8, 8.5 Hz, 1H), 5.04−5.14 (m, 3H), 6.01 (ddd, *J* = 8.4, 10.6, 17.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8 (3C), 17.6 (6C), 20.6, 27.1 (3C), 28.2, 35.7, 38.7, 45.3, 62.4, 71.7, 76.1, 116.2, 136.5, 170.2, 178.5; CI-HRMS m/z calcd for $C_{24}H_{44}O_5NaSi$ $[M + Na]^+$ 463.2856, found 463.2842.

2-((1*R*,2*R*,3*R*,4*R*)-2-Acetoxy-4-formyl-3-(triisopropylsilyloxy)-cyclobutyl)ethyl Pivalate (20). To a solution of **19** (22 mg, 0.049 mmol) in dioxane/water (3:1, 0.5 mL) were added 2,6-lutidine (11.35 μL, 0.248 mmol), OsO_4 (0.05 M in 2-methyl-2-propanol, 50.0 μL, 0.0024 mmol), and $NaIO_4$ (42.0 mg, 0.196 mmol). The reaction mixture was stirred at room temperature for 2 h and then diluted with water (10 mL) and CH_2Cl_2 (10 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extract was washed with aqueous $CuSO_4$ solution and brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the crude residue was purified by silica gel chromatography (1:9 ethyl acetate/hexanes) to afford **20** (15.0 mg, 68%) as a pale-brown oil. R_f 0.41 (15:85 hexanes/ethyl acetate); $[\alpha]_D^{26}$ −53.8 (*c* 1.0, $CHCl_3$); IR (neat) 2944, 2861, 1754, 1724(2) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (s, 21H), 1.19 (s, 9H), 1.54−1.61 (m, 1H), 1.78−1.86 (m, 1H), 2.09 (s, 3H), 2.90−2.97 (m, 1H), 3.13 (d, *J* = 9.3 Hz, 1H), 3.97−4.07 (m, 2H), 4.72 (dd, *J* = 6.8, 9.2 Hz, 1H), 5.24 (dd, *J* = 6.4, 7.9 Hz, 1H), 9.88 (d, *J* = 2.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.7 (3C), 17.5 (6C), 20.5, 27.1 (3C), 27.2, 30.1, 38.7, 52.5, 62.1, 72.7, 75.7, 169.8, 178.4, 200.7; EI-HRMS m/z calcd for $C_{23}H_{42}O_6NaSi$ $[M + Na]^+$ 465.2648, found 465.2659.

2-((1*R*,2*R*,3*R*,4*S*)-2-Acetoxy-4-((*R*)-2-((*tert*-butyldimethylsilyloxy)methyl)-1-hydroxybuta-2,3-dienyl)-3-(triisopropylsilyloxy)cyclobutyl)ethyl Pivalate (22). To a sol-

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ution of **21** (149.0 mg, 0.568 mmol) in 3.0 mL of DMF at room temperature under argon were added $SnCl_2$ (129.0 mg, 0.68 mmol) and NaI (102.0 mg, 0.68 mmol), and the resulting mixture was stirred for 3 h while protected from light in a flask wrapped with aluminum foil. After the foil was removed, the bright-yellow solution was cooled to 0 °C, and a solution of **20** (84.0 mg, 0.189 mmol) in 2.0 mL of DMF was added over a 10 min period. After 30 h of stirring at 0 °C in the absence of light, the reaction mixture was diluted with Et_2O (20 mL) and a satd aqueous solution of NH_4Cl (20 mL) while being vigorously stirred. The separated aqueous layer was extracted with Et_2O (3 × 20 mL), and the combined organic extract was washed with satd aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and filtered. The solvent was removed under reduced pressure, and flash chromatographic purification of the residual oil on silica gel (6:94 ethyl acetate/hexanes) afforded **22** (61.0 mg, 53%) as a colorless oil. R_f 0.50 (85:15 hexanes/ethyl acetate); $[\alpha]_D^{20}$ −53.1 (*c* 1.20, $CHCl_3$); IR (neat) 3540, 2953, 2867, 1960, 1742, 1731, 1458, 1369, 1236, 1151 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.07 (s, 3H), 0.07 (s, 3H), 0.89 (s, 9H), 1.06 (s, 21H), 1.19 (s, 9H), 1.58−1.67 (m, 1H), 1.76−1.85 (m, 1H), 2.07 (s, 3H), 2.48 (td, *J* = 2.7, 9.2 Hz, 1H), 2.68 (dd, *J* = 3.0, 8.5 Hz, 1H), 3.01 (d, *J* = 3.1 Hz, OH), 3.96 (t, *J* = 7.3 Hz, 2H), 4.18 (td, *J* = 2.0, 11.6 Hz, 1H), 4.31 (td, *J* = 2.0, 11.6 Hz, 1H), 4.62 (dd, *J* = 6.2, 9.4 Hz, 1H), 4.69 (pentet, *J* = 2.9 Hz, 1H), 4.91 (qq, *J* = 2.2, 10.5 Hz, 2H), 5.27 (dd, *J* = 5.9, 9.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.4, −5.3, 11.8 (3C), 17.6 (3C), 17.8 (3C), 20.7, 25.8 (3C), 27.1 (3C), 28.9, 29.7, 30.2, 38.6, 44.9, 62.6, 63.1, 66.2, 72.1, 76.5, 78.1, 104.2, 169.8, 178.4, 205.5; CI-HRMS *m*/*z* calcd for $C_{33}H_{63}O_7Si_2$ $[M]^+$ 627.4112, found 627.4088.

2-((1*R*,2*R*,3*R*,4*R*)-2-Acetoxy-4-(2-((*tert*-butyldimethylsilyloxy)methyl)buta-2,3-dienoyl)-3-(triisopropylsilyloxy)cyclobutyl)ethyl Pivalate (23). To a solution of **22** (61.0 mg, 0.097 mmol) in 1.0 mL of CH_2Cl_2 at 0 °C was added $NaHCO_3$ (32.5 mg, 0.38 mmol) followed by Dess−Martin periodinane (82.5 mg, 0.194 mmol). The slurry was stirred at 0 °C for 1 h and then diluted with CH_2Cl_2 (5.0 mL). The reaction was quenched with satd $Na_2S_2O_3$ solution (15 mL) by stirring the biphasic mixture vigorously for 20 min. After the layers were separated, the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic extract was washed with satd $NaHCO_3$ solution, water, and brine and dried over Na_2SO_4. The drying agent was removed by filtration, and the filtrate was concentrated in vacuo. Purification of the crude residue by silica gel chromatography (94:6 hexanes/ethyl acetate) provided **23** (59 mg, 97%) as a yellow oil. R_f 0.50 (85:15 hexanes/ethyl acetate); $[\alpha]_D^{18}$ −14.6 (*c* 0.98, $CHCl_3$); IR (neat) 2953, 2863, 1933, 1750, 1731, 1664, 1466, 1369, 1228 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.08 (s, 9H), 1.01 (s, 21H), 1.17 (s, 9H), 1.50−1.60 (m, 1H), 1.72−1.81 (m, 1H), 2.06 (s, 3H), 2.78−2.85 (m, 1H), 3.90 (dd, *J* = 3.2, 9.8 Hz, 1H), 3.97 (t, *J* = 6.5 Hz, 2H), 4.28 (td, *J* = 3.6, 13.3 Hz, 1H), 4.44 (td, *J* = 3.4, 13.3 Hz, 1H), 4.60 (dd, *J* = 6.5, 9.5 Hz, 1H), 5.24−5.29 (m, 2H), 5.36 (td, *J* = 3.4, 13.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.4, −5.3, 12.1 (3C), 17.6 (3C), 17.7 (3C), 18.2, 20.5, 25.8 (3C), 27.1 (3C), 27.5, 31.9, 38.6, 48.8, 58.4, 62.2, 72.2, 75.9, 82.1, 112.0, 169.6, 178.3, 197.3, 216.3; CI-HRMS *m*/*z* calcd for $C_{33}H_{61}O_7Si_2$ $[M]^+$ 625.3956, found 625.3955.

2-((1*R*,2*R*,3*R*,4*R*)-2-Acetoxy-4-(3-((*tert*-butyldimethylsilyloxy)methyl)furan-2-yl)-3-(triisopropylsilyloxy)cyclobutyl)ethyl Pivalate (24). To a solution of **23** (54.0 mg, 0.086 mmol) in 3.58 mL of hexane and 0.70 mL of CH_2Cl_2 at room temperature was added 73.3 mg of $AgNO_3$ on SiO_2 (10 wt.%, 0.043 mmol) in a single portion. The suspension was stirred at room temperature for 2 h in the absence of light and then diluted with Et_2O and filtered through a short pad of Celite, which was washed with Et_2O (20 mL). The filtrate was concentrated in vacuo, and the crude mixture was purified by silica gel chromatography (96:4 hexanes/ethyl acetate) to furnish **24** (43.0 mg, 79%) as a pale-yellow oil. R_f 0.57 (85:15 hexanes/ethyl acetate); $[\alpha]_D^{18}$ −27.3 (*c* 1.00, $CHCl_3$); IR (neat) 2953, 2863, 1746, 1731, 1462, 1365 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.92 (s, 30H), 1.17 (s, 9H), 1.67−1.73 (m, 1H), 1.84−1.92 (m, 1H), 2.10 (s, 3H), 2.78−2.85 (m, 1H), 3.46 (dd, *J* = 3.2, 9.1 Hz, 1H), 3.97−4.08 (m, 2H), 4.50 (d, *J* = 2.9 Hz, 2H), 4.63 (dd, *J* = 6.6, 8.3 Hz, 1H), 5.52 (dd, *J* = 6.6, 8.8 Hz, 1H), 6.31 (d, *J* = 1.7 Hz, 1H), 7.31 (d, *J* = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.2 (2C), 11.8 (3C), 17.5 (3C), 17.6 (3C), 18.3, 20.6, 25.9 (3C), 27.1 (3C), 28.7, 35.0, 38.6, 39.0, 57.2, 62.2, 72.5, 76.2, 110.6, 121.6, 140.9, 147.8, 170.0, 178.3; CI-HRMS *m*/*z* calcd for $C_{33}H_{61}O_7Si_2$ $[M]^+$ 625.3955, found 625.3938.

2-((1*R*,2*R*,3*R*,4*R*)-2-(3-((*tert*-Butyldimethylsilyloxy)methyl)-furan-2-yl)-4-hydroxy-3-(triisopropylsilyloxy)cyclobutyl)ethyl Pivalate (25). To a stirred solution of **24** (38.0 mg, 0.06 mmol) in dry MeOH (0.6 mL) at 0 °C was added K_2CO_3 (21.0 mg, 0.152 mmol). The mixture was stirred at 0 °C for 3 h, and water (10 mL) was added to the reaction mixture. The separated aqueous layer was extracted with EtOAc (3 × 20 mL), and the combined organic extract was dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude residue was purified by silica gel chromatography (92:8 hexane/ethyl acetate) to afford **25** (29.0 mg, 82%) as a colorless oil. R_f 0.68 (8:2 hexanes/ethyl acetate); $[\alpha]_D^{20}$ −6.0 (*c* 1.45, $CHCl_3$); IR (neat) 3466, 2933, 2871, 1734, 1711, 1454 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.08 (s, 3H), 0.09 (s, 3H), 0.95 (s, 30H), 1.20 (s, 9H), 1.72−1.81 (m, 1H), 2.06−2.14 (m, 1H), 2.16 (d, *J* = 4.7 Hz, 1H), 2.64 (dd, *J* = 3.6, 8.0 Hz, 1H), 3.34 (dd, *J* = 6.2, 8.4 Hz, 1H), 4.06−4.22 (m, 2H), 4.44 (dd, *J* = 6.2, 8.4 Hz, 1H), 4.49 (d, *J* = 2.0 Hz, 2H), 4.66 (dd, *J* = 5.7, 9.4 Hz, 1H), 6.32 (d, *J* = 1.5 Hz, 1H), 7.29 (d, *J* = 1.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.2 (2C), 11.9 (3C), 17.6 (6C), 25.9 (3C), 27.1 (3C), 28.8, 29.7, 38.6, 57.2, 63.1, 75.3, 76.0, 110.7, 121.3, 121.3, 140.6, 148.7, 178.6; CI-HRMS *m*/*z* calcd for $C_{31}H_{58}O_6Si_2Na$ $[M + Na]^+$ 605.3670, found 605.3654.

2-((1*R*,2*R*,3*R*)-2-(3-((*tert*-Butyldimethylsilyloxy)methyl)furan-2-yl)-4-oxo-3-(triisopropylsilyloxy)cyclobutyl)ethyl Pivalate (26). To a CH_2Cl_2 (0.5 mL) solution of **25** (31.0 mg, 0.053 mmol) were added 4 Å molecular sieves, TPAP (1.86 mg, 0.0052 mmol), and NMO (18.69 mg, 0.159 mmol). The reaction mixture was stirred at room temperature for 30 min, after which the suspension was loaded directly on a silica gel column. The crude mixture was purified by chromatography (93:7 hexanes/ethyl acetate) to yield **26** (29.0 mg, 94%) as a colorless oil. R_f 0.75 (2:8 hexanes/ethyl acetate); $[\alpha]_D^{21}$ +38.7 (*c* 1.45, $CHCl_3$); IR (neat) 2957, 2868, 1792, 1733, 1470, 1158 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.10 (s, 6H), 0.93−0.96 (m, 30H), 1.17 (s, 9H), 1.95−2.14 (m, 2H), 3.53−3.59 (m, 1H), 3.69 (dd, *J* = 5.9, 9.1 Hz, 1H), 4.13 (t, *J* = 6.1 Hz, 2H), 4.56 (d, *J* = 7.0 Hz, 2H), 5.18 (dd, *J* = 2.9, 9.3 Hz, 1H), 6.32 (d, *J* = 1.3 Hz, 1H), 7.29 (d, *J* = 1.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.2 (2C), 11.8 (3C), 17.4 (3C), 17.5 (3C), 18.3, 25.9 (3C), 27.1 (3C), 29.9, 36.8, 38.7, 56.2, 57.2, 61.8, 83.2, 110.7, 122.1, 141.3, 147.2, 178.3, 208.4; CI-HRMS *m*/*z* calcd for $C_{31}H_{56}O_6Si_2$ $[M]^+$ 580.3615, found 580.3616.

2-((1*R*,2*R*,3*R*)-2-(3-((*tert*-Butyldimethylsilyloxy)methyl)furan-2-yl)-4-methylene-3-(triisopropylsilyloxy)cyclobutyl)ethyl Pivalate (27) and 2-((1*R*,2*R*,3*R*)-2-(3-((*tert*-Butyldimethylsilyloxy)-methyl)furan-2-yl)-4-methylene-3-(triisopropylsilyloxy)-cyclobutyl)ethanol (28). To a solution of **26** (26.0 mg, 0.044 mmol) in dry THF (1.0 mL) at 0 °C was added $Ph_3P{=}CH_2$ [1.50 mL, 0.179 mmol, 0.119 M in THF, freshly prepared from Ph_3PCH_3Br (200.0 mg, 0.56 mmol) and *n*-BuLi (0.17 mL, 0.47 mmol, 2.7 M solution in hexane) in THF (4.0 mL) at 0 °C], and the mixture was stirred at 0 °C for 10 min and at room temperature for 45 min. The reaction was quenched with satd aqueous NH_4Cl solution (10 mL), and the separated aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic extract was dried (Na_2SO_4), filtered, and concentrated, and the crude residue was purified by silica gel chromatography (3:97 ethyl acetate/hexanes) to give **27** (12.0 mg, 48%) and **28** (3.0 mg, 15%) as colorless oils.

27: R_f 0.8 (9:1 hexanes/ethyl acetate); $[\alpha]_D^{19}$ −4.1 (*c* 0.6, $CHCl_3$); IR (neat) 2953, 2959, 1725, 1466 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.08 (s, 3H), 0.09 (s, 3H), 0.95 (m, 30H), 1.18 (s, 9H), 1.94 (dd, *J* = 6.9, 7.5 Hz, 2H), 3.53 (m, 1H), 3.46 (dd, *J* = 5.9, 7.8 Hz, 1H), 4.10 (t, *J* = 6.7 Hz, 2H), 4.54 (d, *J* = 2.6 Hz, 2H), 5.03 (s, 1H), 5.08 (m, 1H), 5.22 (s, 1H), 6.33 (d, *J* = 1.5 Hz, 1H), 7.30 (d, *J* = 1.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.2 (2C), 12.0 (3C), 17.7 (6C), 25.9 (3C), 27.1 (3C), 29.6, 33.4, 38.6, 41.6, 43.1, 57.3, 62.3, 72.7, 77.1,

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107.3, 110.8, 121.4, 148.8, 154.9, 178.4. CI-HRMS m/z calcd for $C_{32}H_{58}O_5Si_2$ $[M]^+$ 578.3822, found 578.3814.

28: R_f 0.46 (8:2 hexanes/ethyl acetate); $[\alpha]_D^{23}$ −18.0 (c 0.4, $CHCl_3$); IR (neat) 3400, 2941, 2863, 1462, 1246 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.10 (s, 3H), 0.11 (s, 3H), 0.95 (s, 30H), 1.72 (t, J = 4.3 Hz, OH), 1.76−1.85 (m, 1H), 1.90−1.98 (m, 1H), 3.39−3.49 (m, 2H), 3.67 (d, J = 4.3 Hz, 2H), 4.55 (q, J = 1.4, 7.1 Hz, 2H), 5.03 (s, 1H), 5.07 (dd, J = 1.4, 7.1 Hz, 1H), 5.20 (s, 1H), 6.32 (d, J = 1.4 Hz, 1H), 7.30 (d, J = 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.1 (2C), 11.7 (3C), 17.7 (6C), 25.9 (3C), 37.3, 42.6, 43.2, 57.2, 58.8, 61.0, 72.9, 106.8, 111.1, 121.2, 140.8, 149.4, 155.4; EI-HRMS m/z calcd for $C_{27}H_{50}O_4Si_2$ $[M]^+$ 494.3247, found 494.3229.

(*S*,*E*)-5-Iodo-4-methylpent-4-ene-1,2-diol (32). To a suspension of Cp_2ZrCl_2 (334.4 mg, 1.14 mmol) in DCE (1.0 mL) at room temperature was added slowly $AlMe_3$ (0.3 mL, 3.12 mmol), and the mixture was stirred for 15 min. The solution was cooled to 0 °C, and a solution of **31**[24] (105.0 mg, 1.04 mmol) in DCE (1.1 mL) was added via cannula. The mixture was stirred for 41 h at room temperature and then cooled to −30 °C, and a solution of I_2 in Et_2O (3.0 mL) was added. The mixture was stirred for 45 min −30 °C and then allowed to warm to 0 °C, and the reaction was quenched with satd sodium potassium tartrate solution (30 mL) and pentane (20 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (6 × 30 mL). The combined organic extract was dried (Na_2SO_4), filtered, and concentrated, and the crude residue was purified by silica gel chromatography (55:45 ethyl acetate/hexanes) to give **32** (154 mg, 60%) as a colorless oil. R_f 0.25 (3:7 hexanes/ethyl acetate); $[\alpha]_D^{21}$ −10.4 (c 0.65, $CHCl_3$); IR (neat) 3361, 2921, 2871, 1271, 1151 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.91 (d, J = 0.8 Hz, 3H), 2.39 (dd, J = 8.3, 11.1 Hz, 2H), 3.46 (dd, J = 10.6, 6.9 Hz, 1H), 3.88 (m, 1H), 6.06 (q, J = 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.2, 43.2, 66.2, 69.6, 77.6, 144.6; EI-HRMS m/z calcd for $C_6H_{11}IO_2$ $[M]^+$ 241.9804, found 241.9797.

(*S*,*E*)-2-Hydroxy-5-iodo-4-methylpent-4-enyl 4-Methylbenzenesulfonate (33). To a solution of **32** (2.53 g, 10.45 mmol) in pyridine (25.0 mL) at 0 °C was added *p*-toluenesulfonyl chloride (2.19 g, 11.50 mmol), and the mixture was stirred at 4 °C for 20 h. After the reaction was quenched with water (100 mL), the layers were separated, and the aqueous layer was extracted with EtOAc (4 × 50 mL). The combined organic extract was dried over Na_2SO_4, filtered, and concentrated. The crude mixture was purified by silica gel chromatography (22:88 ethyl acetate/hexanes) to afford **33** (3.18 g, 76%) as a colorless oil. R_f 0.66 (7:3 hexanes/ethyl acetate); $[\alpha]_D^{18}$ +5.8 (c 0.85, $CHCl_3$); IR (neat) 3517, 2910, 2848, 1361, 1170, 1096, 976 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.86 (d, J = 0.8 Hz, 3H), 2.38 (d, J = 6.1 Hz, 2H), 2.48 (s, 3H), 3.92 (dd, J = 5.6, 9.4 Hz, 1H), 4.03 (m, 2H), 6.00 (s, 1H), 7.39 (d, J = 8.06 Hz, 2H), 7.82 (d, J = 7.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 24.0, 42,7, 67.1, 72.7, 78.4, 128.0 (2C), 130.0 (2C), 132.4, 143.1, 145.2; CI-HRMS m/z calcd for $C_{13}H_{18}O_4SI$ $[M + H]^+$ 396.9971, found 396.9956.

(*R*,*E*)-5-(3-Iodo-2-methylallyl)dihydrofuran-2(3*H*)-one (34). To a stirred solution of ethoxyacetylene (40% w/w solution in hexanes, 78.9 μL, 0.33 mmol) in THF (2.0 mL) at −78 °C was added a solution of *n*-BuLi (2.5 M) in hexanes (0.13 mL, 0.32 mmol). The mixture was stirred at −78 °C for 1 h, and a solution of **33** (22.0 mg, 0.05 mmol) in THF (1.0 mL) was added dropwise. The reaction mixture was stirred at −78 °C for 2 h and then warmed to 0 °C, and $BF_3{\cdot}OEt_2$ (27.9 μL, 0.22 mmol) was added. The mixture was stirred at 0 °C for 1 h, after which the reaction was quenched by addition of a satd aqueous solution of $NaHCO_3$. The resulting mixture was diluted with Et_2O (10 mL) and water (10 mL), and the separated aqueous phase was extracted with Et_2O (2 × 20 mL). The combined organic extract was dried (Na_2SO_4), filtered, and concentrated to leave a crude oil.

To an EtOH (1.00 mL) solution of the oil obtained above was added *p*-toluenesulfonic acid (10.0 mg), and the mixture was stirred at room temperature for 18 h. The reaction was quenched with satd aqueous $NaHCO_3$, and the mixture was diluted with EtOAc (5 mL). The separated aqueous phase was extracted with EtOAc (2 × 10 mL), and the combined organic extract was dried (Na_2SO_4), filtered, and concentrated. Chromatographic purification of the residue (silica gel, 25:75 ethyl acetate/hexanes) gave **34** (8.0 mg, 57%) as a colorless oil. R_f 0.4 (6:4 hexanes/ethyl acetate); $[\alpha]_D^{20}$ −82.8 (c 0.85, $CHCl_3$); IR (neat) 2923, 2851, 1768, 1456, 1174 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.86−1.90 (m, 1H), 1.92 (d, J = 1.0 Hz, 3H), 2.28−2.38 (m, 1H), 2.51 (dd, J = 8.7, 14.1 Hz, 1H), 2.56 (dd, J = 6.9, 9.5 Hz, 2H), 2.66 (dd, J = 7.2, 14.3 Hz, 1H), 4.63 (m, 1H), 6.11 (q, J = 1.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.4, 27.6, 28.5, 44.9, 78.3, 78.6, 142.7, 176.6; EI-HRMS m/z calcd for $C_8H_{11}O_2I$ $[M]^+$ 265.9804, found 265.9799.

(*S*,*E*)-5-(3-Iodo-2-methylallyl)-3-(phenylselenyl)-dihydrofuran-2(3*H*)-one (35). To a solution of α-phenylselenoacetic acid (**36**) (4.48 g, 20.74 mmol) in anhydrous THF (20 mL) was added slowly LiHMDS (45.6 mL, 45.65 mmol, 1 M solution in THF) at −78 °C. The mixture was stirred at −78 °C for 1 h, and a solution of **33** (3.18 g, 8.01 mmol) in THF (20 mL) was added. The reaction mixture was stirred at −78 °C for 30 min and then at 0 °C for 1 h. The mixture was warmed to room temperature and stirred at room temperature for 2 h. To the mixture was added 1 N NaOH (85 mL), and the layers were separated. The organic layer was discarded, and the aqueous layer was acidified with 1 N HCl (125.0 mL) and extracted with Et_2O (3 × 50 mL). The combined organic extract was dried (Na_2SO_4), filtered, and concentrated to give a crude oil.

The oil obtained above was immediately dissolved in dry benzene (20 mL), and $TsOH{\cdot}H_2O$ (180 mg, 0.94 mmol, 10 mol %) was added to the solution. The mixture was refluxed for 16 h, and the reaction was quenched with satd aqueous $NaHCO_3$ solution. The aqueous layer was extracted with Et_2O (2 × 30 mL), and the organic extract was dried (Na_2SO_4), filtered, and concentrated. Purification of the residual oil by silica gel chromatography (15:85 ethyl acetate/hexanes) gave an inseparable mixture (1.4:1) of stereoisomers **35** (1.82 g, 54% based on **33**) as a viscous yellow oil. R_f 0.31 (8:2 hexanes/ethyl acetate); IR (neat) 2918, 2847, 1767, 1434 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (major isomer) δ 1.85 (s, 3H), 2.35 (dd, J = 5.4, 7.5 Hz, 2H), 2.45 (dd, J = 5.8, 14.4 Hz, 1H), 2.61 (dd, J = 7.1, 14.2 Hz, 1H), 3.96 (t, J = 5.4 Hz, 1H), 4.40 (m, 1H), 6.06 (s, 1H), 7.40−7.50 (m, 3H), 7.65−7.75 (2H); (minor isomer) δ 1.83 (d, J = 1.0 Hz, 3H), 1.96 (ddd, J = 7.9, 9.1, 13.7 Hz, 1H), 2.29−2.36 (m, 1H), 2.48 (dd, J = 7.1, 14.4 Hz, 1H), 2.75 (ddd, J = 6.7, 9.4, 13.7 Hz, 1H), 4.02 (t, J = 9.3 Hz, 1H), 4.55−4.65 (m, 1H), 6.01 (q, J = 1.0 Hz, 1H), 7.40−7.50 (m, 3H), 7.65−7.75 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) (major) δ 24.2, 36.4, 36.7, 44.5, 76.9, 78.7, 126.5, 129.3, 129.5 (2C), 135.9 (2C), 142.3, 175.2; (minor) δ 24.5, 35.2, 36.9, 44.8, 76.9, 78.8, 126.8, 129.1, 129.4 (2C), 135.9 (2C), 142.3, 175.2; CI-HRMS m/z calcd for $C_{14}H_{16}O_2SeI$ $[M + H]^+$ 422.9361, found 422.9350.

(*S*)-5-((2*E*,4*E*)-4-((2*R*,3*R*,4*R*)-3-(3-((*tert*-Butyldimethylsilyloxy)-methyl)furan-2-yl)-2-(2-hydroxyethyl)-4-(triisopropylsilyloxy)-cyclobutylidene)-2-methylbut-2-enyl)-3-(phenylselanyl)-dihydrofuran-2(3*H*)-one (38). To a mixture of vinyl iodide **35** (6.14 mg, 0.014 mmol) and furan **28** (6.0 mg, 0.012 mmol) in 0.2 mL of DMF were added KOAc (2.35 mg, 0.024 mmol) and $Pd(OAc)_2$ (0.26 mg, 0.00012 mmol). The reaction mixture was heated in a sealed vessel at 100 °C for 6 h, cooled, and diluted with water (10 mL). The mixture was extracted with Et_2O (2 × 10 mL), and the combined organic extract was dried (Na_2SO_4), filtered, and concentrated. Purification of the residue by silica gel chromatography (3:7 ethyl acetate/hexanes) afforded **38** (2.0 mg, 34%) as a colorless oil. R_f 0.16 (3:7 hexanes/ethyl acetate); IR (neat) 2925, 2855, 1769 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 0.09−0.10 (m, 14H), 0.93−0.94 (m, 20H), 0.96−0.97 (m, 37H), 1.75 (s, 3H), 1.76 (s, 3H), 1.92−1.96 (m, 4H), 1.9−2.03 (m, 1H), 2.15−2.17 (m, 1H), 2.26−2.29 (m, 1H), 2.38 (dd, J = 5.5, 7.5 Hz, 4H), 2.47−2.50 (m, 1H), 2.76−2.81 (m, 1H), 3.34−3.37 (m, 1H), 3.57−3.60 (m, 1H), 3.66−3.70 (m, 2H), 3.73−3.77 (m, 1H), 3.98 (t, J = 5.9 Hz, 1H), 4.04 (t, J = 8.9 Hz, 1H), 4.42−4.46 (m, 1H), 4.48−4.51 (m, 1H), 4.53 (dd, J = 2.2, 4.0 Hz, 2H), 5.21 (d, J = 7.2 Hz, 1H), 5.88 (d, J = 11.3 Hz, 1H), 5.96 (d, J = 11.5 Hz, 1H), 6.33 (d, J = 1.8 Hz, 1H), 6.34 (d, J = 1.8 Hz, 1H), 6.36 (t, J = 1.6 Hz, 1H), 6.38 (t, J = 2.2 Hz, 1H), 7.31 (d, J = 1.8 Hz, 1H), 7.32 (d, J = 1.8 Hz, 1H), 7.34−7.42 (m, 8H), 7.68−7.71 (m, 5H); ^{13}C NMR (176 MHz, $CDCl_3$) δ −5.1, 11.9, 12.0, 14.1, 16.8, 17.5, 17.7, 17.8, 18.4, 25.9,

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29.7, 30.3, 31.9, 35.5, 36.4, 36.9, 37.2, 37.5, 40.3, 43.6, 45.6, 45.9, 57.3, 61.1, 71.9, 77.3, 110.8, 117.8, 121.3, 124.4, 126.7, 129.2, 129.4, 131.2, 135.8, 135.9, 140.9, 149.3, 149.5, 176.0, 176.1; EI-HRMS m/z calcd for $C_{41}H_{64}O_6SeSi_2Na$ $[M + Na]^+$ 811.3407, found 811.3398.

2-((1*R*,2*R*,3*R*)-2-(3-((*tert*-Butyldimethylsilyloxy)methyl)furan-2-yl)-4-methylene-3-(triisopropylsilyloxy)cyclobutyl)-acetaldehyde (39). To a CH_2Cl_2 solution (0.5 mL) of **28** (15.0 mg, 0.03 mmol) were added 4 Å molecular sieves, TPAP (1.06 mg, 0.003 mmol), and NMO (10.54 mg, 0.09 mmol). The reaction mixture was stirred at room temperature for 1 h, after which the suspension was loaded on a silica gel column and eluted (95:5 hexanes/ethyl acetate) to give aldehyde **39** (9.0 mg, 60%) as a colorless oil. R_f 0.66 (15:85 hexanes/ethyl acetate); $[\alpha]_D^{20}$ −10.2 (c 0.4, $CHCl_3$); IR (neat) 2947, 2866, 1721, 1462 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.08 (s, 3H), 0.09 (s, 3H), 0.92 (s, 9H), 0.95 (s, 21H), 2.72 (dd, J = 1.8, 7.3 Hz, 2H), 3.50 (t, J = 7.0 Hz, 1H), 3.78−3.85 (m, 1H), 4.53 (d, J = 8.2 Hz, 2H), 5.06 (t, J = 2.0 Hz, 1H), 5.09 (dd, J = 2.4, 7.5 Hz, 1H), 5.23 (t, J = 2.0 Hz, 1H), 6.33 (d, J = 1.7 Hz, 1H), 7.32 (d, J = 1.7 Hz, 1H), 9.75 (t, J = 1.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.2, −5.1, 11.9 (3C), 17.7 (6C), 18.3, 25.9 (3C), 39.1, 42.7, 48.1, 57.2, 72.9, 108.3, 110.9, 121.7, 141.1, 148.0, 153.9, 200.7; CI-HRMS m/z calcd for $C_{27}H_{49}O_4Si_2$ $[M + H]^+$ 493.3169, found 493.3172.

(*S*)-3-(2-((1*R*,2*R*,3*R*)-2-(3-((*tert*-Butyldimethylsilyloxy)-methyl)furan-2-yl)-4-methylene-3-(triisopropylsilyloxy)-cyclobutyl)-1-hydroxyethyl)-5-((*E*)-3-iodo-2-methylallyl)furan-2(5*H*)-one (40). To a solution of **35** (13.0 mg, 0.03 mmol) in dry THF (0.2 mL) at −78 °C was added dropwise LiHMDS (46.1 μL, 0.046 mmol, 1.0 M solution in THF). The mixture was stirred at −78 °C for 40 min, and a solution of **39** (9.0 mg, 0.018 mmol) in dry THF (0.2 mL) was added dropwise over 10 min. The mixture was stirred at −78 °C for 1.5 h and then at 0 °C for 15 min. The reaction was quenched with satd aqueous NH_4Cl solution (10 mL), and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL), and the combined organic extract was dried over Na_2SO_4, filtered, and concentrated to leave a crude oil (20.0 mg) that was immediately used for the next reaction.

To a solution of the crude residue obtained above (20.0 mg) in THF (0.3 mL) at 0 °C was added dropwise H_2O_2 (0.10 mL, 30% w/w in water), and the mixture was warmed to room temperature. After the mixture was stirred at room temperature for 20 min, the reaction was quenched with satd aqueous $NaHCO_3$ solution (5.0 mL). The separated aqueous layer was extracted with Et_2O (2 × 5 mL), and the combined organic extract was dried (Na_2SO_4), filtered, and concentrated. The crude mixture was purified by silica gel chromatography (14−16% ethyl acetate in hexanes) to afford separable diastereomers of **40** (less polar 4.0 mg, more polar 3.0 mg, total 51% based on **39**) as colorless oils.

Less Polar Isomer. R_f 0.46 (75:25 hexanes/ethyl acetate); $[\alpha]_D^{23}$ +6.9 (c 0.26, $CHCl_3$); IR (neat) 3464, 2922, 2855, 1752, 1468, 1258 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 0.13 (s, 3H), 0.14 (s, 3H), 0.93−0.94 (m, 30H), 1.92 (d, J = 1.0 Hz, 3H), 1.94 (ddd, J = 7.5, 10.1, 14.0 Hz, 1H), 2.27 (td, J = 5.0, 14.0 Hz, 1H), 2.50 (dd, J = 7.4, 14.9 Hz, 2H), 3.07 (d, J = 5.8 Hz, OH), 3.46−3.50 (m, 1H), 3.53 (dd, J = 7.1, 7.5 Hz, 1H), 4.50 (d, J = 12.2 Hz, 1H), 4.52 (dd, J = 4.8, 11.9 Hz, 1H), 4.60 (d, J = 11.9 Hz, 1H), 4.94 (ddd, J = 1.3, 6.1, 7.6 Hz, 1H), 5.06 (dd, J = 2.0, 4.0 Hz, 1H), 5.08 (t, J = 1.9 Hz, 1H), 5.22 (t, J = 1.9 Hz, 1H), 6.11 (q, J = 1.0 Hz, 1H), 6.33 (d, J = 1.8 Hz, 1H), 6.95 (t, J = 1.4 Hz, 1H), 7.32 (d, J = 1.8 Hz, 1H); ^{13}C NMR (176 MHz, $CDCl_3$) δ −5.1, 11.9, 17.7, 18.5, 24.5, 26.0, 29.7, 30.3, 39.4, 42.7, 42.8, 43.1, 57.1, 66.4, 73.2, 79.3, 79.4, 107.8, 111.4, 121.1, 125.5, 131.7, 136.4, 140.8, 141.8, 149.9, 154.3, 171.7; EI-HRMS m/z calcd for $C_{35}H_{57}IO_6Si_2$ $[M]^+$ 756.2738, found 756.2759.

More Polar Isomer. R_f 0.42 (75:25 hexanes/ethyl acetate); $[\alpha]_D^{23}$ −2.0 (c 0.3, $CHCl_3$); IR (neat) 3457, 2930, 2862, 1752, 1456 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 0.12 (s, 3H), 0.14 (s, 3H), 0.94−0.93 (m, 30H), 1.93 (d, J = 1.0 Hz, 3H), 1.99−2.03 (m, 1H), 2.10 (ddd, J = 3.8, 10.4, 14.0 Hz, 1H), 2.54 (dd, J = 5.9, 10.4 Hz, 2H), 3.52 (dd, J = 7.0, 7.4 Hz, 1H), 3.59−3.63 (m, 1H), 4.47−4.48 (m, 1H), 4.50 (d, J = 12.1 Hz, 1H), 4.67 (d, J = 12.1 Hz, 1H), 4.99 (tt, J = 1.8, 5.7 Hz, 1H), 5.04−5.05 (m, 2H), 5.20 (s, 1H), 6.12 (q, J = 1.0 Hz, 1H), 6.33 (d, J = 1.8 Hz, 1H), 7.09 (t, J = 1.5 Hz, 1H), 7.32 (d, J = 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.1, 12.0, 17.7, 18.5, 24.6, 25.9, 29.7, 30.3, 39.8, 42.6, 42.7, 43.0, 57.2, 65.6, 73.3, 79.3, 79.4, 107.5, 111.5, 121.1, 125.5, 135.7, 136.8, 140.8, 141.8, 147.9, 149.6, 154.2, 171.6.

(*S*)-5-((*E*)-3-(4-((*tert*-Butyldimethylsilyloxy)methyl)-5-((1*R*,2*R*,4*R*)-2-(2-hydroxyethyl)-3-methylene-4-(triisopropylsilyloxy)cyclobutyl)furan-2-yl)-2-methylallyl)-3-(phenylselanyl)dihydrofuran-2(3*H*)-one (42). To a solution of **28** (9.0 mg, 0.018 mmol) in dry THF (0.2 mL) at −78 °C were added dropwise freshly distilled TMEDA (16.0 μL, 0.108 mmol) and *sec*-BuLi (50.0 μL, 0.054 mmol, 1.08 M solution in cyclohexane). The mixture was stirred at −78 °C for 15 min and then at 0 °C for 30 min. The solution was cooled to −78 °C, and Me_3SnCl (90.0 μL, 0.09 mmol, 1.0 M solution in hexane) was added. The reaction mixture was stirred at −78 °C for 1 h and then warmed to room temperature. After the mixture was stirred at room temperature for 1 h, the reaction was quenched with water (10 mL), and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL), and the combined organic extract was dried over Na_2SO_4, filtered, and concentrated to leave a crude oil that was immediately used for the next reaction.

To a solution of the oil obtained above (13.0 mg, 0.019 mmol) and **35** (9.0 mg, 0.021 mmol) in degassed DMF (0.3 mL) under an argon atmosphere were added $Pd(PPh_3)_4$ (1.09 mg, 0.00095 mmol) and CuI (0.36 mg, 0.0019 mg). After 4 h of stirring at room temperature, the mixture was diluted with water (10 mL) and Et_2O (10 mL). The separated aqueous layer was extracted with Et_2O (3 × 10 mL), and the combined organic extract was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel chromatography (3:22:75 NEt_3/ethyl acetate/hexanes) under argon to afford **42** (8.0 mg, 54% based on **28**) as a colorless oil. R_f 0.28 (7:3 hexanes/ethyl acetate); $[\alpha]_D^{22}$ −10.2 (c 0.46, $CHCl_3$); IR (neat) 3478, 2929, 2855, 1769, 1462, 1170 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 0.10−0.12 (m, 19H), 0.92−0.95 (m, 76H), 1.80−1.85 (m, 3H), 1.92−1.94 (m, 2H), 1.96 (s, 6H), 2.00−2.04 (m, 2H), 2.14−2.18 (dd, J = 7.1, 13.6 Hz, 1H), 2.31−2.35 (m, 2H), 2.38−2.42 (m, 1H), 2.54 (dd, J = 5.9, 13.9 Hz, 1H), 2.60 (dd, J = 6.4, 14.4 Hz, 1H), 2.72 (ddd, J = 6.6, 9.3, 13.5 Hz, 1H), 3.37−3.41 (m, 2H), 3.45 (dd, J = 5.9, 7.1 Hz, 2H), 3.66−3.72 (m, 4H), 3.96 (dd, J = 2.5, 8.3 Hz, 1H), 4.04 (t, J = 9.5 Hz, 1H), 4.42−4.46 (m, 1H), 4.49 (d, J = 12.0 Hz, 2H), 4.59 (d, J = 12.0 Hz, 2H), 4.60 (dd, J = 6.5, 7.3 Hz, 1H), 5.00 (s, 2H), 5.08 (d, J = 7.4 Hz, 2H), 5.17 (s, 2H), 5.92 (s, 1H), 5.98 (s, 1H), 6.13−6.15 (m, 2H), 7.34−7.37 (m, 4H), 7.38−7.42 (m, 2H), 7.62−7.64 (m, 2H), 7.68−7.71 (m, 4H); ^{13}C NMR (176 MHz, $CDCl_3$) δ −5.1, 11.9, 17.7, 18.4, 26.0, 26.4, 29.7, 30.3, 35.2, 36.2, 36.9, 37.3, 42.5, 43.2, 45.9, 46.4, 57.2, 61.1, 73.1, 77.6, 77.9, 106.6, 110.4, 117.4, 117.5, 122.6, 126.7, 127.0, 127.7, 128.9, 129.2, 129.4, 130.1, 131.4, 135.7, 135.9, 148.5, 151.0, 155.2, 175.7, 175.8; EI-HRMS m/z calcd for $C_{41}H_{64}O_6SeSi_2$ $[M]^+$ 788.3407, found 788.3388.

2-((1*R*,2*R*,3*R*)-2-(3-((*tert*-Butyldimethylsilyloxy)methyl)-5-((*E*)-2-methyl-3-((*S*)-5-oxo-2,5-dihydrofuran-2-yl)prop-1-enyl)-furan-2-yl)-4-methylene-3-(triisopropylsilyloxy)cyclobutyl)-acetaldehyde (43). To a solution of **42** (6.0 mg, 0.0076 mmol) in 0.15 mL of CH_2Cl_2 at 0 °C was added $NaHCO_3$ (2.0 mg, 0.0152 mmol) followed by Dess−Martin periodinane (4.6 mg, 0.01 mmol). The slurry was stirred at 0 °C for 1.5 h and then diluted with CH_2Cl_2 (5.0 mL). The reaction was quenched with satd $Na_2S_2O_3$ solution (5.0 mL) by stirring the biphasic mixture vigorously for 20 min, and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 5.0 mL), and the combined organic extract was washed with satd $NaHCO_3$ solution, water, and brine and dried over Na_2SO_4. The drying agent was removed by filtration, and the filtrate was concentrated in vacuo. Purification of the residue by silica gel chromatography (72:25:3 hexanes/ethyl acetate/NEt_3) provided **43** (2.0 mg, 43%) as a colorless oil. R_f 0.27 (7:3 hexanes/ethyl acetate); $[\alpha]_D^{25}$ −4.6 (c 0.35, $CHCl_3$); IR (neat) 3478, 2929, 2855, 1746, 1721, 1271 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 0.90 (s, 3H), 0.10 (s, 3H), 0.93−0.95 (m, 30H), 2.09 (d, J = 0.7 Hz, 3H), 2.45 (dd, J = 7.3, 13.7 Hz, 1H), 2.70 (dd, J = 6.6, 13.8 Hz, 1H), 2.75 (dd, J = 1.5, 7.0 Hz, 2H), 3.49 (dd, J = 3.4, 7.6 Hz, 1H), 3.78−3.82 (m, 1H), 4.51 (d, J =

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9.6 Hz, 2H), 5.04 (t, J = 2.0 Hz, 1H), 5.10 (qd, J = 2.0, 7.6 Hz, 1H), 5.19−5.22 (m, 2H), 6.07 (q, J = 0.7 Hz, 1H), 6.16 (dd, J = 1.9, 5.7 Hz, 1H), 6.18 (s, 1H), 7.18 (s, 1H), 7.50 (dd, J = 1.4, 5.7 Hz, 1H), 9.77 (t, J = 1.8 Hz, 1H); ^{13}C NMR (176 MHz, $CDCl_3$) δ −5.1, 11.9, 14.1, 17.7, 18.4, 19.1, 22.7, 25.9, 29.4, 39.0, 42.6, 44.5, 48.1, 57.2, 73.1, 82.2, 108.1, 110.5, 117.9, 121.7, 123.2, 129.5, 147.3, 151.1, 156.1, 172.9, 200.8; CI-HRMS m/z calcd for $C_{35}H_{56}O_6Si_2Na$ $[M + Na]^+$ 651.3513, found 651.3529.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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