Synthesis and Biological Evaluation of Structurally Highly Modified Analogues of the Antimitotic Natural Product Curacin A

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Structure−activity relationship analysis of synthetic analogues of curacin A revealed the lack of activity of traditional heterocyclic replacements of the thiazoline ring or cyclopropyl analogues of the core diene segment. The significance of the C(3)−C(4)−(*Z*)-alkene geometry was established, and a novel oxime analogue was designed that displays biological properties that are a close match of the natural product lead. The much less lipophilic, structurally simplified oxime **50** was only slightly weaker at inhibiting the growth of cultured human tumor cells than the natural product and was found to be more potent than curacin A at inhibiting the assembly of purified tubulin. Accordingly, the oxime moiety is likely to serve as a novel bioisostere of the (*Z*)-alkene group.

Introduction

The heterodimeric protein tubulin readily polymerizes in the presence of guanosine 5′-triphosphate (GTP), and the resulting microtubules form helical arrays that are intrinsically associated with correct chromosome segregation during cell division (mitosis), vesicle movements in secretion, intracellular transport of organelles, ciliar and flagellar movement, and the maintenance of cell shape.[1] Disassembly of microtubules is an equally important part of the dynamics of this process. The ubiquitous biological presence of tubulin and its crucial contribution to cell division renders this protein a prime target for natural product-based chemical defense mechanisms. Many cytotoxic natural products target the dynamic equilibrium between soluble α- and *β*-tubulin heterodimers and polymeric microtubules.[2] In particular, three major binding sites on tubulin have been identified for mostly lipophilic ligands, and some high-affinity agents have been developed as antimitotic anticancer drugs. In recent years, the paclitaxel binding site on the *β*-tubulin subunit of the polymerized microtubule has attracted great interest, and ligands such as the taxanes, epothilones, or discodermolide, which interact at this site, prevent depolymerization and are clinically validated as effective anticancer agents. The vinca alkaloid domain and the colchicine binding site are both located on *β*-tubulin of the unpolymerized heterodimer, and interaction of vinblastine, halichondrin, or spongistatin with the former and colchicine, combretastatin, nocodazole, or podophyllotoxin with the latter site interferes with polymerization, leading to general microtubule disruption. In addition, other natural products bind to somewhat less well-defined sites on tubulin, including covalent interactions with tubulin sulfhydryl groups. Most noteworthy among these alternative binding agents are spindle poisons of the rhizoxin/maytansine class, which include cryptophycin and dolastatins as well as cytochalasins and disulfiram. Low-affinity, unspecific binding to tubulin is common, however, and many lipophilic derivatives of combinatorial library syntheses have been reported to interact with this target.[3]

The marine natural product curacin A demonstrates potent inhibition of tubulin polymerization and an impressive antiproliferative profile.[4] However, structural features such as the presence of a readily oxidized thiazoline heterocycle, four double bonds including a conjugated diene, and, especially, high lipophilicity are strong deterrents from a therapeutic evaluation of curacin A as a new lead for the development of anticancer agents. Traditional chemical analoging of this natural product has also met with limited success.[4b,5] While many natural congeners with closely related structures showed comparable activity to curacin A, all synthetic derivatives were greatly inferior (Figure 1, Table 1).[4,5]

The general trends that could be discerned from this structurally well-defined series were as follows: (i) Activity was relatively independent of replacements of the cyclopropane with other lipophilic side chains. (ii) Ring opening of the thiazoline was not tolerated. (iii) In contrast to the C(15)−C(16) alkene, the C(3)−C(4) double bond could not be saturated without loss in activity; however, the significance of the (*Z*)-configuration of the latter alkene was not clear. (iv) Biological activity was remarkably sensitive to isomerizations or structural modifications of the core lipophilic C(7)−C(10) diene segment. (v) The stereochemistry at C(13) was not significant, but longer chains or acyl groups as oxygen substituents were not tolerated. Little or no information existed regarding the replacement of the thiazoline ring with other heterocycles or structure−activity relationships (SAR) at the C(14)−C(16) terminus of curacin A.

For the design of a series of first generation analogues, we were interested in a comparison of activities for oxazoline and oxazole analogues of the natural product. Because the cyclopropyl substituent did not appear to contribute significantly to the biological

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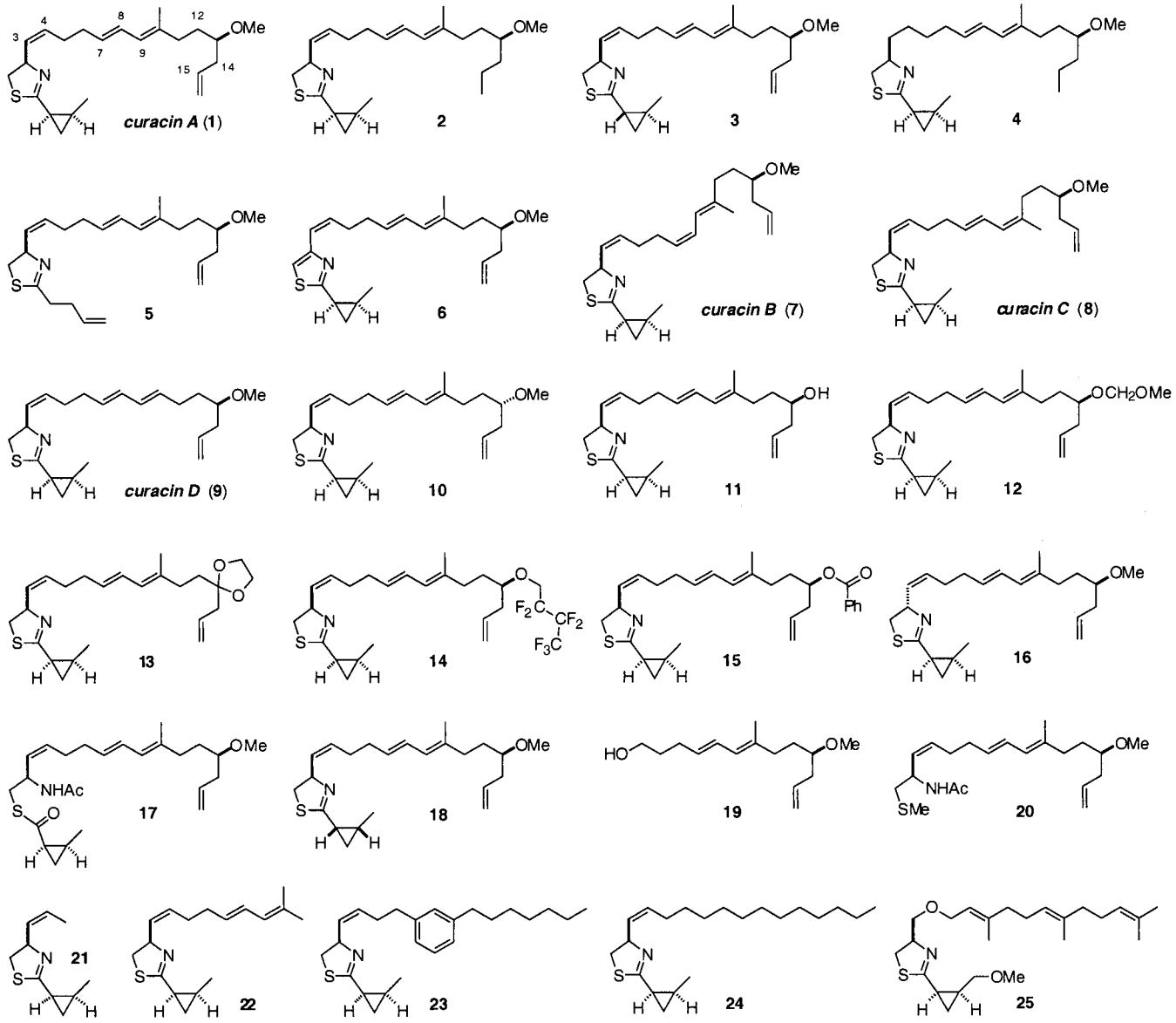


Figure 1. Natural and synthetic analogues of curacin A.

activity of the lead structure, we replaced it with a *tert*-butyl group in order to increase the hydrolytic stability of the azole derivatives due to steric shielding (Figure 2). For appropriate correlations, we also prepared the corresponding thiazoline and thiazole compounds **28** and **29** based on an extension of our approach toward the total synthesis of curacin A reported in 1996 (Scheme 1).[6]

Coupling of serine hydrochloride methyl ester (**30**) with pivalic acid, protection of the side chain alcohol with TBS-Cl, and reduction of the ester to the primary alcohol **31** proceeded in 38% overall yield. Subsequent Swern oxidation and Wittig reaction of **32** with the ylide **33**[6] led to amide **34**, which was cyclized to oxazoline **26** with Deoxo-Fluor[7] after cleavage of the TBS-ether. Dehydrogenation of **26** to the oxazole **27** was accomplished with manganese dioxide.[8] Alternatively, amide **34** could be converted to thiazoline **28** by thionation with Lawesson's reagent,[9] *O*-desilylation, and cyclodehydration of the intermediate β-hydroxythioamide with Deoxo-Fluor.[10] Treatment of thiazoline **28** with manganese dioxide provided thiazole **29** in 46% yield.

As expected, the sulfur-containing compounds **28** and **29** showed competitive effects at the colchicine binding site and inhibited tubulin polymerization in close analogy to curacin A. Furthermore, **28** and **29** inhibited the growth of human breast (MDA-MB231), prostate (PC-3), and ovarian (2008) carcinoma cells with low nanomolar potencies (Table 2). In contrast, the oxazoline and oxazole analogues **26** and **27** lacked any appreciable biological efficacy. A related decrease or even disappearance of biological activity has been noted in other natural product azole derivatives when sulfur atoms were exchanged with oxygen.[11]

Interestingly, while colchicine site binding and tubulin polymerization inhibition (TPI) for oxazoline **26** was insignificant, **26** demonstrated moderate (PC-3) to high (2008) cell line toxicity (Table 2). This activity is likely due to a biological event unrelated to tubulin binding. Oxazole **27** showed moderate TPI but no affinity for the colchicine site or inhibition of cell growth. In addition, while TPI and cell growth inhibition induced by thiazoline **28** and thiazole **29** closely mimicked the effects of curacin A, growth inhibition of the ovarian cancer line

Table 1. CBI, 50% TPI Concentration, and 50% Growth Inhibitory Concentrations (GI_{50}) for Curacin A and Literature Compounds **2**−**25**

compd	CBI (% at 5 μM)	TPI IC_{50} (μM)	GI_{50} (μM) MCF-7
1	94	0.72	0.04
2	85	1.2	0.05
3	88	0.77	0.09
4	1	4.6	3.3
5	83	0.92	0.30
6	74	0.74	0.30
7	56	0.82	0.32
8	10	2.3	3.6
9	53	4.8	0.34
10	56	0.67	0.18
11	82	0.87	0.45
12	81	0.64	0.22
13	92	0.78	0.03
14	12	5.4	>10
15	5	>80	>10
16	3	5.5	>1
17	9	1.5	4.2
18	48	2.1	0.36
19	0	>80	>10
20	12	3.3	5.2
21	inactive	inactive	-
22	-	>50	-
23	-	>50	-
24	-	>50	-
25	-	-	>25[a]

[a] Determined with the A2780 human ovarian carcinoma cell line.

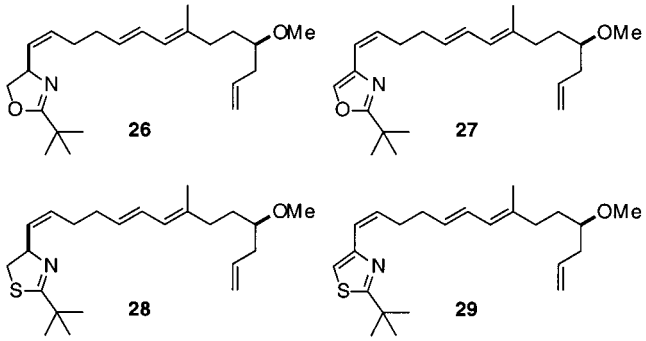
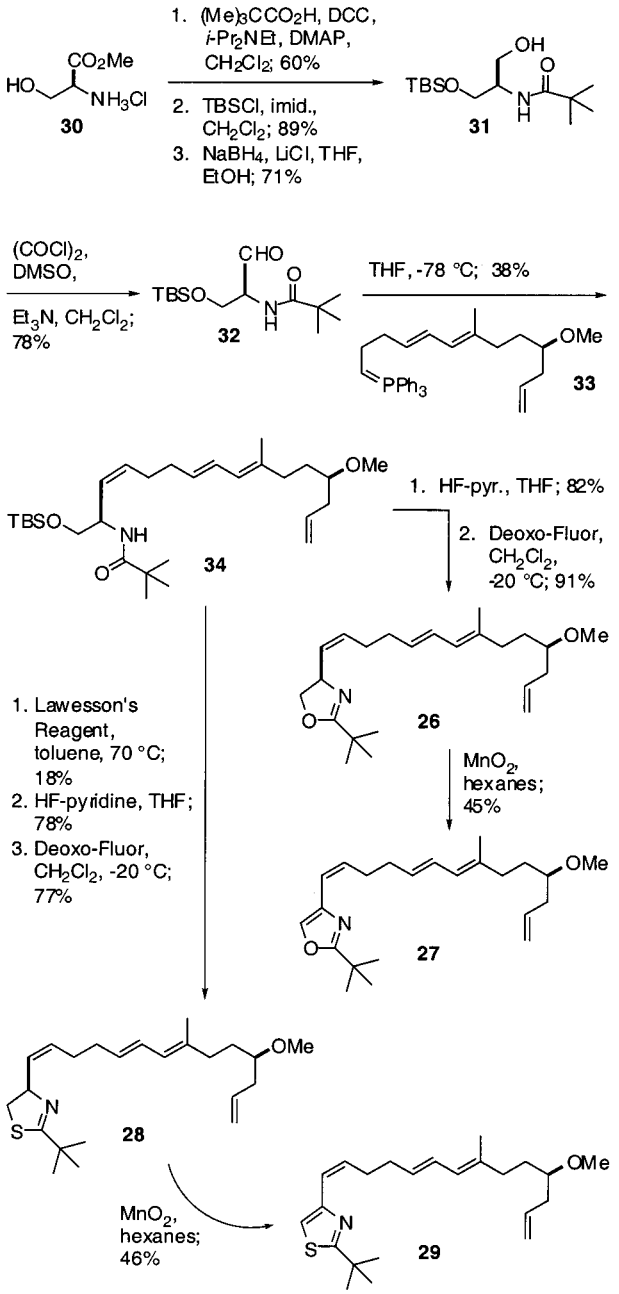


Figure 2. *tert*-Butyl oxazoline, oxazole, thiazoline, and thiazole analogues of curacin A.

and colchicine binding inhibition (CBI) was ca. 10 times and >2 times decreased, respectively. The significant decrease in percent CBI for **28** and **29** is possibly due to differential binding of these agents to more than one site on tubulin. In addition to fast and irreversible binding of curacin A to the colchicine site on tubulin, the natural product has at least two additional lower affinity binding sites on the protein.[12,13] If **28** and **29**, as a consequence of structural modifications in the heterocycle region, display a greater affinity to these alternative binding sites on tubulin, the secondary structure of the protein might be perturbed sufficiently to contribute to a relative stabilization of the tubuline−colchicine interaction.[14]

The SAR data in Table 1 clearly show that the biological activity of curacin A is critically dependent on the nature of the highly lipophilic and oxidation sensitive tetraene chain. As an attractive replacement of the central diene portion, we envisioned the preparation of cyclopropyl derivatives **44** and **45** (Scheme 2). There is encouraging precedence of the use of cyclopropanes as alkene bioisosteres in cancer chemotherapy,[15] and we hoped in this case to decrease the potential for rapid metabolism and biological degradation of curacin A by sequential replacement of alkene moieties with cyclopropane units.

Scheme 1



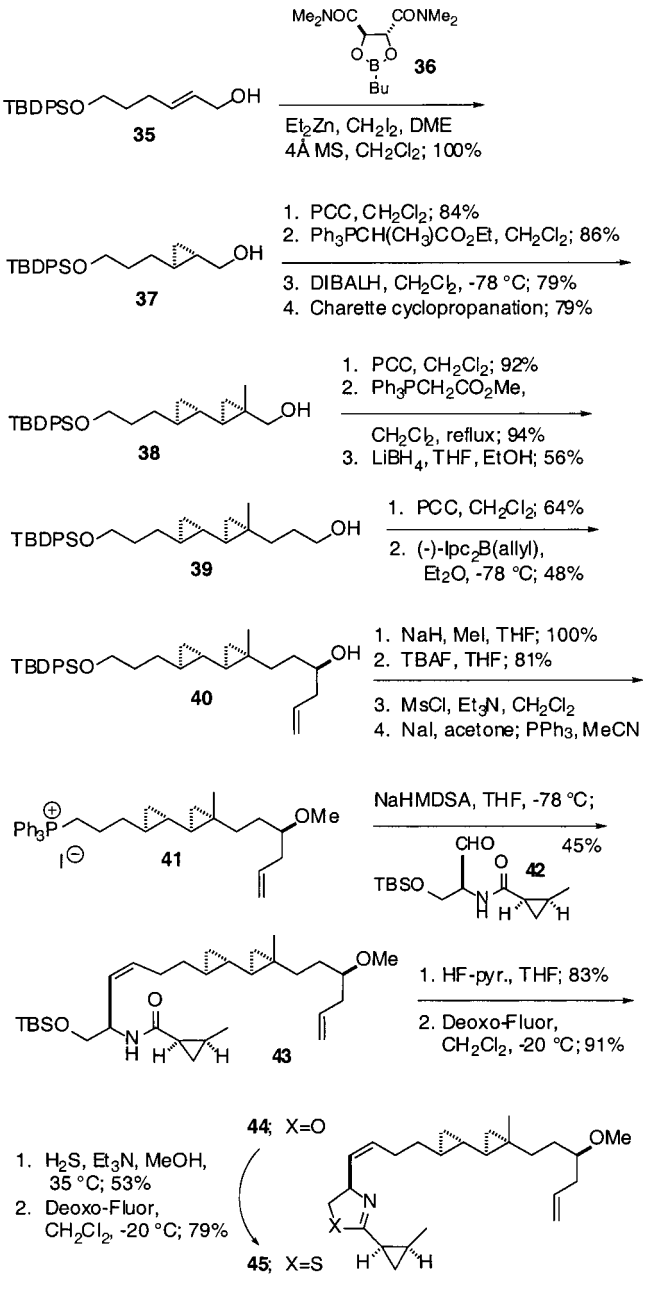
Charette asymmetric cyclopropanation[16] of allylic alcohol **35**[17] in the presence of boronic ester **36** provided cyclopropane **37** in quantitative yield. PCC oxidation to the aldehyde, Wittig chain extension, reduction to the allylic alcohol, and a second directed cyclopropanation led to bis-cyclopropane **38** in 45% overall yield. Another two carbon chain extension followed by allylation[18] of the aldehyde derived from **39** led to the cyclopropane analogue **40** of the lipophilic side chain of curacin A. After *O*-methylation, the ylide derived from phosphonium salt **41** was condensed with serine-derived aldehyde **42**[6] providing the (*Z*)-alkene **43** in 45% yield. This amide was deprotected with HF-pyridine and converted

Table 2. CBI, 50% TPI Concentration, and GI_{50} Values for Curacin A and Analogues **26**−**29**, **44**, and **45**

compd	CBI (% at 5 μM)[a]	TPI (% at 5 μM)[b]	MDA−MB231	GI_{50} (μM) PC-3[c]	2008
1	78 ± 2	98	0.096 ± 0.06	0.050 ± 0.009	0.035 ± 0.007
26	<10	0	1.8 ± 0.3	6.2 ± 1.3	0.45 ± 0.50
27	<10	51	36 ± 22	>50	>50
28	35 ± 2	100	0.20 ± 0.11	0.13 ± 0.08	0.22 ± 0.09
29	38 ± 4	100	0.32 ± 0.20	0.24 ± 0.07	0.30 ± 0.17
44	<10	59	18 ± 4	49 ± 1	18 ± 4
45	<10	0	>50	>50	>50

[a] Values shown are means (N = 9 over four concentrations) ± standard deviations (SD) for incubation at 30 °C for 15 min. [b] Average of two determinations except for curacin A (**1**) and **44**, where N = 7 and 4, respectively. [c] Means (N = 4 over 10 concentrations) ± SD after 48 h of continuous exposure to the agent.

Scheme 2



to oxazoline **44** upon exposure to Deoxo-Fluor. An important objective of our design was to continue to have ready access to both oxygen- and sulfur-containing heterocycles for comparison of their relative biological activities. This was accomplished by a two step oxazoline−thiazoline interconversion methodology.[19] Thiolysis of **44** with hydrogen sulfide in the presence of triethylamine provided the intermediate hydroxy thioamide, which was cyclodehydrated to thiazoline **45**.

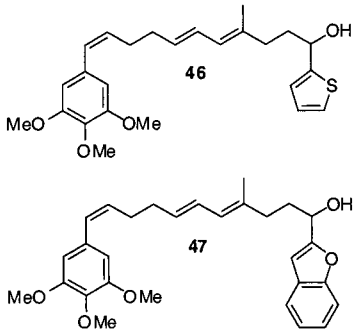


Figure 3. Two second generation curacin A analogues from a mixture library synthesis.[21]

The cyclopropyl group can be an effective bioisostere of alkene functions.[20] In conjugated systems, however, the rotation of the C−C bond connecting two contiguous cyclopropane rings is relatively unhindered, whereas the barrier for rotation of the corresponding diene is 3−4 kcal/mol. The diene moiety of curacin A can thus be expected to exert a strong preference for the planar s-trans conformation and be more rigidified than a 1,3-dicyclopropane. Nonetheless, it is surprising that the biological activity of bis-cyclopropyl curacin A analogue **45** was completely obliterated, in terms of both inhibition of cellular growth and tubulin polymerization (Table 2). This dramatic effect is a further confirmation of the crucial role of the conformation of the lipophilic core in the biological mode of action of the natural product. While the bis-cyclopropyl oxazoline **44** was a somewhat more potent inhibitor of polymerization of isolated tubulin than thiazole **45**, this biological effect was at odds with mediocre effects in antiproliferative activity and lack of displacement of colchicine from its binding site.

We have recently reported a focused combinatorial library approach that identified a new class of structurally simplified analogues approaching the biological activity of curacin A in several in vitro assays.[21] The most active library members, **46** and **47** (Figure 3), inhibited tubulin polymerization with an IC_{50} of ca. 1 μM, showed an average growth inhibition activity GI_{50} of ca. 250 nM, inhibited [^{3}H]colchicine binding to tubulin, and blocked mitotic progression at nanomolar concentrations. This combinatorial approach greatly facilitated the synthesis of further analogues of the natural product since it identified suitable replacements for the heterocyclic and the homoallylic ether termini of the lead structure. Accordingly, we focused our further studies on the identification of a replacement

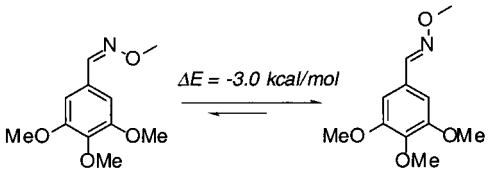


Figure 4. Equilibrium distribution of aromatic cis and trans oximes based on HF 6-31G* calculations.

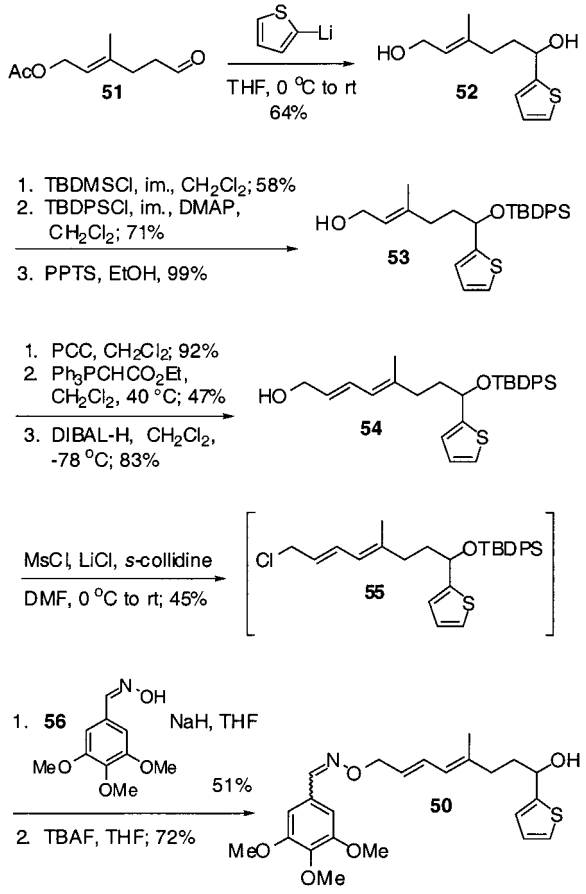
of the (*Z*)-alkene moiety of **46**. The importance of this structural motif in the natural product is clearly indicated by the SAR information shown in Table 1. To date, any modification of this chemically sensitive double bond, in particular saturation, had resulted in inactive derivatives (e.g., **4** and **25**).

While analogues such as **46** and **47** provided effective replacements for the labile cyclopropyl thiazoline moiety and the homoallylic ether terminus of curacin A, they shared the undesirable (*Z*)-alkene moiety with the parent lead structure and were similarly highly lipophilic (*clogP* values[22] of 5.3−6.6; curacin A has a *clogP* of 6.7). In an effort to address both deficiencies, we prepared a novel oxime analogue of curacin A that demonstrated superior bioactivity. The rationale for replacing the (*Z*)-alkene moiety with an oxime was based on an increase in chemical stability, retaining a π-system for conjugation with the arene portion, and introducing a functional group that equilibrates between both cisoid and transoid geometries and lends itself to rapid modular analoging.[23] In contrast to potential (hetero)cyclic (*Z*)-alkene replacements, oximes do not increase steric congestion at this critical site. Quantum chemical calculation at the HF 6-31G* level of the energy difference of model cis and trans oximes **48** and **49** indicated that the trans geometry was favored by 3.0 kcal/mol (Figure 4).[24] While, accordingly, isomer **49** is largely favored in solution, there is considerable experimental evidence that oxime isomerizations in polar media are fast even at ambient temperatures[23,25] and allow for a ready selection of the most active isomer by the biological target.[26]

For a preliminary proof-of-principle for oxime-based analogues of curacin A, we selected peripheral substituents derived from the combinatorially optimized **46**. The synthesis of target molecule **50** is shown in Scheme 3 and was accomplished in 10 steps.

Treatment of aldehyde **51**[27] with excess 2-thienyllithium and selective protection of the resulting diol **52** provided silyl ether **53**. Oxidation of **53** to the α,β-unsaturated aldehyde with PCC[28] and Wittig homologation followed by reduction of the dienyl ester with DIBAL-H led to dienyl alcohol **54**. Mesylation and in

Scheme 3



situ allylic chloride formation gave the sensitive dienyl chloride **55**, which was displaced without purification with the sodium salt of aldoxime **56**[29] to give the oxime ether. Desilylation with TBAF in THF gave the desired oxime **50**.

Compound **50** was found to have potent antiproliferative activity in three human tumor cell lines: breast (MDA-MB231), prostate (PC3), and ovarian (2008) (Table 3). GI_{50} values at 48 h of continuous drug exposure were 0.12, 0.25, and 0.24 μM, respectively. These values are, as those of our previously reported analogues **46** and **47**, closely comparable to those found for **1** under identical conditions, namely, 0.096, 0.050, and 0.035 μM, respectively.[21] Compound **50** was tested for displacement of [^{3}H]colchicine from tubulin at both 30 and 37 °C.[4b,21] Under these experimental conditions, compound **50** displaced the label at ca. 60% of the efficiency of **1**. The most impressive property of **50** was its ability to inhibit the GTP/glutamate-induced polymerization of tubulin (Figure 5).[4b,21] The activity of **50** in this assay was remarkable in that its IC_{50} (0.17 μM)

Table 3. CBI, 50% TPI Concentration, and GI_{50} Values for Analogues **46**, **50**, **57**, and **63**−**65**

compd	CBI (% at 5 μM)[a]	TPI (% at 5 μM)[b]	MDA−MB231	GI_{50} (μM) PC-3[c]	2008
1	78 ± 2	98	0.096 ± 0.06	0.050 ± 0.009	0.035 ± 0.007
46[21]	39 ± 10	>95	0.28 ± 0.04	0.38 ± 0.08	0.28 ± 0.02
50	48 ± 12	100	0.12 ± 0.10	0.25 ± 0.08	0.24 ± 0.18
57	<10	26	0.98 ± 0.20	1.2 ± 1.9	9.9 ± 8.7
63	<10	7	>50	18 ± 10	15 ± 8
64	<10	15	43 ± 7	21 ± 6	26 ± 3
65	<10	25	15 ± 2	35 ± 4	21 ± 0

[a] Values shown are means (N = 9 over four concentrations) ± SD for incubation at 30 °C for 15 min. [b] Average of two determinations except for curacin A (**1**), where N = 7. [c] Means (N = 4 over 10 concentrations) ± SD after 48 h of continuous exposure to the agent.

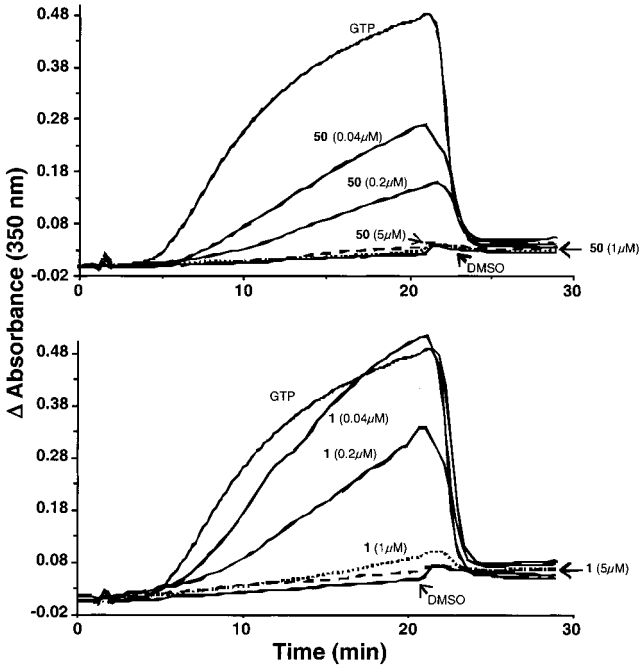


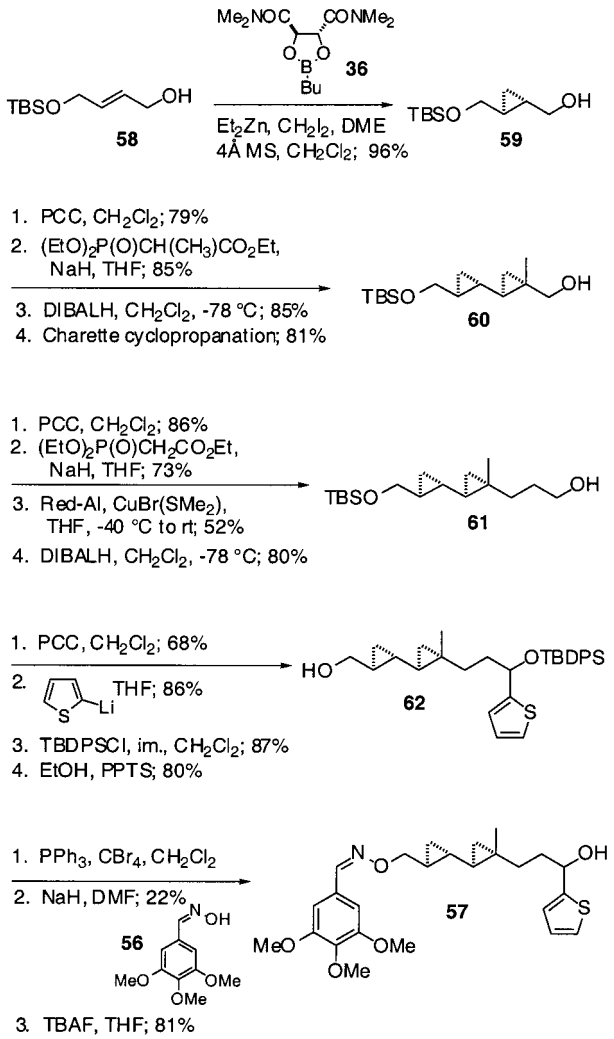
Figure 5. Representative plots comparing inhibition of GTP/glutamate-induced assembly of tublin by 40 nM to 1μM concentrations of **50** and **1**.

was clearly superior to that of **1** (0.52 μM) with the particular batch of tubulin used in these examinations.

For further calibration of the biological effects of **50** vs curacin A, we synthesized the biscyclopropyl derivative **57**, which represented an analogue of the (inactive) biscyclopropane derivative **45** of the natural product. If indeed **50** had a biological mode of action closely related to the natural product, we would expect **57** to match the SAR of curacin A derivatives and be similarly inactive. The preparation of this negative control oxime is shown in Scheme 4. Charette cyclopropanation of allylic alcohol **58** followed by PCC oxidation of **59**, Wadsworth−Emmons chain extension, and a second asymmetric cyclopropanation provided **61** in high overall yield. After a two carbon chain extension at the hydroxyl terminus of **61**, the thiophene was installed and protective groups were switched to give alcohol **62**. Conversion of the alcohol to the bromide and condensation with the sodium salt of oxime **56** led to the target compound **57** after TBAF-mediated cleavage of the *tert*-butyldiphenylsilyl ether protective group. As expected, on the basis of the biological results of **45**, oxime **57** was unable to displace colchicine from its binding site. Oxime **57** was also ca. 10 times less cell growth inhibitory than **50** and had little TPI activity (Table 3); however, it was more potent in these assays than the completely inactive **45**.

To complete our preliminary SAR studies around the newly found, potent lead oxime **50**, we studied the biological activity of two reduced derivatives, e.g., the ether **63** and the per-hydrogenated **64** (Scheme 5). We also prepared the C(3)−C(4) trans alkene derivative **65**, since there were no data in the literature on the biological activity of a trans alkene analogue of curacin A at this position. The convergent synthesis of these derivatives is summarized in Scheme 5. Aldehyde **66**[6] was converted to the primary alcohol **67** by treatment with 2-lithiated thiophene and protective group ma-

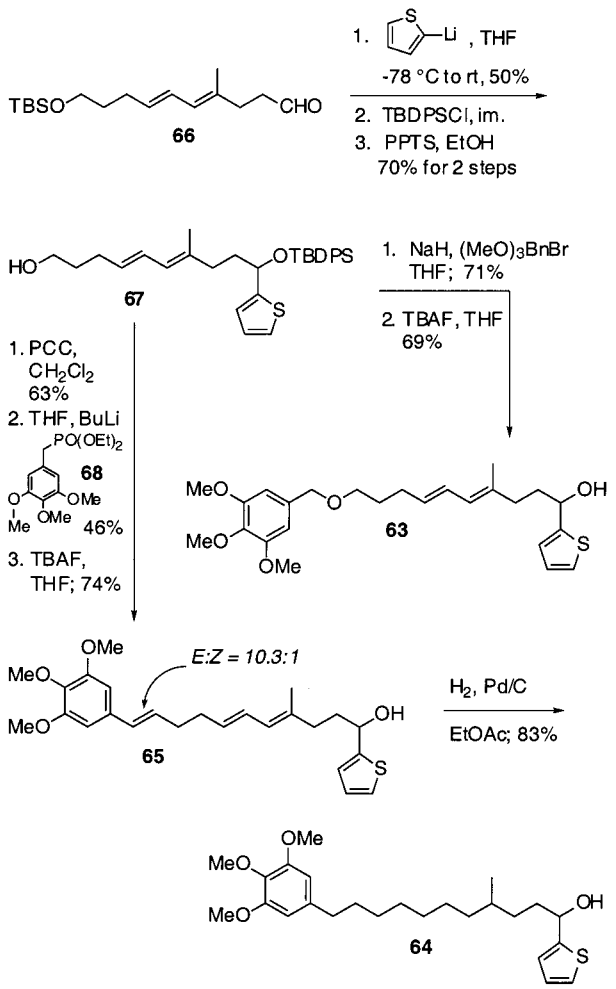
Scheme 4



nipulation. Alkylation of the sodium salt of **67** with 3,4,5-trimethoxybenzyl bromide and desilylation gave ether **63**. Alternatively, alkene **65** and polysaturated derivative **64** were readily obtained from precursor **67** by oxidation, Horner−Wadsworth−Emmons condensation with phosphonate **68**, deprotection, and catalytic hydrogenation. Benzyl ether **63**, the saturated derivative **64**, and the (*E*)-alkene **65** all showed marginal or no biological activity and therefore confirmed the unique ability of oxime **50** to serve as a potent analogue of curacin A (Table 3). In addition, it appears clear from the 100-fold lower activity of *trans*-**65** vs the potent effects of cis isomer **46** that the tolerance of geometric isomerism at the benzylic position is minimal.

In conclusion, we have prepared a series of analogues of the antimitotic marine natural product curacin A that sheds light on some of the more intricate SARs of this structurally novel compound. In particular, closely related oxazoline and oxazole analogues are deprived of significant antitubulin or cell growth inhibitory effects, but the thiazoline moiety can be replaced successfully with an electron-rich aromatic ring. Partially hydrogenated derivatives, (*E*)-alkene isomers at C(4)−C(5), and cyclopropyl analogues of the diene segment in curacin A fail to show any appreciable biological activity in TPI and cell-based assays. The homoallylic ether at the terminus of the lipid chain of curacin A can

Scheme 5



be replaced by a thiophene-substituted alcohol with little or no loss in activity, thus providing a means for increasing water solubility. Most significantly, an oxime group can be used as a bioisostere of the C(3)−C(4) (*Z*)-alkene moiety in the natural product, even though the oxime has a strong preference for the s-trans configuration and a trans alkene analogue at this position is inactive. The potent effects of **50** are therefore likely due to a rapid equilibration of s-trans and s-cis oximes in biological media. Compound **50** displaced label from the colchicine site only half as well as **1** but was only 1.2- to 6.9-fold weaker at inhibiting the growth of cultured human tumor cells. Furthermore, **50** was found to be more potent than **1** at inhibiting the assembly of purified tubulin. Although we have yet to determine the binding stoichiometry and kinetics between **50** and tubulin, the data suggest that **50** binds the protein slightly differently from **1** and perhaps at overlapping but not fully coincident sites near the colchicine binding pocket. Alternatively, as **1** binds with high affinity to the colchicine site and has at least two other sites of interaction with tubulin,[4a] it may be that **50** binds the same sites but with different affinities and/or kinetics. It seems apparent that the potent TPI activity of **50** is not entirely due to binding at the colchicine site. Regardless of the apparent complexities of structure−activity analyses of the molecular mode of interaction with tubulin, **50** represents the most attractive analogue of curacin A reported to date, in terms of both its biological activity and TPI as well as with regard to its physicochemical properties. The *clogP* of **50** was calculated as 3.7, improved by about 3 orders of magnitude over the natural product as well as the second generation analogues **46** and **47**. As oximes as a group are often thought of as highly protein-bound or unstable compounds, **50** was examined for human plasma protein binding and stability in comparison to **1**.[30] Plasma protein binding for **50** was moderate, with unbound fractions ranging from 28 to 40%. Both unbound and protein-bound fractions of **50** showed complete chemical stability over a 4 h period. In contrast, **1** was highly protein-bound, yielding unbound fractions ranging from 0.5 to 5%. Moreover, compound **1** was not totally stable over a 4 h period in the presence of plasma, with 5−17% of the sample becoming oxidized to a species with a molecular mass 2 amu lower than **1**.

Our results validate the feasibility of replacing undesirable structural features of curacin A with more stable and more readily modifiable functional groups that also improve water solubility. This is a remarkable advancement since most tubulin binding agents lose significant activity upon reduction of their hydrophobicity.[1−3] Further biological evaluations of **50** and its congeners, in particular in in vivo mouse antitumor models, will be reported in due course.

Experimental Section

General. All reactions were performed under an atmosphere of N_2, and all glassware was dried in an oven at 140 °C prior to use. THF and Et_2O were dried by distillation over Na/benzophenone. Dry CH_2Cl_2 was obtained by distillation from CaH_2. Unless otherwise stated, solvents or reagents were used without further purification. Nuclear magnetic resonance (NMR) spectra were recorded at 300 MHz/75 MHz ($^1H/^{13}C$ NMR) in $CDCl_3$ on a Bruker DPX-300. Infrared spectra were measured on an ATI Mattson Genesis Series Fourier transform spectrometer. Low-resolution electron ionization (EI) mass spectra were obtained on a Hewlett-Packard-9000 gas chromatography-mass spectrometer (GC-MS), and high-resolution spectra were obtained on a VG 70-G or VG Autospec double focusing instrument under EI or fast atom bombardment (FAB) modes. High-performance liquid chromatography (HPLC) traces were obtained on a Microsorb C_{18} column with UV or ELS (evaporative light scattering) detection. Tubulin without microtubule-associated proteins was prepared from fresh bovine brains.[31]

(2*S*)-2-(2,2-Dimethylpropionylamino)-3-hydroxypropionic Acid Methyl Ester. A solution of trimethylacetic acid (5.14 g, 50.4 mmol) in CH_2Cl_2 (300 mL) was treated with diisopropylethylamine (8.78 mL, 50.4 mmol), L-serine methyl ester hydrochloride **30** (7.85 g, 50.4 mmol), and 4-(dimethylamino)pyridine (576 mg, 5.04 mmol). After 30 min, 1,3-dicyclohexylcarbodiimide (10.4 g, 50.4 mmol) was added, and the reaction mixture was stirred at room temperature overnight and filtered. The filtrate was concentrated and chromatographed on SiO_2 (hexanes/EtOAc, 1:1) to give (2*S*)-2-(2,2-dimethylpropionylamino)-3-hydroxypropionic acid methyl ester (6.13 g, 30.2 mmol, 60%) as a wax. ^1H NMR: δ 6.64 (br d, 1 H, J = 6.8 Hz), 4.60 (dt, 1 H, J = 3.7 Hz), 4.00−3.91 (m, 1 H), 3.89−3.82 (m, 1 H), 3.76 (s, 3 H), 3.34 (t, 1 H, J = 5.6 Hz), 1.21 (s, 9 H).

(2*S*)-3-(*tert*-Butyldimethylsilanyloxy)-2-(2,2-dimethylpropionylamino)propionic Acid Methyl Ester. A solution of (2*S*)-2-(2,2-dimethylpropionylamino)-3-hydroxypropionic acid methyl ester (6.04 g, 29.8 mmol) in CH_2Cl_2 (80 mL) was treated with imidazole (2.23 g, 32.8 mmol) and TBS-Cl (4.49 g, 29.8 mmol). The reaction mixture was stirred at room temperature overnight, diluted with Et_2O, washed with 1 M HCl, H_2O, and brine, dried ($MgSO_4$), concentrated, and chromatographed on

SiO_2 (hexanes/EtOAc, 4:1) to give (2*S*)-3-(*tert*-butyldimethylsilanyloxy)-2-(2,2-dimethylpropionylamino)propionic acid methyl ester (8.41 g, 26.5 mmol, 89%) as an oil. ^{1}H NMR: δ 6.49 (br d, 1 H, J = 7.1 Hz), 4.62 (dt, 1 H, J = 8.1, 2.8 Hz), 4.05 (dd, 1 H, J = 10.0, 2.5 Hz), 3.81 (dd, 1 H, J = 10.0, 3.1 Hz), 3.74 (s, 3 H), 1.22 (s, 9 H), 0.85 (s, 9 H), 0.03 (s, 3 H), 0.01 (s, 3 H).

(2*R*)-*N*-[2-(*tert*-Butyldimethylsilanyloxy)-1-hydroxymethylethyl]-2,2-dimethylpropionamide (31). A solution of (2*S*)-3-(*tert*-butyldimethylsilanyloxy)-2-(2,2-dimethylpropionylamino)propionic acid methyl ester (5.21 g, 16.4 mmol) in THF (30 mL) was treated with LiCl (1.39 g, 32.8 mmol), $NaBH_4$ (1.25 g, 32.8 mmol), and EtOH (60 mL). The reaction mixture was stirred at room temperature overnight, cooled with ice water, adjusted to pH 4 by gradual addition of 10% aqueous citric acid solution, and concentrated. H_2O was added, and the solution was extracted with CH_2Cl_2. The organic layer was washed with saturated $NaHCO_3$, dried ($MgSO_4$), concentrated, and chromatographed on SiO_2 (hexanes/EtOAc, 1:1) to give **31** (3.37 g, 11.7 mmol, 71%) as an oil; $[\alpha]_D$ +11.9 (*c* 1.2, $CHCl_3$). IR (neat): 3450, 3366, 2954, 2859, 1644, 1513, 1469, 1255, 1101, 840 cm^{-1}. ^{1}H NMR: δ 6.34 (br d, 1 H, J = 6.9 Hz), 3.93−3.85 (m, 1 H), 3.79−3.66 (m, 3 H), 3.62−3.53 (m, 2 H), 1.16 (s, 9 H), 0.85 (s, 9 H), 0.03 (2s, 6 H). ^{13}C NMR: δ 179.1, 63.5, 63.1, 51.9, 38.8, 27.5, 25.8, 18.1, −5.5, −5.6. MS (EI) *m*/*z* (relative intensity): 289 (M^+, 1), 232 (35), 84 (100). HRMS (EI) calcd for $C_{14}H_{31}NO_3Si$, 289.2073; found, 289.2071.

(2*S*)-*N*-[2-(*tert*-Butyldimethylsilanyloxy)-1-formylethyl]-2,2-dimethylpropionamide (32). A solution of oxalyl chloride (0.45 mL, 5.2 mmol) in CH_2Cl_2 (5 mL) was treated at −60 °C with dimethyl sulfoxide (DMSO; 0.49 mL, 6.9 mmol) followed by a solution of alcohol **31** (1.01 g, 3.46 mmol) in CH_2Cl_2 (10 mL). After 15 min at −60 °C, Et_3N (1.9 mL, 13.8 mmol) was added dropwise. The reaction mixture was allowed to warm over 20 min, quenched with H_2O, diluted with hexanes, washed with saturated $KHSO_4$ solution, dried ($MgSO_4$), concentrated, and chromatographed on SiO_2 (hexanes/EtOAc, 4:1) to give **32** (775 mg, 2.70 mmol, 78%) as an oil. ^{1}H NMR: δ 9.62 (s, 1 H), 6.60−6.50 (br, 1 H), 4.50 (ddd, 1 H, J = 9.9, 4.2, 3.0 Hz), 4.21 (dd, 1 H, J = 10.4, 3.0 Hz), 3.85 (dd, 1 H, J = 10.4, 4.2 Hz), 1.24 (s, 9 H), 0.86 (s, 9 H), 0.04 (s, 6 H).

(1*R*,2*Z*,6*E*,8*E*,12*R*)-*N*-[1-(*tert*-Butyldimethylsilanyloxymethyl)-12-methoxy-9-methylpentadeca-2,6,8,14-tetraenyl]-2,2-dimethylpropionamide (34). A solution of phosphonium salt **33** (494 mg, 0.810 mmol) in THF (7 mL) was treated dropwise at −78 °C with 2 M solution of NaHMDS in THF (0.50 mL, 1.0 mmol). The reaction mixture was stirred for 45 min at −78 °C and then treated with a solution of aldehyde **32** (459 mg, 1.60 mmol) in THF (3 mL). The reaction mixture was allowed to warm to room temperature overnight, quenched with H_2O, and extracted with Et_2O. The organic extract was dried ($MgSO_4$), concentrated, and chromatographed on SiO_2 (hexanes/EtOAc, 19:1) to give **34** (150 mg, 0.305 mmol, 38%) as an oil; $[\alpha]_D$ +7.5 (*c* 1.8, $CHCl_3$). IR (neat): 3358, 3366, 2931, 1640, 1501, 1255, 1097, 836 cm^{-1}. ^{1}H NMR: δ 6.23 (dd, 1 H, J = 15.1, 10.8 Hz), 6.02 (br d, 1 H, J = 7.3 Hz), 5.88−5.74 (m, 2 H), 5.60−5.39 (m, 3 H), 5.12−5.04 (m, 2 H), 4.73−4.64 (m, 1 H), 3.67 (dd, 1 H, J = 9.8, 3.9 Hz), 3.55 (dd, 1 H, J = 9.8, 3.7 Hz), 3.34 (s 3 H), 3.19 (p, 1 H, J = 8.2 Hz), 2.32−2.23 (m, 4 H), 2.21−2.01 (m, 4 H), 1.72 (s, 3 H), 1.62−1.55 (m, 2 H), 1.18 (s, 9 H), 0.90 (s, 9 H), 0.05 (s, 6 H). ^{13}C NMR: δ 177.4, 136.4, 134.8, 132.5, 131.3, 127.9, 127.3, 124.8, 116.9, 79.9, 77.2, 65.4, 56.5, 48.0, 38.7, 37.7, 35.4, 32.9, 31.6, 27.8, 27.6, 25.8, 18.2, 16.5, −5.5. MS (EI) *m*/*z* (relative intensity): 491 (M^+, 14), 434 (62). HRMS (EI) calcd for $C_{29}H_{53}NO_3Si$, 491.3795; found, 491.3794.

(1*R*,2*Z*,6*E*,8*E*,12*R*)-*N*-(1-Hydroxymethyl-12-methoxy-9-methylpentadeca-2,6,8,14-tetraenyl)-2,2-dimethylpropionamide. A solution of **34** (49 mg, 0.10 mmol) in THF (10 mL) was treated at 0 °C with HF·pyridine complex (0.28 mL). The reaction mixture was stirred at 0 °C for 30 min and then at room temperature for 14 h. The solution was diluted with Et_2O, poured into saturated aqueous $NaHCO_3$, and extracted with EtOAc. The organic extract was dried ($MgSO_4$), concentrated, and chromatographed on SiO_2 (hexanes/EtOAc, 3:2) to give (1*R*,2*Z*,6*E*,8*E*,12*R*)-*N*-(1-hydroxymethyl-12-methoxy-9-methylpentadeca-2,6,8,14-tetraenyl)-2,2-dimethylpropionamide (31 mg, 0.082 mmol, 82%) as an oil. ^{1}H NMR: δ 6.24 (dd, 1 H, J = 15.1, 10.8 Hz), 5.87−5.73 (m, 3 H), 5.65−5.48 (m, 2 H), 5.37−5.30 (m, 1 H), 5.11−5.04 (m, 2 H), 4.75−4.70 (m, 1 H), 3.67−3.55 (m, 2 H), 3.34 (s, 3 H), 3.19 (p, 1 H, J = 5.8 Hz), 3.11 (t, 1 H, J = 5.6 Hz), 2.30−1.98 (m, 8 H), 1.72 (s, 3 H), 1.66−1.55 (m, 2 H), 1.20 (s, 9 H).

(4*R*)-2-*tert*-Butyl-4-[(1*Z*,5*E*,7*E*,11*R*)-11-methoxy-8-methyltetradeca-1,5,7,13-tetraenyl]-4,5-dihydrooxazole (26). A solution of (1*R*,2*Z*,6*E*,8*E*,12*R*)-*N*-(1-hydroxymethyl-12-methoxy-9-methylpentadeca-2,6,8,14-tetraenyl)-2,2-dimethylpropionamide (31 mg, 0.082 mmol) in CH_2Cl_2 (3 mL) was treated dropwise at −25 °C with Deoxo-Fluor (50 μL, 0.54 mmol). After 25 min at −20 °C, the reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic extract was dried ($MgSO_4$), concentrated, and chromatographed on SiO_2 (hexanes/EtOAc, 19:1) to give **26** (26.8 mg, 0.0747 mmol, 91%) as an oil; $[\alpha]_D$ +9.9 (*c* 0.61, $CHCl_3$). IR (neat): 2974, 2922, 1651, 1137, 1097, 962 cm^{-1}. ^{1}H NMR: δ 6.23 (dd, 1 H, J = 14.9, 10.8 Hz), 5.87−5.74 (m, 2 H), 5.58−5.48 (m, 2 H), 5.33 (t, 1 H, J = 9.3 Hz), 5.11−5.04 (m, 2 H), 4.84 (q, 1 H, J = 9.3 Hz), 4.34 (dd, 1 H, J = 9.5, 8.2 Hz), 3.76 (t, 1 H, J = 8.2 Hz), 3.34 (s, 3 H), 3.19 (p, 1 H, J = 5.9 Hz), 2.29−2.02 (m, 8 H), 1.72 (s, 3 H), 1.62−1.55 (m, 2 H), 1.22 (s, 9 H). ^{13}C NMR: δ 136.7, 134.7, 131.4, 131.1, 130.9, 127.3, 124.6, 117.0, 79.8, 72.9, 63.0, 56.5, 37.6, 35.3, 32.8, 31.6, 27.8, 16.5. MS (EI) *m*/*z* (relative intensity): 359 (M^+, 100), 318 (75). HRMS (EI) calcd for $C_{23}H_{37}NO_2$, 359.2824; found, 359.2825. HPLC analysis: (C_{18}, MeCN, ELSD) t_R = 5.58 min, 99.9%; (C_{18}, MeOH/H_2O (9:1), ELSD) t_R = 7.62 min, 100%.

2-*tert*-Butyl-4-[(1*Z*,5*E*,7*E*,11*R*)-11-methoxy-8-methyltetradeca-1,5,7,13-tetraenyl]oxazole (27). A solution of **26** (22 mg, 0.061 mmol) in hexanes (8 mL) was treated with 85% MnO_2 (605 mg, 6.95 mmol). The reaction mixture was stirred at room temperature for 50 h and filtered through a short pad of SiO_2, and the filtrate was concentrated and chromatographed on SiO_2 (hexanes/EtOAc, 24:1) to give **27** (9.8 mg, 0.027 mmol, 45%) as an oil; $[\alpha]_D$ −6.9 (*c* 0.23, $CHCl_3$). IR (neat) 2974, 2927, 1640, 1572, 1461, 1362, 1105, 962 cm^{-1}. ^{1}H NMR: δ 7.46 (s, 1 H), 6.32−6.10 (m, 2 H), 5.87−5.66 (m, 3 H), 5.60 (dt, 1 H, J = 14.2, 6.9 Hz), 5.11−5.03 (m, 2 H), 3.33 (s, 3 H), 3.19 (p, 1 H, J = 5.9 Hz), 2.49−2.41 (m, 2 H), 2.32−2.22 (m, 4 H), 2.15−1.99 (m, 2 H), 1.72 (s, 3 H), 1.62−1.55 (m, 2 H), 1.37 (s, 9 H). ^{13}C NMR δ 170.4, 137.3, 136.6, 134.9, 134.7, 133.0, 131.3, 127.2, 124.6, 119.1, 116.9, 79.8, 56.5, 37.6, 35.3, 33.5, 32.5, 31.5, 29.5, 28.5, 16.5. MS (EI) *m*/*z* (relative intensity): 357 (M^+, 8), 284 (15). HRMS (EI) calcd for $C_{23}H_{35}NO_2$, 357.2668; found, 357.2674. HPLC analysis: (C_{18}, MeCN, ELSD) t_R = 6.11 min, 100%; (C_{18}, MeOH/H_2O (9:1), ELSD) t_R = 11.16 min, 100%.

(1*R*,2*Z*,6*E*,8*E*,12*R*)-*N*-[1-(*tert*-Butyldimethylsilanyloxymethyl)-12-methoxy-9-methylpentadeca-2,6,8,14-tetraenyl]-2,2-dimethylthiopropionamide. A solution of amide **34** (120 mg, 0.244 mmol) in toluene (4 mL) was treated with Lawesson's reagent (59.0 mg, 0.146 mmol). The reaction mixture was heated at 70 °C for 2.5 h, cooled to room temperature, concentrated, and chromatographed on SiO_2 (hexanes/EtOAc, 97:3) to give (1*R*,2*Z*,6*E*,8*E*,12*R*)-*N*-[1-(*tert*-butyldimethylsilanyloxymethyl)-12-methoxy-9-methylpentadeca-2,6,8,14-tetraenyl]-2,2-dimethyl-thiopropionamide (22 mg, 0.043 mmol, 18%) as an oil. ^{1}H NMR: δ 7.75 (br d, 1 H, J = 5.8 Hz), 6.25 (dd, 1 H, J = 15.0, 10.8 Hz), 5.88−5.74 (m, 2 H), 5.66−5.35 (m, 4 H), 5.12−5.04 (m, 2 H), 3.89−3.84 (m, 1 H), 3.65−3.60 (m, 1 H), 3.34 (s, 3 H), 3.23−3.16 (m, 1 H), 2.37−2.00 (m, 8 H), 1.73 (bs, 3 H), 1.60−1.54 (m, 2 H), 1.33 (s, 9 H), 0.90 (s, 9 H), 0.06 (s, 3 H), 0.05 (s, 3 H).

(1*R*,2*Z*,6*E*,8*E*,12*R*)-*N*-(1-Hydroxymethyl-12-methoxy-9-methylpentadeca-2,6,8,14-tetraenyl)-2,2-dimethylthiopropionamide. A solution of (1*R*,2*Z*,6*E*,8*E*,12*R*)-*N*-[1-(*tert*-butyldimethylsilanyloxymethyl)-12-methoxy-9-methylpentadeca-2,6,8,14-tetraenyl]-2,2-dimethylthiopropionamide (22 mg, 0.043 mmol) in THF (9 mL) was treated at 0 °C with HF·pyridine

complex (0.15 mL). The reaction mixture was stirred at 0 °C for 30 min and then at room temperature overnight. The solution was diluted with Et_2O, poured into saturated aqueous $NaHCO_3$, and extracted with EtOAc. The organic extract was dried ($MgSO_4$), concentrated, and chromatographed on SiO_2 (hexanes/EtOAc, 7:3) to give (1*R*,2*Z*,6*E*,8*E*,12*R*)-*N*-(1-hydroxymethyl-12-methoxy-9-methylpentadeca-2,6,8,14-tetraenyl)-2,2-dimethylthiopropionamide (13.3 mg, 3.38 μmol, 78%) as an oil. ^{1}H NMR: δ 7.60−7.50 (br, 1 H), 6.25 (dd, 1 H, J = 15.1, 10.8 Hz), 5.88−5.67 (m, 3 H), 5.59−5.49 (m, 2 H), 5.47−5.40 (m, 1 H), 5.12−5.04 (m, 2 H), 3.89−3.83 (m, 1 H), 3.77−3.70 (m, 1 H), 3.34 (s, 3 H), 3.20 (p, 1 H, J = 6.0 Hz), 2.30−2.00 (m, 9 H), 1.73 (s, 3 H), 1.65−1.53 (m, 2 H), 1.35 (s, 9 H).

(4*R*)-2-*tert*-Butyl-4-[(1*Z*,5*E*,7*E*,11*R*)-11-methoxy-8-methyltetradeca-1,5,7,13-tetraenyl]-4,5-dihydrothiazole (28). A solution of (1*R*,2*Z*,6*E*,8*E*,12*R*)-*N*-(1-hydroxymethyl-12-methoxy-9-methylpentadeca-2,6,8,14-tetraenyl)-2,2-dimethylthiopropionamide (13 mg, 0.033 mmol) in CH_2Cl_2 (4 mL) was treated dropwise at −25 °C with Deoxo-Fluor (25 μL, 0.27 mmol). After 25 min at −20 °C, the reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic extract was dried ($MgSO_4$), concentrated, and chromatographed on SiO_2 (hexanes/EtOAc, 19:1) to give **28** (9.6 mg, 0.026 mmol, 77%) as an oil; $[\alpha]_D$ +12.4 (*c* 0.19, $CHCl_3$). IR (neat): 2964, 2930, 1610, 1457, 1367, 1094 cm^{-1}. ^{1}H NMR: δ 6.26 (dd, 1 H, J = 14.8, 10.8 Hz), 5.88−5.74 (m, 2 H), 5.61−5.47 (m, 3 H), 5.20−5.05 (m, 3 H), 3.39−3.32 (m, 1 H), 3.34 (s, 3 H), 3.19 (p, 1 H, J = 5.9 Hz), 2.89 (dd, 1 H, J = 10.8, 8.6 Hz), 2.32−2.00 (m, 8 H), 1.73 (bs, 3 H), 1.65−1.53 (m, 2 H), 1.25 (s, 9 H). ^{13}C NMR: δ 136.7, 134.7, 131.3, 131.2, 130.0, 127.3, 125.5, 124.6, 117.0, 79.9, 77.2, 73.8, 56.6, 39.2, 37.6, 35.4, 32.8, 31.6, 29.3, 27.9, 16.6. MS (EI) *m*/*z* (relative intensity): 375 (M^+, 32), 182 (100). HRMS (EI) calcd for $C_{23}H_{37}NOS$, 375.2596; found, 375.2597. HPLC analysis: (C_{18}, MeCN, ELSD) t_R = 7.83 min, 98.1%; (C_{18}, MeOH/H_2O (9:1), ELSD) t_R = 10.76 min, 100%.

2-*tert*-Butyl-4-[(1*Z*,5*E*,7*E*,11*R*)-11-methoxy-8-methyltetradeca-1,5,7,13-tetraenyl]thiazole (29). A solution of **28** (2.9 mg, 7.7 μmol) in hexanes (2 mL) was treated with 85% MnO_2 (104 mg, 1.20 mmol). The reaction mixture was stirred at room temperature for 19 h and filtered through a short pad of SiO_2, and the filtrate was concentrated and chromatographed on SiO_2 (hexanes/Et_2O, 19:1) to give **29** (1.3 mg, 3.5 mmol, 46%) as an oil; $[\alpha]_D$ −9.2 (*c* 0.10, $CHCl_3$). IR (neat): 2962, 2923, 1640, 1461, 1362, 1097 cm^{-1}. ^{1}H NMR: δ 6.93 (s, 1 H), 6.41 (dt, 1 H, J = 13.2, 1.5 Hz), 6.34−6.25 (m, 1 H), 5.88−5.59 (m, 4 H), 5.12−5.04 (m, 2 H), 3.34 (s, 3 H), 3.23−3.16 (m, 1 H), 2.75−2.67 (m, 2 H), 2.33−2.24 (m, 4 H), 2.17−1.98 (m, 2 H), 1.71 (bs, 3 H), 1.65−1.56 (m, 2 H), 1.44 (s, 9 H). ^{13}C NMR: δ 179.9, 152.9, 136.4, 134.8, 133.2, 131.8, 127.1, 124.9, 122.6, 117.0, 115.0, 80.0, 56.7, 37.7, 35.4, 32.9, 31.6, 31.0, 30.9, 29.2, 16.6. MS (EI) *m*/*z* (relative intensity): 373 (M^+, 65), 180 (75). HRMS (EI) calcd for $C_{23}H_{35}NOS$, 373.2439; found, 373.2445. Anal. ($C_{23}H_{35}NOS$) C, H.

{(1*S*,2*R*)-2-[3-(*tert*-Butyldiphenylsilanyloxy)propyl]-cyclopropyl}methanol (37). A mixture of freshly distilled 1,2-dimethoxyethane (DME; 4.6 mL, 43.6 mmol), Et_2Zn (4.50 mL, 43.6 mmol), and CH_2Cl_2 (44 mL) was treated dropwise at −15 °C with CH_2I_2 (7.00 mL, 87.2 mmol). The resultant solution was immediately added dropwise at −15 °C to a solution of dioxaborolane **36** (2.60 g, 9.64 mmol), alcohol **35** (3.10 g, 8.76 mmol), and 4 Å molecular sieves (1 g) in CH_2Cl_2 (44 mL). The reaction mixture was stirred at −15 °C for 2 h, quenched with saturated NH_4Cl solution, and extracted with Et_2O. The combined organic layers were dried ($MgSO_4$), concentrated, and chromatographed on SiO_2 (hexanes/EtOAc, 3:1) to give **37** (3.22 g, 8.76 mmol, 100%) as an oil; $[\alpha]_D$ +11.2 (*c* 0.52, $CHCl_3$). IR (neat): 3347, 2931, 2851, 1473, 1426, 1113 cm^{-1}. ^{1}H NMR: δ 7.70−7.66 (m, 4 H), 7.42−7.39 (m, 6 H), 3.70 (t, 2 H, J = 6.4 Hz), 3.40 (d, 2 H, J = 6.9 Hz), 1.66 (p, 2 H, J = 6.9 Hz), 1.38−1.25 (m, 4 H), 1.06 (s, 9 H), 0.86−0.79 (m, 1 H), 0.60−0.54 (m, 1 H), 0.38−0.27 (m, 2 H). ^{13}C NMR: δ 135.6, 134.0, 129.5, 127.6, 67.1, 63.5, 32.5, 29.8, 26.8, 21.2, 19.2, 16.8, 9.9. MS (EI) *m*/*z* (relative intensity): 368 (M^+, 0.2), 311 (3), 67 (100). HRMS (EI) calcd for $C_{23}H_{32}O_2Si$, 368.2172; found, 368.2182.

(1*S*,2*R*)-2-[3-(*tert*-Butyldiphenylsilanyloxy)propyl]-cyclopropanecarbaldehyde. A mixture of 4 Å molecular sieves (500 mg), SiO_2 (3.80 g), alcohol **37** (3.19 g, 8.67 mmol), and CH_2Cl_2 (80 mL) was treated with pyridinium chlorochromate (3.77 g, 17.3 mmol). After 2.5 h, the reaction mixture was diluted with hexanes and filtered through a short plug of SiO_2, and the filtrate was concentrated and chromatographed on SiO_2 (hexanes/EtOAc, 19:1) to give (1*S*,2*R*)-2-[3-(*tert*-butyldiphenylsilanyloxy)propyl]cyclopropanecarbaldehyde (2.67 g, 7.30 mmol, 84%) as an oil. ^{1}H NMR: δ 8.97 (d, 1 H, J = 5.6 Hz), 7.68−7.65 (m, 4 H), 7.44−7.37 (m, 6 H), 3.69 (t, 2 H, J = 6.2 Hz), 1.70−1.58 (m, 3 H), 1.50−1.41 (m, 3 H), 1.30−1.24 (m, 1 H), 1.05 (s, 9 H), 0.95−0.89 (m, 1 H).

(2*E*)-3-{(1*S*,2*R*)-2-[3-(*tert*-Butyldiphenylsilanyloxy)propyl]cyclopropyl}-2-methylacrylic Acid Ethyl Ester. A solution of carboethoxyethylidene triphenylphosphorane (15.11 g, 43.4 mmol), (1*S*,2*R*)-2-[3-(*tert*-butyldiphenylsilanyloxy)propyl]cyclopropanecarbaldehyde (2.67 g, 7.28 mmol), and CH_2Cl_2 (75 mL) was heated at reflux for 19 h, cooled, and concentrated. The residue was triturated with Et_2O several times, and the filtrate was concentrated and chromatographed on SiO_2 (hexanes/EtOAc, 99:1) to give (2*E*)-3-{(1*S*,2*R*)-2-[3-(*tert*-butyldiphenylsilanyloxy)propyl]cyclopropyl}-2-methylacrylic acid ethyl ester (2.82 g, 6.27 mmol, 86%) as an oil. ^{1}H NMR: δ 7.67−7.64 (m, 4 H), 7.42−7.35 (m, 6 H), 6.13 (dd, 1 H, J = 10.6, 1.3 Hz), 4.17 (q, 2 H, J = 7.1 Hz), 3.68 (t, 2 H, J = 6.4 Hz), 1.90 (d, 3 H, J = 1.3 Hz), 1.68−1.60 (m, 2 H), 1.50−1.25 (m, 3 H), 1.28 (t, 3 H, J = 7.1 Hz), 1.05 (s, 9 H), 0.97−0.87 (m, 1 H), 0.76−0.72 (m, 2 H).

(2*E*)-3-{(1*S*,2*R*)-2-[3-(*tert*-Butyldiphenylsilanyloxy)propyl]cyclopropyl}-2-methylprop-2-en-1-ol. A solution of (2*E*)-3-{(1*S*,2*R*)-2-[3-(*tert*-butyldiphenylsilanyloxy)-propyl]-cyclopropyl}-2-methylacrylic acid ethyl ester (2.79 g, 6.20 mmol) in CH_2Cl_2 (50 mL) was treated dropwise at −78 °C with 1 M DIBAL-H in hexanes (15.5 mL, 15.5 mmol). The reaction mixture was stirred at −78 °C for 1 h, quenched with EtOH (3 mL), and stirred with a saturated sodium potassium tartrate solution for 1 h at room temperature. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$), concentrated, and chromatographed on SiO_2 (hexanes/EtOAc, 9:1) to give (2*E*)-3-{(1*S*,2*R*)-2-[3-(*tert*-butyldiphenylsilanyloxy)propyl]-cyclopropyl}-2-methylprop-2-en-1-ol (1.99 g, 4.88 mmol, 79%) as an oil; $[\alpha]_D$ +9.7 (*c* 0.46, $CHCl_3$). IR (neat): 3343, 2927, 2851, 1473, 1426, 1113 cm^{-1}. ^{1}H NMR: δ 7.68−7.65 (m, 4 H), 7.43−7.37 (m, 6 H), 4.80 (dd, 1 H, J = 9.6, 1.2 Hz), 3.96 (d, 2 H, J = 5.1 Hz), 3.69 (t, 2 H, J = 6.5 Hz), 1.75 (d, 3 H, J = 1.2 Hz), 1.70−1.61 (m, 2 H), 1.40−1.32 (m, 2 H), 1.24−1.11 (m, 2 H), 1.05 (s, 9 H), 0.73−0.62 (m, 1 H), 0.56−0.44 (m, 2 H). ^{13}C NMR: δ 135.6, 134.2, 130.4, 129.6, 127.6, 69.0, 63.7, 32.5, 30.2, 26.9, 20.8, 19.3, 17.9, 14.3, 14.0. MS (EI) *m*/*z* (relative intensity): 408 (M^+, 0.4), 351 (1.5), 199 (100). HRMS (EI) calcd for $C_{26}H_{36}O_2Si$, 408.2485; found, 408.2500.

{(1*S*,2*S*,1′*S*,2′*R*)-2′-[3-(*tert*-Butyldiphenylsilanyloxy)-propyl]-2-methylbicyclopropyl-2-yl}methanol (38). A solution of freshly distilled DME (1.0 mL, 9.5 mmol), Et_2Zn (1.0 mL, 9.5 mmol), and CH_2Cl_2 (10 mL) was treated dropwise at −15 °C with CH_2I_2 (1.53 mL, 19.1 mmol). The resultant solution was immediately added dropwise at −15 °C to a solution of dioxaborolane **36** (622 mg, 2.33 mmol), (2*E*)-3-{(1*S*,2*R*)-2-[3-(*tert*-butyldiphenylsilanyloxy)propyl]cyclopropyl}-2-methylprop-2-en-1-ol (866 mg, 2.12 mmol), and 4 Å molecular sieves (200 mg) in CH_2Cl_2 (10 mL). The reaction mixture was stirred at −15 °C for 3 h, quenched with saturated NH_4Cl solution, and extracted with Et_2O. The combined organic layers were dried ($MgSO_4$), concentrated, and chromatographed on SiO_2 (hexanes/EtOAc, 9:1) to give **38** (705 mg, 1.67 mmol, 79%) as an oil; $[\alpha]_D$ +32.1 (*c* 0.31, $CHCl_3$). IR (neat): 3347, 2927, 2855, 1469, 1422, 1109 cm^{-1}. ^{1}H NMR: δ 7.69−7.66 (m, 4 H), 7.43−7.38 (m, 6 H), 3.69 (t, 2 H, 6.5 Hz), 3.35−3.25 (m, 2 H), 1.67 (p, 2 H, J = 6.9 Hz), 1.34−1.20 (m, 3 H), 1.19 (s, 3 H),

1.05 (s, 9 H), 0.53−0.48 (m, 2 H), 0.44−0.34 (m, 2 H), 0.31−0.24 (m, 1 H), 0.23−0.19 (m, 1 H), 0.04 (t, 1 H, J = 4.8 Hz). ^{13}C NMR: δ 135.6, 134.1, 129.5, 127.5, 72.3, 63.7, 32.4, 30.4, 26.8, 24.6, 22.9, 19.2, 18.3, 16.9, 15.8, 15.2, 12.0. MS (EI) *m/z* (relative intensity): 365 ([M−C_4H_9]$^+$, 6), 135 (100). HRMS (EI) calcd for $C_{23}H_{29}O_2Si$ (M − C_4H_9), 365.1937; found, 365.1924.

(1*S*,2*S*,1′*S*,2′*R*)-2′-[3-(*tert*-Butyldiphenylsilanyloxy)propyl]-2-methyl-bicyclopropyl-2-carbaldehyde. A mixture of 4 Å molecular sieves (100 mg), SiO_2 (1.10 g), alcohol **38** (658 mg, 1.56 mmol), and CH_2Cl_2 (20 mL) was treated with pyridinium chlorochromate (1.01 g, 4.70 mmol). After 1 h, the reaction mixture was diluted with hexanes and filtered through a short plug of SiO_2, and the filtrate was concentrated and chromatographed on SiO_2 (hexanes/EtOAc, 19:1) to give (1*S*,2*S*,1′*S*,2′*R*)-2′-[3-(*tert*-butyldiphenylsilanyloxy)propyl]-2-methylbicyclopropyl-2-carbaldehyde (605 mg, 1.44 mmol, 92%) as an oil. ^{1}H NMR: δ 8.62 (s, 1 H), 7.68−7.65 (m, 4 H), 7.43−7.35 (m, 6 H), 3.68 (t, 2 H, J = 6.4 Hz), 1.65 (p, 2 H, J = 7.3 Hz), 1.40−1.20 (m, 4 H), 1.31 (s, 3 H), 1.05 (s, 9 H), 0.70−0.65 (m, 1 H), 0.60−0.50 (m, 1 H), 0.45−0.28 (m, 3 H).

(2*E*)-3-{(1*S*,2*S*,1′*S*,2′*R*)-2′-[3-(*tert*-Butyldiphenylsilanyloxy)propyl]-2-methylbicyclopropyl-2-yl}acrylic Acid Methyl Ester. A solution of methyl triphenylphosphoranylidene acetate (1.41 g, 4.22 mmol), (1*S*,2*S*,1′*S*,2′*R*)-2′-[3-(*tert*-butyldiphenylsilanyloxy)propyl]-2-methylbicyclopropyl-2-carbaldehyde (592 mg, 1.41 mmol), and CH_2Cl_2 (10 mL) was heated at reflux for 28 h, cooled, and concentrated. The residue was triturated with Et_2O several times, and the filtrate was concentrated and chromatographed on SiO_2 (hexanes/EtOAc, 19:1) to give (2*E*)-3-{(1*S*,2*S*,1′*S*,2′*R*)-2′-[3-(*tert*-butyldiphenylsilanyloxy)propyl]-2-methylbicyclopropyl-2-yl}acrylic acid methyl ester (631 mg, 1.33 mmol, 94%) as an oil. ^{1}H NMR: δ 7.68−7.65 (m, 4 H), 7.42−7.35 (m, 6 H), 6.46 (d, 1 H, J = 15.6 Hz), 5.72 (d, 1 H, J = 15.6 Hz), 3.72 (s, 3 H), 3.68 (t, 2 H, J = 6.5 Hz), 1.65 (p, 2 H, J = 7.1 Hz), 1.35−1.26 (m, 2 H), 1.25 (s, 3 H), 1.05 (s, 9 H), 0.98−0.84 (m, 2 H), 0.57−0.50 (m, 2 H), 0.44−0.40 (m, 1 H), 0.37−0.31 (m, 1 H), 0.29−0.25 (m, 1 H).

3-{(1*S*,2*S*,1′*S*,2′*R*)-2′-[3-(*tert*-Butyldiphenylsilanyloxy)propyl]-2-methylbicyclopropyl-2-yl}propan-1-ol (39). A mixture of $NaBH_4$ (221 mg, 5.80 mmol), LiCl (244 mg, 5.80 mmol), EtOH (5 mL), and THF (2 mL) was treated with a solution of (2*E*)-3-{(1*S*,2*S*,1′*S*,2′*R*)-2′-[3-(*tert*-butyldiphenylsilanyloxy)propyl]-2-methylbicyclopropyl-2-yl}acrylic acid methyl ester (554 mg, 1.16 mmol) in THF (2 mL). The reaction mixture was stirred at room temperature for 19 h, quenched with saturated aqueous NH_4Cl solution, and concentrated. The residue was extracted with Et_2O, dried ($MgSO_4$), concentrated, and chromatographed on SiO_2 (hexanes/EtOAc, 9:1) to give **39** (292 mg, 0.649 mmol, 56%) as an oil; $[\alpha]_D$ +30.6 (*c* 0.29, $CHCl_3$). IR (neat): 3336, 2927, 2851, 1422, 1109 cm^{-1}. ^{1}H NMR: δ 7.70−7.67 (m, 4 H), 7.43−7.36 (m, 6 H), 3.70 (t, 2 H, J = 6.5 Hz), 3.65−3.60 (m, 2 H), 1.70−1.60 (m, 4 H), 1.34−1.25 (m, 4 H), 1.16−1.10 (m, 1 H), 1.08 (s, 3 H), 1.06 (s, 9 H), 0.55−0.44 (m, 1 H), 0.35−0.24 (m, 4 H), 0.22−0.16 (m, 1 H), −0.02 - −0.04 (m, 1 H). ^{13}C NMR: δ 135.6, 134.1, 129.5, 127.5, 63.8, 63.1, 37.3, 32.5, 30.5, 30.1, 26.9, 19.6, 19.2, 18.6, 17.8, 17.7, 17.5, 12.0. MS (EI) *m/z* (relative intensity): 393 ([M − C_4H_9]$^+$, 4), 315 (3.5). HRMS (EI) calcd for $C_{25}H_{33}O_2Si$ (M − C_4H_9), 393.2250; found, 393.2256.

3-{(1*S*,2*S*,1′*S*,2′*R*)-2′-[3-(*tert*-Butyldiphenylsilanyloxy)propyl]-2-methylbicyclopropyl-2-yl}propionaldehyde. A mixture of 4 Å molecular sieves (100 mg), SiO_2 (812 mg), alcohol **39** (238 mg, 0.529 mmol), and CH_2Cl_2 (15 mL) was treated with pyridinium chlorochromate (341 mg, 1.59 mmol). After 1.25 h, the reaction mixture was diluted with hexanes and filtered through a short plug of SiO_2, and the filtrate was concentrated and chromatographed on SiO_2 (hexanes/EtOAc, 49:1) to give 3-{(1*S*,2*S*,1′*S*,2′*R*)-2′-[3-(*tert*-butyldiphenylsilanyloxy)propyl]-2-methylbicyclopropyl-2-yl}propionaldehyde (150 mg, 0.335 mmol, 64%) as an oil. ^{1}H NMR: δ 9.76 (t, 1 H, J = 2.0 Hz), 7.69−7.65 (m, 4 H), 7.42−7.35 (m, 6 H), 3.69 (t, 2 H, J = 6.5 Hz), 2.50−2.44 (m, 2 H), 1.70−1.58 (m, 2 H), 1.54−1.35 (m, 2 H), 1.33−1.28 (m, 2 H), 1.06 (s, 3 H), 1.05 (s, 9 H), 0.52−0.40 (m, 1 H), 0.37−0.24 (m, 4 H), 0.21−0.18 (m, 1 H), 0.01 - −0.02 (m, 1 H).

(3*S*)-1-{(1*S*,2*S*,1′*S*,2′*R*)-2′-[3-(*tert*-Butyldiphenylsilanyloxy)propyl]-2-methylbicyclopropyl-2-yl}hex-5-en-3-ol (40). A solution of (−)-*B*-methoxydiisopinocampheylborane (106 mg, 0.335 mmol) in Et_2O (1 mL) was treated dropwise at 0 °C with 1 M allylmagnesium bromide in Et_2O (0.34 mL, 0.34 mmol). The reaction mixture was stirred at room temperature for 1 h, cooled to −78 °C, and treated with a solution of 3-{(1*S*,2*S*,1′*S*,2′*R*)-2′-[3-(*tert*-butyldiphenylsilanyloxy)propyl]-2-methylbicyclopropyl-2-yl}propionaldehyde (150 mg, 0.335 mmol) in Et_2O (1.5 mL). The reaction mixture was stirred at −78 °C for 4 h, treated with ethanolamine (21 μL, 0.34 mmol), and then stirred at room temperature overnight. The reaction mixture was diluted with hexanes and filtered, and the filtrate was washed with saturated aqueous $NaHCO_3$. The organic layer was dried ($MgSO_4$), concentrated, and chromatographed on SiO_2 (hexanes/EtOAc, 19:1) to give **40** (79.2 mg, 0.162 mmol, 48%) as an oil; $[\alpha]_D$ +41.6 (*c* 2.8, $CHCl_3$). IR (neat): 3358, 3069, 2931, 2851, 1430, 1113, 701 cm^{-1}. ^{1}H NMR: δ 7.71−7.68 (m, 4 H), 7.43−7.37 (m, 6 H), 5.91−5.77 (m, 1 H), 5.17−5.12 (m, 2 H), 3.71 (t, 2 H, J = 6.5 Hz), 3.65−3.58 (m, 1 H), 2.35−2.26 (m, 1 H), 2.19−2.06 (m, 1 H), 1.73−1.41 (m, 5 H), 1.35−1.22 (m, 4 H), 1.08 (s, 3 H), 1.07 (s, 9 H), 0.53−0.45 (m, 1 H), 0.40−0.24 (m, 4 H), 0.22−0.16 (m, 1 H), −0.01−0.05 (m, 1 H). ^{13}C NMR: δ 135.5, 134.8, 134.1, 129.5, 127.5, 118.1, 70.7, 63.8, 41.9, 37.2, 33.9, 32.5, 30.5, 26.8, 19.8, 19.2, 18.3, 17.9, 17.8, 17.5, 12.1. MS (EI) *m/z* (relative intensity): 433 ([M − C_4H_9]$^+$, 7), 199 (100). HRMS (EI) calcd for $C_{28}H_{37}O_2Si$ (M − C_4H_9), 433.2563; found, 433.2574.

***tert*-Butyl-{3-[(1*S*,2*R*,1′*S*,2′*S*)-2′-((3*S*)-3-methoxyhex-5-enyl)-2′-methylbicyclopropyl-2-yl]propoxy}diphenylsilane.** A suspension of 60% NaH (21 mg, 0.29 mmol) in THF (0.8 mL) was treated with a solution of alcohol **40** (71.2 mg, 0.145 mmol) in THF (2 mL). After 1 h, methyl iodide (18 μL, 0.29 mmol) was added, and the reaction mixture was stirred at room temperature overnight. The solution was quenched with H_2O, extracted with Et_2O, and the organic extract was dried ($MgSO_4$), concentrated, and chromatographed on SiO_2 (hexanes/EtOAc, 99:1) to give *tert*-butyl-{3-[(1*S*,2*R*,1′*S*,2′*S*)-2′-((3*S*)-3-methoxyhex-5-enyl)-2′-methylbicyclopropyl-2-yl]-propoxy}diphenylsilane (73.0 mg, 0.145 mmol, 100%) as an oil. ^{1}H NMR: δ 7.69−7.66 (m, 4 H), 7.43−7.35 (m, 6 H), 5.89−5.75 (m, 1 H), 5.11−5.05 (m, 2 H), 3.69 (t, 2 H, J = 6.5 Hz), 3.33 (s, 3 H), 3.23−3.15 (m, 1 H), 2.27−2.23 (m, 2 H), 1.71−1.62 (m, 2 H), 1.59−1.47 (m, 2 H), 1.33−1.26 (m, 2 H), 1.22−1.16 (m, 2 H), 1.05 (s, 12 H), 0.53−0.40 (m, 1 H), 0.36−0.23 (m, 4 H), 0.20−0.15 (m, 1 H), −0.04 to −0.06 (m, 1 H).

3-[(1*S*,2*R*,1′*S*,2′*S*)-2′-((3*R*)-3-Methoxyhex-5-enyl)-2′-methylbicyclopropyl-2-yl]propan-1-ol. A solution of *tert*-butyl-{3-[(1*S*,2*R*,1′*S*,2′*S*)-2′-((3*S*)-3-methoxyhex-5-enyl)-2′-methylbicyclopropyl-2-yl]propoxy}diphenylsilane (73.0 mg, 0.145 mmol) in THF (5 mL) was treated dropwise with 1 M TBAF in THF (200 μL, 0.200 mmol). The reaction mixture was stirred at room temperature for 3 h, quenched with saturated $NaHCO_3$ solution, and extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$), concentrated, and chromatographed on SiO_2 (hexanes/EtOAc, 17:3) to give 3-[(1*S*,2*R*,1′*S*,2′*S*)-2′-((3*R*)-3-methoxyhex-5-enyl)-2′-methylbicyclopropyl-2-yl]propan-1-ol (31.1 mg, 0.117 mmol, 81%) as an oil; $[\alpha]_D$ +59.9 (*c* 1.5, $CHCl_3$). IR (neat): 3378, 2935, 1636, 1457, 1354, 1093, 915 cm^{-1}. ^{1}H NMR: δ 5.86−5.72 (m, 1 H), 5.09−5.02 (m, 2 H), 3.64 (t, 2 H, J = 6.6 Hz), 3.30 (s, 3 H), 3.16 (p, 1 H, J = 5.8 Hz), 2.24−2.20 (m, 2 H), 1.70−1.60 (m, 2 H), 1.57−1.46 (m, 2 H), 1.34−1.22 (m, 2 H), 1.20−1.11 (m, 2 H), 1.05 (s, 3 H), 0.55−0.44 (m, 1 H), 0.36−0.25 (m, 4 H), 0.21−0.15 (m, 1 H), −0.05 to −0.07 (m, 1 H). ^{13}C NMR: δ 134.8, 116.8, 80.4, 62.8, 56.4, 37.6, 36.6, 32.6, 30.5, 30.3, 26.8, 19.9, 18.3, 18.0, 17.8, 17.6, 12.1. MS (EI) *m/z* (relative intensity): 266 (M$^+$, 0.4), 234 (2), 71 (100). HRMS (EI) calcd for $C_{17}H_{30}O_2$, 266.2246; found, 266.2244.

{3-[(1*S*,2*R*,1′*S*,2′*S*)-2′-((3*R*)-3-Methoxyhex-5-enyl)-2′-methylbicyclopropyl-2-yl]propyl}triphenylphosphonium Iodide (41). A solution of alcohol 3-[(1*S*,2*R*,1′*S*,2′*S*)-2′-((3*R*)-3-

methoxyhex-5-enyl)-2′-methylbicyclopropyl-2-yl]propan-1-ol (27.4 mg, 0.103 mmol) in CH_2Cl_2 (4 mL) was treated with Et_3N (29 μL, 0.21 mmol) followed by methanesulfonyl chloride (12 μL, 0.15 mmol). The reaction mixture was stirred at room temperature for 14 h, diluted with Et_2O, and filtered through a short pad of SiO_2. The filtrate was concentrated, and the crude mesylate was dissolved in acetone (2.5 mL). NaI (62 mg, 0.41 mmol) was added, and the reaction mixture was heated at reflux for 2 h and concentrated. The residue was washed through a short SiO_2 pad with Et_2O and concentrated to give the crude iodide, which was dissolved in MeCN (2 mL) and treated with PPh_3 (41 mg, 0.16 mmol). The reaction mixture was heated at 90 °C for 6 h, concentrated, and dried in vacuo to give crude **41** as a wax, which was used directly in the next step.

(1*R*,2*S*)-2-Methylcyclopropanecarboxylic Acid {(1*R*,2*Z*)-1-(*tert*-Butyldimethylsilanyloxymethyl)-5-[(1*S*,2*R*,1′*S*,2′*S*)-2′-((3*R*)-3-methoxyhex-5-enyl)2′-methylbicyclopropyl-2-yl]pent-2-enyl}amide (43). A degassed solution of **41** (0.066 mmol) in THF (1 mL) was treated dropwise at −78 °C with 1 M NaHMDS in THF (0.10 mL, 0.10 mmol). The reaction mixture was stirred at −78 °C for 1 h and treated with a solution of aldehyde **42** (86 mg, 0.30 mmol) in THF (1.5 mL). The reaction mixture was allowed to warm to room temperature overnight, quenched with H_2O, and extracted with Et_2O. The organic extract was dried ($MgSO_4$), concentrated, and chromatographed on SiO_2 (hexanes/EtOAc, 24:1) to give **43** (15.2 mg, 294 μmol, 45%) as an oil; $[\alpha]_D$ +26.3 (*c* 0.10, $CHCl_3$). IR (neat): 3316, 2924, 1642, 1527, 1250, 1102, 832 cm^{-1}. ^1H NMR: δ 5.88−5.68 (m, 2 H), 5.64−5.52 (m, 1 H), 5.46−5.40 (m, 1 H), 5.10−5.04 (m, 2 H), 4.83−4.75 (m, 1 H), 3.71−3.66 (m, 1 H), 3.62−3.56 (m, 1 H), 3.32 (s, 3 H), 3.17 (p, 1 H, J = 5.8 Hz), 2.26−2.21 (m, 4 H), 1.67−1.48 (m, 3 H), 1.44−1.32 (m, 2 H), 1.30−1.23 (m, 2 H), 1.21−1.16 (m, 2 H), 1.13 (d, 3 H, J = 1.5 Hz), 1.05 (s, 3 H), 0.98−0.93 (m, 1 H), 0.90−0.83 (m, 11 H), 0.57−0.45 (m, 1 H), 0.37−0.32 (m, 2 H), 0.30−0.22 (m, 2 H), 0.21−0.15 (m, 1 H), 0.05 (s, 6 H), −0.05 to −0.08 (m, 1 H). ^{13}C NMR: δ 170.2, 135.0, 133.2, 127.5, 125.5, 116.7, 80.4, 77.2, 65.6, 56.4, 48.1, 37.7, 36.6, 34.4, 30.6, 27.9, 26.8, 25.9, 20.8, 20.0, 18.4, 18.3, 17.8, 17.6, 14.5, 12.1, −5.4. MS (EI) *m*/*z* (relative intensity): 517 (M^+, 3), 460 (90). HRMS (EI) calcd for $C_{31}H_{55}NO_3Si$, 517.3951; found, 517.3942.

(1*R*,2*S*)-2-Methylcyclopropanecarboxylic Acid {1-Hydroxymethyl-5-[(1*S*,2*R*,1′*S*,2′*S*)-2′-((3*R*)-3-methoxyhex-5-enyl)-2′-methylbicyclopropyl-2-yl]pent-2-enyl}amide. A solution of **43** (15.2 mg, 29.4 mmol) in THF (10 mL) was treated at 0 °C with HF·pyridine complex (0.10 mL). The reaction mixture was stirred at 0 °C for 30 min and then at room temperature for 6 h. The solution was diluted with Et_2O, poured into saturated aqueous $NaHCO_3$, and extracted with EtOAc. The organic extract was dried ($MgSO_4$), concentrated, and chromatographed on SiO_2 (hexanes/EtOAc, 3:2) to give (1*R*,2*S*)-2-methylcyclopropanecarboxylic acid {1-hydroxymethyl-5-[(1*S*,2*R*,1′*S*,2′*S*)-2′-((3*R*)-3-methoxyhex-5-enyl)-2′-methylbicyclopropyl-2-yl]pent-2-enyl}amide (9.8 mg, 0.024 mmol, 83%) as an oil. ^1H NMR: δ 5.89−5.75 (m, 2 H), 5.71−5.62 (m, 1 H), 5.38−5.31 (m, 1 H), 5.12−5.05 (m, 2 H), 4.86−4.78 (m, 1 H), 3.70−3.60 (br, 2 H), 3.33 (s, 3 H), 3.22−3.14 (m, 1 H), 2.30−2.15 (m, 4 H), 1.65−1.19 (m, 9 H), 1.16 (d, 3 H, J = 2.0 Hz), 1.06 (s, 3 H), 1.00−0.85 (m, 3 H), 0.58−0.45 (m, 1 H), 0.40−0.25 (m, 4 H), 0.23−0.17 (m, 1 H), −0.05 (t, 1 H, J = 4.3 Hz).

(4*R*)-4-{(1*Z*)-4-[(1*S*,2*R*,1′*S*,2′*S*)-2′-((3*R*)-3-Methoxyhex-5-enyl)-2′-methyl-bicyclopropyl-2-yl]but-1-enyl}-2-((1*R*,2*S*)-2-methylcyclopropyl)-4,5-dihydrooxazole (44). A solution of (1*R*,2*S*)-2-methylcyclopropanecarboxylic acid {1-hydroxymethyl-5-[(1*S*,2*R*,1′*S*,2′*S*)-2′-((3*R*)-3-methoxy-hex-5-enyl)-2′-methylbicyclopropyl-2-yl]pent-2-enyl}amide (9.8 mg, 24.3 μmol) in CH_2Cl_2 (2 mL) was treated dropwise at −25 °C with Deoxo-Fluor (15 μL, 0.081 mmol). After 30 min at −20 °C, the reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic extract was dried ($MgSO_4$), concentrated, and chromatographed on SiO_2 (hexanes/EtOAc, 9:1) to give **44** (8.5 mg, 0.022 mmol, 91%) as an oil; $[\alpha]_D$ +32.9 (*c* 0.21, $CHCl_3$). IR (neat): 3053, 2929, 1656, 1453, 1401, 1164, 1093 cm^{-1}. ^1H NMR: δ 5.87−5.73 (m, 1 H), 5.57−5.47 (m, 1 H), 5.30−5.23 (m, 1 H), 5.10−5.03 (m, 2 H), 4.94−4.76 (m, 1 H), 4.34 (dd, 1 H, J = 9.5, 8.2 Hz), 3.84 (t, 1 H, J = 7.9 Hz), 3.31 (s, 3 H), 3.17 (p, 1 H, J = 5.8 Hz), 2.25−2.19 (m, 4 H), 1.68−1.45 (m, 3 H), 1.41−1.17 (m, 5 H), 1.14 (d, 3 H, J = 5.5 Hz), 1.05 (s, 3 H), 1,01−0.94 (m, 1 H), 0.88−0.81 (m, 1 H), 0.57−0.47 (m, 1 H), 0.41−0.24 (m, 4 H), 0.21−0.16 (m, 1 H), −0.06 (t, 1 H, J = 3.8 Hz). ^{13}C NMR: δ 167.6, 134.8, 132.0, 130.6, 116.7, 80.3, 72.8, 62.9, 56.3, 37.6, 36.5, 34.4, 30.3, 27.7, 26.7, 19.8, 18.3, 17.8, 17.7, 17.5, 14.1, 13.9, 12.6, 12.5, 12.0. MS (EI) *m*/*z* (relative intensity): 384 ($[M - H]^+$, 9), 370 (21), 354 (42), 344 (47). HRMS (EI) calcd for $C_{25}H_{38}NO_2$ (M − H), 384.2903; found, 384.2907. HPLC analysis: (C_{18}, MeCN, ELSD) t_R = 5.90 min; (C_{18}, 100%; MeOH/H_2O (9:1), ELSD) t_R = 9.57 min, 100%.

(1*R*,2*S*)-2-Methylcyclopropanecarbothioic Acid {1-Hydroxymethyl-5-[(1*S*,2*R*,1′*S*,2′*S*)-2′-((3*R*)-3-methoxyhex-5-enyl)-2′-methylbicyclopropyl-2-yl]pent-2-enyl}amide. Through a solution of **44** (8.5 mg, 0.022 mmol) in Et_3N (1.5 mL) and MeOH (1.5 mL) was bubbled H_2S for 15 min. The flask was sealed and heated at 35 °C for 14.5 h. The reaction mixture was concentrated, and the residue was chromatographed on SiO_2 (hexanes/EtOAc, 13:7) to give (1*R*,2*S*)-2-methylcyclopropanecarbothioic acid {1-hydroxymethyl-5-[(1*S*,2*R*,1′*S*,2′*S*)-2′-((3*R*)-3-methoxyhex-5-enyl)-2′-methylbicyclopropyl-2-yl]pent-2-enyl}amide (4.9 mg, 12 μmol, 53%) as an oil. ^1H NMR: δ 7.39−7.33 (br, 1 H), 5.88−5.70 (m, 2 H), 5.67−5.58 (m, 1 H), 5.46−5.40 (m, 1 H), 5.11−5.05 (m, 2 H), 3.85 (dd, 1 H, J = 10.7, 4.1 Hz), 3.74 (dd, 1 H, J = 10.7, 5.0 Hz), 3.32 (s, 3 H), 3.21−3.13 (m, 1 H), 2.34−2.15 (m, 4 H), 2.10−2.01 (m, 1 H), 1.62−1.48 (m, 2 H), 1.36−1.17 (m, 4 H), 1.14 (d, 3 H, J = 6.1 Hz), 1.06 (s, 3 H), 0.57−0.46 (m, 1 H), 0.42−0.33 (m, 2 H), 0.31−0.25 (m, 2 H), 0.23−0.17 (m, 1 H), −0.06 (t, 1 H, J = 4.4 Hz).

(4*R*)-4-{(1*Z*)-4-[(1*S*,2*R*,1′*S*,2′*S*)-2′-((3*R*)-3-Methoxyhex-5-enyl)-2′-methylbicyclopropyl-2-yl]but-1-enyl}-2-((1*R*,2*S*)-2-methylcyclopropyl)-4,5-dihydrothiazole (45). A solution of (1*R*,2*S*)-2-methylcyclopropanecarbothioic acid {1-hydroxymethyl-5-[(1*S*,2*R*,1′*S*,2′*S*)-2′-((3*R*)-3-methoxyhex-5-enyl)-2′-methylbicyclopropyl-2-yl]pent-2-enyl}amide (4.9 mg, 12 μmol) in CH_2Cl_2 (1 mL) was treated dropwise at −25 °C with Deoxo-Fluor (10 mL, 54 μmol). After 25 min at −20 °C, the reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic extract was dried ($MgSO_4$), concentrated, and chromatographed on SiO_2 (hexanes/EtOAc, 19:1) to give **45** (3.7 mg, 9.2 μmol, 79%) as an oil; $[\alpha]_D$ +47.4 (*c* 0.11, $CHCl_3$). IR (neat): 2919, 1616, 1378, 1073 cm^{-1}. ^1H NMR: δ 5.88−5.74 (m, 1 H), 5.57−5.48 (m, 1 H), 5.45−5.38 (m, 1 H), 5.35−5.27 (m, 1 H), 5.11−5.04 (m, 2 H), 3.46 (dd, 1 H, J = 10.8, 8.2 Hz), 3.32 (s, 3 H), 3.18 (p, 1 H, J = 5.8 Hz), 3.00 (dd, 1 H, J = 10.8, 6.7 Hz), 2.31−2.19 (m, 4 H), 1.86−1.78 (m, 1 H), 1.60−1.16 (m, 4 H), 1.12 (d, 3 H, J = 6.1 Hz), 1.06 (s, 3 H), 1.04−0.92 (m, 1 H), 0.60−0.49 (m, 1 H), 0.38−0.26 (m, 4 H), 0.23−0.18 (m, 1 H), −0.05 (t, 1 H, J = 4.1 Hz). ^{13}C NMR: δ 170.0, 134.9, 131.8, 129.6, 116.8, 80.4, 77.2, 73.5, 56.4, 39.9, 37.7, 36.6, 34.5, 30.4, 27.9, 26.8, 19.7, 18.4, 17.9, 17.8, 17.6, 15.3, 13.8, 12.4, 12.1. MS (EI) *m*/*z* (relative intensity): 401 (M^+, 7), 386 (30), 370 (47). HRMS (EI) calcd for $C_{25}H_{39}NOS$, 401.2752; found, 401.2751. HPLC analysis: (C_{18}, MeCN, ELSD) t_R = 5.77 min; (C_{18}, 100%; MeOH/H_2O (9:1), ELSD) t_R = 8.94 min, 100%.

(2*E*,6*RS*)-3-Methyl-6-thiophen-2-ylhex-2-ene-1,6-diol (52). A solution of aldehyde **51** (2.26 g, 13.3 mmol) in THF (85 mL) was treated at 0° C with a solution of 2-thienyllithium in THF (28.0 mL, 28.0 mmol, 1 M). The reaction mixture was allowed to warm to room temperature overnight and was quenched with a saturated $NaHCO_3$ solution and extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$) and concentrated. Chromatography on SiO_2 (hexanes/EtOAc, 1:1) gave **52** (1.80 g, 8.49 mmol, 64%) as an oil. IR (neat): 3335, 2919, 1663, 1438, 994 cm^{-1}. ^1H NMR: δ 7.21 (t, 1 H, J = 3.3 Hz), 6.95−6.91 (m, 2 H), 5.38 (td, 1 H, J = 6.8, 1.1 Hz), 4.90−4.80 (m, 1 H), 4.09 (bd, 2 H, J = 6.7 Hz), 3.07 (bd, 1 H, J = 2.9 Hz), 2.19−1.80 (m, 5 H), 1.64 (s, 3 H). ^{13}C NMR: δ 148.7, 138.5,

126.5, 124.4, 123.9, 123.6, 69.5, 59.1, 37.0, 35.6, 16.1. MS (EI) *m*/*z* (relative intensity): 194 ([M − H_2O]$^+$, 17), 126 (100), 113 (65). HRMS (EI) calcd for $C_{11}H_{14}OS$, 194.0765; found, 194.0760.

(1*RS*,4*E*)-6-(*tert*-Butyldimethylsilanyloxy)-4-methyl-1-thiophen-2-ylhex-4-en-1-ol. A solution of **52** (555 mg, 2.62 mmol) and imidazole (214 mg, 3.15 mmol) in CH_2Cl_2 (22 mL) was treated at 0° C with a solution of TBS−Cl (395 mg, 2.62 mmol) in CH_2Cl_2 (4 mL). After 2 h, the reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and concentrated. Chromatography on SiO_2 (hexanes/EtOAc, 7:3) gave (1*RS*,4*E*)-6-(*tert*-butyldimethylsilanyloxy)-4-methyl-1-thiophen-2-yl-hex-4-en-1-ol (495 mg, 1.52 mmol, 58%) as an oil. ^{1}H NMR: δ 7.26−7.24 (m, 1 H), 6.98−6.95 (m, 2 H), 5.37−5.32 (m, 1 H), 4.95−4.89 (m, 1 H), 4.19 (d, 1 H, J = 6.3 Hz), 2.20−1.90 (m, 5 H), 1.64 (s, 3 H), 0.90 (s, 9 H), 0.07 (s, 6 H).

2-[(1*RS*,4*E*)-6-(*tert*-Butyldimethylsilanyloxy)-1-(*tert*-butyldiphenylsilanyloxy)-4-methylhex-4-enyl]thiophene. A solution of (1*RS*,4*E*)-6-(*tert*-butyldimethylsilanyloxy)-4-methyl-1-thiophen-2-ylhex-4-en-1-ol (460 mg, 1.41 mmol), imidazole (213 mg, 3.13 mmol), and 4-(dimethylamino)pyridine (22 mg, 0.18 mmol) in CH_2Cl_2 (20 mL) was treated with TBDPS−Cl (0.65 mL, 2.5 mmol). After 2 h, the reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4) and concentrated. Chromatography on SiO_2 (hexanes/EtOAc, 19:1) gave 2-[(1*RS*,4*E*)-6-(*tert*-butyldimethylsilanyloxy)-1-(*tert*-butyldiphenylsilanyloxy)-4-methylhex-4-enyl]thiophene (565 mg, 1.00 mmol, 71%) as an oil. ^{1}H NMR: δ 7.71−7.67 (m, 2 H), 7.52−7.49 (m, 2 H), 7.43−7.34 (m, 5 H), 7.30−7.24 (m, 1 H), 7.17 (dd, 1 H, J = 5.1, 1.1 Hz), 6.83 (dd, 1 H, J = 5.0, 3.5 Hz), 6.63 (bd, 1 H, J = 3.0 Hz), 5.15−5.11 (m, 1 H), 4.92−4.89 (m, 1 H), 4.09 (d, 2 H, J = 6.3 Hz), 1.90−1.75 (m, 4 H), 1.43 (s, 3 H), 1.04 (s, 9 H), 0.88 (s, 9 H), 0.04 (s, 6 H).

(2*E*,6*RS*)-6-(*tert*-Butyldiphenylsilanyloxy)-3-methyl-6-thiophen-2-ylhex-2-en-1-ol (53). A solution of 2-[(1*RS*,4*E*)-6-(*tert*-butyldimethylsilanyloxy)-1-(*tert*-butyldiphenylsilanyloxy)-4-methylhex-4-enyl]thiophene (565 mg, 1.00 mmol) and pyridinium *p*-toluenesulfonate (24 mg, 95 μmol) in EtOH (15 mL) was stirred at room temperature for 18 h, quenched with saturated $NaHCO_3$ solution, and concentrated. The residue was extracted with EtOAc, and the extracts were dried (Na_2SO_4) and concentrated. Chromatography on SiO_2 (hexanes/EtOAc, 4:1) gave **53** (446 mg, 0.991 mmol, 99%) as an oil. IR (neat): 3335, 3069, 2931, 2855, 1426, 1109 cm^{-1}. ^{1}H NMR: δ 7.72−7.69 (m, 2 H), 7.52−7.49 (m, 2 H), 7.46−7.35 (m, 4 H), 7.30−7.25 (m, 2 H), 7.19 (dd, 1 H, J = 5.0, 1.1 Hz), 6.84 (dd, 1 H, J = 5.0, 3.5 Hz), 6.64 (bd, 1 H, J = 3.2 Hz), 5.20 (td, 1 H, J = 6.9, 1.1 Hz), 4.93−4.89 (m, 1 H), 4.03 (t, 2 H, J = 5.6 Hz), 1.93−1.77 (m, 4 H), 1.48 (s, 3 H), 1.04 (s, 9 H). ^{13}C NMR: δ 148.6, 139.2, 135.9, 134.2, 133.5, 129.7, 129.5, 127.6, 127.4, 126.0, 124.0, 123.6, 123.4, 71.5, 59.3, 38.4, 34.7, 26.9, 19.4, 16.1. MS (EI) *m*/*z* (relative intensity): 393 ([M − C_4H_9]$^+$, 4), 375 (4), 199 (100). HRMS (EI) calcd for $C_{23}H_{25}O_2SiS$, 393.1345; found, 393.1353.

(2*E*,6*RS*)-6-(*tert*-Butyldiphenylsilanyloxy)-3-methyl-6-thiophen-2-ylhex-2-enal. A solution of **53** (446 mg, 0.991 mmol) in CH_2Cl_2 (12 mL) was treated with pyridinium chlorochromate (587 mg, 2.73 mmol). After 2 h, the reaction mixture was diluted with hexanes and filtered through a short plug of SiO_2. The filtrate was concentrated to give crude (2*E*,6*RS*)-6-(*tert*-butyldiphenylsilanyloxy)-3-methyl-6-thiophen-2-yl-hex-2-enal (410 mg, 0.915 mmol, 92%) as an oil, which was used directly in the next step. ^{1}H NMR: δ 9.88 (d, 1 H, J = 8.0 Hz), 7.73−7.68 (m, 2 H), 7.52−7.49 (m, 2 H), 7.47−7.36 (m, 4 H), 7.31−7.27 (m, 2 H), 7.21 (dd, 1 H, J = 5.0, 1.0 Hz), 6.87 (dd, 1 H, J = 5.0, 3.5 Hz), 6.68 (d, 1 H, J = 3.4 Hz), 5.68 (dd, 1 H, J = 8.0, 1.1 Hz), 4.97 (t, 1 H, J = 5.9 Hz), 2.06−2.01 (m, 2 H), 1.95 (d, 3 H, J = 1.0 Hz), 1.91−1.81 (m, 2 H), 1.05 (s, 9 H).

(2*E*,4*E*,8*RS*)-8-(*tert*-Butyldiphenylsilanyloxy)-5-methyl-8-thiophen-2-ylocta-2,4-dienoic Acid Ethyl Ester. A solution of (2*E*)-6-(*tert*-butyldiphenylsilanyloxy)-3-methyl-6-thiophen-2-ylhex-2-enal (410 mg, 0.915 mmol) and ethyl (triphenylphosphoranylidene)acetate (1.46 g, 4.20 mmol) in CH_2Cl_2 (15 mL) was heated at 40° C for 14 h and concentrated. Chromatography on SiO_2 (hexanes/EtOAc, 24:1) gave (2*E*,4*E*,8*RS*)-8-(*tert*-butyldiphenylsilanyloxy)-5-methyl-8-thiophen-2-ylocta-2,4-dienoic acid ethyl ester (225 mg, 0.434 mmol, 47%) as an oil. ^{1}H NMR: δ 7.60−7.57 (m, 2 H), 7.41−7.38 (m, 2 H), 7.31−7.25 (m, 5 H), 7.18−7.10 (m, 2 H), 7.06 (dd, 1 H, J = 3.9, 1.1 Hz), 6.73 (dd, 1 H, J = 5.0, 3.5 Hz), 6.53−6.52 (m, 1 H), 5.65 (d, 1 H, J = 11.6 Hz), 5.58 (d, 1 H, J = 15.1 Hz), 4.82 (dd, 1 H, J = 6.7, 5.3 Hz), 4.07 (q, 2 H, J = 7.1 Hz), 1.87−1.83 (m, 2 H), 1.79−1.67 (m, 2 H), 1.55 (s, 3 H), 1.17 (t, 3 H, J = 7.1 Hz), 0.93 (s, 9 H).

(2*E*,4*E*,8*RS*)-8-(*tert*-Butyl-diphenylsilanyloxy)-5-methyl-8-thiophen-2-ylocta-2,4-dien-1-ol (54). A solution of (2*E*,4*E*,8*RS*)-8-(*tert*-butyldiphenylsilanyloxy)-5-methyl-8-thiophen-2-ylocta-2,4-dienoic acid ethyl ester (225 mg, 0.434 mmol) in CH_2Cl_2 (10 mL) was treated dropwise at −78° C with 1 M DIBAL-H in hexanes (1.0 mL, 1.0 mmol). After 1 h, the reaction mixture was quenched with EtOH (1 mL) followed by H_2O (1 mL) and extracted with EtOAc. The combined organic extracts were dried (Na_2SO_4) and concentrated. Chromatography on SiO_2 (hexanes/EtOAc, 4:1) gave **54** (171 mg, 0.359 mmol, 83%) as an oil. IR (neat): 3335, 3069, 2927, 2855, 1655, 1588, 1430, 1109, 1081 cm^{-1}. ^{1}H NMR: δ 7.58−7.55 (m, 2 H), 7.39−7.36 (m, 2 H), 7.30−7.20 (m, 4 H), 7.16−7.11 (m, 2 H), 7.06−7.00 (m, 1 H), 6.70 (dd, 1 H, J = 5.0, 3.5 Hz), 6.50−6.49 (m, 1 H), 6.29−6.19 (m, 1 H), 5.56−5.47 (m, 2 H), 4.81−4.77 (m, 1 H), 4.02 (t, 2 H, J = 5.6 Hz), 1.79−1.60 (m, 4 H), 1.43 (s, 3 H), 1.20 (t, 1 H, J = 5.7 Hz), 0.91 (s, 9 H). ^{13}C NMR: δ 148.6, 139.2, 135.9, 134.1, 133.4, 129.7, 129.5, 129.4, 128.2, 127.6, 127.4, 126.0, 124.0, 123.9, 123.6, 71.5, 63.8, 38.6, 35.0, 26.9, 19.3, 16.5. MS (EI) *m*/*z* (relative intensity): 476 (M$^+$, 0.5), 351 (52), 199 (100). HRMS (EI) calcd for $C_{29}H_{36}O_2SiS$, 476.2205; found, 476.2215.

***tert*-Butyl-(1*RS*,2*E*,4*E*)-(8-chloro-4-methyl-1-thiophen-2-ylocta-4,6-dienyloxy)diphenylsilane (55).** A mixture of **54** (171 mg, 0.359 mmol), LiCl (76.0 mg, 1.84 mmol), and *s*-collidine (0.12 mL, 0.91 mmol) in DMF (3 mL) was treated dropwise at 0° C with methanesulfonyl chloride (70 μL, 0.90 mmol). The reaction mixture was stirred at 0° C for 1 h followed by 1 h at room temperature. Water was added, and the reaction mixture was extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4) and concentrated to give crude **55** (80 mg, 0.162 mmol, 45%) as an oil, which was used directly in the next step.

3,4,5-Trimethoxybenzaldehyde *O*-[(2*E*,4*E*,8*RS*)-8-(*tert*-Butyldiphenylsilanyloxy)-5-methyl-8-thiophen-2-ylocta-2,4-dienyl]oxime. A solution of oxime **56** (169 mg, 0.801 mmol) in THF (1.5 mL) was treated with a suspension of 60% NaH in mineral oil (32 mg, 0.80 mmol). After 1 h, a solution of **55** (80 mg, 0.162 mmol) in THF (2 mL) was added dropwise. After 16 h, the reaction mixture was quenched with H_2O and extracted with Et_2O, and the extracts were dried (Na_2SO_4) and concentrated. Chromatography on SiO_2 (hexanes/EtOAc, 9:1) gave 3,4,5-trimethoxybenzaldehyde *O*-[(2*E*,4*E*,8*RS*)-8-(*tert*-butyldiphenylsilanyloxy)-5-methyl-8-thiophen-2-ylocta-2,4-dienyl]oxime (55 mg, 0.082 mmol, 51%) as an oil. ^{1}H NMR: δ 8.01 (s, 1 H), 7.71−7.68 (m, 2 H), 7.53−7.49 (m, 2 H), 7.44−7.35 (m, 4 H), 7.30−7.25 (m, 2 H), 7.18 (dd, 1 H, J = 5.0, 1.1 Hz), 6.87−6.83 (m, 1 H), 6.81 (s, 2 H), 6.64−6.63 (m, 1 H), 6.47 (dd, 1 H, J = 15.1, 11.0 Hz), 5.76−5.67 (m, 2 H), 4.94−4.91 (m, 1 H), 4.69 (d, 2 H, J = 6.6 Hz), 3.89 (s, 6 H), 3.87 (s, 3 H), 1.91−1.81 (m, 4 H), 1.58 (bs, 3 H), 1.04 (s, 9 H).

3,4,5-Trimethoxybenzaldehyde *O*-((2*E*,4*E*,8*RS*)-8-Hydroxy-5-methyl-8-thiophen-2-ylocta-2,4-dienyl)oxime (50). A solution of 3,4,5-trimethoxybenzaldehyde *O*-[(2*E*,4*E*,8*RS*)-8-(*tert*-butyldiphenylsilanyloxy)-5-methyl-8-thiophen-2-ylocta-2,4-dienyl]oxime (41 mg, 61 μmol) in THF (8 mL) was treated dropwise with 1 M TBAF in THF (1.0 mL, 1.0 mmol). After 21.5 h, the reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2, and the combined organic extracts were dried ($MgSO_4$) and concentrated. Chromatography on SiO_2 (hexanes/EtOAc, 3:1) gave **50** (19 mg, 44 μmol, 72%) as an oil. IR (neat): 3473, 2939, 1572, 1505,

1457, 1414, 1362, 1236, 1129, 982 cm^{-1}. ^1H NMR: δ 8.01 (s, 1 H), 7.26−7.24 (m, 1 H), 6.98−6.96 (m, 2 H), 6.81 (s, 2 H), 6.57 (dd, 1 H, J = 15.1, 10.9 Hz), 5.91 (d, 1 H, J = 10.9 Hz), 5.80 (dt, 1 H, J = 21.7, 6.6 Hz), 4.91 (t, 1 H, J = 6.4 Hz), 4.71 (d, 1 H, J = 6.5 Hz), 3.88 (s, 6 H), 3.86 (s, 3 H), 2.30−2.10 (m, 2 H), 2.10−1.90 (m, 3 H), 1.79 (s, 3 H). ^{13}C NMR: δ 153.4, 148.5, 139.3, 130.5, 127.7, 126.6, 126.1, 124.7, 124.5, 123.8, 104.0, 77.2, 75.0, 69.8, 60.9, 56.1, 37.2, 35.9, 16.7. MS (EI) *m*/*z* (relative intensity): 431 (M^+, 11), 211 (100). HRMS (EI) calcd for $C_{23}H_{29}NO_5S$, 431.1766; found, 431.1773. Anal. ($C_{23}H_{29}NO_5S$) C, H.

[(1*S*,2*R*)-2-(*tert*-Butyldimethylsilanyloxymethyl)-cyclopropyl]methanol (59). A mixture of freshly distilled DME (12.4 mL, 0.119 mol), Et_2Zn (12.0 mL, 0.119 mol), and CH_2Cl_2 (110 mL) was treated dropwise at −15 °C with CH_2I_2 (19.0 mL, 0.238 mol). The resultant solution was immediately added dropwise at −15 °C to a solution of dioxaborolane **36** (7.0 g, 26.1 mmol), alcohol **58** (4.80 g, 23.8 mmol), and 4 Å molecular sieves (1 g) in CH_2Cl_2 (110 mL). The reaction mixture was stirred at −15 °C for 2.5 h, quenched with saturated NH_4Cl solution, and extracted with Et_2O. The combined organic layers were dried ($MgSO_4$), concentrated, and chromatographed on SiO_2 (hexanes/EtOAc, 9:1) to give **59** (4.93 g, 22.8 mmol, 96%) as an oil; $[\alpha]_D$ +12.6 (*c* 0.42, $CHCl_3$). IR (neat): 3366, 2958, 2927, 2887, 2855, 1469, 1255, 1089, 840 cm^{-1}. ^1H NMR: δ 3.60 (dd, 1 H, J = 10.7, 5.8 Hz), 3.50−3.43 (m, 2 H), 3.44 (dd, 1 H, J = 10.7, 6.5 Hz), 1.33 (bt, 1 H, J = 5.4 Hz), 1.06−0.98 (m, 1 H), 0.97−0.90 (m, 1 H), 0.89 (s, 9 H), 0.53−0.41 (m, 2 H), 0.05 (s, 6 H). ^{13}C NMR: δ 66.6, 65.7, 26.0, 19.4, 19.3, 7.8, −5.2. MS (EI) *m*/*z* (relative intensity): 199 ([M − OH]$^+$, 0.5), 105 (100). HRMS (EI) calcd for $C_{11}H_{23}OSi$ (M − OH), 199.1518; found, 199.1520.

(1*S*,2*R*)-2-(*tert*-Butyldimethylsilanyloxymethyl)-cyclopropanecarbaldehyde. A mixture of 4 Å molecular sieves (500 mg), alcohol **59** (4.90 g, 22.7 mmol), and CH_2Cl_2 (120 mL) was treated with pyridinium chlorochromate (10.2 g, 47.4 mmol). After 2 h, the reaction mixture was diluted with hexanes and filtered through a short plug of SiO_2, and the filtrate was concentrated and chromatographed on SiO_2 (hexanes/EtOAc, 19:1) to give (1*S*,2*R*)-2-(*tert*-butyldimethylsilanyloxymethyl)-cyclopropanecarbaldehyde (3.82 g, 17.9 mmol, 79%) as an oil. ^1H NMR: δ 9.09 (d, 1 H, J = 5.4 Hz), 3.67 (ddd, 2 H, J = 20.6, 10.8, 4.7 Hz), 1.88−1.81 (m, 1 H), 1.77−1.68 (m, 1 H), 1.26 (dt, 1 H, J = 13.5, 4.6 Hz), 1.16−1.09 (m, 1 H), 0.87 (s, 9 H), 0.04 (s, 6 H).

(2*E*)-3-[(1*S*,2*R*)-2-(*tert*-Butyldimethylsilanyloxymethyl)cyclopropyl]-2-methylacrylic Acid Ethyl Ester. A mixture of a 60% suspension of NaH in mineral oil (1.57 g, 39.3 mmol) in THF (120 mL) was treated dropwise with triethyl 2-phosphonopropionate (8.40 mL, 39.2 mmol). After 1 h, a solution of (1*S*,2*R*)-2-(*tert*-butyldimethylsilanyloxymethyl)-cyclopropanecarbaldehyde (2.80 g, 13.1 mmol) in THF (5 mL) was added at 0 °C. The reaction mixture was stirred at room temperature for 4 h, quenched with H_2O, and diluted with Et_2O, and the organic layer was washed with H_2O. The organic layer was dried ($MgSO_4$), concentrated, and chromatographed on SiO_2 (hexanes/EtOAc, 19:1) to give (2*E*)-3-[(1*S*,2*R*)-2-(*tert*-butyldimethylsilanyloxymethyl)cyclopropyl]-2-methylacrylic acid ethyl ester (3.32 g, 11.1 mmol, 85%) as an oil. ^1H NMR: δ 6.18 (bd, 1 H, J = 9.4 Hz), 4.17 (q, 2 H, J = 7.1 Hz), 3.70−3.55 (m, 2 H), 1.93 (bs, 3 H), 1.60−1.48 (m, 1 H), 1.27 (t, 3 H, J = 7.1 Hz), 1.00−0.90 (m, 2 H), 0.89 (s, 9 H), 0.80−0.70 (m, 1 H), 0.05 (s, 6 H).

(2*E*)-3-[(1*S*,2*R*)-2-(*tert*-Butyldimethylsilanyloxymethyl)cyclopropyl]-2-methyl-prop-2-en-1-ol. A solution of (2*E*)-3-[(1*S*,2*R*)-2-(*tert*-butyldimethylsilanyloxymethyl)cyclopropyl]-2-methylacrylic acid ethyl ester (3.30 g, 11.0 mmol) in CH_2Cl_2 (150 mL) was treated dropwise at −78 °C with 1 M DIBAL-H in hexanes (33.0 mL, 33.0 mmol). The reaction mixture was stirred at −78 °C for 1.5 h, quenched with EtOH (4 mL), and stirred with a saturated sodium potassium tartrate solution for 1 h at room temperature. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$), concentrated, and chromatographed on SiO_2 (hexanes/EtOAc, 4:1) to give (2*E*)-3-[(1*S*,2*R*)-2-(*tert*-butyldimethylsilanyloxymethyl)cyclopropyl]-2-methylprop-2-en-1-ol (2.39 g, 9.34 mmol, 85%) as an oil. ^1H NMR: δ 4.88 (dd, 1 H, J = 9.4, 1.2 Hz), 3.98 (d, 2 H, J = 5.5 Hz), 3.57 (d, 2 H, J = 6.0 Hz), 1.78 (d, 3 H, J = 1.3 Hz), 1.45−1.32 (m, 1 H), 1.22 (t, 1 H, J = 6.1 Hz), 1.10−1.00 (m, 1 H), 0.89 (s, 9 H), 0.75−0.68 (m, 1 H), 0.56−0.50 (m, 1 H), 0.05 (s, 6 H).

[(1*S*,2*S*,1′*R*,2′*R*)-2′-(*tert*-Butyldimethylsilanyloxymethyl)-2-methylbicyclopropyl-2-yl]methanol (60). A solution of freshly distilled DME (4.7 mL, 39.0 mmol), Et_2Zn (4.6 mL, 39.0 mmol), and CH_2Cl_2 (45 mL) was treated dropwise at −15 °C with CH_2I_2 (7.2 mL, 78.0 mmol). The resultant solution was immediately added dropwise at −15 °C to a mixture of dioxaborolane **36** (2.64 g, 8.58 mmol), (2*E*)-3-[(1*S*,2*R*)-2-(*tert*-butyldimethylsilanyloxymethyl)-cyclopropyl]-2-methylprop-2-en-1-ol (2.00 g, 7.8 mmol), and 4 Å molecular sieves (1 g) in CH_2Cl_2 (45 mL). The reaction mixture was stirred at −15 °C for 3 h, quenched with saturated NH_4Cl solution, and extracted with Et_2O. The combined organic layers were dried ($MgSO_4$), concentrated, and chromatographed on SiO_2 (hexanes/EtOAc, 17:3) to give **60** (1.70 g, 6.30 mmol, 81%) as an oil; $[\alpha]_D$ +29.2 (*c* 0.69, $CHCl_3$). IR (neat): 3358, 2960, 2927, 2856, 1471, 1252, 1096, 836 cm^{-1}. ^1H NMR: δ 3.55−3.40 (m, 2 H), 3.33−3.27 (m, 2 H), 1.40−1.32 (m, 1 H), 1.20 (s, 3 H), 0.88 (s, 9 H), 0.87−0.80 (m, 1 H), 0.60−0.50 (m, 2 H), 0.50−0.42 (m, 1 H), 0.41−0.35 (m, 2 H), 0.08−0.05 (m, 1 H), 0.04 (s, 6 H). ^{13}C NMR: δ 72.1, 66.6, 26.0, 24.1, 22.8, 20.9, 18.4, 15.7, 15.4, 15.1, 10.0, −5.2. MS (EI) *m*/*z* (relative intensity): 253 ([M − OH]$^+$, 50), 215 (60), 157 (100). HRMS (EI) calcd for $C_{15}H_{29}OSi$ (M − OH), 253.1988; found, 253.1990.

(1*S*,2*S*,1′*R*,2′*R*)-2′-(*tert*-Butyldimethylsilanyloxymethyl)-2-methylbicyclopropyl-2-carbaldehyde. A mixture of 4 Å molecular sieves (500 mg), alcohol **60** (1.64 g, 6.08 mmol), and CH_2Cl_2 (120 mL) was treated with pyridinium chlorochromate (1.57 g, 7.30 mmol). After 1 h, the reaction mixture was diluted with hexanes and filtered through a short plug of SiO_2, and the filtrate was concentrated and chromatographed on SiO_2 (hexanes/EtOAc, 19:1) to give (1*S*,2*S*,1′*R*,2′*R*)-2′-(*tert*-butyldimethylsilanyloxymethyl)-2-methylbicyclopropyl-2-carbaldehyde (1.40 g, 5.22 mmol, 86%) as an oil, which was used immediately in the next step.

(2*E*)-3-[(1*S*,2*S*,1′*R*,2′*R*)-2′-(*tert*-Butyldimethylsilanyloxymethyl)-2-methylbicyclopropyl-2-yl]acrylic Acid Ethyl Ester. A suspension of 60% NaH (418 mg, 10.4 mmol) in THF (60 mL) was treated dropwise with triethyl phosphonoacetate (2.10 mL, 10.4 mmol). After 1 h, a solution of (1*S*,2*S*,1′*R*,2′*R*)-2′-(*tert*-butyldimethylsilanyloxymethyl)-2-methylbicyclopropyl-2-carbaldehyde (1.40 g, 5.22 mmol) in THF (5 mL) was added at 0 °C. The reaction mixture was stirred at room temperature for 21 h, quenched with H_2O, and diluted with Et_2O, and the organic layer was washed with H_2O. The organic layer was dried ($MgSO_4$), concentrated, and chromatographed on SiO_2 (hexanes/EtOAc, 30:1) to give (2*E*)-3-[(1*S*,2*S*,1′*R*,2′*R*)-2′-(*tert*-butyldimethylsilanyloxymethyl)-2-methylbicyclopropyl-2-yl]acrylic acid ethyl ester (1.28 g, 3.79 mmol, 73%) as an oil. ^1H NMR: δ 6.45 (d, 1 H, J = 15.6 Hz), 5.70 (d, 1 H, J = 15.6 Hz), 4.16 (q, 2 H, J = 7.1 Hz), 3.61−3.33 (m, 2 H), 1.30−1.25 (m, 3 H), 1.27 (s, 3 H), 1.02−0.85 (m, 3 H), 0.88 (s, 9 H), 0.67−0.56 (m, 2 H), 0.51−0.38 (m, 2 H), 0.03 (s, 6 H).

3-[(1*S*,2*S*,1′*R*,2′*R*)-2′-(*tert*-Butyldimethylsilanyloxymethyl)-2-methylbicyclopropyl-2-yl]-propionic Acid Ethyl Ester. A suspension of $CuBr{\cdot}SMe_2$ (3.72 g, 18.1 mmol) in THF (40 mL) was treated dropwise at room temperature with Red-Al in toluene (5.1 mL, 18.1 mmol, ∼3.5 M). After 30 min, the reaction mixture was cooled to −40 °C and treated dropwise with a solution of (2*E*)-3-[(1*S*,2*S*,1′*R*,2′*R*)-2′-(*tert*-butyldimethylsilanyloxymethyl)-2-methylbicyclopropyl-2-yl]acrylic acid ethyl ester (1.22 g, 3.61 mmol) in THF (4 mL). The reaction mixture was stirred at −20 °C for 2 h, quenched with H_2O, and extracted with Et_2O. The combined organic layers were dried (Na_2SO_4), concentrated, and chromatographed on SiO_2 (hexanes/EtOAc, 99:1) to give 3-[(1*S*,2*S*,1′*R*,2′*R*)-2′-(*tert*-

butyldimethylsilanyloxymethyl)-2-methylbicyclopropyl-2-yl]-propionic acid ethyl ester (642 mg, 1.89 mmol, 52%) as an oil. ^{1}H NMR: δ 4.11 (q, 2 H, J = 7.1 Hz), 3.49 (d, 2 H, J = 6.3 Hz), 2.35 (ddd, 2 H, J = 10.0, 6.7, 3.1 Hz), 1.60−1.35 (m, 2 H), 1.25 (t, 3 H, J = 7.2 Hz), 1.08 (s, 3 H), 0.89 (s, 9 H), 0.88−0.80 (m, 1 H), 0.50−0.32 (m, 5 H), 0.04 (s, 6 H), 0.00 to −0.05 (m, 1 H).

3-[(1*S*,2*S*,1′*R*,2′*R*)-2′-(*tert*-Butyldimethylsilanyloxymethyl)-2-methylbicyclopropyl-2-yl]propan-1-ol (61). A solution of 3-[(1*S*,2*S*,1′*R*,2′*R*)-2′-(*tert*-butyldimethylsilanyloxymethyl)-2-methylbicyclopropyl-2-yl]propionic acid ethyl ester (640 mg, 1.88 mmol) in CH_2Cl_2 (30 mL) was treated dropwise at −78 °C with 1 M DIBAL-H in hexanes (4.7 mL, 4.7 mmol). The reaction mixture was stirred at −78 °C for 1 h, quenched with EtOH (1 mL), and stirred with a saturated sodium potassium tartrate solution for 1 h at room temperature. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$), concentrated, and chromatographed on SiO_2 (hexanes/EtOAc, 7:1) to give **61** (451 mg, 1.51 mmol, 80%) as an oil; $[\alpha]_D$ +27.1 (*c* 0.57, $CHCl_3$). IR (neat): 3350, 2957, 2927, 2849, 1468, 1252, 1096, 836 cm^{-1}. ^{1}H NMR: δ 3.62 (t, 2 H, J = 6.6 Hz), 3.49 (d, 2 H, J = 6.3 Hz), 1.70−1.55 (m, 2 H), 1.34−1.24 (m, 2 H), 1.17−1.10 (m, 1 H), 1.08 (s, 3 H), 0.89 (s, 9 H), 0.55−0.29 (m, 5 H), 0.04 (s, 6 H), 0.00 to −0.03 (m, 1 H). ^{13}C NMR: δ 66.9, 63.1, 37.2, 30.1, 26.4, 26.0, 20.9, 19.6, 18.4, 17.9, 17.7, 15.7, 10.1, −5.2. MS (EI) *m*/*z* (relative intensity): 253 ([M − CH_2CH_2OH]$^+$, 3), 75 (100). HRMS (EI) calcd for $C_{15}H_{29}OSi$ (M − CH_2CH_2OH), 253.1988; found, 253.1980.

3-[(1*S*,2*S*,1′*R*,2′*R*)-2′-(*tert*-Butyldimethylsilanyloxymethyl)-2-methyl-bicyclopropyl-2-yl]propionaldehyde. A mixture of 4 Å molecular sieves (500 mg), alcohol **61** (451 mg, 1.51 mmol), and CH_2Cl_2 (20 mL) was treated with pyridinium chlorochromate (976 mg, 4.54 mmol). After 3 h, the reaction mixture was diluted with hexanes and filtered through a short plug of SiO_2, and the filtrate was concentrated and chromatographed on SiO_2 (hexanes/EtOAc, 19:1) to give 3-[(1*S*,2*S*,1′*R*,2′*R*)-2′-(*tert*-butyldimethylsilanyloxymethyl)-2-methylbicyclopropyl-2-yl]propionaldehyde (305 mg, 1.03 mmol, 68%) as an oil. ^{1}H NMR: δ 9.78 (t, 1 H, J = 3.0 Hz), 3.55−3.38 (m, 2 H), 2.53−2.46 (m, 2 H), 1.60−1.37 (m, 2 H), 1.08 (s, 3 H), 0.89 (s, 9 H), 0.87−0.80 (m, 1 H), 0.51−0.32 (m, 5 H), 0.04 (s, 6 H), 0.04−0.02 (m, 1 H).

(1*RS*)-3-[(1*S*,2*S*,1′*R*,2′*R*)-2′-(*tert*-Butyldimethylsilanyloxymethyl)-2-methylbicyclopropyl-2-yl]-1-thiophen-2-ylpropan-1-ol. A solution of 3-[(1*S*,2*S*,1′*R*,2′*R*)-2′-(*tert*-butyldimethylsilanyloxymethyl)-2-methylbicyclopropyl-2-yl]propionaldehyde (200 mg, 0.676 mmol) in THF (15 mL) was treated at −78 °C with a 1 M solution of 2-thienyllithium in THF (1.0 mL, 1.0 mmol). The reaction mixture was stirred at −78 °C for 2.5 h, quenched with a saturated $NaHCO_3$ solution, and extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$), concentrated, and chromatographed on SiO_2 (hexanes/EtOAc, 9:1) to give (1*RS*)-3-[(1*S*,2*S*,1′*R*,2′*R*)-2′-(*tert*-butyldimethylsilanyloxymethyl)-2-methylbicyclopropyl-2-yl]-1-thiophen-2-ylpropan-1-ol (219 mg, 0.576 mmol, 86%) as an oil; $[\alpha]_D$ +34.6 (*c* 0.94, $CHCl_3$). IR (neat): 3386, 2930, 2859, 1473, 1255, 1089, 840 cm^{-1}. ^{1}H NMR: δ 7.25−7.22 (m, 1 H), 6.96−6.94 (m, 2 H), 4.90−4.83 (m, 1 H), 3.49 (d, 2 H, J = 6.3 Hz), 2.05 (bd, 1 H, J = 4.0 Hz), 2.00−1.80 (m, 2 H), 1.46−1.36 (m, 1 H), 1.30−1.15 (m, 2 H), 1.09 (s, 3 H), 0.89 (s, 9 H), 0.53−0.43 (m, 1 H), 0.43−0.24 (m, 4 H), 0.04 (s, 6 H), 0.00 - −0.04 (m, 1 H). ^{13}C NMR: δ 149.0, 126.6, 124.4, 123.7, 70.5, 70.4, 66.7, 37.2, 36.7, 26.5, 26.0, 21.1, 19.7, 18.4, 18.1, 18.0, 17.8, 15.7, 10.1, −5.1. MS (EI) *m*/*z* (relative intensity): 323 ([M − C_4H_9]$^+$, 3), 75 (100).

2-[(1*RS*)-3-[(1*S*,2*S*,1′*R*,2′*R*)-2′-(*tert*-Butyldimethylsilanyloxymethyl)-2-methylbicyclopropyl-2-yl]-1-(*tert*-butyldiphenylsilanyloxy)propyl]thiophene. A solution of (1*RS*)-3-[(1*S*,2*S*,1′*R*,2′*R*)-2′-(*tert*-butyldimethylsilanyloxymethyl)-2-methylbicyclopropyl-2-yl]-1-thiophen-2-yl-propan-1-ol (202 mg, 0.532 mmol), imidazole (98.0 mg, 1.44 mmol), and 4-(dimethylamino)pyridine (12 mg, 98 μmol) in CH_2Cl_2 (10 mL) was treated with TBDPS−Cl (0.300 mL, 1.06 mmol). After 26 h, the reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with Et_2O, and the extracts were dried (Na_2SO_4) and concentrated. Chromatography on SiO_2 (hexanes/EtOAc, 49:1) gave 2-[(1*RS*)-3-[(1*S*,2*S*,1′*R*,2′*R*)-2′-(*tert*-butyldimethylsilanyloxymethyl)-2-methylbicyclopropyl-2-yl]-1-(*tert*-butyldiphenylsilanyloxy)propyl]thiophene (286 mg, 0.463 mmol, 87%) as an oil. ^{1}H NMR: δ 7.70−7.67 (m, 2 H), 7.52−7.49 (m, 2 H), 7.44−7.34 (m, 4 H), 7.30−7.24 (m, 2 H), 7.26 (d, 1 H, J = 5.1 Hz), 6.84−6.81 (m, 1 H), 6.61−6.59 (m, 1 H), 4.90−4.87 (m, 1 H), 3.52−3.35 (m, 2 H), 1.85−1.65 (m, 2 H), 1.04 (s, 9 H), 0.93−0.91 (m, 3 H), 0.89 (s, 9 H), 0.88−0.65 (m, 2 H), 0.45−0.22 (m, 4 H), 0.20−0.10 (m, 2 H), 0.04 (s, 9 H), −0.12 - −0.20 (m, 1 H).

{(1*R*,2*R*,1′*S*,2′*S*)-2′-[(3*RS*)-3-(*tert*-Butyldiphenylsilanyloxy)-3-thiophen-2-yl-propyl]-2′-methylbicyclopropyl-2-yl}methanol (62). A solution of 2-[(1*RS*)-3-[(1*S*,2*S*,1′*R*,2′*R*)-2′-(*tert*-butyldimethylsilanyloxymethyl)-2-methylbicyclopropyl-2-yl]-1-(*tert*-butyldiphenylsilanyloxy)propyl]thiophene (236 mg, 0.382 mmol), pyridinium *p*-toluenesulfonate (10 mg, 40 μmol), and EtOH (30 mL) was stirred at room temperature for 2 h, quenched with a saturated $NaHCO_3$ solution, and concentrated. The residue was extracted with EtOAc, and the combined organic extracts were dried ($MgSO_4$), concentrated, and chromatographed on SiO_2 (hexanes/EtOAc, 17:3) to give **62** (154 mg, 0.306 mmol, 80%) as an oil; $[\alpha]_D$ +28.8 (*c* 0.66, $CHCl_3$). IR (neat): 3339, 3069, 2931, 2855, 1426, 1113, 701 cm^{-1}. Major isomer: ^{1}H NMR: δ 7.73−7.70 (m, 2 H), 7.54−7.51 (m, 2 H), 7.46−7.36 (m, 4 H), 7.31−7.29 (m, 2 H), 7.17 (dd, 1 H, J = 5.0, 1.1 Hz), 6.84 (ddd, 1 H, J = 6.2, 3.5, 1.1 Hz), 6.63−6.61 (m, 1 H), 4.91 (t, 1 H, J = 6.0 Hz), 3.52−3.35 (m, 2 H), 2.81 (t, 1 H, J = 7.7 Hz), 1.88−1.63 (m, 2 H), 1.45−1.11 (m, 2 H), 1.06 (s, 9 H), 0.93 (s, 3 H), 0.90−0.80 (m, 1 H), 0.50−0.30 (m, 3 H), 0.26−0.13 (m, 2 H), −0.11 to −0.14 (m, 1 H). ^{13}C NMR: δ 149.1, 135.9, 129.7, 129.5, 127.6, 127.4, 126.0, 123.8, 123.3, 72.0, 67.2, 37.6, 36.0, 27.0, 26.0, 21.1, 19.4, 17.8, 17.7, 17.6, 15.9, 10.3. MS (EI) *m*/*z* (relative intensity): 504 (M$^+$, 3), 97 (100). HRMS (EI) calcd for $C_{31}H_{40}O_2SiS$, 504.2518; found, 504.2533.

3,4,5-Trimethoxybenzaldehyde *O*-{(1*R*,2*R*,1′*S*,2′*S*)-2′-[(3*RS*)-3-(*tert*-Butyldiphenylsilanyloxy)-3-thiophen-2-yl-propyl]-2′-methylbicyclopropyl-2-ylmethyl}oxime. A mixture of alcohol **62** (104 mg, 0.206 mmol), CBr_4 (85 mg, 0.26 mmol), and CH_2Cl_2 (8 mL) was treated dropwise at 0 °C with a solution of PPh_3 (65 mg, 0.25 mmol) in CH_2Cl_2 (1 mL). The reaction mixture was stirred for 2 h at 0 °C and concentrated, and the residue was triturated with pentane/Et_2O (1:1), filtered through a short pad of SiO_2, and concentrated to give crude [3-((1*S*,2*S*,1′*R*,2′*R*)-2′-bromomethyl-2-methylbicyclopropyl-2-yl)-1-thiophen-2-ylpropoxy]-*tert*-butyldiphenylsilane, which was used directly for the next step. A solution of oxime **56** (87 mg, 0.41 mmol) in DMF (4 mL) was treated with 60% NaH (17 mg, 0.41 mmol). After 30 min, a solution of the crude bromide in THF (1 mL) was added dropwise. The reaction mixture was stirred at room temperature overnight, quenched with H_2O, diluted with Et_2O, and washed with H_2O. The organic layer was dried ($MgSO_4$) and chromatographed on SiO_2 (hexanes/EtOAc, 9:1) to give 3,4,5-trimethoxybenzaldehyde *O*-{(1*R*,2*R*,1′*S*,2′*S*)-2′-[(3*RS*)-3-(*tert*-butyldiphenylsilanyloxy)-3-thiophen-2-ylpropyl]-2′-methylbicyclopropyl-2-ylmethyl}oxime (31 mg, 0.044 mmol, 22%) as an oil. ^{1}H NMR: δ 8.00−7.98 (m, 1 H), 7.70−7.68 (m, 2 H), 7.52−7.49 (m, 2 H), 7.43−7.33 (m, 4 H), 7.30−7.26 (m, 2 H), 7.19−7.15 (m, 1 H), 6.84−6.80 (m, 3 H), 6.60−6.58 (m, 1 H), 4.88 (t, 1 H, J = 6.3 Hz), 4.07−4.01 (m, 1 H), 3.95−3.92 (m, 1 H), 3.88 (s, 6 H), 3.87 (s, 3 H), 1.85−1.62 (m, 2 H), 1.03 (s, 9 H), 1.02−0.93 (m, 2 H), 0.93, 0.92 (2s, 3 H), 0.88−0.80 (m, 1 H), 0.56−0.37 (m, 3 H), 0.25−0.12 (m, 2 H), −0.10 to −0.15 (m, 1 H).

3,4,5-Trimethoxybenzaldehyde *O*-[(1*R*,2*R*,1′*S*,2′*S*)-2′-((3*RS*)-3-Hydroxy-3-thiophen-2-ylpropyl)-2′-methylbicyclopropyl-2-ylmethyl]oxime (57). A solution of 3,4,5-trimethoxybenzaldehyde *O*-{(1*R*,2*R*,1′*S*,2′*S*)-2′-[(3*RS*)-3-(*tert*-butyldiphenylsilanyloxy)-3-thiophen-2-ylpropyl]-2′-methylbicyclopropyl-2-ylmethyl}oxime (25 mg, 0.036 mmol) in THF (4 mL) was treated dropwise with 1 M TBAF in THF (50

μL, 0.050 mmol). The reaction mixture was stirred at room temperature overnight, quenched with saturated $NaHCO_3$ solution, and extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$) and chromatographed on SiO_2 (hexanes/EtOAc, 17:3) to give **57** (13.2 mg, 0.0289 mmol, 81%) as an oil; $[\alpha]_D$ +33.8 (*c* 1.30, $CHCl_3$). IR (neat): 3473, 2935, 1580, 1505, 1461, 1414, 1358, 1236, 1129 cm^{-1}. ^1H NMR: δ 8.00−7.97 (m, 1 H), 7.24−7.21 (m, 1 H), 6.95−6.91 (m, 2 H), 6.80−6.79 (m, 2 H), 4.89−4.83 (m, 1 H), 3.99 (d, 2 H, J = 7.1 Hz), 3.87 (s, 6 H), 3.86 (s, 3 H), 2.10−2.00 (br, 1 H), 2.00−1.80 (m, 2 H), 1.47−1.18 (2m, 2 H), 1.09 (s, 3 H), 1.06−0.97 (m, 1 H), 0.70−0.53 (m, 1 H), 0.51−0.38 (m, 3 H), 0.35−0.31 (m, 1 H), 0.00 (t, 1 H, J = 4.5 Hz). ^{13}C NMR (major isomer): δ 153.3, 148.0, 127.9, 126.5, 124.5, 123.7, 103.9, 78.4, 70.2, 60.9, 56.1, 37.1, 36.5, 26.1, 19.6, 17.9, 17.7, 16.2, 10.6. MS (EI) *m*/*z* (relative intensity): 459 (M^+, 25), 211 (100). HRMS (EI) calcd for $C_{25}H_{33}NO_5S$, 459.2079; found, 459.2088. Anal. ($C_{25}H_{33}NO_5S$) C, H.

(1*RS*,4*E*,6*E*)-10-(*tert*-Butyldimethylsilanyloxy)-4-methyl-1-thiophen-2-yldeca-4,6-dien-1-ol. A solution of aldehyde **66** (1.45 g, 4.90 mmol) in THF (55 mL) was treated at −78 °C with a 1 M solution of 2-thienyllithium in THF (6.0 mL, 6.0 mmol). The reaction mixture was stirred at −78 °C for 1 h, quenched with a saturated $NaHCO_3$ solution, and extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$), concentrated, and chromatographed on SiO_2 (hexanes/EtOAc, 9:1) to give (1*RS*,4*E*,6*E*)-10-(*tert*-butyldimethylsilanyloxy)-4-methyl-1-thiophen-2-yldeca-4,6-dien-1-ol (939 mg, 2.47 mmol, 50%) as an oil. ^1H NMR: δ 7.26−7.24 (m, 1 H), 6.98−6.95 (m, 2 H), 6.25 (dd, 1 H, J = 15.0, 10.8 Hz), 5.83 (d, 1 H, J = 10.8 Hz), 5.59 (dt, 1 H, J = 14.5, 7.0 Hz), 4.94−4.88 (m, 1 H), 3.62 (t, 2 H, J = 6.4 Hz), 2.25−2.08 (m, 4 H), 2.07−1.93 (m, 3 H), 1.75 (s, 3 H), 1.66−1.56 (m, 2 H), 0.90 (s, 9 H), 0.04 (s, 6 H).

2-[(1*RS*,4*E*,6*E*)-10-(*tert*-Butyldimethylsilanyloxy)-1-(*tert*-butyldiphenylsilanyloxy)-4-methyldeca-4,6-dienyl]thiophene. A solution of (1*RS*,4*E*,6*E*)-10-(*tert*-butyldimethylsilanyloxy)-4-methyl-1-thiophen-2-yldeca-4,6-dien-1-ol (939 mg, 2.47 mmol) and imidazole (336 mg, 4.94 mmol) in CH_2Cl_2 (25 mL) was treated with TBDPS−Cl (0.88 mL, 3.44 mmol). After 24 h, the reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4) and concentrated. Chromatography on SiO_2 (hexanes/Et_2O, 49:1) gave 2-[(1*RS*,4*E*,6*E*)-10-(*tert*-butyldimethylsilanyloxy)-1-(*tert*-butyldiphenylsilanyloxy)-4-methyldeca-4,6-dienyl]thiophene (1.19 g, 1.92 mmol, 78%) as an oil. ^1H NMR: δ 7.71−7.68 (m, 2 H), 7.52−7.49 (m, 2 H), 7.46−7.34 (m, 4 H), 7.29−7.24 (m, 2 H), 7.17 (dd, 1 H, J = 5.1, 1.0 Hz), 6.83 (dd, 1 H, J = 5.1, 3.5 Hz), 6.62 (d, 1 H, J = 3.2 Hz), 6.15 (dd, 1 H, J = 15.0, 10.8 Hz), 5.60 (d, 1 H, J = 10.9 Hz), 5.49 (dt, 1 H, J = 14.6, 7.1 Hz), 4.93−4.89 (m, 1 H), 3.60 (t, 2 H, J = 6.5 Hz), 2.12 (q, 2 H, J = 7.0 Hz), 1.91−1.78 (m, 4 H), 1.64−1.53 (m, 2 H), 1.55 (s, 3 H), 1.04 (s, 9 H), 0.89 (s, 9 H), 0.04 (s, 6 H).

(4*E*,6*E*,10*RS*)-10-(*tert*-Butyldiphenylsilanyloxy)-7-methyl-10-thiophen-2-yldeca-4,6-dien-1-ol (67). A mixture of 2-[(1*RS*,4*E*,6*E*)-10-(*tert*-butyldimethylsilanyloxy)-1-(*tert*-butyldiphenylsilanyloxy)-4-methyldeca-4,6-dienyl]thiophene (1.19 g, 1.92 mmol), pyridinium *p*-toluenesulfonate (100 mg, 0.400 mmol), and EtOH (75 mL) was stirred at room temperature for 7.5 h, quenched with a saturated $NaHCO_3$ solution, and concentrated. The residue was extracted with EtOAc, and the combined organic extracts were dried ($MgSO_4$), concentrated, and chromatographed on SiO_2 (hexanes/EtOAc, 4:1) to give **67** (870 mg, 1.73 mmol, 90%) as an oil. IR (neat): 3350, 2931, 2852, 1586, 1469, 1428, 1110, 1080 cm^{-1}. ^1H NMR: δ 7.68−7.65 (m, 2 H), 7.49−7.46 (m, 2 H), 7.43−7.30 (m, 4 H), 7.26−7.21 (m, 2 H), 7.14 (dd, 1 H, J = 5.0, 1.0 Hz), 6.80 (dd, 1 H, J = 5.0, 3.5 Hz), 6.59 (d, 1 H, J = 3.0 Hz), 6.15 (dd, 1 H, J = 15.0, 10.8 Hz), 5.58 (d, 1 H, J = 10.8 Hz), 5.46 (dt, 1 H, J = 14.5, 7.1 Hz), 4.90−4.87 (m, 1 H), 3.61 (bt, 2 H, J = 5.8 Hz), 2.13 (q, 2 H, J = 7.3 Hz), 1.91−1.70 (m, 4 H), 1.62 (p, 2 H, J = 6.6 Hz), 1.51 (s, 3 H), 1.40−1.30 (br, 1 H), 1.01 (s, 9 H). ^{13}C NMR: δ 148.7, 136.2, 135.9, 134.1, 133.4, 131.3, 129.6, 129.5, 127.6, 127.4, 127.2, 126.0, 125.0, 123.9, 123.6, 71.6, 62.5, 38.7, 35.0, 32.4, 29.2, 26.9, 19.3, 16.4. MS (EI) *m*/*z* (relative intensity): 504 (M^+, 1.5), 199 (100). HRMS (EI) calcd for $C_{31}H_{40}O_2SiS$, 504.2518; found, 504.2511.

***tert*-Butyl-[(1*RS*,4*E*,6*E*)-4-methyl-1-thiophen-2-yl-10-(3,4,5-trimethoxybenzyloxy)deca-4,6-dienyloxy]diphenylsilane.** A solution of alcohol **67** (43 mg, 0.085 mmol) in THF (3.5 mL) was treated with a suspension of 60% NaH in mineral oil (13.6 mg, 0.340 mmol). After 10 min, 3,4,5-trimethoxybenzyl bromide (66 mg, 0.25 mmol) was added. The reaction mixture was stirred at room temperature for 14.5 h, quenched with brine, and extracted with Et_2O, and the organic extract was dried ($MgSO_4$), concentrated, and chromatographed on SiO_2 (hexanes/EtOAc, 17:3) to give *tert*-butyl-[(1*RS*,4*E*,6*E*)-4-methyl-1-thiophen-2-yl-10-(3,4,5-trimethoxybenzyloxy)deca-4,6-dienyloxy]diphenylsilane (41 mg, 0.060 mmol, 71%) as an oil. ^1H NMR: δ 7.71−7.67 (m, 2 H), 7.52−7.49 (m, 2 H), 7.41−7.15 (m, 7 H), 6.83 (dd, 1 H, J = 5.1, 3.5 Hz), 6.62 (d, 1 H, J = 2.9 Hz), 6.57 (s, 2 H), 6.17 (dd, 1 H, J = 15.0, 10.7 Hz), 5.61 (d, 1 H, J = 10.8 Hz), 5.50 (dt, 1 H, J = 14.4, 6.9 Hz), 4.93−4.89 (m, 1 H), 4.43 (s, 2 H), 3.86 (s, 6 H), 3.83 (s, 3 H), 3.48 (t, 2 H, J = 6.5 Hz), 2.17 (q, 2 H, J = 7.5 Hz), 1.92−1.69 (m, 6 H), 1.53 (s, 3 H), 1.03 (s, 9 H).

(1*RS*,4*E*,6*E*)-4-Methyl-1-thiophen-2-yl-10-(3,4,5-trimethoxybenzyloxy)deca-4,6-dien-1-ol (63). A solution of *tert*-butyl-[(1*RS*,4*E*,6*E*)-4-methyl-1-thiophen-2-yl-10-(3,4,5-trimethoxybenzyloxy)deca-4,6-dienyloxy]diphenylsilane (40 mg, 59 μmol) in THF (4 mL) was treated dropwise with 1 M TBAF in THF (0.5 mL, 0.5 mmol). The reaction mixture was stirred at room temperature overnight, quenched with saturated $NaHCO_3$ solution, and extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$), concentrated, and chromatographed on SiO_2 (hexanes/EtOAc, 3:1) to give **63** (18 mg, 0.040 mmol, 69%) as an oil. IR (neat): 3402, 2923, 2848, 1591, 1505, 1457, 1423, 1127 cm^{-1}. ^1H NMR: δ 7.25−7.24 (m, 1 H), 6.97−6.95 (m, 2 H), 6.57 (s, 2 H), 6.25 (dd, 1 H, J = 15.0, 10.8 Hz), 5.83 (d, 1 H, J = 10.8 Hz), 5.59 (dt, 1 H, J = 14.4, 7.0 Hz), 4.90 (bt, 1 H, J = 6.2 Hz), 4.43 (s, 2 H), 3.86 (s, 6 H), 3.83 (s, 3 H), 3.49 (t, 2 H, J = 6.5 Hz), 2.24−1.90 (m, 6 H), 1.78−1.68 (m, 2 H), 1.74 (bs, 3 H). ^{13}C NMR: δ 153.3, 148.7, 137.5, 135.6, 134.3, 131.9, 127.0, 126.6, 125.2, 124.5, 123.7, 104.7, 77.2, 73.1, 70.0, 69.9, 60.8, 56.1, 37.4, 35.9, 29.6, 29.5, 16.5. MS (EI) *m*/*z* (relative intensity): 446 (M^+, 9), 181 (100). HRMS (EI) calcd for $C_{25}H_{34}O_5S$, 446.2127; found, 446.2131. HPLC analysis: (C_{18}, MeCN, ELSD) t_R = 3.35 min, 99.9%; (C_{18}, MeOH/H_2O (9:1), ELSD) t_R = 3.74 min, 99.5%.

(4*E*,6*E*,10*RS*)-10-(*tert*-Butyldiphenylsilanyloxy)-7-methyl-10-thiophen-2-yldeca-4,6-dienal. A mixture of 4 Å molecular sieves (20 mg), SiO_2 (100 mg), alcohol **67** (46 mg, 91 μmol), and CH_2Cl_2 (1.5 mL) was treated with pyridinium chlorochromate (39 mg, 0.18 mmol). After 1.5 h, the reaction mixture was diluted with hexanes and filtered through a short plug of SiO_2, and the filtrate was concentrated to give crude (4*E*,6*E*,10*RS*)-10-(*tert*-butyldiphenylsilanyloxy)-7-methyl-10-thiophen-2-yldeca-4,6-dienal (29 mg, 0.058 mmol, 63%) as an oil, which was used immediately in the next reaction.

***tert*-Butyl-[(1*RS*,4*E*,6*E*,10*E*)-4-methyl-1-thiophen-2-yl-11-(3,4,5-trimethoxyphenyl)undeca-4,6,10-trienyloxy]-diphenylsilane.** A suspension of (3,4,5-trimethoxybenzyl)-diethylphosphonate (**68**, 74 mg, 0.234 mmol) in THF (3 mL) was treated dropwise at −78 °C with 1.6 M *n*-BuLi in hexanes (0.15 mL, 0.24 mmol). After 30 min, a solution of (4*E*,6*E*,10*RS*)-10-(*tert*-butyldiphenylsilanyloxy)-7-methyl-10-thiophen-2-yl-deca-4,6-dienal (29 mg, 58 μmol) in THF (0.5 mL) was added dropwise. The reaction mixture was warmed to room temperature over 1 h, quenched with H_2O, and extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$), concentrated, and chromatographed on SiO_2 (hexanes/EtOAc, 9:1) to give *tert*-butyl-[(1*RS*,4*E*,6*E*,10*E*)-4-methyl-1-thiophen-2-yl-11-(3,4,5-trimethoxyphenyl)undeca-4,6,10-trienyloxy]diphenylsilane (17.8 mg, 0.0267 mmol, 46%, *E*:*Z* = 6.6:1) as an oil. ^1H NMR (major isomer): δ 7.75−7.68 (m, 2 H), 7.53−7.49 (m, 2 H), 7.45−7.34 (m, 4 H), 7.29−7.24 (m, 2 H), 7.21−7.17 (m, 1 H), 6.85−6.82 (m, 1 H), 6.66−6.62 (m, 1 H), 6.57 (s, 2 H), 6.33

(d, 1 H, J = 15.7 Hz), 6.25−6.09 (m, 2 H), 5.70−5.45 (m, 2 H), 4.97−4.86 (m, 1 H), 3.87 (s, 6 H), 3.84 (s, 3 H), 2.33−2.20 (m, 4 H), 1.90−1.80 (m, 4 H), 1.57 (bs, 3 H), 1.04 (s, 9 H).

(1*RS*,4*E*,6*E*,10*E*)-4-Methyl-1-thiophen-2-yl-11-(3,4,5-trimethoxyphenyl)undeca-4,6,10-trien-1-ol (65). A solution of *tert*-butyl-[(1*RS*,4E,6*E*,10*E*)-4-methyl-1-thiophen-2-yl-11-(3,4,5-trimethoxyphenyl)undeca-4,6,10-trienyloxy]diphenylsilane (17.8 mg, 26,7 μmol) in THF (4 mL) was treated dropwise with 1 M TBAF in THF (0.5 mL, 0.5 mmol). The reaction mixture was stirred at room temperature for 24 h, quenched with saturated $NaHCO_3$ solution, and extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$) and chromatographed on SiO_2 (hexanes/EtOAc, 4:1) followed by chromatography on $AgNO_3$-impregnated SiO_2 (hexanes/EtOAc, 6:1) to give **65** (8.5 mg, 19 μmol, 74%, 10*E*:10*Z* = 10.3:1) as an oil. IR (neat): 3440, 2920, 2851, 1580, 1505, 1414, 1124 cm^{-1}. ^1H NMR (major isomer): δ 7.25−7.24 (m, 1 H), 6.98−6.95 (m, 2 H), 6.57 (s, 2 H), 6.39−6.23 (m, 2 H), 6.19−6.09 (m, 1 H), 5.85 (d, 1 H, J = 10.7 Hz), 5.63 (dt, 1 H, J = 21.0, 6.1 Hz), 4.94−4.87 (m, 1 H), 3.87 (s, 6 H), 3.83 (s, 3 H), 2.34−1.92 (m, 8 H), 1.76 (bs, 1 H), 1.57 (s, 3 H). ^{13}C NMR (major isomer): δ 153.3, 135.8, 133.6, 131.7, 130.1, 129.8, 127.1, 126.6, 125.2, 124.6, 123.7, 103.1, 69.9, 60.9, 56.1, 37.3, 35.9, 33.0, 32.8, 16.6. MS (EI) *m*/*z* (relative intensity): 428 (M^+, 14), 334 (80), 176 (100). HRMS (EI) calcd for $C_{25}H_{32}O_4S$, 428.2021; found, 428.2042. HPLC analysis: (C_{18}, MeCN, ELSD) t_R = 3.20 min, 100%; (C_{18}, MeOH/H_2O (9:1), ELSD) t_R = 3.27 min, 100%.

4-Methyl-1-thiophen-2-yl-11-(3,4,5-trimethoxyphenyl)-undecan-1-ol (64). A solution of **65** (4.7 mg, 0.011 mmol) in EtOAc (3 mL) was treated with 10% Pd/C (15 mg), and the reaction mixture was treated with H_2 gas at 1 atm for 40 min. The reaction mixture was filtered through a short pad of SiO_2, and the filtrate was concentrated and chromatographed on SiO_2 (hexanes/EtOAc, 4:1) to give **64** (4.0 mg, 9.2 μmol, 83%) as an oil. IR (neat): 3451, 2930, 2854, 1589, 1510, 1455, 1235, 1127, 1007 cm^{-1}. ^1H NMR: δ 7.24−7.21 (m, 1 H), 6.96−6.93 (m, 2 H), 4.89 (t, 1 H, J = 6.6 Hz), 3.84 (s, 6 H), 3.82 (s, 3 H), 2.64−2.45 (m, 2 H), 2.25−2.18 (br, 1 H), 1.93−1.75 (m, 2 H), 1.65−1.56 (m, 1 H), 1.45−1.39 (m, 3 H), 1.38−1.10 (m, 11 H), 0.93 (d, 3 H, J = 6.2 Hz). ^{13}C NMR: δ 152.9, 148.9, 138.9, 135.7, 126.5, 124.3, 123.6, 105.1, 70.2, 60.8, 55.9, 39.2, 38.9, 36.8, 33.9, 32.5, 29.8, 29.5, 29.3, 26.9, 25.7, 19.6. MS (EI) *m*/*z* (relative intensity): 434 (M^+, 12), 416 (70), 182 (100). HRMS (EI) calcd for $C_{25}H_{38}O_4S$, 434.2491; found, 434.2478. Anal. ($C_{25}H_{38}O_4S$) C, H.

TPI. Reactions were carried out as described previously.[4b,21] Tubulin (final concentration 10 μM; 1 mg/mL) was preincubated with test agents dissolved in DMSO (4% v/v final concentration) and monosodium glutamate (0.8 M final concentration) for 15 min at 30 °C. The reaction mixture was cooled to 0 °C, and GTP (0.4 mM final concentration) was added. Reaction mixtures were transferred to cuvettes held at 0.5−2.5 °C in a Beckmann-Coulter 7400 spectrophotometer reading absorbance (turbidity) at 350 nm. Baselines were established, and temperature was quickly raised to 30 °C (in approximately 1 min) and held there for 20 min. The temperature was then rapidly lowered back to 0.25−2.5 °C. The change in absorbance 20 min after samples reached 30 °C was used to calculate extent of polymerization. The change in absorbance at this time point for vehicle plus no GTP was considered 100% assembly inhibition, while the change in absorbance for GTP plus vehicle was taken as 0% inhibition. Each series of determinations included positive and negative control determinations plus one determination made with 5 μM curacin A.

CBI. Using methods described previously,[4b,21,32] 5 μM [^3H]-colchicine (2.3 TBq/mmol), test agent (1, 5, 10, 50, or 250 μM), or vehicle (DMSO, 5% v/v) were incubated at 30 °C for 15 min or at 37 °C for 10 min with 1 μM tubulin in the presence of 1 M monosodium glutamate, 0.1 M glucose-1-phosphate, 1 mM $MgCl_2$, 1 mM GTP, and 0.5 mg/mL bovine serum albumin. The solutions were filtered through two stacks of DEAE-cellulose filters, and the radioactivity in the filtrate was determined by scintillation spectrometry. Each series of determinations included positive controls of 1, 5, and/or 50 μM curacin A.

Cell Growth Inhibition.[21] Cells were plated (500−2000 cells/well depending on the cell line) in 96 well plates, allowed to attach and grow for 48 h, and then treated with vehicle (DMSO) or test agent (50, 10, 2, 0.4, and 0.08 μM in the first screen; 10, 2, 0.4, 0.08, and 0.016 μM for curacin A; then 1, 0.2, 0.04, 0.008, and 0.0016 μM for the more potent new agents and curacin A) for 48 h. One plate consisted entirely of cells used for a time zero cell number determination. The other plates in a given determination contained eight wells of control cells and eight wells of medium, and each agent concentration was tested in quadruplicate. Cell numbers were obtained spectrophotometrically (absorbance at 490 nm minus that at 630 nm) in a Dynamax plate reader after treatment with 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium (MTS) using phenazine methanesulfonate as the electron acceptor.

Plasma Protein Binding of 50 and 1. Protein binding by **50** and **1** was determined by the equilibrium dialysis method.[30] Whole blood from a healthy donor was purchased from a local blood blank and plasma was prepared by centrifugation. Protein binding was determined using Fisher-Brand dialysis membranes (nominal molecular mass cutoff of 6−8 kDa). Membranes were soaked overnight in 0.1 M phosphate-buffered saline, pH 7.4, and blotted on tissue paper before cell assembly. Dialysates were prepared in plasma and buffer at concentrations of 500 and 5000 ng/mL of test agent and vortexed gently to ensure uniform mixing, and duplicate 50 μL aliquots were collected and analyzed by LC-MS and UV spectrophotometry to verify initial concentrations. Equilibrium dialysis cells were rotated at 15 rpm for 4 h at 37 °C. Following incubation, 50 μL aliquots of both plasma and buffer were withdrawn from each cell and analyzed for the concentration of the respective agent. Compounds **50** and **1** were isolated from samples by protein precipitation with acetonitrile and quantified by LC-MS on a Perkin-Elmer/Sciex API I mass spectrometer with an IonSpray interface after separation on a Hewlett-Packard 1090 HPLC with a Hewlett-Packard 1040 diode array UV−vis detector equipped with a 150 mm × 1 mm Phenomenex Ultracarb 5 μm particle size ODS 20 column. Briefly, internal standard (150 μL of a 250 ng/mL solution of the monodeuterated analogue of compound **46**, in the mobile phase, 3:2 acetonitrile−2 mM aqueous $NH_4O_2CCH_3$, apparent pH 6.5) was added to 50 μL of sample. The mixture was vortexed and centrifuged for 10 min at full speed in an Eppendorf microcentrifuge. An aliquot (10 μL) of the supernatant was injected onto the HPLC-DAD/UV-LC-MS system with the mobile phase flowing at 0.5 mL/min. UV detection wavelengths were 280 nm (aromatic) and 235 (conjugated diene). In the mass spectrometer, positive ions ± 200 *m*/*z* of the mass range comprised by the analytes were monitored. Using a (1/*x*) weighted linear regression analysis of the calibration curve, linear responses in the analyte/internal standard $[M + H - H_2O]^+ + [M + H]^+ + [M + NH_4]^+ + [M + Na]^+$ peaks, as well as UV absorbance, area ratios were observed over the entire concentration ranges examined.

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Supporting Information Available: Copies of ^1H and ^{13}C NMR spectra for **26**−**29**, **44**, **45**, **50**, **57**, and **63**−**65**. This material is available free of charge via the Internet at http://pubs.acs.org.

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