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Featured Article

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Syntheses of Cyclopropyl Analogues of Disorazoles A_1 and B_1 and Their Thiazole Counterparts

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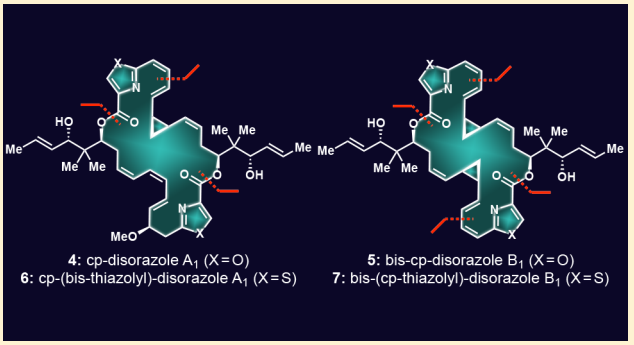
Supporting Information

ABSTRACT: Modular syntheses of disorazoles A_1 and B_1 analogues in which the epoxide moieties of the natural products were replaced with cyclopropyl units have been achieved. Targeted as part of a structure−activity relationships study, these syntheses were successfully extended to the thiazole counterparts of these analogues. The retrosynthetically defined fragments were assembled through Yamaguchi esterification, Cu/Pd-catalyzed cross-coupling, Yamaguchi macrolactonization, and Cu-catalyzed cross-coupling as the key reactions. Further synthetic and biological investigations of such analogues are expected to lead to the discovery and development of potential payloads for antibody−drug conjugates as targeted cancer therapies.



INTRODUCTION

The naturally occurring disorazoles[1] have attracted considerable attention as synthetic targets due to their challenging molecular structures and high potencies against cancer cells.[2] The latter properties elevated these molecules to potential candidates, or lead compounds, for payloads of antibody−drug conjugates (ADCs).[3] Isolated from myxobacterium *Sorangium cellulosum* So ce12,[1] the disorazoles exert their picomolar antitumor properties by interfering with tubulin polymerization dynamics.[4] Disorazoles A_1, B_1, and C_1 (**1**, **2**, and **3**, Figure 1) are representative examples of the structural variations within this class of natural products, with disorazole A_1 (**1**) being the most abundant and well-studied from the biological point of view, and disorazole C_1 (**3**) receiving the most attention from synthetic organic chemists until recently.[2c,d,5] Thus, early synthetic studies led only to the construction of certain fragments,[6] especially of disorazoles C_1 (**3**)[5a−c,e−g] and A_1 (**1**).[5c,6c,7] Subsequent work, however, resulted in three successful and elegant total syntheses of disorazole C_1 (**3**).[5d,h,i] In a recent communication, we reported the first total syntheses of disorazoles A_1 (**1**) and B_1 (**2**) and demystified the full molecular structure of the latter.[8] Herein, we describe the syntheses of the cyclopropyl analogues of disorazoles A_1 and B_1 [cp-disorazole A_1 (**4**) and bis-cp-disorazole B_1 (**5**), Figure 2] and their thiazole counterparts [cp-(bis-thiazolyl)disorazole A_1 (**6**) and bis(cp-thiazolyl)-disorazole B_1 (**7**), Figure 2].

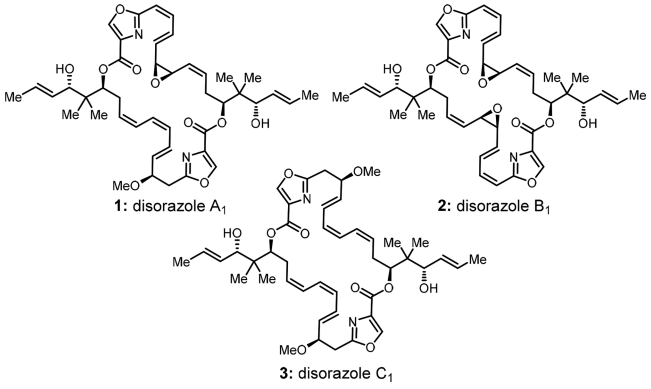


Figure 1. Molecular structures of natural disorazoles A_1 (**1**), B_1 (**2**), and C_1 (**3**).

RESULTS AND DISCUSSION

The design of the targeted oxazole-containing disorazole analogues **4** and **6** was meant to probe the effect of the cyclopropyl substitution for the epoxide structural motif(s) of disorazoles A_1 and B_1 on their biological activities. Their thiazole counterparts, analogues **4** and **6**, were targeted in order to obtain further structure−activity relationships (SARs), namely the effect of replacing, the epoxide and oxazole moieties, with cyclopropyl and thiazole structural motifs, respectively.

Figure 2 indicates, in retrosynthetic format, the general strategies and key building blocks planned for the synthesis of

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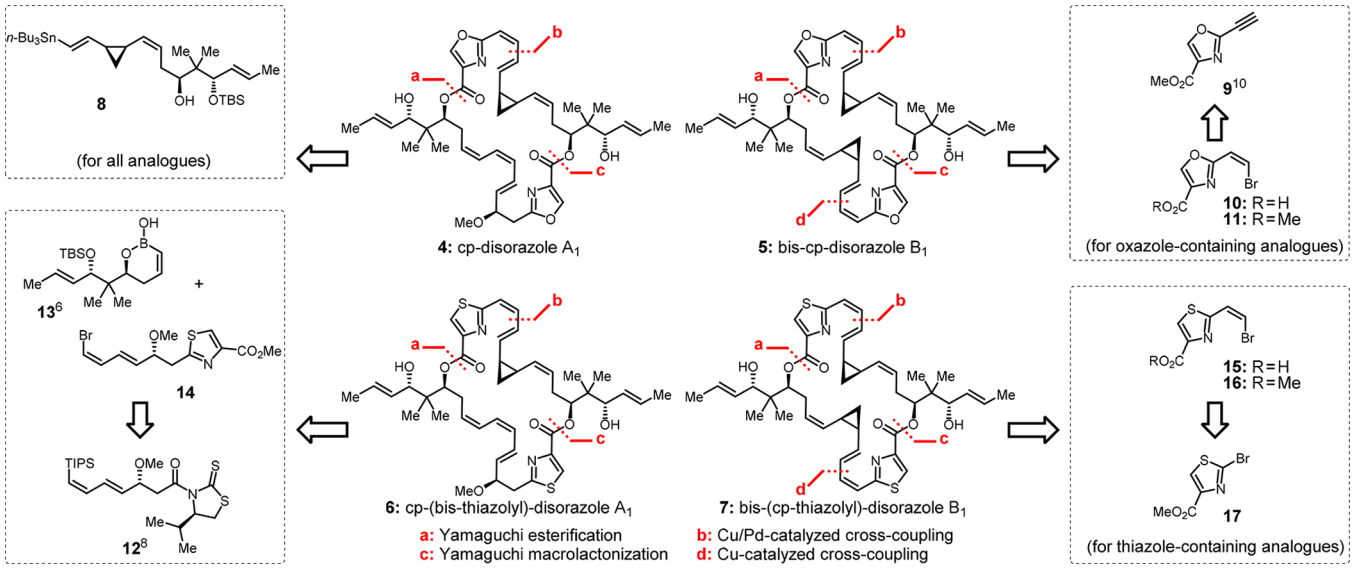

Figure 2. Molecular structures of synthesized designed cyclopropyl and bis-thiazolyl disorazole analogues **4**–**7**, retrosynthetic strategic disconnections (**a**–**d**), defined required building blocks (**8**–**17**) for their synthesis, and key reactions (**a**–**d**) for their assembly.

analogues **4**–**7**, as inspired from our total syntheses of the naturally occurring disorazoles A_1 and B_1 (**1** and **2**, respectively).[8] Thus, cp-disorazole A_1 analogue **4** was planned to be derived from fragments **8**, **30**,[5h,8] and **10**, the latter expected to emerge from appropriate elaboration of oxazole derivative **9**, while its thiazole counterpart (**6**) was traced back to building blocks **13** and **14**, with the latter projected to be generated from thioxothiazolidinyl derivative **12**,[8] as outlined in Figure 2. The bis-cyclopropyl analogues of disorazole B_1 (**5** and **7**) were similarly traced back to building blocks **10** and **11**, both to be derived from **9** (for **5**) and **15** and **16** (for **7**), the latter two building blocks expected to be derived from thiazole derivative **17**, as depicted in Figure 2. The key reactions for assembling these building blocks to the macrocyclic scaffolds of the targeted analogues were (a) Yamaguchi esterification; (b) Cu/Pd-catalyzed cross-coupling; (c) Yamaguchi macrolactonization; and (d) Cu-catalyzed cross-coupling as designated in Figure 2 with the strategic bond disconnections in red.

Synthesis of cp-Disorazole A_1 Analogue 4. The required intermediates for the synthesis of analogue **4**, building blocks **10** and **11** (Figure 2) were synthesized according to previously reported[6c,7b] and standard procedures, whereas the cyclopropyl-containing fragment **8** (Figure 2) was constructed in enantiomerically pure form as shown in Scheme 1. Thus, racemic *cis*-iodocyclopropyl derivative (±)-**18**[9] was coupled with TIPS-acetylene (**19**) under the influence of $PdCl_2(MeCN)_2$ cat., X-Phos, and Cs_2CO_3 to afford hydroxymethyl propyl acetylene (±)-**20** (95% yield), whose DMP oxidation led to aldehyde (±)-**21** (92% yield). The latter was oxidized further ($NaClO_2$, NaH_2PO_4, 2-methyl-2-butene) to carboxylic acid (±)-**22** (quant yield), coupling of which with (*R*)-BINOL (DCC, DMAP cat.) afforded expected mono-BINOL ester diastereoisomer **23** and its (1*R*,2*S*)-isomer (**23a**, not shown). Chromatographic separation of these esters furnished pure diastereoisomers (1*S*,2*R*)-**23** (45% yield) and (1*R*,2*S*)-**23a** (47% yield). The absolute configuration of (1*S*,2*R*)-**23** was confirmed by conversion of the corresponding alcohol [i.e., (−)-**20**] to a known compound[5g] and comparison of its spectroscopic and optical rotation data (see the Experimental Section for details). Cleavage of the BINOL moiety from the desired diastereoisomer (i.e., **23**) with DIBAL-H, followed by DMP oxidation of the resulting primary alcohol, led to aldehyde (−)-**21** in 92% overall yield. This aldehyde was reacted with the ylide derived from TMS,TBS-bis-protected iodide **24**[8] via the corresponding phosphonium salt (PPh_3, *i*-Pr_2EtN, 90 °C) through the action of LiHMDS (DMPU, −78 °C) to afford selectively (*Z*,*E*)-bis-olefin **25** in 83% overall yield. Selective removal of the TMS group from **25** (aq HCl, quant yield) led to hydroxy compound **26**, whose exposure to AgF gave terminal acetylene **27** (85% yield). The latter was brominated (NBS, $AgNO_3$, 84% yield), and the resulting acetylenic bromide (**28**) was selectively stannylated [*n*-Bu_3SnH, $PdCl_2(PPh_3)_2$ cat., *i*-Pr_2EtN] to afford desired (*E*)-vinylstannane **8** in 80% yield as shown in Scheme 1.

With cyclopropyl building block **8** in hand, the completion of the synthesis of cp-disorazole A_1 analogue **4** was initiated with building block **9**[10] and proceeded as summarized in Scheme 2. Thus, acetylenic methyl ester **9**[10] was hydrolyzed (LiOH) to carboxylic acid **29** (96% yield), whose reaction with LiBr and LiOAc in AcOH at 70 °C produced, stereoselectively, carboxylic acid (*Z*)-vinyl bromide **10** (91% yield). The latter was coupled with our previously synthesized hydroxy fragment **30**[5h,8] in the presence of trichlorobenzoyl chloride (TCBC), DMAP, and Et_3N to afford vinyl bromide methyl ester **31** in 88% yield. Palladium-catalyzed cross-coupling [$Pd_2(dba)_3$, $AsPh_3$, CuI, 36% yield] of the latter with vinylstannane fragment **8** (see Scheme 1 for preparation) led to advanced intermediate methyl ester **32**, which upon methyl ester hydrolysis [$Ba(OH)_2$, $MeOH/H_2O$] and Yamaguchi macrocyclization of the resulting hydroxy acid (TCBC, Et_3N, DMAP) furnished protected precursor **33** in 28% overall yield for the two steps. Desilylation of the latter under previously reported conditions (H_2SiF_6) in a similar case[5h] completed the synthesis of the targeted cp-disorazole A_1 analogue **4** in 45% yield.

Synthesis of Bis-cyclopropyl Disorazole B_1 Analogue 5. The bis-cp-disorazole B_1 analogue **5** was synthesized from cyclopropyl vinyl stannane **8** (see Scheme 1 for preparation)

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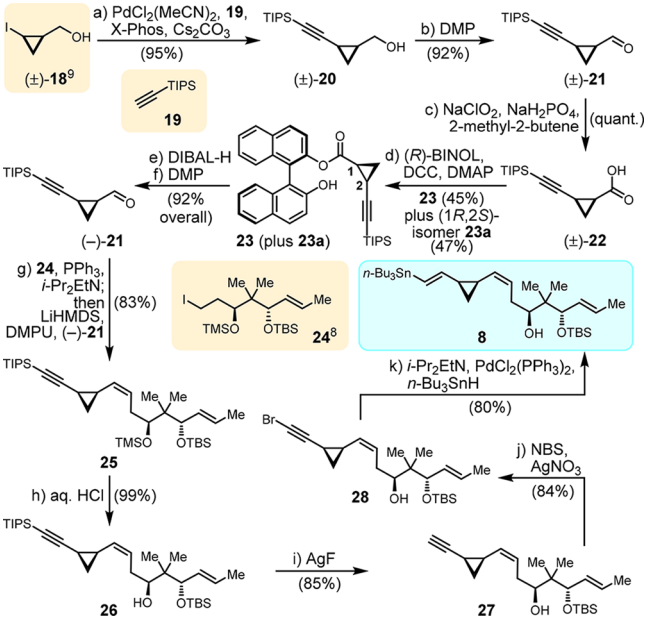
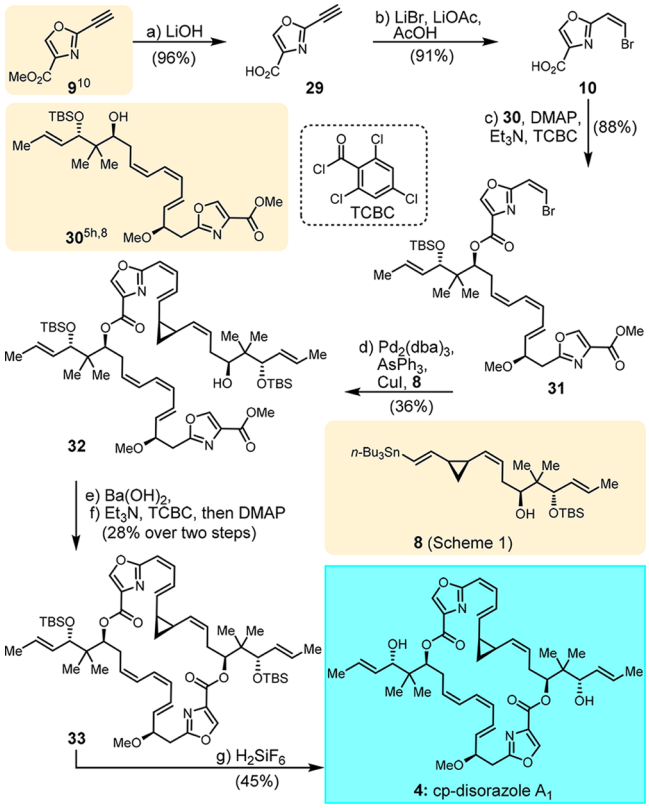
Scheme 1. Synthesis of cp-Disorazole A_1 Building Block Vinyl Stannane 8[a]



[a]Reagents and conditions: (a) Cs_2CO_3 (2.5 equiv), X-Phos (0.06 equiv), $PdCl_2(MeCN)_2$ (0.02 equiv), (±)-**18** (1.0 equiv), **19** (1.5 equiv), THF, 60 °C, 20 h, 95%; (b) DMP (1.1 equiv), CH_2Cl_2, 1 h, 92%; (c) $NaClO_2$ (4.0 equiv), NaH_2PO_4 (8.0 equiv), 2-methyl-2-butene (20 equiv), *t*-BuOH/THF/H_2O (3:3:1, *v*/*v*/*v*), 23 °C, quant; (d) (*R*)-BINOL (3.0 equiv), DCC (1.1 equiv), DMAP (0.8 equiv), 0 to 23 °C, 16 h, 45% (**23**) plus 47% of the corresponding (1*R*,2*S*)-diastereoisomer; (e) DIBAL-H (3.2 equiv), Et_2O, −78 to 23 °C, 3 h, 94%; (f) DMP (1.1 equiv), CH_2Cl_2, 0 to 23 °C, 1 h, 98%; (g) **24** (1.0 equiv), PPh_3 (1.75 equiv), *i*-Pr_2EtN (7.0 equiv), 90 °C, 16 h; then −78 °C, LiHMDS (1.05 equiv), DMPU (0.6 equiv), (−)-**21** (1.1 equiv), THF, 15 min; then 23 °C for 1 h, 83%; (h) Et_2O/4 M aq HCl (1:1, *v*/*v*), 23 °C, 16 h, 99%; (i) AgF (1.3 equiv), MeOH, 23 °C, 0.5 h, 85%; (j) NBS (1.2 equiv), $AgNO_3$ (0.2 equiv), acetone, 23 °C, 84%; (k) $PdCl_2(PPh_3)_2$ (0.05 equiv), *i*-Pr_2EtN (4.0 equiv), *n*-Bu_3SnH (2.2 equiv), THF, −78 °C, 80%. Abbreviations: X-Phos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl, DMP = Dess–Martin periodinane, (*R*)-BINOL = (*R*)-[1,1′-binaphthalene]-2,2′-diol.

Scheme 2. Completion of the Synthesis of cp-Disorazole A_1 (4)[a]



[a]Reagents and conditions: (a) LiOH (1.5 equiv), H_2O/THF (4:3, *v*/*v*), 23 °C, 1.5 h, 96%; (b) LiBr (1.5 equiv), LiOAc (4.5 equiv), AcOH, 70 °C, 16 h, 91%; (c) **30** (1.2 equiv), Et_3N (6.0 equiv), DMAP (8.0 equiv), TCBC, toluene, 0 to 23 °C, 3 h, 88%; (d) **8** (1.3 equiv), $Pd_2(dba)_3$ (0.5 equiv), $AsPh_3$ (2.0 equiv), CuI (4.0 equiv), DMF, 23 °C, 3 h, 36%; (e) $Ba(OH)_2$ (30 equiv) in MeOH/H_2O (3:2, *v*/*v*), THF, 0 to 23 °C, 3 h; (f) TCBC (10 equiv), Et_3N (11 equiv), toluene, 23 °C, 1 h, then DMAP (4.0 equiv), 40 °C, 24 h, 28% from **32**; (g) H_2SiF_6 (65 equiv), MeOH, 4 °C, 120 h; then 23 °C, 24 h, 45%. Abbreviations: TCBC = 2,4,6-trichlorobenzoyl chloride.

and the previously synthesized building blocks **10** (Scheme 1) and **11**[6c,7b] as shown in Scheme 3. Thus, stannane **8** was coupled with vinyl bromide methyl ester **11**[6c,7b] in the presence of CuTC in NMP to afford hydroxy methyl ester **34** (77% yield), which reacted with carboxylic acid vinyl bromide **10** (Scheme 1; TCBC, Et_3N, DMAP) to give vinyl bromide ester **35** in 68% yield. To vinyl bromide **35** was attached the second cyclopropyl-containing domain through CuTC-facilitated coupling with vinyl stannane fragment **8**, leading to hydroxy methyl ester **36** (72% yield). The latter was subjected to the action of $Ba(OH)_2$, resulting in methyl ester hydrolysis. The so-obtained hydroxy acid was treated with TCBC in the presence of Et_3N, and then DMAP, to furnish bis-TBS ether **37** (28% overall yield from **36**). Finally, treatment of **37** with TASF in the presence of H_2O (14 equiv) at 40 °C led to the coveted bis-cyclopropyl disorazole B_1 analogue **5** in 98% yield as shown in Scheme 3.

Synthesis of cp-(Bis-thiazolyl)disorazole A_1 Analogue 6. The thiazole analogues **6** and **7** were targeted for synthesis in order to probe the effect of the thiazole moieties on the biological profile of the molecules. Requiring building blocks **8** (Scheme 1) and **14** and **15** (Scheme 4), the synthesis of cp-(bis-thiazolyl)-disorazole A_1 analogue **6** is summarized in Scheme 4 (construction of building blocks **14** and **15**) and Scheme 6 (completion of the synthesis). Thus, commercially available thiazole bromide **17** (Scheme 4A) was coupled with TIPS-acetylene (**19**) by treatment with catalytic amounts of $Pd(PPh_3)_4$ and CuI in the presence of Et_3N to afford the corresponding TIPS-protected acetylenic product, from which the TIPS group was removed (TBAF), leading to terminal acetylene **38**, in 85% overall yield. Hydrolysis of the methyl ester within **38** (aq LiOH) afforded terminal acetylene carboxylic acid **39** (99% yield), whose hydrobromination was achieved selectively employing LiBr and LiOAc in AcOH at 90 °C, furnishing the desired thiazole (*Z*)-vinyl bromide [**15**, 75% yield, (*Z*)/(*E*) ≥ 20:1]. Processing acetylenic methyl ester **38** through the same hydrobromination conditions as for **39** as indicated in Scheme 4A furnished the corresponding (*Z*)-vinyl bromide methyl ester (**16**) together with small amounts of its (*E*)-isomer, which was removed chromatographically, the former (i.e., **16**) being required for the synthesis of bis(cp-thiazolyl)disorazole B_1 analogue **7** to be discussed below (see Scheme 6). Required for the synthesis of **6** building block **14**

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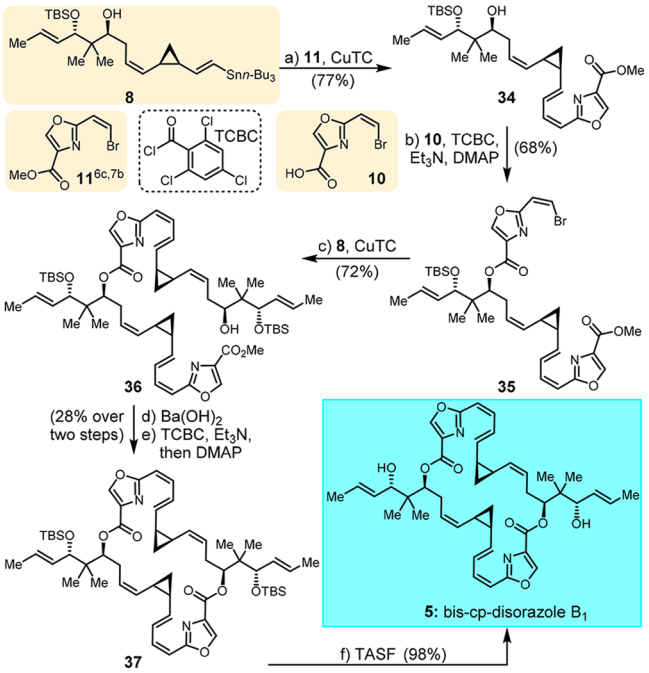
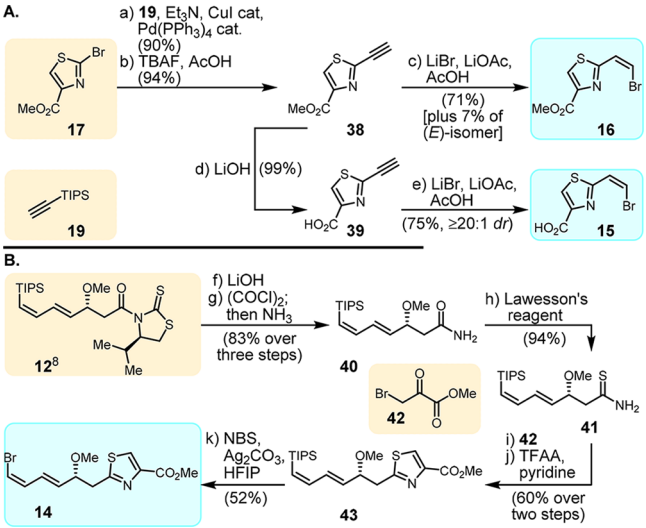
Scheme 3. Synthesis of Bis-cp-disorazole B_1 Analogue 5[a]



[a]Reagents and conditions: (a) **8** (1.0 equiv), **11** (1.0 equiv), CuTC (1.5 equiv), NMP, 23 °C, 1 h, 77%; (b) **34** (1.0 equiv), **10** (2.0 equiv), Et_3N (6.0 equiv), 23 °C, 5 min; then DMAP (8.0 equiv), TCBC (6.0 equiv), 23 °C, 1.5 h, 68%; (c) **8** (1.5 equiv), CuTC (1.5 equiv), NMP, 23 °C, 1 h, 72%; (d) $Ba(OH)_2$ (30 equiv) in MeOH/H_2O (3:2, *v*/*v*), THF, 23 °C, 3 h; (e) TCBC (10 equiv), Et_3N (11 equiv), 23 °C, toluene, 1 h; then dilution with toluene to 7.5 mM, then DMAP (4.0 equiv), 40 °C, 29 h, 28% from **36**; (f) TASF (5.0 equiv), H_2O (14 equiv), DMF, 40 °C, 48 h, 98%.

Scheme 4. Syntheses of cp-(Bis-thiazolyl)disorazole Building Blocks 14−16[a]



[a]Reagents and conditions: (A) (a) **19** (5.0 equiv), $Pd(PPh_3)_4$ (0.05 equiv), CuI (0.05 equiv), DMF/Et_3N (1:1, *v*/*v*), 60 °C, 16 h, 90%; (b) TBAF (2.0 equiv), AcOH (4.0 equiv), THF, 0 °C, 1 h, 94%; (c) LiBr (1.5 equiv), LiOAc (4.5 equiv), AcOH, 90 °C, 16 h, 71% plus 7% (*E*)-isomer; (d) LiOH (1.5 equiv), THF/H_2O (5:4, *v*/*v*), 23 °C, 1 h, 99%; (e) LiBr (1.5 equiv), LiOAc (4.5 equiv), AcOH, 100 °C, 16 h, 75%, ≥20:1 *dr*; (B) (f) LiOH (1.5 equiv), THF/H_2O (25:6, *v*/*v*), 0 to 23 °C, 16 h; (g) $(COCl)_2$ (3.0 equiv), DMF (cat.), Et_2O, 0 to 23 °C, 1 h; then NH_3 (7 M in MeOH, 8.0 equiv), CH_2Cl_2, 0 to 23 °C, 16 h, 83% from **12**; (h) Lawesson's reagent (0.70 equiv), THF, 23 °C, 1 h, 94%; (i) **42** (1.4 equiv), acetone, −10 °C, 2 h; (j) TFAA (1.3 equiv), pyridine (2.5 equiv), CH_2Cl_2, −30 to 23 °C, 2 h, 60% from **41**; (k) NBS (1.25 equiv), Ag_2CO_3 (1.02 equiv), HFIP, 0 °C, 1.5 h, 52%. Abbreviations: HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol, Lawesson's reagent = 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-dithione.

was prepared from TIPS-diene thioxothiazolidine **12**[8] as shown in Scheme 4B. Thus, **12** was hydrolyzed to its carboxylic counterpart (aq LiOH) and thence converted to the corresponding acid chloride [$(COCl)_2$], whose treatment with NH_3 led to primary amide **40** in 83% overall yield for the three steps. This amide was then transformed to the corresponding thioamide (**41**, Lawesson's reagent, 94% yield), which served well as a precursor for the targeted thiazole building block (i.e., **14**) as shown in Scheme 4B. Thus, reaction of **41** with methyl bromopyruvate (**42**) and TFAA/pyridine (60% overall yield for the two steps), followed by replacement of the TIPS group of the resulting thiazole product with a bromide residue (NBS, Ag_2CO_3, HFIP, 52% yield), furnished the required thiazole bromodiene building block **14** via **43**.

With building block **14** readily available, its advancement to the targeted cp-(bis-thiazolyl)disorazole A_1 analogue **6** proceeded as summarized in Scheme 5. Thus, **14** was joined with our previously reported boronic acid fragment **13**[8] through a Suzuki cross-coupling reaction [$Pd(dppf)Cl_2$, Tl_2CO_3, 59% yield] to furnish extended fragment **44**, with which thiazole vinyl bromide carboxylic acid **15** was reacted under esterification conditions (TCBC, Et_3N, DMAP) to afford ester vinyl bromide **45** in 87% yield. The latter was coupled with cyclopropyl vinyl stannane **8** (see Scheme 1 for preparation) through a palladium-catalyzed cross-coupling [$Pd_2(dba)_3$, CuI, $AsPh_3$] leading to advanced methyl ester intermediate **46** in 94% yield. Selective methyl ester hydrolysis within **46** [$Ba(OH)_2$], followed by Yamaguchi macrolactonization (TCBC, Et_3N, then DMAP) of the resulting seco acid then led to bis-TBS protected precursor **47** (41% overall yield for the two steps), from which the targeted cyclopropyl bis-thiazole disorazole A_1 analogue **6** was generated by exposure to H_2SiF_6[5h] in MeOH (43% yield).

Synthesis of Bis(cp-thiazolyl)disorazole B_1 Analogue 7. The bis(cp-thiazolyl)disorazole B_1 analogue **7** was prepared from fragments **8** (Scheme 1) and **15** and **16** (Scheme 4) as depicted in Scheme 6. Thus, vinyl stannane **8** and vinyl bromide **16** were efficiently coupled under the influence of CuTC in NMP to afford hydroxy methyl ester **48** (84% yield), which reacted smoothly with carboxylic acid **15** under Yamaguchi esterification conditions (TCBC, Et_3N, DMAP, 90% yield), leading to vinyl bromide intermediate **49**. The latter was coupled with vinyl stannane fragment **8** in the presence of CuTC in NMP to afford advanced intermediate **50** in 92% yield. Selective methyl ester hydrolysis within **50** [$Ba(OH)_2$], followed by sequential Yamaguchi macrolactonization (TCBC, Et_3N, then DMAP, 24% yield for the two steps) and TASF-induced global desilylation, generated targeted bis(cp-thiazolyl)disorazole B_1 analogue **7** in 46% yield as shown in Scheme 6. Parenthetically, it should be noted that Stille coupling reactions with stannane **8** were performed either under $Pd_2(dba)_3$/CuI/$AsPh_3$ or CuTC conditions aiming for optimal yields due to the capricious behavior of the different reactants and rather labile character of the

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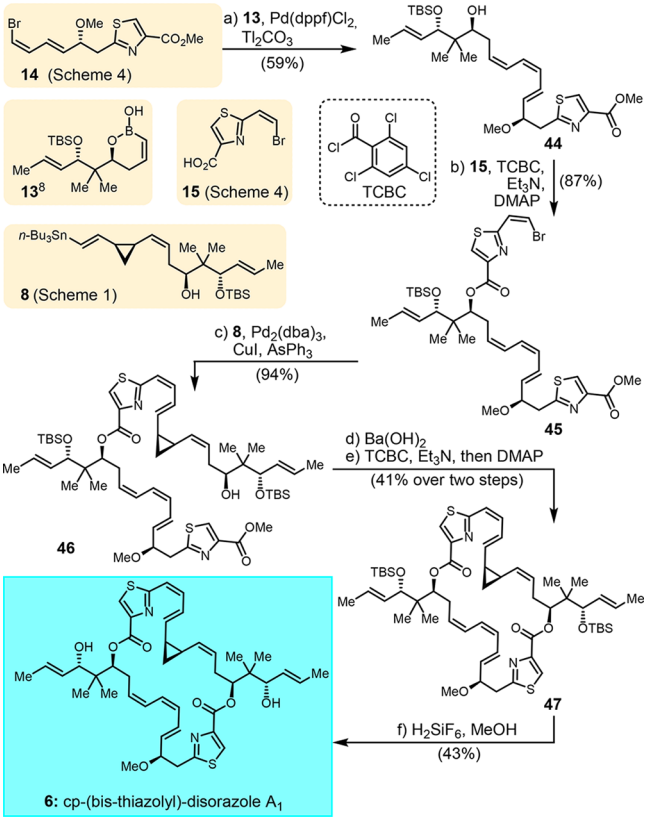
Scheme 5. Completion of the Synthesis of cp-(Bis-thiazolyl)disorazole A_1 (6)[a]



[a]Reagents and conditions: (a) **13** (1.4 equiv), $Pd(dppf)Cl_2$ (0.10 equiv), Tl_2CO_3 (5.0 equiv), 25 °C, THF/H_2O (3:1, *v*/*v*), 16 h, 59%; (b) **15** (1.2 equiv), TCBC (3.0 equiv), DMAP (8.0 equiv), Et_3N (6.0 equiv), toluene, 0 to 23 °C, 3 h, 87%; (c) **8** (1.3 equiv), $Pd_2(dba)_3$ (0.5 equiv), CuI (4.25 equiv), $AsPh_3$ (2.0 equiv), DMF, 23 °C, 3 h, 94%; (d) $Ba(OH)_2$ (30 equiv) in $MeOH/H_2O$ (3:2, *v*/*v*), THF, 23 °C, 3 h; (e) TCBC (10 equiv), Et_3N (11 equiv), toluene, 23 °C, 1 h, then DMAP (4.0 equiv), 30 °C, 19 h, 41% from **45**; (f) H_2SiF_6 (75 equiv), MeOH, 0 to 23 °C, 17 h; then 23 °C, 24 h, 43%.

stannane component. Further investigations with these reactions are in progress and will be reported in due course.

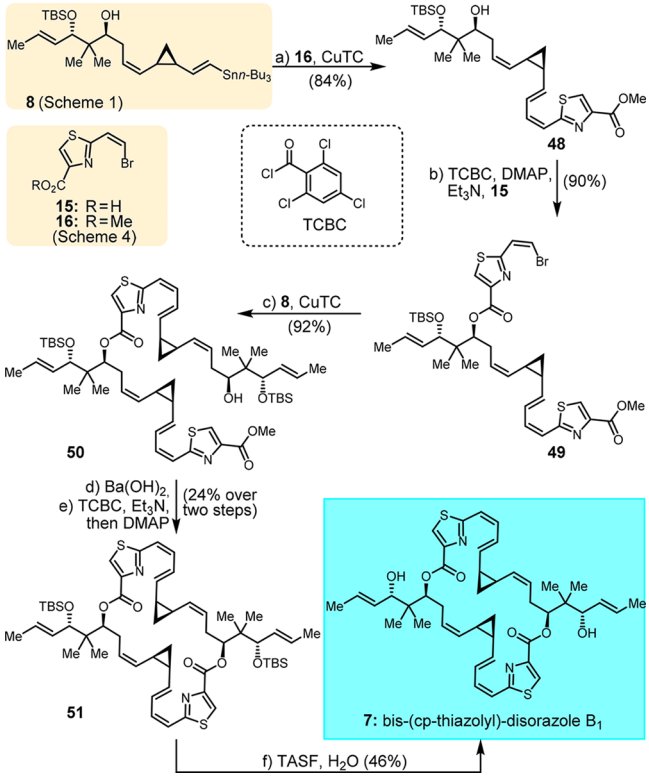
CONCLUSIONS

The described synthetic work renders a number of cyclopropyl disorazoles A_1 and B_1 analogues for biological investigations and sets the stage for further studies involving molecular design, synthesis, and biological evaluation within the disorazole family of compounds. Such studies may provide structurally novel and functionally highly potent cytotoxic compounds as potential payloads for antibody–drug conjugates for personalized and targeted cancer therapies.

EXPERIMENTAL SECTION

General Methods. All reactions were carried out under an argon atmosphere with dry solvent under anhydrous conditions, unless otherwise noted. Dry acetonitrile (MeCN), dimethylformamide (DMF), dichloromethane (CH_2Cl_2), tetrahydrofuran (THF), and toluene were obtained by passing commercially available predried, oxygen-free formulations through activated alumina columns. Anhydrous benzene, acetone, chloroform ($CHCl_3$), methanol (MeOH), and ethanol (EtOH) were purchased from commercial suppliers and stored under argon. Yields refer to chromatographically

Scheme 6. Synthesis of Bis(cp-thiazolyl)disorazole B_1 (7)[a]



[a]Reagents and conditions: (a) **16** (1.0 equiv), CuTC (1.5 equiv), NMP, 23 °C, 1 h, 84%; (b) **15** (2.0 equiv), TCBC (3.0 equiv), Et_3N (6.0 equiv), DMAP (8.0 equiv), toluene, 23 °C, 1.5 h, 90%; (c) **8** (1.0 equiv), CuTC (1.5 equiv), NMP, 23 °C, 1 h, 92%; (d) $Ba(OH)_2$ (30 equiv) in $MeOH/H_2O$ (3:2, *v*/*v*), THF, 23 °C, 5 h; (e) TCBC (10 equiv), Et_3N (11 equiv), 23 °C, toluene, 1 h; then dilution with toluene to 7.5 mM, then DMAP (4.0 equiv), 40 °C, 29 h, 24% for the two steps from **50**; (f) TASF (5.0 equiv), H_2O (14 equiv), DMF, 40 °C, 48 h, 46%.

and spectroscopically (^1H NMR) homogeneous material, unless otherwise stated. Reagents were purchased at the highest commercial quality and were used without further purification, unless otherwise noted. Reactions were monitored by thin-layer chromatography (TLC) carried out on S-2 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and an ethanolic solution of phosphomolybdic acid, an aqueous solution of cerium sulfate, an ethanolic solution of anisaldehyde or a basic aqueous solution of potassium permanganate as developing agents. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. NMR spectra were recorded on a Bruker DRX-600 instrument and calibrated using residual undeuterated solvent ($CDCl_3$, δ_H = 7.26 ppm, δ_C = 77.16 ppm; C_6D_6, δ_H = 7.16 ppm, δ_C = 128.06 ppm, CD_3OD, δ_H = 4.87 ppm, δ_C = 49.00 ppm; DMSO-d_6, δ_H = 2.50 ppm, δ_C = 39.52 ppm; CD_3CN, δ_H = 1.94 ppm, δ_C = 1.32 and 118.26) as an internal reference. The following abbreviations were used to designate multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, br = broad. Infrared (IR) spectra were recorded on a Perkin-Elmer 100 FT-IR spectrometer. High-resolution mass spectra (HR-MS) were recorded on an Agilent ESI-TOF (time-of-flight) mass spectrometer using MALDI (matrix-assisted laser desorption ionization) or ESI (electrospray ionization). Optical rotations were recorded on a Schmidt+Haensch POLARTRONIC M100 polarimeter at 589 nm, using 100 mm cells and the solvent and concentration indicated [in units of 10^{-1} (deg cm^2 g^{-1})].

Experimental Procedures and Characterization Data. *cis-{2-[(Triisopropylsilyl)ethynyl]cyclopropyl}methanol [(±)-20].* A dry round-bottom flask equipped with a stir bar was charged with

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Cs_2CO_3 (6.05 g, 18.56 mmol, 2.50 equiv), and the solid was flame-dried under reduced pressure. Once the solid was cooled back to 23 °C, $PdCl_2(MeCN)_2$ (39.0 mg, 0.148 mmol, 2 mol %), X-Phos (0.212 g, 0.445 mmol, 0.06 equiv), and THF (37.0 mL) were added in this order. The mixture was stirred for 5 min while being degassed with argon, a solution of cyclopropyl iodide (±)-**18** (1.47 g, 7.42 mmol, 1.00 equiv) in THF (2 mL) was added in one portion, and degassing was continued for 5 min before the addition of TIPS-acetylene (**9**; 2.49 mL, 11.1 mmol, 1.50 equiv) to the mixture. The reaction vessel was capped and heated at 60 °C for 20 h. Then the mixture was filtered through a pad of Celite, and the pad was washed with CH_2Cl_2 (20 mL). The crude residue was purified by flash column chromatography (SiO_2, hexanes/EtOAc 9:1, *v*/*v* → 17:3, *v*/*v* → 7:3, *v*/*v*) to yield alcohol (±)-**20** (1.78 g, 7.05 mmol, 95% yield) as a dark oil. Spectral data and the procedure employed to synthesize this material were identical to those reported in the literature.[9]

(±)-**20**: R_f = 0.27 (hexanes/EtOAc 8:2, *v*/*v*); IR (film) ν_{max} = 3349, 2942, 2865, 2165, 1463, 1044, 883, 676 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.93 (dd, *J* = 11.9, 5.2 Hz, 1 H), 3.62 (dd, *J* = 11.9, 8.8 Hz, 1 H), 1.58 (s, 2 H), 1.54 (td, *J* = 8.2, 5.4 Hz, 1 H), 1.41 (qt, *J* = 8.3, 5.5 Hz, 1 H), 1.11−0.97 (m, 21 H), 0.67 (q, *J* = 5.4 Hz, 1 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 108.5, 78.7, 64.3, 21.2, 18.8, 13.8, 11.4, 5.6 ppm; HR-MS (ESI-TOF) calcd for $C_{15}H_{29}OSi^+$ $[M + H]^+$ 253.1982, found 253.1976.

*cis-2-[(Triisopropylsilyl)ethynyl]cyclopropane-1-carbaldehyde [(±)-**21**].* To a stirred solution of cyclopropyl alcohol (±)-**20** (0.360 g, 1.46 mmol, 1.0 equiv) in CH_2Cl_2 (7.1 mL) was added Dess−Martin periodinane (0.665 g, 1.56 mmol, 1.1 equiv) in one portion. The reaction was followed by TLC and showed full conversion after 1 h. The reaction was quenched by addition of a mixture of a saturated aqueous solution of $NaHCO_3$ and a saturated aqueous solution of $Na_2S_2O_3$ (20 mL, 1:1, *v*/*v*). The resulting heterogeneous mixture was vigorously stirred for 0.5 h before the phases were separated. The aqueous phase was extracted three times with CH_2Cl_2 (3 × 20 mL), and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, hexanes/EtOAc 19:1, *v*/*v*) to yield (±)-21 (0.332 g, 1.30 mmol, 92% yield) as a colorless oil.

(±)-21: R_f = 0.25 (hexanes/EtOAc 9:1, *v*/*v*); IR (film) ν_{max} = 2943, 2865, 2171, 1713, 1463, 882, 782 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.19 (d, *J* = 6.8 Hz, 1 H), 2.06 (td, *J* = 8.2, 6.5 Hz, 1 H), 1.91 (tt, *J* = 8.1, 6.1 Hz, 1 H), 1.58−1.52 (m, 1 H), 1.48 (td, *J* = 8.3, 5.1 Hz, 1 H), 1.05−0.97 (m, 21 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 200.7, 104.5, 81.7, 28.4, 18.7, 15.3, 11.3, 10.0 ppm; HR-MS (CI): calcd for $C_{15}H_{26}OSi^+$ $[M + H]^+$: 250.1753, found 250.1745.

*cis-2-[(Triisopropylsilyl)ethynyl]cyclopropane-1-carboxylic Acid [(±)-**22**].* To a stirred solution of aldehyde (±)-**21** (0.500 g, 2.00 mmol, 1.0 equiv) in a mixture of *t*-BuOH/THF/H_2O (20 mL, 3:3:1, *v*/*v*/*v*) were added NaH_2PO_4 (2.49 g, 16.0 mmol, 8.0 equiv), 2-methylbut-2-ene (4.70 mL, 3.11 g, 40.0 mmol, 20.0 equiv), and $NaClO_2$ (720 mg, 8.00 mmol, 4.0 equiv), and the reaction mixture was stirred at 23 °C for 15 min. Then the mixture was diluted with water (100 mL) and extracted with EtOAc (3 × 200 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the crude residue by flash column chromatography (SiO_2, hexanes/EtOAc 9:1, *v*/*v* → 7:3, *v*/*v*) yielded carboxylic acid (±)-**22** (0.532 g, 2.00 mmol, quant. yield).

(±)-**22**: R_f = 0.44 (hexanes/EtOAc 7:3, *v*/*v*); IR (film) ν_{max} = 2942, 2865, 2170, 1698, 1462, 1234, 883, 662 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.00−1.89 (m, 2 H), 1.45 (td, *J* = 6.6, 4.6 Hz, 1 H), 1.26 (td, *J* = 8.2, 4.6 Hz, 1 H), 1.05 (d, *J* = 5.7 Hz, 18 H), 1.04−0.98 (m, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 175.9, 104.5, 80.8, 21.5, 18.7, 15.4, 11.37, 11.35 ppm; HR-MS (ESI-TOF) calcd for $C_{15}H_{26}O_2SiNa^+$ $[M + Na]^+$ 289.1594, found 289.1582.

*(R)-2′-Hydroxy-1,1′-binaphthalen-2-yl (1S,2R)-2-[(triisopropylsilyl)ethynyl]cyclopropane-1-carboxylate (**23**).* To a stirred solution of carboxylic acid (±)-**22** (1.45 g, 5.44 mmol, 1.0 equiv) in CH_2Cl_2 (54 mL) were added DMAP (0.530 g, 4.34 mmol, 0.80 equiv) and (*R*)-BINOL (4.61 g, 16.1 mmol, 3.0 equiv), and the reaction mixture was stirred at 23 °C for 10 min. Then it was cooled to 0 °C and DCC (1.22 g, 5.91 mmol, 1.1 equiv) was added, after which the reaction mixture was allowed to warm to 23 °C over 0.5 h and was then stirred at 23 °C for 16 h. Subsequently, the reaction mixture was cooled to 0 °C, filtered through a fritted funnel, and concentrated under reduced pressure. Purification of the crude residue by flash column chromatography (SiO_2, hexanes/EtOAc 9:1, *v*/*v* → 7:3, *v*/*v*) yielded ester 23 (1.30 g, 2.45 mmol, 45% yield) and diastereomeric ester **23a** (1.36 g, 2.56 mmol, 47% yield) as waxy white solids.

23: R_f = 0.70 (hexanes/EtOAc 7:3, *v*/*v*); $[\alpha]_D^{25}$ = +93.0 (*c* = 1.0, $CHCl_3$); IR (film) ν_{max} = 3504, 2941, 2864, 2166, 1748, 1621, 1382, 1209, 1140, 1118, 745 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.9 Hz, 1 H), 7.97 (d, *J* = 8.2 Hz, 1 H), 7.91 (d, *J* = 8.9 Hz, 1 H), 7.86 (d, *J* = 8.1 Hz, 1 H), 7.53−7.47 (m, 1 H), 7.42 (d, *J* = 8.9 Hz, 1 H), 7.36−7.31 (m, 3 H), 7.27−7.25 (m, 1H) 7.24 (dd, *J* = 9.8, 8.4 Hz, 1 H), 7.05 (d, *J* = 8.4 Hz, 1 H), 5.37 (s, 1 H), 1.86 (td, *J* = 8.6, 7.0 Hz, 1 H), 1.72 (td, *J* = 8.1, 6.2 Hz, 1 H), 1.33 (td, *J* = 6.6, 4.8 Hz, 1 H), 1.20−1.12 (m, 1 H), 1.10−0.99 (m, 21 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.7, 152.1, 148.3, 133.74, 133.68, 132.4, 130.6, 130.4, 129.2, 128.4, 128.1, 127.5, 126.8, 126.3, 125.9, 124.7, 123.6, 123.2, 122.7, 118.7, 114.4, 104.4, 80.9, 21.2, 18.8, 15.3, 11.5, 11.4 ppm; HR-MS (ESI) calcd for $C_{35}H_{38}O_3SiNa^+$ $[M + Na]^+$ 557.2482, found 557.2486.

23a: R_f = 0.59 (hexanes/EtOAc 7:3, *v*/*v*); IR (film) ν_{max} = 3448, 2942, 2892, 2864, 2167, 1758, 1463, 1383, 1214, 1141, 1119 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.9 Hz, 1 H), 7.97 (d, *J* = 8.2 Hz, 1 H), 7.90 (d, *J* = 8.9 Hz, 1 H), 7.85 (dd, *J* = 8.2, 1.2 Hz, 1 H), 7.53−7.47 (m, 2 H), 7.36−7.30 (m, 3 H), 7.28 (dd, *J* = 8.4, 1.1 Hz, 1 H), 7.22 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1 H), 7.06 (dd, *J* = 8.5, 1.0 Hz, 1 H), 5.07 (s, 1 H), 1.83 (td, *J* = 8.6, 7.2 Hz, 1 H), 1.67 (td, *J* = 8.2, 6.2 Hz, 1 H), 1.10−1.04 (m, 23 H), 0.93 (td, *J* = 8.4, 4.7 Hz, 1 H), 0.88 (ddd, *J* = 7.2, 6.2, 4.7 Hz, 1 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.8, 151.7, 148.2, 133.7, 133.6, 132.3, 130.40, 130.37, 129.1, 128.4, 128.0, 127.5, 126.8, 126.3, 125.9, 124.9, 123.6, 122.8, 122.6, 118.2, 114.1, 104.6, 81.5, 21.2, 18.8, 15.6, 11.5, 11.4 ppm; HR-MS (ESI) calcd for $C_{35}H_{38}O_3SiNa^+$ $[M + Na]^+$ 557.2482, found 557.2485.

*{(1S,2R)-2-[(Triisopropylsilyl)ethynyl]cyclopropyl}methanol [(−)-**20**].* To a stirred solution of binol ester **23** (1.00 g, 1.87 mmol, 1.0 equiv) in Et_2O (9.4 mL), cooled to −78 °C, was added DIBAL-H (5.98 mL, 1 M in hexane, 5.98 mmol, 3.2 equiv) dropwise, and the reaction mixture was allowed to warm to 23 °C over 3 h. The reaction was quenched following the Fieser method: the mixture was cooled to 0 °C, and water (0.24 mL) was added dropwise, after which the ice bath was removed and a 15% aqueous solution of NaOH (0.24 mL) was added dropwise followed by water (0.60 mL). The resulting mixture was stirred for 0.5 h and filtered through a pad of Celite. Subsequently, the filter cake was washed with Et_2O (3 × 10 mL). The filtrate was concentrated under reduced pressure, and the crude residue was purified by flash column chromatography (SiO_2, hexanes/EtOAc 9:1, *v*/*v*) to yield alcohol (−)-**20** (0.450 g, 1.75 mmol, 94% yield) as a colorless oil.

(−)-**20**: R_f = 0.27 (hexanes/EtOAc 8:2, *v*/*v*); $[\alpha]_D^{25}$ = −75.3 (*c* = 1.0, $CHCl_3$); IR (film) ν_{max} = 3349, 2942, 2865, 2165, 1463, 1044, 883, 676 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.93 (dd, *J* = 11.9, 5.2 Hz, 1 H), 3.62 (dd, *J* = 11.9, 8.8 Hz, 1 H), 1.82 (s, 1 H), 1.54 (td, *J* = 8.2, 5.4 Hz, 1 H), 1.41 (qt, *J* = 8.3, 5.5 Hz, 1 H), 1.11−0.97 (m, 21 H), 0.67 (q, *J* = 5.4 Hz, 1 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 108.5, 78.7, 64.3, 21.2, 18.8, 13.8, 11.5, 5.6 ppm; HR-MS (ESI-TOF) calcd for $C_{15}H_{29}OSi^+$ $[M + H]^+$ 253.1982, found 253.1976.

Confirmation of the Cp-Ring Stereochemistry. *{[(1R,2S)-2-{[(4-Methoxybenzyl)oxy]methyl}cyclopropyl]ethynyl}(tripropan-2-yl)silane (**S1**).* To a stirred solution of alcohol (−)-**20** (250 mg, 0.980 mmol, 1.0 equiv) and 4-methoxybenzyl 2,2,2-trichloroacetimidate (330 mg, 1.2 mmol, 1.2 equiv) in CH_2Cl_2 (4 mL) was added *p*-toluenesulfonic acid monohydrate (25 mg, 98 μmol, 0.10 equiv), and the reaction mixture was stirred at 23 °C for 24 h. Then water (15 mL) and CH_2Cl_2 (15 mL) were added, the phases were separated, the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL), and the

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combined organic phases were washed with brine (15 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Then, the crude residue was purified by flash column chromatography (SiO_2, hexanes/EtOAc 30:1, *v/v* → 20:1, *v/v*) to yield ether **S1** (230 mg, 0.620 mmol, 63% yield) as a colorless oil.

S1: R_f = 0.35 (hexanes/EtOAc 12:1, *v/v*); $[\alpha]_D^{25}$ = −33.8 (*c* = 1.0, $CHCl_3$); IR (film) ν_{max} = 2941, 2864, 2166, 1613, 1513, 1464, 1247, 1172, 1086, 1038, 883, 810, 677, 662 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.29−7.26 (m, 2 H), 6.88−6.85 (m, 2 H), 4.55 (d, *J* = 11.4 Hz, 1 H), 4.42 (d, *J* = 11.4 Hz, 1 H), 3.80 (s, 3 H), 3.66 (dd, *J* = 10.3, 6.9 Hz, 1 H), 3.55 (dd, *J* = 10.3, 6.8 Hz, 1 H), 1.58−1.53 (m, *J* = 5.5 Hz, 1 H), 1.36−1.29 (m, 1 H), 1.08−0.96 (m, 21 H), 0.56 (td, *J* = 5.9, 4.7 Hz, 1 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.3, 130.8, 129.5, 113.9, 108.3, 78.5, 72.8, 71.1, 55.4, 18.8, 18.2, 13.8, 11.5, 6.3 ppm; HR-MS (ESI-TOF) calcd for $C_{23}H_{37}O_2Si^+$ $[M + H]^+$ 373.2557, found 373.2546.

*1-({[(1S,2R)-2-Ethynylcyclopropyl]methoxy}methyl)-4-methoxybenzene (**S2**).* To a stirred solution of TIPS-alkyne **S1** (225 mg, 0.604 mmol, 1.0 equiv) in MeOH (7 mL) was added silver fluoride (100 mg, 0.785 mmol, 1.3 equiv), and the reaction mixture was stirred at 23 °C for 3 h. Then an aqueous HCl solution (1 M; 15 mL) and CH_2Cl_2 (15 mL) were added, the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were washed with brine (15 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Then, the crude residue was purified by flash column chromatography (SiO_2, hexanes/EtOAc 8:1, *v/v*) to yield alkyne **S2** (121 mg, 0.560 mmol, 93% yield) as a colorless oil.

S2: R_f = 0.29 (hexanes/EtOAc 9:1, *v/v*); $[\alpha]_D^{25}$ = −52.5 (*c* = 1.0, $CHCl_3$); IR (film) ν_{max} = 3290, 2858, 2120, 1612, 1513, 1465, 1302, 1247, 1173, 1084, 1036, 819 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.5 Hz, 2 H), 6.88 (d, *J* = 8.6 Hz, 2 H), 4.51 (s, 2 H), 3.80 (s, 3 H), 3.62−3.54 (m, 2 H), 1.81 (d, *J* = 2.2 Hz, 1 H), 1.50 (tdd, *J* = 8.0, 5.5, 2.2 Hz, 1 H), 1.40−1.30 (m, 1 H), 1.02 (td, *J* = 8.4, 4.7 Hz, 1 H), 0.59−0.54 (m, 1 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.3, 130.7, 129.6, 113.9, 84.2, 72.8, 70.6, 66.3, 55.4, 17.8, 12.8, 5.0 ppm; HR-MS (ESI-TOF) calcd for $C_{14}H_{16}O_2Na^+$ $[M + Na]^+$ 239.1043, found 239.1045.

*1-({[(1S,2S)-2-Ethenylcyclopropyl]methoxy}methyl)-4-methoxybenzene (**S3**).* To a stirred solution of alkyne **S2** (26.0 mg, 0.120 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added Schwartz's reagent [chloridobis(η^5-cyclopentadienyl)hydridozirconium; 62.0 mg, 0.240 mmol, 2.0 equiv], and the reaction mixture was stirred at 23 °C for 2 h. Then an aqueous HCl solution (1 M; 10 mL) and CH_2Cl_2 (10 mL) were added, the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, hexanes/EtOAc 15:1, *v/v* → 10:1, *v/v*) to yield alkene **S3** (23.8 mg, 0.109 mmol, 91% yield) as a colorless oil. Its physical data and sign of optical rotation matched those previously reported, confirming the compound's absolute configuration.[5g]

S3: R_f = 0.60 (hexanes/EtOAc 7:1, *v/v*); $[\alpha]_D^{25}$ = +24.8 (*c* = 1.2, CH_2Cl_2) [lit:[5g] $[\alpha]_D^{24}$ = +12.9 (*c* = 1.2, CH_2Cl_2)]; IR (film) ν_{max} = 3001, 2856, 2120, 1612, 1511, 1301, 1244, 1172, 1079, 1034, 897, 815 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.5 Hz, 2 H), 6.87 (d, *J* = 8.6 Hz, 2 H), 5.57 (ddd, *J* = 17.0, 10.3, 8.3 Hz, 1 H), 5.13 (ddd, *J* = 17.0, 1.9, 0.9 Hz, 1 H), 5.02−4.96 (m, 1 H), 4.49−4.40 (m, 2 H), 3.80 (s, 3 H), 3.51 (dd, *J* = 10.3, 6.5 Hz, 1 H), 3.34 (dd, *J* = 10.3, 8.0 Hz, 1 H), 1.63 (qd, *J* = 8.3, 5.6 Hz, 1 H), 1.35 (qt, *J* = 8.3, 6.1 Hz, 1 H), 0.95 (td, *J* = 8.3, 4.9 Hz, 1 H), 0.42 (q, *J* = 5.5 Hz, 1 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.3, 137.2, 130.8, 129.5, 115.0, 113.9, 72.5, 69.8, 55.4, 19.7, 18.3, 10.7 ppm; HR-MS (ESI-TOF) calcd for $C_{14}H_{18}O_2Na^+$ $[M + Na]^+$ 241.1199, found 241.1193.

*(1S,2R)-2-[(Triisopropylsilyl)ethynyl]cyclopropane-1-carbaldehyde [(−)-**21**].* To a stirred solution of alcohol (−)-**20** (3.00 g, 11.9 mmol, 1.0 equiv) in CH_2Cl_2 (90 mL) at 0 °C was added DMP (6.54 g, 15.4 mmol, 1.3 equiv), and the reaction mixture was stirred at 23 °C for 2 h. Then a mixture of satd aq $Na_2S_2O_3$ and $NaHCO_3$ (50 mL, 1:1, *v/v*) was added, and the reaction mixture was stirred for a further 0.5 h at 25 °C, after which it was extracted with CH_2Cl_2 (3 × 100 mL) and dried over $MgSO_4$, and the combined organic extracts were concentrated under reduced pressure. Purification of the residue by flash column chromatography (SiO_2, hexanes → hexanes/EtOAc 8:2, *v/v*) yielded aldehyde (−)-**21** (2.92 g, 11.6 mmol, 98% yield) as a colorless oil.

(−)-**21**: R_f = 0.25 (hexanes/EtOAc 9:1, *v/v*); $[\alpha]_D^{25}$ = −153.2 (*c* = 1.0, $CHCl_3$); IR (film) ν_{max} = 2943, 2865, 2171, 1713, 1463, 882, 782 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.19 (d, *J* = 6.8 Hz, 1 H), 2.06 (td, *J* = 8.2, 6.5 Hz, 1 H), 1.91 (tt, *J* = 8.1, 6.1 Hz, 1 H), 1.58−1.52 (m, 1 H), 1.48 (td, *J* = 8.3, 5.1 Hz, 1 H), 1.05−0.97 (m, 21 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 200.6, 104.5, 81.7, 28.4, 18.7, 15.3, 11.3, 10.0 ppm; HR-MS (CI) calcd for $C_{15}H_{26}OSi^+$ $[M + H]^+$ 250.1753, found 250.1745.

*(4S,6S)-2,2,5,5,8,8,9,9-Octamethyl-6-[(1E)-prop-1-en-1-yl]-4-[(2Z)-3-{(1R,2R)-2-[(triisopropylsilyl)ethynyl]cyclopropyl}prop-2-en-1-yl]-3,7-dioxa-2,8-disiladecane (**25**).* To a stirred solution of iodide **24** (2.00 g, 4.13 mmol, 1.00 equiv) in *i*-Pr_2EtN (5.03 mL, 28.9 mmol, 7.00 equiv) was added PPh_3 (1.89 g, 7.22 mmol, 1.75 equiv). The reaction vessel was capped and heated at 90 °C for 16 h. Subsequently, the mixture was allowed to cool to 23 °C and pentane (70 mL) was added, resulting in a thick paste material that was carefully separated from the cloudy pentane solution. The paste was washed three times with pentane (3 × 50 mL) and dissolved in THF (41.0 mL), and the stirred solution was cooled to −78 °C. Next, LiHMDS (4.33 mL, 1 M in THF, 4.33 mmol, 1.05 equiv) was added, and the reaction mixture was stirred for 15 min before DMPU (0.299 mL, 2.48 mmol, 0.60 equiv) was added, followed by the addition of a solution of aldehyde (−)-**21** (1.14 g, 4.54 mmol, 1.10 equiv) in THF (4 mL). The reaction mixture was stirred at −78 °C for 15 min and was subsequently allowed to warm to 23 °C over 1 h. Then, the reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (50 mL) and the aqueous phase was extracted three times with Et_2O (3 × 35 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, hexanes:benzene 3:2, *v/v* → 1:1, *v/v* → 2:3, *v/v*; then hexanes/EtOAc 19:1, *v/v* → 17:3, *v/v*) to yield cyclopropyl compound **25** (2.04 g, 3.45 mmol, 83% yield) as a colorless oil.

25: R_f = 0.60 (hexanes/EtOAc 19:1, *v/v*); $[\alpha]_D^{25}$ = −117.5 (*c* = 1.0, $CHCl_3$); IR (film) ν_{max} = 2956, 2864, 2165, 1463, 1249, 1048, 834 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.52−5.39 (m, 3 H), 5.31 (tt, *J* = 10.9, 1.5 Hz, 1 H), 3.90 (d, *J* = 8.2 Hz, 1 H), 3.58 (dd, *J* = 9.0, 2.7 Hz, 1 H), 2.30 (ddt, *J* = 14.6, 6.4, 2.4 Hz, 1 H), 2.26−2.19 (m, 1H), 1.86−1.78 (m, 1 H), 1.71−1.63 (m, 4 H), 1.18 (td, *J* = 8.4, 4.3 Hz, 1 H), 1.07−1.00 (m, 21 H), 0.88 (s, 9 H), 0.85 (s, 3 H), 0.80 (s, 3 H), 0.64 (td, *J* = 5.9, 4.3 Hz, 1 H), 0.09 (s, 9 H), 0.01 (s, 3 H), −0.03 (s, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 132.0, 129.9, 129.7, 127.6, 108.6, 79.1, 78.9, 77.7, 43.9, 31.3, 26.2, 20.0, 19.5, 18.8, 18.4, 17.8, 17.3, 16.9, 11.5, 8.9, 1.2, −3.1, −4.5 ppm; HR-MS (ESI) calcd for $C_{34}H_{66}O_2Si_3Na^+$ $[M + Na]^+$ 613.4263, found 613.4276.

*(1Z,4S,6S,7E)-6-{[tert-Butyl(dimethyl)silyl]oxy}-5,5-dimethyl-1-{(1R,2R)-2-[(triisopropylsilyl)ethynyl]cyclopropyl}nona-1,7-dien-4-ol (**26**).* To a stirred solution tris-silylated derivative **25** (0.623 g, 1.05 mmol, 1.0 equiv) in Et_2O (10 mL) was added aqueous HCl (4 N; 10 mL), and the biphasic solution was stirred 16 h at 23 °C. The resulting mixture was quenched by the addition of a saturated aqueous solution $NaHCO_3$ (30 mL), and the aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, hexanes/EtOAc 19:1, *v/v*) to yield alcohol **26** (0.543 g, 1.04 mmol, 99% yield) as a colorless oil.

26: R_f = 0.31 (hexanes/EtOAc 19:1, *v/v*); $[\alpha]_D^{25}$ = −177.2 (*c* = 1.0, $CHCl_3$); IR (film) ν_{max} = 3317, 1393, 1231, 1021, 821 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.72 (dt, *J* = 10.8, 7.2 Hz, 1 H), 5.61−5.51 (m, 2 H), 5.37 (dd, *J* = 10.9, 9.2 Hz, 1 H), 4.14 (s, 1 H), 3.88 (d, *J* = 6.4 Hz, 1 H), 3.72 (ddd, *J* = 9.9, 2.8, 1.6 Hz, 1 H), 2.32 (dddt, *J* = 13.4, 7.7, 2.9, 1.4 Hz, 1 H), 2.19 (dddd, *J* = 14.5, 9.8, 6.7, 1.6 Hz, 1 H), 1.85−1.77 (m, 1 H), 1.71 (d, *J* = 4.7 Hz, 3 H), 1.65 (td, *J* = 8.3,

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5.7 Hz, 1 H), 1.19 (td, J = 8.4, 4.3 Hz, 1 H), 1.06−0.99 (m, 21 H), 0.98 (s, 3 H), 0.89 (s, 9 H), 0.76 (s, 3 H), 0.66 (td, J = 5.9, 4.3 Hz, 1 H), 0.07 (s, 3 H), 0.01 (s, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 130.5, 130.0, 128.9, 128.7, 108.6, 84.2, 79.2, 76.3, 41.2, 30.5, 26.0, 22.6, 19.7, 18.8, 18.2, 17.9, 17.2, 17.1, 11.5, 8.9, −3.8, −5.0 ppm; HR-MS (ESI) calcd for $C_{31}H_{58}O_2Si_2Na^+$ $[M + Na]^+$ 541.3868, found 541.3870.

*(1Z,4S,6S,7E)-6-{[tert-Butyl(dimethyl)silyl]oxy}-1-[(1R,2R)-2-ethynylcyclopropyl]-5,5-dimethylnona-1,7-dien-4-ol (**27**).* To a stirred solution of alcohol **26** (0.540 g, 1.04 mmol, 1.0 equiv) in MeOH (10 mL) was added AgF (0.172 g, 1.35 mmol, 1.3 equiv), and the reaction vessel was protected from light with aluminium foil. The reaction mixture was stirred for 0.5 h at 23 °C, and the solution was diluted in CH_2Cl_2 (50 mL) and quenched by addition of aqueous HCl (1 M; 20 mL). The aqueous phase was extracted three times with CH_2Cl_2 (3 × 30 mL), and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, hexanes/EtOAc 97:3, v/v → 19:1, v/v) to yield alcohol **27** (0.320 g, 0.880 mmol, 85% yield) as a pale black-yellow oil.

27: R_f = 0.24 (hexanes/EtOAc 19:1, v/v); $[\alpha]_D^{25}$ = −124.7 (c = 1.0, $CHCl_3$); IR (film) ν_{max} = 3483, 3316, 2957, 2930, 2857, 2120, 1471, 1252, 1033, 834 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.68 (dt, J = 10.8, 7.2 Hz, 1 H), 5.49 (dd, J = 5.8, 3.6 Hz, 2 H), 5.25 (ddt, J = 10.8, 9.2, 1.6 Hz, 1 H), 4.08 (s, 1 H), 3.81 (d, J = 6.5 Hz, 1 H), 3.65 (dt, J = 9.9, 2.3 Hz, 1 H), 2.24 (ddt, J = 14.4, 7.6, 1.5 Hz, 1 H), 2.14 (dddd, J = 14.4, 9.8, 6.9, 1.6 Hz, 1 H), 1.82 (d, J = 2.2 Hz, 1 H), 1.80−1.72 (m, 1 H), 1.65 (d, J = 4.8 Hz, 3 H), 1.57−1.49 (m, 1 H), 1.11 (td, J = 8.5, 4.5 Hz, 1 H), 0.92 (s, 3 H), 0.82 (s, 9 H), 0.69 (s, 3 H), 0.61 (td, J = 5.9, 4.5 Hz, 1 H), 0.00 (s, 3 H), −0.05 (s, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 130.5, 129.5, 129.4, 128.7, 84.4, 84.2, 76.3, 67.0, 41.2, 30.5, 26.0, 22.6, 19.7, 18.2, 17.9, 16.7, 16.2, 7.5, −3.8, −5.0 ppm; HR-MS (ESI-TOF) calcd for $C_{22}H_{38}O_2SiNa^+$ $[M + Na]^+$ 385.2534, found 385.2533.

*(1Z,4S,6S,7E)-1-[(1R,2R)-2-(Bromoethynyl)cyclopropyl]-6-{[tert-butyl(dimethyl)silyl]oxy}-5,5-dimethylnona-1,7-dien-4-ol (**28**).* To a stirred solution of terminal alkyne **27** (0.320 g, 0.882 mmol, 1.0 equiv), in acetone (5 mL), were added NBS (0.188 g, 1.05 mmol, 1.2 equiv) and $AgNO_3$ (30.0 mg, 17.6 μmol, 0.20 equiv). The reaction flask was covered with aluminium foil, and the reaction mixture was stirred for 0.5 h before it was concentrated under reduced pressure at low temperature (25 °C). The crude residue was purified directly by flash column chromatography (SiO_2, hexanes:benzene 1:1, v/v → hexanes: EtOAc 19:1, v/v) to yield alkynyl bromide **28** (0.326 g, 0.740 mmol, 84% yield) as a yellow oil.

28: R_f = 0.59 (hexanes/EtOAc 9:1, v/v); $[\alpha]_D^{25}$ = −146.3 (c = 1.0, $CHCl_3$); IR (film) ν_{max} = 2957, 1471, 1252, 1033, 972, 836, 776 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.74 (dt, J = 10.9, 7.2 Hz, 1 H), 5.62−5.51 (m, 2 H), 5.28 (ddt, J = 10.8, 9.2, 1.5 Hz, 1 H), 4.17 (s, 1 H), 3.88 (d, J = 6.5 Hz, 1 H), 3.72 (dd, J = 9.6, 1.6 Hz, 1 H), 2.29 (dd, J = 14.5, 7.1 Hz, 1 H), 2.21 (dddd, J = 14.4, 9.9, 7.1, 1.6 Hz, 1 H), 1.87−1.78 (m, 1 H), 1.72 (d, J = 4.7 Hz, 3 H), 1.61 (ap.td, J = 8.3, 5.7 Hz, 1 H), 1.16 (ap. td, J = 8.5, 4.5 Hz, 1 H), 0.99 (s, 3 H), 0.89 (s, 9 H), 0.76 (s, 2 H), 0.68 (ap. td, J = 5.9, 4.4 Hz, 1 H), 0.07 (s, 3 H), 0.02 (s, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 130.4, 129.6, 129.4, 128.7, 84.3, 80.3, 76.3, 41.1, 36.5, 30.5, 26.0, 22.7, 19.7, 18.2, 17.9, 16.9, 16.0, 8.8, −3.8, −5.0 ppm; HR-MS (ESI-TOF) calcd for $C_{22}H_{37}O_2SiBrNa^+$ $[M + Na]^+$ 463.1638, found 463.1633.

*(1Z,4S,6S,7E)-6-{[tert-Butyl(dimethyl)silyl]oxy}-5,5-dimethyl-1-{(1R,2R)-2-[(E)-2-(tributylstannyl)vinyl]cyclopropyl}nona-1,7-dien-4-ol (**8**).* To a stirred solution of alkynyl bromide **28** (0.155 g, 0.351 mmol, 1.00 equiv) and i-Pr_2EtN (245 μL, 1.40 mmol, 4.0 equiv) in toluene cooled to −78 °C was added $PdCl_2(PPh_3)_2$ (11.0 mg, 0.0156 mmol, 0.045 equiv) in one portion, and argon was bubbled through the solution for 5 min. Then a solution of n-Bu_3SnH (0.208 mL, 0.772 mmol, 2.20 equiv) in THF (1 mL) was added dropwise to the reaction mixture, and it was stirred at this temperature for 10 min before the cooling bath was removed and the mixture was allowed to slowly warm to 23 °C. Once the reaction mixture turned from pale yellow to pale brown the mixture was concentrated under reduced pressure and the crude residue was purified directly by flash column chromatography (deactivated SiO_2 with Et_3N, hexanes) to yield vinyl stannane **8** (0.183 g, 0.280 mmol, 80% yield) as a colorless oil.

8: R_f = 0.31 (hexanes/EtOAc 19:1, v/v); $[\alpha]_D^{25}$ = −82.7 (c = 1.0, $CHCl_3$); IR (film) ν_{max} = 3495, 2956, 2855, 1593, 1463, 1251, 1049, 1033, 835, 775 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.00 (d, J = 18.9 Hz, 1 H), 5.69 (dd, J = 18.8, 7.4 Hz, 1 H), 5.63 (dt, J = 10.7, 7.0 Hz, 1 H), 5.56−5.54 (m, 2 H), 5.19 (dd, J = 10.7, 8.9 Hz, 1 H), 4.10 (s, 1 H), 3.86 (d, J = 6.5 Hz, 1 H), 3.70 (dt, J = 10.0, 2.2 Hz, 1 H), 2.32 (dd, J = 14.6, 7.7 Hz, 1 H), 2.14 (dddd, J = 14.5, 9.9, 6.6, 1.6 Hz, 1 H), 1.78 (dtd, J = 15.8, 8.2, 5.9 Hz, 2 H), 1.70 (d, J = 4.4 Hz, 3 H), 1.54−1.41 (m, 6 H), 1.29 (dt, J = 14.7, 7.4 Hz, 6 H), 1.12 (td, J = 8.2, 4.7 Hz, 1 H), 0.97 (s, 3 H), 0.91−0.85 (m, 24 H), 0.75 (s, 3 H), 0.60 (q, J = 5.5 Hz, 1 H), 0.06 (d, J = 2.3 Hz, 3 H), 0.00 (s, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 148.2, 130.5, 129.9, 128.6, 128.4, 127.9, 84.2, 76.4, 41.2, 30.3, 29.3, 27.4, 26.0, 25.8, 22.6, 19.7, 18.2, 17.92, 17.89, 14.9, 13.9, 9.7, −3.8, −4.9 ppm; HR-MS (ESI-TOF) calcd for $C_{34}H_{66}O_2SiSnNa^+$ $[M + Na]^+$ 677.3753, found 677.3765.

*2-Ethynyl-1,3-oxazole-4-carboxylic Acid (**29**).* To a stirred solution of ester **9**[10] (1.37 g, 8.30 mmol, 1.0 equiv) in a mixture of THF (33 mL) and water (25 mL) was added LiOH hydrate (523 mg, 12.5 mmol, 1.5 equiv), and the reaction mixture was stirred at 25 °C for 1.5 h. Then the reaction mixture was acidified with aqueous HCl (1 M; 50 mL), extracted with EtOAc (3 × 50 mL), and dried over $MgSO_4$, and the organic layer was concentrated under reduced pressure to give carboxylic acid **29** (1.09 g, 7.97 mmol, 96% yield) as a white solid.

29: R_f = 0.07 (EtOAc with 1% formic acid); mp 170 °C (EtOAc, decomposing to brown oil); IR (film) ν_{max} = 3288, 3133, 2585, 1680, 1541, 1439, 1281, 1228, 1162, 1116, 987, 942, 765, 687, 714 cm^{-1}; ^{1}H NMR (600 MHz, CD_3OD) δ 8.53 (s, 1 H), 4.24 (s, 1 H) ppm; ^{13}C NMR (151 MHz, CD_3OD) δ 163.0, 147.5, 146.8, 135.3, 84.0, 71.0 ppm; HR-MS (ESI-TOF) calcd for $C_6H_2NO_3Na^+$ $[M + Na]^+$: 181.9825, found 181.9817.

*2-[(Z)-2-Bromoethenyl]-1,3-oxazole-4-carboxylic Acid (**10**).* To a stirred solution of dry LiBr (132 mg, 1.50 mmol, 1.5 equiv) and dry LiOAc (298 mg, 4.50 mmol, 4.5 equiv) in glacial AcOH (4.0 mL) was added carboxylic acid **22** (138 mg, 1.00 mmol, 1.0 equiv), and the resulting mixture was heated to 70 °C for 16 h. The reaction mixture was then cooled to 25 °C, diluted with water (5 mL), and extracted with EtOAc (5 × 15 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The resulting solid was then azeotropically dried with toluene (3 × 30 mL) under reduced pressure to afford the desired bromide **10** (200 mg, 910 μmol, 91% yield) as a white amorphous solid.

10: R_f = 0.29 (EtOAc with 1% HCO_2 H), IR (film) ν_{max} = 3024, 1682, 1637, 1582, 1420, 1308, 1114, 759 cm^{-1}; ^{1}H NMR (600 MHz, CD_3OD) δ 8.56 (s, 1 H), 7.22 (d, J = 8.6 Hz, 1 H), 7.14 (d, J = 8.6 Hz, 1 H) ppm; ^{13}C NMR (151 MHz, CD_3OD) δ 163.8, 160.9, 145.5, 135.6, 120.3, 116.7 ppm; HR-MS (ESI-TOF) calcd for $C_6H_5NO_3Br^+$ $[M + H]^+$ 217.9447, found 217.9443.

*(2E,4R,6S,8Z,10Z,12E,14R)-4-{[tert-Butyl(dimethyl)silyl]oxy}-14-methoxy-15-[4-(methoxycarbonyl)1,3-oxazol-2-yl]-5,5-dimethylpentadeca-2,8,10,12-tetraen-6-yl 2-[(Z)-2-bromoethenyl]1,3-oxazole-4-carboxylate (**31**).* To a stirred solution of alcohol **30** (0.10 g, 0.19 mmol, 1.0 equiv) and carboxylic acid **10** (49 mg, 0.23 mmol, 1.2 equiv) in toluene (2.0 mL) were added Et_3N (0.16 mL, 1.1 mmol, 6.0 equiv) and DMAP (0.18 g, 1.5 mmol, 8.0 equiv). The solution was cooled to 0 °C, and 2,4,6-trichlorobenzoyl chloride (0.088 mL, 0.56 mmol, 3.0 equiv) was added dropwise before the reaction mixture was allowed to warm to 23 °C. Upon complete consumption of the starting material (about 3 h), the reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$. The aqueous phase was extracted with EtOAc (3 × 10 mL), and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, hexanes/EtOAc 4:1, v/v → 3:1, v/v → 7:3, v/v → 1:1, v/v) to yield vinyl bromide **31** (0.12 g, 0.16 mmol, 88% yield) as a colorless oil.

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31: R_f = 0.28 (hexanes/EtOAc 13:7, *v*/*v*); $[\alpha]_D^{25}$ = −49.0 (*c* = 1.0, $CHCl_3$); IR (film) ν_{max} = 2953, 2856, 1740, 1584, 1322, 1112, 834 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.15 (s, 1 H), 8.14 (s, 1 H), 7.16 (d, *J* = 8.7 Hz, 1 H), 6.88 (d, *J* = 8.7 Hz, 1 H), 6.60 (dd, *J* = 15.2, 11.3 Hz, 1 H), 6.45−6.36 (m, 1 H), 6.24 (t, *J* = 11.4 Hz, 1 H), 5.96 (t, *J* = 11.1 Hz, 1 H), 5.60−5.43 (m, 4 H), 5.23 (dd, *J* = 9.8, 3.3 Hz, 1 H), 4.14 (td, *J* = 7.8, 5.5 Hz, 1 H), 3.90 (s, 3 H), 3.84 (d, *J* = 8.1 Hz, 1 H), 3.23 (s, 3 H), 3.08 (dd, *J* = 15.0, 7.8 Hz, 1 H), 2.98 (dd, *J* = 14.9, 5.6 Hz, 1 H), 2.66−2.57 (m, 1 H), 2.52 (dddd, *J* = 15.2, 6.7, 3.3, 1.7 Hz, 1 H), 1.68 (dd, *J* = 6.1, 1.2 Hz, 3 H), 0.96 (s, 3 H), 0.92 (s, 3 H), 0.87 (s, 9 H), −0.02 (s, 3 H), −0.05 (s, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.9, 161.8, 160.5, 159.4, 144.1, 143.1, 134.6, 133.4, 132.7, 131.3, 129.9, 128.8, 128.6, 128.4, 125.4, 125.3, 119.8, 114.9, 79.6, 79.1, 78.1, 56.7, 52.2, 43.0, 35.0, 28.6, 26.1, 20.2, 19.5, 18.3, 17.9, −3.4, −4.8 ppm; HR-MS (ESI-TOF) calcd for $C_{35}H_{49}N_2O_8SiBrNa^+$ $[M + Na]^+$ 755.2334, found 755.2334.

*Methyl 2-{(2R,3E,5Z,7Z,10S,12R,13E)-12-{[tert-Butyl(dimethyl)-silyl]oxy}-10-[({2-[(1Z,3E)-4-{(1S,2R)-2-[(1Z,4S,6R,7E)-6-{[tert-butyl-(dimethyl)silyl]oxy}-4-hydroxy-5,5-dimethylnona-1,7-dien-1-yl]-cyclopropyl}buta-1,3-dien-1-yl]-1,3-oxazol-4-yl}carbonyl)oxy]-2-methoxy-11,11-dimethylpentadeca-3,5,7,13-tetraen-1-yl}-1,3-oxazole-4-carboxylate (**32**).* To a stirred solution of vinyl bromide **31** (0.12 g, 0.16 mmol, 1.0 equiv) and vinyl stannane **8** (0.14 g, 0.21 mmol, 1.3 equiv) in DMF (1.6 mL) purged with Ar were added CuI (0.13 g, 0.65 mmol, 4.0 equiv), $AsPh_3$ (0.10 g, 0.33 mmol, 2.0 equiv), and $Pd_2(dba)_3$ (75 mg, 0.082 mmol, 0.50 equiv). The resulting mixture was stirred at 23 °C for 3 h, and the reaction mixture was filtered through Celite, diluted with EtOAc (15 mL), and washed with brine (3 × 10 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, hexanes/EtOAc 4:1, *v*/*v* → 3:1, *v*/*v* → 7:3, *v*/*v*). The purified residue was dissolved in CH_2Cl_2 (10 mL) and washed with a solution of aqueous HCl (1 M; 10 mL) and a saturated aqueous solution of $NaHCO_3$ (10 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure before the residue was purified once again by flash column chromatography (SiO_2, hexanes/EtOAc 3:1, *v*/*v* → 7:3, *v*/*v*) to give heterodimer **32** (60 mg, 59 mmol, 36%) as a clear oil.

32: R_f = 0.40 (hexanes/EtOAc 13:7, *v*/*v*); $[\alpha]_D^{25}$ = −23.6 (*c* = 1.0, $CHCl_3$); IR (film) ν_{max} = 3481, 2955, 2856, 1740, 1463, 1321, 1252, 1113 cm^{-1}; ^1H NMR (600 MHz, CD_3CN) δ 8.25 (s, 1 H), 8.25 (s, 1 H), 7.51 (dd, *J* = 15.2, 11.4 Hz, 1 H), 6.68 (dd, *J* = 15.2, 11.4 Hz, 1 H), 6.53 (t, *J* = 11.6 Hz, 1 H), 6.46 (t, *J* = 11.3 Hz, 1 H), 6.32 (t, *J* = 11.3 Hz, 1 H), 5.99 (dt, *J* = 11.2, 5.4 Hz, 2 H), 5.91 (dd, *J* = 15.1, 9.8 Hz, 1 H), 5.66−5.55 (m, 4 H), 5.52 (tddd, *J* = 8.1, 6.5, 4.4, 1.5 Hz, 2 H), 5.26−5.16 (m, 1 H), 5.14 (dd, *J* = 9.5, 3.4 Hz, 1 H), 4.12 (td, *J* = 7.8, 5.5 Hz, 1 H), 4.01 (d, *J* = 8.0 Hz, 1 H), 3.94 (d, *J* = 8.5 Hz, 1 H), 3.81 (s, 3 H), 3.56 (dt, *J* = 10.1, 2.9 Hz, 1 H), 3.51 (d, *J* = 3.4 Hz, 1 H), 3.17 (s, 3 H), 3.00 (dd, *J* = 15.2, 7.7 Hz, 1 H), 2.94 (dd, *J* = 15.2, 5.4 Hz, 1 H), 2.58 (ddt, *J* = 26.1, 17.2, 9.5 Hz, 2 H), 2.38−2.26 (m, 1 H), 1.68 (dd, *J* = 2.8, 1.4 Hz, 3 H), 1.67 (dd, *J* = 2.8, 1.5 Hz, 3 H), 0.97 (s, 3 H), 0.92 (s, 3 H), 0.87 (s, 9 H), 0.86 (s, 12 H), 0.77 (s, 3 H), 0.06 (s, 3 H), 0.00 (s, 3 H), −0.01 (s, 3 H), −0.03 (s, 3 H) ppm; ^{13}C NMR (151 MHz, CD_3CN) δ 163.8, 162.5, 161.6, 145.5, 145.4, 144.4, 138.6, 135.1, 134.2, 133.9, 132.1, 131.7, 130.9, 130.7, 130.0, 129.6, 129.4, 129.3, 128.0, 126.3, 126.2, 110.2, 82.8, 80.0, 79.7, 78.2, 76.8, 56.7, 52.4, 43.6, 42.2, 35.3, 30.9, 29.2, 26.4, 26.3, 23.6, 21.5, 20.4, 20.2, 19.8, 19.5, 18.8, 18.7, 17.89, 17.85, 17.3, −3.2, −3.5, −4.7, −4.8 ppm; HR-MS (ESI-TOF) calcd for $C_{57}H_{88}N_2O_{10}Si_2Na^+$ $[M + Na]^+$ 1039.5870, found 1039.5896.

*(2Z,4E,6S,8R,9Z,12S,20R,21E,23Z,25Z,28S)-12-[(3R,4E)-3-{[tert-Butyl(dimethyl)silyl]oxy}-2-methylhex-4-en-2-yl]-28-[(3S,4E)-3-{[tert-butyl(dimethyl)silyl]oxy}-2-methylhex-4-en-2-yl]-20-methoxy-13,17,29,33-tetraoxa-34,35-diazatetracyclo-[29.2.1.1^{15,18}.0^{6,8}]pentatriaconta-1(34),2,4,9,15,18(35),21,23,25,31-decaene-14,30-dione (**33**).* To a stirred solution of ester **32** (0.060 g, 0.059 mmol, 1.0 equiv) in THF (1.2 mL) cooled to 0 °C was added dropwise a saturated aqueous solution of barium hydroxide octahydrate (0.56 mL, MeOH/H_2O 3:2, *v*/*v*). The reaction mixture was allowed to warm to 23 °C and stirred until all starting material was consumed by TLC (about 3 h). The reaction was quenched by the addition of an aqueous HCl solution (1 N; 3 mL), and the aqueous phase was extracted with EtOAc (6 × 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was used in the next reaction without any further purification.

To a stirred solution of the crude carboxylic acid in toluene (2.4 mL) was added a solution of 2,4,6-trichlorobenzoyl chloride (0.092 mL, 0.59 mmol, 10 equiv) in toluene (1.0 mL) and a solution of Et_3N (0.090 mL, 0.65 mmol, 11 equiv) in toluene (1.0 mL). The mixture was stirred 1 h at 23 °C, and it was diluted to a concentration of 0.0075 M by the addition of toluene (4.4 mL). The latter reaction mixture was added over 5 h, via a syringe pump, to a solution of DMAP (0.029 g, 0.24 mmol, 4.0 equiv) in toluene (11 mL) heated at 40 °C. After the addition was completed, stirring was continued for 24 h before the reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (15 mL). The aqueous phase was extracted with EtOAc (6 × 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, hexanes/EtOAc 3:1, *v*/*v* → 7:3, *v*/*v* → 13:7, *v*/*v*) to give bis-TBS protected cp-disorazole A_1 (**33**; 0.016 g, 0.016 mmol, 28% yield over two steps) as a colorless oil.

33: R_f = 0.33 (hexanes/EtOAc 13:7, *v*/*v*); $[\alpha]_D^{25}$ = −36.0 (*c* = 0.05, MeOH); IR (film) ν_{max} = 2957, 2928, 1740, 1716, 1464, 1142, 1114, 835 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.97 (s, 1 H), 7.89 (s, 1 H), 6.96 (dd, *J* = 14.9, 11.7 Hz, 1 H), 6.42−6.35 (m, 2 H), 6.25 (t, *J* = 11.0 Hz, 1 H), 6.15 (t, *J* = 11.8 Hz, 1 H), 5.97−5.94 (m, 2 H), 5.69 (dd, *J* = 15.2, 8.9 Hz, 1 H), 5.59−5.42 (m, 6 H), 5.39 (td, *J* = 11.0, 4.9 Hz, 1 H), 5.19 (dd, *J* = 11.3, 2.6 Hz, 2 H), 5.03 (t, *J* = 10.7 Hz, 1 H), 3.83 (ddt, *J* = 18.9, 6.4, 3.9 Hz, 3 H), 3.18 (s, 3 H), 2.76 (q, *J* = 11.9 Hz, 1 H), 2.68 (q, *J* = 11.5 Hz, 1 H), 2.59 (dd, *J* = 14.9, 3.8 Hz, 1 H), 2.30−2.20 (m, 2 H), 2.09 (p, *J* = 8.0 Hz, 1 H), 1.83−1.75 (m, 1 H), 1.71 (dd, *J* = 6.2, 1.4 Hz, 6 H), 0.98 (s, 3 H), 0.97 (s, 3 H), 0.94 (s, 3 H), 0.93 (s, 3 H), 0.87 (s, 9 H), 0.87 (s, 9 H), 0.76−0.69 (m, 1H) 0.55 (q, *J* = 5.6 Hz, 1 H), 0.00 (m, 6 H), −0.05 (m, 6 H) ppm; ^{13}C NMR (151 MHz, CD_3CN) δ 163.0, 162.9, 161.5, 161.3, 145.6, 145.3, 144.4, 137.4, 134.6, 134.2, 132.3, 132.1, 131.0, 129.5, 129.4, 129.3, 128.8, 127.6, 127.2, 127.1, 126.6, 110.5, 79.94, 79.90, 79.7, 77.4, 77.1, 56.5, 43.3, 43.2, 35.6, 29.2, 26.4, 26.3, 24.1, 20.6, 20.5, 19.9, 19.53, 19.48, 18.8, 17.9, 17.4, −3.25, −3.26, −4.64, −4.66 ppm; HR-MS (ESI-TOF) calcd for $C_{56}H_{84}N_2O_9Si_2Na^+$ $[M + Na]^+$ 1007.5608, found 1007.5630.

*(2Z,4E,6S,8R,9Z,12S,20R,21E,23Z,25Z,28S)-12,28-Bis[(3S,4E)-3-hydroxy2-methylhex-4-en-2-yl]-20-methoxy-13,17,29,33-tetraoxa-34,35-diazatetracyclo[29.2.1.1^{15,18}.0^{6,8}]pentatriaconta-1(34),2,4,9,-15,18(35),21,23,25,31-decaene-14,30-dione (**4**).* To a stirred solution of bis silyl ether **33** (10 mg, 10 μmol, 1.0 equiv) in MeOH (2 mL) in an argon purged plastic Falcon tube was added hexafluorosilicic acid (0.24 mL, 0.66 mmol, 33−35% in water, 65 equiv) dropwise at 23 °C, and the tube was covered with aluminium foil. The resulting mixture was cooled to 4 °C and stirred for five consecutive days at the same temperature and 1 day at 23 °C. At this point, no starting material and minute amounts of (presumed) monodeprotected intermediates could be observed by TLC. The reaction mixture was diluted with EtOAc (50 mL), followed by the addition of a saturated aqueous solution of $NaHCO_3$ (10 mL). The phases were separated, and the organic phase was washed with a saturated aqueous solution of $NaHCO_3$ (2 × 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, hexanes/EtOAc 7:3, *v*/*v* → 1:1, *v*/*v* → 0:1, *v*/*v*) to yield cp-disorazole A_1 (**4**) (3.5 mg, 4.6 μmol, 45% yield).

4: R_f = 0.13 (hexanes/EtOAc 2:3, *v*/*v*); $[\alpha]_D^{25}$ = −65.7 (*c* = 0.14, $CHCl_3$); IR (film) ν_{max} = 3429, 2967, 2937, 1734, 1628, 1555, 1388, 1317, 1142, 1109 cm^{-1}; ^1H NMR (600 MHz, CD_3OD) δ 8.37 (s, 1 H), 8.28 (s, 1 H), 7.02 (dd, *J* = 14.8, 11.7 Hz, 1 H), 6.52−6.44 (m, 2 H), 6.36 (dd, *J* = 11.0, 11.0 Hz, 1 H), 6.30 (dd, *J* = 11.8, 11.8 Hz, 1 H), 5.99 (dd, *J* = 11.1, 11.1 Hz, 1 H), 5.89 (d, *J* = 11.8 Hz, 1 H), 5.73 (dd, *J* = 15.1, 9.2 Hz, 1 H), 5.69−5.62 (m, 3 H), 5.61−5.51 (m, 2 H),

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5.36 (ddd, J = 11.1, 11.1, 4.8 Hz, 1 H), 5.30 (dd, J = 11.6, 2.9 Hz, 1 H), 5.29 (dd, J = 11.7, 2.9 Hz, 1 H), 5.15 (dd, J = 10.9, 10.9 Hz, 1 H), 3.96 (ddd, J = 8.9, 5.3, 3.4 Hz, 1 H), 3.84 (d, J = 7.8 Hz, 2 H), 3.21 (dd, J = 14.9, 5.4 Hz, 1 H), 3.16 (s, 3 H), 2.88−2.74 (m, 2 H), 2.56 (dd, J = 14.8, 3.5 Hz, 1 H), 2.35−2.29 (m, 1 H), 2.28−2.23 (m, 1 H), 2.23−2.17 (m, 1 H), 2.21 (ddd, J = 15.8, 10.8, 8.2 Hz, 1 H), 1.73−1.67 (m, 6 H), 1.33 (td, J = 8.3, 4.4 Hz, 1 H), 1.03 (s, 3 H), 1.02 (s, 3 H), 0.98 (s, 3 H), 0.97 (s, 3 H), 0.58 (dd, J = 5.5, 5.5 Hz, 1 H) ppm; ^{13}C NMR (151 MHz, CD_3OD) δ 163.9, 163.8, 162.2, 162.0, 146.1, 145.9, 145.6, 138.9, 134.6, 134.1, 133.7, 132.8, 131.7 (2 × C), 131.0, 129.7, 129.54, 129.51, 129.4, 128.1, 127.3, 127.1, 127.0, 109.5, 80.2, 78.4, 78.2, 77.9 (2 × C), 56.6, 42.7, 42.6, 36.0, 29.24, 29.21, 24.5, 20.2, 19.5, 19.43, 19.39, 19.35, 18.0 (2 × C), 17.7 ppm; HR-MS (ESI-TOF) calcd for $C_{44}H_{56}N_2O_9Na^+$ $[M + Na]^+$ 779.3878, found 779.3882.

*Methyl 2-[(1Z,3E)-4-{(1S,2R)-2-[(1Z,4S,6S,7E)-6-{[tert-Butyl(dimethyl)silyl]oxy}-4-hydroxy-5,5-dimethylnona-1,7-dien-1-yl]cyclopropyl}buta-1,3-dien-1-yl]-1,3-oxazole-4-carboxylate (**34**).* To a stirred and degassed solution of vinyl stannane **8** (330 mg, 0.505 mmol, 1.0 equiv) and oxazole methyl ester **11**[10] (117 mg, 0.505 mmol, 1.0 equiv) in NMP (2.5 mL) at 23 °C was added CuTc (144 mg, 0.757 mmol, 1.5 equiv). The resulting mixture was stirred for 1 h at 23 °C and was directly purified by flash column chromatography (SiO_2, hexanes/EtOAc 9:1, v/v → 4:1, v/v) to yield the title compound **34** (202 mg, 0.392 mmol, 77% yield) as a pale yellow oil.

34: R_f = 0.28 (hexanes/EtOAc 17:3, v/v); $[\alpha]_D^{25}$ = +55.3 (c = 1.0, $CHCl_3$); IR (film) ν_{max} = 3486, 2956, 2930, 2857, 1749, 1732, 1630, 1464, 1322, 1116, 1005, 836 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.19 (s, 1 H), 7.41 (dd, J = 15.0, 11.6 Hz, 1 H), 6.47 (t, J = 11.6 Hz, 1 H), 6.01 (d, J = 11.6 Hz, 1 H), 5.82 (dd, J = 15.0, 9.4 Hz, 1 H), 5.70 (dt, J = 10.9, 7.1 Hz, 1 H), 5.60−5.51 (m, 2 H), 5.23 (dd, J = 10.7, 8.7 Hz, 1 H), 4.19 (s, 1 H), 3.92 (s, 3 H), 3.86 (d, J = 6.8 Hz, 1 H), 3.70 (d, J = 9.5 Hz, 1 H), 2.31 (dd, J = 14.6, 7.5 Hz, 1 H), 2.15 (dddd, J = 14.7, 10.1, 6.7, 1.6 Hz, 1 H), 1.96 (ddt, J = 26.4, 14.3, 8.3 Hz, 2 H), 1.71 (d, J = 4.8 Hz, 3 H), 1.33 (td, J = 8.2, 4.8 Hz, 1 H), 0.97 (s, 3 H), 0.88 (s, 9 H), 0.76 (s, 3 H), 0.72 (q, J = 5.7 Hz, 1 H), 0.06 (s, 3 H), 0.00 (s, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.5, 162.0, 144.6, 143.0, 138.2, 134.1, 130.4, 129.9, 129.1, 128.8, 127.2, 109.5, 84.4, 76.4, 52.3, 41.1, 30.3, 26.0, 22.9, 22.7, 19.8, 19.4, 18.2, 17.9, 17.0, −3.8, −5.0 ppm; HR-MS (ESI-TOF) calcd for $C_{29}H_{45}O_5NSiNa^+$ $[M + Na]^+$ 538.2959, found 538.2977.

*(1Z,4S,6S,7E)-6-{[tert-Butyl(dimethyl)silyl]oxy}-1-[(1R,2S)-2-{(1E,3Z)-4-[4-(methoxycarbonyl)-1,3-oxazol-2-yl]buta-1,3-dien-1-yl}cyclopropyl]-5,5-dimethylnona-1,7-dien-4-yl 2-[(Z)-2-bromoethenyl]-1,3-oxazole-4-carboxylate (**35**).* A solution of hydroxy compound **34** (40 mg, 0.078 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL) was added a solution carboxylic acid **10** (34 mg, 0.155 mmol, 2.0 equiv) in CH_2Cl_2 (1.0 mL), and the mixture was concentrated under reduced pressure and dried at high vacuum. Then the resulting thick paste was dissolved in toluene (0.78 mL), and to the resulting stirred solution were subsequently added at 23 °C Et_3N (65 μL, 47 mg, 0.470 mmol, 6.0 equiv), after 5 min, DMAP (76 mg, 0.620 mmol, 8.0 equiv), and then dropwise TCBC (36 μL, 57 mg, 0.470 mmol, 6.0 equiv). After the reaction mixture was stirred at 23 °C for 0.5 h, additional toluene was added (1.0 mL), and the mixture was stirred for an additional 1 h at 23 °C and was then directly purified by flash column chromatography (SiO_2, hexanes/EtOAc 4:1, v/v → 3:2, v/v) to yield title compound **35** (38 mg, 0.053 mmol, 68% yield) as a pale yellow oil.

35: R_f = 0.37 (hexanes/EtOAc 3:1, v/v); $[\alpha]_D^{25}$ = +31.3 (c = 0.8, $CHCl_3$); IR (film) ν_{max} = 3162, 2954, 2856, 1743, 1630, 1573, 1323, 1116, 835, 758 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.19 (s, 1 H), 8.14 (s, 1 H), 7.25 (dd, J = 15.1, 11.5 Hz, 1 H), 7.08 (d, J = 8.6 Hz, 1 H), 6.79 (d, J = 8.7 Hz, 1 H), 6.33 (t, J = 11.7 Hz, 1 H), 5.95 (d, J = 11.6 Hz, 1 H), 5.64 (dd, J = 14.9, 9.9 Hz, 1 H), 5.56−5.42 (m, 3 H), 5.23 (dd, J = 10.1, 3.1 Hz, 1 H), 5.13−5.08 (m, 1 H), 3.93 (s, 3 H), 3.84 (d, J = 7.9 Hz, 1 H), 2.62−2.52 (m, 1 H), 2.49−2.42 (m, 1 H), 2.04−1.95 (m, 1 H), 1.90−1.81 (m, 1 H), 1.67 (d, J = 5.6 Hz, 3 H), 1.31 (td, J = 8.2, 4.9 Hz, 1 H), 0.97 (s, 3 H), 0.92 (s, 3 H), 0.87 (s, 9 H), 0.67 (q, J = 5.6 Hz, 1 H), −0.02 (s, 3 H), −0.05 (s, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.4, 162.0, 160.5, 159.3, 144.0, 143.1, 143.0, 138.0, 134.7, 134.2, 131.4, 130.6, 128.4, 127.5, 127.0, 119.8, 114.7, 109.5, 79.2, 78.2, 52.3, 42.9, 28.6, 26.1, 23.0, 20.2, 19.4, 19.2, 18.3, 17.9, 17.1, −3.4, −4.8 ppm; HR-MS (ESI-TOF) calcd for $C_{35}H_{47}O_7N_2SiBrNa^+$ $[M + Na]^+$ 737.2228, found 737.2238.

*Methyl 2-{(1Z,3E)-4-[(1S,2R)-2-{(1Z,4S,6S,7E)-6-{[tert-Butyl(dimethyl)silyl]oxy}-4-[({2-[(2Z)-4-{(1S,2R)-2-[(1Z,4S,6S,7E)-6-{[tert-butyl(dimethyl)silyl]oxy}-4-hydroxy-5,5-dimethylnona-1,7-dien-1-yl]cyclopropyl}but-2-en-1-yl]-1,3-oxazol-4-yl}carbonyl)oxy]-5,5-dimethylnona-1,7-dien-1-yl}cyclopropyl]buta-1,3-dien-1-yl}-1,3-oxazole-4-carboxylate (**36**).* To a stirred and degassed solution of vinyl stannane **8** (32 mg, 0.048 mmol, 1.5 equiv) and vinyl bromide **35** (23 mg, 0.032 mmol, 1.0 equiv) in NMP (160 μL) at 23 °C was added CuTc (9.2 mg, 0.048 mmol, 1.5 equiv). The resulting mixture was stirred for 1 h at 23 °C and was then directly purified by flash column chromatography (SiO_2, hexanes/EtOAc 9:1, v/v → 4:1, v/v) to yield the title compound **36** (23 mg, 0.023 mmol, 72% yield) as a pale yellow oil.

36: R_f = 0.32 (hexanes/EtOAc 3:1, v/v); $[\alpha]_D^{25}$ = +40.0 (c = 1.0, $CHCl_3$); IR (film) ν_{max} = 3477, 2956, 2929, 2856, 1743, 1630, 1471, 1115, 835, 775 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.20 (s, 1 H), 8.03 (s, 1 H), 7.41 (dd, J = 15.0, 11.5 Hz, 1 H), 7.26 (s, 1 H), 6.37 (t, J = 11.6 Hz, 1 H), 6.32 (t, J = 11.7 Hz, 1 H), 5.94 (d, J = 11.6 Hz, 1 H), 5.90 (d, J = 11.6 Hz, 1 H), 5.77 (dd, J = 15.0, 9.6 Hz, 1 H), 5.69 (dt, J = 11.0, 7.1 Hz, 1 H), 5.64 (dd, J = 15.0, 9.8 Hz, 1 H), 5.58−5.44 (m, 5 H), 5.25−5.19 (m, 2 H), 5.14−5.08 (m, 1 H), 4.21 (s, 1 H), 3.93 (s, 3 H), 3.85 (dd, J = 10.0, 7.2 Hz, 2 H), 3.70 (dt, J = 9.8, 2.2 Hz, 1 H), 2.56 (dt, J = 15.1, 9.2 Hz, 1 H), 2.50−2.43 (m, 1 H), 2.31 (dd, J = 14.7, 7.5 Hz, 1 H), 2.16 (dddd, J = 14.6, 10.1, 6.6, 1.6 Hz, 1 H), 1.98 (dp, J = 16.2, 8.4 Hz, 2 H), 1.91−1.82 (m, 2 H), 1.71 (d, J = 4.7 Hz, 3 H), 1.67 (d, J = 5.5 Hz, 3 H), 1.31 (td, J = 8.3, 4.8 Hz, 2 H), 0.98 (s, 3 H), 0.97 (s, 3 H), 0.92 (s, 3 H), 0.87 (s, 18 H), 0.76 (s, 3 H), 0.70 (q, J = 5.7 Hz, 1 H), 0.68−0.65 (m, 1 H), 0.05 (s, 3 H), 0.00 (s, 3 H), −0.01 (s, 3 H), −0.05 (s, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.5, 162.2, 162.0, 161.0, 144.0, 143.9, 143.2, 142.4, 138.0, 137.7, 134.6, 134.1, 131.5, 130.5, 130.4, 129.7, 129.2, 128.8, 128.3, 127.6, 127.4, 127.1, 109.6, 109.5, 84.4, 79.2, 78.0, 76.4, 52.3, 42.9, 41.1, 30.3, 28.6, 26.1, 26.0, 23.0, 22.8, 22.7, 20.2, 19.8, 19.5, 19.4, 19.2, 18.3, 18.2, 17.91, 17.88, 17.0, 16.8, −3.4, −3.8, −4.8, −5.0 ppm; HR-MS (ESI-TOF) calcd for $C_{57}H_{86}O_9N_2Si_2Na^+$ $[M + Na]^+$ 1021.5764, found 1021.5792.

*(2Z,4E,6R,8R,9Z,12S,19Z,21E,23R,25R,26Z,29S)-12,29-Bis[(3R,4E)-3-{[tert-butyl(dimethyl)silyl]oxy}-2-methylhex-4-en-2-yl]-13,17,30,34-tetraoxa-35,36-diazapentacyclo[30.2.1.-^{15,18}.0^{6,8}.0^{23,25}]hexatriaconta-1(35),2,4,9,15,18(36),19,21,26,32-deca-ene-14,31-dione (**37**).* To a stirred solution of hydroxy methyl ester **36** (14.5 mg, 0.015 mmol, 1.0 equiv) in THF (290 μL) was added a saturated solution of $Ba(OH)_2 \cdot 8H_2O$ (137 mg in MeOH/H_2O 3:2, v/v) at 23 °C, and the reaction mixture was stirred for 3 h. Then the resulting mixture was quenched by the addition of satd aq NH_4Cl solution (5 mL). After separation of the phases, the aqueous layer was extracted with EtOAc (4 × 10 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained residue was used in the next step without further purification.

To a stirred solution of the crude hydroxy carboxylic acid in toluene (1.0 mL) was added a solution of 2,4,6-trichlorobenzoyl chloride (22 μL, 35 mg, 0.142 mmol, 10 equiv) and Et_3N (22 μL, 16 mg, 0.156 mmol, 11.0 equiv) in toluene (1.0 mL). The mixture was stirred for 1 h at 23 °C and then diluted to reach a final concentration of 7.5 mM by the addition of toluene (4.4 mL). The latter reaction mixture was added over 5 h, via a syringe pump, to a solution of DMAP (6.9 mg, 57 μmol, 4.0 equiv) in toluene (2.6 mL) that was heated to 40 °C. After the addition was completed, stirring was continued for 24 h before the reaction was quenched by the addition of satd aq $NaHCO_3$ solution (15 mL). Then the aqueous layer was extracted with EtOAc (6 × 10 mL), and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, hexanes/EtOAc 3:1, v/v → 7:3, v/v → 13:7,

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v/*v*) to give titled compound **37** (1.5 mg, 4.2 μmol, 28% yield over two steps) as a colorless oil.

37: R_f = 0.18 (hexanes/EtOAc 3:1, *v*/*v*); $[\alpha]_D^{25}$ = −160.0 (*c* = 0.15, $CHCl_3$); IR (film) ν_{max} = 2956, 2928, 2855, 1740, 1630, 1142, 1060, 834, 774 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.99 (s, 2 H), 6.85 (dd, *J* = 14.8, 11.6 Hz, 2 H), 6.11 (t, *J* = 11.7 Hz, 2 H), 5.86 (d, *J* = 11.8 Hz, 2 H), 5.58−5.37 (m, 8 H), 5.20 (dd, *J* = 11.5, 2.2 Hz, 2 H), 5.06 (t, *J* = 10.8 Hz, 2 H), 3.82 (d, *J* = 7.9 Hz, 2 H), 2.70 (q, *J* = 12.2 Hz, 2 H), 2.28−2.20 (m, 2 H), 2.06 (ddd, *J* = 14.0, 11.1, 6.8 Hz, 2 H), 1.77−1.70 (m, 2 H), 1.68 (d, *J* = 5.7 Hz, 6 H), 1.30−1.24 (m, 2 H), 0.98 (s, 6 H), 0.92 (s, 6 H), 0.88 (s, 18 H), 0.56 (q, *J* = 5.5 Hz, 2 H), 0.00 (s, 6 H), −0.05 (s, 6 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.9, 160.3, 142.3, 142.0, 136.3, 134.0, 131.4 (2 × C), 128.3, 127.1, 126.2, 110.5, 79.3, 77.4, 42.6, 28.8, 26.1, 23.5, 20.5, 19.4, 18.6, 18.4, 18.0, 17.2, −3.4, −4.8 ppm; HR-MS (ESI-TOF) calcd for $C_{56}H_{82}O_8N_2Si_2Na^+$ $[M + Na]^+$ 989.5502, found 989.5528.

(2Z,4E,6S,8R,9Z,12S,19Z,21E,23S,25R,26Z,29S)-12,29-Bis[(3S,4E)-3-hydroxy-2-methylhex-4-en-2-yl]-13,17,30,34-tetraoxa-35,36-diazapentacyclo[30.2.1.1^{15,18}*.0*^{6,8}*.0*^{23,25}*]hexatriaconta- 1(35),2,4,9,-15,18(36),19,21,26,32-decaene-14,31-dione (**5**).* To a stirred solution of bis-silylated **37** (2.0 mg, 2.1 μmol, 1.0 equiv) in DMF (70 μL) and H_2O (0.5 μL, 29 μmol, 14 equiv) was added TASF (2.9 mg, 10 μmol, 5.0 equiv), and the reaction mixture was heated at 40 °C and stirred for 48 h. The resulting mixture was purified through a small silica pad (10 cm, SiO_2, hexanes/EtOAc 1:1, *v*/*v* → 0:1, *v*/*v*) . The resulting fractions containing the desired products were combined, concentrated and purified again by flash column chromatography (SiO_2, hexanes/EtOAc 1:1, *v*/*v* → 1:4, *v*/*v* → 0:1, *v*/*v*) to yield the titled compound (**5**; 1.5 mg, 2.0 μmol, 98% yield) as colorless oil.

5: R_f = 0.23 (hexanes/EtOAc 2:3, *v*/*v*); $[\alpha]_D^{25}$ = −74.7 (*c* = 0.15, $CHCl_3$); IR (film) ν_{max} = 3428, 2924, 2854, 1736, 1629, 1556, 1323, 1145, 993, 757 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.03 (s, 2 H), 6.89 (dd, *J* = 14.9, 11.6 Hz, 2 H), 6.13 (t, *J* = 11.7 Hz, 2 H), 5.86 (d, *J* = 11.7 Hz, 2 H), 5.64 (dq, *J* = 15.0, 6.3 Hz, 2 H), 5.54 (ddd, *J* = 15.1, 7.5, 1.6 Hz, 2 H), 5.49 (td, *J* = 11.4, 4.9 Hz, 2 H), 5.43 (dd, *J* = 14.8, 10.5 Hz, 2 H), 5.33 (dd, *J* = 11.5, 2.0 Hz, 2 H), 5.10 (t, *J* = 10.8 Hz, 2 H), 3.85 (d, *J* = 7.4 Hz, 2 H), 3.35 (s, 2 H), 2.73 (q, *J* = 11.9 Hz, 2 H), 2.31−2.24 (m, 2 H), 2.13−2.07 (m, 2 H), 1.82−1.74 (m, 2 H), 1.70 (d, *J* = 6.4 Hz, 6 H), 1.30 (td, *J* = 8.4, 4.9 Hz, 2 H), 0.99 (s, 6 H), 0.93 (s, 6 H), 0.60 (q, *J* = 5.5 Hz, 2 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.0, 160.9, 142.41, 142.38, 136.6, 133.5, 131.9, 129.7, 129.4, 126.6, 126.4, 110.3, 77.6, 76.8, 41.6, 28.2, 23.5, 19.6, 18.8, 18.6, 18.1, 17.3 ppm; HR-MS (ESI-TOF) calcd for $C_{44}H_{54}O_8N_2Na^+$ $[M + Na]^+$ 761.3772, found 761.3778.

*Methyl 2-[(Tripropan-2-ylsilyl)ethynyl]-1,3-thiazole-4-carboxylate (**S4**).* To a stirred, degassed solution of bromide **17** (1.00 g, 4.50 mmol, 1.0 equiv) and ethynyltriisopropylsilane (4.96 mL, 4.03 g, 22.1 mmol, 5.0 equiv) in a mixture of DMF and Et_3N (10 mL, 1:1, v/v) were added $Pd(PPh_3)_4$ (102 mg, 0.221 mmol, 0.05 equiv) and CuI (42 mg, 0.221 mmol, 0.05 equiv), and the reaction mixture was degassed by bubbling Ar, sealed, and heated to 60 °C for 16 h. Then the resulting mixture was cooled to 23 °C and partitioned between Et_2O (50 mL) and H_2O (50 mL). Extraction with Et_2O (2 × 50 mL) followed by drying over $MgSO_4$, filtration, and concentration under reduced pressure gave the crude residue which was purified by flash column chromatography (SiO_2, hexanes/EtOAc 9:1, *v*/*v* → 8:1, *v*/*v*) to give thiazole **S4** (1.31 g, 4.05 mmol, 90% yield) as a colorless liquid.

S4: R_f = 0.55 (hexanes/EtOAc 8:2, *v*/*v*), IR (film) ν_{max} = 2944, 2923, 2893, 2865, 1725, 1448, 1242, 1214, 1151, 1086, 994, 881, 779, 750, 677, 661 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.16 (s, 1 H), 3.96 (s, 3 H), 1.17−1.12 (m, 3 H), 1.13 (d, *J* = 5.5 Hz, 18 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 161.5, 149.5, 147.1, 128.7, 100.3, 97.6, 52.8, 18.7, 11.3 ppm; HR-MS (ESI) calcd for $C_{16}H_{25}NO_2SSiNa^+$ $[M + Na]^+$ 346.1267, found 346.1273.

*Methyl 2-Ethynyl-1,3-thiazole-4-carboxylate (**38**).* To a stirred solution of thiazole **S4** (8.59 g, 26.6 mmol, 1.0 equiv) in THF (300 mL) at 0 °C was added AcOH (6.08 mL, 6.38 g, 106 mmol, 4.0 equiv) followed by TBAF (1 M in THF, 53.3 mL, 53.3 mmol, 2.0 equiv), and the reaction mixture was stirred at 0 °C for 1 h. Then the resulting mixture was quenched with by addition of satd aq NH_4Cl (200 mL), extracted with Et_2O (3 × 250 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, hexanes/EtOAc 17:3, *v*/*v* → 1:1, *v*/*v*) to give thiazole **38** (4.18 g, 25.0 mmol, 94% yield) as a white amorphous solid.

38: R_f = 0.21 (hexanes/EtOAc 8:2, *v*/*v*), IR (film) ν_{max} = 3237, 3104, 2111, 1708, 1489, 1442, 1319, 1250, 1139, 988, 764 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.20 (s, 1 H), 3.97 (s, 3 H), 3.51 (s, 1 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 161.3, 148.4, 147.4, 129.1, 83.6, 75.7, 52.8 ppm; HR-MS (ESI) calcd for $C_7H_5NO_2SNa^+$ $[M + Na]^+$ 189.9933, found 189.9933.

*Methyl 2-[(Z)-2-Bromoethenyl]-1,3-thiazole-4-carboxylate (**16**).* A dry round-bottom flask equipped with a stir bar was charged with LiBr (16 mg, 0.18 mmol, 1.5 equiv) and LiOAc (36 mg, 0.54 mmol, 4.5 equiv), and the solids were dried by stirring at 70 °C under high vacuum for 1 h. Once the solids were cooled back to 25 °C, AcOH (1 mL) and thiazole **38** (20 mg, 0.12 mmol, 1.0 equiv) were added, and the sealed reaction mixture was heated to 90 °C for 16 h. After being cooled back to 23 °C, the reaction mixture was diluted with EtOAc (20 mL), washed with 1 M NaOH (2 × 10 mL), $Na_2S_2O_3$ (10 mL), and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, hexanes/EtOAc 8:2, *v*/*v* → 6:4, *v*/*v*) to give thiazole **16** (21 mg, 0.085 mmol, 71% yield) and the corresponding (*E*)-isomer (2.0 mg, 8.1 μmol, 7% yield) as white amorphous solids, respectively.

16: R_f = 0.35 (hexanes/EtOAc 7:3, *v*/*v*), IR (film) ν_{max} = 3118, 1722, 1614, 1496, 1437, 1298, 1260, 1243, 1135, 987, 726 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.27 (s, 1 H), 7.69 (d, *J* = 8.1 Hz, 1 H), 6.91 (d, *J* = 8.1 Hz, 1 H), 3.98 (s, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.4, 162.0, 146.4, 128.0, 127.9, 112.9, 52.8 ppm; HR-MS (ESI) calcd for $C_7H_6BrNO_2SNa^+$ $[M + Na]^+$ 269.9195, found 269.9197.

*Methyl 2-[(E)-2-Bromoethenyl]-1,3-thiazole-4-carboxylate [**S5**; (E)-isomer of **16**]:* R_f = 0.46 (hexanes/EtOAc 7:3, *v*/*v*), IR (film) ν_{max} = 2953, 2924, 1724, 1596, 1498, 1457, 1343, 1324, 1245, 1217, 1094, 929 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.12 (s, 1 H), 7.37 (d, *J* = 14.1 Hz, 1 H), 7.32 (dd, *J* = 14.1, 0.6 Hz, 1 H), 3.96 (s, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.6, 161.7, 147.7, 129.9, 127.3, 115.6, 52.8 ppm; HR-MS (ESI) calcd for $C_7H_6BrNO_2SNa^+$ $[M + Na]^+$ 269.9195, found 269.9200.

*2-Ethynyl-1,3-thiazole-4-carboxylic Acid (**39**).* To a stirred solution of methyl ester **38** (2.72 g, 16.3 mmol, 1.0 equiv) in a THF/H_2O mixture (55:44 mL, *v*/*v*) at 23 °C was added LiOH hydrate (945 mg, 24.5 mmol, 1.5 equiv), and the reaction mixture was stirred for 1 h at 23 °C. Then aq HCl (1 M; 40 mL) was added dropwise until the pH was <2, and the reaction mixture was extracted with EtOAc (5 × 75 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the titled product (**39**; 2.47 g, 16.1 mmol, 99% yield) as a white amorphous solid.

39: R_f = 0.07 (hexanes/EtOAc 1:1, *v*/*v*), IR (film) ν_{max} = 3287, 3094, 1675, 1455, 1245, 1098, 881, 848, 776, 666 cm^{-1}; ^1H NMR (600 MHz, CD_3OD) δ 8.41 (s, 1 H), 4.33 (s, 1 H) ppm; ^{13}C NMR (151 MHz, CD_3OD) δ 163.2, 149.9, 148.9, 130.9, 85.9, 76.2 ppm; HR-MS (CI) calcd for $C_6H_3NO_2S^+$ $[M + H]^+$ 152.9885, found 152.9884.

*2-[(Z)-2-Bromoethenyl]-1,3-thiazole-4-carboxylic Acid (**15**).* A dry round-bottom flask equipped with a stir bar was charged with LiBr (2.15 g, 24.2 mmol, 1.5 equiv) and LiOAc (4.85 g, 72.6 mmol, 4.5 equiv), and the solids were dried while being stirred at 80 °C under high vacuum for 3 h. Once the solids were cooled back to 23 °C, AcOH (66 mL) and thiazole **39** (2.47 g, 16.1 mmol, 1.0 equiv) were added, and the sealed reaction vessel was heated at 100 °C for 16 h. After being cooled to 23 °C, the reaction mixture was diluted with EtOAc (300 mL), washed with aq NaOH (1 M; 2 × 100 mL), $Na_2S_2O_3$ (100 mL), and brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give thiazole **15** (2.86 mg, 12.2 mmol, 75% yield, > 20:1 dr) as a white amorphous solid.

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15: R_f = 0.21 (EtOAc with 1% HCO_2H), IR (film) ν_{max} = 3104, 1673, 1482, 1438, 1375, 1300, 1269, 1236, 1101, 733 cm^{-1}; ^1H NMR (600 MHz, CD_3OD) δ 8.44 (s, 1 H), 7.65 (d, J = 8.1 Hz, 1 H), 7.16 (d, J = 8.1 Hz, 1 H) ppm; ^{13}C NMR (151 MHz, CD_3OD) δ 164.8, 164.1, 148.2, 129.1, 128.3, 114.3 ppm; HR-MS (ESI) calcd for $C_6H_4BrNO_2S^+$ $[M + H]^+$ 233.9219, found 233.9215.

*(3R,4E,6Z)-3-Methoxy-7-(tripropan-2-ylsilyl)hepta-4,6-dienoic Acid (**S6**).* To a stirred solution of **12** (4.40 g, 9.65 mmol, 1.0 equiv) in a THF/H_2O mixture (50:12 mL, *v*/*v*) at 0 °C was added LiOH hydrate (630 mg, 14.5 mmol, 1.5 equiv), and the reaction mixture was allowed to warm to 23 °C and stirred for 16 h. Then aq HCl (1 M; 15 mL) was added dropwise until the pH was <3, and the reaction mixture was extracted with EtOAc (5 × 75 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was then filtered through a plug of silica (SiO_2, hexanes/EtOAc 7:3, *v*/*v* with 1% HCOOH → 1:1, *v*/*v* with 1% HCOOH) to give the crude product (4.16 g, contaminated with the auxiliary), which was used in the next step without further purification. A small aliquot was purified by preparative TLC for analytical purposes of **S6**.

S6: colorless oil; R_f = 0.75 (hexanes/EtOAc 1:1, *v*/*v*), $[\alpha]_D^{25}$ = −12.0 (*c* = 0.5, $CHCl_3$); IR (film) ν_{max} 2941, 2892, 2865, 1714, 1566, 1464, 1301, 1079, 1000, 882, 666 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.95 (dd, J = 14.5, 11.1 Hz, 1 H), 6.38 (dd, J = 15.1, 11.1 Hz, 1 H), 5.66 (d, J = 14.4 Hz, 1 H), 5.59 (dd, J = 15.1, 7.8 Hz, 1 H), 4.09 (td, J = 8.1, 4.8 Hz, 1 H), 3.30 (s, 3 H), 2.65 (dd, J = 15.6, 8.4 Hz, 1 H), 2.55 (dd, J = 15.6, 4.8 Hz, 1 H), 1.16 (h, J = 7.2 Hz, 3 H), 1.06 (d, J = 7.2 Hz, 18 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 175.0, 145.6, 135.2, 133.2, 130.2, 78.2, 56.6, 40.8, 18.9, 12.3 ppm; HR-MS (ESI) calcd for $C_{17}H_{32}O_3SiNa^+$ $[M + Na]^+$ 335.2013, found 335.2017.

*(3R,4E,6Z)-3-Methoxy-7-(tripropan-2-ylsilyl)hepta-4,6-dienamide (**40**).* To a solution of crude acid **S6** (4.16 g) in Et_2O (140 mL) was added $(COCl)_2$ (2.53 mL, 3.74 g, 29.5 mmol, 3.0 equiv) followed by two drops of DMF at 0 °C after which the reaction mixture was allowed to warm to 23 °C and stirred for 1 h. Then the volatiles were removed under reduced pressure, the residue was redissolved in CH_2Cl_2 (100 mL) at 0 °C, and then NH_3 (7 M in MeOH, 11 mL, 77 mmol, 8.0 equiv) was added. The reaction mixture was then allowed to warm to 23 °C and stirred for 16 h before being diluted with brine (100 mL), extracted with CH_2Cl_2 (3 × 100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, hexanes/EtOAc 1:1, *v*/*v* → 0:1, *v*/*v*) to give amide **40** (2.49 g, 7.99 mmol, 83% yield over three steps) as a colorless oil.

40: R_f = 0.18 (hexanes/EtOAc 1:1, *v*/*v*), $[\alpha]_D^{25}$ = +10.3 (*c* = 1.0, $CHCl_3$); IR (film) ν_{max} = 3341, 3200, 2941, 2890, 2865, 1668, 1618, 1566, 1463, 1401, 1096, 1074, 999, 882, 665 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.95 (dd, J = 14.5, 11.1 Hz, 1 H), 6.36 (dd, J = 15.1, 11.1 Hz, 1 H), 6.23 (s, 1 H), 5.64 (d, J = 14.5 Hz, 1 H), 5.59 (dd, J = 15.1, 7.7 Hz, 1 H), 5.50 (s, 1 H), 4.04 (td, J = 7.8, 4.1 Hz, 1 H), 3.30 (s, 3 H), 2.50−2.37 (m, 2 H), 1.15 (h, J = 7.2, 6.8 Hz, 3 H), 1.05 (d, J = 7.3 Hz, 18 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.0, 145.7, 134.7, 133.6, 129.8, 78.6, 56.6, 42.6, 18.9, 12.3 ppm; HR-MS (ESI) calcd for $C_{17}H_{33}NO_2SiNa^+$ $[M + Na]^+$ 334.2173, found 334.2176.

*(3R,4E,6Z)-3-Methoxy-7-(tripropan-2-ylsilyl)hepta-4,6-dienethioamide (**41**).* To a stirred solution of **40** (2.00 g, 6.42 mmol, 1.0 equiv) in THF (50 mL) at 23 °C was added Lawesson's reagent (1.81 g, 4.47 mmol, 0.7 equiv), and the reaction mixture was stirred for 1 h. Then, the resulting mixture was diluted with brine (50 mL), extracted with Et_2O (3 × 50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, hexanes/EtOAc 8:2, *v*/*v* → 6:4, *v*/*v*) to give thioamide **41** (1.97 g, 6.01 mmol, 94% yield) as a yellow oil.

41: R_f = 0.44 (hexanes/EtOAc 7:3, *v*/*v*), $[\alpha]_D^{25}$ = +44.4 (*c* = 0.5, $CHCl_3$); IR (film) ν_{max} = 3306, 3177, 2941, 2891, 2865 1620, 1566, 1462, 1410, 1308, 1230, 1088, 998, 957, 882, 711, 665 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.00 (br s, 1 H), 7.47 (br s, 1 H), 6.95 (dd, J = 14.5, 11.1 Hz, 1 H), 6.37 (dd, J = 15.1, 11.2 Hz, 1 H), 5.66 (d, J = 14.4 Hz, 1 H), 5.57 (dd, J = 15.1, 7.5 Hz, 1 H), 4.07 (td, J = 8.0, 3.2 Hz, 1 H), 3.31 (s, 3 H), 3.01 (dd, J = 15.3, 3.0 Hz, 1 H), 2.90 (dd, J = 15.3, 8.4 Hz, 1 H), 1.21−1.11 (m, 3 H), 1.06 (d, J = 7.2 Hz, 18 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 207.0, 145.6, 135.0, 132.7, 130.2, 80.4, 56.6, 50.8, 19.0, 12.3 ppm; HR-MS (ESI) calcd for $C_{17}H_{33}NOSSiNa^+$ $[M + Na]^+$ 350.1944, found 350.1946.

*Methyl 2-[(2R,3E,5Z)-2-Methoxy-6-(tripropan-2-ylsilyl)hexa-3,5-dien-1-yl]-1,3-thiazole-4-carboxylate (**43**).* To a stirred solution of thioamide **41** (1.95 g, 5.95 mmol, 1.0 equiv) in acetone (30 mL) at −10 °C was added methyl bromopyruvate (**42**; 0.894 mL, 1.52 g, 8.40 mmol, 1.4 equiv), and the mixture was stirred for 2 h at −10 °C. Then, the reaction mixture was quenched by addition of satd aq $NaHCO_3$ solution (50 mL), diluted with $CHCl_3$ (50 mL), and extracted with CH_2Cl_2 (3 × 50 mL) followed by drying with $MgSO_4$ and concentration under reduced pressure.

The crude residue was then dissolved in CH_2Cl_2 (50 mL) at −30 °C, pyridine (1.21 mL, 1.19 g, 15.0 mmol, 2.5 equiv) and TFAA (1.06 mL, 1.60 g, 7.63 mmol, 1.3 equiv) were added sequentially, and the reaction mixture was allowed to warm to 23 °C over 2 h. Then the resulting mixture was quenched by addition of satd aq $NaHCO_3$ solution (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL), followed by drying with $MgSO_4$ and concentration under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, hexanes/EtOAc 8:2, *v*/*v* → 6:4, *v*/*v*) gave thiazole **43** (1.47 g, 3.59 mmol, 60% yield over two steps) as a light brown oil.

43: R_f = 0.42 (hexanes/EtOAc 7:3, *v*/*v*), $[\alpha]_D^{25}$ = +14.8 (*c* = 1.0, $CHCl_3$); IR (film) ν_{max} = 2941, 2890, 2864, 1740, 1721, 1483, 1463, 1238, 1208, 1093, 997, 882, 666 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.09 (s, 1 H), 6.94 (ddd, J = 14.4, 11.2, 0.8 Hz, 1 H), 6.33 (ddt, J = 15.1, 11.1, 1.0 Hz, 1 H), 5.63 (d, J = 14.5 Hz, 1 H), 5.61 (dd, J = 15.1, 7.6 Hz, 2 H), 4.03−3.96 (m, 1 H), 3.95 (s, 3 H), 3.31 (dd, J = 10.2, 4.8 Hz, 1 H), 3.29 (s, 3 H), 3.25 (dd, J = 15.0, 8.4 Hz, 1 H), 1.12 (ddt, J = 13.7, 8.5, 6.6 Hz, 3 H), 1.03 (ap. t, J = 6.8 Hz, 18 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 168.0, 162.1, 146.1, 145.7, 135.2, 133.7, 129.9, 128.4, 80.6, 56.6, 52.6, 39.9, 18.9, 12.3 ppm; HR-MS (ESI) calcd for $C_{21}H_{35}NO_3SSiNa^+$ $[M + Na]^+$ 432.1999, found 432.2006.

*Methyl 2-[(2R,3E,5Z)-6-Bromo-2-methoxyhexa-3,5-dien-1-yl]-1,3-thiazole-4-carboxylate (**14**).* To a stirred solution of thiazole **43** (1.46 g, 3.56 mmol, 1.0 equiv) in HFIP (60 mL) at 0 °C that was protected from light with aluminium foil were sequentially added Ag_2CO_3 (998 mg, 3.62 mmol, 1.02 equiv) and NBS (803 mg, 4.51 mmol, 1.25 equiv), and the reaction mixture was stirred for 1.5 h at 0 °C in the dark. Then, the reaction mixture was quenched by the addition of water (200 mL) and satd aq $Na_2S_2O_3$ (50 mL), extracted with CH_2Cl_2 (3 × 150 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, hexanes/EtOAc 7:3, *v*/*v* → 3:7, *v*/*v*) to yield bromide **14** (0.620 g, 1.87 mmol, 52% yield) as a light brown oil.

14: R_f = 0.34 (hexanes/EtOAc 7:3, *v*/*v*), $[\alpha]_D^{25}$ = +56.0 (*c* = 0.2, $CHCl_3$); IR (film) ν_{max} = 2947, 2864, 2826, 1718, 1483, 1435, 1342, 1320, 1239, 1211, 1092, 980, 778, 755 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.12 (s, 1 H), 6.67−6.56 (m, 2 H), 6.25−6.18 (m, 1 H), 5.86−5.69 (m, 1 H), 4.06 (td, J = 8.0, 4.0 Hz, 1 H), 3.95 (s, 3 H), 3.37−3.28 (m, 4 H), 3.26 (dd, J = 15.0, 8.4 Hz, 1 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.8, 162.1, 146.1, 135.6, 131.5, 129.2, 128.5, 109.8, 80.5, 57.0, 52.6, 39.8 ppm; HR-MS (ESI) calcd for $C_{12}H_{14}BrNO_3SNa^+$ $[M + Na]^+$ 353.9770, found 353.9774.

*Methyl 2-[(2R,3E,5Z,7Z,10S,12S,13E)-12-{[tert-Butyl(dimethyl)-silyl]oxy}-10-hydroxy-2-methoxy-11,11-dimethylpentadeca-3,5,7,13-tetraen-1-yl]-1,3-thiazole-4-carboxylate (**44**).* To a stirred solution of bromide **14** (100 mg, 0.301 mmol, 1.0 equiv) and boronic acid derivative **13** (137 mg, 0.421 mmol, 1.4 equiv) in a mixture of THF/water (1.60 mL, 3:1, *v*/*v*) was added thallium carbonate (706 mg, 1.51 mmol, 5.0 equiv)/ and the solution was degassed for 10 min by bubbling Ar through the mixture. Subsequently, Pd(dppf)Cl_2 (22 mg, 0.030 mmol, 0.10 equiv) was added, and the reaction mixture was stirred at 23 °C for 16 h while shielded from light by aluminum foil. The reaction mixture was then filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, hexanes/

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EtOAc 7:3, *v/v*) to yield compound **44** (100 mg, 0.182 mmol, 59% yield) as a colorless oil.

44: R_f = 0.44 (hexanes/EtOAc 7:3, *v/v*), $[\alpha]_D^{25}$ = +5.5 (*c* = 1.0, $CHCl_3$); IR (film) ν_{max} = 3463, 2955, 2929, 2856, 1725, 1471, 1249, 1214, 1093, 1051, 1002, 972, 836, 776 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.10 (s, 1 H), 6.72 (dd, *J* = 15.2, 11.3 Hz, 1 H), 6.52 (t, *J* = 11.2 Hz, 1 H), 6.30 (t, *J* = 11.4 Hz, 1 H), 5.99 (t, *J* = 11.1 Hz, 1 H), 5.77 (dt, *J* = 10.6, 7.5 Hz, 1 H), 5.62−5.48 (m, 3 H), 4.32 (br. s, 1 H), 4.01 (td, *J* = 8.0, 4.4 Hz, 1 H), 3.94 (s, 3 H), 3.85 (d, *J* = 6.9 Hz, 1 H), 3.71 (dd, *J* = 9.7, 3.0 Hz, 1 H), 3.34−3.29 (m, 1 H), 3.30 (s, 3 H), 3.25 (dd, *J* = 15.1, 8.3 Hz, 1 H), 2.38−2.19 (m, 2 H), 1.71 (d, *J* = 5.2 Hz, 3 H), 1.00 (s, 3 H), 0.88 (s, 9 H), 0.75 (s, 3 H), 0.07 (s, 3 H), 0.01 (s, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 168.1, 162.1, 146.0, 132.4, 132.2, 130.3, 129.1, 128.9, 128.4, 127.8, 126.0, 124.4, 84.7, 80.8, 76.3, 56.7, 52.5, 41.1, 40.1, 30.2, 26.0, 22.9, 19.8, 18.2, 17.9, −3.8, −5.0 ppm; HR-MS (ESI) calcd for $C_{29}H_{47}NO_5SSiNa^+$ $[M + Na]^+$ 572.2836, found 572.2834.

*(2E,4R,6S,8Z,10Z,12E,14R)-4-{[tert-Butyl(dimethyl)silyl]oxy}-14-methoxy-15-[4-(methoxycarbonyl)-1,3-thiazol-2-yl]-5,5-dimethylpentadeca-2,8,10,12-tetraen-6-yl 2-[(Z)-2-Bromoethenyl]-1,3-thiazole-4-carboxylate (**45**).* To a stirred solution of hydroxy compound **44** (90 mg, 0.164 mmol, 1.0 equiv) and carboxylic acid **15** (46 mg, 0.197 mmol, 1.2 equiv) in toluene (5 mL) at 23 °C were added Et_3N (0.14 mL, 0.102 g, 1.00 mmol, 6.0 equiv) and DMAP (0.157 g, 1.29 mmol, 8.0 equiv), and the solution was cooled to 0 °C before 2,4,6-trichlorobenzoyl chloride (77 μL, 120 mg, 0.493 mmol, 3.0 equiv) was added dropwise. Then the reaction mixture was allowed to warm to 23 °C and stirred for 3 h before being quenched by the addition of satd aq $NaHCO_3$ (10 mL). The aqueous layer was extracted with EtOAc (3 × 20 mL), and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, hexanes/EtOAc 7:3, *v/v*) to yield bromide **45** (109 mg, 0.142 mmol, 87% yield) as a colorless oil.

45: R_f = 0.27 (hexanes/EtOAc 7:3, *v/v*), $[\alpha]_D^{25}$ = −59.4 (*c* = 0.5, $CHCl_3$); IR (film) ν_{max} = 2954, 2928, 2885, 1733, 1471, 1303, 1240, 1210, 1093, 1056, 973, 858, 836, 776, 748 cm^{-1}; ^1H NMR (600 MHz, CDCl3) δ 8.09 (s, 1 H), 8.08 (s, 1 H), 7.68 (d, *J* = 8.2 Hz, 1 H), 6.87 (d, *J* = 8.2 Hz, 1 H), 6.59 (dd, *J* = 15.2, 11.3 Hz, 1 H), 6.39 (t, *J* = 11.4 Hz, 1 H), 6.26 (t, *J* = 11.3 Hz, 1 H), 5.95 (t, *J* = 11.1 Hz, 1 H), 5.58−5.50 (m, 3 H), 5.26 (dd, *J* = 9.8, 3.3 Hz, 1 H), 3.97 (dd, *J* = 8.0, 4.1 Hz, 1 H), 3.94 (s, 3 H), 3.86 (d, *J* = 7.4 Hz, 1 H), 3.33−3.27 (m, 1 H), 3.26 (s, 3 H), 3.21 (dd, *J* = 15.1, 8.3 Hz, 1 H), 2.66 (dt, *J* = 15.4, 9.2 Hz, 1 H), 2.60−2.47 (m, 1 H), 1.67 (d, *J* = 5.0 Hz, 3 H), 0.99 (s, 3 H), 0.96 (s, 3 H), 0.87 (s, 9 H), −0.02 (s, 3 H), −0.05 (s, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 168.0, 163.0, 162.1, 160.7, 147.0, 146.0, 132.6, 131.4, 130.0, 128.7, 128.4, 128.3, 128.2, 127.0, 125.5, 125.4, 112.4, 80.6, 79.4, 78.3, 56.7, 52.5, 43.0, 40.0, 28.7, 26.1, 20.4, 19.6, 18.3, 17.9, −3.4, −4.8 ppm; HR-MS (ESI) calcd for $C_{35}H_{49}BrN_2O_6S_2Si^+$ $[M + H]^+$ 765.2057, found 765.2060.

*Methyl 2-{(2R,3E,5Z,7Z,10S,12R,13E)-12-{[tert-Butyl(dimethyl)silyl]oxy}-10-[({2-[(1Z,3E)-4-{(1S,2R)-2-[(1Z,4S,6R,7E)-6-{[tert-butyl(dimethyl)silyl]oxy}-4-hydroxy-5,5-dimethylnona-1,7-dien-1-yl]cyclopropyl}buta-1,3-dien-1-yl]-1,3-thiazol-4-yl}carbonyl)oxy]-2-methoxy-11,11-dimethylpentadeca-3,5,7,13-tetraen-1-yl}-1,3-thiazole-4-carboxylate (**46**).* A stirred solution of bromide **45** (100 mg, 0.131 mmol, 1.0 equiv), stannane **8** (112 mg, 0.171 mmol, 1.3 equiv), CuI (106 mg, 0.557 mmol, 4.25 equiv), $AsPh_3$ (81 mg, 0.264 mmol, 2.0 equiv), and $Pd_2(dba)_3$ (61 mg, 0.067 mmol, 0.5 equiv) in DMF (1.3 mL) degassed three times with Ar by the freeze−pump−thaw method was stirred at 23 °C for 3 h, after which time the reaction mixture was filtered through a pad of Celite, diluted with EtOAc (15 mL), and washed three times with brine (3 × 10 mL), and then the combined aqueous layers were reextracted with EtOAc (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, hexanes/EtOAc 17:3, *v/v* → 7:3, *v/v*) to give compound **46** (129 mg, 0.123 mmol, 94% yield) as a light brown oil.

46: R_f = 0.41 (hexanes/EtOAc 7:3, *v/v*), $[\alpha]_D^{25}$ = −16.5 (*c* = 0.2, $CHCl_3$); IR (film) ν_{max} = 3480, 2956, 2929, 2856, 1721, 1627, 1471, 1246, 1209, 1093, 1055, 1003, 972, 857, 836, 776 cm^{-1}; ^1H NMR (600 MHz, CD_3CN) δ 8.07 (s, 1 H), 8.06 (s, 1 H), 7.57 (dd, *J* = 15.1, 11.4 Hz, 1 H), 6.60 (dd, *J* = 15.2, 11.4 Hz, 1 H), 6.43−6.34 (m, 2 H), 6.31−6.23 (m, 2 H), 5.94−5.82 (m, 2 H), 5.57−5.43 (m, 6 H), 5.18−5.07 (m, 2 H), 3.96 (ap. t, *J* = 7.6 Hz, 2 H), 3.91 (d, *J* = 8.4 Hz, 1 H), 3.79 (s, 3 H), 3.54−3.43 (m, 2 H), 3.16 (s, 3 H), 3.15−3.12 (m, 1 H), 2.63−2.54 (m, 1 H), 2.54−2.47 (m, 1 H), 2.27 (dd, *J* = 14.6, 7.4 Hz, 2 H), 2.10−1.92 (m, 2 H), 1.88−1.80 (m, 1 H), 1.65−1.58 (m, 6 H), 1.25 (td, *J* = 8.2, 4.5 Hz, 1 H), 0.94 (s, 3 H), 0.91 (s, 3 H), 0.81 (s, 9 H), 0.81 (s, 9 H), 0.69 (ap. p, *J* = 5.9 Hz, 1 H), 0.00 (s, 3 H), −0.06 (s, 3 H), −0.08 (s, 3 H), −0.10 (s, 3 H) ppm; ^{13}C NMR (151 MHz, CD_3CN) δ 168.7, 166.2, 162.7, 161.6, 148.7, 146.7, 144.8, 135.8, 134.1, 132.2, 131.7, 131.0, 130.7, 130.0, 129.6, 129.5, 129.4, 129.33, 129.31, 128.5, 128.1, 126.2, 126.1, 117.4, 82.8, 81.2, 79.7, 78.4, 76.9, 56.7, 52.6, 43.7, 42.2, 40.2, 30.9, 29.3, 26.4, 26.3, 23.7, 21.5, 20.31, 20.29, 19.8, 19.5, 18.8, 18.7, 17.88, 17.86, 17.2, −3.2, −3.5, −4.7, −4.8 ppm; HR-MS (ESI) calcd for $C_{57}H_{88}N_2O_8S_2Si_2^+$ $[M + H]^+$ 1049.5593, found 1049.5603.

*(2Z,4E,6S,8R,9Z,12S,20R,21E,23Z,25Z,28S)-12-[(3R,4E)-3-{[tert-Butyl(dimethyl)silyl]oxy}-2-methylhex-4-en-2-yl]-28-[(3S,4E)-3-{[tert-butyl(dimethyl)silyl]oxy}-2-methylhex-4-en-2-yl]-20-methoxy-13,29-dioxa-17,33-dithia-34,35-diazatetracyclo[29.2.1.1^{15,18}.0^{6,8}]pentatriaconta-1(34),2,4,9,15,18(35),21,23,25,31-decaene-14,30-dione (**47**).* To a stirred solution of hydroxy methyl ester **46** (60.0 mg, 57.2 μmol, 1.0 equiv) in THF (2 mL) at 23 °C was added dropwise a satd solution of barium hydroxide octahydrate (0.56 mL, MeOH/H_2O 3:2, *v/v*). The reaction mixture was stirred for 3 h before being quenched by the addition of satd aq NH_4Cl (10 mL), and the aqueous phase was extracted with EtOAc (4 × 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was used crude in the next reaction.

To a stirred solution of the crude carboxylic acid in toluene (2.4 mL) was added a solution of 2,4,6-trichlorobenzoyl chloride (92 μL, 140 mg, 0.57 mmol, 10.0 equiv) in toluene (1.0 mL) and a solution of Et_3N (90 μL, 0.63 mmol, 11.0 equiv) in toluene (1.0 mL). The mixture was stirred for 1 h at 23 °C, and then the resulting mixture was diluted by the addition of toluene (5.0 mL) and added over 3 h, via a syringe pump, to a solution of DMAP (30 mg, 0.24 mmol, 4.0 equiv) in toluene (10 mL) heated at 30 °C. After the addition was completed, stirring was continued for 16 h before the reaction was quenched by the addition of satd aq $NaHCO_3$ (20 mL). The aqueous layer was extracted with EtOAc (4 × 20 mL), and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, hexanes/EtOAc 17:3, *v/v* → 7:3, *v/v*) to give compound **47** (24 mg, 24 μmol, 41% yield over two steps) as a colorless oil.

47: R_f = 0.40 (hexanes/EtOAc 7:3, *v/v*), $[\alpha]_D^{25}$ = −65.3 (*c* = 1.0, $CHCl_3$; IR (film) ν_{max} = 2956, 2928, 2856, 1732, 1627, 1471, 1386, 1361, 1248, 1199, 1094, 1055, 996, 972, 858, 836, 775 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.92 (s, 1 H), 7.83 (s, 1 H), 6.74−6.66 (m, 1 H), 6.47 (d, *J* = 11.8 Hz, 1 H), 6.42−6.33 (m, 2 H), 6.31−6.23 (m, 1 H), 6.22−6.14 (m, 1 H), 5.89 (t, *J* = 11.0 Hz, 1 H), 5.61 (dd, *J* = 15.2, 8.2 Hz, 1 H), 5.57−5.49 (m, 4 H), 5.43 (td, *J* = 10.8, 4.8 Hz, 1 H), 5.23 (ddd, *J* = 16.2, 11.1, 2.6 Hz, 2 H), 5.06 (t, *J* = 10.7 Hz, 1 H), 3.86−3.84 (m, 2 H), 3.41 (dd, *J* = 15.2, 4.8 Hz, 1 H), 3.19 (s, 3 H), 2.99 (dd, *J* = 15.2, 5.7 Hz, 1 H), 2.84−2.68 (m, 2 H), 2.36−2.26 (m, 2 H), 2.13−2.06 (m, 1 H), 1.75 (dtd, *J* = 10.3, 8.3, 5.6 Hz, 1 H), 1.70−1.65 (m, 6 H), 1.67−1.60 (m, 1 H), 1.43 (d, *J* = 5.7 Hz, 1 H), 1.39−1.31 (m, 1 H), 1.32−1.26 (m, 1 H), 1.01 (s, 3 H), 1.00 (s, 3 H), 0.99 (s, 3 H), 0.95 (s, 3 H), 0.88 (s, 9H) 0.87 (s, 9 H), 0.59 (ap. q, *J* = 5.6 Hz, 1 H), 0.01 (s, 3 H), 0.00 (s, 3 H), −0.04 (s, 3 H), −0.05 (s, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.6, 164.3, 161.0, 160.3, 146.9, 146.7, 143.1, 134.2, 133.0, 131.4, 130.5, 130.4, 128.5, 128.2, 127.4, 127.0, 126.6, 126.3, 125.8, 125.4, 119.0, 80.3, 79.6, 79.4, 77.7, 56.8, 42.74, 42.71, 40.6, 29.9, 28.92, 28.90, 28.0, 27.0, 26.1, 23.4, 20.8, 20.5, 19.7, 19.5, 19.4, 18.4, 18.0, 17.9, 17.7, 17.3, 13.8, −3.37, −3.38, −4.73, −4.75 ppm; HR-MS (ESI) calcd for $C_{56}H_{84}N_2O_7S_2Si_2Na^+$ $[M + Na]^+$ 1039.5151, found 1039.5164.

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*(2Z,4E,6S,8R,9Z,12S,20R,21E,23Z,25Z,28S)-12,28-Bis[(3S,4E)-3-hydroxy-2-methylhex-4-en-2-yl]-20-methoxy-13,29-dioxa-17,33-dithia-34,35-diazatetracyclo[29.2.1.1^{15,18}.0^{6,8}]pentatriaconta-1(34),2,4,9,15,18(35),21,23,25,31-decaene-14,30-dione (**6**).* To a stirred solution of compound **47** (24 mg, 23.6 μmol, 1.0 equiv) in degassed MeOH (5 mL), in a plastic Falcon tube, was added hexafluorosilicic acid (33.5−35%, 0.60 mL, 1.80 mmol, 33−35% in water, 75 equiv) dropwise at 0 °C, and the tube was covered with aluminium foil. The resulting mixture was allowed to warm to 23 °C over 1 h and then stirred for 16 h. The resulting mixture was then diluted with EtOAc (30 mL), followed by the addition of a satd aq $NaHCO_3$ (30 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, hexanes/EtOAc 1:1, *v*/*v* → 0:1, *v*/*v*) to yield analogue **6** (8.0 mg, 10.1 μmol, 43% yield) as a white amorphous solid.

6: R_f = 0.48 (hexanes/EtOAc 3:7, *v*/*v*), $[\alpha]_D^{25}$ = −106.8 (*c* = 0.25, MeOH); IR (film) ν_{max} = 3419, 2926, 2854, 1722, 1626, 1464, 1381, 1209, 1094, 971, 744 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.98 (s, 1 H), 7.91 (s, 1 H), 6.75 (dd, *J* = 14.4, 12.0 Hz, 1 H), 6.49 (d, *J* = 11.7 Hz, 1 H), 6.47−6.39 (m, 2 H), 6.34 (t, *J* = 11.1 Hz, 1 H), 6.26 (t, *J* = 11.9 Hz, 1 H), 5.96 (t, *J* = 11.0 Hz, 1 H), 5.71−5.62 (m, 2 H), 5.64−5.55 (m, 2 H), 5.57−5.49 (m, 1 H), 5.46 (td, *J* = 10.7, 4.8 Hz, 1 H), 5.35 (dd, *J* = 11.3, 2.3 Hz, 1 H), 5.28 (dd, *J* = 10.9, 2.4 Hz, 1 H), 5.17−5.10 (m, 1 H), 3.94 (d, *J* = 7.3 Hz, 1 H), 3.91−3.84 (m, 2 H), 3.37−3.30 (m, 1 H), 3.20 (s, 3 H), 3.11 (dd, *J* = 15.2, 6.3 Hz, 1 H), 2.89−2.77 (m, 2 H), 2.53 (d, *J* = 4.0 Hz, 1 H), 2.38−2.29 (m, 1 H), 2.20−2.11 (m, 1 H), 1.83−1.74 (m, 1 H), 1.71 (dd, *J* = 6.3, 1.5 Hz, 3 H), 1.69 (dd, *J* = 6.4, 1.5 Hz, 3 H), 1.35 (dt, *J* = 8.4, 4.2 Hz, 1 H), 1.01 (s, 3 H), 0.98 (s, 3 H), 0.98 (s, 3 H), 0.95 (s, 3 H), 0.88 (t, *J* = 6.9 Hz, 1 H), 0.64 (ap. q, *J* = 5.6 Hz, 1 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.2, 164.7, 161.8, 161.3, 146.1, 146.0, 143.5, 134.5, 133.2, 131.2, 129.9, 129.59, 129.55, 129.4, 129.1, 128.9, 128.6, 128.0, 127.1, 126.87, 126.86, 125.7, 125.4, 119.0, 80.7, 79.3, 77.9, 76.5, 76.4, 56.9, 41.8, 41.7, 40.5, 29.9, 28.3, 23.4, 20.1, 19.6, 19.4, 19.1, 18.7, 18.08, 18.05, 17.4 ppm; ^{1}H NMR (600 MHz, CD_3CN) δ 8.15 (s, 1 H), 8.12 (s, 1 H), 6.88−6.71 (m, 1 H), 6.52−6.41 (m, 2 H), 6.39 (d, *J* = 11.4 Hz, 2 H), 6.30−6.22 (m, 1 H), 5.95 (t, *J* = 10.8 Hz, 1 H), 5.74−5.55 (m, 5 H), 5.42 (td, *J* = 10.8, 4.7 Hz, 1 H), 5.27 (ddd, *J* = 18.3, 11.3, 2.4 Hz, 2 H), 5.16 (t, *J* = 10.8 Hz, 1 H), 3.96 (dt, *J* = 9.1, 4.9 Hz, 1 H), 3.87−3.84 (m, 2 H), 3.36 (dd, *J* = 14.9, 4.8 Hz, 1 H), 3.14 (s, 3 H), 2.94−2.86 (m, 2 H), 2.84−2.79 (m, 2 H), 2.38−2.30 (m, 1 H), 1.86 (dtd, *J* = 10.9, 8.4, 5.8 Hz, 1 H), 1.72−1.70 (m, 3 H), 1.70−1.68 (m, 3 H), 1.02 (s, 3 H), 0.99 (s, 3 H), 0.99 (s, 3 H), 0.96 (s, 3 H), 0.67−0.54 (m, 1 H) ppm; ^{13}C NMR (151 MHz, CD_3CN) δ 167.6, 164.8, 161.8, 161.2, 147.0, 146.8, 144.5, 134.7, 134.3, 132.0, 131.7, 131.6, 131.0, 129.4, 129.34, 129.30, 129.1, 128.9, 128.8, 127.49, 127.47, 126.6, 126.1, 119.4, 80.7, 78.3, 77.7, 77.04, 76.96, 56.7, 42.5, 42.4, 41.4, 29.02, 28.97, 24.1, 20.2, 19.5, 19.4, 19.23, 19.20, 18.00, 17.99 ppm; HR-MS (ESI) calcd for $C_{44}H_{56}N_2O_7S_2Na^+$ [M + Na]$^+$ 811.3421, found 811.3444.

*Methyl 2-[(1Z,3E)-4-{(1S,2R)-2-[(1Z,4S,6S,7E)-6-{[tert-Butyl(dimethyl)silyl]oxy}-4-hydroxy-5,5-dimethylnona-1,7-dien-1-yl]cyclopropyl}buta-1,3-dien-1-yl]-1,3-thiazole-4-carboxylate (**48**).* To a stirred and degassed solution of vinyl stannane **8** (100 mg, 0.153 mmol, 1.0 equiv) and oxazole **16** (38 mg, 0.153 mmol, 1.0 equiv) in NMP (0.77 mL) at 23 °C was added CuTc (44 mg, 0.229 mmol, 1.5 equiv). The resulting mixture was stirred for 1 h at 23 °C and was directly purified by flash column chromatography (SiO_2, hexanes/EtOAc 9:1, *v*/*v* → 4:1, *v*/*v*) to yield alcohol **48** (68 mg, 0.128 mmol, 84% yield) as a pale yellow oil.

48: R_f = 0.52 (hexanes/EtOAc 3:1, *v*/*v*); $[\alpha]_D^{25}$ = +44.5 (*c* = 1.0, $CHCl_3$); IR (film) ν_{max} = 3480, 2956, 2930, 2857, 1741, 1722, 1626, 1471, 1245, 1211, 1069, 836, 776 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.11 (s, 1 H), 7.32−7.20 (m, 1 H), 6.49−6.38 (m, 2 H), 5.86 (dd, *J* = 14.8, 9.4 Hz, 1 H), 5.70 (dt, *J* = 11.3, 7.2 Hz, 1 H), 5.61−5.49 (m, 2 H), 5.23 (t, *J* = 9.9 Hz, 1 H), 4.19 (s, 1 H), 3.95 (s, 3 H), 3.86 (d, *J* = 6.2 Hz, 1 H), 3.74−3.66 (m, 1 H), 2.31 (dd, *J* = 14.8, 7.4 Hz, 1 H), 2.16 (ddd, *J* = 15.3, 9.4, 6.7 Hz, 1 H), 1.99 (p, *J* = 8.2 Hz, 1 H), 1.95−1.88 (m, 1 H), 1.71 (d, *J* = 4.5 Hz, 3 H), 1.33 (td, *J* = 8.2, 4.9 Hz, 1 H), 0.97 (s, 3 H), 0.87 (d, *J* = 1.7 Hz, 9 H), 0.75 (s, 3 H), 0.73 (q, *J* = 5.7 Hz, 1 H), 0.05 (s, 3 H), 0.00 (s, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.7, 162.2, 147.0, 144.0, 135.4, 130.4, 129.8, 129.1, 128.7, 127.0, 126.7, 117.7, 84.4, 76.4, 52.6, 41.1, 30.3, 26.0, 22.9, 22.7, 19.8, 19.5, 18.2, 17.9, 16.9, −3.8, −5.0 ppm; HR-MS (ESI-TOF) calcd for $C_{29}H_{45}O_4NSSiNa^+$ [M + Na]$^+$ 554.2731, found 554.2733.

*(1Z,4S,6R,7E)-6-{[tert-Butyl(dimethyl)silyl]oxy}-1-[(1R,2S)-2-{(1E,3Z)-4-[4-(methoxycarbonyl)-1,3-thiazol-2-yl]buta-1,3-dien-1-yl}cyclopropyl]-5,5-dimethylnona-1,7-dien-4-yl 2-[(Z)-2-bromoethenyl]-1,3-thiazole-4-carboxylate (**49**).* To a stirred solution of alcohol **48** (0.060 g, 0.113 mmol, 1.0 equiv) and carboxylic acid **15** (53 mg, 0.226 mmol, 2.0 equiv) in toluene (1.13 mL) were added Et_3N (0.094 mL, 0.677 mmol, 6.0 equiv) and DMAP (0.110 g, 0.903 mmol, 8.0 equiv). The solution was cooled to 0 °C, and 2,4,6-trichlorobenzoyl chloride (0.088 mL, 0.56 mmol, 3.0 equiv) was added dropwise before the reaction mixture was allowed to warm to 23 °C. Upon complete consumption of the starting material (about 1 h), the reaction mixture was purified by flash column chromatography directly (SiO_2, hexanes/EtOAc 4:1, *v*/*v* → 7:3, *v*/*v*) to yield vinyl bromide **49** (76 mg, 0.102 mmol, 90% yield) as a white film.

49: R_f = 0.26 (hexanes/EtOAc 3:1, *v*/*v*); $[\alpha]_D^{25}$ = +52.3 (*c* = 1.0, $CHCl_3$); IR (film) ν_{max} = 2953, 2855, 1734, 1626, 1471, 1432, 1303, 1242, 1211, 1092, 1057, 972, 836, 775, 743 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.11 (s, 1 H), 8.08 (s, 1 H), 7.62 (d, *J* = 8.1 Hz, 1 H), 7.07 (dd, *J* = 14.7, 11.4 Hz, 1 H), 6.78 (d, *J* = 8.1 Hz, 1 H), 6.35 (d, *J* = 11.7 Hz, 1 H), 6.28 (t, *J* = 11.6 Hz, 1 H), 5.65 (dd, *J* = 14.7, 9.7 Hz, 1 H), 5.54−5.45 (m, 3 H), 5.25 (dd, *J* = 10.1, 3.1 Hz, 1 H), 5.11 (t, *J* = 10.2 Hz, 1 H), 3.96 (s, 3 H), 3.85 (d, *J* = 7.0 Hz, 1 H), 2.61 (dt, *J* = 15.0, 9.4 Hz, 1 H), 2.54−2.45 (m, 1 H), 2.01 (p, *J* = 8.7 Hz, 1 H), 1.81 (qd, *J* = 8.5, 5.6 Hz, 1 H), 1.65 (d, *J* = 4.5 Hz, 3 H), 1.30 (td, *J* = 8.2, 4.8 Hz, 1 H), 0.99 (s, 3 H), 0.95 (s, 3 H), 0.86 (s, 9 H), 0.67 (q, *J* = 5.6 Hz, 1 H), −0.03 (s, 3 H), −0.06 (s, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.6, 162.9, 162.1, 160.7, 147.2, 147.0, 143.4, 135.3, 131.5, 130.5, 128.3, 128.1, 127.6, 127.0, 126.8, 126.5, 117.7, 112.3, 79.3, 78.4, 52.6, 43.0, 28.7, 26.1, 23.0, 20.4, 19.5, 19.3, 18.3, 17.9, 16.9, −3.4, −4.8 ppm; HR-MS (ESI-TOF) calcd for $C_{35}H_{47}BrN_2O_5S_2SiNa^+$ [M + Na]$^+$ 769.1771, found 769.1777.

*Methyl 2-{(1Z,3E)-4-[(1S,2R)-2-{(1Z,4S,6R,7E)-6-{[tert-Butyl(dimethyl)silyl]oxy}-4-[({2-[(1Z,3E)-4-{(1S,2R)-2-[(1Z,4S,6R,7E)-6-{[tert-butyl(dimethyl)silyl]oxy}-4-hydroxy-5,5-dimethylnona-1,7-dien-1-yl]cyclopropyl}buta-1,3-dien-1-yl]-1,3-thiazol-4-yl}carbonyl)oxy]-5,5-dimethylnona-1,7-dien-1-yl}cyclopropyl]buta-1,3-dien-1-yl}-1,3-thiazole-4-carboxylate (**50**).* To a stirred and degassed solution of vinyl stannane **8** (80 mg, 0.122 mmol, 1.2 equiv) and oxazole **49** (76 mg, 1.02 mmol, 1.0 equiv) in NMP (0.51 mL) at 23 °C was added CuTC (29 mg, 0.152 mmol, 1.5 equiv). The resulting mixture was stirred for 1 h at 23 °C and was then directly purified by flash column chromatography (SiO_2, hexanes/EtOAc 17:3, *v*/*v* → 4:1, *v*/*v*) to yield uncyclized dimer **50** (97 mg, 0.094 mmol, 92% yield) as a pale yellow oil.

50: R_f = 0.36 (hexanes/EtOAc 3:1, *v*/*v*); $[\alpha]_D^{25}$ = +87.2 (*c* = 1.0, $CHCl_3$); IR (film) ν_{max} = 3482, 2956, 2930, 2883, 2856, 1737, 1719, 1626, 1471, 1243, 1067, 836, 775 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) 8.12 (s, 1 H), 7.94 (s, 1 H), 7.43 (dd, *J* = 14.8, 11.3 Hz, 1 H), 7.06 (dd, *J* = 14.7, 11.4 Hz, 1 H), 6.37−6.24 (m, 4 H), 5.79 (dd, *J* = 14.8, 9.5 Hz, 1 H), 5.74−5.66 (m, 1 H), 5.65 (dd, *J* = 14.7, 9.8 Hz, 1 H), 5.60−5.46 (m, 5 H), 5.27−5.19 (m, 2 H), 5.11 (t, *J* = 10.2 Hz, 1 H), 4.20 (s, 1 H), 3.96 (s, 3 H), 3.90−3.85 (m, 2 H), 3.71 (d, *J* = 10.0 Hz, 1 H), 2.60 (dt, *J* = 14.9, 9.3 Hz, 1 H), 2.52−2.46 (m, 1 H), 2.32 (dd, *J* = 14.7, 7.5 Hz, 1 H), 2.21−2.12 (m, 1 H), 2.03 (dt, *J* = 15.1, 8.3 Hz, 1 H), 1.96 (p, *J* = 8.3 Hz, 1 H), 1.87 (qd, *J* = 8.6, 5.6 Hz, 1 H), 1.79 (qd, *J* = 8.6, 5.6 Hz, 1 H), 1.71 (d, *J* = 4.5 Hz, 3 H), 1.65 (d, *J* = 4.8 Hz, 3 H), 1.33−1.26 (m, 2 H), 1.00 (s, 3 H), 0.98 (s, 3 H), 0.96 (s, 3 H), 0.87 (s, 9 H), 0.87 (s, 9 H), 0.76 (s, 3 H), 0.71 (q, *J* = 5.6 Hz, 1 H), 0.67 (q, *J* = 5.7 Hz, 1 H), 0.06 (s, 3 H), 0.00 (s, 3 H), −0.03 (s, 3 H), −0.06 (s, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.7, 165.2, 162.2, 161.0, 148.0, 147.0, 143.4, 143.3, 135.4, 135.0, 131.5, 130.5, 130.4, 129.7, 129.2, 128.8, 128.3, 127.5, 127.4, 127.1, 126.5, 126.0, 117.6, 117.3, 84.4, 79.2, 78.1, 76.4, 52.5, 43.0, 41.1, 30.3, 28.7, 26.1, 26.0, 23.0, 22.9, 22.7, 20.3, 19.8, 19.4, 19.3 (2 × C), 18.3, 18.2,

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17.9 (2 × C), 16.9, 16.8, −3.4, −3.8, −4.8, −5.0 ppm; HR-MS (ESI-TOF) calcd for $C_{57}H_{86}O_7N_2S_2Si_2Na^+$ $[M + Na]^+$ 1053.5307, found 1053.5329.

*(2Z,4E,6S,8R,9Z,12S,19Z,21E,23S,25R,26Z,29S)-12,29-Bis[(3S,4E)-3-{[tert-butyl(dimethyl)-silyl]oxy}-2-methylhex-4-en-2-yl]-13,30-dioxa-17,34-dithia-35,36-diazapentacyclo[30.2.1.1^{15,18}.0^{6,8}.0^{23,25}]-hexatriaconta-1(35),2,4,9,15,18(36),19,21,26,32-decaene-14,31-dione (**51**).* To a stirred solution of ester **50** (0.096 g, 0.093 mmol, 1.0 equiv) in THF (1.86 mL) cooled to 0 °C was added dropwise a saturated aqueous solution of barium hydroxide octahydrate (0.88 mL, MeOH/H_2O 3:2, *v*/*v*). The reaction mixture was allowed to warm to 23 °C and stirred until all starting material was consumed by TLC (about 5 h). The reaction mixture was quenched by the addition of a 0.01 N $KHSO_4$ solution (5 mL) and the aqueous phase was extracted six times with EtOAc (6 × 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was used in the next reaction without any further purification.

To a solution of the crude carboxylic acid, stirred in toluene (6.9 mL), were added 2,4,6-trichlorobenzoyl chloride (0.146 mL, 0.934 mmol, 10 equiv) and Et_3N (0.143 mL, 1.07 mmol, 11 equiv). The mixture was stirred 1 h at 23 °C, and it was then diluted to a concentration of 0.0075 M by the addition of toluene (6.9 mL). The resulting mixture was added over 5 h, via a syringe pump, to a stirred solution of DMAP (0.046 g, 0.373 mmol, 4.0 equiv) in toluene (17 mL) heated at 40 °C. After the addition was completed, stirring was continued for 24 h before the reaction was concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, hexanes/EtOAc 3:1, *v*/*v* → 7:3, *v*/*v* → 13:7, *v*/*v*) to give bis-TBS protected cp-disorazole A_1 **51** (0.022 g, 0.022 mmol, 24% yield over two steps) as a white film.

51: R_f = 0.22 (hexanes/EtOAc 3:1, *v*/*v*); $[\alpha]_D^{25}$ = −53.6 (*c* = 0.88, $CHCl_3$); IR (film) ν_{max} = 2956, 2929, 2856, 1732, 1629, 1471, 1201, 1094, 836 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.90 (s, 2 H), 6.47−6.35 (m, 4 H), 6.11 (t, *J* = 11.9 Hz, 2 H), 5.57−5.40 (m, 8 H), 5.20 (d, *J* = 11.5 Hz, 2 H), 5.06 (t, *J* = 10.9 Hz, 2 H), 3.84 (d, *J* = 6.8 Hz, 2 H), 2.72 (q, *J* = 12.2 Hz, 2 H), 2.28 (dd, *J* = 13.5, 4.8 Hz, 2 H), 2.07 (dq, *J* = 14.4, 7.8 Hz, 2 H), 1.65 (d, *J* = 4.6 Hz, 6 H), 1.63−1.59 (m, 2 H), 1.29−1.23 (m, 2 H), 1.01 (s, 6 H), 0.97 (s, 6 H), 0.87 (s, 18 H), 0.55 (q, *J* = 5.5 Hz, 2 H), −0.01 (s, 6 H), −0.06 (s, 6 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.8, 160.0, 147.0, 141.8, 133.9, 131.5, 131.2, 128.2, 127.0, 124.9, 124.8, 119.5, 79.6, 77.3, 42.7, 28.8, 26.1, 23.4, 20.8, 19.5, 18.9, 18.4, 18.0, 17.3, −3.4, −4.8 ppm; HR-MS (ESI-TOF) calcd for $C_{56}H_{82}O_6N_2S_2Si_2Na^+$ $[M + Na]^+$ 1021.5045, found 1021.5073.

*(2Z,4E,6S,8R,9Z,12S,19Z,21E,23S,25R,26Z,29S)-12,29-Bis[(3S,4E)-3-hydroxy-2-methylhex-4-en-2-yl]-13,30-dioxa-17,34-dithia-35,36-diazapentacyclo[30.2.1.1^{15,18}.0^{6,8}.0^{23,25}]hexatriaconta-1(35),2,4,9,15,18(36),19,21,26,32-decaene-14,31-dione (**7**).* To a stirred solution of compound **51** (9.0 mg, 9.0 μmol, 1.0 equiv) in DMF (300 μL) and H_2O (2.3 μL, 130 μmol, 14 equiv) was added TASF (12 mg, 45 μmol, 5.0 equiv), and the reaction mixture was heated at 40 °C and stirred for 48 h. The resulting mixture was filtered through a small silica pad (10 cm, SiO_2, hexanes/EtOAc 1:1, *v*/*v* → 0:1, *v*/*v*). The resulting fractions containing the desired products were combined, concentrated, and purified by flash column chromatography (SiO_2, hexanes/EtOAc 1:1, *v*/*v* → 1:4, *v*/*v* → 0:1, *v*/*v*) to yield bis(cp-thiazolyl)disorazole B_1 (**7**, 3.0 mg, 4.2 μmol, 46% yield) as a white foam. The product was insoluble in most pure solvents, e.g., MeOH, DMSO, CH_2Cl_2, $CHCl_3$, MeCN, etc. The product was found to be soluble in a small aliquot of DMSO when CH_2Cl_2 was added until all product was dissolved and then most of the CH_2Cl_2 was removed under reduced pressure, leaving a cloudy solution of the desired product in DMSO with CH_2Cl_2.

7: R_f = 0.15 (hexanes/EtOAc 2:3, *v*/*v*); $[\alpha]_D^{25}$ = −52.4 (*c* = 0.034, CH_2Cl_2); IR (film) ν_{max} = 3439, 2922, 2852, 1714, 1629, 1212, 1104, 964 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6 with CH_2Cl_2) δ 8.37 (s, 2 H), 6.45−6.37 (m, 2 H), 6.21 (d, *J* = 11.9 Hz, 2 H), 6.15 (t, *J* = 11.8 Hz, 2 H), 5.66 (dd, *J* = 14.1, 11.0 Hz, 2 H), 5.60−5.49 (m, 4 H), 5.39−5.31 (m, 2 H), 5.23−5.11 (m, 4 H), 4.64 (d, *J* = 4.6 Hz, 2 H), 3.73 (t, *J* = 5.3 Hz, 2 H), 2.70 (q, *J* = 12.0 Hz, 2 H), 2.29−2.22 (m, 2 H), 2.10−2.00 (m, 4 H), 1.64 (d, *J* = 4.9 Hz, 6 H), 0.96 (s, 6 H), 0.88 (s, 6 H), 0.60 (dd, *J* = 10.4, 4.9 Hz, 2 H), 0.51 (q, *J* = 5.5 Hz, 2 H) ppm; ^{13}C NMR (151 MHz, CD_2Cl_2) δ 164.8, 160.7, 146.4, 142.1, 133.9, 131.7, 130.1, 128.9, 126.6, 126.1, 125.2, 118.9, 77.7, 76.6, 41.6, 28.1, 23.5, 19.1, 19.0, 18.6, 17.7, 17.3 ppm; HR-MS (ESI-TOF) calcd for $C_{44}H_{54}O_6N_2S_2Na^+$ $[M + Na]^+$ 793.3316, found 793.3322.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b02137.

^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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