Synthesis of Furano-Epothilone D

Dieter Schinzer,*[a] Erika Bourguet,[b] and Sylvie Ducki[c]

Abstract: The total synthesis of furano-epothilone D by a convergent route is reported. The key fragments are available on a large scale to provide sufficient material for biological evaluation. The approach involves a palladium-catalyzed coupling that generates a highly functionalized aldehyde which is connected in a stereoselective aldol reaction to yield the framework of furano-epothilone D. Finally, a macrolactonization provides furano-epothilone D.

Keywords: aldol reactions · antitumor agents · epothilone analogues · macrolides · natural products

Introduction

The bacterial macrolides epothilone A and epothilone B[1] have been found to act as biological analogues of paclitaxel. This discovery has induced intense research activity,[2] resulting in several total syntheses of epothilone A[3] and epothilone B,[4] partial synthesis,[5] and numerous derivatives.[6] In various biochemical assays, paclitaxel and the epothilones were found to be almost identical in their effect on microtubule stabilization and cytotoxic properties. However, against multiple-drug resistant (MDR) human carcinoma cell lines, the epothilones were significantly more potent than paclitaxel. They may even prove to be more promising anticancer drugs than paclitaxel with less undesired side effects.[7] Recent studies with MDR cell lines indicate that epothilone B is the most potent of the naturally occurring epothilones in vitro, whereas deoxyepothilone B (epothilone D) exhibited the best therapeutic results in vivo and is thus regarded as a lead compound for potential clinical development.[8]

In view of the need to synthesize sufficient quantities of epothilone B and its analogues for drug development, we have elaborated an alternative, selective procedure to obtain a series of compounds. This route is based on highly efficient aldol and transition-metal-mediated coupling reactions that yield a *seco*-acid precursor utilized in the macrolactonization route developed by Nicolaou et al.[3g,4d] to epothilone B.[9]

Herein, we have extended this method to obtain furano-epothilone D as an analogue of epothilone D. Careful analysis of the bond angles in the X-ray crystal structure of epothilone B[1] suggested the design of conformationally more stabilized/restricted epothilone analogues with a five-membered ring placed in the region of C8–C10.

Results and Discussion

Scheme 1 depicts the retrosynthetic analysis of furano-epothilone B (**1**) that led to the macrolactonization-based strategy. To obtain the required *seco* acid which would give desoxy-**1** upon macrolactonization[3g,4d], an aldol reaction of the ethyl ketone **2**[10] and aldehyde **3** was designed as the key step. Further disconnection of **3** led to the thiazole fragment **5**[5a,10] and a C7–C12 building block **4**. An efficient palladium-mediated Negishi-type coupling reaction[11] was envisioned for the assembly of **4** and **5** as precursors of aldehyde **3**.

The thiazole building block **5** was synthesized according to an improved sequence that was amenable to a multigram scale-up.[5a,10]

The approach to the C7–C12 fragment **4** started with saponification of 5-acetoxymethyl-2-furfuraldehyde (**6**) with potassium carbonate in MeOH to give **7** in 98% yield, fol-

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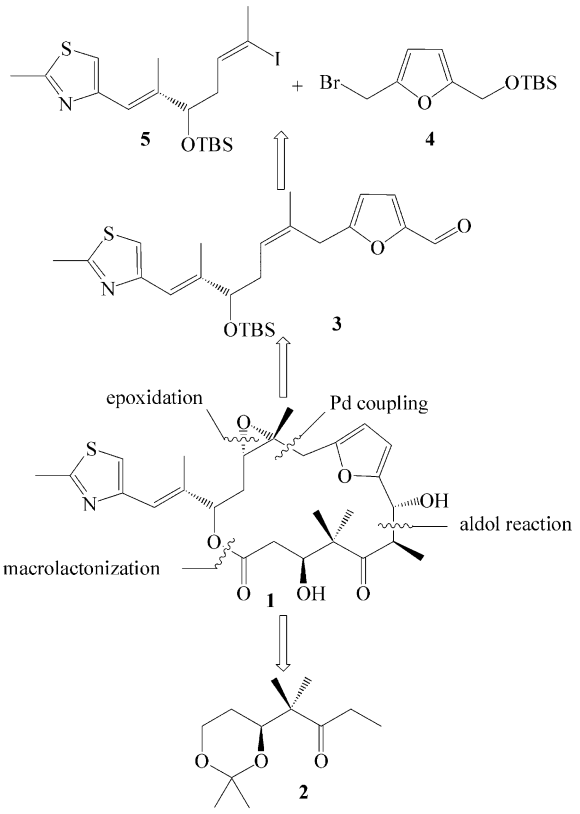


Scheme 1. Retrosynthetic analysis of furano-epothilone B—the macrolactonization approach.

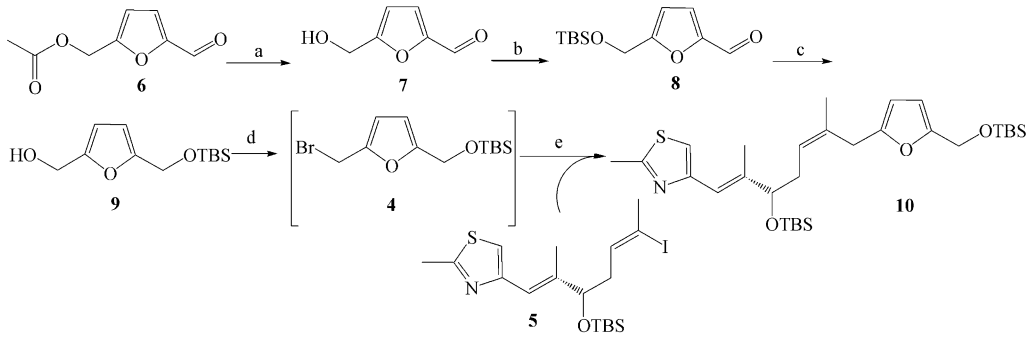
lowed by protection by using *tert*-butyldimethylsilyl chloride, which afforded silyl ether **8** in 89% yield, as described by McNelis et al.[12] (Scheme 2). Reduction with triacetoxyborohydride in benzene led to compound **9** in 93% yield. Fragment **4** was obtained by bromination of **9** in CH_2Cl_2 in the presence of imidazole and triphenylphosphine. Compound **4** is quite unstable and can only be stored in solution under nitrogen in the fridge for a short time. An efficient palladium-mediated coupling[11] of vinyl iodide **5** and the organozinc species derived from **4**[13] using a Zn/Cu couple[14] led to the bis(silyl) ether **10** in 32% yield. Rieke Zn[15] however proved superior, giving compound **10** in 85% yield. The best yields were obtained when both the $Ph_3P{=}O$ formed during the bromination reaction and the excess naphthalene used in the preparation of the Rieke Zn were removed; these otherwise inhibited coupling.

Selective deprotection to yield alcohol **11** was achieved by the action of NH_4F in MeOH (93%). Oxidation of **11** with TPAP/NMO in CH_2Cl_2 as the reagent of choice provided aldehyde **3** in 87% yield, which was needed for the aldol reaction with ketone **2** (Scheme 3).

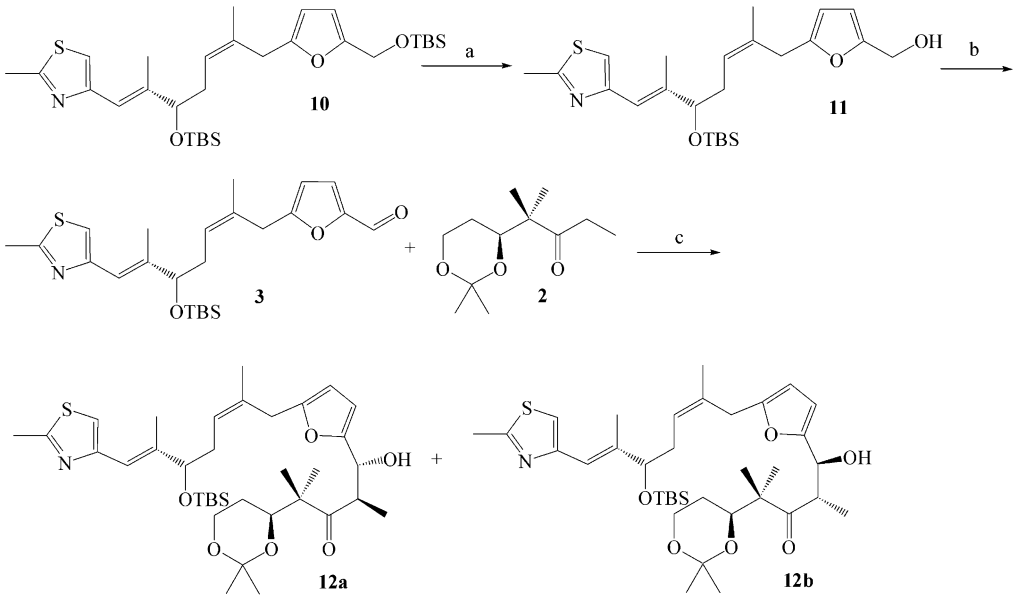
To ensure complete conversion of aldehyde **3** to the desired aldol product **12**, two equivalents of the lithium enolate generated from ketone **2** had to be employed in the reaction. The aldol product **12** was isolated in 91% yield from the reaction mixture. The ratio of *anti*-Cram (6*R*,7*S*) to Cram (6*S*,7*R*) products was found to be 3:1 by ^{1}H NMR spectroscopy. The selectivity in the aldol reaction of the furano series was lower than in the case of epothilone A and epothilone B because no α-chiral aldehyde was used in the coupling.[9] Therefore, no match of chirality can be employed to increase selectivity and the 3:1 ratio observed is a result of the inherent chirality of the chiral enolate used in the aldol reaction.

The first step in the transformation of the intermediate **12a** into the *seco*-acid precursor **16** was cleavage of the ketal protecting group using PPTS in MeOH, leading to the triol **13** in 84% yield. When the reaction was performed in refluxing MeOH, isomerization was observed at the C6 and C7 centers. It can be almost completely suppressed when the reaction mixture is stirred at room temperature. Silylation of compound **13** with TBSOTf and 2,6-lutidine led to the tetrakis(silyl) ether **14** in 71% yield. Selective deprotection of **14** to the primary alcohol **15** was achieved by the action of NH_4F in MeOH in 73% yield. PDC oxidation of **15** in DMF provided *seco*-acid **16** in 80% yield (Scheme 4).

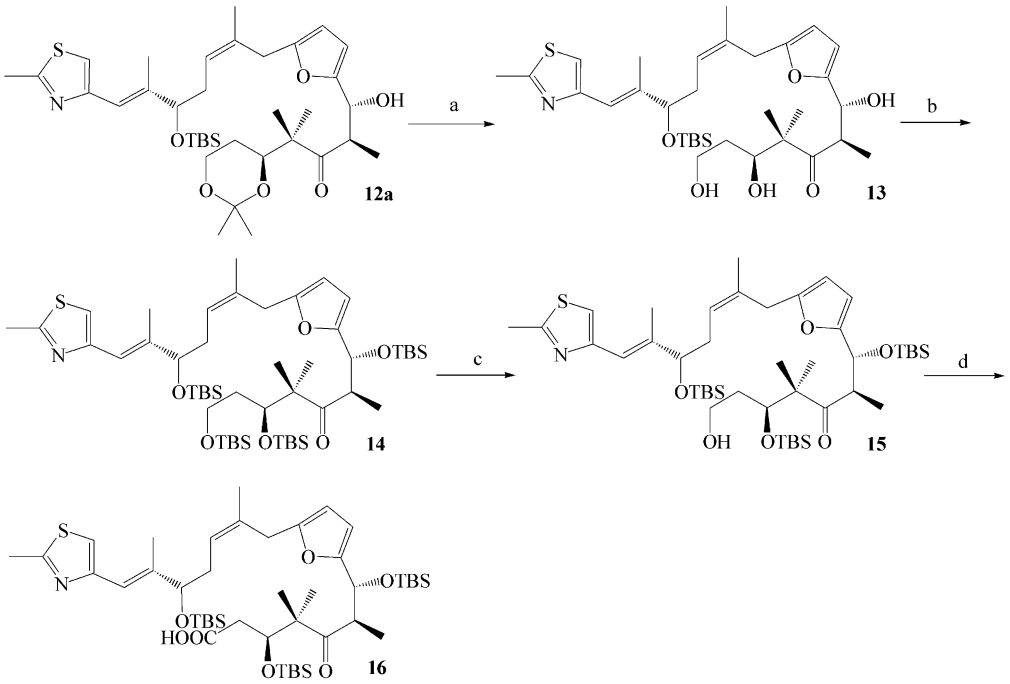
The selective deprotection of the allylic alcohol **16** was not possible under neutral, acidic, or basic conditions. Total deprotection of the hydroxy groups of **16** with aqueous HF (40%) in CH_3CN/Et_2O afforded a mixture of two diastereoisomers **17** (**17a**:**17b** epimerization of C7; ratio 1:2) in 25:47% yield (Scheme 5). Diastereomers **17a** and **17b** were cyclized to macrolactones **18a** and **18b**, respectively, in 51% yield by the Yamaguchi method.[16]



Scheme 2. Synthesis of the C7–C12 fragment **4** and Pd-mediated coupling of building blocks **4** and **5**. a) K_2CO_3 (0.16 equiv), CH_3OH, RT, 18 h, 98%; b) TBSCl (1.2 equiv), imidazole (1.8 equiv), DMF, RT, 18 h, 89%; c) $NaBH(OAc)_3$, benzene, reflux, 3 h, 93%; d) PPh_3 (1.1 equiv), imidazole (1.2 equiv), Br_2 (1.1 equiv), CH_2Cl_2, 0 °C, 10 min, complete by TLC; e) Zn* (6.0 equiv) in THF, −30 °C; then **4** in THF added by syringe pump over 4.5 h, $[Pd(PPh_3)_4]$ (12.5 mol%); then **5** in THF, 60 °C, 1 h, 85%.

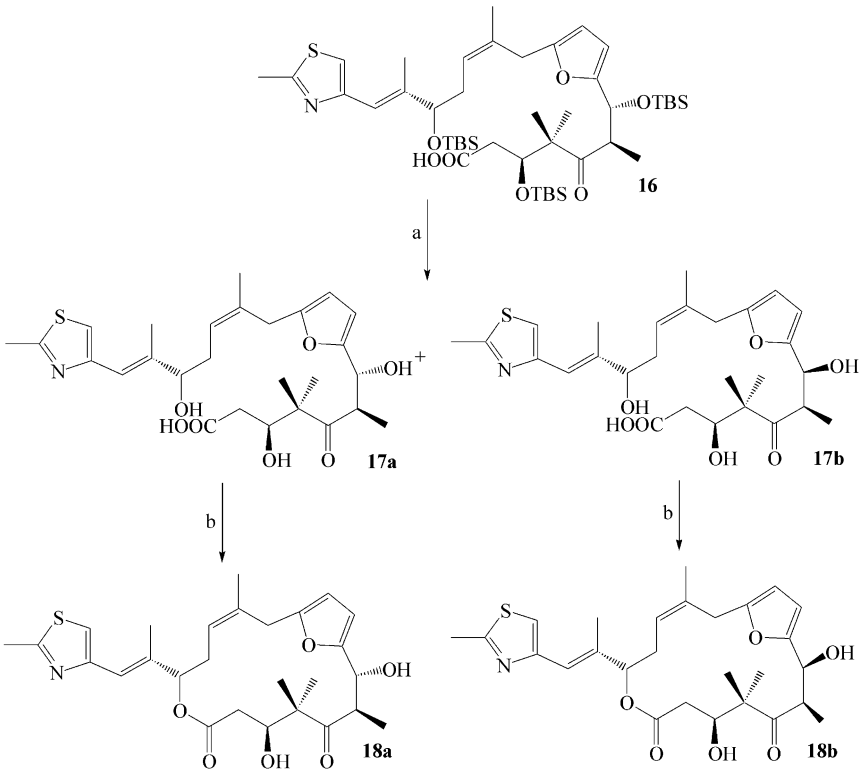


Scheme 3. Aldol reaction. a) NH_4F (40 equiv), MeOH, reflux, 1 h, 93%; b) NMO (1.5 equiv), molecular sieves 4 Å, CH_2Cl_2, 0°C, 15 min, TPAP (0.05 equiv), RT, 15 min, 87%; NMO = 4-methylmorpholine *N*-oxide, TPAP = tetrapropylammonium perruthenate; c) ketone **2** (2.0 equiv), LDA (1.96 equiv), THF, −78°C, 1 h; then aldehyde **3**, −78°C, 15 min, 91%.



Scheme 4. Synthesis of a *seco* acid precursor **16**. a) PPTS (1.0 equiv), MeOH, RT, 48 h, 84%; b) TBSOTf (4.8 equiv), 2,6-lutidine (9.6 equiv), CH_2Cl_2, −50°C, 1 h, 71%; c) NH_4F (49 equiv), MeOH, reflux, 2.5 h, 73%; d) PDC (45 equiv), DMF, RT, 19 h, 80%.

The induction of tubulin polymerization was determined by using the procedure described in the Experimental Section. The results are presented as ED_{50} and ED_{90} values which correspond to the dose of compound required to induce 50% and 90% microtubule assembly, respectively. Paclitaxel was used as a reference assay. Furano-epothilone D (**18a**) showed an $ED_{50} = 2.2\,\mu M$ and an $ED_{90} = 5.5\,\mu M$ (paclitaxel: $ED_{50} = 0.4\,\mu M$; $ED_{90} = 2.0$) and is therefore less potent than paclitaxel. The isomer **18b** showed the same effect on tubulin assembly. However, it was demonstrated for the first time that an epothilone analogue without a chiral center at C8 showed biological activity. This supports our hypothesis that incorporation of a five-membered ring enforces the conformational stability of the region C8–C10.



Scheme 5. Final steps of the macrolactonization approach to furano-epothilone D. a) aqueous HF (40%), CH_3CN/Et_2O, glass splinters, two days, ratio 1:2, 25:47%; b) 2,4,6-trichlorobenzoylchloride (5.0 equiv), Et_3N (6.0 equiv), THF, 0°C, 15 min, then add by using a syringe pump to a solution of 4-DMAP (10 equiv) in toluene, 25°C, 1 h, 51%.

Work is in progress to synthesize more potent analogues, investigate their interaction with tubulin, and establish their cytotoxicity.

Conclusion

In summary, we have presented a convergent synthesis of furano-epothilone D. Our method using stereoselective aldol C–C bond formations, palladium-mediated couplings, and macrolactonization can be extended to synthesize numerous analogues of epothilone D.

In addition, this strategy offers the possibility to synthesize epothilone analogues in sufficient quantities for in vitro and in vivo biological studies. However, the biological data derived from the tubulin assay showed only moderate activity for furano-epothilone D and its isomer. This clearly demonstrated that the correct configuration at C8 is more important than a stabilized conformation in that part of the molecule by incorporation of a five-membered ring.

Experimental Section

General techniques: Solvents were dried by standard procedures and redistilled under N_2 prior to use. All organometallic reactions were performed under N_2 or argon, and pure products were obtained after flash chromatography by using Merck silica gel 60 (40–63 μm). Mass spectra and high-resolution mass spectra were recorded on Finnigan MAT 95 and SSQ 7000 spectrometers (HRMS: reference PKF, peak matching method, accuracy + 2 ppm). IR spectra were recorded on Perkin-Elmer 2000 and Nicolet 320 FT-IR spectrometers. UV spectra were recorded on Hewlett-Packard 8452 A and Perkin-Elmer Lambda 19 spectrometers. NMR spectra were recorded on a Bruker DPX 400 spectrometer. Optical rotations were recorded with a Perkin-Elmer 241 polarimeter.

5-Hydroxymethyl-2-furfuraldehyde (7): A solution of 5-acetoxymethyl-2-furfuraldehyde (**6**; 5 g, 29 mmol) in methanol (45 mL) was treated with potassium carbonate (644 mg, 4.6 mmol) and the progress of the reaction was monitored by TLC (SiO_2, 1:1 pentane/EtOAc). After 18 h, the solvent was evaporated and the residue dissolved in EtOAc. The organic layer was washed with water and dried over anhydrous $MgSO_4$. Filtration and evaporation afforded 5-hydroxymethyl-2-furfuraldehyde (**7**; 3.573 g, 98%) as a yellow oil.

^{1}H NMR (360 MHz, $CDCl_3$): $\delta = 9.55$ (s, 1H; CHO), 7.23 (d, $^3J = 3.5$ Hz, 1H; H-3 furyl), 6.52 (d, $^3J = 3.6$ Hz, 1H; H-4 furyl), 4.70 (s, 2H; -CH_2OH), 3.64 ppm (bs, 1H; -OH); ^{13}C NMR (90 MHz, $CDCl_3$): $\delta = 177.7$, 160.9, 152.1, 109.9, 57.3 ppm.

5-*tert*-Butyldimethylsiloxymethyl-2-furfuraldehyde (8): Imidazole (51 mg, 0.74 mmol, 1.8 equiv) and 5-hydroxymethyl-2-furfuraldehyde (**7**; 52 mg, 0.41 mmol) was added to a solution of *tert*-butyldimethylsilyl chloride (75 mg, 0.49 mmol, 1.2 equiv) in DMF (200 μL) and the mixture was stirred for 19 h. The reaction mixture was then diluted with pentane and washed with water. The organic layer was dried ($MgSO_4$) and filtered through a small plug of silica gel. Evaporation of the solvent afforded 5-*tert*-butyldimethylsiloxymethyl-2-furfuraldehyde (**8**; 87.6 mg, 89%) as a yellow oil.

^{1}H NMR (360 MHz, $CDCl_3$): $\delta = 9.59$ (s, 1H; CHO), 7.22 (d, $^3J = 3.5$ Hz, 1H; 3 furyl), 6.48 (d, $^3J = 3.5$ Hz, 1H; H-4 furyl), 4.74 (s, 2H; -CH_2OH), 0.92 (s, 9H, OSiC$(CH_3)_3$), 0.09 ppm (s, 6H, OSi$(CH_3)_2$); ^{13}C NMR (90 MHz, $CDCl_3$): $\delta = 177.4$, 161.3, 152.1, 109.3, 58.5, 25.6, 18.2, −5.4 ppm.

5-*tert*-Butyldimethylsiloxymethyl-2-furanmethanol (9): A solution of 5-*tert*-butyldimethylsiloxymethyl-2-furfuraldehyde (**8**; 5.588 g, 23 mmol) in benzene (50 mL) was added dropwise to a solution of sodium triacetoxyborohydride (18.61 g, 87 mmol) in benzene (250 mL). After 3 h of heating under reflux, water (50 mL) was added to the solution, which was subsequently extracted with diethyl ether (3×50 mL). The organic phases were washed with brine, dried over $MgSO_4$, evaporated under vacuum, and purified by column chromatography using silica gel (pentane/EtOAc = 3:1) to yield product **9** (5.249 g, 93%) as a colorless oil.

^{1}H NMR (360 MHz, $CDCl_3$): $\delta = 6.21$ (d, $^3J = 2.6$ Hz, 1H; H-3 furyl), 6.17 (d, $^3J = 3$ Hz, 1H; H-4 furyl), 4.61 (s, 2H; -CH_2OH), 4.55 (s, 2H; -CH_2OH), 0.90 (s, 9H, OSiC$(CH_3)_3$), 0.08 ppm (s, 6H, OSi$(CH_3)_2$); ^{13}C NMR (90 MHz, $CDCl_3$): $\delta = 154.2$, 153.5, 108.3, 107.9, 58.1, 57.4, 25.8, 18.3, −5.2 ppm; IR (film): $\tilde{\nu}_{max} = 3351$, 2930, 2858, 2362, 1561, 1472, 1255, 1075, 1014, 837, 778 cm^{-1}; MS (CI, NH_3/CH_4): *m/z* (%): 241 (13.6), 225 (98.4) [*M*−OH]$^+$, 209 (16), 191 (25), 185 (39.2) [*M*−*t*Bu]$^+$, 167 (18.4), 161 (7.2), 110 (28) [*M*−OTBS]$^+$, 80 (6); elemental analysis calcd (%) for $C_{12}H_{22}O_3Si$ (242.13): C 59.46, H 9.15; found: C 59.31, H 9.48.

5-*tert*-Butyldimethylsiloxymethyl-2-bromomethyl-furan (4): Br_2 (20 μL, 0.38 mmol, 1.1 equiv) was added slowly to a solution of 5-*tert*-butyldi-

methylsiloxymethyl-2-furanomethanol (**9**; 83.6 mg, 0.34 mmol), imidazole (28 mg, 0.41 mmol, 1.2 equiv), and PPh_3 (99 mg, 0.38 mmol, 1.1 equiv) in CH_2Cl_2 (2 mL) at 0 °C. After 10 min, the solution was washed with water, 10% Na_2SO_3 (2×4 mL), and dried over $MgSO_4$. The solvent was removed under a flux of nitrogen and replaced by pentane, the solution was cooled to −78 °C, and the white solid was filtered. The solvent was removed under a flux of nitrogen and replaced with THF. The bromide compound **4** is unstable, but can be stored in solution under nitrogen in the fridge for a short time.

4-[(1*E*,3*S*,5*Z*)-3,12-Di(*tert*-butyldimethylsilyloxy)-2,6-dimethyl-1,5-undecadienyl-7-furan]-2-methyl-1,3-thiazole (10): Alkyl bromide **4** in THF was added to a suspension of powdered Zn*[15] (6.0 equiv) in THF (10 mL) at −25 °C by using a syringe pump over 4.5 h. The mixture was stirred at −30 °C for 30 min. $[Pd(PPh_3)]_4$ (12.5 mg, 12.5 mol%) was added and the mixture was stirred for another 5 min. A solution of vinyl iodide **5** (40 mg, 0.08 mmol) in THF (1 mL) was added and the mixture was stirred for 1 h at 60 °C, cooled to room temperature and quenched with saturated aqueous NH_4Cl solution (0.5 mL). The aqueous layer was extracted with MeO*t*Bu (3×3 mL), the combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash chromatography (pentane/Et_2O = 30:1) afforded the coupled product **10** (40 mg, 83%) as a yellow oil.

$[\alpha]_D^{20} = +21.7$ (c = 1.15, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$): δ = 6.92 (s, 1H; H-5′), 6.46 (s, 1H; H-1), 6.09 (d, ^3J = 3 Hz, 1H; CH furyl, H-10), 5.88 (d, ^3J = 3 Hz, 1H; CH furyl, H-9), 5.3 (t, ^3J = 6.8 Hz, 1H; H-5), 4.57 (s, 2H; H-12), 4.12 (t, ^3J = 5.8 Hz, 1H; H-3), 3.4 (d, ^2J = 15.5 Hz, 1H; H-12), 3.25 (d, ^2J = 15.5 Hz, 1H; H-12), 2.70 (s, 3H; C2′-CH_3), 2.48–2.27 (m, 2H; H-4), 1.99 (d, ^4J = 1.2 Hz, 3H; C2-CH_3), 1,70 (d, ^4J = 1 Hz, 3H; C6-CH_3), 0.88 (s, 18H, $OSiC(CH_3)_3$), 0.08 (s, 3H), 0.06 (s, 6H), 0.04 ppm (s, 3H, $OSi(CH_3)_2$); ^{13}C NMR (90 MHz, $CDCl_3$): δ = 164.2, 153.5, 153.2, 152.7, 142.3, 132.7, 123.6, 118.7, 114.9, 107.9, 106.1, 78.7, 58.2, 35.5, 30.9, 25.9, 23.6, 19.1, 18.3, 18.2, 13.9, −4.6, −4.9, −5.1, −5.2 ppm; IR (film): $\tilde{\nu}_{max}$ = 2929, 2857, 2364, 1472, 1376, 1255, 1075, 939, 837, 777 cm^{-1}; UV/Vis (MeOH): λ_{max} = 220,18 nm (ε = 9785.7); MS (CI, NH_3/CH_4): m/z (%): 562 (74.4) $[M+H]^+$, 546 (52) $[M-CH_3]^+$, 504 (36) $[M-t\mathrm{Bu}]^+$, 451 (8), 430 (100) $[M-\mathrm{OTBS}]^+$, 409 (12), 356 (5.6), 335 (26.4), 298 (21.6) [M-2xOTBS] $^+$, 282 (100) $[C_{14}H_{24}NOSSi]^+$, 225 (10.8); HRMS (EI) calcd $C_{30}H_{51}NO_3SSi_2$ 561.31282 ; found 561.3137 (mmu : −0.9); elemental analysis calcd (%) for $C_{30}H_{51}NO_3SSi_2$ (561.97): C 64.12, H 9.15, N 2.49, S 5.71; found: C 57.20, H 8.89, N 2.74, S 4.56.

(7*Z*,10*S*,11*E*)-10-(*tert*-Butyldimethylsilyloxy)-7,11-dimethyl-12-(2-methyl-1,3-thiazol-4-yl)-undeca-7,12-dien-furan-1-ol (11): Ammonium fluoride (1.69 g, 45 mmol, 40 equiv) was added to a solution of the coupled product **10** (641 mg, 1.14 mmol) in MeOH (30 mL). The mixture was heated for 1 h under reflux. The solvent was evaporated and the solid was extracted with diethyl ether. The organic phase was dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography (pentane/Et_2O = 2:1) gave alcohol **11** (472 mg, 93%) as a yellow oil.

$[\alpha]_D^{20} = +59.4$ (c = 0.5, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$): δ = 6.93 (s, 1H; H-5′), 6.49 (s, 1H; H-12), 6.17 (d, ^3J = 3 Hz, 1H; CH furyl, H-3), 5.93 (d, ^3J = 3 Hz, 1H; CH furyl, H-4), 5.33 (t, ^3J = 7 Hz, 1H; H-8), 4.57 (d, ^2J = 13 Hz, 1H; H-1), 4.52 (d, ^2J = 13 Hz, 1H; H-1), 4.18 (t, ^3J = 6 Hz, 1H; H-10), 3.40 (d, ^2J = 15 Hz, 1H; H-6), 3.26 (d, ^2J = 15 Hz, 1H; H-6), 2.78 (bs, 1H, -OH), 2.70 (s, 3H; C2′-CH_3), 2.41–2.27 (m, 2H; H-9), 1.98 (d, ^4J = 1.1 Hz, 3H; C11-CH_3), 1,70 (d, ^4J = 1 Hz, 3H; C7-CH_3), 0.89 (s, 9H, $OSiC(CH_3)_3$), 0.04 (s, 3H), 0.00 ppm (s, 3H; $OSi(CH_3)_2$); ^{13}C NMR (90 MHz, $CDCl_3$): δ = 164.5, 154.0, 153.0, 152.9, 142.4, 132.7, 123.7, 118.9, 114.7, 108.5, 106.4, 79.0, 57.2, 35.5, 31.0, 25.8, 23.7, 19.0, 18.2, 13.7, −4.6, −4.9 ppm; IR (film): $\tilde{\nu}_{max}$ = 3310, 2928, 2856,1508, 1471, 1360, 1251, 1185, 1071, 1012, 939, 837, 777 cm^{-1}; UV/Vis (MeOH): λ_{max} = 212.26 nm (ε = 23087); MS (CI, NH_3/CH_4): m/z (%): 448 (59.2) $[M+H]^+$, 430 (100) $[M-H_2O]^+$, 390 (5.6), 316 (49.6), 298 (63.2), 282 (85.6) $[C_{14}H_{24}NOSSi]^+$, 242 (6.4); HRMS (EI): calcd for $C_{24}H_{37}NO_3SSi$ 447.2263, found 447.2259 (0.4 mmu); elemental analysis calcd (%) for $C_{24}H_{37}NO_3SSi$ (447.22): C 64.39, H 8.33, N 3.13, S 7.16; found: C 60.35, H 8.66, N 3.50, S 6.00.

(7*Z*,10*S*,11*E*)-10-(*tert*-Butyldimethylsilyloxy)-7,11-dimethyl-12-(2-methyl-1,3-thiazol-4-yl)-undeca-7,12-dien-furan-1-al (3): 4-Methylmorpholine-*N*-oxide (621 mg, 5.3 mmol, 1.5 equiv) and 4 Å molecular sieves were added to a solution of alcohol **11** (1.58 g, 3.5 mmol) in CH_2Cl_2 (44 mL). The mixture was cooled to 0 °C and stirred for 15 min. Tetrapropylammonium perruthenate (62 mg, 0.17 mmol, 0.05 equiv) was added, and the mixture was stirred 15 min at room temperature. Purification of the residue by flash chromatography (pentane/Et_2O = 2:1) gave aldehyde **3** (1.348 mg, 87%) as a yellow oil.

$[\alpha]_D^{20} = +28.4$ (c = 1, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$): δ = 9.5 (s, 1H; H-1), 7.13 (d, ^3J = 3.5 Hz, 1H; CH furyl, H-3), 6.92 (s, 1H; H-5′), 6.47 (s, 1H; H-12), 6.20 (d, ^3J = 3.5 Hz, 1H; CH furyl, H-4), 5.40 (td, ^2J = 6.4 Hz, ^3J = 0.7 Hz, 1H; H-8), 4.14 (t, ^3J = 5.7 Hz, 1H; H-10), 3.53 (d, ^2J = 15 Hz, 1H; H-6), 3.37 (d, ^2J = 16 Hz, 1H; H-6), 2.70 (s, 3H; C2′-CH_3), 2.40–2.25 (m, 2H; H-9), 1.98 (d, ^4J = 1.1 Hz, 3H; C11-CH_3), 1,72 (d, ^4J = 1.1 Hz, 3H; C7-CH_3), 0.88 (s, 9H; $OSiC(CH_3)_3$), 0.03 (s, 3H), 0.00 ppm (s, 3H; $OSi(CH_3)_2$); ^{13}C NMR (90 MHz, $CDCl_3$): δ = 177.0, 164.3, 161.5, 153.0, 152.1, 142.0, 130.9, 125.2, 118.9, 115.1, 109.1, 78.4, 35.6, 31.3, 25.8, 23.7, 19.1, 18.2, 13.9, −4.6, −5.0 ppm; IR (film): $\tilde{\nu}_{max}$ = 2928, 2856, 1681, 1513, 1471, 1255, 1184, 1073, 1022, 837, 776 cm^{-1}; UV/Vis (MeOH): λ_{max} = 283.8 nm (ε = 5600); MS (CI, NH_3/CH_4): m/z (%): 446 (100) $[M+H]^+$, 430 (17.6), 388 (8), 314 (27.6), 282 (9.6) $[C_{14}H_{24}NOSSi]^+$; HRMS (EI): calcd for $C_{24}H_{35}NO_3SSi$ 445.21069, found 445.2107 (0.0 mmu); elemental analysis calcd (%) for $C_{24}H_{35}NO_3SSi$ (445.69): C 64.68, H 7.92, N 3.14, S 7.19; found: C 60.79, H 8.21, N 3.10, S 6.42.

(4′*S*,4*S*,5*S*,11*Z*,14*S*,15*E*)-14-[(*tert*-Butyldimethylsilyl)oxy]-2-[(4*R*)-2,2-dimethyl-1,3-dioxan-4-yl]-5-hydroxy-2,4,11,15-pentamethyl-16-(2-methyl-1,3-thiazol-4-yl)-11,15-pentadecadien-furan-3-one (12): A solution of LDA was freshly prepared by addition of *n*BuLi (457 μL, 1.14 mmol, 1.96 equiv of a 2.5 M solution in hexanes) to a solution of diisopropylamine (160 μL, 1.14 mmol) in THF (1.95 mL) at 0 °C and stirring for 30 min. A solution of ethyl ketone **2** (250 mg, 1.16 mmol, 2.0 equiv) in THF (1.95 mL) was then added dropwise at −78 °C to the mixture. This was stirred for 1 h at −78 °C. A solution of aldehyde **3** (260 mg, 0.58 mmol, 1 equiv) in THF (2.4 mL) was added dropwise and stirring was continued for 20 min at −78 °C. The mixture was quenched by the dropwise addition of saturated NH_4Cl solution (7 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3× 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by flash chromatography (pentane/Et_2O = 3:1) afforded *anti*-Cram aldol product **12a** and its corresponding Cram diastereoisomer **12b** (350 mg, 91%, ratio 3:1 by NMR spectroscopy) as colorless oils.

Major isomer **12a**: $[\alpha]_D^{20} = -2.9$ (c = 1, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$): δ = 6.91 (s, 1H; H-5″), 6.43 (s, 1H; H-16), 6.10 (d, ^3J = 3 Hz, 1H; CH furyl, H-8), 5.86 (d, ^3J = 3 Hz, 1H; CH furyl, H-7), 5.33–5.29 (m, 1H; H-12), 4.82 (d, ^3J = 3.8 Hz, 1H; H-5), 4.13–4.1 (m, 1H; H-14), 4.0 (dd, ^3J = 11.6 Hz, ^3J = 2.4 Hz, 1H; H-4′), 3.94 (td, ^3J = 2.8 Hz, ^3J = 11.8 Hz, 1H; H-6′), 3.85 (ddd, ^2J = 11.8 Hz, ^3J = 5.4 Hz, ^3J = 1.7 Hz, 1H; H-6′), 3.43 (qd, ^3J = 6.9 Hz, ^3J = 2.8 Hz; 1H; H-4), 3.38 (d, ^2J = 15.6 Hz, 1H; H-10), 3.24 (d, ^2J = 15.6 Hz, 1H; H-10), 2.70 (s, 3H; C2″-CH_3), 2.34–2.25 (m, 2H; H-13), 1.98 (d, ^4J = 1.1 Hz, 3H; C15-CH_3), 1,70 (d, ^4J = 1.1 Hz, 3H; C11-CH_3), 1.67–1.59 (m, 1H; H-5′), 1.56 (bs, 1H, OH), 1.40 (s, 3H, C2′-CH_3), 1.33 (s, 3H; C2′-CH_3), 1.32–1.25 (m, 1H; H-5′), 1.12 (d, ^3J = 6.8 Hz, 3H; C4-CH_3), 1.12 (s, 3H; H-1), 0.99 (s, 3H; C2-CH_3), 0.88 (s, 9H; $OSiC(CH_3)_3$), 0.04 (s, 3H), 0.00 ppm (s, 3H; $OSi(CH_3)_2$); ^{13}C NMR (90 MHz, $CDCl_3$): δ = 221.2, 164.4, 153.2, 153.1, 152.6, 142.3, 132.6, 123.8, 118.7, 114.9, 107.4, 106.0, 98.4, 78.7, 74.4, 68.7, 59.8, 51.5, 45.2, 35.5, 30.9, 29.6, 25.8, 25.1, 23.8, 20.6, 19.1, 19.0, 18.5, 18.2, 13.9, 12.0, −4.6, −4.9 ppm; IR (film): $\tilde{\nu}_{max}$ = 3475, 2929, 2856, 2363, 1697, 1558, 1472, 1373, 1252, 1195, 1159, 1104, 987, 836, 777 cm^{-1}; MS (70 eV, EI): m/z (%): 659 (1) $[M]^+$, 446 (2), 388 (2), 282 (100) $[C_{14}H_{24}NOSSi]^+$, 225 (4), 156 (6), 115 (8), 73 (30); HRMS (EI): calcd for $C_{36}H_{57}NO_6SSi$ 659.36759, found 659.3672 (0.4 mmu); elemental analysis calcd (%) for $C_{36}H_{57}NO_6SSi$ (659.99): C 65.51, H 8.71, N 2.12, S 4.86; found: C 63.30, H 9.30, N 2.90, S 4.33.

Minor isomer **12b**: ^{1}H NMR (360 MHz, $CDCl_3$): δ = 6.92 (s, 1H; H-5″), 6.45 (s, 1H; H-16), 6.14 (d, ^3J = 3 Hz, 1H; CH furyl, H-7), 5.88 (d, ^3J = 3 Hz, 1H; CH furyl, H-8), 5.33–5.29 (m, 1H; H-12), 4.86 (d, ^3J = 3.6 Hz, 1H; H-5), 4.12–4.0 (m, 2H; H-14; H-4′), 3.94 (td, ^3J = 2.8 Hz, ^3J = 11.8 Hz, 1H; H-6′), 3.85 (ddd, ^2J = 11.8 Hz, ^3J = 5.4 Hz, ^3J = 1.7 Hz, 1H; H-6′), 3.41–3.43 (m, 1H; H-4), 3.37 (d, ^2J = 15.8 Hz, 1H; H-10), 3.23 (d, ^2J = 15.5 Hz, 1H; H-10), 2.70 (s, 3H; C2″-CH_3), 2.34–2.29 (m, 2H; H-13), 1.98 (d, ^4J = 1.2 Hz, 3H; C15-CH_3), 1,70 (d, ^4J = 1.1 Hz, 3H; C11-CH_3), 1.63–1.59 (m, 1H; H-5′), 1.42 (s, 3H, C2′-CH_3), 1.32 (s, 3H; C2′-CH_3), 1.31–1.23 (m, 1H, H-5′), 1.11 (d, ^3J = 6.9 Hz, 3H; C4-CH_3), 1.11 (s, 3H;

H-1), 0.99 (s, 3H; C2-CH_3), 0.89 (s, 9H, $OSiC(CH_3)_3$), 0.04 (s, 3H), 0.00 ppm (s, 3H; $OSi(CH_3)_2$); ^{13}C NMR (90 MHz, $CDCl_3$): $\delta = 192.8$, 164.5, 153.1, 152.8, 142.3, 132.6, 123.8, 118.8, 115.0, 107.4, 106.1, 98.5, 78.7, 74.1, 68.7, 59.9, 51.6, 44.4, 35.5, 30.9, 29.6, 25.8, 25.2, 23.7, 21.1, 19.1, 18.9, 18.3, 18.2, 13.9, 12.2, −4.6, −4.9 ppm; IR (film): $\tilde{\nu}_{max} = 3446$, 2928, 2855, 2358, 1739, 1698, 1558, 1471, 1372, 1251, 1196, 1161, 1104, 986, 836, 777 cm^{-1}; MS (70 eV, EI): *m/z* (%): 659 (1) $[M]^+$, 644 (2), 446 (2), 388 (3), 282 (100) $[C_{14}H_{24}NOSSi]^+$, 226 (4), 156 (9), 115 (11), 73 (36); HRMS (EI): calcd for $C_{36}H_{57}NO_6SSi$ 659.36759, found 659.3696 (-2 mmu).

(3*S*,6*S*,7*S*,13*Z*,16*S*,17*E*)-1,3,7-Trihydroxy-16-[(*tert*-butyldimethylsilyl)-oxy]-4,4,6,13,17-pentamethyl-18-(2-methyl-1,3-thiazol-4-yl)-13,17-hepta-decadien-furan-5-one (13): PPTS (6.0 mg, 23 μmol, 0.6 equiv) was added to a solution of aldol product **12a** (25 mg, 38 μmol) in MeOH (1 mL). The mixture was stirred for 22 h at room temperature. Another portion of PPTS (4.0 mg, 16 μmol, 0.4 equiv) was added and stirring was continued for 24 h. The solvent was removed in vacuo, and the residue was purified by flash chromatography (Et_2O) to give triol **13** (19.7 mg, 84%) as a colorless oil.

$[\alpha]_D^{20} = -1.1$ ($c = 1$, $CHCl_3$); ^1H NMR (360 MHz, $CDCl_3$): $\delta = 6.92$ (s, 1H; H-5′), 6.40 (s, 1H; H-18), 6.07 (d, $^3J = 3$ Hz, 1H; CH furyl, H-9), 5.86 (d, $^3J = 3.1$ Hz, 1H; CH furyl, H-10), 5.34–5.31 (m, 1H; H-14), 4.78 (d, $^3J = 6.3$ Hz, 1H; H-7), 4.13–4.1 (m, 1H; H-16), 3.96 (dd, $^3J = 6.7$ Hz, $^3J = 2.9$ Hz, 1H; H-3), 3.85–3.79 (m; 2H; H-1), 3.46 (qd, $^3J = 6.9$ Hz, $^3J = 2.8$ Hz; 1H; H-6), 3.37 (d, $^2J = 15.5$ Hz, 1H; H-12), 3.23 (d, $^2J = 15.1$ Hz, 1H; H-12), 2.70 (s, 3H; C2′-CH_3), 2.39–2.25 (m, 2H; H-15), 1.96 (d, $^4J = 1.1$ Hz, 3H; C17-CH_3), 1,70 (d, $^4J = 1.1$ Hz, 3H; C13-CH_3), 1.63–1.51 (m; 6H; H-2, -OH), 1.21 (d, $^3J = 6.8$ Hz, 3H; C6-CH_3), 1.06 (s, 3H; C4-CH_3), 0.97 (s, 3H; C4-CH_3), 0.88 (s, 9H, $OSiC(CH_3)_3$), 0.04 (s, 3H), 0.00 ppm (s, 3H, $OSi(CH_3)_2$); ^{13}C NMR (90 MHz, $CDCl_3$): $\delta = 221.3$, 165.6, 153.4, 152.5, 152.5, 141.7, 132.6, 123.9, 118.5, 114.8, 107.8, 106.2, 78.7, 76.3, 69.0, 62.0, 52.5, 45.6, 35.6, 32.5, 30.9, 25.8, 23.8, 21.1, 18.9, 18.2, 18.1, 14.0, 13.9, −4.6, −4.9 ppm; IR (film): $\tilde{\nu}_{max} = 3388$, 2930, 2857, 1693, 1508, 1471, 1387, 1252, 1188, 1072, 1010, 990, 837, 777 cm^{-1}; MS (70 eV, EI): *m/z* (%): 619 (0.03) $[M]^+$, 586 (0.02), 545 (0.07) $[M-t\mathrm{Bu}]^+$, 501 (0.03), 486 (0.01), 470 (0.12), 446 (0.8), 430 (0.32), 388 (1), 328 (0.32), 314 (0.88), 282 (100) $[C_{14}H_{24}NOSSi]^+$, 226 (1), 182 (4), 151 (4), 100 (5), 73 (20); HRMS (EI): calcd for $C_{33}H_{53}NO_6SSi$ 619.3363, found 619.3373 (-1.3 mmu); elemental analysis calcd (%) for $C_{33}H_{53}NO_6SSi$ (619.34): C 63.94, H 8.62, N 2.26, S 5.17; found: C 61.86, H 8.69, N 2.92, S 4.77.

(3*S*,6*S*,7*S*,13*Z*,16*S*,17*E*)-1,3,7,16-Tetra[(*tert*-butyldimethylsilyl)oxy]-4,4,6,13,17-pentamethyl-18-(2-methyl-1,3-thiazol-4-yl)-13,17-heptadeca-dien-furan-5-one (14): 2,6-Lutidine (36 μL, 0.31 mmol, 9.6 equiv) was added to a solution of triol **13** (20.0 mg, 32 μmol) in CH_2Cl_2 (1 mL). The mixture was cooled to −50 °C and TBSOTf (34 μL, 0.15 mmol, 4.8 equiv) was added. The mixture was stirred for an additional hour. The solvent was poured directly on the column and the residue was purified by flash chromatography (pentane/Et_2O = 20:1). The tetrakis silyl ether **14** (22 mg, 71%) was obtained as a colorless oil.

$[\alpha]_D^{20} = -7.9$ ($c = 1$, $CHCl_3$); ^1H NMR (360 MHz, $CDCl_3$): $\delta = 6.91$ (s, 1H; H-5′), 6.46 (s, 1H; H-18), 5.89 (d, $^3J = 3$ Hz, 1H; CH furyl, H-9), 5.76 (d, $^3J = 3.1$ Hz, 1H; CH furyl, H-10), 5.29–5.25 (m, 1H; H-14), 4.6 (d, $^3J = 9.6$ Hz, 1H; H-7), 4.13–4.10 (m, 1H; H-16), 3.71 (dd, $^3J = 7.4$ Hz, $^3J = 2.7$ Hz, 1H; H-3), 3.66–3.46 (m; 3H; H-1, H-6), 3.33 (d, $^2J = 15.5$ Hz, 1H; H-12), 3.20 (d, $^2J = 15.5$ Hz, 1H; H-12), 2.70 (s, 3H; C2′-CH_3), 2.35–2.28 (m, 2H; H-15), 1.96 (d, $^4J = 1.1$ Hz, 3H; C17-CH_3), 1,65 (d, $^4J = 1.1$ Hz, 3H; C13-CH_3), 1.51–1.43 (m; 2H; H-2), 1.17 (d, $^3J = 6.8$ Hz, 3H; C6-CH_3), 1.00 (s, 3H; C4-CH_3), 0.88, 0.86, 0.86, 0.82 (4 s, 4× 9H, $OSiC(CH_3)_3$), 0.52 (s, 3H; C4-CH_3), 0.04, 0.03, 0.01, 0.01, −0.00, −0.02 (6 s, 6× 3H; $OSi(CH_3)_2$), 0.00 ppm (s, 6H; $OSi(CH_3)_2$); ^{13}C NMR (90 MHz, $CDCl_3$): $\delta = 217.5$, 164.3, 153.1, 153.0, 152.9, 142.9, 132.5, 123.6, 117.5, 114.9, 108.3, 105.8, 78.6, 73.7, 70.4, 61.1, 53.6, 48.1, 38.2, 35.4, 30.9, 26.0, 25.9, 25.8, 25.7, 23.5, 23.0, 19.1, 18.2, 18.2, 18.1, 18.1, 15.6, 14.0, 13.9, −3.7, −3.9, −4.6, −4.9, −5.1, −5.1, −5.2, −5.2 ppm; IR (film): $\tilde{\nu}_{max} =$ 2930, 2857, 1695, 1472, 1388, 1361, 1256, 1091, 1007, 990, 836, 776 cm^{-1}; MS (70 eV, EI): *m/z* (%): 961 (0.03) $[M]^+$, 946 (0.01), 904 (0.02), 829 (0.06), 814 (0.01), 772 (0.01), 723 (0.02), 698 (0.02), 662 (0.03), 647 (0.04), 602 (0.04), 560 (10), 453 (2), 428 (8), 338 (7), 282 (100) $[C_{14}H_{24}NOSSi]^+$, 239 (12), 177 (2), 115 (4), 91 (8), 73 (18); HRMS (EI): calcd for $C_{51}H_{95}NO_6SSi_4$ 961.5957, found 961.5965 (-0.8 mmu); elemental analysis calcd (%) for $C_{51}H_{95}NO_6SSi_4$ (962.71): C 63.63, H 9.95, N 1.45, S 3.33; found: C 60.34, H 9.67, N 1.94, S 3.10.

(3*S*,6*S*,7*S*,13*Z*,16*S*,17*E*)-1(Hydroxy)-3,7,16-Tri[(*tert*-butyl-dimethylsilyl)-oxy]-4,4,6,13,17-pentamethyl-18-(2-methyl-1,3-thiazol-4-yl)-13,17-hepta-decadien-furan-5-one (15): Ammonium fluoride (262 mg, 7 mmol, 40 equiv) was added to a solution of the tetrakis silyl ether **14** (170 mg, 0.17 mmol) in MeOH (4.5 mL). The mixture was heated for 1.5 h under reflux. A second portion of ammonium fluoride (58 mg, 1.6 mmol, 9 equiv) was added, and the solution was heated under reflux for an additional hour. The solution was filtered, and the residue was washed with MeOH, CH_2Cl_2, and diethyl ether. The organic phase was dried over celite and concentrated in vacuo. Flash chromatography (pentane/Et_2O = 5:1) of the residue gave alcohol **15** (108 mg, 73%) as a yellow oil.

$[\alpha]_D^{20} = -0.7$ ($c = 1$, $CHCl_3$); ^1H NMR (360 MHz, $CDCl_3$): $\delta = 6.91$ (s, 1H; H-5′), 6.47 (s, 1H; H-18), 5.91 (d, $^3J = 3$ Hz, 1H; CH furyl, H-9), 5.78 (d, $^3J = 3.1$ Hz, 1H; CH furyl, H-10), 5.30–5.27 (m, 1H; H-14), 4.66 (d, $^3J = 9.6$ Hz, 1H; H-7), 4.14–4.11 (m, 1H; H-16), 3.91 (dd, $^3J = 6.3$ Hz, $^3J = 3.8$ Hz, 1H; H-3), 3.62–3.59 (m; 2H; H-1), 3.49–3.42 (m; 1H; H-6), 3.34 (d, $^2J = 15.5$ Hz, 1H; H-12), 3.22 (d, $^2J = 15.5$ Hz, 1H; H-12), 2.71 (s, 3H; C2′-CH_3), 2.40–2.28 (m, 2H; H-15), 1.98 (d, $^4J = 1$ Hz, 3H; C17-CH_3), 1,66 (d, $^4J = 0.9$ Hz, 3H; C13-CH_3), 1.60–1.50 (m; 2H; H-2), 1.20 (d, $^3J = 6.8$ Hz, 3H; C6-CH_3), 1.08 (s, 3H; C4-CH_3) , 0.89, 0.86, 0.83 (3 s, 3× 9H, $OSiC(CH_3)_3$), 0.53 (s, 3H; C4-CH_3), 0.06, 0.05, 0.00, −0.01 (4 s, 4× 3H; $OSi(CH_3)_2$), 0.01 ppm (s, 6H; $OSi(CH_3)_2$); ^{13}C NMR (90 MHz, $CDCl_3$): $\delta = 218.4$, 164.3, 153.1, 153.0, 152.9, 142.9, 132.5, 123.7, 118.8, 114.9, 108.5, 105.9, 78.6, 72.7, 70.2, 60.2, 53.6, 48.1, 38.4, 35.4, 30.9, 26.0, 25.8, 25.7, 23.5, 23.0, 19.1, 18.2, 18.1, 16.8, 15.9, 13.9, −3.9, −4.0, −4.6, −4.9, −5.1, −5.1 ppm; IR (film): $\tilde{\nu}_{max} = 3412$, 2929, 2857, 1694, 1556,1472, 1387, 1361, 1255, 1090, 1010, 990, 836, 776 cm^{-1}; MS (70 eV, EI): *m/z* (%): 847 (1) $[M]^+$, 790 (0.5), 715 (0.5), 658 (1), 560 (1), 526 (0.5), 428 (4), 325 (1), 282 (100) $[C_{14}H_{24}NOSSi]^+$, 213 (4), 147 (6), 131 (9), 75 (30); HRMS (EI): calcd for $C_{45}H_{81}NO_6SSi_3$ 847.5092, found 847.5081 (+1.1 mmu); elemental analysis calcd (%) for $C_{45}H_{81}NO_6SSi_3$ (847.51): C 63.70, H 9.62, N 1.65, S 3.78; found: C 61.49, H 9.74, N 1.84, S 3.38.

(3*S*,6*S*,7*S*,13*Z*,16*S*,17*E*)-3,7,16-Tri[(*tert*-butyldimethylsilyl)oxy]-4,4,6,13,17-pentamethyl-18-(2-methyl-1,3-thiazol-4-yl)-13,17-heptadeca-dien-furan-5-oxoheptanoic acid (16): PDC (3.39 g, 8 mmol, 45 equiv) in DMF (10 mL) was added to a solution of alcohol **15** (170 mg, 0.2 mmol) in DMF (3 mL). The reaction mixture was stirred at room temperature for 19 h. The solution was filtered twice over silica gel (pentane/ether = 4:1). Flash chromatography (pentane/Et_2O = 4:1) of the residue afforded acid **16** (138 mg, 80%) as a yellow oil.

$[\alpha]_D^{20} = -1.6$ ($c = 1$, $CHCl_3$); ^1H NMR (360 MHz, $CDCl_3$): $\delta = 6.92$ (s, 1H; H-5′), 6.52 (s, 1H; H-18), 5.91 (d, $^3J = 3$ Hz, 1H; CH furyl, H-9), 5.80 (d, $^3J = 3$ Hz, 1H; CH furyl, H-10), 5.29–5.28 (m, 1H; H-14), 4.65 (d, $^3J = 9.6$ Hz, 1H; H-7), 4.25 (dd, $^3J = 5.6$ Hz, $^3J = 4.1$ Hz, 1H; H-3), 4.16–4.13 (m, 1H; H-16), 3.50–3.42 (m; 1H; H-6), 3.31 (d, $^2J = 15.5$ Hz, 1H; H-12), 3.22 (d, $^2J = 15.3$ Hz, 1H; H-12), 2.73 (s, 3H; C2′-CH_3), 2.45–2.25 (m, 4H; H-2, H-15), 1.96 (d, $^4J = 1$ Hz, 3H; C17-CH_3), 1,66 (d, $^4J = 0.9$ Hz, 3H; C13-CH_3), 1.20 (d, $^3J = 6.7$ Hz, 3H; C6-CH_3), 1.00 (s, 3H; C4-CH_3) , 0.89, 0.85, 0.83 (3 s, 3× 9H, $OSiC(CH_3)_3$), 0.63 (s, 3H; C4-CH_3), 0.06, 0.03, 0.02, 0.00, −0.00, −0.1 ppm (6 s, 6× 3H; $OSi(CH_3)_2$); ^{13}C NMR (90 MHz, $CDCl_3$): $\delta = 216.8$, 174.9, 165.2, 153.1, 153.0, 153.0, 143.1, 132.6, 123.7, 118.4, 114.7, 108.3, 106.0, 78.6, 73.3, 70.5, 53.6, 48.2, 39.9, 35.5, 30.9, 25.9, 25.8, 25.7, 23.5, 21.5, 18.8, 18.4, 18.2, 16.1, 14.0, −4.0, −4.6, −4.9, −5.0, −5.1 ppm; IR (film): $\tilde{\nu}_{max} = 3285$, 2930, 2857, 1717, 1694, 1505,1472, 1388, 1361, 1255, 1090, 992, 837, 777 cm^{-1}; MS (70 eV, EI): *m/z* (%): 861 (1) $[M]^+$, 804 (1), 729 (1), 672 (2), 560 (2) , 428 (4), 282 (100) $[C_{14}H_{24}NOSSi]^+$, 232 (4), 177 (4), 147 (12), 115 (7), 73 (17); HRMS (EI): calcd for $C_{45}H_{79}NO_7SSi_3$ 861.4885, found 861.4875 (+1 mmu); elemental analysis calcd (%) for $C_{45}H_{79}NO_7SSi_3$ (861.48): C 62.67, H 9.23, N 1.62, S3.72; found: C 60.00, H 9.02, N 3.92, S 3.07.

(3*S*,6*S*,7*S*,13*Z*,16*S*,17*E*)-3,7,16-Trihydroxy-4,4,6,13,17-pentamethyl-18-(2-methyl-1,3-thiazol-4-yl)-13,17-heptadecadien-furan-5-oxoheptanoic acid (17): A solution of trisilylether **16** (16 mg, 0.018 mmol) in MeCN/Et_2O (1:1, 2 mL) at 0 °C was treated with aqueous hydrofluoric acid (280 μL, 40%), ground glass splinters, and the mixture was stirred for 48 h at room temperature. The mixture was then filtered through celite and the residue washed with MeCN. The reaction mixture was concentrated in vacuo to a small volume, and the crude product was purified by preparative thin-layer chromatography (reverse phase silica gel RP 18, 2% MeOH in CH_2Cl_2) to afford pure trihydroxy acid **17** (4.4 mg, 47%; 2.4 mg, 25%, ratio 2:1) as a yellow oil.

Major isomer **17a**: $[\alpha]_D^{20} = -38$ ($c = 0.1$, $CHCl_3$); ^1H NMR (360 MHz, $CDCl_3$): $\delta = 6.99$ (s, 1H; H-5′), 6.86 (s, 1H; H-18), 6.25 (d, $^3J = 3.1$ Hz, 1H; CH furyl, H-9), 6.08 (d, $^3J = 3.1$ Hz, 1H; CH furyl, H-10), 5.29–5.28 (m, 1H; H-14), 4.36 (d, $^3J = 11.3$ Hz, 1H; H-7), 4.28–4.19 (m, 1H; H-16), 4.07 (dd, $^3J = 10.0$ Hz, $^3J = 2.1$ Hz, 1H; H-3), 3.45 (d, $^2J = 15.0$ Hz, 1H; H-12), 3.27 (d, $^2J = 15$ Hz, 1H; H-12), 3.03–2.99 (m; 1H; H-6), 2.74 (s, 3H; C2′-CH_3), 2.62–2.36 (m, 4H; H-2, H-15), 1.97 (s, 3H; C17-CH_3), 1,70 (s, 3H; C13-CH_3), 1.20 (s, 3H; C4-CH_3), 1.08 (s, 3H; C4-CH_3), 0.96 ppm (d, $^3J = 6.6$ Hz, 3H; C6-CH_3); ^{13}C NMR (90 MHz, $CDCl_3$): $\delta = 216.8$, 173.1, 166.2, 152.9, 152.0, 142.8, 135.2, 122.4, 117.0, 114.0, 108.3, 107.4, 80.5, 77.9, 75.7, 48.6, 43.7, 35.8, 34.5, 30.9, 23.6, 19.6, 19.4, 18.1, 16.0, 10.5 ppm; IR (film): $\tilde{\nu}_{max} = 3121$, 2967, 1715, 1556, 1465, 1376, 1247, 1191, 1063, 1014, 909, 793, 732 cm^{-1}; MS (70 eV, EI): *m/z* (%): 501 (4) $[M-H_2O]^+$, 483 (5), 413 (1), 375 (1), 342 (2) , 334 (5), 256 (8), 204 (8), 175 (86), 168 (100), 140 (10), 113 (12), 97 (10); HRMS (EI): calcd for $C_{27}H_{37}NO_7S$ 519.2290, found 501.2185 ($-H_2O$) (+ 0.1 mmu).

Minor isomer **17b**: $[\alpha]_D^{20} = -18$ ($c = 0.1$, $CHCl_3$); ^1H NMR (360 MHz, $CDCl_3$): $\delta = 6.98$ (s, 1H; H-5′), 6.69 (s, 1H; H-18), 6.04 (d, $^3J = 3.1$ Hz, 1H; CH furyl, H-9), 5.97 (d, $^3J = 3.1$ Hz, 1H; CH furyl, H-10), 5.41–5.35 (m, 1H; H-14), 5.23 (d, $^3J = 7.2$ Hz, 1H; H-7), 4.28–4.25 (m, 1H; H-16), 4.00 (dd, $^3J = 10.1$ Hz, $^3J = 2.1$ Hz, 1H; H-3), 3.35 (s, 2H; H-12), 3.33–3.31 (m; 1H; H-6), 2.71 (s, 3H; C2′-CH_3), 2.60–2.54 (m, 1H; H-2), 2.40–2.36 (m, 3H, H-2, H-15), 1.98 (s, 3H; C17-CH_3), 1,76 (s, 3H; C13-CH_3), 1.20 (s, 3H; C4-CH_3), 1.04 (s, 3H; C4-CH_3), 0.99 ppm (d, $^3J = 6.8$ Hz, 3H; C6-CH_3); ^{13}C NMR (90 MHz, $CDCl_3$): $\delta = 212.2$, 173.0, 166.0, 154.0, 148.0, 143.0, 134.6, 122.9, 118.1, 115.0, 112.0, 106.2, 77.9, 74.9, 74.5, 49.9, 42.9, 35.9, 34.1, 31.0, 24.2, 20.7, 19.4, 18.1, 14.7, 10.3; IR (film): $\tilde{\nu}_{max} = 3405$, 2926, 1715, 1549, 1510, 1459, 1378, 1143, 913, 840, 796, 733 cm^{-1}; MS (70 eV, EI): *m/z* (%): 501 (3) $[M-H_2O]^+$, 483 (13), 448 (4), 412 (2), 375 (2), 342 (4) , 334 (7), 324 (10), 282 (5), 256 (9), 233 (13), 204 (16), 185 (18), 175 (76), 168 (100), 147 (42), 97 (22); HRMS (EI): calcd for $C_{27}H_{37}NO_7S$ 519.2290, found 501.2188 ($-H_2O$) (-0.3 mmu).

(3*S*,6*S*,7*S*,13*Z*,16*S*,17*E*)-3,7-Dihydroxy-4,4,6,13-tetramethyl-17-[methyl-(2-methyl-1,3-thiazol-4-yl)-vinyl]-11,16-dioxa-bicyclo[13.2.1]octadeca-8,10,13-trien-1,5-dione (18): A solution of trihydroxy acid **17a** (4.1 mg, 7.8 μmol) in THF (0.5 mL) at 0 °C was treated with Et_3N (7 μL, 47 μmol, 6.0 equiv) and 2,4,6-trichlorobenzoyl chloride (6 μL, 39 μmol, 5.0 equiv). The reaction mixture was stirred at 0 °C for 15 min and then added by syringe pump over a period of 1 h to a solution of 4-DMAP (9.6 mg, 78 μmol, 10 equiv) in toluene (8 mL) at 25 °C. The reaction mixture was stirred for 1 h, concentrated in vacuo to a small volume and filtered through silica gel. The residue was washed with ether and the resulting solution was concentrated to a small volume. The crude product was purified by preparative thin-layer chromatography (reverse phase silica gel RP 18, 2% MeOH in CH_2Cl_2) to afford pure furano-epothilone **18a** (2 mg, 51%).

Major isomer **18a**: $[\alpha]_D^{20} = -24$ ($c = 0.15$, $CHCl_3$); ^1H NMR (360 MHz, C_6D_6): $\delta = 7.02$ (s, 1H; H-18), 6.60 (s, 1H; H-5'), 6.04 (m, 1H; H-16), 5.87 (d, $^3J = 3.1$ Hz, 1H; CH furyl, H-9), 5.76 (d, $^3J = 3.0$ Hz, 1H; CH furyl, H-10), 5.44 (m, 1H; H-14), 4.06 (d, $^3J = 11.2$ Hz, 1H; H-7), 3.89 (dd, $^3J = 11.2$ Hz, $^3J = 2.3$ Hz, 1H; H-3), 3.43 (d, $^2J = 14.5$ Hz, 1H; H-12), 3.20 (m, 1H, H-15), 2.60 (d, $^2J = 14.9$ Hz, 1H; H-12), 2.63–2.56 (m; 2H; H-6, H-15), 2.38–2.33 (m, 1H; H-2), 2.27 (s, 3H; C2′-CH_3), 2.19 (s, 3H; C17-CH_3), 1.93 (dd, $^3J = 12.2$ Hz, $^3J = 2.47$ Hz, 1H, H-2), 1,37 (s, 3H; C13-CH_3), 1.05 (d, $^3J = 6.6$ Hz, 3H; C6-CH_3), 0.87 (s, 3H; C4-CH_3), 0.66 ppm (s, 3H; C4-CH_3); ^{13}C NMR (90 MHz, $CDCl_3$): $\delta = 209.3$, 171.2, 164.3, 153.8, 153.5, 152.4, 136.6, 133.4, 120.9, 119.6, 116.2, 106.2, 105.7, 81.6, 78.0, 76.7, 48.7, 43.0, 36.1, 32.0, 29.8, 24.1, 19.2, 19.1, 18.9, 16.0, 10.7 ppm; IR (film): $\tilde{\nu}_{max} = 3416$, 2864, 1731, 1452, 1373, 1257, 1184, 1131, 1094, 1010, 796 cm^{-1}; MS (70 eV, EI): *m/z* (%): 483 (100) $[M-H_2O]^+$, 439 (9), 396 (4), 354 (2), 324 (60); HRMS (EI): calcd for $C_{27}H_{35}NO_6S$ 501,2185, found 483.2079 ($-H_2O$) (-0.3 mmu).

Minor isomer **18b**: $[\alpha]_D^{20} = -33$ ($c = 0.06$, $CHCl_3$); ^1H NMR (360 MHz, C_6D_6): $\delta = 6.92$ (s, 1H; H-18), 6.59 (s, 1H; H-5'), 6.09 (d, $^3J = 3.3$ Hz, 1H; CH furyl, H-9), 5.66 (d, $^3J = 3.0$ Hz, 1H; CH furyl, H-10), 5.42–5.38 (m, 1H; H-16), 5.11–5.07 (m, 1H; H-14), 4.96 (d, $^3J = 6.5$ Hz, 1H; H-7), 3.74 (dd, $^3J = 9.8$ Hz, $^3J = 2.7$ Hz, 1H; H-3), 3.45 (d, $^2J = 14.5$ Hz, 1H; H-12), 3.19–3.09 (m, 1H, H-15), 2.86–2.81 (m; 1H; H-6), 2.50 (d, $^2J = 15.1$ Hz, 1H; H-12), 2.56–2.48 (m, 1H; H-2), 2.41 (s, 3H; C17-CH_3), 2.28 (s, 3H; C2'-CH_3), 2.21–2.15 (m, 1H, H-2), 2.13–2.10 (m, 1H, H-15), 1,60 (s, 3H; C13-CH_3), 0.99 (d, $^3J = 6.9$ Hz, 3H; C6-CH_3), 0.71 (s, 3H; C4-CH_3), 0.69 ppm (s, 3H; C4-CH_3); ^{13}C NMR (90 MHz, $CDCl_3$): $\delta = 211.2$, 163.7, 139.5, 131.4, 127.9, 124.1, 120.1, 80.6, 75.8, 74.1, 48.3, 43.5, 24.4, 20.9, 19.6, 19.3, 16.6, 12.7 ppm; MS (70 eV, EI): *m/z* (%): 483 (100) $[M-H_2O]^+$, 468 (5), 396 (5), 342 (7), 324 (41), 277 (6), 256 (11), 219 (12), 204 (29); HRMS (EI): calcd for $C_{27}H_{35}NO_6S$ 501,2185, found 483.2079 ($-H_2O$) (0.0 mmu).

Tubulin polymerization assay: The samples were prepared directly in 1.5 mL optical glass cuvettes at 0 °C which contained aqueous "Mes buffer" [0.900 mL (0.1 M 2-(morpholino)ethanesulfonic acid (MES), 1 mM ethyleneglycol-bis-(β-aminoethylether)-*N,N,N′,N′*-tetraacetic acid (EGTA) 0.5 mM $MgCl_2$, pH 6.6)], guanosine 5′-triphosphate (GTP; 10 μL, 100 mM in double distilled water), and tubulin (100 μL, 8–10 mg mL^{-1} in aqueous "Mes buffer"). The cuvettes were thoroughly agitated and immediately placed in a Cary 300 Bio spectrophotometer (Varian), preheated at 37 °C, alongside a blank sample containing aqueous "Mes buffer" (0.990 mL) and GTP (10 μL, 100 mM in double distilled water) and the absorbance at λ 350 nm was recorded. When the absorbance reached a plateau (after 15 min), $CaCl_2$ (10 μL, 400 mM in double distilled water) was added to each cuvette. After another 15 min, a minimum absorbance was reached and the candidate drug in DMSO (2.5 mM) was added to the cuvettes in portions every 15 min and thoroughly shaken to give final concentrations of 0.5, 1.0, 2.0, 5.0, 10, and 20 μM, respectively (final concentrations of the candidate drug in the assay). The results were compared to the untreated control (using the same quantities of DMSO without the candidate drug) to assess the relative change in absorbance due to microtubule assembly. The results are presented as ED_{50} and ED_{90} which correspond to the dosage of candidate drug required to induce 50% and 90% microtubule assembly.

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