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Function oriented synthesis: preparation and initial biological evaluation of new A-ring-modified bryologs

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ABSTRACT

The synthesis and biological evaluation of the first members of a new series of designed bryostatin A-ring analogues (bryologs) are described. An advanced intermediate is produced that allows for step economical access to diverse analogs. The first of these analogues, bearing side chains of completely different polarities from alkyl to hydroxyl and carboxyl functionalities, were evaluated. All exhibit potent protein kinase C binding (54.7–2.4 nM) with affinities increasing with decreasing side chain polarity. This series of bryostatin analogues demonstrates that A-ring surrogates can indeed be used for tuning pharmacophore and ADME characteristics as needed to improve bryolog function.

1. Introduction

The bryostatins are a structurally and biologically unique family of macrocyclic lactones[1] first collected from bryozoa[2] in the Gulf of Mexico in 1968 by Pettit and co-workers.[3] In 1982, the structure of bryostatin 1 (Fig. 1), the lead member of this family, was established by X-ray crystallography.[4] Subsequent studies revealed that bryostatin exhibits promising activity against several cancer cell lines. Significantly, bryostatin promotes apoptosis,[5] reverses multidrug resistance,[6] and synergizes with other anticancer agents.[7] In contrast to many anticancer drugs, bryostatin stimulates the immune system, thus providing the basis for a promising immunotherapeutic approach to cancer.[8] Bryostatin has also been found to facilitate learning and extend memory in animals[9] and has recently been entered into a clinical trial for treating Alzheimer's disease.[10] Remarkably, bryostatin also induces activation of latent HIV reservoirs, thus serving as a lead in efforts to eradicate HIV/AIDS.[11]

Bryostatin's activities arise from binding to the C1 domain of protein kinase C (PKC)[12] and possibly other C1 domain targets.[13] Unlike many kinase-targeting molecules that bind to the ATP binding site and thus serve only to inhibit function, ligands targeting the C1 domain can turn on or turn off function. Bryostatin binds with high affinity (<10 nM) to conventional and novel PKC isozymes.[14] Since different isoforms are associated with various therapeutic indications,[15] bryostatin is a promising lead for drug discovery.

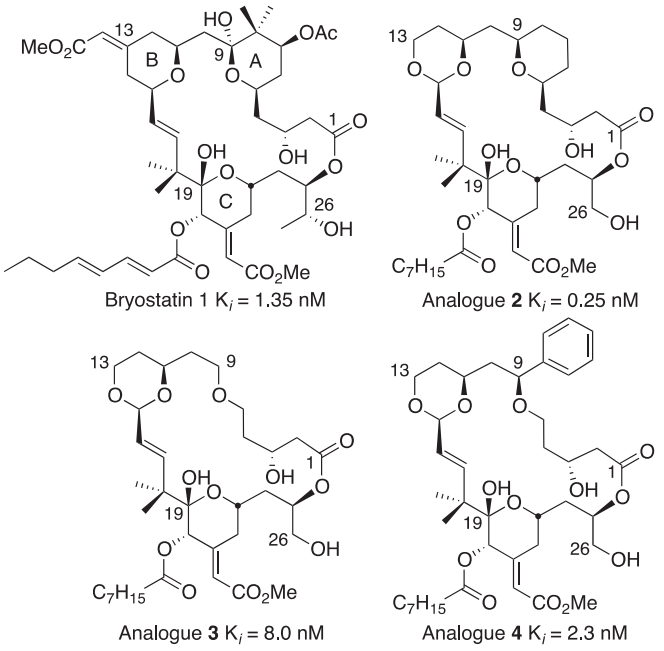

Fig. 1. Bryostatin **1** and lead analogues (K_i=binding affinity to rat brain PKC).

Despite this unique portfolio of biological activities, the study and use of bryostatin has been impeded by its limited supply and challenges associated with systematic modification of its complex

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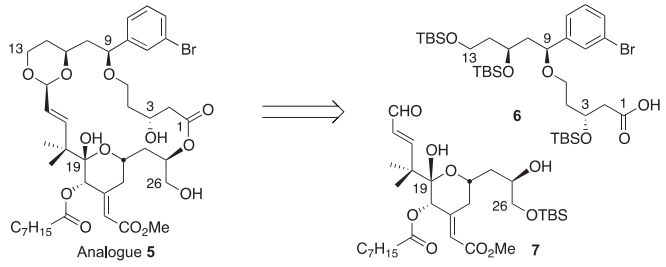
structure. Low isolation yields (18 g are obtained from 14 tons of bryozoa[16]) and environmental concerns about larger scale marine harvesting make it impractical to obtain significant amounts from natural sources. Early research by the groups of Masamune, Evans and Yamamura led to impressive total syntheses of bryostatins 7, 2 and 3, respectively.[17] These syntheses have, however, not been further advanced and are currently too long (>70 steps) to impact supply. Recent advances include a formal total synthesis of bryostatin 7 by the Hale Group[18] and a total synthesis of bryostatin 16 by Trost and Dong.[19] The Keck Group[20] has also reported a notable advance with an approximately 57-step synthesis of bryostatin 1 and recently the Krische Group[21] described a 36-step synthesis of bryostatin 7. Adam Schrier (Wender Group) recently reported a scalable 42-step synthesis of bryostatin 9.[22] Additional groups have contributed substantially to this field, including those of Thomas, Vandewalle, Roy, Burke, Hoffmann, and Yadav.[23]

While efforts to synthesize natural bryostatins continue to impressively advance, in the 1980s we[24] took an alternative approach to the goal of achieving more time- and step economical access to molecules with bryostatin activity, that is, generally applicable to many therapeutically promising complex molecules that are beyond the *immediate* reach of supply-impacting synthesis. Realizing that the demand for bryostatin, not unlike that of many natural products, is driven primarily by its function (i.e., activity) and not its structure and that function is neither evolved nor optimized for human therapy, we sought to use synthesis-informed design to create simpler structures that would be more readily accessible and yet exhibit similar if not superior activity to the natural lead. This function oriented synthesis (FOS) approach[25] has yielded to date over 100 designed bryostatin analogues (bryologs), over 35 of which have comparable or better affinities than bryostatin in binding PKC and are synthetically accessible on scale in under 30 total steps.[26] This FOS approach opens broad opportunities to explore the varied activities of tunable bryostatin-like compounds and is expected to be a preferred strategy for those interested in its function. Moreover, given supply and some off target clinical issues with bryostatin, these analogs and related approaches could offer more effective agents with fewer side effects. The potential of our approach has indeed been recognized in recent clinical studies.[7b]

In computational studies of competitive PKC ligands, we proposed that the affinity of bryostatin could arise in part from the array of hydrogen bond donors and acceptors at C1, C19 and C26.[26] Deletion of groups not in contact with PKC or that do not influence conformational populations led to bryolog **2** (Fig. 1) with a PKC affinity *better* than bryostatin and accessible in <30 steps.[27] Further simplification caused some loss in affinity (**3**) that was largely restored in **4** by introduction of a conformation influencing phenyl group at C9.[28] Encouraged by the significant activity of **4**, the current study sought to create a diversifiable, advanced intermediate **5** (Scheme 1) that would allow systematic investigation of how variations in this part of the molecule would affect PKC affinity with the eventual goal of using this information to design selective PKC regulators.[29]

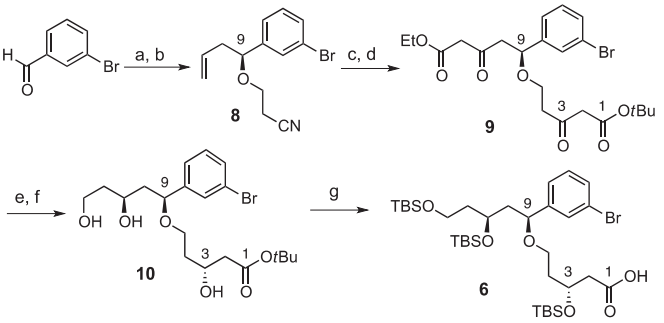


Scheme 1. Retrosynthetic analysis.

Our A-ring analogues have been shown to translocate PKCδ-GFP from the cytosol to cellular membranes in RBL cells, an assay that correlates with biological function.[30] Analogue **4** in particular shows a translocation profile similar to bryostatin.[31] These significant findings warranted further study of how this A-ring region could be used to modulate activity and selectivity. It has been shown that non-polar side chains are tolerated in this region,[32] but little is known about polar side chains. Polarity is however important, since bryostatins 1 (OAc) and 2 (OH) differ in PKC selectivity. Analogue **5** (Scheme 1) was chosen as a diversification node for accessing derivatives with varying polarity in the A-ring region. Based on previous modeling studies of **4** the *meta*-substitution of the phenyl-ring was expected to favor contact with PKC in the vicinity of bryostatin's C7-acetate.

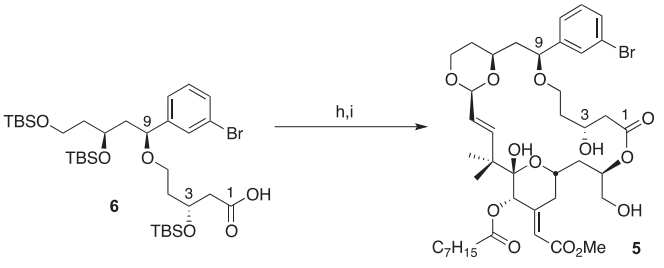
2. Results and discussion

Analogue **5** is synthesized in a highly convergent fashion by coupling a top piece with a known bottom piece **7**[27] in two steps using a macrotransacetalization procedure (Scheme 1). The synthesis of the C1-C13 spacer domain **6** (Scheme 2) began with asymmetric allylation[33] of 3-bromobenzaldehyde to give an alcohol (92% enantiopurity, 76% yield) that on subsequent cyanoethylation with acrylonitrile provided nitrile **8** in 98% yield. Blaise-type conditions with Zn and catalytic Cp_2TiCl_2 converted the nitrile group in **8** into a β-ketoester.[34,35] Ozonolysis followed by addition of ethyl diazoacetate and $SnCl_4$ gave **9** via a Roskamp rearrangement.[36] Asymmetric hydrogenation with (*R*)-BINOL/$RuBr_2$ adjusted the oxidation state of C3 and C11. HPLC analysis established that **10** was obtained in 98% diastereomeric purity. Selective reduction of C13 was achieved with superhydride. Triol **10** was treated with excess TBSOTf/2,6-lutidine, which silylated all three hydroxyl groups and cleaved the *tert*-butyl ester functionality,[37] affording acid **6** in 92% yield. The synthesis of the new top piece **6** was thus achieved in only 7 steps with an overall yield of 24%.



Scheme 2. Top piece synthesis. (a) (*S*)-BINOL/Ti(O*i*-Pr)$_4$ (10 mol %), B(OMe)$_3$, Bu_3Sn(allyl), 4 Å MS, CH_2Cl_2, 76%; (b) acrylonitrile, Triton B in H_2O, CH_2Cl_2, 98%; (c) *t*-Bu-bromoacetate, Zn, cat. Cp_2TiCl_2, THF, 85%; (d) i. O_3, PPh_3 ii. ethyl diazoacetate, $SnCl_4$, 63%; (e) ((*R*)-BINAP) $RuBr_2$, EtOH, H_2, 80%; (f) Superhydride, THF, 81%; (g) TBSOTf, 2,6-lutidine, 92%.

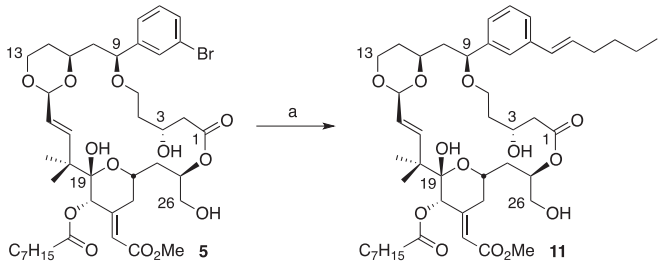
The top and bottom pieces (**6** and **7**) were linked following the Yamaguchi protocol via the mixed anhydride (Scheme 3).[38] Subsequent addition of HF/pyridine cleaved the silyl protecting groups and effected formation of the macrocyclic lactone **5** by



Scheme 3. Coupling and ring closure. (h) Et_3N, 2,4,6-tribenzoyl chloride, then **7**, DMAP, toluene, 91%; (i) 70% HF/pyridine, 83%.

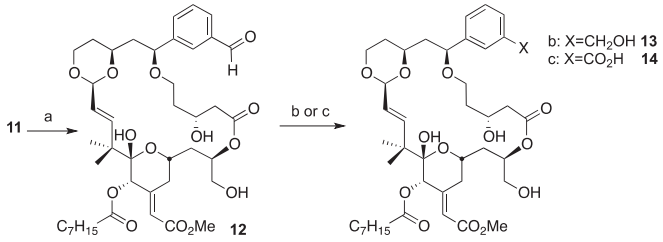
transacetalization. Analogue **5** was synthesized in 19 steps (longest linear sequence) and 2% overall yield.

The diversification of bryolog **5** was addressed next. While aryl bromides are attractive groups for diversification, the presence in **5** of several sensitive groups including free alcohols, three esters, two olefins (one a Michael acceptor), two acetals and one benzyl ether puts severe constraints on reaction choice. Diversification reactions, such as palladium promoted carbonylation, alkynylation and vinylation as well as radical allylations worked well for model systems but did not transfer to reactions with analogue **5**. Alkenylation was finally achieved using a Suzuki coupling protocol employing the *S*-Phos ligand with $Pd(OAc)_2$, CsF and *trans*-1-hexen-1-ylboronic acid (Scheme 4). The resulting vinylated analogue **11** is obtained in 70% yield.



Scheme 4. Suzuki coupling of analogue **5**[a] (a) $Pd(OAc)_2$, *S*-Phos, CsF, *trans*-hex-1-en-1-ylboronic acid, dioxane, 60 °C, 70%.

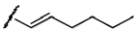
Cleavage of the styrenyl double bond was accomplished chemoselectively with 1 equiv of ozone or alternatively a dihydroxylation—diol cleavage strategy. Subsequent reduction of the resultant aldehyde gave the 9-(3-hydroxymethyl)aryl substituted bryolog (**13**) in 72% yield (Scheme 5). Alternatively, the aldehyde can be oxidized to carboxylic acid **14** upon treatment with *m*-CPBA. Interestingly, the Baeyer—Villiger oxidation only furnishes the 9-(3-carboxy)-aryl substituted analogue (52% yield). The corresponding aryl migration product was not detected by NMR or HPLC.



Scheme 5. Late stage diversification. (a) OsO_4, $NaIO_4$, or O_3 (b) $NaBH_4$, MeOH, 72% (over two steps); (c) *m*-CPBA, 52% (over two steps).

A competitive binding assay was performed with the new A-ring analogues **5**, **11**, **13** and **14** on a mixture of rat brain PKC isozymes (Table 1) used as a preliminary benchmark assay to determine whether further study is warranted. All compounds exhibit potent nanomolar binding affinity to this PKC isozyme mixture. Significantly, decreasing polarity in the side chain results in increased affinity: the parent analogue **4** and its bromo variant **5** have an affinity of 2.3–2.4 nM. The alkenyl substituted analogue **11** shows a similar (4.0 nM) binding affinity. Substitution of these nonpolar groups with oxygen-containing functional groups reduces the binding affinity to 15.5 nM in case of the hydroxyl methyl analogue **13**. Introduction of an even more polar carboxyl group still furnishes a potent compound but with a further reduction in binding affinity (54.7 nM). Although this number constitutes the lowest binding affinity in the series it is striking that such drastic changes in the polarity still led to highly potent compounds.

Table 1
Binding affinities for new A-ring bryologs (rat brain PKC)

Analogue		K_i nM
5	Br	2.4
11		4.0
13		15.5
14		54.7

3. Conclusion

These and previous studies show that simplified A-ring analogs made in uniquely step economical sequences exhibit bryostatin like binding and can be tuned as needed to improve function or suppress undesired side effects. This work provides the shortest synthetic sequence to natural or non-natural compounds with bryostatin-like PKC affinities. This FOS approach provides quantities of diversifiable intermediates that are being explored for preclinical candidacy.

4. Experimental section

4.1. Synthesis of (*S*)-1-(3-bromophenyl)but-3-en-1-ol

To a solution of 0.1 equiv (*S*)-BINOL (1.0 mmol, 288 mg) in 4.6 ml CH_2Cl_2 4 g powdered 4 Å MS were added followed by 0.05 equiv $Ti(Oi\text{-}Pr)_4$ (0.5 mmol, 150 μl). The resulting orange mixture was refluxed for 1 h and then cooled in a water bath to rt. A solution of 1.0 equiv 3-bromo benzcarboxaldehyde (10.0 mmol, 1.17 ml) in 1 ml CH_2Cl_2 followed by 1.2 equiv $B(OMe)_3$ (12 mmol, 1.34 ml) was added. 1.18 equiv $Bu_3SnCH_2CHCH_2$ (11.8 mmol, 3.7 ml) were added dropwise to the deep red suspension over 5 min. The resulting mixture was stirred at rt for 14 h, then the orange mixture was filtered through Celite into saturated $NaHCO_3$ (50 ml). The Celite was washed with Et_2O and the biphasic mixture was stirred for 1 h. Afterwards the aqueous layer was extracted with Et_2O (3×30 ml) and the combined organic layers were dried over Na_2SO_4 and concentrated to an orange oil. The residue was purified by column chromatography (silica gel, Et_2O/pentane 1:4) to yield the (*S*)-1-(3-bromophenyl)but-3-en-1-ol (1.723 g, 7.58 mmol, 76%) as a slightly yellow liquid. R_f=0.55 (pentane/EtOAc=10:1)—one blue spot with *p*-anisaldehyde stain IR (thin film): 3368, 3077, 3009, 2979, 2907, 1642, 1595, 1570, 1476, 1429, 1344, 1298, 1193, 1092, 1070,997, 919, 882, 783, 687, 666 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.52 (m_c, 1H, aryl-H); 7.42–7.37 (m, 1H, aryl-H); 7.29–7.18 (m, 2H, aryl-H); 5.78 (m_c, 1H, H-2); 5.20–5.14 (m, 2H, H-1); 4.69 (m_c, 1H, H-4); 2.54–2.40 (m, 2H, H-3); 2.21–2.16 (m, 1H, OH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.1, 133.8, 130.5, 129.9, 128.9, 124.4, 122.5, 119.0, 72.4, 43.8.HRMS: calculated for $C_{10}H_{11}OBr$ $[M]^+$: 225.9993. Found: 225.9990.$[\alpha]_D^{23}$ −44.5 (*c* 0.93in $CHCl_3$); *op*=87%.

4.2. Synthesis of nitrile 8

To a rt solution of 1.0 equiv (*S*)-1-(3-bromophenyl)but-3-en-1-ol (7.39 mmol, 1.678 g) were added 5.0 equiv acrylonitrile (36.95 mmol, 2.43 ml) followed by 0.1 equiv. Triton B (40% wt in H_2O, 0.74 mmol, 0.29 ml), each via syringe. The reaction was monitored by GC, since the starting material (t_R=12.15 min) and the product (t_R=15.87 min) cospot. After 3.5 h the yellow solution was poured into saturated aq NH_4Cl solution (50 ml). The phases were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo to furnish

a yellow oil. The crude was purified by column chromatography (silica gel, pentane/Et_2O 1:7→1:4) to give nitrile **8** (2.023 g, 7.22 mmol, 98%) as a colourless liquid. R_f=0.24 (pentane/EtOAc=6:1)—one purple-grey spot with *p*-anisaldehyde stain. IR (thin film): 3077, 3011, 2978, 2911, 2878, 2253, 1642, 1595, 1571, 1475, 1429, 1342, 1279, 1222, 1193, 1106, 1071, 997, 921, 787, 699, 666 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.17–7.40 (m, 2H, aryl-H); 7.27–7.22 (m, 2H, aryl-H); 5.76 (m_c, 1H, H-2); 5.08–5.03 (m, 1H, H-1); 4.28 (dd, *J*=6.0, 7.5 Hz, 1H, H-4); 3.53 (dt, *J*=6.5, 9.5 Hz, 1H, H-5); 3.49 (dt, *J*=6.5, 9.5 Hz, 1H, H-5′); 2.60–2.53 (m, 3H, H-6/H-3′); 2.39 (dddt, *J*=1.4, 6.0, 7.0, 13.0, 1H, H-3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.4, 133.6, 131.0, 130.2, 129.5, 125.1, 122.6, 117.70, 117.68, 82.0, 63.4, 42.2, 18.9. HRMS: calculated for $C_{10}H_9NOBr$ $[M-CH_2CHCH_2]^+$: 237.9868. Found: 237.9875. Elemental Analysis: calculated for $C_{13}H_{14}BrNO$: C 55.73; H 5.04; N 5.00. Found: C 55.54; H 5.04; N 5.06. $[\alpha]_D^{23}$ −34.5 (*c* 0.88 in $CHCl_3$).

4.3. Synthesis of di-β-ketoester 9

In a dry flask 1.0 equiv nitrile **8** (5.25 mmol, 1.500 g) was dissolved in 53.5 ml dry THF under N_2 before 15.0 equiv Zn (80.25 mmol, 5.240 g), 0.03 equiv Cp_2TiCl_2 (0.16 mmol, 40 mg) and *tert*-butyl-bromoacetate (1 drop) were added. The green suspension was heated to 60 °C and 10 equiv *tert*-butyl-bromoacetate (53.5 mmol, 7.22 ml) were added in portions over 1 h. The reaction was stirred for an additional 1.5 h and then allowed to cool to rt. The mixture was filtered into 30 ml Et_2O through a pad of Celite, which was washed with Et_2O (a white precipitate initially formed and then dissolved). To the filtrate 70 ml 1 N HCl were added and the biphasic mixture was stirred for 18 h. The layers were separated and the aqueous phase was extracted with Et_2O (3×30 ml). The combined organic layers were dried over Na_2SO_4 and concentrated to give a yellow oil. The crude residue was purified by silica gel column chromatography (pentane/Et_2O 10:1), which furnished the β-ketoester (1.800 g, 4.53 mmol, 85%) as a colourless oil. R_f=0.66 (pentane/EtOAc=6:1)—one brown spot with *p*-anisaldehyde stain. IR (thin film): 3078, 2980, 2934, 2904, 2873, 1734, 1715, 1644, 1595, 1571, 1476, 1452, 1394, 1369, 1316, 1255, 1149, 1101, 997, 951.4, 918.28, 840, 786, 699, 666 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.45–7.37 (m, 2H, aryl-H); 7.23–7.17 (m, 2H, aryl-H); 5.71 (m_c, 1H, H-2); 5.05–4.98 (m, 2H, H-1); 4.22 (dd, *J*=6.0, 7.5 Hz, 1H, H-4); 3.57 (dt, *J*=3.1, 6.0 Hz, 2H, H-5); 3.39 (s, 2H, H-8); 2.80 (dt, *J*=6.5, 17.0 Hz, 1H, H-6); 2.73 (dt, *J*=6.0, 17.0 Hz, 1H, H-6′); 2.49 (ddd, *J*=7.0, 7.5, 14.5 Hz, 1H, H-3); 2.34 (ddd, *J*=6.0, 6.5, 14.5 Hz, 1H, H-3′); 1.47 (s, 9H, *t*-Bu-H). Note: spectrum shows 9% of the enol tautomer present in solution. ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.6, 166.2, 144.1, 134.0, 130.6, 129.9, 129.5, 125.1, 122.4, 117.3, 81.8, 81.7, 63.7, 51.0, 42.8, 42.2, 27.8 (3C). HRMS: calculated for $C_{16}H_{20}O_4Br$ $[M-CH_2CHCH_2]^+$: 355.0545. Found: 355.0553. Elemental Analysis: calculated for $C_{19}H_{25}BrO_4$: C 57.44; H 6.34. Found: C 57.77; H 6.22. $[\alpha]_D^{23}$ −25.8 (*c* 1.38 in $CHCl_3$).

β-Ketoester (1.0 equiv, 1.51 mmol, 600 mg) was dissolved in 15 ml CH_2Cl_2. Ozone was bubbled through the solution at −78 °C (bath temperature) until the blue colour persisted (1 min). Then oxygen was bubbled through until the blue colour disappeared (3 min). To the cooled solution 1.5 equiv solid triphenylphosphine (2.29 mmol, 600 mg) were added in one portion and the mixture was allowed to warm to rt. The mixture was stirred for 2 h at rt before another 0.48 equiv solid triphenylphosphine (0.73 mmol, 191 mg) were added and the reaction was stirred another 1 h to complete reduction of the ozonide. The reaction mixture was recooled to −78 C and 3.0 equiv ethyl diazoacetate (4.53 mmol, 0.65 ml) were added in one portion via syringe followed by 1.5 equiv. $SnCl_4$ (1 M in CH_2Cl_2, 2.27 mmol, 2.3 ml). The mixture was allowed to slowly warm up. At −35 °C the formation of bubbles in the solution was observed. At this temperature another 1.5 equiv. $SnCl_4$ (1 M in CH_2Cl_2, 2.27 mmol, 2.3 ml) was added in small portions over 1 h until a bubble-free solution was observed. Afterwards the reaction mixture was gradually warmed to rt and poured into a mixture of 100 ml saturated aq $NaHCO_3$ solution and 50 ml H_2O. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (5×20 ml). The combined organic layers were dried over Na_2SO_4, concentrated in vacuo and the remaining crude was chromatographed on silica (pentane/EtOAc 4:1→ 3:1) to give the di-β-ketoester **9** (462 mg, 0.95 mmol, 63%). R_f=0.57 (35%OAc in pentane)—one red spot with *p*-anisaldehyde stain. IR (thin film): 3069, 2981, 2935, 1749, 1732, 1715, 1652, 1596, 1573, 1471, 1393, 1369, 1318, 1255, 1151, 1032, 999, 951, 840, 788, 697, 665 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.48–7.40 (m, 2H, aryl-H); 7.28–7.20 (m, 2H, aryl-H); 4.74 (dd, *J*=7.5 Hz, 2H, Et); 4.18 (q, *J*=7.5 Hz, 2H, Et); 3.61 (dt, *J*=6.0, 9.5 Hz, 1H, H-6); 3.55 (dt, *J*=6.0, 9.5 Hz, 1H, H-6′); 3.45 (s, 2H, H-2 or H-9); 3.06 (dd, *J*=9.0, 16.0 Hz, 1H, H-4); 2.75 (dt, *J*=1.9, 6.0 Hz, 2H, H-7); 2.68 (dd, *J*=4.0, 16.0 Hz, 1H, H-4′); 1.46 (s, 9H, *t*-Bu); 1.32 (t, *J*=7.5 Hz, 3H, Et). Note: spectrum shows >16% of enol tautomers present in solution. ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.4, 200.1, 166.8, 166.2, 143.1, 131.2, 130.3, 129.4, 125.1, 122.8, 81.9, 77.4, 63.8, 61.4, 50.9, 50.8, 50.0, 42.6, 27.9, 14.1. HRMS: calculated for $C_{22}H_{29}O_7NaBr$ $[M+Na]^+$: 507.0994. Found: 507.0982. Elemental Analysis: calculated for $C_{22}H_{29}BrO_7$: C 54.44; H 6.02. Found: C 54.00; H 6.16. $[\alpha]_D^{23}$ −36.9 (*c* 1.11 in $CHCl_3$).

4.4. Synthesis of triol 10

The Ruthenium catalyst was prepared as described by Blanc and co-workers.[39] 1.0 equiv (COD)Ru(2-methylallyl)$_2$ (0.013 mmol, 4.21 mg, Acros) and 1.2 equiv (*R*)-BINAP (0.016 mmol, 10.21 mg) were measured into a dry flask under N_2 and a mixture of 0.9 ml degassed anhydrous acetone and 0.09 ml degassed methanol were added. Then 2.2 equiv HBr (48% aq HBr, 0.029 mmol, 3.16 μl) were added and the brown solution was stirred for 1 h at rt. The solvent was blown off with N_2 gas and the brown residue dried under high vacuum for 2.5 h. The flask was refilled with N_2 and used directly for the hydrogenation. To the prepared catalyst di-β-ketoester **9** (0.206 mmol, 100 mg) was added as a solution in degassed EtOH (1.5 ml, 200 proof, Gold Shield Chemical Company) and the reaction flask was placed in a high-pressure bomb, flushed with N_2 and sealed tightly. The apparatus was purged with H_2 (3×20 bar) and then finally pressurized to 40 bar H_2. The apparatus was placed into a 45 °C oil bath on a stir plate and the mixture was stirred for 44 h. Afterwards the apparatus was removed from the bath, allowed to cool to rt and slowly depressurized. The solvent was blown off with N_2 and the black residue was purified by silica gel chromatography (silica gel, pentane/EtOAc 3:2→1:1) to the diol (80.5 mg, 0.164 mmol, 80%) as a pale yellow oil. R_f=0.23 (pentane/EtOAc=3:2)—one black-blue spot with *p*-anisaldehyde stain. IR (thin film): 3445, 2980, 2931, 2873, 1732, 1715, 1595, 1571, 1471, 1428, 1394, 1369, 1300, 1258, 1155, 1098, 952, 845, 787, 700, 666 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.48–7.39 (m, 2H, aryl-H); 7.28–7.20 (m, 2H, aryl-H); 4.49 (dd, *J*=5.5, 8.5 Hz, 1H, H-5); 4.15 (dq, *J*=1.2, 7.0, 2H, Et); 4.11 (m_c, 1 h, H-8); 4.08 (m_c, 1H, H-3); 3.72 (d, *J*=2.3 Hz, 1H, OH); 3.49 (ddd, *J*=6.0, 6.5, 9.5, 1H, H-6); 3.44 (dt, *J*=6.0, 9.5 Hz, 1H, H-6′); 3.40 (d, *J*=3.6 Hz, 1H, OH), 2.51 (dd, *J*=8.0, 16.0 Hz, 1H, H-2); 2.42 (dd, *J*=4.8, 16.0 Hz, 1H, H-2′); 2.38 (dd, *J*=4.5, 16.5, 1H, H-9); 2.33 (dd, *J*=8.0, 16.5 Hz, 1H, H-9′); 2.01 (ddd, *J*=3.5, 9.0, 14.0, 1H, H-4); 1.82–1.66 (m, 3H, H-4′/H-7); 1.46 (s, 9H, *t*-Bu); 1.26 (t, *J*=7.0 Hz, 3H, Et). Note: The spectrum shows 5% of a second diastereomer. ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.2, 172.1, 144.0, 131.0, 130.2, 129.6, 125.2, 122.8, 81.3, 81.1, 66.8, 66.0, 65.9, 60.7, 44.3, 42.2, 41.6, 36.1, 28.8 (3C), 14.1. HRMS: calculated for $C_{22}H_{33}O_7NaBr$ $[M+Na]^+$: 511.1307. Found: 511.1301. $[\alpha]_D^{23}$ −33.2 (*c* 0.78 in $CHCl_3$).

Superhydride (7.0 equiv, 1.0 M solution of lithium triethylborohydride in THF, 0.147 mmol, 147 μl) was added dropwise via 2 min to a solution of 1.0 equiv of the diol (0.02 mmol, 9.8 mg) at 0 °C. The reaction was stirred for 1 h at 0 °C, gradually warmed to rt and then

stirred additional 1.5 h at rt. Afterwards the reaction was recooled to 0 °C followed by addition of H_2O_2 (30% in H_2O, 50 μl) and aq NaOH (1 M, 1 drop). The mixture was allowed to stir for 45 min before 2 ml NH_4Cl and 1 ml H_2O were added at 0 °C. After warming the mixture to rt the layers were separated and the aqueous layer was extracted with EtOAc (3×5 ml). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by chromatography on silica (pentane/EtOAc 70:30→EtOAc 100%) to give triol **10** (7.2 mg, 0.016 mmol, 81%) as a colourless oil. R_f=0.54 (EtOAc 100%)—one bright blue spot with *p*-anisaldehyde stain. IR (thin film): 3387, 2974, 2922, 2872, 1724, 1595, 1571, 1473, 1427, 1368, 1258, 1155, 1099, 997, 955, 885, 786, 700, 665 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): 7.46–7.40 (m, 2H, aryl-H); 7.27–7.22 (m, 2H, aryl-H); 4.48 (dd, *J*=3.3, 10.0 Hz, 1H, H-5); 4.13 (m, 2H, H-3/H-8); 3.99 (s, 1H, OH); 3.83 (m_c, 2H, H-1); 3.53–3.40 (m, 3H, H-6/OH), 2.80 (m_c, 1H, OH(H-1)); 2.39 (dd, *J*=4.0, 16.5 Hz); 2.34 (dd, *J*=8.5, 16.5 Hz, 1H, H-9′); 1.99 (dt, *J*=10.0, 15.0 Hz, 1H, H-4); 1.73–1.65 (m, 5H, H-4′/H-2/H-7); 1.46 (s, 9H, *t*-Bu). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.2, 144.1, 131.0, 130.3, 129.4, 124.9, 122.8, 82.6, 81.5, 71.6, 65.9, 65.5, 61.3, 45.3, 42.2, 38.6, 36.0, 28.1. HRMS: calculated for $C_{20}H_{31}O_6NaBr$ $[M+Na]^+$: 469.1202. Found: 469.1201. $[\alpha]_D^{23}$ −38.5 (*c* 0.66 in $CHCl_3$).

4.5. Synthesis of carboxylic acid 6

2,6-Lutidine (30.0 equiv, 1.95 mmol, 230 μl) was added to a solution of 1.0 equiv triol **10** (0.065 mmol, 29 mg) in 1.5 ml CH_2Cl_2 under N_2 atmosphere. The solution was cooled to 0 °C and 10.0 equiv. TBSOTf (0.65 mmol, 149 μl) were added dropwise via 30 s. The ice bath was removed and the solution was slowly concentrated by blowing with N_2 gas until ~0.3 M solution was obtained. The concentrated mixture was allowed to stir for 22 h at rt. Afterwards first 1.0 ml H_2O and 1.0 ml CH_2Cl_2 were added to the reaction followed by NaOH (1 N in MeOH/THF/H_2O 3:1:1, 0.3 ml). The slightly yellow biphasic mixture was stirred for 2 h and solid $KHSO_4$ was added until a pH of 7 of the aqueous phase was reached. The organic phase was extracted with EtOAc (4×10 ml) and the combined organic layers were dried over Na_2SO_4. After concentration in vacuo the crude residue was purified by chromatography on silica (pentane/EtOAc 80:20) to give the carboxylic acid **6** (43.7 mg, 0.06 mmol, 92%) as a colourless oil. Note: The product is acid sensitive; chromatography on silica with 1% AcOH in the solvent mixture leads to decomposition! R_f=0.30 (pentane/EtOAc=80:20)—one black spot with *p*-anisaldehyde stain. Note: The R_f value is strongly dependent on the concentration. IR (thin film): 2955 (br), 2929, 2856, 1712, 1594, 1571, 1471, 1429, 1361, 1256, 1185, 1097, 940, 836, 776, 699, 664 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): 7.39–7.35 (m, 2H, aryl-H); 7.21–7.15 (m, 2H, aryl-H); 4.26 (dd, *J*=5.0, 8.5 Hz, 1H, H-5); 4.24 (quit, *J*=5.5 Hz, 1H, H-8); 3.87 (tt, *J*=5.5, 6.5 Hz, 1H, H-3); 3.65 (quint, *J*=6.5 Hz, 1H, H-1); 3.64 (quint, *J*=6.5 Hz, 1H, H-1′); 3.26 (m_c, 2H, H-6); 2.49 (dd, *J*=5.0, 15.5 Hz, 1H, H-9); 2.39 (dd, *J*=6.0, 15.5 Hz, 1H, H-9′); 1.94 (ddd, *J*=5.5, 8.5, 13.5 Hz, 1H, H-4); 1.85–1.63 (m, 5H, H-2/H-4′/H-7); 0.87 (s, 9H, O*TB*DMS); 0.84 (s, 9H, O*TB*DMS); 0.83 (s, 9H, O*TB*DMS); 0.07 (s, 3H, OTB*DMS*); 0.06 (s, 3H, OTB*DMS*); 0.02 (s, 3H, OTB*DMS*); 0.01 (s, 3H, OTB*DMS*); 0.00 (s, 3H, OTB*DMS*); −0.02 (s, 3H, OTB*DMS*). ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.1, 145.1, 130.7, 130.2, 129.7, 125.2, 122.7, 79.0, 66.9, 66.5, 64.9, 59.7, 45.8, 41.5, 39.9, 37.1, 25.9 (×6), 25.7 (3C), 18.2, 18.0, 17.9, −0.01, −4.4, −4.7, −4.9, −5.4 (2C). HRMS: calculated for $C_{34}H_{65}O_6BrSi_3Na$ $[M+Na]^+$: 755.3170. Found: 755.3167. $[\alpha]_D^{23}$ −24.1 (*c* 0.82 in $CHCl_3$).

4.6. Synthesis of analogue 5

To a solution of 1.0 equiv carboxylic acid **6** (0.022 mmol, 16.0 mg) in 1.5 ml toluene were added 4.0 equiv. Et_3N (0.088 mmol, 12.5 μl) in one portion at rt under N_2 followed by addition of a solution of 1.1 equiv (0.024 mmol, 3.8 μl) 2,4,6-trichlorobenzoyl chloride. The reaction mixture was allowed to stir at rt for 6 h. DMAP (5.0 equiv, 0.111 mmol, 13.7 mg) and 1.1 equiv alcohol **7** (0.024 mmol, 14.3 mg) were dissolved in a second flask in 0.3 ml toluene and added dropwise over 5 min to the reaction mixture via syringe. The flask and the syringe were washed three times with 0.3 ml toluene. The cloudy mixture was stirred for 1.5 h at rt. Afterwards the solution was concentrated to ~30% by blowing with N_2 gas and the concentrated mixture was directly purified by chromatography on silica (pentane/EtOAc 80:20). The enal (26.1 mg, 0.020 mmol, 91%) was furnished as a colourless oil. R_f=0.84 (pentane/EtOAc=80:20)—one black spot with *p*-anisaldehyde stain. IR (thin film): 3479 (w), 2954, 2920, 2857, 1724, 1692, 1435, 1387, 1361, 1255, 1155, 1104, 1036, 836, 776, 669, 665 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): 9.55 (d, *J*=6.5 Hz 1H, H-11); 7.29 (d, *J*=13.5 Hz, 1H, H-13); 7.28–7.32 (m, 2H, aryl-H); 7.19–7.14 (m, 2H, aryl-H); 6.00 (d, *J*=1.6 Hz, 1H, H-23); 5.94 (dd, *J*=6.5, 13.5 Hz, 1H, H-12); 5.19 (ddt, *J*=1.0, 4.7, 9.0 Hz, 1H, H-21), 5.12 (s, 1H, H-16); 4.25 (dd, 4.7, 6.5 Hz, 1H, H-6); 4.22 (quint, *J*=5.5 Hz, H-3); 3.85 (quint, *J*=4.7 Hz, 1H, H-8); 3.79 (tt, *J*=1.5, 9.5 Hz, 1H, H-19); 3.67 (s, 3H, OMe); 3.66–3.60 (m, 5H, H-10/H-18/H-22); 3.25 (dt, *J*=5.5, 7.5 Hz, 1H, H-5); 3.21 (dt, *J*=7.5, 8.7 Hz, 1H, H-5′); 3.07 (s, 1H, OH(C-15)); 2.35 (dd, *J*=4.8, 5.5 Hz, 1H, H-2); 2.11–1.88 (m, 5H, H-7′/H-18/H-20/H-24/H-24′); 1.77–1.63 (m, 7H, H-4/H-7/H-9/H-20′); 1.47 (dt, *J*=6.5, 12.5 Hz, 1H, H-25); 1.30–1.16 (m, 9H, H-12—H-29); 1.20 (s, 3H, CH_3); 1.14 (s, 3H, CH_3); 0.88 (s, 9H, O*TB*DMS); 0.87 (s, 9H, O*TB*DMS); 0.85 (t, *J*=6.0 Hz, 3H, H-30); 0.84 (s, 9H, O*TB*DMS); 0.78 (s, 9H, O*TB*DMS); 0.048 (s, 3H, OTB*DMS*); 0.044 (s, 3H, OTB*DMS*); 0.026 (s, 3H, OTB*DMS*); 0.014 (s, 3H, OTB*DMS*); 0.005 (s, 3H, OTB*DMS*); −0.012 (s, 3H, OTB*DMS*); −0.017 (s, 3H, OTB*DMS*); −0.021 (s, 3H, OTB*DMS*). ^{13}C NMR (125 MHz, $CDCl_3$): δ 194.6, 172.6, 171.7, 166.6, 166.4, 150.4, 145.3, 130.6, 130.2, 129.8, 127.4, 125.1, 122.6, 120.8, 99.5, 78.9, 72.5, 71.5, 66.52, 66.46, 66.2, 65.0, 64.9, 59.6, 51.2, 45.7 (×2), 42.2, 40.0, 37.5, 37.3, 34.5, 31.6, 30.9, 28.88, 28.86, 25.92 (3C), 25.90 (3C), 25.8 (3C), 25.7 (3C), 24.4, 23.0, 22.5, 20.0, 18.3, 18.2, 18.1, 18.0, 14.1, −4.2, −4.4, −4.7, −4.8, −5.30, −5.32, −5.4 (2C). HRMS: calculated for $C_{65}H_{117}O_{14}NaSi_4Br$ $[M+Na]^+$: 1335.6602. Found: 1335.6584. $[\alpha]_D^{23}$ −27.3 (*c* 1.22 in $CHCl_3$).

Enal (1.0 equiv, 0.02 mmol, 26 mg) was dissolved in 5.5 ml anhydrous THF in a polypropylene vial under N_2 at 0 °C. Then 2.8 equiv HF·pyridine (0.055 mmol, 1.07 ml) were added via syringe and the reaction was stirred at 0 °C for 1 h. Afterwards the bath was removed and the reaction allowed to stir additional 4 h. The reaction mixture was transferred to a separating funnel containing 8 ml H_2O using 5 ml EtOAc. Saturated aq $NaHCO_3$ (~50 ml) was added in portions until the vigorous bubbling stopped. The layers were separated and the aqueous layer was extracted using Et_2O (3×15 ml). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude was purified by column chromatography on silica using pentane/EtOAc 40:60→20:80 as eluents. Purification yielded the bryostatin analogue **5** (14 mg, 0.017 mmol, 83%) as a white solid. R_f=0.48 (pentane/EtOAc=20:80)—one black spot with *p*-anisaldehyde stain. IR (thin film): 3465, 3333, 2926, 2856, 1731, 1715, 1667, 1595, 1573, 1469, 1434, 1403, 1378, 1362, 1285, 1259, 1230, 1159, 1136, 1105, 980, 940, 918, 879, 851, 807, 791, 791, 736, 705 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): 7.44–7.40 (m, 2H, aryl-H); 7.24–7.18 (m, 2H, aryl-H); 6.01 (d, *J*=16.2 Hz, 1H, H-13); 6.01 (d, *J*=1.7 Hz, 1H, H-23); 5.44 (dd, *J*=7.4, 16.2 Hz, 1H, H-12); 5.43–5.38 (m, 1H, H-21); 5.16 (s, 1H H-16 or C15–OH); 5.11 (d, *J*=7.6 Hz, 1H, H-11); 5.08 (s, 1H, H-16 or C15–OH); 4.35 (d, *J*=12.0 Hz, 1H, C3–OH); 4.32 (dd, *J*=2.6, 11.4 Hz, 1H, H-6); 4.32–4.26 (m, 1H, H-3); 4.12–4.01 (m, 3H, H-8/H-10/H-19); 3.90 (dt, *J*=1.9, 12.0 Hz, 1H, H-10); 3.87 (m_c, 1H, H-22); 3.72 (dd, *J*=2.2, 13.8 Hz, 1H, H-18); 3.68 (s, 3H, OMe); 3.70–3.63 (m, 1H, H-22′); 3.45 (ddd, *J*=1.1, 5.0, 9.6 Hz, 1H, H-5); 3.33 (ddd, *J*=2.2, 9.6, 10.2 Hz, 1H, H-5′); 2.56 (dd, *J*=10.8, 12.6 Hz, 1H, H-2); 2.52 (dd, *J*=3.3, 12.6 Hz, 1H, H-2′); 2.30 (m_c, 2H, H-24); 2.24 (ddd, *J*=2.6, 5.2,

10.2, 15.6 Hz, 1H, H-4); 2.14–1.96 (m, 3H, H-7/H-20/H-18′); 1.81 (ddd, *J*=2.6, 11.4, 13.8 Hz, 1H, H-20′); 1.76 (dq, *J*=5.0, 12.6 Hz, 1H, H-9); 1.65–1.53 (m, 3H, H-7′/H-25); 1.51 (d (br), *J*=15.6 Hz, 1H, H-4′); 1.39 (d (br), *J*=12.6 Hz, 1H, H-9′); 1.32–1.21 (m, 8H, H-26–29); 1.20 (s, 3H, -C(CH_3)$_2$); 1.06 (s, 3H, –C(CH_3)$_2$); 0.87 (t, *J*=6.6 Hz, 3H, H-30). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.3, 172.1, 167.0, 151.6, 143.6, 142.6, 131.2, 130.4, 129.5, 125.9, 124.9, 122.8, 119.9, 102.2, 98.9, 83.3, 75.6, 74.1, 71.6, 68.7, 66.2, 66.0, 65.7, 64.5, 51.1, 45.5, 45.1, 42.1, 35.8, 34.6, 33.6, 32.3, 31.6, 31.0, 29.0, 28.9, 24.7, 24.3, 22.6, 19.4, 14.1. HRMS: calculated for $C_{41}H_{59}O_{13}NaBr$ $[M+Na]^+$: 861.3037. Found: 861.3024. $[\alpha]_D^{23}$ –72.7 (*c* 0.43 in $CDCl_3$).

4.7. Synthesis of analogue 11

Aryl bromide **5** (1.0 equiv, 0.012 mmol, 10.0 mg) was measured in a dry vial, which was evacuated and refilled with N_2. Then 7.0 equiv CsF (0.083 mmol, 12.6 mg), which was dried in a 200 °C vacuum oven, were added and the mixture was placed under high vacuum for 30 min. The vial was refilled with N_2 and kept under N_2 atmosphere throughout the reaction. The mixture was dissolved in 0.1 ml dioxane. Then 1.25 equiv $Pd(OAc)_2$ (0.015 mmol, 3.3 mg), 1.8 equiv *S*-Phos (0.021 mmol, 8.8 mg) and 6.0 equiv *trans*-1-hexen-1-ylboronic acid were added via a stock solution in dioxane (0.1 ml solution). The orange-red reaction mixture was sealed with a 2-ply Teflon tape, followed by a plastic screw cap and finally the vial was sealed with parafilm. Afterwards the vial was vortexed and placed in a 60 °C oil bath and stirred for 2 h at 60 °C. The black reaction mixture was filtered through a plug of silica using ethyl acetate and concentrated under a stream of N_2. Purification of the yellow crude by preparative HPLC (MeCN/H_2O 65%→90% at 20 ml/min) furnished the coupling product **11** as a white solid in 70% yield. R_f=0.59 (pentane/EtOAc=30:70)—one blue spot with *p*-anisaldehyde stain. IR (thin film): 3460, 3333, 2925, 2854, 1737, 1731, 1667, 1463, 1434, 1404, 1378, 1362, 1287, 1259, 1230, 1159, 1134, 1105, 1063, 1006, 979, 918, 887, 806, 737 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): 7.26–7.21 (m, 3H, aryl-H); 7.07–7.02 (m, 1H, aryl-H); 6.33 (d, *J*=16.0 Hz, 1H, H-31); 6.23 (d, *J*=6.5 Hz, 1H, H-32); 5.99 (d, *J*=16.0 Hz, 1H, H-13); 5.99 (d, *J*=1.4 Hz, 1H, H-23); 5.44 (dd, *J*=7.5, 16.0 Hz, 1H, H-12); 5.41–5.36 (m, 1H, H-21); 5.14 (s, 1H, H-16 or C15–OH); 5.11 (s, 1H, H-16 or C15–OH); 5.09 (d, *J*=7.5 Hz, 1H, H-11); 4.42 (d, *J*=12.0 Hz, 1H, C3–OH); 4.31 (dd, *J*=2.6, 12.0 Hz, 1H, H-6); 4.30–4.22 (m, 1H, H-3); 4.11–3.98 (m, 3H, H-8/H-10/H-19); 3.89 (m_c, 1H, H-10); 3.85 (md, 1H, H-22); 3.70 (dd, *J*=1.7, 13.5 Hz, 1H, H-18); 3.668 (s, 3H, OMe); 3.68–3.62 (m, 1H, H-22′); 3.44 (ddd, *J*=1.4, 4.7, 9.5 Hz, 1H, H-5); 3.29 (ddd, *J*=1.5, 9.5, 12.0 Hz, 1H, H-5′); 2.56 (t, *J*=12.5 Hz, 1H, H-2); 2.50 (dd, *J*=2.4, 12.5 Hz, 1H, H-2′); 2.28 (dt, *J*=3.7, 7.2 Hz, 2H, H-24); 2.26–2.21 (m, 2H, H-33); 2.19 (m_c, 1H, H-4); 2.12 (m_c, 1H, H-7); 2.05–1.95 (m, 2H, H-20/H-18′); 1.79 (dt, *J*=2.8, 12.0 Hz, 1H, H-20′); 1.73 (dq, *J*=4.7, 12.5 Hz, 1H, H-9); 1.62–1.55 (m, 3H, H-7′/H-25); 1.49–1.41 (m, *J*=15.6 Hz, 1H, H-4′); 1.36 (m_c, 1H, H-9′); 1.30–1.19 (m, 12H, H-26–29/H-34/H-35); 1.18 (s, 3H, –C(CH_3)$_2$); 1.03 (s, 3H, –C(CH_3)$_2$); 0.91 (t, *J*=7.5 Hz, H-36); 0.85 (t, *J*=6.5 Hz, 3H, H-30). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.5, 172.1, 167.0, 151.6, 142.5, 141.4, 138.4, 131.9, 129.2, 128.8, 126.0, 125.7, 124.8, 123.5, 119.9, 102.3, 98.9, 84.1, 76.0, 74.1, 71.6, 68.8, 66.3, 65.7 (2C), 64.5, 51.1, 45.5, 45.1, 42.1, 35.8, 34.6, 33.6, 32.7, 32.3, 31.6, 31.4, 31.0, 29.0, 28.9, 24.7, 24.3, 22.6, 22.3, 19.4, 14.1, 14.0. HRMS: calculated for $C_{47}H_{70}O_{13}Na$ $[M+Na]^+$: 865.4714. Found: 865.4701. $[\alpha]_D^{23}$ –74.3 (*c* 0.42 in $CHCl_3$).

4.8. Synthesis of analogue 13

Analogue **11** (1.0 equiv, 0.0037 mmol, 3.1 mg) was dissolved in 300 μl THF and 60 μl deionized H_2O. Then 0.1 equiv of OsO_4 (0.0004 mmol, 2.5 μl) were added as a 4% stock solution in water via syringe followed by addition of 6.0 equiv of solid $NaIO_4$ (0.0222 mmol, 4.7 mg). The reaction mixture was stirred for 15 min at rt before the product was extracted from the solution using ethyl acetate (3×5 ml). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude was dried in vacuum for 1 h and was then dissolved in 1.0 ml anhydrous methanol and 0.2 ml anhydrous CH_2Cl_2. Afterwards the solution was cooled to 0 °C via ice bath before 8.0 equiv $NaBH_4$ (0.0296 mmol, 1.2 mg) were added as a solid. The reaction mixture was stirred at 0 °C for 30 min, then the ice bath was removed and the mixture was allowed to warm to rt and stirred for 1 h at rt. The reaction mixture was transferred to a separating funnel, which contained 5.0 ml concentrated NH_4Cl solution in water. The layers were separated and the aqueous layer was extracted using CH_2Cl_2 (4×10 ml). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude was filtered through a pad of silica gel using EtOAc/pentane 80:20 as eluent. All fractions containing product were further purified by reverse phase HPLC (see below for conditions) to give 2.1 mg (0.0027 mmol, 72%) **13** as a white amorphous solid. R_f=0.23 (pentane/EtOAc=20:80)—one blue spot with *p*-anisaldehyde stain. IR (thin film): 3459, 3359, 3199, 2922, 2852, 1738, 1731, 1715, 1667, 1660, 1463, 1455, 1434, 1409, 1378, 1361, 1280, 1260, 1231, 1157, 1133, 1103, 1063, 1025, 980, 881, 861, 800, 737, 709 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): 7.36–7.33 (m, 1H, aryl-H); 7.31–7.26 (m, 2H, aryl-H); 7.21–7.19 (m, 1H, aryl-H); 6.01 (d, *J*=15.6 Hz, 1H, H-13); 6.01 (d, *J*=1.9 Hz, 1H, H-23); 5.45 (dd, *J*=7.2, 15.6 Hz, 1H, H-12); 5.43–5.38 (m, 1H, H-21); 5.16 (s, 1H, H-16 or C15–OH); 5.11 (d, *J*=7.2 Hz, 1H, H-11); 5.11 (s, 1H, H-16 or C15–OH); 4.70 (s, 2H, H-31); 4.42 (d, *J*=12.0 Hz, 1H, C3–OH); 4.37 (dd, *J*=2.8, 12.0 Hz, 1H, H-6); 4.32–4.26 (m, 1H, H-3); 4.12–4.02 (m, 3H, H-8/H-10/H-19); 3.91 (dt, *J*=2.3, 12.0 Hz, 1H, H-10′); 3.87 (dd, *J*=3.1, 12.0 Hz, 1H, H-22); 3.72 (dd, *J*=2.0, 13.8 Hz, 1H, H-18); 3.68 (s, 3H, OMe); 3.68–3.63 (m, 1H, H-22′); 3.44 (ddd, *J*=1.2, 4.7, 9.6 Hz, 1H, H-5); 3.32 (ddd, *J*=2.5, 11.4, 15.6 Hz, 1H, H-5′); 2.56 (dd, *J*=12.0, 12.6 Hz, 1H, H-2); 2.52 (dd, *J*=2.7, 12.6 Hz, 1H, H-2′); 2.30 (dt, *J*=4.3, 7.2 Hz, 2H, H-24); 2.27–2.20 (m, 1H, H-4); 2.14 (m_c, 1H, H-7); 2.05 (m_c, 2H, H-20/H-18′); 1.81 (ddd, *J*=2.6, 11.4, 14.4 Hz, 1H, H-20′); 1.73 (dq, *J*=4.9, 12.6 Hz, 1H, H-9); 1.67–1.53 (m, 3H, H-7′/H-25); 1.48 (d (br), *J*=15.6 Hz, 1H, H-4′); 1.39 (d (br), *J*=13.8 Hz, 1H, H-9′); 1.32–1.22 (m, 8H, H-26–29); 1.20 (s, 3H, -C(CH_3)$_2$); 1.06 (s, 3H, -C(CH_3)$_2$); 0.87 (t, *J*=6.6 Hz, 3H, H-30). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.4, 172.1, 167.0, 151.6, 142.5, 141.6, 141.3, 129.0, 126.6, 125.9, 125.6, 124.8, 119.9, 102.3, 98.9, 83.9, 75.8, 74.1, 71.6, 68.8, 66.2, 65.8, 65.7, 65.1, 64.6, 51.1, 45.6, 45.1, 42.1, 35.9, 34.6, 33.7, 32.3, 31.6, 31.0, 29.0, 28.9, 24.7, 24.3, 22.6, 19.4, 14.1. HRMS: calculated for $C_{42}H_{62}O_{14}Na$ $[M+Na]^+$: 813.4037. Found: 813.4028. $[\alpha]_D^{23}$ –38.9 (*c* 0.22.in $CHCl_3$).

4.9. Synthesis of analogue 12

Analogue **11** (1.0 equiv, 0.008 mmol, 6.8 mg) was dissolved in 500 μl THF and 100 μl deionized H_2O. Then 0.1 equiv of OsO_4 (0.0008 mmol, 5.4 μl) were added as a 4% stock solution in water via syringe followed by addition of 6.0 equiv of solid $NaIO_4$ (0.048 mmol, 10.3 mg). The reaction mixture was stirred for 15 min at rt before the product was extracted from the solution using ethyl acetate (3×5 ml). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude was purified by column chromatography on silica gel using ethyl acetate/pentane 90:10 as eluent. The purification yielded the bryostatin analogue **12** (4.8 mg, 0.006 mmol, 75%) as a white solid. R_f=0.45 (pentane/EtOAc=20:80)—one blue spot with *p*-anisaldehyde stain. IR (thin film): 3460, 3359, 2960, 2922, 2851, 1715, 1737, 1731, 1667, 1633, 1463, 1455, 1434, 1403, 1378, 1362, 1280, 1260, 1230, 1157, 1133, 1102, 1063, 1022, 980, 863, 801, 722, 704, 665 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 10.02 (s, 1H, H-31);

7.84.7.76 (m, 2H, aryl-H); 7.60–7.52 (m, 2H, aryl-H); 6.02 (d, J=16.0 Hz, 1H, H-13); 6.01 (d, J=1.9 Hz, 1H, H-23); 5.45 (dd, J=7.5, 16.0 Hz, 1H, H-12); 5.44–5.38 (m, 1H, H-21); 5.16 (s, 1H, H-16 or C15–OH); 5.12 (d, J=7.0 Hz, 1H, H-11); 5.09 (s, 1H, H-16 or C15–OH); 4.46 (dd, J=2.8, 12.0 Hz, 1H, H-6); 4.37 (d, J=12.0 Hz, 1H, C3–OH); 4.34–4.26 (m, 1H, H-3); 4.14–4.03 (m, 3H, H-8/H-10/H-19); 3.92 (dt, J=1.8, 11.5 Hz, 1H, H-10′); 3.87 (dt, J=3.7, 11.5 Hz, 1H, H-22); 3.72 (dd, J=2.5, 14.0 Hz, 1H, H-18); 3.70–3.64 (m, 1H, H-22′); 3.68 (s, 3H, OMe); 3.44–3.39 (m, 1H, H-5); 3.39–3.33 (m, 1H, H-5′); 2.57 (dd, J=10.5, 12.5 Hz, 1H, H-2); 2.53 (dd, J=3.4, 12.5 Hz, 1H, H-2′); 2.30 (dt, J=3.4, 7.5 Hz, 2H, H-24); 2.24 (m, 1H, H-4); 2.13 (m_c, 1H, H-7); 2.09–1.98 (m, 2H, H-20/H-18′); 1.81 (ddd, J=3.0, 10.0, 14.0 Hz, 1H, H-20′); 1.76 (dq, J=4.2, 12.0 Hz, 1H, H-9); 1.66–1.56 (m, 3H, H-7′/H-25); 1.51 (d (br), J=15.0 Hz, 1H, H-4′); 1.41 (d (br), J=13.0 Hz, 1H, H-9′); 1.35–1.17 (m, 8H, H-26–29); 1.20 (s, 3H, $-C(CH_3)_2$); 1.06 (s, 3H, $-C(CH_3)_2$); 0.87 (t, J=7.0 Hz, 3H, H-30). ^{13}C NMR (125 MHz, $CDCl_3$): δ 191.9, 172.3, 172.1, 166.9, 151.6, 142.6, 142.5, 136.8, 132.1, 129.7 (2C), 127.4, 125.9, 119.9, 102.2, 98.9, 83.4, 75.6, 74.1, 71.6, 68.7, 66.2, 66.1, 65.7, 64.6, 51.1, 45.5, 45.1, 42.2, 35.8, 34.6, 33.7, 32.3, 31.6, 31.0, 29.0, 28.9, 24.7, 24.3, 22.6, 19.4, 14.1. HRMS: calculated for $C_{42}H_{60}O_{14}Na$ $[M+Na]^+$: 811.3881. Found: 811.3874. $[\alpha]_D^{23}$ −68.8 (c 0.40 in $CDCl_3$).

4.10. Synthesis of analogue 14

Analogue **12** (1.0 equiv, 0.0036 mmol, 2.8 mg) was dissolved in 100 μl acetonitrile (HPLC grade). Then 10 equiv m-CPBA (0.035 mmol, 6 mg) were added as a solid in three single portions over 5 h. The conversion of the reaction was observed by Maldi-MS. The reaction was stirred at rt. After 7 h 0.1 ml of a saturated solution of sodium thiosulfate in water were added to the reaction mixture and the mixture was further diluted with 1.0 ml water and 1.0 ml acetonitrile. The layers were separated and the aqueous layer was extracted using CH_2Cl_2 (4×5 ml). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude was filtered through a pad of silica gel using ethyl acetate as eluent. All fractions containing product were further purified by reverse phase HPLC to give 1.5 mg (0.002 mmol, 52%) **14** as a white amorphous solid. R_f=0.11 (pentane/EtOAc=20:80)—one blue spot with p-anisaldehyde stain; R_f shows a strong concentration dependency. IR (thin film): 3460, 3424, 2925, 2855, 1722, 1715, 1434, 1403, 1378, 1362, 1288, 1259, 1231, 1160, 1136, 1104, 1063, 1025, 1006, 980, 917, 885, 859, 834, 806, 760, 734, 703, 665 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 8.06–8.02 (m, 1H, aryl-H); 7.99–7.97 (m, 1H, aryl-H); 7.58–7.55 (m, 1H, aryl-H); 7.51–7.47 (m, 1H, aryl-H); 6.25 (d, J=16.0 Hz, 1H, H-13); 6.01 (d, J=2.0 Hz, 1H, H-23); 5.45 (dd, J=7.5, 16.0 Hz, 1H, H-12); 5.45–5.39 (m, 1H, H-21); 5.17 (s, 1H, H-16 or C15–OH); 5.12 (d, J=7.5 Hz, 1H, H-11); 5.11 (s, 1H, H-16 or C15–OH); 4.45 (dd, J=2.4, 12.0 Hz, 1H, H-6); 4.39 (d, J=12.0 Hz, 1H, C3–OH); 4.34–4.26 (m, 1H, H-3); 4.14–4.02 (m, 3H, H-8/H-10/H-19); 3.92 (dt, J=1.8, 12.0 Hz, 1H, H-10′); 3.88 (dd, J=3.2, 12.0 Hz, 1H, H-22); 3.68 (s, 3H, OMe); 3.73 (dd, J=1.9, 13.5 Hz, 1H, H-18); 3.70–3.65 (m, 1H, H-22′); 3.45–3.40 (m, 1H, H-5); 3.36 (m_c, 1H, H-5′); 2.59 (dd, J=11.0, 12.5 Hz, 1H, H-2); 2.53 (dd, J=2.9, 12.5 Hz, 1H, H-2′); 2.30 (dt, J=3.3, 7.5 Hz, 2H, H-24); 2.27–2.22 (m, 1H, H-4); 2.15 (m_c, 1H, H-7); 2.10–1.98 (m_c, 2H, H-20/H-18′); 1.82 (ddd, J=2.8, 12.0, 13.5 Hz, 1H, H-20′); 1.76 (dq, J=4.3, 12.0 Hz, 1H, H-9); 1.67–1.55 (m, 3H, H-7′/H-25); 1.50 (d (br), J=15.0 Hz, 1H, H-4′); 1.40 (d (br), J=13.0 Hz, 1H, H-9′); 1.31–1.23 (m, 8H, H-26–29); 1.20 (s, 3H, $-C(CH_3)_2$); 1.06 (s, 3H, $-C(CH_3)_2$); 0.87 (t, J=7.0 Hz, 3H, H-30). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.4, 172.1, 169.4, 167.0, 151.6, 142.6, 141.9, 131.4, 130.0, 129.5, 129.2, 128.3, 125.9, 119.9, 102.3, 99.0, 83.6, 75.7, 74.1, 71.6, 68.8, 66.2, 66.0, 65.7, 64.6, 51.1, 45.5, 45.1, 42.2, 35.8, 34.6, 33.6, 32.3, 31.6, 31.0, 29.0, 28.9, 24.7, 24.3, 22.6, 19.4, 14.1. HRMS: calculated for $C_{42}H_{60}O_{15}Na$ $[M+Na]^+$: 827.3830. Found: 827.3828. $[\alpha]_D^{23}$ −100.8 (c 0.15 in $CHCl_3$).

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