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A Convergent Total Synthesis of the Potent Cephalostatin/ Ritterazine hybrid - 25-*epi* Ritterostatin G_N1_N

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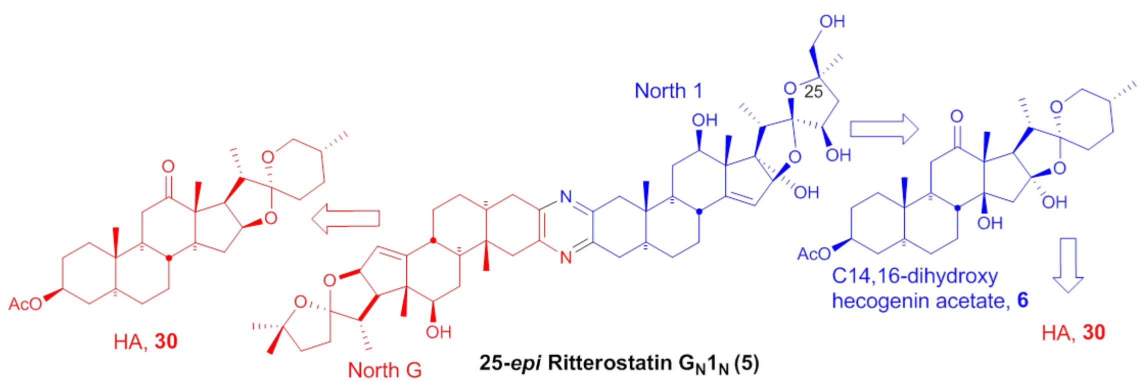


ABSTRACT: The convergent synthesis of 25-*epi* ritterostatin G_N1_N is described for the first time, starting from hecogenin acetate (HA). Stereoselective dihydroxylation employing the chiral ligand $(DHQ)_2$PHAL was used as the key step to introduce the C25 *epi*- stereocenter on the north 1 segment. The title compound was obtained through a coupling reaction between the C3-keto-azide (cstat North 1) and North G.

INTRODUCTION

Cephalostatin 1 (Cstat 1) was isolated by the Petitt group [1] from the marine tubeworm *Cephalodiscus gilchristi,* collected from the Indian Ocean. It is one of the most potent anticancer molecules reported in the NCI 60 cell line testing (Figure 1).[2] Much effort has been devoted to the cephalostatins[3] and very recently a new enantioselective synthesis of this complex molecule has been published[4]. A number of congeners have been isolated from marine sources, including cephalostatins 2-19[5] and ritterazines A-Z.[5] The antineoplastic mechanism of the trisdecacyclic pyrazines is only partly known and the functionality present in these trisdecacyclic steroidal pyrazine bisspiroketals is quite different from that of other anticancer agents, likely indicating a new mechanism of action.[6] Beyond *in vitro* testing, cephalostatin 1 has been shown to be effective in several xenografts including melanoma, sarcoma, leukemia and in a human mammary carcinoma model.[7-8]

Among the series of analogs tested at the NCI (Table 1), 25-*epi* ritterostatin G_N1_N **5** exhibited sub-nanomolar activity (mean GI_{50} 0.48 nM, Table 1 & Figure 1),[8] which is 30 fold more potent than 'natural' epimer **4**. These compounds showed selectivity for CNS, leukemia, and renal cancer cell lines, with ovarian cancer lines relatively resistant.[7-8] As noted previously, this pattern of selectivity is shared with several less potent natural products, including OSW-1, schweinfurthins, and stelletins.[7] Several empirical calculations and docking/modeling studies also supported this higher activity. [6] In order to move agents of the trisdecacyclic pyrazine class to the clinic, a more efficient route to the north 1 hemisphere was required. This issue is addressed herein via a complete synthesis of 25-*epi* ritterostatin G_N1_N in a convergent manner from the readily available hecogenin for both segments, leading to 245 mg of the hybrid molecule.[9] In this synthesis, the north G segment could be readily obtained from hecogenin acetate (HA).[3]

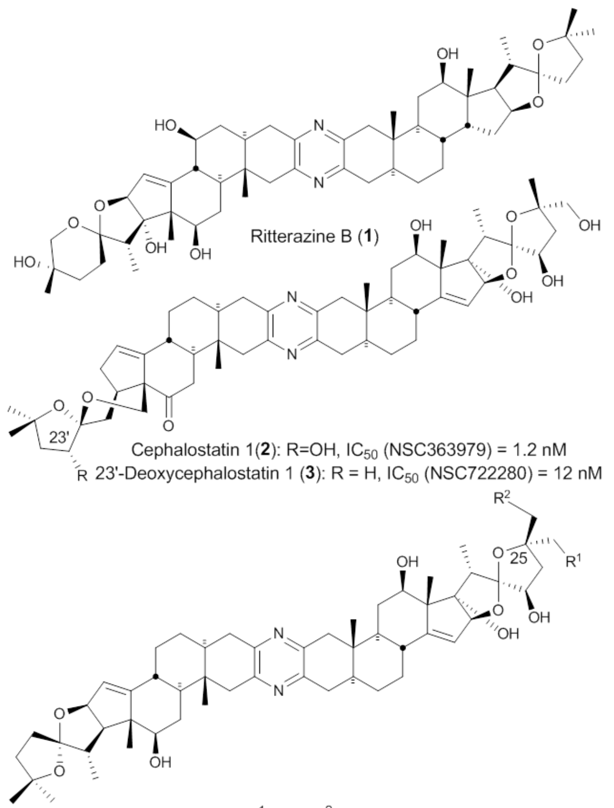


Figure 1. IC_{50} values of Cstat analogs

Table 1. Selected results from NCI-60 cell line testing (IC_{50} values in nM).

Compd	NSC#	Leukemia HL-60	Lung A-549	Colon HT-29	CNS SF-295	Breast MCF-7	Ovary IGROV1	Melanoma M-14	Renal A-498	Prostate PC-3
Cephalostatin 1 (**2**) n = 9	363979	0.4	0.5	1.4	<0.1	0.4	4.0	1.0	1.4	0.3
Ritterostatin G_N1_N (**4**) n = 3	699013	2.4	9.8	79	1.3	28	141	11	>1000	7.2
25-*epi* Ritterostatin G_N1_N (**5**)	720780	<0.1	<0.1	0.3	<0.1	<0.1	<0.1	0.7	0.2	<0.1

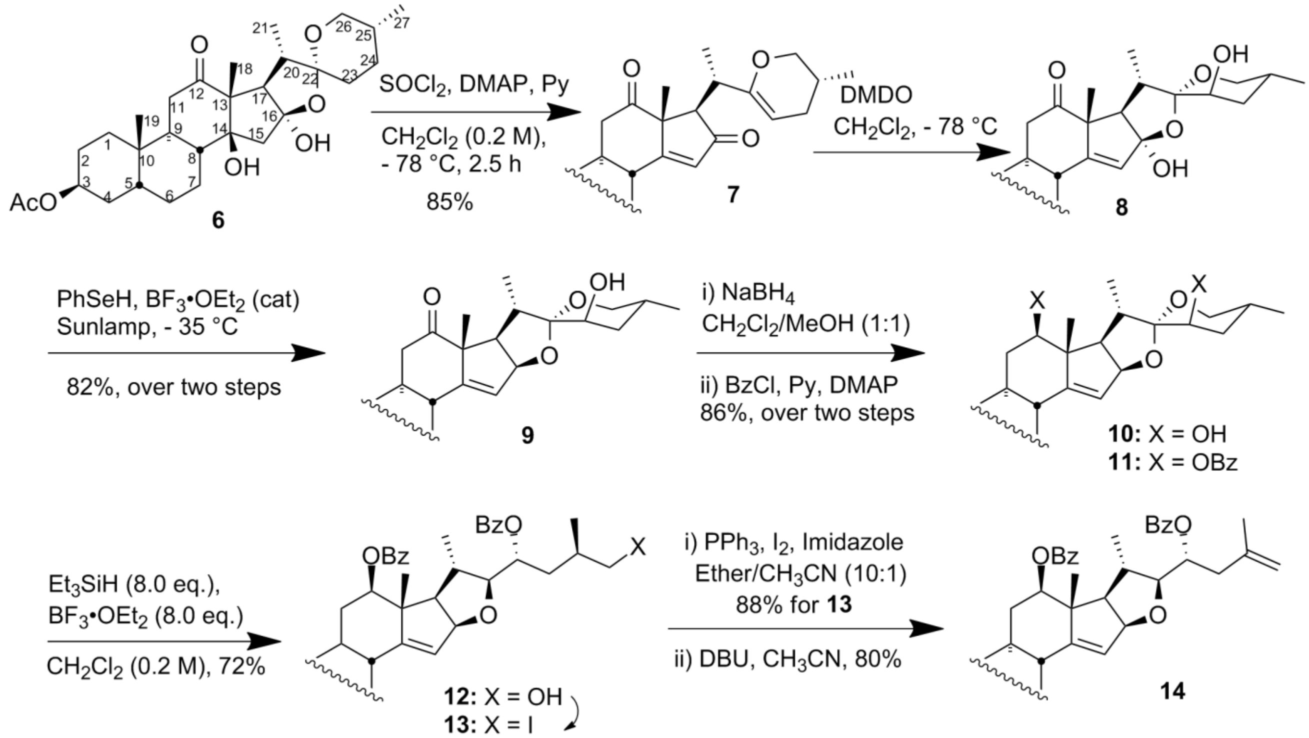
n = 4										

‘n’ is the number of separate full tests- each test was conducted in triplicate at each point (full details in Supporting Information).

Results and Discussion

Synthesis of North 1 Segment. The synthesis began from dihydroxyhecogenin acetate **6** derived from crude hecogenin.[10] The Δ^{14} olefin was formed by $SOCl_2$ mediated dehydration of **6** providing the cyclic vinyl ether **7** in 85% yield. The C23 hydroxyl group (**8)** was introduced via dimethyldioxirane oxidation, followed by reduction of the C16 hydroxyl group using phenylselenol at -45˚C to obtain **9** (Scheme 1).[11] Borohydride reduction of **9** at -78˚C gave the C12 alcohol **10** favoring β (β:α, 8:1) and subsequent bis benzoylation, providing **11** in 86% yield over two steps. Regio- and stereoselective [5,6] spiroketal F-ring reductive opening using triethylsilane[12] to primary alcohol **12** was followed by sequential iodination to **13**, DBU-assisted E2 elimination ultimately provided the terminal olefin **14** (Scheme 1). These reactions were routinely conducted on >10 g scale with highly reproducible yields (72-88%).

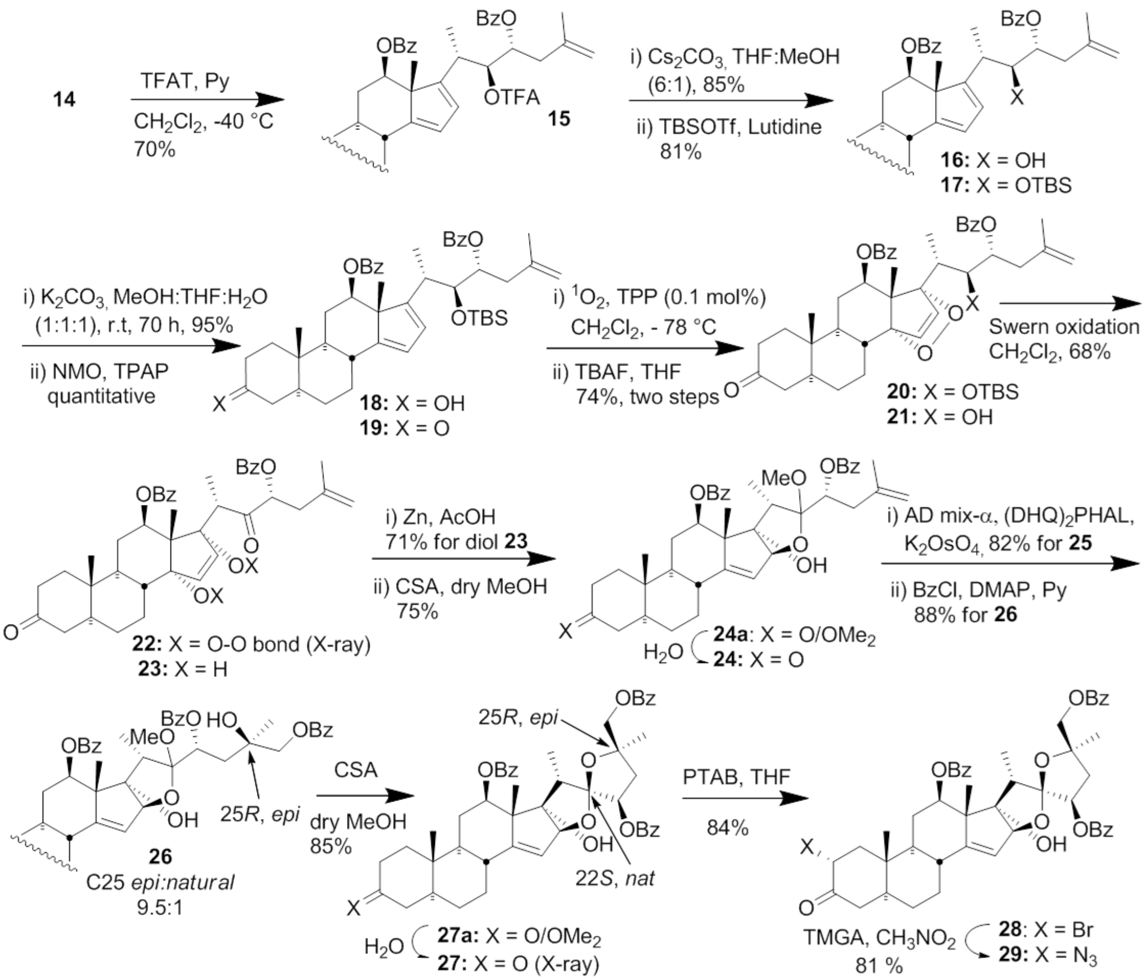
Scheme 1. Synthesis of olefin 14



Treatment of terminal olefin **14** with trifluoroacetyl triflate (TFAT) at -40˚C effected spiroketal ring opening,[13,12] smoothly providing the expected cyclopentadiene as the C22-OTFA ester **15.** Selective deprotection of **15** gave alcohol **16** and its subsequent TBS ether **17** without disturbing the C3-OAc. The C3-keto intermediate **19** was easily obtained in quantitative yield by saponification to **18** followed by oxidation with NMO and catalytic TPAP.[13] Reaction of **19** with singlet oxygen led to the stereospecific α-1,4-adduct **20**.[13] Cleavage of the TBS group at C22 to alcohol **21**, followed by Swern oxidation afforded ketone **22** which was confirmed by X-ray crystallographic analysis (Figure 2).[14] Reductive cleavage of the peroxide bond using Zn/AcOH to diol **23**[12] followed by acid catalyzed cyclization provided olefin **24** (Scheme 2) along with some C3-dimethylacetal **24a** which exhibited two additional methoxy acetal singlets at δ 3.08 &

3.15 in addition to the C22-OMe singlet at δ 3.32. This was easily hydrolyzed to **24** by addition of few drops of water (see experimental section).

Scheme 2. Preparation of Cstat north 1 azide, 29



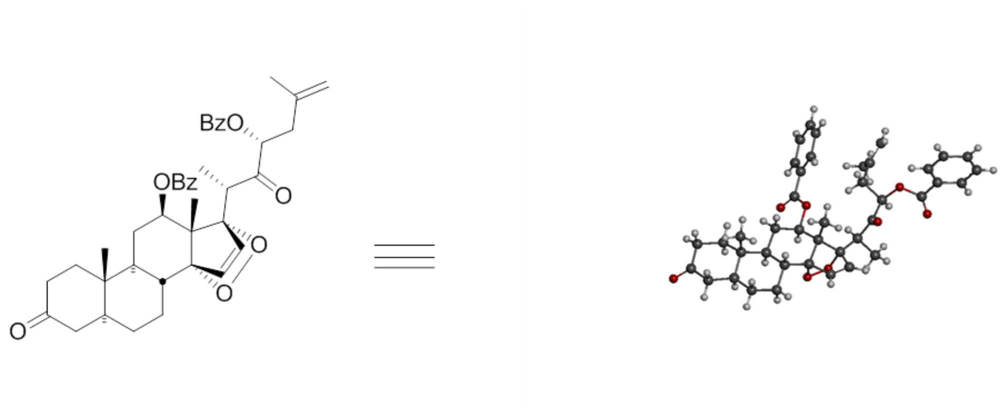
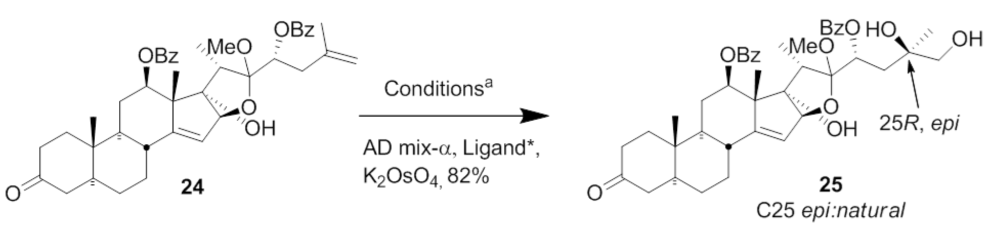


Figure 2. X-Ray structure of peroxide **22**

Asymmetric Dihydroxylation. Several ligands were screened for oxy-functionalization of terminal olefin **24** at C25,26 using Sharpless asymmetric dihydroxylation[15] (Table 2). As expected, a reasonable enantiomeric excess (*ee*) of C25- *epi*, *R*-**25** (9.5:1 ratio, *epi:natural*) was obtained when (DHQ)$_2$PHAL AD-mix-α was used, whereas with other ligands the selectivity was poor (Table 2). The C26 primary alcohol of diol **25** was protected as benzoyl ester **26** in 88% yield, followed by acid catalyzed cyclization to spiroketal **27**[14] in 85% yield (Scheme 2, Figure 3) along with some C3 dimethylacetal [**27a**, X=(OMe)$_2$]. This material was easily hydrolyzed to the C3 ketone (**27**) by addition of a few drops of H_2O to the reaction flask prior to workup (see Supporting Information).

Table 2. Asymmetric dihydroxylation of olefin **24**



Ligands	Compound **25**,

screened*	C25 ratio, *epi:natural* (*R:S*)
None	2.2:1
$(DHQD)_2$PHAL	1:1
$(DHQ)_2$PHAL	**9.5:1** (82%)
$(DHQD)_2$PYR	1:3.8
$(DHQ)_2$PYR	2:1
DHQD	1.8:1
DHQ	2.5:1

[a] Conditions: K_2OsO_4 (2 mol%), ligand (10 mol%), *t*-BuOH/H_2O (1:1), 0˚C, 40 h.

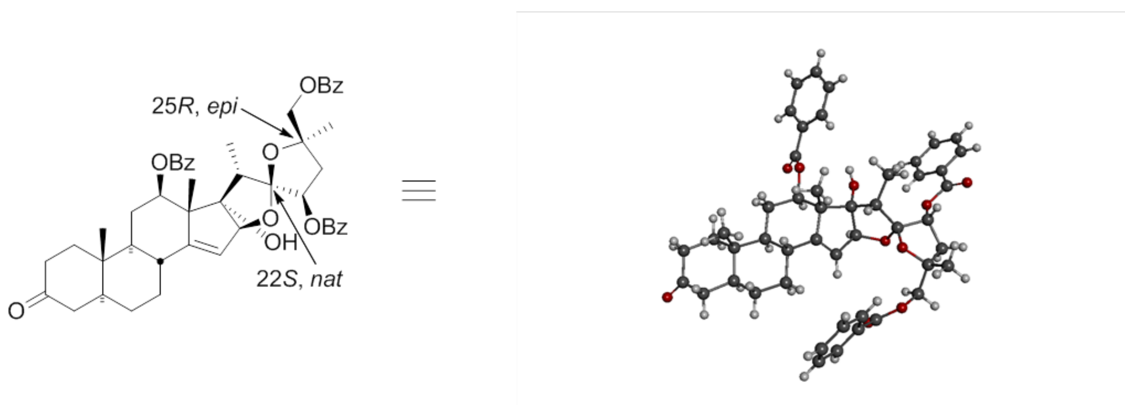
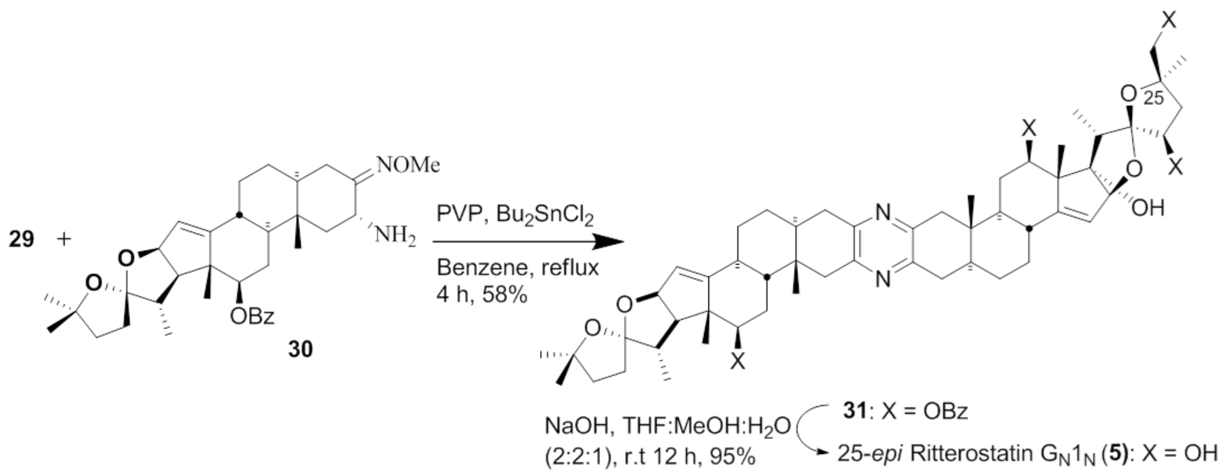


Figure 3. X-Ray structure of **27**

The North 1 coupling partner C3-keto-azide **29**[16] was prepared by bromination of **27** in THF using phenyltrimethylammonium tribromide (PTAB) in 84% yield **(28)** followed by azide formation with tetramethylguanidinium azide (TMGA) (**29)** in 81% yield (Scheme 2). C3-keto-azide **29** of 25-*epi* Cstat North 1 was thus prepared in 23 steps and 1.6% overall yield from C14,16-dihydroxy hecogenin acetate **6**. The North G (**30**) segment was synthesized according to the literature protocol from HA.[3,6]

End game. Coupling of aminomethoxime North G **30** with C3-keto-azide of North 1 **29** using PVP, Bu_2SnCl_2 in refluxing benzene provided trisdecacyclic pyrazine **31** in 58% yield (Scheme 3).[17] Completion of 25-*epi* ritterostatin G_N1_N (**5**) in nearly quantitative yield simply involved global deprotection with NaOH.

Scheme 3. Formation of trisdecacyclic pyrazine 5



In conclusion, the first synthesis of 25-*epi* ritterostatin G_N1_N **5** is reported with excellent stereocontrol. The highly functionalized North 1 hemisphere featured introduction of the C25-*epi* stereocenter *via* asymmetric dihydroxylation as the key step. Reactions were performed at multi-gram scale with reproducible yields.

EXPERIMENTAL SECTION

General Methods. All reagents purchased were used as received. Tetrahydrofuran (THF) and diethyl ether were distilled from benzophenone ketyl. Benzene, toluene, and methylene chloride

(CH_2Cl_2) were distilled from calcium hydride. Acetonitrile (CH_3CN) and methanol were purchased spectral grade and used without further purification. Sodium sulfate (Na_2SO_4) was anhydrous. All recrystallization, chromatographic, and workup solvents were distilled. Unless otherwise indicated, all reactions were carried out under in a positive pressure of nitrogen in anhydrous solvents and the reaction flasks were fitted with rubber septa for the introduction of substrates and reagents via syringe. Progress of reactions was monitored by thin layer chromatography (TLC) using silica gel plates. The TLC plates were visualized with a UV lamp (254 nm) and/or with TLC visualizing solutions activated with heat. The two commonly employed TLC visualizing solutions were: (i) *p*-anisaldehyde solution (1350mL absolute ethanol, 50mL concentrated H_2SO_4, 37mL *p*-anisaldehyde), and (ii) Iodine.

^1H NMR and ^{13}C NMR spectra were recorded on 400-500 MHz spectrometers in $CDCl_3$ solution. Chemical shifts were reported in parts per million (ppm) on the δ scale from an internal standard (NMR descriptions: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; dd, doublet of doublet; td, triplet of doublet and/or quint, quintet). Coupling constants, *J*, are reported in Hertz. Melting points were obtained on a capillary melting point apparatus or automated melting point system and are uncorrected. The high resolution mass measurements were obtained on a LTQ Orbitrap XL mass spectrometer utilizing electrospray ionization (ESI)

C12 Reduction (10) followed by benzoyl protection, 11. C23 alcohol (**9**, 3.1 g, 6.37 mmol) was dissolved in CH_2Cl_2 and MeOH (1:1, 50 mL). The solution was cooled to -78°C (dry ice/acetone) under a nitrogen atmosphere. $NaBH_4$ was added into the mixture in 3 portions in five-minute intervals (200 mg, 5.3 mmol each portion). The solution was maintained at -78°C for

8 hours with vigorous stirring. The temperature was then slowly raised to -20°C. TLC showed the complete absence of starting material (7:3 EtOAc/Hexane, R_f = 0.3). The reaction was quenched with HCl (2 N, 40 mL). CH_2Cl_2 was used to extract the reaction mixture (50 mL x 3). The combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated followed by application of vacuum for 2 h before proceeding to next step with crude **10**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (d, *J* = 6.5, 3H), 0.88 (s, 3H), 1.01 (s, 4H), 1.21 (d, *J* = 6.7, 3H), 1.28-1.39 (m, 6H), 1.43-1.49 (m, 2H), 1.63-1.75 (m, 6H), 1.80-1.88 (m, 2H), 2.02 (s, 6H), 2.13-2.18 (t, 1H), 2.43 (t, 1H), 3.17 (dd, *J* = 4.6, 4.6, 1H), 3.48-3.57 (m, 2H), 3.64 (t, 1H), 4.63-4.70 (m, 1H), 4.89 (d, *J* = 9.5, 1H), 5.37 (s, 1H); LRMS (ESI) *m/z* calc for $C_{29}H_{45}O_6$ (M+H) 489.32, found 489.27.

To crude **10** in CH_2Cl_2 (30 mL) were added DMAP (80 mg 0.1 eq.), pyridine (8 mL) under N_2 and the flask was cooled in an ice water bath. To this solution benzoyl chloride (2.2 mL, 19 mmol) was added and the reaction was stirred for 16 hours, until TLC showed starting material disappeared (3:7 EtOAc/Hexane, R_f = 0.5). The solvent was removed under reduced pressure and the reaction mixture was purified by silica gel column chromatograph by using EtOAc-Hexane to provide the desired product **11** (3:7 EtOAc/Hexane, R_f = 0.5), 3.8 to 3.9 g, yield 86% for two steps. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.79 (d, *J* = 6.6, 3H), 0.89 (s, 3H), 0.94 (d, *J* = 6.7, 3H), 1.01-1.09 (m, 1H), 1.01-1.09 (m, 1H), 1.21 (s, 3H), 1.33-1.43 (m, 3H), 1.46-1.52 (m, 1H), 1.61–1.69 (m, 2H), 1.74-1.84 (m, 3H), 1.88-1.99 (m, 4H), 2.02 (s, 3H), 2.05 (s, 2H), 2.07-2.14 (m, 2H), 2.43 (t, 1H), 3.53 (t, 1H), 3.58-3.62 (m, 1H), 4.63-4.71 (m, 2H), 4.98 (dd, *J* = 2.1, 2.2, 1H), 5.13 (s, 1H), 5.47 (s, 1H), 7.37-7.56 (m, 6H), 7.99 (d, *J* = 8.2, 2H), 8.08 (d, *J* = 8.2, 2H); HRMS (ESI) calcd for $C_{43}H_{53}O_8$ $[M+H]^+$ 697.3740, found 697.3734.

F-ring cleavage compound 12. The C12, 23-dibenzoate (**11**, 10.0 g, 14.35 mmol) and triethylsilane (13.35 g, 114.8 mmol, 8 eq.) were dissolved in CH_2Cl_2 (100 mL) under N_2. BF_3•OEt_2 (14.5 mL, 114.8 mmol, 8 eq.) was added to the reaction mixture at <5°C. The reaction was stirred at room temperature for 40 hours and then quenched with $NaHCO_3$ (200 mL, ice water bath). The reaction mixture was extracted with CH_2Cl_2 (50 mL x 3) and combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The crude mass was subjected to chromatography on silica gel to provide the C26 alcohol (**12)** 7.21 g, yield 72% (3:7 EtOAc/Hexane, R_f= 0.25). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (s, 3H), 0.90-0.92 (m, 4H), 0.95 (d, J = 6.5, 3H), 1.24-1.27 (m, 4H), 1.35 (t, 2H), 1.56 (t, 1H), 1.64-1.76 (m, 3H), 1.90-1.97 (m, 8H), 2.02 (s, 3H), 2.04 (s, 2H), 2.08-2.12 (m, 1H), 2.25 (t, 1H), 3.47 (t, 1H), 3.55-3.59 (m, 1H), 4.65-4.70 (m, 4H), 4.84 (dd, J = 1.5, 1.3, 1H), 5.35-5.39 (m, 1H), 5.45 (t, 1H), 7.43 (t, J = 15.0, 4H), 7.55 (t, J = 14.6, 2H), 7.98-8.15 (m, 4H); HRMS (ESI) calcd for $C_{43}H_{55}O_8$ $[M+H]^+$ 699.3897, found 699.3887.

Iodo compound 13. To the C26 alcohol (**12**, 5.0 g, 7.15 mmol) in diethyl ether (150 mL) and CH_3CN (15 mL) were added triphenylphosphine (4.7 g, 17.9 mmol, 2.5 eq.), imidazole (2.47 g, 35.8 mmol, 5 eq.) followed by iodine (5.45 g, 21.5 mmol, 3 eq.) at <5°C. The reaction was stirred at this temperature for 30 minutes and then at room temperature for an additional 3 hours. Aq. $NaHSO_3$ was added to the reaction and stirred for 30 minutes. The organic solution was separated and the aqueous phase was extracted with ethyl acetate (25 mL x 3). The combined organic layer dried over Na_2SO_4 and removal of the solvent under reduced pressure followed by chromatography on silica gel provided **13** (3:7 EtOAc/Hexane, R_f= 0.65), 5.11 g, yield 88%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84-0.97 (m, 2H), 0.89 (s, 6H), 0.91 (s, 2H), 0.93-0.99 (m, 1H), 1.03

(d, *J* = 6.5, 3H), 1.26 (s, 3H), 1.36 (t, 2H), 1.56-1.63 (m, 6H), 1.64-1.71 (m, 2H), 1.76-1.86 (m, 1H), 1.88-1.99 (m, 1H), 2.01 (s, 3H), 2.04 (s, 1H), 2.07-2.12 (m, 1H), 2.25 (t, 1H), 3.17 (t, 2H), 3.55 (dd, *J* = 5.0, 5.1, 1H), 4.67-4.70 (q, 2H), 4.83 (dd, *J* = 2.2, 2.4, 1H), 5.31-5.35 (m, 1H), 5.46 (t, 1H), 7.41-7.45 (m, 4H), 7.51-7.57 (m, 2H), 8.00-8.06 (m, 4H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ 11.9, 14.1, 16.3, 17.8, 18.3, 19.9, 21.3, 22.5, 25.2, 26.6, 27.2, 28.0, 29.4, 31.2, 31.4, 33.6, 34.0, 34.5, 35.8, 36.4, 37.7, 37.9, 44.0, 51.7, 52.0, 60.0, 73.0, 81.4, 86.5, 87.9, 120.0, 128.3, 129.3, 129.6, 129.8, 130.2, 131.9, 132.0, 132.9, 157.0, 165.6, 165.8, 170.2; LRMS (ESI) calcd for $C_{43}H_{54}IO_7$ $[M+H]^+$ 809.29, found 809.25.

Olefin 14. Iodide (**13**, 901 mg, 1.13 mmol) was dissolved in CH_3CN (25 mL) under argon atmosphere and freshly distilled DBU over CaH_2 (255 µL, 1.7 mmol, 1.5 eq.) was added to the reaction mixture. The reaction was stirred at 55°C for 4 hours and then at room temperature for 10 hours. The solvent was removed under reduced pressure and the crude mass was purified *via* silica gel column chromatography using EtOAc-Hexane (3:7 R_f = 0.45) to provide **14**, 591 mg, yield 80%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.77-0.81 (m, 2H), 0.82 (s, 3H), 0.89 (d, *J* = 6.4, 3H), 0.94-1.04 (m, 2H), 1.10-1.20 (m, 2H) 1.23 (s, 3H), 1.26-1.34 (m, 4H), 1.37-1.45 (m, 1H), 1.57-1.65 (m, 2H), 1.70 (s, 3H), 1.73-1.86 (m, 2H), 1.88-1.91 (m, 1H), 1.92 (s, 3H), 2.02-2.13 (m, 2H), 2.23 (t, 1H), 2.46 (d, *J* = 6.4, 2H), 3.53 (dd, *J* = 5.4, 5.2, 1H), 4.60-4.64 (m, 1H) 4.68 (br, 1H), 4.80 (dd, *J* = 2.3, 2.3, 1H), 5.37-5.41 (m, 1H), 5.42 (t, 1H), 7.30-7.36 (m, 4H), 7.41-7.47 (m, 2H), 7.95-7.99 (m,4H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ 11.8, 14.1, 16.2, 18.3, 20.6, 21.2, 22.4, 25.2, 26.6, 27.1, 28.0, 29.4, 31.4, 33.6, 34.0, 34.3, 34.5, 35.8, 36.4, 38.1, 39.4, 44.0, 51.7, 52.0, 60.1, 73.0, 73.1, 81.4, 86.4, 87.6, 113.1, 120.1, 128.2, 128.3, 129.3, 129.5, 130.2, 130.3, 132.7, 141.2, 157.0, 165.6, 165.7, 170.2; HRMS (ESI) calcd for $C_{43}H_{53}O_7$ $[M+H]^+$ 681.3792, found 681.3778.

Synthesis of D-ring diene 15. The olefin (**14**, 2.8 g, 4.11 mmol) and 2,6-di-*t*-butyl-4-methyl pyridine (3.28 g, 16 mmol, 4 eq.) were dissolved in CH_2Cl_2 (200 mL) and cooled to -40°C. Freshly prepared trifluoroacetyl trifluoromethanesulfonate (TFAT, 1.5 mL, 8 mmol, 2 eq.) was added slowly and stirred for 1 h. A second portion of TFAT (1.5 mL, 2 eq.) was added and stirred another 2.5 h and finally, a 3rd portion of TFAT (0.7 mL, 1 eq.) was added and stirring continued for another 1 h. After disappearance of starting material shown by TLC (3:7 EtOAc/Hexane, R_f = 0.55), the reaction was quenched with aq. $NaHCO_3$ (100 mL). The organic layer was separated and aqueous phase was extracted with CH_2Cl_2 (15 x 3). The combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was loaded on a silica gel column and eluted with hexane followed by EtOAc-Hexanes. The 2,6-di-*t*-butyl-4-methyl pyridine was recovered first by flushing 1:10 to 1:8 and then desired product **15** was isolated with 1:4 EtOAc-Hexanes respectively. The yield was 70%, 2.23 g. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80-0.88 (m, 3H), 0.93 (s, 3H), 0.96 (d, *J* = 6.5, 3H), 1.10-1.15 (m, 1H), 1.21 (s, 3H), 1.26 (t, 1H), 1.34-1.47 (m, 3H), 1.52 (s, 3H), 1.64-1.75 (m, 2H), 1.78-1.86 (m, 1H), 1.96-2.00 (m, 2H), 2.02 (s, 3H), 2.03-2.09 (m, 1H), 2.14-2.24 (m, 2H), 2.49 (q, 1H), 2.96 (dd, *J* = 6.6, 6.7, 1H), 4.46 (dd, *J* = 4.4, 4.4, 1H), 4.63 (br, 1H), 4.67-4.72 (m, 2H), 5.42 (d, *J* = 10.6, 1H), 5.51 (dd, *J* = 2.4, 2.4, 1H), 5.88 (s, 1H), 6.15 (s, 1H), 7.38-7.62 (m, 6H), 7.89 (d, *J* = 8.1, 2H), 8.10 (d, *J* = 8.2, 2H). ^{19}F NMR (376 MHz) δ -76.43; ^{13}CNMR ($CDCl_3$, 100 MHz) δ 11.9, 13.7, 13.8, 19.2, 20.7, 21.0, 21.8, 27.1, 27.9, 28.9, 32.9, 33.6, 34.5, 35.2, 35.6, 36.8, 44.0, 53.1, 56.6, 60.0, 70.8, 73.0, 76.9, 77.2, 77.5, 79.0, 81.5, 113.1, 114.0, 115.9, 120.6, 125.4, 128.2, 129.2, 130.3, 132.9, 133.1, 140.0, 155.9, 156.2, 156.6, 165.1, 165.2, 170.1, 170.6; LRMS (ESI) calcd for $C_{45}H_{52}F_3O_8$ $[M+H]^+$ 777.36, found 777.31.

Synthesis of C22 alcohol 16. The C22-OTFA (**15**) was dissolved in THF/MeOH (70 mL, 6:1) and Cs_2CO_3 (1.3 g, 1 eq.) was added to the reaction and stirred at room temperature. After ensuring the consumption of starting material by TLC (3:7 EtOAc/Hexane, $R_f = 0.3$), the reaction was diluted by EtOAc (80 mL), followed by water (60 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (30 mL x 3). The combined organic phase was washed once with brine (20 mL), dried (Na_2SO_4) and concentrated. After evaporation of the solvent under reduced pressure, the crude product was purified on a silica gel column using EtOAc-Hexane (1:4) to provide C23 alcohol, **16**, 2.38 g in 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84-0.88 (m, 2H), 0.91 (d, J = 6.4, 3H), 0.93 (s, 3H), 1.05-1.15 (m, 1H), 1.20-1.25 (m, 2H), 1.27 (s, 3H), 1.34-1.50 (m, 3H), 1.65-1.73 (m, 1H), 1.75-1.85 (m, 2H), 2.0-2.07 (m, 9H), 2.13-2.25 (m, 3H), 2.61-2.74 (m, 2H), 3.90 (dd, J = 2.5, 2.4, 1H), 4.46 (dd, J = 4.5, 4.4, 1H), 4.68 (br, 3H), 5.30-5.33 (m, 1H), 5.96 (s, 1H), 6.21 (s, 1H), 7.39-7.47 (m, 4H), 7.52-7.59 (m, 2H), 8.01 (d, J = 8.1, 2H), 8.09 (d, J = 8.2, 2H); LRMS (ESI) calcd for $C_{43}H_{52}NaO_7$ $[M+Na]^+$ 703.36, found 703.33.

Formation of C-22 OTBS ether 17. To the C22 alcohol (**16**, 2.36 g, 3.47 mmol) in CH_2Cl_2 (35 mL) were added 2,6-Lutidine (2.1 mL, 18 mmol, 5.0 eq.) followed by TBSOTf (4 eq.) in three portions under N_2 at room temperature and the reaction was stirred for 3 h. The reaction mixture was quenched by adding aq. $NaHCO_3$ solution (20 mL), the aqueous phase was extracted with CH_2Cl_2 (15 mL x 3) and the combined organic phases were dried over Na_2SO_4

and concentrated under reduced pressure. The crude product was subjected to chromatography on silica gel to provide **17** (3:7 EtOAc/Hexane, R_f = 0.65), 2.21 g in 81% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (s, 6H), 0.88 (br, 12H), 0.90-0.95 (m, 5H), 1.04-1.12 (m, 1H), 1.19-1.24 (m, 1H), 1.28 (s, 3H), 1.33-1.42 (m, 3H), 1.44-1.50 (m, 2H), 1.62-1.71 (m, 2H), 1.74-1.80 (m, 1H), 1.97-2.00 (m, 4H), 2.16-2.23 (m, 2H), 2.49 (s, 4H), 2.61-2.70 (m, 1H), 2.72-2.80 (m, 1H), 3.99 (dd, *J* = 1.4, 1.5, 1H), 4.40 (dd, *J* = 4.4, 4.2, 1H), 4.66 (br, 2H), 5.29 (d, *J* = 10.1, 1H), 5.93 (s, 1H), 6.21 (s, 1H), 6.91 (d, *J* = 7.6, 1H), 7.35-7.56 (m, 6H), 7.98 (d, *J* = 7.8, 2H), 8.08 (d, *J* = 8.1, 2H; ^{13}CNMR ($CDCl_3$, 100 MHz) δ -4.6, -3.8, -3.6, 12.1, 12.8, 17.9, 18.3, 20.3, 21.3, 22.0, 24.1, 25.6, 26.0, 27.1, 27.3, 28.1, 29.1, 33.7, 34.6, 35.7, 36.2, 36.4, 36.9, 44.2, 53.2, 56.8, 73.3, 75.1, 78.3, 80.0, 113.0, 120.2, 121.1, 125.6, 128.2, 128.4, 129.3, 129.6, 130.5, 132.7, 132.9, 136.7, 141.7, 154.6, 157.3, 158.5, 165.6, 166.4, 170.5; LRMS (ESI) calcd for $C_{49}H_{67}O_7Si$ $[M+H]^+$ 795.46, found 795.41.

Synthesis of C-3 alcohol 18. C3-acetyl compound (**17**, 2.21 g, 2.78 mmol) was dissolved in THF: MeOH: H_2O (1:1:1, 30 mL), K_2CO_3 (4.28 g, 30 mmol) was added in one portion and the reaction mixture was stirred for 70 h at room temperature. After ensuring the absence of starting material from TLC (3:7 EtOAc/Hexane, R_f = 0.2), the mixture was diluted with EtOAc (60 mL) followed by H_2O (30 ml). The organic phase was separated and aqueous phase was extracted with EtOAc (20 x 3). The combined organic phase was dried over Na_2SO_4, the solvent was evaporated under reduced pressure and the resulting crude product was subjected to chromatography on silica gel using EtOAc-Hexane to provide the C3-OH, **18** (3:7 EtOAc/Hexane, R_f = 0.2), 1.99 g and yield 95%. ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.23 (s, 3H), -0.07 (s, 3H), 0.79-0.81(m, 1H), 0.86 (s, 9H), 0.91 (s, 3H), 0.92-0.95 (m, 3H), 1.02-1.17 (m, 3H), 1.21-1.25 (m, 2H), 1.28 (s, 3H), 1.31-1.36 (m, 1H), 1.41-1.44 (m, 3H), 1.57-1.71 (m, 3H), 1.75-1.82 (m, 1H), 1.97-2.04 (m, 4H), 2.17-2.27 (m, 2H), 2.64-2.70 (m, 1H), 2.75-2.80 (m, 1H), 3.56-3.65 (m, 1H), 4.01(dd, *J* = 1.5, 1.5, 1H), 4.40 (dd, *J* = 4.4, 4.2, 1H), 4.67 (br, 2H), 5.30 (d, *J* = 10.7, 1H), 5.94 (t, *J* = 4.1, 1H), 6.22 (d, *J* = 2.2, 1H), 7.38-7.59 (m, 6H), 7.99 (d, *J* = 8.1, 2H), 8.10 (d, *J* = 7.9, 2H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ -4.5, -3.8, -0.03, 12.3, 12.8, 14.2, 18.9, 20.4, 21.0, 22.2, 26.1, 27.4, 28.3, 29.2, 31.2, 34.7, 35.8, 36.2, 36.5, 37.2, 37.8, 44.5, 53.4, 56.9, 60.4, 71.0, 75.2, 78.4, 80.2, 113.0, 121.1, 125.6, 128.2, 128.5, 129.4, 129.6, 130.5, 130.6, 132.8, 133.0, 141.9, 154.6, 158.6, 165.7, 166.5; LRMS (ESI) calcd for $C_{47}H_{65}O_6Si$ $[M+H]^+$ 753.45, found 753.41.

Synthesis of C3 ketone 19. The C3 alcohol (**18**, 781 mg, 1.04 mmol) was dissolved in CH_2Cl_2 (10 mL) under N_2 and NMO (240 mg, 2 mmol, 2.0 eq.) followed by tetrapropylammonium perruthenate (TPAP, 17.5 mg, 0.05 mmol) was added at room temperature and the mixture was stirred for 3 h. After ensuring the disappearance of starting material by TLC (3:7 EtOAc/Hexane, R_f = 0.55), the solvent was removed and the crude product was subjected to flash chromatography on a short silica gel column to provide C3 ketone **19**, 744 mg in 99% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.24 (s, 3H), -0.07 (s, 3H), 0.85 (s, 12H), 0.93 (d, *J* = 6.5, 2H), 1.05 (s, 3H), 1.31 (s, 3H), 1.36-1.45 (m, 6H), 1.87-1.95 (m, 2H), 1.98-2.11 (m, 4H), 2.19-2.31 (m, 5H), 2.64-2.71 (m, 1H), 2.79 (t, 1H), 4.01 (d, *J* = 7.4, 1H), 4.40 (dd, *J* = 4.5, 4.2, 1H), 4.66 (d, *J* = 5.3, 2H), 5.31 (dd, *J* = 2.7, 2.8, 1H), 5.94 (s, 1H), 6.21 (s, 1H), 7.33-7.53 (m, 6H), 7.98 (d, *J* = 8.2, 2H), 8.09 (d, *J* = 8.1, 2H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ -4.5, -3.8, 11.3, 12.7, 18.3, 20.3, 22.1, 26.1, 27.5, 28.4, 28.8, 34.5, 35.8, 36.2, 36.4, 37.7, 38.4, 44.3, 46.0, 52.8, 56.9, 75.0, 78.3, 79.7, 113.0, 121.5, 125.5, 128.2, 128.4, 129.3, 129.5, 130.4, 132.7, 133.0, 141.7, 154.0, 158.8, 165.4, 166.2, 210.4; LRMS (ESI) calcd for $C_{47}H_{63}O_6Si$ $[M+H]^+$ 751.43, found 751.40.

Peroxide formation (20) followed by deprotection of C22-OTBS (21). The diene (**19**, 500 mg, 0.64 mmol) in CH_2Cl_2 (40 mL) was cooled to -78°C. 5,10,15,20-Tetraphenyl-*21H,23H*-porphine (TPP) (0.1 mol %) was added and oxygen was bubbled into the solution *via* a balloon with photoactivation (GE Sunlamp 300 W) at a distance of approximately 8 to 9 inches from the reaction flask. The reaction was stirred with irradiation at -78°C for 2 hours. After ensuring the disappearance of starting material by TLC (3:7 EtOAc/Hexane, R_f = 0.4), solvent was removed and the crude peroxide (**20**) was directly used in the next step after drying for 1 h under high vacuum.

In the second step, crude product **20** was dissolved in THF (7 mL) under N_2 and TBAF (tetrabutylammonium fluoride, 1.0 M in THF, 1.5 mL) was added at room temperature and the reaction was stirred for 3 h. The reaction was quenched with brine and extracted with ethyl acetate (10 mL x 3). The combined organics were dried over Na_2SO_4, the solvent evaporated under reduced pressure and crude product was subjected to column chromatography on neutral alumina using EtOAc-Hexane (3:7 EtOAc/Hexane, R_f = 0.22) to provide C22 alcohol (**21**), 263 mg, 74% for two steps. ^{1}H NMR (400 MHz, CDCl3) δ 0.85 (s, 4H), 0.90-0.96 (m, 3H) 1.04-1.08 (t, 3H), 1.13 (s, 3H), 1.20-1.29 (m, 3H), 1.62-1.69 (m, 1H), 1.74-1.80 (m, 3H), 1.83 (s, 3H), 1.88-1.96 (m, 3H), 2.02-2.11 (m, 4H), 2.24-2.33 (m, 1H), 2.35-2.42 (m, 1H), 3.37 (s, 1H), 4.47 (d, *J* = 5.2, 2H), 5.22 (d, *J* = 8.9, 1H), 5.48 (dd, *J* = 4.4, 5.9, 1H), 6.25 (d, *J* = 5.6, 1H), 6.44 (d, *J* = 5.4, 1H), 7.18-7.27 (m, 4H), 7.33-7.43 (m, 2H), 7.80 (d, *J* = 8.1, 2H), 7.87 (d, *J* = 8.3, 2H); ^{13}CNMR (CDCl3, 100 MHz) δ 10.6, 10.7, 11.6, 13.4, 14.0, 20.8, 22.2, 22.3, 26.4, 26.8, 28.5, 33.3, 35.0, 35.4, 35.6, 37.5, 37.9, 44.0, 44.9, 45.4, 60.1, 63.3, 72.0, 73.4, 73.6, 97.5, 98.2, 113.1, 128.1, 128.2, 129.2, 129.5, 129.9, 130.0, 132.0, 132.8, 135.9, 141.1, 165.3, 165.5, 170.8, 210.8; LRMS (ESI) calcd for $C_{41}H_{49}O_8$ $[M+H]^+$ 669.34, found 669.29.

Synthesis of C-22 ketone 22.[14] A flame dried flask was charged with DMSO (118 µL, 1.65 mmol) in CH_2Cl_2 (8 mL) and cooled to -78°C under argon atmosphere. TFAA (175 µL, 1.24 mmol) was added to the solution dropwise and stirred for 45 minutes. To the reaction was added C22-alcohol (**21**, 263 mg, 0.413 mmol) in CH_2Cl_2 (6 mL) *via* syringe over 4 minutes and the reaction stirred another 50 minutes at -78°C. Diisopropylethyl amine (456 µL) was added to the reaction and the temperature was allowed to warm to -30°C over 1.5 h. TLC (3:7 EtOAc/Hexane, R_f = 0.5) showed no starting material remaining and the reaction was quenched by adding brine. The organic layer was separated and aqueous phase was extracted with CH_2Cl_2 (10 mL x 3). The combined organics were dried over Na_2SO_4, concentrated and crude product was subjected to flash column chromatography on neutral Al_2O_3 by using EtOAc-Hexane to provide C3, 22-diketone (**22**), 187 mg, yield 68%. An X-ray structure was obtained which confirmed the singlet oxygen Diels-Alder reaction proceeded with the desired stereochemistry.[14] However, due to the potential instability of the peroxide, this material was normally used immediately. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01-1.23 (m, 10H), 1.28-1.34 (m, 1H), 1.50-1.56 (m, 1H), 1.64-1.73 (m, 2H), 1.78-1.87 (m, 3H), 1.94-2.09 (m, 5H), 2.35 (s, 7H), 3.05-3.14 (m, 1H), 4.32 (s, 1H), 4.38 (s, 1H), 5.04 (dd, J = 3.6, 3.3, 1H), 5.40 (dd, J = 4.7, 4.6, 1H), 6.15 (d, J = 5.8, 1H), 6.41 (d, J = 6.0, 1H), 7.12-7.19 (m, 4H), 7.28-7.34 (m, 2H), 7.63 (d, J = 8.2, 2H), 7.68 (d, J = 7.9, 2H); LRMS (ESI) calcd for $C_{41}H_{47}O_8$ $[M+H]^+$ 667.32, found 667.28.

Synthesis of diol 23. To the C3,22-diketone (**22**) in CH_2Cl_2 (6 mL) were added activated Zn powder[18] (260 mg, 4 mmol) followed by AcOH (50 μL). The mixture was stirred at roon temperature for 2 h. After disappearance of starting material from TLC (1:1 EtOAc/Hexane, R_f = 0.3), $NaHCO_3$ (aq. 10 mL) was added to quench the reaction. The organic layer was separated and aqueous phase was extracted with CH_2Cl_2 (10 mL x 3). Combined organics were dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified by chromatography on silica gel to provide **23**, 196 mg, yield 71%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (s, 3H), 1.04 (s, 2H), 1.17 (t, 3H), 1.22 (d, J = 6.5, 3H), 1.34-1.41 (m, 1H), 1.62-1.68 (m, 1H), 1.72 (s, 3H), 1.80-1.86 (m, 3H), 1.95 (s, 3H), 1.98-2.07 (m, 2H), 2.12-2.27 (m, 3H), 2.45-2.57 (m, 2H), 3.02 (q, 1H), 3.78 (s, 1H), 4.75 (s, 1H), 4.81 (d, J = 10.7, 2H), 5.42 (dd, J = 3.8, 3.6, 1H), 5.73 (d, J = 5.8, 1H), 6.03-6.07 (m, 1H), 6.28 (d, J = 6.0, 1H), 7.34-7.38 (m, 4H), 7.46-7.52 (m, 2H), 7.92 (d, J = 8.2, 2H), 7.98 (d, J = 8.1, 2H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ 10.8, 12.2, 14.2, 14.8, 21.0, 22.1, 26.0, 26.9, 28.7, 34.6, 35.9, 37.8, 37.9, 38.7, 44.4, 45.2, 46.1, 54.5, 60.3, 71.1, 75.7, 87.3, 88.6, 114.8, 128.4, 128.5, 128.9, 129.6, 129.7, 130.6, 132.9, 135.5, 137.7, 138.4, 139.6, 165.4, 165.6, 170.9, 211.2, 213.0; LRMS (ESI) calcd for $C_{41}H_{49}O_8$ $[M+H]^+$ 669.34, found 669.30.

Synthesis of methoxy ketal 24. To the C14, 16 diol (**23**, 196 mg, 0.29 mmol) dissolved in dry MeOH (5 mL) was added camphor sulfonic acid (CSA, 6.8 mg, 0.03 mmol) and the reaction was stirred for 4 to 5 hours at room temperature. After ensuring the disappearance of starting material from TLC (3:7 EtOAc/Hexane, R_f = 0.45), the solvent was evaporated under reduced pressure and CH_2Cl_2 (30 mL) was added to the reaction and the mixture was washed with aq. $NaHCO_3$ (5 mL), brine (10 ml) and dried over Na_2SO_4 and concentrated. The crude product was subjected to chromatography (EtOAc-Hexane) on silica gel to provide **24**, 181 mg in 75% yield. **Data for**

C3-ketone, 24: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82-0.86 (m, 1H), 0.88-0.94 (m, 3H), 1.01 (s, 3H), 1.13 (d, *J* = 6.8, 3H), 1.20-1.30 (m, 3H), 1.37 (s, 3H), 1.40-1.47 (m, 1H), 1.52-1.63 (m, 1H), 1.76 (s, 3H), 1.85-1.92 (m, 1H), 1.95-2.01 (m, 2H), 2.04-2.10 (m, 1H), 2.17-2.22 (m, 3H), 2.24-2.30 (m, 2H), 2.39-2.43 (m, 1H), 2.63-2.68 (q, 1H), 3.32 (s, 3H), 4.70 (d, *J* = 8.0, 2H), 5.10 (t, *J* = 3.6, 1H), 5.23 (dd, *J* = 4.4, 4.0, 1H), 5.68 (dd, *J* = 4.6, 4.8, 1H), 7.38-7.44 (m, 4H), 7.49-7.54 (m, 2H), 7.97 (d, *J* = 8.2, 2H), 8.02 (d, *J* = 8.0, 2H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ 8.5, 11.1, 15.0, 22.0, 27.4, 28.1, 33.6, 35.9, 37.7, 38.3, 42.7, 44.2, 45.8, 48.8, 51.8, 53.9, 69.8, 74.9, 91.4, 93.7, 109.8, 113.4, 119.9, 128.1, 128.2, 129.4, 129.6, 130.3, 131.0, 132.6, 141.2, 152.9, 165.5, 165.7, 210.9; LRMS (ESI) calcd for $C_{42}H_{51}O_8$ $[M+H]^+$ 683.35, found 683.31.

Data for C3-dimethylketal (24a)§: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (s, 3H), 0.85-0.89 (m, 1H), 1.04-1.08 (m, 1H), 1.14 (d, *J* = 6.8, 3H), 1.19-1.28 (m, 6H), 1.35 (s, 3H), 1.43-1.48 (m, 1H), 1.60-1.63 (m, 1H), 1.77 (s, 3H), 1.80-1.85 (m, 1H), 1.92-1.97 (m, 2H), 2.02 (s, 2H), 2.40-2.45 (m, 2H), 2.55 (s, 1H), 2.63-2.68 (q, 1H), 3.08 (s, 3H), 3.15 (s, 3H), 3.32 (s, 3H), 4.70 (t, *J* = 3.5, 1H), 4.73 (d, *J* = 7.1, 2H), 5.10 (t, 1H), 5.24 (dd, *J* = 5.1, 5.0, 1H), 5.69 (dd, *J* = 5.0, 4.8, 1H), 7.38-7.44 (m, 4H), 7.50-7.54 (m, 2H), 7.98 (d, *J* = 8.2, 2H), 8.03 (d, *J* = 7.9, 2H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ 8.5, 11.3, 14.1, 14.9, 20.9, 22.0, 27.2, 27.6, 28.1, 28.3, 33.8, 34.6, 35.2, 36.1, 38.3, 41.8, 42.7, 47.3, 47.4, 48.8, 52.1, 53.9, 60.3, 69.8, 75.2, 91.4, 93.8, 99.9, 109.8, 113.4, 119.4, 128.1, 128.2, 129.4, 129.5, 130.3, 131.0, 132.5, 132.6, 141.2, 153.5, 165.5, 165.7; LRMS (ESI) calcd for $C_{44}H_{57}O_9$ $[M+H]^+$ 729.40, found 729.37.

§ The C3-dimethylketal, **24a** was easily converted to C3 ketone **24** by stirring (1-2 h) with a few drops of water in CH_2Cl_2:MeOH and then subjected to the work-up procedure above.

Asymmetric dihydroxylation 25. The olefin **24** (190 mg 0.278 mmol) was mixed with K_2OsO_4 (2 mg, 0.0056 mmol 2 mol %), $(DHQ)_2$PHAL (20 mg, 0.026 mmol, 5 eq. relative to Osmium) and AD mix-α (390 mg). The reaction flask was placed in a 0°C cooling bath and *tert*-butyl alcohol-water (16 mL, 1:1) was added to the flask while stirring was continued for 40 h at this temperature. The reaction was monitored by TLC (1:1 EtOAc/Hexane, R_f = 0.2) by quenching (aq. $NaHSO_3$) reaction mixture aliquots. After ensuring disappearance of starting material, the reaction was quenched using aq. $NaHSO_3$ (10 mL) and stirred at room temperature for 1 h. The reaction mixture was extracted with EtOAc (15 mL) and CH_2Cl_2 (20 mL x 3), the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The crude product was chromatographed on silica gel using EtOAc-Hexane followed by 2% MeOH in $CHCl_3$ to provide product **25**[§], 164 mg and yield 82%. The selectivity is 9.5*:1, C25 epi-natural* favor to *'R'* configuration at C25. **Data for C3-keto compound, 25:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82-0.88 (m, 1H), 1.01 (s, 3H), 1.13 (d, *J* = 6.9, 3H), 1.15 (s, 2H), 1.17-1.20 (m, 1H), 1.22-1.24 (m, 2H), 1.24 (s, 3H), 1.25-1.26 (m, 1H), 1.27-1.31 (m, 1H), 1.36 (s, 3H), 1.42-1.49 (m, 1H), 1.79-1.90 (m, 1H), 1.92-1.99 (m, 1H), 2.03 (s, 2H), 2.06-2.21 (m, 2H), 2.25-2.32 (m, 2H), 2.52 (s, 1H), 2.63 (q, 1H), 3.32 (s, 3H), 3.15 (s, 3H), 3.39 (s, 2H), 4.72 (t, *J* = 1.8, 1H), 5.03 (s, 1H), 5.21 (dd, *J* = 5.2, 4.9, 1H), 5.78 (d, *J* = 9.7, 1H), 7.40-7.44 (m, 4H), 7.52-7.56 (m, 2H), 7.98 (d, *J* = 8.2, 2H), 8.02 (d, *J* = 8.4, 2H); LRMS (ESI) calcd for $C_{42}H_{53}O_{10}$ $[M+H]^+$ 717.36, found 717.33.

Data for C3-dimethylacetal $(OMe)_2$ compound, 25a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (s, 3H), 0.85-0.91 (m, 1H), 1.04-1.10 (m, 1H), 1.12 (d, *J* = 6.9, 3H), 1.16 (s, 2H), 1.20-1.23 (m, 2H), 1.24-1.28 (m, 7H), 1.34 (s, 3H), 1.54-1.63 (m, 1H), 1.76-1.86 (m, 2H), 1.89-1.97 (m, 2H), 2.04 (s, 1H), 2.10-2.18 (m, 1H), 2.38 (br, 1H), 2.53 (s, 1H), 2.64 (q, 1H), 2.73 (br, 1H), 3.08 (s, 3H), 3.16 (s, 3H), 3.32 (s, 3H), 3.40 (s, 2H), 4.73 (t, 1H), 5.03 (s, 1H), 5.21 (dd, J = 5.1, 5.0, 1H), 5.78 (d, J = 10.8, 1H), 7.40-7.44 (m, 4H), 7.51-7.55 (m, 2H), 7.98 (d, J = 7.6, 2H), 8.03 (d, J = 7.9, 2H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ 8.6, 11.3, 14.1, 14.7, 23.4, 27.2, 27.6, 28.1, 28.3, 29.6, 33.7, 34.6, 35.1, 36.1, 37.5, 41.8, 42.9, 47.3, 47.4, 48.8, 52.1, 53.8, 68.9, 70.1, 71.7, 75.3, 91.5, 93.8, 100.0, 109.9, 119.3, 128.1, 128.2, 129.4, 129.6, 130.1, 131.0, 132.5, 132.9, 153.5, 165.7, 166.2; LRMS (ESI) calcd for $C_{44}H_{59}O_{11}$ $[M+H]^+$ 763.40, found 763.37.

[§]The selectivity is 9.5*:1, C25 epi-natural* favoring the *'R'* configuration at C25, whereas, in another case the selectivity is 3.8:1, *C25 natural-epi* when the ligand was $(DHQD)_2$PYR and Na_2CO_3, K_3FeCN_6, (see Table 1 in the manuscript).

Synthesis of benzoate 26. To the diol (**25**, 164 mg, 0.25 mmol) in CH_2Cl_2 (10 mL) were added pyridine (2.5 mL), DMAP (5 mg, 0.025 mmol, 0.1 eq.) followed by benzoyl chloride (50 µL, 0.4 mmol, 1.5 eq.) under N_2 at room temperature and stirred for 16 h. After ensuring the disappearance of starting material via TLC (3:7 EtOAc/Hexane, R_f = 0.45), the solvent was removed under reduced pressure, and the crude product was purified by column chromatography on silica gel using EtOAc-Hexane to provide **26**, 0.123 g in 88% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.77-0.84 (m, 3H), 0.98 (s, 3H), 1.12 (d, J = 6.5, 3H), 1.21 (t, 5H), 1.26 (s, 4H), 1.32 (s, 3H), 1.37-1.45 (m, 1H), 1.83-1.88 (m, 1H), 1.91-1.97 (m, 3H), 2.02-2.07 (m, 1H), 2.14-2.28 (m, 4H), 2.53 (br, 1H), 2.62 (q, 1H), 3.30 (s, 3H), 4.19 (d, J = 4.2, 1H), 4.70 (t, J = 2.8, 1H), 5.00 (t, J = 3.9, 1H), 5.18 (dd, J = 5.5, 5.0, 1H), 5.87 (d, J = 8.6, 1H), 7.34-7.42 (m, 6H), 7.46-7.54 (m, 3H), 7.94-8.02 (m, 6H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ 8.5, 11.1, 14.1, 20.9, 23.8, 27.3, 28.0, 33.5, 35.9, 37.7, 37.8, 38.0, 44.2, 45.8, 48.8, 51.8, 53.4, 53.8, 60.3, 68.4, 70.7, 71.6, 74.9, 91.4, 93.7, 109.9, 119.8, 128.1, 128.2, 128.3, 129.4, 129.5, 129.6, 129.7, 129.8, 130.1, 130.9, 132.6, 132.8, 133.0, 152.8, 165.7, 165.8, 166.2, 171.1, 211.0; LRMS (ESI) calcd for $C_{49}H_{57}O_{11}$ $[M+H]^+$ 821.39, found 821.35.

Synthesis of spiroketal 27.[14] To **26** in CH_2Cl_2: MeOH (1:1, 10 mL) was added camphor sulfonic acid (CSA, 6 mg) at room temperature and the reaction was stirred for 4 h. H_2O (0.5 mL) was added and the reaction was stirred for another 1 h (to hydrolyze the C3-dimethylketal, **27a** to C3-ketone **27**). After removal of the solvent, the reaction was diluted by adding CH_2Cl_2 (10 mL) and H_2O (5 mL) and extracted with CH_2Cl_2 (10 mL x 3). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified on silica gel column chromatography to provide **27**[14] (3:7 EtOAc/Hexane, R_f = 0.55), 0.101 g and yield 85%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87-0.94 (m, 1H), 1.02 (s, 3H), 1.11 (d, J = 6.4, 3H), 1.23 (t, 3H), 1.30-1.36 (m, 3H), 1.38 (s, 3H), 1.42 (s, 3H), 1.46-1.51 (m, 1H), 1.81-1.83 (m, 1H), 1.89-1.95 (m, 2H), 2.04-2.13 (m, 3H), 2.19-2.23 (m, 1H), 2.25-2.30 (m, 2H), 2.33-2.37 (m, 1H), 2.60-2.65 (q, 1H), 4.33 (d, J = 11.0, 1H), 4.50 (d, J = 11.2, 1H), 4.82 (d, J = 2.2, 1H), 5.19 (dd, J = 4.9, 4.8, 1H), 5.38 (d, J = 7.7, 1H), 5.41 (t, J = 3.8, 1H), 7.37-7.45 (m, 7H), 7.50-7.56 (m, 2H), 7.95-8.0 (m, 3H), 8.06-8.10 (m, 3H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ 8.3, 11.1, 14.1, 14.8, 21.0, 25.1, 27.3, 28.2, 28.4, 33.8, 35.9, 37.8, 37.9, 38.2, 44.3, 45.5, 45.9, 51.7, 54.7, 60.3, 70.1, 72.9, 75.5, 79.6, 89.3, 93.3, 116.4, 121.2, 128.2, 128.3, 128.4, 128.5, 129.3, 129.4, 129.7, 130.0, 130.6, 132.8, 132.9, 133.3, 152.6, 165.7, 166.3, 211.1; LRMS (ESI) calcd for $C_{48}H_{53}O_{10}$ $[M+H]^+$ 789.36, found 789.32.

Synthesis of α-bromoketone 28. C3-ketone (**27**, 148 mg, 0.188 mmol) was dissolved in dry THF (3 mL) under N_2 and was cooled to -5°C. Phenyltrimethylammonium tribromide (PTAB, 70.5 mg, 0.188 mmol, 1 eq.) was added to the reaction in one portion while stirring. In about 5 minutes, the orange solution turned cloudy, and then turned to a light red color. The reaction mixture was stirred for an additional 15 minutes and then quenched with aq. $NaHSO_3$. The reaction was diluted and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was chromatographed on silica gel using EtOAc-Hexane to provide C2-bromide **28** (3:7 EtOAc/Hexane, R_f = 0.6), 142 mg in 84 yield %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93-1.00 (m, 1H), 1.11 (s, 8H), 1.24 (t, 1H), 1.30-1.36 (m, 1H), 1.38 (s, 3H), 1.42 (s, 3H), 1.44-1.50 (m, 1H), 1.57-1.66 (m, 1H), 1.74-1.87 (m, 2H), 2.04-2.11 (m, 1H), 2.29-2.38 (m, 2H), 2.39-2.44 (m, 2H), 2.54 (dd, J = 6.2, 6.4, 1H), 2.61 (q, 1H), 2.79 (br, 1H), 4.33 (d, J = 11.0, 1H), 4.59 (d, J = 10.9, 1H), 4.67 (dd, J = 6.0, 6.2, 1H), 4.80 (d, J = 2.3, 1H), 5.19 (dd, J = 5.1, 5.1, 1H), 5.38 (d, J = 7.3, 1H), 5.42 (t, 1H), 7.40-7.46 (m, 7H), 7.52-7.57 (m, 3H), 7.95-7.99 (m, 3H), 8.07-8.09 (m, 2H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ 8.3, 11.8, 14.1, 14.8, 21.0, 25.1, 27.3, 27.6, 28.2, 33.4, 38.2, 39.0, 43.5, 45.6, 45.7, 50.8, 51.3, 53.7, 54.7, 60.3, 70.0, 73.0, 75.2, 79.6, 89.3, 93.2, 116.4, 121.5, 128.2, 128.3, 128.5, 129.3, 129.4, 129.7, 130.0, 130.5, 132.9, 133.3, 133.4, 152.0, 165.7, 166.1, 163.3, 200.4; LRMS (ESI) calcd for $C_{48}H_{52}BrO_{10}$ $[M+H]^+$ 867.27, found 867.23.

Synthesis of α-azidoketone 29. C2-bromide (**28**, 142 mg, 0.164 mmol) was dissolved in dry nitromethane (12 mL, freshly distilled) under N_2 and cooled in an ice-water bath. A clear solution of tetramethyl guanidinium azide (TMGA, 103 mg, 0.66 mmol, 4.0 eq.) in nitromethane (3 mL) was added to the reaction mixture dropwise. After five minutes, the cooling bath was removed and the reaction was stirred at room temperature for 14 h. The reaction was quenched by adding brine, diluted and extracted with EtOAc (15 mL x 3). The combined organics were dried (Na_2SO_4), and concentrated under reduced pressure at room temperature. The crude product was subjected to chromatography on silica gel using EtOAc-Hexane to provide azide **29** (3:7 EtOAc/Hexane, $R_f = 0.5$) (C25 *epi: natural*, >9.5:1) favoring C25-*epi*, 110 mg and a yield of 81%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85-0.93 (m, 1H), 0.94-1.11 (s, 2H), 1.12 (s, 6H), 1.26 (t, 1H), 1.31-1.36 (m, 2H), 1.38 (s, 4H), 1.43 (s, 3H), 1.46-1.60 (m, 2H), 1.84-1.91 (m, 1H), 2.04-2.13 (m, 1H), 2.19-2.27 (m, 1H), 2.30 (d, *J* = 4.2, 1H), 2.32-2.40 (m, 2H), 2.58-2.67 (q, 1H), 2.75 (br, 1H), 3.93 (dd, *J* = 6.3, 6.1, 1H), 4.33 (d, *J* = 10.9, 1H), 4.50 (d, *J* = 11.0, 1H), 4.80 (d, *J* = 2.2, 1H), 5.19 (dd, *J* = 5.2, 5.0, 1H), 5.38 (t, 1H), 5.42 (s, 1H), 7.40-7.45 (m, 7H), 7.52-7.58 (m, 3H), 7.95-8.01 (m, 3H), 8.08-8.10 (m, 2H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ 8.3, 12.1, 14.1, 14.8, 20.9, 25.1, 27.3, 27.6, 28.2, 33.3, 37.1, 38.2, 43.3, 44.8, 45.6, 46.8, 51.4, 54.7, 60.3, 63.5, 70.0, 73.0, 75.2, 79.6, 89.3, 93.2, 116.4, 121.5, 128.2, 128.3, 128.4, 128.6, 129.3, 129.4, 129.5, 129.7, 130.0, 130.5, 132.8, 132.9, 133.3, 152.0, 165.7, 166.1, 166.2, 171.0, 204.5; LRMS (ESI) calcd for $C_{48}H_{52}N_3O_{10}$ $[M+H]^+$ 830.36, found 830.33.

Pyrazine formation – C12, 12', 23 & 26-tetra-O-Benzoyl protected 25-*epi* Ritterostatin G_N1_N (31). To the mixture of North G aminomethoxime **30** (17 mg, 0.029 mmol, 1.2 eq.) and North 1 azidoketone **29** (20 mg, 0.024 mmol, 1.0 eq.) in benzene (8 mL) were added polyvinyl pyridine, PVP (37 mg) and dichlorodibutylstannane (catalytic) at room temperature. The reaction flask was heated to 90°C using a Dean-Stark trap and continued for 4 h at this temperature under N_2. TLC (3:7 EtOAc/Hexane, $R_f = 0.4$) showed the non-polar ketoazide was almost absent. The reaction was filtered through a short plug of celite, the solvent was evaporated under reduced pressure and the crude mass was purified by silica gel column chromatography using EtOAc-Hexane to provide **31** (3:7 EtOAc/Hexane, $R_f = 0.4$), 18.3 mg in 58% yield. ^{1}H NMR (400 MHz,

$CDCl_3$): δ 0.83 (d, *J* = 6.7, 5H), 0.95 (d, *J* = 6.4, 2H), 1.11 (s, 9H), 1.25 (s, 1H), 1.26 (s, 3H), 1.34 (s, 3H), 1.39 (s, 3H), 1.42 (s, 7H), 1.65-1.74 (m, 8H), 1.92-2.01 (m, 6H), 2.02-2.07 (m, 1H), 2.10-2.20 (m, 3H), 2.32-2.40 (m, 2H), 2.46-2.64(m, 7H), 2.75-2.87 (m, 3H), 4.33 (d, *J* = 11.0, 1H), 4.49 (d, *J* = 11.0, 1H), 4.64 (dd, *J* = 4.4, 4.7, 1H), 4.82 (s, 1H), 4.96 (d, *J* = 8.2, 1H), 5.20 (dd, *J* = 5.2, 4.8, 1H), 5.39 (t, 1H), 5.44 (d, *J* = 2.1, 1H), 5.49 (d, *J* = 2.2, 1H), 7.40-7.46 (m, 8H), 7.52-7.56 (m, 4H), 7.95-8.05 (m, 6H), 8.09 (d, *J* = 8.1, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 8.3, 11.6, 11.7, 14.0, 14.6, 14.8, 25.1, 26.4, 26.9, 27.1, 27.6, 27.8, 28.3, 29.1, 29.9, 33.1, 33.7, 34.9, 35.0, 35.8, 35.9, 37.1, 38.1, 41.1, 41.2, 41.3, 45.5, 51.4, 51.7, 54.6, 55.8, 70.1, 72.8, 75.7, 79.5, 81.3, 81.9, 84.1, 89.4, 93.3, 108.6, 116.3, 117.2, 121.0, 121.3, 128.2, 128.3, 128.5, 129.3, 129.4, 129.7, 130.1, 130.6, 130.7, 132.7, 132.8, 132.9, 133.2, 148.1, 148.2, 148.3, 148.4, 152.7, 155.7, 165.3, 166.1, 166.2; HRMS (ESI) calcd for $C_{82}H_{93}N_2O_{13}$ $[M+H]^+$ 1313.6677, found 1313.6703.

Global deprotection of all OBz groups – Synthesis of 25-*epi* Ritterostatin G_N1_N, (5).[9] C-12, 12', 23, 26-tetra-O-benzoyl protected 25-*epi* ritterostatin G_N1_N (**31**, 15 mg, 0.0114 mmol) was dissolved in 1.5 mL of THF/MeOH/H_2O (2:2:1). NaOH (5.0 mg, 10 eq.) was added and the reaction was stirred for 12 h at room temperature. The solvent was evaporated under reduced pressure and the crude product was diluted, extracted with EtOAc (5 mL x 2) and CH_2Cl_2 (5 mL x 4). Combined organics dried over Na_2SO_4, concentrated and crude product was purified by flash chromatography on silica gel with 3% MeOH in CH_2Cl_2 to provide **5** as a colorless solid (10.1 mg, 98%), m.p 222-225 °C. R_f = 0.25 (2 % MeOH:EtOAc). ^1H NMR (400 MHz, $CDCl_3$): δ 0.83 (s, 3H), 0.85 (s, 3H), 0.87 (s, 1H), 0.95 (s, 1H), 0.97 (s, 1H), 0.99 (br, 2H), 1.06 (s, 6H), 1.09 (d, *J* = 6.8, 3H), 1.15 (s, 4H), 1.18 (s, 3H), 1.19 (s, 3H), 1.23-1.28 (t, 2H), 1.50-1.65 (m, 5H), 1.68-1.75 (m, 3H), 1.80-1.88 (m, 3H), 1.90-1.95 (m, 3H), 1.97-2.10 (m, 3H), 2.31-2.41 (m

2H), 2.43-2.48 (m, 2H), 2.49-2.55 (m, 4H), 2.59 (d, *J* = 5.6, 1H), 2.60 (s, 1H), 2.63 (s, 1H), 2.78 (d, *J* = 4.8, 1H), 2.82 (d, *J* = 5.6, 1H), 2.85 (s, 1H), 2.90 (s, 1H), 3.24 (dd, *J* = 16.0, 7.8, 1H), 3.32 (m, 1H), 3.55 (d, *J* = 12.0, 1H), 3.62 (d, *J* = 12.0, 1H), 3.82-3.86 (m, 1H), 3.99 (br, 1H), 4.18 (m, 1H), 4.69 (s, 1H), 4.81 (s, 1H), 4.93 (d, *J* = 8.2, 1H), 5.35 (s, 1H), 5.39 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 8.5, 11.6, 11.7, 11.9, 13.3, 13.9, 14.0, 20.6, 22.5, 24.4, 25.2, 27.7, 27.8, 27.9, 28.0, 28.2, 28.4, 28.7, 28.9, 29.1, 29.6, 29.8, 30.0, 31.5, 34.5, 35.9, 36.0, 37.1, 41.2, 45.3, 45.4, 52.0, 52.7, 54.7, 55.7, 67.9, 70.8, 75.0, 78.6, 81.9, 82.6, 84.2, 91.7, 92.7, 116.0, 117.4, 119.8, 120.6, 147.9, 148.3, 148.5, 148.6, 153.1, 156.9; HRMS (ESI) calcd for $C_{54}H_{77}N_2O_9$ $[M+H]^+$ 897.5629, found 897.5615.

ASSOCIATED CONTENT

Supporting Information. Copies of all NMR (^1H, ^{13}C and ^{19}F) spectra, x-ray data and NCI 60 cell line full data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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