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Synthesis and antiproliferative evaluation of new zampanolide mimics†

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Abstract

(–)-Zampanolide is a marine microtubule-stabilizing macrolide that has been shown by *in vitro* experiments to be a promising anticancer lead compound. Through its unique covalent-binding with β -tubulin, zampanolide exhibits cytotoxic potency towards multi-drug resistant cancer cells that is superior to paclitaxel. However, the limited availability of zampanolide impedes its further *in vivo* evaluation as a viable drug candidate. Zampanolide is envisioned to become more drug-like if its chemically fragile side chain can be stabilized; hence, this project aims to develop mimics of zampanolide with a stable side chain using straightforward synthetic methods. To this end, twelve novel zampanolide mimics (**51–62**) with conjugated and planar side chains have been synthesized via a 24-step sequence for each mimic from commercially available 2-butyne-1-ol as starting material. A Horner-Wadsworth-Emmons reaction incorporates the α,β -unsaturated ketone side chain and also closes the core macrocycle. WST-1 cell proliferation assays in three docetaxel-sensitive and two docetaxel-resistant human prostate cancer cell models confirm that a suitably designed side chain can serve as a bioisostere for the *N*-acyl hemiaminal side chain in zampanolide. Mimic **52** with a 17*R* chiral center was identified as the optimal candidate with IC₅₀ values of 0.29–0.46 μ M against both docetaxel-sensitive (PC-3 and DU145) and docetaxel-resistant prostate cancer cell lines (PC-3/DTX and DU145/DTX). Zampanolide mimic **52** exhibited equivalent antiproliferative potency towards both docetaxel-sensitive and docetaxel-resistant cell lines, with relative resistance in the range of 0.9–1.6.

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Conflicts of interest

There are no conflicts to declare.

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Keywords

Natural product; zampanolide; prostate cancer; docetaxel-resistant cell

Introduction

Prostate cancer has the highest incidence and the second highest mortality rate of all cancers in American men.¹ Approximately 30,000 US men die each year of castration-resistant prostate cancer (CRPC) due to progression of resistance to the current treatments. Two microtubule-stabilizing cytotoxic agents (MSA), docetaxel and cabazitaxel, are the only chemotherapeutic agents that show a survival benefit for patients with prostate cancer. Currently, they are standard first-line and second-line treatments for CRPC.^{2–4} Two mechanisms responsible for the action of MSAs as anti-prostate cancer agents are (1) promotion of mitotic arrest, and (2) suppression of nuclear accumulation of androgen receptor that is the driving force for prostate cancer cell growth and progression.^{5–6}

The marine macrolide (–)-zampanolide (**1**, Fig. 1)⁷ is a unique MSA with covalent-binding to β -tubulin and low nanomolar cytotoxic potency against multi-drug resistant cancers.⁸ Its mechanism of action is similar to that of the clinically proven drug paclitaxel (Taxol®) and its sister drugs docetaxel and cabazitaxel which bind to the taxane luminal pocket of β -tubulin.⁹ However, the covalent nature of zampanolide binding to tubulin distinguishes it from paclitaxel which involves non-covalent binding to β -tubulin. A 1.8 Å high-resolution crystal structure of α,β -tubulin in complex with (–)-zampanolide (**1**) established that the macrolide binds covalently at residues Asn228 and His229 at the taxane luminal site.¹⁰ (–)-zampanolide (**1**) is therefore an extremely promising drug candidate and/or lead compound for clinical treatment of both drug-sensitive and resistant prostate cancer. This expectation is based on the fact that covalently bound agents in contrast to their non-covalently bound counterparts are effective in P-glycoprotein overexpressing cells because (1) they cannot be pumped out of the cell after they bind, and (2) they are not affected by upregulation of tubulin isotypes or by mutations in tubulin.¹¹

Although (–)-zampanolide is a unique and promising MSA that opens new routes to more effective chemotherapeutics for CRPC, this important lead compound needs further investigation of its *in vivo* anticancer efficacy, pharmacokinetics, and toxicity, in order to guide the compound towards a clinical chemotherapeutic. Unfortunately, the limited supply of (–)-zampanolide creates a serious obstacle for its further evaluation as a viable drug candidate. (–)-zampanolide was isolated from marine sponge sources in only 0.001% yield

at best^{8,12} and its syntheses proceed with a highest overall yield at barely 0.9%.^{13–19} Equally important is the probability that zampanolide will possess poor pharmacokinetic profiles as a drug candidate, due in part to its chemically fragile side chain. Thus, Smith and co-workers reported that synthetic (+)-zampanolide (**7**) decomposed at 85 °C into (+)-dactylolide (**8**) by cleavage of the *N*-acetyl hemiaminal side chain (Scheme 1)¹⁵ and Higa and co-workers described the instability of (–)-zampanolide in CDCl₃ when they initially characterized its structure.¹² Furthermore, four synthetic approaches to zampanolide encountered difficulties in assembling the *N*-acyl hemiaminal side chain of the molecule.^{13,15–18} The *N*-acyl hemiaminal side chain of **1** is critical for its nanomolar antiproliferative potency in certain cell models, and removal of the side chain results in a loss of 10- to 1000-fold potency in those cell models.^{8,9,20} This report describes the synthesis and antiproliferative evaluation of zampanolide mimics in which the *N*-acyl hemiaminal side chain is replaced by more stable and easily accessible planar and conjugated appendages (**6**, Fig. 2).

Results and Discussion

Design of zampanolide mimics

Our set of side chains was inspired by the fact that the side chains of (–)-zampanolide (**1**) and epothilone A (**2**) bind to the same M-loop of β -tubulin (Fig. 3). Six side chains with different aromatic rings were selected as bioisosteric substitutions for the zampanolide *N*-acyl hemiaminal side chain and were designed to have the chemically unstable hemiaminal moiety (blue circle in Fig. 3) replaced by an α,β -unsaturated ketone. Since the epothilone side chain (Fig. 3) does not contain a hydroxyl substituent, the C20 alcohol of zampanolide is removed to afford a more facile synthesis. The carbonyl oxygen of the zampanolide side chain is preserved in order to retain hydrogen bonding to the NH group of Thr276 in β -tubulin and the conjugated *E,Z*-pentadiene moiety of zampanolide is replaced by planar benzenoid and heteroaromatic rings to retain hydrophobic contacts between the mimic side chain and residues in the M-loop of β -tubulin. For the macrolactone core, we have adopted Altmann's (17*S*)-desTHPdactylolide (**4**) and its (17*R*)-enantiomer (**5**) as our template on the ground that desTHP-zampanolide (**3**) in which the tetrahydropyran subunit is replaced by a direct ether linkage, exhibits submicromolar activity.¹⁸ This simplification which removes two stereogenic centers enables a more practical synthesis of our mimics. A generalized structure (**6**) representing our target mimics is shown in Fig. 2.

Synthesis

Our synthetic strategy envisioned attachment of side chains to (17*S*) and (17*R*) aldehydes **13** and **14** prior to closure of the macrolactone by intramolecular Horner-Wadsworth-Emmons (HWE) condensation since this would avoid potential interference by latent functional groups within the ester framework (Scheme 2). Esters **9** and **10** have been previously synthesized by us from commercially available 2-butyne-1-ol via a 17-step sequence²¹ and were used as source materials for **13** and **14**. As shown in Scheme 2, debenzoylation of *p*-methoxybenzyl ethers **9** and **10** with DDQ followed by oxidation of the resulting primary alcohols **11** and **12** with Dess-Martin periodinane (DMP) yielded aldehydes **13** and **14** in an overall 48% yield.

Commercially available methyl aryl carboxylates **15-20** were used as starting materials to prepare six keto phosphonates **21-26** (Scheme 3). Treatment of the carboxylates with the lithium anion of diethyl methyl phosphonate, obtained by exposure of the phosphonate to *n*-butyllithium in THF, gave the keto phosphonates in 50–99% yield as illustrated in Scheme 3. In order to avoid a difficult separation of the keto phosphonate products **21-26** from unreacted diethyl methyl phosphonate, it was necessary to restrict the quantity of the latter reagent to no more than 1.2 equivalents. Horner-Wadsworth-Emmons (HWE) condensation of each keto phosphonate with aldehydes **13** and **14** gave *trans* α,β -unsaturated ketones **27-38** containing six terminal aryl units represented as Ar1-Ar6 (Scheme 4). Since extractive work-up of these reactions resulted in partial hydrolysis of the ester, the reaction mixture in each case was filtered through a pad of anhydrous sodium sulfate and silica gel which was rinsed with THF. The crude product was then purified by preparative-layer TLC. Global deprotection of bis-TBS ethers **27-38** with HF-pyridine complex furnished diols **39-50** which were oxidized with Dess-Martin periodinane to the corresponding keto aldehydes. Since chromatographic purification of these keto aldehydes caused significant decomposition, they were used directly in an intramolecular HWE condensation mediated by Ba(OH)₂ to produce zampanolide mimics **51-62**. As with ketones **27-38**, extractive work-up again caused partial hydrolysis of the ester and purification of **51-62** was therefore carried out as before by filtration followed by preparative TLC.

Anti-proliferative activity towards prostate cancer cell lines and structure-activity relationships.

The anti-proliferative activity of twelve zampanolide mimics (**51-62**, six pairs of enantiomers) has been evaluated in three docetaxel-sensitive prostate-cancer cell lines (PC-3, DU145, and LNCaP) and two docetaxel-resistant prostate cancer cell lines (PC-3/DTX and DU145/DTX) using the WST-1 cell proliferation assay with docetaxel as a positive control. As illustrated in Table 1, the IC₅₀ values for our twelve zampanolide mimics are in the range of 0.29–5.59 μ M. These values are smaller than those of desTHPdactylolides **4** and **5**, suggesting that the side chain can make a significant contribution to the potency of this group of compounds. Mimics **51** and **52** are the optimal mimics with IC₅₀ values of 0.29–0.86 μ M towards docetaxel-sensitive prostate cancer cell lines (PC-3, DU145, and LNCaP). It is noteworthy that our (17*S*) zampanolide mimic **51** has potency similar to the known zampanolide analog (**3**),¹⁸ with mimic **51** showing about 13–18 times increased potency against three docetaxel-sensitive prostate cancer cell lines and **3** exhibiting 18-fold greater potency towards PC-3 cells compared to (17*S*) desTHPdactylolide (**4**) (Fig. 4). This indicates that an appropriately designed side chain can serve as a bioisostere for the chemically unstable *N*-acetyl hemiaminal side chain of zampanolide. Interestingly, inversion of the C17 chiral center of **51** as its (17*R*)-enantiomer **52** resulted in significantly improved potency towards five human prostate cancer cell lines, especially against docetaxel-resistant cell lines. Compound **52** was therefore identified as the optimal mimic with IC₅₀ values of 0.29–0.46 μ M against both docetaxel-sensitive (PC-3 and DU145) and docetaxel-resistant prostate cancer cell lines (PC-3/DTX and DU145/DTX). The relative resistance of PC-3/DTX over PC-3 is 0.9 while the relative resistance of DU145/DTX over DU145 is 1.6.

Effects of **52** on PC-3 cell apoptosis

The F2N12S and SYTOX AADvanced double staining assay in a flow cytometer was used for discrimination between early apoptotic PC-3 cells and late apoptotic/necrotic PC-3 cells when treated with **52** at 0, 1, 5, 10, 20, 30, 50, and 100 μM concentrations for 16 h. As shown in Fig. 5, mimic **52** can significantly induce apoptotic cell death in the androgen-insensitive PC-3 prostate cancer cell line in a dose-dependent manner after a 16-h treatment. Specifically, treatment of **52** at 1–10 μM led to 13–18% of PC-3 cells in the early phase of apoptosis as compared with control cells; exposure of PC-3 cells to **52** at 20–50 μM induces 43–51% early apoptotic cells together with 9–16% late apoptotic/necrotic cells.

Conclusion

In summary, twelve new zampanolide mimics with different planar and conjugated side chains have been synthesized via a 24-step sequence for each mimic starting from commercially available 2-butyne-1-ol. Horner-Wadsworth-Emmons reactions were used for incorporating the stable mimic side chains and for closing the macrolactone ring. All mimics showed greater potency than desTHPdactylolide in both docetaxel-sensitive and docetaxel-resistant prostate cancer cell lines, suggesting that the planar, conjugated side chains of these compounds do make a significant contribution to their potency. Our findings indicate that an appropriately designed side chain can serve as a bioisostere for the chemically unstable *N*-acetyl hemiaminal side chain in (–)-zampanolide. The IC_{50} values of the optimal mimic **52** fall in the range 0.29–0.46 μM against both docetaxel-sensitive (PC-3 and DU145) and docetaxel-resistant prostate cancer cell lines (PC-3/DTX and DU145/DTX). The relative resistance of **52** towards docetaxel-resistant prostate cancer cell lines falls in the range 0.9–1.6.

Experimental section

General information

Optical rotations were measured on a RUDOLPH Research Analytical Autopol III Automatic Polarimeter. IR spectra were recorded on a Nicolet Nexus 470 FTIR spectrophotometer. HRMS were obtained on an Orbitrap mass spectrometer with electrospray ionization (ESI). NMR spectra were obtained on a Bruker Fourier 300 spectrometer in CDCl_3 . The chemical shifts are given in ppm referenced to the respective solvent peak, and coupling constants are reported in Hz. Anhydrous THF and dichloromethane were purified by a PureSolv MD 7 Solvent Purification System from Innovative Technologies (MB-SPS-800). All other reagents and solvents were purchased from commercial sources and were used without further purification. Silica gel column chromatography was performed using silica gel (32–63 μm). Preparative thin-layer chromatography (PTLC) separations were carried out on thin layer chromatography plates loaded with silica gel 60 GF254 (EMD Millipore Corporation). Starting materials **9** and **10** were synthesized using the procedure previously described by us.²¹

General procedure for the synthesis of diethyl (2-oxo-2-arylethyl)phosphonates (21-26)

To a solution of diethyl methyl phosphonate (182 mg, 1.2 mmol) in anhydrous THF (2.5 mL) at -78°C was added dropwise *n*-butyllithium (0.48 mL, 2.5 M, 1.2 mmol), and the solution was stirred at -78°C for 30 min prior to addition of a solution of the relevant methyl arylcarboxylate in anhydrous THF (1 mL). The resulting mixture was stirred at -78°C for an additional 5 h before being quenched with saturated ammonium chloride (20 mL). The mixture was extracted with ethyl acetate (10 mL $\times$ 3), and the combined organic extract was dried over anhydrous sodium sulfate and was concentrated *in vacuo*. The crude product was subjected to PTLC purification, eluting with dichloromethane/methanol (95:5) three times, and the pure compound was retrieved from PTLC silica gel by extraction with acetone. Characterization, yield and NMR data for each product are given below:

Diethyl (2-(1-methyl-1*H*-imidazol-5-yl)-2-oxoethyl)phosphonate (21).

Pale yellow oil; 64% yield. ^1H NMR (300 MHz, CDCl_3) δ 7.97 (s, 1H, imidazole-H), 7.26 (overlapped, 1H, imidazole-H), 4.22–4.12 (m, 4H, $2 \times \text{OCH}_2\text{CH}_3$), 4.00 (s, 3H, *N*- CH_3), 3.45 (d, $J = 22.5$ Hz, 2H, COCH_2PO), 1.33 (t, $J = 6.9$ Hz, 6H, $2 \times \text{OCH}_2\text{CH}_3$). ^{13}C NMR (75 MHz, CDCl_3) δ 181.8 (d, $J = 6.8$ Hz), 144.1, 140.4, 130.8, 62.8 (d, $J = 6.0$ Hz), 39.9 (d, $J = 127.5$ Hz), 35.1, 16.5 (d, $J = 6.0$ Hz).

Diethyl (2-(oxazol-4-yl)-2-oxoethyl)phosphonate (22).

Pale yellow oil; 70% yield. ^1H NMR (300 MHz, CDCl_3) δ 8.31 (d, $J = 0.9$ Hz, 1H, oxazole-H), 7.89 (d, $J = 0.6$ Hz, 1H, oxazole), 4.11 (q, $J = 7.2$ Hz, 2H, $1 \times \text{OCH}_2\text{CH}_3$), 4.09 (q, $J = 7.2$ Hz, 2H, $1 \times \text{OCH}_2\text{CH}_3$), 3.58 (d, $J = 22.8$ Hz, 2H, COCH_2PO), 1.24 (t, $J = 7.2$ Hz, 6H, $2 \times \text{OCH}_2\text{CH}_3$). ^{13}C NMR (75 MHz, CDCl_3) δ 186.8 (d, $J = 6.8$ Hz), 151.6, 144.1, 140.7 (d, $J = 2.3$ Hz), 63.3 (d, $J = 6.0$ Hz), 39.5 (d, $J = 128.3$ Hz), 16.8 (d, $J = 6.3$ Hz).

Diethyl (2-oxo-2-phenylethyl)phosphonate (23).

Colorless oil; 50% yield. ^1H NMR (300 MHz, CDCl_3) δ 8.01 (d, $J = 7.2$ Hz, 2H, phenyl-H), 7.59 (tt, $J = 7.2, 1.5$ Hz, 1H, phenyl-H), 7.48 (t, $J = 7.8$ Hz, 2H, phenyl-H), 4.15 (q, $J = 7.2$ Hz, 2H, $1 \times \text{OCH}_2\text{CH}_3$), 4.12 (q, $J = 7.2$ Hz, 2H, $1 \times \text{OCH}_2\text{CH}_3$), 3.63 (d, $J = 22.8$ Hz, COCH_2PO), 1.28 (t, $J = 7.2$ Hz, 6H, $2 \times \text{OCH}_2\text{CH}_3$). ^{13}C NMR (75 MHz, CDCl_3) δ 192.0, 136.6, 133.7, 129.1, 128.6, 62.7 (d, $J = 6.0$ Hz), 38.5 (d, $J = 135$ Hz), 16.3, 16.2.

Diethyl (2-oxo-2-(4-fluorophenyl)ethyl)phosphonate (24).

Colorless oil; 86% yield. ^1H NMR (300 MHz, CDCl_3) δ 8.06 (dd, $J = 9.0, 5.4$ Hz, 2H, phenyl-H), 7.15 (t, $J = 9.0$ Hz, 2H, phenyl-H), 4.18–4.09 (m, 4H, $2 \times \text{OCH}_2\text{CH}_3$), 3.60 (d, $J = 22.8$ Hz, 2H, COCH_2PO), 1.29 (t, $J = 7.2$ Hz, 6H, $2 \times \text{OCH}_2\text{CH}_3$). ^{13}C NMR (75 MHz, CDCl_3) δ 190.4 (d, $J = 6.8$ Hz), 166.1 (d, $J = 255$ Hz), 133.0, 131.9 (d, $J = 3.0$ Hz), 115.8 (d, $J = 21.8$ Hz), 62.8 (d, $J = 6.8$ Hz), 38.7 (d, $J = 129$ Hz), 16.3 (d, $J = 6.0$ Hz).

Diethyl (2-oxo-2-(2-fluorophenyl)ethyl)phosphonate (25).

Colorless oil; 86% yield. ^1H NMR (300 MHz, CDCl_3) δ 7.88 (dt, $J = 7.8, 2.1$ Hz, 1H, phenyl-H), 7.60–7.52 (m, 1H, phenyl-H), 7.28–7.22 (m, 1H, phenyl-H), 7.17 (dt, $J = 8.1, 0.9$ Hz, 1H, phenyl-H), 4.19–4.10 (m, 4H, $2 \times \text{OCH}_2\text{CH}_3$), 3.73 (dd, $J = 22.2, 1.2$ Hz, 2H,

COCH₂PO), 1.28 (t, *J* = 6.9 Hz, 6H, 2 × OCH₂CH₃). ¹³C NMR (75 MHz, CDCl₃) δ 189.9 (dd, *J* = 7.5, 3.0 Hz), 161.8 (d, *J* = 247.5 Hz), 135.2 (d, *J* = 9.0 Hz), 131.0, 125.5 (dd, *J* = 11.3, 2.3 Hz), 124.5 (d, *J* = 3.8 Hz), 116.6 (d, *J* = 24.0 Hz), 62.5 (d, *J* = 6.0 Hz), 42.4 (dd, *J* = 129.8, 8.3 Hz), 16.2 (d, *J* = 6.0 Hz).

Diethyl (2-oxo-2-(3-fluorophenyl)ethyl)phosphonate (26).

Colorless oil; 99% yield. ¹H NMR (300 MHz, CDCl₃) δ 7.81 (ddd, *J* = 7.5, 1.5, 0.9 Hz, 1H, phenyl-H), 7.70 (ddd, *J* = 9.3, 2.4, 1.8 Hz, 1H, phenyl-H), 7.47 (dt, *J* = 8.1, 5.4 Hz, 1H, phenyl-H), 7.29 (ddt, *J* = 8.4, 2.7, 1.2 Hz, 1H, phenyl-H), 4.20–4.09 (m, 4H, 2 × OCH₂CH₃), 3.51 (d, *J* = 22.8 Hz, 2H, COCH₂PO), 1.29 (t, *J* = 7.2 Hz, 6H, 2 × OCH₂CH₃). ¹³C NMR (75 MHz, CDCl₃) δ 190.8 (dd, *J* = 6.8, 2.3 Hz), 162.8 (d, *J* = 246.8 Hz), 138.6 (dd, *J* = 6.2, 1.7 Hz), 130.4 (d, *J* = 7.5 Hz), 125.0 (d, *J* = 3.0 Hz), 120.8 (d, *J* = 22.5 Hz), 115.7 (d, *J* = 22.5 Hz), 62.8 (d, *J* = 6.8 Hz), 38.8 (d, *J* = 129.0 Hz), 16.3 (d, *J* = 6.0 Hz).

Synthesis of alcohols 11 and 12

To a solution of **9** (99 mg, 0.12 mmol) in dichloromethane (3 mL) was added water (0.6 mL) followed by 2,3-dichloro-5,6-cyano-1,4-benzoquinone (54 mg, 0.24 mmol), and the reaction mixture was stirred vigorously at room temperature for 1 h before being quenched by saturated aqueous sodium bicarbonate (20 mL). The mixture was extracted with dichloromethane (20 mL × 3), and the combined organic extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was purified by PTLC, using hexane/ethyl acetate (1:1) as eluent, to yield pure **11** as a colorless oil in 74% yield. ¹H NMR (300 MHz, CDCl₃) δ 7.81 (7.79) (dd, *J* = 16.2, 11.7 Hz, 1H, H-3), 6.07 (6.03) (d, *J* = 12.0 Hz, 1H, H-4), 5.70 (d, *J* = 15.0 Hz, 1H, H-2), 5.39 (t, *J* = 6.6 Hz, 1H, H-14), 5.06–4.95 (m, 1H, H-17), 4.17–3.99 (m, 5H, 2 × OCH₂CH₃ & H-7), 3.94 (d, *J* = 6.6 Hz, 2H, H₂-13), 3.80–3.59 (m, 2H, H₂-18), 3.68 (t, *J* = 6.3 Hz, 2H, H₂-11), 3.44 (t, *J* = 6.3 Hz, 2H, H₂-9), 2.98 (2.72) (dd, *J* = 13.5, 3.0 Hz, 1H, H-16), 2.59 (2.43) (dd, *J* = 13.5, 7.2 Hz, 1H, H-16), 2.43–2.23 (m, 2H, H₂-8), 2.06–1.89 (m, 2H, H₂-6), 1.94 (1.93) (s, 3H, 5-CH₃), 1.80–1.72 (m, 2H, H₂-10), 1.74 (s, 3H, 15-CH₃), 1.33 (t, *J* = 6.9 Hz, 6H, 2 × OCH₂CH₃), 0.88 (s, 9H, TBS), 0.86 (s, 9H, TBS), 0.06 (0.05) (s, 3H, TBS), 0.04 (s, 6H, TBS), 0.02 (0.01) (s, 3H, TBS). ¹³C NMR (75 MHz, CDCl₃) δ 167.2, 147.5 (147.1), 141.7 (141.4), 135.6, 126.9 (126.3), 125.0, 119.9 (119.8), 73.6 (73.5), 68.7 (67.9), 67.3, 67.0, 63.7 (63.6), 62.0, 60.2, 41.1 (d, *J* = 36.8 Hz), 40.6, 34.8 (34.3) (d, *J* = 135.0 Hz), 26.6 (26.3), 26.1, 25.9 (25.8), 18.5 (18.0), 16.8, 16.6 (16.5), 16.4 (16.5), –3.4 (–4.7), –4.8 (–5.2).

Antipode **12** was prepared from **10** in a similar way as a colorless oil in 83% yield. ¹H NMR (300 MHz, CDCl₃) δ 7.84 (7.82) (dd, *J* = 15.0, 11.7 Hz, 1H, H-3), 6.07 (6.05) (d, *J* = 12.0 Hz, 1H, H-4), 5.72 (d, *J* = 15.3 Hz, 1H, H-2), 5.41 (t, *J* = 6.6 Hz, 1H, H-14), 5.06–4.97 (m, 1H, H-17), 4.21–3.92 (m, 5H, 2 × OCH₂CH₃ & H-7), 3.93 (d, *J* = 6.6 Hz, 2H, H₂-13), 3.81–3.57 (m, 2H, H₂-18), 3.68 (t, *J* = 6.3 Hz, 2H, H₂-11), 3.45 (t, *J* = 6.6 Hz, 2H, H₂-9), 2.97 (2.71) (dd, *J* = 13.5, 3.3 Hz, 1H, H-16), 2.58 (2.42) (dd, *J* = 13.2, 6.9 Hz, 1H, H-16), 2.42–2.22 (m, 2H, H₂-8), 2.05–1.88 (m, 2H, H₂-6), 1.94 (1.92) (s, 3H, 5-CH₃), 1.83–1.71 (m, 2H, H₂-10), 1.73 (s, 3H, 15-CH₃), 1.33 (1.32) (t, *J* = 6.9 Hz, 6H, 2 × OCH₂CH₃), 0.88 (s, 9H, TBS), 0.86 (s, 9H, TBS), 0.06 (0.04) (s, 3H, TBS), 0.03 (s, 6H, TBS), 0.01 (–0.02) (s, 3H, TBS). ¹³C NMR (75 MHz, CDCl₃) δ 167.2, 147.6 (147.2), 141.8 (141.5), 135.6, 126.9

(126.3), 125.0, 112.0 (119.8), 73.64 (73.59), 68.8 (68.0), 67.4, 67.0, 63.7, 61.9, 60.2, 41.2 (d, $J = 37.5$ Hz), 40.7 (40.6), 34.8 (34.3) (d, $J = 135.0$ Hz), 26.6 (26.4), 26.1, 25.9 (25.8), 18.5 (18.0), 16.8, 16.6 (16.5), 16.4 (16.5), -4.65 (-4.69), -4.7 (-5.2).

Synthesis of aldehydes (17S) **13** and (17R) **14**

To a solution of **11** (134 mg, 0.19 mmol) in dichloromethane (2 mL) at room temperature was added Dess-Martin periodinane (118 mg, 0.28 mmol) and the reaction mixture was stirred for 10 min after which a second portion of Dess-Martin periodinane (118 mg, 0.28 mmol) was added. The resulting mixture was stirred for an additional 30 min, and saturated sodium bicarbonate (8 mL) and saturated sodium thiosulfate (8 mL) were added. The suspension was stirred for 15 min and was extracted with dichloromethane (10 mL $\times$ 3). The combined organic extracts were dried over anhydrous sodium sulfate and the dried extract was concentrated under vacuum. The crude product was subjected to PTLC purification, eluting with hexane/ethyl acetate (40:60, v/v), to give pure **13** as a pale yellow oil in 74% yield. ^1H NMR (300 MHz, CDCl_3) δ 9.55 (d, $J = 6.3$ Hz, 1H, H-18), 7.67 (dd, $J = 15.0, 11.7$ Hz, H-3), 6.11 (d, $J = 11.1$ Hz, 1H, H-4), 5.84 (d, $J = 15.0$ Hz, 1H, H-2), 5.45 (t, $J = 6.3$ Hz, 1H, H-14), 5.19–5.13 (m, 1H, H-17), 4.18–4.06 (m, 5H, $2 \times \text{OCH}_2\text{CH}_3$ & H-7), 3.96 (d, $J = 6.3$ Hz, 2H, H₂-13), 3.68 (t, $J = 6.3$ Hz, 2H, H₂-11), 3.47 (t, $J = 6.3$ Hz, 2H, H₂-9), 2.61–2.42 (m, 4H, H₂-16 & H₂-8), 2.05–1.97 (m, 2H, H₂-6), 1.92 (s, 3H, 5-CH₃), 1.81–1.74 (m, 2H, H₂-10), 1.72 (s, 3H, 15-CH₃), 1.33 (t, $J = 6.0$ Hz, 6H, $2 \times \text{OCH}_2\text{CH}_3$), 0.89 (s, 9H, TBS), 0.83 (s, 9H, TBS), 0.05 (s, 3H, TBS), 0.04 (s, 6H, TBS), -0.03 (s, 3H, TBS). ^{13}C NMR (75 MHz, CDCl_3) δ 198.8, 167.0 (166.9), 148.0 (147.9), 143.2, 133.6, 126.6, 126.1, 117.9, 76.53 (76.49), 67.2, 67.1, 67.0 (66.9), 61.9 (61.8), 60.1, 41.8, 39.1, 36.3, 34.5, 33.1, 26.1, 25.9, 18.0, 16.8, 16.63 (16.55), -4.59 (-4.66), -5.20.

Antipode **14** was prepared from **12** in a similar way as a colorless oil in 80% yield. ^1H NMR (300 MHz, CDCl_3) δ 9.52 (d, $J = 2.1$ Hz, 1H, H-18), 7.64 (dd, $J = 15.0, 11.7$ Hz, H-3), 6.08 (d, $J = 11.7$ Hz, 1H, H-4), 5.81 (d, $J = 15.0$ Hz, 1H, H-2), 5.43 (t, $J = 6.6$ Hz, 1H, H-14), 5.16–5.11 (m, 1H, H-17), 4.15–4.02 (m, 5H, $2 \times \text{OCH}_2\text{CH}_3$ & H-7), 3.93 (d, $J = 6.6$ Hz, 2H, H₂-13), 3.65 (t, $J = 6.3$ Hz, 2H, H₂-11), 3.44 (t, $J = 6.3$ Hz, 2H, H₂-9), 2.61–2.39 (m, 4H, H₂-16 & H₂-8), 2.02–1.92 (m, 2H, H₂-6), 1.89 (s, 3H, 5-CH₃), 1.73 (quin, $J = 6.3$ Hz, 2H, H₂-10), 1.69 (s, 3H, 15-CH₃), 1.30 (t, $J = 6.9$ Hz, 6H, $2 \times \text{OCH}_2\text{CH}_3$), 0.86 (s, 9H, TBS), 0.80 (s, 9H, TBS), 0.03 (s, 3H, TBS), 0.01 (s, 6H, TBS), -0.06 (s, 3H, TBS). ^{13}C NMR (75 MHz, CDCl_3) δ 198.8 (198.7), 166.9 (166.8), 148.0 (147.9), 143.1, 133.5, 126.6, 126.1, 117.9, 76.5 (76.4), 67.2, 67.1, 67.0 (66.9), 61.8 (61.7), 60.1, 41.8, 39.1, 36.3, 34.5, 33.1, 26.1, 25.9, 18.0 (17.9), 16.8, 16.62 (16.54), -4.611 (-4.69), -5.2.

General procedure for synthesis of α,β -unsaturated ketones **27–38**

To a solution of the relevant diethyl (2-oxo-2-arylethyl)phosphonate (0.11 mmol, **21–26**) in THF (0.4 mL) and water (16 μL) was added activated barium hydroxide (18.4 mg, 0.10 mmol). After stirring the mixture for 15 min at 0 $^\circ\text{C}$, aldehyde **13** or **14** (60 mg, 0.083 mmol) in THF (0.4 mL) was added dropwise to the solution. The ice-bath was removed after 30 min and the reaction was allowed to proceed with stirring at room temperature for 2.5 h. The reaction mixture was filtered through a pad of anhydrous sodium sulfate and silica gel which was rinsed with THF. The filtrate was concentrated under vacuum to give the crude

product which was subjected to PTLC purification, using dichloromethane/methanol (95/5, v/v) as eluent, to give pure product. Characterization, yield and NMR data for each product are given below:

(17S) Di-TBS ether 27.—Pale yellow oil, 73.5% yield. ^1H NMR (300 MHz, CDCl_3) δ 8.30 (s, 1H, imidazole-H), 7.92 (s, 1H, imidazole-H), 7.65 (dd, J = 14.4, 11.7 Hz, 1H, H-3), 7.02 (7.01) (dd, J = 15.3 Hz, 1H, H-19), 6.75 (dd, J = 15.0, 4.2 Hz, 1H, H-18), 6.12 (d, J = 11.7 Hz, 1H, H-4), 5.83 (d, J = 15.0 Hz, 1H, H-2), 5.75–5.68 (m, 1H, H-17), 5.45 (t, J = 6.3 Hz, H-14), 4.16–4.03 (m, 5H, $2 \times \text{OCH}_2\text{CH}_3$ & H-7), 4.06 (s, 3H, $N\text{-CH}_3$), 3.95 (d, J = 6.6 Hz, 2H, H₂-15), 3.68 (t, J = 6.3 Hz, 2H, H₂-11), 3.47 (t, J = 6.3 Hz, 2H, H₂-9), 2.67–2.37 (m, 4H, H₂-16 & H₂-8), 2.13–1.95 (m, 2H, H₂-6), 1.93 (s, 3H, 5- CH_3), 1.80–1.72 (m, 2H, H₂-10), 1.74 (s, 3H, 15- CH_3), 1.33 (t, J = 7.2 Hz, 6H, $2 \times \text{OCH}_2\text{CH}_3$), 0.88 (s, 9H, TBS), 0.83 (0.81) (s, 9H, TBS), 0.06 (s, 3H, TBS), 0.04 (s, 6H, TBS), –0.02 (s, 3H, TBS). ^{13}C NMR (300 MHz, CDCl_3) δ 179.7, 166.5, 147.33 (147.29), 144.02 (143.98), 142.4, 139.0, 136.7, 134.21 (134.17), 127.8, 126.72 (126.68), 126.1, 125.85 (125.75), 118.7, 70.86 (70.79), 67.2, 67.1, 66.94 (66.85), 61.75 (61.67), 60.1, 44.6, 41.8, 36.2, 35.0, 34.4, 34.3, 33.1, 26.1, 25.9, 25.28 (25.22), 18.5, 17.9, 16.9, 16.6 (16.5), –4.6, –4.7, –5.2.

(17R) Di-TBS ether 28.—Yellow oil, 63% yield. ^1H NMR (300 MHz, CDCl_3) δ 8.32 (8.31) (d, J = 0.9 Hz, 1H, oxazole-H), 7.94 (7.92) (d, J = 0.9 Hz, 1H, oxazole-H), 7.63 (7.62) (dd, J = 15.0, 11.7 Hz, 1H, H-3), 7.164 (7.158) (dd, J = 15.9, 4.8 Hz, H-18), 7.04 (7.03) (dd, J = 15.6, 1.2 Hz, 1H, H-19), 6.09 (d, J = 11.7 Hz, 1H, H-4), 5.82 (d, J = 15.0 Hz, 1H, H-2), 5.75–5.68 (m, 1H, H-17), 5.43 (t, J = 6.6 Hz, 1H, H-14), 4.21–4.03 (m, 5H, $2 \times \text{OCH}_2\text{CH}_3$, H-7), 3.94 (d, J = 6.6 Hz, 2H, H₂-13), 3.67 (t, J = 6.0 Hz, 2H, H₂-11), 3.45 (t, J = 6.6 Hz, 2H, H₂-9), 2.62–2.42 (m, 4H, H₂-16 & H₂-8), 2.05–1.95 (m, 2H, H₂-6), 1.91 (s, 3H, 5- CH_3), 1.76–1.70 (m, 2H, H₂-10), 1.72 (s, 3H, 15- CH_3), 1.34–1.28 (m, 6H, $2 \times \text{OCH}_2\text{CH}_3$), 0.87 (s, 9H, TBS), 0.86 (s, 3H, TBS), 0.82 (s, 3H, TBS), 0.80 (s, 3H, TBS), 0.04 (s, 3H, TBS), 0.03 (s, 6H, TBS), –0.03 (s, 3H). ^{13}C NMR (300 MHz, CDCl_3) δ 183.1, 166.5, 151.2, 147.2 (147.1), 146.2, 143.6, 142.3, 140.7, 134.2, 126.8 (126.7), 126.1, 125.5 (125.4), 118.9, 88.7, 70.9, 67.3, 67.1, 61.8 (61.7), 60.2, 44.58 (44.55), 41.84 (41.78), 36.2 (34.4), 33.2, 26.1, 26.0 (25.9), 25.3 (25.2), 18.5, 17.9, 16.91 (16.88), 16.7 (16.6), –4.5 (–4.6), –5.2.

(17S) Di-TBS ether 29.—Pale yellow oil, 42% yield. ^1H NMR (300 MHz, CDCl_3) δ 7.80 (d, J = 3.9 Hz, 1H, imidazole-H), 7.78 (d, J = 3.9 Hz, 1H, imidazole-H), 7.62 (dd, J = 15.3, 11.7 Hz, 1H, H-3), 6.94 (6.93) (dd, J = 15.3, 4.8 Hz, 1H, H-19), 6.75 (6.74) (dd, J = 15.3, 3.9 Hz, 1H, H-18), 6.09 (d, J = 11.7 Hz, 1H, H-4), 5.80 (d, J = 14.7 Hz, 1H, H-2), 5.72–5.66 (m, 1H, H-17), 5.42 (t, J = 5.7 Hz, H-14), 4.14–4.02 (m, 5H, $2 \times \text{OCH}_2\text{CH}_3$ & H-7), 3.95 (s, 3H, $N\text{-CH}_3$), 3.92 (d, J = 6.6 Hz, 2H, H₂-15), 3.65 (t, J = 6.0 Hz, 2H, H₂-11), 3.44 (t, J = 6.0 Hz, 2H, H₂-9), 2.65–2.34 (m, 4H, H₂-16 & H₂-8), 2.03–1.95 (m, 2H, H₂-6), 1.89 (s, 3H, 5- CH_3), 1.75–1.68 (m, 2H, H₂-10), 1.71 (s, 3H, 15- CH_3), 1.30 (1.29) (t, J = 7.2 Hz, 6H, $2 \times \text{OCH}_2\text{CH}_3$), 0.85 (s, 9H, TBS), 0.80 (0.78) (s, 9H, TBS), 0.02 (s, 3H, TBS), 0.01 (s, 6H, TBS), –0.05 (s, 3H, TBS). ^{13}C NMR (300 MHz, CDCl_3) δ 179.5, 166.5, 147.39 (147.35), 144.5, 143.5, 142.5, 137.6, 134.17 (134.13), 131.3, 126.7, 126.1, 125.6 (125.5), 118.7, 70.79 (70.75), 67.2, 67.1, 66.92 (66.85), 61.76 (61.67), 60.1, 44.5, 41.7, 36.2, 35.2, 34.4, 33.1, 26.1, 25.9, 25.28 (25.24), 18.4, 17.9, 16.8, 16.6 (16.5), –4.6, –4.7, –5.2.

(17R) Di-TBS ether 30.—Yellow oil, 93% yield. ^1H NMR (300 MHz, CDCl_3) δ 8.31 (8.30) (d, $J = 0.9$ Hz, 1H, oxazole-H), 7.94 (7.92) (d, $J = 0.9$ Hz, 1H, oxazole-H), 7.62 (7.61) (dd, $J = 15.0, 11.7$ Hz, 1H, H-3), 7.16 (7.15) (dd, $J = 15.6, 4.8$ Hz, H-18), 7.04 (7.03) (dd, $J = 15.6, 1.2$ Hz, 1H, H-19), 6.08 (d, $J = 11.7$ Hz, 1H, H-4), 5.81 (d, $J = 15.0$ Hz, 1H, H-2), 5.74–5.67 (m, 1H, H-17), 5.42 (t, $J = 5.4$ Hz, 1H, H-14), 4.22–4.03 (m, 5H, $2 \times \text{OCH}_2\text{CH}_3$, H-7), 3.93 (d, $J = 6.3$ Hz, 2H, H₂-13), 3.66 (t, $J = 6.0$ Hz, 2H, H₂-11), 3.44 (t, $J = 6.3$ Hz, 2H, H₂-9), 2.61–2.41 (m, 4H, H₂-16 & H₂-8), 2.04–1.96 (m, 2H, H₂-6), 1.90 (s, 3H, 5-CH₃), 1.77–1.71 (m, 2H, H₂-10), 1.72 (s, 3H, 15-CH₃), 1.33–1.28 (m, 6H, $2 \times \text{OCH}_2\text{CH}_3$), 0.87 (s, 9H, TBS), 0.86 (s, 3H, TBS), 0.81 (s, 3H, TBS), 0.79 (s, 3H, TBS), 0.04 (s, 3H, TBS), 0.02 (s, 6H, TBS), –0.04 (s, 3H). ^{13}C NMR (300 MHz, CDCl_3) δ 183.1, 166.5, 151.1, 147.2 (147.1), 146.2, 143.5, 142.3, 140.7, 134.2, 126.8 (126.7), 126.1, 125.3, 118.9, 88.9, 70.9, 67.3 (67.1), 61.8 (61.7), 60.1, 44.5, 41.8, 36.2 (34.4), 33.1, 26.1, 25.92 (25.90), 25.3 (25.2), 18.5, 18.0, 16.90 (16.87), 16.64 (16.56), –4.5, –4.6, –5.2.

(17S) Di-TBS ether 31.—Pale yellow oil; 74% yield. ^1H NMR (300 MHz, CDCl_3) δ 7.91 (d, $J = 6.9$ Hz, 2H, phenyl-H), 7.65 (dd, $J = 15.3, 11.7$ Hz, 1H, H-3), 7.56 (t, $J = 7.2$ Hz, 1H, phenyl-H), 7.46 (t, $J = 6.9$ Hz, 2H, phenyl-H), 7.01 (7.00) (d, $J = 15.6$ Hz, 1H, H-19), 6.93 (6.92) (dd, $J = 15.0, 1.8$ Hz, 1H, H-18), 6.11 (d, $J = 11.7$ Hz, H-4), 5.83 (d, $J = 15.0$ Hz, 1H, H-2), 5.76–5.70 (m, 1H, H-17), 5.45 (t, $J = 6.9$ Hz, 1H, H-14), 4.19–4.06 (m, 5H, $2 \times \text{OCH}_2\text{CH}_3$ and H-7), 3.95 (d, $J = 6.6$ Hz, 2H, H₂-13), 3.67 (t, $J = 6.3$ Hz, 2H, H₂-11), 3.46 (t, $J = 6.3$ Hz, 2H, H₂-9), 2.62–2.39 (m, 4H, H₂-16 & H₂-8), 2.04 (1.98) (d, $J = 6.3$ Hz, 2H, H₂-6), 1.92 (s, 3H, 5-CH₃), 1.77 (quin., $J = 6.3$ Hz, 2H, H₂-10), 1.74 (s, 3H, 15-CH₃), 1.35–1.28 (m, 6H, $2 \times \text{OCH}_2\text{CH}_3$), 0.88 (s, 9H, TBS), 0.82 (0.80) (s, 9H, TBS), 0.04 (s, 6H, TBS), –0.03 (–0.04) (s, 6H, TBS). ^{13}C NMR (75 MHz, CDCl_3) δ 190.5, 166.5, 147.2, 145.5, 142.4, 137.7, 134.3 (134.2), 133.1, 128.8, 128.7, 126.8 (126.7), 126.1, 125.6 (125.5), 118.8, 71.1 (71.0), 67.3, 67.1, 66.9 (66.8), 61.8 (61.7), 60.1, 44.6, 41.8, 36.2 (34.5), 33.2, 26.1, 25.9 (25.8), 25.3 (25.2), 18.5, 18.0 (17.9), 17.0 (16.9), 16.7 (16.6), –4.56 (–4.63), –5.2.

(17R) Di-TBS ether 32.—Pale yellow oil; 43% yield. ^1H NMR (300 MHz, CDCl_3) δ 7.90 (dt, $J = 6.9, 1.8$ Hz, 2H, phenyl-H), 7.63 (dd, $J = 15.0, 11.7$ Hz, 1H, H-3), 7.55 (tt, $J = 7.5, 1.2$ Hz, 1H, phenyl-H), 7.45 (tt, $J = 7.8, 1.2$ Hz, 2H, phenyl-H), 7.02–6.93 (m, 2H, H-18 & H-19), 6.10 (d, $J = 11.7$ Hz, H-4), 5.82 (d, $J = 15.3$ Hz, 1H, H-2), 5.85–5.69 (m, 1H, H-17), 5.44 (t, $J = 6.3$ Hz, 1H, H-14), 4.18–4.04 (m, 5H, $2 \times \text{OCH}_2\text{CH}_3$ and H-7), 3.94 (d, $J = 6.3$ Hz, 2H, H₂-13), 3.66 (t, $J = 6.0$ Hz, 2H, H₂-11), 3.45 (t, $J = 6.3$ Hz, 2H, H₂-9), 2.61–2.41 (m, 4H, H₂-16 & H₂-8), 2.04–1.94 (m, 2H, H₂-6), 1.91 (s, 3H, 5-CH₃), 1.75 (quin., $J = 6.3$ Hz, 2H, H₂-10), 1.72 (s, 3H, 15-CH₃), 1.33–1.26 (m, 6H, $2 \times \text{OCH}_2\text{CH}_3$), 0.87 (s, 9H, TBS), 0.82 (0.79) (s, 9H, TBS), 0.03 (s, 6H, TBS), –0.03 (–0.04) (s, 6H, TBS). ^{13}C NMR (75 MHz, CDCl_3) δ 190.5, 166.5, 147.3 (147.2), 145.5 (145.4), 142.4, 137.8, 134.3 (134.2), 133.1, 128.8, 128.7, 126.8, 126.1, 125.6 (125.5), 118.9, 71.1 (71.0), 67.3, 67.1, 66.9 (66.8), 61.8 (61.7), 60.1, 44.6, 41.8, 36.3 (34.5), 33.2, 26.1, 25.9 (25.8), 25.3 (25.2), 18.5, 18.0 (17.9), 16.9, 16.7 (16.6), –4.5 (–4.6), –5.2.

(17S) Di-TBS ether 33.—Colorless oil; 73% yield. ^1H NMR (300 MHz, CDCl_3) δ 7.94 (dd, $J = 8.4, 5.4$ Hz, 2H, phenyl-H), 7.63 (dd, $J = 15.0, 11.7$ Hz, 1H, H-3), 7.13 (t, $J = 8.7$ Hz, 2H, phenyl-H), 6.97 (dd, $J = 15.6, 0.6$ Hz, 1H, H-19), 6.91 (6.90) (dd, $J = 16.5, 2.1$ Hz,

1H, H-18), 6.10 (d, J = 11.7 Hz, 1H, H-4), 5.82 (d, J = 15.3 Hz, 1H, H-2), 5.74–5.68 (m, 1H, H-17), 5.44 (t, J = 7.2 Hz, 1H, H-14), 4.16–4.05 (m, 5H, $2 \times \text{OCH}_2\text{CH}_3$ & H-7), 3.94 (d, J = 6.3 Hz, 2H, H₂-13), 3.66 (t, J = 6.0 Hz, 2H, H₂-11), 3.45 (t, J = 6.3 Hz, 2H, H₂-9), 2.61–2.42 (m, 4H, H₂-16 & H₂-8), 2.03 (1.97) (d, J = 6.3 Hz, 2H, H₂-6), 1.91 (s, 3H, 5-CH₃), 1.74 (quin, J = 5.4 Hz, 2H, H₂-10), 1.73 (s, 3H, 15-CH₃), 1.34–1.27 (m, 6H, $2 \times \text{OCH}_2\text{CH}_3$), 0.87 (s, 9H, TBS), 0.81 (0.79) (s, 9H, TBS), 0.04 (0.03) (s, 3H, TBS), 0.03 (s, 6H, TBS), –0.03 (–0.04) (s, 3H, TBS). ¹³C NMR (75 MHz, CDCl₃) δ 188.79 (188.75), 166.5, 165.9 (d, J = 253 Hz), 147.4 (d, J = 3.0 Hz), 145.7 (d, J = 3.0 Hz), 142.5, 134.2 (d, J = 2.2 Hz), 131.4 (d, J = 9.3 Hz), 128.8, 126.1, 125.1 (d, J = 8.6 Hz), 118.8, 116.1, 115.8, 71.0, 67.3, 67.1, 66.9 (66.8), 61.8 (61.7), 60.1, 44.5, 41.8, 36.2 (34.5), 33.2, 26.1, 25.93 (25.91), 25.3 (25.2), 18.5, 18.0, 16.9, 16.7 (16.6), –4.56 (–4.63), –5.2.

(17R) Di-TBS ether 34.—Colorless oil; 51% yield. ¹H NMR (300 MHz, CDCl₃) δ 7.94 (dd, J = 8.4, 5.4 Hz, 2H, phenyl-H), 7.63 (dd, J = 14.7, 11.7 Hz, 1H, H-3), 7.12 (t, J = 8.4 Hz, 2H, phenyl-H), 7.00–6.88 (overlapped, 2H, H-18 & H-19), 6.10 (d, J = 11.7 Hz, 1H, H-4), 5.82 (d, J = 15.3 Hz, 1H, H-2), 5.74–5.66 (m, 1H, H-17), 5.44 (t, J = 6.3 Hz, 1H, H-14), 4.22–4.05 (m, 5H, $2 \times \text{OCH}_2\text{CH}_3$ & H-7), 3.94 (d, J = 6.6 Hz, 2H, H₂-13), 3.66 (t, J = 6.3 Hz, 2H, H₂-11), 3.45 (t, J = 6.3 Hz, 2H, H₂-9), 2.61–2.42 (m, 4H, H₂-16 & H₂-8), 2.03 (1.97) (d, J = 6.0 Hz, 2H, H₂-6), 1.91 (s, 3H, 5-CH₃), 1.79–1.70 (m, 2H, H₂-10), 1.73 (s, 3H, 15-CH₃), 1.34–1.27 (m, 6H, $2 \times \text{OCH}_2\text{CH}_3$), 0.87 (s, 9H, TBS), 0.81 (0.78) (s, 9H, TBS), 0.06 (s, 3H, TBS), 0.02 (s, 6H, TBS), –0.04 (–0.05) (s, 3H, TBS). ¹³C NMR (75 MHz, CDCl₃) δ 188.79 (188.75), 166.5, 165.9 (d, J = 253 Hz), 147.4 (d, J = 3.0 Hz), 145.7 (d, J = 3.0 Hz), 142.5, 134.2 (d, J = 2.2 Hz), 131.4 (d, J = 9.8 Hz), 126.7, 126.1, 125.1 (d, J = 8.3 Hz), 118.8, 116.0, 115.7, 71.1, 67.3, 67.1, 66.9 (66.8), 61.8 (61.7), 60.1, 44.5, 41.8, 36.2 (34.4), 33.1, 26.1, 25.92 (25.90), 25.3 (25.2), 18.5, 18.0, 16.9, 16.7 (16.6), –4.57 (–4.64), –5.2.

(17S) Di-TBS ether 35.—Colorless oil; 76% yield. ¹H NMR (300 MHz, CDCl₃) δ 7.72 (tt, J = 7.2, 1.8 Hz, 1H, phenyl-H), 7.62 (dd, J = 15.0, 11.7 Hz, 1H, H-3), 7.53–7.45 (m, 1H, phenyl-H), 7.22 (dt, J = 7.5, 0.9 Hz, 1H, phenyl-H), 7.12 (tt, J = 9.6, 1.5 Hz, 1H, phenyl-H), 6.91 (6.88) (dd, J = 15.3, 3.3 Hz, 1H, H-18), 6.85 (6.84) (d, J = 15.0 Hz, 1H, H-19), 6.09 (d, J = 11.7 Hz, 1H, H-4), 5.81 (d, J = 15.0 Hz, 1H, H-2), 5.74–5.67 (m, 1H, H-17), 5.43 (t, J = 6.0 Hz, 1H, H-14), 4.18–4.05 (m, 5H, $2 \times \text{OCH}_2\text{CH}_3$ & H-7), 3.94 (d, J = 6.6 Hz, 2H, H₂-13), 3.67 (t, J = 6.0 Hz, 2H, H₂-11), 3.46 (t, J = 6.3 Hz, 2H, H₂-9), 2.62–2.37 (m, 4H, H₂-8 & H₂-16), 2.05–1.90 (m, 2H, H₂-6), 1.91 (s, 3H, 5-CH₃), 1.75 (quin, J = 6.3 Hz, 2H, H₂-10), 1.73 (s, 3H, 15-CH₃), 1.35–1.29 (m, 6H, $2 \times \text{OCH}_2\text{CH}_3$), 0.88 (s, 9H, TBS), 0.81 (0.80) (s, 9H, TBS), 0.03 (s, 9H, TBS), –0.03 (–0.04) (s, 3H, TBS). ¹³C NMR (75 MHz, CDCl₃) δ 188.9, 166.5, 161.5 (d, J = 266.6 Hz), 147.2 (147.1), 145.8, 142.3, 140.4, 134.2, 131.1, 128.8 (128.7), 126.8 (126.7), 126.1, 124.6, 118.9, 116.9 (116.6), 70.9, 67.3, 67.1, 61.8, 61.7, 60.2, 44.5, 41.8, 36.3, 34.5, 33.2, 26.1, 25.9, 18.5, 18.0, 16.7, 16.6, –4.6, –5.2.

(17R) Di-TBS ether 36.—Pale yellow oil; 50% yield. ¹H NMR (300 MHz, CDCl₃) δ 7.72 (tt, J = 7.5, 1.8 Hz, 1H, phenyl-H), 7.62 (dd, J = 15.0, 11.7 Hz, 1H, H-3), 7.53–7.46 (m, 1H, phenyl-H), 7.22 (dt, J = 7.5, 0.9 Hz, 1H, phenyl-H), 7.12 (tt, J = 9.3, 1.5 Hz, 1H, phenyl-H), 6.91 (6.90) (dd, J = 15.6, 3.6 Hz, 1H, H-18), 6.85 (6.84) (d, J = 15.6 Hz, 1H, H-19), 6.09 (d,

$J = 11.7$ Hz, 1H, H-4), 5.81 (d, $J = 15.0$ Hz, 1H, H-2), 5.73–5.68 (m, 1H, H-17), 5.43 (t, $J = 6.3$ Hz, 1H, H-14), 4.18–4.05 (m, 5H, $2 \times \text{OCH}_2\text{CH}_3$ & H-7), 3.94 (d, $J = 6.3$ Hz, 2H, H₂-13), 3.67 (t, $J = 6.3$ Hz, 2H, H₂-11), 3.46 (t, $J = 6.3$ Hz, 2H, H₂-9), 2.63–2.37 (m, 4H, H₂-8 & H₂-16), 2.05–1.90 (m, 2H, H₂-6), 1.91 (s, 3H, 5-CH₃), 1.75 (quin, $J = 6.3$ Hz, 2H, H₂-10), 1.73 (s, 3H, 15-CH₃), 1.35–1.29 (m, 6H, $2 \times \text{OCH}_2\text{CH}_3$), 0.88 (s, 9H, TBS), 0.81 (0.79) (s, 9H, TBS), 0.03 (s, 9H, TBS), -0.03 (-0.04) (s, 3H, TBS). ¹³C NMR (75 MHz, CDCl₃) δ 188.9, 166.5, 161.5 (d, $J = 245$ Hz), 147.2 (147.1), 145.8, 142.4, 140.4, 134.2, 131.2, 128.7 (128.6), 126.9 (126.8), 126.1, 124.7, 118.9, 116.9 (116.6), 71.0, 67.2, 67.1, 61.9, 61.8, 60.2, 44.5, 41.8, 36.2, 34.4, 33.2, 26.1, 25.9, 18.5, 18.0, 16.7, 16.6, -4.6 , -5.2 .

(17S) Di-TBS ether 37.—Pale yellow oil; 57% yield. ¹H NMR (300 MHz, CDCl₃) δ 7.69–7.56 (m, 3H, $2 \times$ phenyl-H & H-3), 7.47–7.40 (m, 1H, phenyl-H), 7.30–7.22 (m, 1H, phenyl-H), 6.98 (d, $J = 15.3$ Hz, 1H, H-19), 6.91 (dd, $J = 15.6$, 3.0 Hz, H-18), 6.10 (d, $J = 11.7$ Hz, 1H, H-4), 5.82 (d, $J = 15.0$ Hz, 1H, H-2), 5.75–5.69 (m, 1H, H-17), 5.44 (t, $J = 7.5$ Hz, 1H, H-14), 4.15–4.05 (m, 4H, $2 \times \text{OCH}_2\text{CH}_3$), 4.01–3.93 (m, 2H, H₂-13), 3.66 (t, $J = 6.3$ Hz, 2H, H₂-11), 3.45 (t, $J = 6.3$ Hz, 2H, H₂-9), 2.62–2.42 (m, 4H, H₂-8 & H₂-16), 2.03–1.96 (m, 2H, H₂-6), 1.91 (s, 3H, 5-CH₃), 1.76 (quin., $J = 6.0$ Hz, 2H, H₂-10), 1.73 (s, 3H, 15-CH₃), 1.31 (t, $J = 6.9$ Hz, 6H, $2 \times \text{OCH}_2\text{CH}_3$), 0.87 (s, 9H, TBS), 0.81 (0.78) (s, 9H, TBS), 0.034 (0.026) (s, 3H, TBS), 0.02 (s, 6H, TBS), -0.04 (-0.05) (s, 3H, TBS). ¹³C NMR (75 MHz, CDCl₃) δ 189.0, 166.5, 162.9 (d, $J = 246.8$ Hz), 147.4 (d, $J = 3.8$ Hz), 146.3 (d, $J = 3.0$ Hz), 139.8 (d, $J = 6.8$ Hz), 134.15 (134.12), 130.5 (130.4), 126.7 (126.1), 125.0 (124.9), 124.5, 120.2, 119.6, 118.7, 115.6 (115.3), 70.9, 67.2, 67.1, 66.9 (66.8), 61.8 (61.7), 60.1, 44.5, 41.8, 36.3, 34.4, 33.1, 26.1, 25.9, 18.5, 17.9, 16.61, 16.53, -4.7 , -5.2 .

(17R) Di-TBS ether 38.—Pale yellow oil; 55% yield. ¹H NMR (300 MHz, CDCl₃) δ 7.69–7.56 (m, 3H, $2 \times$ phenyl-H & H-3), 7.47–7.40 (m, 1H, phenyl-H), 7.28–7.21 (m, 1H, phenyl-H), 6.97 (d, $J = 15.9$ Hz, 1H, H-19), 6.91 (dd, $J = 15.9$, 3.0 Hz, H-18), 6.10 (d, $J = 11.4$ Hz, 1H, H-4), 5.82 (d, $J = 15.3$ Hz, 1H, H-2), 5.76–5.69 (m, 1H, H-17), 5.44 (t, $J = 6.0$ Hz, 1H, H-14), 4.16–4.04 (m, 4H, $2 \times \text{OCH}_2\text{CH}_3$), 3.94 (d, $J = 6.6$ Hz, 2H, H₂-13), 3.66 (t, $J = 6.0$ Hz, 2H, H₂-11), 3.45 (t, $J = 6.3$ Hz, 2H, H₂-9), 2.62–2.42 (m, 4H, H₂-8 & H₂-16), 2.03–1.96 (m, 2H, H₂-6), 1.91 (s, 3H, 5-CH₃), 1.76 (quin., $J = 6.0$ Hz, 2H, H₂-10), 1.73 (s, 3H, 15-CH₃), 1.35–1.29 (m, 6H, $2 \times \text{OCH}_2\text{CH}_3$), 0.87 (s, 9H, TBS), 0.81 (0.78) (s, 9H, TBS), 0.034 (0.026) (s, 3H, TBS), 0.02 (s, 6H, TBS), -0.04 (-0.05) (s, 3H, TBS).

General procedure for synthesis of diols 39 – 50:

To a solution of the relevant di-TBS ether (**27–38**, 0.041 mmol) in THF (1.7 mL) at 0 °C in a plastic bottle was added dropwise hydrogen fluoride-pyridine complex (70%, 0.41 mL). The solution was stirred at 0 °C for 5 min and then at room temperature for 16 h. Saturated sodium bicarbonate (30 mL) was added to quench the reaction and the suspension was extracted with ethyl acetate (20 mL $\times$ 3). The combined organic extracts were dried over anhydrous sodium sulfate and the dried extract was concentrated under vacuum. The crude product was purified by PTLC, eluting with dichloromethane/methanol (93:7; v/v), and the pure diol was retrieved by extracting the PTLC silica gel with acetone. Characterization, yield and NMR data for each diol are listed below:

(17S) Diol 9.—¹H NMR (300 MHz, CDCl₃) δ 7.80 (s, 1H, imidazole-H), 7.66–7.55 (overlapped, 2H, imidazole-H & H-3), 6.92 (dd, *J* = 15.3, 3.6 Hz, 1H, H-18), 6.76 (d, *J* = 15.3 Hz, 1H, H-19), 6.15 (d, *J* = 11.4 Hz, H-4), 5.84 (d, *J* = 15.0 Hz, 1H, H-2), 5.77–5.65 (m, 1H, H-17), 5.41 (t, *J* = 5.4 Hz, 1H, H-14), 4.14–4.03 (m, 5H, 2 × OCH₂CH₃ & H-7), 3.96–3.92 (overlapped, 2H, H₂-13), 3.92 (s, 3H, *N*-CH₃), 3.69 (t, *J* = 5.4 Hz, 2H, H₂-11), 3.52 (t, *J* = 4.8 Hz, 2H, H₂-9), 2.67–2.36 (m, 4H, H₂-8 & H₂-16), 2.14 (br.s, 2H, 2 × OH), 1.96–1.89 (m, 2H, H₂-6), 1.93 (s, 3H, 5-CH₃), 1.77 (quin, *J* = 6.0 Hz, 2H, H₂-10), 1.72 (s, 3H, 15-CH₃), 1.30 (t, *J* = 6.9 Hz, 6H, 2 × OCH₂CH₃). ¹³C NMR (75 MHz, CDCl₃) δ 179.8, 166.5, 146.79 (146.75), 143.92, 143.85, 141.5 (141.4), 134.6, 134.5, 126.7 (126.6), 126.0, 125.9, 125.87 (125.80), 119.22 (119.15), 70.8 (70.7), 68.73 (68.70), 67.3, 65.4 (65.3), 62.3 (62.2), 62.1 (62.0), 61.3 (61.2), 54.0, 44.5, 41.5 (41.3), 35.0 (34.6), 32.8 (31.9), 32.4, 25.2 (25.0), 16.94 (16.91), 16.6 (16.5).

(17R) Diol 40.—¹H NMR (300 MHz, CDCl₃) δ 7.86 (7.83) (s, 1H, imidazole-H), 7.83 (7.80) (s, 1H, imidazole-H), 7.62 (7.60) (dd, *J* = 16.5, 11.7 Hz, H-3), 6.94 (6.93) (dd, *J* = 15.3, 4.5 Hz, 1H, H-18), 6.77 (6.76) (d, *J* = 15.3 Hz, 1H, H-19), 6.15 (d, *J* = 11.7 Hz, H-4), 5.84 (d, *J* = 15.3 Hz, 1H, H-2), 5.76–5.67 (m, 1H, H-17), 5.42 (t, *J* = 5.7 Hz, 1H, H-14), 4.17–4.05 (m, 5H, 2 × OCH₂CH₃ & H-7), 3.96–3.90 (overlapped, 2H, H₂-13), 3.96 (3.95) (s, 3H, *N*-CH₃), 3.69 (t, *J* = 6.0 Hz, 2H, H₂-11), 3.53 (3.52) (t, *J* = 6.0 Hz, 2H, H₂-9), 2.70–2.36 (m, 4H, H₂-8 & H₂-16), 1.98–1.89 (m, 2H, H₂-6), 1.94 (s, 3H, 5-CH₃), 1.77 (quin, *J* = 5.7 Hz, 2H, H₂-10), 1.72 (s, 3H, 15-CH₃), 1.31 (t, *J* = 6.9 Hz, 6H, 2 × OCH₂CH₃). ¹³C NMR (75 MHz, CDCl₃) δ 179.7, 166.5, 146.8, 144.4, 144.2, 141.5 (141.4), 134.6, 134.5, 126.7, 126.0, 125.9, 125.8, 119.2, 70.7, 68.8, 67.3, 65.3, 62.3, 62.1 (62.0), 61.3 (61.2), 53.5, 44.4, 41.5 (41.3), 35.2, 32.4, 25.2 (25.1), 16.9, 16.6 (16.5).

(17S) Diol 41.—¹H NMR (300 MHz, CDCl₃) δ 8.32 (s, 1H, oxazole-H), 7.98 (7.96) (s, 1H, oxazole-H), 7.61 (dd, *J* = 15.3, 12.0 Hz, 1H, H-3), 7.18 (dd, *J* = 15.6, 4.5 Hz, 1H, H-18), 7.07 (d, *J* = 15.6 Hz, 1H, H-19), 6.16 (d, *J* = 11.7 Hz, 1H, H-4), 5.88 (5.85) (d, *J* = 15.0 Hz, 1H, H-2), 5.79–5.72 (m, 1H, H-17), 5.41 (t, *J* = 6.3 Hz, 1H, H-14), 4.23–4.05 (m, 5H, 2 × OCH₂CH₃ and 7-H), 3.96 (d, *J* = 6.6 Hz, 2H, H₂-13), 3.71 (t, *J* = 5.4 Hz, 2H, H₂-11), 3.53 (dt, *J* = 6.9, 1.8 Hz, 2H, H₂-9), 2.69–2.57 (m, 2H, H₂-8), 2.52–2.40 (m, 2H, H₂-16), 1.98–1.91 (m, 2H, H₂-6), 1.95 (s, 3H, 5-CH₃), 1.82–1.73 (m, 2H, H₂-10), 1.73 (s, 3H, 15-CH₃), 1.35–1.24 (m, 6H, 2 × OCH₂CH₃). ¹³C NMR (75 MHz, CDCl₃) δ 183.1, 166.5 (166.4), 151.4 (151.3), 146.6 (146.5), 146.2 (146.1), 143.6, 141.4 (141.3), 140.7, 134.8 (134.7), 126.8, 125.8 (125.7), 125.3 (125.2), 119.4, 70.8, 69.0, 67.4, 65.4, 62.3 (62.1) (d, *J* = 6.8 Hz), 61.7 (d, *J* = 9.0 Hz), 44.5, 41.5 (41.3), 34.6 (34.5), 32.8, 25.3 (25.1), 17.0, 16.6 (16.5).

(17R) Diol 42.—¹H NMR (300 MHz, CDCl₃) δ 8.32 (s, 1H, oxazole-H), 7.98 (7.95) (d, *J* = 0.9 Hz, 1H, oxazole-H), 7.64 (dd, *J* = 15.0, 11.7 Hz, 1H, H-3), 7.17 (dd, *J* = 15.6, 4.5 Hz, 1H, H-18), 7.07 (d, *J* = 15.6 Hz, 1H, H-19), 6.16 (d, *J* = 11.7 Hz, 1H, H-4), 5.86 (5.85) (d, *J* = 15.0 Hz, 1H, H-2), 5.79–5.73 (m, 1H, H-17), 5.40 (t, *J* = 6.6 Hz, 1H, H-14), 4.23–4.05 (m, 5H, 2 × OCH₂CH₃ and 7-H), 3.96 (d, *J* = 6.6 Hz, 2H, H₂-13), 3.70 (t, *J* = 5.4 Hz, 2H, H₂-11), 3.52 (dt, *J* = 6.0, 2.1 Hz, 2H, H₂-9), 2.69–2.57 (m, 2H, H₂-8), 2.52–2.40 (m, 2H, H₂-16), 1.98–1.91 (m, 2H, H₂-6), 1.94 (s, 3H, 5-CH₃), 1.77 (quin, *J* = 5.7 Hz, 2H, H₂-10), 1.73 (s, 3H, 15-CH₃), 1.34–1.28 (m, 6H, 2 × OCH₂CH₃). ¹³C NMR (75 MHz, CDCl₃) δ

183.1, 166.6 (166.5), 151.4 (151.3), 146.6 (146.5), 146.2 (146.1), 143.6, 141.4 (141.3), 140.7, 134.8 (134.7), 126.8, 125.8 (125.7), 125.3 (125.2), 119.4, 70.8, 68.9, 67.3, 65.4, 62.2 (62.1), 61.7 (d, $J = 9.0$ Hz), 44.5, 41.5 (41.3), 34.8, 32.4, 25.3 (25.1), 17.0, 16.6 (16.5).

(17S) Diol 43.— ^1H NMR (300 MHz, CDCl_3) δ 7.91 (d, $J = 8.1$ Hz, 2H, phenyl-H), 7.60 (dd, $J = 14.7, 11.7$ Hz, 1H, H-3), 7.56 (tt, $J = 7.5, 1.2$ Hz, 1H, phenyl-H), 7.46 (tt, $J = 7.5, 1.2$ Hz, 2H, phenyl-H), 7.02 (dd, $J = 15.6, 2.7$ Hz, 1H, H-19), 6.94 (ddd, $J = 15.3, 4.5, 1.2$ Hz, 1H, H-18), 6.16 (d, $J = 11.7$ Hz, 1H, H-4), 5.86 (dd, $J = 15.0, 1.8$ Hz, 1H, H-2), 5.79–5.72 (m, 1H, H-17), 5.42 (t, $J = 5.4$ Hz, 1H, H-14), 4.19–4.05 (m, 5H, $2 \times \text{OCH}_2\text{CH}_3$, H-7), 3.97 (d, $J = 6.6$ Hz, 2H, H₂-13), 3.71 (3.60) (t, $J = 5.7$ Hz, 2H, H₂-11), 3.53 (3.52) (t, $J = 5.7$ Hz, 2H, H₂-9), 2.69–2.38 (m, 4H, H₂-16 & H₂-8), 1.95 (s, 3H, 5-CH₃), 1.97–1.89 (m, 2H, H₂-6), 1.77 (quin, $J = 6.0$ Hz, 2H, H₂-10), 1.73 (s, 3H, 15-CH₃), 1.35–1.24 (m, 6H, $2 \times \text{OCH}_2\text{CH}_3$). ^{13}C NMR (75 MHz, CDCl_3) δ 190.4, 166.6, 146.7, 145.3, 141.3, 137.6, 134.8, 134.7, 133.2, 128.8, 126.7, 125.8, 125.4, 119.3, 71.0, 69.7, 69.0, 67.4, 62.2, 61.7, 54.0, 44.6, 32.3, 31.9, 29.4, 16.6, 16.5.

(17R) Diol 44.— ^1H NMR (300 MHz, CDCl_3) δ 7.90 (d, $J = 7.8$ Hz, 2H, phenyl-H), 7.60 (dd, $J = 14.4, 11.7$ Hz, 1H, H-3), 7.56 (tt, $J = 7.2, 1.2$ Hz, 1H, phenyl-H), 7.46 (tt, $J = 7.8, 1.5$ Hz, 2H, phenyl-H), 7.02 (dd, $J = 16.2, 2.4$ Hz, 1H, H-19), 6.93 (ddd, $J = 15.8, 4.5, 1.2$ Hz, 1H, H-18), 6.16 (d, $J = 11.4$ Hz, 1H, H-4), 5.86 (dd, $J = 15.0, 1.5$ Hz, 1H, H-2), 5.79–5.72 (m, 1H, H-17), 5.41 (t, $J = 6.6$ Hz, 1H, H-14), 4.19–4.05 (m, 5H, $2 \times \text{OCH}_2\text{CH}_3$, H-7), 3.96 (d, $J = 6.3$ Hz, 2H, H₂-13), 3.70 (3.69) (t, $J = 5.7$ Hz, 2H, H₂-11), 3.52 (3.51) (t, $J = 6.0$ Hz, 2H, H₂-9), 2.69–2.38 (m, 4H, H₂-16 & H₂-8), 1.94 (s, 3H, 5-CH₃), 1.98–1.89 (m, 2H, H₂-6), 1.76 (quin, $J = 5.7$ Hz, 2H, H₂-10), 1.73 (s, 3H, 15-CH₃), 1.34–1.28 (m, 6H, $2 \times \text{OCH}_2\text{CH}_3$). ^{13}C NMR (75 MHz, CDCl_3) δ 190.4, 166.7 (166.6), 146.8, 145.3, 141.4, 137.6, 134.8, 134.7, 133.2, 128.8, 126.7, 125.8, 125.4, 119.3, 71.0, 68.8, 67.3, 62.2, 62.1, 61.6, 50.8, 44.5, 32.8, 32.3, 25.2 (25.0), 17.0, 16.6 (16.5).

(17S) Diol 45.— ^1H NMR (300 MHz, CDCl_3) δ 7.96 (ddd, $J = 9.0, 5.4, 1.2$ Hz, 2H, phenyl-H), 7.61 (7.56) (ddd, $J = 15.0, 11.7$ Hz, 1H, H-3), 7.14 (t, $J = 8.7$ Hz, 2H, phenyl-H), 7.01 (7.00) (d, $J = 15.3$ Hz, 1H, H-19), 6.95 (6.94) (dd, $J = 14.7, 3.0$ Hz, 1H, H-18), 6.17 (d, $J = 11.7$ Hz, 1H, H-4), 5.87 (d, $J = 14.4$ Hz, 1H, H-2), 5.79–5.72 (m, 1H, H-17), 5.42 (t, $J = 5.4$ Hz, 1H, H-14), 4.22–4.06 (m, 5H, $2 \times \text{OCH}_2\text{CH}_3$ & H-7), 3.97 (d, $J = 6.6$ Hz, 2H, H₂-13), 3.72 (t, $J = 5.7$ Hz, 2H, H₂-11), 3.54 (3.53) (t, $J = 6.0$ Hz, H₂-9), 2.69–2.39 (m, 4H, H₂-8 & H₂-16), 1.97–1.89 (overlapped, 2H, H₂-6), 1.95 (s, 3H, 5-CH₃), 1.78 (quin, $J = 6.0$ Hz, 2H, H₂-10), 1.74 (s, 3H, 15-CH₃), 1.32 (t, $J = 6.9$ Hz, 6H, $2 \times \text{OCH}_2\text{CH}_3$). ^{13}C NMR (75 MHz, CDCl_3) δ 188.7, 165.9 (d, $J = 253.5$ Hz), 166.5, 146.7, 145.6 (d, $J = 5.3$ Hz), 141.5 (d, $J = 6.0$ Hz), 134.7 (d, $J = 5.3$ Hz), 134.0 (d, $J = 3.0$ Hz), 131.5 (d, $J = 9.0$ Hz), 126.74 (126.69), 125.84 (125.76), 124.99 (124.93), 119.33 (119.28), 116.1, 115.8, 71.0, 69.10 (69.05), 67.4, 65.45 (65.38), 65.34 (65.28), 62.32 (62.24), 62.21 (62.13), 61.83 (61.78), 44.5, 41.5 (41.3), 34.6, 32.8, 32.3, 25.2 (25.1), 17.00 (16.96), 16.63 (16.55).

4.6.8 (17R) Diol 46.— ^1H NMR (300 MHz, CDCl_3) δ 7.95 (ddd, $J = 9.0, 5.4, 1.2$ Hz, 2H, phenyl-H), 7.61 (7.60) (dd, $J = 15.0, 11.7$ Hz, 1H, H-3), 7.14 (t, $J = 8.7$ Hz, 2H, phenyl-H), 7.01 (7.00) (d, $J = 15.6$ Hz, 1H, H-19), 6.95 (6.94) (dd, $J = 15.6, 3.0$ Hz, 1H, H-18), 6.17 (d,

$J = 11.7$ Hz, 1H, H-4), 5.86 (d, $J = 15.0$ Hz, 1H, H-2), 5.79–5.73 (m, 1H, H-17), 5.42 (t, $J = 5.4$ Hz, 1H, H-14), 4.21–4.06 (m, 5H, $2 \times \text{OCH}_2\text{CH}_3$ & H-7), 3.97 (d, $J = 6.6$ Hz, 2H, H₂-13), 3.71 (t, $J = 5.7$ Hz, 2H, H₂-11), 3.54 (3.53) (t, $J = 6.0$ Hz, H₂-9), 2.69–2.38 (m, 4H, H₂-8 & H₂-16), 1.97–1.89 (overlapped, 2H, H₂-6), 1.95 (s, 3H, 5-CH₃), 1.78 (quin, $J = 6.0$ Hz, 2H, H₂-10), 1.74 (s, 3H, 15-CH₃), 1.32 (t, $J = 7.2$ Hz, 6H, $2 \times \text{OCH}_2\text{CH}_3$). ¹³C NMR (75 MHz, CDCl₃) δ 188.7, 165.9 (d, $J = 255$ Hz), 166.6 (166.5), 146.7, 145.6 (d, $J = 5.3$ Hz), 141.5 (d, $J = 6.0$ Hz), 134.7 (d, $J = 5.3$ Hz), 134.0 (d, $J = 3.0$ Hz), 131.5 (d, $J = 9.0$ Hz), 126.7, 125.8, 124.9, 119.3, 116.1, 115.8, 70.9, 69.1, 67.4, 65.4, 65.3, 62.3 (62.2), 62.2 (62.1), 61.8 (61.7), 44.5, 41.5 (41.3), 34.6, 32.8, 32.3, 25.2 (25.1), 17.00 (16.96), 16.63, 16.55.

(17S) Diol 47.—¹H NMR (300 MHz, CDCl₃) δ 7.73 (dt, $J = 7.5$, 1.8 Hz, 1H, phenyl-H), 7.59 (7.58) (dd, $J = 15.0$, 11.7 Hz, 1H, H-3), 7.53–7.46 (m, 1H, phenyl-H), 7.22 (dt, $J = 7.5$, 0.9 Hz, 1H, phenyl-H), 7.13 (dd, $J = 10.8$, 8.4 Hz, 1H, phenyl-H), 6.91–6.89 (overlapped, 2H, H-18 & H-19), 6.15 (d, $J = 11.7$ Hz, 1H, H-4), 5.84 (5.83) (d, $J = 15.0$ Hz, 1H, H-2), 5.77–5.70 (m, 1H, H-17), 5.41 (t, $J = 5.4$ Hz, 1H, H-14), 4.19–4.02 (m, 5H, $2 \times \text{OCH}_2\text{CH}_3$ & H-7), 3.97 (d, $J = 6.6$ Hz, 2H, H₂-13), 3.71 (t, $J = 5.7$ Hz, 1H, H₂-11), 3.53 (3.52) (t, $J = 6.0$ Hz, 2H, H₂-9), 2.65–2.43 (m, 4H, H₂-8 & H₂-16), 1.97–1.89 (m, 2H, H₂-6), 1.94 (s, 3H, 5-CH₃), 1.78 (quin., $J = 5.7$ Hz, 2H, H₂-10), 1.73 (s, 3H, 15-CH₃), 1.32 (t, $J = 7.2$ Hz, 6H, $2 \times \text{OCH}_2\text{CH}_3$). ¹³C NMR (75 MHz, CDCl₃) δ 188.9, 166.6 (166.5), 161.4 (d, $J = 252.0$ Hz), 146.6, 145.6, 141.4 (141.2), 134.8 (134.7), 134.4 (134.3), 131.2 (131.1), 128.7 (128.6), 126.7, 126.6, 125.8 (125.7), 124.7 (124.6), 119.3, 116.9, 70.8, 69.02 (68.98), 67.4, 65.5 (65.4), 65.4 (65.3), 62.33 (62.25), 62.21 (62.13), 61.79 (61.76), 44.5, 41.5 (41.3), 35.6, 32.7, 32.3, 25.2 (25.1), 16.96, 16.61 (16.55).

(17R) Diol 48.—¹H NMR (300 MHz, CDCl₃) δ 7.73 (dt, $J = 7.8$, 1.8 Hz, 1H, phenyl-H), 7.60 (7.59) (dd, $J = 14.7$, 11.7 Hz, 1H, H-3), 7.54–7.46 (m, 1H, phenyl-H), 7.23 (dt, $J = 7.8$, 1.2 Hz, 1H, phenyl-H), 7.13 (dd, $J = 10.8$, 8.4 Hz, 1H, phenyl-H), 6.91–6.89 (overlapped, 2H, H-18 & H-19), 6.16 (d, $J = 11.7$ Hz, 1H, H-4), 5.85 (5.84) (d, $J = 15.0$ Hz, 1H, H-2), 5.77–5.70 (m, 1H, H-17), 5.41 (t, $J = 6.6$ Hz, 1H, H-14), 4.19–4.02 (m, 5H, $2 \times \text{OCH}_2\text{CH}_3$ & H-7), 3.97 (d, $J = 6.9$ Hz, 2H, H₂-13), 3.72 (t, $J = 5.7$ Hz, 1H, H₂-11), 3.54 (3.53) (t, $J = 6.0$ Hz, 2H, H₂-9), 2.68–2.39 (m, 4H, H₂-8 & H₂-16), 1.98–1.89 (m, 2H, H₂-6), 1.95 (s, 3H, 5-CH₃), 1.79 (quin., $J = 6.0$ Hz, 2H, H₂-10), 1.73 (s, 3H, 15-CH₃), 1.33 (1.32) (t, $J = 6.9$ Hz, 6H, $2 \times \text{OCH}_2\text{CH}_3$). ¹³C NMR (75 MHz, CDCl₃) δ 188.9, 166.6, 161.4 (d, $J = 251.3$ Hz), 146.6, 145.6, 141.4, 134.8 (134.7), 134.5 (134.3), 131.1, 128.7 (128.6), 126.7, 126.5, 125.8 (125.7), 124.7 (124.6), 119.4 (119.3), 116.9 (116.6), 70.8, 69.1 (69.0), 67.4, 65.4 (65.3), 62.25 (62.22), 62.13 (62.09), 61.9, 44.5, 41.5 (41.3), 34.6, 32.7, 32.3, 25.2 (25.1), 16.96, 16.61 (16.55).

(17S) Diol 49.—¹H NMR (300 MHz, CDCl₃) δ 7.70–7.56 (m, 3H, $2 \times$ phenyl-H & H-3), 7.48–7.41 (m, 1H, phenyl-H), 7.29–7.22 (m, 1H, phenyl-H), 6.97–6.96 (overlapped, 2H, H-18 & H-19), 6.17 (d, $J = 11.7$ Hz, 1H, H-4), 5.87 (5.86) (d, $J = 15.3$ Hz, 1H, H-2), 5.78–5.73 (m, 1H, H-17), 5.42 (t, $J = 7.5$ Hz, 1H, H-14), 4.15–4.06 (m, 5H, $2 \times \text{OCH}_2\text{CH}_3$ & H-7), 3.97 (d, $J = 6.6$ Hz, 2H, H₂-13), 3.71 (t, $J = 5.7$ Hz, 2H, H₂-11), 3.53 (dt, $J = 6.0$, 2.1 Hz, 2H, H₂-9), 2.69–2.38 (m, 4H, H₂-8 & H₂-16), 1.97–1.89 (m, 2H, H₂-6), 1.95 (s, 3H, 5-

CH₃), 1.77 (quin, $J = 5.7$ Hz, 2H, H₂-10), 1.74 (s, 3H, 15-CH₃), 1.32 (t, $J = 6.9$ Hz, 6H, 2 × OCH₂CH₃). ¹³C NMR (75 MHz, CDCl₃) δ 189.03 (189.00), 166.60 (166.55), 163.0 (d, $J = 247.5$ Hz), 146.9 (146.8), 146.23 (146.17), 141.6 (141.5), 139.8 (139.7), 134.7 (134.6), 130.5 (130.4), 126.71 (126.66), 125.9 (125.8), 124.91 (124.86), 124.55 (124.52), 120.4 (120.1), 119.23 (119.16), 115.7 (115.4), 70.9, 69.0, 67.4, 65.4, 62.3 (62.2), 61.7, 44.5, 41.5 (41.3), 34.6, 32.3, 25.2 (25.1), 17.0, 16.6 (16.5).

(17R) Diol 50.—¹H NMR (300 MHz, CDCl₃) δ 7.72–7.56 (m, 3H, 2 × phenyl-H & H-3), 7.48–7.41 (m, 1H, phenyl-H), 7.29–7.22 (m, 1H, phenyl-H), 6.97–6.96 (overlapped, 2H, H-18 & H-19), 6.16 (d, $J = 11.4$ Hz, 1H, H-4), 5.87 (5.86) (d, $J = 15.3$ Hz, 1H, H-2), 5.79–5.70 (m, 1H, H-17), 5.42 (t, $J = 6.3$ Hz, 1H, H-14), 4.15–4.06 (m, 5H, 2 × OCH₂CH₃ & H-7), 3.96 (d, $J = 6.6$ Hz, 2H, H₂-13), 3.72 (3.71) (t, $J = 5.7$ Hz, 2H, H₂-11), 3.53 (3.52) (t, $J = 6.0$ Hz, 2H, H₂-9), 2.66–2.38 (m, 4H, H₂-8 & H₂-16), 1.97–1.89 (m, 2H, H₂-6), 1.94 (s, 3H, 5-CH₃), 1.78 (quin, $J = 5.7$ Hz, 2H, H₂-10), 1.73 (s, 3H, 15-CH₃), 1.32 (1.31) (t, $J = 6.9$ Hz, 6H, 2 × OCH₂CH₃). ¹³C NMR (75 MHz, CDCl₃) δ 189.0, 166.6 (166.5), 163.0 (d, $J = 246.8$ Hz), 146.8, 146.2, 141.6, 139.8 (139.7), 134.7 (134.6), 130.4, 126.7, 125.8 (125.7), 124.9 (124.8), 124.5, 120.4 (120.1), 119.2, 115.7 (115.4), 70.9, 69.0, 67.3, 65.4, 62.3 (62.2), 62.2 (62.1), 61.7, 44.5, 41.5 (41.3), 34.6, 32.8, 32.3, 25.7 (25.1), 16.9, 16.6 (16.5).

General procedure for synthesis of zampanolide mimics 51–62

To a solution of the relevant diol (**39–50**, 0.05 mmol) in dichloromethane (3 mL) at room temperature was added Dess-Martin periodinane (64 mg, 0.15 mmol). The reaction mixture was stirred for 30 min before a second portion of Dess-Martin periodinane (64 mg, 0.15 mmol) was added. The reaction was allowed to proceed with stirring at room temperature for an additional 1 h. The reaction mixture was poured into a stirred mixture of saturated sodium bicarbonate (10 mL) and saturated sodium thiosulfate (10 mL), and the resulting suspension was stirred for 30 min before being extracted with dichloromethane (20 mL × 3). The combined organic extracts were dried over anhydrous sodium sulfate and the dried extract was concentrated under vacuum. The crude product was used for the next reaction without further purification.

To a solution of the crude diketone (0.05 mmol) obtained above in THF (50 mL) at 0 °C was added water (1.05 mL) followed by activated barium hydroxide (7.4 mg, 0.04 mmol). The reaction mixture was stirred at 0 °C for 30 min and at room temperature for 2.5, then was filtered through a pad of sodium sulfate and a pad of silica gel which was rinsed with THF. After evaporation of the solvent, the crude product was subjected to PTLC purification, using dichloromethane/methanol (95:5) as eluent, to yield the pure zampanolide mimic. Characterization, yield and NMR data for each mimic are given below:

(17S) Zampanolide mimic 51.—Colorless oil. Yield: 52%. $[\alpha]_D^{20}$: + 17.8 ($c = 0.18$). ¹H NMR (300 MHz, CDCl₃) δ 7.86 (s, 1H, imidazole-H), 7.69 (s, 1H, imidazole-H), 7.66 (dd, $J = 15.0, 11.4$ Hz, 1H, H-3), 7.01 (dd, $J = 15.3, 4.5$ Hz, 1H, H-18), 6.88 (dt, $J = 16.2, 6.6$ Hz, 1H, H-9), 6.84 (d, $J = 15.3$ Hz, 1H, H-19), 6.17 (d, $J = 11.7$ Hz, 1H, H-4), 6.08 (d, $J = 15.9$ Hz, 1H, H-8), 5.95 (d, $J = 15.3$ Hz, 1H, H-2), 5.90–5.84 (m, 1H, H-15), 5.37 (t, $J = 6.6$ Hz, 1H, H-14), 4.03 (dd, $J = 12.0, 7.8$ Hz, 1H, H-13), 3.98 (s, 3H, *N*-CH₃), 3.90 (dd, $J = 12.0$,

4.5 Hz, 1H, H-13), 3.71 (d, $J = 12.9$ Hz, 1H, H-6), 3.54–3.43 (m, 2H, H₂-11), 3.37 (d, $J = 13.0$ Hz, H-6), 2.44–2.31 (m, 4H, H₂-10 & H₂-16), 1.87 (s, 3H, 5-CH₃), 1.74 (s, 3H, 15-CH₃). ¹³C NMR (75 MHz, CDCl₃) δ 197.0, 179.6, 166.1, 146.9, 144.2, 144.1, 143.2, 140.1, 140.0, 139.1, 133.6, 131.4, 130.3, 125.9, 125.6, 120.7, 69.8, 68.1, 67.7, 54.0, 46.0, 44.9, 33.0, 24.3, 16.8. IR (film) ν_{max} : 1708, 1666, 1624, 1532, 1140 cm⁻¹. HRMS (ESI): m/z calculated for C₂₅H₃₁N₂O₅ [M+H]⁺: 439.2233. Found: 439.2231.

(17R) Zampanolide mimic 52.—Yellow oil. Yield: 45%. $[\alpha]_{\text{D}}^{20}$: -35.6 ($c = 0.18$, MeOH).

¹H NMR (300 MHz, CDCl₃) δ 7.85 (s, 1H, imidazole-H), 7.73 (s, 1H, imidazole-H), 7.66 (dd, $J = 15.0, 11.4$ Hz, 1H, H-3), 7.00 (dd, $J = 15.3, 4.5$ Hz, 1H, H-18), 6.86 (dt, $J = 16.2, 6.6$ Hz, 1H, H-9), 6.83 (dd, $J = 15.3, 1.2$ Hz, 1H, H-19), 6.17 (d, $J = 11.7$ Hz, 1H, H-4), 6.07 (d, $J = 16.2$ Hz, 1H, H-8), 5.94 (d, $J = 15.3$ Hz, 1H, H-2), 5.92–5.83 (m, 1H, H-15), 5.36 (t, $J = 6.0$ Hz, 1H, H-14), 4.03 (dd, $J = 12.0, 7.8$ Hz, 1H, H-13), 3.98 (s, 3H, *N*-CH₃), 3.89 (dd, $J = 12.3, 4.8$ Hz, 1H, H-13), 3.71 (d, $J = 12.9$ Hz, 1H, H-6), 3.54–3.41 (m, 2H, H₂-11), 3.37 (d, $J = 13.2$ Hz, H-6), 2.45–2.32 (m, 4H, H₂-10 & H₂-16), 1.86 (s, 3H, 5-CH₃), 1.74 (s, 3H, 15-CH₃). ¹³C NMR (75 MHz, CDCl₃) δ 196.9, 179.6, 166.1, 146.9, 144.5, 144.0, 143.3, 140.2, 140.1, 138.4, 133.6, 131.5, 130.4, 126.0, 125.6, 120.7, 69.8, 68.1, 67.7, 54.0, 46.0, 44.8, 33.0, 24.3, 16.8. IR (film) ν_{max} : 2916, 2855, 1706, 1664, 1622, 1533, 1378, 1357, 1140 cm⁻¹. HRMS (ESI): m/z calculated for C₂₅H₃₁N₂O₅ [M+H]⁺: 439.2233. Found: 439.2223.

(17S) Zampanolide mimic 53.—Colorless oil. Yield: 72%. $[\alpha]_{\text{D}}^{20}$: +59.6 ($c = 0.07$, MeOH).

¹H NMR (300 MHz, CDCl₃) δ 8.33 (s, 1H, oxazole-H), 7.94 (s, 1H, oxazole-H), 7.66 (dd, $J = 15.0, 11.7$ Hz, 1H, H-3), 7.23 (dd, $J = 15.9, 4.2$ Hz, H, H-18), 7.13 (d, $J = 15.9$ Hz, 1H, H-19), 6.87 (dt, $J = 15.9, 6.6$ Hz, 1H, H-9), 6.16 (d, $J = 11.4$ Hz, 1H, H-4), 6.07 (d, $J = 16.2$ Hz, 1H, H-8), 5.96 (d, $J = 15.0$ Hz, 1H, H-2), 5.91 – 5.86 (m, 1H, H-17), 5.35 (t, $J = 6.3$ Hz, 1H, H-14), 4.02 – 3.88 (m, 2H, H₂-13), 3.72 (d, $J = 13.2$ Hz, 1H, H-6), 3.53 – 3.42 (m, 2H, H₂-11), 3.37 (d, $J = 12.9$ Hz, 1H, H-6), 2.47 – 2.38 (m, 4H, H₂-10 & H₂-16), 1.86 (s, 3H, 5-CH₃), 1.74 (s, 3H, 15-CH₃). ¹³C NMR (75 MHz, CDCl₃) δ 197.1, 183.1, 166.1, 151.1, 146.9, 146.5, 143.6, 143.1, 140.7, 140.0, 133.7, 130.4, 126.0, 125.9, 125.2, 120.8, 69.9, 68.1, 67.7, 46.0, 44.8, 33.0, 24.2, 16.9. IR (film) ν_{max} : 2924, 1716, 1683, 1635, 1559, 1507, 1250 cm⁻¹; HRMS (ESI): m/z calculated for C₂₄H₂₈NO₆ [M+H]⁺: 426.1917. Found: 426.1915.

(17R) Zampanolide mimic 54.—Colorless oil. Yield: 15%. $[\alpha]_{\text{D}}^{20}$: -55.1 ($c = 0.05$, MeOH).

¹H NMR (300 MHz, CDCl₃) δ 8.33 (d, $J = 0.9$ Hz, 1H, oxazole-H), 7.93 (d, $J = 1.2$ Hz, 1H, oxazole-H), 7.66 (dd, $J = 15.3, 11.7$ Hz, 1H, H-3), 7.24 (dd, $J = 15.6, 4.2$ Hz, H, H-18), 7.12 (dd, $J = 15.9, 1.5$ Hz, 1H, H-19), 6.87 (dt, $J = 16.2, 6.6$ Hz, 1H, H-9), 6.16 (d, $J = 11.4$ Hz, 1H, H-4), 6.07 (d, $J = 16.2$ Hz, 1H, H-8), 5.96 (d, $J = 15.0$ Hz, 1H, H-2), 5.91 – 5.86 (m, 1H, H-17), 5.36 (t, $J = 5.7$ Hz, 1H, H-14), 4.32 (dd, $J = 12.3, 7.8$ Hz, 1H, H-13), 3.89 (dd, $J = 12.0, 5.1$ Hz, 1H, H-13), 3.71 (d, $J = 13.2$ Hz, 1H, H-6), 3.53 – 3.42 (m, 2H, H₂-11), 3.38 (d, $J = 13.2$ Hz, 1H, H-6), 2.47 – 2.38 (m, 4H, H₂-10 & H₂-16), 1.86 (s, 3H, 5-CH₃), 1.74 (s, 3H, 15-CH₃). ¹³C NMR (75 MHz, CDCl₃) δ 197.0, 183.1, 166.1, 151.1, 146.9, 146.5, 143.6, 143.1, 140.8, 140.0, 133.7, 130.4, 126.0, 125.9, 125.3, 120.9, 70.0, 68.1, 67.8, 46.0, 44.8, 33.0, 24.3, 16.9. IR (film) ν_{max} : 2922, 2853, 1708, 1676, 1628, 1560,

1092 cm⁻¹; HRMS (ESI): *m/z* calculated for C₂₄H₂₈NO₆ [M+H]⁺: 426.1917. Found: 426.1910.

(17S) Zampanolide mimic 55.—Colorless oil. Yield: 24%. [α]_D²⁰: +47.2 (*c* = 0.06, MeOH). ¹H NMR (300 MHz, CDCl₃) δ 7.94 (d, *J* = 6.9 Hz, 2H, phenyl-H), 7.67 (dd, *J* = 15.3, 11.7 Hz, 1H, H-3), 7.58 (t, *J* = 7.8 Hz, 1H, phenyl-H), 7.48 (t, *J* = 7.5 Hz, 2H, phenyl-H), 7.09 (d, *J* = 15.6 Hz, 1H, H-19), 7.00 (dd, *J* = 15.3, 4.2 Hz, 1H, H-18), 6.87 (dt, *J* = 15.9, 6.9 Hz, 1H, H-10), 6.17 (d, *J* = 11.1 Hz, 1H, H-4), 6.07 (d, *J* = 16.2 Hz, 1H, H-8), 5.96 (d, *J* = 14.7 Hz, 1H, H-2), 5.93–5.81 (m, 1H, H-17), 5.37 (t, *J* = 5.4 Hz, 1H, H-14), 4.04 (dd, *J* = 12.0, 8.1 Hz, 1H, H-13), 3.90 (dd, *J* = 12.3, 4.8 Hz, 1H, H-13), 3.72 (d, *J* = 12.6 Hz, 1H, H-6), 3.54–3.39 (m, 2H, H₂-11), 3.37 (d, *J* = 12.9 Hz, 1H, H-6), 2.45–2.35 (m, 4H, H₂-10 & H₂-16), 1.87 (s, 3H, 5-CH₃), 1.75 (s, 3H, 15-CH₃). ¹³C NMR (75 MHz, CDCl₃) δ 197.0, 190.4, 166.2, 146.9, 145.6, 143.2, 140.0, 137.7, 133.8, 133.3, 130.4, 128.9, 128.8, 126.0, 125.9, 125.2, 120.8, 70.1, 68.1, 67.7, 46.0, 44.9, 33.0, 24.3, 16.9. IR (film) $\nu_{\max}$: 2923, 2853, 1715, 1670, 1628, 1597 cm⁻¹; HRMS (ESI): *m/z* calculated for C₂₇H₃₁O₅ [M+H]⁺: 435.2172. Found: 435.2170.

(17R) Zampanolide mimic 56.—Colorless oil. Yield: 29%. [α]_D²⁰: -56.0 (*c* = 0.08, MeOH). ¹H NMR (300 MHz, CDCl₃) δ 7.94 (dt, *J* = 7.2, 2.1 Hz, 2H, phenyl-H), 7.66 (dd, *J* = 15.0, 11.7 Hz, 1H, H-3), 7.58 (tt, *J* = 7.2, 1.2 Hz, 1H, phenyl-H), 7.48 (tt, *J* = 7.8, 1.5 Hz, 2H, phenyl-H), 7.08 (dd, *J* = 15.3, 0.9 Hz, 1H, H-19), 7.00 (dd, *J* = 15.36, 4.2 Hz, 1H, H-18), 6.87 (dt, *J* = 15.9, 6.6 Hz, 1H, H-10), 6.17 (d, *J* = 11.4 Hz, 1H, H-4), 6.07 (d, *J* = 16.2 Hz, 1H, H-8), 5.96 (d, *J* = 15.3 Hz, 1H, H-2), 5.90–5.87 (m, 1H, H-17), 5.37 (t, *J* = 5.1 Hz, 1H, H-14), 4.04 (dd, *J* = 12.0, 7.8 Hz, 1H, H-13), 3.90 (dd, *J* = 12.3, 5.1 Hz, 1H, H-13), 3.72 (d, *J* = 12.9 Hz, 1H, H-6), 3.54–3.42 (m, 2H, H₂-11), 3.37 (d, *J* = 12.9 Hz, 1H, H-6), 2.45–2.35 (m, 4H, H₂-10 & H₂-16), 1.87 (s, 3H, 5-CH₃), 1.75 (s, 3H, 15-CH₃). ¹³C NMR (75 MHz, CDCl₃) δ 197.0, 190.4, 166.2, 146.9, 145.6, 143.2, 140.0, 137.7, 133.7, 133.3, 130.4, 128.8, 128.8, 126.0, 126.0, 125.2, 120.8, 70.1, 68.1, 67.7, 45.9, 44.9, 33.0, 24.3, 16.9. IR (film) $\nu_{\max}$: 2918, 1709, 1672, 1629 cm⁻¹; HRMS (ESI): *m/z* calculated for C₂₇H₃₁O₅ [M+H]⁺: 435.2172. Found: 435.2162.

(17S) Zampanolide mimic 57.—Pale yellow oil. Yield: 89%. [α]_D²⁰: +55.3 (*c* = 0.2, MeOH). ¹H NMR (300 MHz, CDCl₃) δ 7.97 (dd, *J* = 9.0, 5.4 Hz, 2H, phenyl-H), 7.66 (dd, *J* = 15.3, 11.7 Hz, 1H, H-3), 7.15 (t, *J* = 8.7 Hz, 2H, phenyl-H), 7.06 (d, *J* = 15.9 Hz, 1H, H-19), 6.99 (dd, *J* = 15.3, 3.6 Hz, 1H, H-18), 6.87 (dt, *J* = 16.2, 6.6 Hz, 1H, H-9), 6.17 (d, *J* = 11.1 Hz, 1H, H-4), 6.07 (d, *J* = 16.2 Hz, 1H, H-8), 5.95 (d, *J* = 15.0 Hz, 1H, H-2), 5.93–5.86 (m, 1H, H-17), 5.37 (t, *J* = 6.6 Hz, 1H, H-14), 4.04 (dd, *J* = 12.0, 7.8 Hz, 1H, H-13), 3.90 (dd, *J* = 12.0, 4.8 Hz, 1H, H-13), 3.72 (d, *J* = 13.2 Hz, 1H, H-6), 3.54–3.43 (m, 2H, H₂-11), 3.37 (d, *J* = 13.2 Hz, 1H, H-6), 2.43–2.39 (m, 4H, H₂-10 & H₂-16), 1.87 (s, 3H, 5-CH₃), 1.74 (s, 3H, 15-CH₃). ¹³C NMR (75 MHz, CDCl₃) δ 196.9, 188.6, 166.1, 166.0 (d, *J* = 259.0 Hz), 146.9, 145.8, 143.3, 140.1, 134.0 (d, *J* = 2.9 Hz), 133.7, 131.5, 131.4, 130.4, 125.9 (d, *J* = 2.3 Hz), 124.8, 120.7, 116.0 (d, *J* = 21.8 Hz), 70.0, 68.1, 67.7, 45.9, 44.8, 33.0, 24.3, 16.8. IR (film) $\nu_{\max}$: 2923, 2853, 1712, 1663, 1629, 1597, 1507 cm⁻¹. HRMS (ESI): *m/z* calculated for C₂₇H₃₀FO₅ [M+H]⁺: 453.2077. Found: 453.2064.

(17R) Zampanolide mimic 58.—Pale yellow oil. Yield: 33%. $[\alpha]_{\text{D}}^{20}$: - 65.0 ($c = 0.10$, MeOH). ^1H NMR (300 MHz, CDCl_3) δ 7.98 (dd, $J = 8.7, 5.4$ Hz, 2H, phenyl-H), 7.66 (dd, $J = 15.0, 11.4$ Hz, 1H, H-3), 7.16 (t, $J = 8.4$ Hz, 2H, phenyl-H), 7.06 (d, $J = 15.6$ Hz, 1H, H-19), 6.99 (dd, $J = 15.3, 3.6$ Hz, 1H, H-18), 6.87 (dt, $J = 15.9, 6.9$ Hz, 1H, H-9), 6.17 (d, $J = 11.4$ Hz, 1H, H-4), 6.07 (d, $J = 16.2$ Hz, 1H, H-8), 5.95 (d, $J = 15.3$ Hz, 1H, H-2), 5.92–5.86 (m, 1H, H-17), 5.37 (t, $J = 6.3$ Hz, 1H, H-14), 4.04 (dd, $J = 12.0, 7.8$ Hz, 1H, H-13), 3.90 (dd, $J = 12.0, 4.8$ Hz, 1H, H-13), 3.72 (d, $J = 13.2$ Hz, 1H, H-6), 3.54–3.42 (m, 2H, H_2 -11), 3.37 (d, $J = 13.2$ Hz, 1H, H-6), 2.45 – 2.39 (m, 4H, H_2 -10 & H_2 -16), 1.87 (s, 3H, 5- CH_3), 1.74 (s, 3H, 15- CH_3). ^{13}C NMR (75 MHz, CDCl_3) δ 196.9, 188.6, 166.1, 165.9 (d, $J = 255.0$ Hz), 146.9, 145.8, 143.3, 140.1, 134.0 (d, $J = 3.0$ Hz), 133.7, 131.5, 131.4, 130.4, 126.0, 124.8, 120.7, 116.1 (d, $J = 22.5$ Hz), 70.1, 68.1, 67.7, 46.0, 44.8, 33.0, 24.3, 16.9. IR (film) ν_{max} : 2916, 2857, 1709, 1672, 1628, 1597, 1507 cm^{-1} . HRMS (ESI): m/z calculated for $\text{C}_{27}\text{H}_{30}\text{FO}_5$ $[\text{M}+\text{H}]^+$: 453.2077. Found: 453.2068.

(17S) Zampanolide mimic 59.—Red-brown oil. Yield: 38%. $[\alpha]_{\text{D}}^{20}$: +83.1 ($c = 0.06$, MeOH). ^1H NMR (300 MHz, CDCl_3) δ 7.75 (dt, $J = 7.5, 1.8$ Hz, 1H, phenyl-H), 7.65 (dd, $J = 15.3, 11.7$ Hz, 1H, H-3), 7.56–7.48 (m, 1H, phenyl-H), 7.27–7.21 (overlapped, 1H, phenyl-H), 7.14 (ddd, $J = 10.8, 8.4, 0.9$ Hz, 1H, phenyl-H), 6.96–6.95 (overlapped, 2H, H-18 & H-19), 6.86 (dt, $J = 15.9, 6.9$ Hz, 1H, H-9), 6.16 (d, $J = 11.4$ Hz, 1H, H-4), 6.07 (d, $J = 16.2$ Hz, 1H, H-8), 5.94 (d, $J = 15.0$ Hz, 1H, H-2), 5.87 (dt, $J = 5.9, 2.4$ Hz, 1H, H-17), 5.36 (t, $J = 6.3$ Hz, 1H, H-14), 4.03 (dd, $J = 12.0, 7.8$ Hz, 1H, H-13), 3.90 (dd, $J = 12.0, 4.8$ Hz, 1H, H-13), 3.69 (d, $J = 13.2$ Hz, 1H, H-6), 3.53–3.40 (m, 2H, H_2 -11), 3.38 (d, $J = 12.9$ Hz, 1H, H-6), 2.45–2.39 (m, 4H, H_2 -16 & H_2 -10), 1.86 (s, 3H, 5- CH_3), 1.73 (s, 3H, 15- CH_3). ^{13}C NMR (75 MHz, CDCl_3) δ 197.0, 188.9, 166.1, 161.5 (d, $J = 259.5$ Hz), 146.9, 145.8, 143.1, 140.0, 134.4 (d, $J = 8.3$ Hz), 133.7, 131.2 (d, $J = 2.3$ Hz), 130.4, 128.6 (d, $J = 6.8$ Hz), 126.7 (d, $J = 12.8$ Hz), 126.0 (d, $J = 7.5$ Hz), 124.7 (d, $J = 3.8$ Hz), 120.8, 116.9, 116.6, 69.9, 68.0, 67.7, 45.9, 44.7, 33.0, 24.3, 16.9. IR (film) ν_{max} : 2923, 2855, 1712, 1671, 1628, 1610, 1480, 1452, 1279 cm^{-1} . HRMS (ESI): m/z calculated for $\text{C}_{27}\text{H}_{30}\text{FO}_5$ $[\text{M}+\text{H}]^+$: 453.2077. Found: 453.2074.

(17R) Zampanolide mimic 60.—Light yellow oil. Yield: 20%. $[\alpha]_{\text{D}}^{20}$: -91.0 ($c = 0.05$, MeOH). ^1H NMR (300 MHz, CDCl_3) δ 7.75 (dt, $J = 7.8, 2.1$ Hz, 1H, phenyl-H), 7.65 (dd, $J = 15.0, 11.4$ Hz, 1H, H-3), 7.56–7.48 (m, 1H, phenyl-H), 7.24 (dt, $J = 7.5, 0.9$ Hz, 1H, phenyl-H), 7.14 (ddd, $J = 11.1, 8.4, 1.2$ Hz, 1H, phenyl-H), 6.96–6.95 (overlapped, 2H, H-18 & H-19), 6.87 (dt, $J = 16.2, 6.6$ Hz, 1H, H-9), 6.16 (d, $J = 11.7$ Hz, 1H, H-4), 6.07 (d, $J = 16.2$ Hz, 1H, H-8), 5.94 (d, $J = 15.0$ Hz, 1H, H-2), 5.87 (dt, $J = 8.1, 3.6$ Hz, 1H, H-17), 5.36 (t, $J = 5.4$ Hz, 1H, H-14), 4.03 (dd, $J = 12.0, 7.8$ Hz, 1H, H-13), 3.90 (dd, $J = 12.0, 5.1$ Hz, 1H, H-13), 3.69 (d, $J = 12.9$ Hz, 1H, H-6), 3.53–3.40 (m, 2H, H_2 -11), 3.39 (d, $J = 13.2$ Hz, 1H, H-6), 2.45–2.39 (m, 4H, H_2 -16 & H_2 -10), 1.86 (s, 3H, 5- CH_3), 1.73 (s, 3H, 15- CH_3). ^{13}C NMR (75 MHz, CDCl_3) δ 197.0, 188.9, 166.1, 161.5 (d, $J = 268.5$ Hz), 146.9, 145.8, 143.1, 134.4 (d, $J = 9.8$ Hz), 133.7, 131.2, 130.4, 128.6, 126.6, 126.0 (d, $J = 6.0$ Hz), 124.7, 120.8, 116.8, 116.6, 69.9, 68.0, 67.7, 45.9, 44.7, 33.0, 24.3, 16.9. IR (film) ν_{max} : 2919, 2852, 1709, 1669, 1627, 1609, 1481, 1452 cm^{-1} . HRMS (ESI): m/z calculated for $\text{C}_{27}\text{H}_{30}\text{FO}_5$ $[\text{M}+\text{H}]^+$: 453.2077. Found: 453.2068.

(17S) Zampanolide mimic 61.—Red-brown oil. Yield: 50%. $[\alpha]_D^{20}$: +57.7 ($c = 0.08$, MeOH). ^1H NMR (300 MHz, CDCl_3) δ 7.71 (dt, $J = 7.8, 1.2$ Hz, 1H, phenyl-H), 7.67–7.60 (m, 2H, phenyl-H & H-3), 7.50–7.43 (m, 1H, phenyl-H), 7.31–7.24 (m, 1H, phenyl-H), 7.03–7.02 (overlapped, 2H, H-19 & H-18), 6.87 (dt, $J = 16.2, 6.6$ Hz, 1H, H-9), 6.17 (d, $J = 11.4$ Hz, 1H, H-4), 6.07 (d, $J = 16.2$ Hz, 1H, H-8), 5.96 (d, $J = 15.0$ Hz, 1H, H-2), 5.92–5.87 (m, 1H, H-17), 5.36 (t, $J = 6.6$ Hz, 1H, H-14), 4.04 (dd, $J = 12.3, 7.8$ Hz, 1H, H-13), 3.90 (dd, $J = 12.3, 4.8$ Hz, 1H, H-13), 3.72 (d, $J = 12.9$ Hz, 1H, H-6), 3.54–3.42 (m, 2H, H₂-11), 3.37 (d, $J = 12.9$ Hz, 1H, H-6), 2.45–2.34 (m, 4H, H₂-16 & H₂-10), 1.87 (s, 3H, 5-CH₃), 1.74 (s, 3H, 15-CH₃). ^{13}C NMR (75 MHz, CDCl_3) δ 196.9, 188.9, 166.1, 163.0 (d, $J_{\text{CF}} = 246.8$ Hz), 146.9, 146.5, 143.3, 140.11, 140.07, 139.8 (139.7), 133.6, 130.6 (130.5), 130.4, 125.9, 124.7, 124.5, 120.7, 120.4 (120.2), 115.7 (115.4), 70.0, 68.1, 67.7, 45.9, 44.8, 33.0, 24.3, 16.9. IR (film) ν_{max} : 2921, 2851, 1716, 1675, 1628, 1521, 1507 cm^{-1} . HRMS (ESI): m/z calculated for $\text{C}_{27}\text{H}_{30}\text{FO}_5$ $[\text{M}+\text{H}]^+$: 453.2077. Found: 453.2075.

(17R) Zampanolide mimic 62.—Red-brown oil. Yield: 29%. $[\alpha]_D^{20}$: -69.0 ($c = 0.10$, MeOH). ^1H NMR (300 MHz, CDCl_3) δ 7.71 (dt, $J = 8.4, 1.5$ Hz, 1H, phenyl-H), 7.67–7.60 (m, 2H, phenyl-H & H-3), 7.50–7.43 (m, 1H, phenyl-H), 7.31–7.24 (m, 1H, phenyl-H), 7.03–7.02 (overlapped, 2H, H-19 & H-18), 6.87 (dt, $J = 16.2, 6.6$ Hz, 1H, H-9), 6.17 (d, $J = 11.4$ Hz, 1H, H-4), 6.07 (d, $J = 16.2$ Hz, 1H, H-8), 5.96 (d, $J = 15.3$ Hz, 1H, H-2), 5.96–5.89 (m, 1H, H-17), 5.36 (t, $J = 7.2$ Hz, 1H, H-14), 4.04 (dd, $J = 12.0, 7.8$ Hz, 1H, H-13), 3.90 (dd, $J = 12.6, 5.1$ Hz, 1H, H-13), 3.72 (d, $J = 13.2$ Hz, 1H, H-6), 3.54–3.42 (m, 2H, H₂-11), 3.37 (d, $J = 13.2$ Hz, 1H, H-6), 2.45–2.33 (m, 4H, H₂-16 & H₂-10), 1.87 (s, 3H, 5-CH₃), 1.74 (s, 3H, 15-CH₃). ^{13}C NMR (75 MHz, CDCl_3) δ 197.0, 189.0, 166.1, 163.1 (d, $J_{\text{CF}} = 250.5$ Hz), 146.9, 146.5, 143.3, 143.1, 140.1, 139.7, 133.6, 130.4, 126.0, 124.7, 124.6, 120.7, 120.2, 115.7, 70.0, 68.1, 67.7, 45.9, 44.8, 33.0, 24.3, 16.9. HRMS (ESI): m/z calculated for $\text{C}_{27}\text{H}_{30}\text{FO}_5$ $[\text{M}+\text{H}]^+$: 453.2077. Found: 453.2075.

Cell culture

All cell lines were initially purchased from American Type Culture Collection (ATCC). The PC-3 and LNCaP prostate cancer cell lines were routinely cultured in RPMI-1640 medium supplemented with 10% FBS and 1% penicillin/streptomycin. Cultures were maintained in a high humidity environment supplemented with 5% carbon dioxide at a temperature of 37 °C. The DU-145 prostate cancer cells were routinely cultured in Eagle's Minimum Essential Medium (EMEM) supplemented with 10% FBS and 1% penicillin/ streptomycin.

Docetaxel-resistant prostate cancer cell lines were established based on the procedure illustrated in the literature.^{22–23} Docetaxel resistant DU145 and PC-3 cell lines (DU145/DTX and PC-3/DTX) were developed over a period of one year by stepwise increased concentrations of docetaxel. Cells were continuously maintained in docetaxel, with treatments beginning at the initial IC₅₀ of the respective parent cell lines. Media containing docetaxel were changed every 2–3 days. As cells displayed resistance to treatments of docetaxel the concentration was increased.

WST-1 cell proliferation assay.

PC-3, DU-145, or LNCaP cells were plated in 96-well plates at a density of 3,200 each well in 200 μ L of culture medium. The cells were then treated with positive reference, or synthesized mimics separately at different doses for 3 days, while equal treatment volumes of DMSO were used as vehicle control. The cells were cultured in a CO₂ incubator at 37 °C for three days. 10 μ L of the premixed WST-1 cell proliferation reagent (Clontech) was added to each well. After mixing gently for one min on an orbital shaker, the cells were incubated for an additional 3 h at 37 °C. To ensure homogeneous distribution of color, it was important to mix gently on an orbital shaker for 1 min. The absorbance of each well was measured using a microplate-reader (Synergy HT, BioTek) at a wavelength of 430 nm. The IC₅₀ value is the concentration of each compound that inhibits cell proliferation by 50% under the experimental conditions and is the average from triplicate determinations that were reproducible and statistically significant. For calculating the IC₅₀ values, a linear proliferative inhibition was made based on at least five dosages for each compound.

F2N12S and CYTOX AADvanced double staining assay

PC-3 cells were plated in 24-well plates at a density of 200,000 each well in 400 μ L of culture medium. After 3 h of cell attachment, the cells were treated with the test compound at different concentrations and cultured in a CO₂ incubator at 37 °C for 16 h while equal treatment volumes of DMSO were used as vehicle control. Both attached and floating cells were collected in a centrifuge tube by centrifugation at rcf value of 450 g for 5 min. The collected cells were re-suspended with 500 μ L HBSS to remove proteins which may affect flow signal and centrifuged again. After discarding the supernatant, the collected cells were re-suspended with 300 μ L HBSS and stained with 0.3 μ L of F2N12S for 3–5 min followed by 0.3 μ L SYTOX AADvanced for an additional 5 min. The fluorescence intensity of the two probes was further measured in individual PC-3 cells using an Attune flow cytometer (Life Technologies) within 0.5–1 h after staining.

Statistical analysis

All data are represented as the mean $\pm$ standard deviation (S.D.) for the number of experiments indicated. Other differences between treated and control groups were analyzed using the Student's t-test. A p-value < 0.05 was considered statistically significant.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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(-)-zampanolide (1)

epothilone A (2)

Fig. 1.
Structures of (-)-zampanolide (1) and epothilone A (2)

Fig. 2.
Structures of (17S)-desTHPzampanolide (**3**), desTHPdactylolides (**4** & **5**) and generalized structure (**6**) for target mimics

Fig. 3.
Design of stabilized side chains

Fig. 4.
Potency of mimics **51** and **3**

Fig. 5. Evolution of viable, apoptotic, and necrotic PC-3 cells populations in response to increasing dosages of 52.

Scheme 1. Thermolysis of (+)-zampanolide (**7**) to (+)-dactylolide (**8**)

Scheme 2. Synthesis of key intermediates (17*S*)-**13** and (17*R*)-**14**.

Scheme 3.
Synthesis of side chain precursors (**21-26**).

Scheme 4.
Synthesis of zampanolide mimics (**51** - **62**)

Table 1.

Anti-proliferative activity of zampanolide mimics **51-62**

Compounds	IC ₅₀ : (μM) ^a		R/S ^d	IC ₅₀ : (μM) ^a		R/S ^c	IC ₅₀ : (μM) ^a
	PC-3 ^b	PC-3/DTX ^c		DU145 ^e	DU145/DTX ^f		LNCaP ^g
Docetaxel	0.0019 ± 0.0006	2.34 ± 0.25	1232	0.0012 ± 0.0003	8.58 ± 0.39	7150	0.0002 ± 0.00005
4 (17S)	11.91 ± 3.68	15.42 ± 1.23	1.3	11.58 ± 0.21	15.33 ± 1.24	1.3	13.46 ± 0.90
51 (17S)	0.88 ± 0.19	2.97 ± 0.09	3.4	0.86 ± 0.25	2.78 ± 0.16	3.2	0.76 ± 0.29
53 (17S)	2.17 ± 0.19	4.07 ± 1.41	1.9	2.70 ± 0.91	2.24 ± 0.22	0.8	1.78 ± 0.52
55 (17S)	2.30 ± 0.57	2.55 ± 0.63	1.1	2.94 ± 0.09	2.31 ± 0.20	0.8	3.85 ± 0.43
57 (17S)	2.10 ± 0.28	2.13 ± 0.50	1.0	5.59 ± 0.91	4.87 ± 1.44	0.9	4.04 ± 0.49
59 (17S)	2.85 ± 0.11	2.17 ± 0.02	0.8	3.16 ± 0.38	1.92 ± 0.10	0.6	2.10 ± 0.20
61 (17S)	2.25 ± 0.83	1.72 ± 0.12	0.8	2.30 ± 0.04	2.25 ± 0.67	1.0	2.19 ± 0.66
5 (17R)	5.27 ± 0.65	4.41 ± 0.44	0.8	5.41 ± 0.11	8.03 ± 0.13	1.5	3.22 ± 0.31
52 (17R)	0.35 ± 0.05	0.30 ± 0.05	0.9	0.29 ± 0.03	0.46 ± 0.10	1.6	0.35 ± 0.02
54 (17R)	3.04 ± 0.25	2.75 ± 0.05	0.9	3.06 ± 0.24	3.35 ± 0.27	1.1	3.19 ± 0.98
56 (17R)	0.61 ± 0.01	0.94 ± 0.05	1.5	3.73 ± 0.72	2.57 ± 0.76	0.7	1.39 ± 0.18
58 (17R)	1.03 ± 0.08	1.09 ± 0.10	1.0	2.09 ± 0.48	1.66 ± 0.32	0.8	3.00 ± 0.53
60 (17R)	2.90 ± 0.30	2.91 ± 0.20	1.0	4.50 ± 0.49	4.43 ± 0.23	1.0	4.60 ± 0.76
62 (17R)	2.65 ± 0.30	2.31 ± 0.40	0.9	2.93 ± 0.65	3.43 ± 0.16	1.2	3.74 ± 1.43

^aIC₅₀ is the compound concentration effective in inhibiting 50% of cell viability measured by WST-1 cell proliferation assay after 3 days of exposure. The data are presented as the mean ± standard deviation of the mean.

^bHuman androgen-insensitive prostate cancer cell line derived from bone metastasis of prostate tumor

^cDocetaxel-resistant PC-3 prostate cancer cell line

^dThe relative resistance of the two cell lines obtained by dividing the IC₅₀ value of the resistance cell line by that of the parental cell line.

^eHuman androgen-insensitive prostate cancer cell line derived from brain metastasis of prostate tumor

^fDocetaxel-resistant DU145 prostate cancer cell line

^gHuman androgen-sensitive prostate cancer cell line