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Total Synthesis and Selective Activity of a New Class of Conformationally Restrained Epothilones

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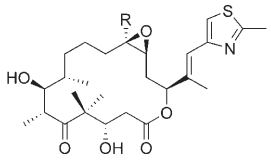
Abstract: Stereoselective total syntheses of two novel conformationally restrained epothilone analogues are described. Evans asymmetric alkylation, Brown allylation, and a diastereoselective aldol reaction served as the key steps in the stereoselective synthesis of one of the two key fragments of the convergent synthetic approach. Enzyme resolution was employed to obtain the second fragment as a single enantiomer. The molecules were assembled by esterification, followed by ring-closing metathesis. In preliminary cytotoxicity studies, one of the analogues showed strong and selective growth inhibitory activity against two leukemia cell lines over solid human tumor cell lines. The precise biological mechanism of action and high degree of selectivity of this analogue remain to be examined.

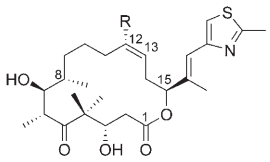
Keywords: antitumor agents · epothilone analogues · macrolide · natural products · total synthesis

Introduction

The clinically used anticancer drug paclitaxel (taxol) exerts its cytotoxic activity by a mechanism invoking the stabilization of microtubules.[1,2] However, the susceptibility of the drug to multiple drug resistance has stimulated extensive research on molecules with a paclitaxel-like mechanism of action.[3,4] The most extensively investigated of the new molecular entities discovered are the epothilones, a class of macrolide natural products initially isolated from a soil bacterium.[3,5,6] Some epothilones exhibit more potent anticancer activity than paclitaxel and have favorable attributes that may improve their pharmacological profile.[7,8]



R = H epothilone A
R = CH_3 epothilone B



R = H epothilone C
R = CH_3 epothilone D

Replacing the thiazole ring in epothilone B by methylpyridine rings, in which the nitrogen atom is *ortho* to the pyridine-vinyl linker attachment, produced analogues with higher potencies against drug-resistant tumor cells.[9] The role of the N atom at an *ortho*-position in the heterocycle has been attributed to a hydrogen-bond interaction between the thiazole N atom and a protonated His residue in tubulin.[10–13] The 16-Me and 19-H adopt a *syn* orientation, liberating the thiazole N atom from the steric bulk of the 16-Me, making it more accessible for potential hydrogen bonding. Rigidification of the aromatic side chain through incorporation of the C-16–C-17 olefinic double bond into a fused heteroaromatic ring system such as benzothiazole resulted in analogues more potent than parent epothilone B and D.[14,15] Interestingly, in contrast to the pyridine analogues, there was no dependence of the tubulin-polymerizing activity of these rigidified analogues on the position of the nitrogen atom in the heterocycles.[16] Antiproliferative activity, on the other hand, showed a strong dependence on the position of

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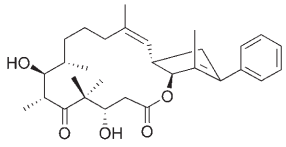
Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author: General methods, syntheses of intermediates **3** and **4**, spectral data for all compounds, and cytotoxicity data for compound **1b**.

the nitrogen atom, as in the pyridine analogues. Attempts to rigidify the southern C-1–C-8 sector of the molecule have resulted in loss of biological activity.[17,18] Analogues made by rigidification of some parts of the northern C-9–C-13 sector have retained biological activity.[19–21] A series of conformationally rigidified analogues bridging the northern and southern sectors across the macrocycle were prepared recently. However, their biological activities have not been reported.[22]

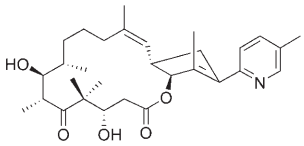
The extensive database on SAR for epothilone has led to the discovery of potent epothilones.[23,24] At least five analogues are currently in different stages of clinical development.[7] Most of the current potent epothilone analogues bear close structural resemblance to the parent compounds. While largely uninvestigated, compounds with more stringent structural modifications of the epothilone scaffold may produce new lead structures with altered pharmacological profiles for drug discovery.[25,26]

Results and Discussion

We designed a new class of conformationally restrained analogues of epothilones (compounds **1a** and **1b**) by restricting



1a



1b

the mobility of the aromatic side chain. In doing so, we retained the C-1–C-8 sector unchanged, in view of its seemingly crucial role in biological activity. A single methylene bridge was introduced between C-14 and C-17. The resulting cyclopentene moiety, which incorporated the C-16–C-17 double bond, was designed to rigidify the side chain while still permitting sufficient mobility of the pyridine ring to allow for the preferred N-atom orientation for a hydrogen bonding interaction with the receptor.[11]

The choice of a *S* configuration at the new chiral center at C-14 in the designed analogues was based on molecular modeling studies, and is consistent with the observations of Taylor et al.,[27,28] whose extensive studies on the bioactive conformation of epothilones have shown that the (*S*)-C-14-Me analogue of epothilone D is far more active than the corresponding *R* epimer. We performed energy minimizations for **1b** (C-14-*S*) as well as for its C-14-(*R*) epimer and for epothilone D by using Gaussian 03[29] at the B3LYP/6—311++G(d,p) level (Figure 1). Compound **1b** was found to be more stable than the C-14-(*R*) epimer by 8.8 kcal mol^{-1}. The main ring configuration in the minimized structure of epothilone D remained very similar to the X-ray crystal structure of 14-(*S*)-methyl-epothilone D (Figure 1).[27] In Figure 1, the energy-minimized structures of **1b** and its C-14-(*R*) epimer are aligned with the minimum-energy structure of epothilone D by using the heavy atoms in the large ring and the root-mean-square deviations were found to be 0.287 and 0.283 Å for **1b** and its C-14-(*R*) epimer, respectively. In comparison, the root mean deviation of the heavy-atom alignment for epothilone D and the X-ray crystal structure of 14-(*S*) -methyl-epothilone D was found to be 0.186 Å. As can be seen from Figure 1, the side chain heteroaromatic ring segment in **1b**, compared to its C-14-(*R*) epimer, can adopt an overall configuration close to those of epothilone D and 14-(*S*)-methyl-epothilone D. The conformational flexibility of the heteroaromatic ring-containing side chains of these analogues permit the N atoms in the heteroaromatic rings to come within 1 Å of each other. In contrast, the heteroaromatic ring-containing side chain of the C-14-(*R*) epimer of **1b** is virtually perpendicular to the plane of the macrocycle.

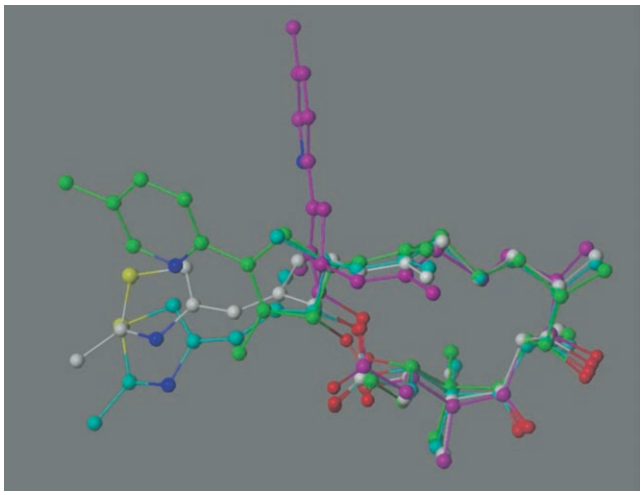
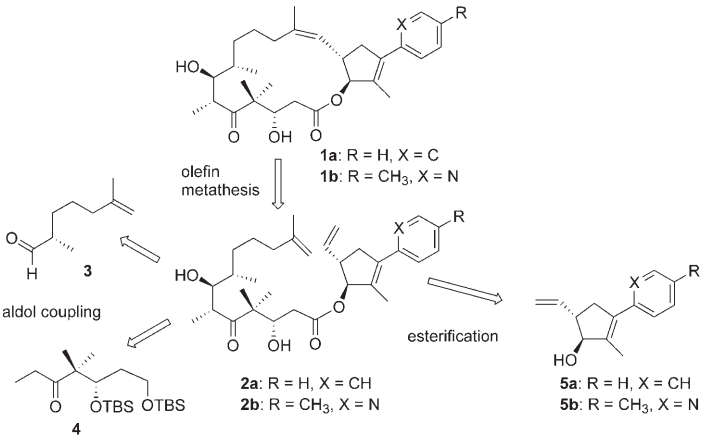


Figure 1. Energy-minimized epothilone D (gray); X-ray crystal structure of 14-(*S*)-methyl-epothilone D (cyan); compound **1b** (green); and C-14-(*R*)-**1b** (magenta). The nitrogen atoms are shown in blue, the oxygen atoms are in red, and the sulfur atoms are in yellow. Main-ring heavy atoms were used in the alignment and the energy-minimized epothilone D was used as the reference structure. The figure was created by using Sybyl 7.3 (Tripos, St. Louis, MO).

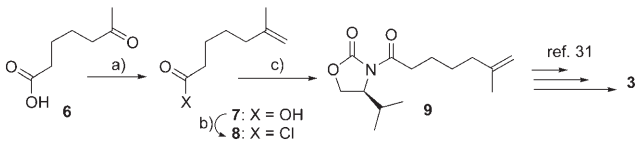
A convergent synthetic approach with ring-closing metathesis (RCM) of **2a** and **2b** in the final step was adapted (Scheme 1). Retrosynthetic disconnection of **2a** and **2b** led to the three key synthons **3**, **4**, and either **5a** or **5b**. The stereoselective aldol coupling product between aldehyde **3** and ketone **4** would be converted to the corresponding carboxylic acid and then esterified with alcohols **5a** and **5b** to give **2a** and **2b**. This intermediate would then undergo RCM to yield the desired macrolide skeleton.

Aldehyde **3** was made by using the Evans asymmetric alkylation protocol (Scheme 2).[30] Wittig olefination of the keto acid **6** gave the alkene **7**. It was converted to the aldehyde **3** via the imide **9**, following Schinzer's procedure.[31]

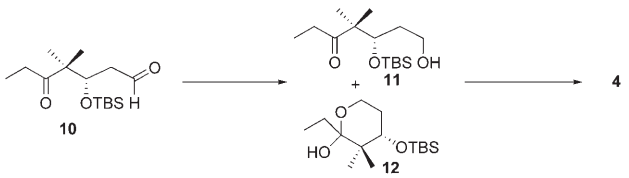
The bis-silyl ether ketone **4** was made as shown in Scheme 3. Compound **10** was synthesized as reported earlier.[32] Selective reduction of the aldehyde group of **10** with



Scheme 1. Retrosynthetic analysis of the designed epothilones.



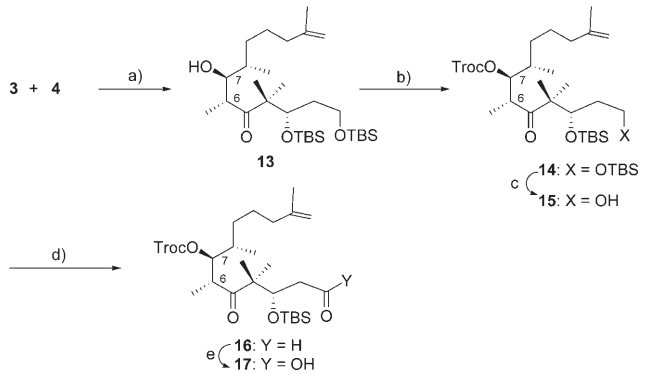
Scheme 2. a) $MeP^{+}(Ph)_3Br^{-}$, *n*BuLi, DMSO/THF, RT, 48 h, 78%; b) $(COCl)_2$, benzene; c) (*S*)-4-isopropyl-2-oxazolidonone, *n*BuLi, THF, −78°C.



Scheme 3. a) $NaBH_4$, CH_2Cl_2, EtOH, −78°C; b) TBSCl, imidazole, CH_2Cl_2, 0°C. TBSCl = *tert*-butyldimethylsilyl chloride.

$NaBH_4$ gave the primary alcohol **11** as a mixture with its hemiacetal **12**, and was converted to the bis-silyl ether **4** with TBSCl and imidazole.

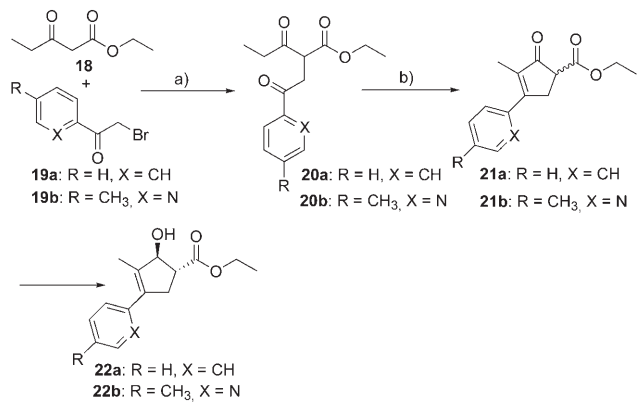
A highly diastereoselective aldol reaction between the aldehyde **3** and ketone **4** under kinetic control generated aldol **13** (Scheme 4). The desired *syn* aldol **13** was formed together with the unwanted *syn* diastereomer (10:1) without any detectable formation of the *anti* product.[33] The *syn* diastereomers were separated by column chromatography. The *S* stereochemistry at C-7 in **13** was confirmed by Mosher's ester analysis.[34] The hydroxyl function was protected with a Troc group to give compound **14**. The use of the Troc group[35] in this context was based on an earlier failed sequence. We had initially approached the synthesis of **1a** by employing Suzuki coupling for making the C-12–C-13 double bond and Yamaguchi macrolactonization for final ring closure and with a TBS (and later TES) protecting group at this position instead of Troc. However, desilylation of these groups in the final step proved problematic. Milder desilylating agents were ineffective and harsher conditions gave decomposition products. Thus, the present protocol was adopted with olefin metathesis for final ring closure. Se-



Scheme 4. a) LDA, THF, −78°C, 83%; b) TrocCl, pyridine, CH_2Cl_2, 0°C, 1 h, 93%; c) CSA, CH_2Cl_2/MeOH, 0°C, 7 h, 87%; d) DMP, CH_2Cl_2, RT, 15 min; e) $NaClO_2$, NaH_2PO_4, H_2O/*t*BuOH, 2-methyl-2-butene, RT, 1 h, 90% (2 steps). TrocCl = 2,2,2-trichloroethyl chloroformate, CSA = (1*S*)-(+)-10-camphorsulfonic acid, LDA = lithium diisopropylamide, DMP = Dess–Martin periodinane.

lective desilylation of **14**, followed by sequential DMP and Pinnick's oxidations gave the carboxylic acid **17**.

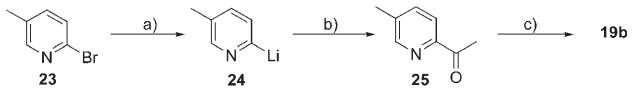
The synthesis of enantiomerically pure β-ketoalcohols **22a** and **22b** by means of diastereoselective reduction of the corresponding β-ketoesters **21a** and **21b** seemed a logical and convenient approach to this moiety as the racemate of these β-ketoesters could be very conveniently prepared by aldol cyclization of the corresponding γ-aryl-substituted β-ketoesters **20a** and **20b** (Scheme 5). We investigated the conversion of **21a** and **21b** to **22a** and **22b** in high enantiomeric purity.



Scheme 5. a) NaH, THF, 0°C, 82% (**20a**), 76% (**20b**); b) NaOH, anhydrous EtOH, 78% (**21a**), 73% (**21b**).

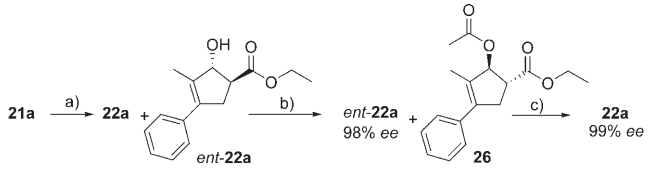
The diketoesters **20a** and **20b** were synthesized from ethyl propionylacetate **18** and α-bromoacetoaromatic derivatives **19a** and **19b** (Scheme 5). Direct intramolecular aldol condensation led to the cyclopentenones **21a** and **21b**. The 2-bromoketone **19b** was prepared as shown in Scheme 6.[36] Bromination of **25** to **19b** was carried out conveniently and reproducibly by using commercially available polymer-supported tribromide (Amberlyst A26-Br_3^-).[37]

After a number of unsuccessful attempts at stereoselective reduction of the ketone **21a**,[38,39] including reduction with high catalyst loading of Corey's oxazaborolidine CBS re-



Scheme 6. a) *n*BuLi, Et_2O, −78 °C; b) *N*,*N*-dimethyl-acetamide, Et_2O, −78 °C, 72 % (2 steps); c) polymer-supported Amberlyst A26-Br_3^-, THF, 91 %.

agent,[40] the desired *trans* product **22a** and its enantiomer *ent*-**22a** were finally obtained in equal amounts by reduction under chelation control by using $Zn(BH_4)_2$ (Scheme 7).[41]

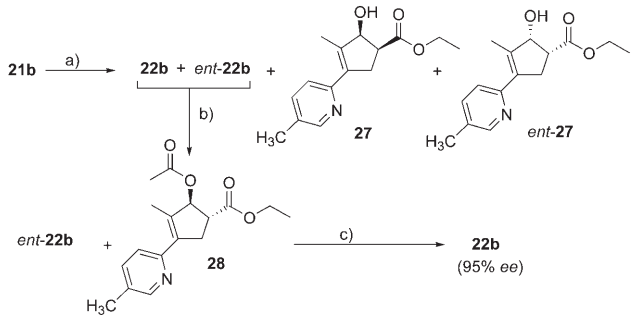


Scheme 7. a) $Zn(BH_4)_2$/ether, 4 °C, 75 %; b) PS-D lipase, vinyl acetate, 4 Å MS, pentane, RT, 4 d, 48 % (*ent*-**22a**), 49 % (26); c) anhydrous K_2CO_3, anhydrous EtOH, RT, 12 h, 92 %. MS = molecular sieves.

The *trans* racemate mixture **22a**/*ent*-**22a** was efficiently separated by enzymatic resolution by using Amano PS-D Lipase enzyme (Scheme 7). Alcohol **22a** was acetylated to form **26**, whilst *ent*-**22a** remained unchanged. They were separated by column chromatography (49 % **26** and 48 % *ent*-**22a**). The stereochemistry at the secondary hydroxyl carbon atom of the *ent*-**22a** isomer and its enantiomeric purity were determined by Mosher's ester analysis (*R*, 99 % *ee*).[34] Ethanolysis of **26** gave the desired alcohol **22a** (*S*, 98 % ee by Mosher's ester analysis).[34] The *trans* configuration of **22a** was confirmed by NOE experiment (vide infra).

Compound **21b** was found to be much more resistant to reducing agents, including $Zn(BH_4)_2$. Indeed, using even an excess of $NaBH_4$ resulted in only partial reduction. We speculated that altering electronic effects exerted by the basic nitrogen atom could render the molecule susceptible to reduction. Gratifyingly, prior conversion of **21b** to the corresponding trifluoroacetate salt by treatment with two equivalents of trifluoroacetic acid (TFA) allowed rapid $NaBH_4$ reduction producing a mixture of all four diastereomers (Scheme 8). The product mixture was separated into the *cis* and *trans* enantiomeric pairs by column chromatography (*trans*/*cis* 2:1, determined by ^{1}H NMR spectroscopy). The fraction containing the pair of *trans* enantiomers (**22b** and *ent*-**22b**) was resolved by using Amano PS-D Lipase enzyme as described earlier for the phenyl analogue.

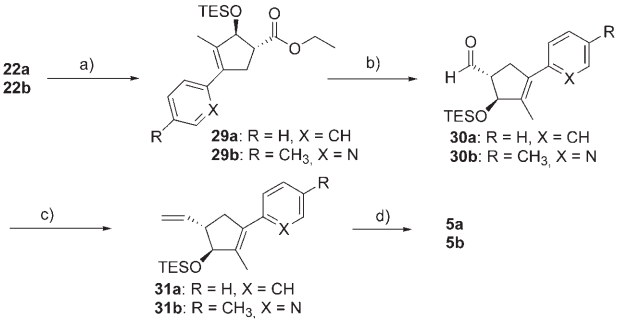
As with the phenyl analogue, the desired enantiomer **22b** was acetylated to **28** while the enantiomer *ent*-**22b** remained unchanged. They were separated by column chromatography and **28** was subjected to ethanolysis as before to obtain **22b** (*S*, 95 % *ee* by Mosher's ester analysis).[34] NOE experiments confirmed the *trans* configuration of the molecule. The *cis* isomers **27** and *ent*-**27**, isolated by a similar enzyme-mediated resolution protocol, showed a strong NOE be-



Scheme 8. a) i) TFA, CH_2Cl_2, solvent evaporated, ii) residue in MeOH, $NaBH_4$, 0 °C, 30 min; b) PS-D lipase, vinyl acetate, 4 Å MS, pentane, RT, 3 d, 48 % (*ent*-**22b**), 49 % (**28**); c) anhydrous K_2CO_3, anhydrous EtOH, RT, 12 h, 94 %. TFA = trifluoroacetic acid.

tween the two protons at the two stereogenic centers, and no such NOE was observed between the two corresponding protons in **22b** or *ent*-**22b**.

Reduction of the esters **29a** and **29b** with DIBAL-H gave the corresponding aldehydes **30a** and **30b**, which were subjected to Wittig olefination to obtain the olefins **31a** and **31b** (Scheme 9). Desilylation with TBAF gave the desired



Scheme 9. a) TESCl, imidazole, CH_2Cl_2, 0 °C, 2 h, 93 % (**29a**), 92 % (**29b**); b) DIBAL-H, toluene, −78 °C, 1 h; c) $MeP^+(Ph)_3Br^-$, *n*BuLi, THF, 0 °C, 30 min, 71 % (**31a**), 73 % (**31b**); d) TBAF, THF, 0 °C, 30 min, 80 % (**5a**), 83 % (**5b**). TESCl = triethylsilyl chloride, DIBAL-H = diisobutylaluminum hydride, TBAF = tetrabutylammonium fluoride.

alcohols **5a** and **5b**. At this stage, we confirmed the relative *trans* stereochemistry of the protons H-1 and H-5 in the cyclopentene moiety **5a** and the absolute stereochemistry of the molecule as shown based on NOE correlations (Figure 2) in conjunction with the already-established *S* configuration of the secondary hydroxyl carbon atom.[34]

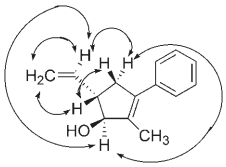
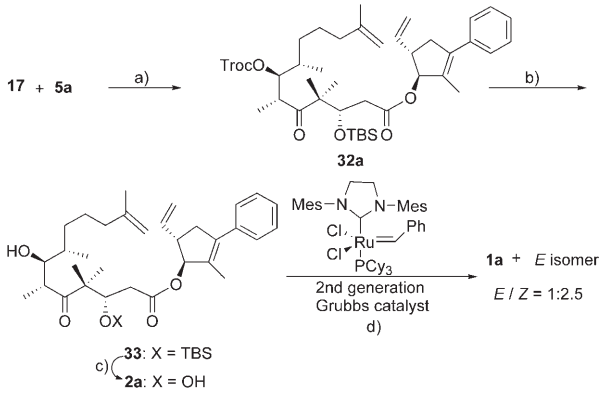


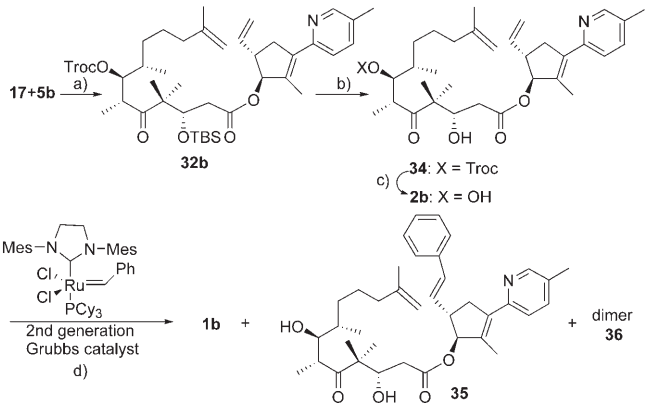
Figure 2. NOE correlations of (1*S*,5*S*)-2-methyl-3-phenyl-5-vinylcyclopent-2-enol (**5a**).

The carboxylic acid **17** was esterified to **32a** with alcohol **5a** by using DCC/DMAP (Scheme 10). The Troc and TBS protecting groups were sequentially removed with zinc dust/ammonium chloride in dry ethanol and TAS-F,[42] respectively, to give intermediate **2a**. Finally, RCM of **2a** by using second-generation Grubbs catalyst gave the desired *Z*-alkene **1a**, accompanied by what appeared to be the *E* isomer as a minor product. A strong NOE correlation between the C-12-methyl protons and the C-13 olefinic proton confirmed the *Z* stereochemistry of the double bond of **1a**.



Scheme 10. a) DCC, DMAP, CH_2Cl_2, 0 °C (15 min), RT (16 h), 64 %; b) Zn, NH_4Cl, anhydrous EtOH, RT, 45 min; c) TAS-F, DMF, 2 d, 62 % (2 steps); d) CH_2Cl_2, 50 °C, 16 h, 50 % (Z+E). DCC = 1,3-dicyclohexylcarbodiimide, DMAP = 4-dimethylaminopyridine, TAS-F = tris(dimethylamino)sulfur (trimethylsilyl)difluoride.

A similar approach to synthesize the pyridine analogue **1b** by starting from the carboxylic acid **17** and the alcohol **5b** was complicated by an unexpected retroaldol decoupling of the alcohol obtained by the removal of the Troc protecting group upon treatment with TAS-F. Gratifyingly, this was easily overcome by changing the order of removal of the two protecting groups (Scheme 11). Thus, the TBS protecting group was removed first with TAS-F[42] to give **34** which was then treated directly with zinc dust and ammonium chloride in dry ethanol to give intermediate **2b**. Finally, RCM of **2b** by using second-generation Grubbs catalyst gave the desired product **1b**. The *Z* configuration of the double bond was confirmed by NOESY. The phenyl analogue **35** and a dimerlike product from **2b** were isolated as byproducts. A large coupling constant between the two olefinic protons and the absence of NOE correlations established the *E* configuration of the nonterminal double bond of **35**. Formation of **35** can be attributed to high catalyst loading required to overcome the sluggishness of the RCM reaction.



Scheme 11. a) DCC, DMAP, CH_2Cl_2, 0 °C (15 min), RT (16 h), 85 %; b) TAS-F, DMF, 2 d; c) Zn, NH_4Cl, anhydrous EtOH, RT, 45 min, 62 % (2 steps); d) CH_2Cl_2, 50 °C, 16 h, 55 %.

Cytotoxic activity: In preliminary in vitro cytotoxicity studies in the NCI-60 cell line human tumor screen, compound **1b** showed strong growth inhibitory activity on CCRF-CEM and SR leukemia cell lines with GI_{50} values of 2.7 and 2.9 nM, respectively (Table 1 and Figure 3 A). Surprisingly, it showed no significant activity on any of the other cell lines, including those derived from breast (MCF-7) and ovarian (SK-OV-3) cancers (Table 1 and Figure 3B,C). Although activity data of natural epothilone D against the NCI-60 cell lines is not available, Danishefsky et al. reported a potent and nonselective cytotoxic activity of epothilone D against these cell lines (Table 1).[43] It is also significant to note that the mechanistically analogous cancer drug paclitaxel (taxol) is slightly less effective (GI_{50} of 12.6 nM for CCRF-CEM and 15.8 nM for SR) and less selective against these cell lines (NCI-60 cell line screen data). The reason for the highly selective inhibition of compound **1b** against leukemia cell growth over solid tumor cell lines is still under investigation. We also tested the open-chain analogue **35**, which was isolated as a byproduct of the RCM reaction along with **1b**, and it showed no significant activity on any of the NCI-60 cell lines (Table 1). This is in accordance with our previous data on acyclic epothilone analogues which showed weak cytotoxic activity.[44] So far we have subjected analogue **1a** only to a preliminary growth inhibition assay on MCF-7 breast cancer cells, in which it showed no activity. We are currently generating more material for testing in the NCI-60 cell line tumor screen.

Table 1. In vitro cytotoxicities (GI_{50} and IC_{50}) against human tumor cell lines.[a]

	GI_{50} [μM]				IC_{50} [μM]
Cell line	**1b**	**1a**	**35**	Paclitaxel	Epothilone D[b]
CCRF-CEM	0.0027	nd	> 12.5	0.0126	0.0095
SR	0.0029	nd	> 12.5	0.0158	nd
MCF-7	> 15	192	> 12.5	0.0100	0.0029
SK-OV-3	> 15	nd	> 12.5	0.0251	0.0069

[a] In vitro cell growth inhibition was measured by using the NCI-60 cell line screen (SRB assay). CCRF-CEM and SR are leukemia cell lines, MCF-7 is breast cancer cell line, and SK-OV-3 is ovarian cancer cell line. [b] Data from reference [43] (measured by SRB assay). nd: Not Determined.

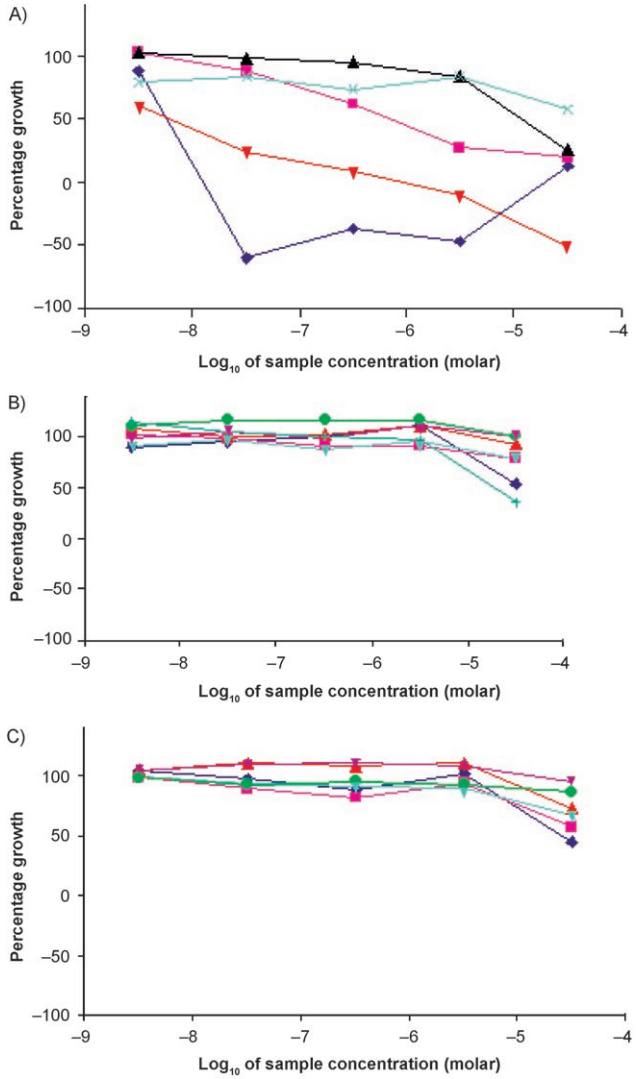


Figure 3. NCI in vitro 60 cell line human tumor screen (dose response curves for A) leukemia (◆: CCRF-CEM, ■: HL-60(TB), ▲: K-562, ×: RPMI-8226, ▼: SR) B) breast cancer (◆: MCF7, ■: NCI/ADR-RES, ▲: MDA-MB-231/, ×: HS 578T, ▼: MDA-MB-435, ●: BT-549), and C) ovarian cancer (◆: IGROV1, ■: OVCAR-3, ▲: OVCAR-4, ×: OVCAR-5, ▼: OVCAR-8, ●: SK-OV-3.

Conclusion

Two novel conformationally restrained epothilones **1a** and **1b** were synthesized. The strategy developed should be applicable to the synthesis of other important analogues of the series. The strong and selective growth inhibitory effect exhibited by analogue **1b** on two leukemia cell lines, while not suppressing the proliferation of breast cancer and ovarian cancer cells which are very sensitive to natural epothilones, indicates that it may be possible to also develop new lead molecules of varying pharmacological profile by substantial modification of the epothilone scaffold. Our future efforts will focus on a more detailed investigation of this new class of conformationally restrained epothilone analogues to elucidate the biological mechanism in relation to selective activity.

Experimental Section

General methods: NMR spectra were recorded on Varian INOVA 600, Varian VXRS-400, Bruker AC-F 300 MHz, or Nicolet NM-500 MHz (modified with a Tecmag Libra interface) instruments and calibrated using residual undeuterated solvent as internal reference. Optical rotations were recorded on an AUTOPOL III 589/546 polarimeter. High-resolution mass spectra (HRMS) were recorded on a Micromass LCT Electrospray mass spectrometer performed at the Mass Spectrometry and Proteomics Facility, The Ohio State University.

(3*S*,6*R*,7*S*,8*S*)-1,3-Bis(*tert*-butyldimethylsilanyloxy)-7-hydroxy-4,4,6,8,12-pentamethyltridec-12-en-5-one (13): A solution of ketone **4** (1.8 g, 4.48 mmol, 2.3 equiv) in THF (5 mL) was added dropwise to a solution of freshly prepared LDA in THF (prepared by adding *n*BuLi (2.92 mL of 1.6 M solution in hexanes, 4.67 mmol) to diisopropylamine (4.67 mmol, 0.655 mL) in THF (5 mL) at −78 °C, then warming the solution to 0 °C for 20 min, and finally cooling back to −78 °C). The reaction mixture was stirred at −78 °C for 1 h and at −40 °C for 30 min and was then cooled back to −78 °C. A precooled (−78 °C) solution of aldehyde **3** (0.272 g, 1.95 mmol, 1 equiv) in THF (10 mL) was added by the use of a cannula to the mixture over 2 min. The reaction mixture was stirred at −78 °C for 15 min before it was quenched rapidly by injection of a solution of acetic acid (0.55 mL) in THF (1.64 mL). The mixture was stirred at −78 °C for 5 min and brought to room temperature. Saturated aqueous ammonium chloride (20 mL) and Et_2O (25 mL) were added and the layers were separated. The aqueous layer was extracted with Et_2O (3×25 mL) and the organic extracts were combined, dried over anhydrous sodium sulfate, and concentrated in vacuo. Flash column chromatography (4–20 % Et_2O/hexanes) gave recovered ketone **4** (0.78 g) followed by *syn* aldol **13** (0.87 g, 83 %) as the pure diastereomer along with the other *syn* aldol diastereomer (74 mg, 7 %) as colorless oils.

Data for ***13***: $[\alpha]_D^{22} = -39.6$ ($c = 0.7$ in $CHCl_3$); $R_f = 0.57$ (silica gel, 20 % Et_2O/hexanes); ^1H NMR (600 MHz, $CDCl_3$): $\delta = 4.66$ (s, 1H), 4.65 (s, 1H), 3.88 (dd, $J = 2.4$, 7.8 Hz, 1H), 3.67–3.63 (m, 1H), 3.60–3.55 (m, 1H), 3.30–3.27 (m, 2H), 2.05–1.95 (m, 2H), 1.69 (s, 3H), 1.76–1.26 (m, 7H), 1.19 (s, 3H), 1.07 (s, 3H), 1.01 (d, $^3J = 6.6$ Hz, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.82 (d, $J = 7.2$ Hz, 3H), 0.09 (s, 3H), 0.06 (s, 3H), 0.02 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 222.7$, 146.5, 109.9, 75.1, 74.3, 60.7, 54.2, 41.5, 38.4, 35.7, 32.8, 26.4, 26.3, 26.2, 25.0, 23.1, 22.6, 20.7, 18.6, 18.5, 15.6, 9.8, −3.5, −3.8, −5.0 ppm; HRMS (ESI): *m/z*: calcd for $C_{30}H_{62}O_4Si_2 + Na^+$: 565.4084 [$M$+$Na^+$]; found: 565.4067.

(3*S*,6*R*,7*S*,8*S*)-Carbonic acid-1-[4,6-bis(*tert*-butyldimethylsilanyloxy)-1,3,3-trimethyl-2-oxohexyl]-2,6-dimethyl-1-hept-6-enyl ester 2,2,2-trichloroethyl ester (14): To a solution of aldol **13** (0.80 g, 1.48 mmol) in methylene chloride (30 mL) at 0 °C was added pyridine (0.96 mL, 11.84 mmol, 8 equiv) followed by 2,2,2-trichloroethyl chloroformate (0.8 mL, 5.92 mmol, 4 equiv), and the reaction mixture was stirred at 0 °C for 1 h. Saturated aqueous sodium bicarbonate (50 mL) was added and the organic layer was separated. The aqueous layer was extracted with methylene chloride (3×50 mL), and the combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo. Purification by flash column chromatography (2 % EtOAc/hexanes) afforded protected aldol **14** (0.98 g, 93 %) as a colorless oil. $[\alpha]_D^{22} = -51.5$ ($c = 1.6$ in $CHCl_3$); $R_f = 0.72$ (silica gel, 17 % EtOAc/hexanes); ^1H NMR (600 MHz, $CDCl_3$): $\delta = 4.85$ (d, $J = 12.0$ Hz, 1H), 4.78 (dd, $J = 4.2$, 7.8 Hz, 1H), 4.66 (d, $J = 12.0$ Hz, 1H), 4.66 (s, 1H), 4.62 (s, 1H), 3.72 (dd, $J = 2.4$, 7.8 Hz, 1H), 3.63–3.59 (m, 1H), 3.58–3.53 (m, 1H), 3.50–3.45 (m, 1H), 1.98–1.91 (m, 2H), 1.72–1.61 (m, 2H), 1.67 (s, 3H), 1.51–1.42 (m, 2H), 1.34 (s, 3H), 1.31–1.24 (m, 3H), 1.04 (d, $J = 6.6$ Hz, 3H), 0.99 (s, 3H), 0.94 (d, $J = 6.6$ Hz, 3H), 0.88 (s, 9H), 0.85 (s, 9H), 0.082 ppm (s, 6H), 0.001 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 215.8$, 154.5, 145.8, 110.3, 95.0, 83.1, 76.8, 75.8, 60.5, 53.8, 42.7, 38.2, 34.9, 31.5, 26.4, 26.1, 24.9, 23.7, 22.6, 21.2,

18.6, 16.3, 11.3, −3.3, −4.1, −5.0, −5.1 ppm; HRMS (ESI): *m/z*: calcd for $C_{33}H_{63}Cl_3O_6Si_2+Na^+$ 739.3126; found: 739.3163 [$M+Na^+$].

(3*S*,6*R*,7*S*,8*S*)-Carbonic acid-1-[4-(*tert*-butyldimethylsilanyloxy)-6-hydroxy-1,3,3-trimethyl-2-oxohexyl]-2,6-dimethyl-1-hept-6-enyl ester 2,2,2-trichloroethyl ester (15): A solution of bis-silyl compound **14** (0.8 g, 1.11 mmol, 1 equiv) in methylene chloride (30 mL) and methanol (20 mL) was cooled to 0 °C. A solution of (1*S*)-(+)-10-camphorsulfonic acid (77 mg, 0.33 mmol, 0.3 equiv) in methanol (10 mL) was added to this solution. The reaction mixture was stirred at 0 °C for 7 h before it was quenched with saturated aqueous sodium bicarbonate (10 mL). The solid precipitate was filtered and the filtrate was concentrated in vacuo. The residue was diluted with Et_2O (100 mL) and washed with brine. The organic layer was separated and the aqueous layer was extracted with Et_2O (3×20 mL). The combined organic phases were dried over anhydrous sodium sulfate and concentrated in vacuo. Purification by flash column chromatography (10% EtOAc/hexanes) afforded the unstable alcohol **15** (0.583 g, 87%). It was used directly in the next step. $R_f=0.57$ (silica gel, 33% EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta=4.87$–4.80 (m, 2H), 4.69–4.61 (m, 3H), 3.92 (dd, $J=3.0$ Hz, 7.8 Hz, 1H), 3.67–3.59 (m, 2H), 3.45–3.40 (m, 1H), 1.98–1.90 (m, 2H), 1.66 (s, 3H), 1.70–1.42 (m, 8H), 1.26 (s, 3H), 1.07–1.06 (m, 6H), 0.95 (d, $J=6.6$ Hz, 3H), 0.89 (s, 9H), 0.10 (s, 3H), 0.08 ppm (s, 3H); HRMS (ESI): *m/z*: calcd for $C_{27}H_{49}Cl_3O_6Si+Na^+$: 625.2262 [$M+Na^+$]; found: 625.2260.

(3*S*,6*R*,7*S*,8*S*)-3-(*tert*-Butyldimethylsilanyloxy)-4,4,6,8,12-pentamethyl-5-oxo-7-(2,2,2-trichloroethoxycarbonyloxy)tridec-12-enoic acid (17): Dess–Martin periodinane (0.545 g, 1.28 mmol, 1.4 equiv) was added to a solution of alcohol **15** (0.550 g, 0.914 mmol) in methylene chloride (4 mL). The mixture was stirred at room temperature for 15 min. An additional amount of Dess–Martin reagent (0.23 g, 0.6 equiv) was added and the reaction mixture was stirred for 15 min and was then subjected to flash column chromatography (10% EtOAc/hexanes) to furnish crude aldehyde **16** which was used directly in the next step. A solution of sodium dihydrogenphosphate (270 mg, 2.25 mmol, 2.46 equiv) and sodium chlorite (270 mg, 3 mmol, 3.27 equiv) in distilled water (5 mL) was added to the crude aldehyde **16** (ca. 0.914 mmol) in *tert*-butanol (25 mL) and 2-methyl-2-butene (6 mL). The mixture was stirred at room temperature for 1 h and quenched by the addition of saturated aqueous ammonium chloride (50 mL) and water (50 mL). The mixture was extracted with ethyl acetate (3×60 mL) and the combined organic extracts were dried over anhydrous sodium sulfate and concentrated in vacuo. Purification by flash column chromatography (10% EtOAc/hexanes) afforded the pure carboxylic acid **17** (0.505 g, 90% over two steps) as a colorless oil. $[\alpha]_D^{22}=-53.7$ ($c=0.8$ in $CHCl_3$); $R_f=0.58$ (silica gel, 40% EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta=4.85$ (d, $J=12.0$ Hz, 1H), 4.76 (dd, $J=4.2$, 7.2 Hz, 1H), 4.66 (d, $J=12.0$ Hz, 1H), 4.66 (s, 1H), 4.62 (s, 1H), 4.22 (dd, $J=3.6$, 6.6 Hz, 1H), 3.47–3.41 (m, 1H), 2.60 (dd, $J=3.6$, 17.4 Hz, 1H), 2.21 (dd, $J=6.6$, 16.8 Hz, 1H), 1.96–1.91 (m, 2H), 1.74 −1.68 (m, 1H), 1.66 (s, 3H), 1.52–1.42 (m, 2H), 1.31 (s, 3H), 1.28 (d, $J=16.8$ Hz, 3H), 1.06 (s, 6H), 0.94 (d, $J=7.2$ Hz, 3H), 0.86 (s, 9H), 0.1 (s, 3H), 0.03 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=215.5$, 177.7, 154.5, 145.8, 110.3, 94.9, 82.7, 76.9, 75.0, 53.8, 42.4, 39.9, 38.2, 34.9, 31.5, 26.3, 26.2, 24.8, 23.0, 22.6, 20.3, 18.4, 16.3, 11.5, −4.3 ppm; HRMS (ESI): *m/z*: calcd for $C_{27}H_{47}Cl_3O_7Si+Na^+$: 639.2054 [$M+Na^+$]; found: 639.2079.

3-Oxo-2-(2-oxo-2-phenylethyl)pentanoic acid ethyl ester (20a): Ethyl propionylacetate **18** (10 g, 69.4 mmol) was added slowly to a stirred suspension of sodium hydride (60% dispersion in mineral oil, 3.33 g, 83.3 mmol, 1.2 equiv) in THF (100 mL) at 0 °C and the mixture was stirred for 30 min. 2-Bromoacetophenone **19a** (15.2 g, 76.34 mmol, 1.1 equiv) in THF (10 mL) was added dropwise and the reaction mixture was stirred at room temperature for 16 h. Saturated aqueous ammonium chloride (60 mL) was added and the mixture was subsequently extracted with Et_2O (3×70 mL). The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. The solvent was removed in vacuo to give a dark-yellow oil that was purified by flash column chromatography (10% EtOAc/hexane) to give the diketoester **20a** (14.8 g, 82%) as a yellow oil. $R_f=0.50$ (silica gel, 25% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.98$ (d, $J=8.4$ Hz, 2H), 7.58 (m, 1H), 7.46 (m, 2H), 4.22 (q, $J=7.2$ Hz, 3H), 3.74 (dd, $J=8.4$, 18.4 Hz, 1H), 3.53 (dd, $J=5.2$, 18.4 Hz, 1H), 2.91–2.70 (m, 2H), 1.28 (t, $J=7.2$ Hz, 3H), 1.12 ppm (t, $J=7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=205.4$, 197.4, 169.3, 136.3, 133.6, 128.8, 128.3, 61.9, 53.2, 37.7, 36.6, 14.2, 7.8 ppm; HRMS (ESI): *m/z*: calcd for $C_{15}H_{18}O_4+Na^+$ 285.1103; found: 285.1093 [$M+Na^+$].

3-Methyl-2-oxo-4-phenylcyclopent-3-enecarboxylic acid ethyl ester (21a): A solution of the diketoester **20a** (12 g, 45.8 mmol) in dry ethanol (150 mL) was added dropwise to a solution of sodium hydroxide (1.83 g, 45.8 mmol) in dry ethanol (75 mL) with vigorous stirring. The solution was heated to 50 °C and stirred overnight at that temperature. Et_2O (1.5 L) was added and the organic phase was washed with HCl (2 N, 3× 300 mL) and dried over anhydrous sodium sulfate. The solvent was removed in vacuo to give an oil that was purified by flash column chromatography (6% EtOAc/hexane) to give the cyclic β-ketoester **21a** (8.7 g, 78%) as a yellow oil. $R_f=0.40$ (silica gel, 25% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.56$–7.52 (m, 2H), 7.50–7.42 (m, 3H), 4.26 (q, $J=7.2$ Hz, 2H), 3.58 (dd, $J=3.2$, 7.6 Hz, 1H), 3.38–3.31 (m, 1H), 3.15–3.07 (m, 1H), 1.99 (s, 3H), 1.32 ppm (t, $J=7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=202.6$, 169.6, 166.5, 135.8, 134.9, 130.2, 128.9, 127.9, 61.9, 51.3, 33.7, 14.5, 10.5 ppm; HRMS (ESI): *m/z*: calcd for $C_{15}H_{16}O_3+Na^+$: 267.0997 [$M+Na^+$]; found: 267.0974.

1-(5-Methylpyridin-2-yl)ethanone (25): *n*BuLi (6.25 mL of 1.6 M solution in hexanes, 10 mmol, 1 equiv) was added dropwise to a solution of 2-bromo-5-methyl pyridine **23** (1.73 g, 10 mmol) in dry Et_2O (20 mL), cooled to −78 °C. The reaction mixture was allowed to warm to −40 °C for 15 min, then cooled back to −78 °C again. *N*,*N*-Dimethylacetamide (1.023 mL, 11 mmol, 1.1 equiv) was added dropwise and the mixture was stirred at −78 °C for 2 h. Saturated aqueous ammonium chloride (10 mL) was added and the organic layer was separated. The aqueous layer was extracted with Et_2O (3×10 mL) and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to give an oily residue that was subjected to flash column chromatography by using (5% methanol/methylene chloride) to give compound **25** (0.977 g, 72%) as a yellow oil. $R_f=0.48$ (silica gel, 25% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=8.50$–8.48 (brs, 1H), 7.94 (d, $J=8.0$ Hz, 1H), 7.63–7.60 (m, 1H), 2.70 (s, 3H), 2.41 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=200.2$, 151.7, 149.7, 137.8, 137.4, 121.7, 26.0, 18.9 ppm; HRMS (ESI): *m/z*: calcd for $C_8H_9NO+Na^+$: 158.0582 [$M+Na^+$]; found: 158.0580.

2-Bromo-1-(5-methylpyridin-2-yl)ethanone (19b): Amberlyst A26-Br_3^- (Aldrich, 1.26 mmol Br_3 per g; 4.76 g, 6 mmol, 0.9 equiv) was added in one portion to a solution of compound **25** (0.9 g, 6.67 mmol) in THF (25 mL). The mixture was stirred at 50 °C for 10 h and the decolored resin was filtered off and washed with ethyl acetate. The organic solution was washed with water, dried over anhydrous sodium sulfate, and concentrated in vacuo to give an oily residue that was chromatographed on silica gel with (10–30% methylene chloride/hexanes) to give compound **19b** (1.29 g, 91%) as a yellow oil. $R_f=0.62$ (silica gel, 20% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=8.50$ (brs, 1H), 8.01 (d, $J=8.0$ Hz, 1H), 7.66 (dd, $J=1.6$, 8.0 Hz, 1H), 4.84 (s, 2H), 2.44 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=192.5$, 149.8, 149.3, 138.7, 137.6, 122.6, 32.5, 18.9 ppm; HRMS (ESI): *m/z*: calcd for $C_8H_8BrNO+Na^+$: 235.9687 [$M+Na^+$]; found: 235.9676.

3-Oxo-2-(2-oxo-2-pyridin-2-ylethyl)pentanoic acid ethyl ester (20b): Ethyl propionylacetate **18** (5 g, 34.7 mmol) was added slowly to a stirred suspension of sodium hydride (60% dispersion in mineral oil, 1.665 g, 41.65 mmol, 1.2 equiv) in THF (50 mL) at 0 °C and the mixture was stirred for 30 min. Compound **19b** (8.092 g, 38.17 mmol, 1.1 equiv) in THF (5 mL) was added dropwise and the reaction mixture was stirred at room temperature for 16 h. Saturated aqueous ammonium chloride (30 mL) was added and the mixture was subsequently extracted with Et_2O (3×30 mL). The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. The solvent was removed in vacuo to give a dark-yellow oil that was purified by flash column chromatography (10% EtOAc/hexanes) to give the diketoester **20b** (7.3 g, 76%) as a yellow oil: TLC $R_f=0.33$ (silica gel, 20% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=8.50$ (brs, 1H), 7.89 (d, $J=8.0$ Hz, 1H), 7.66 (dd, $J=1.6$, 8.0 Hz, 1H), 4.20 (q, $J=7.2$ Hz, 2H), 4.15 (dd, $J=6.0$, 8.0 Hz,

1H), 3.92 (dd, $J=8.4$, 18.8 Hz, 1H), 3.74 (dd, $J=6.0$, 18.8 Hz, 1H), 2.85–2.66 (m, 2H), 2.41 (s, 3H), 1.27 (t, $J=7.2$ Hz, 3H), 1.10 ppm (t, $J=7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=205.5$, 198.9, 169.6, 150.7, 149.8, 138.1, 137.3, 121.7, 61.8, 53.5, 37.1, 36.2, 18.9, 14.2, 7.9 ppm; HRMS (ESI): m/z: calcd for $C_{15}H_{19}NO_4+Na^+$: 300.1212; found: 300.1200 [$M+Na^+$].

3-Methyl-2-oxo-4-pyridin-2-ylcyclopent-3-ene carboxylic acid ethyl ester (21b): A solution of the diketoester **20b** (3.1 g, 11.19 mmol) in dry ethanol (35 mL) was added dropwise to a solution of sodium hydroxide (0.447 g, 11.19 mmol) in dry ethanol (15 mL) with vigorous stirring. The solution was stirred at room temperature overnight. Et_2O (200 mL) was added and the organic phase was washed with HCl (2N, 3×100 mL). The aqueous layer was cooled to 0°C and made slightly basic by the addition of sodium bicarbonate. The aqueous layer was then extracted with ethyl acetate (3×300 mL) and the organic phase was dried over anhydrous sodium sulfate. The solvent was removed in vacuo to give an oil that was purified by flash column chromatography (10% EtOAc/hexanes) to give the cyclic β-ketoester **21b** (2.115 g, 73%) as a yellow oil. $R_f=0.35$ (silica gel, 33% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=8.59$ (s, 1H), 7.62–7.60 (m, 1H), 7.54–7.52 (m, 1H), 4.24 (q, $J=7.2$ Hz, 2H), 3.56 (dd, $J=2.8$, 7.2 Hz, 1H), 3.42–3.25 (m, 2H), 2.41 (s, 3H), 2.12 (s, 3H), 1.31 ppm (t, $J=7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=203.2$, 169.5, 164.4, 151.4, 150.6, 136.8, 136.5, 134.2, 123.3, 61.7, 51.1, 32.5, 18.6, 14.3, 10.6 ppm; HRMS (ESI): m/z: calcd for $C_{15}H_{17}NO_3+Na^+$: 282.1106 [$M+Na^+$]; found: 282.1109.

(1*R,2*S**,3*E*)-2-Hydroxy-3-methyl-4-phenylcyclopent-3-enecarboxylic acid ethyl ester (22a) and (*ent*-22a)**: A solution of zinc borohydride (150 mL of 0.3 M solution in Et_2O, 45 mmol, 4 equiv) was added dropwise at 0°C to a stirred solution of β-ketoester (+/-)-**21a** (2.75 g, 11.25 mmol) in THF (5 mL). The mixture was stirred overnight at 4°C, quenched by slow addition of water and stirred for an additional 1 h. Anhydrous sodium sulfate was added and the resulting suspension was filtered and the filtrate was concentrated. The residue was dissolved in methylene chloride and filtered again and dried. Purification by flash column chromatography (8% EtOAc/hexanes) gave recovered starting material (0.27 g, 10%) and racemic β-hydroxyesters **22a** and *ent*-**22a** (2.1 g, 75%) as a yellow oil. $R_f=0.17$ (silica gel, 25% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.37$–7.24 (m, 5H), 4.98 (s, 1H), 4.22 (q, $J=7.2$ Hz, 2H), 3.03–2.94 (m, 3H), 2.32 (d, $J=5.6$ Hz, 1H), 1.90 (s, 3H), 1.31 ppm (t, $J=7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=174.9$, 137.2, 135.7, 135.1, 128.4, 127.9, 127.3, 83.9, 61.1, 51.8, 37.1, 14.5, 12.8 ppm; HRMS (ESI): m/z: calcd for $C_{15}H_{18}O_3+Na^+$: 269.1154 [$M+Na^+$]; found: 269.1143.

(1*R*,2*S*,3*E*)-2-Acetoxy-3-methyl-4-phenylcyclopent-3-ene carboxylic acid ethyl ester (26) and (1*R*,2*R*,3*E*)-2-hydroxy-3-methyl-4-phenyl-cyclopent-3-ene carboxylic acid ethyl ester (*ent*-22a): Vinyl acetate (7.5 mL, 81.4 mmol) was added to a solution of **22a** and *ent*-**22a** (2 g, 8.13 mmol) in anhydrous pentane (30 mL). Amano PS-D lipase (2.0 g) and 4 Å MS (2.0 g) were added and the suspension was stirred at room temperature. The reaction was monitored by TLC and ^{1}H NMR spectroscopy and after 4 d, 48–50% conversion of **22a** to the acetate was achieved. The sieves and lipase were filtered and washed with Et_2O. The solvent was removed and crude product was purified by flash column chromatography (20% Et_2O/hexanes) to give **26** (1.15 g, 49%) as a slightly yellow oil and *ent*-**22a** (0.96 g, 48%, 98% *ee*).

Data for **26**: $[\alpha]_D^{22}=-50.5$ ($c=0.6$ in $CHCl_3$); $R_f=0.38$ (silica gel, 25% EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta=7.40$–7.25 (m, 5H), 6.06 (s, 1H), 4.20 (q, $J=7.2$ Hz, 2H), 3.08–2.95 (m, 3H), 2.11 (s, 3H), 1.80 (s, 3H), 1.28 ppm (t, $J=7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=174.2$, 170.9, 138.4, 136.7, 131.8, 128.5, 128.0, 127.7, 85.9, 61.2, 48.7, 38.6, 21.3, 14.4, 12.9 ppm; HRMS (ESI): m/z: calcd for $C_{17}H_{20}O_4+Na^+$: 311.1259 [$M+Na^+$]; found: 311.1240.

Data for ent-**22a**: $[\alpha]_D^{22}=-15.2$ ($c=0.6$ in $CHCl_3$); see **22a** below for ^{1}H and ^{13}C NMR spectroscopic data.

(1*R*,2*S*,3*E*)-2-Hydroxy-3-methyl-4-phenylcyclopent-3-ene carboxylic acid ethyl ester (22a): Anhydrous potassium carbonate (240 mg, 1.74 mmol) was added at 0°C to a solution of **26** (500 mg, 1.74 mmol) in dry ethanol (15 mL) and the solution was stirred at room temperature for 12 h. Ethanol was removed under reduced pressure and the residue was dissolved in methylene chloride and washed with a saturated aqueous solution of ammonium chloride. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed in vacuo. The residue was purified by flash column chromatography (25% EtOAc/hexane) to give compound **22a** (393 mg, 92%, 99% *ee*) as a slightly yellow oil. $[\alpha]_D^{22}=+14.8$ ($c=0.8$ in $CHCl_3$); $R_f=0.17$ (silica gel, 25% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.37$–7.25 (m, 5H), 4.99 (s, 1H), 4.23 (q, $J=7.2$ Hz, 2H), 3.05–2.94 (m, 3H), 2.33 (d, $J=5.6$ Hz, 1H), 1.90 (s, 3H), 1.32 ppm (t, $J=7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=174.9$, 137.2, 135.8, 135.1, 128.4, 127.9, 127.3, 84.0, 61.1, 51.7, 37.1, 14.5, 12.9 ppm; HRMS (ESI): m/z: calcd for $C_{15}H_{18}O_3+Na^+$ 269.1154 [$M+Na^+$]; found: 269.1148.

(1*R,2*S**,3*E*)-2-Hydroxy-3-methyl-4-pyridin-2-ylcyclopent-3-ene carboxylic acid ethyl ester (22b/*ent*-22b) and (27/*ent*-27)**: Trifluoroacetic acid (0.297 mL, 3.86 mmol) was added to a stirred solution of compound **21b** (0.5 g, 1.93 mmol) in methylene chloride (6 mL). The solvent was removed in vacuo and the resulting salt was dissolved in methanol (7 mL) and cooled to 0°C. Sodium borohydride (0.73 g, 19.3 mmol) was added rapidly at once to this solution at 0°C. After stirring at the same temperature for 30 min, chloroform was added and the mixture was washed with saturated aqueous sodium bicarbonate solution and brine. The organic layer was dried over anhydrous sodium sulfate and concentrated. The residue (0.459 g, 91%, *cis*/*trans* 1:2, determined by ^{1}H NMR spectroscopy) was separated by using silica-gel chromatography (16–25% EtOAc/hexane) to obtain **22b**/*ent*-**22b** (0.306 g, 67%) and **27**/*ent*-**27** (0.153 g, 33%).

Data for **27**/ent-**27**: $R_f=0.29$ (silica gel, 20% EtOAc/hexane); ^{1}H NMR (C_6D_6, 600 MHz): $\delta=8.38$ (s, 1H), 6.88–6.87 (m, 2H), 4.61 (s, 1H), 3.99–3.89 (m, 2H), 3.54–3.49 (m, 1H), 3.05–3.01 (m, 1H), 2.88–2.84 (m, 1H), 2.33 (d, $J=7.8$ Hz, 1H), 2.13 (s, 3H), 1.77 (s, 3H), 0.90 ppm (t, $J=14.4$, 3H); ^{13}C NMR (C_6D_6, 400 MHz): $\delta=172.9$, 153.5, 149.9, 138.6, 136.2, 135.9, 130.7, 121.9, 82.0, 60.4, 46.5, 36.2, 17.8, 14.1, 13.8 ppm; HRMS (ESI): m/z: calcd for $C_{15}H_{19}NO_3+Na^+$: 284.1263 [$M+Na^+$]; found: 284.1248.

(1*R*,2*S*,3*E*)-2-Acetoxy-3-methyl-4-pyridin-2-ylcyclopent-3-ene carboxylic acid ethyl ester (28) and (1*R*,2*R*,3*E*)-2-hydroxy-3-methyl-4-pyridin-2-yl-cyclopent-3-ene carboxylic acid ethyl ester (*ent*-22b): Vinyl acetate (0.95 mL, 10.3 mmol) was added to a solution of **22b**/*ent*-**22b** (0.27 g, 1.03 mmol) in anhydrous pentane (3 mL). Amano PS-D lipase (0.27 g) and 4 Å MS (0.27 g) were added and the suspension was stirred at room temperature. The reaction was monitored by TLC and ^{1}H NMR spectroscopy and after 3 d, 49–50% conversion of **22b**/*ent*-**22b** to acetate **28** was achieved. The sieves and lipase were filtered off and washed with Et_2O. The solvent was removed and the crude product was purified by column chromatography (17% EtOAc/hexane) to give **28** (0.154 g, 49%) as a pale-yellow oil and *ent*-**22b** (0.130 g, 48%).

Data for **28**: $[\alpha]_D^{22}=-40.6$ ($c=1.0$ in $CHCl_3$); $R_f=0.26$ (silica gel, 75% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 600 MHz): $\delta=8.44$ (s, 1H), 7.47 (d, $J=7.8$ Hz, 1H), 7.20 (d, $J=7.8$ Hz, 1H), 6.07 (s, 1H), 4.19 (q, $J=14.4$ Hz, 2H), 3.22–3.16 (m, 1H), 3.05–3.01 (m, 2H), 2.32 (s, 3H), 2.09 (s, 3H), 1.94 (s, 3H), 1.26 ppm (t, $J=7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz): $\delta=174.1$, 170.9, 152.5, 150.0, 137.2, 136.7, 135.0, 137.8, 122.5, 85.9, 61.1, 48.5, 37.5, 21.3, 18.5, 14.4, 13.2 ppm; HRMS (ESI): m/z: calcd for $C_{17}H_{21}NO_4+Na^+$: 326.1368 [$M+Na^+$]; found: 326.1354.

Data for ent-**22b**: $[\alpha]_D^{22}=+7.8$ ($c=1.0$ in $CHCl_3$). See **22b** below for ^{1}H and ^{13}C NMR spectroscopic data.

(1*R*,2*S*,3*E*)-2-Hydroxy-3-methyl-4-pyridin-2-ylcyclopent-3-ene carboxylic acid (22b): Anhydrous potassium carbonate (45.6 mg, 0.33 mmol) was added at 0°C to a solution of **28** (100 mg, 0.33 mmol) in dry ethanol (2.8 mL) and the solution was stirred at room temperature for 12 h. Ethanol was removed under reduced pressure and the residue was dissolved in methylene chloride and washed with a saturated aqueous solution of ammonium chloride. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed in vacuo. The residue was purified by flash column chromatography (25% EtOAc/hexane) to give compound **22b** (81 mg, 94%, 95% *ee*) as a pale-yellow oil. $[\alpha]_D^{20}=-8.1$ ($c=0.26$ in $CHCl_3$); TLC $R_f=0.27$ (silica gel, 75% EtOAc/hexanes);

^{1}H NMR (C_6D_6, 600 MHz): δ = 8.48 (s, 1H), 6.97–6.92 (m, 2H), 5.03 (s, 1H), 4.04–4.00 (m, 2H), 3.22–3.21 (m, 2H), 3.02–2.98 (m, 1H), 2.18 (s, 3H), 1.87 (s, 3H), 0.98 ppm (t, J = 14.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ = 174.6, 153.1, 149.9, 138.4, 136.7, 134.9, 131.4, 122.4, 84.1, 61.0, 51.7, 35.9, 18.5, 14.5, 13.1 ppm; HRMS (ESI): m/z: calcd for $C_{15}H_{19}NO_3+Na^+$: 284.1263 [M+Na$^+$]; found: 284.1279.

(1*R*,2*S*,3*E*)-3-Methyl-4-phenyl-2-triethylsilanyloxycyclopent-3-ene carboxylic acid ethyl ester (29a): Triethylsilyl chloride (876 μL, 5.22 mmol, 1.5 equiv) was added dropwise to a solution of alcohol **22a** (856 mg, 3.48 mmol) and imidazole (711 mg, 10.44 mmol, 3 equiv) in methylene chloride (25 mL) at 0 °C. After stirring at 0 °C for 2 h, the reaction was quenched with water (15 mL) and extracted with ethyl acetate (3× 30 mL). The organic extracts were washed with brine (20 mL) and dried over anhydrous sodium sulfate. Filtration and evaporation of the solvents in vacuo furnished an oily crude product which was purified by flash column chromatography (2% EtOAc/hexanes) to give TES ether **29a** (1.16 g, 93%) as a yellow oil. $[\alpha]_D^{22}$ = −34.2 (c = 0.6 in $CHCl_3$); R_f = 0.53 (silica gel, 10% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.22 (m, 5H), 5.11 (s, 1H), 4.21 (q, J = 7.2 Hz, 2H), 3.08–2.82 (m, 3H), 1.83 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H), 1.00 (t, J = 8.0 Hz, 9H), 0.68 ppm (q, J = 8.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.5, 137.5, 135.7, 134.9, 128.3, 128.0, 127.2, 84.5, 60.9, 51.8, 38.6, 14.5, 12.9, 7.1, 5.1, 0.2 ppm; HRMS (ESI): m/z: calcd for $C_{21}H_{32}O_3Si+Na^+$: 383.2018 [M+Na$^+$]; found: 383.2019.

(1*R*,2*S*,3*E*)-3-Methyl-4-phenyl-2-triethylsilanyloxycyclopent-3-enecarbaldehyde (30a): A solution of DIBAL-H (2.2 mL, 1.0 M in hexane, 2.2 mmol, 1.1 equiv) was added dropwise to a solution of silyl ether **29a** (720 mg, 2 mmol) in toluene (10 mL) at −78 °C. The reaction was stirred at that temperature for 1 h and quenched by dropwise addition of saturated NH_4Cl (1.0 mL). The reaction was allowed to reach room temperature and a saturated aqueous solution of Rochelle salt (3.0 mL) and brine (2.0 mL) were added. The mixture was extracted with ethyl acetate (3×7 mL) and the combined organic extracts were dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo to give crude aldehyde **30a** as a colorless liquid which was used in the next step without further purification; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.86 (d, J = 2.0 Hz, 1H), 7.38–7.25 (m, 5H), 5.08 (s, 1H), 3.12–2.98 (m, 2H), 2.90–2.84 (m, 1H), 1.84 (s, 3H), 1.00 (t, J = 8.0 Hz, 9H), 0.68 ppm (q, J = 8.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.2, 135.5, 133.9, 133.7, 126.6, 126.3, 125.6, 79.6, 57.4, 33.1, 11.3, 5.3, 3.4 ppm.

(1*S*,2*E*,5*S*)-Triethyl-(2-methyl-3-phenyl-5-vinylcyclopent-2-enyloxy)silane (31a): *n*BuLi (0.775 mL of 1.6 M solution in hexanes, 1.24 mmol, 1.95 equiv) was added dropwise to a precooled (0 °C) solution of methyltriphenylphosphonium bromide (455 mg, 1.27 mmol, 2 equiv) in THF (5 mL). The reaction mixture was stirred at 0 °C for 30 min. A solution of aldehyde **30a** (0.2 g, 0.633 mmol) in THF (2 mL) was added and the mixture was stirred at 0 °C for 30 min and quenched with saturated aqueous ammonium chloride (5 mL). The solvent was removed under reduced pressure and the aqueous residue was extracted with ethyl acetate (3× 5 mL). The combined organic extract was dried over anhydrous sodium sulfate and concentrated in vacuo. Purification by flash column chromatography (5% Et_2O/hexanes) afforded pure olefin **31a** (0.14 g, 71%) as a colorless oil. $[\alpha]_D^{22}$ = −14.3 (c = 0.4 in $CHCl_3$); R_f = 0.73 (silica gel, 10% Et_2O/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.34–7.21 (m, 5H), 5.94–5.88 (m, 1H), 5.12 (d, J = 16.8 Hz, 1H), 5.04 (dd, J = 1.8, 10.2 Hz, 1H), 4.52 (d, J = 4.8 Hz, 1H), 2.88–2.82 (m, 1H), 2.74–2.68 (m, 1H), 2.52–2.47 (m, 1H), 1.82 (s, 3H), 0.98 (t, J = 7.8 Hz, 9H), 0.66 ppm (q, J = 7.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.1, 138.1, 136.3, 135.7, 128.3, 127.9, 126.9, 115.2, 87.0, 52.1, 40.4, 13.1, 7.2, 5.5 ppm; HRMS (ESI): m/z: calcd for $C_{20}H_{30}OSi+Na^+$: 337.1964 [M+Na$^+$]; found: 337.1970.

(1*S*,2*E*,5*S*)-2-Methyl-3-phenyl-5-vinyl-cyclopent-2-enol (5a): Tetrabutylammonium fluoride (1.53 mL of 1 M solution in THF, 1.53 mmol) was added dropwise to a solution of compound **31a** (0.48 g, 1.53 mmol) in THF (7 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then water (6 mL) and ethyl acetate (10 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (2×10 m). The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo. Purification by flash column chromatography (10% EtOAc/hexanes) afforded pure alcohol **5a** (0.245 g, 80%) as a white solid. $[\alpha]_D^{22}$ = −14.17 (c = 1.2 in $CHCl_3$); R_f = 0.45 (silica gel, 33% EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.36–7.23 (m, 5H), 6.00–5.94 (m, 1H), 5.18 (dd, J = 1.2, 16.8 Hz, 1H), 5.08 (dd, J = 0.6, 10.2 Hz, 1H), 4.48 (d, J = 6.6 Hz, 1H), 2.85–2.81 (m, 1H), 2.71–2.65 (m, 1H), 2.59–2.54 (m, 1H), 1.89 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.4, 137.8, 136.3, 135.9, 128.4, 127.9, 127.2, 115.4, 86.4, 52.4, 39.8, 12.9 ppm; HRMS (ESI): m/z: calcd for $C_{14}H_{16}O+Na^+$: 223.1099 [M+Na$^+$]; found: 223.1100.

(1*R*,2*S*)-3-Methyl-4-(5-methylpyridin-2-yl)-2-triethylsilanyloxycyclopent-3-ene carboxylic acid ethyl ester (29b): Triethylsilyl chloride (145 μL, 0.863 mmol, 1.5 equiv) was added dropwise to a solution of alcohol **22b** (150 mg, 0.575 mmol) and imidazole (17 mg, 1.72 mmol, 3 equiv) in methylene chloride (4 mL) at 0 °C. After stirring at 0 °C for 2 h, the reaction was quenched with water (2.5 mL) and extracted with ethyl acetate (3× 5 mL). The organic extracts were washed with brine (3.5 mL) and dried over anhydrous sodium sulfate. Filtration and evaporation of the solvents in vacuo furnished an oily crude product which was purified by flash column chromatography on silica (2–7% EtOAc/hexanes) to give **29b** (198 mg, 92%) as a yellow oil. $[\alpha]_D^{22}$ = −51.04 (c = 0.7 in $CHCl_3$); R_f = 0.29 (silica gel, 25% EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.41 (s, 1H), 7.44 (dd, J = 1.8, 8.4 Hz, 1H), 7.19 (d, J = 7.8 Hz, 1H), 5.12 (d, J = 4.8 Hz, 1H), 4.18 (dd, J = 7.2, 14.4 Hz, 2H), 3.17–3.12 (m, 1H), 3.00–2.89 (m, 2H), 2.30 (s, 3H), 1.97 (s, 3H), 1.28 (t, J = 14.4 Hz, 3H), 0.96 (t, J = 7.8 Hz, 9H), 0.65 ppm (q, J = 7.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.3, 153.3, 149.9, 139.1, 136.5, 134.1, 131.1, 122.4, 84.5, 60.8, 51.6, 37.4, 18.4, 14.5, 13.3, 7.0, 5.2 ppm; HRMS (ESI): m/z: calcd for $C_{21}H_{33}NO_3Si+H^+$: 376.2308 [M+H$^+$]; found: 376.2302.

(3*S*,4*S*)-5-Methyl-2-(2-methyl-3-triethylsilanyloxy-4-vinylcyclopent-1-enyl)pyridine (31b): A solution of DIBAL-H (0.44 mL, 1.0 M in hexane, 0.44 mmol, 1.1 equiv) was added dropwise to a solution of silyl ether **29b** (150 mg, 0.4 mmol) in toluene (2 mL) at −78 °C. The reaction mixture was stirred at that temperature for 1 h and quenched by dropwise addition of saturated aqueous ammonium chloride solution (0.2 mL). The reaction mixture was allowed to reach room temperature and a saturated aqueous solution of Rochelle salt (1 mL) and brine (0.4 mL) were added. The mixture was extracted with ethyl acetate (3×2 mL) and the combined organic extracts were dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo to give crude aldehyde **30b** as a yellow liquid which was used in the next step without further purification. *n*BuLi (0.49 mL of 1.6 M solution in hexanes, 0.78 mmol, 1.95 equiv) was added dropwise to a precooled (0 °C) solution of methyltriphenylphosphonium bromide (286 mg, 0.8 mmol, 2 equiv) in THF (3 mL). The reaction mixture was stirred at 0 °C for 30 min. A solution of crude aldehyde **30b** (ca. 0.4 mmol) in THF (1.5 mL) was added and the mixture was stirred at 0 °C for 30 min and then quenched with saturated aqueous ammonium chloride solution (3 mL). The solvent was removed under reduced pressure and the aqueous residue was extracted with ethyl acetate (3×3 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated in vacuo. Purification by flash column chromatography on silica (7% EtOAc/hexanes) afforded pure olefin **31b** (96 mg, 73%) as a yellowish oil. $[\alpha]_D^{22}$ = −21.29 (c = 0.7 in $CHCl_3$); R_f = 0.66 (silica gel, 33% EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.42 (s, 1H), 7.44 (dd, J = 1.8, 7.8 Hz, 1H), 7.18 (d, J = 7.8 Hz, 1H), 5.95–5.88 (m, 1H), 5.12 (d, J = 16.8 Hz, 1H), 5.04 (d, J = 10.8 Hz, 1H), 4.54 (d, J = 5.4 Hz, 1H), 2.97–2.93 (m, 1H), 2.74–2.68 (m, 1H), 2.60–2.56 (m, 1H), 2.30 (s, 3H), 1.96 (s, 3H), 0.98 (t, J = 7.8 Hz, 9H), 0.64 ppm (q, J = 7.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.9, 149.8, 140.9, 139.8, 136.5, 135.0, 130.9, 122.4, 115.2, 87.2, 51.8, 39.2, 18.4, 13.4, 7.2, 5.5 ppm; HRMS (ESI): m/z: calcd for $C_{20}H_{31}NOSi+H^+$: 330.2253 [M+H$^+$]; found: 330.2258.

(1*S*,5*S*)-2-Methyl-3-(5-methylpyridin-2-yl)-5-vinylcyclopent-2-enol (5b): Tetrabutylammonium fluoride (0.152 mL of 1 M solution in THF, 0.152 mmol) was added dropwise to a solution of compound **31b** (50 mg, 0.152 mmol) in THF (1 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then water (1 mL) and ethyl acetate (2 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (2×2 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo. Purification

by flash column chromatography on silica (16–50% EtOAc/hexanes) afforded pure alcohol **5b** (28 mg, 83%) as a white solid. $[\alpha]_D^{22}=-26.0$ ($c=0.3$ in $CHCl_3$); $R_f=0.25$ (silica gel, 50% EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta=8.43$ (s, 1H), 7.46 (dd, $J=1.8$ Hz, 7.8 Hz, 1H), 7.18 (d, $J=7.8$ Hz, 1H), 6.0–5.95 (m, 1H), 5.14 (d, $J=16.8$ Hz, 1H), 5.08 (d, $J=10.2$ Hz, 1H), 4.48 (s, 1H), 2.96–2.91 (m, 1H), 2.69–2.60 (m, 2H), 2.32 (s, 3H), 2.03 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=153.6$, 149.9, 140.2, 139.4, 136.7, 135.6, 131.2, 122.3, 115.4, 86.4, 52.3, 38.5, 18.5, 13.2 ppm; HRMS (ESI): m/z: calcd for $C_{14}H_{17}NO+Na^+$: 238.1208 [M+Na$^+$]; found: 238.1191.

(3*S*,6*R*,7*S*,8*S*)-3-(*tert*-Butyldimethylsilanyloxy)-4,4,6,8,12-pentamethyl-5-oxo-7-(2,2,2-trichloroethoxycarbonyloxy)tridec-12-enoic acid (1*S*,2*E*,5*S*)-2-methyl-3-phenyl-5-vinylcyclopent-2-enyl ester (32a): DCC (0.027 mL of 1 M solution in CH_2Cl_2, 0.027 mmol, 1.3 equiv) was added dropwise to a solution of acid **17** (13 mg, 0.021 mmol), alcohol **5a** (4.6 mg, 0.023 mmol, 1.1 equiv), and DMAP (1 mg, 0.008 mmol, 0.4 equiv) in methylene chloride (0.5 mL) at 0 °C. The reaction mixture was stirred for 15 min at 0 °C and for 16 h at room temperature. The solid precipitate was filtered off and the filtrate was concentrated in vacuo. Purification by flash column chromatography (5% Et_2O/hexanes) afforded ester **32a** (11 mg, 64%) as a colorless oil. $[\alpha]_D^{22}=-53.2$ ($c=0.85$ in $CHCl_3$); TLC $R_f=0.67$ (silica gel, 25% EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta=7.36$–7.25 (m, 5H), 5.98–5.91 (m, 1H), 5.70 (d, $J=4.2$ Hz, 1H), 5.10 (d, $J=17.4$ Hz, 1H), 5.03 (d, $J=10.2$ Hz, 1H), 4.88–4.85 (m, 1H), 4.70 (dd, $J=3.0$, 8.4 Hz, 1H), 4.66–4.60 (m, 3H), 4.29 (t, $J=4.2$ Hz, 1H), 3.50–3.46 (m, 1H), 2.96–2.92 (m, 1H), 2.86–2.81 (m, 1H), 2.68 (dd, $J=3.6$, 17.4 Hz, 1H), 2.59–2.55 (m, 1H), 2.23 (dd, $J=5.4$, 17.4 Hz, 1H), 1.95–1.87 (m, 2H), 1.75 (s, 3H), 1.66 (s, 3H), 1.54–1.53 (m, 6H), 1.33–1.27 (m, 5H), 1.06–1.04 (m, 3H), 0.96 (d, $J=6.6$ Hz, 3H), 0.87 (s, 9H), 0.13 (s, 3H), 0.05 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=215.4$, 172.3, 154.4, 145.8, 139.3, 137.3, 132.4, 128.4, 127.9, 127.4, 115.3, 110.3, 95.0, 88.2, 82.4, 76.9, 75.0, 56.0, 54.0, 47.6, 42.2, 40.5, 40.3, 38.2, 35.2, 34.9, 31.8, 31.2, 26.2, 25.7, 24.9, 24.8, 22.7, 22.6, 20.6, 18.4, 16.1, 13.1, 11.1, −4.1, −4.5 ppm; HRMS (ESI): m/z: calcd for $C_{41}H_{61}Cl_3O_7Si+Na^+$: 821.3150 [$M$+Na$^+$]; found: 821.3178.

(3*S*,6*R*,7*S*,8*S*)-3,7-Dihydroxy-4,4,6,8,12-pentamethyl-5-oxotridec-12-enoic acid (1*S*,2*E*,5*S*)-2-methyl-3-phenyl-5-vinylcyclopent-2-enyl ester (2a): Anhydrous ammonium chloride (75 mg) followed by zinc dust (75 mg) was added to a solution of ester **32a** (12 mg, 0.015 mmol) in dry ethanol (1.5 mL). The reaction mixture was stirred at room temperature for 45 min before it was diluted with ethyl acetate (5 mL) and filtered though a plug of Celite. The solution was concentrated and passed though a small plug of silica gel to give compound **33** which was used in the next step without further purification. To the crude solution of compound **33** was added a solution of tris(dimethylamino)sulfur (trimethylsilyl)difluoride (TAS-F) (5 mg, 0.187 mmol, 1 equiv) in *N*,*N*-dimethylformamide (0.2 mL). After 24 h, another 5 mg of TAS-F were added and the mixture was stirred for an additional 24 h after which it was diluted with ethyl acetate (5 mL) and washed with phosphate buffer pH 7 (5 mL). The aqueous layer was extracted with ethyl acetate (3×5 mL) and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude oil was purified by silica gel chromatography (10% EtOAc/hexanes) to give pure compound **2a** (4.7 mg, 62% over two steps) as a colorless material. $[\alpha]_D^{22}=-77.5$ ($c=0.2$ in $CHCl_3$); $R_f=0.74$ (silica gel, 50% EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta=7.37$–7.25 (m, 5H), 6.0–5.92 (m, 1H), 5.76 (d, $J=3.6$ Hz, 1H), 5.13 (d, $J=16.8$ Hz, 1H), 5.06 (d, $J=10.2$ Hz, 1H), 4.66 (d, $J=10.2$ Hz, 2H), 4.29–4.26 (m, 1H), 3.39–3.35 (m, 2H), 3.27–3.23 (m, 2H), 2.99–2.93 (m, 1H), 2.88–2.83 (m, 1H), 2.61–2.57 (m, 1H), 2.52 (dd, $J=1.8$, 16.2 Hz, 1H), 2.44 (dd, $J=10.2$, 16.2 Hz, 1H), 2.04–1.96 (m, 2H), 1.79 (s, 3H), 1.75–1.72 (m, 1H), 1.69 (s, 3H), 1.54–1.52 (m, 1H), 1.36–1.30 (m, 1H), 1.20–1.18 (s overlapping with m, 4H), 1.15 (s, 3H), 1.06 (d, $J=7.2$ Hz, 3H), 0.84 ppm (d, $J=7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=222.5$, 173.2, 146.4, 139.8, 139.4, 137.1, 131.8, 128.5, 127.9, 127.6, 115.5, 109.9, 88.6, 75.0, 72.7, 52.3, 47.8, 41.1, 40.4, 38.4, 36.9, 35.7, 32.7, 25.0, 22.6, 21.5, 19.2, 15.7, 13.1, 10.2 ppm; HRMS (ESI): m/z: calcd for $C_{32}H_{46}O_5+Na^+$: 533.3243 [M+Na$^+$]; found: 533.3213.

2*E*,4*S*,7*S*,10*R*,11*S*,12*S*,16*Z*,18*S*)-7,11-Dihydroxy-3,8,8,10,12,16-hexamethyl-2-phenyl-3a,7,8,10,11,12,13,14,15,17a-decahydro-1*H*,6*H*-4-oxacyclopentacyclohexadecene-5,9-dione (1a): A solution of the second-generation Grubbs catalyst (1.5 mg, 0.0018 mmol; weighed under argon) in methylene chloride (1.5 mL) was added to a solution of compound **2a** (1.5 mg, 0.0032 mmol) in methylene chloride (0.5 mL). The reaction mixture was heated at 50 °C for 16 h and applied directly to a preparative TLC plate (25% EtOAc/hexanes) to give the target (*Z*)-**1a** and slightly impure (*E*)-**1a** (0.2 mg) separately (≈50% overall yield). The *Z* isomer was purified by a second preparative TLC by using (3% methanol/methylene chloride) to remove the last traces of the catalyst and to furnish the desired target molecule (*Z*)-**1a** (0.5 mg). ^{1}H NMR (600 MHz, $CDCl_3$): $\delta=7.36$–7.33 (m, 2H), 7.27–7.24 (m, 3H), 5.82 (d, $J=7.2$ Hz, 1H), 5.24 (d, $J=10.2$ Hz, 1H), 4.2–4.17 (m, 1H), 3.69–3.66 (m, 1H), 3.22–3.15 (m, 2H), 2.81 (dd, $J=8.4$, 15.6 Hz, 1H), 2.66 (d, $J=4.2$ Hz, 1H), 2.58 (dd, $J=10.8$, 16.8 Hz, 2H), 2.52–2.47 (m, 1H), 2.39–2.31 (m, 2H), 1.80–1.75 (s overlapping with m, 4H), 1.68 (s, 3H), 1.66–1.62 (m, 3H), 1.36 (s, 3H), 1.18 (d, $J=6.6$ Hz, 3H), 1.07 (s, 3H), 0.98 ppm (d, $J=7.2$ Hz, 3H); HRMS (ESI): m/z: calcd for $C_{30}H_{42}O_5+Na^+$: 505.2930 [M+Na$^+$]; found: 505.2893.

(3*S*,6*R*,7*S*,8*S*,1′*S*,5′*S*)-3-(*tert*-Butyldimethylsilanyloxy)-4,4,6,8,12-pentamethyl-5-oxo-7-(2,2,2-trichloroethoxycarbonyloxy)tridec-12-enoic acid 2-methyl-3-(5-methylpyridin-2-yl)-5-vinylcyclopent-2-enyl ester (32b): DCC (0.017 mL of 1 M solution in CH_2Cl_2, 0.017 mmol, 1.3 equiv) was added dropwise to a solution of acid **17** (8.0 mg, 0.013 mmol), alcohol **5b** (3.0 mg, 0.014 mmol, 1.1 equiv), and DMAP (1 mg, 0.008 mmol, 0.6 equiv) in methylene chloride (0.5 mL) at 0 °C. The reaction mixture was stirred for 15 min at 0 °C and for 16 h at room temperature. After this time, the solid precipitate was filtered off and the filtrate was concentrated in vacuo. Purification by flash column chromatography on silica (5% EtOAc/hexanes) afforded ester **32b** (9 mg, 85%) as a colorless oil. $[\alpha]_D^{22}=-29.8$ ($c=1$ in $CHCl_3$); $R_f=0.48$ (silica gel, 25% EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta=8.43$ (s, 1H), 7.46 (dd, $J=1.8$, 7.8 Hz, 1H), 7.18 (d, $J=7.8$ Hz, 1H), 5.98–5.91 (m, 1H), 5.73 (d, $J=4.8$ Hz, 1H), 5.11 (d, $J=16.8$ Hz, 1H), 5.02 (d, $J=10.2$ Hz, 1H), 4.86 (d, $J=12.0$ Hz, 1H), 4.73–4.70 (m, 1H), 4.67–4.61 (m, 3H), 4.30–4.28 (m, 1H), 3.50–3.45 (m, 1H), 3.06–3.02 (m, 1H), 2.88–2.83 (m, 1H), 2.70–2.65 (m, 1H), 2.33 (s, 3H), 2.23 (dd, $J=5.4$, 17.4 Hz, 1H), 1.98–1.91 (m, 2H), 1.95 (s, 3H), 1.76–1.74 (m, 1H), 1.66 (s, 3H), 1.50–1.22 (m, 5H), 1.10–1.04 (m. 6H), 0.96 (d, $J=7.2$ Hz, 3H), 0.87 (m, 12H), 0.13 (s, 3H), 0.05 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=215.4$, 172.3, 154.4, 153.1, 149.9, 145.8, 139.5, 138.3, 136.7, 135.7, 131.5, 125.5, 122.5, 115.4, 110.3, 95.0, 88.2, 82.4, 75.0, 54.0. 47.5, 42.2, 40.2, 39.2, 38.2, 34.9, 31.8, 29.9, 26.3, 24.8, 22.6, 22.5, 20.7, 18.5, 18.4, 16.1, 13.4, 11.1, −4.1, −4.5 ppm; HRMS (ESI): m/z: calcd for $C_{41}H_{62}Cl_3NO_7Si+H^+$: 814.3434 [$M$+H$^+$]; found: 814.3481.

(3*S*,6*R*,7*S*,8*S*,1′*S*,5′*S*)-3,7-Dihydroxy-4,4,6,8,12-pentamethyl-5-oxotridec-12-enoic acid 2-methyl-3-(5-methyl-pyridin-2-yl)-5-vinylcyclopent-2-enyl ester (2b): A solution of tris(dimethylamino)sulfur (trimethylsilyl)difluoride (TAS-F) (1.7 mg, 0.008 mmol, 1 equiv) in *N*,*N*-dimethylformamide (0.2 mL) was added to a solution of ester **32b** (5 mg, 0.006 mmol) in DMF (0.2 mL). After 24 h, another 1.7 mg of TAS-F were added and the mixture was diluted with ethyl acetate (3 mL) and washed with phosphate buffer pH 7 (5 mL). The aqueous layer was extracted with ethyl acetate (3×5 mL) and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude oil was purified by silica-gel chromatography (10% EtOAc/hexanes) to give compound **34** which was dissolved in dry ethanol (1.2 mL) and treated with anhydrous ammonium chloride (62 mg) followed by zinc dust (62 mg). The reaction mixture was stirred at room temperature for 45 min before it was diluted with ethyl acetate (3 mL) and filtered though a plug of Celite. The solution was concentrated and purified by silica-gel chromatography (20% EtOAc/hexanes) to give pure compound **2b** (2 mg, 62% over two steps) as a colorless material. $R_f=0.36$ (silica gel, 33% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=8.47$ (s, 1H), 7.50 (d, $J=8.0$ Hz, 1H), 7.21 (d, $J=8.5$ Hz, 1H), 6.02–5.95 (m, 1H), 5.81 (d, $J=4.5$ Hz, 1H), 5.16 (d, $J=17.5$ Hz, 1H), 5.07 (d, $J=10.5$ Hz, 1H), 4.68 (d, $J=9.0$ Hz, 2H), 4.30 (d, $J=10.5$ Hz, 1H), 3.41–3.37 (m, 2H), 3.30–3.27 (m, 1H), 3.25 (d, $J=3.5$ Hz, 1H), 3.10–3.3.06 (m, 1H), 2.91–2.88 (m, 1H), 2.71–2.69 (m, 1H), 2.54 (dd, $J=2.5$, 16.5 Hz, 1H), 2.46 (dd,

J=10.5, 16.5 Hz, 1H), 2.35 (s, 3H), 2.06–2.02 (m, 2H), 1.98 (s, 3H), 1.78–1.76 (m, 1H), 1.72 (s, 3H), 1.33–1.31 (m, 2H), 1.22 (s, 3H), 1.17 (s, 3H), 1.08 (d, J=6.5 Hz, 3H), 0.87 ppm (d, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=222.1, 172.9, 152.8, 149.8, 146.2, 139.1, 136.5, 135.0, 131.4, 122.2, 115.3, 109.7, 88.3, 74.9, 72.5, 52.1, 47.5, 41.0, 38.9, 38.2, 36.8, 35.5, 32.5, 29.7, 24.9, 22.4, 21.3, 19.0, 18.3, 15.6, 13.2, 10.0 ppm; HRMS (ESI): m/z: calcd for $C_{32}H_{47}NO_5+Na^+$: 548.3352 [M+Na^+]; found: 548.3331.

(3*S*,6*R*,7*S*,8*S*,1′*S*,5′*S*)-7,11-Dihydroxy-3,8,8,10,12,16-hexamethyl-2-(5-methylpyridin-2-yl)-3a,7,8,10,11,12,13,14,15,17a-decahydro-1*H*,6*H*-4-oxa-cyclopentacyclohexadecene-5,9-dione (1b): A solution of the second-generation Grubbs catalyst (2.5 mg, 0.003 mmol; weighed under argon) in methylene chloride (1.5 mL) was added to a solution of compound **2b** (2.5 mg, 0.0052 mmol) in methylene chloride (0.5 mL). The reaction mixture was heated at 50 °C for 16 h and applied directly to a preparative TLC plate and developed (25% EtOAc/hexanes) to give the target (*Z*)-**1b** (0.5 mg) along with phenyl analogue **35** and the dimer **36** (≈0.5 mg each; ≈55 overall yield).

*Data for compound **1b***: R_f=0.23 (silica gel, 50% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.60 (s, 1H), 8.16 (d, J=8.0 Hz, 1H), 7.54 (d, J=8.0 Hz, 1H), 5.84 (d, J=7.0 Hz, 1H), 5.25 (d, J=10.0 Hz, 1H), 4.53 (d, J=10.0 Hz, 1H), 3.64–3.62 (m, 1H), 3.47–3.40 (m, 2H), 3.26–3.21 (m, 2H), 2.81 (dd, J=2.5, 16.5 Hz, 1H), 2.65 (dd, J=10.5, 16.5 Hz, 1H), 2.59 (s, 3H), 2.38–2.31 (m, 1H), 2.00 (s overlapping with m, 5H), 1.84–1.79 (m, 2H), 1.72 (s, 3H), 1.42 (s, 3H), 1.35–1.31 (m, 2H), 1.16 (d, J=6.5 Hz, 3H), 1.06 (s, 3H), 1.02 ppm (d, J=7.0 Hz, 3H); HRMS (ESI): m/z: calcd for $C_{30}H_{43}NO_5+H^+$: 498.3219 [M+H^+]; found: 498.3231.

3,7-Dihydroxy-4,4,6,8,12-pentamethyl-5-oxotridec-12-enoic acid 2-methyl-3-(5-methylpyridin-2-yl)-5-styrylcyclopent-2-enyl ester (35): R_f=0.61 (silica gel, 50% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.48 (d, J=2.0 Hz, 1H), 7.51 (dd, J=2.0, 8.0 Hz, 1H), 7.37–7.30 (m, 4H), 7.25–7.21 (m, 2H), 6.52 (d, J=16.0 Hz, 1H), 6.34 (dd, J=8.0, 16.0 Hz, 1H), 5.87 (d, J=4.5 Hz, 1H), 4.68 (d, J=9.0 Hz, 2H), 4.31–4.28 (m, 1H), 3.42–3.36 (m, 2H), 3.30–3.26 (m, 1H), 3.24 (d, J=4.0 Hz, 1H), 3.19–3.04 (m, 2H), 2.81–2.76 (m, 1H), 2.55 (dd, J=2.5, 16.0 Hz, 1H), 2.46 (dd, J=10.5, 16.0 Hz, 1H), 2.36 (s, 3H), 2.01 (s overlapping with m, 5H), 1.72 (m, 2H), 1.71 (s, 3H), 1.35 (m, 2H), 1.22 (s, 3H), 1.17 (s, 3H), 1.07 (d, J=7.0 Hz, 3H), 0.86 (d, J=7.0 Hz, 3H); HRMS (ESI): m/z: calcd for $C_{38}H_{51}NO_5+Na^+$: 624.3665 [M+Na^+]; found: 624.3713.

Dimer 36: R_f=0.37 (silica gel, 50% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.45 (d, J=2.0 Hz, 1H), 7.48 (dd, J=2.0, 8.0 Hz, 1H), 7.17 (d, J=8.0 Hz, 1H), 5.81–5.78 (m, 1H), 5.66 (dd, J=2.5, 5.5 Hz, 1H), 4.66 (d, J=7.5 Hz, 2H), 4.45–4.41 (m, 1H), 4.20–4.17 (m, 1H), 3.55 (s, 1H), 3.40 (d, J=9.0 Hz, 1H), 3.35 (dd, J=6.5, 13.5 Hz, 1H), 2.98–2.93 (m, 1H), 2.87–2.83 (m, 1H), 2.65–2.60 (m, 1H), 2.54–2.51 (m, 2H), 2.34 (s, 3H), 2.05–1.94 (m, 3H), 1.91 (s, 3H), 1.70 (s, 3H), 1.26 (s overlapping with m, 5H), 1.18 (s, 3H), 1.09 (d, J=7.0 Hz, 3H), 0.87 ppm (d, J=7.0 Hz, 3H); HRMS (ESI): m/z: calcd for $C_{62}H_{90}N_2O_{10}+Na^+$: 1045.6493 [$M$+$Na^+$]; found: 1045.6522.

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