Total Synthesis of Oxazole- and Cyclopropane-Containing Epothilone A Analogues by the Olefin Metathesis Approach

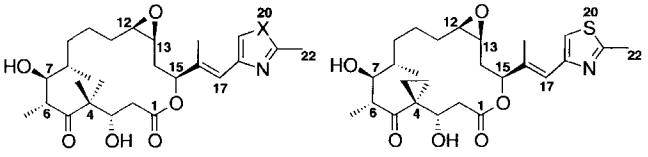
K. C. Nicolaou,* Hans Vallberg, N. Paul King, Frank Roschangar, Yun He, Dionisios Vourloumis, and Christopher G. Nicolaou

Abstract: For structure–activity relationship studies, two series of epothilone A (**1**) analogues have been designed and synthesized, one containing an oxazole moiety instead of the thiazole heterocycle and the other containing a spirocyclopropane moiety in place of the *gem*-dimethyl group at position C-4 (4,4-ethano-epothilones). The olefin metathesis strategy in solution was utilized for the chemical synthesis of these compounds starting with key building blocks **7**–**9** for the oxazole series (compounds **2**, **14**–**18**, **21**–**26**) and building blocks **8**, **30**, and **31** for the 4,4-ethano series (compounds **3**, **39**–**43**, **46**–**51**). The convergent strategy towards the designed epothilone A series involved a) an aldol condensation reaction, b) an esterification reaction, c) an olefin metathesis reaction catalyzed by [$RuCl_2$(=CHPh)-(PCy_3)$_2$], and d) epoxidation of the macrocycle double bond.

Keywords
epothilone · oxazoles · cyclopropanes · metathesis · total synthesis

Introduction

Amongst the most exciting antitumor agents of recent times are the naturally occurring epothilones A (**1**) (Figure 1) and B.[1–2] Isolated[1] from fermentation broths of myxobacteria *Sorangium cellulosum* strain 90 found in a soil sample originally collected from the banks of the Zambezi River in southern Africa, these substances exhibit potent antifungal and cytotoxic properties against a variety of cell lines.[1–3] Of particular interest is their demonstrated ability to cause death in Taxol™-resistant tumor cells and their Taxol-like mechanism of action, which involves tubulin assembly and stabilization of microtubules.[4] Following the disclosure of their stereostructure by spectroscopic and X-ray crystallographic techniques in 1996,[5] numerous synthetic studies[6] and several total syntheses of epothilones A (**1**)[7–11,13] and B[10,12,13] have been reported. In addition, several analogues of these compounds have already been synthesized and studied.[6a,7,10–15] In this article we wish to describe the details of the total synthesis of a series of epothilone A analogues, in which either the thiazole has been replaced by an oxazole moiety or the *gem*-dimethyl group has been substituted with a cyclopropane ring. Minimized structures of (12*R*,13*S*)-epothilone A (**1**), (12*R*,13*S*)-20-oxa-epothilone A (**2**), and (12*R*,13*S*)-4,4-ethanoepothilone A (**3**) are shown in Figure 2. As expected, these modeling studies confirmed the strong conformational similarities between **1** and **2**, but revealed some differences with the 4,4-ethano analogue **3**. It was, therefore, of interest to synthesize these and related compounds for biological investigations in order to establish structure–activity relationships for drug design purposes. In the accompanying article,[16] we describe an analogous series of epothilone B-related compounds.



1: X = S : epothilone A
2: X = O : 20-oxa-epothilone A
3: 4,4-ethano-epothilone A

Figure 1. Structure and numbering of epothilone A (**1**) and analogues **2** and **3**.

Results and Discussion

The oxazole series of epothilone A analogues: Based on our original olefin metathesis approach to epothilones published in 1996,[6a] we undertook the synthesis of an oxazole series of epothilone A analogues, represented by structure **2**, outlined retrosynthetically in Scheme 1. Thus, building blocks **8**, **9**, and **10** were to be assembled and converted to the more advanced intermediates **6** and **7** by means of an aldol condensation and an asymmetric allylboration reaction, respectively. The latter compounds were then to be joined by an esterification and the cou-

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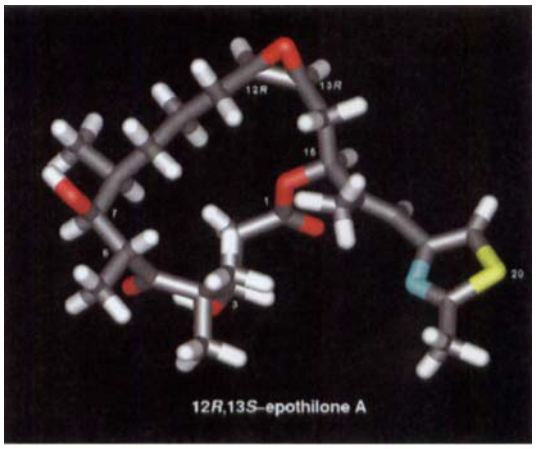
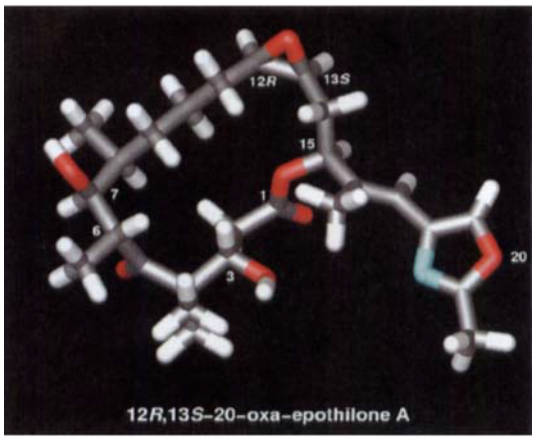




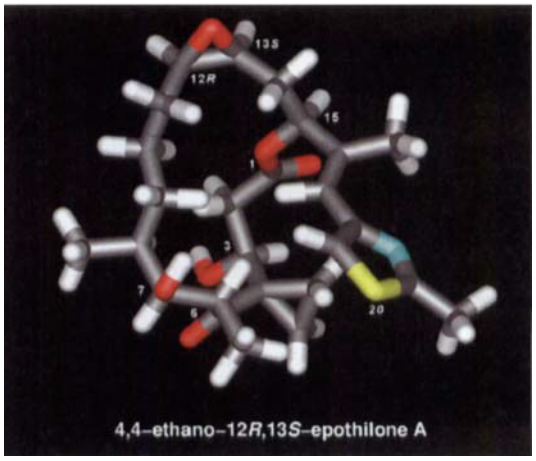
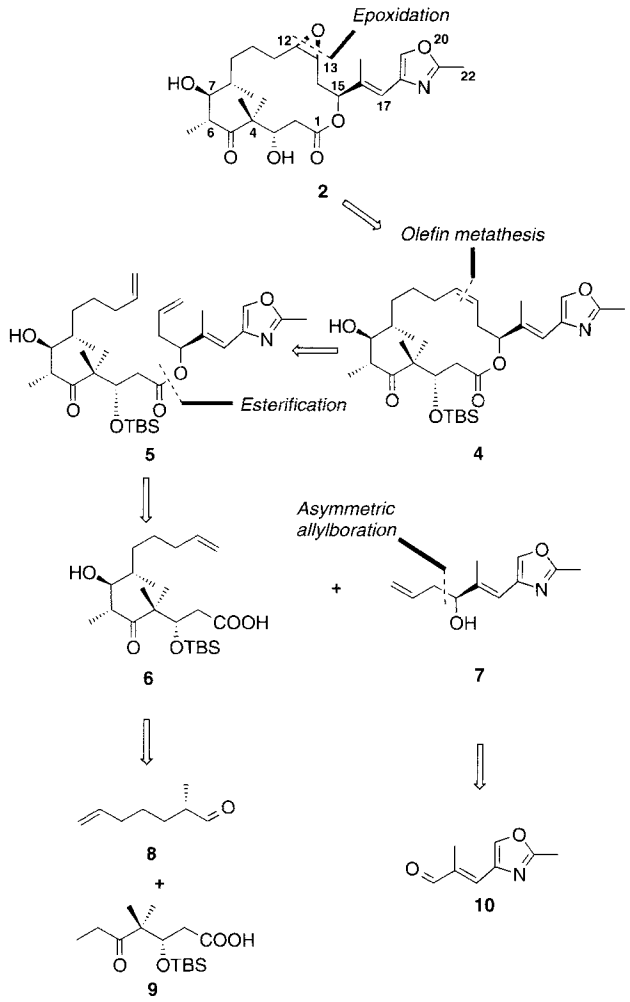


Figure 2. Computer-generated, minimized structures of (12*R*,13*S*)-epothilone A (**1**, top), (12*R*,13*S*)-20-oxa-epothilone A (**2**, center), and 4,4-ethano-(12*R*,13*S*)-epothilone A (**3**, bottom). The epothilone atoms are colored according to the following code: carbon, grey; hydrogen, white; oxygen, red; nitrogen, blue; sulfur, yellow.

pled product cyclized by an olefin metathesis reaction leading to olefinic precursor **4**. Finally, deprotection and epoxidation of **4** was expected to give the desired target molecule **2**. The expected lack of stereoselectivity at the aldol and olefin metathesis stages of the sequence was a desirable feature, since the immediate goal of our research program was to generate as diverse a library of compounds as possible for biological screening.

Scheme 2 summarizes the construction of olefin metathesis precursors **5** and **12**. Thus, condensation of aldehyde **8**[11] with the dianion of **9**,[13] generated by the action of 2.4 equiv of LDA



Scheme 1. Retrosynthetic analysis of 20-oxa-epothilone A analogue **2**.

(for abbreviations, see legends in schemes) in THF at $-40\,^{\circ}C$, yielded aldols **6** and **11** in a ratio of approximately 5:3. Reaction of the known oxazole derivative **10**[17] with (+)-Ipc$_2$B(allyl) in ether at $-100\,^{\circ}C$[18] furnished allylic alcohol **7** in 92% yield and $\geq 95\%$ *ee* (as determined by formation of the Mosher ester).[19]

Abstract in Greek: *Δυο καινουργιες σειρες αναλογων της εποθειλονης Α (**1**) σχεδιαστηκαν και συντεθηκαν αποσκοποντας στην μελετη της σχεσης μεταξυ δομης και βιολογικης δρασης: η πρωτη περιεχει μια οξαζολη αντι του ετεροκυκλικου δακτηλιου της θειαζολης, ενω η δευτερη περιεχει μια σπιρο-εθανικη ομαδα αντι των δυο μεθυλιων στη θεση 4 (4,4-εθανο-εποθειλονες). Η στρατηγικη της ολεφινικης μεταθεσης χρησιμοποιηθηκε για τη συνθεση αυτων των ουσιων ξεκινωντας απο τις δομικες ουσιες **7–9** για τη σειρα οξαζολης (ουσιες **2**, **14–18**, **21–26**) και τις δομικες ουσιες **8**, **30** και **31** για τη σειρα 4,4-εθανο (ουσιες **3**, **39–43**, **46–51**). Η ευελικτη στρατηγικη που ακολουθειται για τη συνθεση των αναλογων αυτων της εποθειλονης Α αποτελειται απο: α) μια αντιδραση αλδοολικης συμπυκνωσης, β) μια αντιδραση εστεροποιησης, γ) μια καταλυτικη αντιδραση ολεφινικης μεταθεσης παρουσια [$RuCl_2(=CHPh)(PCy_3)_2$], και τελος δ) εποξειδωση του μακροκυκλικου διπλου δεσμου.*

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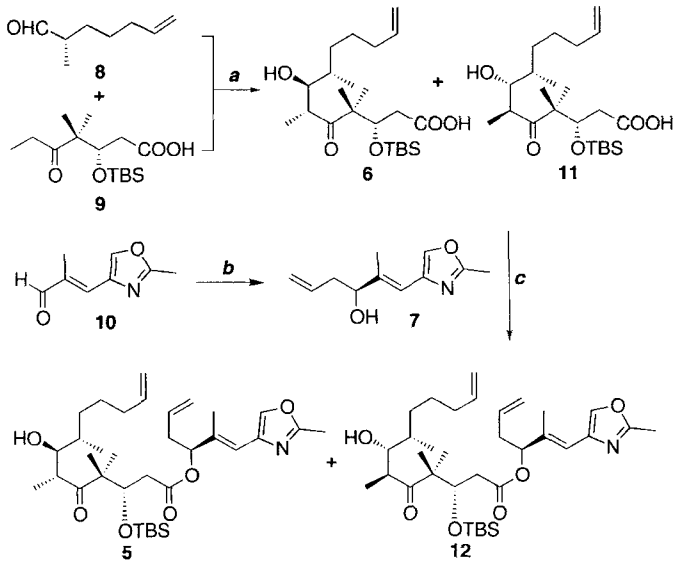
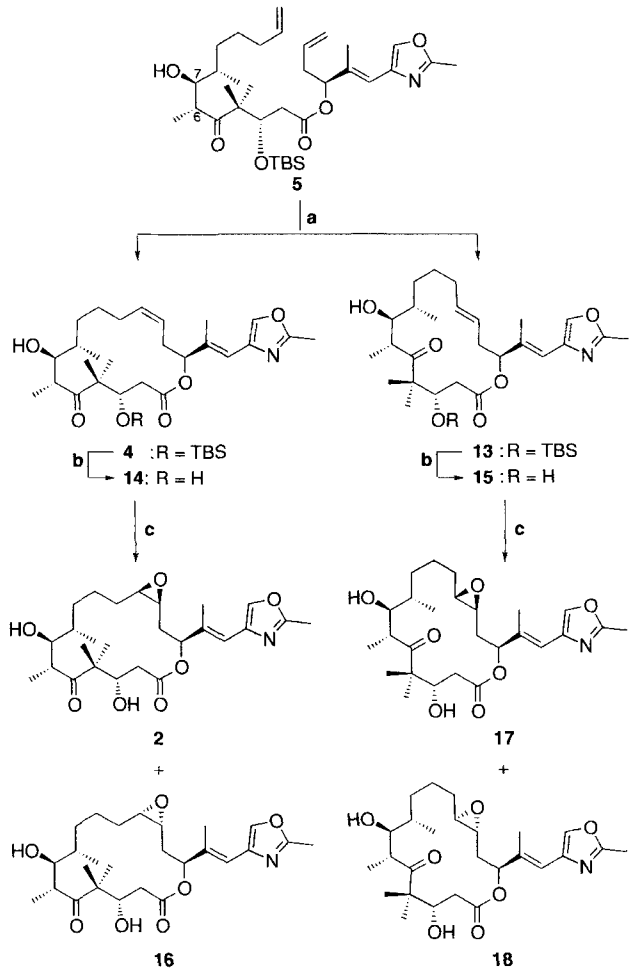


Scheme 2. Coupling of building blocks and construction of precursors **5** and **12**. Reagents and conditions: a) 2.2 equiv of LDA, −40 °C, THF, 1.5 h, then **8** in THF, −40 °C, 0.5 h (**6**:**11** ca. 5:3); b) 1.2 equiv of (+)-Ipc_2B(allyl), Et_2O, −100 °C, 0.5 h, 92%; c) 2.5 equiv of **7**, 3.0 equiv of EDC, 0.1 equiv of 4-DMAP, CH_2Cl_2, 0→25 °C, 12 h, 44% (**5**) plus 28% (**12**) for two steps. TBS = *tert*-butyldimethylsilyl; Ipc = isopinocampheyl; LDA = lithium diisopropylamide; EDC = 1-ethyl-(3-dimethylaminopropyl)-3-carbodiimide hydrochloride; 4-DMAP = 4-dimethylaminopyridine.

Coupling of **7** with the mixture of **6** and **11**, in the presence of EDC and 4-DMAP, followed by chromatographic separation furnished pure **5** (44% yield from **8**+**9**) and **12** (28% yield from **8**+**9**).

The olefin metathesis of **5** (Scheme 3) was facilitated by [$RuCl_2$(=CHPh)(PCy_3)$_2$] catalyst (Cy = cyclohexyl)[20–22] and led to a mixture of *cis* and *trans* cyclic olefins. Chromatographic purification furnished pure compounds **4** (40% yield) and **13** (32% yield), which were processed separately. Thus, exposure of **4** to 20% TFA in CH_2Cl_2 at ambient temperature gave diol **14** (89% yield), and similar treatment of **13** furnished **15** (95% yield). Reaction of **14** with methylperoxycarboximidic acid [CH_3C(=NH)OOH, prepared in situ from acetonitrile and 35% aq. H_2O_2 in the presence of $KHCO_3$][23] resulted in the formation of epoxide **2** (52% yield based on ca. 50% conversion) along with a trace amount of **16** (ratio of **2**:**16** > 20:1 by ^{1}H NMR), whereas similar reaction of **15** led to **17** (17% yield) and **18** (24% yield) (based on ca. 50% conversion).[24] These epoxides were purified by preparative thin-layer chromatography, and their stereochemistry was assigned by comparison of their NMR spectra with the original epothilone A series, the stereochemistry of which was determined by ^{1}H–^{1}H NOESY and ^{1}H–^{1}H COSY experiments and molecular modeling,[11] and in accordance with the higher potencies of **2** and **17** in tubulin polymerization experiments as compared to those of **16** and **18**, respectively.[25] However, it must be emphasized that these stereochemical assignments are tentative, requiring further experimental evidence. It is worth noting that application of these epoxidation conditions to the actual epothilone A (**1**) olefinic precursor resulted in improved diastereoselectivity (ca. 13:1 in favor of the desired isomer, 65% combined yield based on ca. 75% conversion) over our previously reported methods.[11]

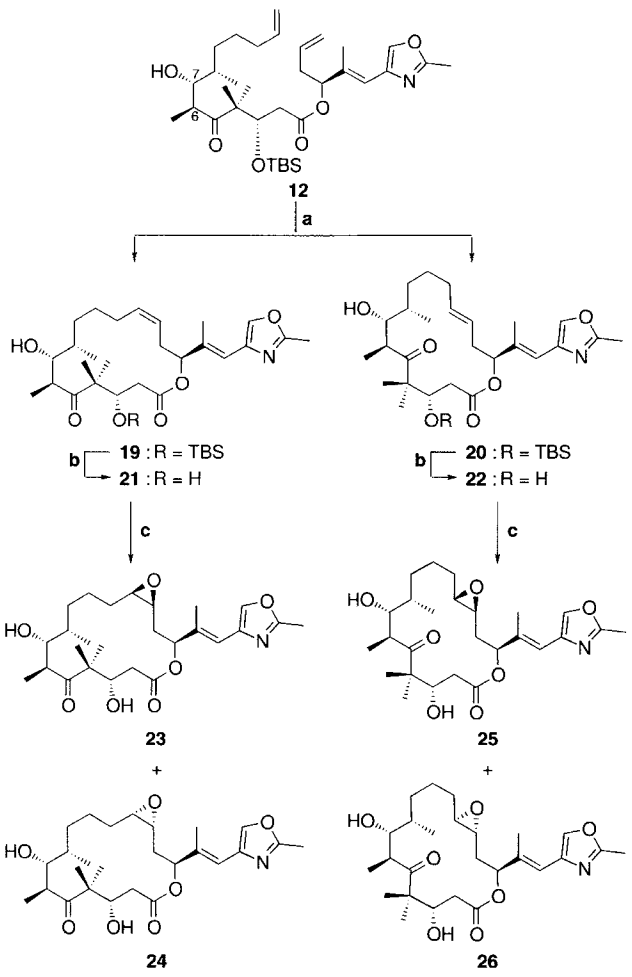


Scheme 3. Olefin metathesis of precursor **5** and synthesis of 20-oxa-epothilone A analogues **2**, **16**–**18**. Reagents and conditions: a) 20 mol% of [$RuCl_2$(=CHPh)(PCy_3)$_2$], CH_2Cl_2, 25 °C, 16 h, 40% (**4**) plus 32% (**13**); b) 20% TFA in CH_2Cl_2, 25 °C, 2 h, 89% (**14**), 95% (**15**); c) 35% H_2O_2, CH_3CN, $KHCO_3$, MeOH, 25 °C, 52% (**2**) plus trace of **16**; 17% (**17**) plus 24% (**18**) (all yields based on ca. 50% conversion). TFA = trifluoroacetic acid. The tentative stereochemical assignments of epoxides **2** and **17** were based on NMR comparisons with members of the natural epothilone A series as well as the higher potencies of **2** and **17** in the tubulin polymerization assay as compared to those of **16** and **18**, respectively.

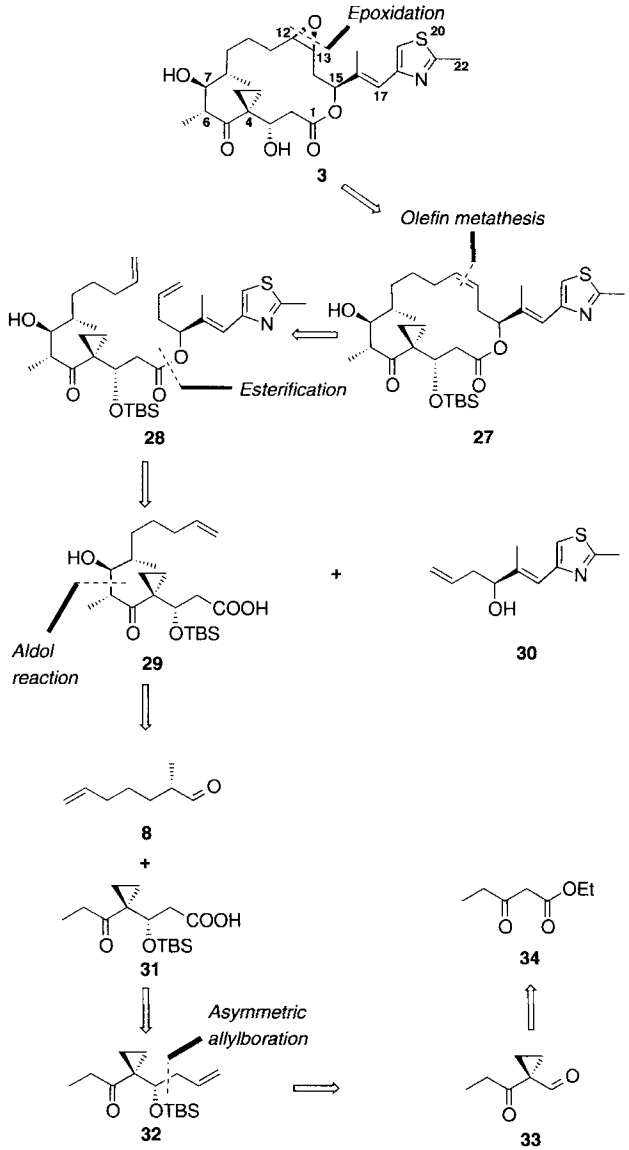
Processing of the (6*S*,7*R*) diastereomeric aldol product **12** in the same way as described above for **5**, led to the oxazole-containing epothilone A analogues **19**–**26**, as summarized in Scheme 4. The tentative stereochemical assignments of epoxides **23**–**26** were based on NMR correlations to the corresponding epothilone A analogues.

The 4,4-ethano series of epothilone A analogues: Following the same retrosynthetic rationale as the one outlined above for the oxazole analogues, the 4,4-ethano-epothilone A was analyzed as shown in Scheme 5. This time, the analysis led to building blocks **30**, **8**, and **31**. Compound **31** was further broken down into β-ketoester **34** via intermediates **32** and **33**.

We began with the synthesis of cyclopropylketoacid **31** (Scheme 6). Thus, reaction of 1,2-dibromoethane with ethyl propionylacetate (**34**) in the presence of K_2CO_3 at ambient temperature resulted in the formation of cyclopropylketoester **35** (60% yield).[26] Reduction of the ester and keto groups with $LiAlH_4$ (93% yield) followed by Swern oxidation of the result-



Scheme 4. Olefin metathesis of C6–C7 diastereomeric precursor **12** and synthesis of 20-oxa-epothilone A analogues **23**–**26**. Reagents and conditions: a) 20 mol% of $[RuCl_2(=CHPh)(PCy_3)_2]$, CH_2Cl_2, 25 °C, 20 h, 25% (**19**) plus 63% (**20**); b) 20% TFA in CH_2Cl_2, 25 °C, 2 h, 75% (**21**), 72% (**22**); c) 35% H_2O_2, CH_3CN, $KHCO_3$, MeOH, 25 °C, 24% (**23** or **24**) plus 9% (**24** or **23**), 15% (**25** or **26**) plus 19% (**26** or **25**).

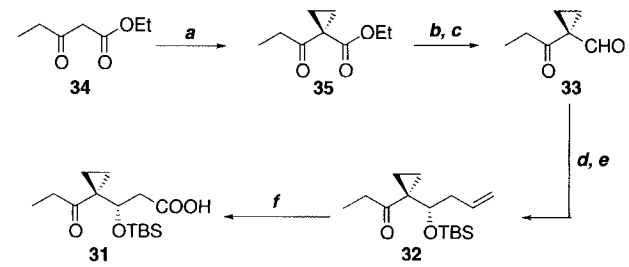


Scheme 5. Retrosynthetic analysis of 4,4-ethano-epothilone A analogue **3**.

ing diol [$(COCl)_2$; DMSO; Et_3N] furnished ketoaldehyde **33** in 64% yield. Chemo- and stereoselective addition of (+)-$Ipc_2B(allyl)$[18] to aldehyde **33** (> 85% *ee* by Mosher ester analysis),[19] followed by silylation (TBSOTf; 2,6-lutidine) of the generated secondary alcohol, gave silyl ether **32**. Finally, cleavage of the terminal olefin in **32** with $NaIO_4$ in the presence of catalytic amounts of $RuCl_3 \cdot H_2O$ in $MeCN/H_2O/CCl_4$ (2:3:2) at 25 °C[27] yielded the desired ketoacid **31** in 43% overall yield from cyclopropylketoaldehyde **33**.

The dianion of ketoacid **31** (LDA in THF at −30 °C) reacted with aldehyde **8** to form aldols **29** and **36** in a ratio of approximately 2:3 (determined by ^1H NMR) (Scheme 7). The coupling of the mixture of **29** and **36** with fragment **30**[13] was facilitated by EDC and 4-DMAP, and the resulting hydroxyesters were chromatographically separated to afford pure **28** (15%) and **37** (36%).

Ring closure of advanced intermediate **28** and epoxidation of the desilylated cyclic diols are shown in Scheme 8. Thus, stirring of **28** with $[RuCl_2(=CHPh)(PCy_3)_2]$ catalyst in CH_2Cl_2 at 25 °C followed by chromatographic separation (silica gel, preparative thin layer) furnished *cis* and *trans* olefins **27** (37% yield) and **38** (35% yield), respectively. The corresponding diols **39** (65% yield) and **40** (62% yield) were obtained by treating the respective silyl ethers with 25% HF·pyridine in THF at ambient temperature. Finally, epoxidation of **39** with methyl(trifluoro-



Scheme 6. Synthesis of ketoacid **31**. Reagents and conditions: a) 1.3 equiv of $BrCH_2CH_2Br$, 3.0 equiv of K_2CO_3, DMF, 25 °C, 15 h, 60%; b) 2.0 equiv of $LiAlH_4$, Et_2O, −20 → 0 °C, 2.5 h, 93%; c) 4.0 equiv of DMSO, 3.0 equiv of $(COCl)_2$, 8.0 equiv of Et_3N, CH_2Cl_2, −78 → 0 °C, 64%; d) 1.1 equiv of (+)-$Ipc_2B(allyl)$, Et_2O, −100 °C; e) 3.8 equiv of TBSOTf, 4.6 equiv of 2,6-lutidine, CH_2Cl_2, −78 °C; f) 4.1 equiv of $NaIO_4$, 0.05 equiv of $RuCl_3 \cdot H_2O$, $MeCN:H_2O:CCl_4$ (2:3:2), 25 °C, 43% for three steps. DMSO = dimethyl sulfoxide; TBS = *tert*-butyldimethylsilyl; Ipc = isopinocampheyl.

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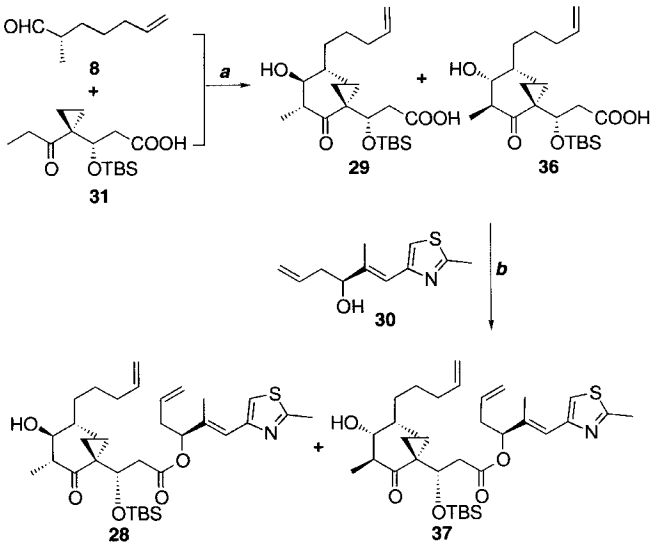
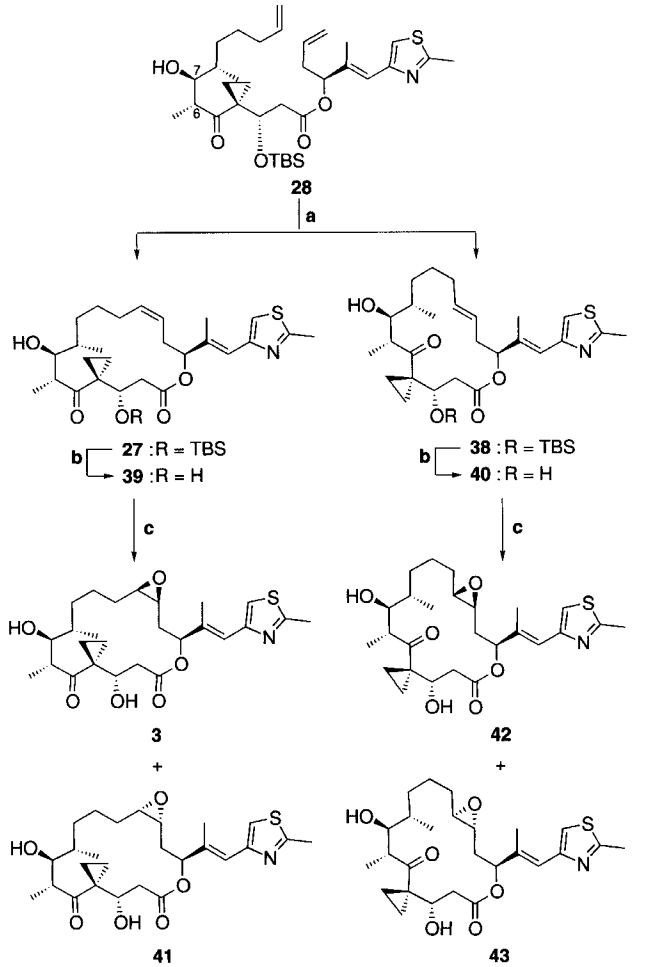


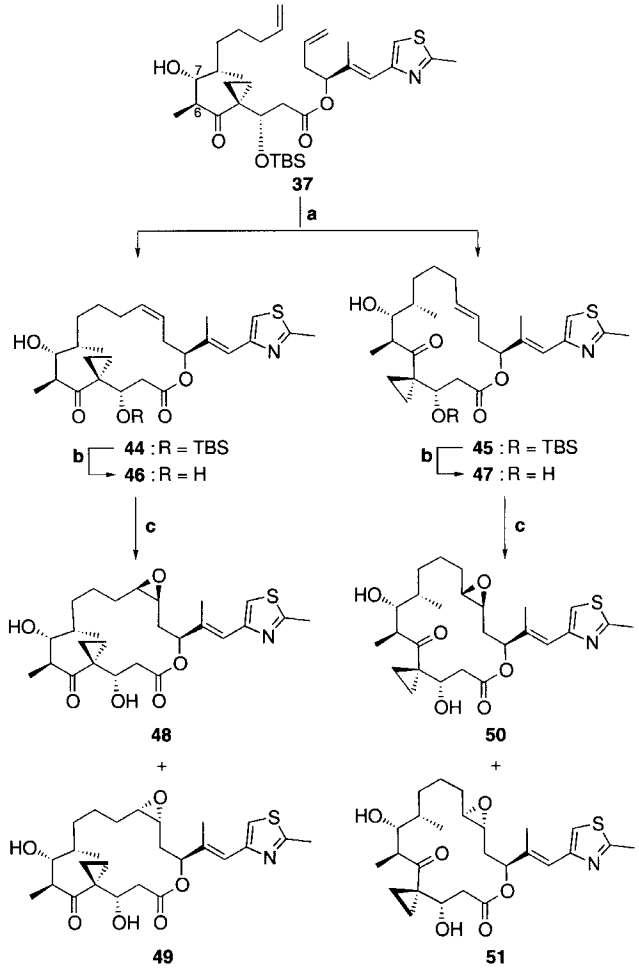
Scheme 7. Coupling of building blocks and construction of advanced intermediates **28** and **37**. Reagents and conditions: a) 2.4 equiv of LDA, −30 °C, THF, 2 h, then **8** in THF, −30 °C, 0.5 h, (**29**:**36** ca. 2:3); c) 2.5 equiv of **30**, 1.2 equiv of EDC, 0.1 equiv of 4-DMAP, CH_2Cl_2, 0→25 °C, 2 h, 15% (**28**) plus 36% (**37**) for two steps. TBS = *tert*-butyldimethylsilyl; LDA = lithium diisopropylamide; EDC = 1-ethyl-(3-dimethylaminopropyl)-3-carbodiimide hydrochloride; 4-DMAP = 4-dimethylaminopyridine.



Scheme 8. Olefin metathesis of diene **28** and synthesis of 4,4-ethano-epothilone A analogues **3** and **41**–**43**. Reagents and conditions: a) 10 mol% of $[RuCl_2(=CHPh)(PCy_3)_2]$, CH_2Cl_2, 25 °C, 2 h, 37% (**27**) plus 35% (**38**); b) 25% HF·Py in THF, 0→25 °C, 28 h, 65% (**39**), 62% (**40**); c) CH_2Cl_2:CH_3CN:Na_2EDTA (1:2:1.5), 50 equiv of CF_3COCH_3, 11 equiv of $NaHCO_3$, 7.0 equiv of Oxone®, 0 °C, 50% (**3** or **41**) plus 29% (**41** or **3**); 11% (**42** or **43**) plus 31% (**43** or **42**).

methyl)dioxirane[10, 28] gave epoxides **3** and **41** (stereochemistries not assigned, 50 and 29% yields), whereas similar treatment of **40** furnished **42** and **43** (stereochemistries not assigned, 11 and 31% yields).

The other aldol product, compound **37**, was processed in a similar way as described above for **28**, furnishing the 4,4-ethano-epothilone A analogues **46**–**51** as shown in Scheme 9. Again, the stereochemical details of these compounds remain unassigned.



Scheme 9. Olefin metathesis of C6–C7 diastereomeric diene **37** and synthesis of 4,4-ethano-epothilone A analogues **48**–**51**. Reagents and conditions: a) 9 mol% of $[RuCl_2(=CHPh)(PCy_3)_2]$, CH_2Cl_2, 25 °C, 1 h, 18% (**44**) plus 58% (**45**); b) 25% HF·Py in THF, 0→25 °C, 22 h, 54% (**46**), 76% (**47**); c) CH_2Cl_2:CH_3CN:Na_2EDTA (4:4:1), 50 equiv of CF_3COCH_3, 16 equiv of $NaHCO_3$, 10 equiv of Oxone®, 0 °C, 39% (**48** or **49**) plus 35% (**49** or **48**); 22% (**50** or **51**) plus 27% (**51** or **50**).

Conclusion

Applying the olefin metathesis approach to epothilones, we have synthesized a series of oxazole- and cyclopropane-containing epothilone A analogues. These compounds considerably enrich the known epothilone libraries in terms of molecular diversity and numbers. Biological investigations with these analogues established[25] useful structure–activity relationships within this important class of compounds. Interestingly, while the oxazole series of compounds exhibited comparable tubulin polymerization activity and cytotoxicity to the corresponding thia-

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zole series, the 4,4-ethano-epothilones proved inactive.[25] These results underscore the importance of conformational precision in these compounds for biological action. In the accompanying article[16] we describe the design and chemical synthesis of a corresponding series of epothilone B analogues with oxazole and cyclopropyl moieties utilizing the macrolactonization approach.

Experimental Section

General Techniques: All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Tetrahydrofuran (THF), toluene, and diethyl ether (ether) were distilled from sodium benzophenone, and methylene chloride (CH_2Cl_2) from calcium hydride. Anhydrous solvents were also obtained by passing them through commercially available alumina column. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at highest commercial quality and used without further purification unless otherwise stated. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60 F-254) using UV light as visualizing agent and 7% ethanolic phosphomolybdic acid or *p*-anisaldehyde solution and heat as developing agents. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 0.25, 0.50, or 1 mm E. Merck silica gel plates (60 F-254). NMR spectra were recorded on Bruker DRX-600, AMX-500, AMX-400, or AC-250 instruments and calibrated with residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. IR spectra were recorded on a Perkin-Elmer 1600 series FT-IR spectrometer. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter. High-resolution mass spectra (HRMS) were recorded on a VG ZAB-ZSE mass spectrometer under fast atom bombardment (FAB) conditions with NBA as the matrix. Melting points (m.p.) are uncorrected and were recorded on a Thomas Hoover Unimelt capillary melting point apparatus.

Hydroxyacids 6 and 11—aldol condensation of acid 9 with aldehyde 8: A solution of ketoacid **9** (1.131 g, 3.75 mmol, 1.0 equiv) in THF (30 mL) was added dropwise at −78 °C to a freshly prepared solution of LDA [formed by addition of *n*BuLi (5.27 mL, 1.6 M solution in hexanes, 8.44 mmol, 2.25 equiv) to a solution of diisopropylamine (1.16 mL, 8.25 mmol, 2.2 equiv) in THF (30 mL) at −10 °C and stirring for 30 min]. After stirring at the same temperature for 15 min, the reaction mixture was allowed to warm to −30 °C and stirred at that temperature for 1.5 h. The reaction mixture was cooled back to −78 °C and a solution of aldehyde **8** (0.757 g, 6.00 mmol, 1.6 equiv) in THF (15 mL) was added through a cannula. The resulting mixture was stirred for 15 min at −78 °C, then warmed to −40 °C and stirred for 1 h, cooled to −78 °C, and quenched by slow addition of saturated aqueous NH_4Cl (50 mL) solution. The reaction mixture was warmed to 0 °C, and a solution of aqueous 4 N HCl (1.9 mL, 7.50 mmol, 2.0 equiv) was added, followed by warming to 25 °C. Then the pH was adjusted to ≈2–3 by dropwise addition of aqueous 4 N HCl. Extractions with EtOAc (6 × 25 mL), filtration through a short plug of silica gel, and concentration afforded, in high yield, a mixture of aldol products **6** and **11** along with unreacted starting acid **9** in a 56:36:8 ratio (^{1}H NMR). This crude material was used without further purification. R_f = 0.20 (silica gel, 50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$; only signals for **6** and **11** are reported): δ = 5.88–5.73 (m, 1H, CH_2CH=CH_2), 5.04–4.92 (m, 2H, CH_2CH=CH_2), 4.51–4.47 (m, 0.4H, CHOTBS), 4.44–4.40 (m, 0.6H, $(CH_3)_2CCH$(OTBS)), 3.42 (d, J = 8.0 Hz, 0.4H, $CHOH(CHCH_3)$), 3.32 (d, J = 9.0 Hz, 0.6H, $CHOH(CHCH_3)$), 3.30–3.20 (m, 1H, CH_3CH(C=O), 2.51–2.45 (m, 1H, CH_2COOH), 2.38 (dd, J = 16.5, 6.5 Hz, 0.4H, CH_2COOH), 2.35 (dd, J = 16.5, 6.5 Hz, 0.6H, CH_2COOH), 2.11–1.98 (m, 2H), 1.80–1.21 (m, 5H), 1.20 (s, 1.8H, $C(CH_3)_2$), 1.19 (s, 1.2H, $C(CH_3)_2$), 1.16 (s, 1.8H, $C(CH_3)_2$), 1.14 (s, 1.2H, $C(CH_3)_2$), 1.06 (d, J = 6.5 Hz, 1.2H), 1.05 (d, J = 6.5 Hz, 1.8H), 1.00 (d, J = 6.5 Hz, 1.2H), 0.89 (s, 5.4H, $SiC(CH_3)_3(CH_3)_2$), 0.87 (s, 3.6H, $SiC(CH_3)_3(CH_3)_2$), 0.85 (d, J = 7.0 Hz, 1.8H), 0.11 (s, 1.8H, $SiC(CH_3)_3(CH_3)_2$), 0.09 (s, 1.2H, $SiC(CH_3)_3(CH_3)_2$), 0.08 (s, 1.2H, $SiC(CH_3)_3(CH_3)_2$), 0.07 (s, 1.8H, $SiC(CH_3)_3(CH_3)_2$); HRMS (FAB): calcd for $C_{23}H_{44}NaO_5Si$ (M + Na^+) 451.2856, found 451.2867.

Alcohol 7—allylboration of aldehyde 10: Aldehyde **10** (24.6 g, 163 mmol) was dissolved in anhydrous ether (550 mL, 0.3 M) and the solution was cooled to −100 °C. (+)-Allyldiisopinocampheylborane (0.15 M in pentane; 1.3 L, 196 mmol, 1.2 equiv; prepared from (−)-Ipc_2BOMe and 1.0 equiv of allylmagnesium bromide) was added dropwise under vigorous stirring, and the reaction mixture was allowed to stir for 1 h at the same temperature. Methanol was added at −100 °C, and the reaction mixture was allowed to warm to room temperature. Amino ethanol (50 mL, 0.81 mol, 5.0 equiv) was added, and stirring was continued for 15 h. The workup procedure was completed by the addition of saturated aqueous NH_4Cl solution, extraction with EtOAc and drying of the combined organic layers with $MgSO_4$. Filtration, followed by evaporation of the solvents under reduced pressure and flash column chromatography (silica gel, 35% ether in hexanes until all the boron complexes were removed; then 70% ether in hexanes) provided alcohol **7** (28.8 g, 92%). R_f = 0.41 (silica gel, 33% EtOAc in hexanes); $[\alpha]_D^{22}$ = −22.2 (c = 1.10, $CHCl_3$); IR (film): $\tilde{\nu}_{max}$ = 3342, 2977, 2930, 2858, 1584, 1107 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.48 (s, 1H, ArH), 6.30 (s, 1H, $ArCH$=CCH_3), 5.84–5.76 (m, 1H, CH_2CH=CH_2), 5.17–5.12 (m, 2H, CH_2CH=CH_2), 4.21 (dd, J = 7.5, 5.0 Hz, 1H, $CHOH$)), 2.46 (s, 3H, CH_3Ar), 2.46–2.31 (m, 2H, CH_2CH=CH_2), 1.94 (s, 3H, $ArCH$=CCH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 160.7, 141.3, 137.8, 135.3, 134.5, 117.8, 115.2, 76.1, 39.9, 14.6, 13.7; HRMS (FAB): calcd for $C_{11}H_{16}NO_2$ (M + H^+) 194.1181, found 194.1186.

Esters 5 and 12—EDC coupling of alcohol 7 with the mixture of ketoacids 6 and 11: A solution of ketoacids **6** and **11** (981 mg, 2.30 mmol, 1.0 equiv), 4-(dimethylamino)pyridine (4-DMAP, 28 mg, 0.23 mmol, 0.1 equiv), and alcohol **7** (1.11 g, 5.74 mmol, 2.5 equiv) in CH_2Cl_2 (1.2 mL, 2 M) was cooled to 0 °C and then treated with 1-ethyl-(3-dimethylaminopropyl)-3-carbodiimide hydrochloride (EDC, 1.32 g, 6.90 mmol, 3.0 equiv). The reaction mixture was stirred at 0 °C for 2 h and then at 25 °C for 12 h. The solution was concentrated to dryness in vacuo, and the residue was taken up in EtOAc (10 mL) and water (10 mL). The organic layer was separated, washed with saturated NH_4Cl solution (10 mL) and water (10 mL), and dried ($MgSO_4$). Evaporation of the solvents followed by flash column chromatography (silica gel, 15% EtOAc in hexanes) resulted in the isolation of the pure hydroxyesters **5** (0.608 g, 44% from ketoacid **9**) and **12** (0.387 g, 28% from ketoacid **9**).

5: R_f = 0.70 (silica gel, 50% EtOAc in hexanes); $[\alpha]_D^{22}$ = −36.6 (c = 1.31, $CHCl_3$); IR (film): $\tilde{\nu}_{max}$ = 3508, 2945, 2857, 1737, 1685, 1587, 1095 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.43 (s, 1H, ArH), 6.21 (s, 1H, $ArCH$=CCH_3), 5.80–5.72 (m, 1H, CH_2CH=CH_2), 5.70–5.62 (m, 1H, CH_2CH=CH_2), 5.25 (dd, J = 7.0, 6.5 Hz, 1H, CO_2CH), 5.06 (d, J = 17.0 Hz, 1H, CH_2CH=CH_2), 5.01 (d, J = 10.0 Hz, 1H, CH_2CH=CH_2), 4.95 (d, J = 17.0 Hz, 1H, CH_2CH=CH_2), 4.88 (d, J = 10.5 Hz, 1H, CH_2CH=CH_2), 4.37 (dd, J = 6.0, 3.5 Hz, 1H, $(CH_3)_2CCH$(OTBS)), 3.44 (s, 1H, CHO-$H(CHCH_3)$), 3.27–3.22 (m, 2H, CH_3CH(C=O) and $CHOH(CHCH_3)$), 2.45–2.38 (m, 3H), 2.40 (s, 3H, CH_3Ar), 2.29 (dd, J = 17.5, 6.0 Hz, 1H, CH_2COO), 2.02–1.90 (m, 2H, CH_2CH=CH_2), 1.91 (s, 3H, $ArCH$=CCH_3), 1.74–1.67 (m, 1H), 1.52–1.36 (m, 2H), 1.29–0.95 (m, 2H), 1.16 (s, 3H, $C(CH_3)_2$), 1.07 (s, 3H, $C(CH_3)_2$), 1.00 (d, J = 7.0 Hz, 3H, CH_3CH(C=O)), 0.85 (s, 9H, $SiC(CH_3)_3(CH_3)_2$), 0.79 (d, J = 7.0 Hz, 3H, CH_3CHCH_2), 0.08 (s, 3H, $SiC(CH_3)_3(CH_3)_2$), 0.02 (s, 3H, $SiC(CH_3)_3(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 221.7, 170.8, 160.7, 139.0, 137.5, 136.3, 135.8, 133.1, 117.8, 117.3, 114.1, 78.4, 74.5, 73.3, 53.8, 41.2, 40.1, 37.4, 35.4, 34.1, 32.3, 26.0, 25.9, 21.9, 19.8, 18.1, 15.2, 14.8, 13.7, 9.7, −4.4, −4.9; HRMS (FAB): calcd for $C_{34}H_{57}CsNO_6Si$ (M + Cs^+) 736.3010, found 736.3036.

12: R_f = 0.63 (silica gel, 50% EtOAc in hexanes); $[\alpha]_D^{22}$ = −11.0 (c = 0.77, $CHCl_3$); IR (film): $\tilde{\nu}_{max}$ = 3501, 2931, 2872, 1738, 1692, 1587, 1090 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.44 (s, 1H, ArH), 6.21 (s, 1H, $ArCH$=CCH_3), 5.81–5.72 (m, 1H, CH_2CH=CH_2), 5.71–5.62 (m, 1H, CH_2CH=CH_2), 5.28 (dd, J = 7.0, 7.0 Hz, 1H, CO_2CH), 5.06 (d, J = 17.5 Hz, 1H, CH_2CH=CH_2), 5.01 (d, J = 11.5 Hz, 1H, CH_2CH=CH_2), 4.98 (d, J = 17.0 Hz, 1H, CH_2CH=CH_2), 4.92 (d, J = 10.0 Hz, 1H, CH_2CH=CH_2), 4.46 (dd, J = 6.0, 4.0 Hz, 1H, $(CH_3)_2CCH$(OTBS)), 3.44–3.38 (m, 2H, $CHOH(CHCH_3)$ and $CHOH(CHCH_3)$), 3.19 (qd, J = 7.0, 1.5 Hz, 1H, CH_3CH(C=O)), 2.48–2.39 (m, 3H), 2.40 (s, 3H, CH_3Ar), 2.33 (dd, J = 17.0, 6.0 Hz, 1H, CH_2COO), 2.06–1.92 (m, 2H), 1.92 (s, 3H, $ArCH$=CCH_3), 1.51–0.95 (m, 5H), 1.12 (s, 3H, $C(CH_3)_2$), 1.08 (s, 3H, $C(CH_3)_2$), 0.99 (d, J = 7.0 Hz, 3H, CH_3CH(C=O)), 0.96 (d, J = 7.0 Hz, 3H, CH_3CHCH_2), 0.83

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(s, 9H, $SiC(CH_3)_3(CH_3)_2$), 0.05 (s, 3H, $SiC(CH_3)_3(CH_3)_2$), 0.03 (s, 3H, $SiC(CH_3)_3(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 220.7, 170.9, 160.7, 138.6, 137.6, 136.4, 135.8, 133.1, 117.8, 117.3, 114.5, 78.4, 74.8, 72.5, 53.9, 41.4, 40.1, 37.4, 35.3, 33.8, 32.1, 26.0, 25.9, 21.7, 19.6, 18.1, 15.4, 14.8, 13.7, 10.6, −4.4, −4.8; HRMS (FAB): calcd for $C_{34}H_{57}CsNO_6Si$ (M + Cs^+) 736.3010, found 736.3035.

Hydroxylactones 4 and 13—cyclization of diene 5 by olefin metathesis: To a solution of diene **5** (145 mg, 0.24 mmol) in CH_2Cl_2 (240 mL, 0.001 M) was added $[RuCl_2(=CHPh)(PCy_3)_2]$ (40 mg, 0.048 mol, 0.2 equiv), and the reaction mixture was allowed to stir at 25 °C for 16 h. After completion of the reaction (established by TLC), the solvent was removed under reduced pressure, and the crude products were purified by flash chromatography (silica gel, 20% EtOAc in hexanes) to give *cis*-hydroxylactone **4** (55 mg, 40%) and *trans*-hydroxylactone **13** (44 mg, 32%).

4: R_f = 0.19 (silica gel, 30% EtOAc in hexanes); $[\alpha]_D^{22}$ = − 37.5 (c = 1.41, $CHCl_3$); IR (film): $\tilde{\nu}_{max}$ = 3449, 2930, 2857, 1741, 1694, 1585, 1099, 733 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.47 (s, 1H, ArH), 6.27 (s, 1H, ArC*H*=CCH$_3$), 5.44 (ddd, J = 10.5, 10.5, 2.5 Hz, 1H, C*H*=CHCH$_2$), 5.33 (ddd, J = 10.5, 10.5, 5.0 Hz, 1H, C*H*=CHCH$_2$), 5.00 (d, J = 10.5 Hz, 1H, CO_2CH), 4.04 (t, J = 6.5 Hz, 1H, $(CH_3)_2CCH$(OTBS)), 3.92 (brs, 1H, C*H*OH(CHCH$_3$)), 3.05–3.01 (m, 2H, C*H*$_3$CH(C=O) and CHO-*H*(CHCH$_3$)), 2.78 (d, J = 6.5 Hz, 2H, CH_2COO), 2.68 (ddd, J = 14.0, 10.5, 10.5 Hz, 1H, CH=CHC*H*$_2$), 2.44 (s, 3H, CH_3Ar), 2.36–2.29 (m, 1H), 2.06 (dd, J = 14.5, 5.0 Hz, 1H, CH=CHC*H*$_2$), 1.98 (s, 3H, ArCH=CC*H*$_3$), 1.98–1.91 (m, 1H), 1.78–1.73 (m, 1H), 1.66–1.59 (m, 1H), 1.48–1.41 (m, 1H), 1.28–1.13 (m, 2H), 1.16 (s, 6H, $C(CH_3)_2$), 1.12 (d, 3H, J = 6.5 Hz, C*H*$_3$CH(C=O)), 1.00 (d, 3H, J = 7.0 Hz, C*H*$_3$CHCH$_2$), 0.81 (s, 9H, $SiC(CH_3)_3(CH_3)_2$), 0.10 (s, 3H, $SiC(CH_3)_3(CH_3)_2$), −0.07 (s, 3H, $SiC(CH_3)_3(CH_3)_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 218.0, 170.9, 160.8, 138.0, 137.6, 135.7, 134.7, 123.9, 115.8, 78.7, 76.3, 73.2, 53.5, 43.0, 39.0, 38.8, 33.5, 31.9, 28.4, 27.8, 26.1, 24.8, 22.9, 18.6, 16.5, 15.5, 14.1, 13.8, −3.6, −5.5; HRMS (FAB): calcd for $C_{32}H_{53}CsNO_6Si$ (M + Cs^+) 708.2697, found 708.2732.

13: R_f = 0.46 (silica gel, 30% EtOAc in hexanes); $[\alpha]_D^{22}$ = − 40.0 (c = 0.67, $CHCl_3$); IR (film): $\tilde{\nu}_{max}$ = 3465, 2932, 2873, 1741, 1693, 1586, 1096, 835 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.51 (s, 1H, ArH), 6.33 (s, 1H, ArC*H*=CCH$_3$), 5.35 (ddd, J = 14.5, 7.0, 7.0 Hz, 1H, C*H*=CHCH$_2$), 5.24 (ddd, J = 14.5, 7.0, 7.0 Hz, 1H, C*H*=CHCH$_2$), 5.17 (dd, J = 6.5, 3.5 Hz, 1H, CO_2CH), 4.41 (dd, J = 8.0, 3.5 Hz, 1H, $(CH_3)_2CCH$(OTBS)), 3.85 (brs, 1H, C*H*OH(CHCH$_3$)), 3.38 (brs, 1H, CHO*H*(CHCH$_3$)), 3.18 (qd, J = 7.0, 5.5 Hz, 1H, CH$_3$C*H*(C=O)), 2.65 (dd, J = 15.5, 8.0 Hz, 1H, CH_2COO), 2.60 (dd, J = 15.5, 3.5 Hz, 1H, CH_2COO), 2.54 (ddd, J = 14.5, 7.0, 3.5 Hz, 1H, CH=CHC*H*$_2$), 2.46–2.41 (m, 1H), 2.44 (s, 3H, CH_3Ar), 2.37 (ddd, J = 14.5, 7.0, 7.0 Hz, 1H, CH=CHC*H*$_2$), 2.19–2.11 (m, 1H), 1.96 (s, 3H, C*H*$_3$C=CH), 1.67–1.52 (m, 2H), 1.45 (dddd, J = 13.0, 13.0, 3.5, 3.5 Hz, 1H), 1.31–0.99 (m, 2H), 1.22 (d, 3H, J = 7.0 Hz, C*H*$_3$CH(C=O)), 1.14 (s, 3H, $C(CH_3)_2$), 1.09 (s, 3H, $C(CH_3)_2$), 1.02 (d, 3H, J = 7.0 Hz, C*H*$_3$CHCH$_2$), 0.84 (s, 9H, $SiC(CH_3)_3(CH_3)_2$), 0.08 (s, 3H, $SiC(CH_3)_3(CH_3)_2$), −0.01 (s, 3H, $SiC(CH_3)_3(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 218.3, 170.1, 160.9, 137.5, 136.3, 135.2, 134.6, 125.0, 115.8, 77.1, 75.1, 74.1, 54.0, 43.6, 40.7, 38.4, 35.3, 32.9, 30.9, 26.8, 26.1, 23.2, 21.8, 18.4, 16.8, 16.2, 14.6, 13.7, −3.9, −4.5; HRMS (FAB): calcd for $C_{32}H_{54}NO_6Si$ (M + H^+) 576.3720, found 576.3735.

***cis*-Dihydroxylactone 14—desilylation of compound 4**: Silyl ether **4** (55 mg, 0.096 mmol) was treated with a freshly prepared solution of 20% (v/v) trifluoroacetic acid (TFA)/CH_2Cl_2 (9.6 mL, 0.01 M) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min (completion of the reaction by TLC), and the solvents were evaporated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (silica gel, ether) to obtain *cis*-dihydroxylactone **14** (39 mg, 89%). R_f = 0.21 (silica gel, 50% EtOAc in hexanes); $[\alpha]_D^{22}$ = − 46.5 (c = 0.71, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$ = 3406, 2930, 1733, 1686, 1584, 1251, 733 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.47 (s, 1H, ArH), 6.31 (s, 1H, ArC*H*=C(CH$_3$)), 5.43 (ddd, J = 10.5, 10.5, 4.0 Hz, 1H, C*H*=CHCH$_2$), 5.36 (ddd, J = 10.5, 10.5, 4.5 Hz, 1H, C*H*=CHCH$_2$), 5.28 (d, J = 9.5 Hz, 1H, CO_2CH), 4.15 (d, J = 11.0 Hz, 1H, $(CH_3)_2CCH$(OH)), 3.72 (m, 1H, C*H*OH(CHCH$_3$)), 3.11 (qd, J = 7.0, 2.5 Hz, 1H, C*H*$_3$CH(C=O)), 3.02 (brs, 2H, OH), 2.66(ddd, J = 15.0, 10.0, 10.0 Hz, 1H, CH=CHC*H*$_2$), 2.50 (dd, J = 15.5, 11.0 Hz, 1H, CH_2COO), 2.43 (s, 3H, CH_3Ar), 2.38 (dd, J = 15.5, 2.5 Hz, 1H, CH_2COO), 2.26–2.13 (m, 2H), 2.07–1.98 (m, 1H), 1.98 (s, 3H, ArCH=CC*H*$_3$), 1.80–1.60 (m, 2H), 1.37–1.13 (m, 3H), 1.31 (s, 3H, $C(CH_3)_2$), 1.17 (d, J = 7.0 Hz, 3H, C*H*$_3$CH(C=O)), 1.07 (s, 3H, $C(CH_3)_2$), 0.98 (d, J = 7.0 Hz, 3H, C*H*$_3$CHCH$_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 220.3, 170.3, 160.9, 137.8, 137.4, 135.6, 133.5, 124.8, 115.9, 78.3, 74.2, 72.6, 53.0, 42.0, 39.0, 38.5, 32.4, 31.6, 27.6, 27.5, 22.5, 19.3, 15.9, 15.6, 13.8, 13.7; HRMS (FAB): calcd for $C_{26}H_{40}NO_6$ (M + H^+) 462.2856, found 462.2844.

***trans*-Dihydroxylactone 15—desilylation of compound 13**: Silyl ether **13** (27 mg, 0.047 mmol) was treated with a freshly prepared solution of 20% (v/v) trifluoroacetic acid (TFA)/CH_2Cl_2 (4.7 mL, 0.01 M) at 0 °C for 40 min, according to the procedure described for *cis*-dihydroxylactone **14**, to yield, after flash column chromatography (silica gel, 50% EtOAc in hexanes), *trans*-dihydroxyester **15** (29 mg, 95%). R_f = 0.22 (silica gel, ether); $[\alpha]_D^{22}$ = − 37.9 (c = 0.70, $CHCl_3$); IR (film): $\tilde{\nu}_{max}$ = 3400, 2933, 1733, 1688, 1583, 1466, 1251, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.49 (s, 1H, ArH), 6.29 (s, 1H, ArC*H*=CCH$_3$), 5.50 (ddd, J = 15.0, 7.5, 7.5 Hz, 1H, C*H*=CHCH$_2$), 5.37 (dd, J = 5.5, 5.5 Hz, 1H, CO_2CH), 5.34 (ddd, J = 15.0, 7.5, 7.5 Hz, 1H, C*H*=CHCH$_2$), 4.19 (d, J = 10.0, 3.0 Hz, 1H, $(CH_3)_2CCH$(OH)), 3.73 (dd, J = 5.5, 2.5 Hz, 1H, C*H*OH(CHCH$_3$)), 3.26 (qd, J = 7.0, 5.5 Hz, 1H, CH$_3$C*H*(C=O)), 3.01 (brs, 1H, OH), 2.86 (brs, 1H, OH), 2.55 (dd, J = 15.5, 10.0 Hz, 1H, CH_2COO), 2.49 (dd, J = 15.5, 3.0 Hz, 1H, CH_2COO), 2.45 (s, 3H, CH_3Ar), 2.46–2.40 (m, 2H), 2.23–2.14 (m, 1H), 2.00–1.92 (m, 1H), 1.96 (s, 3H, ArCH=CC*H*$_3$), 1.64–1.56 (m, 2H), 1.47 (dddd, J = 12.5, 12.5, 4.0, 4.0 Hz, 1H), 1.40–1.00 (m, 2H), 1.26 (s, 3H, $C(CH_3)_2$), 1.18 (d, J = 7.0 Hz, 3H, C*H*$_3$CH(C=O)), 1.06 (s, 3H, $C(CH_3)_2$), 0.98 (d, J = 6.5 Hz, 3H, C*H*$_3$CHCH$_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 219.9, 170.5, 161.0, 137.4, 136.8, 135.6, 134.5, 125.6, 116.1, 77.2, 76.1, 72.5, 52.3, 43.8, 38.8, 37.6, 36.1, 32.6, 30.3, 27.2, 21.5, 20.4, 16.6, 16.0, 15.1, 13.7; HRMS (FAB): calcd for $C_{26}H_{40}NO_6$ (M + H^+) 462.2856, found 462.2866.

20-Oxa-epothilone A analogues 2 and 16—epoxidation of *cis*-dihydroxylactone 14: To a solution of *cis*-dihydroxylactone **14** (15.7 mg, 0.034 mmol) in methanol (170 μL, 0.2 M) was added acetonitrile (36 μL, 0.680 mmol, 20 equiv), potassium hydrogen carbonate (10.0 mg, 0.102 mmol, 3 equiv), and hydrogen peroxide (35 wt% solution in water; 33.0 μL, 0.374 mmol, 11 equiv), and the reaction mixture was stirred at ambient temperature for 3 h. Additional acetonitrile (36 μL, 0.680 mmol, 20 equiv), potassium hydrogen carbonate (10.0 mg, 0.102 mmol, 3 equiv), and hydrogen peroxide (35 wt% solution in water; 33.0 μL, 0.374 mmol, 11 equiv) were added, and the stirring was continued for 3 more hours, until a ca. 1:1 ratio of product(s) and starting material was indicated by TLC. The reaction mixture was then immediately passed through a short pad of silica gel with ether and concentrated. Purification by preparative thin-layer chromatography (250 μm silica gel plate, 50% EtOAc in hexanes) provided epoxide **2** (5.5 mg, 34%) and a trace amount of its α-isomeric epoxide **16** along with unreacted starting material **14** (5.2 mg, 33%).

2: R_f = 0.23 (silica gel, Ether); $[\alpha]_D$ = − 25.2 (c = 0.31, $CHCl_3$); IR (film): $\tilde{\nu}_{max}$ = 3417, 2927, 2866, 1731, 1692, 1584, 1260, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.50 (s, 1H, ArH), 6.35 (s, 1H, ArC*H*=CCH$_3$), 5.44 (dd, 1H, J = 8.0, 2.5 Hz, CO_2CH), 4.12 (dd, 1H, J = 10.0, 3.0 Hz, $(CH_3)_2CCH$(OH), 3.81 (dd, J = 5.0, 4.0 Hz, 1H, C*H*OH(CHCH$_3$)), 3.66 (brs, 1H, OH), 3.23 (qd, J = 7.0, 5.5 Hz, 1H, CH$_3$C*H*(C=O)), 3.02 (ddd, J = 7.0, 5.0, 5.0 Hz, 1H, CH_2CH-O(epoxide)CH), 2.90 (ddd, J = 7.0, 4.0, 4.0 Hz, 1H, CH_2CH-O(epoxide)CH), 2.54 (dd, J = 14.5, 10.0 Hz, 1H, CH_2COO), 2.46 (s, 3H, CH_3Ar), 2.45 (dd, J = 14.5, 3.0 Hz, 1H, CH_2COO), 2.08 (ddd, J = 15.0, 5.0, 3.0 Hz, 1H, C*H*$_2$CH-O(epoxide)CH), 2.01 (s, 3H, ArCH=CC*H*$_3$), 1.88 (ddd, J = 15.0, 7.5, 7.5 Hz, 1H, C*H*$_2$CH-O(epoxide)CH), 1.78–1.72 (m, 1H), 1.72–1.65 (m, 1H), 1.60–1.15 (m, 5H), 1.36 (s, 3H, $C(CH_3)_2$), 1.17 (d, 3H, J = 7.0 Hz, C*H*$_3$CH(C=O)), 1.11 (s, 3H, $C(CH_3)_2$), 1.00 (d, J = 7.0 Hz, 3H, C*H*$_3$CHCH$_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 220.6, 170.9, 161.3, 137.5, 136.8, 136.1, 116.5, 76.3, 74.8, 73.7, 57.4, 54.2, 52.4, 43.6, 38.5, 36.0, 31.1, 30.2, 26.7, 23.6, 21.1, 20.9, 17.0, 15.5, 14.1, 13.6; HRMS (FAB): calcd for $C_{26}H_{40}NO_7$ (M + H^+) 478.2805, found 478.2790.

Larger amounts of epoxide **16** were synthesized by utilizing the method described for the epoxidation of *cis*-dihydroxylactone **39**. **16**: R_f = 0.22 (silica gel, 2 × 50% EtOAc in hexanes); $[\alpha]_D^{22}$ = − 22.0 (c = 0.10, $CHCl_3$); IR (film): $\tilde{\nu}_{max}$ = 3486, 2926, 2856, 1735, 1689, 1460, 1256, 1148, 982 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.49 (s, 1H, ArH), 6.35 (s, 1H, ArC*H*=CCH$_3$), 5.68 (d, J = 8.5 Hz, 1H, CO_2CH), 4.11 (dd, J = 11.0, 2.0 Hz, 1H, $(CH_3)_2CCH$(OH)), 4.03–4.00 (m, 1H, C*H*OH(CHCH$_3$)), 3.86

(brs, 1H), 3.32 (qd, $J = 7.0$, 2.0 Hz, 1H, $CH_3CH(C{=}O)$), 3.23 (ddd, $J = 10.0$, 4.0, 4.0 Hz, 1H, CH_2CH-O(epoxide)CH), 2.96 (ddd, $J = 10.0$, 4.0, 3.0 Hz, 1H, CH_2CH-O(epoxide)CH), 2.67 (brs, 1H), 2.49 (dd, $J = 12.5$, 11.0, 1H, CH_2COO), 2.45 (s, 3H, CH_3Ar), 2.40 (dd, $J = 12.5$, 2.0 Hz, 1H, CH_2COO), 2.02 (dddd, $J = 15.0$, 2.5, 1.5, 1.5 Hz, 1H, CH_2CH-O(epoxide)CH), 2.01 (s, 3H, $ArCH{=}CCH_3$), 1.86 (ddd, $J = 15.0$, 9.0, 9.0 Hz, 1H), 1.85–1.72 (m, 2H), 1.70–1.00 (m, 5H), 1.36 (s, 3H, $C(CH_3)_2$), 1.12 (d, $J = 7.0$ Hz, 3H, $CH_3CH(C{=}O)$), 1.04 (s, 3H, $C(CH_3)_2$), 0.94 (d, $J = 7.0$ Hz, 3H, CH_3CHCH_2); ^{13}C NMR (150.9 MHz, $CDCl_3$): $\delta = 222.9$, 170.8, 161.3, 137.7, 137.2, 136.1, 116.2, 75.9, 74.2, 72.1, 57.7, 56.9, 51.5, 42.6, 38.6, 37.8, 32.7, 30.9, 27.5, 23.9, 21.4, 18.5, 16.1, 15.4, 13.6, 13.0; HRMS (FAB): calcd for $C_{26}H_{39}NO_7$ ($M + Cs^+$) 610.1781, found 610.1787.

20-Oxa-epothilone A analogues 17 and 18—epoxidation of *trans*-dihydroxylactone 15: As described in the procedure for the epoxidation of *cis*-dihydroxylactone **14**, acetonitrile (261 μL, 4.998 mmol, 60 equiv), potassium hydrogen carbonate (75 mg, 0.747 mmol, 9 equiv), and hydrogen peroxide (35 wt% solution in water; 243 μL, 2.748 mmol, 33 equiv) were added portionwise, over a period of 9 h, to a solution of *trans*-dihydroxylactone **15** (38.4 mg, 0.083 mmol) in methanol (420 μL, 0.2 M) to yield, after purification by preparative thin-layer chromatography (250 μm silica gel plate, 50% EtOAc in hexanes), epoxides **17** (4.9 mg, 12%) and **18** (7.2 mg, 18%) along with unreacted starting compound **15** (10.1 mg, 26%).

17: $R_f = 0.36$ (silica gel, 75% EtOAc in hexanes); $[\alpha]_D^{22} = -22.5$ ($c = 0.20$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 3418$, 2927, 1732, 1691, 1584, 1460, 1251, 1150, 1105, 981 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.50$ (s, 1H, ArH), 6.34 (s, 1H, $ArCH{=}C(CH_3)$), 5.49 (dd, $J = 7.5$, 2.0 Hz, 1H, CO_2CH), 4.28 (dd, $J = 9.5$, 4.0 Hz, 1H, $(CH_3)_2CCH(OH)$), 3.80 (brs, 1H, OH), 3.76 (dd, $J = 5.5$, 3.5 Hz, 1H, $CHOH(CHCH_3)$), 3.13 (qd, $J = 7.0$, 5.5 Hz, 1H, $CH_3CH(C{=}O)$), 2.88 (brs, 1H, OH), 2.82 (ddd, $J = 5.5$, 5.5, 2.5 Hz, 1H, CH_2CH-O(epoxide)CH), 2.78 (ddd, $J = 6.5$, 4.0, 2.5 Hz, 1H, CH_2CH-O(epoxide)CH), 2.55 (dd, $J = 14.0$, 9.5 Hz, 1H, CH_2COO), 2.45 (s, 3H, CH_3Ar), 2.44 (dd, $J = 14.0$, 4.0 Hz, 1H, CH_2COO), 2.07 (ddd, $J = 15.0$, 7.5, 6.0 Hz, 1H, CH_2CH-O(epoxide)CH), 1.96 (s, 3H, $ArCH{=}CCH_3$), 1.96–1.88 (m, 2H), 1.75–1.00 (m, 6H), 1.33 (s, 3H, $C(CH_3)_2$), 1.18 (d, $J = 7.0$ Hz, 3H, $CH_3CH(C{=}O)$), 1.06 (s, 3H, $C(CH_3)_2$), 0.98 (d, $J = 7.0$ Hz, 3H, CH_3CHCH_2); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 220.1$, 170.8, 161.0, 137.2, 136.2, 135.6, 115.8, 76.2, 75.5, 72.8, 58.4, 55.6, 52.5, 43.9, 38.9, 36.6, 34.9, 30.8, 30.3, 22.4, 20.7, 20.4, 16.9, 16.0, 14.5, 13.7.

18: $R_f = 0.33$ (silica gel, 75% EtOAc in hexanes); $[\alpha]_D^{22} = -25.3$ ($c = 0.30$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 3442$, 2931, 1732, 1691, 1584, 1461, 1378, 1255, 980 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.49$ (s, 1H, ArH), 6.32 (s, 1H, $ArCH{=}C(CH_3)$), 5.53 (dd, $J = 9.5$, 2.0 Hz, 1H, CO_2CH), 4.16–4.11 (m, 1H, $(CH_3)_2CCH(OH)$), 3.81 (brs, 1H, $CHOH(CHCH_3)$), 3.60 (brs, 1H, OH), 3.53, (brs, 1H, OH), 3.35 (dq, $J = 7.0$, 7.0 Hz, 1H, $CH_3CH(C{=}O)$), 2.84–2.78 (m, 2H, CH_2CH-O(epoxide)CH), 2.60 (dd, $J = 15.0$, 10.0 Hz, 1H, CH_2COO), 2.52 (dd, $J = 15.0$, 3.5 Hz, 1H, CH_2COO), 2.45 (s, 3H, CH_3Ar), 2.22–2.16 (m, 1H, CH_2CH-O(epoxide)CH), 1.97 (s, 3H, $ArCH{=}CCH_3$), 1.80 (ddd, $J = 15.5$, 9.0, 7.0, 1H, CH_2CH-O(epoxide)CH), 1.74–1.05 (m, 7H), 1.36 (s, 3H, $C(CH_3)_2$), 1.18 (d, $J = 7.0$ Hz, 3H, $CH_3CH(C{=}O)$), 1.09 (s, 3H, $C(CH_3)_2$), 0.98 (d, $J = 7.0$ Hz, 3H, CH_3CHCH_2); ^{13}C NMR (150.9 MHz, $CDCl_3$): $\delta = 219.1$, 170.9, 160.1, 136.7, 136.3, 136.2, 116.5, 76.2, 75.1, 72.8, 58.2, 56.2, 52.8, 44.4, 38.3, 36.0, 35.3, 31.5, 30.0, 22.1, 21.0, 20.9, 16.6, 15.3, 14.1, 13.5; HRMS (FAB): calcd for $C_{26}H_{39}NO_7$ ($M + Cs^+$) 610.1781, found 610.1789.

Hydroxylactones 19 and 20—cyclization of diene 12 by olefin metathesis: A solution of compound **12** (125 mg, 0.21 mmol) in CH_2Cl_2 (210 mL, 0.001 M) was treated at 25 °C with $[RuCl_2(=CHPh)(PCy_3)_2]$ (17 mg, 0.021 mmol, 0.1 equiv), according to the procedure described for the cyclization of **5**, producing hydroxylactones **19** (30 mg, 25%) and **20** (75 mg, 63%), after consecutive flash column chromatography (silica gel, 20% EtOAc in hexanes) and preparative thin-layer chromatography (25 μm silica gel plate, 20% EtOAc in hexanes).

19: $R_f = 0.33$ (silica, 30% EtOAc in hexanes); $[\alpha]_D^{22} = -58.2$ ($c = 0.28$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 3512$, 2930, 2857, 1738, 1682, 1586, 1089 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.47$ (s, 1H, ArH), 6.12 (s, 1H, $ArCH{=}CCH_3$), 5.49 (ddd, $J = 10.0$, 8.0, 8.0 Hz, 1H, $CH{=}CHCH_2$), 5.33–5.27 (m, 2H, $CH{=}CHCH_2$ and CO_2CH), 4.17 (dd, $J = 9.0$, 3.5 Hz, 1H, $(CH_3)_2CCH(OTBS)$), 3.63–3.58 (m, 2H, $CHOH(CHCH_3)$ and $CH_3CH(C{=}O)$), 3.52–3.40 (brs, 1H, $CHOH(CHCH_3)$), 2.50 (dd, $J = 15.0$, 3.5 Hz, 1H, CH_2COO), 2.50–2.40 (m, 2H), 2.44 (s, 3H, CH_3Ar), 2.39 (dd, $J = 15.0$, 9.0 Hz, 1H, CH_2COO), 2.14–2.00 (m, 2H), 1.97 (s, 3H, $CH_3C{=}CH$), 1.63–1.58 (m, 1H), 1.46–1.00 (m, 4H), 1.24 (s, 3H, $C(CH_3)_2$), 1.13 (d, 3H, $J = 7.0$ Hz, $CH_3CH(C{=}O)$), 1.04 (s, 3H, $C(CH_3)_2$), 1.02 (d, 3H, $J = 6.5$ Hz, CH_3CHCH_2), 0.93 (s, 9H, $SiC(CH_3)_3(CH_3)_2$), 0.15 (s, 3H, $SiC(CH_3)_3(CH_3)_2$), 0.08 (s, 3H, $SiC(CH_3)_3(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 222.8$, 170.4, 160.8, 137.6, 136.6, 135.6, 133.5, 123.6, 115.4, 77.2, 75.0, 73.7, 54.1, 43.4, 39.8, 34.7, 33.1, 30.6, 27.7, 26.3, 25.5, 23.3, 22.3, 18.5, 16.2, 15.5, 13.8, 12.0, −3.6, −4.5; HRMS (FAB): calcd for $C_{32}H_{54}NO_6Si$ ($M + H^+$) 576.3720, found 576.3735.

20: $R_f = 0.35$ (silica gel, 30% EtOAc in hexanes); $[\alpha]_D^{22} = -42.2$ ($c = 1.44$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 3512$, 2932, 2858, 1739, 1680, 1586, 1088 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.44$ (s, 1H, ArH), 6.22 (s, 1H, $ArCH{=}CCH_3$), 5.33 (ddd, $J = 15.0$, 8.0, 4.0 Hz, 1H, $CH{=}CHCH_2$), 5.31 (ddd, $J = 15.0$, 10.5, 5.0 Hz, 1H, $CH{=}CHCH_2$), 5.17 (dd, $J = 7.0$, 6.5 Hz, 1H, CO_2CH), 4.17 (dd, $J = 8.5$, 3.0 Hz, 1H, $(CH_3)_2CCH(OTBS)$), 3.64 (q, $J = 7.0$ Hz, 1H, $CH_3CH(C{=}O)$), 3.56 (s, 1H, $CHOH(CHCH_3)$), 3.42 (d, $J = 9.0$ Hz, 1H, $CHOH(CHCH_3)$), 2.52–2.38 (m, 3H), 2.50 (dd, $J = 15.5$, 3.0 Hz, 1H, CH_2COO), 2.42 (s, 3H, CH_3Ar), 2.23–2.17 (m, 1H), 1.99–1.93 (m, 1H), 1.95 (s, 3H, $CH_3C{=}CH$), 1.57–1.47 (m, 2H), 1.36–1.28 (m, 2H), 1.21 (s, 3H, $C(CH_3)_2$), 1.10 (d, 3H, $J = 7.0$ Hz, $CH_3CH(C{=}O)$), 1.05–0.96 (m, 1H), 1.02 (s, 3H, $C(CH_3)_2$), 0.98 (d, 3H, $J = 6.5$ Hz, CH_3CHCH_2), 0.91 (s, 9H, $SiC(CH_3)_3(CH_3)_2$), 0.15 (s, 3H, $SiC(CH_3)_3(CH_3)_2$), 0.11 (s, 3H, $SiC(CH_3)_3(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 223.0$, 170.4, 160.7, 137.6, 137.3, 135.6, 133.9, 125.8, 115.7, 77.6, 75.7, 74.8, 54.1, 42.7, 39.3, 37.0, 35.0, 32.5, 32.1, 26.4, 25.5, 23.7, 22.2, 18.5, 15.4, 15.3, 13.8, 11.9, −3.4, −4.5; HRMS (FAB): calcd for $C_{32}H_{54}NO_6Si$ ($M + H^+$) 576.3720, found 576.3741.

***cis*-Dihydroxylactone 21—desilylation of compound 19**: Silyl ether **19** (71 mg, 0.12 mmol) was treated with a freshly prepared solution of 20% (*v*/*v*) trifluoroacetic acid (TFA)/CH_2Cl_2 (12 mL, 0.01 M) at 0 °C for 3 h, according to the procedure described for the synthesis of *cis*-dihydroxylactone **14**, to yield, after flash column chromatography (silica gel, 50% EtOAc in hexanes), *cis*-dihydroxyester **21** (43 mg, 75%). $R_f = 0.13$ (silica gel, 33% EtOAc in hexanes); $[\alpha]_D^{22} = -82.7$ ($c = 0.49$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3499$, 2930, 1731, 1687, 1585 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.49$ (s, 1H, ArH), 6.24 (s, 1H, $ArCH{=}CCH_3$), 5.58–5.52 (m, 2H, CO_2CH and $CH{=}CHCH_2$), 5.35 (ddd, $J = 10.5$, 9.0, 4.5 Hz, 1H, $CH{=}CHCH_2$), 4.24 (ddd, $J = 10.0$, 3.0, 2.0 Hz, 1H, $(CH_3)_2CCH(OH)$), 3.55 (d, $J = 10.0$ Hz, 1H, $CHOH(CHCH_3)$), 3.40 (s, 1H, $CHOH(CHCH_3)$), 3.31 (q, $J = 7.0$ Hz, 1H, $CH_3CH(C{=}O)$), 2.94 (d, $J = 3.0$ Hz, 1H, $(CH_3)_2CCH(OH)$), 2.64 (ddd, $J = 16.0$, 9.5, 9.5 Hz, 1H, $CH{=}CHCH_2$) 2.60 (dd, $J = 16.0$, 1.5 Hz, 1H, CH_2COO), 2.45 (s, 3H, CH_3Ar), 2.42–2.36 (m, 1H, $CH{=}CHCH_2$), 2.41 (dd, $J = 16.0$, 10.0 Hz, 1H, CH_2COO), 2.19–2.12 (m, 1H, $CH{=}CHCH_2$), 1.98 (s, 3H, $ArCH{=}CCH_3$), 1.98–1.93 (m, 1H, $CH{=}CHCH_2$), 1.59–1.55 (m, 1H), 1.48–1.32 (m, 3H), 1.18 (s, 3H, $C(CH_3)_2$), 1.13–1.07 (m, 1H), 1.11 (d, $J = 7.0$ Hz, 3H, $CH_3CH(C{=}O)$), 1.03 (s, 3H, $C(CH_3)_2$), 1.02 (d, $J = 6.5$ Hz, 3H, CH_3CHCH_2); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 221.7$, 170.7, 160.9, 137.4, 136.4, 135.9, 133.1, 124.7, 116.2, 78.1, 74.1, 72.9, 52.6, 40.8, 38.1, 34.7, 32.9, 31.4, 27.8, 25.1, 22.5, 17.7, 15.8, 15.8, 13.8, 11.7; HRMS (FAB): calcd for $C_{26}H_{40}NO_6$ ($M + H^+$) 462.2856, found 462.2867.

***trans*-Dihydroxylactone 22—desilylation of compound 20**: Silyl ether **20** (27 mg, 0.047 mmol) was treated with a freshly prepared solution of 20% (*v*/*v*) trifluoroacetic acid (TFA)/CH_2Cl_2 (4.7 mL, 0.01 M) at 0 °C for 8 h, according to the procedure described for the synthesis of *cis*-dihydroxylactone **14**, to yield, after flash column chromatography (silica gel, 33% EtOAc in hexanes), *trans*-dihydroxyester **22** (16 mg, 72%). $R_f = 0.15$ (silica gel, 33% EtOAc in hexanes); m.p. 124–125 °C; $[\alpha]_D^{22} = -67.7$ ($c = 0.62$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 3509$, 2974, 2930, 2859, 1731, 1693, 1585, 757 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.47$ (s, 1H, ArH), 6.24 (s, 1H, $ArCH{=}CCH_3$), 5.50–5.45 (m, 2H, CO_2CH and $CH{=}CHCH_2$), 5.32 (ddd, $J = 14.5$, 7.0, 7.0 Hz, 1H, $CH{=}CHCH_2$), 4.22 (ddd, $J = 10.5$, 3.0, 1.0 Hz, 1H, $(CH_3)_2CCHOH$), 3.53 (d, $J = 9.5$ Hz, 1H, $CHOH(CHCH_3)$), 3.49 (s, 1H, $CHOH(CHCH_3)$), 3.36 (q, $J = 7.0$ Hz, 1H, $CH_3CH(C{=}O)$), 2.98 (d, $J = 3.0$ Hz, 1H, $(CH_3)_2CCHOH$), 2.57 (dd, $J = 15.5$, 1.0 Hz, 1H, CH_2COO), 2.48–2.42 (m, 2H, $CH{=}CHCH_2$), 2.44 (s, 3H, CH_3Ar), 2.38 (dd, $J = 15.5$, 10.5 Hz, 1H, CH_2COO) 2.14–2.09 (m, 1H, $CH{=}CHCH_2$), 1.97 (s, 3H, $ArCH{=}CCH_3$), 1.97–1.91 (m, 1H, $CH{=}CHCH_2$), 1.61–1.56 (m, 1H), 1.42–1.05 (m, 4H), 1.19 (s, 3H, $C(CH_3)_2$), 1.11 (d, $J = 7.0$ Hz, 3H, $CH_3CH(C{=}O)$), 1.02 (s, 3H, $C(CH_3)_2$), 0.99 (d, $J = 7.0$ Hz, 3H,

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CH_3CHCH_2); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 221.9, 171.0, 160.9, 137.5, 136.5, 135.8, 134.3, 124.8, 116.0, 77.8, 74.6, 73.2, 52.7, 41.0, 38.2, 36.1, 34.5, 32.9, 32.8, 24.8, 23.0, 17.8, 16.0, 15.7, 13.8, 11.6; HRMS (FAB): calcd for $C_{26}H_{40}NO_6$ ($M + H^+$) 462.2856, found 462.2843.

20-Oxa-epothilone A analogues 23 and 24—epoxidation of *cis*-dihydroxylactone 21: As described in the procedure for the epoxidation of *cis*-dihydroxylactone **14**, acetonitrile (96 μL, 1.840 mmol, 40 equiv), potassium hydrogen carbonate (27.6 mg, 0.276 mmol, 6 equiv), and hydrogen peroxide (35 wt% solution in water; 90 μL, 1.012 mmol, 22 equiv) were added portionwise, over a period of 6 h, to a solution of *cis*-dihydroxylactone **21** (21.0 mg, 0.046 mmol) in methanol (230 μL, 0.2 M) to yield, after purification by preparative thin-layer chromatography (250 μm silica gel plate, 50% EtOAc in hexanes), epoxides **23** (or **24**) (5.2 mg, 24%) and **24** (or **23**) (2.0 mg, 9%) along with unreacted starting compound **21** (5.0 mg, 24%).

23 (or **24**): R_f = 0.45 (silica gel, 75% EtOAc in hexanes); $[\alpha]_D^{22} = -25.6$ (c = 0.25, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$ = 3454, 2927, 1731, 1689, 1585, 1460, 1381, 1288, 1152, 1109, 1056, 979, 920 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.51 (s, 1H, ArH), 6.44 (s, 1H, ArC*H*=CCH$_3$), 5.62–5.58 (m, 1H, CO_2CH), 4.43 (d, J = 2.1 Hz, 1H, $(CH_3)_2CCH(OH)$), 4.30–4.26 (m, 1H, $(CH_3)_2CCH(OH)$), 3.82 (d, J = 8.5 Hz, 1H, C*H*OH(CHCH$_3$)), 3.35 (brs, 1H, CHO*H*(CHCH$_3$)), 3.21 (q, J = 7.0 Hz, 1H, $CH_3CH(C{=}O)$), 3.09 (ddd, J = 10.5, 4.0, 3.5 Hz, 1H, CH_2CH-O(epoxide)CH), 2.89 (ddd, J = 10.5, 4.5, 2.5 Hz, 1H, CH_2CH-O(epoxide)CH), 2.55–2.46 (m, 2H, CH_2COO), 2.45 (s, 3H, CH_3Ar), 2.17 (ddd, J = 15.5, 3.5, 3.5 Hz, 1H, CH_2CH-O(epoxide)CH), 2.07 (s, 3H, ArCH=CC*H*$_3$), 1.92 (ddd, J = 15.5, 10.5, 3.5 Hz, 1H, CH_2CH-O(epoxide)CH), 1.80–1.10 (m, 7H), 1.14 (s, 3H, $C(CH_3)_2$), 1.14 (d, J = 7.0 Hz, 3H, $CH_3CH(C{=}O)$), 1.06 (s, 3H, $C(CH_3)_2$), 1.02 (d, J = 7.0 Hz, 3H, CH_3CHCH_2); ^{13}C NMR (125.7 MHz, $CHCl_3$): δ = 221.2, 171.7, 160.9, 137.6, 136.0, 134.2, 115.8, 75.8, 74.4, 72.8, 56.5, 53.9, 53.1, 40.2, 39.2, 34.2, 32.8, 29.6, 28.2, 22.9, 21.1, 16.4, 16.1, 15.2, 13.9, 12.0; HRMS (FAB): calcd for $C_{26}H_{40}NO_7$ ($M + H^+$) 478.2805, found 478.2820.

24 (or **23**): R_f = 0.42 (silica gel, 75% EtOAc in hexanes); $[\alpha]_D^{22} = -30.0$ (c = 0.06, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$ = 3416, 2924, 1733, 1687, 1585, 1459, 1380, 1149, 1068, 929 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.50 (s, 1H, ArH), 6.33 (s, 1H, ArC*H*=CCH$_3$), 5.87 (d, J = 10.5 Hz, 1H, CO_2CH), 4.73 (d, J = 9.0 Hz, 1H, $(CH_3)_2CCH(OH)$), 3.71 (brs, 1H, OH), 3.68 (d, J = 9.5 Hz, 1H, C*H*OH(CHCH$_3$)), 3.43 (brs, 1H, OH), 3.42 (q, J = 7.0 Hz, 1H, $CH_3CH(C{=}O)$), 3.19 (ddd, J = 10.0, 4.0, 2.0 Hz, 1H, CH_2CH-O(epoxide)CH), 3.08 (ddd, J = 9.0, 4.5, 4.5 Hz, 1H, CH_2CH-O(epoxide)CH), 2.51 (d, J = 14.0, 1H, CH_2COO), 2.45 (s, 3H, CH_3Ar), 2.45 (dd, J = 14.0, 9.0 Hz, 1H, CH_2COO), 2.13 (ddd, J = 14.5, 2.0, 2.0 Hz, 1H, CH_2CH-O(epoxide)CH), 2.03–1.97 (m, 1H, CH_2CH-O(epoxide)CH), 2.00 (s, 3H, ArCH=CC*H*$_3$), 1.80–0.96 (m, 7H), 1.16 (s, 3H, $C(CH_3)_2$), 1.13 (d, J = 7.0 Hz, 3H, $CH_3CH(C{=}O)$), 1.04 (s, 3H, $C(CH_3)_2$), 1.03 (d, J = 7.0 Hz, 3H, CH_3CHCH_2); HRMS (FAB): calcd for $C_{26}H_{39}NO_7$ (M + Cs^+) 610.1781, found 610.1793.

20-Oxa-epothilone A analogues 25 and 26—epoxidation of *trans*-dihydroxylactone 22: As described in the procedure for the epoxidation of *cis*-dihydroxylactone **14**, acetonitrile (62.6 μL, 1.200 mmol, 40 equiv), potassium hydrogen carbonate (18.0 mg, 0.180 mmol, 6 equiv), and hydrogen peroxide (35 wt% solution in water; 59 μL, 0.668 mmol, 22 equiv) were added portionwise, over a period of 6 h, to a solution of *trans*-dihydroxylactone **22** (14.0 mg, 0.030 mmol) in methanol (150 μL, 0.2 M) to yield, after purification by preparative thin-layer chromatography (250 μm silica gel plate, 50% EtOAc in hexanes), epoxides **25** (or **26**) (2.2 mg, 15%) and **26** (or **25**) (2.8 mg, 19%) along with unreacted starting material **22** (4.2 mg, 30%).

25 (or **26**): R_f = 0.36 (silica gel, 50% EtOAc in hexanes); $[\alpha]_D^{22} = -23.5$ (c = 0.55, $CHCl_3$); IR (film): $\tilde{\nu}_{max}$ = 3445, 2931, 1731, 1583, 1460, 1374, 1287, 1214, 1151, 1108, 1064, 983 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.48 (s, 1H, ArH), 6.31 (s, 1H, ArC*H*=CCH$_3$), 5.71 (d, J = 10.0 Hz, 1H, CO_2CH), 4.39 (dd, J = 9.5, 4.0 Hz, 1H, $(CH_3)_2CCH(OH)$), 4.27 (d, J = 4.5 Hz, 1H, OH), 3.75 (d, J = 6.0 Hz, 1H, C*H*OH(CHCH$_3$)), 3.26 (q, J = 7.0 Hz, 1H, $CH_3CH(C{=}O)$, 2.92 (brs, 1H, OH), 2.91 (ddd, J = 9.0, 2.5, 2.5 Hz, 1H, CH_2CH-O(epoxide)CH), 2.71 (ddd, J = 8.5, 2.5, 2.5 Hz, 1H, CH_2CH-O(epoxide)CH), 2.50 (d, J = 13.0 Hz, 1H, CH_2COO), 2.44 (s, 3H, CH_3Ar), 2.39 (dd, J = 13.0, 10.0 Hz, 1H, CH_2COO), 2.13 (ddd, J = 15.0, 2.5, 2.5 Hz, 1H, CH_2CH-O(epoxide)CH), 1.98 (s, 3H, ArCH=CC*H*$_3$), 1.95–1.88 (m, 1H), 1.73–1.35 (m, 7H), 1.16 (s, 3H, $C(CH_3)_2$), 1.14 (d, 3H, J = 7.0 Hz, $CH_3CH(C{=}O)$), 1.03 (s, 3H, $C(CH_3)_2$), 0.93 (d, 3H, J = 7.0 Hz, CH_3CHCH_2); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 220.7, 172.2, 161.0, 137.4, 136.4, 136.0, 116.6, 76.7, 74.6, 73.6, 58.0, 55.9, 53.0, 42.1, 39.1, 36.1, 34.6, 33.0, 29.2, 22.2, 21.7, 16.0, 15.3, 13.8, 13.5, 12.3.

26 (or **25**): R_f = 0.35 (silica gel, 50% EtOAc in hexanes); $[\alpha]_D^{22} = -23.5$ (c = 0.55, $CHCl_3$); IR (film): $\tilde{\nu}_{max}$ = 3418, 2930, 1733, 1686, 1584, 1460, 1376, 1152, 1049, 921 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.49 (s, 1H, ArH), 6.33 (s, 1H, ArC*H*=CCH$_3$), 5.54 (dd, J = 9.0, 3.0 Hz, 1H, CO_2CH), 4.20 (dd, J = 10.5, 1.5 Hz, 1H, $(CH_3)_2CCH(OH)$), 3.73 (d, J = 7.5 Hz, 1H, C*H*OH(CHCH$_3$)), 3.51 (brs, 1H), 3.35 (dq, J = 7.0, 1.5 Hz, 1H, $CH_3CH(C{=}O)$), 3.11 (brs, 1H, OH), 2.74 (dt, J = 5.5, 2.0 Hz, 2H, CH_2CH-O(epoxide)CH), 2.70 (dt, J = 5.5, 2.5 Hz, 1H, CH_2CH-O(epoxide)CH), 2.60 (dd, J = 15.5, 1.5 Hz, 1H, CH_2COO), 2.45 (s, 3H, CH_3Ar), 2.40 (dd, J = 15.5, 10.5 Hz, 1H, CH_2COO), 2.10 (ddd, J = 14.5, 5.5, 3.0 Hz, 1H, CH_2CH-O(epoxide)CH), 1.98 (s, 3H, ArCH=CC*H*$_3$), 1.91 (ddd, J = 14.5, 9.0, 5.5 Hz, 1H, CH_2CH-O(epoxide)CH), 1.68–1.25 (m, 7H), 1.29 (s, 3H, $C(CH_3)_2$), 1.12 (d, J = 7.0 Hz, 3H, $CH_3CH(C{=}O)$), 1.03 (s, 3H, $C(CH_3)_2$), 0.97 (d, J = 7.0 Hz, 3H, CH_3CHCH_2); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 221.5, 171.4, 161.0, 137.4, 136.1, 135.7, 116.5, 76.7, 74.1, 72.8, 58.7, 55.7, 52.6, 42.4, 38.3, 35.2, 35.1, 32.9, 31.7, 22.6, 21.9, 18.5, 15.5, 15.0, 13.8, 12.1; HRMS (FAB): calcd for $C_{26}H_{40}NO_7$ ($M + H^+$) 478.2805, found 478.2823.

Spirocyclopropane ketoester 35—cyclopropanation of ethyl propionylacetate 34: Ethyl propionylacetate **34** (75.0 mL, 0.526 mol) was added to a solution of dry K_2CO_3 (218.0 g, 1.579 mol, 3.0 equiv) in DMF (526 mL, 1 M) at ambient temperature. This mixture was treated with 1,2-dibromoethane (60.0 mL, 0.684 mol, 1.3 equiv) over a period of 15 min and then rapidly stirred for 15 h, after which time completion of the reaction was indicated by NMR. Following filtration through Celite and washing with ether, the solvents were removed in vacuo. Vacuum distillation (b.p. 64 °C/6 mm Hg) of the crude product resulted in the isolation of the pure spirocyclopropane ketoester **35** (53.9 g, 60%) as a colorless oil. R_f = 0.45 (silica gel, 17% EtOAc in hexanes); IR (film): $\tilde{\nu}_{max}$ = 2981, 2940, 1726, 1703, 1372, 1314, 1183, 1098 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 4.20 (q, J = 7.1 Hz, 2H, CH_3CH_2O), 2.86 (q, J = 7.3 Hz, 2H, CH_3CH_2), 1.43 (s, 4H, $C(CH_2)_2$), 1.29 (t, J = 7.1 Hz, 3H, CH_3CH_2O), 1.08 (t, J = 7.3 Hz, 3H, CH_3CH_2); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 206.0, 171.1, 61.2, 35.1, 34.6, 18.5, 14.0, 8.3.

Spirocyclopropane ketoaldehyde 33—$LiAlH_4$ reduction/Swern oxidation of spirocyclopropane ketoester 35: To a solution of spirocyclopropane ketoester **35** (53.9 g, 0.316 mol) in ether (1.5 L, 0.2 M) was added a solution of lithium aluminum hydride (LAH; 1 M solution in THF, 632 mL, 0.632 mol, 2.0 equiv) at −20 °C over a period of 2 h, and the reaction mixture stirred at −20 °C for 2 h. The reaction mixture was then diluted with ether (250 mL) and quenched by the sequential dropwise addition of water (24 mL), 15% aqueous sodium hydroxide solution (24 mL) and additional water (72 mL). The resulting slurry was allowed to warm to 25 °C over 10 h, and the aluminum salts were removed by filtration through Celite. The filtrate was dried ($MgSO_4$), and the solvent removed in vacuo to yield the crude diol (38.5 g, 93%), which was used in the oxidation step without further purification. An analytical sample was prepared by flash column chromatography (silica gel, 33 → 50% EtOAc in hexanes); R_f = 0.17 (silica gel, 50% EtOAc in hexanes); IR (film): $\tilde{\nu}_{max}$ = 3355, 2964, 2934, 2877, 1462, 1433, 1101, 1029, 969 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 4.11 (ddd, J = 11.3, 3.9, 1.3 Hz, 1H, CH_3CH_2CHOH), 3.03 (dd, J = 11.3, 5.9 Hz, 1H, CH_2OH), 2.97–2.85 (m, 3H, CH_2OH, CH_2OH and CHOH), 1.75–1.59 (m, 2H, CH_3CH_2), 0.97 (t, J = 7.5 Hz, 3H, CH_3CH_2), 0.61–0.53 (m, 2H, $C(CH_2)_2$), 0.43–0.36 (m, 2H, $C(CH_2)_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 80.1, 67.2, 27.3, 25.4, 10.7, 9.9, 7.9; HRMS (FAB): calcd for $C_7H_{14}NaO_2$ (M + Na^+) 153.0892, found 153.0894.

To a solution of oxalyl chloride (35.5 mL, 0.407 mol, 3.0 equiv) in CH_2Cl_2 (360 mL) was added dropwise DMSO (38.5 mL, 0.543 mol, 4.0 equiv) in CH_2Cl_2 (100 mL) at −78 °C over 1 h. After the mixture had been stirred for 35 min, a solution of crude diol (17.7 g, 0.136 mol) in CH_2Cl_2 (200 mL) was added dropwise at −78 °C over a period of 1.5 h. The solution was stirred for a further 1 h at −78 °C, before Et_3N (151 mL, 1.085 mol, 8.0 equiv) was added over 40 min. After a further 15 min at −78 °C the resulting slurry was allowed to warm to 0 °C over 1 h. Ether (700 mL) and saturated aqueous NH_4Cl solution (500 mL) were then added and the organic phase separated. The aqueous phase was again extracted with ether (500 mL), and the combined organic solution washed with saturated aqueous NH_4Cl solution (1.0 L), dried (Na_2SO_4), filtered, and concentrated under reduced pressure.

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Purification by flash column chromatography (silica gel, 25% ether in hexanes) afforded spirocyclopropane ketoaldehyde **33** (10.9 g, 64%). $R_f = 0.57$ (silica gel, 50% EtOAc in hexanes); (b.p. 45 °C/1.5 mm Hg); IR (film): $\tilde{\nu}_{max} = 2974, 2939, 1723, 1699, 1318, 1176, 1099\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 9.83$ (s, 1H, CHO), 2.70 (q, $J = 7.2$ Hz, 2H, CH_3CH_2), 1.70–1.68 (m, 2H, $C(CH_2)_2$), 1.57–1.54 (m, 2H, $C(CH_2)_2$), 1.09 (t, $J = 7.2$ Hz, 3H, CH_3CH_2); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 205.9, 197.8, 40.9, 33.7, 21.2, 7.7$; HRMS (FAB): calcd for $C_7H_{11}O_2$ ($M + H^+$) 127.0759, found 127.0765.

Silyl ether 32—allylboration of spirocyclopropane ketoaldehyde 33 and silylation: Allylmagnesium bromide (1 M solution in ether, 80 mL, 80.0 mmol, 1.0 equiv) was added dropwise to a well-stirred solution of (−)-Ipc_2BOMe (27.2 g, 86.0 mmol, 1.1 equiv) in ether (500 mL) at 0 °C. After the completion of the addition, the gray slurry was stirred at room temperature for 1 h, and the solvent removed under reduced pressure. Pentane (400 mL) was added to the residual solids, and the mixture stirred for 10 min. The stirring was discontinued to allow precipitation of the magnesium salts, and the clear supernatant pentane solution was transferred through a cannula carefully avoiding the transfer of any solid materials. This process was repeated four times. The combined pentane fractions were concentrated to a volume of ca. 500 mL and then added dropwise, without further purification, to a solution of ketoaldehyde **33** (10.1 g, 79.7 mmol, 1.0 equiv) in ether (250 mL) at −100 °C. After the addition was complete, the mixture was stirred at the same temperature for 30 min. Methanol (10 mL) was added at −100 °C, and the reaction mixture was allowed to warm to −40 °C over 40 min. Saturated aqueous $NaHCO_3$ solution (125 mL), followed by H_2O_2 (50 wt% solution in H_2O, 50 mL) were added, and the reaction mixture was allowed to stir at room temperature for 12 h. The organic phase was separated, and the aqueous phase extracted with EtOAc (3 × 250 mL). The combined organic extracts were washed with saturated aqueous NH_4Cl solution (500 mL), dried (Na_2SO_4), and the solvents removed in vacuo to yield the crude allylic alcohol, which was used without further purification. An analytical sample was prepared by flash column chromatography (silica gel, 3% acetone in CH_2Cl_2); $R_f = 0.14$ (silica gel, 17% EtOAc in hexanes); $[\alpha]_D^{22} = -93.6$ ($c = 0.92$, $CHCl_3$), IR (film): $\tilde{\nu}_{max} = 3472, 2978, 2938, 1678, 1641, 1376, 1068, 994, 972, 914\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 5.84$ (dddd, $J = 17.0$, 10.0, 7.0, 7.0 Hz, 1H, $CH_2CH{=}CH_2$), 5.10–5.03 (m, 2H, $CH_2CH{=}CH_2$), 3.30 (dd, $J = 6.5$, 6.5 Hz, 1H, CHOH), 3.18 (brs, 1H, CHOH), 2.42–2.37 (m, 2H, $CH_2CH{=}CH_2$), 2.12 (q, $J = 7.5$ Hz, 2H, CH_3CH_2), 1.26 (ddd, $J = 9.5$, 7.0, 5.0 Hz, 1H, $C(CH_2)_2$), 1.16 (ddd, $J = 9.5$, 7.0, 5.0 Hz, 1H, $C(CH_2)_2$), 1.07 (ddd, $J = 9.0$, 7.0, 5.0 Hz, 1H, $C(CH_2)_2$), 1.00 (t, $J = 7.5$ Hz, 3H, CH_3CH_2), 0.94 (ddd, $J = 9.0$, 7.0, 5.0 Hz, 1H, $C(CH_2)_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 212.5, 135.4, 117.0, 74.9, 39.7, 35.4, 29.4, 14.0, 12.6, 8.0$; HRMS (FAB): calcd for $C_{10}H_{16}NaO_2$ ($M + Na^+$) 191.1048, found 191.1042.

This crude alcohol was dissolved in CH_2Cl_2 (750 mL, 0.3 M), and the solution was cooled to −78 °C. The solution was treated with 2,6-lutidine (40 mL, 0.368 mol, 4.6 equiv), and after stirring for 5 min, *tert*-butyldimethylsilyl triflate (70 mL, 0.305 mmol, 3.8 equiv) was added dropwise. The reaction mixture was allowed to stir at −78 °C for 35 min, after which time no starting material was detected by TLC. Saturated aqueous NH_4Cl solution (500 mL) was added, and the reaction mixture was allowed to warm to room temperature. The organic phase was separated, and the aqueous layer extracted with ether (3 × 300 mL). The combined organic extracts were dried ($MgSO_4$) and filtered through Celite, and the solvents were removed in vacuo to yield the crude silyl ether **32**, which was used without further purification. An analytical sample was prepared by flash column chromatography (silica gel, 2 → 17% ether in hexanes); $R_f = 0.50$ (silica gel, 17% EtOAc in hexanes); $[\alpha]_D^{22} = +20.3$ ($c = 0.94$, $CHCl_3$), IR (film): $\tilde{\nu}_{max} = 2955, 2932, 2890, 2857, 1687, 1256, 1086, 838, 776\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.79$ (dddd, $J = 17.0$, 10.0, 7.0, 7.0 Hz, 1H, $CH_2CH{=}CH_2$), 5.01–4.94 (m, 2H, $CH_2CH{=}CH_2$), 4.16 (dd, $J = 5.5$, 5.5 Hz, 1H, CHOTBS), 2.38–2.21 (m, 2H, $CH_2CH{=}CH_2$), 2.30 (q, $J = 7.5$ Hz, 2H, CH_3CH_2), 1.13–1.09 (m, 1H, $C(CH_2)_2$), 1.00 (t, $J = 7.5$ Hz, 3H, CH_3CH_2), 0.98–0.90 (m, 3H, $C(CH_2)_2$), 0.86 (s, 9H, $SiC(CH_3)_3(CH_3)_2$), 0.04 (s, 3H, $SiC(CH_3)_3(CH_3)_2$), 0.01 (s, 3H, $SiC(CH_3)_3(CH_3)_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 210.5, 135.5, 116.8, 70.2, 41.6, 36.3, 31.0, 25.8, 18.0, 12.6, 11.3, 8.3, -4.3, -4.6$; HRMS (FAB): calcd for $C_{16}H_{31}O_2Si$ ($M + H^+$) 283.2093, found 283.2087.

Spirocyclopropane ketoacid 31—oxidation of olefin 32: The crude alkene **32** was dissolved in MeCN (143 mL), CCl_4 (143 mL), and H_2O (214 mL), and the mixture cooled to 0 °C. Sodium periodate (70 g, 327 mmol, 4.1 equiv) and ruthenium(III) chloride hydrate (898 mg, 3.98 mmol, 0.05 equiv) were added, and the mixture was stirred at 0 °C for 10 min. The dark mixture was allowed to warm to ambient temperature and stirred for 3 h, after which time the disappearance of starting material was indicated by TLC. CH_2Cl_2 (1.5 L) and saturated aqueous NaCl solution (1.5 L) were added, and the layers were separated. Extractions of the aqueous phase with CH_2Cl_2 (3 × 750 mL), filtration through Celite, concentration and flash column chromatography (2 → 80% EtOAc in hexanes) yielded pure spirocyclopropane ketoacid **31** (10.2 g, 43% for three steps); $R_f = 0.39$ (silica gel, 50% EtOAc in hexanes); $[\alpha]_D^{22} = -0.8$ ($c = 1.19$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 2955, 2930, 2857, 1712, 1687, 1255, 1090, 838, 778\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 4.45$ (dd, $J = 5.5$, 5.5 Hz, 1H, CHOTBS), 2.62 (dd, $J = 15.5$, 5.5 Hz, 1H, CH_2CHOTBS), 2.61 (dd, $J = 15.5$, 5.5 Hz, 1H, CH_2CHOTBS), 2.39 (dq, $J = 17.5$, 7.0 Hz, 1H, CH_3CH_2), 2.28 (dq, $J = 17.5$, 7.0 Hz, 1H, CH_3CH_2), 1.01 (t, $J = 7.0$ Hz, 3H, CH_3CH_2), 0.84 (s, 9H, $SiC(CH_3)_3(CH_3)_2$), 0.06 (s, 3H, $SiC(CH_3)_3(CH_3)_2$), 0.04 (s, 3H, $SiC(CH_3)_3(CH_3)_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$): $\delta = 210.2, 177.4, 68.7, 42.2, 36.4, 30.9, 25.7, 18.0, 13.0, 12.6, 8.2, -4.6, -4.9$; HRMS (FAB): calcd for $C_{15}H_{28}NaO_4Si$ ($M + Na^+$) 323.1655, found 323.1650.

Hydroxyacids 29 and 36—aldol condensation of ketoacid 31 with aldehyde 8: In accordance with the procedure described for the preparation of aldols **6** and **11**, ketoacid **31** (1.581 g, 5.26 mmol) in THF (18 mL) was treated with lithium diisopropylamide [LDA; freshly prepared from *n*BuLi (7.73 mL, 1.6 M solution in hexanes, 12.37 mmol, 2.35 equiv) and diisopropylamine (1.70 mL, 12.10 mmol, 2.3 equiv) in THF (53 mL)] and aldehyde **8** (1.13 g, 8.94 mmol, 1.7 equiv) in THF (53 mL) to afford a mixture of aldol products **29** and **36** in a ratio of ca. 2:3 (^1H NMR). This crude material was used without further purification.

Esters 28 and 37—EDC coupling of alcohol 30 with the mixture of ketoacids 29 and 36: By analogy to the procedure described above for the synthesis of esters **5** and **12**, a solution of the mixture of ketoacids **29** and **36** (2.289 g crude), 4-DMAP (66 mg, 0.540 mmol), and alcohol **30** (2.81 g, 13.43 mmol) in CH_2Cl_2 (8.0 mL) was treated with EDC (1.23 g, 6.42 mmol) to provide, after column chromatography (silica gel, 33 → 50% ether in hexanes), ester **28** (488 mg, 15% from ketoacid **31**) and ester **37** (1.171 g, 36% from ketoacid **31**).

28: $R_f = 0.38$ (silica gel, 50% ether in hexanes); IR (film): $\tilde{\nu}_{max} = 3508, 3078, 2926, 2855, 1737, 1675, 1378, 1255, 1170, 1095, 987, 836\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.96$ (s, 1H, ArH), 6.50 (s, 1H, $ArCH{=}CCH_3$), 5.87–5.65 (m, 2H, $2CH_2CH{=}CH_2$), 5.28 (dd, $J = 6.8$, 6.8 Hz, 1H, CO_2CH), 5.10 (d, $J = 17.0$ Hz, 1H, $CH_2CH{=}CH_2$), 5.04 (d, $J = 10.0$ Hz, 1H, $CH_2CH{=}CH_2$), 5.00 (d, $J = 17.0$ Hz, 1H, $CH_2CH{=}CH_2$), 4.93 (d, $J = 10.0$ Hz, 1H, $CH_2CH{=}CH_2$), 4.30 (dd, $J = 6.2$, 5.0 Hz, 1H, $(CH_2)_2$CCHOTBS), 3.48 (brs, 1H, $CHOH(CHCH_3)$), 3.42 (d, $J = 9.2$ Hz, 1H, CHOH$(CHCH_3)$), 2.98 (q, $J = 6.5$ Hz, 1H, $CH_3CH(C{=}O)$), 2.70 (s, 3H, CH_3Ar), 2.66 (dd, $J = 15.0$, 6.8 Hz, 1H, CH_2COO), 2.56 (dd, $J = 15.0$, 5.0 Hz, 1H, CH_2COO), 2.51–2.45 (m, 2H, $CH_2CH{=}CH_2$), 2.09–2.02 (m, 2H, $CH_2CH{=}CH_2$), 2.06 (d, $J = 1.0$ Hz, 3H, $ArCH{=}CCH_3$), 1.78–1.74 (m, 1H), 1.73–1.63 (m, 1H), 1.63–1.48 (m, 2H), 1.34–0.96 (m, 5H), 1.01 (d, $J = 7.0$ Hz, 3H, $CH_3CH(C{=}O)$), 0.87 (s, 9H, $SiC(CH_3)_3(CH_3)_2$), 0.84 (d, $J = 7.0$ Hz, 3H, CH_3CHCH_2), 0.08 (s, 3H, $SiC(CH_3)_3(CH_3)_2$), 0.07 (s, 3H, $SiC(CH_3)_3(CH_3)_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 216.0, 170.2, 164.5, 152.3, 138.9, 136.6, 133.2, 121.1, 117.7, 116.3, 114.0, 78.6, 74.3, 69.2, 42.6, 40.5, 37.4, 35.9, 35.4, 34.1, 32.3, 26.0, 25.6, 19.1, 17.9, 15.3, 14.6, 14.0, 12.5, 10.0, -4.5, -5.0$; HRMS (FAB): calcd for $C_{34}H_{55}CsNO_5SSi$ ($M + Cs^+$) 750.2625, found 750.2649.

37: $R_f = 0.30$ (silica gel, 50% ether in hexanes); $[\alpha]_D^{22} = -12.7$ ($c = 1.38$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 3499, 3077, 2931, 2857, 1738, 1674, 1375, 1254, 1169, 1096, 982, 836\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.96$ (s, 1H, ArH), 6.50 (s, 1H, $ArCH{=}CCH_3$), 5.83–5.69 (m, 2H, $2CH_2CH{=}CH_2$), 5.29 (dd, $J = 6.8$, 6.8 Hz, 1H, CO_2CH), 5.10 (d, $J = 17.0$ Hz, 1H, $CH_2CH{=}CH_2$), 5.04 (d, $J = 10.5$ Hz, 1H, $CH_2CH{=}CH_2$), 5.00 (d, $J = 17.0$ Hz, 1H, $CH_2CH{=}CH_2$), 4.95 (d, $J = 10.0$ Hz, 1H, $CH_2CH{=}CH_2$), 4.32 (dd, $J = 6.5$, 4.8 Hz, 1H, $(CH_2)_2$CCHOTBS), 3.50–3.46 (m, 1H, CHOH$(CHCH_3)$), 3.24 (brd, $J = 2.0$ Hz, 1H, CHOH$(CHCH_3)$), 2.94 (qd, $J = 7.0$, 2.5 Hz, 1H, $CH_3CH(C{=}O)$), 2.70 (s, 3H, CH_3Ar), 2.65 (dd, $J = 15.1$, 6.5 Hz, 1H, CH_2COO), 2.56 (dd, $J = 15.1$, 4.8 Hz, 1H, CH_2COO), 2.51–2.45 (m, 2H, $CH_2CH{=}CH_2$), 2.06 (d, $J = 1.0$ Hz, 3H, $ArCH{=}CCH_3$),

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2.06–1.96 (m, 2H, $CH_2CH=CH_2$), 1.66–1.01 (m, 9H), 1.04 (d, $J = 7.0$ Hz, 3H, $CH_3CH(C=O)$), 0.99 (d, $J = 6.5$ Hz, 3H, CH_3CHCH_2), 0.87 (s, 9H, $SiC(CH_3)_3(CH_3)_2$), 0.08 (s, 3H, $SiC(CH_3)_3(CH_3)_2$), 0.07 (s, 3H, $SiC(CH_3)_3(CH_3)_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 215.5$, 170.3, 164.6, 152.4, 138.7, 136.7, 133.3, 121.2, 117.8, 116.3, 114.6, 78.7, 74.7, 69.2, 42.7, 41.1, 37.4, 36.1, 35.3, 33.9, 32.3, 26.0, 25.8, 19.2, 18.0, 15.4, 14.7, 13.8, 12.5, 11.4, −4.5, −4.8 ; HRMS (FAB): calcd for $C_{34}H_{55}CsNO_5SSi$ ($M + Cs^+$) 750.2625, found 750.2649.

Hydroxylactones 27 and 38—cyclization of diene 28 by olefin metathesis: As described for the cyclization of diene **5**, a solution of diene **28** (79 mg, 0.128 mmol, 1.0 equiv) in CH_2Cl_2 (128 mL, 0.001 M) was treated with [$RuCl_2$(=CHPh)(PCy_3)$_2$] (10.5 mg, 0.013 mmol, 0.1 equiv) for 2 h, to furnish, after preparative thin-layer chromatography (250 μm silica gel plate, 17% EtOAc in hexanes) *cis*-hydroxylactone **27** (28 mg, 37%) and *trans*-hydroxylactone **38** (27 mg, 35%).

27: $R_f = 0.61$ (silica, 50% EtOAc in hexanes); $[\alpha]_D^{22} = -121.3$ ($c = 0.67$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 2928$, 2855, 1738, 1678, 1461, 1381, 1254, 1165, 1104, 1064, 835 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.93$ (s, 1H, ArH), 6.44 (s, 1H, ArC*H*=C(CH_3)), 5.52–5.45 (m, 1H, C*H*=$CHCH_2$) 5.30 (ddd, $J = 10.5$, 10.5, 6.5 Hz, 1H, C*H*=$CHCH_2$), 5.20 (d, $J = 8.5$ Hz, 1H, CO_2CH), 4.07–4.00 (m, 1H), 3.86 (brs, 1H, CHO*H*($CHCH_3$)), 3.56–3.53 (m, 1H), 2.83 (dd, $J = 16.0$, 11.5 Hz, 1H, CH_2COO), 2.87–2.77 (m, 1H), 2.70 (s, 3H, CH_3Ar), 2.67–2.56 (m, 1H), 2.55 (dd, $J = 16.0$, 2.0 Hz, 1H, CH_2COO), 2.31–2.19 (m, 2H), 2.15–2.09 (m, 1H), 2.06 (s, 3H, ArCH=CC*H*$_3$), 1.77–1.73 (m, 1H), 1.67–1.52 (m, 2H), 1.43–1.23 (m, 2H), 1.15 (d, $J = 7.0$ Hz, 3H, $CH_3CH(C=O)$), 1.05–0.85 (m, 3H), 1.00 (d, $J = 7.0$ Hz, 3H, CH_3CHCH_2), 0.92 (s, 9H, $SiC(CH_3)_3(CH_3)_2$), 0.50–0.44 (m, 1H, $C(CH_2)_2$), 0.15 (s, 3H, $SiC(CH_3)_3(CH_3)_2$), 0.15 (s, 3H, $SiC(CH_3)_3(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ; 217.5, 169.5, 164.4, 152.3, 138.3, 133.5, 124.5, 119.0, 115.8, 77.4, 74.1, 73.9, 44.5, 41.1, 39.1, 35.0, 32.8, 31.3, 29.6, 27.7, 25.8, 21.2, 19.1, 18.0, 15.5, 15.3, 14.7, 11.8, −3.0, −5.9; HRMS (FAB): calcd for $C_{32}H_{52}NO_5SSi$ ($M + H^+$) 590.3335, found 590.3347.

38: $R_f = 0.63$ (silica gel, 50% EtOAc in hexanes); $[\alpha]_D^{22} = -71.6$ ($c = 0.57$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 2929$, 2855, 1738, 1668, 1380, 1254, 1167, 1105, 1066, 1105, 837 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.93$ (s, 1H, ArH), 6.49 (s, 1H, ArC*H*=C(CH_3)), 5.38 (ddd, $J = 15.0$, 11.5, 4.0 Hz, 1H, C*H*=$CHCH_2$), 5.26 (ddd, $J = 15.0$, 7.5, 7.0 Hz, 1H, C*H*=$CHCH_2$), 5.11 (dd, $J = 7.5$, 7.0 Hz, 1H, CO_2CH), 4.15–4.07 (m, 1H), 3.87 (d, $J = 4.5$ Hz, 1H), 3.60–3.50 (m, 2H), 2.81 (dd, $J = 16.5$, 11.5 Hz, 1H, CH_2COO), 2.70 (s, 3H, CH_3Ar), 2.57 (dd, $J = 16.5$, 2.0 Hz, 1H, CH_2COO), 2.42–2.36 (m, 3H), 2.04 (s, 3H, ArCH=CC*H*$_3$), 1.93–1.82 (m, 2H), 1.79–1.72 (m, 1H), 1.63–1.53 (m, 2H), 1.28–1.21 (m, 1H), 1.12 (d, $J = 7.0$ Hz, 3H, $CH_3CH(C=O)$), 1.03–0.84 (m, 3H), 1.01 (d, $J = 7.0$ Hz, 3H, CH_3CHCH_2), 0.93 (s, 9H, $SiC(CH_3)_3(CH_3)_2$), 0.49–0.42 (m, 1H, $C(CH_2)_2$), 0.16 (s, 6H, $SiC(CH_3)_3(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 218.8$, 169.5, 164.4, 152.3, 137.8, 134.2, 126.2, 119.4, 115.9, 77.8, 73.8, 73.1, 43.0, 41.1, 39.0, 37.6, 35.1, 33.3, 32.6, 29.6, 26.9, 25.9, 19.1, 18.1, 14.8, 14.2, 13.6, 11.5, −3.4, −5.7; HRMS (FAB): calcd for $C_{32}H_{52}NO_5SSi$ ($M + H^+$) 590.3335, found 590.3351.

***cis*-Dihydroxylactone 39—desilylation of compound 27**: Silyl ether **27** (62 mg, 0.105 mmol) in THF (3.0 mL, 0.035 M) was treated with hydrogen fluoride·pyridine (1.2 mL, 0.1 M) at 0 °C for 30 min. The mixture was allowed to warm to room temperature over 28 h, after which time TLC indicated the disappearance of starting material. The resulting solution was added dropwise to a mixture of saturated aqueous $NaHCO_3$ (20 mL) and EtOAc (20 mL), and the mixture stirred until effervesence ceased. The two layers were then separated, and the aqueous layer again extracted with EtOAc (2 × 20 mL). The combined organic phases were washed with $NaHCO_3$ (30 mL) and brine (30 mL) and dried ($MgSO_4$). Concentration followed by flash column chromatography (silica gel, 17 → 50% EtOAc in hexanes) furnished *cis*-dihydroxylactone **39** (32 mg, 65%). $R_f = 0.28$ (silica gel, 50% EtOAc in hexanes); $[\alpha]_D^{22} = -105.5$ ($c = 0.55$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3465$, 2929, 1732, 1675, 1372, 1171, 983, 733 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.97$ (s, 1H, ArH), 6.53 (s, 1H, ArC*H*=C(CH_3)), 5.61 (ddd, $J = 10.0$, 8.5, 7.5 Hz, 1H, C*H*=$CHCH_2$), 5.54 (dd, $J = 9.0$, 2.5 Hz, 1H, CO_2CH), 5.37 (ddd, $J = 10.5$, 10.5, 5.5 Hz, 1H, C*H*=$CHCH_2$), 3.87–3.82 (m, 1H), 3.67 (ddd, $J = 9.5$, 3.5, 3.5 Hz, 1H), 3.62–3.56 (m, 2H), 2.78 (dd, $J = 17.5$, 10.0 Hz, 1H, CH_2COO), 2.71 (s, 3H, CH_3Ar), 2.67 (dd, $J = 17.5$, 3.0 Hz, 1H, CH_2COO), 2.63 (ddd, $J = 15.0$, 9.5, 9.5 Hz, 1H, $CH=CHCH_2$), 2.38–2.31 (m, 1H, $CH=CHCH_2$), 2.29–2.20 (m, 1H, $CH=CHCH_2$), 2.07 (s, 3H, ArCH=CC*H*$_3$), 2.01–1.94 (m, 1H, $CH=CHCH_2$), 1.70–1.50 (m, 2H), 1.48–1.40 (m, 2H), 1.48–1.40 (m, 2H), 1.21 (d, $J = 7.0$ Hz, 3H, $CH_3CH(C=O)$), 1.11 (ddd, $J = 9.5$, 7.0, 4.0 Hz, 1H, $C(CH_2)_2$), 1.03 (d, $J = 7.0$ Hz, 3H, CH_3CHCH_2), 0.99 (ddd, $J = 9.5$, 6.5, 4.5 Hz, 1H, $C(CH_2)_2$), 0.65 (ddd, $J = 10.0$, 7.0, 4.5 Hz, 1H, $C(CH_2)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ; 215.4, 171.9, 164.7, 152.1, 136.8, 133.2, 124.7, 119.7, 116.2, 77.3, 75.5, 70.7, 45.6, 38.5, 37.5, 34.0, 31.5, 30.4, 27.7, 27.0, 19.1, 18.2, 16.6, 15.9, 15.4, 11.2; HRMS (FAB): calcd for $C_{26}H_{38}NO_5S$ ($M + H^+$) 476.2471, found 476.2482.

***trans*-Dihydroxylactone 40—desilylation of compound 38**: Silyl ether **38** (62 mg, 0.105 mmol), in THF (3.0 mL, 0.035 M) was treated with hydrogen fluoride·pyridine (1.2 mL, 0.1 M) at room temperature for 25 h, according to the procedure described for *cis*-dihydroxylactone **39**, to yield, after flash column chromatography (silica gel, 17 → 50% EtOAc in hexanes), *trans*-dihydroxylactone **40** (31 mg, 62%). $R_f = 0.38$ (silica gel, 50% EtOAc in hexanes); $[\alpha]_D^{22} = -72.5$ ($c = 0.24$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3502$, 2922, 2852, 1730, 1672, 1456, 1373, 1179, 976 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.96$ (s, 1H, ArH), 6.53 (s, 1H, ArC*H*=C(CH_3)), 5.49–5.44 (m, 2H, C*H*=$CHCH_2$ and CO_2CH), 5.35 (ddd, $J = 15.0$, 7.5, 7.5 Hz, 1H, C*H*=$CHCH_2$), 3.81 (m, 1H), 3.77 (d, $J = 3.0$, 1H), 3.72 (qd, $J = 7.0$, 2.5 Hz, 1H, $CH_3CH(C=O)$), 3.67 (m, 1H), 3.03 (brs, OH), 2.77 (dd, $J = 17.5$, 10.5 Hz, 1H, CH_2COO), 2.70 (s, 3H, CH_3Ar), 2.64 (dd, $J = 17.5$, 2.5 Hz, 1H, CH_2COO), 2.46–2.43 (m, 2H), 2.34–2.27 (m, 1H), 2.10–2.05 (m, 1H), 2.07 (d, $J = 1.5$ Hz, 3H, ArCH=CC*H*$_3$), 1.96–1.88 (m, 1H), 1.79–1.63 (m, 1H), 1.60–1.00 (m, 3H), 1.47 (ddd, $J = 9.5$, 7.0, 4.0 Hz, 1H, $C(CH_2)_2$), 1.17 (d, $J = 7.0$ Hz, 3H, $CH_3CH(C=O)$), 1.11 (ddd, $J = 9.5$, 7.0, 4.0 Hz, 1H, $C(CH_2)_2$), 1.01 (d, $J = 7.0$ Hz, 3H, CH_3CHCH_2), 0.97 (ddd, $J = 9.5$, 7.0, 4.5 Hz, 1H, $C(CH_2)_2$), 0.61 (ddd, $J = 9.5$, 6.5, 4.0 Hz, 1H, $C(CH_2)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ; 217.2, 171.8, 164.7, 152.1, 136.9, 134.4, 125.5, 120.0, 116.3, 77.8, 73.9, 70.9, 44.0, 38.6, 38.1, 37.0, 32.6, 32.3, 29.6, 26.7, 19.1, 18.7, 15.0, 14.9, 13.9, 11.4; HRMS (FAB): calcd for $C_{26}H_{37}CsNO_5S$ ($M + Cs^+$) 608.1447, found 608.1471.

4,4-Ethano-epothilone A analogues 3 and 41—epoxidation of *cis*-dihydroxylactone 39: To a solution of *cis*-dihydroxylactone **39** (8.2 mg, 0.017 mmol) in acetonitrile (200 μL) and CH_2Cl_2 (100 μL) was added a 0.4 mM aqueous solution of disodium salt of ethylenediaminetetraacetic acid (Na_2EDTA, 150 μL), and the reaction mixture was cooled to 0 °C. Excess of 1,1,1-trifluoroacetone (100 μL) was added, followed by a portionwise addition of Oxone® (18.0 mg, 0.029 mmol, 1.7 equiv) and $NaHCO_3$ (4.0 mg, 0.048 mmol, 2.8 equiv) with stirring, until the disappearance of most of the starting material was indicated by TLC. The reaction mixture was then immediately passed through a short pad of silica gel with 80% EtOAc in hexanes and concentrated. Purification by preparative thin-layer chromatography (250 μm silica gel plate, 75% EtOAc in hexanes) provided a mixture of diastereomeric epoxides, epoxide **3** (or **41**) (4.2 mg, 50%) and α-isomeric epoxide **41** (or **3**) (2.5 mg, 29%).

3 (or **41**): $R_f = 0.13$ (silica gel, 67% EtOAc in hexanes); $[\alpha]_D^{22} = -89.4$ ($c = 0.18$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3472$, 2927, 2871, 1739, 1675, 1453, 1377, 1158, 1091, 985 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.98$ (s, 1H, ArH), 6.50 (s, 1H, ArC*H*=C(CH_3)), 5.69–5.66 (m, 1H, CO_2CH), 3.87 (d, $J = 8.5$ Hz, 1H), 3.86–3.81 (m, 1H), 3.56 (dq, $J = 7.0$, 7.0 Hz, 1H, $CH_3CH(C=O)$), 3.44 (d, $J = 3.0$ Hz, 1H), 3.03 (ddd, $J = 8.5$, 4.5, 4.5 Hz, 1H, CH_2CH-O(epoxide)CH), 2.93 (ddd, $J = 8.0$, 4.0, 4.0 Hz, 1H, CH_2CH-O(epoxide)CH), 2.83 (dd, $J = 17.5$, 9.5 Hz, 1H, CH_2COO), 2.72 (dd, $J = 17.5$, 3.0 Hz, 1H, CH_2COO), 2.71 (s, 3H, CH_3Ar), 2.27 (ddd, $J = 15.0$, 5.0, 5.0 Hz, 1H, CH_2CH-O(epoxide)CH), 2.12 (s, 3H, ArCH=CC*H*$_3$), 1.79 (ddd, $J = 15.0$, 8.5, 3.5 Hz, 1H, CH_2CH-O(epoxide)CH), 1.75–1.15 (m, 8H), 1.22 (d, 3H, $J = 6.5$ Hz, $CH_3CH(C=O)$), 1.12 (ddd, $J = 9.5$, 7.0, 4.5 Hz, 1H, $C(CH_2)_2$), 1.06 (d, $J = 7.0$ Hz, 3H, CH_3CHCH_2), 1.00 (ddd, $J = 10.0$, 7.0, 4.5 Hz, 1H, $C(CH_2)_2$), 0.72–0.69 (m, 1H, $C(CH_2)_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$): $\delta = 214.5$, 171.4, 164.9, 151.9, 135.7, 118.9, 116.3, 76.2, 74.8, 70.5, 57.2, 53.4, 46.4, 38.7, 36.6, 34.5, 30.3, 30.0, 29.7, 27.2, 24.2, 19.2, 17.7, 16.6, 16.3, 10.9; HRMS (FAB): calcd for $C_{26}H_{37}CsNO_6S$ ($M + Cs^+$) 624.1396, found 624.1374.

41 (or **3**): $R_f = 0.06$ (silica gel, 67% EtOAc in hexanes); $[\alpha]_D^{22} = -43.4$ ($c = 0.13$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3472$, 2924, 2855, 1734, 1677, 1457, 1376, 1159, 1091, 1042, 983 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.98$ (s, 1H, ArH), 6.55 (s, 1H, ArC*H*=C(CH_3)), 5.61 (dd, $J = 9.5$, 2.5 Hz, 1H, CO_2CH), 3.88–3.84 (m, 1H), 3.84–3.81 (m, 1H), 3.51 (d, $J = 2.5$ Hz, 1H),

3.38 (dq, $J = 7.0$, 7.0 Hz, 1H, $CH_3CH(C{=}O)$), 3.10–3.01 (m, 2H, CH_2CH-O(epoxide)CH), 2.80 (dd, $J = 17.0$, 8.0 Hz, 1H, CH_2COO), 2.70 (s, 3H, CH_3Ar), 2.68 (dd, $J = 17.0$, 3.5 Hz, 1H, CH_2COO), 2.18–2.12 (ddd, 1H, $J = 14.7$, 3.0, 3.0 Hz, 1H, CH_2CH-O(epoxide)CH), 2.08 (s, 3H, $ArCH{=}CCH_3$), 2.05–1.95 (m, 1H, CH_2CH-O(epoxide)CH), 1.86–1.75 (m, 1H, CH_2CH-O(epoxide)CH), 1.85 (ddd, $J = 14.8$, 9.4, 9.4 Hz, 1H, CH_2CH-O(epoxide)CH), 1.70–1.15 (m, 6H), 1.19 (d, $J = 6.5$ Hz, 3H, $CH_3CH(C{=}O)$), 1.12 (ddd, $J = 9.5$, 7.0, 4.5 Hz, 1H, $C(CH_2)_2$), 1.03 (d, $J = 7.0$ Hz, 3H, CH_3CHCH_2), 1.01–0.97 (m, 1H, $C(CH_2)_2$), 0.85–0.75 (m, 1H, $C(CH_2)_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 214.1$, 171.9, 166.2, 152.0, 136.2, 120.7, 116.9, 77.3, 75.8, 69.6, 56.1, 55.0, 45.6, 38.4, 36.3, 34.6, 31.0, 29.7, 29.3, 27.7, 22.5, 17.4, 16.3, 16.1, 15.0, 10.6; HRMS (FAB): calcd for $C_{26}H_{37}CsNO_6S$ ($M + Cs^+$) 624.1396, found 624.1376.

4,4-Ethano-epothilone A analogues 42 and 43—epoxidation of *trans*-dihydroxylactone 40: As described in the procedure for the epoxidation of *cis*-dihydroxylactone **39**, *trans*-hydroxylactone **40** (19.0 mg, 0.040 mmol) in MeCN (200 μL) and CH_2Cl_2 (150 μL) was treated with a 0.4 mM aqueous solution of Na_2EDTA (120 μL), 1,1,1-trifluoroacetone (200 μL), Oxone® (172 mg, 0.280 mmol, 7.0 equiv), and $NaHCO_3$ (38 mg, 0.452 mmol, 11 equiv), to yield, after purification by preparative thin-layer chromatography (250 μm silica gel plate, 6% MeOH in $CHCl_3$), epoxides **42** (or **43**) (2.1 mg, 11%) and **43** (or **42**) (6.0 mg, 31%).

42 (or **43**): $R_f = 0.06$ (silica gel, 50% EtOAc in hexanes); $[\alpha]_D^{22} = -47.1$ ($c = 0.05$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3472$, 2919, 2850, 1730, 1672, 1460, 1164 1053, 732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.98$ (s, 1H, ArH), 6.55 (s, 1H, $ArCH{=}C(CH_3)$), 5.54 (dd, $J = 10.5$, 2.5 Hz, 1H, CO_2CH), 4.07–4.02 (m, 1H), 3.87–3.84 (m, 1H), 3.75 (d, $J = 5.0$ Hz, 1H), 3.25 (dq, $J = 6.5$, 6.5 Hz, 1H, $CH_3CH(C{=}O)$), 2.86 (dd, $J = 17.5$, 7.5 Hz, 1H, CH_2COO), 2.77–2.75 (m, 1H, CH_2CH-O(epoxide)CH), 2.73–2.69 (m, 1H, CH_2CH-O(epoxide)CH), 2.71 (s, 3H, CH_3Ar), 2.70 (dd, $J = 17.5$, 3.5 Hz, 1H, CH_2COO), 2.37–2.34 (m, 1H), 2.07 (s, 3H, $ArCH{=}CCH_3$), 2.07–1.98 (m, 1H), 1.95–1.87 (m, 1H), 1.87–1.78 (m, 1H), 1.73–0.80 (m, 9H), 1.16 (d, 3H, $J = 6.5$ Hz, $CH_3CH(C{=}O)$), 0.98 (d, $J = 7.0$ Hz, 3H, CH_3CHCH_2); HRMS (FAB): calcd for $C_{26}H_{37}CsNO_6S$ ($M + Cs^+$) 624.1396, found 624.1377.

43 (or **42**): $R_f = 0.04$ (silica gel, 50% EtOAc in hexanes); $[\alpha]_D^{22} = -87.2$ ($c = 0.11$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3493$, 2921, 2851, 1736, 1674, 1451, 1374, 1162, 982, 731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.98$ (s, 1H, ArH), 6.54 (s, 1H, $ArCH{=}C(CH_3)$), 5.49–5.46 (m, 1H, CO_2CH), 4.06–4.00 (m, 1H), 3.88–3.84 (m, 1H), 3.70–3.65 (m, 1H), 3.30 (dq, 1H, $J = 7.0$, 7.0 Hz, 1H, $CH_3CH(C{=}O)$), 2.86 (dd, $J = 17.5$, 7.5 Hz, 1H, CH_2COO), 2.82–2.73 (m, 3H, CH_2CH-O(epoxide)CH and CH_2COO), 2.71 (s, 3H, CH_3Ar), 2.29 (ddd, $J = 15.0$, 6.5, 4.0 Hz, 1H, CH_2CH-O(epoxide)CH), 2.10–2.02 (m, 1H, CH_2CH-O(epoxide)CH), 2.09 (s, 3H, $ArCH{=}CCH_3$), 1.84–1.73 (m, 2H), 1.66–0.82 (m, 9H), 1.19 (d, 3H, $J = 7.0$ Hz, $CH_3CH(C{=}O)$), 1.01 (d, $J = 6.5$ Hz, 3H, CH_3CHCH_2); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 214.0$, 172.0, 164.9, 152.0, 136.0, 119.5, 116.5, 75.7, 75.0, 69.3, 57.8, 55.0, 44.6, 38.1, 36.2, 34.4, 31.4, 30.0, 29.7, 29.3, 22.2, 19.2, 16.9, 15.7, 15.2, 10.6; HRMS (FAB): calcd for $C_{26}H_{37}CsNO_6S$ ($M + Cs^+$) 624.1396, found 624.1417.

Hydroxylactones 44 and 45—cyclization of diene 37 by olefin metathesis: As described for the cyclization of diene **5**, a solution of diene **37** (525 mg, 0.85 mmol) in CH_2Cl_2 (850 mL, 0.001 M) was treated with [$RuCl_2(=CHPh)(PCy_3)_2$] (64 mg, 0.085 mmol, 0.1 equiv), to furnish, after flash column chromatography (silica gel, 33% ether in hexanes), *cis*-hydroxylactone **44** (88 mg, 18%) and *trans*-hydroxylactone **45** (284 mg, 58%).

44: $R_f = 0.70$ (silica gel, 50% EtOAc in hexanes); $[\alpha]_D^{22} = -95.7$ ($c = 0.44$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 2917$, 2849, 1737, 1662, 1164, 1100, 834, 777 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.94$ (s, 1H, ArH), 6.44 (s, 1H, $ArCH{=}C(CH_3)$), 5.47–5.40 (m, 1H, $CH{=}CHCH_2$), 5.37–5.31 (m, 1H, $CH{=}CHCH_2$), 5.25–5.24 (m, 1H, CO_2CH), 4.15–4.08 (m, 1H), 3.8 (brs, 1H, $CHOH(CHCH_3)$), 3.61–3.54 (m, 1H), 3.47 (d, $J = 10.5$ Hz, 1H, $CHOH(CHCH_3)$), 2.99 (dd, $J = 15.5$, 12.5 Hz, 1H, CH_2COO), 2.70 (s, 3H, CH_3Ar), 2.56 (dd, $J = 15.5$, 2.5 Hz, 1H, CH_2COO), 2.40–2.30 (m, 1H), 2.18–2.13 (m, 3H), 2.07 (s, 3H, $ArCH{=}CCH_3$), 1.70–0.85 (m, 8H), 1.08 (d, $J = 6.5$ Hz, 3H, $CH_3CH(C{=}O)$), 1.06 (d, $J = 7.0$ Hz, 3H, CH_3CHCH_2), 0.92 (s, 9H, $SiC(CH_3)_3(CH_3)_2$), 0.65–0.56 (m, 1H, $C(CH_2)_2$), 0.14 (s, 3H, $SiC(CH_3)_3(CH_3)_2$), 0.13 (s, 3H, $SiC(CH_3)_3(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 219.4$, 169.4, 164.4, 152.3, 137.2, 133.2, 124.6, 118.8, 115.7, 77.1, 76.8, 74.1, 43.0, 41.2, 37.4, 35.1, 35.0, 32.6, 30.9, 29.6, 27.8, 25.8, 23.1, 19.1, 17.9, 15.8, 15.3, 10.5, −2.9, −6.1; HRMS (FAB): calcd for $C_{32}H_{52}NO_5SSi$ ($M + H^+$) 590.3335, found 590.3355.

45: $R_f = 0.71$ (silica gel, 50% EtOAc in hexanes); $[\alpha]_D^{22} = -86.0$ ($c = 1.75$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 2928$, 2855, 1738, 1664, 1382, 1165, 1103, 1061, 970, 836, 777 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.93$ (s, 1H, ArH), 6.51 (s, 1H, $ArCH{=}C(CH_3)$), 5.31 (ddd, $J = 15.0$, 8.0, 2.0 Hz, 1H, $CH{=}CHCH_2$), 5.29 (ddd, $J = 15.0$, 7.5, 2.0 Hz, 1H, $CH{=}CHCH_2$), 5.12 (dd, $J = 10.5$, 4.0 Hz, 1H, CO_2CH), 4.17 (q, $J = 6.0$ Hz, 1H, $CH_3CH(C{=}O)$), 3.81 (m, 1H, OH), 3.56 (d, $J = 11.5$ Hz, 1H, $(CH_2)_2CCH(OTBS)$), 3.39 (d, $J = 9.5$ Hz, 1H, $CHOH(CHCH_3)$), 2.92 (dd, $J = 16.0$, 11.5 Hz, 1H, CH_2COO), 2.69 (s, 3H, CH_3Ar), 2.57 (dd, $J = 16.0$, 2.0 Hz, 1H, CH_2COO), 2.48–2.33 (m, 3H, $3CH{=}CHCH_2$), 2.05 (s, 3H, $ArCH{=}CCH_3$), 1.97–1.89 (m, 1H, $CH{=}CHCH_2$), 1.65–0.90 (m, 8H), 1.05 (d, $J = 6.0$ Hz, 3H, $CH_3CH(C{=}O)$), 1.04 (d, $J = 7.0$ Hz, 3H, CH_3CHCH_2), 0.92 (s, 9H, $SiC(CH_3)_3(CH_3)_2$), 0.63–0.57 (m, 1H, $C(CH_2)_2$), 0.17 (s, 3H, $SiC(CH_3)_3(CH_3)_2$), 0.14 (s, 3H, $SiC(CH_3)_3(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 219.5$, 169.4, 164.4, 152.3, 137.8, 133.9, 126.1, 119.3, 115.9, 77.8, 75.1, 74.1, 42.5, 40.9, 37.5, 35.4, 35.1, 32.6, 31.6, 29.6, 25.9, 25.7, 19.1, 18.0, 15.6, 15.0, 14.9, 10.2, −2.9, −6.0; HRMS (FAB): calcd for $C_{32}H_{52}NO_5SSi$ ($M + H^+$) 590.3335, found 590.3353.

***cis*-Dihydroxylactone 46—desilylation of compound 44**: Silyl ether **44** (24 mg, 0.041 mmol), in THF (1.4 mL, 0.03 M), was treated with hydrogen fluoride·pyridine (0.35 mL, 0.1 M) at room temperature for 15 h, according to the procedure described for *cis*-dihydroxylactone **39**, to yield, after flash column chromatography (silica gel, 50% EtOAc in hexanes), *trans*-dihydroxylactone **46** (10.5 mg, 54%). $R_f = 0.41$ (silica gel, 50% EtOAc in hexanes); $[\alpha]_D^{22} = -147.4$ ($c = 0.62$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3510$, 2925, 2855, 1735, 1672, 1452, 1375, 1244, 1165, 1087, 980, 732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.97$ (s, 1H, ArH), 6.55 (s, 1H, $ArCH{=}C(CH_3)$), 5.55 (dd, $J = 8.5$, 2.0 Hz, 1H, CO_2CH), 5.50 (ddd, $J = 10.0$, 10.0, 6.0 Hz, 1H, $CH{=}CHCH_2$), 5.37 (ddd, $J = 10.0$, 10.0, 5.5 Hz, 1H, $CH{=}CHCH_2$), 3.82 (q, $J = 7.0$ Hz, 1H, $CH_3CH(C{=}O)$), 3.68 (dd, $J = 11.5$, 3.0 Hz, 1H, $(CH_2)_2CCHOH$), 3.62 (1H, brs, $CHOH(CHCH_3)$), 3.50 (d, $J = 10.0$ Hz, 1H, $CHOH(CHCH_3)$), 3.19 (d, $J = 3.0$ Hz, 1H, $(CH_2)_2CCHOH$), 2.82 (dd, $J = 17.0$, 11.5 Hz, 1H, CH_2COO), 2.71 (s, 3H, CH_3Ar), 2.70–2.58 (m, 1H, $CH{=}CHCH_2$), 2.66 (dd, $J = 17.0$, 3.0 Hz, 1H, CH_2COO), 2.42–2.35 (m, 1H, $CH{=}CHCH_2$), 2.21–2.13 (m, 1H, $CH{=}CHCH_2$), 2.12–2.01 (m, 1H, $CH{=}CHCH_2$), 2.09 (s, 3H, $ArCH{=}CCH_3$), 1.64–1.59 (m, 1H), 1.54–1.44 (m, 3H), 1.41–1.35 (m, 1H), 1.15–1.00 (m, 3H), 1.11 (d, $J = 7.0$ Hz, 3H, $CH_3CH(C{=}O)$), 1.07 (d, $J = 6.5$ Hz, 3H, CH_3CHCH_2), 0.65–0.61 (m, 1H, $C(CH_2)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 218.4$, 171.0, 164.7, 152.1, 136.8, 133.1, 124.5, 119.5, 116.0, 77.3, 74.2, 71.4, 43.8, 39.7, 34.7, 33.8, 32.2, 31.5, 27.6, 25.3, 19.7, 19.1, 15.8, 15.7, 13.3, 10.6; HRMS (FAB): calcd for $C_{26}H_{38}NO_5S$ ($M + H^+$) 476.2471, found 476.2485.

***trans*-Dihydroxylactone 47—desilylation of compound 45**: Silyl ether **45** (9.0 mg, 0.015 mmol, 1.0 equiv), in THF (0.45 mL, 0.03 M), was treated with hydrogen fluoride·pyridine (0.15 mL, 0.1 M) at room temperature for 22 h, according to the procedure described for *cis*-dihydroxylactone **39**, to yield, after flash column chromatography (silica gel, 50% EtOAc in hexanes), *cis*-dihydroxylactone **47** (5.5 mg, 76%). $R_f = 0.43$ (silica gel, 50% EtOAc in hexanes); $[\alpha]_D^{22} = -89.1$ ($c = 1.09$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3485$, 2930, 2856, 1732, 1665, 1374, 1173, 1092, 1014, 974, 732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.96$ (s, 1H, ArH), 6.54 (s, 1H, $ArCH{=}C(CH_3)$), 5.54 (dd, $J = 10.0$, 4.0 Hz, 1H, CO_2CH), 5.39 (ddd, $J = 15.5$, 9.0, 3.5 Hz, 1H, $CH{=}CHCH_2$), 5.30 (ddd, 1H, $J = 15.5$, 7.5, 4.5 Hz, 1H, $CH{=}CHCH_2$), 3.88 (q, $J = 7.0$ Hz, 1H, $CH_3CH(C{=}O)$), 3.72 (brs, 1H, OH), 3.63 (brs, 1H, OH), 3.58 (d, $J = 11.5$ Hz, 1H, $(CH_2)_2CCHOH$), 3.42 (d, $J = 10.0$ Hz, 1H, $CHOH(CHCH_3)$), 2.82 (dd, $J = 17.5$, 11.5 Hz, 1H, CH_2COO), 2.70 (s, 3H, CH_3Ar), 2.64 (dd, $J = 17.5$, 2.5 Hz, 1H, CH_2COO), 2.50–2.41 (m, 2H, $CH{=}CHCH_2$), 2.30–2.22 (m, 1H, $CH{=}CHCH_2$), 2.08 (s, 3H, $ArCH{=}CCH_3$), 1.98 dddd, $J = 14.0$, 9.5, 9.5, 4.5 Hz, 1H, $CH{=}CHCH_2$), 1.63–1.59 (m, 1H), 1.52–1.43 (m, 2H), 1.41–1.32 (m, 1H), 1.30–1.00 (m, 4H), 1.11 (d, $J = 6.5$ Hz, 3H, $CH_3CH(C{=}O)$), 1.02 (d, $J = 6.5$ Hz, 3H, CH_3CHCH_2), 0.60 (ddd, $J = 9.0$, 7.0, 4.0 Hz, 1H, $C(CH_2)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 218.7$, 171.6, 164.7, 152.1, 137.0, 134.1, 125.4, 120.0, 116.3, 77.6, 75.0, 71.7, 43.6, 39.0, 37.0, 35.0, 33.7, 33.0, 32.0, 25.4, 20.5, 19.1, 15.9, 15.1, 13.4, 10.4; HRMS (FAB): calcd for $C_{26}H_{37}CsNO_5S$ ($M + Cs^+$) 608.1447, found 603.1423.

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4,4-Ethano-epothilone A analogues 48 and 49—epoxidation of *cis*-dihydroxylactone 46: As described in the procedure for the epoxidation of *cis*-dihydroxylactone **39**, *cis*-hydroxylactone **46** (11.0 mg, 0.023 mmol) in MeCN (200 μL) and CH_2Cl_2 (300 μL) was treated with a 0.4 mM aqueous solution of Na_2EDTA (120 μL), 1,1,1-trifluoroacetone (200 μL), Oxone® (114 mg, 0.185 mmol, 8.0 equiv), and $NaHCO_3$ (25 mg, 0.296 mmol, 12.8 equiv), to yield, after purification by preparative thin-layer chromatography (250 μm silica gel plate, 17% acetone in CH_2Cl_2), epoxides **48** (or **49**) (4.0 mg, 39%) and **49** (or **48**) (4.5 mg, 35%).

48 (or **49**): $R_f = 0.30$ (silica gel, 50% EtOAc in hexanes); $[\alpha]_D^{22} = -92.1$ ($c = 0.14$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3468, 2922, 2854, 1735, 1668, 1456, 1378, 1257, 1161, 1093, 980, 733\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.97$ (s, 1H, ArH), 6.54 (s, 1H, ArC*H*=C(CH_3)), 5.78 (dd, $J = 5.0$, 4.5 Hz, 1H, CO_2CH), 4.12 (br d, $J = 11.0$ Hz, 1H, $(CH_2)_2CCHOH$), 3.73 (q, $J = 7.0$ Hz, 1H, CH_3CH(C=O)), 3.62 (d, $J = 10.0$ Hz, 1H, C*H*O-H($CHCH_3$)), 3.59 (br s, 1H, OH), 3.51–3.47 (m, 1H, OH), 3.12 (ddd, $J = 6.5$, 6.5, 4.0 Hz, 1H, CH_2CH-O(epoxide)CH), 3.00 (ddd, $J = 6.5$, 6.5, 4.0 Hz, 1H, CH_2CH-O(epoxide)CH), 2.72 (dd, $J = 16.0$, 11.0 Hz, 1H, CH_2COO), 2.70 (s, 3H, CH_3Ar), 2.55 (dd, $J = 16.0$, 2.5 Hz, 1H, CH_2COO), 2.11 (d, $J = 1.0$ Hz, 3H, ArCH=CCH_3), 2.00–1.93 (m, 2H), 1.75–1.06 (m, 8H), 1.13 (d, $J = 7.0$ Hz, 3H, CH_3CH(C=O)), 1.06 (d, $J = 6.5$ Hz, 3H, CH_3CHCH_2), 1.06–0.95 (m, 2H, $C(CH_2)_2$), 0.71–0.68 (m, 1H, $C(CH_2)_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$): $\delta = 218.4, 171.1, 160.5, 152.0, 136.2, 119.7, 116.5, 75.7, 73.7, 70.1, 56.6, 54.8, 43.3, 39.5, 34.2, 32.4, 31.9, 31.0, 29.7, 26.5, 21.4, 19.2, 15.8, 15.7, 11.3, 11.2$; HRMS (FAB): calcd for $C_{26}H_{38}NO_6S$ ($M + H^+$) 492.2420, found 492.2434.

49 (or **48**): $R_f = 0.30$ (silica gel, 50% EtOAc in hexanes); $[\alpha]_D^{22} = -98.0$ ($c = 0.21$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3460, 2923, 2855, 1736, 1669, 1454, 1378, 1240, 1159, 1040, 977, 733\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.97$ (s, 1H, ArH), 6.59 (s, 1H, ArC*H*=C(CH_3)), 5.62 (dd, $J = 6.0$, 3.5 Hz, 1H, CO_2CH), 4.26 (d, $J = 10.5$ Hz, 1H, $(CH_2)_2CCHOH$), 3.87 (br s, 1H, OH), 3.71 (d, $J = 9.2$ Hz, 1H, C*H*OH($CHCH_3$)), 3.64–3.56 (m, 2H, CH_3CH(C=O) and OH), 3.09 (ddd, $J = 6.0$, 6.0, 4.0 Hz, 1H, CH_2CH-O-(epoxide)CH), 2.97 (ddd, $J = 6.0$, 6.0, 4.5, 1H, CH_2CH-O(epoxide)CH), 2.70 (s, 3H, CH_3Ar), 2.62 (dd, $J = 15.5$, 10.5 Hz, 1H, CH_2COO), 2.41 (dd, $J = 15.5$, 2.5 Hz, 1H, CH_2COO), 2.13 (s, 3H, ArCH=CCH_3), 2.08–1.97 (m, 2H), 1.75–1.03 (m, 8H), 1.09 (d, $J = 7.0$ Hz, 3H, CH_3CH(C=O)), 1.07 (d, $J = 6.5$ Hz, 3H, CH_3CHCH_2), 1.00–0.90 (m, 2H, $C(CH_2)_2$), 0.74 (ddd, $J = 9.5$, 7.0, 4.5 Hz, 1H, $C(CH_2)_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$): $\delta = 217.7, 170.8, 164.9, 152.1, 135.6, 119.9, 116.7, 76.4, 73.6, 69.8, 56.6, 54.8, 42.6, 39.7, 34.6, 32.7, 30.9, 30.5, 29.7, 28.2, 21.2, 19.2, 17.1, 16.1, 15.8, 11.2$; HRMS (FAB): calcd for $C_{26}H_{38}NO_6S$ ($M + H^+$) 492.2420, found 492.2431.

4,4-Ethano-epothilone A analogues 50 and 51—epoxidation of *trans*-dihydroxylactone 47: As described in the procedure for the epoxidation of *cis*-dihydroxylactone **39**, *trans*-hydroxylactone **47** (20 mg, 0.042 mmol) in MeCN (400 μL) and CH_2Cl_2 (600 μL) was treated with a 0.4 mM aqueous solution of Na_2EDTA (400 μL), 1,1,1-trifluoroacetone (250 μL), Oxone® (207 mg, 0.334 mmol, 8.0 equiv), and $NaHCO_3$ (45 mg, 0.538 mmol, 12.8 equiv), to yield, after purification by preparative thin-layer chromatography (250 μm silica gel plate, 50% EtOAc in hexanes), epoxides **50** (or **51**) (4.5 mg, 22%) and **51** (or **50**) (5.6 mg, 27%).

50 (or **51**): $R_f = 0.20$ (silica gel, 50% EtOAc in hexanes); $[\alpha]_D^{22} = -49.5$ ($c = 0.33$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3472, 2923, 2855, 1734, 1666, 1457, 1374, 1263, 1163, 1089, 981, 910, 731\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.99$ (s, 1H, ArH), 6.56 (s, 1H, ArC*H*=C(CH_3)), 5.49 (dd, $J = 9.0$, 2.5 Hz, 1H, CO_2CH), 4.28–4.25 (m, 1H, $(CH_2)_2CCHOH$), 3.87 (d, $J = 3.5$ Hz, 1H, OH), 3.69 (qd, $J = 7.0$, 2.0 Hz, 1H, CH_3CH(C=O)), 3.63 (d, $J = 8.5$ Hz, 1H, C*H*OH($CHCH_3$)), 3.59 (br s, 1H, OH), 2.89 (ddd, $J = 5.5$, 5.5, 2.0 Hz, 1H, CH_2CH-O(epoxide)CH), 2.78 (ddd, $J = 5.5$, 5.5, 2.0 Hz, 1H, CH_2CH-O(epoxide)CH), 2.71 (s, 3H, CH_3Ar), 2.63 (dd, $J = 15.5$, 10.5 Hz, 1H, CH_2COO), 2.51 (dd, $J = 15.5$, 2.5 Hz, 1H, CH_2COO), 2.15 (ddd, $J = 15.0$, 9.0, 6.0 Hz, 1H, CH_2CH-O(epoxide)CH), 2.09 (d, $J = 1$ Hz, 3H, ArCH=CCH_3), 1.95 (ddd, $J = 15.0$, 5.0, 2.5 Hz, 1H, CH_2CH-O(epoxide)CH), 1.66–1.20 (m, 8H), 1.16 (d, $J = 7.0$ Hz, 3H, CH_3CH(C=O)), 1.03 (d, $J = 6.5$ Hz, 3H, CH_3CHCH_2), 1.02–0.96 (m, 2H, $C(CH_2)_2$), 0.65–0.61 (m, 1H, $C(CH_2)_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$): $\delta = 217.5, 171.4, 165.0, 152.0, 136.3, 119.9, 116.6, 76.4, 74.5, 69.5, 57.7, 55.5, 44.0, 39.7, 34.9, 34.6, 34.9, 32.7, 30.6, 29.7, 22.5, 19.2, 16.2, 15.3, 11.6, 10.6$; HRMS (FAB): calcd for $C_{26}H_{37}CsNO_6S$ ($M + Cs^+$) 624.1396, found 624.1421.

51 (or **50**): $R_f = 0.15$ (silica gel, 50% EtOAc in hexanes); $[\alpha]_D^{22} = -73.5$ ($c = 0.14$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3463, 2917, 2852, 1735, 1668, 1456, 1377, 1259, 1160, 1095, 910, 734\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.97$ (s, 1H, ArH), 6.55 (s, 1H, ArC*H*=C(CH_3)), 5.63 (dd, $J = 11.5$, 2.5 Hz, 1H, CO_2CH), 3.81 (br s, 1H, OH), 3.73 (q, $J = 7.0$ Hz, 1H, CH_3CH(C=O)), 3.69 (d, $J = 11.0$ Hz, 1H, $(CH_2)_2CCHOH$), 3.66 (d, $J = 9.0$ Hz, 1H, C*H*OH($CHCH_3$)), 3.38 (br s, 1H, OH), 2.79 (dd, $J = 17.0$, 11.0 Hz, 1H, CH_2COO), 2.73–2.69 (m, 1H, CH_2CH-O(epoxide)CH), 2.70 (s, 3H, CH_3Ar), 2.68–2.64 (m, 2H, CH_2CH-O(epoxide)CH and CH_2COO), 2.24 (ddd, $J = 14.5$, 2.5, 2.5 Hz, 1H, CH_2CH-O(epoxide)CH), 2.08 (d, $J = 1$ Hz, 3H, ArCH=CCH_3), 2.06–1.99 (m, 1H), 1.93–1.85 (m, 1H), 1.77 (ddd, $J = 14.5$, 11.5, 8.0 Hz, 1H, CH_2CH-O(epoxide)CH), 1.72–1.68 (m, 1H), 1.67–1.08 (m, 5H), 1.53 (ddd, $J = 9.5$, 7.0, 4.5 Hz, 1H, $C(CH_2)_2$), 1.15 (d, $J = 7.0$ Hz, 3H, CH_3CH(C=O)), 1.09 (d, $J = 7.0$ Hz, 3H, CH_3CHCH_2), 0.94 (ddd, $J = 9.5$, 7.0, 4.5 Hz, 1H, $C(CH_2)_2$), 0.59 (ddd, $J = 9.5$, 6.5, 4.5 Hz, 1H, $C(CH_2)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 217.9, 171.3, 164.9, 151.9, 136.2, 120.6, 116.8, 76.7, 73.2, 71.4, 60.0, 57.2, 44.3, 39.3, 35.9, 34.7, 34.2, 32.5, 32.3, 29.6, 21.5, 19.1, 18.8, 16.1, 14.7, 11.1$; HRMS (FAB): calcd for $C_{26}H_{37}CsNO_6S$ ($M + Cs^+$) 624.1396, found 624.1431.

Molecular dynamics and minimization calculations (CV Force Field) were performed on a SGI Indigo-2 workstation using Insight II (Biosym Technologies, Inc., San Diego, CA). Pictures were created using AVS (AVS Inc., Waltham, MA) and locally developed modules running on a DEC Alpha 3000/500 with a Kubota Pacific Denali graphics card (we thank Chris Boddy and Stefan Bräse for their assistance in these modeling studies).

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