Total Synthesis of Oxazole- and Cyclopropane-Containing Epothilone B Analogues by the Macrolactonization Approach

K. C. Nicolaou,* Francisco Sarabia, M. Ray V. Finlay, Sacha Ninkovic, N. Paul King, Dionisios Vourloumis, and Yun He

Abstract: In order to probe structure–activity relationships in the epothilone area, two series of epothilone B analogues have been designed and synthesized. The first series containing an oxazole moiety in place of a thiazole on the side chain was constructed by utilizing key intermediates **7**–**9** or **10**, **12**, and **13** (Scheme 1), whereas the second series containing an ethano group instead of the *gem*-dimethyl group at position 4 was synthesized from fragments **42** and **43**. A Yamaguchi-type macrolactonization reaction was used to construct the macrocycle from a seco-acid, which was assembled, in both cases, by means of a) an aldol reaction, b) an Enders alkylation, and c) a Wittig-type reaction. This convergent strategy provided access to oxazole analogues **2**, **4**, **29**–**32** and 4,4-ethano derivatives **3**, **40**, **60**–**63** for biological studies.

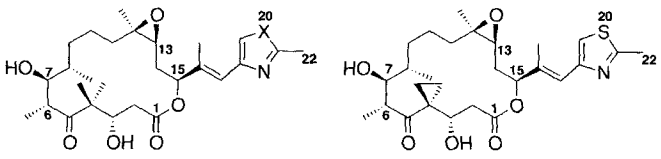
Keywords
epothilone · oxazoles · cyclopropanes · total synthesis · macrolactonizations

Introduction

The recent disclosures of the isolation, structural elucidation, and biological properties of epothilones, which have been shown to be potent tubulin-assembly and microtubule-stabilizing agents,[1–4] have elicited strong interest in scientific and medical circles.[6–15] The impressive cytotoxic effectiveness of epothilone B (**1**, Figure 1), in particular, against Taxol™-resistant tumor cells[3, 4] and its Taxol-like mechanism of action[2, 18] prompted intense investigations into its total synthesis[11, 12, 14] and analogue design.[11, 12, 14] In the preceding paper[17] we described the synthesis of a series of epothilone A analogues with oxazole and cyclopropyl groups. In this article we wish to describe the chemical synthesis of a series of oxazole- and 4,4-ethano-containing analogues of epothilone B (**1**), represented by structures **2** and **3**, respectively (Figure 1).

Results and Discussion

Oxazole-containing analogues of epothilone B: The replacement of the sulfur atom in the side-chain heterocycle of epothilone B (**1**, Figure 1) with an oxygen atom was considered important for structure–activity relationships, and, therefore, compounds of type **2** (Figure 1) were targeted for synthesis. Scheme 1 depicts the retrosynthetic analysis that led to the formulation of the strategy for the synthesis of **2** and related compounds. Thus, in this macrolactonization-based approach,[9, 14, 16] it was envisioned that **2** would be derived by epoxidation of olefinic diol **4**, the assembly of which would rely upon the cyclization of hydroxyacid **5**. Sequential disconnection of precursor **5** by a retro aldol reaction (to afford **6** and **7**) and a retro Wittig condensation (to afford **8** and **9**) pointed to route a (Scheme 1) as a possible means of construction. On the other hand, a retro Enders alkylation[19] of **6** unravelled hydrazone **10** and iodide **11** as potential precursors, whereas further disconnections of **11** by a retro Wittig-type olefination led to aldehyde **12** and stabilized phosphorane **13** as viable starting materials.



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

Figure 1. Structure and numbering of epothilone B (**1**), 20-oxa-epothilone B (**2**) and 4,4-ethano-epothilone B (**3**).

The implementation of the macrolactonization strategy towards the oxazole series of epothilones B proceeded along a similar path to that developed for the corresponding thiazole series of epothilones.[9, 12, 14] Scheme 2 shows the stereoselective construction of the requisite aldehyde **12** and phosphonium salt **9** starting with the readily available oxazole derivative **14**.[20]

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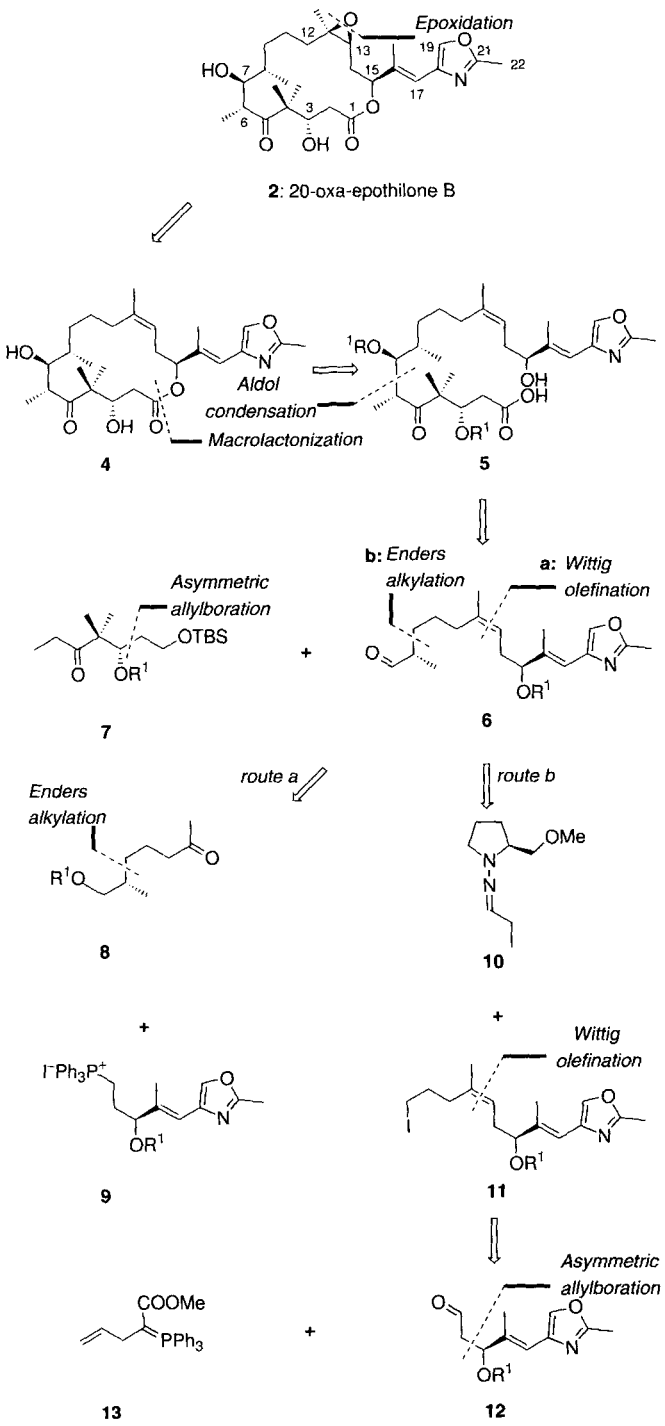
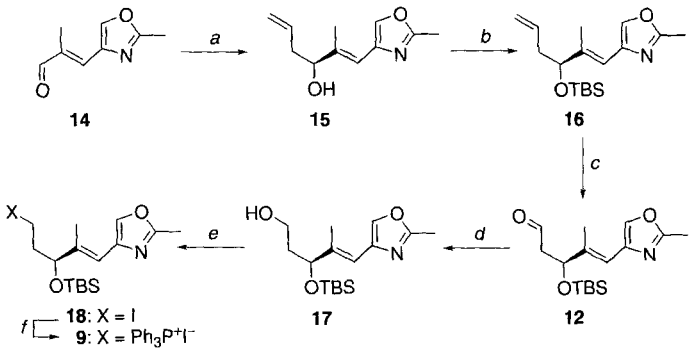


Scheme 1. Molecular structure and retrosynthetic analysis of 20-oxa-epothilone B (**2**). R^1 = TBS = SitBuMe$_2$.

Thus, asymmetric addition of (+)-Ipc$_2$B(allyl) to aldehyde **14**[21] (see Scheme 2), as described in the preceding paper,[17] gave alcohol **15**. Silylation of **15** with TBSCl (for abbreviations, see legends in schemes) and imidazole gave 99% yield of silyl ether **16**. Selective dihydroxylation of the terminal olefin in **16** employing the Upjohn procedure (NMO–OsO_4 cat.),[22] followed by $NaIO_4$ cleavage of the resulting diol led to aldehyde **12** in excellent yield (93%). Reduction of the aldehyde group in **12** with $NaBH_4$ (99% yield) followed by exposure to Ph_3P/I_2/imidazole furnished iodide **18** (87% yield) via primary alcohol **17**.



Scheme 2. Synthesis of phosphonium salt **9** and aldehyde **12**. Reagents and conditions: a) 1.5 equiv of (+)-Ipc$_2$B(allyl), Et_2O, −100 °C, 0.5 h, 91%; b) 1.2 equiv TBSCl, 1.5 equiv of imidazole, DMF, 0 → 25 °C, 2 h, 99%; c) i. 1.0 mol% OsO_4, 1.1 equiv of 4-methylmorpholine *N*-oxide (NMO), THF:*t*BuOH:H_2O (1:1:0.1), 0 → 25 °C, 12 h, 95%; ii. 6.0 equiv of $NaIO_4$, MeOH/H_2O (2:1), 0 °C, 0.5 h, 98%; d) 1.5 equiv of $NaBH_4$, MeOH, 0 °C, 15 min, 99%; e) 2.0 equiv of I_2, 4.0 equiv of imidazole, 2.0 equiv of Ph_3P, Et_2O:MeCN (3:1), 0 °C, 0.5 h, 87%; f) 2.0 equiv Ph_3P, neat, 100 °C, 2 h, 90%.

Finally, heating of **18** with Ph_3P at 100 °C gave phosphonium salt **9** in 90% yield.

In order to obtain both the (12*E*) and (12*Z*) isomers of epothilone B analogues, we initially undertook the nonstereoselective synthesis depicted in Scheme 3 in which the first step involves a Wittig reaction, yielding a 1:1 mixture of geometrical isomers. Thus, generation of the ylide from phosphonium salt **9** by the action of NaHMDS in THF at −20 °C, followed by addition of ketone **8**,[14] furnished compound **19′** in 68% yield as a 1:1 mixture of (*E*)/(*Z*) isomers. Preparation of the desired aldehyde **6′** from **19′** required selective desilylation of the primary hydroxyl group[23] (CSA, CH_2Cl_2/MeOH, 0 → 25 °C, 92% yield) and oxidation of the resulting alcohol (**20′**) with SO_3·pyridine/DMSO/Et_3N[24] (98% yield).

The condensation of aldehyde **6′** (mixture of (12*E*) and (12*Z*) geometrical isomers, Scheme 3) with the anion derived from ketone **7**[14] (LDA, THF) proceeded smoothly at −78 °C to afford a mixture of diastereomeric aldols **21′** and **22′** (ca. 4:1 ratio) in 73% combined yield. Chromatographic separation (silica, preparative layer) led to pure **21′** and **22′**, each consisting of (*E*) and (*Z*) geometrical isomers (ca. 1:1). Only the (6*R*,7*S*) diastereoisomer **21′** (less polar mixture of $\Delta^{12,13}$ geometrical

Abstract in Greek: *Δυο νεες σειρες αναλογων της εποθειλονης B (1) σχεδιαστηκαν και συντεθηκαν με σκοπο την εξερευνηση της σχεσης μεταξυ δομης και βιολογικης δρασης. Η πρωτη σειρα περιεχει μια οξαζολη αντι της θειαζολης στην πλευρικη αλυσιδα και συντεθηκε χρισιμοποιωντας τις δομικες ουσιες 7–9 η τις ουσιες 10, 12 και 13, ενω η δευτερη σειρα η οποια περιεχει ενα κυκλοπροπανιο αντι των δυο μεθυλιων στη θεση 4 συντεθηκε απο τα ενδιαμεσα 42 και 43. Μια μακρο-λακτονοποιηση τυπου Yamaguchi χρησιμοποιηθηκε για την κατασκευη του δακτυλιου απο το αντιστοιχο υδροξυ-οξυ το οποιο συντεθηκε και στις δυο περιπτωσεις με: α) μια αντιδραση αλδοολικης συμπυκνωσης, β) μια αλκυλιωση Enders και γ) μια αντιδραση τυπου Wittig. Η ευελικτη αυτη στρατηγικη επετρεψε τη συνθεση των αναλογων οξαζολης (2, 4, 29–32) και 4,4-εθανο αναλογων 3, 40, 60, 63 για βιολογικες μελετες.*

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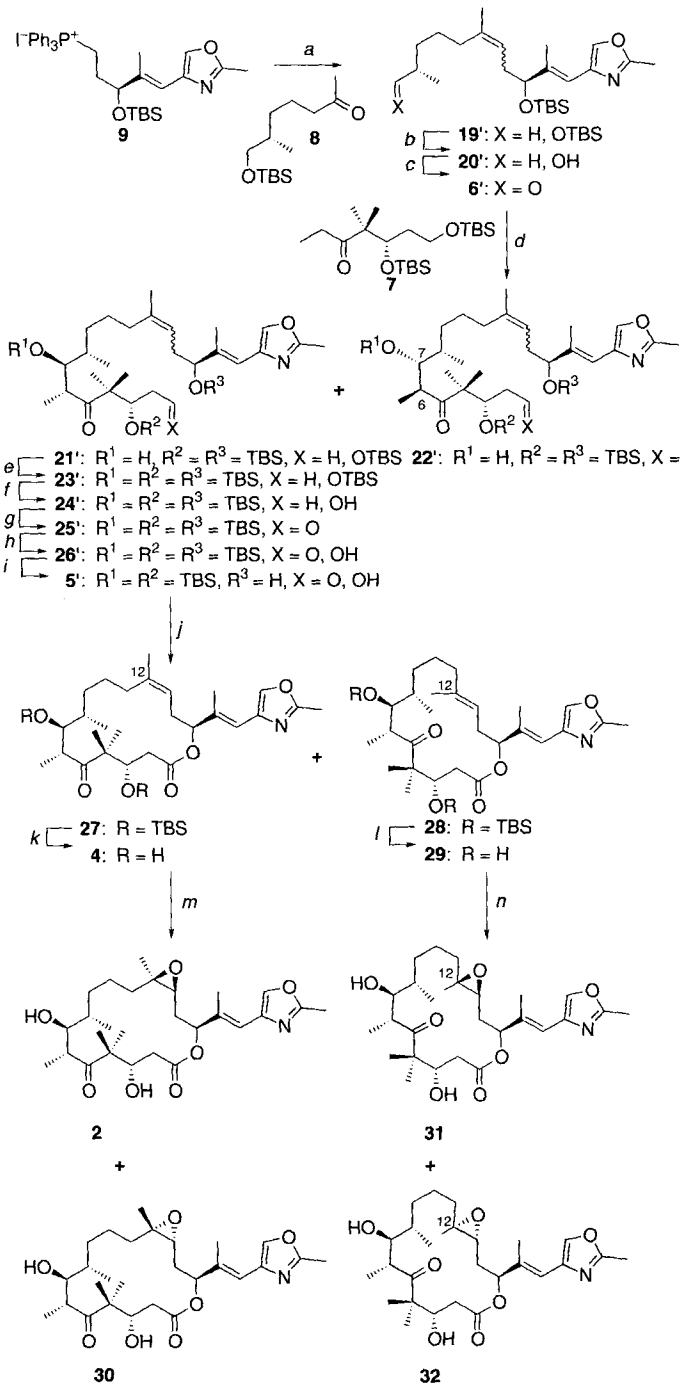
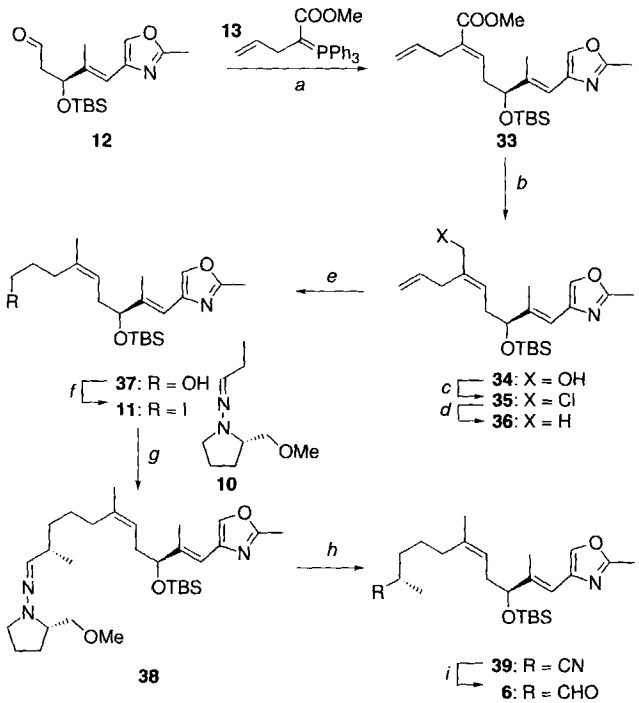


Scheme 3. Total synthesis of 20-oxa-epothilone B (**2**) and analogues. Reagents and conditions: a) 1.2 equiv of **9**, 1.2 equiv of NaHMDS, THF, 0 °C, 15 min, then add 1.0 equiv of ketone **8**, −20 °C, 12 h, 68% ((*Z*):(*E*) ca. 1:1); b) 1.0 equiv of CSA, CH_2Cl_2:MeOH (1:1), 0 °C, 0.5 h; then 25 °C, 1.0 h, 92%; c) 2.0 equiv of SO_3·pyridine, 10.0 equiv of DMSO, 5.0 equiv of Et_3N, CH_2Cl_2, 25 °C, 0.5 h, 98%; d) 1.2 equiv of LDA, THF, 0 °C, 15 min; then 1.2 equiv of **7** in THF, −78 °C, 1.5 h; then 1.0 equiv of **6'** in THF at −78 °C, 15 min, 59% of **21'** and 14% of its (6*S*,7*R*)-diastereoisomer **22'** (ca. 4:1 ratio); e) 1.5 equiv of TBSOTf, 2.0 equiv of 2,6-lutidine, CH_2Cl_2, 0 °C, 1 h, 97%; f) 1.0 equiv of CSA portionwise over 0.5 h, CH_2Cl_2:MeOH (1:1), 0 → 25 °C, 1.0 h, 85%; g) 2.0 equiv of $(COCl)_2$, 4.0 equiv of DMSO, 6.0 equiv of Et_3N, CH_2Cl_2, −78 → 0 °C, 1.5 h, 94%; h) 6.0 equiv of $NaClO_2$, 10.0 equiv of 2-methyl-2-butene, 3.0 equiv of NaH_2PO_4, *t*BuOH:H_2O (5:1), 0 °C, 15 min., 99%; i) 6.0 equiv of TBAF, THF, 25 °C, 10 h, 78%; j) 1.3 equiv of 2,4,6-trichlorobenzoyl chloride, 2.2 equiv of Et_3N, THF, 0 °C, 0.5 h; then add to a solution of 2.0 equiv of 4-DMAP in toluene (0.002 M based on **5'**), 25 °C, 12 h, 35% of **27**; and 42% of **28**; k) 20% HF·pyridine (by volume) in THF, 25 °C, 24 h, 62%; l) same as step k, 82%; m) 2.0 equiv of *m*CPBA, $CHCl_3$, 0 °C, 3 h, 40% (**2**:**30** ca 5:1 ratio of diastereoisomers); n) same as step m, 45% (**31**:**32** ca 5:1 ratio of diastereoisomers).

isomers) was taken forward (polarity and comparison with the natural series was used as a guide to choose the desired (6*R*,7*S*) diastereoisomer at this stage). The geometrical isomers were separated after the macrolactonization reaction (vide infra).

The next task in the synthesis was to prepare hydroxyacid **5'** (Scheme 3). To this end, the hydroxyl group in **21'** was silylated (TBSOTf-2,6-lutidine, 97%) to afford tetra(silyl ether) **23'** and selectively deprotected at the primary position by exposure to CSA in $MeOH/CH_2Cl_2$ at 0 → 25 °C leading to **24'** (85% yield). A stepwise protocol was used to oxidize primary alcohol **24'** to the desired carboxylic acid: 1) $(COCl)_2$/DMSO/Et_3N, −78 → 0 °C, yielding aldehyde **25'** (94% yield) and 2) $NaClO_2$/2-methyl-2-butene, NaH_2PO_4, furnishing acid **26'** (99% yield). Selective desilylation at the allylic position with TBAF in THF then gave hydroxyacid **5'** in 78% yield.

Yamaguchi macrolactonization of **5'** as in the natural series (2,4,6-trichlorobenzoyl chloride/Et_3N/4-DMAP, high dilution, 25 °C),[25] followed by preparative thin-layer chromatography (silica, 20% ether/hexanes) led to lactones **27** (R_f = 0.24, 35%) and **28** (R_f = 0.20, 42%). The identity of **27** was proven by comparison with an authentic sample prepared by a stereoselective route (see Scheme 5 and following discussion). Deprotection of **27** and **28** was carried out with HF·pyridine in THF[26] at 25 °C and furnished diols **4** (62% yield) and **29** (82% yield), respectively. Finally, epoxidation of **4** and **29** with *m*CPBA in $CHCl_3$ at 0 °C furnished the corresponding α- and β-epoxides (**2**+**30**, 40% total yield, ca. 5:1



Scheme 4. Stereoselective synthesis of aldehyde **6** for 20-oxa-epothilone B (**2**). Reagents and conditions: a) 3.0 equiv of **13**, benzene, reflux, 1 h, 90%; b) 3.0 equiv of DIBAL, CH_2Cl_2, −78 °C, 3 h, 99%; c) 2.5 equiv of Ph_3P, CCl_4, reflux, 24 h, 81%; d) 2.0 equiv of $LiEt_3BH$, THF, 0 °C, 1 h, 97%; e) 1.1 equiv of 9-BBN, THF, 0 °C, 2 h, 92%; f) 2.5 equiv of I_2, 5.0 equiv of imidazole, 2.5 equiv of Ph_3P, Et_2O:MeCN (3:1), 0 °C, 0.5 h, 89%; g) 1.3 equiv of **10**, 1.4 equiv of LDA, THF, 0 °C, 16 h; then 1.0 equiv of **11** in THF, −100 → −20 °C, 10 h, 86%; h) 2.5 equiv of monoperoxyphthalic acid, magnesium salt (MMPP), MeOH/phosphate buffer pH 7 (2:1), 0 °C, 1 h, 46%; i) 2.0 equiv DIBAL, toluene, −78 °C, 1 h, 84%.

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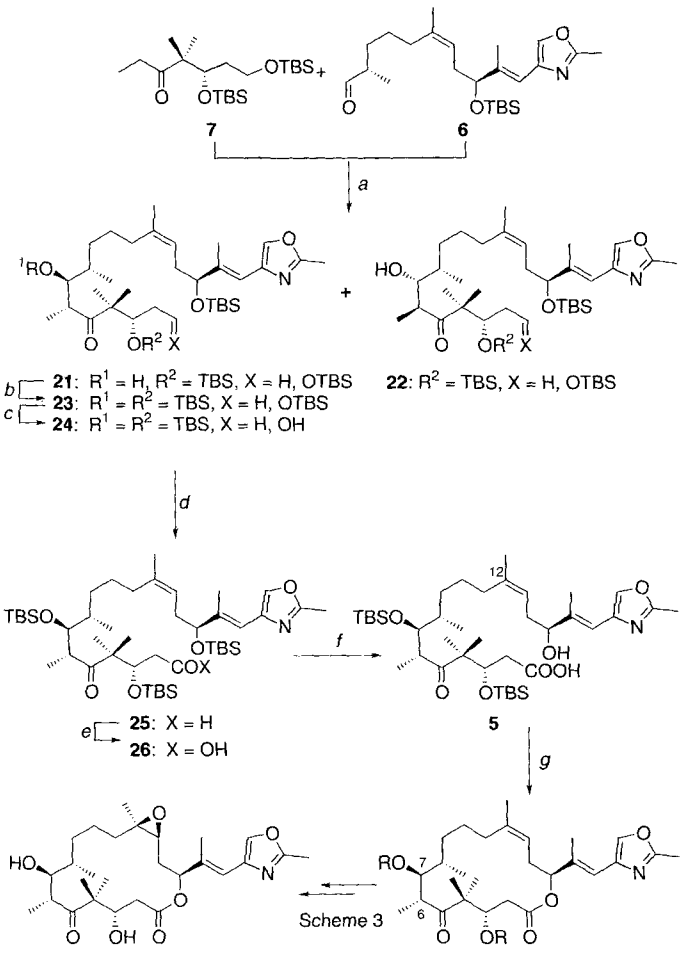
ratio, and **31** + **32**, 45% total yield, ca. 6:1 ratio). The stereochemical assignments shown in Scheme 3 for these compounds are tentative and are exclusively based on comparisons with the series related to natural epothilone B (**1**).[12, 14]

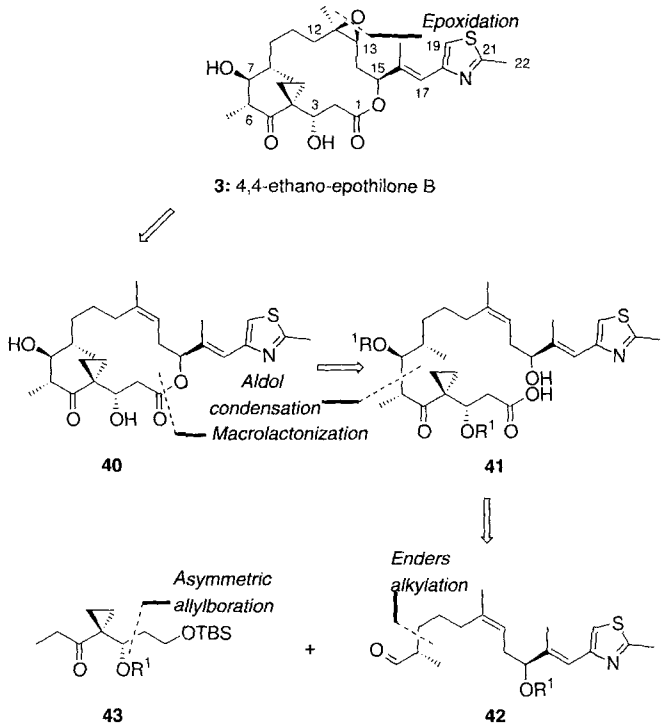
A stereoselective synthesis of the $\Delta^{12,13}$ series of the oxazole-containing epothilones (**4**, **2**, and **30**) was also developed and is shown in Schemes 4 and 5. Thus, the desired geometry of the $\Delta^{12,13}$ position was fixed by condensation of the stabilized ylide **13**[27] (Scheme 4) with aldehyde **12** (benzene, Δ), a reaction that led to 90% yield of compound **33**. Subsequent reduction of the ester group of **33** (DIBAL, CH_2Cl_2, −78 °C, 99% yield), chlorination (Ph_3P, CCl_4, Δ, 81%), and further reduction (Li-Et_3BH,[28] THF, 0 °C, 97% yield) furnished intermediate **36** via allylic alcohol **34** and chloride **35**. Selective hydroboration of **36** at the terminal olefin site was achieved by the use of 9-BBN, and after oxidative workup, primary alcohol **37** was obtained in 92% yield. Conversion of **37** to iodide **11** was subsequently carried out by the standard I_2/imidazole/Ph_3P procedure (89% yield). The iodide **11** was then used to alkylate the SAMP hydrazone **10**[29] (LDA, THF, −100 → −20 °C), furnishing hydrazone **38** in 86% yield. The latter compound was then transformed to nitrile **39** (MMPP, MeOH/phosphate buffer pH 7, 0 °C, 46% yield), and thence to aldehyde **6** (DIBAL, toluene, −78 °C, 84% yield).[30]

The aldol condensation of the lithio derivative of **7** with stereochemically homogeneous aldehyde **6** (Scheme 5) proceeded in a similar fashion to the case of the (*E*)/(*Z*) mixture described above, leading to pure compounds **21** and **22**. After chromatographic separation, the pure (6*R*,7*S*) diastereoisomer **21** [tentative assignment of stereochemistry based on polarity (less polar) and comparison to the natural series] was taken through the sequence, and on to the final products **27**, **2**, and **30** as detailed in Scheme 5.



Scheme 5. Stereoselective total synthesis of 20-oxa-epothilone B (**2**). Reagents and conditions: a) 1.4 equiv of LDA, THF, 0 °C, 15 min; then 1.4 equiv of **7** in THF, −78 °C, 2 h; then 1.0 equiv of **6** in THF at −78 °C, 59% of **21** and 14% of its (6*S*,7*R*) diastereoisomer **22** (ca. 4:1 ratio, 73%); b) 1.6 equiv of TBSOTf, 2.0 equiv of 2,6-lutidine, CH_2Cl_2, 0 °C, 2 h, 93%; c) 1.0 equiv of CSA portionwise over 5 min, CH_2Cl_2:MeOH (1:1), −5 °C, 3 h, 95%; d) 2.0 equiv of $(COCl)_2$, 4.0 equiv of DMSO, 6.0 equiv of Et_3N, CH_2Cl_2, −78 → 0 °C, 1.5 h, 80%; e) 6.0 equiv of $NaClO_2$, 44.0 equiv of 2-methyl-2-butene, 3.0 equiv of NaH_2PO_4, *t*BuOH:H_2O (5:1), 25 °C, 1 h, 97%; f) 6.0 equiv of TBAF, THF, 25 °C, 8 h, 65%; g) 1.3 equiv of 2,4,6-trichlorobenzoyl chloride, 2.2 equiv of Et_3N, THF, 0 °C, 1 h; then add to a solution of 2.0 equiv of 4-DMAP in toluene (0.002 M based on **5**), 25 °C, 10 h, 70%.

The 4,4-ethano series of epothilone B analogues: The 4,4-ethano analogues of epothilones B were designed in order to test the tolerance of the receptor site for the substitution of the *gem*-dimethyl group in the natural substance. As the retrosynthetic analysis of Scheme 6 succinctly shows, the requisite fragments



Scheme 6. Molecular structure and retrosynthetic analysis of the 4,4-ethano analogue of epothilone B (**3**). R^1 = TBS = Si*t*BuMe_2.

for the synthesis of the designed 4,4-ethano-epothilone B (**3**) and its relatives, are defined as fragments **42** and **43**. The synthesis of building block **42** has already been described[14] in connection with a stereoselective total synthesis of epothilone B (**1**), whereas that of building block **43** is shown in Scheme 7.

Thus, the ketocyclopropane derivative **44** (Scheme 7), described in the preceding article,[17] was subjected to ozonolysis and subsequent reduction with Ph_3P to afford aldehyde **45** in

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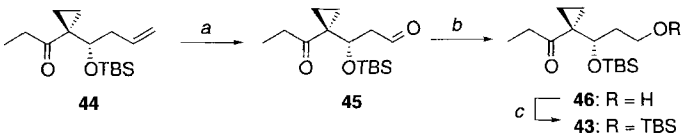


Scheme 7. Synthesis of ketone **43**. Reagents and conditions: a) O_3, CH_2Cl_2, $-78\,^\circ C$, 0.5 h; then 1.2 equiv Ph_3P, $-78 \rightarrow 25\,^\circ C$, 1 h, 90%; b) 1.1 equiv of $LiAl(OtBu)_3H$, THF, $-78 \rightarrow 0\,^\circ C$, 15 min; c) 2.0 equiv of TBSCl, 3.0 equiv of Et_3N, 0.02 equiv of 4-DMAP, CH_2Cl_2, $0 \rightarrow 25\,^\circ C$, 12 h, 83% for 2 steps.

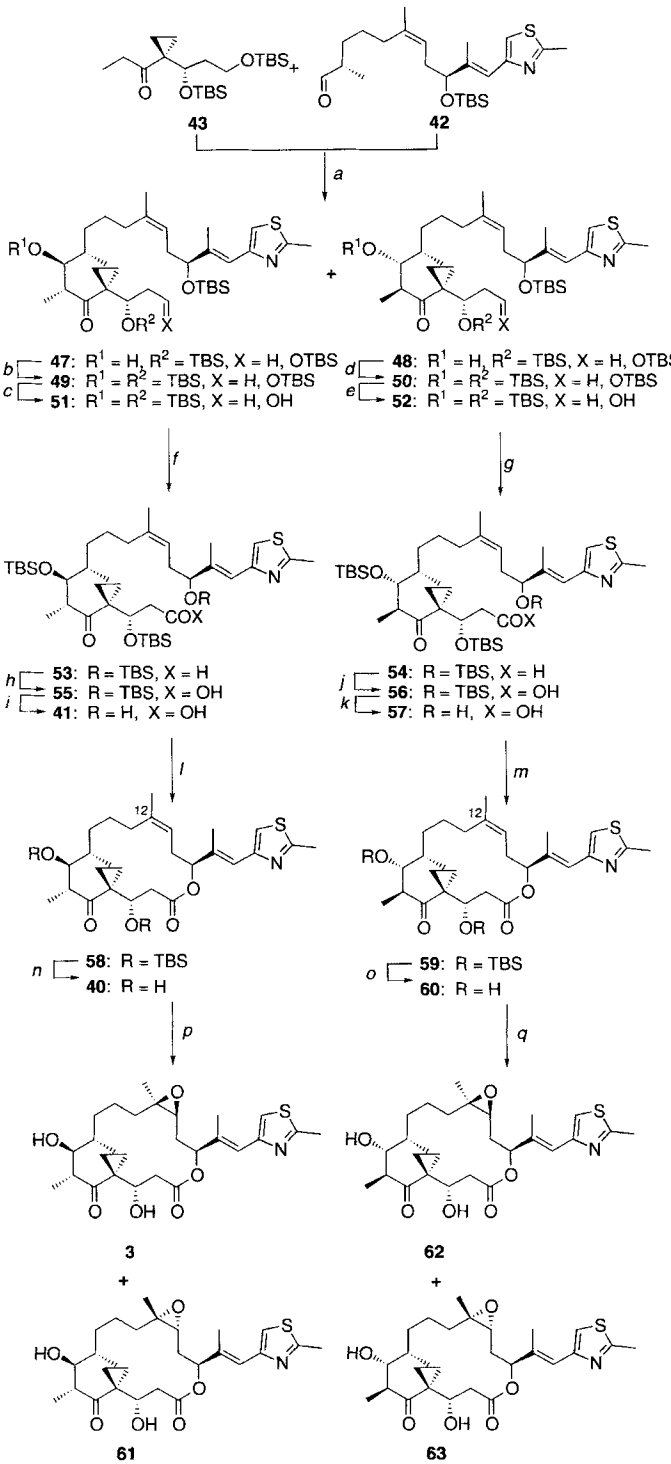
90% yield. Further reduction [$LiAl(OtBu)_3H$, THF, $-78\,^\circ C$], followed by silylation of the resulting primary alcohol **46** (TBSCl, Et_3N, 4-DMAP) furnished ketocyclopropane fragment **43** in 83% overall yield.

Scheme 8 details the coupling of fragments **43** and **42** and the assembly of a series of 4,4-ethano-epothilone B analogues. Thus, generation of the lithium enolate of ketone **43** with LDA in THF at $-78 \rightarrow -60\,^\circ C$, followed by addition of aldehyde **42** resulted in the formation of aldols **47** and **48** in ca. 1:2 ratio and 71% total yield. Stereochemical assignments were based on a X-ray crystallographic analysis of a subsequent intermediate (**59**), and will be discussed below. The difference in the ratio of aldol products between fragments **43** (ca. 1:2, Scheme 8) and **7** (ca. 4:1, Scheme 5) is rather striking, and it may have its origin in the effect of the cyclopropane ring on the transition state of the reaction. The two diastereomeric aldol products **47** and **48** were chromatographically separated (silica, flash column chromatography) and processed separately in order to obtain both the (6*S*,7*R*) and (6*R*,7*S*) series of compounds.

Thus, stereoisomer **47** (Scheme 8) was silylated with TBSOTf and 2,6-lutidine affording tetra(silyl ether) **49** in 92% yield, and then exposed to the action of CSA in CH_2Cl_2/MeOH at $0 \rightarrow 25\,^\circ C$ to give hydroxy tris(silyl ether) **51** (74% yield) in which only the primary hydroxyl group was liberated. Stepwise oxidation of **51** with 1) $(COCl)_2$, DMSO, Et_3N, $-78 \rightarrow 0\,^\circ C$ (96% yield) and 2) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4 (91% yield) gave sequentially aldehyde **53** and carboxylic acid **55**. Selective desilylation of **55** with TBAF in THF at $25\,^\circ C$ furnished the desired hydroxyacid **41** in 62% yield.

The intended macrolactonization of **41** was accomplished by the Yamaguchi method (2,4,6-trichlorobenzoyl chloride, Et_3N, 4-DMAP, toluene, $25\,^\circ C$, high dilution),[25] furnishing compound **58** in 70% yield. Exposure of **58** to HF·pyridine in THF at $25\,^\circ C$ resulted in the removal of both silyl groups, leading to diol **40** in 92% yield. Finally, epoxidation of **40** with methyl(trifluoromethyl)dioxirane[12, 14, 31] in MeCN resulted in the formation of epothilone B analogues **3** and **61** in ca. 8:1 ratio (by ^1H NMR) and 86% total yield. Preparative thin-layer chromatography (silica, 5% MeOH in CH_2Cl_2) gave pure epothilone B analogues **3** and **61**.

The same chemistry was performed with diastereoisomer **48** (Scheme 8) leading to epothilone B analogues **60**, **62**, and **63** via intermediates **50**, **52**, **54**, **56**, **57**, and **59** in similar yields to those described for **47**. The latter compound (**59**) crystallized as long needles from MeOH/EtOH (m.p. 157 °C) and yielded to X-ray crystallographic analysis, which revealed its stereochemical structure (see ORTEP drawing in Figure 2).[33]



Scheme 8. Total synthesis of 4,4-ethano analogues of epothilone B. Reagents and conditions: a) 1.5 equiv of LDA, THF, 0 °C, 15 min; then 1.4 equiv of **43** in THF, $-78 \rightarrow -60\,^\circ C$, 1 h; then 1.0 equiv of **42** in THF at $-78\,^\circ C$, 24% of **47** and 47% of its (6*S*,7*R*) diastereoisomer **48** (ca. 1:2 ratio); b) 1.2 equiv of TBSOTf, 2.0 equiv of 2,6-lutidine, CH_2Cl_2, 0 °C, 2 h, 92%; c) 1.0 equiv of CSA portionwise, CH_2Cl_2:MeOH (1:1), $0 \rightarrow 25\,^\circ C$, 0.5 h, 74%; d) same as step b, 89%; e) same as step c, 60%; f) 2.0 equiv of $(COCl)_2$, 4.0 equiv of DMSO, 6.0 equiv of Et_3N, CH_2Cl_2, $-78 \rightarrow 0\,^\circ C$, 1.0 h, 96%; g) same as step f, 69%; h) 6.0 equiv of $NaClO_2$, 10.0 equiv of 2-methyl-2-butene, 3.0 equiv of NaH_2PO_4, *t*BuOH:H_2O (5:1), 25 °C, 0.5 h, 91%; i) 6.0 equiv of TBAF, THF, 25 °C, 8 h, 62%; j) same as step h, 99%; k) same as step i, 50%; l) 1.1 equiv of 2,4,6-trichlorobenzoyl chloride, 2.2 equiv of Et_3N, THF, 0 °C, 1 h; then add to a solution of 2.0 equiv of 4-DMAP in toluene (0.002 M based on **41**), 25 °C, 3 h, 70%; m) same as step l, 72%; n) 20% HF·pyridine (by volume) in THF, $0 \rightarrow 25\,^\circ C$, 24 h, 92%; o) same as step n, 90%; p) methyl(trifluoromethyl)dioxirane, MeCN, 0 °C, 86% (**3**:**61** ca. 8:1 ratio of diastereoisomers); q) same as step p, 89% (**62**:**63** ca. 2:1 ratio of diastereoisomers).

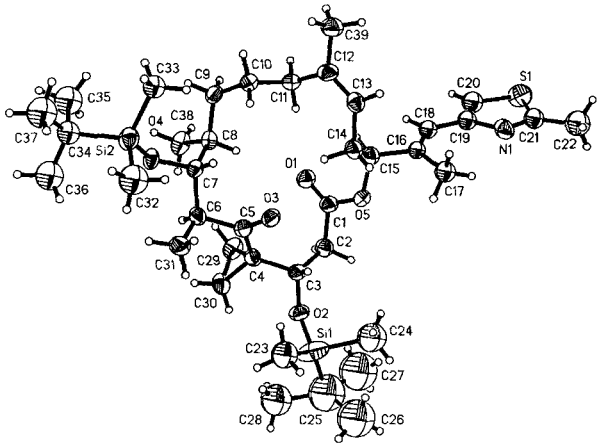


Figure 2. ORTEP view of compound **59**.

Conclusion

In this article, we have described the total synthesis of a series of epothilone B (**1**) analogues in which either the sulfur atom of the side-chain heterocycle of the natural substance was replaced by an oxygen atom (the oxazole series) or the 4,4-*gem*-dimethyl moiety was substituted with a 4,4-ethano system (4,4-ethano or 4-spirocyclopropyl series). Biological investigations with these compounds reported elsewhere[32] added important information to our knowledge of structure–activity relationships within the epothilone family of compounds. These studies[32] revealed potent tubulin polymerization abilities and cytotoxicities for **2** and some of its relatives, whereas the 4,4-ethano-epothilones proved inactive in these assays.

Experimental Section

General Techniques: See preceding article.[17]

Compound 16—silylation of alcohol 15: Alcohol **15**[17] (6.4 g, 0.033 mol) was dissolved in DMF (35 mL, 1.0 M), the solution was cooled to 0 °C and imidazole (3.5 g, 0.050 mol, 1.5 equiv) was added. After stirring for 5 min, *tert*-butyldimethylsilyl chloride (6.02 g, 0.040 mol, 1.2 equiv) was added portionwise and the reaction mixture was allowed to stir at 0 °C for 45 min, and then at 25 °C for 2.5 h, after which time no starting alcohol was detected by TLC. Methanol (2 mL) was added at 0 °C, and the solvent was removed under reduced pressure. Ether (100 mL) was added, followed by saturated aqueous NH_4Cl solution (20 mL), the organic phase separated, and the aqueous phase extracted with ether (2 × 20 mL). The combined organic solution was dried ($MgSO_4$) and filtered over Celite, and the solvents were removed under reduced pressure. Flash column chromatography (silica gel, 10 → 20% ether in hexanes) provided pure **16** (10.0 g, 99%): $R_f = 0.65$ (20% ether in hexanes); $[\alpha]_D^{22} = -2.10$ ($c = 1.3$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 2937$, 2859, 1586, 1459, 1381, 1313, 1244, 1079, 918, 830, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.45$ (s, 1H, OCH=C), 6.18 (s, 1H, C*H*=CCH$_3$), 5.79–5.71 (m, 1H, C*H*=CH$_2$), 5.03 (ddd, $J = 17.0$, 2.0, 1.4 Hz, 1H, CH=C*H*$_2$), 4.99 (ddd, $J = 17.0$, 2.2, 1.1 Hz, 1H, CH=C*H*$_2$), 4.14 (t, $J = 6.3$ Hz, 1H, C*H*OSi), 2.44 (s, 3H, N=C(O)CH$_3$), 2.35–2.31 (m, 1H, CH$_2$=CHC*H*$_2$), 2.31–2.23 (m, 1H, CH$_2$=CHC*H*$_2$), 1.86 (s, 3H, CH=CC*H*$_3$), 0.88 (s, 9H, SiC(CH$_3$)$_3$), 0.05 (s, 3H, Si(CH$_3$)$_2$), −0.01 (s, 3H, Si(CH$_3$)$_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 160.5$, 141.7, 137.9, 135.0, 116.5, 115.0, 77.9, 41.2, 25.7, 18.1, 14.1, 13.7, −4.8, −5.1; FAB HRMS (NBA): $m/e = 308.2057$, $M+H^+$ calcd for $C_{17}H_{29}NO_2Si$ 308.2046.

Aldehyde 12—dihydroxylation of olefin 16 and 1,2-glycol cleavage: Olefin **16** (14.0 g, 45.5 mmol) was dissolved in THF/*t*BuOH (1:1, 500 mL) and H_2O (50 mL). 4-Methylmorpholine *N*-oxide (NMO) (5.8 g, 50.0 mmol, 1.1 equiv) was added at 0 °C, followed by OsO_4 (4.55 mL, solution in *t*BuOH, 1.0 mol%, 2.5% by weight). The mixture was vigorously stirred for 2.5 h at 0 °C and then for 12 h at 25 °C. After completion of the reaction, Na_2SO_3 (6.0 g) was added at 0 °C, followed by H_2O (100 mL). Stirring was continued for another 30 min and then EtOAc (1 L) was added, followed by saturated aqueous NaCl solution (2 × 100 mL). The organic phase was separated, and the aqueous phase extracted with EtOAc (2 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and filtered, and the solvents were removed under reduced pressure. Flash column chromatography (silica gel, EtOAc) provided 14.72 g (95%) of the expected 1,2-diol as a 1:1 mixture of diastereoisomers: $R_f = 0.65$ (silica gel, EtOAc); IR (thin film): $\tilde{\nu}_{max} = 3380$, 2950, 2873, 1585, 1465, 1460, 1253, 1106, 1074, 837, 777 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.50$ and 7.46 (singlets, 1H total, OCH=C), 6.30 and 6.22 (singlets, 1H total, C*H*=CCH$_3$), 4.45–4.42 (m, 1H), 3.95–3.84 (m, 1H), 3.60–3.56 and 3.48–3.43 (m, 4H total), 2.44 (s, 3H, N=C(O)CH$_3$), 1.87 and 1.86 (s, 3H), 1.80–1.79 and 1.70–1.67 (m, 2H total), 0.90 and 0.87 (singlets, 9H total, SiC(CH$_3$)$_3$), 0.09, 0.08, 0.02 and −0.01 (singlets, 3H total, Si(CH$_3$)$_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 160.7$, 141.3, 141.2, 137.8, 137.5, 135.2, 135.1, 115.7, 114.7, 77.9, 75.1, 70.6, 68.8, 66.8, 66.5, 38.9, 38.5, 25.7, 25.6, 18.0, 17.9, 14.9, 13.9, 13.7, 13.6, −4.7, −4.9, −5.3, −5.4; FAB HRMS (NBA/NaI): $m/e = 364.1909$, $M+Na^+$ calcd for $C_{17}H_{31}NO_4Si$ 364.1920.

The diol obtained from **16** as described above (5.0 g, 14.6 mmol) was dissolved in MeOH/H_2O (2:1, 165 mL, 0.09 M) and cooled to 0 °C. $NaIO_4$ (18.8 g, 87.9 mmol, 6.0 equiv) was then added portionwise over 10 min, and the mixture was vigorously stirred for 30 min at 0 °C. After completion of the reaction, the mixture was diluted with water (200 mL) and extracted with ether (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and filtered, and the solvents were removed under reduced pressure. Flash column chromatography (silica gel, 20% ether in hexanes) provided pure aldehyde **12** (4.4 g, 98%): $R_f = 0.76$ (silica gel, 50% ether in hexanes); $[\alpha]_D^{22} = -19.2$ ($c = 0.7$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 2929$, 2873, 1726, 1586, 1255, 1096, 837, 778 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 9.77$ (dd, $J = 2.5$, 2.4 Hz, 1H, CHO), 7.47 (s, 1H, OCH=C), 6.30 (s, 1H, C*H*=CCH$_3$), 4.66 (dd, $J = 5.2$, 3.9 Hz, 1H, CHOSi), 2.70 (ddd, $J = 15.7$, 8.2, 2.9 Hz, 1H, CHOC*H*$_2$), 2.47 (ddd, $J = 15.7$, 4.0, 2.0 Hz, 1H, CHOC*H*$_2$), 2.44 (s, 3H, N=C(O)CH$_3$), 1.91 (s, 3H, CH=CC*H*$_3$), 0.87 (s, 9H, SiC(CH$_3$)$_3$), 0.06 (s, 3H, Si(CH$_3$)$_2$), 0.01 (s, 3H, Si(CH$_3$)$_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 201.4$, 161.2, 140.1, 137.6, 135.5, 115.5, 73.5, 49.9, 25.6, 18.0, 14.2, 13.7, −4.8, −5.4; FAB HRMS (NBA): $m/e = 310.1828$, $M+H^+$ calcd for $C_{16}H_{27}NO_3Si$ 310.1838.

Alcohol 17—reduction of aldehyde 12: A solution of aldehyde **12** (4.0 g, 12.92 mmol) in MeOH (120 mL, 0.1 M) was treated with $NaBH_4$ (736 mg, 19.38 mmol, 1.5 equiv) at 0 °C for 15 min. The solution was diluted with ether (300 mL), and then saturated aqueous NH_4Cl solution (100 mL) was carefully added. The organic phase was washed with brine (100 mL), dried ($MgSO_4$), and concentrated. Flash column chromatography (silica gel, 50% ether in hexanes) gave alcohol **17** (4.0 g, 99%) as a colorless oil. **17**: $R_f = 0.30$ (silica gel, 50% ether in hexanes); $[\alpha]_D^{22} = -31.7$ ($c = 0.9$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3388$, 2956, 2871, 1582, 1485, 1382, 1320, 1252, 1085, 1014, 835, 777 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.46$ (s, 1H, OCH=C), 6.25 (s, 1H, C*H*=CCH$_3$), 4.37 (dd, $J = 7.5$, 5.4 Hz, 1H, CHOSi), 3.73–3.70 (m, 2H, C*H*$_2$OH), 2.44 (s, 3H, N=C(O)CH$_3$), 2.39 (s, 1H, OH), 1.89 (s, 3H, CH=CC*H*$_3$), 1.86–1.82 (m, 1H, C*H*$_2$CH$_2$OH), 1.79–1.74 (m, 1H, C*H*$_2$CH$_2$OH), 0.89 (s, 9H, SiC(CH$_3$)$_3$), 0.09 (s, 3H, Si(CH$_3$)$_2$), 0.01 (s, 3H, Si(CH$_3$)$_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 160.9$, 141.3, 137.9, 135.2, 115.0, 76.9, 60.2, 37.9, 25.7, 18.0, 14.5, 13.7, −4.8, −5.4; FAB HRMS (NBA/NaI): $m/e = 334.1825$, $M+Na^+$ calcd for $C_{16}H_{29}NO_3Si$ 334.1814.

Iodide 18—iodination of alcohol 17: A solution of alcohol **17** (3.90 g, 12.52 mmol) in ether:MeCN (3:1, 80 mL, 0.16 M) was cooled to 0 °C. Imidazole (3.40 g, 50.08 mmol, 4.0 equiv), Ph_3P (6.57 g, 25.04 mmol, 2.0 equiv), and iodine (6.35 g, 25.04 mmol, 2.0 equiv) were sequentially added, and the mixture was stirred for 0.5 h at 0 °C. A saturated aqueous solution of $Na_2S_2O_3$ (50 mL) was added, followed by the addition of ether (200 mL). The organic phase was washed with brine (50 mL) and dried ($MgSO_4$), and the solvents were removed under vacuum. Flash column chromatography (silica gel, 10% ether in hexanes) gave pure iodide **18** (4.60 g, 87%) as a colorless oil: $R_f = 0.62$ (silica gel, 50% ether in hexanes); $[\alpha]_D^{22} = +6.3$ ($c = 0.7$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 2954$, 2857, 1586, 1462, 1386, 1315,

0947-6539/97/0312-1976 $ 17.50+.50/0 *Chem. Eur. J.* **1997**, *3*, No. 12

1254, 1169, 1080, 933, 835, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.46$ (s, 1H, OCH=C), 6.25 (s, 1H, C*H*=CCH$_3$), 4.20 (dd, $J = 7.6$, 4.5 Hz, 1H, CHOSi), 3.21–3.14 (m, 2H, CH_2I), 2.44 (s, 3H, N=C(O)CH_3), 2.11–2.04 (m, 1H, CH_2CH$_2$I), 2.01–1.94 (m, 1H, CH_2CH$_2$I), 1.87 (s, 3H, CH=CCH_3), 0.89 (s, 9H, SiC(CH$_3$)$_3$), 0.09 (s, 3H, Si(CH$_3$)$_2$), 0.00 (s, 3H, Si(CH$_3$)$_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 160.6$, 140.7, 137.8, 135.3, 115.7, 77.6, 40.2, 25.7, 18.0, 14.1, 13.7, 2.83, −4.7, −5.0; FAB HRMS (NBA): $m/e = 422.1027$, $M+H^+$ calcd for $C_{16}H_{28}INO_2Si$ 422.1012.

Phosphonium salt 9: A mixture of iodide **18** (4.50 g, 10.68 mmol) and Ph_3P (5.70 g, 21.73 mmol, 2.0 equiv) was heated neat at 100 °C for 4 h. Purification by flash column chromatography (silica gel, CH_2Cl_2; then 10% MeOH in CH_2Cl_2) provided phosphonium salt **9** (6.50 g, 90%) as a yellow solid: $R_f = 0.43$ (silica gel, 10% MeOH in CH_2Cl_2); $[\alpha]_D^{22} = -2.4$ ($c = 0.9$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 2928$, 2852, 1560, 1437, 1249, 1111, 1073, 836, 749 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.81–7.42$ (m, 16H, aromatic, OCH=C), 6.37 (s, 1H, C*H*=CCH$_3$), 4.51 (dd, $J = 6.6$, 4.5 Hz, 1H, CHOSi), 3.82–3.75 (m, 1H, CH_2P), 3.36–3.27 (m, 1H, CH_2P), 2.40 (s, 3H, N=C(O)CH_3), 1.97–1.89 (m, 1H, CH_2CH$_2$P), 1.85 (s, 3H, CH=CCH_3), 1.83–1.75 (m, 1H, CH_2CH$_2$P), 0.86 (s, 9H, SiC(CH$_3$)$_3$), 0.10 (s, 3H, Si(CH$_3$)$_2$), 0.01 (s, 3H, Si(CH$_3$)$_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 161.4$, 139.8, 139.5, 137.5, 135.2, 133.3, 133.2, 130.5, 130.4, 128.4, 118.2, 117.5, 116.1, 75.8, 75.7, 28.9, 25.8, 18.0, 14.9, 13.7, −4.7.

Olefin 19′: Phosphonium salt **9** (6.3 g, 9.21 mmol, 1.2 equiv) was dissolved in THF (90 mL, 0.1 M) and the solution was cooled to 0 °C. Sodium bis(trimethylsilyl)amide (NaHMDS, 1.0 M solution in THF, 9.10 mL, 9.10 mmol, 1.18 equiv) was slowly added and the resulting mixture was stirred at 0 °C for 15 min. The reaction mixture was then cooled to −20 °C before ketone **8**[11, 17] (2.0 g, 7.73 mmol, 1.0 equiv) in THF (10 mL) was added. The reaction mixture was stirred at the same temperature for 12 h. Saturated aqueous NH_4Cl solution (50 mL) was added, and the mixture extracted with ether (200 mL). The organic phase was washed with brine (2 × 100 mL), dried ($MgSO_4$), and concentrated to afford, after flash column chromatography (silica gel, 2% ether in hexanes), olefins **19′** (2.8 g, 68%, (*Z*):(*E*) ca. 1:1 by ^1H NMR): $R_f = 0.58$ (silica gel, 20% ether in hexanes); IR (thin film): $\tilde{\nu}_{max} = 2936$, 2886, 1586, 1465, 1360, 1253, 1089, 945, 838, 775 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.44$, 7.43 (singlets, 1H total, *OCH=C*), *6.16* (*s, 1H, CH=CCH$_3$*), *5.12–5.07* (*m, 1H, C(CH$_3$)=CH*), 4.08 (dd, $J = 6.4$, 5.4 Hz, 0.5H, CHOSi), 4.06 (dd, $J = 6.4$, 5.4 Hz, 0.5H, CHOSi), 3.44–3.40 (m, 1H, CH_2OSi), 3.33 (dd, $J = 10.7$, 6.9 Hz, 0.5H, CH_2OSi), 3.32 (dd, $J = 9.8$, 7.0 Hz, 0.5H, CH_2OSi), 2.43 (s, 3H, N=C(O)CH_3), 2.27–2.20 (m, 2H, CH_2CHOSi), 2.03–1.98 (m, 1H, CH_2C(CH$_3$)=CH), 1.95–1.92 (m, 1H, CH_2C(CH$_3$)=CH), 1.86 (s, 3H, CH=CCH_3), 1.64 (s, 1.5H, C(CH_3)=CH), 1.57 (s, 1.5H, C(CH_3)=CH), 1.56–1.51 (m, 1H), 1.39–1.29 (m, 3H), 1.04–0.99 (m, 1H), 0.88, 0.87 (singlets, 18H total, 2SiC(CH$_3$)$_3$), 0.85 (d, $J = 7.0$ Hz, 1.5H, CH_3CH), 0.83 (d, $J = 6.7$ Hz, 1.5H, CH_3CH), 0.02, 0.01, −0.03 (singlets, 12H total, 2Si(CH$_3$)$_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 160.4$, 142.3, 142.2, 138.1, 138.0, 136.8, 136.7, 134.9, 121.1, 120.3, 115.0, 114.8, 78.5, 78.3, 68.2, 40.0, 35.6, 35.5, 35.3, 35.1, 33.0, 32.7, 32.1, 25.9, 25.7, 25.3, 25.2, 23.3, 18.2, 18.1, 16.5, 16.0, 14.1, 13.7, −4.9, −5.1, −5.5; FAB HRMS (NBA): $m/e = 536.3939$, $M+H^+$ calcd for $C_{30}H_{57}NO_3Si_2$ 536.3955.

Hydroxyolefins 20′—desilylation of silyl ether 19′: Silyl ether **19′** (2.50 g, 4.66 mmol) was dissolved in CH_2Cl_2/MeOH (1:1, 100 mL, 0.05 M), and the solution was cooled to 0 °C prior to addition of CSA (1.14 g, 4.89 mmol, 1.05 equiv) over a 5 min period. The resulting solution was stirred for 30 min at 0 °C, and then for 1 h at 25 °C. Et_3N (0.68 mL, 4.89 mmol, 1.05 equiv) was added, and the solvents were removed under reduced pressure. Flash column chromatography (silica gel, 50% ether in hexanes) furnished pure hydroxy compound **20′** (1.80 g, 92%): $R_f = 0.35$ (silica gel, 50% ether in hexanes); IR (thin film): $\tilde{\nu}_{max} = 3380$, 2929, 2872, 1584, 1482, 1384, 1319, 1252, 1075, 938, 837, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (mixture of (*Z*):(*E*) olefins, ca. 1:1): $\delta = 7.45$, 7.44 (singlets, 1H total, OCH=C), 6.15, 6.11 (singlets, 1H total, C*H*=CCH$_3$), 5.10 (dd, $J = 7.1$, 7.1 Hz, 0.5H, C(CH$_3$)=C*H*), 5.03 (dd, $J = 7.2$, 7.1 Hz, 0.5H, C(CH$_3$)=C*H*), 4.06 (dd, $J = 6.7$, 6.2 Hz, 1H, CHOSi), 3.47 (dd, $J = 8.9$, 5.9 Hz, 0.5H, CH_2OH), 3.42–3.37 (m, 1.5H, CH_2OH), 2.42 (s, 3H, N=C(O)CH_3), 2.28–2.15 (m, 2H, CH_2CHOSi), 2.03–1.94 (m, 2H, CH_2C(CH$_3$)=CH), 1.84, 1.82 (singlets, 3H total, CH=CCH_3), 1.64 (s, 1.5H, C(CH_3)=CH), 1.60–1.58 (m, 1H), 1.55 (s, 1.5H, C(CH_3)=CH), 1.46–1.31 (m, 3H), 1.07–0.98 (m, 1H), 0.89 (d, $J = 6.9$ Hz, 1.5H, CH_3CH), 0.87–0.85 (m, 10.5H, SiC(CH$_3$)$_3$), CH_3CH), 0.03, 0.02 (singlets, 3H total, Si(CH$_3$)$_2$), −0.02, −0.03 (singlets, 3H total, Si(CH$_3$)$_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 160.7$, 160.5, 142.4, 142.0, 137.9, 137.8, 136.7, 136.6, 134.9, 134.8, 121.3, 120.3, 115.1, 114.8, 78.6, 78.3, 68.0, 67.9, 39.6, 35.6, 35.5, 35.2, 35.0, 32.9, 32.3, 32.0, 25.7, 25.2, 24.7, 23.3, 18.1, 16.5, 16.2, 15.8, 14.1, 13.9, 13.6, 13.5, −4.8, −5.1; FAB HRMS (NBA/NaI): $m/e = 444.2921$, $M+Na^+$ calcd for $C_{24}H_{43}NO_3Si$ 444.2910.

Aldehyde 6′—oxidation of alcohol 20′: Alcohol **20′** (mixture of (*Z*) and (*E*) geometrical isomers, 1.00 g, 2.37 mmol) was dissolved in CH_2Cl_2 (25 mL, 0.1 M). DMSO (8.30 mL), Et_3N (1.65 mL, 11.85 mmol, 5.0 equiv), and SO_3·pyridine (0.75 g, 4.74 mmol, 2.0 equiv) were added at 25 °C, and the resulting mixture was stirred for 30 min. Saturated aqueous NH_4Cl solution (20 mL) and ether (100 mL) were added, and the organic phase was separated and washed with brine (2 × 30 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Flash column chromatography (silica gel, 20% ether in hexanes) furnished aldehyde **6′** (0.97 g, mixture of (*Z*):(*E*) isomers, ca 1:1, 98%): $R_f = 0.47$ (silica gel, 50% ether in hexanes); IR (thin film): $\tilde{\nu}_{max} = 2943$, 2860, 1719, 1584, 1455, 1378, 1249, 1073, 937, 832, 773 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 9.60$ (d, $J = 2.0$ Hz, 0.5H, CHO), 9.53 (d, $J = 1.9$ Hz, 0.5H, CHO), 7.44, 7.43 (singlets, 1H total, OCH=C), 6.15, 6.13 (singlets, 1H total, C*H*=CCH$_3$), 5.12–5.07 (m, 1H, CH$_2$C*H*=CCH$_3$), 4.07 (dd, $J = 6.4$, 6.3 Hz, 0.5H, CHOSi), 4.05 (dd, $J = 6.6$, 6.2 Hz, 0.5H, CHOSi), 2.42 (s, 3H, N=C(O)CH_3), 2.32–2.15 (m, 2H, CH_2CHOSi), 2.05–1.93 (m, 2H, CH_2C(CH$_3$)=CH), 1.84 (s, 3H, CH=CCH_3), 1.68–1.58 (m, 2H), 1.63 (s, 1.5H, CH$_2$CH=CCH_3), 1.55 (s, 1.5H, CH$_2$CH=CCH_3), 1.41–1.23 (m, 3H), 1.05 (d, $J = 7.1$ Hz, 1.5H, CH_3CH), 1.02 (d, $J = 6.9$ Hz, 1.5H, CH_3CH), 0.84 (s, 9H, SiC(CH$_3$)$_3$), 0.01, 0.00 (singlets, 3H total, Si(CH$_3$)$_2$), −0.04 (s, 3H, Si(CH$_3$)$_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 205.0$, 204.9, 160.4, 142.1, 138.0, 136.0, 135.9, 134.9, 121.8, 120.9, 114.9, 78.4, 78.2, 46.1, 46.0, 39.5, 35.2, 31.7, 30.2, 29.8, 25.7, 25.1, 24.9, 23.2, 18.1, 15.9, 14.1, 14.0, 13.7, 13.1, 13.0, −4.9, −5.1; FAB HRMS (NBA/NaI): $m/e = 442.2743$, $M+Na^+$ calcd for $C_{24}H_{41}NO_3Si$ 442.2753.

Tris(silyl ethers) 21′ and 22′—aldol reaction of ketone 7 with aldehyde 6′: A solution of ketone **7** (1.34 g, 3.33 mmol, 1.2 equiv) in THF (5.0 mL) was added dropwise to a freshly prepared solution of LDA [diisopropylamine (468 μL, 3.36 mmol) was added to *n*BuLi (2.10 mL, 1.6 M solution in hexanes, 3.36 mmol) in 10.0 mL of THF at 0 °C] in THF (10.0 mL) at −78 °C. After the mixture had been stirred for 1.5 h at −78 °C, a solution of aldehyde **6′** (1.16 g, 2.77 mmol, 1.0 equiv) in THF (5.0 mL) was added dropwise. The resulting mixture was stirred for 15 min at −78 °C, and then quenched by dropwise addition of saturated aqueous NH_4Cl solution (20 mL). The aqueous phase was extracted with ether (3 × 50 mL), and the combined organic layer was dried ($MgSO_4$) and concentrated. Purification by flash column chromatography (silica gel, 20% ether in hexanes) provided pure aldol products **21′** (1.33 g, 59%) and **22′** (0.33 g, 14%) (73% overall yield, ca. 4:1).

21′: colorless oil; $R_f = 0.40$ (silica gel, 20% ether in hexanes); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.43$ (s, 1H, OCH=C), 6.14 (s, 1H, C*H*=CCH$_3$), 5.08 (dd, $J = 10.4$, 7.0 Hz, 1H, C(CH$_3$)=C*H*CH$_2$), 4.05 (dd, $J = 13.0$, 6.5 Hz, 1H, (CH$_3$)$_2$CC*H*OSi), 3.89 (dd, $J = 7.5$, 2.5 Hz, 1H, CH$_2$C*H*OSi), 3.68–3.62 (m, 1H, CH(CH$_3$)C*H*OH), 3.59 (dd, $J = 7.5$, 7.4 Hz, 2H, CH_2OSi), 3.53 (d, $J = 12.5$ Hz, 1H), 3.32–3.25 (m, 1H, C(O)C*H*(CH$_3$)), 2.42 (s, 3H, N=C(CH$_3$)O), 2.30–2.19 (m, 2H, C(CH$_3$)=CHCH_2), 2.05–1.90 (m, 2H, CH_2C(CH$_3$)=CH), 1.84 (s, 3H, CH=C(CH_3)), 1.65 (s, 1.5H, C(CH_3)=CHCH$_2$), 1.54 (s, 1.5H, C(CH_3)=CHCH$_2$), 1.80–1.46 (m, 5H), 1.34–1.25 (m, 2H), 1.19 (s, 3H, C(CH$_3$)$_2$), 1.07 (s, 3H, C(CH$_3$)$_2$), 1.01 (d, $J = 6.8$ Hz, 3H, CH(CH_3)), 0.89 (s, 18H, 2SiC(CH$_3$)$_3$), 0.87 (s, 9H, SiC(CH$_3$)$_3$), 0.81 (d, $J = 6.8$ Hz, 3H, CH(CH_3)), 0.09 (s, 3H, Si(CH$_3$)$_2$), 0.06 (s, 3H, Si(CH$_3$)$_2$), 0.01 (s, 9H, Si(CH$_3$)$_2$), −0.04 (s, 3H, Si(CH$_3$)$_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 222.1$, 222.0, 160.4, 142.3, 142.2, 138.0, 136.8, 134.9, 121.1, 120.3, 114.8, 78.5, 78.3, 74.7, 74.0, 60.3, 53.8, 41.3, 41.2, 40.0, 37.7, 35.4, 35.3, 35.1, 32.8, 32.5, 32.2, 26.0, 25.8, 25.6, 25.0, 24.9, 23.4, 22.8, 18.2, 18.1, 18.0, 16.3, 15.2, 14.1, 13.7, 9.5, 9.4, −3.9, −4.2, −4.9, −5.1, −5.4; FAB HRMS (NBA/CsI): $m/e = 954.4935$, $M+Cs^+$ calcd for $C_{45}H_{87}NO_6Si_3$ 954.4896.

22′: colorless oil; $R_f = 0.37$ (silica gel, 20% ether in hexanes); IR (thin film): $\tilde{\nu}_{max} = 3490$, 2942, 2932, 2873, 1683, 1463, 1382, 1249, 1090, 840, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.45$ (s, 1H, OCH=C), 6.16 (s, 0.5H, C*H*=CCH$_3$), 6.15 (s, 0.5H, C*H*=CCH$_3$), 5.14–5.07 (m, 1H, C(CH$_3$)=C*H*CH$_2$), 4.09–4.05 (m, 1H), 3.65–3.58 (m, 3H), 3.42–3.38 (m,

1H), 3.24–3.19 (m, 1H), 2.43 (s, 3H, N=C(CH$_3$)O), 2.31–2.18 (m, 2H, C(CH$_3$)=CHCH_2), 1.85 (s, 3H, CH=C(CH_3)), 1.99–1.88 (m, 2H, CH_2C(CH$_3$)=CH), 1.67 (s, 1.5H, C(CH_3)=CHCH$_2$), 1.58 (s, 1.5H, C(CH_3)=CHCH$_2$), 1.55–1.40 (m, 5H), 1.35–0.81 (m, 41H), 0.10 (s, 1.5H, Si(CH$_3$)$_2$), 0.09 (s, 1.5H, Si(CH$_3$)$_2$), 0.07 (s, 1.5H, Si(CH$_3$)$_2$), 0.05 (s, 1.5H, Si(CH$_3$)$_2$), 0.02 (s, 9H, Si(CH$_3$)$_2$), −0.03 (s, 3H, Si(CH$_3$)$_2$); ^{13}C NMR (125.7 MHz, CDCl$_3$): δ = 222.3, 222.1, 160.5, 142.1, 138.2, 136.5, 134.9, 121.4, 120.5, 114.9, 78.5, 78.3, 78.2, 74.9, 73.8, 72.5, 60.5, 60.0, 54.2, 53.8, 41.8, 41.6, 41.3, 39.9, 37.8, 37.6, 35.4, 35.3, 35.2, 32.7, 32.5, 32.1, 26.0, 25.9, 25.8, 25.7, 25.0, 24.9, 23.4, 22.7, 19.9, 19.4, 18.2, 18.1, 18.0, 15.4, 15.0, 14.1, 13.7, 10.9, 10.8, −3.9, −4.1, −4.2, −4.9, −5.1, −5.4; FAB HRMS (NBA): m/e = 822.5948, M+H$^+$ calcd for $C_{45}H_{87}NO_6Si_3$ 822.5920.

Tetra(silyl ether) 23′: Compound **21′** (0.72 g, 1.14 mmol) was dissolved in CH_2Cl_2 (10.0 mL, 0.11 M), cooled to 0 °C, and treated with 2,6-lutidine (0.26 mL, 2.28 mmol, 2.0 equiv) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.38 mL, 1.71 mmol, 1.5 equiv). After stirring for 1 h at 0 °C, the reaction mixture was quenched with methanol (5.0 mL) and treated with saturated aqueous NH_4Cl solution (10 mL). The aqueous phase was extracted with ether (3 × 10 mL), and the combined organic solution was washed with brine (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 3% ether in hexanes) provided tetra(silyl ether) **23′** (1.04 g, 97%) as a colorless oil. **23′**: R_f = 0.56 (silica gel, 10% ether in hexanes); ^{1}H NMR (500 MHz, CDCl$_3$): δ = 7.42 (s, 1H, OCH=C), 6.15 (s, 1H, CH=CCH$_3$), 5.10 (dd, J = 13.2, 7.2 Hz, 1H, C(CH$_3$)=CHCH$_2$), 4.05 (dd, J = 10.4, 5.6 Hz, 1H, (CH$_3$)$_2$CCHOSi), 3.90–3.85 (m, 1H, CH$_2$CHOSi), 3.74 (dd, J = 5.6, 1.9 Hz, 1H), 3.69–3.62 (m, 1H, CH(CH$_3$)CHOSi), 3.56 (dd, J = 13.2, 6.2 Hz, 2H, CH$_2$OSi), 3.12 (dq, J = 5.6, 1.6 Hz, 1H, C(O)CH(CH$_3$)), 2.41 (s, 3H, N=C(CH$_3$)O), 2.28–2.15 (m, 2H, C(CH$_3$)=CHCH_2), 1.98–1.89 (m, 2H, CH_2C(CH$_3$)=CH), 1.85 (s, 1.5H, CH=C(CH_3)), 1.84 (s, 1.5H, CH=C(CH_3)), 1.62 (s, 3H, C(CH_3)=CHCH$_2$), 1.55 (s, 3H, C(CH_3)=CHCH$_2$), 1.76–0.81 (m, 46H), 0.07 (s, 3H, Si(CH$_3$)$_2$), 0.04 (s, 9H, Si(CH$_3$)$_2$), 0.01 (s, 9H, Si(CH$_3$)$_2$), −0.04 (s, 3H, Si(CH$_3$)$_2$); ^{13}C NMR (125.7 MHz, CDCl$_3$): δ = 218.0, 160.3, 142.3, 142.1, 138.1, 136.6, 134.9, 121.3, 120.5, 114.8, 114.7, 78.4, 78.3, 77.3, 73.8, 73.7, 60.8, 53.5, 44.9, 40.2, 38.8, 38.7, 37.9, 35.4, 35.1, 32.4, 31.5, 30.8, 30.6, 26.2, 26.0, 25.8, 25.7, 24.4, 24.3, 23.4, 19.3, 19.1, 18.4, 18.2, 18.1, 18.0, 17.4, 16.1, 15.1, 14.1, 13.7, −3.8, −3.9, −4.1, −4.9, −5.1, −5.4; FAB HRMS (NBA/CsI): m/e = 1068.5720, M+Cs$^+$ calcd for $C_{51}H_{101}NO_6Si_4$ 1068.5760.

Alcohol 24′ (370 mg, 85%) was obtained from compound **23′** (500 mg, 0.53 mmol) according to the procedure described above for **20′**. **24′**: colorless oil; R_f = 0.37 (silica gel, 50% ether in hexanes); IR (thin film): $\tilde{\nu}_{max}$ = 3392, 2935, 2865, 1689, 1463, 1378, 1357, 1252, 1083, 988, 867, 835, 772, 730 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ = 7.43 (s, 1H, OCH=C), 6.14 (s, 1H, CH=CCH$_3$), 5.12–5.05 (m, 1H, C(CH$_3$)=CH), 4.10–4.04 (m, 2H, (CH$_3$)$_2$CCHOSi, CH$_2$CHOSi), 3.76 (dd, J = 7.0, 1.4 Hz, 1H, CH(CH$_3$)CHOSi), 3.61 (t, J = 7.0 Hz, 2H, CH_2OH), 3.11 (dd, J = 7.0, 6.8 Hz, 1H, C(O)CH(CH$_3$)), 2.42 (s, 3H, N=C(CH$_3$)O), 2.25–2.12 (m, 2H, C(CH$_3$)=CHCH_2), 1.99–1.87 (m, 2H, CH_2C(CH$_3$)=CH), 1.84 (d, J = 1.0 Hz, 3H, CH=C(CH_3)), 1.63 (s, 1.5H, C(CH_3)=CH), 1.57–1.52 (m, 2H), 1.55 (s, 1.5H, C(CH_3)=CH), 1.37–1.25 (m, 3H), 1.19 (s, 3H, C(CH$_3$)$_2$), 1.18–1.10 (m, 2H), 1.03 (s, 3H, C(CH$_3$)$_2$), 0.88–0.85 (m, 33H, 2CH(CH_3), 3SiC(CH$_3$)$_3$), 0.09, 0.08, 0.07, 0.05, 0.04, 0.01, −0.01 (singlets, 18H total, 3Si(CH$_3$)$_2$); ^{13}C NMR (125.7 MHz, CDCl$_3$): δ = 219.3, 160.4, 142.3, 142.2, 138.0, 136.6, 134.9, 121.3, 120.5, 114.8, 114.7, 78.4, 78.3, 77.5, 77.4, 72.9, 72.8, 59.9, 53.6, 53.3, 44.9, 40.2, 38.5, 38.4, 38.2, 35.3, 35.1, 32.3, 30.6, 30.3, 26.1, 25.9, 25.7, 24.7, 23.4, 18.4, 18.1, 18.0, 17.7, 17.6, 16.1, 15.6, 15.5, 14.1, 13.7, −3.7, −3.9, −4.0, −4.8, −5.1; FAB HRMS (NBA/CsI): m/e = 954.4878, M+Cs$^+$ calcd for $C_{45}H_{87}NO_6Si_3$ 954.4896.

Aldehyde 25′—oxidation of alcohol 24′: To a solution of oxalyl chloride (82 μL, 0.85 mmol, 2.0 equiv) in CH_2Cl_2 (5.0 mL) was added dropwise DMSO (120 μL, 1.70 mmol, 4.0 equiv) at −78 °C. After the mixture had been stirred for 15 min at −78 °C, a solution of alcohol **24′** (350 mg, 0.425 mmol, 1.0 equiv) in CH_2Cl_2 (2.0 mL) was added dropwise at −78 °C over a period of 5 min. The solution was stirred at −78 °C for 30 min, and then Et_3N (350 μL, 2.55 mmol, 6.0 equiv) was added. The reaction mixture was allowed to warm to 0 °C over a period of 30 min, and then ether (20 mL) was added, followed by saturated aqueous NH_4Cl solution (10 mL). The organic phase was separated, and the aqueous phase extracted with ether (2 × 10 mL). The combined organic solution was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 20% ether in hexanes) provided aldehyde **25′** (326 mg, 94%) as a colorless oil. **25′**: R_f = 0.63 (silica gel, 50% ether in hexanes); IR (thin film): $\tilde{\nu}_{max}$ = 2943, 2849, 1725, 1690, 1461, 1384, 1249, 1079, 985, 832, 773 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ = 9.74–9.73 (m, 1H, CHO), 7.43 (s, 1H, OCH=C), 6.15 (s, 1H, CH=CCH$_3$), 5.12–5.05 (m, 1H, C(CH$_3$)=CH), 4.45 (dd, J = 4.7, 4.6 Hz, 1H, (CH$_3$)$_2$CCHOSi), 4.05 (dd, J = 7.1, 6.9 Hz, 1H, CH$_2$CHOSi), 3.74 (dd, J = 7.4, 1.6 Hz, 1H, CH(CH$_3$)CHOSi), 3.10 (dq, J = 7.2, 7.0 Hz, 1H, C(O)CH(CH$_3$)), 2.52–2.46 (m, 1H, CH_2CHO), 2.42 (s, 3H, N=C(CH$_3$)O), 2.37 (ddd, J = 17.0, 5.5, 2.8 Hz, 1H, CH_2CHO), 2.23–2.16 (m, 2H, C(CH$_3$)=CHCH_2), 1.97–1.88 (m, 2H, CH_2C(CH$_3$)=CH), 1.85 (s, 1.5H, CH=C(CH_3)), 1.84 (S, 1.5H, CH=C(CH_3)), 1.63 (s, 1.5H, C(CH_3)=CH), 1.55 (s, 1.5H, C(CH_3)=CH), 1.48–1.25 (m, 5H), 1.22 (s, 3H, C(CH$_3$)$_2$), 1.05 (s, 3H, C(CH$_3$)$_2$), 1.01 (d, J = 6.9 Hz, 1.5H, CH(CH_3)), 1.00 (d, J = 6.9 Hz, 1.5H, CH(CH_3)), 0.89–0.85 (m, 30H, CH(CH_3), 3SiC(CH$_3$)$_3$), 0.07, 0.04, 0.03, 0.02, 0.01, 0.00, −0.04 (singlets, 18H total, 3Si(CH$_3$)$_2$); ^{13}C NMR (125.7 MHz, CDCl$_3$): δ = 218.3, 200.9, 160.4, 142.3, 142.1, 138.0, 136.6, 136.5, 134.9, 121.3, 120.5, 114.8, 114.7, 78.4, 78.3, 77.5, 77.4, 71.1, 71.0, 53.3, 49.4, 44.9, 40.2, 38.6, 38.5, 35.3, 35.1, 32.4, 30.6, 30.3, 26.2, 25.7, 25.6, 23.9, 23.4, 18.6, 18.5, 18.4, 18.1, 17.9, 17.6, 16.1, 15.4, 14.1, 13.7, −3.7, −3.8, −4.3, −4.6, −4.8, −4.9, −5.1.

Carboxylic acid 26′—oxidation of aldehyde 25′: Aldehyde **25′** (325 mg, 0.39 mmol), *t*BuOH (15.0 mL, 0.03 M), 2-metyl-2-butene (11.0 mL, 2 M solution in THF, 22.0 mmol), H_2O (3.0 mL), $NaClO_2$ (217 mg, 2.38 mmol, 6.0 equiv), and NaH_2PO_4 (143 mg, 1.19 mmol, 3.0 equiv) were combined and stirred at 0 °C for 15 min. The reaction mixture was concentrated under reduced pressure, and the residue diluted with EtOAc (50 mL) and washed with brine (20 mL). The aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic solution was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 6% MeOH in CH_2Cl_2) afforded carboxylic acid **26′** (330 mg, 99%). **26′**: R_f = 0.27 (silica gel, 5% MeOH in CH_2Cl_2); IR (thin film): $\tilde{\nu}_{max}$ = 3358, 2932, 2857, 1711, 1466, 1254, 1088, 988, 835 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ = 7.47 (s, 1H, OCH=C), 6.32, 6.15 (singlets, 1H total, CH=CCH$_3$), 5.16 (t, J = 7.5 Hz, 0.5H, C(CH$_3$)=CH), 5.09 (t, J = 7.5 Hz, 0.5H, C(CH$_3$)=CH), 4.41 (dd, J = 7.0, 3.1 Hz, 0.5H, (CH$_3$)$_2$CCHOSi), 4.36 (dd, J = 7.1, 2.7 Hz, 0.5H, (CH$_3$)$_2$CCHOSi), 4.13 (dd, J = 7.7, 5.3 Hz, 0.5H, CH$_2$CHOSi), 4.06 (dd, J = 6.7, 6.5 Hz, 0.5H, CH$_2$CHOSi), 3.79 (dd, J = 6.5, 1.5 Hz, 0.5H, CH(CH$_3$)CHOSi), 3.72 (dd, J = 5.5, 3.2 Hz, 0.5H, CH(CH$_3$)CHOSi), 3.19 (dq, J = 7.2, 7.0 Hz, 0.5H, C(O)CH(CH$_3$)), 3.15 (dq, J = 7.2, 7.0 Hz, 0.5H, C(O)CH(CH$_3$)), 2.54–2.47 (m, 1H, CH_2COOH), 2.46 (s, 3H, N=C(CH$_3$)O), 2.42 (dd, J = 16.4, 3.1 Hz, 1H, CH_2COOH), 2.36–2.28 (m, 1H, C(CH$_3$)=CHCH_2), 2.24–2.17 (m, 1H, C(CH$_3$)=CHCH_2), 2.00–1.85 (m, 2H, CH_2C(CH$_3$)=CH), 1.83 (s, 1.5H, CH=C(CH_3)), 1.81 (s, 1.5H, CH=C(CH_3)), 1.67 (s, 1.5H, C(CH_3)=CH), 1.53 (s, 1.5H, C(CH_3)=CH), 1.49–1.25 (m, 5H), 1.21 (s, 3H, C(CH$_3$)$_2$), 1.06 (s, 3H, C(CH$_3$)$_2$), 1.05 (d, J = 6.9 Hz, 3H, CH(CH_3)), 0.89–0.85 (m, 30H, CH(CH_3), 3SiC(CH$_3$)$_3$), 0.14, 0.12, 0.10, 0.08, 0.07, 0.06, 0.05, 0.03, 0.02, −0.01, −0.02, −0.03 (singlets, 18H total, 3Si(CH$_3$)$_2$); ^{13}C NMR (150.9 MHz, CDCl$_3$): δ = 218.6, 218.4, 174.9, 161.0, 142.8, 142.7, 137.9, 136.9, 135.1, 121.4, 120.5, 114.8, 78.5, 78.3, 77.6, 77.3, 73.7, 73.6, 69.1, 53.3, 53.2, 45.1, 44.7, 40.2, 39.8, 38.6, 38.4, 35.2, 35.0, 32.2, 30.7, 25.9, 25.7, 25.5, 23.2, 23.0, 19.8, 19.2, 19.1, 18.2, 18.1, 17.8, 17.5, 17.1, 15.9, 15.4, 15.2, 13.9, 13.3, −4.0, −4.1, −4.2, −4.3, −4.5, −4.6, −5.1, −5.2, −5.4.

Hydroxyacid 5′—selective desilylation of tris(silyl ether) 26′: A solution of tris(silyl ether) **26′** (325 mg, 0.39 mmol) in THF (8.0 mL, 0.05 M) at 25 °C was treated with TBAF (2.34 mL, 1.0 M solution in THF, 2.34 mmol, 6.0 equiv). After stirring for 10 h, the reaction mixture was diluted with EtOAc (10 mL) and washed with aqueous HCl (10 mL, 1.0 N solution). The aqueous solution was extracted with EtOAc (4 × 10 mL), and the combined organic phase washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The crude mixture was purified by flash column chromatography (silica gel, 5% MeOH in CH_2Cl_2) to provide hydroxyacid **5′** (220 mg, 78%) as a yellow oil: R_f = 0.38 (silica gel, 12% MeOH in CH_2Cl_2); IR (thin film): $\tilde{\nu}_{max}$ = 3358, 2932, 2857, 1722, 1466, 1380, 1254, 1088, 988, 835 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ = 7.45 (s, 1H, OCH=C), 6.29, 6.25 (singlets, 1H total, CH=CCH$_3$), 5.15–5.10 (m, 1H, C(CH$_3$)=CH), 4.39–4.35 (m, 1H, (CH$_3$)$_2$CCHOSi), 4.12 (dd, J = 7.5, 7.0 Hz, 1H, CH$_2$CHOH), 3.73 (dd, J = 6.9, 1.0 Hz, 1H, CH(CH$_3$)CHOSi), 3.15–3.11 (m, 1H, C(O)CHCH$_3$),

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2.43 (s, 3H, N=C(CH_3)O), 2.41–2.39 (m, 1H, CH_2COOH), 2.31–2.20 (m, 3H, CH_2COOH, C(CH_3)=CHCH_2), 2.03–1.95 (m, 2H, CH_2C(CH_3)=CH), 1.88, 1.87 (singlets, 3H total, CH=C(CH_3)), 1.67 (s, 1.5H, C(CH_3)=CH), 1.63–1.59 (m, 3H), 1.58 (s, 1.5H, C(CH_3)=CH), 1.49–1.40 (m, 2H), 1.19 (s, 3H, C(CH_3)$_2$), 1.07 (s, 3H, C(CH_3)$_2$), 1.03 (d, J = 7.0 Hz, 1.5H, CH(CH_3)), 1.02 (d, J = 7.1 Hz, 1.5H, CH(CH_3)), 0.89–0.83 (m, 21H, CH(CH_3), SiC(CH_3)$_3$), 0.08, 0.07, 0.04, 0.03, 0.02 (singlets, 12H total, 2Si(CH_3)$_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 217.8, 175.8, 160.8, 141.7, 141.6, 139.0, 138.9, 137.6, 135.1, 120.0, 119.2, 115.0, 114.9, 77.6, 77.5, 76.8, 76.7, 73.8, 53.5, 53.4, 45.1, 44.8, 40.5, 40.3, 38.7, 38.6, 34.0, 33.9, 32.4, 30.8, 30.4, 26.0, 25.9, 25.1, 23.4, 23.1, 22.9, 19.9, 19.7, 18.3, 18.0, 17.6, 17.3, 15.7, 15.6, 14.6, 14.5, −3.7, −3.8, −3.9, −4.0, −4.3, −4.8; FAB HRMS (NBA/CsI): m/e = 854.3848, M+Cs$^+$ calcd for $C_{39}H_{71}NO_7Si_2$ 854.3823.

Lactones 27 and 28—macrolactonization of hydroxyacid 5′: A solution of hydroxyacid **5′** (130 mg, mixture of (*Z*) and (*E*) isomers, ca. 1:1, 0.180 mmol) in THF (2.6 mL, 0.07 M) was treated at 0 °C with Et_3N (55 μL, 0.396 mmol, 2.2 equiv) and 2,4,6-trichlorobenzoyl chloride (28 μL, 0.234 mmol, 1.3 equiv). The reaction mixture was stirred at 0 °C for 0.5 h, and then added to a solution of 4-DMAP (44.2 mg, 0.360 mmol, 2.0 equiv) in toluene (83.0 mL, 0.002 M) at 25 °C and stirred at this temperature for 12 h. The solvents were removed in vacuo, and the crude product obtained was suspended in 40% ether in hexanes and filtered through silica gel. Concentration, followed by preparative thin-layer chromatography (silica gel, 5% MeOH in CH_2Cl_2), gave pure lactones **27** (44 mg, 35%) and **28** (53 mg, 42%) as colorless oils.

27: R_f = 0.24 (silica gel, 20% ether in hexanes); $[\alpha]_D^{22}$ = −18.0 (c = 1.5, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$ = 2931, 2856, 1740, 1695, 1463, 1381, 1252, 1156, 1064, 833, 775 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.47 (s, 1H, OCH=C), 6.28 (s, 1H, CH=CCH$_3$), 5.14 (dd, J = 8.4, 7.5 Hz, 1H, CH$_3$C=CHCH$_2$), 4.95 (d, J = 10.0 Hz, 1H, CH_2COOCH), 4.01 (d, J = 9.9 Hz, 1H, CHOSi), 3.88 (d, J = 9.0 Hz, 1H, CHOSi), 3.00 (dq, J = 6.9, 6.7 Hz, 1H, C(O)CHCH$_3$), 2.79 (d, J = 16.2 Hz, 1H, CH_2COOCH), 2.70–2.61 (m, 2H), 2.48–2.40 (m, 1H), 2.44 (s, 3H, N=C(CH_3)O), 2.05–2.00 (m, 2H), 1.98 (s, 3H, CH=C(CH_3)), 1.75–1.68 (m, 2H), 1.66 (s, 3H, CH_2C(CH_3)=CH), 1.64–1.45 (m, 3H), 1.18 (s, 3H, C(CH_3)$_2$), 1.13 (s, 3H, C(CH_3)$_2$), 1.09 (d, J = 6.7 Hz, 3H, CH(CH_3)), 0.96 (d, J = 6.9 Hz, 3H, CH(CH_3)), 0.93 (s, 9H, SiC(CH_3)$_3$), 0.83 (s, 9H, SiC(CH_3)$_3$), 0.09 (s, 6H, Si(CH_3)$_2$), 0.07 (s, 3H, Si(CH_3)$_2$), −0.13 (s, 3H, Si(CH_3)$_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 216.0, 172.1, 161.6, 139.4, 138.6, 136.4, 119.8, 116.4, 80.4, 77.1, 54.2, 40.0, 33.2, 32.8, 32.2, 30.5, 28.2, 27.2, 27.0, 25.4, 25.1, 24.0, 19.5, 19.4, 16.4, 14.7, −2.4, −2.8, −4.8; FAB HRMS (NBA): m/e = 704.4767, M+H$^+$ calcd for $C_{39}H_{69}NO_6Si_2$ 704.4742.

28: R_f = 0.20 (silica gel, 20% ether in hexanes); $[\alpha]_D^{22}$ = −24.2 (c = 1.7, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$ = 2931, 2857, 1740, 1695, 1465, 1378, 1252, 1169, 1102, 1029, 832, 775 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.46 (s, 1H, OCH=C), 6.27 (s, 1H, CH=CCH$_3$), 5.24 (dd, J = 8.0, 3.2 Hz, 1H, CH_2COOCH), 5.13 (dd, J = 6.9, 6.8 Hz, 1H, CH$_3$C=CHCH$_2$), 4.44 (dd, J = 5.1, 5.1 Hz, 1H, CHOSi), 3.87 (dd, J = 6.3, 2.1 Hz, 1H, CHOSi), 3.03 (dq, J = 6.8, 6.7 Hz, 1H, C(O)CHCH$_3$), 2.59 (dd, J = 15.4, 5.7 Hz, 1H, CH_2COOCH), 2.45 (dd, J = 15.4, 4.9 Hz, 1H, CH_2COOCH), 2.43 (s, 3H, N=C(CH_3)O), 2.15–2.08 (m, 1H, CH$_3$C=CHCH_2), 2.02 (s, 3H, CH=C(CH_3)), 2.00–1.85 (m, 3H, CH$_3$C=CHCH_2, CH_2C(CH_3)=CH), 1.55 (s, 3H, CH_2C(CH_3)=CH), 1.54–1.46 (m, 2H), 1.29–1.21 (m, 3H), 1.17 (s, 3H, C(CH_3)$_2$), 1.12 (d, J = 6.9 Hz, 3H, CH(CH_3)), 1.07 (s, 3H, C(CH_3)$_2$), 0.90 (d, J = 6.9 Hz, 3H, CH(CH_3)), 0.89 (s, 9H, SiC(CH_3)$_3$), 0.88 (s, 9H, SiC(CH_3)$_3$), 0.09 (s, 3H, Si(CH_3)$_2$), 0.08 (s, 3H, Si(CH_3)$_2$), 0.06 (s, 3H, Si(CH_3)$_2$), 0.04 (s, 3H, Si(CH_3)$_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 216.4, 170.5, 160.7, 137.9, 137.5, 135.7, 119.9, 115.5, 78.8, 76.2, 73.0, 53.9, 44.0, 41.9, 40.2, 39.3, 31.9, 30.7, 26.1, 26.0, 24.7, 22.8, 20.2, 18.3, 18.2, 16.9, 15.9, 15.7, 15.6, 13.8, −3.6, −3.7, −4.3, −4.4; FAB HRMS (NBA): m/e = 704.4742, M+H$^+$ calcd for $C_{39}H_{69}NO_6Si_2$ 704.4767.

Dihydroxylactone 4: To a solution of lactone **27** (38 mg, 0.054 mmol) in THF (4.0 mL) was added HF·pyridine (1.4 mL). After stirring at room temperature for 24 h, the reaction was quenched by the careful addition of saturated aqueous $NaHCO_3$ solution (10 mL). The layers were separated, and the aqueous phase extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to give a yellow oil, which was subjected to preparative thin-layer chromatography (silica gel, 50% ether in hexanes) to give the diol **4** as a colourless oil (16 mg, 62%): R_f = 0.38 (silica gel, 50% EtOAc in hexanes); $[\alpha]_D^{22}$ = −68.5 (c = 0.2, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$ = 3431, 2933, 1731, 1688, 1584, 1455, 1379, 1306, 1252, 1151, 1104, 1045, 1009, 934, 733 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.47 (s, 1H, OCH=C), 6.30 (s, 1H, CH=CCH$_3$), 5.21 (dd, J = 9.5, 1.5 Hz, 1H, CH_2COOCH), 5.12 (dd, J = 9.7, 5.0 Hz, 1H, CH$_3$C=CHCH$_2$), 4.22 (dd, J = 11.0, 2.6 Hz, 1H, (CH$_3$)$_2$CCHOH), 3.70 (dd, J = 3.4, 2.5 Hz, 1H, CHOH), 3.13 (qd, J = 6.9, 2.4 Hz, 1H, C(O)CHCH$_3$), 2.99 (brs, 1H, OH), 2.58 (ddd, J = 15.3, 9.8, 5.3 Hz, 1H, CH_2CH=CCH$_3$), 2.47 (buried m, 1H, CH_2COOCH), 2.44 (s, 3H, N=C(CH_3)O), 2.33–2.24 (m, 1H), 2.27 (dd, J = 15.0, 3.0 Hz, CH_2COOCH), 2.22 (d, J = 14.8 Hz, 1H, CH_2C(CH_3)=CHCH_2), 1.95 (s, 3H, CH=CCH_3), 1.90–1.84 (m, 1H), 1.77–1.68 (m, 1H), 1.64 (s, 3H, CH_2C(CH_3)=CH), 1.31 (s, 3H, C(CH_3)$_2$), 1.32–1.22 (m, 4H), 1.18 (d, J = 6.7 Hz, 3H, CH(CH_3)), 1.05 (s, 3H, C(CH_3)$_2$), 0.98 (d, J = 7.0 Hz, 3H, CH(CH_3)); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 222.0, 171.4, 162.0, 139.4, 138.3, 136.5, 121.7, 116.4, 79.5, 75.0, 73.2, 54.0, 42.4, 40.1, 39.2, 32.9, 32.4, 32.0, 26.0, 23.4, 23.2, 18.9, 16.6, 16.2, 14.3, 14.1; FAB HRMS (NBA/NaI): m/e = 498.2852, M+Na$^+$ calcd for $C_{27}H_{41}NO_6$ 498.2832.

Dihydroxylactone 29 (9 mg, 82%) was obtained from compound **28** (17 mg, 0.024 mmol) according to the procedure described above for **27**. **29**: R_f = 0.40 (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]_D^{22}$ = −59.1 (c = 0.5, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$ = 3425, 2937, 1732, 1685, 1580, 1458, 1380, 1254, 1095, 1008, 978, 733 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.50 (s, 1H, OCH=C), 6.31 (s, 1H, CH=CCH$_3$), 5.39 (dd, J = 6.2, 3.8 Hz, 1H, O=COCH), 5.06 (dd, J = 7.1, 7.0 Hz, 1H, CH$_3$C=CHCH$_2$), 4.38 (dd, J = 7.5, 1.5 Hz, 1H, CHOH), 3.67 (br, 1H, CHOH), 3.52 (br, 1H, OH), 3.31 (dq, J = 6.8, 4.8 Hz, 1H, C(O)CHCH$_3$), 3.12 (br, 1H, OH), 2.54–2.46 (m, 2H, CH_2COOCH), 2.45 (s, 3H, N=C(CH_3)O), 2.43–2.37 (m, 1H, CH$_3$C=CHCH_2), 2.20–2.15 (m, 1H, CH$_3$C=CHCH_2), 2.00–1.95 (m, 1H, CH_2C(CH_3)=CH), 1.95 (s, 3H, CH=C(CH_3)), 1.89–1.83 (m, 1H, CH_2C(CH_3)=CH), 1.67–1.61 (m, 3H), 1.59 (s, 3H, CH_2C(CH_3)=CH), 1.40–1.30 (m, 2H), 1.25 (s, 3H, C(CH_3)$_2$), 1.16 (d, J = 6.7 Hz, 3H, CH(CH_3)), 1.04 (s, 3H, C(CH_3)$_2$), 0.98 (d, J = 7.0 Hz, 3H, CH(CH_3)); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 220.1, 170.5, 160.6, 138.6, 136.9, 136.2, 135.1, 119.2, 115.6, 76.7, 71.8, 53.7, 43.2, 39.7, 38.9, 37.2, 30.6, 30.4, 24.5, 20.6, 20.2, 16.5, 16.4, 15.5, 14.9, 13.6; FAB HRMS (NBA/CsI): m/e = 608.1970, M+Cs$^+$ calcd for $C_{27}H_{41}NO_6$ 608.1988.

20-Oxa-epothilone B (2) and its α-epoxide epimer 30—epoxidation of lactone 4: To a stirred solution of diol **4** (17.0 mg, 0.036 mmol) in chloroform (800 μL) at 0 °C was added dropwise a solution of *m*CPBA (200 μL, 0.357 M solution in chloroform, 0.072 mmol, 2.0 equiv). The reaction mixture was maintained at this temperature for 3 h before being quenched by dropwise addition of dimethyl sulfide (400 μL) and Et_3N (500 μL). Volatiles were removed in vacuo, and the resulting residue was purified by preparative thin-layer chromatography (silica gel, 5% methanol in dichloromethane) to give the epoxide **2** (6.0 mg, 34%) and its diasteroisomer **30** (1.1 mg, 6%) as colorless oils.

2: R_f = 0.17 (silica gel, 80% ethyl acetate in hexanes); $[\alpha]_D^{22}$ = −30.4 (c = 0.1, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$ = 3436, 2927, 1733, 1690, 1451, 1382, 1253, 1150, 1106, 979 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.49 (s, 1H, OCH=C), 6.34 (s, 1H, CH=CCH$_3$), 5.43 (dd, J = 6.9, 3.4 Hz, 1H, CH_2COOCH), 4.14 (dd, J = 10.6, 2.6 Hz, 1H, (CH$_3$)$_2$CCHOH), 3.77 (dd, J = 4.3, 4.2 Hz, 1H, CHOH), 3.30 (dq, J = 6.9, 6.7 Hz, 1H, C(O)CHCH$_3$), 2.78 (dd, J = 6.7, 5.7 Hz, 1H, CHOCCH$_3$), 2.54 (dd, J = 14.2, 10.1 Hz, 1H, CH_2COOCH), 2.44 (s, 3H, N=C(CH_3)O), 2.39 (dd, J = 14.3, 3.1 Hz, CH_2COOCH), 2.02 (m, 1H, (CH$_3$)COCHCH_2CHO), 2.00 (s, 3H, CH=CCH_3), 1.91 (m, 1H, (CH$_3$)COCHCH_2CHO), 1.75–1.66 (m, 3H), 1.53–1.36 (m, 4H), 1.35 (s, 3H, C(CH_3)OCHCH$_2$), 1.27 (s, 3H, C(CH_3)$_2$), 1.16 (d, J = 6.9 Hz, 3H, CH(CH_3)), 1.07 (s, 3H, C(CH_3)$_2$), 0.99 (d, J = 7.0 Hz, 3H, CH(CH_3)); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 220.4, 170.3, 164.8, 137.2, 136.4, 135.7, 116.1, 76.4, 74.4, 73.3, 61.3, 61.2, 52.7, 43.4, 39.0, 36.5, 32.0, 31.9, 30.7, 22.9, 22.7, 21.1, 20.7, 17.3, 16.0, 14.3, 14.1, 13.9; FAB HRMS (NBA): m/e = 492.2972, M+H$^+$ calcd for $C_{27}H_{42}NO_7$ 492.2961.

30: R_f = 0.17 (silica gel, 50% EtOAc in hexanes); $[\alpha]_D^{22}$ = −30.4 (c 0.1, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$ = 3418, 2930, 1735, 1689, 1583, 1460, 1382, 1254, 1152, 1056 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.49 (s, 1H, OCH=C), 6.35 (s, 1H, CH=CCH$_3$), 5.66 (d, J = 9.1 Hz, 1H, CH_2COOCH), 4.11 (brm, 1H, (CH$_3$)$_2$CCHOH), 4.05 (brd, J = 2.7 Hz, 1H, CHOH), 3.32 (dq, J = 7.1, 0.7 Hz, 1H, C(O)CHCH$_3$), 3.05 (dd, J = 10.6, 3.4 Hz, 1H, CHOCCH$_3$), 2.76 (brs, 1H, OH), 2.47 (buried m, 1H, CH_2COOCH), 2.45 (s, 3H, N=C(CH_3)O), 2.39, (dd, J = 12.7, 0.8 Hz,

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CH_2COOCH), 2.06 (dd, J = 15.4, 3.5 Hz, 1H, $(CH_3)COCHCH_2CHO$), 2.00 (s, 3H, $CH{=}CCH_3$), 1.82 (m, 1H, $(CH_3)COCHCH_2CHO$), 1.77–1.70 (m, 3H), 1.51–1.34 (m, 4H), 1.35 (s, 3H, $C(CH_3)OCHCH_2$), 1.25 (s, 3H, $C(CH_3)_2$), 1.09 (d, J = 7.0 Hz, 3H, $CH(CH_3)$), 1.02 (s, 3H, $C(CH_3)_2$), 0.92 (d, J = 7.1 Hz, 3H, $CH(CH_3)$); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 223.2, 170.8, 161.3, 137.7, 137.5, 136.1, 116.2, 75.9, 74.4, 71.0, 65.4, 62.5, 51.3, 42.3, 38.5, 38.4, 33.3, 31.7, 31.2, 22.9, 21.6, 21.3, 18.2, 15.9, 15.3, 13.6, 12.5; FAB HRMS (NBA/CsI): m/e = 624.1921, $M+Cs^+$ calcd for $C_{27}H_{42}NO_7$ 624.1937.

Epoxides 31 and 32: epoxidation of lactone 29: Compound **29** (4.3 mg, 9.0 μmol) was epoxidized with *m*CPBA according to the procedure described above for **4** to yield a mixture of 20-oxa-epothilone B (**31**) and its α-epoxy diastereoisomer **32** (2.2 mg, 50% total yield, ca 5:1 by ^{1}H NMR). Purification by preparative thin-layer chromatography (silica gel, 5% MeOH in CH_2Cl_2) gave pure epoxide **31** (1.7 mg, 38%) as a white solid and epoxide **32** (0.3 mg, 7%).

31: R_f = 0.29 (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]_D^{22} = -28.0$ (c = 0.1, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$ = 3460, 2931, 1731, 1684, 1578, 1455, 1378, 1255, 1149, 1102, 1049, 978, 914, 726 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.56 (s, 1H, OCH=C), 6.34 (s, 1H, $CH{=}CCH_3$), 5.48 (dd, J = 8.4, 3.5 Hz, 1H, CH_2COOCH), 4.25 (br, 1H, $(CH_3)_2CCHOH$), 3.86 (br s, 1H, OH), 3.76 (br, 1H, $CHOH$), 3.31 (dq, J = 6.8, 6.7 Hz, 1H, $C(O)CHCH_3$), 2.86 (dd, J = 6.7, 4.2 Hz, 1H, $CHOCCH_3$), 2.62 (br, 1H, OH), 2.55 (dd, J = 13.5, 10.3 Hz, 1H, CH_2COOCH), 2.46 (dd, J = 13.5, 3.9 Hz, 1H, CH_2COOCH), 2.45 (s, 3H, $N{=}C(CH_3)O$), 2.05–1.99 (m, 2H), 1.97 (s, 3H, $CH{=}C(CH_3)$), 1.96–1.92 (m, 1H), 1.75–1.67 (m, 1H), 1.49–1.42 (m, 2H), 1.38 (s, 3H, $C(CH_3)OCHCH_2$), 1.27 (s, 3H, $C(CH_3)_2$), 1.26–1.24 (m, 1H), 1.14 (d, J = 6.8 Hz, 3H, $CH(CH_3)$), 1.13–1.08 (m, 2H), 1.05 (s, 3H, $C(CH_3)_2$), 0.95 (d, J = 7.0 Hz, 3H, $CH(CH_3)$); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 220.2, 171.0, 161.2, 137.5, 136.5, 135.9, 116.1, 77.1, 75.7, 73.2, 60.9, 59.7, 52.5, 43.8, 38.3, 36.7, 35.9, 32.4, 30.8, 21.3, 20.9, 19.1, 17.4, 16.8, 15.5, 14.3, 13.5; FAB HRMS (NBA/CsI): m/e = 624.1958, $M+Cs^+$ calcd for $C_{27}H_{41}NO_7$ 624.1937.

32: R_f = 0.27 (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]_D^{22} = -20.0$ (c = 0.02, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$ = 3458, 2931, 1729, 1681, 1578, 1458, 1378, 1256, 1152, 1102, 1049, 978, 914, 726 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.48 (s, 1H, OCH=C), 6.30 (s, 1H, $CH{=}CCH_3$), 5.45 (dd, J = 6.7, 6.1 Hz, 1H, CH_2COOCH), 4.25 (br, 1H, $(CH_3)_2CCHOH$), 3.74 (br, 1H, $CHOH$), 3.50 (br s, 1H, OH), 3.25 (dq, J = 6.7, 3.4 Hz, 1H, $C(O)CHCH_3$), 2.92 (t, J = 5.7 Hz, 1H, $CHOCCH_3$), 2.54 (dd, J = 15.2, 9.8 Hz, 1H, CH_2COOCH), 2.48 (dd, J = 15.2, 3.5 Hz, 1H, CH_2COOCH), 2.45 (s, 3H, $N{=}C(CH_3)O$), 2.00 (dd, J = 7.3, 5.8 Hz, 1H), 1.98 (s, 3H, $CH{=}C(CH_3)$), 1.90–1.70 (m, 2H), 1.69–1.67 (m, 1H), 1.45–1.38 (m, 2H), 1.35 (s, 3H, $C(CH_3)OCHCH_2$), 1.25 (s, 3H, $C(CH_3)_2$), 1.27–1.25 (m, 1H), 1.14 (d, J = 6.8 Hz, 3H, $CH(CH_3)$), 1.12–1.08 (m, 2H), 1.08 (s, 3H, $C(CH_3)_2$), 0.95 (d, J = 7.0 Hz, 3H, $CH(CH_3)$); FAB HRMS (NBA/NaI): m/e = 514.2795, $M+Na^+$ calcd for $C_{27}H_{41}NO_7$ 514.2781.

α,β-Unsaturated ester 33: A mixture of aldehyde **12** (13.35 g, 43.1 mmol) and stabilized ylide **13** (48.45 g, 129.4 mmol, 3.0 equiv [prepared from 4-bromo-1-butene by: 1) phosphonium salt formation, 2) anion formation with NaHMDS, and 3) quenching with MeOC(O)Cl])[27] in benzene (500 mL) was heated at reflux for 1 h. After the mixture had cooled to 25 °C, the solvent was removed under reduced pressure, and the residue was subjected to flash column chromatography (silica gel, 60% ether in hexanes) to afford α,β-unsaturated ester **33** (15.74 g, 90%): R_f = 0.53 (silica gel, 60% ether in hexanes); $[\alpha]_D^{22} = +8.8$ (c = 0.7, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$ = 2929, 2856, 1716, 1639, 1586, 1436, 1437, 1074, 835, 777 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.45 (s, 1H, OCH=C), 6.87 (dd, J = 7.4, 7.4 Hz, 1H, $CH{=}CCOOCH_3$), 6.21 (s, 1H, $CH{=}CCH_3$), 5.81–5.74 (m, 1H, $CH{=}CH_2$), 5.01–4.92 (m, 2H, $CH{=}CH_2$), 4.19 (dd, 1H, J = 7.6, 5.1 Hz, CHOSi), 3.70 (s, 3H, $COOCH_3$), 3.05 (d, J = 5.9 Hz, 2H, $CH_2CH{=}CH_2$), 2.44 (partially obscured m, 1H, CH_2CHOSi), 2.43 (s, 3H, $N{=}C(O)CH_3$), 2.36 (ddd, J = 12.6, 7.5, 5.1 Hz, 1H, CH_2CHOSi), 1.87 (s, 3H, $CH{=}CCH_3$), 0.86 (s, 9H, $SiC(CH_3)_3$), 0.02 (s, 3H, $Si(CH_3)_2$), −0.03 (s, 3H, $Si(CH_3)_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 167.8, 160.6, 141.3, 140.4, 137.87, 135.3, 130.7, 115.4, 115.0, 77.2, 51.7, 36.0, 30.9, 25.7, 18.1, 14.2, 13.8, −4.7, −5.1; FAB HRMS (NBA): m/e = 406.2430, $M+H^+$ calcd for $C_{22}H_{36}NO_4Si$ 406.2414.

Allylic alcohol 34: Methyl ester **33** (14.1 g, 34.7 mmol) was dissolved in THF (200 mL, 0.17 M) and cooled to −78 °C. DIBAL (122.0 mL, 1.0 M solution in CH_2Cl_2, 122.0 mmol, 3.0 equiv) was added dropwise at −78 °C, and the reaction mixture was stirred for 3 h. The reaction was quenched with MeOH (10.0 mL) at −78 °C, and then ether (300 mL) was added, followed by saturated aqueous sodium–potasium tartrate solution (300 mL). The resulting mixture was allowed to warm to room temperature and then stirred for 12 h. The organic layer was separated, and the aqueous phase extracted with ether (2 × 500 mL). The combined organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Flash column chromatography (silica gel, 60% ether in hexanes) furnished alcohol **34** (13.1 g, 99%): R_f = 0.22 (silica gel, 60% ether in hexanes); $[\alpha]_D^{22} = +5.2$ (c = 1.0, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$ = 3379, 2930, 1637, 1583, 1462, 1252, 1071, 837, 777 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.47 (s, 1H, OCH=C), 6.16 (s, 1H, $CH{=}CCH_3$), 5.77–5.72 (m, 1H, $CH{=}CH_2$), 5.49 (dd, J = 7.2, 7.1 Hz, 1H, $CH{=}CCH_2OH$), 5.03 (ddd, J = 18.3, 17.1, 1.3 Hz, 1H, $CH{=}CH_2$), 4.98 (ddd, J = 11.5, 10.0, 1.3 Hz, 1H, $CH{=}CH_2$), 4.13 (dd, J = 6.5, 6.3 Hz, 1H, CHOSi), 3.99 (s, 2H, CH_2OH), 2.84 (d AB q, J = 15.2, 6.6 Hz, 2H, $CH_2CH{=}CH_2$), 2.43 (s, 3H, $N{=}C(O)CH_3$), 2.32 (ddd, J = 14.4, 7.2, 7.2 Hz, 1H, CH_2CHOSi), 2.26 (ddd, J = 14.3, 7.1, 7.1 Hz, 1H, CH_2CHOSi), 1.84 (s, 3H, $CH{=}CCH_3$), 0.86 (s, 9H, $SiC(CH_3)_3$), 0.02 (s, 3H, $Si(CH_3)_2$), −0.02 (s, 3H, $Si(CH_3)_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 162.5, 142.8, 138.9, 136.6, 136.0, 125.0, 116.3, 116.1, 78.8, 67.9, 35.6, 33.4, 26.6, 19.0, 15.0, 14.7, −3.8, −4.1; FAB HRMS (NBA): m/e = 378.2458, $M+H^+$ calcd for $C_{21}H_{36}NO_3Si$ 378.2464.

Compound 35—chlorination of alcohol 34: Alcohol **34** (13.69 g, 36.3 mmol) was dissolved in CCl_4 (400 mL, 0.09 M) and Ph_3P (24.0 g, 91 mmol, 2.5 equiv) was added. The reaction mixture was stirred at 100 °C for 24 h and cooled to room temperature. The solvent was removed under reduced pressure. Flash column chromatography (silica gel, 10 → 60% ether in hexanes) furnished pure **35** (11.64 g, 81%): R_f = 0.68 (silica gel, 60% ether in hexanes); $[\alpha]_D^{22} = +7.8$ (c = 0.6, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$ = 2952, 2857, 1639, 1585, 1440, 1078, 836, 777, 637 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.48 (s, 1H, OCH=C), 6.19 (s, 1H, $CH{=}CCH_3$), 5.74–5.69 (m, 1H, $CH{=}CH_2$), 5.63 (dd, J = 7.3, 7.2 Hz, 1H, $CH_2CH{=}CCH_2Cl$), 5.56 (ddd, J = 17.1, 3.3, 1.6 Hz, 1H, $CH{=}CH_2$), 5.03 (ddd, J = 10.1, 2.9, 1.6 Hz, 1H, $CH{=}CH_2$), 4.14 (dd, J = 6.9, 5.9 Hz, 1H, CHOSi), 4.00 (s, 2H, CH_2Cl), 2.95 (dd, J = 15.3, 6.3 Hz, 1H, $CH_2CH{=}CH_2$), 2.91 (dd, J = 15.3, 6.5 Hz, 1H, $CH_2CH{=}CH_2$), 2.44 (s, 3H, $N{=}C(O)CH_3$), 2.34 (ddd, J = 14.8, 7.4, 7.4 Hz, 1H, CH_2CHOSi), 2.27 (ddd, J = 14.7, 7.1, 7.1 Hz, 1H, CH_2CHOSi), 1.87 (s, 3H, $CH{=}CCH_3$), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.03 (s, 3H, $Si(CH_3)_2$), −0.02 (s, 3H, $Si(CH_3)_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 161.5, 150.5, 142.5, 138.9, 136.1, 135.7, 129.6, 117.1, 116.2, 78.6, 50.7, 36.1, 33.2, 26.7, 19.0, 15.1, 14.7, −3.9, −4.1; FAB HRMS (NBA): m/e = 396.2144, $M+H^+$ calcd for $C_{21}H_{35}ClNO_2Si$ 396.2126.

Compound 36—reduction of 35: Compound **35** (11.64 g, 29.4 mmol) was dissolved in THF (400 mL, 0.07 M) and cooled to 0 °C. $LiEt_3BH$ (59.0 mL, 1.0 M solution in THF, 59.0 mmol, 2.0 equiv) was added dropwise, and the reaction mixture stirred at 0 °C for 1 h. Aqueous NaOH (10 mL, 3.0 N) solution was added, followed by ether (500 mL). The organic phase was washed with brine (2 × 100 mL), dried ($MgSO_4$), and concentrated. Flash column chromatography (silica gel, 20% ether in hexanes) furnished pure **36** (10.25 g, 97%): R_f = 0.40 (silica gel, 20% ether in hexanes); $[\alpha]_D^{22} = +8.7$ (c = 0.3, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$ = 2931, 2856, 1636, 1585, 1442, 1252, 1076, 776 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.47 (s, 1H, OCH=C), 6.16 (s, 1H, $CH{=}CCH_3$), 5.77–5.69 (m, 1H, $CH{=}CH_2$), 5.19 (dd, J = 7.2, 7.2 Hz, 1H, $CH_2CH{=}CCH_3$), 5.01 (ddd, J = 17.0, 3.5, 1.9 Hz, 1H, $CH{=}CH_2$), 4.96 (ddd, J = 10.1, 2.9, 1.5 Hz, 1H, $CH{=}CH_2$), 4.08 (dd, J = 6.5, 6.5 Hz, 1H, CHOSi), 2.78 (dd, J = 14.6, 6.5 Hz, 1H, $CH_2CH{=}CH_2$), 2.70 (dd, J = 14.7, 6.3 Hz, 1H, $CH_2CH{=}CH_2$), 2.43 (s, 3H, $N{=}C(O)CH_3$), 2.28 (ddd, J = 14.8, 7.4, 7.4 Hz, 1H, CH_2CHOSi), 2.21 (ddd, J = 14.5, 7.1, 7.1 Hz, 1H, CH_2CHOSi), 1.85 (s, 3H, $CH{=}CCH_3$), 1.65 (s, 3H, $CH_2CH{=}CCH_3$), 0.87 (s, 9H, $SiC(CH_3)_3$), 0.02 (s, 3H, $Si(CH_3)_2$), −0.02 (s, 3H, $Si(CH_3)_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 161.4, 143.1, 139.0, 136.9, 135.9, 135.3, 123.2, 115.9, 79.3, 37.4, 36.1, 26.7, 24.3, 19.0, 15.0, 14.7, −3.9, −4.1; FAB HRMS (NBA): m/e = 396.2144, $M+H^+$ calcd for $C_{21}H_{34}ClNO_2Si$ 396.2126.

Primary alcohol 37—selective hydroboration of olefinic compound 36: Compound **36** (10.25 g, 28.34 mmol) was dissolved in THF (30.0 mL, 0.95 M), and the solution cooled to 0 °C. 9-BBN (62.36 mL, 0.5 M solution in THF, 62.36 mmol, 1.1 equiv) was added, and the reaction mixture stirred for 2 h at

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0 °C. Aqueous NaOH (57 mL, 3 N solution, 171 mmol, 7.2 equiv) was added with stirring, followed by H_2O_2 (20 mL, 30%, aqueous solution). Stirring was continued for 0.5 h at 0 °C, and the reaction mixture was then diluted with ether (300 mL). The organic solution was separated, and the aqueous phase extracted with ether (2 × 200 mL). The combined organic layer was washed with brine (2 × 50 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash column chromatography (silica gel, 60% ether in hexanes) furnished primary alcohol **37** as a colorless oil (9.9 g, 92%): $R_f = 0.22$ (silica gel, 60% ether in hexanes); $[\alpha]_D^{22} = +1.3$ ($c = 0.3$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3407$, 2929, 1694, 1584, 1461, 1252, 1098, 669 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 7.45$ (s, 1H, OCH=C), 6.16 (s, 1H, C*H*=CCH$_3$), 5.15 (dd, $J = 7.2$, 7.2 Hz, 1H, CH$_2$C*H*=CCH$_3$), 4.10 (dd, $J = 6.7$, 6.2 Hz, 1H, CHOSi), 3.60 (dd, $J = 10.4$, 6.0 Hz, 2H, C*H*$_2$OH), 2.43 (s, 3H, N=C(O)CH$_3$), 2.30 (ddd, $J = 14.2$, 7.4, 7.4 Hz, 1H, C*H*$_2$CHOSi), 2.21 (ddd, $J = 14.4$, 7.3, 7.3 Hz, 1H, C*H*$_2$CHOSi), 2.09 (dd, $J = 7.7$, 7.6 Hz, 2H, C*H*$_2$CH$_2$CH$_2$OH), 1.86 (s, 3H, CH=CC*H*$_3$), 1.67 (s, 3H, CH$_2$CH=CC*H*$_3$), 1.65–1.58 (m, 2H, C*H*$_2$CH$_2$OH), 0.87 (s, 9H, SiC(CH$_3$)$_3$), 0.03 (s, 3H, Si(CH$_3$)$_2$), −0.01 (s, 3H, Si(CH$_3$)$_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$): $\delta = 161.5$, 143.2, 138.9, 137.1, 136.0, 123.0, 115.8, 79.4, 63.4, 36.2, 31.6, 28.9, 26.7, 24.2, 19.1, 15.2, 14.6, −3.9, −4.1; FAB HRMS (NBA): $m/e = 380.2636$, $M+H^+$ calcd for $C_{21}H_{38}NO_3Si$ 380.2621.

Iodide 11—iodination of alcohol 37: Iodide **11** (10.58 g, 89%) was obtained from alcohol **37** (9.9 g, 26.0 mmol) according to the procedure described above for **17**: $R_f = 0.65$ (silica gel, 60% ether in hexanes); $[\alpha]_D^{22} = +3.0$ ($c = 0.4$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 2928$, 1585, 1461, 1096, 837 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 7.46$ (s, 1H, OCH=C), 6.17 (s, 1H, C*H*=CCH$_3$), 5.17 (dd, $J = 7.5$, 6.9 Hz, 1H, CH$_2$C*H*=CCH$_3$), 4.08 (dd, $J = 6.8$, 6.1 Hz, 1H, CHOSi), 3.14 (dd, $J = 7.1$, 7.0 Hz, 2H, CH$_2$I), 2.44 (s, 3H, N=C(O)CH$_3$), 2.30 (ddd, $J = 14.2$, 7.0, 7.0 Hz, 1H, C*H*$_2$CHOSi), 2.21 (ddd, $J = 14.3$, 7.1, 7.1 Hz, 1H, C*H*$_2$CHOSi), 2.14–2.03 (m, 2H), 1.93–1.86 (m, 2H), 1.87 (s, 3H, CH=CC*H*$_3$), 1.66 (s, 3H, CH$_2$CH=CC*H*$_3$) 0.87 (s, 9H, SiC(CH$_3$)$_3$), 0.03 (s, 3H, Si(CH$_3$)$_2$), −0.02 (s, 3H, Si(CH$_3$)$_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$): $\delta = 161.4$, 143.1, 139.0, 135.9, 135.6, 123.8, 115.9, 79.3, 36.3, 33.6, 32.8, 26.7, 24.3, 19.0, 15.2, 14.7, 7.4, −3.9, −4.1; FAB HRMS (NBA): $m/e = 490.1627$, $M+H^+$ calcd for $C_{21}H_{37}INO_2Si$ 490.1639.

Hydrazone 38—alkylation of SAMP hydrazone 10 with iodide 11: SAMP hydrazone **10** (4.78 g, 28.1 mmol, 1.3 equiv) in THF (15.0 mL) was added to a freshly prepared solution of LDA [diisopropylamine (4.0 mL, 30.5 mmol, 1.4 equiv) was added to *n*BuLi (18.9 mL, 1.60 M solution in hexanes, 30.5 mmol, 1.4 equiv) in 30.0 mL of THF at 0 °C] at 0 °C. After stirring at this temperature for 16 h, the resulting yellow solution was cooled to −100 °C, and a solution of iodide **11** (10.58 g, 21.6 mmol, 1.0 equiv) in THF (30.0 mL) was added dropwise over a period of 5 min. The mixture was allowed to warm to −20 °C over 10 h, and then poured into saturated aqueous NH_4Cl solution (50 mL) and extracted with ether (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated. Purification by flash column chromatography on silica gel (40% ether in hexanes) provided hydrazone **38** (9.91g, 86%, de >98% by ^1H NMR) as a yellow oil: $R_f = 0.22$ (silica gel, 40% ether in hexanes); $[\alpha]_D^{22} = -28.0$ ($c = 0.7$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 2930$, 1726, 1585, 1460, 1100, 837, 777 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 7.44$ (s, 1H, OCH=C), 6.47 (d, $J = 6.5$ Hz, 1H, CNH), 6.16 (s, 1H, C*H*=CCH$_3$), 5.10 (dd, $J = 7.1$, 6.9 Hz, 1H, CH$_2$C*H*=CCH$_3$), 4.06 (dd, $J = 6.6$, 6.3 Hz, 1H, CHOSi), 3.56 (dd, $J = 6.2$, 3.8 Hz, 1H, C*H*$_2$OCH$_3$), 3.41 (dd, $J = 9.2$, 6.9 Hz, 1H, C*H*$_2$OCH$_3$), 3.36 (s, 3H, CH$_2$OC*H*$_3$), 3.35–3.32 (m, 2H, CH$_2$N), 2.74–2.64 (m, 1H), 2.43 (s, 3H, N=C(O)CH$_3$), 2.31–2.17 (m, 3H), 2.04–1.84 (m, 5H), 1.84 (s, 3H, CH=CC*H*$_3$), 1.77–1.72 (m, 1H), 1.63 (s, 3H, CH$_2$CH=CC*H*$_3$), 1.42–1.22 (m, 4H), 1.01 (d, $J = 6.7$ Hz, CHC*H*$_3$), 0.87 (s, 9H, SiC(CH$_3$)$_3$), 0.02 (s, 3H, Si(CH$_3$)$_2$), −0.02 (s, 3H, Si(CH$_3$)$_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$): $\delta = 160.5$, 144.4, 142.4, 138.1, 136.8, 135.0, 121.4, 115.0, 78.6, 74.8, 63.6, 59.2, 50.5, 37.1, 35.4, 35.2, 32.0, 26.5, 25.8, 25.5, 23.4, 22.1, 19.00, 14.2, 13.8, −4.7, −5.0; FAB HRMS (NBA/CsI): $m/e = 664.2933$, $M+Cs^+$ calcd for $C_{30}H_{53}N_3O_3Si$ 664.2911.

Nitrile 39: The magnesium salt of monoperoxyphthalic acid (MMPP·6H_2O, 2.82 g, 45.6 mmol, 2.5 equiv) was suspended in a rapidly stirred mixture of MeOH and pH 7 phosphate buffer (2:1, 300 mL) at 0 °C. Hydrazone **38** (9.7 g, 18.23 mmol, 1.0 equiv) in MeOH (20 mL) was added dropwise, and the mixture was stirred at 0 °C until the reaction was complete by TLC (ca. 1 h). The resulting suspension was placed in a separating funnel along with ether (150 mL) and saturated aqueous $NaHCO_3$ solution (50 mL). The organic layer was separated, and the aqueous phase extracted with ether (100 mL). The combined organic solution was washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$), and concentrated. Flash column chromatography (silica gel, 40% ether in hexanes) afforded nitrile **39** (3.5 g, 46%) as a colorless oil: $R_f = 0.42$ (silica gel, 40% ether in hexanes); $[\alpha]_D^{22} = +10.6$ ($c = 1.0$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 2931$, 2237, 1584, 1452, 1099, 940, 837, 777 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 7.46$ (s, 1H, OCH=C), 6.16 (s, 1H, C*H*=CCH$_3$), 5.14 (dd, $J = 7.3$, 6.8 Hz, 1H, CH$_2$C*H*=CCH$_3$), 4.06 (dd, $J = 6.6$, 6.1 Hz, 1H, CHOSi), 2.57 (m, 1H, C(*H*)CH$_3$), 2.43 (s, 3H, N=C(O)CH$_3$), 2.22 (ddd, $J = 14.1$, 7.3, 7.3, 1H, C*H*$_2$CHOSi), 2.18 (ddd, $J = 14.4$, 7.5, 7.5 Hz, 1H, C*H*$_2$CHOSi), 2.00 (m, 2H), 1.85 (s, 3H, CH=CC*H*$_3$), 1.65 (s, 3H, CH$_2$CH=CC*H*$_3$) 1.64–1.43 (m, 4H), 1.29 (d, $J = 7.0$ Hz, CHC*H*$_3$), 0.86 (s, 9H, SiC(CH$_3$)$_3$), 0.02 (s, 3H, Si(CH$_3$)$_2$), −0.03 (s, 3H, Si(CH$_3$)$_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 161.5$, 143.1, 138.9, 136.5, 136.0, 123.8, 123.1, 115.9, 79.3, 36.2, 34.6, 32.4, 26.7, 26.3, 26.1, 24.2, 19.0, 18.9, 15.1, 14.7, −3.8, −4.1; FAB HRMS (NBA): $m/e = 417.2953$, $M+H^+$ calcd for $C_{24}H_{41}N_2O_2Si$ 417.2937.

Aldehyde 6: Nitrile **39** (1.30 g, 3.1 mmol) was dissolved in toluene (50 mL, 0.06 M) and cooled to −78 °C. DIBAL (6.3 mL, 1.0 M solution in toluene, 6.3 mmol, 2.0 equiv) was added dropwise at −78 °C, and the reaction mixture was stirred at this temperature until its completion was verified by TLC (ca. 1 h). Methanol (5 mL) and aqueous HCl (5 mL, 1.0 N solution) were sequentially added, and the resulting mixture was brought up to 0 °C and stirred at that temperature for 30 min. Ether (50 mL) and water (20 mL) were added, and the organic layer was separated. The aqueous phase was extracted with ether (2 × 50 mL) and the combined organic solution was washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Flash column chromatography (silica gel, 40% ether in hexanes) furnished pure aldehyde **6** (1.09 g, 84%): $R_f = 0.41$ (silica gel, 40% ether in hexanes); $[\alpha]_D^{22} = +8.0$ ($c = 0.4$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 2931$, 2849, 1725, 1584, 1461, 1384, 1251, 1101, 837, 776, 671 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 9.60$ (d, $J = 2.0$ Hz, 1H, CHO), 7.47 (s, 1H, OCH=C), 6.17 (s, 1H, C*H*=CCH$_3$), 5.14 (dd, $J = 6.1$, 5.5 Hz, 1H, CH$_2$C*H*=CCH$_3$), 4.07 (dd, $J = 6.5$, 6.5 Hz, 1H, CHOSi), 2.45 (s, 3H, N=C(O)CH$_3$), 2.33–2.20 (m, 3H), 2.03–2.01 (m, 2H), 1.87 (s, 3H, CH=CC*H*$_3$), 1.71–1.65 (m, 1H), 1.66 (d, $J = 1.0$ Hz, 3H, CH$_2$CH=CC*H*$_3$), 1.42–1.29 (m, 3H), 1.08 (d, $J = 7.0$ Hz, 3H, C*H*$_3$CH), 0.88 (s, 9H, SiC(CH$_3$)$_3$), 0.03 (s, 3H, Si(CH$_3$)$_2$), −0.01 (s, 3H, Si(CH$_3$)$_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 206.0$, 161.4, 143.1, 139.0, 137.0, 135.9, 122.8, 115.9, 79.4, 47.1, 36.2, 32.7, 31.2, 26.7, 26.1, 24.2, 19.1, 15.1, 14.7, 14.2, −3.8, −4.1.

Tris(silyl ethers) 21 and 22—aldol reaction of ketone 7 with aldehyde 6: A solution of ketone **7** (1.34 g, 3.3 mmol, 1.4 equiv) in THF (5.0 mL) was added dropwise to a freshly prepared solution of LDA [diisopropylamine (468 μL, 3.6 mmol) was added to *n*BuLi (2.23 mL, 1.60 M solution in hexanes, 3.7 mmol) in 10 mL of THF at 0 °C] in THF (5.0 mL) at −78 °C. After the mixture had been stirred for 2 h at −78 °C, a solution of aldehyde **6** (1.0 g, 2.4 mmol, 1.0 equiv) in THF (5.0 mL) was added dropwise. The resulting mixture was stirred for 15 min at −78 °C, and then quenched by dropwise addition of saturated aqueous NH_4Cl solution (7 mL). The aqueous phase was extracted with ether (3 × 20 mL), and the combined organic layer was dried ($MgSO_4$) and concentrated. Purification by flash column chromatography (silica gel, 20% ether in hexanes) provided pure **21** (1.154 g, 59%) and **22** (273 mg, 14%).

21: colorless oil; $R_f = 0.46$ (silica gel, 40% ether in hexanes); $[\alpha]_D^{22} = -17.8$ ($c = 0.5$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3494$, 2925, 2861, 1683, 1583, 1253, 1099 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 7.43$ (s, 1H, OCH=C), 6.15 (s, 1H, C*H*=CCH$_3$), 5.08 (dd, $J = 7.0$, 6.7 Hz , 1H, C(CH$_3$)=C*H*CH$_2$), 4.05 (dd, $J = 6.5$, 6.4 Hz, 1H, (CH$_3$)$_2$CC*H*OSi), 3.89 (dd, $J = 7.5$, 2.8 Hz, 1H, CH$_2$C*H*OSi), 3.67–3.62 (m, 1H, CH(CH$_3$)C*H*OH), 3.68–3.55 (m, 2H, CH$_2$OSi), 3.28 (m, 1H, C(O)C*H*(CH$_3$)), 2.42 (s, 3H, N=C(CH$_3$)O), 2.27–2.15 (m, 2H, C(CH$_3$)=CHC*H*$_2$), 2.13–1.94 (m, 2H, C*H*$_2$C(CH$_3$)=CH), 1.84 (s, 3H, CH=C(CH$_3$)), 1.64 (s, 3H, C(CH$_3$)=CHCH$_2$), 1.80–1.46 (m, 5H), 1.34–1.25 (m, 2H), 1.19 (s, 3H, C(CH$_3$)$_2$), 1.07 (s, 3H, C(CH$_3$)$_2$), 1.01 (d, $J = 6.9$ Hz, 3H, CH(CH$_3$)), 0.88 (s, 9H, SiC(CH$_3$)$_3$), 0.87 (s, 9H, SiC(CH$_3$)$_3$), 0.86, (s, 9H, SiC(CH$_3$)$_3$), 0.80 (d, $J = 6.7$ Hz, 3H, CH(CH$_3$)), 0.10 (s, 3H, Si(CH$_3$)$_2$), 0.09 (s, 3H, Si(CH$_3$)$_2$), 0.06 (s, 3H, Si(CH$_3$)$_2$), 0.02 (s, 6H, Si(CH$_3$)$_2$), 0.01 (s, 3H, Si(CH$_3$)$_2$), −0.03 (s, 3H, Si(CH$_3$)$_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$): $\delta = 222.9$, 161.2, 143.1, 139.0, 137.7, 135.8, 122.1, 115.8, 79.6, 75.7, 75.0, 61.4, 54.9, 42.3, 38.8, 36.5, 36.2, 33.9, 33.3, 27.0, 26.9, 26.8, 24.5, 23.9, 21.5, 19.3, 19.2, 19.1, 16.4, 15.2, 14.8, 10.6, −2.7, −3.0,

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−3.7, −3.9, −4.2; FAB HRMS (NBA/CsI): m/e = 954.4932, $M+Cs^+$ calcd for $C_{45}H_{87}NO_6Si_3$ 954.4896.

22: colorless oil; R_f = 0.43 (silica gel, 40% ether in hexanes); IR (thin film): $\tilde{\nu}_{max}$ = 3501, 2927, 1687, 1585, 1464, 1253, 1098, 776 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 7.44 (s, 1H, OCH=C), 6.16 (s, 1H, C*H*=CCH$_3$), 5.11 (dd, J = 8.4, 7.2 Hz, 1H, C(CH$_3$)=C*H*CH$_2$), 4.08–4.04 (m, 1H, (CH$_3$)$_2$CC*H*OSi), 3.67–3.57 (m, 3H, CH$_2$C*H*OSi, CH$_2$OSi), 3.38–3.34 (m, 1H, CH(CH$_3$)C*H*OH), 3.31–3.24 (m, 1H, C(O)C*H*(CH$_3$)), 2.43 (s, 3H, N=C(CH$_3$)O), 2.32–2.16 (m, 2H, C(CH$_3$)=CHC*H*$_2$), 1.85 (s, 3H, CH=C(C*H*$_3$)), 1.99–1.84 (m, 2H, C*H*$_2$C(CH$_3$)=CH), 1.65 (s, 3H, C(C*H*$_3$)=CHCH$_2$), 1.55–1.44 (m, 5H), 1.35–1.27 (m, 2H), 1.20 (s, 3H, C(CH$_3$)$_2$), 1.11 (s, 3H, C(CH$_3$)$_2$), 1.08 (d, J = 6.9 Hz, 3H, CH(C*H*$_3$)), 0.96 (d, J = 7.0 Hz, 3H, CH(C*H*$_3$)), 0.89 (s, 9H, SiC(CH$_3$)$_3$), 0.87 (s, 9H, SiC(CH$_3$)$_3$), 0.86 (s, 9H, SiC(CH$_3$)$_3$), 0.09 (s, 3H, Si(CH$_3$)$_2$), 0.07 (s, 3H, Si(CH$_3$)$_2$), 0.04 (s, 3H, Si(CH$_3$)$_2$), 0.03 (s, 6H, Si(CH$_3$)$_2$), −0.03 (s, 3H, Si(CH$_3$)$_2$); FAB HRMS (NBA/CsI): m/e = 954.4928, $M+Cs^+$ calcd for $C_{43}H_{83}NO_6Si_3$ 954.4896.

Tetra(silyl ether) 23: Tetra(silyl ether) **23** (1.22 g, 93%) was obtained from compound **21** (1.154 g, 1.4 mmol) according to the procedure described above for **21′**. **23**: R_f = 0.64 (silica gel, 40% ether in hexanes); $[\alpha]_D^{22}$ = −15.8 (c = 0.5, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$ = 2931, 1695, 1587, 1465, 1384, 1253, 1098, 942, 671 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 7.44 (s, 1H, OCH=C), 6.16 (s, 1H, C*H*=CCH$_3$), 5.09 (dd, J = 6.9, 6.7 Hz, 1H, C(CH$_3$)=C*H*CH$_2$), 4.06 (dd, J = 6.8, 6.0 Hz, 1H, (CH$_3$)$_2$CC*H*OSi), 3.88 (dd, J = 7.5, 2.5 Hz, 1H, CH$_2$C*H*OSi), 3.75 (dd, J = 6.5, 1.9 Hz, 1H, CH(CH$_3$)C*H*OSi), 3.68–3.64 (m, 1H, CH$_2$OSi), 3.60–3.54 (m, 1H, CH$_2$OSi), 3.13 (dd, J = 6.8, 6.7 Hz, 1H, C(O)C*H*(CH$_3$)), 2.43 (s, 3H, N=C(CH$_3$)O), 2.25–2.15 (m, 2H, C(CH$_3$)=CHC*H*$_2$), 2.01–1.94 (m, 2H, C*H*$_2$C(CH$_3$)=CH), 1.85 (s, 3H, CH=C(C*H*$_3$)), 1.64 (s, 3H, C(C*H*$_3$)=CHCH$_2$), 1.50–1.44 (m, 5H), 1.34–1.23 (m, 2H), 1.21 (s, 3H, C(CH$_3$)$_2$), 1.03 (d, J = 6.8 Hz, 3H, CH(C*H*$_3$)), 1.01 (s, 3H, C(CH$_3$)$_2$), 0.91–0.83 (m, 39H, CH(C*H*$_3$), 4SiC(CH$_3$)$_3$), 0.08 (s, 3H, Si(CH$_3$)$_2$), 0.06 (s, 3H, Si(CH$_3$)$_2$), 0.05 (s, 3H, Si(CH$_3$)$_2$), 0.02 (s, 3H, Si(CH$_3$)$_2$), 0.02 (s, 6H, Si(CH$_3$)$_2$), 0.01 (s, 3H, Si(CH$_3$)$_2$), −0.03 (s, 3H, Si(CH$_3$)$_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 219.1, 161.4, 143.1, 139.1, 137.6, 135.9, 122.2, 115.8, 79.4, 78.3, 74.9, 61.8, 54.5, 45.9, 39.8, 38.9, 36.1, 33.4, 31.9, 27.1, 27.0, 26.8, 26.7, 25.3, 24.3, 19.3, 19.2, 19.1, 19.0, 18.3, 16.0, 15.1, 14.7, −2.8, −2.9, −3.1, −3.8, −4.1, −4.4, −4.5; FAB HRMS (NBA/CsI): m/e = 1068.5807, $M+Cs^+$ calcd for $C_{51}H_{101}NO_6Si_4Cs$ 1068.5760.

Alcohol 24: Compound **23** (1.12 g, 1.2 mmol) was dissolved in CH_2Cl_2/MeOH (1:1, 18.0 mL, 0.07 M). The solution was cooled to 0 °C and CSA (278 mg, 1.2 mmol, 1.0 equiv) was added over a 5 min period. The mixture was then stirred for 3 h at −5 °C. Et_3N (2.0 mL) was added, and the solvents were removed under reduced pressure. Flash column chromatography (silica gel, 40% ether in hexanes) furnished the desired alcohol **24** (934 mg, 95%). **24**: R_f = 0.32 (silica gel, 40% ether in hexanes); $[\alpha]_D^{22}$ = −11.0 (c = 0.2, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$ = 3432, 2934, 2856, 1692, 1464, 1378, 1254, 1075, 988, 775 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.45 (s, 1H, OCH=C), 6.17 (s, 1H, C*H*=CCH$_3$), 5.10 (dd, J = 7.0, 7.0 Hz , 1H, C(CH$_3$)=C*H*CH$_2$), 4.10–4.05 (m, 2H, (CH$_3$)$_2$CC*H*OSi, CH$_2$C*H*OSi), 3.78 (dd, J = 7.0, 1.0 Hz, 1H, CH(CH$_3$)C*H*OSi), 3.63 (br m, 2H, C*H*$_2$OH), 3.12 (p, J = 7.5 Hz, 1H, C(O)C*H*(CH$_3$)), 2.44 (s, 3H, N=C(CH$_3$)O), 2.26–2.19 (m, 2H, C(CH$_3$)=CHC*H*$_2$), 1.85 (s, 3H, CH=C(C*H*$_3$)), 2.14–1.92 (m, 2H, C*H*$_2$C(CH$_3$)=CH), 1.64 (s, 3H, C(C*H*$_3$)=CHCH$_2$), 1.70–1.55 (m, 2H), 1.42–1.21 (m, 3H), 1.22 (s, 3H, C(CH$_3$)$_2$), 1.19–1.04 (m, 2H), 1.06 (s, 3H, C(CH$_3$)$_2$), 1.05 (d, J = 6.7 Hz, 3H, CH(C*H*$_3$)), 0.92–0.85 (m, 30H, CH(C*H*$_3$), 3SiC(CH$_3$)$_3$), 0.10 (s, 3H, Si(CH$_3$)$_2$), 0.06 (s, 9H, Si(CH$_3$)$_2$), 0.03 (s, 3H, Si(CH$_3$)$_2$), −0.02 (s, 3H , Si(CH$_3$)$_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 219.1, 162.1, 142.2, 134.9, 130.7, 128.7, 121.3, 114.8, 77.4, 72.9, 60.1, 53.6, 44.9, 38.6, 38.2, 35.2, 32.4, 30.6, 26.1, 25.9, 24.7, 23.6, 19.1, 18.4, 18.1, 18.0, 17.6, 15.5, 13.9, −3.7, −3.9, −4.0, −4.8, −5.1; FAB HRMS (NBA/CsI): m/e = 954.4860, $M+Cs^+$ calcd for $C_{45}H_{87}NO_6Si_3$ 954.4896.

Aldehyde 25—oxidation of alcohol 24: Aldehyde **25** (736 mg, 80%) was obtained from alcohol **24** (930 mg, 0.305 mmol, 1.0 equiv) according to the procedure described above for **24′**. **25**: R_f = 0.25 (silica gel, 20% ether in hexanes); $[\alpha]_D^{22}$ = −11.6 (c = 0.3, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$ = 2932, 2857, 1727, 1692, 1465, 1384, 1253, 1093, 990, 837, 776 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 9.75 (m, 1H, CHO), 7.44 (s, 1H, OCH=C), 6.16 (s, 1H, C*H*=CCH$_3$), 5.09 (dd, J = 7.1, 6.8 Hz, 1H, C(CH$_3$)=C*H*CH$_2$), 4.46 (dd, 1H, J = 5.1, 4.9 Hz, (CH$_3$)$_2$CC*H*OSi), 4.05 (dd, J = 6.4, 5.7 Hz, 1H, CH$_2$C*H*OSi), 3.75 (dd, J = 7.3, 1.9 Hz, 1H, CH(CH$_3$)C*H*OSi), 3.11 (p, J = 7.1 Hz, 1H, C(O)C*H*(CH$_3$)), 2.50 (ddd, J = 15.4, 4.5, 1.5 Hz, 1H, C*H*$_2$CHO), 2.43 (s, 3H, N=C(CH$_3$)O), 2.39 (ddd, J = 15.5, 5.5, 2.6 Hz, 1H, C*H*$_2$CHO), 2.24–2.13 (m, 2H, C(CH$_3$)=CHC*H*$_2$), 1.97–1.89 (m, 2H, C*H*$_2$C(CH$_3$)=CH), 1.84 (s, 3H, CH=C(C*H*$_3$)), 1.63 (s, 3H, C(C*H*$_3$)=CHCH$_2$), 1.50–1.20 (m, 5H), 1.22 (s, 3H, C(CH$_3$)$_2$), 1.05 (s, 3H, C(CH$_3$)$_2$), 1.02 (d, J = 6.9 Hz, 3H, CH(C*H*$_3$)), 0.88–0.82 (m, 30H, CH(C*H*$_3$), 3SiC(CH$_3$)$_3$), 0.08 (s, 3H, Si(CH$_3$)$_2$), 0.05 (s, 3H, Si(CH$_3$)$_2$), 0.04 (s, 3H, Si(CH$_3$)$_2$), 0.03 (s, 3H, Si(CH$_3$)$_2$), 0.02 (s, 3H, Si(CH$_3$)$_2$), −0.03 (s, 3H, Si(CH$_3$)$_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 219.3, 202.0, 161.4, 143.1, 139.0, 137.6, 135.9, 122.3, 115.9, 79.4, 78.4, 72.1, 54.3, 50.4, 46.0, 39.6, 36.1, 33.4, 31.6, 27.0, 26.7, 26.6, 24.9, 24.3, 19.6, 19.3, 18.9, 16.4, 15.0, 14.7, −2.7, −2.9, −3.2, −3.6, −3.8, −4.1; FAB HRMS (NBA/CsI): m/e = 952.4702, $M+Cs^+$ calcd for $C_{45}H_{85}NO_6Si_3$ 952.4739.

Carboxylic acid 26—oxidation of aldehyde 25: Carboxylic acid **26** (727 mg, 97%) was obtained from aldehyde **25** (736 mg, 0.90 mmol) according to the procedure described above for **25′**. **26**: R_f = 0.27 (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]_D^{22}$ = + 0.4 (c = 0.3, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$ = 3335, 2857, 1711, 1465, 1253, 1085, 835 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 7.46 (s, 1H, OCH=C), 6.31 (s, 1H, C*H*=CCH$_3$), 5.14 (dd, J = 7.6, 7.4 Hz, 1H, (CH$_3$)C=C*H*CH$_2$), 4.40 (dd, J = 6.9, 2.9 Hz, 1H, (CH$_3$)$_2$CC*H*OSi), 4.11 (dd, J = 7.9, 5.2 Hz, 1H, CH$_2$C*H*OSi), 3.72 (dd, J = 5.5, 2.1 Hz, 1H, CH(CH$_3$)C*H*OSi), 3.14 (p, J = 6.6 Hz, 1H, C(O)C*H*(CH$_3$)), 2.44 (s, 3H, N=C(CH$_3$)O), 2.42 (dd, J = 16.6, 2.8 Hz, C*H*$_2$COOH), 2.44 (dd, J = 16.4, 3.1 Hz, 1H, C*H*$_2$COOH), 2.32 (dd, J = 16.4, 7.0 Hz, 1H, C*H*$_2$COOH), 2.26–2.04 (m, 3H, C*H*$_2$C(CH$_3$)=CH, CH$_2$C(CH$_3$)=CHC*H*$_2$), 1.82 (s, 3H, CH=C(C*H*$_3$)), 1.92–1.80 (m, 1H), 1.66 (s, 3H, CH$_2$C(C*H*$_3$)=CH), 1.51–1.36 (m, 4H), 1.15 (s, 3H, C(CH$_3$)$_2$), 1.14 (s, 3H, C(CH$_3$)$_2$), 1.21–1.09 (m, 1H), 1.05 (d, J = 6.7 Hz, 3H, CH(C*H*$_3$)), 0.90–0.85 (m, 30H, CH(C*H*$_3$), 3SiC(CH$_3$)$_3$), 0.10 (s, 3H, Si(CH$_3$)$_2$), 0.07 (s, 3H, Si(CH$_3$)$_2$), 0.06 (s, 3H, Si(CH$_3$)$_2$), 0.02 (s, 3H, Si(CH$_3$)$_2$), 0.00 (s, 3H, Si(CH$_3$)$_2$), −0.04 (s, 3H, Si(CH$_3$)$_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 219.4, 176.1, 161.9, 144.3, 138.5, 138.1, 135.7, 122.3, 115.3, 79.7, 73.9, 54.8, 45.1, 40.8, 40.2, 36.2, 33.3, 32.4, 27.1, 27.0, 26.9, 24.4, 24.3, 19.4, 19.3, 19.1, 17.4, 16.5, 15.1, 14.4, −3.0, −3.2, −3.3, −3.7, −3.9, −4.1; FAB HRMS (NBA/CsI): m/e = 968.4720, $M+Cs^+$ calcd for $C_{45}H_{85}NO_7Si_3$ 968.4688.

Hydroxyacid 5—selective desilylation of tris(silyl ether) 26: Hydroxyacid **5** (130 mg, 65%) was obtained from tris(silyl ether) **26** (234 mg, 0.28 mmol) according to the procedure described above for **26′**. **5**: R_f = 0.38 (silica gel, 12% MeOH in CH_2Cl_2); $[\alpha]_D^{22}$ = − 23.5 (c = 0.2, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$ = 3387, 2932, 2854, 1721, 1695, 1460, 1380, 1253, 1088, 1087, 835, 776 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 7.47 (s, 1 H OCH=C), 6.36 (s, 1H, C*H*=CCH$_3$), 5.15 (dd, 1H, J = 7.2, 7.0 Hz, CH$_3$C=C*H*CH$_2$), 4.39 (dd, J = 6.2, 3.8 Hz, 1H, (CH$_3$)$_2$CC*H*OSi), 4.13 (dd, J = 6.8, 6.6 Hz, 1H, CH$_2$C*H*OH), 3.75 (d, J = 6.6 Hz, 1H, CH(CH$_3$)C*H*OSi), 3.13 (dq, J = 6.9, 6.7 Hz, 1H, C(O)C*H*CH$_3$), 2.45 (s, 3H, N=C(CH$_3$)O), 2.44 (obscured m, 1H, C*H*$_2$COOH), 2.33–2.28 (m, 3H, C*H*$_2$C(CH$_3$)=CH, C*H*$_2$COOH), 2.13–2.08 (m, 1H, C(CH$_3$)=CHC*H*$_2$), 1.97–1.90 (m, 1H, C(CH$_3$)=CHC*H*$_2$), 1.88 (s, 3H, CH=C(C*H*$_3$)), 1.69 (s, 3H, CH$_2$C(C*H*$_3$)=CH), 1.53–1.35 (m, 5H), 1.17 (s, 3H, C(CH$_3$)$_2$), 1.11 (s, 3H, C(CH$_3$)$_2$), 1.05 (d, J = 6.8 Hz, 3H, CH(C*H*$_3$)), 0.92–0.83 (m, 21H, CH(C*H*$_3$), SiC(CH$_3$)$_3$), 0.09 (s, 3H, Si(CH$_3$)$_2$), 0.05 (s, 6H, Si(CH$_3$)$_2$), 0.03 (s, 3H, Si(CH$_3$)$_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 218.9, 175.9, 161.9, 142.8, 140.4, 138.4, 136.0, 120.9, 115.8, 74.3, 53.3, 45.5, 41.0, 39.9, 35.0, 33.3, 32.1, 27.0, 26.9, 26.1, 24.5, 24.0, 19.3, 19.0, 17.9, 16.8, 15.8, 15.1, 14.4, −2.9, −3.1, −3.2, −3.7; FAB HRMS (NBA/CsI): m/e = 854.3854, $M+Cs^+$ calcd for $C_{39}H_{71}NO_7Si_2$ 854.3823.

Lactone 27—macrolactonization of hydroxyacid 5: A solution of hydroxyacid **5** (30 mg, 0.041 mmol) in THF (600 μL) was treated at 0 °C with Et_3N (13 μL, 0.093 mmol, 2.2 equiv) and 2,4,6-trichlorobenzoyl chloride (8.5 μL, 0.054 mmol, 1.3 equiv). The reaction mixture was stirred at 0 °C for 1 h, and then added by means of a syringe pump over 3 h to a solution of 4-DMAP (10 mg, 0.083 mmol, 2.0 equiv) in toluene (25 mL, 0.002 M) at 25 °C. The mixture was stirred at that temperature for 10 h. The solvents were removed in vacuo, and the crude product so obtained was suspended in 40% ether in hexanes and filtered through silica gel. Concentration, followed by preparative thin-layer chromatography (silica gel, 20% ether in hexanes), gave lac-

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tone **27** (20 mg, 70%) with spectroscopic data identical to those exhibited by **27** obtained above.

Ketoaldehyde 45—ozonolysis of ketone 44: Alkene **44**[17] (3.6 g, 12.7 mmol) was dissolved in CH_2Cl_2 (50.0 mL, 0.25 M), and the solution cooled to −78 °C. Oxygen was bubbled through for 2 min, after which time ozone was passed through until the reaction mixture adopted a blue color (ca. 30 min). The solution was then purged with oxygen for 2 min at −78 °C (disappearance of blue color), and Ph_3P (6.75 g, 25.4 mmol, 1.2 equiv) added. The cooling bath was removed, and the reaction mixture allowed to reach room temperature and stirred for an additional 1 h. The solvent was removed under reduced pressure, and the mixture purified by flash column chromatography (silica gel, 30% ether in hexanes) to provide pure ketoaldehyde **45** (3.26 g, 90%). **45**: $R_f = 0.40$ (silica gel, 40% ether in hexanes); $[\alpha]_D^{22} = +15.7$ ($c = 5.4$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 2933, 2858, 1726, 1686, 1465, 1379, 1256, 1089, 1040, 1005, 972, 837, 778\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 9.78$ (dd, $J = 2.8, 2.4$ Hz, CHO), 4.66 (dd, $J = 5.8, 4.8$ Hz, 1H, CHOSi), 2.68–2.57 (m, 2H, $CH_2CH{=}O$), 2.29–2.09 (m, 2H, CH_2CH_3), 1.23–0.97 (m, 7H, $C(CH_2)_2$, CH_3CH_2), 0.83 (s, 9H, $(CH_3)_3C$), 0.05 (s, 3H, $Si(CH_3)_2$), 0.03 (s, 3H, $Si(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 210.1, 201.3, 66.0, 51.0, 36.5, 29.8, 25.6, 17.9, 12.5, 11.1, 8.1, -4.7, -4.8$; FAB HRMS (NBA/NaI): $m/e = 307.1705$, $M+Na^+$ calcd for $C_{15}H_{28}O_3Si$ 307.1716.

Ketone 43: To a solution of aldehyde **45** (2.9 g, 10.2 mol) in THF (50 mL, 0.2 M) at −78 °C was added dropwise lithium tri-*tert*-butoxyaluminohydride (11.2 mL, 1.0 M solution in THF, 11.2 mmol, 1.1 equiv). After 5 min, the reaction mixture was brought up to 0 °C and stirred at that temperature for 15 min, before quenching with saturated aqueous solution of sodium–potassium tartrate (25 mL). The aqueous phase was extracted with ether (3 × 75 mL), and the combined organic layer dried ($MgSO_4$), filtered, and concentrated. The crude primary alcohol so obtained was dissolved in CH_2Cl_2 (50 mL, 0.2 M) and cooled to 0 °C. Et_3N (68.1 mL, 30.6 mmol, 3.0 equiv), 4-DMAP (120 mg, 0.18 mmol, 0.02 equiv), and *tert*-butyldimethylsilyl chloride (3.0 g, 20.4 mmol, 2.0 equiv) were added. The reaction mixture was allowed to stir at 0 °C for 2 h and then at 25 °C for 10 h. MeOH (5 mL) was added, and the solvents were removed under reduced pressure. Ether (100 mL) was added, followed by saturated aqueous NH_4Cl solution (25 mL), and the organic phase was separated. The aqueous phase was extracted with ether (2 × 50 mL), and the combined organic solution dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 5% ether in hexanes) provided pure bis(silyl ether) **43** (1.26 g, 83% yield from **45**). **43**: $R_f = 0.45$ (silica gel, 5% ether in hexanes); $[\alpha]_D^{22} = -7.1$ ($c = 0.6$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 2941, 2856, 1690, 1467, 1387, 1255, 1095, 1034, 837, 776\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 3.98$ (dd, $J = 7.6, 4.1$ Hz, 1H, CHOSi), 3.67–3.59 (m, 2H, CH_2OSi), 2.76 (dq, $J = 17.6, 7.3$ Hz, 1H, CH_2CH_3), 2.44 (dq, $J = 17.6, 7.3$ Hz, 1H, CH_2CH_3), 1.83–1.73 (m, 2H, CH_2CH_2OSi), 1.14 (ddd, $J = 9.6, 6.1, 3.4$ Hz, 1H, $C(CH_2)_2$), 1.00 (t, $J = 7.3$ Hz, 3H, CH_3CH_2), 1.03–0.98 (m, 1H, $C(CH_2)_2$), 0.87 (s, 18H, $SiC(CH_3)_3$), 0.89–0.83 (m, 1H, $C(CH_2)_2$), 0.81(ddd, $J = 9.5, 6.7, 3.6$ Hz, 1H, $C(CH_2)_2$), 0.06 (s, 3H, $Si(CH_3)_2$), 0.03 (s, 3H, $Si(CH_3)_2$), 0.02 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 210.6, 69.3, 59.6, 40.2, 36.4, 32.5, 25.9, 25.8, 18.2, 18.0, 13.7, 13.5, 8.2, -4.3, -4.8, -5.4, -5.5$; FAB HRMS (NBA): $m/e = 401.2923$, $M+H^+$ calcd for $C_{21}H_{44}O_3Si_2$ 401.2907.

Tris(silyl ethers) 47 and 48—aldol reaction of ketone 43 with aldehyde 42: The aldol reaction of ketone **43** (682 mg, 1.7 mmol, 1.4 equiv) with aldehyde **42**[14] (530 mg, 1.2 mmol, 1.0 equiv) was carried out exactly as described for ketone **7** and aldehyde **6'** above, and yielded pure **47** (270 mg, 24%) and **48** (480 mg, 47%).

47: colorless oil; $R_f = 0.40$ (silica gel, 20% ether in hexanes); $[\alpha]_D^{22} = +1.5$ ($c = 0.8$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3493, 2942, 2872, 1671, 1505, 1462, 1386, 1254, 1091, 836, 776\ cm^{-1}$; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 6.87$ (s, 1H, SCH=C), 6.41 (s, 1H, $CH{=}CCH_3$), 5.10 (dd, $J = 7.2, 7.1$ Hz, 1H, $C(CH_3){=}CHCH_2$), 4.04 (dd, $J = 6.7, 5.8$ Hz, 1H, $(CH_2)_2CCHOSi$), 3.77 (br, 1H, CH_2CHOSi), 3.65–3.51 (m, 1H, $CH(CH_3)CHOH$), 3.61 (dd, $J = 7.3, 7.3$ Hz, 2H, CH_2OSi), 3.32–3.23 (m, 1H, $C(O)CH(CH_3)$), 2.65 (s, 3H, $N{=}C(CH_3)S$), 2.30–2.19 (m, 2H), 2.10–1.90 (m, 2H), 1.96 (s, 3H, $CH{=}C(CH_3)$), 1.76–1.68 (m, 2H), 1.63 (s, 3H, $C(CH_3){=}CHCH_2$), 1.50–1.40 (m, 2H), 1.26–1.15 (m, 2H), 1.01–0.75 (m, 35H, $CH(CH_3)$, $SiC(CH_3)_3$), $Si(CH_2)_2$), 0.04 (s, 3H, $Si(CH_3)_2$), 0.03 (s, 3H, $Si(CH_3)_2$), 0.00 (s, 3H, $Si(CH_3)_2$), −0.01 (s, 6H, $Si(CH_3)_2$), −0.04 (s, 3H, $Si(CH_3)_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$): $\delta = 216.0, 164.1, 153.1, 142.4, 136.7, 121.3, 118.5, 114.8, 78.9, 74.7, 59.3, 40.4, 35.4, 35.1, 32.8, 32.3, 25.8, 25.2, 23.5, 19.0, 18.1, 17.9, 17.0, 16.5, 15.3, 13.8, 12.6, 10.4, -4.1, -4.8, -4.9, -5.0, -5.4$; FAB HRMS (NBA/CsI): $m/e = 968.4473$, $M+Cs^+$ calcd for $C_{45}H_{85}NO_5SSi_3$ 968.4511.

48: colorless oil; $R_f = 0.33$ (silica gel, 20% ether in hexanes); IR (thin film): $\tilde{\nu}_{max} = 3492, 2954, 2872, 1672, 1462, 1386, 1255, 1092, 836, 776\ cm^{-1}$; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 6.88$ (s, 1H, SCH=C), 6.44 (s, 1H, $CH{=}CCH_3$), 5.11 (dd, $J = 7.1, 7.0$ Hz, 1H, $C(CH_3){=}CHCH_2$), 4.06 (dd, $J = 5.8, 5.8$ Hz, 1H, $(CH_3)_2CCHOSi$), 3.85 (br, 1H), 3.61 (dd, $J = 6.5, 6.4$ Hz, 2H, CH_2OSi), 3.42–3.38 (m, 1H, $CH(CH_3)CHOH$), 3.24–3.19 (m, 1H, $C(O)CH(CH_3)$), 2.66 (s, 3H, $N{=}C(CH_3)S$), 2.31 2.18 (m, 2H, $C(CH_3){=}CHCH_2$), 1.96 (s, 3H, $CH{=}C(CH_3)$), 1.97–1.89 (m, 2H, $CH_2C(CH_3){=}CH$), 1.78–1.69 (m, 2H), 1.64 (s, 3H, $C(CH_3){=}CHCH_2$), 1.51–1.10 (m, 6H), 1.04 (d, $J = 6.9$ Hz, 3H, $CH(CH_3)$), 0.95 (d, $J = 6.5$ Hz, 3H, $CH(CH_3)$), 1.05–0.6 (m, 8H), 0.86 (s, 9H, $SiC(CH_3)_3$), 0.85 (s, 18H, $2SiC(CH_3)_3$), 0.04 (s, 3H, $Si(CH_3)_2$), 0.02 (s, 3H, $Si(CH_3)_2$), 0.01 (s, 3H, $Si(CH_3)_2$), 0.00 (s, 3H, $Si(CH_3)_2$), −0.01 (s, 3H, $Si(CH_3)_2$), −0.03 (s, 3H, $Si(CH_3)_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$): $\delta = 216.8, 164.2, 153.1, 142.4, 136.5, 121.6, 118.6, 114.8, 78.9, 59.4, 42.0, 40.4, 35.9, 35.4, 35.3, 33.0, 32.1, 25.8, 25.7, 25.3, 23.5, 19.1, 18.1, 18.0, 15.3, 13.9, 12.4, 11.8, -4.2, -4.8, -4.9, -5.0, -5.4$; FAB HRMS (NBA/CsI): $m/e = 968.4546$, $M+Cs^+$ calcd for $C_{45}H_{85}NO_5SSi_3$ 968.4511.

Tetra(silyl ether) 49: Compound **49** (271 mg, 92%) was obtained from compound **47** (260 mg, 0.31 mmol) according to the procedure described above for **21'**. **49**: $R_f = 0.75$ (silica gel, 6% ether in hexanes); $[\alpha]_D^{22} = +7.3$ ($c = 0.5$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 2942, 2856, 1679, 1506, 1462, 1386, 1361, 1254, 1090, 1031, 1007, 985, 939, 836, 775, 727, 669\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.90$ (s, 1H, SCH=C), 6.45 (s, 1H, $CH{=}CCH_3$), 5.12 (dd, $J = 7.1, 7.0$ Hz, 1H, $C(CH_3){=}CHCH_2$), 4.19 (br, 1H), 4.07 (dd, $J = 6.5, 6.2$ Hz, 1H, $(CH_2)_2CCHOSi$), 3.82 (d, $J = 8.1$ Hz, 1H, CH_2CHOSi), 3.64 (dd, $J = 6.8, 6.8$ Hz, 2H, CH_2OSi), 2.88–2.68 (m, 1H, $C(O)CH(CH_3)$), 2.69 (s, 3H, $N{=}C(CH_3)S$), 2.30–2.17 (m, 2H, $C(CH_3){=}CHCH_2$), 1.99 (s, 3H, $CH{=}C(CH_3)$), 1.98–1.90 (m, 2H, $CH_2C(CH_3){=}CH$), 1.78–1.72 (m, 1H), 1.66 (s, 3H, $C(CH_3){=}CHCH_2$), 1.68–1.61 (m, 1H), 1.45–1.00 (m, 7H), 1.03 (d, $J = 6.7$ Hz, 3H, $CH(CH_3)$), 0.92–0.83 (m, 41H, $CH(CH_3)$, $(CH_2)_2CCHOSi$, $4SiC(CH_3)_3$), 0.06 (s, 3H, $Si(CH_3)_2$), 0.05 (s, 3H, $Si(CH_3)_2$), 0.04 (s, 3H, $Si(CH_3)_2$), 0.03 (s, 3H, $Si(CH_3)_2$), 0.02 (s, 6H, $Si(CH_3)_2$), 0.01 (s, 3H, $Si(CH_3)_2$), −0.01 (s, 3H, $Si(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 212.9, 164.2, 153.2, 142.4, 136.7, 121.4, 118.7, 114.9, 78.9, 77.8, 67.2, 59.9, 43.4, 40.3, 38.9, 37.9, 35.3, 32.5, 30.9, 26.4, 26.1, 25.9, 25.8, 23.6, 19.2, 18.4, 18.2, 18.1, 18.0, 17.4, 17.3, 13.9, 13.8, 12.4, -3.9, -4.2, -4.7, -4.8, -5.0, -5.3$.

Tetra(silyl ether) 50: Compound **50** (567 mg, 89%) was obtained from compound **48** (560 mg, 0.67 mmol) according to the procedure described above for **21'**. **50**: $R_f = 0.75$ (silica gel, 6% ether in hexanes); $[\alpha]_D^{22} = +5.7$ ($c = 0.8$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 2955, 2930, 2857, 1678, 1505, 1462, 1386, 1361, 1254, 1090, 1031, 1007, 985, 939, 836, 775\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.91$ (s, 1H, SCH=C), 6.45 (s, 1H, $CH{=}CCH_3$), 5.12 (dd, $J = 7.0, 6.9$ Hz, 1H, $C(CH_3){=}CHCH_2$), 4.21 (br, 1H), 4.07 (dd, $J = 6.6, 6.2$ Hz, 1H, $(CH_2)_2CCHOSi$), 3.82 (d, $J = 8.8$ Hz, 1H, CH_2CHOSi), 3.64 (dd, $J = 7.2, 7.1$ Hz, 2H, CH_2OSi), 2.88–2.73 (m, 1H, $C(O)CH(CH_3)$), 2.70 (s, 3H, $N{=}C(CH_3)S$), 2.29–2.18 (m, 2H, $C(CH_3){=}CHCH_2$), 1.99 (s, 3H, $CH{=}C(CH_3)$), 1.98–1.90 (m, 1H), 1.78–1.72 (m, 1H), 1.65 (s, 3H, $C(CH_3){=}CHCH_2$), 1.67–1.61 (m, 1H), 1.45–1.00 (m, 8H), 1.04 (d, $J = 6.7$ Hz, 3H, $CH(CH_3)$), 0.92–0.83 (m, 39H, $CH(CH_3)$, $4SiC(CH_3)_3$), 0.07 (s, 3H, $Si(CH_3)_2$), 0.05 (s, 3H, $Si(CH_3)_2$), 0.04 (s, 3H, $Si(CH_3)_2$), 0.03 (s, 6H, $Si(CH_3)_2$), 0.02 (s, 6H, $Si(CH_3)_2$), −0.01 (s, 3H, $Si(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 215.3, 164.2, 153.2, 142.5, 136.7, 121.5, 118.7, 114.9, 79.0, 76.9, 67.2, 59.8, 44.5, 40.3, 38.4, 37.5, 35.3, 34.7, 32.2, 26.2, 26.1, 25.9, 25.8, 23.5, 19.2, 18.5, 18.3, 18.2, 18.0, 17.6, 14.2, 13.9, 13.0, -3.6, -3.8, -4.2, -4.6, -4.7, -5.0, -5.3$; FAB HRMS (NBA/CsI): $m/e = 1082.5330$, $M+Cs^+$ calcd for $C_{51}H_{99}NO_5SSi_4$ 1082.5375.

Alcohol 51: Compound **49** (272 mg, 0.29 mmol) was dissolved in CH_2Cl_2/MeOH (1:1, 2.9 mL, 0.1 M). The solution was cooled to 0 °C and CSA (67 mg, 0.29 mmol, 1.0 equiv) was added. The mixture was stirred for 30 min at 0 °C, and then for 1 h at 10 °C. Et_3N (0.3 mL) was added, and the solvents were removed under reduced pressure. Flash column chromatography (silica gel, 40% ether in hexanes) furnished the desired alcohol **51** (180 mg, 74%). **51**:

colorless oil; $R_f = 0.60$ (silica gel, 40% ether in hexanes); $[\alpha]_D^{22} = +7.8$ ($c = 0.3$, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$): $\delta = 6.90$ (s, 1H, SCH=C), 6.44 (s, 1H, CH=CCH_3), 5.13 (dd, $J = 7.0$, 6.9 Hz, 1H, $C(CH_3)$=$CHCH_2$), 4.43 (br, 1H), 4.07 (dd, $J = 6.9$, 5.8 Hz, 1H, $(CH_2)_2CCHOSi$), 3.80 (d, $J = 8.1$ Hz, 1H, CH_2CHOSi), 3.71–3.59 (m, 2H, CH_2OSi), 2.69 (s, 3H, N=$C(CH_3)$S), 2.52 (q, $J = 7.2$ Hz, 1H, C(O)$CH(CH_3)$), 2.30–2.17 (m, 2H, $C(CH_3)$=$CHCH_2$), 2.05–1.90 (m, 2H, $CH_2C(CH_3)$=CH), 1.98 (s, 3H, CH=$C(CH_3)$), 1.78–1.70 (m, 2H), 1.66 (s, 3H, $C(CH_3)$=$CHCH_2$), 1.40–1.00 (m, 7H), 1.02 (d, $J = 6.7$ Hz, 3H, $CH(CH_3)$), 0.92–0.83 (m, 32H, $CH(CH_3)$, $(CH_2)_2CCHOSi$, $3SiC(CH_3)_3$), 0.07 (s, 3H, $Si(CH_3)_2$), 0.05 (s, 3H, $Si(CH_3)_2$), 0.04 (s, 3H, $Si(CH_3)_2$), 0.03 (s, 3H, $Si(CH_3)_2$), 0.02 (s, 3H, $Si(CH_3)_2$), −0.01 (s, 3H, $Si(CH_3)_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$): $\delta = 213.8$, 164.3, 153.0, 142.5, 136.5, 121.5, 118.5, 114.8, 78.8, 76.9, 67.2, 59.4, 42.4, 39.4, 38.8, 36.4, 35.2, 32.3, 31.1, 26.3, 26.0, 25.8, 25.7, 25.6, 23.4, 19.0, 18.3, 18.1, 17.9, 17.6, 17.1, 17.0, 13.8, 11.9, 11.1, −3.9, −4.0, −4.6, −4.8, −4.9, −5.1; FAB HRMS (NBA/CsI): $m/e = 968.4552$, $M+Cs^+$ calcd for $C_{45}H_{85}NO_5SSi_3$ 968.4511.

Alcohol 52: Alcohol **52** (300 mg, 60%) was obtained from compound **50** (567 mg, 0.60 mmol) according to the procedure described above for **49**. **52**: colorless oil; $R_f = 0.60$ (silica gel, 40% ether in hexanes); $[\alpha]_D^{22} = +12.3$ ($c = 0.3$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3441$, 2955, 2930, 2856, 1679, 1462, 1366, 1361, 1254, 1072, 836, 775 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 6.89$ (s, 1H, SCH=C), 6.42 (s, 1H, CH=CCH_3), 5.10 (dd, $J = 6.9$, 6.8 Hz, 1H, $C(CH_3)$=$CHCH_2$), 4.45 (br, 1H), 4.05 (dd, $J = 6.7$, 6.0 Hz, 1H, $(CH_2)_2CCHOSi$), 3.79 (d, $J = 9.0$ Hz, 1H, CH_2CHOSi), 3.71–3.59 (m, 2H, CH_2OSi), 2.66 (s, 3H, N=$C(CH_3)$S), 2.49 (q, $J = 7.5$ Hz, 1H, C(O)$CH(CH_3)$), 2.30–2.17 (m, 2H, $C(CH_3)$=$CHCH_2$), 1.99–1.83 (m, 2H, $CH_2C(CH_3)$=CH), 1.96 (s, 3H, CH=$C(CH_3)$), 1.78–1.70 (m, 2H), 1.62 (s, 3H, $C(CH_3)$=$CHCH_2$), 1.25–0.98 (m, 7H), 1.00 (d, $J = 6.7$ Hz, 3H, $CH(CH_3)$), 0.92–0.83 (m, 32H, $CH(CH_3)$, $(CH_2)_2CCHOSi$, $3SiC(CH_3)_3$), 0.06 (s, 3H, $Si(CH_3)_2$), 0.03 (s, 3H, $Si(CH_3)_2$), 0.02 (s, 3H, $Si(CH_3)_2$), 0.01 (s, 3H, $Si(CH_3)_2$), 0.00 (s, 3H, $Si(CH_3)_2$), −0.03 (s, 3H, $Si(CH_3)_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$): $\delta = 213.9$, 164.2, 153.1, 142.5, 136.5, 121.3, 118.5, 114.8, 78.9, 76.9, 66.7, 59.5, 43.1, 39.4, 38.3, 36.6, 35.2, 34.5, 31.9, 26.3, 26.0, 25.8, 25.7, 23.4, 19.0, 18.4, 18.1, 17.9, 17.6, 14.0, 13.8, 11.9, 10.8, −3.7, −3.8, −4.6, −4.7, −4.8, −5.0.

Aldehyde 53—oxidation of alcohol 51: Aldehyde **53** (172 mg, 96%) was obtained from alcohol **51** (182 mg, 0.218 mmol, 1.0 equiv) according to the procedure described above for **24′**. **53**: $R_f = 0.45$ (silica gel, 20% ether in hexanes); $[\alpha]_D^{22} = +15.9$ ($c = 0.7$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 2943$, 2859, 1728, 1675, 1462, 1255, 1074, 837, 776 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 9.74$ (dd, $J = 3.3$, 2.1 Hz, 1H, CHO), 6.90 (s, 1H, SCH=C), 6.44 (s, 1H, CH=CCH_3), 5.12 (dd, $J = 6.6$, 5.0 Hz, 1H, $C(CH_3)$=$CHCH_2$), 4.77 (dd, $J = 6.0$, 4.4 Hz, 1H, $(CH_2)_2CCHOSi$), 4.07 (dd, $J = 6.8$, 6.2 Hz, 1H, CH_2CHOSi), 3.75 (dd, $J = 8.5$, 1.3 Hz, 1H, $CH(CH_3)CHOSi$), 2.69 (s, 3H, N=$C(CH_3)$S), 2.61 (ddd, $J = 15.5$, 4.2, 2.1 Hz, 1H, CH_2CHO), 2.51 (ddd, $J = 15.4$, 6.1, 3.5 Hz, 1H, CH_2CHO), 2.41–2.16 (m, 3H, C(O)$CH(CH_3)$, $C(CH_3)$=$CHCH_2$), 1.97 (s, 3H, CH=$C(CH_3)$), 1.99–1.90 (m, 2H), 1.65 (s, 3H, $C(CH_3)$=$CHCH_2$), 1.50–1.25 (m, 7H), 1.08–0.98 (m, 4H), 1.02 (d, $J = 6.7$ Hz, 3H, $CH(CH_3)$), 0.89–0.84 (m, 32H, $(CH_2)_2CHOSi$, $CH(CH_3)$, $3SiC(CH_3)_3$), 0.05 (s, 9H, $Si(CH_3)_2$), 0.03 (s, 6H, $Si(CH_3)_2$), 0.02 (s, 6H, $Si(CH_3)_2$), −0.01 (s, 3H, $Si(CH_3)_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$): $\delta = 214.0$, 202.0, 165.2, 154.1, 143.3, 137.5, 122.4, 119.6, 115.8, 79.8, 79.0, 65.7, 52.3, 42.6, 39.8, 37.6, 36.1, 33.3, 32.1, 27.2, 27.0, 26.7, 26.6, 24.4, 20.1, 19.3, 19.1, 18.8, 18.6, 18.1, 14.7, 12.6, 11.2, −2.9, −3.0, −3.6, −3.8, −4.1; FAB HRMS (NBA/CsI): $m/e = 966.4392$, $M+Cs^+$ calcd for $C_{45}H_{83}NO_5SSi_3$ 966.4354.

Aldehyde 54—oxidation of alcohol 52: Aldehyde **54** (200 mg, 69%) was obtained from alcohol **52** (290 mg, 0.35 mmol) according to the procedure described above for **24′**. **54**: colorless oil; $R_f = 0.80$ (silica gel, 20% ether in hexanes); $[\alpha]_D^{22} = +26.7$ ($c = 0.1$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 2943$, 2873, 1728, 1674, 1505, 1462, 1383, 1255, 1075, 1032, 989, 940, 837, 776 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 9.78$ (dd, $J = 3.4$, 2.2 Hz, 1H, CHO), 6.89 (s, 1H, SCH=C), 6.43 (s, 1H, CH=CCH_3), 5.10 (dd, $J = 6.8$, 6.6 Hz, 1H, $C(CH_3)$=$CHCH_2$), 4.73 (dd, $J = 5.6$, 4.6 Hz, 1H, $(CH_2)_2CCHOSi$), 4.05 (dd, $J = 6.7$, 6.2 Hz, 1H, CH_2CHOSi), 3.78 (d, $J = 9.0$ Hz, 1H, $CH(CH_3)CHOSi$), 2.67 (s, 3H, N=$C(CH_3)$S), 2.60 (ddd, $J = 15.4$, 4.4, 2.1 Hz, 1H, CH_2CHO), 2.53 (ddd, $J = 15.4$, 5.9, 3.4 Hz, 1H, CH_2CHO), 2.36 (dq, $J = 9.0$, 6.8 Hz, C(O)$CH(CH_3)$), 2.22 (ddd, $J = 14.5$, 7.2, 7.0 Hz, 1H, $C(CH_3)$=$CHCH_2$), 2.19 (ddd, $J = 14.5$, 6.8, 6.6 Hz, 1H, $C(CH_3)$=$CHCH_2$), 1.97 (s, 3H, CH=$C(CH_3)$), 1.99–1.88 (m, 2H, $CH_2C(CH_3)$=CH), 1.63 (s, 3H, $C(CH_3)$=$CHCH_2$), 1.35–1.00 (m, 11H), 1.00 (d, $J = 6.9$ Hz, 3H, $CH(CH_3)$), 0.86 (s, 18H, $2SiC(CH_3)_3$), 0.89–0.85 (m, 2H, $(CH_2)_2CHOSi$), 0.86 (d, $J = 6.8$ Hz, 3H, $CH(CH_3)$), 0.82 (s, 9H, $SiC(CH_3)_3$), 0.04 (s, 3H, $Si(CH_3)_2$), 0.03 (s, 3H, $Si(CH_3)_2$), 0.02 (s, 6H, $Si(CH_3)_2$), −0.03 (s, 3H, $Si(CH_3)_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$): $\delta = 213.1$, 201.0, 164.2, 153.1, 142.4, 136.6, 121.5, 119.6, 118.6, 114.9, 78.9, 76.9, 65.0, 51.3, 42.5, 38.3, 36.7, 35.2, 34.3, 32.1, 26.1, 26.0, 25.8, 25.7, 23.4, 19.1, 18.4, 18.2, 17.9, 17.8, 14.2, 13.8, 11.6, 10.3, −3.7, −3.8, −4.6, −4.7, −5.0.

Carboxylic acid 55—oxidation of aldehyde 53: Carboxylic acid **55** (160 mg, 91%) was obtained from aldehyde **53** (172 mg, 0.206 mmol) according to the procedure described above for **25′**. **55**: $R_f = 0.15$ (silica gel, 20% ether in hexanes); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.90$ (s, 1H, SCH=C), 6.50 (s, 1H, CH=CCH_3), 5.12 (dd, $J = 7.8$, 6.6 Hz, 1H, $C(CH_3)$=$CHCH_2$), 4.54 (br, 1H, $(CH_2)_2CCHOSi$), 4.09 (dd, $J = 6.4$, 6.2 Hz, 1H, CH_2CHOSi), 3.90 (d, $J = 5.8$ Hz, 1H, $CH(CH_3)CHOSi$), 2.73 (s, 3H, N=$C(CH_3)$S), 2.60 (m, 1H, CH_2COOH), 2.50 (m, 1H, CH_2COOH), 2.41–2.16 (m, 3H, C(O)$CH(CH_3)$, $C(CH_3)$=$CHCH_2$), 1.99–1.90 (m, 2H), 1.90 (s, 3H, CH=$C(CH_3)$), 1.69 (s, 3H, $C(CH_3)$=$CHCH_2$), 1.50–1.25 (m, 7H), 1.08–0.98 (m, 4H), 1.05 (d, $J = 6.8$ Hz, 3H, $CH(CH_3)$), 0.92–0.83 (m, 32H, $(CH_2)_2CHOSi$, $CH(CH_3)$, $3SiC(CH_3)_3$), 0.07 (s, 3H, $Si(CH_3)_2$), 0.06 (s, 3H, $Si(CH_3)_2$), 0.05 (s, 3H, $Si(CH_3)_2$), 0.04 (s, 3H, $Si(CH_3)_2$), 0.03 (s, 3H, $Si(CH_3)_2$), −0.01 (s, 3H, $Si(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 212.8$, 175.1, 165.2, 152.5, 143.3, 136.7, 121.5, 117.9, 114.5, 78.7, 77.5, 67.9, 42.4, 39.1, 36.3, 35.2, 32.2, 31.6, 31.0, 26.3, 26.0, 25.7, 23.4, 18.6, 18.2, 18.1, 17.9, 17.6, 16.5, 13.9, 12.0, −4.0, −4.1, −4.5, −4.8, −5.7; FAB HRMS (NBA/CsI): $m/e = 982.4264$, $M+Cs^+$ calcd for $C_{45}H_{83}NO_6SSi_3$ 982.4303.

Carboxylic acid 56—oxidation of aldehyde 54: Acid **56** (204 mg, 99%) was obtained from aldehyde **54** (200 mg, 0.24 mmol) according to the procedure described above for **25′**. **56**: colorless oil; $R_f = 0.15$ (silica gel, 20% ether in hexanes); $[\alpha]_D^{22} = +20.0$ ($c = 0.3$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 2955$, 2888, 2856, 1713, 1680, 1509, 1462, 1384, 1254, 1183, 1077, 1031, 987, 941, 837, 776 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 6.90$ (s, 1H, SCH=C), 6.46 (s, 1H, CH=CCH_3), 5.12 (dd, $J = 7.0$, 6.8 Hz, 1H, $C(CH_3)$=$CHCH_2$), 4.58 (br, 1H, $(CH_2)_2CCHOSi$), 4.06 (dd, $J = 7.7$, 5.4 Hz, 1H, CH_2CHOSi), 3.84 (d, $J = 9.3$ Hz, 1H, $CH(CH_3)CHOSi$), 2.71 (s, 3H, N=$C(CH_3)$S), 2.60 (dd, $J = 15.1$, 4.0 Hz, 1H, CH_2COOH), 2.60–2.52 (m, 1H, C(O)$CH(CH_3)$), 2.53 (dd, $J = 15.0$, 6.9 Hz, 1H, CH_2COOH), 2.30–2.15 (m, 2H, $C(CH_3)$=$CHCH_2$), 1.95–1.88 (m, 2H, $CH_2C(CH_3)$=CH), 1.92 (s, 3H, CH=$C(CH_3)$), 1.65 (s, 3H, $C(CH_3)$=$CHCH_2$), 1.35–1.00 (m, 11H), 1.02 (d, $J = 6.8$ Hz, 3H, $CH(CH_3)$), 0.87 (s, 18H, $2SiC(CH_3)_3$), 0.89–0.85 (m, 2H, $(CH_2)_2CHOSi$), 0.84 (s, 9H, $SiC(CH_3)_3$), 0.82 (d, $J = 6.7$ Hz, 3H, $CH(CH_3)$), 0.07 (s, 3H, $Si(CH_3)_2$), 0.04 (s, 9H, $Si(CH_3)_2$), 0.03 (s, 3H, $Si(CH_3)_2$), −0.01 (s, 3H, $Si(CH_3)_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$): $\delta = 213.0$, 175.2, 165.1, 152.6, 143.4, 136.9, 121.4, 118.1, 114.5, 78.9, 67.3, 53.4, 43.5, 42.3, 38.2, 36.5, 35.3, 34.9, 32.2, 26.4, 26.2, 25.8, 25.7, 23.7, 18.7, 18.5, 18.2, 18.0, 17.7, 14.1, 13.9, 11.6, 11.3, −3.6, −3.7, −4.6, −4.7, −4.8, −5.0; FAB HRMS (NBA, CsI): $m/e = 982.4278$, $M+Cs^+$ calcd for $C_{45}H_{83}NO_6SSi_3$ 982.4303.

Lactone 58—selective desilylation of tris(silyl ether) 55 and macrolactonization of hydroxyacid 41: A solution of tris(silyl ether) **55** (75 mg, 0.088 mmol) in THF (1.8 mL, 0.05 M) at 25 °C was treated with TBAF (0.53 mL, 1.0 M solution in THF, 0.53 mmol, 6.0 equiv). After stirring for 8 h, the reaction mixture was diluted with EtOAc (10 mL) and washed with saturated aqueous NH_4Cl (5 mL). The aqueous solution was extracted with EtOAc (2 × 10 mL), and the combined organic phase washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The crude mixture was purified by flash column chromatography (silica gel, 5% MeOH in CH_2Cl_2) to provide hydroxyacid **41** (40 mg, 62%) as a yellow oil [$R_f = 0.40$ (silica gel, 5% MeOH in CH_2Cl_2)]. A solution of hydroxyacid **41** (40 mg, 0.054 mmol) in THF (0.8 mL, 0.07 M) was treated at 0 °C with Et_3N (17 μL, 0.12 mmol, 2.2 equiv) and 2,4,6-trichlorobenzoyl chloride (14.5 μL, 0.06 mmol, 1.1 equiv). The reaction mixture was stirred at 0 °C for 1 h, and then added to a solution of 4-DMAP (1.4 mg, 0.11 mmol, 2.0 equiv) in toluene (28 mL, 0.002 M) at 25 °C and stirred at that temperature for 3 h. The reaction mixture was concentrated under reduced pressure to a small volume and filtered through silica gel. The residue was washed with 40% ether in hexanes, and the resulting solution concentrated. Purification by flash column chromatography (silica gel, 2% MeOH in

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CH_2Cl_2) furnished lactone **58** (27 mg, 70%) as a white solid. **58**: $R_f = 0.35$ (silica gel, 30% ether in hexanes); m.p. 81 °C (from CH_2Cl_2/hexanes); $[\alpha]_D^{22} = -134.3$ ($c = 0.9$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 2931$, 2856, 1740, 1683, 1462, 1380, 1252, 1164, 1102, 1060, 1011, 834, 774 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 6.90$ (s, *1H, SCH=C*), 6.36 (brs, *1H, CH=CCH₃*), 5.16 (br, 1H), 5.04 (br, 1H), 3.95 (d, $J = 7.3$ Hz, 1H, CHOSi), 3.55 (br, 1H, $C(CH_2)_2CHOSi$), 2.80–2.78 (m, 1H, $C(O)CHCH_3$), 2.68 (s, 3H, $N=C(CH_3)S$), 2.55–2.38 (m, 4H, CH_2COOCH, $CH_3C=CHCH_2$), 2.03 (s, 3H, $CH=C(CH_3)$), 1.70 (s, 3H, $C(CH_3)=CHCH_2$), 1.78–1.03 (m, 7H), 1.11 (d, $J = 6.6$ Hz, 3H, $CH(CH_3)$), 1.01 (d, $J = 6.6$ Hz, 3H, $CH(CH_3)$), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.88 (s, 9H, $SiC(CH_3)_3$), 0.94–0.83 (m, 3H, $C(CH_2)_2CHOSi$), 0.40–0.33 (m, 1H, $C(CH_2)_2CHOSi$), 0.14 (s, 3H, $Si(CH_3)_2$), 0.13 (s, 3H, $Si(CH_3)_2$), 0.08 (s, 3H, $Si(CH_3)_2$), 0.04 (s, 3H, $Si(CH_3)_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$): $\delta = 214.6$, 170.0, 164.7, 152.8, 139.0, 137.9, 121.3, 118.8, 116.2, 74.5, 53.3, 48.7, 41.0, 39.4, 35.2, 31.9, 31.8, 31.1, 26.6, 25.9, 25.6, 23.5, 19.7, 19.0, 18.2, 18.1, 17.8, 15.5, 10.0, −3.1, −3.8, −4.2, −6.2; FAB HRMS (NBA): $m/e = 718.4357$, $M+H^+$ calcd for $C_{39}H_{67}NO_5SSi_2$ 718.4357.

Hydroxyacid 57—selective desilylation of tris(silyl ether) 56: Carboxylic acid **56** (200 mg, 0.235 mmol) was converted to hydroxyacid **57** (85 mg, 50%) according to the procedure described above for **26′**. **57**: Yellow oil; $R_f = 0.45$ (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]_D^{22} = +10.0$ ($c = 0.3$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3440$, 2955, 2930, 2871, 1713, 1679, 1462, 1383, 1254, 1185, 1097, 986, 836, 775, 734 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.95$ (s, 1H, SCH=C), 6.60 (s, 1H, $CH=CCH_3$), 5.15 (dd, $J = 6.9$, 6.7 Hz, 1H, $C(CH_3)=CH$), 4.66 (dd, $J = 6.4$, 3.7 Hz, 1H, $(CH_2)_2CCHOSi$), 4.13 (dd, $J = 6.8$, 6.1 Hz, 1H, CH_2CHOH), 3.84 (d, $J = 9.2$ Hz, 1H, $CH(CH_3)CHOSi$), 2.73 (s, 3H, $N=C(CH_3)S$), 2.58–2.53 (m, 2H, CH_2COOH, $C(O)CHCH_3$), 2.45 (dd, $J = 15.0$, 6.6 Hz, 1H, CH_2COOH), 2.34–2.29 (m, 2H, $C(CH_3)=CHCH_2$), 2.30 (dd, $J = 16.3$, 6.4 Hz, 1H, CH_2COOH), 2.05–1.91 (m, 2H, $CH_2C(CH_3)=CH$), 1.98 (s, 3H, $CH=C(CH_3)$), 1.71 (s, 3H, $C(CH_3)=CHCH_2$), 1.38–1.17 (m, 7H), 1.05 (d, $J = 6.8$ Hz, 3H, $CH(CH_3)$), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.85–0.82 (m, 23H, $(CH_2)_2CHOSi$, $CH(CH_3)$, $SiC(CH_3)_3$), 0.09 (s, 3H, $Si(CH_3)_2$), 0.06 (s, 6H, $Si(CH_3)_2$), 0.05 (s, 3H, $Si(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 213.4$, 174.0, 165.3, 152.2, 142.4, 139.5, 120.1, 118.2, 114.9, 77.1, 66.9, 43.5, 42.7, 38.0, 36.9, 35.1, 34.1, 32.2, 26.4, 26.2, 25.8, 23.9, 18.6, 18.5, 18.0, 17.7, 14.8, 13.9, 11.6, 11.0, −3.6, −3.7, −4.6, −4.7; FAB HRMS (NBA/CsI): $m/e = 856.3402$, $M+Cs^+$ calcd for $C_{38}H_{69}NO_6SSi_2$ 856.3439.

Lactone 59—macrolactonization of hydroxyacid 57: The cyclization of hydroxyacid **57** (80 mg, 0.11 mmol) was carried out exactly as described for **5′** above and yielded lactone **59** (56 mg, 72%) as a crystalline solid: $R_f = 0.65$ (silica gel, 20% ether in hexanes); m.p. 157 °C (from MeOH/EtOH); $[\alpha]_D^{22} = -40.5$ ($c = 0.2$, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$): $\delta = 6.97$ (s, 1H, SCH=C), 6.46 (s, 1H, $CH=CCH_3$), 5.02 (m, 2H, $CH_3C=CHCH_2$, CH_2COOCH), 3.87 (d, $J = 8.8$ Hz, 1H, CHOSi), 3.88 (d, $J = 8.9$ Hz, 1H, *CHOSi*), 2.69 (s, 3H, $N=C(CH_3)S$), 2.62 (dd, $J = 12.7$, 4.4 Hz, 1H, CH_2COOCH), 2.58–2.50 (m, 2H), 2.44–2.36 (m, 1H), 2.31–2.24 (m, 1H), 2.17–2.10 (m, 1H), 2.14 (s, 3H, $CH=C(CH_3)$), 1.74–1.68 (m, 1H), 1.64 (s, 3H, $CH_2C(CH_3)=CH$), 1.48–1.23 (m, 7H), 1.14–1.07 (m, 1H), 1.02 (d, $J = 6.8$ Hz, 3H, $CH(CH_3)$), 0.97 (d, $J = 6.8$ Hz, 3H, $CH(CH_3)$), 0.88 (s, 9H, $SiC(CH_3)_3$), 0.85 (s, 9H, $SiC(CH_3)_3$), 0.91–0.82 (m, 2H), 0.06 (s, 3H, $Si(CH_3)_2$), 0.05 (s, 3H, $Si(CH_3)_2$), 0.04 (s, 3H, $Si(CH_3)_2$), 0.03 (s, 3H, $Si(CH_3)_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$): $\delta = 212.5$, 169.2, 164.5, 152.6, 139.3, 136.8, 121.6, 118.8, 116.2, 80.4, 75.9, 42.9, 42.6, 36.5, 35.1, 33.4, 30.7, 30.5, 26.3, 25.8, 24.2, 23.2, 19.2, 18.6, 18.1, 17.8, 14.5, 14.2, 12.4, −3.2, −3.6, −4.8, −5.3; FAB HRMS (NBA): $m/e = 718.4330$, $M+H^+$ calcd for $C_{39}H_{67}NO_5SSi_2$ 718.4357.

Dihydroxylactone 40: Dihydroxylactone **40** (11.0 mg, 92%) was prepared from bis(silyl ether) **58** (17.6 mg, 0.024 mmol) by treatment with HF·pyridine according to the same procedure described above for the preparation of **4′**. **40**: $R_f = 0.20$ (silica gel, 4% MeOH in CH_2Cl_2); m.p. 67 °C (from CH_2Cl_2/hexanes); $[\alpha]_D^{22} = -108.7$ (c 0.1, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3458$, 2931, 1730, 1674, 1451, 1375, 1169, 1040, 980, 911, 732 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 6.95$ (s, 1H, SCH=C), 6.47 (s, 1H, $CH=CCH_3$), 5.46 (dd, $J = 6.8$, 3.3 Hz, 1H, CH_2COOCH), 5.10 (dd, $J = 8.0$, 7.0 Hz, 1H, $CH_3C=CHCH_2$), 3.82 (dd, $J = 6.3$, 2.2 Hz, 1H, *CHOH*), 3.75 (br, 1H), 3.55–3.48 (m, 2H), 2.78 (dd, $J = 17.2$, 9.2 Hz, 1H, CH_2COOCH), 2.69 (s, 3H, $N=C(CH_3)S$), 2.67 (dd, $J = 17.3$, 3.4 Hz, 1H, CH_2COOCH), 2.54–2.45 (m, 1H), 2.44–2.35 (m, 1H), 2.19–2.13 (m, 1H), 2.06 (s, 3H, $CH=CCH_3$), 2.11–2.01 (m, 1H), 1.95–1.86 (m, 1H), 1.73–1.62 (m, 1H), 1.71 (s, 3H, $CH_2C(CH_3)=CH$), 1.62–1.52 (m, 2H), 1.49–1.35 (m, 2H), 1.29–1.23 (m, 2H), 1.25 (d, $J = 6.7$ Hz, 3H, $CH(CH_3)$), 1.30–1.20 (m, 1H), 1.19–1.10 (s, *1H, C(CH₂)₂*), 1.00 (d, $J = 6.9$ Hz, 3H, $CH(CH_3)$), 1.00–0.96 (m, 1H, $C(CH_2)_2$), 0.75–0.69 (m, 1H, $C(CH_2)_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$): $\delta = 216.6$, 173.0, 165.8, 153.4, 140.1, 137.9, 120.6, 117.0, 77.9, 75.7, 70.3, 45.3, 38.5, 37.3, 34.1, 31.7, 31.6, 30.7, 26.0, 23.9, 19.0, 17.1, 16.5, 15.6, 15.4, 10.9; FAB HRMS (NBA): $m/e = 490.2639$, $M+H^+$ calcd for $C_{27}H_{39}NO_5S$ 490.2627.

Dihydroxylactone 60: Dihydroxylactone **60** (19.0 mg, 90%) was prepared from bis(silyl ether) lactone **59** (31 mg, 0.043 mmol) by treatment with HF·pyridine according to the same procedure described above for the preparation of **4′**. **60**: $R_f = 0.45$ (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]_D^{22} = -122.9$ (c 0.1, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3457$, 2934, 2360, 1731, 1667, 1449, 1377, 1242, 1165, 1070, 1039, 978, 911, 732 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 6.95$ (s, 1H, SCH=C), 6.53 (s, 1H, $CH=CCH_3$), 5.51 (d, $J = 6.8$ Hz, 1H, CH_2COOCH), 5.15 (dd, $J = 8.1$, 7.6 Hz, 1H, $CH_3C=CHCH_2$), 3.84 (dd, $J = 13.4$, 6.7 Hz, 1H, *CHOH*), 3.77 (d, $J = 11.3$ Hz, 1H, *CHOH*), 3.47 (d, $J = 6.9$ Hz, 1H), 3.46 (s, 1H), 3.00 (s, 1H), 2.78 (dd, $J = 16.7$, 11.5 Hz, 1H, CH_2COOCH), 2.70 (s, 3H, $N=C(CH_3)S$), 2.65 (dd, $J = 16.7$, 3.0 Hz, 1H, CH_2COOCH), 2.60–2.55 (m, 1H), 2.44–2.35 (m, 1H), 2.35–2.26 (m, 1H), 2.25–2.17 (m, 1H), 2.07 (s, 3H, $CH=CCH_3$), 2.05–1.98 (m, 1H), 1.66 (s, 3H, $CH_2C(CH_3)=CH$), 1.67–1.55 (m, 3H), 1.48–1.41 (m, 3H), 1.10–0.99 (m, 8H, $2CH(CH_3)$, $C(CH_2)_2$), 0.96–0.88 (m, 1H, $C(CH_2)_2$), 0.70–0.64 (m, 1H, $C(CH_2)_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$): $\delta = 218.7$, 171.3, 165.1, 152.5, 137.7, 137.6, 121.4, 119.5, 116.1, 77.9, 74.6, 70.9, 43.5, 40.1, 35.4, 33.9, 32.0, 31.3, 30.8, 26.0, 23.4, 22.1, 18.9, 18.5, 15.8, 15.6, 13.6, 10.1; FAB HRMS (NBA/CsI): $m/e = 622.1580$, $M+Cs^+$ calcd for $C_{27}H_{39}NO_5S$ 622.1603.

Epothilones 3 and 61—epoxidation of lactone 40 with methyl(trifluoromethyl)dioxirane: To a solution of **40** (10 mg, 21.0 μmol) in MeCN (200 μL) was added 4×10^{-4} M aqueous solution of disodium ethylenediaminetetraacetate (Na_2EDTA, 120 μL), and the reaction mixture was cooled to 0 °C. 1,1,1-Trifluoroacetone (200 μL) was added, followed by a mixture of Oxone® (61 mg, 0.10 mmol, 5.0 equiv) and $NaHCO_3$ (14.0 mg, 0.17 mmol, 8.0 equiv) with stirring until completion of the reaction was revealed by TLC. The reaction mixture was treated with excess Me_2S (100 μL) and water (500 μL) and was then extracted with EtOAc (4 × 2 mL). The combined organic phase was dried ($MgSO_4$), filtered, and concentrated. Purification by preparative thin-layer chromatography (silica gel, 80% EtOAc in hexanes) furnished pure (6*S*,7*R*)-4,4-cyclopropyl-epothilone B **3** (7.7 mg, 76%) and its α-epoxide epimer **61** (1.0 mg, 10%).

3: $R_f = 0.45$ (silica gel, 80% EtOAc in hexanes); m.p. 82 °C (from CH_2Cl_2/hexanes); $[\alpha]_D^{22} = -45.0$ ($c = 0.02$, MeOH); IR (thin film): $\tilde{\nu}_{max} = 3443$, 2929, 1739, 1674, 1379, 1158, 1093, 754 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 6.94$ (s, 1H, SCH=C), 6.49 (s, 1H, $CH=CCH_3$), 5.64 (dd, $J = 4.1$, 3.1 Hz, 1H, O=COCH), 3.88 (br, 1H), 3.82 (d, $J = 7.9$ Hz, 1H), 3.52–3.44 (m, 2H), 2.97 (s, 2H), 2.85 (dd, $J = 17.1$, 9.1 Hz, 1H, CH_2COO), 2.85 (dd, $J = 7.7$, 5.9 Hz, 1H), 2.70 (s, 3H, $N=C(CH_3)S$), 2.71–2.67 (m, 1H), 2.20–2.13 (m, 1H), 2.11 (s, 3H, $CH=C(CH_3)$), 1.85 (ddd, $J = 11.7$, 8.0, 3.7 Hz, 1H, CH_2CHO), 1.82–1.74 (m, 1H), 1.63–1.55 (m, 1H), 1.53–1.49 (m, 3H), 1.52–1.37 (m, 6H), 1.33–1.25 (m, 2H), 1.29 (s, 3H, $C(CH_3)$), 1.04 (d, $J = 6.8$ Hz, 3H, $CH(CH_3)$), 1.12 (ddd, $J = 6.7$, 4.4, 2.3 Hz, 3H, $C(CH_2)_2$), 1.03 (d, $J = 6.8$ Hz, 3H, $CH(CH_3)$), 1.03–0.98 (m, 1H, $C(CH_2)_2$), 0.78–0.72 (m, 1H, $C(CH_2)_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$): $\delta = 215.1$, 171.9, 165.2, 152.4, 136.0, 119.4, 116.5, 76.0, 75.2, 70.0, 61.0, 60.7, 45.8, 42.5, 38.5, 36.3, 34.3, 31.7, 31.4, 29.8, 22.9, 22.5, 19.0, 17.4, 17.0, 15.9, 15.7, 10.6; FAB HRMS (NBA): $m/e = 506.2561$, $M+H^+$ calcd for $C_{27}H_{39}NO_6S$ 506.2576.

61: $R_f = 0.50$ (silica gel, 80% EtOAc in hexanes); $[\alpha]_D^{22} = -31.1$ ($c = 0.05$, MeOH); IR (thin film): $\tilde{\nu}_{max} = 3463$, 2926, 1735, 1378, 1158 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 7.00$ (s, 1H, SCH=C), 6.60 (s, 1H, $CH=CCH_3$), 5.45 (dd, $J = 6.3$, 5.0 Hz, 1H, O=COCH), 4.45 (br, *1H*), 3.74–3.68 (m, 2H), 3.01–2.95 (m, 1H), 2.83 (dd, $J = 16.3$, 5.6 Hz, 1H, CH_2COO), 2.79 (dd, $J = 6.3$, 6.0 Hz, 1H), 2.70 (s, 3H, $N=C(CH_3)S$), 2.62 (dd, $J = 16.3$, 4.5 Hz, 1H, CH_2COO), 2.39 (br, 1H), 2.10 (s, 3H, $CH=C(CH_3)$), 2.10–1.94 (m, 2H), 1.60–1.21 (m, 10H), 1.10–1.05 (m, 2H), 1.07 (d, $J = 6.8$ Hz, 3H, $CH(CH_3)$), 0.94 (d, $J = 7.0$ Hz, 3H, $CH(CH_3)$), 0.88–0.81 (m, 2H, $C(CH_2)_2$); FAB HRMS (NBA): $m/e = 506.2576$, $M+H^+$ calcd for $C_{27}H_{39}NO_6S$ 506.2593.

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Epothilones 62 and 63—epoxidation of lactone 60: Compound **60** (10.0 mg, 21.0 μmol) was epoxidized according to the procedure described above for **40** to yield a mixture of (6*R*,7*S*)-4,4-cyclopropyl-epothilone B (**62**) (6.2 mg, 60%) and its α-epoxy diastereoisomer **63** (2.8 mg, 29%).

62: $R_f = 0.40$ (silica gel, 60% EtOAc in hexanes); m.p. 143–145 °C (from CH_2Cl_2/hexanes); $[\alpha]_D^{22} = -60.0$ ($c = 0.1$, MeOH); IR (thin film): $\tilde{\nu}_{max} = 3450, 2929, 1736, 1671, 1451, 1379, 1240, 1155, 977, 732\ cm^{-1}$; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 6.97$ (s, 1H, SCH=C), 6.58 (s, 1H, CH=CCH_3), 5.60 (dd, $J = 4.1, 3.1$ Hz, 1H, O=COCH), 4.53 (d, $J = 9.7$ Hz, 1H), 4.45 (br, 1H), 3.73 (d, $J = 9.1$ Hz, 1H), 3.59 (dd, $J = 14.6, 7.5$ Hz, 1H), 3.54, (s, 1H, OH), 2.90 (dd, $J = 8.3, 4.5$ Hz, 1H), 2.70 (s, 3H, N=C(CH_3)S), 2.50 (dd, $J = 14.9, 10.2$ Hz, 1H, CH_2COO), 2.85 (dd, $J = 14.8, 1.6$ Hz, 1H, CH_2COO), 2.19 (dd, $J = 5.0, 5.0$ Hz, 1H), 2.16 (s, 3H, CH=C(CH_3)), 1.94 (ddd, $J = 15.2, 8.3, 3.5$ Hz, 1H, CH_2CHO), 1.73–1.23 (m, 7H), 1.27 (s, 3H, C(CH_3)), 1.10 (d, $J = 7.0$ Hz, 3H, CH(CH_3)), 1.08 (d, $J = 6.8$ Hz, 3H, CH(CH_3)), 0.97–0.84 (m, 3H, C(CH_2)$_2$), 0.78–0.70 (m, 1H, C(CH_2)$_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$): $\delta = 218.1, 171.0, 165.2, 152.6, 135.5, 119.7, 116.9, 76.4, 73.5, 68.5, 61.8, 60.9, 41.6, 39.4, 34.7, 34.5, 32.9, 32.6, 30.7, 21.6, 19.7, 19.0, 16.1, 15.8, 15.7, 13.9, 10.7, 9.2$; FAB HRMS (NBA): $m/e = 506.2589$, calcd for $C_{27}H_{39}NO_6S$ ($M+H^+$) 506.2576.

63: $R_f = 0.37$ (silica gel, 80% EtOAc in hexanes); ^1H NMR (600 MHz, $CDCl_3$): $\delta = 6.99$ (s, 1H, SCH=C), 6.53 (s, 1H, CH=CCH_3), 5.75 (d, $J = 7.5$ Hz, 1H, O=COCH), 4.12 (d, $J = 9.3$ Hz, 1H), 3.66 (m, 1H), 3.58 (d, $J = 9.0$ Hz, 1H), 3.43 (s, 1H, OH), 3.35 (s, 1H, OH), 2.88–2.79 (m, 1H), 2.74 (dd, $J = 16.1, 5.7$ Hz, 1H, CH_2COO), 2.70 (s, 3H, N=C(CH_3)S), 2.57 (d, $J = 16.1$ Hz, 1H, CH_2COO), 2.10 (s, 3H, CH=C(CH_3)), 2.10–1.84 (m, 2H), 1.62–1.01 (m, 11H), 1.31 (s, 3H, C(CH_3)), 1.14 (d, $J = 6.8$ Hz, 3H, CH(CH_3)), 1.03 (d, $J = 6.7$ Hz, 3H, CH(CH_3)), 0.75–0.70 (m, 1H, C(CH_2)$_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$): $\delta = 218.5, 171.4, 165.2, 152.4, 135.6, 120.1, 116.7, 76.8, 74.1, 69.8, 61.6, 60.4, 43.4, 39.3, 34.4, 34.2, 32.9, 33.2, 32.2, 31.6, 23.2, 20.8, 19.0, 17.1, 15.5, 15.3, 13.9, 11.4, 10.9$; FAB HRMS (NBA): $m/e = 506.2583$, $M+H^+$ calcd for $C_{27}H_{39}NO_6S$ 506.2576.

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[1] a) G. Höfle, N. Bedorf, K. Gerth, H. Reichenbach (GBF), DE-4138042, **1993** (*Chem. Abstr.* **1993**, *120*, 52841); b) K. Gerth, N. Bedorf, G. Höfle, H. Irschik, H. Reichenbach, *J. Antibiot.* **1996**, *49*, 560–563.

[2] D. M. Bollag, P. A. McQueney, J. Zhu, O. Hensens, L. Koupal, J. Liesch, M. Goetz, E. Lazarides, C. M. Woods, *Cancer Res.* **1995**, *55*, 2325–2333.

[3] R. J. Kowalski, P. Giannakakou, E. Hamel, *J. Biol. Chem.* **1997**, *272*, 2534–2541.

[4] G. Höfle, N. Bedorf, H. Steinmetz, D. Schomburg, K. Gerth, H. Reichenbach, *Angew. Chem.* **1996**, *108*, 1671–1673; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1567–1569.

[5] a) K. C. Nicolaou, Y. He, D. Vourloumis, H. Vallberg, Z. Yang, *Angew. Chem.* **1996**, *108*, 2554–2556; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2399–2401; b) D. Meng, E. J. Sorensen, P. Bertinato, S. J. Danishefsky, *J. Org. Chem.* **1996**, *61*, 7998–7999; c) P. Bertinato, E. J. Sorensen, D. Meng, S. J. Danishefsky, *ibid.* **1996**, *61*, 8000–8001; d) D. Schinzer, A. Limberg, O. M. Böhm, *Chem. Eur. J.* **1996**, *2*, 1477–1482; e) J. Mulzer, A. Mantoulidis, *Tetrahedron Lett.* **1996**, *37*, 9179–9182; f) E. Claus, A. Pahl, P. G. Jones, H. M. Meyer, M. Kalesse, *ibid.* **1997**, *38*, 1359–1362; g) T. Gabriel, L. Wessjohann, *ibid.* **1997**, *38*, 1363–1366; h) R. E. Taylor, J. D. Haley, *ibid.* **1997**, *38*, 2061–2064.

[6] A. Balog, D. Meng, T. Kamenecka, P. Bertinato, D.-S. Su, E. J. Sorensen, S. J. Danishefsky, *Angew. Chem.* **1996**, *108*, 2976–2978; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2801–2803.

[7] D. Meng, D.-S. Su, A. Balog, P. Bertinato, E. J. Sorensen, S. J. Danishefsky, Y.-H. Zheng, T.-C. Chou, L. He, S. B. Horwitz, *J. Am. Chem. Soc.* **1997**, *119*, 2733–2734.

[8] Z. Yang, Y. He, D. Vourloumis, H. Vallberg, K. C. Nicolaou, *Angew. Chem.* **1997**, *109*, 170–172; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 166–168.

[9] K. C. Nicolaou, F. Sarabia, S. Ninkovic, Z. Yang, *Angew. Chem.* **1997**, *109*, 539–540, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 525–526.

[10] D. Schinzer, A. Limberg, A. Bauer, O. M. Böhm, M. Cordes, *Angew. Chem.* **1997**, *109*, 543–544; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 523–524.

[11] D.-S. Su, D. Meng, P. Bertinato, A. Balog, E. J. Sorensen, S. J. Danishefsky, Y.-H. Zheng, T.-C. Chou, L. He, S. B. Horwitz, *Angew. Chem.* **1997**, *109*, 775–777; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 757–759.

[12] K. C. Nicolaou, N. Winssinger, J. A. Pastor, S. Ninkovic, F. Sarabia, Y. He, D. Vourloumis, Z. Yang, T. Li, P. Giannakakou, E. Hamel, *Nature* **1997**, *387*, 268–272.

[13] K. C. Nicolaou, Y. He, D. Vourloumis, H. Vallberg, F. Roschangar, F. Sarabia, S. Ninkovic, Z. Yang, J. I. Trujillo, *J. Am. Chem. Soc.* **1997**, *119*, 7960–7973.

[14] K. C. Nicolaou, S. Ninkovic, F. Sarabia, D. Vourloumis, Y. He, H. Vallberg, M. R. V. Finlay, Z. Yang, *J. Am. Chem. Soc.* **1997**, *119*, 7974–7991.

[15] G. Höfle, personal communication.

[16] A. Balog, P. Bertinato, D.-S. Su, D. Meng, E. J. Sorensen, S. J. Danishefsky, Y.-H. Zheng, T.-C. Chou, L. He, S. B. Horwitz, *Tetrahedron Lett.* **1997**, *38*, 4529–4532.

[17] K. C. Nicolaou,H. Vallberg, N. P. King, F. Roschangar, Y. He, D. Vourloumis, C. G. Nicolaou, *Chem. Eur. J.* **1997**, *3*, 1957–1970.

[18] S. B. Horwitz, J. Fant, P. B. Schiff, *Nature* **1979**, *277*, 665–667.

[19] a) D. Enders, *Asymmetric Synthesis* **1984**, *Vol 3*, 275–339, Academic Press, Inc.; b) D. Enders, M. Klatt, *Synthesis* **1996**, 1403–1418.

[20] D. P. Provencal, C. Gandelli, J. A. Lafontaine, J. W. Leahy, *Tetrahedron Lett.* **1995**, *36*, 6033–6039.

[21] a) U. S. Racherla, H. C. Brown, *J. Org. Chem.* **1991**, *56*, 401–404; b) P. Jadhav, K. S. Bhat, P. T. Perumal, H. C. Brown, *J. Org. Chem.* **1967**, *32*, 404–407.

[22] a) W. P. Schneider, A. V. McIntosh, US Patent 2,769,824 Nov 6, **1956**; b) V. VanRheenen, R. C. Kelly, D. Y. Cha, *Tetrahedron Lett.* **1976**, *17*, 1973–1976; c) H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483–2547.

[23] T. D. Nelson, R. D. Crouch, *Synthesis* **1996**, 1031–1069.

[24] J. R. Parikh, W. E. von Doering, *J. Am. Chem. Soc.* **1967**, *89*, 5505–5507.

[25] a) J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989; b) J. Mulzer, P. A. Mareski, J. Buschmann, P. Luger, *Synthesis* **1992**, 215–228; c) K. C. Nicolaou, A. P. Patron, K. Ajito, P. K. Richter, H. Khatuya, P. Bertinato, R. A. Miller, M. J. Tomaszewski, *Chem. Eur. J.* **1996**, *2*, 847–868.

[26] K. C. Nicolaou, S. E. Webber, *Synthesis*, **1986**, 453–461.

[27] a) J. A. Marshall, B. S. DeHoff, D. G. Cleary, *J. Org. Chem.* **1986**, *51*, 1735–1741; b) H. J. Bestmann, *Angew. Chem. Int. Ed. Engl.* **1965**, *4*, 645–660.

[28] D. Heissler, T. Jenn, H. Nagano, *Tetrahedron Lett.* **1991**, *32*, 7587–7590.

[29] a) D. Enders, H. Eichenauer, *Chem. Ber.* **1979**, *112*, 2933–2960; b) D. Enders, J. Tiebes, N. De Kimpe, M. Keppens, C. Stevens, G. Smagghe, O. Betz, *J. Org. Chem.* **1993**, *58*, 4881–4884; c) D. Enders, A. Plant, D. Backhaus, U. Reinhold, *Tetrahedron* **1995**, *51*, 10699–10714. We thank Prof. Enders for a generous gift of SAMP.

[30] D. Enders, D. Backhaus, J. Runsink, *Tetrahedron* **1996**, *52*, 1503–1528.

[31] D. Yang, M.-K. Wong, Y.-C. Yip, *J. Org. Chem.* **1995**, *60*, 3887–3889.

[32] K. C. Nicolaou, D. Vourloumis, T. Li, J. Pastor, N. Winssinger, Y. He, S. Ninkovic, F. Sarabia, H. Vallberg, F. Roschangar, N. P. King, M. R. V. Finlay, T. Fojo, P. Giannakakou, P. Verdier-Pinard, E. Hamel, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2097–2103.

[33] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. *CCDC-100708*. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB21EZ, UK (Fax: Int. code + (1223)336-033; e-mail: deposit@chemcrys.cam.ac.uk).

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