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Total Synthesis of Phorboxazole B

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Abstract: An efficient and highly convergent total synthesis of the potent antitumor agent phorboxazole B has been achieved. The synthetic strategy of this synthesis features: 1) a highly efficient substrate-controlled hydrogenation to construct the functionalized *cis*-tetrahydropyrane unit; 2) iterative crotyl addition to synthesize the segment that contains alternating hydroxyl and methyl substituents; 3) $Hg(OAc)_2$/I_2-induced cyclization to establish the *cis*-tetrahydropyrane moiety; 4) 1,3-asymmetric induction in the Mukaiyama aldol reaction to afford the stereogenic centers at C9 and C3; and 5) the exploration of the Still–Gennari olefination reaction to complete the macrolide ring of phorboxazoloe B.

Keywords: antitumor agents · natural products · phorboxazole B · total synthesis

Introduction

Marine sponges have been extensively investigated as important sources of architecturally complex, biologically active natural products. Phorboxazole A (**1**) and its epimer phorboxazole B (**2**) were isolated from the Indian ocean sponge *Phorbas sp*. by Molinski and co-workers.[1] The relative and absolute stereochemistries of the phorboxazoles have been determined by extensive NMR spectroscopic analysis, degradation studies, and synthetic correlation. Phorboxazoles represent a new class of 21-membered macrolides, accommodating four heavily functionalized oxanes and two 2,4-disubstituted oxazoles.[2] In addition to their potent antifungal activity against *Candida albicans* and *Saccharomyces carlsbergensis*, phorboxazoles have also demonstrated exceptional inhibition of cell growth.[1] These metabolites are ranked among the most cytostatic natural products ever known, exhibiting extraordinary potency (mean $GI_{50} = < 1.6 \times 10^{-9}$ M; GI_{50}: 50% inhibition of cell growth) when bioassayed for 60 human tumor cell strains at the National Cancer Institute (NCI).[1] Although the exact mechanism of action of the phorboxazoles remains unknown, studies have shown that they do not inhibit or promote tubulin polymerization; a process that is known to play an important role in the mechanism of action of several antitumor natural products, such as taxol and the epothilones.[3] The unprecedented structural features and the remarkable antitumor activities of the phorboxazoles have attracted great attention in the synthetic community,[4] with excellent total syntheses reported by Forsyth,[5] Evans,[6] Smith,[7] Pattenden,[8] and Williams.[9] In connection with our previous work on phorboxazole B,[4o–p,q,s] we herein wish to report our total synthesis.

Retrosynthetic analysis: Our retrosynthetic analysis of phorboxazole B (Scheme 1) began with the disconnection of the C2=C3 and C19=C20 double bonds, which led us to the key building blocks **3** and **4**. In the synthetic sense, segments **3** and **4** could be combined by an *E*-selective Wittig reaction, as reported by the Evans group.[6] It was desirable to construct the C2=C3 *Z*-double bond by employing the Still–Gennari olefination that was reported by Forsyth,[5] Smith,[7] Pattenden,[8] and Williams,[9] in their synthesis of phorboxazole A. By further continuing with this analysis, disconnection of the C32–C33 bond and the C41=C42 double bond would separate **4** into tetrahydropyranyl oxazole **5**, lactone **6**, and the known sulfone **7**.[6] It was envisaged that the coupling of lactone **5** with **6**, by using a metalation reaction (nucleophilic addition),[6] followed by Julia olefination with sulfone **7**, would lead to the formation of the C20–C46 segment **4**.

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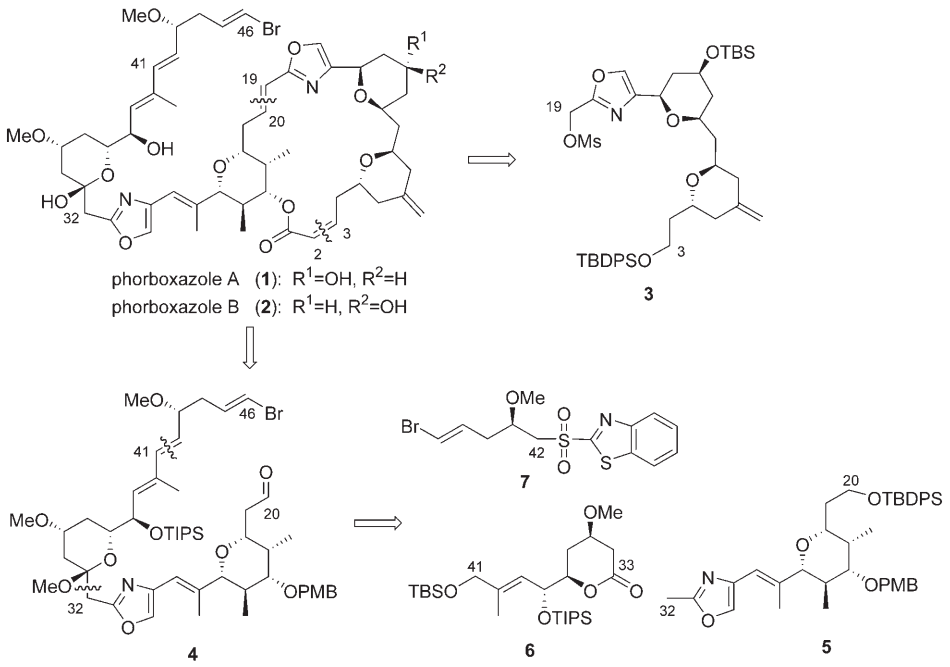
Supporting information for this article (copies of ^1H and ^{13}C NMR spectra) is available on the WWW under http://www.chemeurj.org/ or from the author.

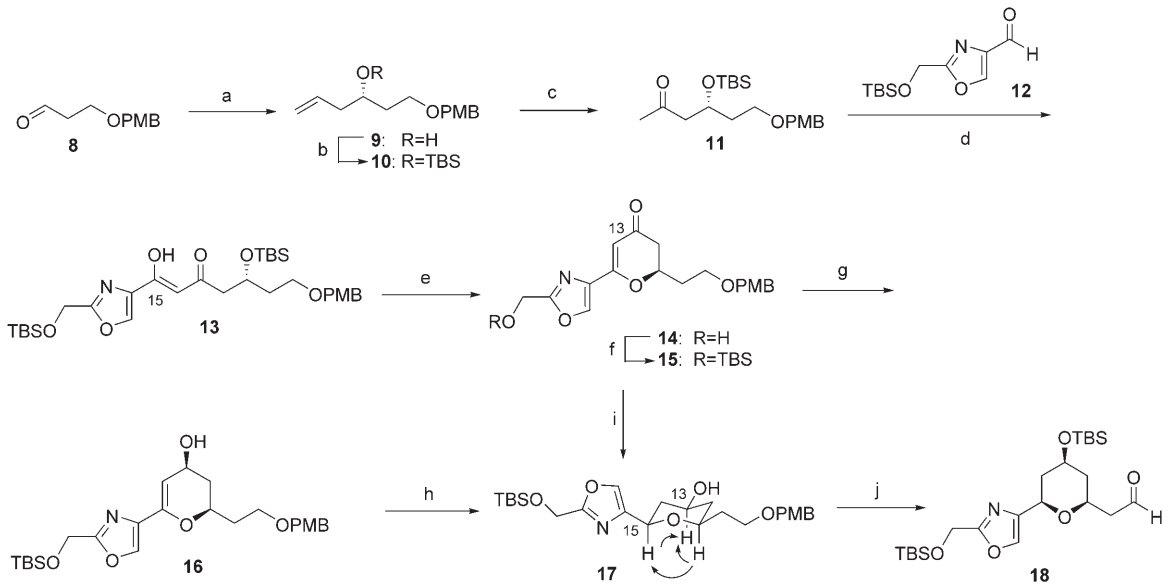


Scheme 1. Retrosynthetic analysis of phorboxazole B.

Results and Discussion

Synthesis of the C3–C19 bistetrahydropyrane segment 3: Brown asymmetric allylation[10] of aldehyde **8** produced the chiral alcohol **9**[7d] with 87% *ee* (*ee* = enantiomeric excess, determined by HPLC analysis, Scheme 2), which was followed by TBS (*tert*-butyldimethylsilyl) ether protection[11] to furnish compound **10**. Exposure of the chiral building block **10** to Wacker oxidation[12] produced the methyl ketone **11** in 89% yield. Treatment of the lithium enolate of **11** with aldehyde **12**[13] in THF at −78 °C led to a mixture of two C15 epimeric isomers of β-hydroxy ketone, which were transformed to the β-diketone **13** by the oxidation with Dess–Martin periodinane (DMP).[14] ^{1}H NMR spectroscopy showed that the β-diketone **13** existed entirely as the enol-ketone. As was expected, exposure of **13** to a 5% solution of hydrofluoric acid[15] in acetonitrile at room temperature led to the production of the cyclodehydrated product **14** in excellent yield (90%). The primary hydroxyl of **14** was then reprotected with a TBS group to afford 2*H*-pyranone **15** in 97% yield.

With a quantity of **15** in hand, we focused our attention on the construction of the C13 and C15 stereogenic centers by substrate-controlled hydrogenation chemistry.[16] Thus, stereoselective Luche reduction[17] of 2*H*-pyranone **15** in



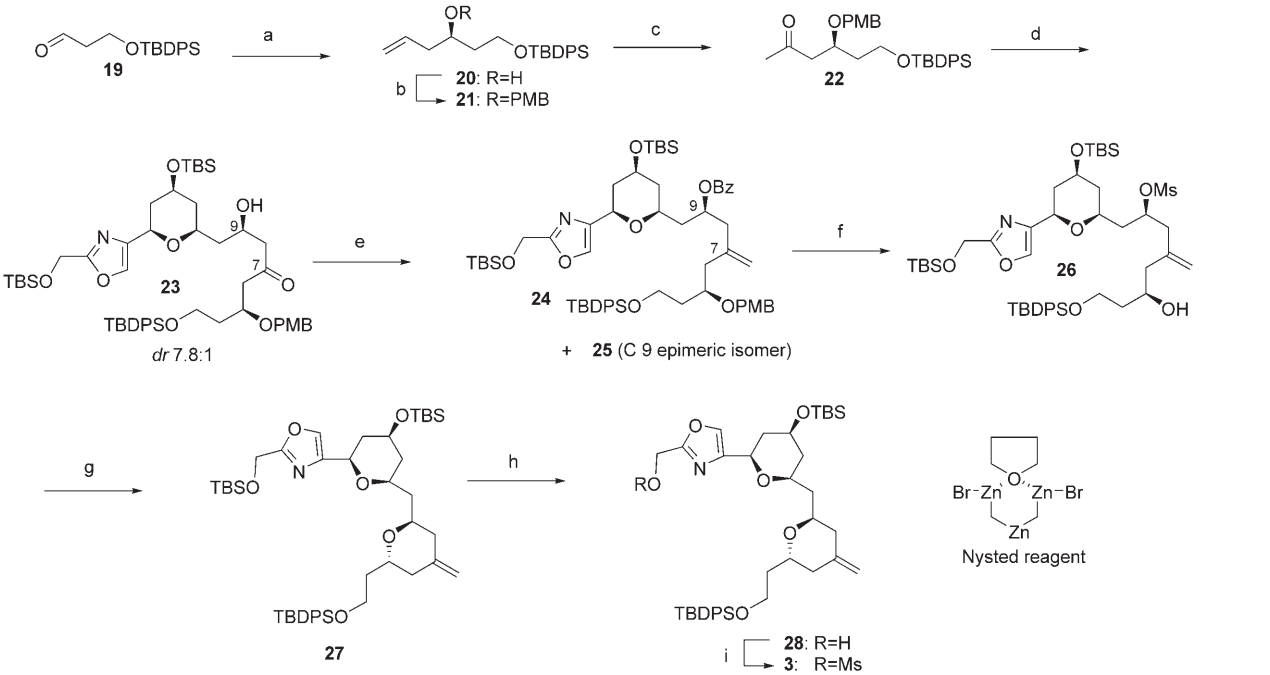
Scheme 2. Synthesis of the C9–C19 segment **18**. a) (−)-Ipc$_2$BAllyl, Et$_2$O, −78 °C, 87% *ee*, 71%; b) TBSCl, imidazole, DMF, 96%; c) PdCl$_2$ (cat), CuCl, O$_2$, DMF/H$_2$O, RT, 6 h, 89%; d) 1) LDA, **12**, THF, −78 °C; 2) Dess–Martin periodinane, CH$_2$Cl$_2$, RT, 90% for the two steps; e) 5% HF in CH$_3$CN, RT, 12 h, 90%; f) TBSCl, imidazole, DMF, RT, 97%; g) NaBH$_4$, CeCl$_3$, MeOH, −78 °C, 95%; h) H$_2$, 10% Pd/C, EtOAc, 8 h, 95%; i) H$_2$, 10% Pd/C, EtOAc (saturated with 0.1 N HCl), 8 h, 65%; j) 1) TBSCl, imidazole, DMF, RT; 2) DDQ, CH$_2$Cl$_2$, RT; 3) Dess–Martin periodinane, CH$_2$Cl$_2$, RT, 82% for the three steps.

methanol at −78 °C provided **16** in 95 % yield as a single isomer.

The next step involved the creation of the *cis*-tetrahydropyrane (C11/C15) ring by means of a stereoselective substrate-controlled hydrogenation of the C14=C15 double bond. In the presence of a catalytic amount of palladium on charcoal, compound **16** was readily hydrogenated to give the *cis*-tetrahydropyrane **17** in 95 % yield as a single isomer. The NOE effect between H-11, H-13, and H-15 confirmed the *cis*-tetrahydropyrane structure of **17**. We then decided to explore the possibility of constructing the C13 and C15 stereocenters in one pot. To our delight, direct hydrogenation of **15** in ethyl acetate also delivered the desired *cis*-tetrahydropyrane **17**, although the yield was initially very low. By conducting the reaction in ethyl acetate, saturated with HCl (0.1 N), the yield was optimized to 65 % yield. Thus, the C9–C19 *cis*-tetrahydropyrane unit was stereoselectively synthesized from 2*H*-pyranone **15** by a one-pot substrate-directed hydrogenation. Protection (TBSCl) of the C13 hydroxy group of compound **17** and subsequent removal of the PMB-protecting group (PMB = *p*-methoxybenzyl),[18] followed by oxidation of the resulting primary hydroxy, afforded the corresponding aldehyde **18** in 82 % yield (overall yield for the three steps).

The next step involved the synthesis of the C3–C19 segment **3** from the TBDPS-protected propionaldehyde **19** (TBDPS = *tert*-butyldiphenylsilyl, Scheme 3). Brown asymmetric allylation[10] of **19** (87 % *ee*, as determined by analysis of the corresponding Mosher's ester), followed by protection[19] (PMB) of the resulting chiral alcohol **20**[20] and Wacker oxidation of the PMB ether **21**, furnished the C3–C8 segment **22** of phorboxazole B. An aldol reaction of aldehyde **18** with the silyl enol ether of **22**, under Mukaiyama's conditions,[21] produced the β-hydroxyl ketone **23** as an inseparable mixture of C9 epimeric isomers (7.8:1).[22] The next step in the synthesis was to convert the ketone at C7 to a methylene moiety. Unfortunately, methylenation of the ketone in **23** did not result in the desired product, despite the employment of various reaction conditions, such as those reported by Petasis,[23] Lombardo,[24] and Takai.[25] This was probably due to the susceptibility of the β-hydroxyl ketone moiety to the reaction conditions. Thus, to suppress undesirable side reactions, **23** was first shielded with a benzoyl group[26] and then methylenated with Nysted reagent (*cyclo*-dibromodi-μ-methylene [μ-(tetrahydrofuran)]trizinc)[27] to give **24** in 66 % yield and the C9 epimer **25** in 8 % yield.

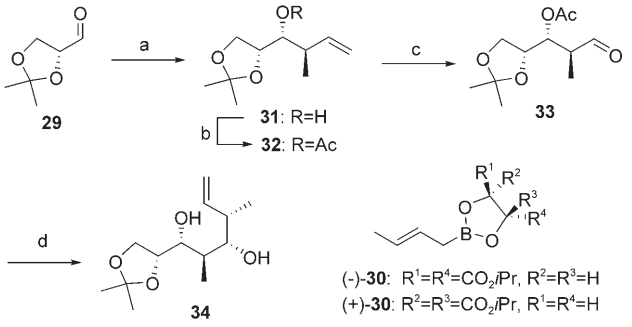
These two isomers were conveniently separated by flash-column chromatography on silica gel. Removal of the benzoyl-protecting group by reduction with DIBAL (diisobutylaluminumhydride) and subsequent mesylation[28] of the resulting hydroxyl, followed by cleavage of the PMB-protecting group, provided **26** in 68 % yield (overall yield for the three steps). Finally, a solution of compound **26** in acetonitrile was refluxed for 12 h with excess triethylamine (conducted according to Forsyth's method)[5] to produce compound **27** (83 % yield) and thus complete the construction of the desired bistetrahydropyrane moiety. The *cis* configura-



Scheme 3. Completion of the C3–C19 segment **3**. a) (+)-$Ipc_2BAllyl$, Et_2O, −78 °C, 87 % *ee*, 74 %; b) $PMBOC(=NH)CCl_3$, cyclohexane/CH_2Cl_2, $BF_3{\cdot}OEt_2$, 0 °C, 87 %; c) $PdCl_2$ (cat), CuCl, O_2, DMF/H_2O, RT, 6 h, 86 %; d) 1) LHDMS, TMSCl, THF, −78 °C; 2) **18**, $TiCl_4$, −78 °C, 68 %; e) 1) BzCl, py (pyridine), RT; 2) Nysted reagent, $TiCl_4$, RT, 30 min, 66 % for the two steps; f) 1) DIBAL, CH_2Cl_2, −78 °C; 2) MsCl (Ms = mesyl), Et_3N, CH_2Cl_2, 0 °C; 3) DDQ, CH_2Cl_2/H_2O, 67 % for the three steps; g) Et_3N, CH_3CN, reflux, 83 %; h) NH_4F, MeOH, 50 °C, 81 %; i) DIPEA, MsCl, 90 %.

tion of the newly formed tetrahydropyrane was confirmed by 2D NOESY spectroscopic analysis. Selective deprotection (NH_4F/MeOH, 50°C)[29] of the TBS ether at C19, followed by subsequent mesylation completed the synthesis of segment **3**.

Synthesis of the C20–C32 tetrahydropyrane-oxazole segment 5: As segment **5** contained contiguous stereogenic centers bearing alternating hydroxyl and methyl substituents, it was planned to utilize asymmetric crotyl addition reactions for their construction (Scheme 4). Thus, the asymmetric crotyl

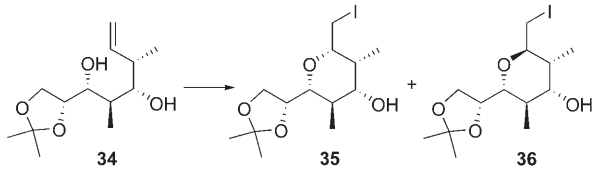


Scheme 4. Iterative crotyl addition reactions. a) (−)-**30**, 4 Å MS, toluene, −78°C, 7 h, 65%; b) Ac_2O, Et_3N, DMAP (cat), CH_2Cl_2, RT, overnight, 95%; c) O_3, MeOH, −78°C; then PPh_3, RT, 85%; d) (+)-**30**, 4 Å MS, toluene, −78°C, 6 h, 70%.

addition of chiral boronate (−)-**30** to **29** (generated from D-mannitol),[30] under Roush's conditions,[31] afforded homoallylic alcohol **31**.[32] This compound was subsequently transformed to its acetate **32**, according to the standard procedure.[33] Asymmetric crotylation of aldehyde **33**, obtained from the ozonolysis of **32**, was performed with (+)-**30**, followed by treatment with sodium hydroxide.

To our surprise, ^{1}H NMR spectroscopy of the product indicated that the B−O bond was not cleaved by the usual workup procedure.[31] This problem was solved by treating the product mixture with 10% NaOH in diethyl ether, instead of toluene. This method resulted in the simultaneous hydrolysis of the acetate to provide diol **34**. For the construction of the *cis*-tetrahydropyrane unit of **5**, we first explored the iodocyclization[34] reaction of **34**. However, iodocyclization of diol **34** with iodine in acetonitrile yielded a complex mixture (Table 1, entry 1), probably due to the lability of the acetonide to the HI generated during the cyclization process. Therefore, $NaHCO_3$ was added to the reaction mixture (entry 2) and, to our delight, the desired *cis*-tetrahydropyrane **35** and minor *trans* isomer **36** were obtained in an overall yield of 46% (**35**:**36** 2.6:1). To optimize the stereochemical outcome, NIS (*N*-iodosuccinimide) was employed (entry 3); however, despite an increase in the ratio of **35**/**36** to 7.7:1, the overall yield of the reaction was still unsatisfactory (52% based on a 40% recovery of the starting material). With this in mind, our attention turned to the $Hg(OAc)_2$-induced cyclization, which is also known to be a general method for preparing tetrahydropyrane systems.[35]

Table 1. Construction of the *cis*-tetrahydropyrane moiety of **5**.



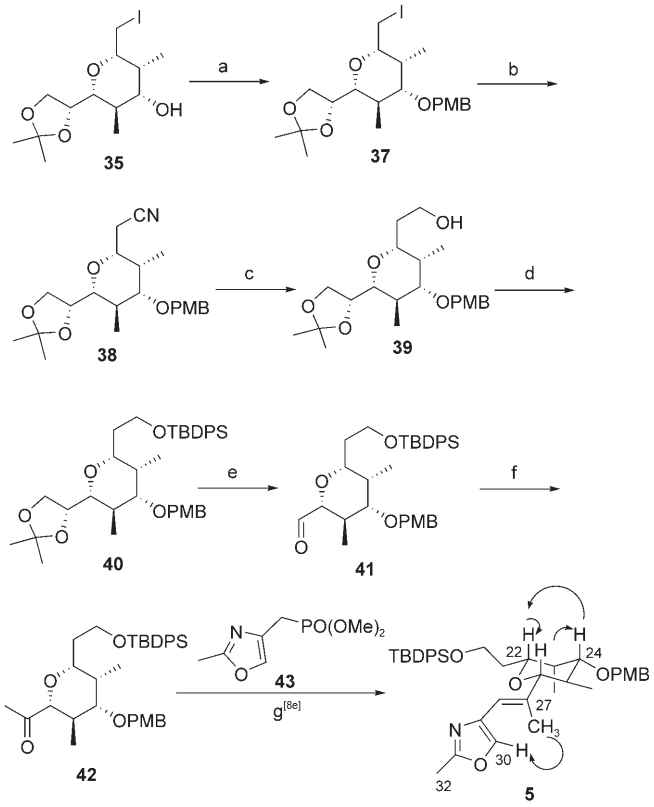
Entry	Conditions	**35**:**36**[a]	Yield [%][b]
1	I_2, CH_3CN, −35 to 0°C	–	–[c]
2	I_2, $NaHCO_3$, CH_3CN, 0°C	2.6:1	46
3	NIS, CH_2Cl_2, 30°C	7.7:1	52[d]
4	$Hg(OAc)_2$, toluene, 0°C; I_2, 30°C	5:1	86

[a] The product ratio was determined by ^{1}H NMR spectral analysis (300 MHz). [b] Isolated yield. [c] Complex mixture. [d] Based on a 40% recovery of the starting material.

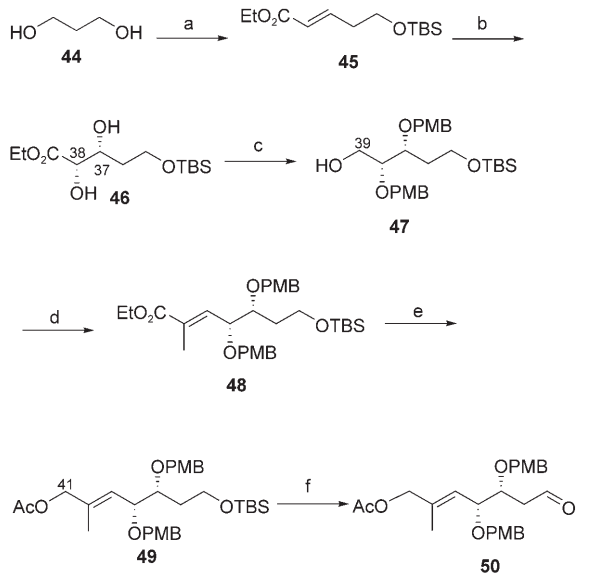
After screening various solvents and reaction conditions, we found that the treatment of diol **34** with $Hg(OAc)_2$ in dry toluene at 0°C, followed by the treatment of the resulting organomercurate with iodine, produced the *cis*-tetrahydropyrane **35** in 86% yield with a 5:1 *dr* (*dr* = diastereomeric ratio). Isolation of compound **35** was achieved by flash chromatography over silica gel, producing **35** in a 71% yield as the major diastereomer. The configuration of **35** was later confirmed by 2D NOESY spectroscopic analysis of oxazole **5**.

Protection of the hydroxyl group in **35** with *p*-methoxybenzyl trichloroacetimidiate[19] in the presence of $BF_3{\cdot}OEt_2$ produced the PMB ether **37** (Scheme 5). This compound **37** was then converted to the nitrile **38**, which was successively reduced with DIBAL and $NaBH_4$ to give alcohol **39**.[36] Protection of the hydroxyl group in **39** with TBDPSCl[37] provided the ether **40**, which was converted to aldehyde **41** by the use of periodic acid.[38] Addition of MeLi to aldehyde **41**, followed by Dess–Martin oxidation, afforded methyl ketone **42**. To complete the synthesis of oxazole **5**, an *E*-selective olefination reaction was required to construct the C27=C28 trisubstituted double bond. Although the Wittig[39] and Julia olefination[40] reactions have been successfully employed in the construction of *E*-double bonds, we found that our methyl ketone reacted sluggishly under these reaction conditions. Ultimately, we resorted to the procedure described by Pattenden, in which the oxazole phosphonate ester **43** was employed.[8e] To our delight, when the phosphonate ester **43** was deprotonated with LDA (lithium diisopropylamide) at −78°C, followed by treatment with methyl ketone **42**, the desired THP-oxazole (THP = tetrahydropyran) segment **5** was obtained in 78% yield (based on 20% recovery of the starting material). The *cis* configuration of the tetrahydropyrane in compound **5** was confirmed by the NOE effect observed between H22, H24, and H26. The NOE effect between the C27 methyl group and H30 confirmed the *E* configuration of the C27=C28 double bond.

Synthesis of the C33–C41 lactone segment 6: Monosilylation of 1,3-propanediol **44** and subsequent oxidation with PCC (pyridinium chlorochromate), followed by olefination of the



Scheme 5. Synthesis of oxazole **5**. a) PMBOC(=NH)CCl_3, $BF_3{\cdot}OEt_2$, 0 °C, 79 %; b) NaCN, DMSO, 70 °C, 81 %; c) 1) DIBAL, CH_2Cl_2, 0 °C; then 1 N HCl; 2) $NaBH_4$, MeOH, 72 % for the two steps; d) TBDPSCl, Et_3N, CH_2Cl_2, 92 %; e) HIO_4, EtOAc; f) 1) MeLi, THF, −78 °C; 2) Dess–Martin periodinane, CH_2Cl_2, RT, 58 % for the three steps; g) LDA, THF, −78 °C, 78 % based on the recovery of **42**.

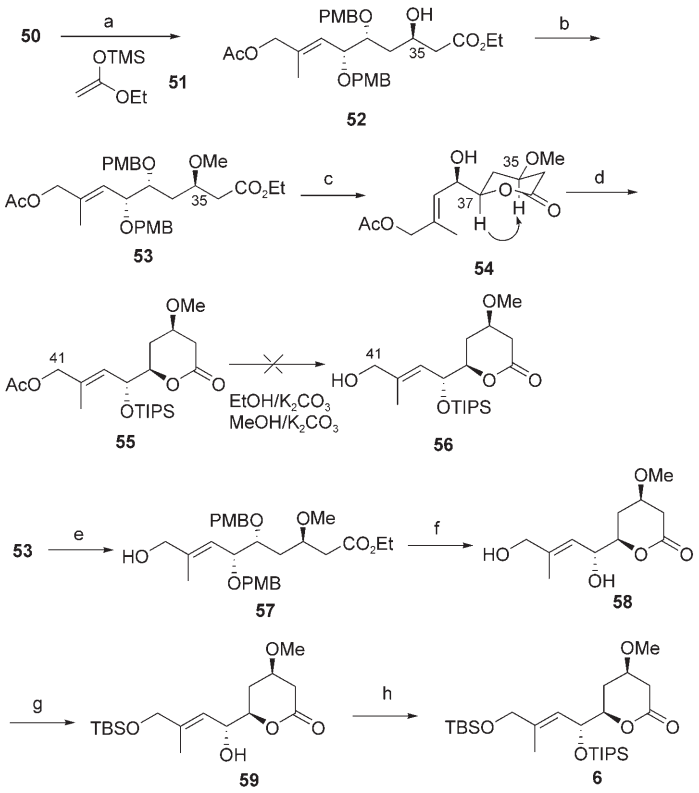


Scheme 6. Synthesis of the C35–C41 segment. a) 1) NaH, TBSCl, THF, 0 °C; 2) PCC, CH_2Cl_2, RT; 3) $Ph_3P{=}CHCO_2Et$, benzene, reflux, 51 % for the three steps; b) AD-mix β, *t*BuOH/H_2O, RT, 86 % *ee*, 87 %; c) 1) PMBOC(=NH)CCl_3, cyclohexane/CH_2Cl_2, $BF_3{\cdot}OEt_2$, 0 °C; 2) $LiAlH_4$, Et_2O, RT, 72 % for the two steps; d) 1) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; then Et_3N; 2) $CH_3C(PPh_3)CO_2Et$, CH_2Cl_2, reflux, 84 % for the two steps; e) 1) DIBAL, CH_2Cl_2, −78 °C; 2) Ac_2O, Et_3N, CH_2Cl_2, RT, 90 % for two steps; f) 1) Bu_4NF, THF, RT; 2) Dess–Martin periodinane, CH_2Cl_2, 86 % for the two steps.

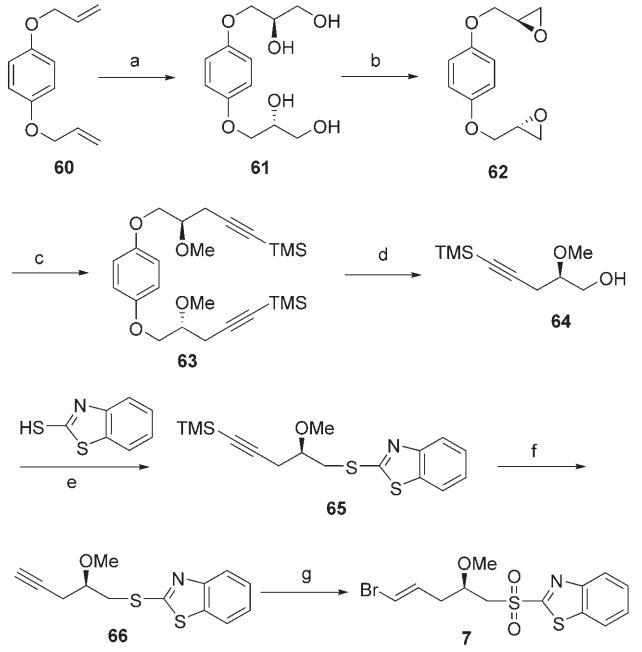
resultant aldehyde, produced the unsaturated ester **45**[41] (*E*/*Z* > 95:5, Scheme 6).[42] Sharpless asymmetric dihydroxylation of **45** set the stereogenic centers at C37 and C38 in place, affording the diol **46** in 87 % yield (86 % *ee*, as determined by chiral GC analysis).[43] Protection of the hydroxyl groups of **46** with *p*-methoxybenzyl trichloroacetimidiate in the presence of $BF_3{\cdot}OEt_2$,[19] followed by reduction with LAH (lithium aluminum hydride) afforded the alcohol **47**. As the PMB ether group appeared from the literature to produce the best 1,3-stereoinduction in the Mukaiyama aldol reaction, we selected this group for the protection of the hydroxyl groups at C37 and C38.[21a,b] Swern oxidation[44] of the hydroxyl group at C39 in **47**, followed by Wittig olefination of the resulting aldehyde with $CH_3C(PPh_3)CO_2Et$, incorporated the *E*-unsaturated ester in **48**.[8a] Ester **48** was conveniently transformed to the acetate **49** by reduction with DIBAL and acylation of the resultant C41 hydroxyl group.[33]

Hydrolysis of the TBS ether of **49**, followed by oxidation of the alcohol under Dess–Martin conditions yielded **50**, a β-OPMB-protected aldehyde suitable for the 1,3-*anti* Mukaiyama aldol reaction. The aldol condensation of 1-ethoxy-1-[(trimethylsilyl)oxy]ethane **51**[45] with aldehyde **50** (Scheme 7) afforded **52** with modest stereoselectivity under standard conditions ($BF_3{\cdot}OEt_2$, $MgBr_2{\cdot}OEt_2$). The use of strong Lewis acids, such as $TiCl_4$, did not promote a clean reaction; however, the use of the mixed titanium species $TiCl_2(O\mathit{i}Pr)_2$ (toluene, −78 °C) delivered a high-yielding, stereoselective reaction (87 %, 4:1 *dr*)[42] that was consistent with the results reported by Evans et al.[46] Compound **52** was isolated in 61 % yield as the major diastereomer. The orientation of the C35 hydroxyl group was assigned as β, based on 2D NOESY spectroscopy of the succeeding lactone **54**. Several methylation methods to protect the free hydroxyl group in **52** proved unsuccessful; these methods included the use of NaH/CH_3I[47] and a catalyzed diazomethane procedure.[48] However, treatment of **52** with Meerwein's salt (Me_3OBF_4)[6b] and 1,8-bis(dimethylamino)naphthalene (proton sponge) produced the desired methyl ether **53** in 85 % yield.

Oxidative deprotection of the two vicinal PMB ethers in **53**[49] proved difficult with reagents, such as DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone)[18] and CAN (ceric ammonium nitrate).[50] Fortunately, when compound **53** was treated with 10 % CF_3CO_2H in CH_2Cl_2,[51] the PMB ethers were removed and the resultant diol was spontaneously cyclized to afford lactone **54** in excellent yield (95 %). The NOE effect between H35 and H37 in lactone **54** convinced us of the configuration of C35. Protection of the C38 free hydroxyl as its TIPS (triisopropylsilyl) ether furnished lactone **55**.[52] The next step in the synthesis of lactone **6** was to replace the C41 acetoxyl moiety in **55** with a TBS ether. Unfortunately, deprotection of the C41 acetoxy group in **55**



Scheme 7. Synthesis of lactone **6**. a) $TiCl_2(OiPr)_2$, toluene, −78 °C; then compound **51**, 87 %, 4:1 *dr*; b) Me_3OBF_4, proton sponge, CH_2Cl_2, RT, 85 %; c) 10 % CF_3CO_2H, CH_2Cl_2, RT, 95 %; d) TIPSCl, imidazole, DMAP (cat), DMF, RT, 78 %; e) K_2CO_3, EtOH, 97 %; f) 10 % CF_3CO_2H, CH_2Cl_2; then Et_3N, 85 %; g) TBSCl, Et_3N, CH_2Cl_2, 75 %; h) TIPSCl, $AgNO_3$, py, 78 %.

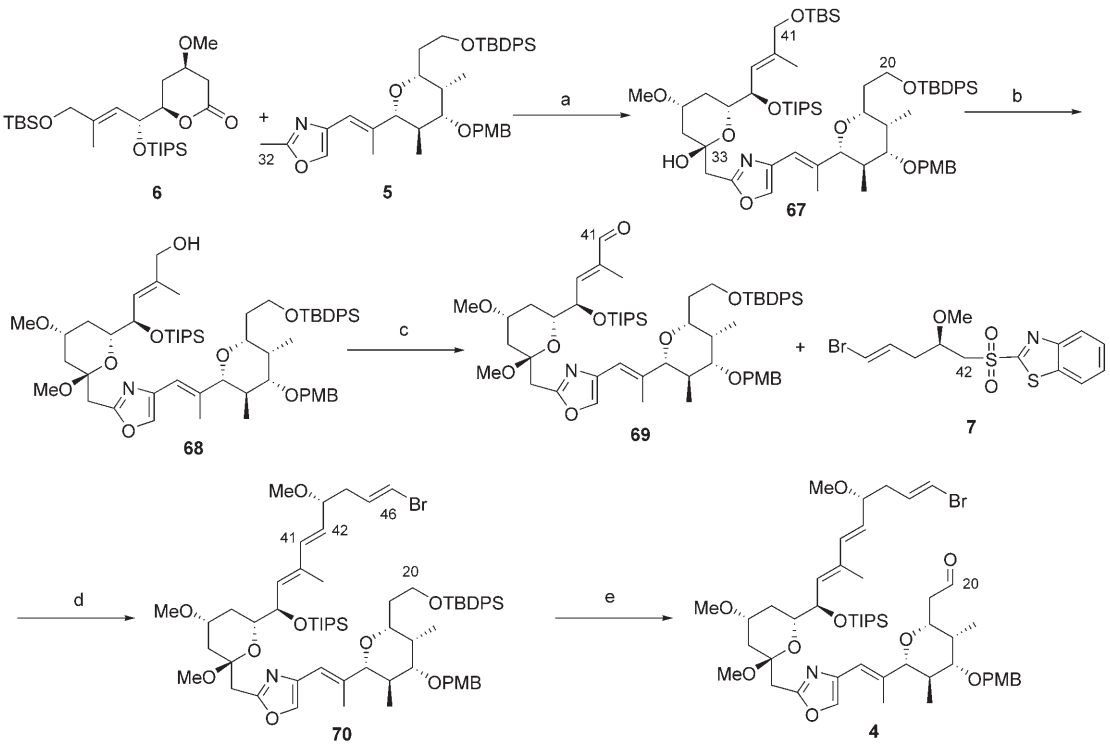


Scheme 8. Synthesis of sulfone **7**. a) AD-mix-α, *t*BuOH/H_2O, RT, 87 % *ee*, 66 %; b) 1) HBr, AcOH; 2) K_2CO_3, MeOH, 88 %; c) 1) TMSC≡CH, BuLi, $BF_3{\cdot}OEt_2$, THF, −78 °C; 2) Me_3OBF_4, proton sponge, CH_2Cl_2, RT, 70 % for the two steps; d) CAN, CH_3CN/H_2O, RT, 91 %; e) 2-mercaptobenzothiazole, PPh_3, DEAD (diethyl azodicarboxylate), THF, 0 °C, 81 %; f) TBAF, THF, RT, 99 %; g) 1) Cp_2ZrHCl, THF; then NBS; 2) $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, 30 % H_2O_2, EtOH, 56 % for the two steps.

under basic conditions, such as K_2CO_3/EtOH[53] or K_2CO_3/MeOH, did not afford the desired product **56**, possibly as a result of the susceptibility of the lactone moiety in **55** to these reaction conditions. Alternatively, deprotection of the acetoxy group in **53** with K_2CO_3/EtOH[53] afforded alcohol **57** in 97 % yield. When compound **57** was treated with 10 % CF_3CO_2H in CH_2Cl_2,[51] the PMB-protecting groups were removed, and the resultant triol concomitantly cyclized to afford the lactone **58**. As lactone **58** was highly soluble in water, the reaction mixture was directly neutralized with Et_3N, concentrated, and then purified by flash-column chromatography without extraction. Selective protection of the primary hydroxyl group in **58** with TBSCl/Et_3N[54] delivered the mono-TBS ether **59**. Whilst protection of **59** with a TIPS group under routine conditions (TIPSCl, imidazole, DMAP (4-dimethylaminopyridine, cat), DMF)[52] was unsuccessful, the use of TIPSCl/$AgNO_3$[55] afforded the desired lactone **6**.

Synthesis of sulfone 7:[6,8,9] Following the procedure reported by Wang,[56] Sharpless asymmetric dihydroxylation of **60** was carried out to produce alcohol **61** (87 % *ee*, as determined by HPLC analysis); this was followed by epoxide formation to give the optically active bis-3C building block **62** (Scheme 8). Ring opening of **62** by the use of lithium TMS acetylide in the presence of $BF_3{\cdot}OEt_2$, followed by methylation of the resulting diol with Meerwein's salt (Me_3OBF_4), produced the corresponding methyl ether **63**.[6b] Treatment of **63** with CAN[56] removed the hydroquinone and produced two equivalents of the known alcohol **64**.[7d,8e] Displacement of the primary alcohol of **64** with 2-mercaptobenzothiazole and desilylation of the TMS group furnished the alkyne **66**. Finally, introduction of the vinyl bromide by hydrozirconation of the alkyne and treatment with NBS (*N*-bromosuccinimide),[57] followed by oxidation of the sulfide with ammonium molybdate,[6d] afforded the desired sulfone **7**.

Completion of the total synthesis of phorboxazole B: With segments **5**, **6**, and **7** in hand, the stage was set for the completion of the synthesis of phorboxazole B (Scheme 9). Thus, oxazole **5** was deprotonated with lithium diethylamide at −78 °C,[6a] and then treated with lactone **6** to produce the desired cyclic hemiketal **67** in 61 % yield as the sole isomer. Selective deprotection of the TBS ether at C41 in **67** and spontaneous methyl protection of the hemiketal was accomplished with PPTS (pyridinium *p*-toluene sulfonate)/MeOH to afford the allylic primary alcohol **68**. Careful oxidation of **68** with Dess–Martin periodinane,[14] followed by Julia olefination of the resulting aldehyde **69** with sulfone **7**, furnished the desired *E*-diene moiety ($E/Z > 95:5$),[42] thus completing the synthesis of the C20–C46 segment **70** of phorboxazole B. Selective deprotection[29] of the TBDPS ether at C20 in **70**,



Scheme 9. Synthesis of the C20–C46 segment. a) $LiNEt_2$, THF, −78 °C; then **6**, 61 %; b) PPTS, MeOH, 30 °C, 81 %; c) Dess–Martin periodinane, py, CH_2Cl_2, RT, 93 %; d) NaHMDS, THF, −78 °C, 78 %; e) 1) NH_4F, MeOH, 50 °C; 2) Dess–Martin periodinane, py, CH_2Cl_2, RT, 71 % for the two steps.

followed by subsequent oxidation gave the key aldehyde **4** in an overall 71 % yield for the two steps.

By using a strategy similar to that employed by Evans,[6] Smith,[7] Pattenden,[8] and Williams,[9] we utilized an *E*-selective Wittig reaction to construct the C19=C20 double bond (Scheme 10). Thus, treatment of the mesylate **3** with tributyl phosphine led to the resulting phosphonium salt, which was subsequently treated with aldehyde **4** and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene to afford the *E*-alkene **71** ($E/Z > 95:5$).[42]

Following an extensive study, selective deprotection of the TBDPS ether at C3 was achieved by using NH_4F in MeOH (50 °C) to afford **72**. Oxidation of the alcohol and deprotection of the PMB ether at C24 with DDQ[18] produced compound **73** in 73 % yield. We envisaged using Still–Gennari olefination[58] to construct the macrolide ring of phorboxazoloe B; the same strategy that had been used in the synthesis of phorboxazole A.[5,7–9] Thus, esterification[59] of the C24 alcohol with dimethyl phosphonoacetic acid provided phosphonate **74**. Intramolecular olefination of **74** in toluene (K_2CO_3, [18]crown-6) effected a *Z*-selective macrolization to afford a mixture of macrocycles (*Z*/*E* 5:1, a similar ratio to that obtained in the synthesis of phorboxazole A[5,7–9]), which were easily separated on silica gel to give *Z*-macrolide **75** in 56 % yield.

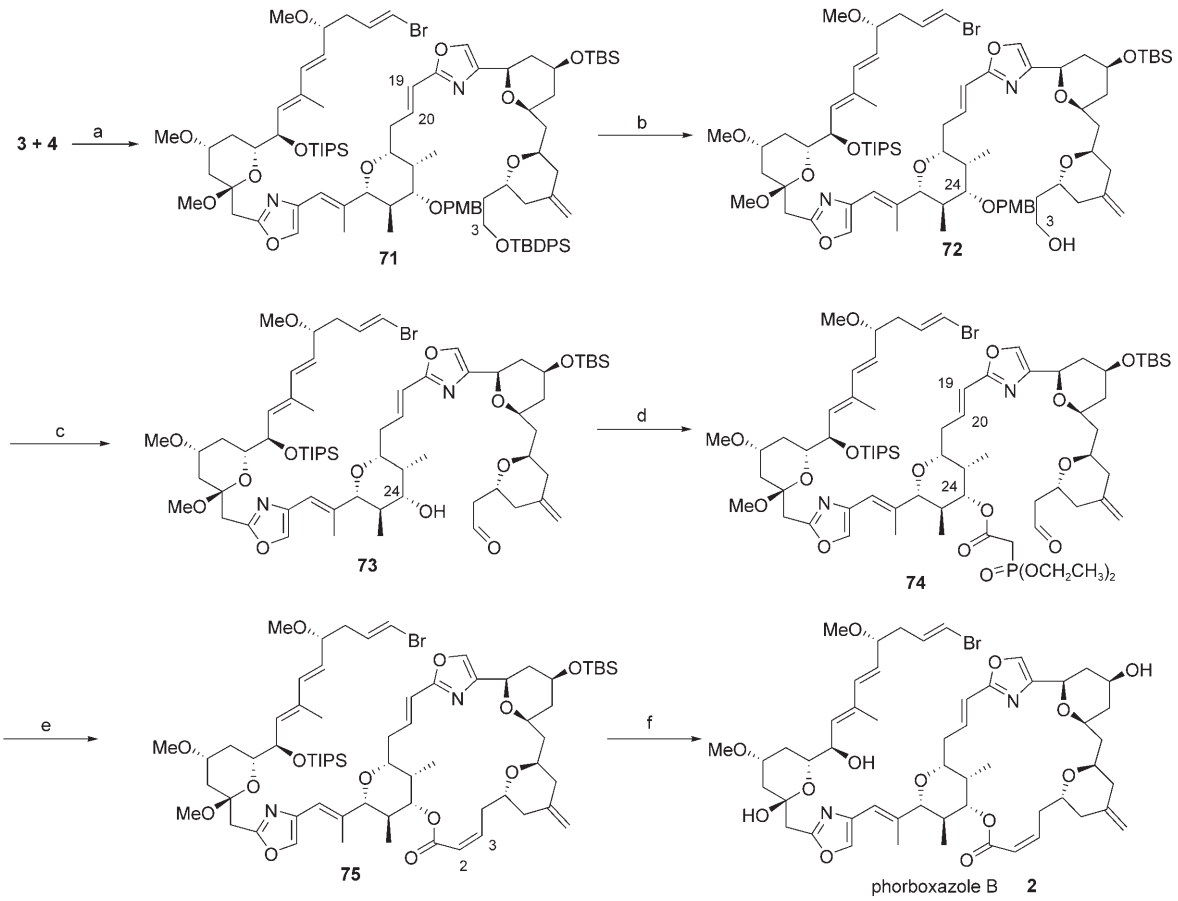
Finally, cleavage of the silyl ethers and the mixed methyl acetal by sequential treatment of **75** with TBAF (tetrabutylammonium fluoride)/THF and 6 % aqueous HCl/THF[5] produced phorboxazole B. The spectral data (^{1}H NMR, COSY (500 MHz), HRMS, and IR spectra; $[\alpha]_D$) of our synthetic material were identical to the corresponding spectral data reported for phorboxazole B.[1,6d]

Conclusion

We have accomplished the total synthesis of the potent antitumor marine natural product phorboxazole B, based on an efficient and convergent synthetic strategy. This synthesis features: 1) a highly efficient substrate-controlled hydrogenation to construct the functionalized *cis*-tetrahydropyrane unit; 2) iterative crotyl addition to synthesize the segment containing the alternating hydroxyl and methyl substituents; 3) $Hg(OAc)_2/I_2$-induced cyclization to establish the *cis*-tetrahydropyrane moiety; 4) 1,3-asymmetric induction in the Mukaiyama aldol reaction to generate the stereogenic centers at C9 and C35; and 5) Still–Gennari olefination to complete the macrolide ring of phorboxazoloe B.

Experimental Section

Optical rotations were measured by using a Perkin–Elmer 241 MC polarimeter in the solvent indicated. IR spectra were recorded on an AVATAR-360 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on MERCURY300, Bruker DRX-400, and Bruker AV-500 spectrometers with TMS as the internal standard. HRMS were recorded by using either FTMS-7 or IonSpec 4.7 spectrometers. Flash-column chromatography was carried out on silica gel (300–400 mesh). Yields refer to chroma-



Scheme 10. Completion of the synthesis of phorboxazole B. a) Bu_3P, DMF; then **4**, DBU, RT, 70%; b) NH_4F, MeOH, 50°C, 71%; c) 1) Dess–Martin periodinane, py, CH_2Cl_2, RT; 2) DDQ, CH_2Cl_2, buffer (pH 7), 73% for the two steps; d) dimethyl phosphonoacetic acid, DCC, CH_2Cl_2, 85%; e) K_2CO_3, [18]crown-6, toluene, −20°C, *Z*/*E* 5:1, 67%; f) 1) TBAF, THF, RT; 2) 6% HCl, THF, 51% for the two steps.

tographically and spectroscopically pure compounds, unless otherwise indicated.

Alcohol 9: A solution of allylmagnesium bromide (46.2 mmol) in Et_2O (80 mL) was added dropwise to a well-stirred solution of (−)-Ipc_2BOMe (15.4 g, 48.5 mmol) in anhydrous Et_2O (300 mL). Following completion of the addition, the reaction mixture was stirred for 1 h at RT, and was then cooled to −78°C. A solution of the aldehyde **8** (8.0 g, 41.0 mmol) in anhydrous Et_2O (80 mL) was added dropwise to this mixture, which was subsequently stirred for a further 4 h at −78°C. After this time, NaOH (3 N, 100 mL) was slowly added, followed by the addition of H_2O_2 (30%, 5 mL). The completion of the oxidation was ensured by refluxing the reaction mixture for 2 h. Once the reaction was complete, water (100 mL) was added and extracted with Et_2O (2×200 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Chromatography of the residue on silica gel (petroleum ether/EtOAc 10:1) provided alcohol **9** (6.91 g, 71%) as a colorless oil. The enantiomeric excess was determined as 87% (AS, 230 nm, hexane/2-propanol 60:40, 0.7 mL min^{-1}). R_f = 0.46 (petroleum ether/EtOAc 4:1); $[\alpha]_D^{20}$ = −5.8 (*c* = 1.37 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.23 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 5.86–5.77 (m, 1H), 5.11–5.09 (m, 1H), 5.05 (d, *J* = 1.2 Hz, 1H), 4.43 (s, 2H), 3.86–3.82 (m, 1H), 3.77 (s, 3H), 3.70–3.55 (m, 2H), 3.02 (br s, 1H), 2.24–2.20 (m, 2H), 1.75–1.69 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.1, 134.7, 129.9, 129.1 (2C), 117.3, 113.6 (2C), 72.7, 70.1, 68.4, 55.0, 41.7, 35.6 ppm; IR (film): $\tilde{\nu}$ = 3435, 3075, 2973, 2862, 1614, 1515, 1249 cm^{-1}; HRMS (ESI): calcd for $C_{14}H_{20}O_3Na$: 259.1305 $[M+Na]^+$; found: 259.1306.

Compound 10: *tert*-Butyldimethylsilyl chloride (4.13 g, 27.4 mmol) was added to a stirred solution of alcohol **9** (5.38 g, 22.8 mmol) and imidazole (3.88 g, 57.0 mmol) in DMF (12 mL). After stirring at RT for 3 h, the reaction mixture was poured into water (100 mL) and extracted with Et_2O (3×200 mL). The combined organic extracts were then washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Chromatography of the residue on silica gel (petroleum ether/EtOAc 20:1) provided **10** (7.66 g, 96%) as a colorless oil. R_f = 0.60 (petroleum ether/EtOAc 6:1); $[\alpha]_D^{20}$ = +15.7 (*c* = 1.65 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.36 (m, 2H), 7.02–6.98 (m, 2H), 6.01–5.80 (m, 1H), 5.19–5.17 (m, 1H), 5.15–5.13 (m, 1H), 4.57 (d, *J* = 11.4 Hz, 1H; B of AB), 4.51 (d, *J* = 11.4 Hz, 1H, A of AB), 4.08–3.95 (m, 1H), 3.91 (s, 3H), 3.66–3.62 (m, 2H), 2.38–2.33 (m, 2H), 1.91–1.81 (m, 2H), 1.03 (s, 9H), 0.18 ppm (d, *J* = 2.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.0, 134.9, 130.6, 129.2 (2C), 116.9, 113.7 (2C), 72.6, 68.9, 66.7, 55.2, 42.3, 36.7, 25.8 (3C), 18.0, −4.4, −4.8 ppm; IR (film): $\tilde{\nu}$ = 3076, 2956, 2930, 2858, 1614, 1515, 1250 cm^{-1}; HRMS (ESI): calcd for $C_{20}H_{34}O_3SiNa$: 373.2169 $[M+Na]^+$; found: 373.2169.

Ketone 11: Oxygen was bubbled into a mixture of $PdCl_2$ (18 mg, 0.1 mmol), CuCl (99 mg, 1.0 mmol), DMF (7 mL), and water (1 mL) at RT. The reaction mixture was stirred at RT for 30 min to give a deep-green mixture, and then compound **10** (350 mg, 1.0 mmol) was added. After the mixture had been vigorously stirred for a further 6 h under an atmosphere of oxygen, water (5 mL) was added to quench the reaction, and the resulting mixture was extracted with Et_2O (4×15 mL). The combined organic phases were washed with water (10 mL) and brine, dried over Na_2SO_4, and concentrated in vacuo. Chromatography of the residue on silica gel (petroleum ether/EtOAc 20:1) provided **11** (326 mg, 89%) as a colorless oil. R_f = 0.60 (petroleum ether/EtOAc 4:1); $[\alpha]_D^{20}$ = −6.9 (*c* = 0.85 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.23–7.21 (m, 2H),

6.86–6.83 (m, 2H), 4.38–4.26 (m, 3H), 3.77 (s, 3H), 3.46 (m, 2H), 2.55 (m, 2H), 2.08 (s, 3H), 1.73 (m, 2H), 0.82 (s, 9H), 0.02 (s, 3H), 0.00 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 207.7, 159.0, 139.3, 129.1 (2C), 113.6 (2C), 72.4, 66.5, 66.1, 55.1, 51.1, 37.2, 31.5, 25.7 (3C), 17.8, −4.7, −4.8 ppm; IR (film): $\tilde{\nu}$ = 3001, 1718, 1614, 1587, 1515, 1250 cm^{-1}; HRMS (ESI): calcd for $C_{20}H_{34}O_4SiNa$: 389.2118 $[M+Na]^+$; found: 389.2117.

Aldehyde 12: DIBAL (10.5 mmol, 1 N solution in toluene) was added dropwise to a solution of ethyl 2-[(*tert*-butyldimethylsilyloxy)methyl]oxazole-4-carboxylate (2 g, 7.0 mmol) in anhydrous CH_2Cl_2 (20 mL) at −78 °C. After the reaction mixture had been stirred for 30 min, MeOH (3 mL) was added at −78 °C. The mixture was then diluted with CH_2Cl_2 (100 mL), and the organic layer was washed with HCl (1 N), saturated $NaHCO_3$ solution, and brine. Finally, the organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography on silica gel (petroleum ether/EtOAc 10:1) provided **12** (1.43 g, 85 %) as a colorless oil. R_f = 0.52 (petroleum ether/EtOAc 6:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.83 (s, 1H), 8.14 (s, 1H), 4.66 (s, 2H), 0.79 (s, 9H), 0.00 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 184.1, 163.9, 144.4, 140.7, 58.1, 25.7, 18.3 (3C), −5.4 ppm (2C); IR (film): $\tilde{\nu}$ = 3001, 1718, 1614, 1587, 1515, 1250 cm^{-1}; HRMS (ESI): calcd for $C_{11}H_{19}O_3NSiNa$: 264.1026 $[M+Na]^+$; found: 264.1030.

Diketone 13: A solution of ketone **11** (2.48 g, 6.8 mmol) in THF (6 mL) was added dropwise to a freshly prepared LDA solution [*n*BuLi (5.13 mL, 8.2 mmol, 1.6 M solution in hexanes) was added to a solution of diisopropylamine (1.26 mL, 9 mmol) in THF (8 mL) at −78 °C under argon]. The resulting mixture was warmed to 0 °C for 15 min and then cooled to −78 °C. After stirring for 30 min at −78 °C, a solution of aldehyde **12** (1.49 g, 6.2 mmol) in THF (6 mL) was added dropwise. This mixture was stirred for 3 h at −78 °C, and was then quenched with a phosphate buffer solution (10 mL, pH 7). The aqueous phase was extracted with Et_2O (3 × 100 mL), and the combined organic layers were dried ($MgSO_4$) and then concentrated in vacuo to give a residue. For the next step in the synthesis, Dess–Martin periodinane (2.89 g, 6.82 mmol) was added at RT to a solution of the residue in CH_2Cl_2 (100 mL), and the resulting reaction mixture was stirred at RT for 30 min. After this time, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$/$Na_2S_2O_3$ (5:1, 30 mL) and stirred for a further 15 min. Finally, the mixture was extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography on silica gel (petroleum ether/EtOAc 20:1) provided ketone **13** (3.36 g, 90 % overall yield for the two steps) as a colorless oil. R_f = 0.67 (petroleum ether/EtOAc 4:1); $[\alpha]_D^{20}$ = −16.9 (c = 1.51 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.14 (s, 1H), 7.26 (d, J = 10.5 Hz, 2H), 6.87 (d, J = 10.5 Hz, 2H), 6.28 (d, J = 1.8 Hz, 1H), 4.77 (s, 2H), 4.44 (AB, J = 11.4 Hz, 1H; B of AB), 4.35 (AB, J = 11.4 Hz, 1H; A of AB), 4.34–4.29 (m, 1H), 3.80 (s, 3H), 3.53 (t, J = 6.6 Hz, 2H), 2.56–2.54 (m, 2H), 1.85–1.80 (m, 2H), 1.60 (br s, 1H), 0.91 (s, 9H), 0.83 (s, 9H), 0.12 (s, 6H), 0.03 ppm (d, J = 9.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.6, 176.3, 163.0, 159.1, 141.5, 137.9, 130.4 (2C), 129.2 (2C), 113.7, 99.0, 72.6, 67.3, 66.1, 58.1, 55.1, 47.4, 37.6, 25.7 (6C), 18.3, 18.0, −4.8 (2C), −5.4 ppm (2C); IR (film): $\tilde{\nu}$ = 3157, 1614, 1514, 1472, 1464, 1251, 1095 cm^{-1}; HRMS (ESI): calcd for $C_{31}H_{51}O_7NSi_2Na$: 628.3081 $[M+Na]^+$; found: 628.3096.

Alcohol 14: HF (1 mL, 40 %) was added to a solution of ketone **13** (1.20 g, 1.98 mmol) in acetonitrile (20 mL) at RT. The resulting mixture was stirred at RT for 24 h, and was then diluted with EtOAc (60 mL) and neutralized with saturated aqueous $NaHCO_3$ solution. The aqueous phase was extracted with Et_2O (3 × 5 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Chromatography of the residue on silica gel (petroleum ether/EtOAc 2:1) provided **14** (640 mg, 90 %) as a colorless oil. R_f = 0.47 (petroleum ether/EtOAc 1:4); $[\alpha]_D^{20}$ = +112.6 (c = 1.45 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.77 (s, 1H), 7.45 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 6.11 (s, 1H), 4.75 (d, J = 6.3 Hz, 2H), 4.72–4.71 (m, 1H), 4.49 (AB, J = 11.4 Hz, 1H; B of AB), 4.41 (AB, J = 11.4 Hz, 1H; A of AB), 3.80 (s, 3H), 3.70–3.55 (m, 2H), 2.80 (t, J = 6.0 Hz, 1H), 2.56 (d, J = 4.2 Hz, 1H), 2.54 (s, 1H), 2.19–2.10 (m, 1H), 2.05–1.96 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.7, 163.9, 162.8, 158.7, 139.1, 134.8, 129.5 (2C), 128.9 (2C), 113.3, 102.1, 76.4, 72.1, 64.4, 59.9, 56.4, 41.0, 34.0 ppm; IR (film): $\tilde{\nu}$ = 3379, 1661, 1629, 1587, 1539, 1514 cm^{-1}; HRMS (ESI): calcd for $C_{19}H_{21}O_6NNa$: 382.1244 $[M+Na]^+$; found: 382.1261.

Pyranone 15: Imidazole (802 mg, 11.8 mmol) was added to a solution of alcohol **14** (2.1 g, 5.9 mmol) in DMF (15 mL) under argon. After the mixture had been stirred for 5 min, TBSCl (1.14 g, 7.6 mmol) was added and the reaction mixture was stirred for a further 5 h at RT. After this time, the mixture was quenched with water (10 mL) and extracted with Et_2O (4 × 30 mL). The combined organic extracts were washed with water (2 × 10 mL) and brine, dried over Na_2SO_4, and then concentrated in vacuo. Chromatography of the residue on silica gel (petroleum ether and EtOAc 4:1) provided **15** (2.71 g, 97 %) as a colorless oil. R_f = 0.39 (petroleum ether/EtOAc 2:1); $[\alpha]_D^{20}$ = +98.1 (c = 1.47 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.78 (s, 1H), 7.26–7.22 (m, 2H), 6.89–6.85 (m, 2H), 6.11 (s, 1H), 4.76 (s, 2H), 4.74–4.70 (m, 1H), 4.49 (AB, J = 11.7 Hz, 1H; B of AB), 4.42 (AB, J = 11.7 Hz, 1H; A of AB), 3.80 (s, 3H), 3.69–3.57 (m, 2H), 2.56 (d, J = 3.6 Hz, 1H), 2.54 (s, 1H), 2.16–2.12 (m, 1H), 2.04–1.99 (m, 1H), 0.90 (s, 9H), 0.11 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.5, 163.3, 162.9, 159.2, 139.1, 135.4, 129.3 (4C), 113.7, 102.8, 76.6, 72.7, 64.8, 58.1, 55.2, 41.6, 34.6, 25.6 (3C), 18.2, −5.5 ppm (2C); IR (film): $\tilde{\nu}$ = 3136, 3000, 1667, 1633, 1587 1514 cm^{-1}; HRMS (ESI): calcd for $C_{25}H_{35}O_6NSiNa$: 496.2118 $[M+Na]^+$; found: 496.2126.

Compound 16: $CeCl_3 \cdot 7H_2O$ (440 mg, 1.2 mmol) was added to a solution of **15** (1.42 g, 3.0 mmol) in MeOH (20 mL) at RT. The resulting mixture was then cooled to −78 °C and sodium borohydride (114 mg, 3.0 mmol) was added. This mixture was stirred at −78 °C for 20 min, and was then quenched with saturated aqueous NH_4Cl solution (10 mL). Finally, the mixture was extracted with EtOAc (2 × 20 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. Chromatography of the residue on silica gel (petroleum ether/EtOAc 4:1) provided **16** (1.35 g, 95 %) as a colorless oil. R_f = 0.42 (petroleum ether/EtOAc 1:1); $[\alpha]_D^{20}$ = +28.2 (c = 1.30 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.51 (m, 1H), 7.26–7.23 (m, 2H), 6.88–6.84 (m, 2H), 5.56 (s, 1H), 4.63 (s, 2H), 4.58–4.52 (m, 1H), 4.44 (AB, J = 12.0 Hz, 1H; B of AB), 4.41 (AB, J = 12.0 Hz, 1H; A of AB), 4.30–4.21 (m, 1H), 3.78 (s, 3H), 3.67–3.53 (m, 2H), 2.25–2.18 (m, 1H), 2.17–1.95 (br s, 1H), 1.95–1.84 (m, 2H), 1.71–1.59 (m, 1H), 0.90 (s, 9H), 0.11 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.5, 159.1, 146.0, 135.5, 135.3, 130.2 (2C), 129.2 (2C), 113.7, 102.6, 72.6, 72.4, 65.6, 63.2, 58.2, 55.2, 37.6, 35.0, 25.7 (3C), 18.3, −5.4 ppm (2C); IR (film): $\tilde{\nu}$ = 3412, 1687, 1613, 1585, 839, 780 cm^{-1}; HRMS (ESI): calcd for $C_{25}H_{37}O_6NSiNa$: 498.2293 $[M+Na]^+$; found: 498.2282.

Pyrane 17

Method A: Palladium on carbon (150 mg, 50 % wet weight) was added to a solution of **16** (521 mg, 1.1 mmol) in EtOAc (30 mL). Hydrogen was then bubbled into the suspension, which was stirred for 8 h at RT. After this time, the mixture was filtered through Celite and the resulting filtrate was concentrated in vacuo. Chromatography of the residue on silica gel (petroleum ether/EtOAc 4:1) provided **17** (R_f = 0.29, petroleum ether/EtOAc 1:1; 498 mg, 95 %) as a colorless oil.

Method B: Palladium on carbon (150 mg, 50 % wet weight) was added to a solution of **15** (300 mg, 0.6 mmol) in EtOAc (30 mL, saturated with 0.1 N HCl). Hydrogen was then bubbled into the reaction mixture, which was stirred for 8 h at RT. After this time, the mixture was filtered through Celite and the resulting filtrate was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Chromatography of the residue on silica gel (petroleum ether/EtOAc 4:1) provided **17** (200 mg, 65 %) as a colorless oil. R_f = 0.29 (petroleum ether/EtOAc 1:1); $[\alpha]_D^{20}$ = +29.6 (c = 0.75 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.51 (s, 1H), 7.14 (d, J = 8.7 Hz, 2H), 6.75 (d, J = 8.7 Hz, 2H), 4.73 (s, 2H), 4.42 (s, 2H), 4.36 (d, J = 10.5 Hz, 1H), 3.90–3.85 (m, 1H), 3.80 (s, 3H), 3.67–3.64 (m, 1H), 3.62–3.60 (m, 1H), 3.56–3.53 (m, 1H), 2.28 (dt, J = 12.6, 2.4 Hz, 1H), 2.01 (dt, J = 12.3, 2.4 Hz, 1H), 1.93–1.88 (m, 1H), 1.83–1.78 (m, 1H), 1.34 (app q, J = 11.7 Hz, 1H), 1.28 (app q, J = 10.5 Hz, 1H), 0.92 (s, 9H), 0.10 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.5, 159.1, 141.2, 135.2, 130.5 (2C), 129.2 (2C), 113.7, 73.1, 72.5, 71.0, 67.8, 66.1, 58.3, 55.2, 40.9, 40.0, 36.0, 25.7 (3C), 18.3, −5.4 ppm (2C); IR (film): $\tilde{\nu}$ = 3400, 1613,

1586, 1514, 1250, 1095, 839, 780 cm^{-1}; HRMS (ESI): calcd for $C_{25}H_{39}O_6NSiNa$: 500.2430 $[M+Na]^+$; found: 500.2439.

Aldehyde 18: Imidazole (355 mg, 5.2 mmol) and DMAP (24 mg, 0.2 mmol) were added sequentially to a solution of **17** (415 mg, 0.85 mmol) in DMF (5 mL) under argon. After the reaction mixture had been stirred for 5 min, *tert*-butyldimethylsilyl chloride (523 mg, 3.5 mmol) was added, and the resulting mixture was stirred at RT overnight. After this time, water (5 mL) was added to the mixture, which was subsequently extracted with Et_2O (4×30 mL). The combined organic extracts were washed with water (10 mL) and brine, dried over Na_2SO_4, and then concentrated in vacuo to give a residue. DDQ (194 mg, 0.85 mmol) was added to a solution of the dissolved residue in CH_2Cl_2 (10 mL) and buffer (0.5 mL, pH 7) at RT. After the reaction mixture had been stirred for 2 h at RT, the reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL) and then extracted with CH_2Cl_2 (2×20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo to give a second residue. Dess–Martin periodinane (300 mg, 0.7 mmol) was added to a solution of the dissolved residue in CH_2Cl_2 (10 mL) at RT. After the mixture had been stirred at RT for 30 min, a mixture of saturated aqueous $NaHCO_3/Na_2SO_3$ 5:1 was added, and the resulting mixture was stirred for a further 20 min until the two phases were clear. Once this had occurred, the mixture was extracted with CH_2Cl_2 (2×20 mL), and the combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Chromatography of the residue on silica gel (petroleum ether/EtOAc 20:1) provided compound **18** (326 mg, 82% overall yield for the three steps) as a colorless oil. R_f=0.56 (petroleum ether/EtOAc 4:1); $[\alpha]_D^{20}$=+3.7 (c=0.59 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=9.80 (t, J=2.4 Hz, 1H), 7.51 (s, 1H), 4.71 (s, 2H), 4.42 (dd, J=11.4, 1.2 Hz, 1H), 4.05–4.01 (m, 1H), 3.93–3.89 (m, 1H), 2.73 (ddd, J=18.0, 7.5, 2.4 Hz, 1H), 2.54 (ddd, J=16.8, 5.1, 1.5 Hz, 1H), 2.17 (dt, J=12.9, 2.1 Hz, 1H), 1.92 (dt, J=10.8, 2.4 Hz, 1H), 1.82 (br s, 1H), 1.58 (app q, J=12.0 Hz, 1H), 1.38 (app q, J=12.0 Hz, 1H), 0.89 (s, 9H), 0.87 (s, 9H), 0.08 (s, 6H), 0.06 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=200.7, 162.5, 141.0, 135.2, 71.5, 71.2, 67.9, 58.3, 49.4, 41.1, 40.1, 25.9 (6C), 18.3, 17.9, −4.5 (2C), −4.6 ppm (2C); IR (film): $\tilde{\nu}$=2728, 1729, 1576, 1473, 1464, 1257, 1096, 838, 778 cm^{-1}; HRMS (ESI): calcd for $C_{23}H_{43}O_5NSi_2Na$: 492.2565 $[M+Na]^+$; found: 492.2572.

Alcohol 20: A solution of allylmagnesium bromide (46.2 mmol) in Et_2O (80 mL) was added dropwise to a well-stirred solution of (+)-Ipc_2BOMe (15.4 g, 48.5 mmol) in anhydrous Et_2O (300 mL) at 0°C under argon. After completion of the addition, the reaction mixture was stirred for 1 h at RT, and then cooled to −78°C and a solution of aldehyde **19** (13.0 g, 41.7 mmol) in anhydrous Et_2O (80 mL) was added dropwise to the mixture. The resulting reaction mixture was stirred for 4 h at −78°C, and then NaOH (3 N, 100 mL) was slowly added, followed by 30% H_2O_2 (5 mL). The completion of the oxidation was ensured by refluxing the reaction mixture for 2 h. After this time, water (100 mL) was added to the reaction mixture, which was subsequently extracted with Et_2O (2× 200 mL), washed with brine, dried over Na_2SO_4, and then concentrated in vacuo. Chromatography of the residue on silica gel (petroleum ether/EtOAc 20:1) provided alcohol **20** (10.9 g, 74%) with 87% *ee* (determined by analysis of the corresponding Mosher's ester) as a colorless oil. R_f= 0.51 (petroleum ether/EtOAc 10:1); $[\alpha]_D^{20}$=+3.6 (c=2.11 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.71–7.66 (m, 4H), 7.46–7.36 (m, 6H), 5.89–5.80 (m, 1H), 5.14–5.10 (m, 1H), 5.07 (s, 1H), 3.98–3.94 (m, 1H), 3.90–3.83 (m, 2H), 3.31 (d, J=1.5 Hz, 1H), 2.29–2.24 (m, 2H), 1.75–1.67 (m, 2H), 1.05 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=135.5 (4C), 134.9, 133.1, 133.0, 129.8 (2C), 127.7 (4C), 117.4, 70.7, 63.2, 41.9, 37.9, 26.8 (3C), 19.0 ppm; IR (film): $\tilde{\nu}$=3352, 3074, 3053, 2935, 2860, 1429 cm^{-1}; HRMS (ESI): calcd for $C_{22}H_{30}O_2SiNa$: 377.1907 $[M+Na]^+$; found: 377.1906.

Compound 21: $BF_3{\cdot}Et_2O$ (3 mL, 0.1 M in CH_2Cl_2) was added dropwise to a mixture of the alcohol **20** (3.54 g, 10.0 mmol) and $Cl_3CC(NH)OPMB$ (30 mL, 0.4 M in hexane) in dry CH_2Cl_2 (15 mL) at 0°C under a nitrogen atmosphere. A significant quantity of a white solid immediately precipitated, and the mixture was stirred at 0°C for 30 min. After this time, the suspension was filtered and the solid was washed with a mixture of CH_2Cl_2/hexane (1:2, 2×5 mL). The filtrate was washed with saturated aqueous $NaHCO_3$ solution. The organic extracts were then combined, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Chromatography of the residue on silica gel (petroleum ether/EtOAc 40:1) provided **21** (4.07 g, 87%) as a colorless oil. R_f=0.44 (petroleum ether/EtOAc 20:1); $[\alpha]_D^{20}$=−10.8 (c=0.40 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.68–7.64 (m, 4H), 7.43–7.35 (m, 6H), 7.23–7.19 (m, 2H), 6.85–6.82 (m, 2H), 5.88–5.77 (m, 1H), 5.09 (d, J=6.3 Hz, 1H), 5.05 (t, J=1.2 Hz, 1H), 4.49 (AB, J=11.1 Hz, 1H; B of AB), 4.38 (AB, J= 11.1 Hz, 1H; A of AB), 3.78 (s, 3H), 3.80–3.72 (m, 3H), 2.34–2.29 (m, 2H), 1.76 (app q, J=6.0 Hz, 2H), 1.05 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=159.0, 135.5 (4C), 134.9, 134.0, 133.9, 131.0, 129.7 (2C), 129.5 (2C), 127.6 (4C), 116.9, 113.7 (2C), 75.1, 70.8, 60.5, 55.2, 38.5, 37.0, 26.9 (3C), 19.2 ppm; IR (film): $\tilde{\nu}$=3072, 3000, 1614, 1588, 1514, 1248, 1112 cm^{-1}; HRMS (MALDI): calcd for $C_{30}H_{38}O_4SiNa$: 497.2482 $[M+Na]^+$; found: 497.2500.

Ketone 22: Oxygen was bubbled into a mixture of $PdCl_2$ (56 mg, 0.31 mmol), CuCl (312 mg, 3.15 mmol), DMF (56 mL), and distilled water (8 mL) to activate the reaction mixture. This mixture was then stirred for 30 min and was observed to turn black. Compound **21** (1.49 g, 3.14 mmol) was added to this mixture, which was vigorously stirred for 12 h. After this time, water (30 mL) was added to quench the reaction, and the resulting mixture was extracted with Et_2O (4×80 mL). The combined organic phases were washed with water (10 mL) and brine, dried over Na_2SO_4, and then concentrated in vacuo. Chromatography of the residue on silica gel (petroleum ether/EtOAc 20:1) provided **22** (1.33 g, 86%) as a colorless oil. R_f=0.47 (petroleum ether/EtOAc 4:1); $[\alpha]_D^{20}$= +4.8 (c=1.49 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.68–7.65 (m, 4H), 7.43–7.38 (m, 6H), 7.15 (d, J=9.0 Hz, 2H), 6.82 (d, J=8.1 Hz, 2H), 4.42 (s, 2H), 4.16 (app q, J=6.0 Hz, 1H), 3.79 (s, 3H), 3.69–3.86 (m, 2H), 2.74 (dd, J=8.1, 16.2 Hz, 1H; B of AB-d), 2.54 (dd, J=4.8, 16.2 Hz, 1H; A of AB-d), 2.13 (s, 3H), 1.82–1.71 (m, 2H), 1.05 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=207.3, 159.2, 135.6 (4C), 133.8, 133.7, 130.6, 129.6 (2C), 129.3 (2C), 127.6 (4C), 113.7 (2C), 72.6, 71.4, 60.3, 55.2, 48.9, 37.2, 31.0, 26.8 (3C), 19.1 ppm; IR (film): $\tilde{\nu}$=3072, 3000, 1718, 1614, 1588, 1515 cm^{-1}; HRMS (ESI): calcd for $C_{30}H_{38}O_4SiNa$: 513.2427 $[M+Na]^+$; found: 513.2432.

Compound 23: LiHMDS (lithium hexamethyldisilazide, 0.6 mmol, 1.0 M in THF) and TMSCl (0.075 mL, 0.6 mmol) were added sequentially to a precooled solution of compound **22** (303 mg, 0.6 mmol) in anhydrous THF (5 mL) at −78°C. The reaction was then quenched with buffer solution (5 mL, pH 7) and extracted with Et_2O (4×80 mL). The combined organic phases were washed with water (10 mL) and brine, dried over Na_2SO_4, and then concentrated in vacuo. For the next step in the synthesis, $TiCl_4$ (0.066 mL, 0.6 mmol) was added to a precooled solution of aldehyde **18** (243 mg, 0.5 mmol) in THF (5 mL) at −78°C. The resulting mixture was stirred for 30 min at −78°C, and then a solution of the TMS ether (produced above) in THF (3 mL) was added. After the reaction had been stirred at −78°C for 2 h, the reaction was quenched with buffer solution (5 mL, pH 7), and the aqueous phase was extracted with Et_2O (3×20 mL). The combined organic layers were dried (Na_2SO_4) and then concentrated in vacuo. Purification by flash-column chromatography on silica gel (petroleum ether/EtOAc 10:1) provided **23** (334 mg, 68%) as a colorless oil. R_f=0.39 (petroleum ether/EtOAc 4:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.67–7.63 (m, 4H), 7.52 (s, 1H), 7.43–7.37 (m, 6H), 7.13 (d, J=8.7 Hz, 2H), 6.81 (d, J=8.4 Hz, 2H), 4.71 (d, J=1.2 Hz, 2H), 4.39 (br s, 2H), 4.40–4.22 (m, 2H), 4.15 (m, 1H), 3.89 (m, 1H), 3.78 (s, 3H), 3.80–3.62 (m, 3H), 3.37 (br s, 1H), 2.71 (dd, J=15.3, 7.5 Hz, 1H), 2.54–2.49 (m, 3H), 2.17 (m, 1H), 1.81–1.59 (m, 6H), 1.38 (m, 1H), 1.04 (s, 9H), 0.90 (s, 9H), 0.88 (s, 9H), 0.09 (s, 6H), 0.07 ppm (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=210.3, 162.4, 159.2, 141.6, 135.5 (4C), 135.0, 133.7, 133.6, 130.4, 129.6 (2C), 129.4 (2C), 127.6 (4C), 113.8 (2C), 72.9, 72.5, 71.5, 71.4, 68.4, 64.5, 60.2, 58.3, 55.2, 50.7, 48.7, 42.3, 41.7, 40.5, 37.1, 26.9 (3C), 25.8 (3C), 25.7(3C), 19.1, 18.3, 18.0, −4.5 (2C), −5.3 ppm (2C); IR (film): $\tilde{\nu}$=3500, 3072, 1710, 1614, 1588, 1515, 1251, 1112, 838, 778 cm^{-1}; HRMS (ESI): calcd for $C_{53}H_{81}O_9NSi_2Na$: 982.5132 $[M+Na]^+$; found: 982.5111.

Compound 24: DMAP (12 mg) and benzoyl chloride (0.14 mL, 1.2 mmol) were added sequentially to a solution of **23** (575 mg, 0.6 mmol)

in dry pyridine (2 mL). After the reaction mixture had been stirred at RT for 3 h, it was diluted with EtOAc (100 mL), washed with saturated $CuSO_4$ solution and brine, dried over Na_2SO_4, and concentrated in vacuo to give a residue. For the next step in the synthesis, powdered molecular sieves (400 mg, 4 Å) and a preprepared quantity of the methylenation reagent [a solution of $TiCl_4$ (3.8 mL, 1.2 mmol) in anhydrous THF (8 mL) was stirred at 0 °C under argon for 10 min and then at RT for 20 min; Nysted reagent (5.2 mL, 4.2 mmol) was then added at 0 °C, and the resulting mixture was stirred for a further 30 min at RT to afford the methylenation reagent as a brown/red mixture] were added sequentially at 0 °C to a solution of the residue in anhydrous THF (10 mL). The reaction mixture produced was stirred at 0 °C for 15 min and then at RT for 3 h; after which time, the mixture was poured into saturated aqueous $NaHCO_3$ (30 mL, ice-cold). Finally, the mixture was extracted with EtOAc (30 mL), and the organic layer was dried (Na_2SO_4) and concentrated in vacuo. Chromatography of the residue on silica gel (petroleum ether/EtOAc 60:1) provided **24** (411 mg, 66 % overall yield for the two steps) as a colorless oil. $R_f = 0.60$ (petroleum ether/EtOAc 7:1); $[\alpha]_D^{20} = +13.3$ ($c = 1.10$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.01$ (d, $J = 6.6$ Hz, 2H), 7.66–7.62 (m, 4H), 7.52–7.50 (m, 2H), 7.43–7.35 (m, 8H), 7.10 (d, $J = 8.4$ Hz, 2H), 6.78 (d, $J = 8.4$ Hz, 2H), 5.62–5.51 (m, 1H), 4.89 (s, 1H), 4.86 (s, 1H), 4.69 (s, 2H), 4.40 (d, $J = 10.8$ Hz, 1H; B of AB), 4.29 (d, $J = 10.8$ Hz, 1H; A of AB), 4.28 (d, $J = 11.7$ Hz, 1H), 3.86–3.68 (m, 4H), 3.76 (s, 3H), 3.57–3.51 (brt, 1H), 2.49–2.35 (m, 3H), 2.23–2.16 (m, 2H), 2.00–1.62 (m, 5H), 1.51 (app q, $J = 12.0$ Hz, 1H), 1.35 (app q, $J = 11.4$ Hz, 1H), 1.03 (s, 9H), 0.90 (s, 9H), 0.84 (s, 9H), 0.09 (s, 6H), 0.08 ppm (d, $J = 3.6$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 166.1$, 162.4, 159.2, 142.6, 142.6, 141.7, 135.8 (4C), 135.4, 134.1, 133.0, 131.1, 130.8, 129.8 (2C), 129.7 (2C), 129.6 (2C), 129.5 (2C), 128.5, 127.8 (2C), 115.6, 113.9 (4C), 74.6, 73.2, 71.7, 71.0, 70.5, 68.5, 60.7, 58.6, 55.4, 42.2, 42.1, 41.0, 40.8, 37.4, 27.1 (3C), 26.0 (6C), 19.4, 18.6, 18.2, −4.4 (2C), −5.2 ppm (2C); IR (film): $\tilde{\nu} = 3072$, 1717, 1647, 1613, 1587 cm^{-1}; HRMS (ESI): calcd for $C_{61}H_{87}O_9NSi_3Na$: 1062.5760 $[M+Na]^+$; found: 1062.5761.

Compound 26: DIBAL (0.25 mL, 0.25 mmol, 1 M in toluene) was added dropwise at −78 °C to a solution of **24** (56 mg, 0.054 mmol) in dry CH_2Cl_2 (3 mL). After the reaction mixture had been stirred at −78 °C for 1 h, the reaction was quenched with MeOH (0.25 mL), and then $MgSO_4$ (3 g) and Et_2O (100 mL) were added. The resulting suspension was stirred at RT for 3 h, and then filtered through Celite. This filtrate was concentrated in vacuo to give a residue. For the next step in the synthesis, triethylamine (0.3 mL) was added to a solution of the residue in anhydrous CH_2Cl_2 (3 mL). Methanesulfonyl chloride (0.1 mL, 1.4 mmol) was added to the mixture above, which had been precooled to 0 °C, and the mixture was stirred at 0 °C for a further 30 min. After this time, the mixture was diluted with EtOAc (50 mL), washed with water (10 mL) and brine, dried over Na_2SO_4, and then concentrated in vacuo to give a second residue. Buffer (0.5 mL, pH 7) and DDQ (18 mg, 0.08 mmol) were added to a solution of this residue in CH_2Cl_2 (2 mL) at RT. The mixture was stirred vigorously for 2 h, and then quenched with saturated aqueous sodium bicarbonate (2 mL). The separated aqueous phase was extracted with CH_2Cl_2 (20 mL), and the combined organic extracts were dried and then evaporated to dryness in vacuo. Purification by chromatography (EtOAc/petroleum ether 10:1) gave **26** (32 mg, 67 % yield for three steps) as a colorless oil. $R_f = 0.58$ (petroleum ether/EtOAc 4:1); $[\alpha]_D^{20} = +13.0$ ($c = 0.3$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.68$–7.65 (m, 4H), 7.56 (s, 1H), 7.44–7.37 (m, 6H), 5.12–5.02 (m, 1H), 4.97 (s, 1H), 4.95 (s, 1H), 4.71 (s, 2H), 4.34 (d, $J = 12.6$ Hz, 1H), 4.11–4.02 (m, 1H), 3.93–3.83 (m, 3H), 3.66 (brt, $J = 10.2$ Hz, 1H), 3.41 (d, $J = 1.8$ Hz, 1H), 3.00 (s, 3H), 2.63 (dd, $J = 14.1$, 5.7 Hz, 1H), 2.48 (dd, $J = 14.1$, 7.2 Hz, 1H), 2.31–2.16 (m, 3H), 1.94–1.64 (m, 5H), 1.58 (app q, $J = 12.0$ Hz, 1H), 1.34 (app q, $J = 11.4$ Hz, 1H), 1.04 (s, 9H), 0.90 (s, 9H), 0.88 (s, 9H), 0.09 (s, 6H), 0.07 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 162.5$, 141.8, 141.4, 135.5 (4C), 135.3, 133.0, 129.8 (2C), 127.7 (4C), 116.3, 78.8, 71.6, 71.2, 71.1, 69.6, 68.2, 63.2, 58.3, 44.1, 42.6, 41.5, 40.5, 40.2, 38.3, 38.1, 26.8 (3C), 25.8 (3C), 25.7 (3C), 19.0, 18.3, 18.0, −4.6 (2C), −5.4 ppm (2C); IR (film): $\tilde{\nu} = 3359$, 3073, 1653, 1590 cm^{-1}; HRMS (ESI): calcd for $C_{47}H_{77}O_8NSSi_3Na$: 922.4570 $[M+Na]^+$; found: 922.4575.

Compound 27: A solution of **26** (22.0 mg, 0.024 mmol), acetonitrile (5 mL), and triethylamine (1 mL) was refluxed for 24 h. After this time, water (5 mL) was added to the reaction mixture, which was then extracted with EtOAc (2 × 15 mL), washed with brine, dried over Na_2SO_4, and finally concentrated in vacuo. Purification of the residue by flash chromatography (petroleum ether 20:1) provided **27** (16 mg, 83 %) as a colorless oil. $R_f = 0.49$ (petroleum ether/EtOAc 10:1); $[\alpha]_D^{25} = -14.2$ ($c = 0.35$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.68$–7.65 (m, 4H), 7.47 (s, 1H), 7.40–7.37 (m, 6H), 4.72 (d, $J = 5.4$ Hz, 2H), 4.72 (s, 2H), 4.27 (d, $J = 10.8$ Hz, 1H), 4.02 (app q, $J = 6.0$ Hz, 1H), 3.93 (app q, $J = 6.0$ Hz, 1H), 3.83–3.67 (m, 3H), 3.55–3.49 (m, 1H), 2.36 (brs, 1H), 2.35 (brs, 1H), 2.16–2.12 (m, 1H), 2.07–1.95 (m, 3H), 1.92–1.88 (m, 1H), 1.85–1.79 (m, 1H), 1.70–1.62 (m, 1H), 1.54–1.48 (m, 2H), 1.33–1.20 (m, 1H), 1.04 (s, 9H), 0.89 (s, 9H), 0.86 (s, 9H), 0.09 (s, 6H), 0.034 (s, 3H), 0.028 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 162.4$, 142.2, 141.8, 135.7 (4C), 135.2, 135.0, 134.0, 129.7 (2C), 127.8 (2C), 127.7 (2C), 110.4, 73.0, 71.4, 69.0, 68.7, 68.6, 60.7, 58.5, 41.2, 40.8, 40.0, 39.6, 39.4, 36.5, 27.0 (3C), 25.8 (6C), 19.3, 18.5, 18.1, −4.4 (2C), −5.3 ppm (2C); IR (film): $\tilde{\nu} = 3073$, 1655, 1429, 1255, 1093, 1112 cm^{-1}; HRMS (ESI): calcd for $C_{46}H_{73}O_6NSi_3Na$: 842.4633 $[M+Na]^+$; found: 842.4638.

Alcohol 28: NH_4F (77 mg, 2.1 mmol) was added to a solution of **27** (107 mg, 0.13 mmol) in MeOH (2.0 mL). The resulting mixture was immediately heated to 50 °C and then stirred for another 25 min. After this time, the mixture was quenched with saturated NH_4Cl solution and then diluted with EtOAc (200 mL). The organic layer produced was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Chromatography of the residue on silica gel (petroleum ether/EtOAc 4:1) provided **28** (74 mg, 81 %) as a colorless oil. $R_f = 0.40$ (petroleum ether/EtOAc 2:1); $[\alpha]_D^{25} = -19.0$ ($c = 0.55$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.70$–7.65 (m, 4H), 7.47 (s, 1H), 7.45–7.27 (m, 6H), 4.74 (s, 2H), 4.70 (s, 2H), 4.28 (d, $J = 11.7$ Hz, 1H), 4.04 (m, 1H), 3.93 (s, 1H), 3.72–3.38 (m, 3H), 3.54–3.50 (m, 1H), 3.15 (brs, 1H), 2.77–2.33 (m, 2H), 2.10–0.80 (m, 6H), 1.80–1.60 (m, 3H), 1.30–1.10 (m, 1H), 1.04 (s, 9H), 0.87 (s, 9H), 0.04 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 163.0$, 142.0, 141.7, 135.5 (4C), 135.1, 133.8 (2C), 129.6 (2C), 127.6 (4C), 110.3, 72.9, 71.1, 68.9, 68.6, 68.4, 60.5, 57.5, 41.1, 40.6, 39.7, 39.5, 39.3, 36.4, 26.9 (3C), 25.8 (3C), 19.2, 18.0, −4.5 ppm (2C); IR (film): $\tilde{\nu} = 3300$, 2952, 2931, 1473 cm^{-1}; HRMS (ESI): calcd for $C_{40}H_{59}O_6NSi_2Na$: 728.3773 $[M+Na]^+$; found: 728.3774.

Segment 3: Diisopropylethylamine (DIPEA, 130 μL, 0.78 mmol) and methanesulfonyl chloride (36 μL, 0.47 mmol) were added to a solution of **28** (280 mg, 0.39 mmol) in dry CH_2Cl_2 (8 mL), which had been precooled in an ice-salt bath. The resulting mixture was stirred for another 1.5 h, and then run through a short pad of silica gel, eluting with petroleum ether/EtOAc 10:1, to provide **3** (331 mg, 90 %) as a colorless oil. $R_f = 0.39$ (petroleum ether/EtOAc 4:1); $[\alpha]_D^{25} = -20.1$ ($c = 0.45$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.69$–7.65 (m, 4H), 7.56 (s, 1H), 7.45–7.36 (m, 6H), 5.26 (s, 2H), 4.47 (s, 2H), 4.28 (d, $J = 10.8$ Hz, 1H), 4.06–4.03 (m, 1H), 3.96–3.88 (m, 1H), 3.88–3.71 (m, 3H), 3.61–3.50 (m, 1H), 3.08 (s, 3H), 2.35 (dd, $J = 13.2$, 3.6 Hz, 2H), 2.20–1.80 (m, 6H), 1.78–1.40 (m, 3H), 1.39–1.20 (m, 1H), 1.04 (s, 9H), 0.87 (s, 9H), 0.05 (s, 3H), 0.05 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 156.5$, 142.9, 142.0, 136.6, 135.5 (4C), 133.9 (2C), 129.6 (2C), 127.6 (4C), 110.3, 73.0, 71.0, 68.9, 68.6, 68.3, 61.9, 60.5, 41.1, 40.6, 39.7, 39.5, 39.3, 38.4, 36.4, 26.9(3C), 25.8 (3C), 19.2 (2C), −4.4 ppm (2C); IR (film): $\tilde{\nu} = 2953$, 2931, 2858, 1363 cm^{-1}; HRMS (ESI): calcd for $C_{41}H_{62}O_8NSSi_2$: 784.3729 $[M+H]^+$; found: 784.3728.

Alcohol 31: Compound (−)-**30** (158 mL, 158 mmol, 1.0 M solution in toluene) was added dropwise to a slurry of powdered molecular sieves (14 g, 4 Å) in anhydrous toluene (50 mL) under argon at RT. After the resulting reaction mixture had been stirred for 30 min at RT, it was cooled to −78 °C and a solution of **29** (10.19 g, 78.3 mmol) in toluene (75 mL) was added dropwise over 1 h. The reaction mixture was stirred at −78 °C for 10 h, and was then quenched with NaOH (2 N, 145 mL). This mixture was stirred for a further 15 min at RT, before being filtered. The aqueous layer was extracted with Et_2O (3 × 200 mL), and the resulting organic extracts were combined and concentrated in vacuo. Chromatography of the residue on silica gel (petroleum ether/EtOAc 20:1) provided **31** as colorless oil (9.46 g, 65 %). $R_f = 0.46$ (petroleum ether/EtOAc 10:1); $[\alpha]_D^{25} = +20.3$ ($c = 0.80$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.94$–5.82 (m,

1H), 5.10–5.02 (m, 2H), 4.11 (q, $J=6.3$ Hz, 1H), 4.01 (dd, $J=8.1$, 6.3 Hz, 1H), 3.74 (dd, $J=7.8$, 7.2 Hz, 1H), 3.40 (q, $J=5.1$ Hz, 1H), 2.30–2.22 (m, 1H), 1.43 (s, 3H), 1.37 (s, 3H), 1.11 ppm (d, $J=6.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=139.5$, 115.3, 109.1, 77.1, 75.2, 66.0, 41.2, 26.5, 25.4, 16.7 ppm; IR (film): $\tilde{\nu}=3490$, 2986, 1640, 1457, 1372 cm^{-1}; HRMS (ESI): calcd for $C_{10}H_{18}O_3Na$: 209.1148 $[M+Na]^+$; found: 209.1148.

Ester 32: DMAP (0.060 g, 0.049 mmol) and triethylamine (3.0 mL, 21.24 mmol) were added sequentially to a solution of **31** (0.658 g, 3.54 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was then cooled to 0°C, and acetyl anhydride (1.0 mL, 10.62 mmol) was added dropwise; this mixture was stirred at RT overnight. After this time, the mixture was diluted with CH_2Cl_2 (100 mL) and washed with H_2O (3×10 mL), saturated aqueous $NaHCO_3$ solution (10 mL), and brine (10 mL). Finally, the mixture was dried over Na_2SO_4 and then concentrated in vacuo. Chromatography of the residue on silica gel (petroleum ether/EtOAc 20:1) provided **32** (0.766 g, 95%) as a colorless oil. $R_f=0.53$ (petroleum ether/EtOAc 10:1); $[\alpha]_D^{20}=+9.8$ ($c=1.0$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=5.79$–5.67 (m, 1H), 5.08–5.01 (m, 2H), 4.88 (t, $J=6.0$ Hz, 1H), 4.23 (q, $J=6.3$ Hz, 1H), 4.01 (dd, $J=8.4$, 6.6 Hz, 1H), 3.66 (dd, $J=8.1$, 6.3 Hz, 1H), 2.50–2.40 (m, 1H), 2.10 (s, 3H), 1.42 (s, 3H), 1.35 (s, 3H), 1.06 ppm (d, $J=4.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=170.6$, 139.1, 115.7, 109.5, 75.8, 75.2, 65.7, 39.8, 26.1, 25.5, 20.9, 16.8 ppm; IR (film): $\tilde{\nu}=1742$, 1643, 1238, 1065, 1025 cm^{-1}; HRMS (ESI): calcd for $C_{12}H_{20}O_4Na$: 251.1254 $[M+Na]^+$; found: 251.1257.

Aldehyde 33: A solution of **32** (3.0 g, 13.2 mmol) in MeOH (120 mL) was cooled to −78°C, and then a stream of ozone/oxygen was bubbled into the reaction mixture until it turned light blue. Oxygen was bubbled into the reaction mixture for 1 h, and then Ph_3P (4.2 g, 15.8 mmol) was added at −78°C. This mixture was then warmed to RT and stirred for a further 2 h, before being concentrated in vacuo. Chromatography of the residue on silica gel (petroleum ether/EtOAc 20:1) provided **33** (2.55 g, 85%) as a colorless oil. $R_f=0.59$ (petroleum ether/EtOAc 4:1); $[\alpha]_D^{20}=+41.4$ ($c=1.0$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=9.71$ (d, $J=2.4$ Hz, 1H), 5.16 (dd, $J=6.6$, 3.0 Hz, 1H), 4.33 (m, 1H), 4.03 (dd, $J=8.7$, 6.9 Hz, 1H), 3.74 (dd, $J=8.4$, 5.4 Hz, 1H), 2.81 (m, 1H), 2.10 (s, 3H), 1.43 (s, 3H), 1.34 (s, 3H), 1.16 ppm (d, $J=7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=201.9$, 170.6, 109.8, 75.3, 72.8, 65.5, 48.0, 25.9, 25.3, 20.7, 11.1 ppm; IR (film): $\tilde{\nu}=2989$, 1747, 1695, 1374 cm^{-1}; HRMS (ESI): calcd for $C_{11}H_{18}O_5K$: 269.0785 $[M+K]^+$; found: 269.0787.

Diol 34: Compound (+)-**30** (30 mL, 30 mmol, 1.0 M solution in toluene) was added dropwise to a slurry of powdered molecular sieves (3 g, 4 Å) in anhydrous toluene (10 mL) under argon at RT. After the reaction mixture had been stirred for 30 min at RT, the mixture was cooled to −78°C, and then a solution of aldehyde **33** (3.37 g, 14.6 mmol) in toluene (20 mL) was added dropwise over 30 min at −78°C. The reaction mixture was stirred at −78°C for 8 h, and was then warmed to RT overnight. After this time, the mixture was quenched with NaOH solution (2 N, 20 mL) and filtered. The aqueous layer was extracted with Et_2O (3× 50 mL), and the combined organic layers were concentrated in vacuo to give a residue. NaOH solution (2 N, 20 mL) was then added to a solution of the residue in diethyl ether (200 mL), and the resulting mixture was heated to reflux for 24 h. After this time, the mixture was extracted with diethyl ether (3×100 mL), washed with brine, dried over Na_2SO_4, and then concentrated in vacuo. Chromatography of the residue on silica gel (petroleum ether/EtOAc 4:1) provided **34** (2.49 g, 70%) as a colorless oil. $R_f=0.40$ (petroleum ether/EtOAc 1:1); $[\alpha]_D^{20}=+9.9$ ($c=0.45$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=5.68$–5.80 (m, 1H), 5.11–5.18 (m, 2H), 4.24–4.30 (m, 1H), 4.03 (dd, $J=8.1$, 6.9 Hz, 1H), 3.80 (dd, $J=8.1$, 7.2 Hz, 1H), 3.69 (dt, $J=9.6$, 1.8 Hz, 1H), 3.52–3.58 (m, 1H), 2.25–2.28 (m, 1H), 1.73–1.78 (m, 1H), 1.46 (s, 3H), 1.40 (s, 3H), 1.01 (d, $J=7.2$ Hz, 3H), 0.95 ppm (d, $J=6.6$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=141.70$, 115.77, 109.10, 76.74, 74.54, 73.45, 66.12, 41.83, 36.62, 26.29, 25.17, 16.16, 9.44 ppm; IR (film): $\tilde{\nu}=3457$, 1641 cm^{-1}; HRMS (ESI): calcd for $C_{13}H_{24}O_4Na$: 267.1567 $[M+Na]^+$; found: 267.1565.

Alcohol 35: A solution of diol **34** (0.982 g, 4.0 mmol) in dry toluene (30 mL) was added dropwise to a mixture of $Hg(OAc)_2$ (1.91 g, 6.0 mmol) in dry toluene (70 mL) at 0°C under a nitrogen atmosphere. After the mixture had been stirred at 0°C for 8 h, I_2 (2.13 g, 8.4 mmol) was added. The resulting mixture was then warmed to RT and stirred for 12 h. After this time, the mixture was quenched with a mixture of saturated aqueous $NaHCO_3/Na_2S_2O_3$ 5:1, and the organic and aqueous layers were separated. The aqueous phase was extracted with EtOAc (100 mL), and then the organic extracts were combined and washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Chromatography of the residue on silica gel (petroleum ether/EtOAc 4:1) provided **35** (1.06 g, 71%) and **36** (0.212 g, 14%) as colorless oils.

Compound 35: $R_f=0.36$ (petroleum ether/EtOAc 2:1); $[\alpha]_D^{20}=+70.3$ ($c=0.65$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=4.32$–4.21 (m, 2H), 4.00 (dd, $J=6.9$, 6.9 Hz, 1H), 3.59–3.54 (m, 1H), 3.45–3.38 (m, 1H), 3.28 and 3.10 (AB of ABX, $J_{AB}=9.9$, $J_{AX}=9.9$, $J_{BX}=5.4$ Hz), 2.92 (dd, $J=10.2$, 1.8 Hz, 1H), 2.22–2.14 (m, 1H), 1.94–1.84 (m, 1H), 1.68 (d, $J=5.7$ Hz, 1H), 1.39 (d, $J=5.4$ Hz, 6H), 1.01 (d, $J=6.3$ Hz, 3H), 0.87 ppm (d, $J=6.6$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=109.1$, 79.9, 78.8, 76.3, 74.7, 65.3, 38.2, 33.5, 26.1, 25.7, 12.4, 5.8, 5.5 ppm; IR (film): $\tilde{\nu}=3455$, 2983, 1458, 1379 cm^{-1}; HRMS (ESI): calcd for $C_{13}H_{23}O_4NaI$: 393.0533 $[M+Na]^+$; found: 393.0535.

Compound 36: $R_f=0.34$ (petroleum ether/EtOAc 2:1); $[\alpha]_D^{20}=+4.1$ ($c=0.97$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=4.34$–4.31 (m, 1H), 4.13–4.02 (m, 2H), 3.63–3.59 (m, 1H), 3.52–3.44 (m, 2H), 3.30–3.22 (m, 2H), 1.99–1.88 (m, 2H), 1.49 (s, 3H), 1.41 (s, 1H; OH), 1.39 (s, 3H), 1.17 (d, $J=7.2$ Hz, 3H), 0.96 ppm (d, $J=6.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=109.8$, 77.7, 75.0, 72.8, 72.6, 66.0, 37.0, 35.5, 26.4, 25.5, 17.6, 13.3, 10.7 ppm; IR (film): $\tilde{\nu}=3468$, 2982, 2880, 1458, 1380 cm^{-1}; HRMS (ESI): calcd for $C_{13}H_{23}O_4NaI$: 393.0533 $[M+Na]^+$; found: 393.0529.

PMB ether 37: A solution of $BF_3{\cdot}Et_2O$ (0.42 mL, 1 M in CH_2Cl_2) was slowly added to a mixture of alcohol **35** (716 mg, 1.93 mmol) and $Cl_3CC(NH)OPMB$ reagent (6 mL, approximately 2.7 mmol) in dry CH_2Cl_2 (3 mL) at 0°C under a nitrogen atmosphere. A significant amount of a white solid was observed to immediately precipitate. After the mixture had been stirred at 0°C for 30 min, the suspension was filtered, the solid was washed with a mixture of CH_2Cl_2/hexane (1:2, 2× 5 mL), and the filtrate was washed with saturated aqueous $NaHCO_3$ solution (20 mL). The organic extracts were then combined, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Chromatography of the residue on silica gel (petroleum ether/EtOAc 20:1) provided **37** (750 mg, 79.3%) as colorless oil. $R_f=0.60$ (petroleum ether/EtOAc 4:1); $[\alpha]_D^{20}=+58.4$ ($c=1.55$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.27$ (d, $J=7.5$ Hz, 2H), 6.88 (d, $J=7.5$ Hz, 2H), 4.59 and 4.30 (AB, $J_{AB}=10.8$ Hz), 4.29–4.19 (m, 2H), 3.98 (dd, $J=6.9$ Hz, 6.0 Hz, 1H), 3.80 (s, 3H), 3.50 (dd, $J=7.2$, 1.8 Hz, 1H), 3.29 (dd, $J=9.9$, 1.5 Hz, 1H), 3.13–3.08 (m, 2H), 2.90 (d, $J=10.2$ Hz, 1H), 2.35 (m, 1H), 2.05–1.98 (m, 1H), 1.39 (s, 3H), 1.36 (s, 3H), 0.97 (d, $J=6.3$ Hz, 3H), 0.86 ppm (d, $J=6.6$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=159.2$, 130.6, 129.1 (2C), 113.8 (2C), 109.1, 82.7, 80.4, 78.7, 74.9, 69.7, 65.3, 55.3, 34.0, 32.2, 26.1, 25.9, 12.8, 6.3, 4.8 ppm; IR (film): $\tilde{\nu}=2982$, 1614, 1587, 1514, 1459 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{31}O_5NaI$: 513.1108 $[M+Na]^+$; found: 513.1110.

Nitrile 38: NaCN (157 mg, 4.05 mmol) was added to a solution of **37** (750 mg, 1.53 mmol) in DMSO (3 mL). The mixture was then heated to 75°C and stirred for 12 h at this temperature. After this time, the mixture was cooled to RT, diluted with Et_2O (200 mL), washed with H_2O and brine, dried over Na_2SO_4, and then concentrated in vacuo. Chromatography of the residue on silica gel (petroleum ether/EtOAc 8:1) provided **38** (482 mg, 81%) as a colorless oil. $R_f=0.29$ (petroleum ether/EtOAc 4:1); $[\alpha]_D^{20}=+52.8$ ($c=0.57$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.27$ (d, $J=8.6$ Hz, 2H), 6.87 (d, $J=8.6$ Hz, 2H), 4.58 and 4.29 (AB, $J_{AB}=11.1$ Hz), 4.27 (m, 1H), 4.08 and 3.97 (AB of ABX, $J_{AB}=8.1$, $J_{AX}=6.6$, $J_{BX}=8.1$ Hz), 3.81 (s, 3H), 3.70–3.65 (m, 1H), 3.15 (dd, $J=10.8$, 4.8 Hz, 1H), 2.97 (dd, $J=10.5$, 2.1 Hz, 1H), 2.67 and 2.46 (AB of ABX, $J_{AB}=16.2$, $J_{AX}=7.2$, $J_{BX}=6.6$ Hz), 2.23 (m, 1H), 2.10–1.95 (m, 1H), 1.36 (d, $J=6.6$ Hz, 6H), 0.98 (d, $J=6.6$ Hz, 3H), 0.93 ppm (d, $J=6.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=159.2$, 130.3, 129.2 (2C), 117.5, 113.8 (2C), 109.2, 82.2, 80.6, 74.7, 74.0, 69.7 (2C), 65.2, 55.3, 33.6, 32.1, 25.9, 21.7, 12.8, 5.3 ppm; IR (film): $\tilde{\nu}=2983$, 2251, 1614, 1587, 1514 cm^{-1}; HRMS (ESI): calcd for $C_{22}H_{31}O_5NaN$: 412.2094 $[M+Na]^+$; found: 412.2098.

Alcohol 39: DIBAL (1.65 mL, 1.65 mmol, 1 M in toluene) was added dropwise to a solution of **38** (248 mg, 0.64 mmol) in dry CH_2Cl_2 (10 mL) under argon at −78 °C. After the mixture had been stirred at −78 °C for 1 h, it was quenched with HCl (1 N, 15 mL) and extracted with Et_2O (3× 50 mL). The combined organic extracts were then washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated in vacuo to give a residue. $NaBH_4$ (24 mg, 0.64 mmol) was added to a solution of the residue in MeOH (2 mL) at 0 °C, and the mixture was stirred for 30 min. After this time, the mixture was quenched with saturated aqueous NH_4Cl and extracted with Et_2O (3×50 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Chromatography of the residue on silica gel (petroleum ether/EtOAc 4:1) provided **39** (181 mg, 72% overall yield for the two steps) as colorless oil. R_f=0.41 (petroleum ether/EtOAc 1:1); $[\alpha]_D^{20}$=+43.7 (c=1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.27 (d, J=8.6 Hz, 2H), 6.87 (d, J=8.6 Hz, 2H), 4.57 and 4.27 (AB, J_{AB}=11.3 Hz), 4.26 (m, 1H), 4.07 and 3.97 (AB of ABX, J_{AB}=8.1, J_{AX}=6.6, J_{BX}=3.9 Hz), 3.81 (s, 3H), 3.80–3.76 (m, 2H), 3.55 (ddd, J=10.8, 2.7, 2.7 Hz, 1H), 3.32–3.29 (m, 1H), 3.12 (dd, J=10.5, 5.1 Hz, 1H), 2. (dd, J=10.2, 2.4 Hz, 1H), 2.10–1.90 (m, 3H), 1.53 (m, 1H), 1.46 (s, 3H), 1.31 (s, 3H), 0.97 (d, J=2.1 Hz, 3H), 0.94 ppm (d, J=1.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=159.2, 130.7, 129.3 (2C), 113.9 (2C), 110.0, 83.3, 82.8, 80.1, 74.8, 69.6, 66.5, 62.5, 55.4, 35.2, 34.8, 32.1, 26.0, 25.5, 12.9, 6.4 ppm; IR (film): $\tilde{\nu}$=3485, 2979, 1614, 1587, 1514 cm^{-1}; HRMS (ESI): calcd for $C_{22}H_{34}O_6Na$ 417.2247 $[M+Na]^+$; found: 417.2249.

TBDPS ether 40: Triethylamine (0.107 mL, 0.76 mmol), TBDPSCl (0.182 mL, 0.663 mmol), and DMAP (6.2 mg, 0.051 mmol) were added to a solution of **39** (200 mg, 0.51 mmol) in CH_2Cl_2 (4 mL) under argon. The reaction mixture was stirred at RT for 3 h and then diluted with Et_2O (150 mL), washed with brine (×2), dried over Na_2SO_4, and concentrated in vacuo. Chromatography of the residue on silica gel (petroleum ether/EtOAc 30:1) provided **40** (296 mg, 92%) as a colorless oil. R_f=0.57 (petroleum ether/EtOAc 10:1); $[\alpha]_D^{20}$=+43.6 (c=0.375 in $CHCl_3$); H NMR (300 MHz, $CDCl_3$): δ=7.66 (m, 4H), 7.45–7.36 (m, 6H), 7.27 (d, J=8.7 Hz, 2H), 6.87 (d, J=8.7 Hz, 2H), 4.57 and 4.27 (AB, J_{AB}=11.4 Hz), 4.22 (ddd, J=6.0, 6.0, 1.5 Hz, 1H), 3.92–3.75 (m, 4H), 3.81 (s, 3H), 3.51 (m, 1H), 3.11 (dd, J=10.5, 4.5 Hz, 1H), 2.77 (dd, J=9.9, 1.5 Hz, 1H), 2.02–1.97 (m, 2H), 1.90–1.75 (m, 1H), 1.60–1.55 (m, 1H), 1.33 (s, 6H), 1.05 (s, 9H), 0.95 (d, J=6.6 Hz, 3H), 0.87 ppm (d, J=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=159.0, 135.4 (4C), 133.9, 133.8, 130.8, 129.5 (2C), 129.0 (2C), 127.6 (4C), 113.6 (2C), 108.9, 83.4, 79.9, 75.1, 74.4, 69.3, 65.1, 60.8, 55.2, 36.1, 34.4, 32.3, 26.8 (3C), 26.0, 25.7, 19.2, 13.0, 5.8 ppm; IR (film): $\tilde{\nu}$=3702, 2959, 1614, 1588, 1514 cm^{-1}; HRMS (ESI): calcd for $C_{38}H_{52}O_6NaSi$: 655.3425 $[M+Na]^+$; found: 655.3427.

Ketone 42: HIO_4 (71 mg, 0.315 mmol) was added to a solution of **40** (94 mg, 0.15 mmol) in EtOAc (4 mL) at 0 °C. The resulting solution was stirred at 0 °C for 6 h, and was then quenched by the addition of a mixture of saturated aqueous $NaHCO_3/Na_2S_2O_3$ (5:1, 10 mL). The resulting mixture was then diluted with Et_2O (150 mL), and the organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo to give a residue. MeLi (0.2 mL, 0.32 mmol, 1.6 M solution in Et_2O) was added to a precooled solution of this residue in THF (4 mL) at −78 °C under argon. The resulting mixture was stirred at −78 °C for 1 h, and was then quenched with aqueous NH_4Cl solution at −78 °C and extracted with Et_2O (150 mL). The organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo to give a second residue. Dess–Martin periodinane (83 mg, 0.2 mmol) was added to a solution of this residue in CH_2Cl_2 (3 mL) at RT. This reaction mixture was stirred at RT for 2 h. After this time, the reaction was quenched with saturated aqueous $NaHCO_3/Na_2S_2O_3$ (10 mL, 5:1) and extracted with Et_2O (150 mL). As above, the organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Chromatography of the residue on silica gel (petroleum ether/EtOAc 20:1) provided **42** (49 mg, 58% overall yield for the three steps) as colorless oil. R_f=0.69 (petroleum ether/EtOAc 6:1); $[\alpha]_D^{20}$=+53.6 (c=0.55 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.66–7.62 (m, 4H), 7.41–7.36 (m, 6H), 7.27 (d, J=8.7 Hz, 2H), 6.87 (d, J=8.7 Hz, 2H), 4.56 and 4.29 (AB, J_{AB}=11.1 Hz), 3.80 (s, 3H), 3.78–3.73 (m, 2H), 3.64 (m, 1H), 3.31 (d, J=10.5 Hz, 1H), 3.17 (dd, J=9.9, 4.2 Hz, 1H), 2.12 (s, 3H), 2.11 (m, 1H), 1.86–1.68 (m, 3H), 1.05 (s, 9H), 0.94 (d, J=6.9 Hz, 3H), 0.89 ppm (d, J=6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=206.9, 158.6, 134.9 (4C), 134.2 (2C), 129.8, 129.1 (2C), 128.8 (2C), 127.1 (4C), 113.2 (2C), 87.2, 82.4, 74.2, 69.1, 59.9, 54.7, 35.3, 33.7, 31.8, 26.3 (3C), 24.8, 18.7, 12.3, 5.5 ppm; IR (film): $\tilde{\nu}$=3072, 2932, 1720, 1614, 1588, 1515 cm^{-1}; HRMS (ESI): calcd for $C_{35}H_{46}O_5NaSi$: 597.3006 $[M+Na]^+$; found: 597.2994.

Oxazole 5: LDA (0.23 mL, 0.138 mmol, 0.6 M solution in THF) was added to a solution of **43** (29 mg, 0.14 mmol) in THF (0.5 mL) at −78 °C under argon. The resulting mixture was stirred for 30 min at −78 °C, and then a solution of ketone **42** (13 mg, 0.023 mmol) in anhydrous THF (0.3 mL) was added. After the addition, the reaction mixture was warmed to RT, quenched with saturated aqueous NH_4Cl solution, and extracted with Et_2O (2×50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Chromatography of the residue on silica gel (petroleum ether/EtOAc 10:1) provided **5** (8.6 mg, 78% yield, 3.4 mg of **42** was recovered) as a colorless oil. R_f=0.56 (petroleum ether/EtOAc 4:1); $[\alpha]_D^{20}$=+38 (c=0.13 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.68–7.64 (m, 4H), 7.49 (s, 1H), 7.40–7.35 (m, 6H), 7.28 (d, J=8.5 Hz, 2H), 6.88 (d, J=8.5 Hz, 2H), 6.17 (s, 1H), 4.56 and 4.28 (AB, J_{AB}=11.1 Hz), 3.81 (s, 3H), 3.79–3.66 (m, 3H), 3.41 (d, J=10.5 Hz, 1H), 3.20 (dd, J=10.8, 4.8 Hz, 1H), 2.45 (s, 3H), 2.15–2.09 (m, 1H), 1.88 (d, J=1.5 Hz, 3H), 1.86–1.70 (m, 3H), 1.05 (m, 9H), 0.94 (d, J=6.9 Hz, 3H), 0.82 ppm (d, J=6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=160.5, 159.1, 138.2, 137.9, 135.5 (4C), 134.0, 133.9, 130.7, 129.5 (2C), 129.3 (3C), 127.6 (5C), 118.4, 113.8 (2C), 88.9, 83.5, 74.8, 69.6, 60.8, 55.3, 35.8, 34.2, 33.3, 26.9 (3C), 19.2, 14.2, 13.8, 13.7, 6.0 ppm; IR (film): $\tilde{\nu}$=3072, 2931, 1614, 1587, 1514, 1462 cm^{-1}; HRMS (ESI): calcd for $C_{40}H_{51}O_5NSiNa$: 676.3428 $[M+Na]^+$; found: 676.3411.

Ester 45: 1,3-Propanediol (7.6 g, 100 mmol) in THF (50 mL) was added to a suspension of NaH (4.0 g, 100 mmol, 60% in oil) in THF (100 mL) at RT. After the mixture had been stirred for 45 min, a solution of TBSCl (15 g, 100 mmol) in THF (50 mmol) was added dropwise at 0 °C. The mixture was stirred for a further 1 h, before being quenched with saturated aqueous $NaHCO_3$ (200 mL). This mixture was extracted with Et_2O (3×300 mL) and the combined organic phases were washed with brine (×2), dried (Na_2SO_4), filtered, and concentrated in vacuo to give a residue. For the next step in the synthesis, PCC (43.2 g, 200 mmol) was added to a solution of the residue in CH_2Cl_2 (150 mL) at 0 °C, and the resulting mixture was stirred at RT overnight. After this time, the CH_2Cl_2 was removed in vacuo and the residue produced was dissolved in Et_2O (400 mL). The mixture was stirred for 1 h, before being filtered through netural Al_2O_3 and concentrated in vacuo to give a residue. Ph_3PCHCO_2Et (38 g, 100 mmol) was added to a solution of this residue in freshly distilled benzene (400 mL), and the resulting mixture was refluxed for 24 h. After this time, the solvent was removed under reduced pressure, and the residue produced was dissolved in CH_2Cl_2 (20 mL), before being further diluted with petroleum ether (400 mL). At this point a substantial quantity of Ph_3PO precipitated out of the reaction mixture. After filtration, the filtrate was concentrated in vacuo, and the resultant residue was treated as above one more time. Chromatography of the residue on silica gel (petroleum ether/EtOAc 60:1) provided **45** (13.2 g, 51% overall yield for the three steps) as a colorless oil. R_f=0.63 (petroleum ether/EtOAc 20:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.97 (dt, J=15.3, 7.2 Hz, 1H), 5.87 (dt, J=15.9, 1.5 Hz, 1H), 4.19 (q, J=6.9z, 2H), 3.74 (t, J=6.9 Hz, 2H), 2.42 (qd, J=6.6, 1.2 Hz, 2H), 1.29 (t, J=6.9 Hz, 3H), 0.89 (s, 9H), 0.06 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=166.4, 145.7, 122.9, 61.5, 60.0, 35.6, 25.8 (3C), 18.2, 14.2, −5.4 ppm (2C); IR (film): $\tilde{\nu}$=2952, 2117, 1650, 1471, 1018 cm^{-1}; HRMS (ESI): calcd for $C_{13}H_{26}O_3SiNa$: 281.1543 $[M+Na]^+$; found: 281.1548.

Diol 46: (Dihydroquinidine)$_2$-phthalazine [(DHQD)$_2$-PHAL, 290 mg, 0.4 mmol, 1 mol%] and potassium osmate (29 mg, 0.08 mmol, 0.2 mol%) were added to a solution of potassium ferricyanide (32 g, 120 mmol) and potassium carbonate (16.6 g, 120 mmol) in a mixture of *t*BuOH and water (1:1, 400 mL) at RT. Compound **45** (10.3 g, 40 mmol) was then added to the mixture, and it was vigorously stirred at RT until the reaction had finished (approximately 12 h). After this time, the reaction was quenched with sodium sulfite (60 g). The aqueous phase was extracted with EtOAc (4×300 mL), and the combined organic layers were washed

with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Chromatography of the residue on silica gel (petroleum ether/EtOAc 4:1) provided **46** as a colorless oil (10.2 g, 87% yield, 86% *ee* as determined by chiral GC analysis). $R_f = 0.64$ (petroleum ether/EtOAc 2:1); $[\alpha]_D^{20} = -3.5$ ($c = 0.66$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 4.28$ (q, $J = 7.5$ Hz, 2H), 4.20 (m, 1H), 4.07 (d, $J = 1.8$ Hz, 1H), 3.87 (m, 2H), 3.32 (br s, 2H; OH), 1.94 (m, 1H), 1.75 (m, 1H), 1.32 (t, $J = 6.9$ Hz, 3H), 0.89 (s, 9H), 0.07 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 173.1$, 73.6, 71.9, 61.7, 61.4, 35.2, 25.7 (3C), 18.1, 14.0, −5.6 ppm (2C); IR (film): $\tilde{\nu} = 3442$, 2937, 2859, 1740, 1256, 1101, 837 cm^{-1}; HRMS (ESI): calcd for $C_{13}H_{28}O_5SiNa$: 315.1598 $[M+Na]^+$; found: 315.1614.

Alcohol 47: $BF_3{\cdot}Et_2O$ (1.1 mL, 0.1 M in CH_2Cl_2) was added to a mixture of diol **46** (1.1 g, 3.76 mmol) and $Cl_3CC(NH)OPMB$ reagent (39 mL, approximately 17.7 mmol) in dry CH_2Cl_2 (15 mL) at 0 °C under a nitrogen atmosphere. A substantial quantity of a white solid was observed to immediately precipitate out of the reaction mixture. After the reaction mixture had been stirred at 0 °C for 30 min, the suspension was filtered. The solid was washed with a mixture of CH_2Cl_2/hexane (1:2, 2×5 mL), and the filtrate was washed with saturated aqueous $NaHCO_3$ solution (20 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, and then concentrated in vacuo to give a residue. Finally, $LiAlH_4$ (571 mg, 15 mmol) was added to a solution of the residue in dry Et_2O (100 mL) at 0 °C. After the addition, the mixture was stirred at RT for 1 h, and then the mixture was quenched with H_2O (3 mL), filtered, and the resulting filtrate was concentrated in vacuo. Chromatography of the residue on silica gel (petroleum ether/EtOAc 6:1) provided **47** (1.33 g, 72% overall yield for the two steps) as a colorless oil. $R_f = 0.33$ (petroleum ether/EtOAc 3:1); $[\alpha]_D^{20} = +5.4$ ($c = 1.45$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.20$ (d, $J = 8.4$ Hz, 2H), 7.19 (d, $J = 9$ Hz, 2H), 6.81 (d, $J = 8.4$ Hz, 4H), 4.57–4.43 (m, 4H), 3.75 (s, 6H), 3.74 (m, 2H), 3.60 (m, 4H), 1.79 (m, 1H), 1.60 (m, 1H), 0.89 (s, 9H), 0.06 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 159.1$ (2C), 130.3, 130.2, 129.5 (2C), 129.4 (2C), 113.7 (4C), 78.9, 75.2, 72.4, 72.0, 61.6, 59.2, 55.1 (2C), 32.9, 25.8 (3C), 18.1, −5.3, −5.4 ppm; IR (film): $\tilde{\nu} = 3456$, 2955, 1614, 1587, 1515, 1250, 835, 777 cm^{-1}; HRMS (ESI): calcd for $C_{27}H_{42}O_6SiNa$: 513.2643 $[M+Na]^+$; found: 513.2636.

Ester 48: A solution of dimethyl sulfoxide (DMSO, 0.24 mL, 3.42 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a stirred solution of oxalyl chloride (0.95 mL, 2.3 mmol) in CH_2Cl_2 (4 mL) at −78 °C under a nitrogen atmosphere. The mixture was stirred at −78 °C for 10 min, and then a solution of the alcohol **47** (560 mg, 1.13 mmol) in CH_2Cl_2 (3 mL) was added dropwise. The mixture was stirred at −78 °C for a further 1 h, and then triethylamine (0.96 mL) was added dropwise. Once the two additions had been completed, the mixture was warmed to RT and then quenched with a solution of saturated aqueous potassium hydrogenphosphate (60 mL). The aqueous layer was extracted with dichloromethane (2×50 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to give a residue. For the next step in the synthesis, Ph_3PCHCO_2Et (517 mg, 1.42 mmol) was added to a solution of the residue in dry CH_2Cl_2 (20 mL), and the mixture was refluxed for 4 h. After this time, silica gel (4 g) was added and the solvent removed in vacuo. Chromatography on silica gel (the residue produced was directly loaded onto the column and eluted with petroleum ether/EtOAc 10:1) provided **48** (546 mg, 84% yield for two steps) as a colorless oil. $R_f = 0.67$ (petroleum ether/EtOAc 4:1); $[\alpha]_D^{20} = -6.6$ ($c = 0.57$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 7.24 (d, $J = 9$ Hz, 2H), 7.23 (d, $J = 9$ Hz, 2H), 6.87 (d, $J = 9$ Hz, 2H), 6.84 (d, $J = 9$ Hz, 2H), 6.72 (dd, $J = 9.3$, 1.5 Hz, 1H), 4.65 and 4.50 (AB, $J_{AB} =$ 11.1 Hz), 4.55 and 4.31 (AB, $J_{AB} = 11.7$ Hz), 4.26 (m, 1H), 4.22 (q, $J =$ 6.9 Hz, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 3.72 (m, 1H), 3.62 (m, 2H), 1.82 (d, $J = 1.5$ Hz, 3H), 1.78–1.63 (m, 2H), 1.32 (t, $J = 6.9$ Hz, 3H), 0.89 (s, 9H), 0.04 (s, 3H), 0.02 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 167.4, 159.0 (2C), 139.0 (2C), 131.2, 130.6, 130.1, 129.6 (2C), 129.4 (2C), 113.6 (2C), 113.5 (2C), 77.2, 76.9, 73.3, 70.4, 60.7, 59.2, 55.1, 33.9, 25.8 (3C), 18.1, 14.1, 13.2, −5.4 ppm (2C); IR (film): $\tilde{\nu} = 2956$, 1714, 1614, 1587, 1465, 1249 cm^{-1}; HRMS (ESI): calcd for $C_{32}H_{48}O_7NaSi$: 595.3062 $[M+Na]^+$; found: 595.3066.

Ester 49: DIBAL (4.77 mL, 4.77 mmol, 1 M in toluene) was added dropwise to a solution of **48** (1.3 g, 2.3 mmol) in dry Et_2O (30 mL) at −78 °C. After the reaction mixture had been stirred at −78 °C for 2 h, the mixture was quenched with H_2O (2 mL) and $MgSO_4$ (10 g) was added. The mixture was then vigorously stirred at RT for 10 h. After this time, the mixture was filtered and the resulting filtrate concentrated in vacuo to give a residue. Triethylamine (5.61 mL, 40 mmol), acetyl anhydride (1.8 mL, 20 mmol), and DMAP (cat) were then added to a solution of the residue in dry CH_2Cl_2 (30 mL) at 0 °C under argon. Once the reaction mixture had been warmed to RT and stirred for 3 h, it was quenched with saturated aqueous $NaHCO_3$ solution. This mixture was then extracted with EtOAc (3×80 mL), and the combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Chromatography of the residue on silica gel (petroleum ether/EtOAc 8:1) provided **49** (1.18 g, 90% overall yield for the two steps) as a colorless oil. $R_f = 0.53$ (petroleum ether/EtOAc 4:1); $[\alpha]_D^{20} = -4.0$ ($c = 0.66$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.25$ (d, $J = 9.0$ Hz, 2H), 7.24 (d, $J = 9.0$ Hz, 2H), 6.85 (d, $J = 9.0$ Hz, 2H), 6.84 (d, $J = 9.0$ Hz, 2H), 5.45 (dd, $J = 9.3$, 1.2 Hz, 1H), 4.68 and 4.30 (AB, $J_{AB} = 10.5$ Hz), 4.52 and 4.48 (AB, $J_{AB} = 9.9$ Hz), 4.49 (br s, 2H), 4.15 (dd, $J = 9.6$, 6.3 Hz, 1H), 3.79 (s, 6H), 3.66–3.60 (m, 3H), 2.09 (s, 3H), 1.70 (m, 1H), 1.63 (d, $J = 1.2$ Hz, 3H), 1.60 (m, 1H), 0.87 (s, 9H), 0.03 (s, 3H), 0.02 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.9$, 159.2 (2C), 135.1, 131.2, 130.8, 129.8 (2C), 129.5 (2C), 126.1, 113.8 (4C), 77.9, 77.3, 73.6, 70.1, 69.0, 59.7, 55.4 (2C), 34.4, 26.1 (3C), 21.1, 18.4, 14.8, −5.1 ppm (2C); IR (film): $\tilde{\nu} = 2955$, 1743, 1614, 1515, 1249 cm^{-1}; HRMS (ESI): calcd for $C_{32}H_{48}O_7SiNa$: 595.3062 $[M+Na]^+$; found: 595.3069.

Aldehyde 50: TBAF (15 mL, 1 M in THF) was added to a solution of **49** (5.43 g, 9.49 mmol) in dry THF (10 mL) at RT. The resulting mixture was then stirred at RT for 24 h, before being quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc (3×80 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, and then concentrated in vacuo to give a residue. Dess–Martin periodinane (4.2 g, 10.0 mmol) was added to a solution of this residue in CH_2Cl_2 (50 mL) at RT. The mixture was stirred at RT for 3 h and then quenched with a mixture of saturated aqueous $NaHCO_3/Na_2S_2O_3$ (5:1, 150 mL), before being extracted with CH_2Cl_2 (2×200 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Chromatography of the residue on silica gel (petroleum ether/EtOAc 10:1) provided **50** (3.76 g, 86.4% overall yield for two steps) as a colorless oil. $R_f = 0.50$ (petroleum ether/EtOAc 4:1); $[\alpha]_D^{20} = -11.8$ ($c =$ 0.59 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 9.65$ (d, $J = 1.5$ Hz, 1H), 7.22 (d, $J = 8.4$ Hz, 2H), 7.20 (d, $J = 8.4$ Hz, 2H), 6.86 (d, $J = 8.4$ Hz, 2H), 6.84 (d, $J = 8.4$ Hz, 2H), 5.43 (dd, $J = 9.6$, 1.5 Hz, 1H), 4.63 and 4.53 (AB, $J_{AB} = 11.1$ Hz), 4.52 and 4.27 (AB, $J_{AB} = 11.4$ Hz), 4.49 (s, 2H), 4.21 (dd, $J = 9.6$, 5.7 Hz, 1H), 4.05–3.99 (m, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 2.58 (m, 2H), 2.10 (s, 3H), 1.63 ppm (d, $J = 0.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 201.1$, 170.8, 159.5, 159.4, 136.4, 130.3 (2C), 129.8 (2C), 129.6 (2C), 124.9, 113.9 (4C), 76.2, 76.0, 73.2, 70.2, 68.8, 55.4 (2C), 45.5, 21.1, 14.9 ppm; IR (film): $\tilde{\nu} = 3000$, 2937, 2839, 2731, 1737, 1613 cm^{-1}; HRMS (ESI): calcd for $C_{26}H_{32}O_7Na$: 479.2040 $[M+Na]^+$; found: 479.2051.

Alcohol 52: $TiCl_4$ (0.16 mL, 1.46 mmol) was added to a solution of $Ti(OiPr)_4$ (0.475 mL) in dry toluene (15 mL) at RT. After the completion of addition, the mixture was stirred at RT for 10 min and then cooled to −78 °C. A solution of aldehyde **50** (1.2 g, 2.65 mmol) in toluene (7 mL) was then added to the mixture. After the mixture had been stirred for 10 min, a solution of 1-ethoxy-1-[(trimethylsilyl)oxy]ethane **51** (763 mg, 4.77 mmol) in toluene (3 mL) was added. This mixture was stirred at −78 °C for 2 h and then quenched with saturated aqueous $NaHCO_3$ solution, before being extracted with EtOAc (3×50 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Chromatography of the residue on silica gel (petroleum ether/EtOAc 6:1) provided **52** (879 mg, 61%) as colorless oil. $R_f = 0.37$ (petroleum ether/EtOAc 3:1); $[\alpha]_D^{20} = -3.6$ ($c = 0.49$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.25$ (d, $J = 9.0$ Hz, 2H), 7.24 (d, $J = 9.0$ Hz, 2H), 6.86 (d, $J = 9.0$ Hz, 2H), 6.85 (d, $J = 9.0$ Hz, 2H), 5.42 (dd, $J = 9.9$, 1.2 Hz, 1H), 4.73 and 4.53 (AB, $J_{AB} = 11.1$ Hz), 4.53 and 4.30 (AB, $J_{AB} = 11.7$ Hz), 4.49 (s, 2H), 4.20 (dd, $J = 9.3$, 6.0 Hz, 1H), 4.14 (q, $J = 7.2$ Hz, 2H), 3.81–3.78 (m, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.13 (d, $J = 3.9$ Hz, 1H), 2.41 (s; OH), 2.39 (d, $J = 2.7$ Hz, 1H), 2.09 (s, 3H), 1.65 (d, $J = 1.2$ Hz, 3H), 1.61–1.51 (m, 2H), 1.25 ppm (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$):

δ = 175.2, 173.3, 161.9, 161.8, 138.3, 133.4, 133.2, 132.5 (2C), 132.0 (2C), 128.1, 116.5 (2C), 116.4 (2C), 80.7, 76.3, 72.6, 71.5, 67.7 (2C), 63.2, 57.9 (2C), 44.6, 40.4, 23.6, 17.4, 16.8 ppm; IR (film): $\tilde{\nu}$ = 3506, 2937, 2839, 1737, 1613, 1587 cm^{-1}; HRMS (ESI): calcd for $C_{30}H_{40}O_9Na$: 567.2564 $[M+Na]^+$; found: 567.2572.

C35 epimer of 52: R_f = 0.36 (petroleum ether/EtOAc 3:1); $[\alpha]_D^{20} = -2.8$ (c = 0.39 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 7.28–7.19 (m, 4H), 6.88–6.82 (m, 4H), 5.43 (dd, J = 10.2, 1.8 Hz, 1H), 4.71 (d, J = 10.8 Hz, 1H), 4.55–4.48 (m, 3H), 4.27 (d, J = 10.8 Hz, 1H), 4.26–4.01 (m, 4H), 3.80 (s, 3H), 3.79 (s, 3H), 3.70–3.65 (m, 2H), 3.56 (d, J = 2.4 Hz, 1H), 2.45–2.35 (m, 2H), 2.10 (s, 3H), 1.75–1.55 (m, 2H), 1.65 (d, J = 0.9 Hz, 3H), 1.25 ppm (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.1, 170.7, 159.3 (2C), 135.9, 130.3, 130.1, 129.8 (2C), 129.5 (2C), 125.2, 113.8 (2C), 113.7 (2C), 79.8, 76.2, 72.9, 69.9, 68.8, 66.9, 60.5, 55.2 (2C), 41.7, 37.0, 20.9, 14.7, 14.2 ppm; IR (film): $\tilde{\nu}$ = 3497, 2936, 1735, 1613, 1587, 1514 cm^{-1}; HRMS (ESI): calcd for $C_{30}H_{40}O_9Na$: 567.2564 $[M+Na]^+$; found: 567.2565.

Ether 53: 1,8-Bis(dimethylamino)naphthalene (599 mg, 2.8 mmol) and Me_3OBF_4 (414 mg, 2.8 mmol) were added to a solution of **52** (190 mg, 0.35 mmol) in dry CH_2Cl_2 (6 mL) at 0 °C. The mixture was stirred at 0 °C for 6 h, and then the reaction was quenched with *i*PrOH (0.5 mL) at 0 °C. The resultant mixture was diluted with Et_2O (200 mL), and the organic phase was washed with HCl (1 N), saturated aqueous $NaHCO_3$, and brine. The organic layer was then dried over Na_2SO_4 and concentrated in vacuo. Chromatography of the residue on silica gel (petroleum ether/EtOAc 6:1) provided **53** (165 mg, 85%) as colorless oil. R_f = 0.60 (petroleum ether/EtOAc 2:1); $[\alpha]_D^{20} = +4.5$ (c = 0.48 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 7.24 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 8.4 Hz, 4H), 5.42 (dd, J = 9.9, 1.2 Hz, 1H), 4.73 and 4.47 (AB, J_{AB} = 10.5 Hz), 4.52 and 4.29 (AB, J_{AB} = 11.4 Hz), 4.49 (br s, 2H), 4.17 (dd, J = 9.6, 6.3 Hz, 1H), 4.12 (q, J = 7.5 Hz, 2H), 3.81–3.68 (m, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.25 (s, 3H), 2.51 and 2.40 (AB of ABX, J_{AB} = 15.0, J_{AX} = 6.3, J_{BX} = 5.7 Hz), 2.09 (s, 3H), 1.73–1.49 (m, 2H), 1.63 (d, J = 1.2 Hz, 3H), 1.24 ppm (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.4, 170.7, 159.2, 159.1, 135.4, 130.9, 130.6, 129.6 (2C), 129.3 (2C), 125.8, 113.8 (2C), 113.7 (2C), 77.8, 76.6, 74.6, 73.4, 69.9, 68.9, 60.4, 56.7, 55.3, 55.2, 39.8, 36.7, 20.9, 14.7, 14.2 ppm; IR (film): $\tilde{\nu}$ = 2936, 2838, 1737, 1613, 1587, 1515 cm^{-1}; HRMS (ESI): calcd for $C_{31}H_{42}O_9Na$: 581.2721 $[M+Na]^+$; found: 581.2724.

Lactone 54: CF_3COOH (10% in CH_2Cl_2, 8.1 mL) was added dropwise to a solution of **53** (360 mg, 0.65 mmol) in CH_2Cl_2 (2 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h, and then poured into a mixture of saturated aqueous $NaHCO_3$ and CH_2Cl_2 (1:1, 100 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL), and then the combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Chromatography of the residue on silica gel (petroleum ether/EtOAc 1:1) provided **54** (168 mg, 95%) as colorless oil. R_f = 0.40 (petroleum ether/EtOAc 1:2); $[\alpha]_D^{20} = -5.2$ (c = 0.60 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 5.52 (d, J = 8.3 Hz, 1H), 4.50 (s, 2H), 4.47 (m, 1H), 4.15 (ddd, J = 11.5, 6.2, 3.4 Hz, 1H), 3.77 (m, 1H), 3.37 (s, 3H), 2.86 (dd, J = 17.2, 5.6 Hz, 1H), 2. 71 (d, J = 3.7 Hz, 1H), 2.56 (dd, J = 17.2, 7.2 Hz, 1H), 2.24 (ddd, J = 13.7, 4.3, 4.3 Hz, 1H), 2.09 (s, 3H), 1.77 (s, 3H), 1.67–1.55 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.7, 169.5, 136.9, 124.1, 79.9, 72.2, 70.1, 68.5, 56.1, 36.3, 30.7, 20.9, 14.8 ppm; IR (film): $\tilde{\nu}$ = 3446, 2933, 1739, 1668, 1442, 1378 cm^{-1}; HRMS (ESI): calcd for $C_{13}H_{20}O_6Na$: 295.1152 $[M+Na]^+$; found: 295.1157.

Compound 55: Imidazole (171 mg, 2.4 mmol), TIPSCl (0.25 mL, 1.2 mmol), and DMAP (cat) were added to a solution of **54** (108 mg, 0.39 mmol) in anhydrous DMF (1 mL) at RT. Whilst stirring, the reaction mixture was heated to 40 °C and then stirred for 20 h. After this time, the mixture was cooled to RT and diluted with Et_2O (150 mL). This mixture was then washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. Chromatography of the residue on silica gel (petroleum ether/EtOAc 10:1) provided **55** (132 mg, 78%) as a colorless oil. R_f = 0.43 (petroleum ether/EtOAc 4:1); $[\alpha]_D^{20} = -6.3$ (c = 0.49 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 5.46 (d, J = 8.7 Hz, 1H), 4.73 (dd, J = 8.7, 4.8 Hz, 1H), 4.47 (s, 2H), 4.24 (ddd, J = 12.0, 3.3, 3.3 Hz, 1H), 3.71–3.67 (m, 1H), 3.37 (s, 3H), 2.91 (ddd, J = 17.4, 5.7, 1.2, 1H), 2.46–2.37 (m, 2H), 2.08 (s, 3H), 1.72 (s, 3H), 1.63–1.48 (m, 1H), 1.10–0.98 ppm (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.1, 169.6, 134.3, 126.4, 80.0, 72.4, 69.6, 68.7, 55.9, 36.9, 29.2, 20.8, 17.9 (3C), 17.8 (3C), 15.0, 12.2 ppm (3C); IR (film): $\tilde{\nu}$ = 2945, 2868, 1745, 1231 cm^{-1}; HRMS (ESI): calcd for $C_{22}H_{40}O_6SiNa$: 451.2486 $[M+Na]^+$; found: 451.2480.

Alcohol 57: K_2CO_3 (17 mg, 0.12 mmol) was added to a stirred solution of **53** (53 mg, 0.93 mmol) in EtOH (1 mL) at RT. After the reaction mixture had been stirred for 2 h at RT, the mixture was quenched with saturated aqueous NH_4Cl solution. The mixture was then diluted with EtOAc (100 mL), washed with brine (×2), dried over Na_2SO_4, and concentrated in vacuo. Chromatography of the residue on silica gel (petroleum ether/EtOAc 4:1) provided **57** (47 mg, 97%) as a colorless oil. R_f = 0.43 (petroleum ether/EtOAc 2:1); $[\alpha]_D^{20} = +5.5$ (c = 0.47 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 7.23(d, J=8.4 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.4 Hz, 4H), 5.41 (d, J = 9.3 Hz, 1H), 4.74 and 4.32 (AB, J_{AB} = 10.5 Hz), 4.52 and 4.48 (AB, J_{AB} = 11.4 Hz), 4.20 (dd, J = 9.3, 6.0 Hz, 1H), 4.12 (q, J = 7.2 Hz, 2H), 4.02 (s, 2H), 3.80 (s, 6H), 3.76–3.68 (m, 2H), 3.26 (s, 3H), 2.51 and 2.41 (AB of ABX, J_{AB} = 14.4, J_{AX} = 5.4, J_{BX} = 5.7 Hz), 2.02 (s, 1H; OH), 1.78–1.50 (m, 2H), 1.65 (s, 3H), 1.27 ppm (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.1, 158.8, 158.6, 140.3, 130.5, 130.4, 129.3 (2C), 128.9 (2C), 122.3, 113.3 (2C), 113.2 (2C), 76.7, 76.2, 74.2, 72.9, 69.5, 67.6, 60.1, 56.4, 54.9 (2C), 39.2, 36.2, 14.1, 13.8 ppm; IR (film): $\tilde{\nu}$ = 3449, 2935, 1734, 1613, 1587, 1515 cm^{-1}; HRMS (ESI): calcd for $C_{29}H_{40}O_8Na$: 539.2615 $[M+Na]^+$; found: 539.2621.

Diol 58: A solution of CF_3COOH in CH_2Cl_2 (4.7 mL, 10%) was added dropwise to a solution of **57** (191 mg, 0.37 mmol) in CH_2Cl_2 (0.7 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h, before being quenched with Et_3N (0.86 mL) and directly concentrated in vacuo. Chromatography of the residue on silica gel (petroleum ether/EtOAc 1:1) provided **58** (72 mg, 85%) as colorless oil. R_f = 0.28 (petroleum ether/EtOAc 1:2); $[\alpha]_D^{20} = -27.6$ (c = 0.61 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 5.34 (dd, J = 9.0, 1.2 Hz, 1H), 4.47 (dd, J = 8.1, 8.1 Hz, 1H), 4.16 (ddd, J = 11.4, 6.3, 3.3 Hz, 1H), 4.09 (d, J = 2.2 Hz, 2H), 3.77 (m, 1H), 3.36 (s, 3H), 3.19 (d, J = 1.8 Hz, 1H; OH), 2.87 (dd, J = 17.1, 5.7 Hz, 1H), 2.57 (dd, J = 17.1, 4.5 Hz, 1H), 2.27 (ddd, J = 14.1, 4.5, 4.5 Hz, 1H), 1.98 (s, 1H; OH), 1.74 (s, 3H), 1.68–1.56 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.1, 141.7, 120.7, 80.1, 72.2, 69.9, 67.2, 56.1, 36.3, 30.7, 14.4 ppm; IR (film): $\tilde{\nu}$ = 3400, 2926, 1728, 1253 cm^{-1}; HRMS (ESI): calcd for $C_{11}H_{18}O_5Na$: 253.1046 $[M+Na]^+$; found: 253.1047.

TBS ether 59: Triethylamine (194 μL, 1.38 mmol), TBSCl (190 mg, 1.26 mmol), and DMAP (11 mg, 0.088 mmol) were added sequentially to a solution of **58** (290 mg, 1.26 mmol) in dry CH_2Cl_2 at RT. The reaction mixture was stirred at RT for 3 h, and then diluted with ether (150 mL), washed brine (×2), dried over Na_2SO_4, and concentrated in vacuo. Chromatography of the residue on silica gel (petroleum ether/EtOAc 4:1) provided **59** (325 mg, 75%) as a colorless oil. R_f = 0.50 (petroleum ether/EtOAc 1:1); $[\alpha]_D^{20} = -9.2$ (c = 0.48 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 5.50 (d, J = 8.7 Hz, 1H), 4.48 (dd, J = 7.2, 7.2 Hz, 1H), 4.14 (ddd, J = 10.8, 6.9, 3.3 Hz, 1H), 4.04 (br s, 2H), 3.74 (m, 1H), 3.35 (s, 3H), 2.86 and 2.54 (AB of ABX, J_{AB} = 17.4, J_{AX} = 6.0, J_{BX} = 7.2 Hz), 2.26 (ddd, J = 13.8, 4.5, 4.5 Hz, 1H), 1.70 (s, 3H), 1.59–1.50 (m, 1H), 0.92 (m, 9H), 0.07 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.6, 141.9, 119.8, 80.2, 72.3, 70.3, 67.3, 56.1, 36.4, 30.7, 25.9 (3C), 18.4, 14.3, −5.2, −5.3 ppm; IR (film): $\tilde{\nu}$ = 3425, 2956, 1737, 1253 cm^{-1}; HRMS (ESI): calcd for $C_{17}H_{32}O_5SiNa$: 367.1911 $[M+Na]^+$; found: 367.1924.

Lactone 6: TIPSCl (0.256 mL, 1.2 mmol) and $AgNO_3$ (210 mg, 1.2 mmol) were added to a solution of **59** (142 mg, 0.41 mmol) in dry pyridine (2 mL). The reaction mixture was kept in darkness and stirred for 24 h at RT. After this time, the reaction mixture was diluted with Et_2O (200 mL), washed with saturated $CuSO_4$ solution and brine, dried over Na_2SO_4, and then concentrated in vacuo. Chromatography of the residue on silica gel (petroleum ether/EtOAc 15:1) provided **6** as a colorless oil (159 mg, 78%). R_f = 0.67 (petroleum ether/EtOAc 6:1); $[\alpha]_D^{20} = -10.5$ (c = 0.25 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 5.45 (dd, J = 8.7, 1.5 Hz, 1H), 4.74 (dd, J = 9.0, 5.1 Hz, 1H), 4.24 (ddd, J = 14.7, 7.5, 2.7 Hz, 1H), 3.99 (s, 2H), 3.69 (m, 1H), 3.36 (s, 3H), 2.91 (m, 1H), 2.39 (m, 1H), 1.64 (s, 3H), 1.53 (m, 1H), 1.04 (m, 22H), 0.90 (s, 9H), 0.05 ppm (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.9, 138.9, 121.7, 80.4, 72.6, 69.9, 67.3,

56.0, 37.0, 25.9 (3C), 18.4, 18.1 (3C), 18.0 (4C), 14.5, 12.3 (3C), −5.2 ppm (2C); IR (film): $\tilde{\nu}$ = 2931, 2866, 1749, 1464, 1386 cm^{-1}; HRMS (ESI): calcd for $C_{26}H_{52}O_5NaSi_2$: 523.3245 $[M+Na]^+$; found: 523.3234.

Diol 61: Allylether **60** (3.8 g, 20 mmol) was added to a well-stirred solution of $(dihydroquinine)_2$-phthalazine [$(DHQ)_2$-PHAL, 311 mg, 2 mol%], potassium osmate (19 mg, 0.25 mol%), potassium ferricyanide (39.6 g), and potassium carbonate (33.2 g) in a mixture of *t*BuOH and water (1:1, 400 mL) at 0°C. The mixture was stirred at 0°C until the reaction was completed (approximately 15 h), and was then quenched with sodium sulfite (60 g). This mixture was stirred at RT for 4 h and then filtered. The solid was dried in vacuo, before being boiled in EtOH (250 mL) for 30 min. After this time, the insoluble material was quickly filtered off, and the filtrate was concentrated in vacuo. Recrystallization from EtOH/*i*PrOH gave **61** as colorless solid (3.4 g, 66%) with 87% *de* (*de* = diastereomeric excess, measured after acetylation of the alcohol, AD, Vu214, hexane/2-propanol 80:20). M.p. 123–124°C; $[\alpha]_D^{20} = -11.6$ (c = 2.35 in EtOH); ^{1}H NMR (500 MHz, DMSO): δ = 6.84 (brs, 4H), 4.88 (brs, 1H), 4.63 (brs, 1H), 3.93–3.90 (m, 2H), 3.80–3.73 (m, 4H), 3.45–3.40 (m, 4H), 3.34 ppm (d, J = 11.5 Hz, 2H); ^{13}C NMR (125 MHz, DMSO): δ = 152.7 (2C), 115.3 (4C), 70.0 (2C), 69.9 (2C), 62.7 ppm (2C); IR (KBr): $\tilde{\nu}$ = 3492, 3255, 1512, 1462 ppm; HRMS (ESI): calcd for $C_{12}H_{18}O_6Na$: 281.0996 $[M+Na]^+$; found: 281.0995.

Compound 62: A solution of HBr in acetic acid (2.2 mL, 30%) was added dropwise to tetrol **61** (500 mg, 1.94 mmol) at RT, and the reaction mixture was stirred at 50°C for 1 h. After this time, saturated aqueous $NaHCO_3$ and EtOAc were added, and the resulting mixture was extracted with EtOAc (200 mL). The organic layer was washed with brine, dried over Na_2SO_4, and then concentrated in vacuo to give a residue. K_2CO_3 (580 mg, 4.2 mmol) was added to a solution of this residue in MeOH (4.5 mL) at RT. The mixture was stirred at RT for 4 h and then filtered. The filtrate was concentrated in vacuo, and the resulting residue was diluted with EtOAc (100 mL). This solution was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Chromatography of the residue on silica gel (petroleum ether/EtOAc 6:1) provided **62** (390 mg, 88%) as a colorless solid. R_f = 0.30 (petroleum ether/EtOAc 4:1); m.p. 72–73°C; $[\alpha]_D^{20} = -8.1$ (c = 0.71 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.85 (brs, 4H), 4.17 (dd, J = 10.8, 3.0 Hz, 2H), 3.90 (dd, J = 10.8, 5.4 Hz, 2H), 3.36–3.31 (m, 2H), 2.90 (dd, J = 5.1, 4.2 Hz, 2H), 2.74 ppm (dd, J = 4.5, 2.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.1 (2C), 115.7 (4C), 69.4 (2C), 50.2 (2C), 44.6 ppm (2C); IR (KBr): $\tilde{\nu}$ = 3010, 2931, 1510, 1453 cm^{-1}; HRMS (ESI): calcd for $C_{12}H_{14}O_4Na$ $[M+Na]^+$: 245.0784; found: 245.0784.

Compound 63: *n*BuLi (13.1 mL, 21.0 mmol, 1.6 M solution in hexane) was added to a solution of trimethylsilylethyne (2.96 mL, 21 mmol) in dry THF (40 mL) at −78°C under argon. The mixture was stirred for 30 min at −78°C, and then $BF_3{\cdot}Et_2O$ (2.66 mL, 21 mmol) was added. After the resulting mixture had been stirred for 20 min at −78°C, a solution of **62** (1.59 g, 7.0 mmol) in THF (10 mL) was added dropwise. The reaction mixture was warmed to RT, quenched with saturated NH_4Cl solution, and extracted with EtOAc (300 mL). The organic phase was washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give a residue. 1,8-Bis(dimethylamino)naphthalene (6.06 g, 28.4 mmol) and Me_3OBF_4 (4.18 g, 28.4 mmol) were then added sequentially to a solution of this residue in dry CH_2Cl_2 (130 mL) at 0°C. After the mixture had been stirred at 0°C for 3 h, it was quenched with *i*PrOH (13 mL) at 0°C and diluted with EtOAc (800 mL). The organic layer was washed with HCl (1 N), saturated aqueous $NaHCO_3$, and brine, and then dried over Na_2SO_4 and concentrated in vacuo. Chromatography of the residue on silica gel (petroleum ether/EtOAc 15:1) provided **63** (2.21 g, 70% yield for two steps) as a colorless oil. R_f = 0.60 (petroleum ether/EtOAc 6:1); $[\alpha]_D^{20} = -21.8$ (c = 0.65 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.86 (m, 4H), 4.09 (m, 2H), 4.01 (m, 2H), 3.68 (m, 2H), 3.48 (s, 3H), 3.47 (s, 3H), 2.56 (m, 4H), 0.12 ppm (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.0 (2C), 115.5 (4C), 102.8 (2C), 86.8 (2C), 78.0 (2C), 69.5 (2C), 57.9 (2C), 22.2 (2C), 0.0 ppm (6C); IR (film): $\tilde{\nu}$ = 3402, 2949, 2837, 1653, 1451, 1027 cm^{-1}; HRMS (ESI): calcd for $C_{24}H_{38}Si_2O_4Na$: 469.2201 $[M+Na]^+$; found: 469.2182.

Alcohol 64: CAN (1.2 g, 2.22 mmol) was added to a solution of **63** (328 mg, 0.74 mmol) in a mixture of CH_3CN and H_2O (2:1, 4.5 mL) at 0°C. After the mixture had been stirred at 0°C for 20 min, it was quenched with a mixture of saturated aqueous $NaHCO_3/Na_2SO_3$ solution 5:1 and diluted with EtOAc (200 mL). The organic extracts were washed with brine (×2), dried over Na_2SO_4, and then concentrated in vacuo. Chromatography of the residue on silica gel (petroleum ether/EtOAc 4:1) provided **64** (248 mg, 91%) as a colorless oil. R_f = 0.32 (petroleum ether/EtOAc 3:1); $[\alpha]_D^{20} = -36.6$ (c = 0.91 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.75 (m, 1H), 3.59 (m, 1H), 3.41 (s, 3H), 3.40 (m, 1H), 2.50 (dd, J = 16.5, 5.1 Hz, 1H), 2.34 (dd, J = 16.5, 7.5 Hz, 1H), 2.32 (brs, 1H; OH), 0.10 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 102.6, 86.9, 79.9, 63.7, 57.5, 21.4, 0.0 ppm (3C); IR (film): $\tilde{\nu}$ = 3431, 2960, 2831, 2171, 1251, 844 cm^{-1}; HRMS (ESI): calcd for $C_9H_{18}Si_1O_2Na$: $[M+Na]^+$: 209.0968; found: 209.0969.

Compound 65: Triphenylphosphine (283 mg, 1.08 mmol), 2-mercaptobenzothiazole (180 mg, 1.08 mmol), and diisopropyl azodicarboxylate (0.569 mL, 1.08 mmol, 40% in toluene) were added sequentially to a solution of the alcohol **64** (192 mg, 1.03 mmol) in THF (6 mL). The resulting reaction mixture was stirred at RT for 1 h, and then loaded onto silica gel (4 g). Chromatography of the residue on silica gel (petroleum ether/EtOAc 30:1) provided **65** (280 mg, 81%) as a colorless oil. R_f = 0.69 (petroleum ether/EtOAc 10:1); $[\alpha]_D^{20} = -9.0$ (c = 0.58 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86 (m, 1H), 7.75 (m, 1H), 7.42 (m, 1H), 7.28 (m, 1H), 3.76–3.68 (m, 2H), 3.60–3.48 (m, 1H), 3.47 (s, 3H), 2.71–2.54 (m, 2H), 0.16 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.6, 153.1, 135.2, 125.9, 124.1, 121.4, 120.9, 102.2, 87.4, 78.1, 57.9, 36.6, 24.5, 0.0 ppm (3C); IR (film): $\tilde{\nu}$ = 3064, 2959, 2178, 1462, 1429, 1249 cm^{-1}; HRMS (ESI): calcd for $C_{16}H_{21}NOS_2SiNa$: 358.0726 $[M+Na]^+$; found: 358.0743.

Compound 66: TBAF (2.4 mL, 1.0 M in THF) was added to a stirred solution of the silylethyne **65** (663 mg, 1.98 mmol) in THF (2 mL) at RT. The mixture was stirred at RT for 1 h, and was then diluted with diethyl ether (200 mL), washed with brine (×2), dried over Na_2SO_4, and concentrated in vacuo. Chromatography of the residue on silica gel (petroleum ether/EtOAc 15:1) provided **66** (517 mg, 99%) as a colorless oil. R_f = 0.60 (petroleum ether/EtOAc 10:1); $[\alpha]_D^{20} = -8.6$ (c = 2.87 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85 (m, 1H), 7.75 (m, 1H), 7.41 (m, 1H), 7.29 (m, 1H), 3.77 (m, 1H), 3.64 (d, J = 5.7 Hz, 2H), 3.50 (s, 3H), 2.62 (q, J = 2.7 Hz, 2H), 2.07 ppm (t, J = 2.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.4, 153.1, 135.3, 126.0, 124.2, 121.4, 121.0, 79.8, 77.7, 70.8, 57.8, 36.1, 22.9 ppm; IR (film): $\tilde{\nu}$ = 3298, 3063, 2932, 2121, 1460, 1428 cm^{-1}; HRMS (ESI): calcd for $C_{13}H_{13}NOS_2Na$: 286.0331 $[M+Na]^+$; found: 286.0342.

Sulfone 7: Cp_2ZrHCl (Schwartz reagent, 370 mg, 1.36 mmol) was added to a solution of the alkyne **66** (327 mg, 1.24 mmol) in dry benzene (15 mL) at RT. The mixture was stirred for 30 min at RT, and then NBS (243 mg, 1.36 mmol) was added. Once the reaction was complete, the mixture was diluted with Et_2O (100 mL), washed with brine (×2), dried over Na_2SO_4, and concentrated in vacuo to give a residue. Ammonium molybdate (1.07 g, 0.87 mmol) and 30% hydrogen peroxide (3 mL) were then added sequentially to a solution of the residue in MeOH (20 mL) at RT. The reaction mixture was stirred for 24 h at RT, and then extracted with EtOAc (300 mL). The organic phase was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Chromatography of the residue on silica gel (CH_2Cl_2/MeOH 1:1) provided **7** (260 mg, 56% yield for the two steps). R_f = 0.50 (petroleum ether/EtOAc 4:1); $[\alpha]_D^{20} = +26.4$ (c = 0.6 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85 (m, 1H), 7.75 (m, 1H), 7.41 (m, 1H), 7.29 (m, 1H), 3.77 (m, 1H), 3.64 (d, J = 5.7 Hz, 2H), 3.50 (s, 3H), 2.62 (q, J = 2.7 Hz, 2H), 2.07 ppm (t, J = 2.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.3, 153.0, 135.3, 133.1, 126.0, 124.3, 121.5, 121.0, 107.2, 78.6, 57.6, 36.4, 30.1 ppm; IR (film): $\tilde{\nu}$ = 3298, 3063, 2932, 2121, 1460, 1428 cm^{-1}; HRMS (ESI): calcd for $C_{13}H_{15}BrNOS_2$: 375.9671 $[M+H]^+$; found: 375.9671.

Compound 67: $LiNEt_2$ [0.050 mL, prepared at −78°C from diethylamine (0.056 mL, 0.59 mmol), BuLi (0.315 mL, 0.504 mmol, 1.60 M in hexane), and THF (0.6 mL)] was added dropwise to a precooled solution of oxazole **5** (12 mg, 0.018 mmol) in THF (0.4 mL) at −78°C. After the resulting solution had been stirred for 10 min at −78°C, a solution of lactone **6**

(12 mg, 0.024 mmol) in THF (0.15 mL) was added dropwise. The reaction mixture was stirred at −78 °C for 40 min, and then quenched with saturated aqueous NH_4Cl and extracted with EtOAc (3×30 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, and then concentrated in vacuo. Chromatography of the residue on silica gel (petroleum ether/EtOAc 8:1) provided **67** (12 mg, 61%) as a colorless oil. R_f=0.52 (petroleum ether/EtOAc 6:1); $[\alpha]_D^{20}$=+42 (c=0.09 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.68–7.64 (m, 4H), 7.48 (s, 1H), 7.42–7.33 (m, 6H), 7.27 (d, J=9.0 Hz, 2H), 6.89 (d, J=9.0 Hz, 2H), 6.16 (s, 1H), 5.33 (dd, J=7.5, 1.2 Hz, 1H), 5.29 (d, J=1.8 Hz, 1H), 4.57 and 4.28 (AB, J_{AB}=10.8 Hz), 4.38 (dd, J=9.0, 5.7 Hz, 1H), 3.96 (s, 2H), 3.94–3.87 (m, 1H), 3.80 (s, 3H), 3.79–3.66 (m, 4H), 3.40 (d, J=10.2 Hz, 1H), 3.36 (s, 3H), 3.19 (dd, J=10.2, 4.5 Hz, 1H), 3.04 and 2.96 (AB, J_{AB}=15.0 Hz), 2.27 (dd, J=12.0, 3.6 Hz, 1H), 2.14–2.08 (m, 2H), 1.90 (s, 3H), 1.86–1.62 (m, 3H), 1.44 (s, 3H), 1.32–1.23 (m, 1H), 1.05 (s, 10H), 0.94 (s, 22H), 0.90 (s, 11H), 0.82 (d, J=6.6 Hz, 3H), 0.053 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=160.3, 159.2, 138.7, 137.8, 136.7, 135.6 (3C), 135.3, 134.0, 133.9, 130.8, 129.6 (2C), 129.3 (4C), 127.6 (4C), 124.3, 117.9, 113.8 (2C), 96.5, 89.0, 83.5, 75.0, 73.7, 73.6, 70.9, 69.6, 68.0, 60.8, 55.5, 55.3, 40.9, 39.9, 35.9, 34.2, 33.3, 31.6, 26.9 (3C), 25.9 (3C), 19.3, 18.0 (3C), 17.9 (3C), 14.2 (2C), 13.8, 12.7 (3C), 6.0, −5.1, −5.2 ppm; IR (film): $\tilde{\nu}$=2930, 2860, 1614, 1514, 1463 cm^{-1}; HRMS (ESI): calcd for $C_{66}H_{103}O_{10}Si_3NaN$: 1176.6786 $[M+Na]^+$; found: 1176.6744.

Alcohol 68: PPTS (5 mg) was added to a solution of **67** (7 mg, 0.006 mmol) in anhydrous MeOH (1 mL). The mixture was stirred at 30 °C for 12 h, and then quenched with saturated aqueous $NaHCO_3$ solution and extracted with EtOAc (2×50 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, and then concentrated in vacuo. Chromatography of the residue on silica gel (petroleum ether/EtOAc 4:1) provided **68** (5 mg, 81%) as a colorless oil. R_f=0.31 (petroleum ether/EtOAc 3:1); $[\alpha]_D^{20}$=+5 (c=0.26 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.64–7.63 (m, 4H), 7.52 (s, 1H), 7.45–7.33 (m, 6H), 7.28 (d, J=8.7 Hz, 2H), 6.88 (d, J=8.7 Hz, 2H), 6.20 (s, 1H), 5.38 (d, J=8.7 Hz, 1H), 4.57 and 4.28 (AB, J_{AB}=11.1 Hz), 4.57–4.51 (m, 1H), 3.98 (d, J=3.9 Hz, 2H), 3.80 (s, 3H), 3.76–3.54 (m, 5H), 3.41 (d, J=10.2 Hz, 1H), 3.35 (s, 3H), 3.29 (s, 3H), 3.27 and 2.97 (AB, J_{AB}=14.7 Hz), 3.20 (dd, J=10.5, 4.5 Hz, 1H), 2.25–2.19 (m, 1H), 2.12–2.09 (m, 1H), 2.02–1.98 (m, 1H), 1.89 (s, 3H), 1.85–1.72 (m, 3H), 1.68 (s, 3H), 1.43–1.36 (m, 1H), 1.05 (s, 31H), 0.93 (d, J=6.6 Hz, 3H), 0.82 ppm (d, J=6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=159.2 (2C), 138.4, 138.1, 135.9, 135.6 (4C), 134.0, 133.9, 130.8, 129.5 (2C), 129.3 (2C), 128.7, 127.6 (4C), 125.7, 118.5, 114.6 (2C), 100.1, 89.0, 83.5, 74.9, 73.8, 73.5, 71.3, 69.6, 68.7, 60.8, 55.5, 55.3, 47.9, 39.3, 35.8, 35.6, 34.2, 33.3, 31.9, 26.9 (3C), 19.3, 18.1 (3C), 18.0 (3C), 17.9, 14.7, 13.8, 12.4 (3C), 6.1 ppm; IR (film): $\tilde{\nu}$=2985, 2857, 1514, 1464, 1287 cm^{-1}; HRMS (ESI): calcd for $C_{61}H_{91}O_{10}Si_2NaN$: calcd for: 1076.6073 $[M+Na]^+$; found: 1076.6067.

Aldehyde 69: Pyridine (50 μL, 0.64 mmol) and Dess–Martin periodinane (70 mg, 0.166 mmol) were added sequentially to a solution of alcohol **68** (135 mg, 0.128 mmol) in CH_2Cl_2 (6 mL). The resulting solution was stirred at RT for 2 h, by which point, none of the starting material was detectable by TLC. After this time, the reaction was quenched by the addition of saturated aqueous $NaHCO_3/Na_2S_2O_3$ 5:1. This mixture was stirred for 15 min, and was then extracted with CH_2Cl_2 (2×300 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and then concentrated in vacuo. Chromatography of the residue on silica gel (petroleum ether/EtOAc 8:1) provided **69** (126 mg, 93%) as a colorless oil. R_f=0.61 (petroleum ether/EtOAc 4:1); $[\alpha]_D^{20}$=+8.5 (c=1.30 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=9.44 (s, 1H), 7.68–7.64 (m, 4H), 7.48 (s, 1H), 7.42–7.35 (m, 6H), 7.28 (d, J=8.4 Hz, 2H), 6.88 (d, J=8.4 Hz, 2H), 6.38 (d, J=8.7 Hz, 1H), 6.18 (s, 1H), 4.83 (dd, J=8.4 Hz, 5.4 Hz, 1H), 4.57 (d, J=11.1 Hz, 1H), 4.29 (d, J=11.1 Hz, 1H), 3.80 (s, 3H), 3.80–3.64 (m, 5H), 3.41 (d, J=10.5 Hz, 1H), 3.33 (s, 3H), 3.30 (s, 3H), 3.24 (d, J=15.0 Hz, 1H), 3.20 (dd, J=9.9, 4.8 Hz, 1H), 2.97 (d, J=15.02 Hz, 1H), 2.23 (dd, J=12.9, 4.2 Hz, 1H), 2.11–2.04 (m, 2H), 1.89 (s, 3H), 1.85–1.64 (m, 5H), 1.67 (m, 1H), 1.38 (apps t, J=11.7 Hz, 1H), 1.05 (brs, 31H), 0.94 (d, J=6.6 Hz, 3H), 0.83 ppm (d, J=6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=194.8, 159.1, 158.8, 152.2, 139.7, 138.5, 138.1, 136.0, 135.9 (2C), 135.6 (2C), 134.0, 133.9, 130.8, 129.5 (2C), 129.3 (2C), 127.6 (4C), 118.3, 113.8 (2C), 100.1, 88.9, 83.5, 74.8, 73.4, 73.1, 71.0, 69.1, 60.8, 55.5, 55.2, 47.9, 39.2, 35.8, 35.5, 34.2, 33.3, 31.4, 26.9 (3C), 19.2, 17.9 (3C), 17.8 (3C), 14.2, 13.7, 12.2 (3C), 10.2, 6.0 ppm; IR (film): $\tilde{\nu}$=2867, 1716, 1695, 1514, 1248, 1111 cm^{-1}; HRMS (ESI): calcd for $C_{61}H_{89}NO_{10}Si_2Na$: 1074.5917 $[M+Na]^+$; found: 1074.5906.

Diene 70: NaHMDS (82 μL, 0.165 mmol, 2 M in THF) was added dropwise to a precooled mixture of **7** (63 mg, 0.167 mmol) and aldehyde **69** (170 mg, 0.162 mmol) in THF (2.6 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 40 min, and then quenched with buffer solution (pH 7) and extracted with EtOAc (2×150 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Chromatography of the residue on silica gel (petroleum ether/EtOAc 10:1) provided **70** (168 mg, 78%) as a colorless oil. R_f=0.58 (petroleum ether/EtOAc 4:1); $[\alpha]_D^{20}$=−4 (c=0.18 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.68–7.63 (m, 4H), 7.51 (s, 1H), 7.40–7.35 (m, 6H), 7.26 (d, J=9.0 Hz, 2H), 6.88 (d, J=9.0 Hz, 2H), 6.20–6.06 (m, 4H), 5.43 (dd, J=15.6, 7.8 Hz, 1H), 5.42 (d, J=7.8 Hz, 1H), 4.61 (dd, J=8.7, 6.6 Hz, 1H), 4.56 and 4.28 (AB, J_{AB}=10.8 Hz), 3.80 (s, 3H), 3.77–3.54 (m, 6H), 3.41 (d, J=9.9 Hz, 1H), 3.35 (s, 3H), 3.32 and 2.94 (AB, J_{AB}=14.7 Hz), 3.28 (s, 3H), 3.26 (s, 3H), 3.20 (dd, J=10.2, 3.9 Hz, 1H), 2.38–2.20 (m, 3H), 2.13–2.09 (m, 1H), 2.02–1.94 (m, 1H), 1.88 (s, 3H), 1.85–1.68 (m, 2H), 1.77 (s, 3H), 1.47–1.33 (m, 2H), 1.05 (s, 31H), 0.94 (d, J=6.6 Hz, 3H), 0.82 ppm (d, J=6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=159.2, 159.1, 138.4, 138.0, 137.4, 136.0, 135.6 (2C), 135.5 (2C), 134.1, 134.0, 133.9, 133.8, 133.2, 130.8, 129.5 (2C), 129.3 (2C), 127.9, 127.6 (4C), 118.5, 113.8 (2C), 106.2, 99.9, 89.0, 83.5, 81.2, 74.8, 73.9, 73.5, 71.8, 69.6, 60.8, 56.3, 55.5, 55.3, 47.9, 39.2, 39.1, 35.8, 35.6, 34.2, 33.3, 32.2, 26.9 (3C), 19.2, 18.0 (3C), 17.9 (3C), 14.2, 13.8, 13.6, 12.4 (3C), 6.0 ppm; IR (film): $\tilde{\nu}$=2957, 2930, 1724, 1614, 1514, 1463 cm^{-1}; HRMALDI: calcd for $C_{67}H_{98}NO_{10}Si_2BrNa$: 1234.5804 $[M+Na]^+$; found: 1234.5802.

Aldehyde 4: NH_4F (134 mg, 3.63 mmol) was added to a solution of **70** (127 mg, 0.1 mmol) in MeOH (5 mL) at RT. The resulting mixture was stirred at 50 °C for 3 h, and then quenched with saturated NH_4Cl solution and extracted with EtOAc (150 mL). The organic extracts were washed with brine, dried over Na_2SO_4, and then concentrated in vacuo to give a residue. Pyridine (39.5 μL) and Dess–Martin periodinane (51 mg, 0.12 mmol) were then added to a solution of this residue in CH_2Cl_2 (4 mL) at RT. The mixture was stirred at RT for 1 h, and quenched with saturated aqueous $NaHCO_3/Na_2S_2O_3$ 5:1. This mixture was stirred for 15 min, and then extracted with CH_2Cl_2 (2×60 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Chromatography of the residue on silica gel (petroleum ether/EtOAc 4:1) provided **4** (71 mg, 71% overall yield for the two steps) as a colorless oil. R_f=0.66 (petroleum ether/EtOAc 2:1); $[\alpha]_D^{20}$=+11.85 (c=0.40 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=9.76 (m, 1H), 7.51 (s, 1H), 7.27 (d, J=11.1 Hz, 2H), 6.88 (d, J=8.4 Hz, 2H), 6.20 (s, 1H), 6.17–6.06 (m, 3H), 5.43 (dd, J=15.6, 7.8 Hz, 1H), 5.42 (d, J=7.8 Hz, 1H), 4.63–4.56 (m, 2H), 4.31 (d, J=11.1 Hz, 1H), 4.02 (m, 1H), 3.81 (s, 3H), 3.60–3.49 (m, 4H), 3.34 (s, 3H), 3.33–3.24 (m, 2H), 3.29 (s, 3H), 3.24 (s, 3H), 2.97 (d, J=15 Hz, 1H), 2.80 (ddd, J=15.6, 8.4, 1.8 Hz, 1H), 2.47–2.14 (m, 5H), 1.93 (m, 1H), 1.89 (s, 3H), 1.82 (m, 1H), 1.69 (s, 3H), 1.36 (apps t, J=11.1 Hz, 1H), 1.04 (brs, 22H), 0.98 (d, J=6.6 Hz, 3H), 0.83 ppm (d, J=6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=201.1, 159.3, 159.2, 137.8, 137.6, 137.3, 136.1, 134.0, 133.9, 133.8, 133.1, 129.3 (2C), 127.8, 118.9, 113.8 (2C), 106.2, 99.9, 89.1, 82.7, 81.2, 73.9, 73.4, 73.2, 71.7, 69.8, 56.2, 55.5, 55.2, 47.8, 46.9, 39.2, 39.1, 35.5, 34.3, 33.0, 32.1, 18.0 (3C), 17.9 (3C), 14.0, 13.7, 13.6, 12.3 (3C), 6.1 ppm; IR (film): $\tilde{\nu}$=2941, 2867, 1728, 1614, 1514 cm^{-1}; HRMALDI: calcd for $C_{51}H_{78}NO_{10}SiBrNa$: 994.4471 $[M+Na]^+$; found: 994.4484.

Compound 71: Bu_3P (92 μL, 0.371 mmol) was added to a solution of the mesylate **3** (83 mg, 0.106 mmol) in dry DMF (2.5 mL) at RT. The resulting mixture was stirred for 15 h at this temperature, and then the mixture was added a solution of aldehyde **4** (89 mg, 0.092 mmol) in dry DMF (1.5 mL), followed by DBU (28 μL, 0.184 mmol). This mixture was stirred at RT for 2 h. Removal of the solvent in vacuo, followed by chromatography of the resulting residue on silica gel (petroleum ether/EtOAc 6:1) provided **71** (137 mg, 91%) as a colorless oil. R_f=0.45 (petroleum ether/EtOAc 4:1); $[\alpha]_D^{20}$=+2.03 (c=0.40 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.68–7.65 (m, 4H), 7.51 (s, 1H), 7.42–7.35 (m 7H), 7.31 (d,

J=9.7 Hz, 2H), 6.84 (d, J=8.6 Hz, 2H), 6.63 (ddd, J=15.5, 8.2, 6.4 Hz, 1H), 6.33 (d, J=16.0 Hz, 1H), 6.21–6.07 (m, 4H), 5.43 (dd, J=15.9, 8.2 Hz, 1H), 5.42 (d, J=10.2 Hz, 1H), 4.72 (br s, 2H), 4.60 (dd, J=8.7, 6.2 Hz, 1H), 4.57 (d, J=11.0 Hz, 1H), 4.27 (d, J=10.9 Hz, 2H), 4.03 (m, 1H), 3.92 (m, 1H), 3.79 (s, 3H), 3.78–3.68 (m, 3H), 3.63 (app q, J= 7.4 Hz, 1H), 3.59–3.51 (m, 3H), 3.45 (d, J=10.2 Hz, 1H), 3.34 (s, 3H), 3.31–3.28 (m, 2H), 3.29 (s, 3H), 3.26 (s, 3H), 3.18 (dd, J=10.3, 4.4 Hz, 1H), 2.94 (d, J=14.9 Hz, 1H), 2.47 (m, 1H), 2.40–2.20 (m, 6H), 2.14 (m, 2H), 2.05–1.91 (m, 5H), 1.91 (s, 3H), 1.84–1.79 (m, 2H), 1.77 (s, 3H), 1.68 (m, 1H), 1.56–1.48 (m, 2H), 1.37 (app t, J=11.4 Hz, 1H), 1.20 (m, 1H), 1.05 (br s, 31H), 0.99 (d, J=6.9 Hz, 3H), 0.86 (s, 9H), 0.83 (d, J= 6.4 Hz, 3H), 0.03 (s, 3H), 0.02 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=160.8, 159.1 (2C), 142.6, 142.0, 138.0, 137.9, 137.3, 136.0, 135.6, 135.5 (4C), 134.0 (2C), 133.9 (2C), 133.8, 133.1, 130.6, 129.5 (2C), 129.3 (2C), 127.8, 127.6 (4C), 118.7, 118.6, 113.8 (2C), 110.2, 106.2, 99.9, 89.1, 83.2, 81.2, 77.2, 73.9, 73.4, 72.8, 71.7, 71.3, 69.7, 68.9, 68.5, 68.4, 60.5, 56.2, 55.5, 55.2, 47.8, 41.0, 40.7, 39.6, 39.5, 39.3, 39.2, 39.1 (2C), 36.4, 36.3, 35.5, 33.6, 33.3, 32.1, 26.8 (3C), 25.7 (3C), 19.2, 18.0 (3C), 17.9 (3C), 14.1, 13.7, 13.6, 12.3 (3C), 5.7, −4.5 ppm (2C); IR (film): $\tilde{\nu}$=2932, 2859, 1718, 1514, 1463 cm^{-1}: HRMALDI: calcd for $C_{91}H_{135}N_2O_{14}Si_3BrNa$: 1665.8297 $[M+Na]^+$; found: 1665.8304.

Alcohol 72: NH_4F (134 mg, 3.62 mmol) was added to a solution of **71** (18 mg, 0.011 mmol) in MeOH (1 mL) at RT. The resulting mixture was stirred at 50 °C for another 3.5 h, and then quenched with saturated NH_4Cl solution and extracted with EtOAc (100 mL). The organic extracts were washed with brine, dried over Na_2SO_4, and then concentrated in vacuo. Chromatography of the residue on silica gel (petroleum ether/EtOAc 2:1) provided **72** (11 mg, 71%) as a colorless oil. R_f=0.49 (petroleum ether/EtOAc 1:1); $[\alpha]_D^{20}$=+2.89 (c=0.25 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.51 (s, 1H), 7.46 (s, 1H), 7.28 (d, J=8.7 Hz, 2H), 6.87 (d, J=8.7 Hz, 2H), 6.65 (ddd, J=15.4, 8.4, 6.3 Hz, 1H), 6.34 (d, J= 16.0 Hz, 1H), 6.22–6.08 (m, 4H), 5.43 (dd, J=15.8, 8.1 Hz, 1H), 5.42 (d, J=11.0 Hz, 1H), 4.75 (d, J=16.9 Hz, 2H), 4.61 (dd, J=8.8, 6.3 Hz, 1H), 4.57 (d, J=11.0 Hz, 1H), 4.36 (d, J=11.7 Hz, 1H), 4.28 (d, J=11.0 Hz, 1H), 4.09–4.06 (m, 2H), 4.01–3.99 (m, 1H), 3.88 (m, 1H), 3.80 (s, 3H), 3.80–3.70 (m, 2H), 3.64 (dd, J=15.0, 7.5 Hz, 1H), 3.59–3.51 (m, 4H), 3.46 (d, J=10.2 Hz, 1H), 3.34 (s, 3H), 3.31–3.28 (m, 2H), 3.29 (s, 3H), 3.26 (s, 3H), 3.18 (dd, J=10.4, 4.5 Hz, 1H), 2.94 (d, J=15.0 Hz, 1H), 2.58 (ddd, J=13.0, 5.4, 5.4 Hz, 1H), 2.41–2.21 (m, 6H), 2.15–2.10 (m, 3H), 2.08–1.95 (m, 3H), 1.91 (s, 3H), 1.85–1.76 (m, 2H), 1.76 (s, 3H), 1.63–1.58 (m, 2H), 1.52 (m, 1H), 1.37 (m, 2H), 1.09–1.04 (m, 22H), 0.98 (d, J=6.8 Hz, 3H), 0.88 (s, 9H), 0.82 (d, J=6.4 Hz, 3H), 0.08 (s, 3H), 0.07 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=161.0, 159.7, 159.1, 142.3, 141.5, 138.0, 137.9, 137.3, 136.1, 136.0, 134.1, 133.9, 133.8, 133.1, 130.6, 129.3 (2C), 127.8, 118.7, 118.4, 113.8 (2C), 110.5, 106.2, 99.9, 89.1, 83.2, 81.2, 77.2, 73.9, 73.7, 73.4, 71.7, 71.2, 70.9, 69.8, 69.7, 68.4, 60.5, 56.2, 55.5, 55.2, 47.9, 41.4, 40.2, 40.1, 39.2, 39.1 (2C), 38.5, 36.3, 36.2, 35.5, 33.7, 33.3, 32.1, 25.8 (3C), 18.0 (4C), 17.9 (3C), 14.1, 13.7, 13.6, 12.3 (3C), 5.7, −4.5 ppm (2C); IR (film): $\tilde{\nu}$=2944, 2866, 1614, 1514, 1464, 1250, 1091 cm^{-1}; HRMALDI: calcd for $C_{75}H_{117}N_2O_{14}Si_2BrNa$: 1427.7119 $[M+Na]^+$; found: 1427.7124.

Aldehyde 73: Pyridine (6.7 μL) and Dess–Martin periodinane (10.8 mg, 0.026 mmol) were added to a solution of **72** (24 mg, 0.017 mmol) in CH_2Cl_2 (2.5 mL) at RT. The mixture was stirred at RT for 1 h, and then quenched with saturated aqueous $NaHCO_3$/$Na_2S_2O_3$ (5:1, 1 mL). This mixture was stirred for 5 min, and then extracted with CH_2Cl_2 (2× 60 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and then filtered through a short pad of silica gel. Finally, the filtrate was concentrated in vacuo to give a residue. DDQ (16 mg, 0.08 mmol) was then added to a solution of the residue in CH_2Cl_2 (2.5 mL) and buffer (0.25 mL, pH 7) at RT. The resulting mixture was stirred vigorously for 2 h, before being quenched with saturated aqueous $NaHCO_3$ (2 mL). The separated aqueous phase was extracted with CH_2Cl_2 (2×30 mL), and the combined organic extracts were washed with brine, dried over Na_2SO_4, and then concentrated in vacuo. Chromatography of the residue on silica gel (petroleum ether/EtOAc 2:1) provided **73** (15 mg, 73% overall yield for the two steps) as a colorless oil. R_f=0.50 (petroleum ether/EtOAc 1:1); $[\alpha]_D^{20}$=−0.67 (c=0.75 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ=9.75 (m, 1H), 7.52 (s, 1H), 7.44 (s, 1H), 6.62 (ddd, J=13.6, 8.4, 6.3 Hz, 1H), 6.32 (d, J=16.1 Hz, 1H), 6.21–6.14 (m, 3H), 6.09 (d, J=13.6 Hz, 1H), 5.44 (dd, J=15.7, 8.1 Hz, 1H), 5.43 (d, J= 9.0 Hz, 1H), 4.79 (s, 2H), 4.62 (dd, J=8.9, 6.3 Hz, 1H), 4.40–4.34 (m, 2H), 3.98 (m, 1H), 3.87 (m, 1H), 3.63 (dd, J=14.0, 6.4 Hz, 1H), 3.59–3.52 (m, 4H), 3.49–3.45 (m, 2H), 3.34 (s, 3H), 3.31–3.28 (m, 2H), 3.29 (s, 3H), 3.26 (s, 3H), 2.96 (d, J=15.0 Hz, 1H), 2.68 (ddd, J=16.2, 8.4, 3.0 Hz, 1H), 2.56 (m, 1H), 2.47 (ddd, J=16.1, 5.1, 1.6 Hz, 1H), 2.40–2.32 (m, 4H), 2.27–2.21 (m, 2H), 2.13–1.97 (m, 3H), 1.96–1.89 (m, 3H), 1.93 (s, 3H), 1.77 (s, 3H), 1.75–1.69 (m, 1H), 1.64–1.50 (m, 4H), 1.37 (dd, J= 12.5, 11.2 Hz, 1H), 1.29 (dd, J=23.4, 11.3 Hz, 1H), 1.12–1.04 (m, 21H), 0.99 (d, J=6.9 Hz, 3H), 0.88 (s, 9H), 0.85 (d, J=6.5 Hz, 3H), 0.08 (s, 3H), 0.07 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=200.6, 160.9, 159.2, 142.6, 140.8, 137.9, 137.8, 137.4, 136.1, 135.7, 134.0, 133.9, 133.8, 133.1, 127.9, 118.8, 118.6, 111.3, 106.2, 99.9, 88.8, 81.2, 77.5, 77.2, 76.5, 73.9, 73.5, 72.9, 71.8, 71.4, 69.4, 68.4, 67.3, 56.3, 55.6, 47.9, 47.6, 41.1, 40.6, 39.5, 39.3, 39.2, 39.1, 39.0, 37.9, 36.1, 35.5, 34.7, 32.1, 25.8 (3C), 18.0 (3C), 17.9 (3C), 14.3, 13.6, 13.4, 12.4 (3C), 5.5, −4.5 ppm (2C); IR (film): $\tilde{\nu}$= 2945, 2866, 1716, 1463, 1361, 1253 cm^{-1}; HRMALDI: calcd for $C_{67}H_{107}N_2O_{13}Si_2BrNa$: 1305.6387 $[M+Na]^+$; found: 1305.6390.

Compound 74: $(EtO)_2PCH_2COOH$ (0.18 mL, 0.1 M in CH_2Cl_2) and DCC (*N*,*N*-dicyclohexylcarbodiimide, 0.18 mL, 0.1 M in CH_2Cl_2) were added sequentially to a solution of **73** (16 mg, 0.012 mmol) in dry CH_2Cl_2 (2 mL) at RT. This mixture was stirred for 1 h, and then quenched with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and then concentrated in vacuo. Chromatography of the residue on silica gel (petroleum ether/EtOAc 1:1) provided **74** (15 mg, 85%) as a colorless oil. R_f= 0.30 (petroleum ether/EtOAc 1:2); $[\alpha]_D^{20}$=−4.5 (c=0.15 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ=9.76 (s, 1H), 7.52 (s, 1H), 7.43 (s, 1H), 6.59 (ddd, J=8.9, 8.3, 1.5 Hz, 1H), 6.31 (d, J=16.0 Hz, 1H), 6.22–6.08 (m, 3H), 5.44 (dd, J=15.7, 8.1 Hz, 1H), 5.42 (d, J=1.5 Hz, 1H), 4.81 (s, 2H), 4.78 (dd, J=18.5, 13.2 Hz, 1H), 4.62 (dd, J=8.6, 6.2 Hz, 1H), 4.38–4.33 (m, 2H), 4.19–4.14 (m, 4H), 3.99 (m, 1H), 3.86 (m, 1H), 3.64 (m, 2H), 3.58–3.53 (m, 3H), 3.34 (s, 3H), 3.34–3.31 (m, 2H), 3.29 (s, 3H), 3.26 (s, 3H), 2.98 (d, J=21.6 Hz, 2H), 2.95 (d, J=13.4 Hz, 1H), 2.70–2.66 (m, 1H), 2.60–2.54 (m, 1H), 2.50–2.48 (m, 1H), 2.47–2.22 (m, 6H), 2.15–1.97 (m, 6H), 1.95 (s, 3H), 1.90–1.84 (m, 1H), 1.77 (s, 3H), 1.68–1.50 (m, 9H), 1.37 (m, 7H), 1.10–0.96 (m, 21H), 0.88 (s, 9H), 0.79 (d, J=6.4 Hz, 3H), 0.08 (s, 3H), 0.07 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ= 200.6, 160.8, 159.2, 142.6, 140.8, 137.8, 137.4, 137.1, 136.2, 135.3, 134.0, 133.9, 133.8, 133.2, 132.5, 127.9, 119.0, 118.8, 111.3, 106.3, 99.9, 88.8, 81.3, 80.0, 73.9, 73.5, 72.9, 71.8, 71.4, 69.4, 68.4, 67.3, 62.7, 62.6, 56.3, 55.6, 47.9, 47.6, 41.1, 40.7, 39.5, 39.3, 39.2, 39.1, 39.0, 36.0, 35.6, 35.4, 33.9, 32.2, 32.1, 29.3, 29.2, 25.8 (3C), 18.0 (3C), 17.9(3C), 16.3, 16.2, 14.2, 13.6, 13.2, 12.4 (3C), 6.2, −4.5 ppm (2C); IR (film): $\tilde{\nu}$=2929, 2857, 1732, 1464, 1259 cm^{-1}; HRMALDI: calcd for $C_{73}H_{118}N_2O_{17}Si_2BrPNa$: 1483.6782 $[M+Na]^+$; found: 1483.6745.

Macrolide 75: A mixture of K_2CO_3 (11.4 mg, 82.6 μmol) and [18]crown-6 (90 mg, 0.34 mmol) in toluene (5 mL) was vigorously stirred at RT for 5 h, before being added a solution of **74** (10 mg, 6.8 μmol) in dry toluene (3.5 mL) at −20 °C. The resulting mixture was stirred for 2 h at −20 °C, and was then warmed to 0 °C over 10 h. After this time, the mixture was extracted with EtOAc (150 mL) and the organic layer was washed with brine (×2), dried over Na_2SO_4, and then concentrated in vacuo. Chromatography of the residue on silica gel (petroleum ether/EtOAc 4:1) provided **75** (5 mg, 56%) as a colorless oil. R_f=0.60 (petroleum ether/EtOAc 2:1); $[\alpha]_D^{20}$=+3.7 (c=0.2 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ= 7.53 (s, 1H), 7.48 (s, 1H), 6.67 (ddd, J=16.0, 9.7, 6.5 Hz, 1H), 6.29 (d, J=15.9 Hz, 1H), 6.26 (s, 1H), 6.20–6.14 (m, 2H), 6.09 (d, J=13.6 Hz, 1H), 5.91 (s, 2H), 5.46–5.41 (m, 2H), 4.97 (s, 1H), 4.62 (m, 2H), 4.51 (dd, J=11.2, 4.5 Hz, 1H), 4.20 (d, J=12.1 Hz, 1H), 4.18–4.11 (m, 1H), 3.98–3.96 (m, 1H), 3.94–3.88 (m, 1H), 3.64 (dd, J=13.6, 6.2 Hz, 1H), 3.59–3.52 (m, 5H), 3.52–3.43 (m, 1H), 3.34 (s 3H), 3.30 (d, J=14.9 Hz, 1H), 3.29 (s, 3H), 3.26 (s, 3H), 2.96 (d, J=14.9 Hz, 1H), 2.63 (d, J= 12.0 Hz, 1H), 2.60–2.50 (m, 1H), 2.43–2.38 (m, 2H), 2.36–2.31 (m, 2H), 2.26 (m, 1H), 2.24–2.20 (m, 1H), 2.14 (dd, J=7.7, 4.5 Hz, 1H), 2.08–1.93 (m, 6H), 1.98 (s, 3H), 1.84 (m, 2H), 1.77 (s, 3H), 1.68 (m, 1H), 1.45–1.32 (m, 3H), 1.06–1.04 (m, 21H), 0.96 (d, J=6.9 Hz, 3H), 0.9 (s, 9H), 0.77 (d, J=6.4 Hz, 3H), 0.09 ppm (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=

165.6, 161.2, 159.2, 144.3, 141.7, 137.9, 137.4, 137.2, 136.3, 134.2, 134.0, 133.9, 133.8, 133.2, 127.6, 121.0, 119.3, 119.2, 110.1, 106.3, 99.9, 89.3, 81.2, 79.5, 78.0, 73.9, 73.5, 72.3, 71.8, 70.8, 69.0, 68.6, 56.3, 55.6, 47.9, 42.0, 41.2, 39.2, 39.1, 39.0, 37.7, 36.9, 35.6, 34.3, 33.9, 32.6, 32.2, 31.8, 30.4, 25.8 (3C), 25.6, 24.9, 18.0 (3C), 17.9 (3C), 14.2, 13.6, 13.3, 12.4 (3C), 5.9, −4.5 ppm (2C); IR (film): $\tilde{\nu}$ = 2945, 2865, 1722, 1464, 1188, 1158, 1112, 1091 cm^{-1}; HRMALDI: calcd for $C_{69}H_{107}N_2O_{13}Si_2BrNa$: 1329.6387 $[M+Na]^+$; found: 1329.6392.

Compound 2: TBAF (15 μL, 1.0 M solution in THF) was added to a solution of **75** (5 mg, 0.0038 mmol) in THF (2 mL) at RT. The resulting mixture was stirred at RT for 10 h, and was then filtered through a pad of silica gel (eluted with EtOAc). The filtrate produced was concentrated in vacuo to give a residue. Aqueous HCl solution (0.3 mL, 6%) was added to a solution of the residue in THF (0.8 mL) at RT. The resulting mixture was stirred at RT for 70 h, and was then quenched with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Chromatography of the residue on silica gel (EtOAc/MeOH 150:1) provided **2** (2 mg, 51%) as an amorphous solid. R_f = 0.60 (EtOAc/MeOH 15:1); $[\alpha]_D^{20}$ = +35 (c = 0.1 in CH_2Cl_2; lit.[6d] = +32.0, c = 0.2 in CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$): δ = 7.57 (s, 1H; $C_{30}H$), 7.47 (s, 1H; $C_{17}H$), 6.67 (ddd, J = 16.3, 9.8, 6.7 Hz, 1H; $C_{20}H$), 6.29 (d, J = 16.0 Hz, 1H; $C_{19}H$), 6.24 (s, 1H; $C_{28}H$), 6.19 (d, J = 15.8 Hz, 1H; $C_{41}H$), 6.19–6.15 (m, 1H; $C_{45}H$), 6.09 (d, J = 13.6 Hz, 1H; $C_{46}H$), 5.92 (m, 2H; C_2H and C_3H), 5.50 (dd, J = 15.8, 7.9 Hz, 1H; $C_{42}H$), 5.36 (d, J = 9.2 Hz, 1H; $C_{39}H$), 5.27 (d, J = 2.0 Hz, 1H; $C_{33}OH$), 4.96 (s, 1H; $C_{51}H$), 4.62 (s, 1H; $C_{51}H$), 4.51 (dd, J = 11.1, 4.5 Hz, 1H; $C_{24}H$), 4.31 (dd, J = 8.8, 8.8 Hz, 1H; $C_{38}H$), 4.23 (d, J = 11.8 Hz, 1H; $C_{15}H$), 4.17 (m, 1H; C_5H), 4.00–3.94 (m, 2H; C_9H and $C_{13}H$), 3.82–3.74 (m, 2H; $C_{35}H$ and $C_{37}H$), 3.64 (ddd, J = 6.9, 6.2, 6.2 Hz, 1H; $C_{43}H$), 3.60–3.43 (m, 3H), 3.58 (d, J = 10.1 Hz, 1H; $C_{26}H$), 3.36 (s, 3H; $C_{35}OMe$), 3.26 (s, 3H; $C_{43}OMe$), 3.15 (d, J = 15.5 Hz, 1H; $C_{32}H$), 3.07 (d, J = 15.7 Hz, 1H; $C_{32}H$), 2.63 (d, J = 11.8 Hz, 1H; C_8H), 2.54 (m, 1H; $C_{21}H$), 2.43 (m, 2H), 2.36–2.22 (m, 6H), 2.06 (br d, J = 13.6 Hz, 1H; C_6H), 2.06–1.95 (m, 4H), 1.98 (s, 3H; $C_{48}H_3$), 1.85 (dd, J = 15.7, 11.2 Hz, 1H; C_8H), 1.81 (s, 3H, $C_{47}H_3$), 1.64 (app q, J = 11.3 Hz, 1H; $C_{14}H$), 1.50 (m, 1H), 1.38–1.29 (m, 2H), 1.11 (app q, J = 11.6 Hz, 1H; $C_{36}H$), 0.96 (d, J = 6.9 Hz, 3H; $C_{50}H_3$), 0.77 ppm (d, J = 6.4 Hz, 3H; $C_{49}H_3$); IR (film): $\tilde{\nu}$ = 3409, 2932, 2854, 1718, 1439, 1360, 1194 cm^{-1}; HRMALDI: calcd for $C_{53}H_{71}N_2O_{13}BrNa$: 1045.4032 $[M+Na]^+$; found: 1045.4072.

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