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Stereocontrolled Second Generation Syntheses of the ABC and FG Ring Systems of Brevetoxin B§

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Abstract: Stereocontrolled, second generation syntheses of the ABC and FG ring systems of brevetoxin B (**1**) are described. The two key intermediates **2** and **3**, representing the ABC and FG ring frameworks, were prepared from 2-deoxy-D-ribose via short and efficient sequences. The synthesis of **2** proceeded via the epoxy alcohol cyclization precursors **6** and **7**, and the Horner-Emmons cyclization precursor **5**, to give the desired tricyclic system in 3.6% overall yield. The synthesis of **3** proceeded via the epoxy alcohol cyclization precursors **10** and **11** to give the desired bicyclic system in a 11.5% overall yield . Both syntheses represent improvements over the previous procedures and allow for rapid and facile entries into the ABC and FG ring systems of this complex natural product.

Introduction

The "red tide" phenomenon, originating from the Gulf of Mexico and the Florida coastal waters, has received much attention in recent years.[1] Several interesting neurotoxins are produced by the organisms responsible for these catastrophic outbreaks. As one of the first structures to be elucidated from this class of marine natural products, brevetoxin B (**1**) has stimulated a

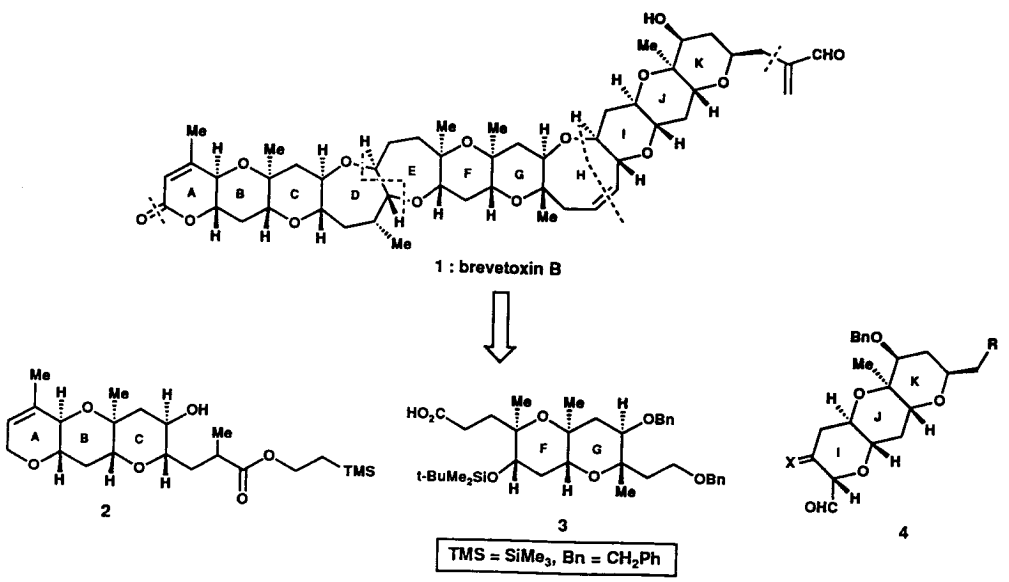
§This paper is dedicated to Professor David Ollis on the occasion of his 65th birthday.

considerable body of scientific activity.[2] Recent studies have led to a proposed biosynthetic pathway to brevetoxin B (**1**) and related compounds.[3] The biological action of this and related compound has been extensively investigated and reviewed.[4] Brevetoxin B (**1**) is one of the most potent neurotoxins known with a LC_{50} = 16 ng; it binds to a unique receptor site on the sodium channel causing inhibition of sodium uptake and repetitive firing of neurons. Other related compounds in this class include brevetoxin A[5], hemibrevetoxin[6] and ciguatoxin.[7]

The structure of brevetoxin B (**1**) was determined by X-ray crystallographic analysis[8] and its absolute stereochemistry was established by the dibenzoate chirality method[9]. This molecule exhibited an unprecedented array of *trans*-fused rings connected in a ladder-like structure, 30 Å long, 6 Å high and 6 Å wide, with twenty three stereogenic centers. The eleven-ring framework is essentially flat and quite rigid except at the bis(oxepane) region where it is somewhat flexible.

The novel structure and striking biological activity of brevetoxin B (**1**) prompted us to explore synthetic routes towards this class of compounds. New synthetic methods for the construction of pyrans[10], oxepanes[11], and oxocenes[12], all relevant to brevetoxin B (**1**) and its relatives, have been described from these laboratories. Furthermore, syntheses of the ABC[13], FG[14] and IJK[15] ring systems of brevetoxin B (**1**) have been reported by us. In this article we describe second generation syntheses of the ABC and FG ring systems that can deliver the optically active fragments in large quantities and with high stereocontrol. The present sequences are more efficient than the first generation routes and, are therefore, the preferred pathways to these intermediates. Both constructions begin with 2-deoxy-D-ribose as the starting material.

Scheme 1 [a]



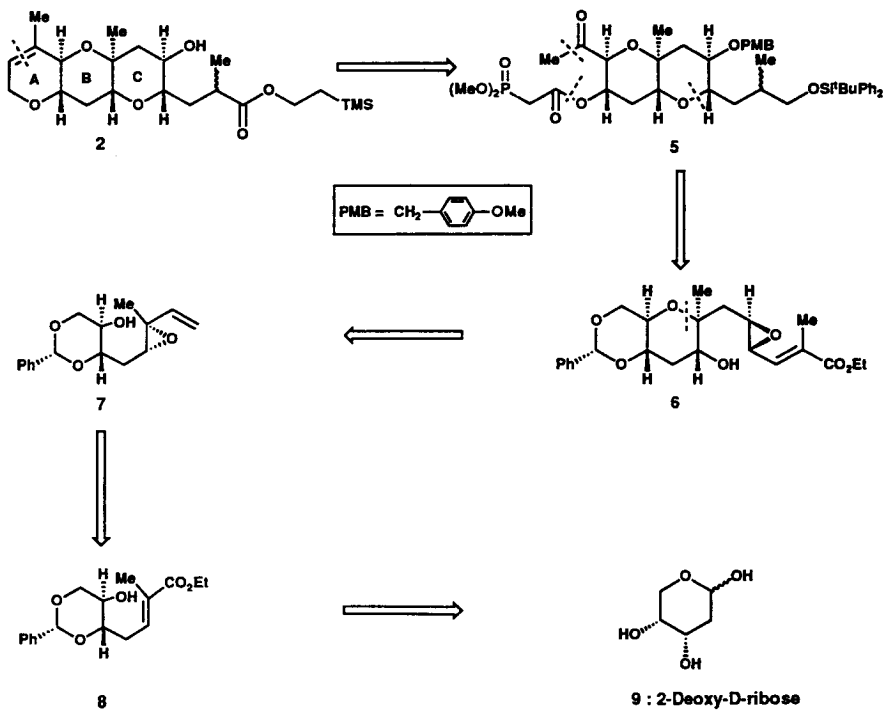
[a] A Possible retrosynthetic analysis of brevetoxin B (1)

Retrosynthetic analysis

A potentially attractive retrosynthetic analysis of brevetoxin B (**1**) is shown in **Scheme 1**. Thus, disconnection of the indicated strategic bonds, followed by a number of standard functional group manipulations, disassembles the seven- and eight-membered rings and leads to the three key intermediates **2**, **3**, and **4**. These disconnections allow for a highly convergent approach involving intermediates that contain only tetrahydropyran rings and thus simplify the problem at hand.

Scheme 2 outlines the retrosynthetic analysis of the ABC ring system as the trimethylsilylethyl ester alcohol **2**. Thus, disassembly of the A ring double bond leads to the ketophosphonate methyl ketone **5** which, in turn, can be traced to the hydroxy epoxide **6**. Finally, disconnection of the remaining tetrahydropyran ring in **6** leads to the hydroxy epoxide **7** which can be related to the α,β-unsaturated ester **8** and, thence, to 2-deoxy-D-ribose (**9**) by obvious chemistry.

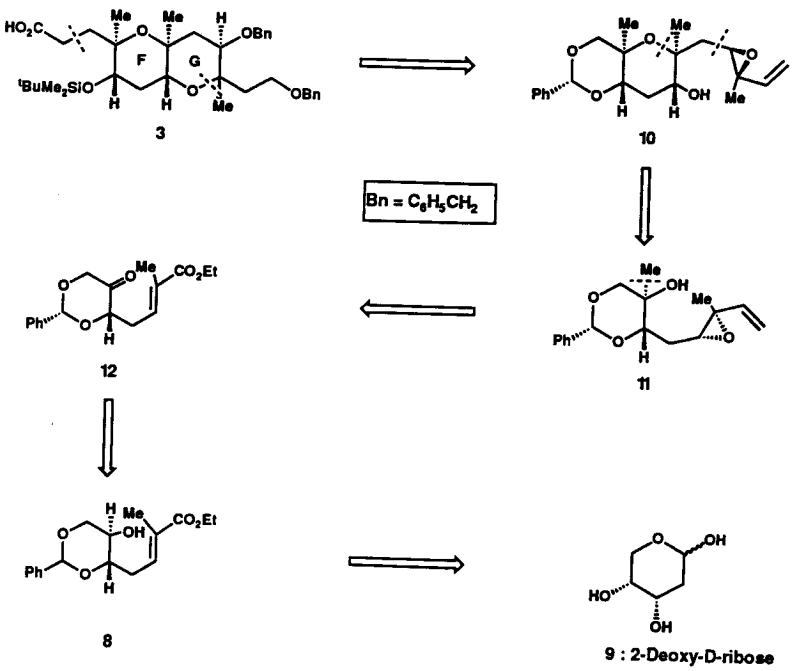
Scheme 2 [a]



[a] Retrosynthetic analysis of the ABC ring system of brevetoxin B (**1**).

The retrosynthesis of the FG ring system, as the protected derivative **3**, is outlined in **Scheme 3**. Once again, the cornerstone of the present analysis is the facile construction of tetrahydropyrans via 6-endo activated ring closures of hydroxy epoxides. Thus, disconnection of the subtarget **3** as indicated, followed by simple functional group manipulations, leads to hydroxy epoxide **10** which can be further disconnected as shown to reveal compound **11** as a potential precursor. Removal of the methyl group from **11** leads to ketone **12** which can be derived from 2-deoxy-D-ribose (**9**) via intermediate **8** using standard chemistry. The successful execution of the synthetic strategies for the synthesis of the ABC (**2**) and FG (**3**) fragments of brevetoxin B (**1**), developed from the above analysis, is described below.

Scheme 3 [a]

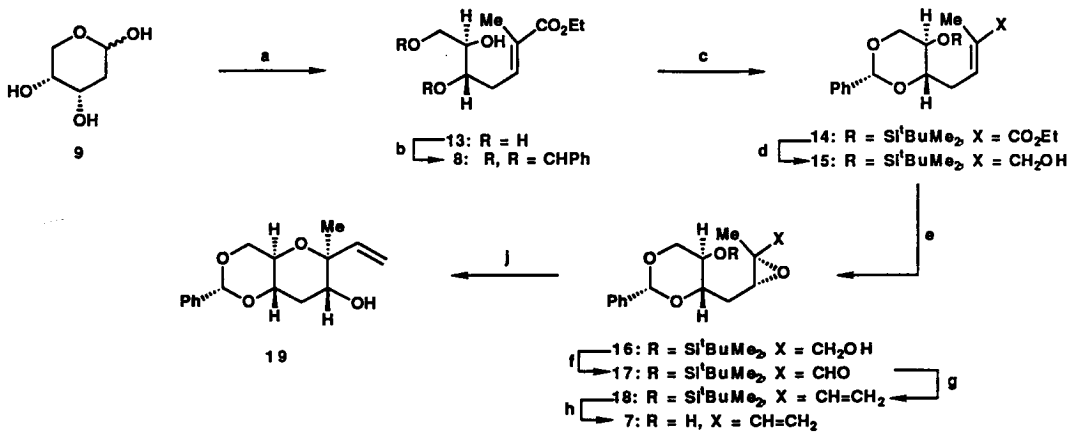


[a] Retrosynthetic analysis of the FG ring system of brevetoxin B (1).

Synthesis of the ABC ring system 2

The initial steps for the synthesis of the ABC ring system **2** are shown in **Scheme 4**. Treatment of 2-deoxy-D-ribose (**9**) with (carbethoxyethylidene)triphenylphosphorane in refluxing tetrahydrofuran (THF) provided the α,β-unsaturated ester triol **13** in 97% yield. The thermodynamically favored six-membered benzylidene **8** was obtained by exposure to excess benzaldehyde dimethyl acetal and

Scheme 4 [a]

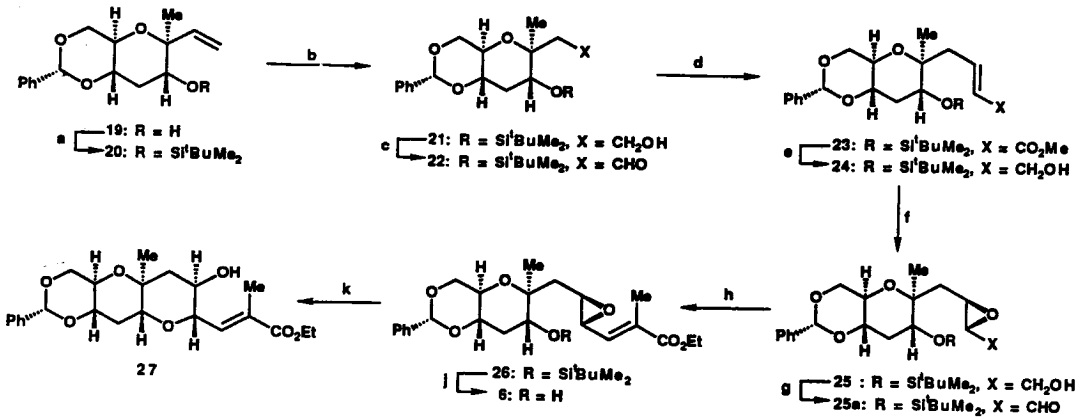


[a] **Reagents and conditions**: (a) 1.2 equiv of $Ph_3P{=}C(Me)CO_2Et$, THF, 65 °C, 4.5 h, 97%; (b) 1.3 equiv of $PhCH(OMe)_2$, 0.3 equiv of CSA, CH_2Cl_2, 25 °C, 12 h, 96%; (c) 1.1 equiv of $^tBuMe_2SiCl$, 1.5 equiv imidazole, DMF, 25 °C, 5 h, 98%; (d) 2.2 equiv of DIBAL, CH_2Cl_2, -78 °C, 1 h, 98%; (e) 0.2 equiv of (-)-diethyl tartrate, 0.15 equiv $Ti(O^iPr)_4$, 1.5 equiv of ^tBuOOH, CH_2Cl_2, -27 °C, 14 h, 89%; (f) 4.0 equiv of SO_3·pyr, 5.0 equiv of Et_3N, CH_2Cl_2:DMSO (4:1), 0 °C, 3.5 h, 94%; (g) 1.5 equiv of $CH_3P^+Ph_3Br^-$, 1.3 equiv of $NaN(SiMe_3)_2$, THF, 0 °C, 1 h, 88%; (h) 1.5 equiv of $^nBu_4NF$, THF, 25 °C, 0.5 h, 98%; (j) 0.85 equiv of PPTS, CH_2Cl_2, 0 →25 °C, 3 h, 86%.

camphorsulfonic acid (CSA) in dichloromethane (CH_2Cl_2) at 25 °C in 96% yield. Protection of the remaining hydroxyl function was achieved with *tert*-butyldimethylsilyl chloride (TBDMSCl) and imidazole in dimethylformamide (DMF) at 25 °C leading to silyl ether **14** in 98% yield. Reduction of the α,β-unsaturated ester using diisobutylaluminum hydride (DIBAL) in CH_2Cl_2 at -78 °C gave the allylic alcohol **15** in 98% yield. Sharpless epoxidation[16] of alcohol **15** with (–)-diethyl tartrate gave the epoxy alcohol **16** in 89% yield. Conversion of the epoxy alcohol to the olefin was carried out in two steps. Oxidation using SO_3·pyridine complex[17] in CH_2Cl_2:DMSO (4:1), gave the epoxy aldehyde **17**; subsequent olefination of the crude aldehyde gave the epoxy olefin **18** in 83% yield for the two steps. The epoxy alcohol **7** was obtained after deprotection of the silyl ether with tetrabutylammonium fluoride (TBAF) in THF at 25 °C in 98% yield. This epoxy alcohol was now

properly functionalized to give the desired 6-endo cyclization product preferentially over the 5-exo isomer upon suitable activation. The activation of epoxy alcohols to give preferential 6-endo cyclization has been elaborated upon previously.[10] Thus, subjecting **7** to 0.85 equiv pyridinium p-toluenesulfonate (PPTS) in CH_2Cl_2 at 0 °C for 3 h gave the cyclized product **19** in 86% yield. This sequence secured the proper B ring stereochemistry and functionality.

Scheme 5 [a]



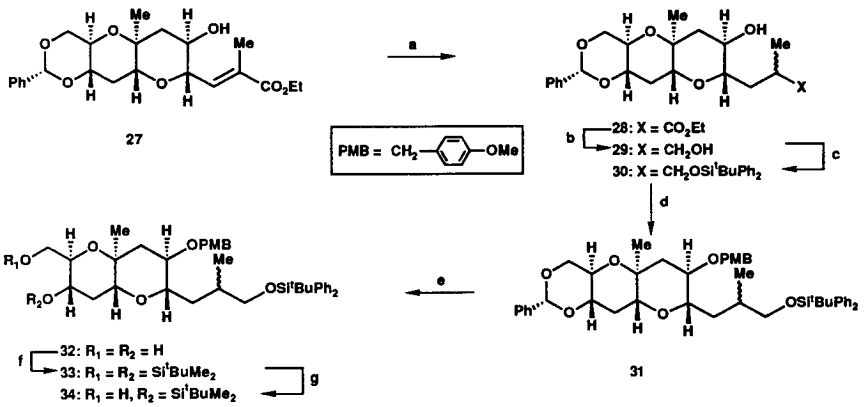
[a]**Reagents and conditions:** (a) 1.1 equiv of $^tBuMe_2SiCl$, 1.5 equiv imidazole, DMF, 50 °C, 10.5 h, 97%; (b) 1.5 equiv of 9-BBN, THF, 0 °C, 1.5 h, then 2.1 equiv of H_2O_2, 2.5 equiv of NaOH, 0 °C, 1 h, 93%; (c) 1.5 equiv oxalyl chloride, 2.0 equiv DMSO, 5.0 equiv of Et_3N, CH_2Cl_2, -78 °C, 1 h, 98%; (d) 1.2 equiv of $Ph_3P{=}CHCO_2Me$, C_6H_6, 50 °C, 0.5 h, 88%; (e) 2.2 equiv of DIBAL, CH_2Cl_2, -78°C, 0.5 h, 98%; (f) 0.2 equiv of (-)-diethyl tartrate, 0.15 equiv of $Ti(O^iPr)_4$, 1.5 equiv of ^tBuOOH, CH_2Cl_2, -28 °C, 14 h, 87%; (g) 4.0 equiv of SO_3-pyr, 5.0 equiv of Et_3N, CH_2Cl_2:DMSO (4:1), 0 °C, 3 h, 93%; (h) 1.1 equiv of $Ph_3P{=}C(Me)CO_2Et$, 0.1 equiv of $PhCO_2H$, C_6H_6, 25 °C, 0.5 h, 88%; (j) 1.5 equiv of $^nBu_4NF$, THF, 25 °C, 0.5 h, 95%; (k) 0.8 equiv of PPTS, CH_2Cl_2, 25 °C, 13 h, 84%.

Further elaboration to provide the C ring is shown in **Scheme 5**. The alcohol **19** was once again protected as the silyl ether using TBDMSCl in DMF to give **20** in 97% yield. The olefin was hydroborated using 9-BBN in THF followed by oxidative work-up leading to alcohol **21** in 93% yield. Swern oxidation[18] of this alcohol gave the aldehyde **22** in 98% yield. Subjecting the crude aldehyde **22** to reaction with methyl(triphenylphosphoranylidene) acetate in benzene at 50 °C gave the α,β-unsaturated ester **23** in 88% yield. DIBAL reduction of the ester gave the allylic alcohol **24** in 98% yield. Sharpless epoxidation of alcohol **24** using (–)-diethyl tartrate as the chiral auxiliary gave the epoxy alcohol **25** in 87% yield. SO_3·pyridine oxidation of the allylic alcohol, followed by treatment with (carbethoxyethylidene)triphenylphosphorane in benzene gave the α,β-unsaturated ester **26** in 82% yield. Deprotection of the silyl ether with TBAF in THF gave the epoxy alcohol **6** in 95% yield. Finally, preferential 6-endo cyclization of this intermediate using PPTS in CH_2Cl_2 proceeded smoothly to give the BC ring system **27** in 84% yield. With the bicyclic intermediate **27**

at hand, it was necessary to adjust the oxidation state of the ester functionality and selectively protect it as a silyl ether. To this end, the secondary alcohol was protected with a suitable protecting group to allow differentiation of the hydroxy groups and pave the way for manipulation of the left hand side of the molecule to construct the A ring.

The adopted sequence is shown in **Scheme 6**. Selective hydrogenation of the double bond with 10% palladium on carbon in ethyl acetate (EtOAc) gave a mixture of diastereomeric esters **28** in quantitative yield. The remaining sequence was carried out with a diastereomeric mixture of compounds. Lithium aluminum hydride reduction of the ethyl ester gave the diol **29** in 95% yield. The primary alcohol was then selectively protected using *tert*-butyldiphenylsilyl chloride (TBDPSCl) in DMF at 0 °C to give the silyl ether **30** in 89% yield. The secondary alcohol was protected as the p-methoxybenzyl ether (PMB) by treatment with potassium hydride (KH) and p-methoxybenzyl chloride in THF at 50 °C in 84% yield. With the right hand side fully protected, it was possible to begin construction of the A ring. Thus, removal of the benzylidene was achieved using 0.25 equiv of CSA in MeOH at 0 °C to give the diol **32** in 86% yield. The primary alcohol in **32** was then differentiated by the following two-step procedure. Silylation of both hydroxy groups with excess

Scheme 6 [a]



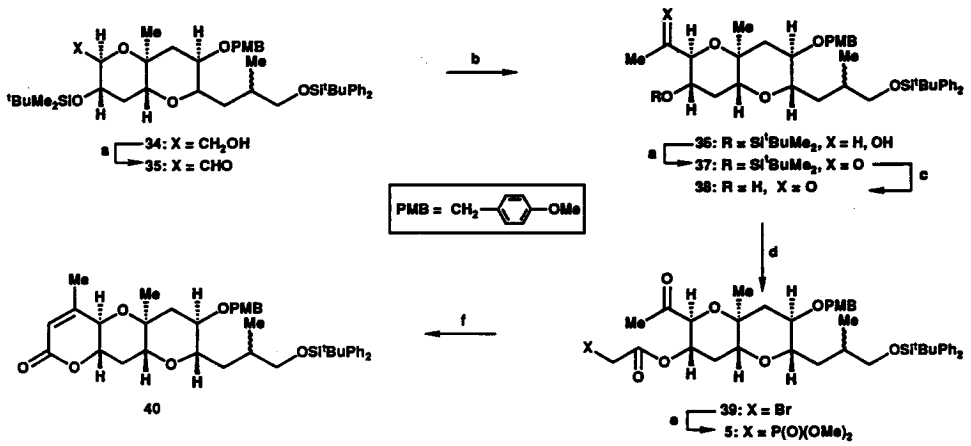
[a]**Reagents and conditions:** (a) H_2, 10% Pd/C, EtOAc, 48 h, 100%; (b) 2.5 equiv of $LiAlH_4$, Et_2O, 0 °C, 0.5 h, 95%; (c) 1.2 equiv of $^tBuPh_2SiCl$, 1.5 equiv of imidazole, DMF, 0 °C, 0.5 h, 89%; (d) 1.5 equiv of KH, 1.3 equiv of p-$MeOC_6H_4$-CH_2Cl, THF, 50 °C, 1 h, 84%; (e) 0.25 equiv of CSA, MeOH, 0 °C, 1 h, 86%; (f) 2.5 equiv of $^tBuMe_2SiCl$, 3.0 equiv of imidazole, DMF, 50 °C, 12 h, 92%; (g) 0.2 equiv of CSA, MeOH, 0 °C, 1 h, 81%.

TBDMSCl in DMF gave the disilylated compound **33** in 92% yield, which was selectively deprotected at the primary position by removal of the TBDMS group with 0.2 equiv of CSA in MeOH at 0 °C furnishing the alcohol **34** in 81% yield.

Elaboration of the generated primary alcohol to the methyl ketone functionality, needed for the Horner-Emmons reaction, is shown in **Scheme 7**. Swern oxidation of alcohol **34** gave the aldehyde **35** in 90% yield which was treated immediately with methylmagnesium bromide in THF at 0 °C to give a 1:1 mixture of diastereomeric alcohols **36** in 91% yield. Reoxidation of this mixture

using the Swern oxidation conditions gave the methyl ketone **37** in 88% yield. The secondary TBDMS ether was then selectively removed in the presence of the primary TBDPS ether by exposure to 1.2 equiv of TBAF in THF at 0 °C to furnish the hydroxy ketone **38** in 90% yield. Dicyclohexylcarbodiimide (DCC) mediated coupling[19] of this alcohol with bromoacetic acid gave the Arbuzov precursor **39** in 89% yield. Treatment of **39** with neat trimethylphosphite at 70 °C for 3 h gave the phosphonate **5** in quantitative yield. Finally, using the Masamune-Rousch[20] modification of the Horner-Emmons reaction, phosphonate **5** was converted to the lactone **40** in 92% yield.

Scheme 7 [a]



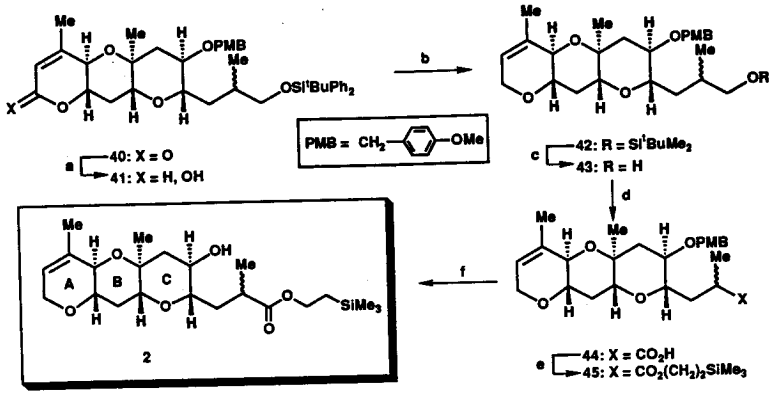
[a] **Reagents and conditions:** (a) 1.5 equiv oxallyl chloride, 2.0 equiv DMSO, 5.0 equiv of Et_3N, CH_2Cl_2, -78 °C, 1 h, 90%; (b) 1.5 equiv of MeMgBr, THF, 0 °C, 0.5 h, 91%; (c) 1.2 equiv of $^nBu_4NF$, THF, 0 °C, 0.5 h, 90%; (d) 1.2 equiv of $BrCH_2CO_2H$, 1.5 equiv of DCC, CH_2Cl_2, 25 °C, 12 h, 89%; (e) neat $(MeO)_3P$, 70 °C, 3 h, 100%; (f) 1.3 equiv of Hunig's base, 1.5 equiv of LiCl, CH_3CN, 25 °C, 2 h, 92%.

With the ABC ring framework in place, all that remained to complete the synthesis was deoxygenation of the lactone, reconstruction of the ester group on the "right side" and removal of the p-methoxybenzyl protecting group. The successful sequence is shown in **Scheme 8**. Reduction of lactone **40** with DIBAL gave the lactol **41** in quantitative yield. Treatment of the lactol with borontrifluoride etherate and excess triethylsilane in CH_2Cl_2 at -10 °C led to the pyran **42** in 90% yield. Treatment of silyl ether **42** with TBAF in THF at 45 °C furnished the alcohol **43** in 93% yield. Jones oxidation of the alcohol at -15 °C gave the free acid **44** in 84% yield. Compound **44** was identical to an authentic sample prepared previously[13] by chromatographic and spectroscopic criteria. Esterification of acid **44** with 2-(trimethylsilyl)ethanol gave the ester **45** in 89% yield. Finally, removal of the p-methoxybenzyl ether using DDQ gave the ABC ring system **2** in 85% yield.

Synthesis of the FG ring system 3

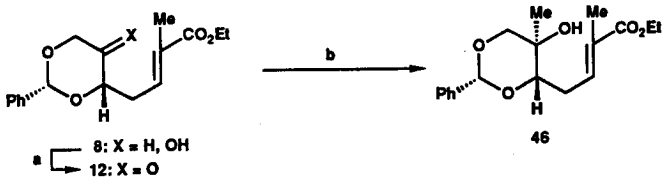
The initial steps in preparing the FG ring system **3** are shown in **Scheme 9.** Thus, Swern oxidation of alcohol **8** provided ketone **12** in 89% yield. Introduction of the axial methyl group stereoselectively was achieved by treating ketone **12** with an excess of trimethylaluminum in CH_2Cl_2 at -20 °C to give the tertiary alcohol **46** as a single diastereomer. None of the other isomer was detected. The high stereospecificity of this reaction is understood by inspection of molecular models. Thus, axial attack from the bottom face of the carbonyl group (**Figure 1**) is completely unhindered, whereas equatorial attack from the top face encounters torsional strain,[21] due to the presence of the 2,6-axial hydrogens.

Scheme 8 [a]



[a]**Reagents and conditions:** (a) 1.5 equiv of DIBAL, CH_2Cl_2, -78 °C, 0.5 h, 100%; (b) 0.8 equiv of BF_3-Et_2O, 5.0 equiv of Et_3SiH, CH_2Cl_2, -10 °C, 0.5 h, 90%; (c) 1.5 equiv of $^nBu_4NF$, THF, 45 °C, 2.5 h, 93%; (d) excess Jones reagent, acetone, -15 °C, 0.5 h, 84%; (e) 1.2 equiv of $Me_3Si(CH_2)_2OH$, 1.5 equiv of DCC, CH_2Cl_2, 12 h, 89%; (f) 1.5 equiv of DDQ, CH_2Cl_2-H_2O (3:1), 25 °C, 0.5 h, 85%.

Scheme 9 [a]



[a]**Reagents and conditions:** (a) 1.8 equiv of oxalyl chloride, 2.2 equiv of DMSO, 5.0 equiv of Et_3N, CH_2Cl_2, -78 °C, 1.5 h, 89%; (b) 1.6 equiv of $AlMe_3$, CH_2Cl_2, -20 °C, 2.5 h, 84%.

Completion of the construction of the F ring is shown in **Scheme 10**. Silylation of the tertiary alcohol with 1-(trimethylsilyl) imidazole in CH_2Cl_2 gave **47** in quantitative yield. DIBAL reduction of the α,β-unsaturated ester furnished the allylic alcohol **48** in 96% yield. Sharpless epoxidation with (–)-diethyl tartrate led to the epoxy alcohol **49** in 89% yield. Oxidation of the epoxy alcohol, using SO_3·pyridine in CH_2Cl_2:DMSO (4:1) at 0 °C, gave the epoxy aldehyde **50** which was immediately subjected to olefination to give the allylic epoxide **51** in 82% yield. Deprotection of the silyl ether, using TBAF in THF, gave the 6-endo activated epoxy alcohol **11** in 95% yield. Finally, acid induced cyclization of this epoxy alcohol with PPTS in CH_2Cl_2 led to the pyran **52** in 94% yield.

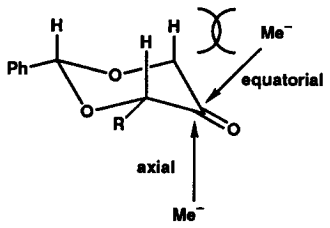
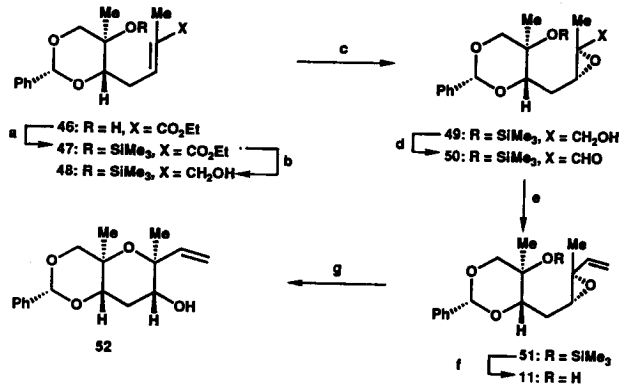


Figure 1: Rational for preferential axial attack at carbonyl of ketone **12**

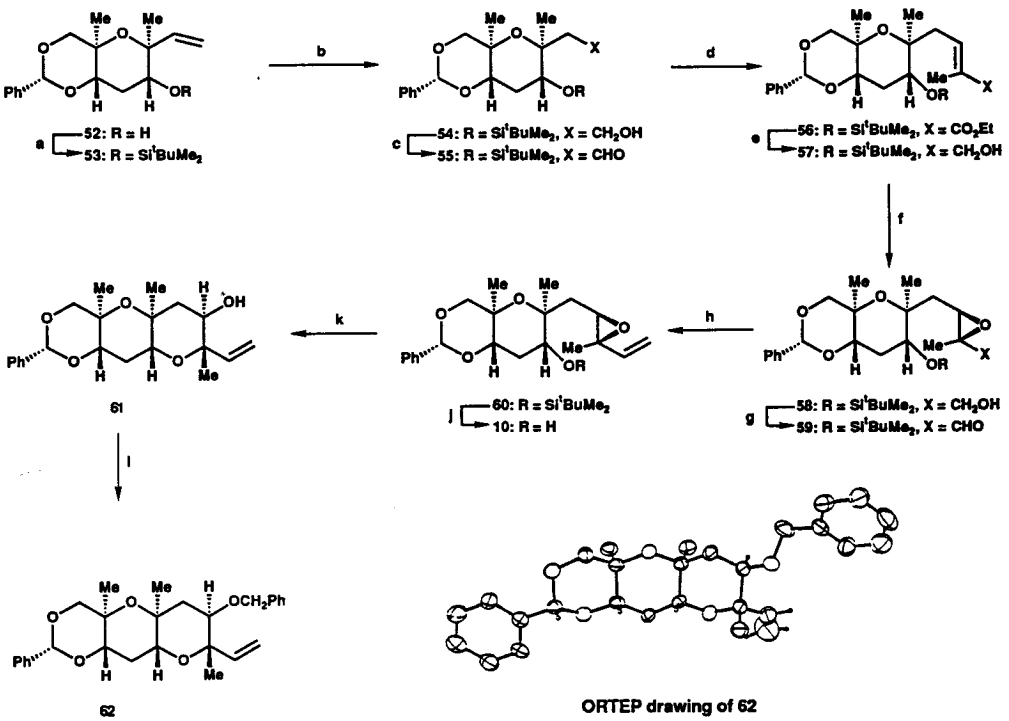
Scheme 10 [a]



[a] **Reagents and conditions:** (a) 1.5 equiv of TMS-imidazole, CH_2Cl_2, 25 °C, 0.5 h, 100%; (b) 2.3 equiv of DIBAL, CH_2Cl_2, -78 °C, 0.5 h, 96%, (c) 0.2 equiv of (-)-diethyl tartrate, 0.15 equiv of $Ti(O^iPr)_4$, 1.5 equiv of ^tBuOOH, CH_2Cl_2, -25 °C, 14 h, 89%; (d) 4.0 equiv of SO_3-pyr, 5.0 equiv of Et_3N, CH_2Cl_2:DMSO (4:1), 0 °C, 2.5 h, 93%; (e) 1.5 equiv of $CH_3P^+Ph_3Br^-$, 1.3 equiv of $NaN(SiMe_3)_2$, THF, 0 °C, 1 h, 88%, (f) 1.3 equiv of $^nBu_4NF$, THF, 25 °C, 0.5 h, 95%; (g) 0.8 equiv of PPTS, CH_2Cl_2, 0 →25 °C, 12 h, 94%.

Scheme 11 presents the sequence leading to the construction of the G ring. Silylation of alcohol **52** using TBDMSCl in DMF provided the silyl ether **53** in 95% yield. Hydroboration of the olefin with 9-BBN followed by oxidative work-up gave the alcohol **54** in 93% yield, which was subjected to Swern oxidation leading to aldehyde **55** in 95% yield. Treatment of the crude aldehyde with (carbethoxyethylidene)triphenylphosphorane in the presence of a catalytic amount of benzoic acid in benzene at 50 °C gave the ester **56** in 90% yield. DIBAL reduction of the α,β–unsaturated ester led to the allylic alcohol **57** in 97% yield. Sharpless epoxidation of allylic alcohol **57** gave an unfavorable mixture of the two diastereomeric epoxides. In contrast to previous results however,[13] hydroxyl directed epoxidation using m-chloroperbenzoic acid in CH_2Cl_2 at 0 °C provided the desired epoxide **58** in 97% yield as a single compound.

Scheme 11 [a]



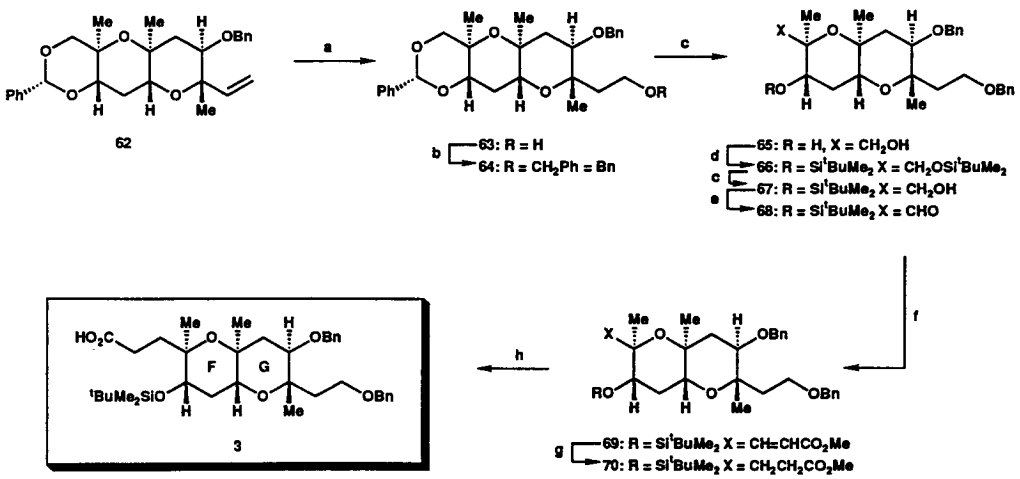
[a]**Reagents and conditions:** (a) 1.2 equiv of ^{t}BuMe$_2$SiCl, 1.5 equiv of imidazole DMF, 50 °C, 12 h, 95%; (b) 1.5 equiv of 9-BBN, THF, 25 °C, then 2.1 equiv of H_2O_2, 2.5 equiv of NaOH, 0 °C, 1 h, 93%; (c) 1.5 equiv of oxalyl chloride, 2.0 equiv of DMSO, 5.0 equiv of Et_3N, CH_2Cl_2, -78 °C, 1 h, 95%; (d) 1.1 equiv of $Ph_3P{=}C(Me)CO_2Et$, 0.1 equiv of $PhCO_2H$, C_6H_6, 50 °C, 0.5 h, 90%; (e) 2.2 equiv of DIBAL, CH_2Cl_2, -78 °C, 0.5 h, 97%; (f) 1.2 equiv of mCPBA, CH_2Cl_2, 0 °C, 0.5 h, 97%; (g) 4.0 equiv of SO_3-pyr, 5.0 equiv of Et_3N, CH_2Cl_2:DMSO (4:1), 0 °C, 3.5 h, 92%; (h) 1.5 equiv of $CH_3P^+Ph_3Br^-$, 1.3 equiv of $NaN(SiMe_3)_2$, THF, 0 °C, 1 h, 88%; (i) 1.2 equiv of ^{n}Bu$_4$NF, THF, 25 °C, 0.5 h, 93%; (k) 0.85 equiv of PPTS, CH_2Cl_2, 0 → 25 °C, 14 h, 92%; (l) 1.5 equiv of benzyl bromide, 1.3 equiv of KH, THF, 45 °C, 1 h, 90%.

Apparently, the presence of the benzylidene ring induces a rigid conformation of the F ring which, in turn results in the observed stereoselectivity. The stereochemistry of epoxide **58** was at this stage tentatively assigned as shown, and was confirmed later as will be described below. Oxidation of the epoxy alcohol **58** using SO_3·pyridine in CH_2Cl_2:DMSO (4:1) at 0 °C gave the epoxy aldehyde **59**, which was subjected immediately to olefination to give epoxy olefin **60** in 81% overall yield. Removal of the TBDMS group with TBAF in THF then led to the epoxy alcohol **10** in 93% yield. Cyclization of the epoxy alcohol **10** using PPTS in CH_2Cl_2 proceeded smoothly as expected, leading to compound **61** in 92% yield. Assuming that 6-endo cyclization of **10** occurs through a

chair-like transition state, the stereochemistry assigned to epoxide **58** must be correct since the other isomer requires a boat-like transition state in order to cyclize to the pyran. Final proof of the stereochemical assignments came from X-ray crystallographic data obtained with the benzyl ether **62**, prepared from **61** by exposure to benzyl bromide in THF at 45 °C (90%, m.p. 204 °C, ether/hexane). The ORTEP drawing of **62** is shown in **Scheme 11**.

Elaboration of **62** to the desired FG ring intermediate **3** is shown in **Scheme 12**. Hydroboration of the olefin using 9-BBN gave the alcohol **63** (92% yield), which was benzylated using KH and benzyl bromide, to give the ether **64** (89% yield). Removal of the benzylidene with CSA in MeOH at 0 °C provided the diol **65** in 90% yield. Differentiation of the primary alcohol by disilylation followed by selective monodesilylation as described above gave alcohol **67** in 86% overall yield. Swern oxidation provided aldehyde **68** in 93% yield which was treated with methyl (triphenylphosphoranylidene) acetate in benzene at 50 °C overnight to give the α,β-unsaturated ester **69** in 90% yield. Selective hydrogenation of the double bond was accomplished using 5% palladium on carbon in EtOAc to give the saturated ester **70** in quantitative yield. Finally, saponification of the methyl ester using excess lithium hydroxide in THF:MeOH:H_2O (1:1:1) at 55 °C provided the acid **3** in 95% yield, and completed the synthesis of the FG ring system.

Scheme 12 [a]



[a] **Reagents and conditions:** (a) 1.5 equiv of 9-BBN, THF, 25 °C, 1 h, then 2.1 equiv of H_2O_2, 2.5 equiv of NaOH, 0 °C, 1 h, 92%; (b) 1.3 equiv of KH, 1.5 equiv of benzyl bromide, THF, 50 °C, 1 h, 89%; (c) 0.2 equiv of CSA, MeOH, 0 °C, 1 h, 90%; (d) 2.5 equiv of $^tBuMe_2SiCl$, 3.0 equiv of imidazole, DMF, 50 °C, 14 h, 95%; (e) 1.5 equiv of oxalyl chloride, 2.0 equiv of DMSO, 5.0 equiv of Et_3N, CH_2Cl_2, -78 °C, 1 h, 93%; (f) 1.1 equiv of $Ph_3P{=}CHCO_2Me$, C_6H_6, 50 °C, 12 h, 90%; (g) H_2, 5% Pd/C, EtOAc, 25 °C, 6 h, 100%; (h) 1.7 equiv of LiOH, THF:MeOH, H_2O (1:1:1), 55 °C, 2.5 h, 95%.

Conclusion

Stereocontrolled and efficient syntheses of the ABC and FG ring systems of brevetoxin B (**1**) (intermediates **2** and **3**) were developed starting from 2-deoxy-D-ribose. The sequences deliver these intermediates in enantiomerically pure forms (**2**: 38 steps, 3.6% overall yield; **3**: 28 steps, 11.5% overall yield). Both routes represent considerable improvements over the previously reported sequences and are, therefore, the preferred ones for preparing large quantities of these key intermediates. These studies are expected to facilitate the projected total synthesis of brevetoxin B (**1**) and related compounds.

EXPERIMENTAL SECTION

General Techniques. NMR spectra were recorded on a Brucker WM-250. IR spectra were recorded on a Perkin-Elmer Model 781 infrared spectrophotometer.

High-resolution mass spectra (HRMS) were recorded on a VG 7070 HS mass spectrometer under chemical ionization (CI) conditions or on a VC ZAB E instrument under FAB conditions.

All reactions were monitored by thin-layer chromatography carried out on 0.25-mm E. Merck silica gel plates (60F-254) by using UV light and 7% ethanolic phosphomolybdic acid-heat as a developing reagent. Preparative layer chromatography was preformed on 0.5 or 0.25 mm x 20 cm x 20 cm E. Merck silica gel plates (60F-254). E. Merck silica gel (60, particle size 0.040-0.063 mm) was used for flash chromatography.

All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated.

Triol 13.

A mixture of 2-deoxy-D-ribose (25 g, 186.5 mmol) and (carbethoxyethylidene) triphenylphosphorane (75 g, 205 mmol) in THF (370 mL) was refluxed for 3 h. Concentration and flash chromatography (silica, 5→20% MeOH in CH_2Cl_2) gave the triol **13** (39.6 g, 97%). **13**: oil; TLC, Rf= 0.31 (silica, 10% MeOH in CH_2Cl_2); IR (neat) n_{max} 3460-3280(OH), 2940, 1710(C=O), 1650, 910 cm^{-1} ; ^{1}H NMR ($CDCl_3$) d 6.80 (dt, J=7.5, 1.4 Hz, 1 H, $\underline{H}C=C$), 4.17 (q, J=7.2 Hz, 2 H, $CH_3C\underline{H}_2O_2C$), 3.87, 3.78, 3.64 (m, 4 H, $C\underline{H}$-O, $C\underline{H}_2O$), 2.75 (bs, 1 H, $O\underline{H}$), 2.49 (bs, 1 H, $O\underline{H}$), 2.44 (t, J=6.6 Hz, 2 H, $C\underline{H}_2$), 1.85 (d, J=1.25 Hz, 3 H, $C\underline{H}_3C=C$), 1.28 (t, J=7.2 Hz, 3 H, $C\underline{H}_3CH_2O_2C$); HRMS, calcd for $C_{10}H_{19}O_5$ (M+H): 219.1232, found: 219.1261.

Ester 8.

A mixture of triol **13** (39 g, 179.0 mmol), benzaldehyde dimethylacetal (35.3 g, 232.6 mmol) and camphorsulfonic acid (8.3 g, 35.8 mmol) in CH_2Cl_2 (600 mL) was stirred for 12 h at 25 °C. The reaction mixture was quenched with triethylamine (6 mL), concentrated and the residue subjected to flash chromatography (silica, 10→70% ether in petroleum ether) to afford the benzylidene **8** (52.8 g, 96%). **8**: solid; m.p. 89–91 °C; TLC, Rf=0.42 (silica, 60% ether in petroleum ether); IR ($CDCl_3$) ν_{max} 3600, 3450, 2980, 2870, 1700(C=O), 1650, 1460, 1385, 1370, 1280, 1230, 1115, 1075, 1030, 980, 910, 650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.45, 7.34 (2 x m, 5 H, aromatic), 6.92 (dt, J=7.3, 1.4 Hz, 1 H, C<u>H</u>=C), 5.47 (s, 1 H, C<u>H</u>Ar), 4.24 (m, 1 H, C<u>H</u>-O), 4.17 (q, J=7.2 Hz, 2 H, $CH_3C\underline{H}_2O_2C$), 3.65 (m, 3 H, C<u>H</u>-O, $C\underline{H}_2O$), 2.75 (dd, J=14.1, 7.4 Hz, 1 H, $C\underline{H}_2$), 2.56 (m, 1 H, $C\underline{H}_2$), 1.95 (bs, 1 H, O<u>H</u>), 1.86 (d, J=0.96 Hz, 3 H, $C\underline{H}_3C$=C), 1.27 (t, J=7.2 Hz, 3 H, $C\underline{H}_3CH_2O_2C$); HRMS, calcd for $C_{17}H_{23}O_5$ (M+H): 307.1545, found: 307.1532.

Silyl ether 14.

To a stirred solution of **8** (52.3 g, 170.9 mmol) and imidazole (17.4 g, 256 mmol) in DMF (285 mL) at 25 °C was added *tert*-butyldimethylsilyl chloride (33.5 g, 222.2 mmol) in one portion. The reaction mixture was stirred at 25 °C for 5 h. After cooling to room temperature, the reaction mixture was quenched with MeOH (9.4 mL), diluted with ether (1 L) and washed with water (2 x 300 mL). Drying ($MgSO_4$), concentration and flash chromatography (silica, 10% ether in petroleum ether) gave the silyl ether **14** (71.1 g, 98%). **14**: oil; TLC, Rf=0.78 (silica, 10% ether in petroleum ether); IR (neat) ν_{max} 2960, 2940, 2870, 1715(C=O), 1655, 1470, 1395, 1370, 1280, 1270, 1110, 1030, 980, 840, 780, 750, 715, 700, 680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.51, 7.38 (2 x m, 5 H, aromatic), 6.93 (dt, J=7.3, 1.4 Hz, 1 H, C<u>H</u>=C), 5.47 (s, 1 H, C<u>H</u>Ar), 4.17 (q, J=7.2 Hz, 2 H, $CH_3C\underline{H}_2O_2C$), 3.58 (m, 4 H, C<u>H</u>-O, $C\underline{H}_2O$), 2.75 (dd, J=14.1, 7.4 Hz, 1 H, $C\underline{H}_2$), 2.38 (m, 1 H, $C\underline{H}_2$), 1.84 (d, J=1.1 Hz, 3 H, $C\underline{H}_3C$=C), 1.55 (t, J=7.2 Hz, 3 H, $C\underline{H}_3CH_2O_2C$), 0.88 (s, 9 H, $(C\underline{H}_3)_3CSi$), 0.09, 0.07 (2 x s, 2 x 3H, $C\underline{H}_3Si$); HRMS, calcd for $C_{23}H_{40}O_5NSi$ ($M+NH_4$): 438.2676, found: 438.2637.

Allylic alcohol 15.

To a stirred solution of **14** (71.0 g, 168.6 mmol) in CH_2Cl_2 (190 mL) at -78 °C was added DIBAL (370 mL, 370 mmol, 1.0 M in CH_2Cl_2) over a 20 min period. After 40 min, the mixture was quenched with MeOH (5 mL), the cooling bath was removed, and the reaction mixture was allowed to reach room temperature. The mixture was diluted with EtOAc (400 mL) and washed with aqueous saturated sodium potassium tartrate (300 mL). The aqueous phase was extracted with EtOAc (2 x 100 mL). The combined organic layers were dried ($MgSO_4$), concentrated and subjected to flash chromatography (silica, 30% ether in petroleum ether) to give the allylic alcohol **15** (62.1 g, 98%). **15**: oil; TLC, Rf=0.27 (silica, 30% ether in petroleum ether); IR (neat) ν_{max} 3460(OH), 2960, 2860, 1465, 1300, 1250, 830, 775, 745, 715, 690, 670, 640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.41, 7.32 (2 x m, 5 H, aromatic), 5.62 (dt, J=7.3, 1.4 Hz, 1 H, C<u>H</u>=C), 5.45 (s, 1 H, C<u>H</u>Ar), 4.18 (m, 1 H, C<u>H</u>-O), 4.01 (d, J=4.1 Hz, 2 H, $C\underline{H}_2O$), 3.55 (m, 3 H, C<u>H</u>-O, $C\underline{H}_2O$), 2.62 (dd, J=14.1, 7.4 Hz, 1 H, $C\underline{H}_2$), 2.29 (m, 1 H,

CH_2), 1.68 (s, 3 H, CH_3C=C), 1.50 (bs,1 H, OH), 0.89 (s, 9 H, $(CH_3)_3CSi$), 0.09, 0.07 (2 x s, 2 x 3 H, CH_3Si); HRMS, calcd for $C_{21}H_{35}O_4Si$ (M+H): 379.2305, found: 379.2317.

Epoxide 16.

A solution of alcohol **15** (61.9 g, 163.8 mmol) in CH_2Cl_2 (380 mL) was added dropwise over 20 min to a cooled (-27 °C) mixture of diethyl-D-tartrate (6.9 mL, 40.9 mmol), 4 Å molecular sieves (20 g), and titanium (IV) isopropoxide (10.8 mL, 36.1 mmol) in CH_2Cl_2 (120 mL). After 30 min, *tert*-butylhydroperoxide (81.9 mL, 245.7 mmol, 3.0 M in 2,2,4-trimethylpentane) was added and the reaction mixture stored at -20 °C for 14 h. The cooling was removed and the reaction mixture filtered. The filtrate was diluted with EtOAc (500 mL), washed with saturated aqueous sodium sulfate (500 mL), dried ($MgSO_4$) and filtered through a celite pad. The filtrate was concentrated and subjected to flash chromatography (silica, 30% ether in petroleum ether) to give the epoxide **16** (57.4 g, 89%). **16**: oil; TLC, Rf=0.21 (silica, 30% ether in petroleum ether); IR (neat) ν_{max} 3440(OH), 2950, 2920, 2850, 1460, 1390, 1250, 1100, 1030, 975, 880, 845, 835, 775, 755, 700, 675, 650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46, 7.33 (2 x m, 5 H, aromatic), 5.49 (s, 1 H, CHAr), 4.19 (dd, J=10.0, 6.4 Hz,1 H, CH-O), 3.69-3.53 (m, 5 H, CH-O, CH_2O), 3.33 (t, J=6.2 Hz, 1 H, H-epox.), 2.01 (m, 1 H, CH_2), 1.64 (dd, J=8.4, 4.8 Hz, 1 H, CH_2), 1.55 (s, 3 H, CH_3-epox.), 0.87 (s, 9 H, $(CH_3)_3CSi$), 0.10, 0.08 (2 x s, 2 x 3 H, CH_3Si); HRMS, calcd for $C_{21}H_{38}O_5NSi$ ($M+NH_4$): 412.2519, found: 412.2493.

Olefin 18.

To a stirred mixture of alcohol **16** (57.1 g, 144.9 mmol), dry DMSO (80 mL) and triethylamine (100 mL, 725 mmol) in CH_2Cl_2 (300 mL) at 0 °C was added sulfur trioxide-pyridine complex (69.2 g, 435 mmol) in four portions. After 3.5 h the reaction mixture was diluted with ether (600 mL), washed with saturated aqueous ammonium chloride solution (500 mL), dried ($MgSO_4$) and concentrated to give the epoxy aldehyde **17** (54 g, 94%) which was used directly. To a stirred solution of methyl triphenylphosphonium bromide (77.7 g, 217.5 mmol) in THF (50 mL) at 0 °C was dropwise added sodium bis(trimethylsilyl)amide (174 mL, 174 mmol, 1.0 M in THF) over 20 min. After stirring for 10 min, the bright yellow ylide was treated with the crude aldehyde **17** (54 g, 137.7 mmol) in THF (350 mL) dropwise over a period of 20 min. After 15 min, the reaction mixture was quenched with acetone (5 mL), diluted with ether (500 mL), washed with water (400 mL), dried ($MgSO_4$) and concentrated. The residue was triturated with 25% ether in petroleum ether, followed by filtration to remove triphenylphosphonium oxide. After solvent removal and flash chromatography (silica, 5→10% ether in petroleum ether), the olefin **18** was obtained (48 g, 88%). **18**: oil; TLC, Rf=0.33 (silica, 10% ether in petroleum ether); IR (neat) ν_{max} 2950, 2920, 2850, 1640, 1460, 1385, 1360, 1295, 1250, 1100, 1020, 985, 915, 870, 840, 830, 775, 750, 700, 680, 660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46, 7.33 (2 x m, 5 H, aromatic), 5.68 (dd, J=17.4, 10.6 Hz, 1 H, $CH=CH_2$), 5.51 (s, 1 H, CHAr), 5.30 (dd, J=17.4, 1.1 Hz, 1 H, CH_2=CH), 5.17 (dd, J=10.6, 1.1 Hz, 1 H, CH_2=CH), 4.20 (dd, J=10.0, 6.4 Hz,1 H, CH-O), 3.70 (m, 2 H, CH-O), 3.57 (m, 1 H, CH-O), 3.16 (t, J=6.2 Hz, 1 H, H-epox.), 2.02 (m, 2 H, CH_2), 1.42 (s, 3 H, CH_3-epox.), 0.89 (s, 9 H, $(CH_3)_3CSi$), 0.12, 0.10 (2 x s, 2 x 3 H, CH_3Si); HRMS, calcd for $C_{22}H_{35}O_4Si$ (M+H): 391.2304, found: 391.2325.

Epoxy alcohol 7.

To a stirred solution of olefin **18** (47.9 g, 122.8 mmol) in THF (225 mL) at 25 °C was added dropwise tetrabutylammonium fluoride (185 mL, 185.0 mmol, 1.0 M in THF) over 10 min. After 20 min, the reaction mixture was diluted with ether (500 mL), washed with water (450 mL), dried ($MgSO_4$) and the solvent evaporated. Flash chromatography (silica, 30→70% ether in petroleum ether) gave the epoxy alcohol **7** (33.2 g, 98%). **7**: oil; TLC, Rf=0.49 (silica, 50% ether in petroleum ether); IR (neat) ν_{max} 3440(OH), 2960, 2920, 2850, 1450, 1400, 1075, 1020, 920, 830, 760, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46, 7.33 (2 x m, 5 H, aromatic), 5.68 (dd, J=17.4, 10.6 Hz, 1 H, C<u>H</u>=CH_2), 5.50 (s, 1 H, C<u>H</u>Ar), 5.30 (dd, J=17.4, 1.1 Hz, 1 H, C<u>H</u>$_2$=CH), 5.17 (dd, J=10.6, 1.1 Hz, 1 H, C<u>H</u>$_2$=CH), 4.30 (dd, J=10.0, 6.4 Hz,1 H, C<u>H</u>-O), 3.91 (m, 1 H, C<u>H</u>-O), 3.79 (m, 1 H, C<u>H</u>-O), 3.61 (t, J=10.5 Hz, 1 H, C<u>H</u>-O), 3.18 (dd, J=7.9, 3.8 Hz, 1 H, H-epox.), 2.29 (d, J=4.7 Hz, 1 H, O<u>H</u>), 2.20 (m, 1 H, C<u>H</u>$_2$), 2.01 (m, 1 H, C<u>H</u>$_2$), 1.42 (s, 3 H, CH_3-epox.); HRMS, calcd for $C_{16}H_{21}O_4$ (M+H): 277.1440, found: 277.1409.

Pyran 19.

A solution of epoxide **7** (33.1 g, 119.9 mmol) in CH_2Cl_2 (1.1 L) at 0 °C was treated with pyridinium p-toluenesulfonate (23.9 g, 95.2 mmol) in one portion. After 3 h, triethylamine (16.6 mL, 120 mmol) was added and the solvent evaporated. Flash chromatography (silica, 70% ether in petroleum ether) gave the cyclized product **19** (28.5 g, 86%). **19**: solid; m.p. 97°C; TLC, Rf=0.53 (silica, 50% ether in petroleum ether); IR (neat) ν_{max} 3450(OH), 2990, 2960, 2870, 1470, 1290, 1190, 1100, 1020, 760, 700, 655 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46, 7.33 (2 x m, 5 H, aromatic), 5.68 (dd, J=17.4, 10.6 Hz, 1 H, C<u>H</u>=CH_2), 5.52 (s, 1 H, C<u>H</u>Ar), 5.33 (dd, J=17.4, 1.1 Hz, 1 H, C<u>H</u>$_2$=CH), 5.16 (dd, J=10.6, 1.1 Hz, 1 H, C<u>H</u>$_2$=CH), 4.26 (m,1 H, C<u>H</u>-O), 3.69-3.42 (m, 4 H, C<u>H</u>-O, C<u>H</u>$_2$O), 2.29 (m, 1 H, C<u>H</u>$_2$), 1.83 (q. J=11.6 Hz, 1 H, C<u>H</u>$_2$), 1.71 (d, J=4.7 Hz, 1 H, O<u>H</u>), 1.36 (s, 3 H, C<u>H</u>$_3$); HRMS, calcd for $C_{16}H_{21}O_4$ (M+H): 277.1440, found: 277.1418.

Silyl ether 20.

To a stirred solution of pyran **19** (28.4 g, 102.9 mmol) and imidazole (10.5 g, 154.3 mmol) in DMF (200 mL) at 25 °C was added *tert*-butyldimethylsilyl chloride (18.4 g, 122.4 mmol) in one portion. The reaction mixture was heated at 50 °C and stirred for 10.5 h. After cooling to room temperature the reaction mixture was quenched with MeOH (9 mL), diluted with ether (500 mL) and washed with water (300 mL). Drying ($MgSO_4$), concentration and flash chromatography (silica, 10% ether in petroleum ether) gave the silyl ether **20** (39 g, 97%). **20**: oil; TLC, Rf=0.36 (silica, 10% ether in petroleum ether); IR (neat) ν_{max} 2960, 2940, 2860, 1480, 1410, 1370, 1300, 1260, 1195, 1100, 1030, 930, 840, 790, 700, 675, 650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46, 7.33 (2 x m, 5 H, aromatic), 5.68 (dd, J=17.4, 10.6 Hz, 1 H, C<u>H</u>=CH_2), 5.51 (s, 1 H, C<u>H</u>Ar), 5.33 (dd, J=17.4, 1.1 Hz, 1 H, C<u>H</u>$_2$=CH), 5.16 (dd, J=10.6, 1.1 Hz, 1 H, C<u>H</u>$_2$=CH), 4.26 (m,1 H, C<u>H</u>-O), 3.69-3.42 (m, 4 H, C<u>H</u>-O, C<u>H</u>$_2$O), 2.17 (m, 1 H, C<u>H</u>$_2$), 1.83 (q, J=11.6 Hz, 1 H, C<u>H</u>$_2$), 1.31 (s, 3 H, C<u>H</u>$_3$), 0.85 (s, 9 H, (C<u>H</u>$_3$)$_3$CSi), 0.04, 0.02 (2 x s, 2 x 3 H, C<u>H</u>$_3$Si); HRMS, calcd for $C_{22}H_{35}O_4Si$ (M+H): 391.2304, found: 391.2281.

Alcohol 21.

A stirred solution of olefin **20** (38.9 g, 99.7 mmol) in THF (80 mL) at 25 °C was treated with 9-BBN (300 mL, 150 mmol, 0.5 M in THF) over 30 min. After 40 min, the reaction mixture was cooled to 0 °C and treated dropwise with 3 N NaOH (75 mL, 225 mmol) and 30% hydrogen peroxide (20 mL, 165 mmol) over 20 min. The cooling bath was removed and the reaction mixture was stirred for another 30 min. The reaction mixture was diluted with ether (500 mL), washed with water (300 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (silica, 20→50% ether in petroleum ether) gave the alcohol **21** (38 g, 93%). **21**: oil; TLC, Rf=0.28 (silica, 50% ether in petroleum ether); IR (neat) ν_{max} 3460(OH), 2960, 2940, 2860, 1475, 1390, 1370, 1260, 1100, 840, 780, 700, 670, 650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.41, 7.32 (2 x m, 5 H, aromatic), 5.49 (s, 1 H, C<u>H</u>Ar), 4.19 (d, J=5.7 Hz, 1 H, C<u>H</u>$_2$O), 3.84-3.39 (m, 6 H, C<u>H</u>-O, C<u>H</u>$_2$O), 2.19 (m, 1 H, C<u>H</u>$_2$), 1.88-1.63 (m, 3 H, C<u>H</u>$_2$), 1.56 (s, 3 H, C<u>H</u>$_3$), 1.50 (bs, 1 H, O<u>H</u>), 0.84 (s, 9 H, (C<u>H</u>$_3$)$_3$CSi), 0.06, 0.04 (2 x s, 2 x 3 H, C<u>H</u>$_3$Si); HRMS, calcd for $C_{22}H_{37}O_5Si$ (M+H): 409.2410, found: 409.2401.

Aldehyde 22.

A solution of alcohol **21** (37.9 g, 92.9 mmol) in CH_2Cl_2 (365 mL) was added dropwise to a mixture of oxalyl chloride (12.2 mL, 139.4 mmol) and DMSO (13.1 mL, 185.8 mmol) in CH_2Cl_2 (85 mL) at -78 °C over 25 min. After 40 min, triethylamine (65 mL, 464.5 mmol) was added slowly and the cooling bath removed. When the reaction mixture reached 0 °C, it was diluted with ether (500 mL) and washed with saturated aqueous ammonium chloride (450 mL), dried ($MgSO_4$) and concentrated. The crude aldehyde **22** (37.5 g, 98%) was taken to the next step without purification. **22**: oil; TLC, Rf=0.82 (silica, 50% ether in petroleum ether); IR (neat) ν_{max} 2960, 2940, 2860, 1720 (C=O), 1470, 1390, 1370, 1260, 1100, 1030, 840, 780, 700, 670, 650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.83 (t, J= 2.9 Hz, 1 H, H-aldehyde), 7.46, 7.32 (2 x m, 5 H, aromatic), 5.49 (s, 1 H, C<u>H</u>Ar), 4.21 (m, 1 H, C<u>H</u>-O), 3.74-3.36 (m, 4 H, C<u>H</u>-O, C<u>H</u>$_2$-O), 2.52 (2 x d, J=2.9 Hz, 2 x 1 H, C<u>H</u>$_2$C=O), 2.16 (m, 1 H, C<u>H</u>$_2$), 1.82 (q, J=11.6 Hz, 1 H, C<u>H</u>$_2$), 1.36 (s, 3 H, C<u>H</u>$_3$), 0.85 (s, 9 H, (C<u>H</u>$_3$)$_3$CSi), 0.06, 0.058 (2 x s, 2 x 3 H, C<u>H</u>$_3$Si); HRMS, calcd for $C_{22}H_{35}O_5Si$ (M+H): 407.2251, found: 407.2291.

Unsaturated ester 23.

A mixture of the crude aldehyde **22** (37.4 g, 92.1 mmol), methyl (triphenylphosphoranylidene) acetate (36.9 g, 110.5 mmol) and benzoic acid (0.2 g) in benzene (185 mL) was stirred at 50 °C for 30 min. Concentration and flash chromatography (silica, 15% ether in petroleum ether) gave the α,β–unsaturated ester **23** (37.6 g, 88%). **23**: oil; TLC, Rf=0.42 (silica, 20% ether in petroleum ether); IR (neat) ν_{max} 2960, 2940, 2860, 1730(C=O), 1660, 1470, 1435, 840, 780, 700, 680, 660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46, 7.32 (2 x m, 5 H, aromatic), 6.94 (m, 1 H, C<u>H</u>=CH), 5.84 (d, J=15.8 Hz, 1 H, C<u>H</u>=CH), 5.49 (s, 1 H, C<u>H</u>Ar), 4.21 (dd, J=10.0, 6.4 Hz, 1 H, C<u>H</u>-O), 3.73 (s, 3 H, C<u>H</u>$_3$O$_2$C), 3.69-3.37 (m, 4 H, C<u>H</u>-O, C<u>H</u>$_2$-O), 2.41 (m, 2 H, C<u>H</u>$_2$), 2.14 (m, 1 H, C<u>H</u>$_2$), 1.82 (m, 1 H, C<u>H</u>$_2$), 1.20 (s, 3 H, C<u>H</u>$_3$), 0.86 (s, 9 H, (C<u>H</u>$_3$)$_3$CSi), 0.046, 0.043 (2 x s, 2 x 3 H, C<u>H</u>$_3$Si); HRMS, calcd for $C_{25}H_{39}O_6Si$ (M+H): 463.2516, found: 463.2479.

Alcohol 24.

DIBAL (178.6 mL, 178.6 mmol, 1.0 M in CH_2Cl_2) was added dropwise to a stirred solution of ester **23** (37.5 g, 81.2 mmol) in CH_2Cl_2 (100 mL) at -78 °C over 20 min. After 15 min, the mixture was quenched with MeOH (5 mL), the cooling bath removed, and the reaction mixture was allowed to reach room temperature. The mixture was diluted with EtOAc (400 mL) and washed with aqueous saturated sodium potassium tartrate (350 mL). The aqueous phase was extracted with EtOAc (2 x 1000 mL). The combined organic layers were dried ($MgSO_4$), concentrated and subjected to flash chromatography (silica, 60% ether in petroleum ether) to give the allylic alcohol **24** (34.8 g, 98%). **24**: oil; TLC, Rf=0.43 (silica, 60% ether in petroleum ether); IR (neat) ν_{max} 3390(OH), 2950, 2860, 1465, 1365, 1255, 835, 780, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46, 7.32 (2 x m, 5 H, aromatic), 5.71 (m, 2 H, C<u>H</u>=CH), 5.49 (s, 1 H, C<u>H</u>Ar), 4.21 (dd, J=10.0, 6.4 Hz, 1 H, C<u>H</u>-O), 4.12 (t, J=5.3 Hz, 1 H, C<u>H</u>-O), 3.64-3.38 (m, 5 H, C<u>H</u>-O, C<u>H</u>$_2$O), 2.36-2.04 (m, 3 H, C<u>H</u>$_2$), 1.79 (m, 1 H, C<u>H</u>$_2$), 1.16 (s, 3 H, C<u>H</u>$_3$), 0.86 (s, 9 H, (C<u>H</u>$_3$)$_3$CSi), 0.04 (s, 6 H, (C<u>H</u>$_3$)$_2$Si); HRMS, calcd for $C_{24}H_{39}O_5Si$ (M+H): 435.2567, found: 435.2532.

Epoxide 25.

A solution of alcohol **24** (34.7 g, 80.0 mmol) in CH_2Cl_2 (200 mL) was added dropwise over 10 min to a cooled (-28 °C) mixture of diethyl-D-tartrate (3.4 mL, 20.0 mmol), 4 Å molecular sieves (12 g), and titanium (IV) isopropoxide (4.8 mL, 16.0 mmol) in CH_2Cl_2 (60 mL). After 30 min, *tert*-butylhydroperoxide (40 mL, 120.0 mmol, 3.0 M in 2,2,4-trimethylpentane) was added and the reaction mixture was stored at -20 °C for 14 h. Cooling was stopped and the reaction mixture was filtered. The filtrate was diluted with EtOAc (400 mL), washed with saturated aqueous sodium sulfate (320 mL), dried ($MgSO_4$) and filtered through a celite pad. The filtrate was concentrated and subjected to flash chromatography (silica, 50% ether in petroleum ether) to give the epoxide **25** (31.3 g, 87%). **25**: oil; TLC, Rf=0.38 (silica, 60% ether in petroleum ether); IR (neat) ν_{max} 3450 (OH), 2960, 2850, 1470, 1395, 1265, 850, 780, 700, 670, 665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46, 7.32 (2 x m, 5 H, aromatic), 5.50 (s, 1 H, C<u>H</u>Ar), 4.21 (m, 1 H, C<u>H</u>-O), 3.94-3.72 (m, 2 H, C<u>H</u>-O, C<u>H</u>$_2$O), 3.68-3.41 (m, 4 H, C<u>H</u>-O, C<u>H</u>$_2$O), 3.18 (m, 1 H, H-epox.), 2.86 (m, 1 H, H-epox.), 2.17 (m, 1 H, C<u>H</u>$_2$), 1.78 (m, 3 H, C<u>H</u>$_2$), 1.24 (s, 3 H, C<u>H</u>$_3$), 0.83 (s, 9 H, (C<u>H</u>$_3$)$_3$CSi), 0.06, 0.05 (2 x s, 2 x 3 H, C<u>H</u>$_3$Si); HRMS, calcd for $C_{24}H_{39}O_6Si$ (M+H): 435.2567, found: 435.2532.

Unsaturated ester 26.

To a stirred mixture of alcohol **25** (31.2 g, 69.3 mmol), dry DMSO (50 mL) and triethylamine (48 mL, 345 mmol) in CH_2Cl_2 (250 mL) at 0 °C was added sulfur trioxide-pyridine complex (33.1 g, 208 mmol) in four portions. After 3 h, the reaction mixture was diluted with ether (350 mL), washed with saturated aqueous ammonium chloride solution (250 mL), dried ($MgSO_4$) and concentrated to give the crude epoxy aldehyde **25a** (30.3 g, 93%) which was used directly. The crude aldehyde was taken up in benzene (140 mL), treated with (carbethoxyethylidene) triphenylphosphorane (30.4 g, 83.2 mmol) and catalytic benzoic acid (0.2 g) and stirred for 30 min at 25 °C. Concentration and flash chromatography (silica, 20% ether in petroleum ether) gave the α,β–unsaturated ester **26**

(30.1 g, 88%). **26**: oil; TLC, Rf=0.34 (silica, 20% ether in petroleum ether); IR (neat) ν_{max} 2960, 2860, 1720(C=O), 1660, 1465, 1370, 1250, 1100, 915, 840, 780, 750, 700, 680, 660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46, 7.32 (2 x m, 5 H, aromatic), 6.28 (d, J=8.8 Hz, 1 H, C<u>H</u>=C), 5.50 (s, 1 H, C<u>H</u>Ar), 4.20 (m, 3 H, C<u>H</u>-O, $CH_3C\underline{H}_2O_2C$), 3.82 (m, 1 H, C<u>H</u>-O), 3.61-3.39 (m, 3 H, C<u>H</u>-O, $C\underline{H}_2O$), 3.31 (dd, J=8.8, 2.2 Hz, 1 H, H-epox.), 3.18 (m, 1 H, H-epox.), 2.18 (m, 1 H, $C\underline{H}_2$), 1.98 (d, J=1.3 Hz, 3 H, $C\underline{H}_3C$=C), 1.83-1.72 (m, 3 H, $C\underline{H}_2$), 1.27 (t, J=7.2 Hz, 3 H, $C\underline{H}_3CH_2O_2C$), 1.24 (s, 3 H, $C\underline{H}_3$), 0.84 (s, 9 H, $(C\underline{H}_3)_3CSi$), 0.07 (s, 6 H, $C\underline{H}_3Si$); HRMS, calcd for $C_{29}H_{45}O_7Si$ (M+H): 533.2934, found: 533.2941.

Epoxy ester 6.

To a stirred solution of ester **26** (30.0 g, 56.4 mmol) in THF (105 mL) at 25 °C was added dropwise tetrabutylammonium fluoride (84.6 mL, 84.6 mmol, 1.0 M in THF) over 10 min. After 20 min, the reaction mixture was diluted with ether (200 mL), washed with water (250 mL), dried ($MgSO_4$) and the solvent evaporated. Flash chromatography (silica, 30→70% ether in petroleum ether) gave the epoxy alcohol **6** (21.7 g, 95%). **6**: oil; TLC, Rf=0.31 (silica, 60% ether in petroleum ether); IR (neat) ν_{max} 3490(OH), 2990, 1710(C=O), 1470, 920, 700, 640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46, 7.32 (2 x m, 5 H, aromatic), 6.28 (d, J=8.8 Hz, 1 H, C<u>H</u>=C), 5.51 (s, 1 H, C<u>H</u>Ar), 4.20 (m, 3 H, C<u>H</u>-O, $CH_3C\underline{H}_2O_2C$), 3.94 (m, 1 H, C<u>H</u>-O), 3.59 (m, 3 H, C<u>H</u>-O, $C\underline{H}_2O$), 3.38 (dd, J=8.8, 2.2 Hz, 1 H, H-epox.), 3.22 (m, 1 H, H-epox.), 2.21 (m, 1 H, $C\underline{H}_2$), 1.98 (d, J=1.3 Hz, 3 H, $C\underline{H}_3C$=C), 1.92-1.64 (m, 3 H, $C\underline{H}_2$), 1.28 (t, J=7.2 Hz, 3 H, $C\underline{H}_3CH_2O_2C$), 1.25 (s, 3 H, $C\underline{H}_3$); HRMS, calcd for $C_{23}H_{31}O_7$ (M+H): 419.2070, found: 419.2072.

Bicycle 27.

A solution of epoxide **6** (21.6 g, 51.7 mmol) in CH_2Cl_2 (520 mL) at 25 °C was treated with pyridinium p-toluenesulfonate (10.4 g, 41.3 mmol) in one portion. After 13 h, triethylamine (7.2 mL) was added and the solvent evaporated. Flash chromatography (silica, 60% ether in petroleum ether) gave the cyclized product **27** (18.1 g, 84%). **27**: oil; TLC, Rf=0.28 (silica, 60% ether in petroleum ether); IR (neat) ν_{max} 3490(OH), 2990, 2950, 2870, 1715(C=O), 1660, 1460, 1375, 1310, 1265, 1100, 1030, 920, 735, 700, 650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46, 7.32 (2 x m, 5 H, aromatic), 6.61 (d, J=8.8 Hz, 1 H, C<u>H</u>=C), 5.52 (s, 1 H, C<u>H</u>Ar), 4.20-3.96 (m, 4 H, C<u>H</u>-O, $CH_3C\underline{H}_2O_2C$), 3.80-3.49 (m, 4 H, C<u>H</u>-O), 3.30 (dd, J=8.8, 2.2 Hz, 1 H, C<u>H</u>-O), 2.23 (m, 2 H, $C\underline{H}_2$), 1.96 (d, J=1.3 Hz, 3 H, $C\underline{H}_3C$=C), 1.81 (m, 2 H, $C\underline{H}_2$), 1.34 (s, 3 H, $C\underline{H}_3$), 1.28 (t, J=7.2 Hz, 3 H, $C\underline{H}_3CH_2O_2C$); HRMS, calcd for $C_{23}H_{31}O_7$ (M+H): 419.2070, found: 419.2066.

Saturated ester 28.

10% palladium on carbon (3.6 g, 20% by wt.) was added to a stirred solution of ester **27** (18.0 g, 43.1 mmol) in EtOAc (140 mL). A hydrogen atmosphere was introduced using a hydrogen-filled balloon by repeated evacuations (water aspirator). After 48 h, the hydrogen was replaced by argon and the reaction mixture was filtered through a celite pad. The filtrate was concentrated to give a diastereomeric mixture of esters **28** (18.0 g, 100%.). **28**: oil; TLC, Rf=0.21 (silica, 60% ether in

petroleum ether); IR (neat) ν_{max} 3480(OH), 2990, 2940, 2860, 1725(C=O), 1470, 1380, 920, 740, 705, 655 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46, 7.32 (2 x m, 5 H, aromatic), 5.52 (s, 1 H, C<u>H</u>Ar), 4.26-4.02 (m, 3 H, C<u>H</u>-O, $CH_3C\underline{H}_2O_2C$), 3.69-3.35 (m, 4 H, C<u>H</u>-O, $C\underline{H}_2O$), 3.14 (m, 2 H, C<u>H</u>-O), 2.72 (m, 1 H, C<u>H</u>CH_3), 2.19 (m, 2 H, $C\underline{H}_2$), 1.93-1.51 (m, 4 H, $C\underline{H}_2$), 1.29 (s, 3 H, $C\underline{H}_3$), 1.19 (m, 3 H, $CH_3C\underline{H}_2O_2C$), 1.04 (d, J=6.6 Hz, 3 H, $C\underline{H}_3CH$); HRMS, calcd for $C_{23}H_{33}O_7$ (M+H): 421.2226, found: 421.2246.

Diol 29.

A stirred solution of ester **28** (17.9 g, 42.6 mmol) in ether (140 mL) at 0 °C was treated with small portions of lithium aluminum hydride (1.62 g, 42.6 mmol) over 15 min. After 30 min, water (2 mL) and 3 N NaOH (2 mL) were added slowly. The reaction mixture was diluted with EtOAc (200 mL) and $MgSO_4$ (12 g) was added. After 10 min, the reaction mixture was filtered through a celite pad and the solids were washed well with EtOAc. Concentration of the filtrate gave the diol **29** (15.3 g, 95%). **29**: oil; TLC, Rf=0.23 (silica, 100% EtOAc); IR (neat) ν_{max} 3420(OH), 2970, 2860, 1455, 1370, 1110, 1090, 1060, 1020, 850, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46, 7.32 (2 x m, 5 H, aromatic), 5.50 (s, 1 H, C<u>H</u>Ar), 4.22 (m, 1 H, C<u>H</u>-O), 3.68 (m, 2 H, C<u>H</u>-O, $C\underline{H}_2O$), 3.60-3.33 (m, 4 H, C<u>H</u>-O), 3.23 (m, 2 H, C<u>H</u>-O, $C\underline{H}_2O$), 2.52 (m, 1 H, O<u>H</u>), 2.18 (m, 2 H, $C\underline{H}_2$), 1.93-1.42 (m, 5 H, $C\underline{H}_2$, $C\underline{H}CH_3$), 1.28 (s, 3 H, $C\underline{H}_3$), 0.94 (d, J=6.6 Hz, 3 H, $C\underline{H}_3CH$); HRMS, calcd for $C_{21}H_{31}O_6$ (M+H): 379.2120, found: 379.2141.

Silyl ether 30.

To a stirred solution of diol **29** (15.2 g, 40.2 mmol) and imidazole (4.1 g, 60.3 mmol) in DMF (80 mL) at 0 °C was added *tert*-butyldiphenylsilyl chloride (12.5 mL, 48.2 mmol) in one portion. After 20 min, the reaction mixture was quenched with MeOH (2 ml), diluted with ether (300 mL) and washed with water (200 mL). Drying ($MgSO_4$), concentration and flash chromatography (silica, 50→70% ether in petroleum ether) gave the silyl ether **30** (22.0 g, 89%). **30**: oil; TLC, Rf=0.68 (silica, 70% ether in petroleum ether); IR (neat) ν_{max} 3470(OH), 2960, 2870, 1470, 1430, 1390, 1295, 1195, 1100, 915, 825, 740, 705, 650, 620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.67, 7.46, 7.32 (3 x m, 15 H, aromatic), 5.51 (s, 1 H, C<u>H</u>Ar), 4.21 (m, 1 H, C<u>H</u>-O), 3.69-3.41 (m, 6 H, C<u>H</u>-O, $C\underline{H}_2O$), 3.14-2.95 (m, 2 H, C<u>H</u>-O), 2.19-1.38 (m, 7 H, $C\underline{H}_2$, $C\underline{H}CH_3$), 1.23 (s, 3 H, $C\underline{H}_3$), 1.09 (s, 9 H, $(C\underline{H}_3)_3CSi$), 0.94 (d, J=6.6 Hz, 3 H, $C\underline{H}_3CH$); HRMS, calcd for $C_{37}H_{49}O_6Si$ (M+H): 617.3298, found: 617.3355.

p-Methoxy benzyl ether 31.

To a stirred solution of alcohol **30** (21.9 g, 35.6 mmol) in THF (70 mL) at 50 °C was added potassium hydride (4.9 g, 42.7 mmol, 35% by wt. in mineral oil). After 40 min, p-methoxybenzyl chloride (6.3 mL, 46.3 mmol) was added dropwise over 1 min. After 10 min, MeOH (2 mL) was added and the reaction mixture was diluted with ether (120 mL), washed with water (100 mL), dried ($MgSO_4$) and concentrated. Flash chromatography (silica, 5→20% ether in petroleum ether) gave the benzyl ether **31** (22.0 g, 84%). **31**: oil; TLC, Rf=0.52 (silica, 30% ether in petroleum ether); IR (neat) ν_{max} 2950, 2860, 1610, 1590, 1515, 1465 1430, 1390, 1300, 1250, 1175, 1090, 1030, 910,

820, 735, 700, 650, 610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.67, 7.46, 7.32 (3 x m, 15 H, aromatic), 7.20, 6.82 (2 x m, 4 H, $C_6\underline{H}_4OMe$), 5.52 (s, 1 H, C<u>H</u>Ar), 4.50, 4.37 (2 x d, J=11.1 Hz, 2 x 1 H, C<u>H</u>Ar), 4.22 (m, 1 H, C<u>H</u>-O), 3.77 (s, 3 H, $OC\underline{H}_3$), 3.69-3.05 (m, 8 H, C<u>H</u>-O, $C\underline{H}_2O$), 2.30-1.29 (m, 7 H, $C\underline{H}_2$, $C\underline{H}CH_3$), 1.23 (s, 3 H, $C\underline{H}_3$), 1.05 (s, 9 H, $(C\underline{H}_3)_3CSi$), 0.96 (d, J=6.6 Hz, 3 H, $C\underline{H}_3CH$); HRMS, calcd for $C_{45}H_{57}O_7Si$ (M+H): 737.3873, found: 737.3807.

Diol 32.

Camphorsulfonic acid (1.7 g, 7.45 mmol) was added to a stirred solution of benzylidene **31** (21.9 g, 29.8 mmol) in MeOH (200 mL) at 0 °C. After 1 h, triethylamine (1.3 mL, 9 mmol) was added and the solvent evaporated. Flash chromatography (silica, 30→100% ether in petroleum ether) gave the diol **32** (16.6 g, 86%). **32**: oil; TLC, Rf=0.21 (silica, 100% ether); IR (neat) ν_{max} 3410(OH), 2900, 2860, 1615, 1590, 1515, 820, 745, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.65, 7.34 (m, 10 H, aromatic), 7.18, 6.80 (2 x m, 4 H, $C_6\underline{H}_4OMe$), 4.50, 4.37 (2 x d, J=11.1 Hz, 2 x 1 H, C<u>H</u>Ar), 3.77 (s, 3 H, $OC\underline{H}_3$), 3.74 (m, 3 H, C<u>H</u>-O, $C\underline{H}_2O$), 3.62-3.41 (m, 3 H, C<u>H</u>-O, $C\underline{H}_2O$), 3.19 (m, 2 H, C<u>H</u>-O), 2.92 (m, 1 H, $C\underline{H}_2$), 2.23 (m, 1 H, $C\underline{H}_2$), 1.94 (m, 4 H, $C\underline{H}_2$, $C\underline{H}CH_3$), 1.59-1.20 (m, 4 H, $C\underline{H}_2$, O<u>H</u>), 1.14 (s, 3 H, $C\underline{H}_3$), 1.02 (s, 9 H, $(C\underline{H}_3)_3CSi$), 0.98 (d, J=6.6 Hz, 3 H, $C\underline{H}_3CH$); HRMS, calcd for $C_{38}H_{56}NO_7Si$ ($M+NH_4$): 666.3826, found: 666.3781.

Bis-silyl ether 33.

To a stirred solution of diol **32** (16.5 g, 25.5 mmol) and imidazole (5.2 g, 76.5 mmol) in DMF (50 mL) at 25 °C was added *tert*-butyldimethylsilyl chloride (9.6 g, 63.8 mmol) in one portion. The reaction mixture was heated at 50 °C for 12 h. The reaction mixture was cooled and quenched with MeOH (5 mL), diluted with ether (300 mL) and washed with water (200 mL). Drying ($MgSO_4$), concentration and flash chromatography (silica, 10% ether in petroleum ether) gave the bis-silyl ether **33** (20.6 g, 92%). **33**: oil; TLC, Rf=0.78 (silica, 20% ether in petroleum ether); IR (neat) ν_{max} 2960, 2880, 1615, 1520, 1470, 1255, 1070, 940, 830, 780, 705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.65, 7.34 (m, 10 H, aromatic), 7.20, 6.82 (2 x m, 4 H, $C_6\underline{H}_4OMe$), 4.50, 4.37 (2 x d, J=11.1 Hz, 2 x 1 H, C<u>H</u>Ar), 3.77 (s, 3 H, $OC\underline{H}_3$), 3.71-2.86 (m, 9 H, C<u>H</u>-O, $C\underline{H}_2O$), 2.26 (m, 1 H, $C\underline{H}_2$), 2.07-1.38 (m, 6 H, $C\underline{H}_2$, $C\underline{H}CH_3$), 1.12 (d, J=6.6Hz, 3 H, $C\underline{H}_3CH$), 1.02 (s, 3 H, $C\underline{H}_3$), 0.87, 0.86, 0.85 (3 x s, 3 x 9 H, $(C\underline{H}_3)_3CSi$), 0.05, 0.03, 0.02, 0.01 (4 x s, 4 x 3 H, $C\underline{H}_3Si$); HRMS, calcd for $C_{50}H_{80}O_7Si_3Na$ (M+Na): 899.5110, found: 899.5227.

Alcohol 34.

Camphorsulfonic acid (0.8 g, 3.5 mmol) was added to a stirred solution of the silyl ether **33** (20.5 g, 23.4 mmol) in MeOH (200 mL) at 0 °C. After 1 h, triethylamine (0.6 mL, 4.2 mmol) was added and the solvent evaporated. Flash chromatography (silica, 20→50% ether in petroleum ether) gave the alcohol **34** (14.4 g, 81%). **34**: oil; TLC, Rf=0.53 (silica, 50% ether in petroleum ether); IR (neat) ν_{max} 3500 (OH), 2980, 2860, 1615, 1595, 1520, 1465, 1430, 1390, 1365, 1265, 1070, 840, 780, 740, 705, 615 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.65, 7.34 (m, 10 H, aromatic), 7.20, 6.82 (2 x m, 4 H, $C_6\underline{H}_4OMe$), 4.50, 4.37 (2 x d, J=11.1 Hz, 2 x 1 H, C<u>H</u>Ar), 3.81 (m, 1 H, C<u>H</u>-O), 3.78 (s, 3 H, $OC\underline{H}_3$), 3.70-2.92 (m,

8 H, C<u>H</u>-O, C<u>H</u>$_2$O), 2.26 (m, 1 H, C<u>H</u>$_2$), 2.07-1.38 (m, 7 H, C<u>H</u>$_2$, C<u>H</u>CH$_3$, O<u>H</u>), 1.12 (d, J=6.6Hz, 3 H, C<u>H</u>$_3$CH), 1.07 (s, 3 H, C<u>H</u>$_3$), 0.87, 0.86 (2 x s, 2 x 9 H, (C<u>H</u>$_3$)$_3$CSi), 0.05, 0.03 (2 x s, 2 x 3 H, C<u>H</u>$_3$Si); HRMS, calcd for $C_{44}H_{66}O_7Si_2Na$ (M+Na): 785.4245, found: 785.4298.

Methyl alcohol 36.

A solution of alcohol **34** (14.3 g, 18.8 mmol) in CH_2Cl_2 (120 mL) was added dropwise to a mixture of oxalyl chloride (2.5 mL, 28.2 mmol) and DMSO (2.7 mL, 37.6 mmol) in CH_2Cl_2 (80 mL) at -78 °C over 25 min. After 40 min, triethylamine (13.1 mL, 94 mmol) was added slowly and the cooling bath removed. When the reaction mixture reached 0 °C, it was diluted with ether (200 mL), washed with saturated aqueous ammonium chloride (300 mL), dried ($MgSO_4$) and concentrated. The crude aldehyde **35** (13 g, 90%) was taken to the next step without purification. A cooled (0 °C) solution of the aldehyde in THF (50 mL) was treated with methylmagnesium bromide (7.4 mL, 22.2 mmol, 3.0 M in THF) dropwise over 5 min. After 30 min, MeOH (2 mL) was added and the reaction mixture was diluted with ether (100 mL), washed with water (100 mL), dried ($MgSO_4$) and concentrated. Flash chromatography (silica, 30% ether in petroleum ether) gave the methyl alcohol **36** (11.9 g, 91%). **36**: oil; TLC, Rf=0.37 (silica, 30% ether in petroleum ether); IR (neat) ν_{max} 3500(OH), 2980, 2860, 1615, 1595, 1440, 1390, 1260, 1070, 830, 780, 740, 705, 615 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.65, 7.34 (m, 10 H, aromatic), 7.20, 6.82 (2 x m, 4 H, C$_6$<u>H</u>$_4$OMe), 4.50, 4.37 (2 x d, J=11.1 Hz, 2 x 1 H, C<u>H</u>Ar), 3.81 (m, 1 H, C<u>H</u>-O), 3.78 (s, 3 H, OC<u>H</u>$_3$), 3.70-2.92 (m, 7 H, C<u>H</u>-O, C<u>H</u>$_2$O), 2.26 (m, 1 H, C<u>H</u>$_2$), 2.07-1.38 (m, 7 H, C<u>H</u>$_2$, C<u>H</u>CH$_3$, O<u>H</u>), 1.12 (m, 2 x 3 H, C<u>H</u>$_3$CH), 1.07 (s, 3 H, C<u>H</u>$_3$), 0.87, 0.86 (2 x s, 2 x 9 H, (C<u>H</u>$_3$)$_3$CSi), 0.05, 0.03 (2 x s, 2 x 3 H, C<u>H</u>$_3$Si); HRMS, calcd for $C_{45}H_{68}O_7Si_2Na$ (M+Na): 799.4402, found: 799.4434.

Methyl ketone 37.

A solution of alcohol **36** (11.8 g, 15.2 mmol) in CH_2Cl_2 (120 mL) was added dropwise to a mixture of oxalyl chloride (2.0 mL, 22.8 mmol) and DMSO (2.2 mL, 30.4 mmol) in CH_2Cl_2 (80 mL) at -78 °C over 25 min. After 60 min, triethylamine (10.6 mL, 76 mmol) was added slowly and the cooling bath removed. When the reaction mixture reached 0 °C, it was diluted with ether (200 mL), washed with saturated aqueous ammonium chloride (300 mL), dried ($MgSO_4$) and concentrated. Flash chromatography (silica, 20% ether in petroleum ether) gave the methyl ketone **37** (10.4 g, 88%). **37**: oil; TLC, Rf=0.69 (silica, 30% ether in petroleum ether); IR (neat) ν_{max} 2970, 2860, 1735(C=O), 1615, 1590, 1520, 1470, 1430, 1370, 1305, 1255, 1100, 840, 780, 740, 705, 615 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.65, 7.34 (m, 10 H, aromatic), 7.20, 6.82 (2 x m, 4 H, C$_6$<u>H</u>$_4$OMe), 4.50, 4.37 (2 x d, J=11.1 Hz, 2 x 1 H, C<u>H</u>Ar), 3.83 (m, 1 H, C<u>H</u>-O), 3.78 (s, 3 H, OC<u>H</u>$_3$), 3.61-2.88 (m, 6 H, C<u>H</u>-O, C<u>H</u>$_2$O), 2.26 (m, 1 H, C<u>H</u>$_2$), 2.18 (s, 3 H, C<u>H</u>$_3$C=O), 2.16-1.38 (m, 6 H, C<u>H</u>$_2$, C<u>H</u>CH$_3$), 1.03 (s, 3 H, C<u>H</u>$_3$), 1.02, (s, 9 H, (C<u>H</u>$_3$)$_3$CSi), 0.97 (d, J=6.6Hz, 3 H, C<u>H</u>$_3$CH), 0.83 (s, 9 H, (C<u>H</u>$_3$)$_3$CSi), 0.05, 0.03 (2 x s, 2 x 3 H, C<u>H</u>$_3$Si); HRMS, calcd for $C_{45}H_{66}O_7Si_2Na$ (M+Na): 797.4245, found: 797.4317.

Alcohol 38.

To a stirred solution of methyl ketone **37** (9.5 g, 12.3 mmol) in THF (25 mL) at 0 °C was added dropwise tetrabutylammonium fluoride (15 mL, 15 mmol, 1.0 M in THF) over 10 min. After 20 min, the reaction mixture was diluted with ether (100 mL), washed with water (100 mL), dried ($MgSO_4$) and the solvent evaporated. Flash chromatography (silica, 30→70% ether in petroleum ether) gave the alcohol **38** (7.3 g, 90%). **38**: oil; TLC, Rf=0.64 (silica, 70% ether in petroleum ether); IR (neat) ν_{max} 3500(OH), 2960, 2860, 1720(C=O), 1615, 1590, 1520, 1430, 1260, 1110, 1085, 1040, 825, 730, 705, 615 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.65, 7.34 (m, 10 H, aromatic), 7.20, 6.82 (2 x m, 4 H, $C_6\underline{H}_4OMe$), 4.50, 4.37 (2 x d, J=11.1 Hz, 2 x 1 H, C<u>H</u>Ar), 3.78 (s, 3 H, $OC\underline{H}_3$), 3.72-2.84 (m, 7 H, C<u>H</u>-O, $C\underline{H}_2O$), 2.18 (s, 3 H, $C\underline{H}_3C{=}O$), 2.26-1.19 (m, 8 H, $C\underline{H}_2$, $C\underline{H}CH_3$, O<u>H</u>), 1.03 (s, 3 H, $C\underline{H}_3$), 1.02 (s, 9 H, $(C\underline{H}_3)_3CSi$), 0.97 (d, J=6.6Hz, 3 H, $C\underline{H}_3CH$); HRMS, calcd for $C_{39}H_{52}O_7SiNa$ (M+Na): 683.3380, found: 683.3301.

Bromo ester 39.

A solution of alcohol **38** (7.2 g, 10.9 mmol), bromoacetic acid (1.7 g, 12 mmol) and dimethylamino pyridine (0.27 g, 2.2 mmol) in CH_2Cl_2 (25 mL) at 25 °C was treated with 1,3-dicyclohexylcarbodiimide (3.4 g, 16.4 mmol) in one portion. After 12 h, the reaction mixture was diluted with ether (50 mL) and filtered through a celite pad. Concentration and flash chromatography (silica, 30% ether in petroleum ether) gave bromoester **39** (7.6 g, 89%). **39**: oil; TLC, Rf=0.78 (silica, 70% ether in petroleum ether); IR (neat) ν_{max} 2950, 1740(C=O), 1615, 1515, 910, 830, 740, 705, 610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.65, 7.34 (m, 10 H, aromatic), 7.20, 6.82 (2 x m, 4 H, $C_6\underline{H}_4OMe$), 4.90 (m, 1 H, $C\underline{H}O_2C$), 4.50, 4.37 (2 x d, J=11.1 Hz, 2 x 1 H, C<u>H</u>Ar), 3.83 (m, 1 H, C<u>H</u>-O), 3.78 (s, 3 H, $OC\underline{H}_3$), 3.75 (s, 2 H, $C\underline{H}_2Br$), 3.69-2.92 (m, 5 H, C<u>H</u>-O, $C\underline{H}_2O$), 2.18 (s, 3 H, $C\underline{H}_3C{=}O$), 2.26-1.21 (m, 7 H, $C\underline{H}_2$, $C\underline{H}CH_3$), 1.03 (s, 3 H, $C\underline{H}_3$), 1.02 (s, 9 H, $(C\underline{H}_3)_3CSi$), 0.97 (d, J=6.6Hz, 3 H, $C\underline{H}_3CH$); HRMS, calcd for $C_{41}H_{53}O_8BrSiNa$ (M+Na): 803.2591, found: 803.2683.

Phosphonate 5.

A stirred solution of bromoester **39** (7.5 g, 9.6 mmol) and trimethyl phosphite (22.6 mL, 192 mmol) was heated at 70 °C for 3 h. Excess trimethyl phosphite was removed at reduced pressure and the resulting phosphonate **5** (7.8 g, 100%) was used without purification. **5**: oil; TLC, Rf=0.32 (silica, 100% EtOAc); IR (neat) ν_{max} 2950, 2920, 2850, 1740(C=O), 1610, 1585, 1510, 1460, 1430, 1385, 1360, 1250, 1180, 1050, 820, 740, 700, 610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.65, 7.34 (m, 10 H, aromatic), 7.20, 6.82 (2 x m, 4 H, $C_6\underline{H}_4OMe$), 4.91 (m, 1 H, $C\underline{H}O_2C$), 4.50, 4.37 (2 x d, J=11.1 Hz, 2 x 1 H, C<u>H</u>Ar), 3.83 (m, 1 H, C<u>H</u>-O), 3.79 (s, 3 H, $OC\underline{H}_3$), 3.76, 3.75 (2 x s, 2 x 3 H, $(C\underline{H}_3O)_2P{=}O$), 3.75 (s, 2 H, $C\underline{H}_2P{=}O$), 3.74-2.86 (m, 5 H, C<u>H</u>-O, $C\underline{H}_2O$), 2.18 (s, 3 H, $C\underline{H}_3C{=}O$), 2.26-1.20 (m, 7 H, $C\underline{H}_2$, $C\underline{H}CH_3$), 1.03 (s, 3 H, $C\underline{H}_3$), 1.02 (s, 9 H, $(C\underline{H}_3)_3CSi$), 0.97 (d, J=6.6Hz, 3 H, $C\underline{H}_3CH$); HRMS, calcd for $C_{43}H_{59}O_{11}PSiNa$ (M+Na): 833.3462, found: 833.3441.

Lactone 40.

A stirred solution of phosphonate **5** (7.7 g, 9.5 mmol) and dry lithium chloride (0.81 g, 19 mmol) in CH_3CN (100 mL) at 25 °C was treated dropwise with diisopropylethyl amine (3.3 mL, 19 mmol) over 5 min. After 2 h, the reaction mixture was diluted with ether (200 mL), washed with water (100 mL), dried ($MgSO_4$) and concentrated. Flash chromatography (silica, 50% ether in petroleum ether) gave the lactone **40** (5.9 g, 92%). **40**: oil; TLC, Rf=0.52 (silica, 30% EtOAc in petroleum ether); IR (neat) ν_{max} 2960, 2860, 1730(C=O), 1620, 1590, 1520, 1470, 1430, 1385, 1310, 1250, 1080, 910, 825, 740, 705, 615 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.65, 7.34 (m, 10 H, aromatic), 7.20, 6.82 (2 x m, 4 H, $C_6\underline{H}_4OMe$), 5.71 (bs, 1 H, C$\underline{H}$=CMe), 4.50, 4.37 (2 x d, J=11.1 Hz, 2 x 1 H, C$\underline{H}$Ar), 4.21 (m, 1 H, C$\underline{H}O_2C$), 3.94 (m, 1 H, C$\underline{H}$-O), 3.79 (s, 3 H, $OC\underline{H}_3$), 3.58-2.94 (m, 5 H, C$\underline{H}$-O, $C\underline{H}_2O$), 2.32 (s, 1 H, $C\underline{H}_2$), 2.14 (m, 1 H, $C\underline{H}_2$), 1.98 (bs, 3 H, $C\underline{H}_3C$=C), 1.82-1.16 (m, 5 H, $C\underline{H}_2$, $C\underline{H}CH_3$), 1.03 (s, 3 H, $C\underline{H}_3$), 1.02 (s, 9 H, $(C\underline{H}_3)_3CSi$), 0.97 (d, J=6.6Hz, 3 H, $C\underline{H}_3CH$); HRMS, calcd for $C_{41}H_{52}O_7SiNa$ (M+Na): 707.3380, found: 707.3336.

Lactol 41.

DIBAL (12.7 mL, 12.7 mmol, 1.0 M in CH_2Cl_2) was added dropwise to a stirred solution of lactone **40** (5.8 g, 8.5 mmol) in CH_2Cl_2 (25 mL) at -78 °C over 10 min. After 15 min, the mixture was quenched with MeOH (1 mL), the cooling bath removed, and the reaction mixture was allowed to reach room temperature. The mixture was diluted with EtOAc (100 mL) and washed with aqueous saturated sodium potassium tartrate (150 mL). The aqueous phase was extracted with EtOAc (2 x 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to give the lactol **41** (5.8 g, 100%). **41**: oil; TLC, Rf=0.49 (silica, 30% EtOAc in petroleum ether); IR (neat) ν_{max} 3420(OH), 2960, 2860, 1680, 1615, 1590, 1520, 1465, 1430, 1385, 1305, 1255, 1180, 1100, 910, 825, 740, 700, 610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.65, 7.34 (m, 10 H, aromatic), 7.20, 6.82 (2 x m, 4 H, $C_6\underline{H}_4OMe$), 5.46 (bs, 1 H, C$\underline{H}$=CMe), 5.32 (m, 1 H, C$\underline{H}$(OH)C-O), 4.50, 4.37 (2 x d, J=11.1 Hz, 2 x 1 H, C$\underline{H}$Ar), 3.83 (m, 1 H, C$\underline{H}$-O), 3.79 (s, 3 H, $OC\underline{H}_3$), 3.70-2.94 (m, 6 H, C$\underline{H}$-O, $C\underline{H}_2O$), 2.32 (m, 1 H, $C\underline{H}_2$), 1.92 (m, 2 H, $C\underline{H}_2$, $C\underline{H}CH_3$), 1.73 (bs, 3 H, $C\underline{H}_3C$=C), 1.67-1.19 (m, 5 H, $C\underline{H}_2$), 1.03 (s, 3 H, $C\underline{H}_3$), 1.02 (s, 9 H, $(C\underline{H}_3)_3CSi$), 0.97 (d, J=6.6Hz, 3 H, $C\underline{H}_3CH$); HRMS, calcd for $C_{41}H_{54}O_7SiNa$ (M+Na): 709.3536, found: 709.3509.

Tricycle 42.

A stirred solution of lactol **41** (5.7 g, 8.3 mmol) and triethylsilane (6.6 mL, 41.5 mmol) in CH_2Cl_2 (30 mL) at -10 °C was treated with borontrifluoride etherate (1.0 mL, 8.3 mmol) dropwise over 5 min. After 20 min, triethylamine (1.4 mL, 10.0 mmol) was added, the reaction mixture was diluted with ether (80 mL), washed with water (50 mL), dried ($MgSO_4$) and concentrated. Flash chromatography (silica, 20% ether in petroleum ether) gave the tricycle **42** (5.0 g, 90%). **42**: oil; TLC, Rf=0.57 (silica, 30% ether in petroleum ether); IR (neat) ν_{max} 2960, 2860, 1680, 1615, 1590, 1520, 1465, 1430, 1385, 1305, 1255, 1180, 1100, 910, 825, 740, 700, 610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.65, 7.34 (m, 10 H, aromatic), 7.20, 6.82 (2 x m, 4 H, $C_6\underline{H}_4OMe$), 5.33 (bs, 1 H, C$\underline{H}$=CMe), 4.50, 4.37 (2 x d, J=11.1 Hz, 2 x 1 H, C$\underline{H}$Ar), 4.18 (m, 2 H, C$\underline{H}$(O)C=C), 3.94 (m, 1 H, C$\underline{H}$-O), 3.79 (s, 3 H, $OC\underline{H}_3$), 3.58-3.09

(m, 6 H, C<u>H</u>-O, C<u>H</u>$_2$O), 2.36 (m, 1 H, C<u>H</u>$_2$), 2.07 (m, 1 H, C<u>H</u>$_2$), 1.91-1.40 (m, 5 H, C<u>H</u>$_2$, C<u>H</u>CH$_3$), 1.69 (s, 3 H, C<u>H</u>$_3$C=C), 1.20 (s, 3 H, C<u>H</u>$_3$), 1.04 (s, 9 H, (C<u>H</u>$_3$)$_3$CSi), 0.90 (d, J=6.6Hz, 3 H, C<u>H</u>$_3$CH); HRMS, calcd for $C_{41}H_{55}O_6Si$ (M+H): 671.3768, found: 671.3659.

Alcohol 43.

To a stirred solution of tricycle **42** (4.9 g, 7.3 mmol) in THF (20 mL) at 45 °C was added dropwise tetrabutylammonium fluoride (11 mL, 11 mmol, 1.0 M in THF) over 1 min. After 2.5 h, the reaction mixture was diluted with ether (50 mL), washed with water (50 mL), dried ($MgSO_4$) and the solvent evaporated. Flash chromatography (silica, 50→80% ether in petroleum ether) gave the alcohol **43** (2.9 g, 93%). **43**: oil; TLC, Rf=0.47 (silica, 100% ether); IR (neat) ν_{max} 3450(OH), 2940, 2865, 1610, 1520, 1465, 1380, 1300, 1240, 1000, 980, 820, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.20, 6.82 (2 x m, 4 H, C$_6$<u>H</u>$_4$OMe), 5.33 (bs, 1 H, C<u>H</u>=CMe), 4.50, 4.37 (2 x d, J=11.1 Hz, 2 x 1 H, C<u>H</u>Ar), 4.18 (m, 2 H, C<u>H</u>$_2$(O)C=C), 3.94 (m, 1 H, C<u>H</u>-O), 3.79 (s, 3 H, OC<u>H</u>$_3$), 3.58-3.12 (m, 6 H, C<u>H</u>-O, C<u>H</u>$_2$O), 2.36 (m, 1 H, C<u>H</u>$_2$), 2.07 (m, 1 H, C<u>H</u>$_2$), 1.91-1.40 (m, 6 H, C<u>H</u>$_2$, C<u>H</u>CH$_3$, O<u>H</u>), 1.69 (s, 3 H, C<u>H</u>$_3$C=C), 1.20 (s, 3 H, C<u>H</u>$_3$), 0.90 (d, J=6.6Hz, 3 H, C<u>H</u>$_3$CH); HRMS, calcd for $C_{25}H_{37}O_6$ (M+H): 433.2590, found: 433.2578.

Acid 44.

A stirred solution of alcohol **43** (2.5 g, 5.8 mmol) in acetone (20 mL) at -15 °C was treated with Jones reagent (3.6 mL, prepared from 11 g of CrO_3, 9.6 mL of conc. H_2SO_4 and 25 mL of H_2O) dropwise over 5 min. After 20 min, isopropyl alcohol (2 mL) was added slowly, the reaction mixture was diluted with ether (100 mL), washed with water (3 x 50 mL), dried ($MgSO_4$) and concentrated to give the free acid **44** (2.2 g, 84%). **44**: oil; TLC, Rf=0.74 streak (silica, 50% EtOAc in petroleum ether); IR (neat) ν_{max} 3500-2600, 1740, 1710, 1615, 1520, 1480, 1385, 1305, 1255, 1175, 1100, 1040, 825, 710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.20, 6.82 (2 x m, 4 H, C$_6$<u>H</u>$_4$OMe), 5.34 (bs, 1 H, C<u>H</u>=CMe), 4.50, 4.37 (2 x d, J=11.1 Hz, 2 x 1 H, C<u>H</u>Ar), 4.25, 4.14 (2 x bd, J=16.0 Hz, 2 x 1 H, C<u>H</u>$_2$(O)C=C), 3.94 (m, 1 H, C<u>H</u>-O), 3.79 (s, 3 H, OC<u>H</u>$_3$), 3.40-3.11 (m, 4 H, C<u>H</u>-O, C<u>H</u>$_2$O), 2.69 (m, 1 H, C<u>H</u>CH$_3$), 2.40-2.21 (m, 2 H, C<u>H</u>$_2$), 2.15-1.35 (m, 4 H, C<u>H</u>$_2$), 1.70 (s, 3 H, C<u>H</u>$_3$C=C), 1.20 (s, 3 H, C<u>H</u>$_3$), 1.16 (d, J=6.6Hz, 3 H, C<u>H</u>$_3$CH); HRMS, calcd for $C_{25}H_{35}O_7$ (M+H): 447.2383, found: 447.2328.

Ester 45.

A stirred solution of acid **44** (2.1 g, 4.7 mmol), 2-(trimethylsilyl)ethanol (0.8 mL, 5.6 mmol), dimethylamino pyridine (0.17 g, 1.4 mmol) and camphorsulfonic acid (0.33 g, 1.4 mmol) in CH_2Cl_2 (10 mL) at 25 °C was treated with 1,3-dicyclohexyl carbodiimide (1.5 g, 7.1 mmol) in one portion. After 12 h, ether (20 mL) was added and the reaction mixture was filtered through a celite pad. Concentration and flash chromatography (silica, 20% ether in petroleum ether) gave ester **45** (2.3 g, 89%). **45**: oil; TLC, Rf=0.68 (silica, 50% ether in petroleum ether); IR (neat) ν_{max} 2960, 2880, 1730, 1520, 1480, 1385, 1305, 1255, 1175, 1100, 1040, 825, 710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.20, 6.82 (2 x m, 4 H, C$_6$<u>H</u>$_4$OMe), 5.34 (bs, 1H, C<u>H</u>=CMe), 4.50, 4.37 (2 x d, J=11.1 Hz, 2 x 1 H, C<u>H</u>Ar),

4.13 (m, 4 H, C<u>H</u>$_2$(O)C=C, C<u>H</u>$_2$O$_2$C), 3.92 (m, 1 H, C<u>H</u>-O), 3.79 (s, 3 H, OC<u>H</u>$_3$), 3.36-3.04 (m, 4 H, C<u>H</u>-O, C<u>H</u>$_2$O), 2.64 (m, 1 H, C<u>H</u>CH$_3$), 2.43-1.36 (m, 6 H, C<u>H</u>$_2$), 1.70 (bs, 3 H, C<u>H</u>$_3$C=C), 1.20 (s, 3 H, C<u>H</u>$_3$), 1.16 (d, J=6.6Hz, 3 H, C<u>H</u>$_3$CH), 0.94 (m, 2 H, C<u>H</u>$_2$Si(CH$_3$)$_3$), 0.06 (s, 9 H, (C<u>H</u>$_3$)$_3$Si); HRMS, calcd for $C_{30}H_{47}O_7Si$ (M+H): 547.3091, found: 547.3062.

ABC system 2.

A stirred solution of ester **45** (2.2 g, 4.0 mmol) in CH_2Cl_2 (10 mL) and H_2O (3 mL) was treated with DDQ (1.2 g, 5.2 mmol) at 25 °C. After 40 min, ether (50 mL) was added and the reaction mixture was washed with saturated aqueous sodium bicarbonate solution (4 x 50 mL), dried ($MgSO_4$) and concentrated. Flash chromatography (silica, 30→70% ether in petroleum ether) gave the alcohol **2** (1.45 g, 85%). **2**: oil; TLC, Rf=0.27 (silica, 50% ether in petroleum ether); IR (neat) ν_{max} 3460(OH), 2960, 2880, 1730, 1540, 1490, 830, 770, 695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.34 (bs, 1 H, C<u>H</u>=CMe), 4.18 (m, 4 H, C<u>H</u>$_2$(O)C=C, C<u>H</u>$_2$O$_2$C), 3.93 (m, 1 H, C<u>H</u>-O), 3.51 (m, 1 H, C<u>H</u>-O), 3.21-3.01 (m, 3 H, C<u>H</u>-O), 2.74 (m, 2 H, C<u>H</u>$_2$CO$_2$), 2.24-1.41 (m, 8 H, C<u>H</u>$_2$, C<u>H</u>CH$_3$, O<u>H</u>), 1.70 (bs, 3 H, C<u>H</u>$_3$C=C), 1.21 (s, 3 H, C<u>H</u>$_3$), 1.17 (m, 3 H, C<u>H</u>$_3$CH), 0.94 (m, 2 H, C<u>H</u>$_2$Si(CH$_3$)$_3$), 0.06 (s, 9 H, (C<u>H</u>$_3$)$_3$Si); HRMS, calcd for $C_{22}H_{41}O_6Si$ (M+H): 429.2672, found: 429.2646.

Ketone 12.

A solution of alcohol **8** (45 g, 146.6 mmol) in CH_2Cl_2 (550 mL) was added dropwise to a mixture of oxalyl chloride (19.2 mL, 220 mmol) and DMSO (20.7 mL, 293 mmol) in CH_2Cl_2 (200 mL) at -78 °C over 25 min. After 60 min, triethylamine (102 mL, 730 mmol) was added slowly and the cooling bath removed. When the reaction mixture reached 0 °C, it was diluted with ether (1 L), washed with saturated aqueous ammonium chloride (2 x 450 mL), dried ($MgSO_4$) and concentrated to give the crude ketone **12** (39.8 g, 89%) which was used without purification. **12**: oil; TLC, Rf=0.78 streak (silica, 70% ether in petroleum ether); IR ($CDCl_3$) ν_{max} 3600, 3450, 2980, 2870, 1700(C=O), 1650, 1460, 1385, 1370, 1280, 1230, 1115, 1075, 1030, 980, 910, 650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.45, 7.34 (2 x m, 5 H, aromatic), 6.83 (dt, J=7.3, 1.4 Hz, 1 H, C<u>H</u>=C), 5.96 (s, 1 H, C<u>H</u>Ar), 4.55 (dd, J= Hz, 1 H, C<u>H</u>(O)C=O), 4.43 (s, 2 H, C<u>H</u>$_2$(O)C=O), 4.17 (q, J=7.2 Hz, 2 H, CH$_3$C<u>H</u>$_2$O$_2$C), 2.84 (m, 1 H, C<u>H</u>$_2$C=C), 2.69 (m, 1 H, C<u>H</u>$_2$C=C), 1.86 (d, J=1.4 Hz, 3 H, C<u>H</u>$_3$C=C), 1.27 (t, J=7.2 Hz, 3 H, C<u>H</u>$_3$CH$_2$O$_2$C); HRMS, calcd for $C_{17}H_{21}O_5$ (M+H): 305.1389, found: 305.1356.

Methyl alcohol 46.

A stirred solution of ketone **12** (39.7 g, 130.2 mmol) at -20 °C was treated dropwise with trimethylaluminum (78 mL, 156 mmol, 2.0 M in hexanes) over 15 min. After 2 h, MeOH (4 mL) was added and the cooling bath removed. Work up was carried out as for **41**. Flash chromatography (silica, 70% ether in petroleum ether) gave methyl alcohol **46** (35 g, 84%). **46**: oil; TLC, Rf=0.31 (silica, 70% ether in petroleum ether); IR ($CDCl_3$) ν_{max} 3470(OH), 2980, 2870, 1715(C=O), 1655, 1460, 1375, 1280, 1105, 1030, 750, 720, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.45, 7.34 (2 x m, 5 H, aromatic), 6.85 (dt, J=7.3, 1.4 Hz, 1 H, C<u>H</u>=C), 5.48 (s, 1 H, C<u>H</u>Ar), 4.17 (q, J=7.2 Hz, 2 H, CH$_3$C<u>H</u>$_2$O$_2$C), 3.88 (d, J=10.7 Hz, 1 H, C<u>H</u>-O), 3.67 (m, 2 H, C<u>H</u>-O), 2.61 (m, 1 H, C<u>H</u>$_2$C=C), 2.39

(m, 1 H, C<u>H</u>$_2$C=C), 1.85 (d, J=1.4 Hz, 3 H, C<u>H</u>$_3$C=C), 1.70 (s, 1 H, O<u>H</u>), 1.42 (s, 3 H, C<u>H</u>$_3$), 1.27 (t, J=7.2 Hz, 3 H, C<u>H</u>$_3$CH$_2$O$_2$C); HRMS, calcd for $C_{18}H_{25}O_5$ (M+H): 321.1702, found: 321.1646.

Silyl ether 47.

A stirred solution of alcohol **46** (34.9 g, 109.1 mmol) in CH_2Cl_2 (200 mL) at 25 °C was treated dropwise with 1-(trimethylsilyl)imidazole (20.8 mL, 141.7 mmol) over 5 min. After 15 min, MeOH (4 mL) was added and the solvent evaporated to give the crude silyl ether **47** (42.7 g, 100%) that was used without purification. **47**: oil; TLC, Rf=0.67 (silica, 20% ether in petroleum ether); IR ($CDCl_3$) ν_{max} 2980, 2880, 1715(C=O), 1650, 1455, 1370, 1265, 1100, 1030, 845, 750, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.45, 7.34 (2 x m, 5 H, aromatic), 6.85 (dt, J=7.3, 1.4 Hz, 1 H, C<u>H</u>=C), 5.48 (s, 1 H, C<u>H</u>Ar), 4.17 (q, J=7.2 Hz, 2 H, CH$_3$C<u>H</u>$_2$O$_2$C), 3.88 (d, J=10.7 Hz, 1 H, C<u>H</u>-O), 3.65 (m, 2 H, C<u>H</u>-O), 2.62 (m, 1 H, C<u>H</u>$_2$C=C), 2.39 (m, 1 H, C<u>H</u>$_2$C=C), 1.85 (d, J=1.4 Hz, 3 H, C<u>H</u>$_3$C=C), 1.42 (s, 3 H, C<u>H</u>$_3$), 1.27 (t, J=7.2 Hz, 3 H, C<u>H</u>$_3$CH$_2$O$_2$C), 0.12 (s, 9 H, (C<u>H</u>$_3$)$_3$Si); HRMS, calcd for $C_{21}H_{33}O_5Si$ (M+H): 393.2097, found: 393.2101.

Alcohol 48.

DIBAL (240 mL, 240 mmol, 1.0 M in CH_2Cl_2) was added dropwise to a stirred solution of ester **47** (42.6 g, 108.7 mmol) in CH_2Cl_2 (120 mL) at -78 °C over 20 min. After 15 min, the mixture was quenched with MeOH (3 mL), the cooling bath removed, and the reaction mixture was allowed to reach room temperature. The mixture was diluted with EtOAc (400 mL) and washed with aqueous saturated sodium potassium tartrate (2 x 150 mL). The aqueous phase was extracted with EtOAc (2 x 500 mL). The combined organic layers were dried ($MgSO_4$), concentrated and subjected to flash chromatography (silica, 30% ether in petroleum ether) to give the alcohol **48** (36.5 g, 96%). **48**: oil; TLC, Rf=0.47 (silica, 50% ether in petroleum ether); IR ($CDCl_3$) ν_{max} 3380(OH), 2970, 2930, 2860, 1405, 1255, 1100, 1030, 845, 755, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.45, 7.34 (2 x m, 5 H, aromatic), 5.56 (dt, J=7.3, 1.4 Hz, 1 H, C<u>H</u>=C), 5.46 (s, 1 H, C<u>H</u>Ar), 3.98 (bs, 2 H, C<u>H</u>$_2$OH), 3.85 (d, J=10.7 Hz, 1 H, C<u>H</u>-O), 3.60 (m, 2 H, C<u>H</u>-O), 2.50 (m, 1 H, C<u>H</u>$_2$C=C), 2.22 (m, 1 H, C<u>H</u>$_2$C=C), 1.91 (s, 1 H, O<u>H</u>), 1.68 (s, 3 H, C<u>H</u>$_3$C=C), 1.40 (s, 3 H, C<u>H</u>$_3$), 0.12 (s, 9 H, (C<u>H</u>$_3$)$_3$Si); HRMS, calcd for $C_{19}H_{31}O_4Si$ (M+H): 351.1991, found: 351.1990.

Epoxide 49.

A solution of alcohol **48** (36.4 g, 104 mmol) in CH_2Cl_2 (280 mL) was added dropwise over 20 min to a cooled (-25 °C) mixture of diethyl-D-tartrate (4.5 mL, 26 mmol), 4 Å molecular sieves (11 g), and titanium (IV) isopropoxide (6.5 mL, 20.8 mmol) in CH_2Cl_2 (90 mL). After 30 min, *tert*-butylhydroperoxide (52 mL, 156 mmol, 3.0 M in 2,2,4-trimethylpentane) was added and the reaction mixture was stored at -20 °C for 14 h. Cooling was stopped and the reaction mixture was filtered. The filtrate was diluted with EtOAc (400 mL), washed with saturated aqueous sodium sulfate (2 x 200 mL), dried ($MgSO_4$) and filtered through a celite pad. The filtrate was concentrated and subjected to flash chromatography (silica, 30% ether in petroleum ether) to give the epoxide **49** (33.9 g, 89%). **49**: oil; TLC, Rf=0.42 (silica, 50% ether in petroleum ether); IR ($CDCl_3$) ν_{max}

3440(OH), 2950, 2930, 2850, 1450, 1385, 1310, 1250, 1155, 1110, 1025, 980, 860, 840, 750, 695, 655 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46, 7.33 (2 x m, 5 H, aromatic), 5.50 (s, 1 H, C<u>H</u>Ar), 3.93 (d, J=10.5 Hz, 1 H, C<u>H</u>-O), 3.66 (m, 4 H, C<u>H</u>-O, C<u>H_2</u>O), 3.28 (t, J=6.2 Hz, 1 H, H-epox.), 1.90 (m, 2 H, C<u>H_2</u>), 1.70 (bs, 1 H, O<u>H</u>), 1.42 (s, 3 H, CH_3-epox.), 1.30 (s, 3 H, C<u>H_3</u>), 0.12 (s, 9 H, (C<u>H_3</u>)$_3$Si); HRMS, calcd for $C_{19}H_{29}O_5Si$ (M-H): 365.1784, found: 365.1791.

Olefin 51.

To a stirred mixture of alcohol **49** (33.8 g, 92.3 mmol), dry DMSO (90 mL) and triethylamine (64 mL, 462 mmol) in CH_2Cl_2 (370 mL) at 0 °C was added sulfur trioxide-pyridine complex (44.0 g, 277 mmol) in four portions. After 2 h, the reaction mixture was diluted with ether (500 mL), washed with saturated aqueous ammonium chloride solution (2 x 400 mL), dried ($MgSO_4$) and concentrated to give the epoxy aldehyde **50** (31.6 g, 93%) which was used directly. To a stirred solution of methyl triphenylphosphonium bromide (46.5 g, 130.2 mmol) in THF (50 mL) at 0 °C was added dropwise sodium bis(trimethylsilyl)amide (108.5 mL, 108.5 mmol, 1.0 M in THF) over 20 min. After stirring for 10 min, the bright yellow ylide was treated with the crude aldehyde **50** (31.6 g, 86.8 mmol) in THF (280 mL) dropwise over 20 min. After 35 min, the reaction mixture was quenched with acetone (5 mL), diluted with ether (500 mL), washed with water (400 mL), dried ($MgSO_4$) and concentrated. The residue was triturated with 25% ether in petroleum ether, followed by filtration to remove triphenylphosphonium oxide. After solvent removal and flash chromatography (silica, 5→10% ether in petroleum ether), the olefin **51** was obtained (26.7 g, 88%). **51**: oil; TLC, Rf=0.72 (silica, 20% ether in petroleum ether); IR (neat) ν_{max} 2960, 2920, 2860, 1460, 1390, 1255, 1065, 1015, 925, 840, 755, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46, 7.33 (2 x m, 5 H, aromatic), 5.58 (dd, J=17.4, 10.6 Hz, 1 H, C<u>H</u>=CH_2), 5.50 (s, 1 H, C<u>H</u>Ar), 5.34 (dd, J=17.4, 1.1 Hz, 1 H, C<u>H_2</u>=CH), 5.18 (dd, J=10.6, 1.1 Hz, 1 H, C<u>H_2</u>=CH), 3.94 (d, J=10.0 Hz, 1 H, C<u>H</u>-O), 3.64 (m, 2 H, C<u>H</u>-O), 3.17 (t, J=6.2 Hz, 1 H, H-epox.), 1.91 (m, 2 H, C<u>H_2</u>), 1.44 (s, 3 H, CH_3-epox.), 1.42 (s, 3 H, C<u>H_3</u>), 0.12 (s, 9 H, (C<u>H_3</u>)$_3$Si); HRMS, calcd for $C_{20}H_{31}O_4Si$ (M+H): 363.1991, found: 363.2019.

Alcohol 11.

To a stirred solution of olefin **51** (26.6 g, 73.5 mmol) in THF (130 mL) at 25 °C was added dropwise tetrabutylammonium fluoride (110 mL, 110.0 mmol, 1.0 M in THF) over 10 min. After 20 min, the reaction mixture was diluted with ether (250 mL), washed with water (200 mL), dried ($MgSO_4$) and the solvent evaporated. Flash chromatography (silica, 30→70% ether in petroleum ether) gave the epoxy alcohol **11** (20.2 g, 95%). **11**: oil; TLC, Rf=0.32 (silica, 70% ether in petroleum ether); IR (neat) ν_{max} 3310, 3060, 2970, 2860, 1590, 1440, 1310, 1180, 1100, 1030, 990, 920, 740, 720, 700, 640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46, 7.33 (2 x m, 5 H, aromatic), 5.63 (dd, J=17.4, 10.6 Hz, 1 H, C<u>H</u>=CH_2), 5.49 (s, 1 H, C<u>H</u>Ar), 5.30 (dd, J=17.4, 1.1 Hz, 1 H, C<u>H_2</u>=CH), 5.16 (dd, J=10.6, 1.1 Hz, 1 H, C<u>H_2</u>=CH), 3.87 (d, J=10.0 Hz, 1 H, C<u>H</u>-O), 3.74 (dd, J=8.7, 3.7 Hz, 1 H, C<u>H</u>-O), 3.66 (d, J=10.5 Hz, 1 H, C<u>H_2</u>O), 3.08 (t, J=6.2 Hz, 1 H, H-epox.), 1.99-1.85 (m, 3 H, C<u>H_2</u>, O<u>H</u>), 1.40 (s, 3 H, CH_3-epox.), 1.39 (s, 3 H, C<u>H_3</u>); HRMS, calcd for $C_{17}H_{23}O_4$ (M+H): 291.1596, found: 291.1604.

Pyran 52.

A solution of epoxide **11** (20.1 g, 69.3 mmol) in CH_2Cl_2 (650 mL) at 0 °C was treated with pyridinium p-toluenesulfonate (13.9 g, 55.4 mmol) in one portion. After 12 h, triethylamine (9.3 mL) was added and the solvent evaporated. Flash chromatography (silica, 70% ether in petroleum ether) gave the cyclized product **52** (19 g, 94%). **52**: solid; m.p. 86-88 °C; TLC, Rf=0.36 (silica, 70% ether in petroleum ether); IR (neat) ν_{max} 3460(OH), 2980, 2860, 1445, 1385, 755, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46, 7.33 (2 x m, 5 H, aromatic), 5.89 (dd, J=17.4, 10.6 Hz, 1 H, C<u>H</u>=CH_2), 5.56 (s, 1 H, C<u>H</u>Ar), 5.35 (dd, J=17.4, 1.1 Hz, 1 H, C<u>H</u>$_2$=CH), 5.15 (dd, J=10.6, 1.1 Hz, 1 H, C<u>H</u>$_2$=CH), 3.91 (d, J=10.0 Hz, 1 H, C<u>H</u>-O), 3.74-3.48 (m, 3 H, C<u>H</u>-O, C<u>H</u>$_2$O), 2.11 (m, 1 H, C<u>H</u>$_2$), 1.95 (q, J=11.5 Hz, 1 H, C<u>H</u>$_2$), 1.79 (d, J=5.1 Hz, 1 H, O<u>H</u>), 1.57 (s, 3 H, C<u>H</u>$_3$), 1.40 (s, 3 H, C<u>H</u>$_3$); HRMS, calcd for $C_{17}H_{23}O_4$ (M+H): 291.1596, found: 291.1587.

Silyl ether 53.

To a stirred solution of **52** (18.9 g, 65.2 mmol) and imidazole (6.7 g, 97.8 mmol) in DMF (130 mL) at 25 °C was added *tert*-butyldimethylsilyl chloride (12.8 g, 84.8 mmol) in one portion. The reaction mixture was heated at 50 °C for 12 h. The reaction mixture was cooled and quenched with MeOH (5 mL), diluted with ether (300 mL) and washed with water (240 mL). Drying ($MgSO_4$), concentration and flash chromatography (silica, 10% ether in petroleum ether) gave the silyl ether **53** (25 g, 95%). **53**: solid; m.p. 91 °C; TLC, Rf=0.64 (silica, 20% ether in petroleum ether); IR (neat) ν_{max} 2950, 2850, 1470, 1375, 1255, 1095, 855, 835, 775, 755, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46, 7.33 (2 x m, 5 H, aromatic), 5.89 (dd, J=17.4, 10.6 Hz, 1 H, C<u>H</u>=CH_2), 5.51 (s, 1 H, C<u>H</u>Ar), 5.37 (dd, J=17.4, 1.1 Hz, 1 H, C<u>H</u>$_2$=CH), 5.19 (dd, J=10.6, 1.1 Hz, 1 H, C<u>H</u>$_2$=CH), 3.92-3.70 (m, 2 H, C<u>H</u>-O), 3.58 (m, 2 H, C<u>H</u>-O, C<u>H</u>$_2$O), 2.04-1.71 (m, 2 H, C<u>H</u>$_2$), 1.53 (s, 3 H, C<u>H</u>$_3$), 1.33 (s, 3 H, C<u>H</u>$_3$), 0.84 (s, 9 H, (C<u>H</u>$_3$)$_3$Si), 0.07, 0.04 (2 x s, 2 x 3 H, (C<u>H</u>$_3$)$_2$Si); HRMS, calcd for $C_{23}H_{37}O_4Si$ (M+H): 405.2461, found: 405.2419.

Alcohol 54.

A stirred solution of olefin **53** (24.9 g, 61.6 mmol) in THF (50 mL) at 25 °C was treated with 9-BBN (185 mL, 92.5 mmol, 0.5 M in THF) over 30 min. After 40 min, the reaction mixture was cooled to 0 °C and treated dropwise with 3 N NaOH (46 mL, 139 mmol) and 30% hydrogen peroxide (12.4 mL, 102 mmol) over 10 min. The cooling bath was removed and the reaction mixture was stirred for another 30 min. The reaction mixture was diluted with ether (300 mL), washed with water (200 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (silica, 20→50% ether in petroleum ether) gave the alcohol **54** (24.2 g, 93%). **54**: oil; TLC, Rf=0.27 (silica, 30% ether in petroleum ether); IR (neat) ν_{max} 3440(OH), 2920, 2850, 1465, 1370, 1250, 1200, 1085, 1020, 850, 830, 770, 750, 690, 660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46, 7.33 (2 x m, 5 H, aromatic), 5.54 (s, 1 H, C<u>H</u>Ar), 3.88-3.69 (m, 4 H, C<u>H</u>-O, C<u>H</u>$_2$O), 3.55 (m, 2 H, C<u>H</u>-O, C<u>H</u>$_2$O), 2.38 (m, 1 H, C<u>H</u>$_2$), 2.09-1.54 (m, 3 H, C<u>H</u>$_2$), 1.53 (s, 3 H, C<u>H</u>$_3$), 1.33 (s, 3 H, C<u>H</u>$_3$), 0.84 (s, 9 H, (C<u>H</u>$_3$)$_3$Si), 0.07, 0.04 (2 x s, 2 x 3 H, (C<u>H</u>$_3$)$_2$Si); HRMS, calcd for $C_{23}H_{42}O_5NSi$ ($M+NH_4$): 440.2832, found: 440.2903.

Aldehyde 55.

A solution of alcohol **54** (24.1 g, 57.1 mmol) in CH_2Cl_2 (200 mL) was added dropwise to a mixture of oxalyl chloride (7.4 mL, 85.7 mmol) and DMSO (8.1 mL, 114.2 mmol) in CH_2Cl_2 (85 mL) at -78 °C over 25 min. After 40 min, triethylamine (38 mL) was added slowly and the cooling bath removed. When the reaction mixture reached 0 °C, it was diluted with ether (400 mL), washed with saturated aqueous ammonium chloride (350 mL), dried ($MgSO_4$) and concentrated. The crude aldehyde **55** (22.9 g, 95%) was taken to the next step without purification. **55**: oil; TLC, Rf=0.55 (silica, 30% ether in petroleum ether); IR (neat) ν_{max} 2960, 2860, 1720(C=O), 1470, 1390, 1260, 1100, 1030, 840, 780, 700, 670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.81 (t, J= 2.9 Hz, 1 H, H-aldehyde), 7.46, 7.32 (2 x m, 5 H, aromatic), 5.50 (s, 1 H, C<u>H</u>Ar), 4.21 (m, 1 H, C<u>H</u>-O), 3.76-3.36 (m, 3 H, C<u>H</u>-O, C<u>H</u>$_2$-O), 2.51 (2 x d, J=2.9 Hz, 2 x 1 H, C<u>H</u>$_2$C=O), 2.16 (m, 1 H, C<u>H</u>$_2$), 1.85 (q, J=11.6 Hz, 1 H, C<u>H</u>$_2$), 1.36, 1.19 (2 x s, 2 x 3 H, C<u>H</u>$_3$), 0.87 (s, 9 H, (C<u>H</u>$_3$)$_3$CSi), 0.06, 0.05 (2 x s, 2 x 3 H, C<u>H</u>$_3$Si); HRMS, calcd for $C_{23}H_{37}O_5Si$ (M+H): 421.2410, found: 421.2422.

Ester 56.

A mixture of the crude aldehyde **55** (22.8 g, 54.3 mmol), (carbethoxyethylidene) triphenylphosphorane (23.8 g, 65.1 mmol) and benzoic acid (0.1 g) in benzene (110 mL) was heated at 50 °C for 30 min. Concentration and flash chromatography (silica, 15% ether in petroleum ether) gave the α,β–unsaturated ester **56** (29.5 g, 90%). **56**: oil; TLC, Rf=0.61 (silica, 30% ether in petroleum ether); IR (neat) ν_{max} 2950, 2860, 1715(C=O), 1475, 1380, 1255, 1100, 860, 840, 775, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46, 7.33 (2 x m, 5 H, aromatic), 6.90 (dt, J=7.0, 1.4 Hz, 1 H, C<u>H</u>=CCO_2), 5.55 (s, 1 H, C<u>H</u>Ar), 4.19 (q, J=7.2 Hz, 2 H, $CH_3C\underline{H}_2O_2C$), 3.84 (d, J=10.0 Hz, 1 H, C<u>H</u>$_2$O), 3.68 (dd, J=10.3, 5.5 Hz, 1 H, C<u>H</u>-O), 3.53 (m, 2 H, C<u>H</u>-O, C<u>H</u>$_2$O), 2.49-1.90 (m, 4 H, C<u>H</u>$_2$), 1.80 (d, J=1.0 Hz, 3 H, C<u>H</u>$_3$C=C), 1.51, 1.26 (2 x s, 2 x 3 H, C<u>H</u>$_3$), 1.30 (t, J=7.2 Hz, 3 H, $C\underline{H}_3CH_2O_2C$), 0.86 (s, 9 H, (C<u>H</u>$_3$)$_3$Si), 0.06, 0.04 (2 x s, 2 x 3H, C<u>H</u>$_3$Si); HRMS, calcd for $C_{28}H_{48}O_6NSi$ (M+NH_4): 522.3250, found: 522.3281.

Allylic alcohol 57.

DIBAL (128 mL, 128 mmol, 1.0 M in CH_2Cl_2) was added dropwise to a stirred solution of ester **56** (29.4 g, 58.3 mmol) in CH_2Cl_2 (80 mL) at -78 °C over 20 min. After 15 min, the mixture was quenched with MeOH (3 mL), the cooling bath removed, and the reaction mixture was allowed to reach room temperature. The mixture was diluted with EtOAc (300 mL) and washed with aqueous saturated sodium potassium tartrate (2 x 150 mL). The aqueous phase was extracted with EtOAc (2 x 50 mL). The combined organic layers were dried ($MgSO_4$), concentrated and subjected to flash chromatography (silica, 30% ether in petroleum ether) to give the alcohol **57** (26.4 g, 97%). **57**: oil; TLC, Rf=0.52 (silica, 60% ether in petroleum ether); IR (neat) ν_{max} 3400(OH), 2930, 2860, 1480, 1380, 1250, 1100, 840, 775, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46, 7.33 (2 x m, 5 H, aromatic), 5.55 (bs, 2 H, C<u>H</u>Ar, C<u>H</u>=C), 4.02 (s, 2 H, C<u>H</u>$_2$O), 3.74 (m, 1 H, C<u>H</u>O), 3.68 (m, 1 H, C<u>H</u>-O), 3.52 (m, 2 H, C<u>H</u>-O, C<u>H</u>$_2$O), 2.35-1.70 (m, 5 H, C<u>H</u>$_2$, O<u>H</u>), 1.64 (s, 3 H, C<u>H</u>$_3$C=C), 1.50, 1.22 (2 x s, 2 x 3 H, C<u>H</u>$_3$),

0.86 (s, 9 H, ($C\underline{H}_3$)$_3$Si), 0.06, 0.04 (2 x s, 2 x 3 H, ($C\underline{H}_3$)$_2$Si); HRMS, calcd for $C_{26}H_{43}O_5Si$ (M+H): 463.2880, found: 463.2861.

Epoxide 58.

m-Chloroperbenzoic acid (14.7 g, 68.3 mmol, 80% by wt.) was added in five portions to a stirred, cooled (0 °C) solution of allylic alcohol **57** (26.3 g, 56.9 mmol) in CH_2Cl_2 (200 mL). After 30 min, dimethyl sulfide (3 mL) and triethylamine (15 mL) were added and the reaction mixture was concentrated. Flash chromatography (silica, 50% ether in petroleum ether) gave the epoxy alcohol **58** (26.4 g, 97%) as a single diastereomer. **58**: oil; TLC, Rf=0.48 (silica, 60% ether in petroleum ether); IR (neat) ν_{max} 3440(OH), 2930, 2860, 1475, 1380, 1255, 1100, 860, 840, 780, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.46, 7.33 (2 x m, 5 H, aromatic), 5.56 (s, 1 H, C$\underline{H}$Ar), 3.95 (dd, J=10.6, 5.2 Hz, 1 H, C$\underline{H}$-O), 3.84 (d, J=10.0 Hz, 1 H, C$\underline{H}_2$O), 3.71-3.49 (m, 4 H, C$\underline{H}$-O, C$\underline{H}_2$O), 3.28 (t, J=6.3 Hz, 1 H, H-epox.), 2.01-1.63 (m, 5 H, C$\underline{H}_2$, O$\underline{H}$), 1.53 (s, 3 H, C$\underline{H}_3$-epox.), 1.26, 1.24 (2 x s, 2 x 3 H, C$\underline{H}_3$), 0.84 (s, 9 H, ($C\underline{H}_3$)$_3$Si), 0.06, 0.04 (2 x s, 2 x 3 H, ($C\underline{H}_3$)$_2$Si); HRMS, calcd for $C_{26}H_{43}O_6Si$ (M+H): 479.2829, found: 479.2853.

Olefin 60.

To a stirred mixture of **58** (26.g, 55.0 mmol), dry DMSO (55 mL) and triethylamine (38 mL, 275 mmol) in CH_2Cl_2 (220 mL) at 0 °C was added sulfur trioxide pyridine complex (26.2 g, 165 mmol) in four portions. After 3.5 h, the reaction mixture was diluted with ether (300 mL), washed with saturated aqueous ammonium chloride solution (250 mL), dried ($MgSO_4$) and concentrated to give the epoxy aldehyde **59** (25 g, 92%) which was used directly. To a stirred solution of methyl triphenylphosphonium bromide (28.4 g, 79.4 mmol) in THF (50 mL) at 0 °C was added dropwise sodium bis(trimethylsilyl)amide (68.8 mL, 68.8 mmol, 1.0 M in THF) over 20 min. After stirring for 10 min, the bright yellow ylide was treated with the crude aldehyde **59** (25 g, 52.9 mmol) in THF (100 mL) dropwise over 20 min. After 10 min, the reaction mixture was quenched with acetone (5 mL), diluted with ether (250 mL), washed with water (200 mL), dried ($MgSO_4$) and concentrated. The residue was triturated with 25% ether in petroleum ether, followed by filtration to remove triphenylphosphonium oxide. After solvent removal and flash chromatography (silica, 5→10% ether in petroleum ether), the olefin **60** was obtained (22.6 g, 88%). **60**: oil; TLC, Rf=0.81 (silica, 20% ether in petroleum ether); IR (neat) ν_{max} 2960, 2930, 2860, 1475, 1380, 1255, 1100, 860, 840, 780, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.46, 7.33 (2 x m, 5 H, aromatic), 5.65 (dd, J=17.4, 10.6 Hz, 1 H, C$\underline{H}$=CH_2), 5.56 (s, 1 H, C$\underline{H}$Ar), 5.35 (dd, J=17.4, 1.1 Hz, 1 H, C$\underline{H}_2$=CH), 5.18 (dd, J=10.6, 1.1 Hz, 1 H, C$\underline{H}_2$=CH), 3.96 (dd, J=10.6, 5.2 Hz, 1 H, C$\underline{H}$-O), 3.83 (d, J=10.0 Hz, 1 H, C$\underline{H}_2$O), 3.55 (m, 2 H, C$\underline{H}$-O, C$\underline{H}_2$O), 3.07 (t, J=6.2 Hz, 1 H, H-epox.), 2.04-1.68 (m, 4 H, C$\underline{H}_2$), 1.52 (s, 3 H, CH_3-epox.), 1.34, 1.26 (2 x s, 2 x 3 H, C$\underline{H}_3$), 0.84 (s, 9 H, ($C\underline{H}_3$)$_3$CSi), 0.09 (s, 6 H, ($C\underline{H}_3$)$_2$Si); HRMS, calcd for $C_{27}H_{43}O_5Si$ (M+H): 475.2880, found: 475.2864.

Alcohol 10.

To a stirred solution of olefin **60** (22.5 g, 47.5 mmol) in THF (100 mL) at 25° C was added dropwise tetrabutylammonium fluoride (71.3 mL, 71.3 mmol, 1.0 M in THF) over 10 min. After 20 min, the reaction mixture was diluted with ether (200 mL), washed with water (100 mL), dried ($MgSO_4$) and the solvent evaporated. Flash chromatography (silica, 30→70% ether in petroleum ether) gave the epoxy alcohol **10** (15.9 g, 93%). **10**: oil; TLC, Rf=0.29 (silica, 30% ether in petroleum ether); IR (neat) ν_{max} 3440(OH), 2960, 2930, 2870, 1475, 1390, 910, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46, 7.33 (2 x m, 5 H, aromatic), 5.65 (dd, J=17.4, 10.6 Hz, 1 H, C<u>H</u>=CH_2), 5.57 (s, 1 H, C<u>H</u>Ar), 5.32 (dd, J=17.4, 1.1 Hz, 1 H, C<u>H</u>$_2$=CH), 5.20 (dd, J=10.6, 1.1 Hz, 1 H, C<u>H</u>$_2$=CH), 4.07 (m, 1 H, C<u>H</u>-O), 3.84 (d, J=10.0 Hz, 1 H, C<u>H</u>$_2$O), 3.58 (m, 2 H, C<u>H</u>-O, C<u>H</u>$_2$O), 3.07 (dd, J=7.6, 3.3 Hz, 1 H, H-epox.), 2.30 (bs, 1 H, O<u>H</u>), 2.12-1.61 (m, 4 H, C<u>H</u>$_2$), 1.54 (s, 3 H, CH_3-epox.), 1.38, 1.32 (2 x s, 2 x 3 H, C<u>H</u>$_3$); HRMS, calcd for $C_{21}H_{29}O_5$ (M+H): 361.2015, found: 361.2029.

Bicycle 61.

A solution of epoxide **11** (15.8 g, 43.9 mmol) in CH_2Cl_2 (400 mL) at 0 °C was treated with pyridinium p-toluenesulfonate (9.4 g, 37.3 mmol) in one portion. After 14 h, triethylamine (6.2 mL) was added and the solvent evaporated. Flash chromatography (silica, 70% ether in petroleum ether) gave the cyclized product **61** (14.5 g, 92%). **61**: oil; TLC, Rf=0.24 (silica, 30% EtOAc in petroleum ether); IR (neat) ν_{max} 3470(OH), 2950, 2930, 2870, 1460, 1385, 735, 700, 650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46, 7.33 (2 x m, 5 H, aromatic), 5.95 (dd, J=17.4, 10.6 Hz, 1 H, C<u>H</u>=CH_2), 5.57 (s, 1 H, C<u>H</u>Ar), 5.37 (dd, J=17.4, 1.1 Hz, 1 H, C<u>H</u>$_2$=CH), 5.18 (dd, J=10.6, 1.1 Hz, 1 H, C<u>H</u>$_2$=CH), 3.84 (d, J=10.0 Hz, 1 H, C<u>H</u>$_2$O), 3.74 (m, 2 H, C<u>H</u>-O, C<u>H</u>$_2$O), 3.56 (d, J=10.0 Hz, 1 H, H-epox.), 3.54 (m, 1 H, C<u>H</u>-O), 2.00 (m, 5 H, C<u>H</u>$_2$, O<u>H</u>), 1.59 (s, 3 H, C<u>H</u>$_3$), 1.37, 1.34 (2 x s, 2 x 3 H, C<u>H</u>$_3$); HRMS, calcd for $C_{21}H_{29}O_5$ (M+H): 361.2015, found: 361.2019.

Benzyl ether 62.

To a stirred solution of alcohol **61** (14.4 g, 40.0 mmol) in THF (85 mL) at 45 °C was added potassium hydride (6.9 g, 52 mmol, 35% by wt. in mineral oil). After 40 min, benzyl bromide (7.0 mL, 60 mmol) was added dropwise over 1 min. After 10 min, the reaction mixture was cooled and MeOH (2 mL) was added. The reaction mixture was diluted with ether (150 mL), washed with water (100 mL), dried ($MgSO_4$) and concentrated. Flash chromatography (silica, 5→20% ether in petroleum ether) gave the benzyl ether **62** (16.2 g, 90%). **62**: colorless plates; m.p. 204 °C (ether/hexane); TLC, Rf=0.58 (silica, 20% ether in petroleum ether); IR (neat) ν_{max} 2980, 2950, 2870, 1455, 1385, 1100, 1030, 995, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46, 7.33 (2 x m, 10 H, aromatic), 6.00 (dd, J=17.4, 10.6 Hz, 1 H, C<u>H</u>=CH_2), 5.57 (s, 1 H, C<u>H</u>Ar), 5.35 (dd, J=17.4, 1.1 Hz, 1 H, C<u>H</u>$_2$=CH), 5.10 (dd, J=10.6, 1.1 Hz, 1 H, C<u>H</u>$_2$=CH), 4.55, 4.40 (2 x d, J=11.7 Hz, 2 x 1 H, C<u>H</u>$_2$Ar), 3.85 (d, J=10.0 Hz, 1 H, C<u>H</u>$_2$O), 3.70 (m, 1 H, C<u>H</u>-O), 3.52 (m, 3 H, C<u>H</u>-O, C<u>H</u>$_2$O), 2.15 (dd, J=11.7, 5.4 Hz, 1 H, C<u>H</u>$_2$), 1.92 (m, 3 H, C<u>H</u>$_2$), 1.58 (s, 3 H, C<u>H</u>$_3$), 1.37, 1.34 (2 x s, 2 x 3 H, C<u>H</u>$_3$); HRMS, calcd for $C_{28}H_{35}O_5$ (M+H): 451.2484, found: 451.2506.

Alcohol 63.

A stirred solution of olefin **61** (16.1 g, 35.8 mmol) in THF (80 mL) at 25 °C was treated with 9-BBN (108 mL, 54 mmol, 0.5 M in THF) over 30 min. After 40 min, the reaction mixture was cooled to 0 °C and treated dropwise with 3 N NaOH (30 mL, 89.5 mmol) and 30% hydrogen peroxide (8.1 mL, 66.5 mmol) over 20 min. The cooling bath was removed and the reaction mixture was stirred for another 30 min. The reaction mixture was diluted with ether (200 mL), washed with water (2 x 100 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (silica, 20→50% ether in petroleum ether) gave the alcohol **63** (15.4 g, 92%). **63**: oil; TLC, Rf=0.19 (silica, 50% ether in petroleum ether); IR (neat) ν_{max} 3460(OH), 2940, 1465, 1385, 1085, 750, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46, 7.33 (2 x m, 10 H, aromatic), 5.56 (s, 1 H, C<u>H</u>Ar), 4.60, 4.35 (2 x d, J=11.7 Hz, 2 x 1 H, C<u>H</u>$_2$Ar), 3.84 (d, J=10.0 Hz, 1 H, C<u>H</u>$_2$O), 3.71-3.48 (m, 6 H, C<u>H</u>-O, C<u>H</u>$_2$O), 2.19 (dd, J=11.7, 5.4 Hz, 1 H, C<u>H</u>$_2$), 1.92-1.70 (m, 6 H, C<u>H</u>$_2$, O<u>H</u>), 1.57 (s, 3 H, C<u>H</u>$_3$), 1.35, 1.34 (2 x s, 2 x 3 H, C<u>H</u>$_3$); HRMS, calcd for $C_{28}H_{37}O_6$ (M+H): 469.2590 found: 469.2566.

Benzyl ether 64.

To a stirred solution of alcohol **63** (15.3 g, 32.7 mmol) in THF (85 mL) at 50 °C was added potassium hydride (5.2 g, 39.2 mmol, 35% by wt. in mineral oil). After 60 min, benzyl bromide (5.3 mL, 45.8 mmol) was added dropwise over 1 min. After 10 min, the reaction mixture was cooled and MeOH (2 mL) was added. The reaction mixture was diluted with ether (150 mL), washed with water (100 mL), dried ($MgSO_4$) and concentrated. Flash chromatography (silica, 5→20% ether in petroleum ether) gave the benzyl ether **64** (16.2 g, 89%). **64**: oil; TLC, Rf=0.74 (silica, 30% ether in petroleum ether); IR (neat) ν_{max} 2960, 2880, 1460, 1390, 1100, 915, 735, 700, 645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46, 7.33 (m, 15 H, aromatic), 5.57 (s, 1 H, C<u>H</u>Ar), 4.57, 4.38 (2 x d, J=11.7 Hz, 2 x 1 H, C<u>H</u>$_2$Ar), 4.46 (s, 2 H, C<u>H</u>$_2$Ar), 3.87 (d, J=10.0 Hz, 1 H, C<u>H</u>$_2$O), 3.72-3.44 (m, 6 H, C<u>H</u>-O, C<u>H</u>$_2$O), 2.14 (dd, J=11.7, 5.4 Hz, 1 H, C<u>H</u>$_2$), 2.00-1.70 (m, 5 H, C<u>H</u>$_2$), 1.57 (s, 3 H, C<u>H</u>$_3$), 1.29, 1.27 (2 x s, 2 x 3 H, C<u>H</u>$_3$); HRMS, calcd for $C_{35}H_{43}O_6$ (M+H): 559.3059 found: 559.3037.

Diol 65.

Camphorsulfonic acid (1.3 g, 5.8 mmol) was added to a stirred solution of benzylidene **64** (16.1 g, 28.9 mmol) in MeOH (150 mL) at 0 °C. After 1 h, triethylamine (1.0 mL) was added and the solvent evaporated. Flash chromatography (silica, 50→100% ether in petroleum ether) gave the diol **65** (12.2 g, 90%). **65**: oil; TLC, Rf=0.19 (silica, 100% ether); IR (neat) ν_{max} 3420(OH), 2940, 2880, 1500, 910, 735, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30 (m, 10 H, aromatic), 4.55, 4.37 (2 x d, J=11.7 Hz, 2 x 1 H, C<u>H</u>$_2$Ar), 4.44 (s, 2 H, C<u>H</u>$_2$Ar), 3.94 (dd, J=11.6, 6.7 Hz, 1 H, C<u>H</u>-O), 3.64-3.20 (m, 6 H, C<u>H</u>-O, C<u>H</u>$_2$O), 2.25 (bs, 1 H, O<u>H</u>), 2.07 (dd, J=11.7, 5.4 Hz, 1 H, C<u>H</u>$_2$), 1.96-1.60 (m, 5 H, C<u>H</u>$_2$), 1.42 (t, J=12.1 Hz, 1 H, O<u>H</u>), 1.22, 1.19, 1.18 (3 x s, 3 x 3 H, C<u>H</u>$_3$); HRMS, calcd for $C_{28}H_{39}O_6$ (M+H): 471.2746 found: 471.2731.

Bis-silyl ether 66.

To a stirred solution of diol **65** (12.1 g, 25.7 mmol) and imidazole (5.3 g, 77.2 mmol) in DMF (50 mL) at 25 °C was added *tert*-butyldimethylsilyl chloride (9.7 g, 64.3 mmol) in one portion. The reaction mixture was heated at 50 °C for 14 h. The reaction mixture was cooled and quenched with MeOH (2 mL), diluted with ether (300 mL) and washed with water (140 mL). Drying ($MgSO_4$), concentration and flash chromatography (silica, 10% ether in petroleum ether) gave the silyl ether **65** (16.5 g, 95%). **65**: oil; TLC, Rf=0.69 (silica, 20% ether in petroleum ether); IR (neat) ν_{max} 2960, 2930, 2860, 1475, 1385, 1260, 1080, 840, 780, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30 (m, 10 H, aromatic), 4.56, 4.37 (2 x d, J=11.7 Hz, 2 x 1 H, C$\underline{H}_2$Ar), 4.44 (s, 2 H, C$\underline{H}_2$Ar), 4.09 (m, 1 H, C$\underline{H}$-O), 3.58 (m, 3 H, C$\underline{H}$-O, C$\underline{H}_2$O), 3.25 (m, 3 H, C$\underline{H}$-O, C$\underline{H}_2$O), 2.07-1.88 (m, 2 H, C$\underline{H}_2$), 1.74-1.39 (m, 4 H, C$\underline{H}_2$), 1.42 (t, J=12.1 Hz, 1 H, O$\underline{H}$), 1.21, 1.16, 1.04 (3 x s, 3 x 3 H, C$\underline{H}_3$), 0.88, 0.84 (2 x s, 2 x 9 H, (C$\underline{H}_3$)$_3$Si), 0.06, 0.04, 0.03, 0.01 (4 x s, 4 x 3 H, C$\underline{H}_3$Si); HRMS, calcd for $C_{40}H_{67}O_6Si_2$ (M+H): 699.4476 found: 699.4491.

Alcohol 67.

Camphorsulfonic acid (1.1 g, 4.7 mmol) was added to a stirred solution of the silyl ether **66** (16.4 g, 23.5 mmol) in MeOH (100 mL) at 0 °C. After 1 h, triethylamine (1.0 mL) was added and the solvent evaporated. Flash chromatography (silica, 20→60% ether in petroleum ether) gave the primary alcohol **67** (12.9 g, 94%). **67**: oil; TLC, Rf=0.21 (silica, 30% ether in petroleum ether); IR (neat) ν_{max} 3500(OH), 2960, 2930, 2860, 1460, 1385, 1085, 870, 840, 780, 735, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30 (m, 10 H, aromatic), 4.56, 4.37 (2 x d, J=11.7 Hz, 2 x 1 H, C$\underline{H}_2$Ar), 4.44 (s, 2 H, C$\underline{H}_2$Ar), 4.00 (m, 1 H, C$\underline{H}$-O), 3.59 (m, 3 H, C$\underline{H}$-O, C$\underline{H}_2$O), 3.27 (m, 3 H, C$\underline{H}$-O, C$\underline{H}_2$O), 2.07 (m, 2 H, C$\underline{H}_2$), 1.95 (t, J=6.9 Hz, 2 H, C$\underline{H}_2$), 1.78-1.38 (m, 3 H, C$\underline{H}_2$, O$\underline{H}$), 1.23, 1.19, 1.10 (3 x s, 3 x 3 H, C$\underline{H}_3$), 0.85 (s, 9 H, (C$\underline{H}_3$)$_3$Si), 0.07, 0.06 (2 x s, 2 x 3 H, C$\underline{H}_3$Si); HRMS, calcd for $C_{34}H_{53}O_6Si$ (M+H): 585.3611 found: 585.3594.

Aldehyde 68.

A solution of alcohol **67** (16.3 g, 27.9 mmol) in CH_2Cl_2 (120 mL) was added dropwise to a mixture of oxalyl chloride (3.7 mL, 41.9 mmol) and DMSO (4.0 mL, 55.8 mmol) in CH_2Cl_2 (80 mL) at -78 °C over 25 min. After 40 min, triethylamine (19.5 mL, 139.5 mmol) was added slowly and the cooling bath removed. When the reaction mixture reached 0 °C, it was diluted with ether (250 mL) and washed with saturated aqueous ammonium chloride (200 mL), dried ($MgSO_4$) and concentrated to give the crude aldehyde **68** (15.1 g, 93%) which was used directly. **68**: oil; TLC, Rf=0.78 streak (silica, 30% ether in petroleum ether); IR (neat) ν_{max} 2960, 2940, 2860, 1720(C=O), 1470, 1390, 1370, 1260, 1100, 1030, 840, 780, 700, 670, 650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.83 (s, 1 H, H-aldehyde), 7.30 (m, 10 H, aromatic), 4.56, 4.37 (2 x d, J=11.7 Hz, 2 x 1 H, C$\underline{H}_2$Ar), 4.44 (s, 2 H, C$\underline{H}_2$Ar), 4.00 (m, 1 H, C$\underline{H}$-O), 3.59 (m, 2 H, C$\underline{H}$-O), 3.27 (m, 2 H, C$\underline{H}$-O), 2.07 (m, 2 H, C$\underline{H}_2$), 1.95 (t, J=6.9 Hz, 2 H, C$\underline{H}_2$), 1.78-1.38 (m, 2 H, C$\underline{H}_2$), 1.23, 1.19, 1.10 (3 x s, 3 x 3 H, C$\underline{H}_3$), 0.85 (s, 9 H, (C$\underline{H}_3$)$_3$Si), 0.07, 0.06 (2 x s, 2 x 3 H, C$\underline{H}_3$Si); HRMS, calcd for $C_{34}H_{50}O_6Si$ (M+): 584.3533, found: 584.3551.

Unsaturated ester 69.

A mixture of the crude aldehyde **68** (15 g, 25.8 mmol), methyl (triphenylphosphoranylidene) acetate (10.4 g, 31.0 mmol) and benzoic acid (0.2 g) in benzene (55 mL) was heated at 50 °C for 12 h. Concentration and flash chromatography (silica, 15% ether in petroleum ether) gave the α,β–unsaturated ester **69** (14.8 g, 90%). **69**: oil; TLC, Rf=0.58 (silica, 5% EtOAc in benzene); IR (neat) ν_{max} 2960, 2930, 2860, 1735(C=O), 1660, 1365, 855, 830, 780, 735, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30 (m, 10 H, aromatic), 6.95, 6.00 (2 x d, J=15.6 Hz, 2 x 1 H, C<u>H</u>=CHCO$_2$Me), 4.56, 4.37 (2 x d, J=11.7 Hz, 2 x 1 H, C<u>H</u>$_2$Ar), 4.45 (s, 2 H, C<u>H</u>$_2$Ar), 3.72 (s, 3 H, C<u>H</u>$_3$O$_2$C), 3.60 (m, 4 H, C<u>H</u>-O, C<u>H</u>$_2$O), 3.31 (m, 1 H, C<u>H</u>-O), 2.11 (dd, J=11.7, 5.4 Hz, 1 H, C<u>H</u>$_2$), 1.95 (t, J=6.9 Hz, 2 H, C<u>H</u>$_2$), 1.78-1.44 (m, 3 H, C<u>H</u>$_2$), 1.33, 1.23, 1.21 (3 x s, 3 x 3 H, C<u>H</u>$_3$), 0.88 (s, 9 H, (C<u>H</u>$_3$)$_3$Si), 0.06, 0.05 (2 x s, 2 x 3 H, C<u>H</u>$_3$Si); HRMS, calcd for $C_{37}H_{55}O_7Si$ (M+H): 639.3717 found: 639.3752.

Saturated ester 70.

5% palladium on carbon (2.9 g, 20% by wt.) was added to a stirred solution of ester **69** (14.7 g, 23 mmol) in EtOAc (100 mL). A hydrogen atmosphere was introduced using a hydrogen-filled balloon by repeated evacuations (water aspirator). After 6 h, the hydrogen was replaced by argon and the reaction mixture was filtered through a celite pad. The filtrate was concentrated to give pure ester **70** (14.7 g, 100%). **70**: oil; TLC, Rf=0.56 (silica, 5% EtOAc in benzene); IR (neat) ν_{max} 2970, 2930, 2840, 1745(C=O), 1460, 1385, 1255, 1085, 865, 835, 775, 735, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30 (m, 10 H, aromatic), 4.56, 4.37 (2 x d, J=11.7 Hz, 2 x 1 H, C<u>H</u>$_2$Ar), 4.43 (s, 2 H, C<u>H</u>$_2$Ar), 3.62 (s, 3 H, C<u>H</u>$_3$O$_2$C), 3.61-3.49 (m, 4 H, C<u>H</u>-O, C<u>H</u>$_2$O), 3.20 (m, 1 H, C<u>H</u>-O), 2.39 (t, J=7.7 Hz, 2 H, C<u>H</u>$_2$CO$_2$Me), 2.01-1.61 (m, 8 H, C<u>H</u>$_2$), 1.22, 1.17, 1.12 (3 x s, 3 x 3 H, C<u>H</u>$_3$), 0.84 (s, 9 H, (C<u>H</u>$_3$)$_3$Si), 0.06, 0.04 (2 x s, 2 x 3 H, C<u>H</u>$_3$Si); HRMS, calcd for $C_{37}H_{57}O_7Si$ (M+H): 641.3873 found: 641.3861.

FG ring system 3.

A stirred solution of ester **70** (14.6 g, 22.8 mmol) in THF:MeOH:H_2O 1:1:1 (45 mL) was treated with lithium hydroxide (1.1 g, 45.6 mmol) in one portion and heated at 55 °C for 2.5 h. The reaction mixture was cooled, diluted with EtOAc (100 mL) and carefully acidified with 2 N HCl until pH 5. The organic layer was separated and the aqueous layer extracted with EtOAc (2 x 50 mL). The extracts were combined, dried ($MgSO_4$) and concentrated to give the acid **3** (13.6 g, 95%). **3**: oil; TLC, Rf=0.61 streak (silica, 30% ether in petroleum ether); IR (neat) ν_{max} 3420, 2900, 1720(C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30 (m, 10 H, aromatic), 4.56, 4.37 (2 x d, J=11.7 Hz, 2 x 1 H, C<u>H</u>$_2$Ar), 4.42 (s, 2 H, C<u>H</u>$_2$Ar), 3.55 (m, 4 H, C<u>H</u>-O, C<u>H</u>$_2$O), 3.22 (m, 1 H, C<u>H</u>-O), 2.48 (m, 2 H, C<u>H</u>$_2$CO$_2$H), 1.94-1.62 (m, 8 H, C<u>H</u>$_2$), 1.21, 1.18, 1.14 (3 x s, 3 x 3 H, C<u>H</u>$_3$), 0.83 (s, 9 H, (C<u>H</u>$_3$)$_3$Si), 0.05, 0.03 (2 x s, 2 x 3 H, C<u>H</u>$_3$Si); HRMS, calcd for $C_{36}H_{55}O_7Si$ (M+H): 627.3717 found: 627.3689.

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