Synthesis of *iso*-epoxy-amphidinolide N and *des*-epoxy-caribenolide I structures. Revised strategy and final stages

K. C. Nicolaou, *^{*a,b*} Paul G. Bulger^{*a*} and William E. Brenzovich^{*a*}

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A general and highly convergent synthetic route to the macrocyclic core structures of the antitumour agents amphidinolide N (1) and caribenolide I (2) has been developed, and the total synthesis of *iso*-epoxy-amphidinolide N and *des*-epoxy-caribenolide I structures is described. Central to the revised strategy was the use of a Horner–Wadsworth–Emmons olefination between β-ketophosphonate **51** and aldehyde **14** to construct the C1–C13 sector common to both **1** and **2**. Stereoselective alkylation of hydrazone **11** with iodide **65** and then with bromide **56** allowed for the rapid assembly of the complete caribenolide I carbon skeleton. Key steps in the completion of the synthesis of *des*-epoxy-caribenolide I structure **78** included hydrolysis of a sensitive methyl ester using Me₃SnOH, followed by regioselective macrolactonisation of the resulting diol *seco*-acid and global deprotection. Coupling of hydrazone **11**, bromide **56** and iodide **64** was followed by an analogous sequence of late-stage manoeuvres to arrive at the fully deprotected *des*-epoxy-amphidinolide N framework, obtained as a mixture of hemiacetal **83** and bicyclic acetal **84**. Regio- and diastereo-selective epoxidation of the C6 methylene group in bicyclic acetal **84** provided access to *iso*-epoxy-amphidinolide N stereoisomer **89**.

Introduction

In the preceding paper in this issue,¹ we described studies on two synthetic approaches to the macrocyclic frameworks of the marine-derived antitumour agents amphidinolide N² (1) and caribenolide I³ (2, Scheme 1). The primary goal of this work was to establish a flexible and convergent synthetic route to the core structures of both natural products 1 and 2. In turn, this would allow for some (or ideally all) of the stereochemical uncertainties surrounding amphidinolide N (1) and caribenolide I (2) to be addressed, as well as enabling further biological investigations of this important class of compounds. In this paper we detail the third and final route investigated towards amphidinolide N (1) and caribenolide I (2), which successfully provided an enantioselective access to advanced intermediates related to both target compounds 1 and 2.

Results and discussion

In the originally proposed route to the amphidinolide N structure (1), a variety of alkynes of general structure 3 [Scheme 1(a)], representing the complete C6–C29 carbon skeleton of the target compound 1, were readily prepared in a highly convergent manner. However, it did not prove to be possible to append the required C1–C5 unit 4 onto the terminal alkyne group through enyne metathesis-based methods,⁴ in either an intermolecular or intramolecular fashion. The inability to form the final carbon–carbon bond in this manner was the undoing of the 'enyne

metathesis approach'. In the second-generation strategy it was envisaged that one of the array of palladium-catalysed crosscoupling reactions⁵ could be enlisted to generate the C5–C6 bond that was ultimately required to reach 1 or 2. A route to C6vinyl bromides such as 5 [Scheme 1(b)], this time representing the caribenolide I (2) C6–C29 substructure, was therefore developed. Disappointingly, at this point the 'cross-coupling approach' also foundered, due to the stubborn reluctance of the bromide unit to engage in the relevant cross-coupling with a variety of C1–C5 acceptor units such as 6 or 7.

We therefore sought to incorporate the key C1-C5 unit at an earlier point in the proposed synthesis of 1 and 2, and arrived at the retrosynthetic blueprint illustrated in Scheme 1(c). In this 'Horner-Wadsworth-Emmons approach', much of the developed chemistry that had served so dutifully in the construction of both alkynes 3 and bromides 5 would be conserved, in particular the Enders hydrazone alkylation fragment coupling methodology⁶ for the stereoselective assembly of the C14-C16 sector. This time, however, a complete C1-C13 allylic bromide fragment 8 would be called for, rather than the corresponding truncated C6-C13 coupling partners that were employed in the syntheses of 3 and 5. Since enantioselective routes to both the amphidinolide N C17-C29 iodide 9 and the caribenolide I C17-C29 iodide 10 had been developed during the course of the synthesis of 3 and 5, respectively,¹ the initial focus then became the synthesis of bromide 8. Given that generation of the C5-C6 bond in diene systems such as that contained within 8 by fragment coupling processes had been found to be a thorny challenge, the point of disconnection was moved one bond along the chain to the C4–C5 (E)-alkene. This then invited the possibility of forming 8 by means of Horner–Wadsworth–Emmons olefination between phosphonate 12 and aldehyde 13, followed by Wittig olefination to install the C6 methylene group and functional group manipulation at the C13 position.

^aDepartment of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, USA. E-mail: kcn@scripps.edu; Fax: 858-784-2469; Tel: 858-784-2400

^bDepartment of Chemistry and Biochemistry, University of California San Diego, 9500 Gilman Drive, La Jolla, California 92093, USA



Scheme 1 Structures of amphidinolide N (1), caribenolide I (2) and retrosynthetic analysis: (a) enyne metathesis approach, (b) cross-coupling approach and (c) Horner–Wadsworth–Emmons approach.

The potential viability of this Horner–Wadsworth–Emmons olefination strategy was assessed by the model study illustrated in Scheme 2. It was found that aldehyde **14**, prepared without difficulty from ester **15** in 88% yield by ozonolysis of the terminal alkene,¹ underwent smooth olefination with β -ketophosphonate **16** [prepared in two steps from methyl (*S*)-(–)-lactate]⁷ employing the Masamune–Roush conditions (LiCl, *i*-Pr₂NEt, MeCN),⁸ to give the desired α , β -unsaturated ketone **17** as a single stereoisomer and in an excellent yield of 93%. Despite the rather hindered nature of the ketone group in compound **17**, standard Wittig methylenation could be effected with remarkable ease, to furnish diene **18** in 94% yield.

Buoyed by this small measure of success, we began the synthesis of the more elaborate β -ketophosphonate required for the target compounds 1 and 2. As shown in Scheme 3, 1,5-cyclooctadiene (19) was converted into aldehyde 20 through two sequential ozonolysis reactions, following the procedure of Zhao and Wang,⁹ in an overall yield (40%) best described as workable. In contrast with the literature protocol, it was found to be necessary to purify



Scheme 2 Synthesis of model diene 18. Reagents and conditions: a) O₃, CH₂Cl₂, -78 °C, then PPh₃ (1.5 equiv.), $-78 \rightarrow 25$ °C, 1 h, 88%; b) 16 (1.0 equiv.), LiCl (1.5 equiv.), MeCN, 25 °C, 10 min, then *i*-Pr₂NEt (1.5 equiv.), 25 °C, 10 min, then 14 (1.2 equiv.), 25 °C, 36 h, 93%; c) Ph₃PCH₃Br (1.6 equiv.), KHMDS (1.5 equiv.), THF, 25 °C, 30 min, then 17, $-78 \rightarrow 25$ °C, 1 h, 94%. KHMDS = potassium bis(trimethylsilyl)amide.



Scheme 3 Synthesis of alcohol 22. *Reagents and conditions*: a) O₃, MeOH/CH₂Cl₂ (1 : 1), -78 °C, then TsOH·H₂O (0.08 equiv.), -78 \rightarrow 25 °C, 2 h, then Me₂S, 25 °C, 18 h, 50%; b) O₃, CH₂Cl₂, -78 °C, then PPh₃ (1.5 equiv.), -78 \rightarrow 25 °C, 1 h, 79%; c) KO*t*-Bu (1.6 equiv.), *trans*-2-butene (3.0 equiv.), *n*-BuLi (1.6 equiv.), THF, -45 °C, 15 min, then (+)-Ipc₂BOMe (1.6 equiv.), -78 °C, 1 h, then BF₃·OEt₂ (1.6 equiv.), -78 °C, 30 min, then 20, -78 °C, 4 h, 69%; d) (*S*)-MTPA-Cl (1.5 equiv.), Et₃N (3.0 equiv.), 4-DMAP (1.0 equiv.), CH₂Cl₂, 25 °C, 2 h, 97%; e) (*R*)-MTPA-Cl (1.5 equiv.), Et₃N (3.0 equiv.), 4-DMAP (1.0 equiv.), CH₂Cl₂, 25 °C, 2 h, 95%. 4-DMAP = 4-dimethylaminopyridine; Ipc = isopinocampheyl; MTPA = methoxy- α -(trifluromethyl)phenylacetyl; Ts = 4-toluenesulfonyl.

the intermediate ring-opened product **21** prior to the second step, as subjecting the crude material from the first step to the second ozonolysis led to an intractable mixture from which none of the desired aldehyde (**20**) could be isolated. A Brown crotylboration reaction¹⁰ of aldehyde **20** then provided secondary alcohol **22** and installed the C9/C10 stereodiad in 69% yield. NMR spectroscopic analysis of the Mosher ester derivatives **23** and **24** indicated that alcohol **22** was formed in 94% *ee*.¹¹

Alcohol 22 was then protected as the corresponding PMB ether 25 under basic conditions (Scheme 4). Unexpectedly, a significant degree of hydrolysis of the dimethyl acetal group occurred during this step, which yielded a 4 : 1 mixture of the dimethyl acetal 25 and aldehyde 26. Therefore, the crude reaction mixture was subjected to acetalisation conditions [cat. La(OTf)₃, (MeO)₃CH, MeOH] prior to purification. This led to the reprotection of the minor aldehyde component (26), with the desired fully protected dimethyl acetal 25 being isolated in 96% yield for the two steps. Ozonolysis of the terminal alkene in compound 25 then provided the corresponding aldehyde (27) which was found to be somewhat sensitive to epimerisation at the C10 stereocentre, and was thus immediately subjected to an (E)-selective Wittig reaction using stabilised phosphorane 28, to give trisubstituted alkene 29 as a single geometrical isomer (78% yield from alkene 25). Alkene 29 was converted into aldehyde 32 by a three-step sequence of ester reduction $(29 \rightarrow 30)$, acetal hydrolysis $(30 \rightarrow 31)$ and TBS ether formation $(31 \rightarrow 32)$ in excellent overall yield (91%). At this point, the intention was to install the C7 hydroxy group through the enantioselective α -oxygenation of aldehyde 32 employing the organocatalytic protocol recently developed by several independent research groups.12 Thus, exposure of aldehyde



Scheme 4 Elaboration of alkene 22 to give aldehyde 32, and attempted organocatalytic *a*-oxygenation. *Reagents and conditions*: a) NaH (1.6 equiv.), THF, 0 °C, 30 min, then PMBCl (1.6 equiv.), 70 °C, 16 h; b) La(OTf)₃ (0.02 equiv.), HC(OMe)₃, MeOH, $0 \rightarrow 25$ °C, 16 h, 96% (two steps); c) O₃, CH₂Cl₂, -78 °C, then PPh₃ (1.5 equiv.), -78 $\rightarrow 25$ °C, 1 h; d) 28 (1.6 equiv.), C₆H₆, 70 °C, 32 h, 78% (two steps); e) DIBAL-H (3.0 equiv.), THF, -78 °C, 2.5 h, 96%; f) TsOH·H₂O (0.15 equiv.), acetone–H₂O (4 :1), 25 °C, 3 h; g) TBSCl (1.7 equiv.), imidazole (2.6 equiv.), 4-DMAP (cat.), CH₂Cl₂, 25 °C, 1.5 h, 95% (two steps). DIBAL-H = diisobutylaluminium hydride; 4-DMAP = 4-dimethylaminopyridine; PMB = 4-methoxybenzyl; TBS = *tert*-butyldimethylsilyl; Tf = trifluoromethanesulfonyl; Ts = 4-toluenesulfonyl.

32 to nitrosobenzene (33) and a catalytic amount of D-proline (34) would generate α -aminoxy aldehyde 35; N–O bond cleavage would then yield the corresponding α -hydroxy aldehyde (36). Unfortunately, this methodology proved to be inapplicable in this case; the instability of the α -aminoxy adduct (35) precluded its isolation, and we were unable to find a satisfactory single-step method for the *in situ* conversion of adduct 35 into the desired alcohol 36.

Introduction of the C7 hydroxy group would therefore have to be postponed until after the oxidation of aldehyde **32** to acid **37** (NaClO₂, 78%) and its subsequent esterification (MeI, K₂CO₃, 97%) to give ester **38**, as shown in Scheme 5. Enolate formation followed by addition of the Davis oxaziridine **39**¹³ afforded α hydroxy ester **40** as an inseparable 3 : 1 mixture of (7*S*)- : (7*R*)epimers in 96% yield. That the major epimer was indeed the (7*S*)stereoisomer was confirmed by comparison of this mixture to an authentic sample of stereochemically pure (7*S*) material (*vide infra*). Interestingly, the stereoselectivity of this reaction was not improved by using the chiral camphor-derived oxaziridine **41**,¹⁴ which provided the same 3 : 1 epimeric mixture but in only 44% yield. Protection of the hydroxy group in compound **40** as the



Scheme 5 Conversion of aldehyde 32 to β-ketophosphonate 44. *Reagents and conditions*: a) NaClO₂ (1.8 equiv.), NaH₂PO₄ (3.5 equiv.), 2-methyl-2-butene (20.0 equiv.), *t*-BuOH–H₂O (4 : 1), 25 °C, 2 h, 78%; b) MeI (4.0 equiv.), K₂CO₃ (2.5 equiv.), acetone, 25 °C, 16 h, 97%; c) KHMDS (2.0 equiv.), THF, -78 °C, 30 min, then 39 (3.0 equiv.), -78 °C, 1 h, 96% [(7*S*) : (7*R*), 3 : 1]; d) TBSCl (2.5 equiv.), imidazole (5.0 equiv.), CH₂Cl₂, 25 °C, 16 h, 88%; e) dimethyl methylphosphonate (3.1 equiv.), *n*-BuLi (3.0 equiv.), THF, -78 °C, 30 min, then 42, -78 °C, 1 h, 96%. KHMDS = potassium bis(trimethylsilyl)amide; TBS = *tert*-butyldimethylsilyl.

corresponding TBS ether **42** was followed by the addition of α lithio phosphonate **43** to give the required β -ketophosphonate **44** in 84% overall yield, albeit still as a 3 : 1 mixture of C7 epimers.

Based upon the well-established α -hydroxylation chemistry of *N*-acyl oxazolidinones,¹⁵ a more highly stereoselective route to the β -ketophosphonate structure was also investigated, as is illustrated in Scheme 6. Acid **37** was first converted into oxazolidinone **45** (*via* mixed anhydride **46**) in an unoptimised yield of 44%. Hydroxylation of oxazolidinone **45** then proceeded smoothly with >98% diastereoselectivity, and was followed by methanolic cleavage¹⁵ of the chiral auxiliary to give (7*S*)-ester **49** in stereochemically pure form (56% from **45**). Ester **49** could then be converted into β -ketophosphonate **51** in two steps as described above (79% overall).

Completion of the synthesis of the C1–C13 bromide fragment could be achieved from either of phosphonates **44** or **51**, as shown in Scheme 7. Olefination of phosphonate **44** [Scheme 7(a)] with aldehyde **14** gave enone **52** (92%) exclusively as the C4–C5 (*E*)isomer, which underwent Wittig methylenation to yield diene **53** (95%). Selective removal¹⁶ of the primary TBS group using PPTS in warm EtOH then allowed for the chromatographic separation of the C7 epimers (**54** and **55**), with the major (7*S*)-product (**54**) being isolated in 56% yield. The enantiopure phosphonate **51** could also be converted into alcohol **54** through the same three-step sequence of Horner–Wadsworth–Emmons olefination, Wittig methylenation and TBS ether cleavage, to give **54** as a single stereoisomer in 79% overall yield [Scheme 7(b)]. Finally,



Scheme 6 Conversion of acid 37 to enantiomerically pure β -ketophosphonate 51. *Reagents and conditions*: a) *t*-BuCOCl (1.1 equiv.), Et₃N (1.1 equiv.), THF, -78 °C, 1 h; b) 47 (1.2 equiv.), -78 °C, 3 h, 44%; c) NaHMDS (1.2 equiv.), THF, -78 °C, 5 min, then 39 (1.5 equiv.), -78 °C, 5 min; d) Mg(OMe)₂ (0.5 equiv.), MeOH, 0 °C, 30 min, 56% (two steps); e) TBSCl (3.0 equiv.), imidazole (6.0 equiv.), 4-DMAP (cat.), CH₂Cl₂, 25 °C, 86%; f) dimethyl methylphosphonate (3.1 equiv.), *n*-BuLi (3.0 equiv.), THF, -78 °C, 30 min, then 50, -78 °C, 1 h, 92%. 4-DMAP = 4-dimethylaminopyridine; NaHMDS = sodium bis(trimethylsilyl)amide; TBS = tert-butyldimethylsilyl.

allylic alcohol **54** was converted into the corresponding bromide **56** in 95% yield, employing the optimum conditions previously established for similar substrates (MsCl, Et_3N then LiBr).¹

The availability of the complete C1-C13 carbon framework also presented us with the opportunity of validating potential methods for the generation of the C4-C5 allylic epoxide group. As illustrated in Scheme 8(a) for the case of amphidinolide N (1), it was proposed to install this delicate motif in the final step of the synthesis, through the selective epoxidation of a fully deprotected diene precursor molecule (e.g. 59). Model epoxidation substrate 61 was therefore prepared in two steps from ester 54 [Scheme 8(b)] through exposure to $TsOH \cdot H_2O$ in MeOH to give triol 60 (79%) followed by selective reprotection of the primary hydroxy group as the corresponding TBDPS ether (77%). Treatment of diene 61 with mCPBA led to a multitude of unidentified products arising from the non-selective epoxidation of each of the three alkenes in the starting material, even if a sub-stoichiometric amount of oxidant was used at low temperature. Hydroxy-directed epoxidation methods were then investigated, with the view that these would offer greater potential for controlling chemo- and diastereofacial-selectivity. To our delight, the Katsuki-Sharpless



Scheme 7 Completion of the synthesis of C1–C13 allylic bromide coupling partner from either (a) β-ketophosphonate 44, or (b) β-ketophosphonate 51. *Reagents and conditions*: a) 44 (1.0 equiv.), LiCl (1.5 equiv.), MeCN, 25 °C, 10 min, then *i*-Pr₂NEt (1.5 equiv.), 25 °C, 10 min, then 14 (1.15 equiv.), 25 °C, 48 h, 92%; b) Ph₃PCH₃Br (1.6 equiv.), KHMDS (1.5 equiv.), THF, 25 °C, 45 min, then 52, $-78 \rightarrow 25$ °C, 1 h, 95%; c) PPTS (0.06 equiv.), EtOH, 45 °C, 16 h, 56% 54 + 14% 55; d) MsCl (2.0 equiv.), Et₃N (4.0 equiv.), THF, 0 → 25 °C, 1 h, then LiBr (10.0 equiv.), 25 °C, 30 min, 95%; e) 51 (1.0 equiv.), LiCl (1.5 equiv.), MeCN, 25 °C, 10 min, then *i*-Pr₂NEt (1.5 equiv.), 25 °C, 30 min, 95%; e) 51 (1.0 equiv.), LiCl (1.5 equiv.), MeCN, 25 °C, 10 min, then *i*-Pr₂NEt (1.5 equiv.), 25 °C, 10 min, then 14 (1.15 equiv.), 25 °C, 30 min, 95%; e) 51 (1.0 equiv.), LiCl (1.5 equiv.), THF, 25 °C, 10 min, then *i*-Pr₂NEt (1.5 equiv.), 25 °C, 10 min, then 14 (1.15 equiv.), 25 °C, 30 min, 95%; e) 51 (1.0 equiv.), LiCl (1.5 equiv.), THF, 25 °C, 10 min, then *i*-Pr₂NEt (1.5 equiv.), 25 °C, 30 min, 95%; f) Ph₃PCH₃Br (1.6 equiv.), KHMDS (1.5 equiv.), THF, 25 °C, 30 min, then 57, $-78 \rightarrow 25$ °C, 1 h, 94%; g) PPTS (0.06 equiv.), EtOH, 45 °C, 20 h, 87%. KHMDS = potassium bis(trimethylsilyl)amide; Ms = methanesulfonyl; PPTS = pyridinium *para*-toluenesulfonate.

epoxidation¹⁷ of diene **61** indeed resulted in selective epoxidation of the desired C4–C5 alkene. Using Ti(Oi-Pr)₄ (4.0 equiv.), (S,S)-(-)-diisopropyl tartrate (4.5 equiv.) and t-BuOOH (7.5 equiv.) in CH₂Cl₂ at -25 °C for 75 min, the product 62 could be isolated in 31% yield, with unreacted diene starting material (61) being recovered in 34% yield. Compound 62 was formed as a single diastereomer, indicating that only one face of the C4-C5 alkene had undergone epoxidation. The stereochemistry of the newly-introduced epoxide group is assumed to be as shown in Scheme 8(a) on the basis of the (S,S)-chirality of the tartrate employed. While longer reaction times led to complete consumption of the starting diene 61, the yield of product 62 dropped precipitously, presumably due to Lewis acid-catalysed opening of the epoxide ring upon prolonged exposure to the reaction conditions. Lower reaction temperatures or the use of catalytic quantities of reagents¹⁸ resulted in unacceptably slow rates of conversion. The moderate isolated yield of epoxide 62 is also due in part due to the difficulties encountered during its isolation and purification, particularly its susceptibility to decomposition during silica gel chromatography. Although this epoxidation protocol was by no means optimal, and recognising that its application to the real systems [e.g. 59, Scheme 8(a), orthe corresponding caribenolide I-type diene] would represent a considerable increase in the demands placed upon it, we were,

nevertheless, greatly encouraged by the success and enabling power of the Katsuki–Sharpless epoxidation in this instance. It is interesting to note that epoxidation of diene **61** using *t*-BuOOH (2.2 equiv.) and a catalytic amount of VO(acac)₂ (20 mol %)¹⁹ in CH₂Cl₂ at 0 °C afforded nearly exclusively the regioisomeric allylic epoxide **63**, which was formed in 56% yield and as a 9 : 1 mixture of diastereoisomers (stereochemistry unassigned).

The origins of the superb regio- and stereo-selectivity exhibited in the conversion of diene **61** to allylic epoxide **62** can be rationalised using the highly predictable empirical model proposed by Sharpless and co-workers for the kinetic resolution of secondary allylic alcohols,²⁰ as depicted in Scheme 9. According to this model, delivery of an oxygen atom to the top face of the C4–C5 alkene by the titanium/(*S*,*S*)-(–)-tartrate catalyst system is predicted to be fast, whilst the rate of epoxidation of the C6 1,1-disubstituted alkene would be slowed by the steric encumbrance imposed by the C7 alkyl chain. The rate difference between the two processes is apparently such that only the desired mode of epoxidation, namely that at the C4–C5 alkene, is observed experimentally.

Assembly of the complete carbon frameworks of both target compounds 1 and 2 from their composite building block fragments was made possible in an extremely concise and efficient manner using the Enders chiral hydrazone alkylation methodology (Scheme 10).⁶ Our previous studies had established optimum



Scheme 8 (a) Proposed epoxidation of amphidinolide N precursor diene 59, (b) regioselective epoxidation of model diene 61 to give either of allylic epoxides 62 or 63. *Reagents and conditions*: a) TsOH·H₂O (1.0 equiv.), MeOH, 25 °C, 16 h, 79%; b) TBDPSCl (1.1 equiv.), Et₃N (1.4 equiv.), 4-DMAP (0.1 equiv.), CH₂Cl₂, 25 °C, 16 h, 77%; c) (*S*,*S*)-(-)-DIPT (4.5 equiv.), Ti(O*i*-Pr)₄ (4.0 equiv.), 4 Å MS, CH₂Cl₂, -25 °C, 30 min, then *t*-BuOOH (7.5 equiv.), -25 °C, 30 min, then 61, -25 °C, 75 min, 31% 62 + 34% recovered 61; d) VO(acac)₂ (0.2 equiv.), *t*-BuOOH (2.2 equiv.), CH₂Cl₂, 0 °C, 40 min, 56% (dr 9 : 1). acac = acetylacetonyl; DIPT = diisopropyl tartrate; 4-DMAP = 4-dimethylaminopyridine; MS = molecular sieves; TBDPS = *tert*-butyldiphenylsilyl; Ts = 4-toluenesulfonyl.



Scheme 9 An empirical model to rationalise the Katsuki–Sharpless epoxidation of model diene 61. DIPT = diisopropyl tartrate.

conditions for the alkylation of hydrazone **11** with iodides **64** or **65**;¹ nevertheless, the compatibility of this technology with the highly functionalised C1–C13 bromide fragment **56** was far from secure. Of particular concern was the potential for epimerisation at the C2 position adjacent to the ester group in bromide **56** under the basic conditions of the reaction. Pleasingly, however, any such fears proved to be unfounded, following the simple reversal of the order of the fragement coupling steps from our initial forays.¹ Thus, as shown in Scheme 10, hydrazone **11** was smoothly coupled first with caribenolide I C17–C29 iodide fragment **65** to give **66** in

88% yield, and then with bromide **56** to give, following cleavage of the hydrazone auxiliary using aqueous oxalic acid,²¹ ketone **68** as a single observable stereoisomer (49% from **66**). These latter two reactions are particularly illustrative of the mildness and functional group tolerance of the Enders hydrazone alkylation and hydrolysis steps, and represent the state of the art in terms of their application in complex molecule synthesis. Through a similar three-step sequence, the whole C1–C29 skeleton of amphidinolide N (**1**), represented by ketone **71**, could be assembled from the three fragments **11**, **56** and **64**. Thus, alkylation of hydrazone **11** with iodide **64** proceeded in excellent yield (93%) to give **69**, which was alkylated again with bromide **56** and then treated with aqueous oxalic acid to furnish ketone **71** in 59% yield for the two steps.

From ketones 68 or 71, relatively few manipulations were required to reach the fully deprotected core structures of amphidinolide N (1) or caribenolide I (2), respectively, again taking advantage of some of the end-game chemistry developed during the unsuccessful first-generation envne metathesis approach. Thus, as is shown in Scheme 11 for the case of caribenolide I-type ketone 68, removal of both PMB protecting groups was effected by treatment with DDQ under biphasic conditions in 70% yield. Hydrolysis of the resulting ester (72) to the corresponding acid (73) proved to be unexpectedly problematic. A wide variety of reaction conditions were screened, but were invariably plagued by competing elimination of the C3 silyloxy group and/or epimerisation at the C14 or C16 positions. A selection of the methods tried includes aq. LiOH/THF, aq. KOH/MeOH, aq. NaOH/ EtOH, LiOOH/THF,22 NaSePh/EtOH,23 NaSPh/DMF,24 (n-Bu₃Sn)₂O/PhMe²⁵ and (Me₂AlTeMe)₂/PhMe.²⁶ Fortunately, our recently developed protocol27 for the mild and selective hydrolysis of esters using Me₃SnOH²⁸ provided a timely solution to this



Scheme 10 Assembly of the complete caribenolide I and amphidinolide N carbon frameworks in ketones 68 and 71, respectively, through hydrazone alkylation fragment coupling reactions. *Reagents and conditions*: a) LDA (1.2 equiv.), THF, -78 °C, 1.75 h, then 65 (1.2 equiv.), -78 °C, 45 min, 88%; b) LDA (1.2 equiv.), THF, -78 °C, 1 h, then 56 (1.2 equiv.), -78 °C, 1 h; c) sat. aq. (CO₂H)₂, Et₂O, 25 °C, 48 h, 49% (two steps); d) LDA (1.2 equiv.), THF, -78 °C, 2.5 h, then 64 (1.2 equiv.), -78 °C, 1 h, 93%; e) LDA (1.1 equiv.), THF, -78 °C, 1 h, then 56 (1.1 equiv.), -78 °C, 1 h, 93%; e) LDA (1.1 equiv.), THF, -78 °C, 1 h, then 56 (1.1 equiv.), -78 °C, 1 h; f) sat. aq. (CO₂H)₂, Et₂O, 25 °C, 48 h, 59% (two steps).

problem, allowing for the conversion of ester 72 to acid 73 in 68% yield. It should be noted that these were the only conditions found that allowed for the clean and reproducible hydrolysis of ester 72. In contrast to the difficulties experienced with the step preceding it, macrolactonisation of acid 73 was found to be remarkably facile, proceeding under standard Yamaguchi conditions²⁹ to afford cyclised compound 75 in 80% yield. The success of this cyclisation may be partly due to the anchoring effect of the acetonide, tetrahydrofuran and alkene groups in acid 73, which serve to restrict the rotational degrees of freedom available to the substrate, minimising the entropic cost of cyclisation. Moreover, and as anticipated, this macrolactonisation reaction was superbly siteselective, with cyclisation occurring exclusively at the C25 hydroxy group. No trace of the corresponding C9 hydroxy-cyclised material (76) was detected, possibly due to there being a prohibitively high enthalpic barrier to forming a ten-membered ring containing an (E)-alkene, relative to forming the larger macrocycle (75). The structure of 75 was confirmed by 2-D NMR analysis, with an HMBC correlation being observed between the C25 methine proton and the ester carbonyl group. An added benefit of the siteselectivity of the macrolactonisation reaction was that the free C9 hydroxy group in the product (75) could be directly oxidised to the corresponding ketone 77 using TPAP/NMO³⁰ (92%). Finally, global deprotection of ketone 77, employing aqueous HF in

acetonitrile– CH_2Cl_2 (9 : 1) was accompanied by spontaneous intramolecular hemiacetal formation at the C15 carbonyl group, to generate tricyclic compound **78** (a *des*-epoxy-caribenolide I stereoisomer) as an inseparable 6 : 1 mixture of anomers (*vide infra*).

An analogous five-step sequence could also be applied to the amphidinolide N-type ketone 71, as illustrated in Scheme 12. Oxidative cleavage of the two PMB groups in ketone 71 using DDQ gave methyl ester 79 (78%), which was hydrolysed to the corresponding acid (80) using Me₃SnOH (45% isolated yield of 80, 66% based on recovered starting material 79). Yamaguchi macrolactonisation then afforded alcohol 81 (65%), which was oxidised to give ketone 82 in 80% yield. Global deprotection of ketone 82 [aqueous HF, acetonitrile–CH₂Cl₂ (4 : 1), $0 \rightarrow 25$ °C, 7 h] proceeded in excellent yield (94%) to generate a mixture of two products in a ratio of 1.6:1. Separation of the product mixture by careful flash column chromatography followed by comprehensive spectroscopic analysis indicated that the minor component was the expected hemiacetal (83, a des-epoxy-amphidinolide N stereoisomer), whilst the major product was the bicyclic acetal 84 derived from closure of both the C19 and C21 hydroxy groups onto the C15 ketone. Hemiacetal 83 was formed exclusively as the α -anomer. While stable under ambient conditions, hemiacetal 83 was slowly converted into bridged bicyclic compound 84 upon



Scheme 11 Completion of the total synthesis of *des*-epoxy-caribenolide I stereoisomer 78. *Reagents and conditions*: a) DDQ (3.0 equiv.), CH₂Cl₂-sat. aq. NaHCO₃ (15 : 1), 0 °C, 1 h, 70%; b) Me₃SnOH (4 × 10 equiv.), 1,2-dichloroethane, 80 °C, 96 h, 68%; c) 74 (30.0 equiv.), Et₃N (40.0 equiv.), toluene, 25 °C, 16 h, then add to 4-DMAP (30.0 equiv.), toluene, 25 °C, 22 h, 80%; d) TPAP (0.5 equiv.), NMO (4.0 equiv.), 4 Å MS, CH₂Cl₂, 25 °C, 2 h, 92%; e) 48% aq. HF, MeCN–CH₂Cl₂ (9 : 1), $0 \rightarrow 25$ °C, 5 h, 65% ($\alpha : \beta, 6 : 1$). 4-DMAP = 4-dimethylaminopyridine; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; MS = molecular sieves; NMO = 4-methylmorpholine *N*-oxide; TPAP = tetra-*n*-propylammonium perruthenate.



Scheme 12 Completion of the total syntheses of *des*-epoxy-amphidinolide N stereoisomer 83 and bicyclic acetal 84. *Reagents and conditions*: a) DDQ (3.0 equiv.), $CH_2Cl_2-pH 7$ aq. buffer (2 : 1), 0 °C, 20 min, 78%; b) Me₃SnOH (5 × 10 equiv.), 1,2-dichloroethane, 80 °C, 60 h, 45% 80 + 21% 79; c) 74 (30.0 equiv.), Et₃N (40.0 equiv.), toluene, 25 °C, 16 h, then add to 4-DMAP (30.0 equiv.), toluene, 25 °C, 22 h, 65%; d) TPAP (0.2 equiv.), NMO (3.0 equiv.), 4 Å MS, CH_2Cl_2 , 25 °C, 2 h, 80%; e) 48% aq. HF, MeCN– CH_2Cl_2 (4 : 1), 0 \rightarrow 25 °C, 7 h, 94% (83 : 84, 1 : 1.6). 4-DMAP = 4-dimethylaminopyridine; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; MS = molecular sieves; NMO = 4-methylmorpholine *N*-oxide; TPAP = tetra-*n*-propylammonium perruthenate.

exposure to mildly acidic conditions (*e.g.* cat. PPTS in CH_2Cl_2), providing further evidence for the formulations of **83** and **84** being as shown in Scheme 12.

Analysis of the ROESY spectra of intermediates **78**, **83** and **84** revealed some interesting relationships between the conformations of the C13–C21 sector within this class of compounds. The tetrahydropyran portion of amphidinolide N (**1**) has been proposed to adopt the chair conformation illustrated in Fig. 1(a), in which the C14 side-chain resides in an axial position on the ring.² The natural product is presumably biased towards this seemingly unfavourable scenario either by intramolecular hydrogen-bonding or the steric compression imposed by the rest of the macrocyclic system in its natural configuration. In contrast, we propose the major anomer of synthetic caribenolide-type compound **78** to have the opposite



Fig. 1 Conformational analysis of the C13–C21 tetrahydropyran sectors of (a) amphidinolide N (1), (b) *des*-epoxy-caribenolide I stereoisomer **78**, (c) bicyclic acetal **84** and (d) *des*-epoxy-amphidinolide N stereoisomer **83**.

stereochemistry at the C15 position, as shown in Fig. 1(b), a conjecture based largely on the absence of observable ROESY cross-peaks between either the C14 and C19 protons, or between the C13 and C16 protons. More substantial differences can be seen between amphidinolide N (1) and its synthetic analogues 83 and 84. The bridged bicyclic nature of acetal 84 means that it is forced to adopt the conformation depicted in Fig. 1(c), in which the C15-C19 tetrahydropyran has undergone a chair-flip compared to the corresponding structure in amphidinolide N (1). The remaining tetrahydropyran ring in compound 84 adopts a boat conformation, to avoid placing the C21 side-chain directly in contact with the axial C17 proton. It should be noted that the propensity for the formation of bicyclic compound 84 suggests that naturally-occurring amphidinolide N (1) has the opposite configuration at the C21 stereocentre [i.e. is (21R), rather than (21S) as in 84]. However, the remote effects of one or more of the remaining stereocentres on the macrocyclic perimeter most likely not being in the naturally-occurring configuration cannot be ruled out as contributing to the favourable formation of the bicyclic system. Clear ROESY cross-peaks between the C14 and C21 protons, and between the C13 and C16 protons, indicate that the C13/C14 unit is oriented as shown in Fig. 1(c), allowing for a stabilising hydrogen-bonding interaction between the C14 and the (now equatorial) C16 hydroxy groups. Somewhat to our initial surprise, the C15–C19 tetrahydropyran portion of hemiacetal 83 [Fig. 1(d)] was found to adopt a conformation analogous to that of bicyclic acetal 84. On closer inspection, it can be argued that the energetic 'cost' of placing the C19 side-chain in an axial position is more than compensated for by the hydrogen-bonding network that can be set up between the C14, C15 and C16 hydroxy groups in this chair conformation. Thus, while the C14-C19 sector of this compound (83) has the same relative stereochemical relationship as is found in amphidinolide N [compare 1, Fig. 1(a), with 83, Fig. 1(d)], such two-dimensional representations disguise the major conformational differences between these two materials.

From diene 78, completion of the total synthesis of the first caribenolide I stereoisomer then required the selective epoxidation of the C4-C5 alkene. Unfortunately, it has not proved to be possible to effect this transformation to date [Scheme 13(a)]. The Katsuki-Sharpless epoxidation conditions which were successful for the model system (cf. Scheme 8) did not lead to any detectable levels of conversion of diene 78 to epoxide 85. Increasing the number of equivalents of reagents, temperature or reaction time did nothing to rectify this situation, with the starting diene 78 invariably being recovered unchanged. In stark contrast, the use of reagents such as *m*-CPBA or *t*-BuOOH/cat. VO(acac)₂ rapidly generated a multitude of unidentifiable oxidation products, resulting from non-chemoselective alkene epoxidation and/or epoxide opening. An exhaustive survey of epoxidation methods then ensued, but yielded no favourable results. A similar story unfolded with diene 83 [Scheme 13(b)]; to date this compound could not be converted into the corresponding amphidinolide N stereoisomer 86.

An alternative route to caribenolide I stereoisomer **85** from one of the advanced intermediates in hand would be to effect the epoxidation of protected substrate **77** to give compound **87** [Scheme 13(a)], followed by global deprotection. However, with diene **77** containing no real handles for controlling the



Scheme 13 (a) Attempted completion of the total synthesis of caribenolide I stereoisomer 85 through epoxidation of dienes 77 or 78, (b) attempted completion of the total synthesis of amphidinolide N stereoisomer 86 through epoxidation of diene 83.

chemoselectivity of the epoxidation, we feared for the viability of this particular strategy. Indeed, epoxidation of diene **77**, under a variety of conditions, was found to be even less selective than that of the corresponding protecting group-free substrate **78**, therefore this strategy was not pursued any further.

In a similar vein, the Katsuki–Sharpless epoxidation of bicyclic acetal **84** to give the amphidinolide N analogue **88** was unsuccessful (Scheme 14). Eventually, after much experimentation, it was found that exposure of acetal **84** to freshly prepared DMDO³¹ in CH₂Cl₂/acetone at 0 °C resulted in selective epoxidation of the C6 exocyclic methylene group, affording the regioisomeric *iso*-epoxy-amphidinolide N stereoisomer **89** in 31% yield. Minor amounts of unidentified side-products were formed during this reaction, but the moderate isolated yield of allylic epoxide **89** primarily reflects its tendency towards decomposition during purification. Compound **89** was formed as a single epoxide diastereomer, although the configuration of the newly-formed chiral centre could not be determined unambiguously. Treat-

ment of either of dienes **78** or **83** with DMDO under the same conditions did not lead to the formation of any recognisable products in synthetically useful yields, indicating that the precise three-dimensional conformation of the macrocyclic system is essential to attaining selectivity in this epoxidation process.

The compounds illustrated in Fig. 2 (for the preparation of hemiacetal **92** from ketone **90** see Scheme 15, and for the preparation of **90**, **93** and **94** see the preceding paper in this issue¹) were screened for cytotoxicity *in vitro* against the following human tumour cell lines: 1A9 and PTX10 (ovarian), MCF-7 and MDA-MB-231 (breast), HCT-116 (colon), A459 (lung) and PC3 (prostate). None of these compounds showed activity against any of the cell lines at concentrations below 1.5 μ M. In comparison, caribenolide I (2) has an IC₅₀ value of 1.6 nM against the HCT-116 cell line,³ while amphidinolide N (1) has IC₅₀ values of 0.08 and 0.09 nM against murine lymphoma L1210 and human epidermoid carcinoma KB-31 cell lines, respectively.²



Scheme 14 Epoxidation of bicyclic acetal 84 using DMDO to generate *iso*-epoxy-amphidinolide N stereoisomer 89. *Reagents and conditions*: a) DMDO (1.4 equiv.), CH_2Cl_2 -acetone (4.5 : 1), 0 °C, 40 min, 31%. DMDO = dimethyldioxirane.



Fig. 2 Amphidinolide N and caribenolide I synthetic intermediates and analogues screened for cytotoxicity in vitro.



Scheme 15 Deprotection of ketone 90 to give hemiacetal 92. *Reagents and conditions*: a) DDQ (3.0 equiv.), CH₂Cl₂–pH 7 aq. buffer (4 : 1), 0 °C, 20 min, 91%; b) 48% aq. HF, MeCN, $0 \rightarrow 25$ °C, 7.5 h, 56% (α : β , 10 : 1). DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

Conclusion

Highly convergent and enantioselective routes to the macrocyclic frameworks of amphidinolide N (1) and caribenolide I (2) have been developed, culminating in the total synthesis of *des*-epoxy-caribenolide I structure **78**, *des*-epoxy-amphidinolide N structures **83** and **84**, and *iso*-epoxy-amphidinolide N structure **89**. The success of these endeavours required the advancement of a number of synthetic strategies and tactics, most notably the Enders hydrazone alkylation methodology for the stereoselective construction of 1,3-dihydroxyketone derivatives, and further verified the mildness and utility of our protocol for the hydrolysis of esters using Me₃SnOH. Installment of the C4–C5 allylic epoxide

group required to complete the synthesis of amphidinolide N (1) or caribenolide I (2) remains problematic. Nevertheless, the flexibility and efficiency of the described strategy should allow for its adaptation to the generation of a wide variety of analogues and stereoisomers of the target compounds 1 and 2. This work has opened the door for both the eventual determination of stereostructure of 1 and 2, and further biological evaluation of this important class of natural products.

Experimental

For general experimental details, see the preceding paper in this issue.¹

Aldehyde 14

A solution of alkene 15¹ (4.00 g, 15.5 mmol) in CH₂Cl₂ (150 mL) was cooled to -78 °C and a stream of ozone (*ca.* 10% in oxygen) was bubbled through the mixture until a deep blue color persisted. Oxygen was then bubbled through the solution for an additional 20 min to remove excess ozone. PPh₃ (6.11 g, 23.3 mmol) was added to the solution, which was then stirred and warmed to room temperature over 1 h. The mixture was then concentrated under reduced pressure, and triturated with 4 : 1 hexanes-Et₂O. The precipitated Ph₃PO was then removed by filtration, and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography on silica gel (gradient: 2.5–10% Et₂O in hexanes) to give 14 (3.563 g, 88%) as a colourless oil. $R_{\rm f} = 0.12$ (silica gel, 23 : 2 hexanes–Et₂O); $[a]_{D}^{25}$ +33.4° (c 1.31 in CH₂Cl₂); v_{max}/cm^{-1} (film) 2950, 2862, 1739, 1252, 1031, 836; $\delta_{\rm H}$ (500 MHz, C₆D₆) 9.41 (1 H, s, H-4), 4.26 (1 H, d, J 3.6 Hz, H-3), 3.34 (3 H, s, CO₂CH₃), 2.72 (1 H, qd, J 7.0, 3.6 Hz, H-2), 1.05 (3 H, d, J 7.0 Hz, 2-CH₃), 0.86 [9 H, s, SiC(CH₃)₃], -0.03 (3 H, s, SiCH₃), -0.07 (3 H, s, SiCH₃); $\delta_{\rm C}$ (125 MHz, C₆D₆) 201.5, 173.2, 78.6, 51.4, 42.7, 25.8,

18.3, 10.8, -4.6, -5.3; HRMS (ES⁺) m/z calc. for C₁₂H₂₄O₄SiNa ([MNa]⁺): 283.1336, found: 283.1331.

α,β-Unsaturated ketone 17

A solution of phosphonate 16^7 (0.403 g, 1.30 mmol) in acetonitrile (10 mL) was added to flame-dried LiCl (0.085 g, 2.0 mmol) in a round-bottomed flask at room temperature. After 10 min, i-Pr₂NEt (0.36 mL, 2.0 mmol) was added, and the mixture stirred for a further 10 min before the addition of a solution of aldehyde 14 (0.406 g, 1.56 mmol) in acetonitrile (4 mL). The mixture was then allowed to stir for 36 h at room temperature, before being quenched by the addition of water (35 mL). The mixture was then extracted with Et₂O (3×20 mL), and the combined organic layers were washed with brine (1 \times 35 mL), dried (MgSO₄), filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (5% Et₂O in hexanes) to give 17 (0.540 g, 93%) as a colourless oil. $R_f = 0.41$ (silica gel, 4 : 1 hexanes-Et₂O); $[a]_{D}^{25}$ -3.8° (c 1.25 in CHCl₃); v_{max} /cm⁻¹ (film) 2954, 1746, $1698, 1634, 1435, 1362, 1081, 837; \delta_{\rm H}$ (600 MHz, CDCl₃) 6.90 (1 H, dd, J 15.6, 5.0 Hz, 4-H), 6.68 (1 H, d, J 15.6 Hz, 5-H), 4.71 (1 H, dd, J 5.0, 4.7 Hz, 3-H), 4.28 (1 H, q, J 6.7 Hz, 7-H), 3.66 (3 H, s, CO₂CH₃), 2.57 (1 H, qd, J 7.0, 4.7 Hz, 2-H), 1.29 (3 H, d, J 6.7 Hz, 7-CH₃), 1.11 (3 H, d, J 7.0 Hz, 2-CH₃), 0.89 [9 H, s, SiC(CH₃)₃], 0.88 [9 H, s, SiC(CH₃)₃], 0.06 (3 H, s, SiCH₃), 0.06 (3 H, s, SiCH₃), 0.01 (3 H, s, SiCH₃), -0.01 (3 H, s, SiCH₃); $\delta_{\rm C}$ (150 MHz, CDCl₃) 201.9, 174.8, 148.8, 124.8, 75.3, 73.8, 52.6, 46.4, 26.7, 26.8, 21.7, 19.1, 18.9, 11.5, -3.4, -4.0, -4.0, -4.4; HRMS (ES⁺) m/z calc. for C₂₂H₄₅O₅Si₂ ([MH]⁺): 445.2800, found: 445.2791.

Diene 18

Methyltriphenylphosphonium bromide (0.693 g, 1.94 mmol) was dried under high vacuum (0.1 mmHg) for 16 h at room temperature, then THF (6 mL) was added. KHMDS (3.65 mL, 0.5 M in toluene, 1.82 mmol) was then added dropwise to the stirred suspension at room temperature. After 30 min, the bright yelloworange solution was cooled to -78 °C, where a solution of ketone 17 (0.540 g, 1.21 mmol) in THF (2 mL) was added dropwise. After stirring for 1 h, the mixture was warmed to room temperature and then quenched by the addition of sat. aq. NH₄Cl (15 mL). The mixture was then extracted with Et_2O (3 × 10 mL), and the combined organic layers were washed with brine $(1 \times 15 \text{ mL})$, dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was triturated with 9 : 1 hexanes-Et₂O, and the precipitated Ph₃PO was then removed by filtration. The filtrate was concentrated under reduced pressure, and then the residue was purified by flash chromatography on silica gel (5% Et_2O in hexanes) to give 18 (0.498 g, 94%) as a colourless oil. $R_{\rm f} = 0.66$ (silica gel, 4 : 1 hexanes-Et₂O); $[a]_{D}^{25}$ -18.7° (c 1.23 in CHCl₃); v_{max} /cm⁻¹ (film) 2955, 1742, 1433, 1361, 1094, 837; $\delta_{\rm H}$ (600 MHz, CDCl₃) 6.12 (1 H, d, J 16.1 Hz, 5-H), 5.70 (1 H, dd, J 16.1, 7.0 Hz, 4-H), 5.22 (1 H, s, 6=CH₂), 5.00 (1 H, s, 6=CH₂), 4.45 (1 H, q, J 6.3 Hz, 7-H), 4.39 (1 H, dd, J 7.0, 6.5 Hz, 3-H), 3.63 (3 H, s, CO₂CH₃), 2.54 (1 H, qd, J 7.0, 6.5 Hz, 2-H), 1.26 (3 H, d, J 6.3 Hz, 7-CH₃), 1.16 (3 H, d, J 7.0 Hz, 2-CH₃), 0.89 (9 H, s, SiC(CH₃)₃), 0.87 $[9 \text{ H}, \text{ s}, \text{SiC}(CH_3)_3], 0.04 (3 \text{ H}, \text{ s}, \text{SiC}H_3), 0.03 (3 \text{ H}, \text{ s}, \text{SiC}H_3),$ 0.02 (3 H, s, SiCH₃), 0.00 (3 H, s, SiCH₃); $\delta_{\rm C}$ (150 MHz, CDCl₃) 174.7, 149.8, 130.3, 130.0, 113.3, 75.1, 68.8, 51.5, 47.1, 25.8, 25.7,

24.6, 18.3, 18.1, 11.8, -4.2, -4.9, -5.1; HRMS (ES⁺) m/z calc. for $\rm C_{23}H_{47}O_4Si_2$ ([MH]⁺): 443.3007, found: 443.3002.

4,4-Dimethoxybutanal 20⁹

A solution of alkene 21 (9.5 g, 40.9 mmol) was dissolved in CH₂Cl₂ (300 mL), and the mixture was cooled to -78 °C. A stream of ozone (ca. 10% in oxygen) was bubbled through the solution until a deep blue color persisted, then argon was bubbled through the solution for an additional 15 min to remove excess ozone. PPh3 (16.1 g, 61.3 mmol) was added in one portion to the solution, which was then stirred and warmed to room temperature over 1 h. The mixture was then concentrated under reduced pressure, and triturated with 4 : 1 hexanes- Et_2O . The precipitated Ph_3PO was then removed by filtration, and the filtrate was concentrated in vacuo. The residue was purified by distillation under reduced pressure (bp 66-75 °C, 13 mmHg) to give 20 (8.54 g, 79%) as a colourless oil, the spectroscopic data of which were in agreement with those reported in the literature.⁹ $R_{\rm f} = 0.16$ (silica gel, 4 : 1 hexanes–Et₂O); $\delta_{\rm H}$ (400 MHz, CDCl₃) 9.72 (1 H, t, J 1.5 Hz, 1-H), 4.35 (1 H, t, J 5.6 Hz, 4-H), 3.30 [6 H, s, CH(OCH₃)₂], 2.48 (2 H, td, J 7.2, 1.5 Hz, 2-H and 2-H), 1.92 (2 H, td, J 7.2, 5.6 Hz, 3-H and 3-H).

(4Z)-1,1,8,8-Tetramethoxyoct-4-ene 21

1,5-Cyclooctadiene (40.0 g, 369.6 mmol) was dissolved in 1 : 1 CH₂Cl₂-MeOH (800 mL), and the mixture was cooled to -78 °C. A stream of ozone (ca. 10% in oxygen) was bubbled through the solution for 2.5 h, then argon was bubbled through the solution for an additional 10 min to remove any residual ozone. TsOH·H₂O (5.32 g, 28.0 mmol) was added to the mixture, which was then stirred and allowed to warm to room temperature over 2 h under an atmosphere of argon. Me₂S (200 mL) was then added, and stirring continued for a further 18 h. The mixture was then concentrated under reduced pressure, and the residue was taken up in sat. aq. NaHCO₃ (800 mL) and extracted with CH_2Cl_2 (3 × 500 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (gradient: 20-33%) Et_2O in hexanes) to give 21 (43.1 g, 50%) as a pale yellow oil. $R_{\rm f} = 0.24$ (silica gel, 2 : 1 hexanes–Et₂O); $v_{\rm max}/{\rm cm}^{-1}$ (film) 2943, 2829, 1447, 1365, 1124, 916; $\delta_{\rm H}$ (500 MHz, CDCl₃) 5.38 (2 H, t, J 4.6 Hz, 9-H and 9'-H), 4.36 (2 H, t, J 5.8 Hz, 6-H and 6'-H), 3.32 [12 H, s, CH(OCH₃)₂ and CH(OCH₃)₂], 2.10 (4 H, td, J 7.8, 4.6 Hz, 8-H, 8-H, 8'-H and 8'-H), 1.65 (4 H, td, J 7.8, 5.8 Hz, 7-H, 7-H, 7'-H and 7'-H); δ_c (125 MHz, CDCl₃) 129.2, 103.8, 52.5, 32.2, 22.2; HRMS (ES⁺) m/z calc. for C₁₂H₂₄O₄Na ([MNa]⁺): 255.1567, found: 255.1574.

Alcohol 22

To a stirred solution of KOt-Bu (10.77 g, 96.0 mmol) in THF (95 mL) at -45 °C was added *trans*-2-butene (17.0 mL, 180 mmol) followed by the dropwise addition of *n*-BuLi (60.0 mL, 1.6 M in hexanes, 96.0 mmol) over 25 min. After 15 min, the bright yellow solution was cooled to -78 °C where a solution of (+)-Ipc₂BOMe (30.37 g, 96.0 mmol) in THF (75 mL) was added, and the mixture stirred at that temperature for 1 h before the addition of BF₃·OEt₂ (12.2 mL, 96.0 mmol). After an additional 30 min, a solution

of aldehyde 20 (8.02 g, 60.0 mmol) in THF (30 mL) was added dropwise, and stirring continued for 4 h at -78 °C before the reaction mixture was quenched by the addition of MeOH (20 mL) and warmed to 0 °C. A mixture of 3 M aq. NaOH (300 mL) and 35% aq. H₂O₂ (65 mL) was added dropwise over 30 min, and the solution was warmed to room temperature overnight, before being extracted with Et₂O (3 \times 200 mL). The combined organic layers were washed with water $(1 \times 200 \text{ mL})$, brine $(1 \times 200 \text{ mL})$, dried (MgSO₄), filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (gradient: 20-60% Et₂O in hexanes) to give 22 (7.79 g, 69%) as a light yellow oil. $R_{\rm f} = 0.23$ (silica gel, 1 : 1 hexanes-Et₂O); $[a]_{\rm D}^{25} - 2.4^{\circ}$ (c 1.08 in CH₂Cl₂); v_{max}/cm⁻¹ (film) 3459, 3073, 2952, 1455, 1369, 1126, 999; δ_H (500 MHz, C₆D₆) 5.70 (1 H, ddd, J 16.6, 11.0 and 8.2 Hz, 11-H), 4.92–4.97 (2 H, m, 12-H and 12-H), 4.30 (1 H, t, J 5.6 Hz, 6-H), 3.22–3.26 (1 H, m, 9-H), 3.14 [6 H, s, CH(OCH₃)₂], 2.01– 2.07 (1 H, m, 10-H), 1.89 (1 H, dddd, J 13.9, 9.7, 5.7 and 5.6 Hz, 7-H), 1.72 (1 H, dddd, J 13.9, 9.6, 5.8 and 5.6 Hz, 7-H), 1.65 (1 H, br s, OH), 1.49-1.55 (1 H, m, 8-H), 1.42-1.47 (1 H, m, 8-H), 0.94 (3 H, d, J 6.7 Hz, 10-CH₃); $\delta_{\rm C}$ (125 MHz, C₆D₆) 140.8, 115.6, 104.8, 74.5, 52.4, 52.2, 44.7, 29.6, 29.4, 16.4; HRMS (ES⁺) m/z calc. for C₁₀H₂₀O₃Na ([MNa]⁺): 211.1305, found 211.1299.

(R)-Mosher's ester 23

To a stirred solution of alcohol 22 (35 mg, 0.186 mmol) in CH₂Cl₂ (2.5 mL) were added 4-DMAP (23 mg, 0.186 mmol), Et₃N (78 µL, 0.558 mmol) and (S)-(+)-methoxy- α -(trifluromethyl)phenylacetyl chloride (52 µL, 0.279 mmol) sequentially at room temperature. After 2 h the mixture was poured into sat. aq. NaHCO₃ (20 mL) and CH₂Cl₂ (20 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL), and the combined organic layers were washed with brine $(1 \times 20 \text{ mL})$, dried (MgSO₄), filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (gradient: 15-20% Et₂O in hexanes) to give 23 (73 mg, 97%) as a colourless oil. The ee of this material was determined to be 94% by ¹H- and ¹⁹F-NMR studies. $R_{\rm f} = 0.49$ (silica gel, 1 : 1 hexanes-Et₂O); $[a]_{\rm D}^{25} - 16.4^{\circ}$ (c 1.4 in CH₂Cl₂); v_{max}/cm⁻¹ (film) 2950, 2831, 1744, 1641, 1451, 1262, 1169, 1125, 1081, 923, 720, 500; $\delta_{\rm H}$ (500 MHz, C₆D₆) 7.71 (2 H, d, J 7.8 Hz, ArH), 7.07-7.10 (2 H, m, ArH), 7.01-7.05 (1 H, m, ArH), 5.60 (1 H, ddd, J 17.0, 10.5 and 8.0 Hz, H-11), 5.08-5.11 (1 H, m, 9-H), 4.87-4.88 (1 H, m, 12-H), 4.85 (1 H, ddd, J 10.5, 1.7 and 0.8 Hz, 12-H), 4.17-4.19 (1 H, m, 6-H), 3.43 (3 H, s, F₃CCOCH₃), 3.09 [3 H, s, CH(OCH₃)₂], 3.08 [3 H, s, CH(OCH₃)₂], 2.23–2.30 (1 H, m, 10-H), 1.58–1.70 (4 H, m, 7-H, 7-H, 8-H and 8-H), 0.77 (3 H, d, J 7.0 Hz, 10-CH₃); $\delta_{\rm C}$ (125 MHz, C_6D_6) 166.4, 138.7, 133.0, 129.7, 128.5, 127.9, 124.3 (q, ${}^1J_{19}_{F^{-13}C}$ 288.5 Hz), 116.3, 104.2, 85.1 (q, ${}^{2}J_{19}_{F^{-13}C}$ 27.5 Hz), 79.9, 55.4, 52.6, 52.4, 41.3, 28.9, 26.5, 15.8; $\delta_{\rm F}$ (376 MHz, C₆D₆) -70.98 (major diasteroisomer), -70.95 (minor diastereoisomer); HRMS (ES+) m/z calc. for C₂₀H₂₇F₃O₅Na ([MNa]⁺): 427.1703, found 427.1702.

(S)-Mosher's ester 24

To a stirred solution of alcohol **22** (41 mg, 0.218 mmol) in CH₂Cl₂ (3.5 mL) were added 4-DMAP (27 mg, 0.218 mmol), Et₃N (91 μ L, 0.653 mmol) and (*R*)-(–)-methoxy- α -(trifluromethyl)phenylacetyl chloride (61 μ L, 0.327 mmol) sequentially at room temperature.

After 2 h the mixture was poured into sat. aq. NaHCO₃ (20 mL) and CH₂Cl₂ (20 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL), and the combined organic layers were washed with brine $(1 \times 20 \text{ mL})$, dried (MgSO₄), filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (gradient: 15-20% Et₂O in hexanes) to give 24 (84 mg, 95%) as a colourless oil. The ee of this material was determined to be 94% by ¹H- and ¹⁹F-NMR studies. $R_{\rm f} = 0.47$ (silica gel, 1 : 1 hexanes–Et₂O); $[a]_{\rm D}^{25} - 35.3^{\circ}$ (c 1.62 in CH₂Cl₂); v_{max}/cm⁻¹ (film) 3075, 2954, 2832, 1746, 1643, 1452, 1259, 1122, 1017, 924, 720; *δ*_H (500 MHz, C₆D₆) 7.71 (2 H, d, J 7.7 Hz, ArH), 7.07-7.11 (2 H, m, ArH), 7.02-7.06 (1 H, m, ArH), 5.63 (1 H, ddd, J 17.0, 10.5 and 8.0 Hz, 11-H), 5.08-5.11 (1 H, m, 9-H), 4.91-4.92 (1 H, m, 12-H), 4.88-4.90 (1 H, m, 12-H), 4.16 (1 H, t, J 5.3 Hz, 6-H), 3.42 (3 H, s, F₃CCOCH₃), 3.05 [3 H, s, CH(OCH₃)₂], 3.03 [3 H, s, CH(OCH₃)₂], 2.26–2.32 (1 H, m, 10-H), 1.42–1.64 (4 H, m, 7-H, 7-H, 8-H and 8-H), 0.86 (3 H, d, J 7.0 Hz, 10-CH₃); $\delta_{\rm C}$ (125 MHz, C₆D₆) 166.5, 139.1, 133.0, 129.7, 128.5, 127.9, 124.4 (q, ${}^{1}J_{19}_{F^{-13}C}$ 288.3 Hz), 116.2, 104.1, 85.2 (q, ${}^{2}J_{19}_{F^{-13}C}$ 27.5 Hz), 55.5, 52.6, 52.1, 41.5, 28.5, 26.3, 16.0; δ_F (376 MHz, C₆D₆) -70.97 (major diasteroisomer), -71.00 (minor diastereoisomer); HRMS (ES⁺) m/z calc. for C₂₀H₂₇F₃O₅Na ([MNa]⁺): 427.1703, found 427.1703.

p-Methoxybenzyl ether 25

To a stirred suspension of NaH (2.40 g, 60% dispersion in mineral oil, 60.0 mmol) in THF (125 mL) was added a solution of alcohol 22 (7.06 g, 37.5 mmol) in THF (50 mL) dropwise at 0 °C. After 30 min, PMBC1 (8.2 mL, 60.0 mmol) and n-Bu₄NI (0.70 g, 1.9 mmol) were added, and the solution was heated to reflux for 16 h. After cooling to room temperature, the reaction was quenched by the careful addition of water (200 mL), and was then extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with brine (1 \times 150 mL), dried (MgSO₄), filtered and concentrated in vacuo. The residue was then taken up in MeOH (50 mL) and cooled to 0 °C, where HC(OMe)₃ (20 mL) and La(OTf)₃ (0.33 g, 0.56 mmol) were added. The stirred solution was allowed to warm to room temperature over 16 h. The reaction mixture was then concentrated to half its original volume under reduced pressure, and sat. aq. NaHCO₃ (150 mL) was added. The mixture was extracted with Et_2O (3 × 150 mL), and the combined organic layers were washed with brine (1 \times 150 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (10% Et_2O in hexanes) to give 25 (11.20 g, 96% from 22) as a colourless oil. $R_{\rm f} = 0.53$ (silica gel, 1 : 1 hexanes-Et₂O); $[a]_{\rm D}^{25} - 11.8^{\circ}$ (c 1.00 in CH₂Cl₂); v_{max}/cm⁻¹ (film) 2941, 2830, 1613, 1511, 1461, 1242, 1126, 958; δ_H (500 MHz, C₆D₆) 7.23 (2 H, d, J 8.6 Hz, ArH), 6.79 (2 H, d, J 8.6 Hz, ArH), 5.81-5.93 (1 H, m, 11-H), 5.01-5.04 (2 H, m, 12-H and 12-H), 4.30–4.39 (3 H, m, 6-H and OCH₂Ar), 3.31 (3 H, s, ArOCH₃), 3.21 (1 H, dt, J 7.4, 4.3 Hz, 9-H), 3.15 [6 H, s, CH(OCH₃)₂], 2.42–2.48 (1 H, m, 10-H), 1.85–1.93 (1 H, m, 7-H), 1.64-1.74 (3 H, m, 7-H, 8-H and 8-H), 1.04 (3 H, d, J 6.9 Hz, 10-CH₃); δ_C (125 MHz, C₆D₆) 159.6, 141.3, 131.6, 129.4, 114.5, 114.0, 104.7, 82.3, 71.5, 54.7, 52.3, 52.1, 40.8, 29.3, 26.0, 15.0; HRMS (ES⁺) m/z calc. for C₁₈H₂₈O₄Na ([MNa]⁺): 331.1880, found: 331.1883.

α,β-Unsaturated ester 29

A solution of alkene 25 (29.0 g, 94.0 mmol) in CH₂Cl₂ (500 mL) was cooled to -78 °C and a stream of ozone (ca. 10% in oxygen) was bubbled through the mixture until TLC analysis confirmed the complete consumption of starting material, then oxygen was bubbled through the solution for an additional 20 min to remove excess ozone. PPh₃ (37.0 g, 141 mmol) was added to the solution, which was then stirred and warmed to room temperature over 1 h. The mixture was then concentrated under reduced pressure, and triturated with 4 : 1 hexanes- Et_2O . The precipitated Ph_3PO was then removed by filtration, and the filtrate was concentrated in vacuo. Quick filtration through silica gel with 20:1 hexanes-Et₂O removed the excess PPh₃, the filtrate was concentrated, and the residue was taken up in benzene (400 mL). Phosphorane 28 (43.3 g, 119 mmol) was added in one portion, and the solution was heated to 70 °C for 16 h. An additional portion of phosphorane 28 (12.0 g, 33.1 mmol) was then added, and stirring continued for an additional 24 h at 70 °C. The solution was then cooled to room temperature and concentrated in vacuo. The residue was triturated with 5:1 hexanes-Et₂O, and the precipitated Ph₃PO was removed by filtration. The filtrate was concentrated under reduced pressure, and then purified by flash chromatography on silica gel (gradient: 9-20% Et₂O in hexanes) to give 29 (28.9 g, 78% from 25) as a colourless oil. $R_{\rm f} = 0.35$ (silica gel, 1 : 1 hexanes-Et₂O); $[a]_{\rm D}^{25} + 1.1^{\circ}$ (c 0.72 in CH₂Cl₂); v_{max}/cm⁻¹ (film) 2953, 2928, 1707, 1647, 1510, 1450, 1364, 1068, 823; δ_H (500 MHz, C₆D₆) 7.20 (2 H, d, J 8.6 Hz, ArH), 7.04 (1 H, dq, J 10.0, 1.4 Hz, 11-H), 6.78 (2 H, d, J 8.6 Hz, ArH), 4.36 (1 H, d, J 11.3 Hz, OCH₂Ar), 4.32 (1 H, d, J 11.3 Hz, OCH₂Ar), 4.24 (1 H, t, J 5.4 Hz, 6-H), 4.03 (2 H, app qd, J 7.1, 2.7 Hz, CO₂CH₂CH₃), 3.29 (3 H, s, ArOCH₃), 3.14–3.20 (1 H, m, 9-H), 3.13 [6 H, s, CH(OCH₃)₂], 2.66–2.70 (1 H, m, 10-H), 1.91 (3 H, d, J 1.4 Hz, 12-CH₃), 1.79-1.83 (1 H, m, 7-H), 1.61-1.70 (2 H, m, 7-H and 8-H), 1.55–1.59 (1 H, m, 8-H), 0.96 (3 H, t, J 7.1 Hz, CO₂CH₂CH₃), 0.93 (3 H, d, J 6.8 Hz, 10-CH₃); $\delta_{\rm C}$ (125 MHz, C₆D₆) 167.7, 159.7, 144.2, 131.3, 129.5, 128.4, 114.0, 104.6, 81.6, 71.8, 60.3, 54.7, 52.4, 52.2, 36.9, 28.9, 26.7, 15.8, 14.3, 12.9; HRMS (ES⁺) *m*/*z* calc. for C₂₂H₃₄O₆Na ([MNa]⁺): 417.2247, found: 417.2249.

Allylic alcohol 30

To a stirred solution of ethyl ester 29 (9.60 g, 24.3 mmol) in THF (120 mL) was added DIBAL-H (48.0 mL, 1.5 M in toluene, 73.0 mmol) dropwise at -78 °C. After 2.5 h, the reaction was quenched by the careful addition of MeOH (10 mL) and then warmed to 0 °C, where sat. aq. Rochelle's salt (250 mL) was added. After stirring vigorously at room temperature for 2 h, the mixture was extracted with EtOAc (3 \times 125 mL), and the combined organic layers were washed with brine $(1 \times 200 \text{ mL})$, dried (MgSO₄), filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (gradient: 20– 60% EtOAc in hexanes) to give 30 (8.22 g, 96%) as a colourless oil. $R_{\rm f} = 0.30$ (silica gel, 1 : 1 hexanes–EtOAc); $[a]_{\rm D}^{25} - 18.0^{\circ}$ (c 0.35 in CH₂Cl₂); v_{max}/cm⁻¹ (film) 3433, 2932, 1611, 1455, 1370, 1176, 1067, 954; δ_H (500 MHz, C₆D₆) 7.25 (2 H, d, J 8.6 Hz, ArH), 6.79 (2 H, d, J 8.6 Hz, ArH), 5.44 (1 H, dq, J 9.5, 1.2 Hz, 11-H), 4.43 (1 H, d, J 11.3 Hz, OCH₂Ar), 4.39 (1 H, d, J 11.3 Hz, OCH₂Ar), 4.31 (1 H, t, J 5.5 Hz, 6-H), 3.80 (2 H, d, J 5.3 Hz, 13-H and

13-H), 3.30 (3 H, s, ArOCH₃), 3.21 (1 H, dt, J 7.5, 4.4 Hz, 9-H), 3.14 [6 H, s, CH(OCH₃)₂], 2.71 (1 H, dqd, J 9.5, 6.8 and 4.4 Hz, 10-H), 1.86–1.91 (1 H, m, 7-H), 1.67–1.73 (2 H, m, 7-H and 8-H), 1.60 (3 H, s, 12-CH₃), 1.59–1.64 (1 H, m, 8-H), 1.42 (1 H, t, J 5.3 Hz, OH), 1.06 (3 H, d, J 6.8 Hz, 10-CH₃); $\delta_{\rm C}$ (125 MHz, C₆D₆) 159.6, 135.7, 131.6, 129.5, 127.7, 114.0, 104.8, 82.4, 71.7, 68.7, 54.8, 52.5, 52.1, 35.3, 29.3, 26.4, 16.5, 14.0; HRMS (ES⁺) m/z calc. for C₂₀H₃₂O₅Na ([MNa]⁺): 375.2142, found: 375.2142.

Aldehyde 32

TsOH·H₂O (1.86 g, 9.79 mmol) was added in one portion to a stirred solution of dimethyl acetal 30 (23.0 g, 65.25 mmol) in 4 : 1 acetone-water (600 mL) at room temperature. After 3 h, the mixture was concentrated in vacuo to remove most of the acetone, and was then partitioned between sat. aq. NaHCO₃ (200 mL) and EtOAc (200 mL). The mixture was extracted with EtOAc $(3 \times 200 \text{ mL})$, the combined organic layers washed with brine $(1 \times 200 \text{ mL})$, dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was filtered through silica gel with 15% Et_2O in hexanes, and the filtrate was concentrated in vacuo. The resulting oil was then dissolved in CH₂Cl₂ (300 mL), and imidazole (11.51 g, 169 mmol), a catalytic amount of 4-DMAP and TBSCI (15.68 g, 104 mmol) were added sequentially to the stirred solution at room temperature. After 90 min, the reaction was quenched with water (300 mL), the layers were separated, and the aqueous layer was extracted with Et₂O (3×200 mL). The combined organic layers were washed with brine $(1 \times 300 \text{ mL})$, dried (MgSO₄), filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (gradient: 9-33% Et₂O in hexanes) to give 32 (25.84 g, 95% from 30) as a colourless oil. $R_{\rm f} = 0.52$ (silica gel, 1 : 1 hexanes– Et_2O); $[a]_D^{25} - 14.0^\circ$ (c 1.00 in CH₂Cl₂); $v_{\rm max}/{\rm cm}^{-1}$ (film) 2943, 2716, 1720, 1609, 1466, 1440, 1245, 1076, 775; δ_H (500 MHz, C₆D₆) 9.36 (1 H, dd, J 1.9, 1.1 Hz, 6-H), 7.22 (2 H, d, J 8.6 Hz, ArH), 6.81 (2 H, d, J 8.6 Hz, ArH), 5.42 (1 H, dd, J 9.5, 1.3 Hz, 11-H), 4.37 (1 H, d, J 11.1 Hz, OCH₂Ar), 4.24 (1 H, d, J 11.1 Hz, OCH₂Ar), 3.97 (2 H, s, 13-H and 13-H), 3.30 (3 H, s, ArOCH₃), 3.07 (1 H, dt, J 8.6 Hz, 4.1 Hz, 9-H), 2.61–2.66 (1 H, m, 10-H), 2.08 (1 H, dtd, J 16.6, 7.4 and 1.9 Hz, 7-H), 1.97 (1 H, dtd, J 16.6, 7.0 and 1.1 Hz, 7-H), 1.59 (3 H, s, 12-CH₃), 1.55–1.71 (2 H, m, 8-H and 8-H), 0.98 [12 H, m, 10-CH₃ and SiC(CH₃)₃], 0.06 (6 H, s, SiCH₃ and SiCH₃); $\delta_{\rm C}$ (125 MHz, C₆D₆) 200.7, 159.7, 135.2, 131.3, 129.6, 127.2, 114.0, 81.6, 71.7, 68.9, 54.7, 40.7, 35.1, 26.1, 24.0, 18.6, 16.0, 13.8, -5.0, -5.1; HRMS (ES⁻) m/z calc. for $C_{24}H_{39}O_4Si$ ([M – H]⁻): 419.2623, found: 419.2621.

Carboxylic acid 37

Solid NaH₂PO₄ (3.99 g, 33.3 mmol) and NaClO₂ (1.93 g, 17.12 mmol) were added sequentially to a stirred solution of aldehyde **32** (4.00 g, 9.51 mmol) and 2-methyl-2-butene (20.15 mL, 190.18 mmol) in 4 : 1 *t*-BuOH–H₂O (60 mL) at room temperature. After 2 h, the reaction was quenched by the addition of sat. aq. Na₂SO₃ (30 mL) and sat. aq. NH₄Cl (30 mL). The mixture was then acidified to a pH of 3.0 using 1 M aq. KHSO₄, and extracted with EtOAc (4 × 60 mL). The combined organic layers were washed with brine (1 × 100 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient: 20–50% EtOAc in hexanes) to give **37** (3.247 g,

78%) as a colourless oil. $R_{\rm f} = 0.47$ (silica gel, 1 : 1 hexanes–EtOAc); [a]₂₅²⁵ -14.9° (c 0.61 in CH₂Cl₂); $v_{\rm max}/{\rm cm}^{-1}$ (film) 3520, 2949, 2851, 1730, 1708, 1509, 1459, 1247, 1071, 936; $\delta_{\rm H}$ (500 MHz, C₆D₆) 7.23 (2 H, d, J 8.6 Hz, Ar*H*), 6.81 (2 H, d, J 8.6 Hz, Ar*H*), 5.45 (1 H, d, J 9.6 Hz, 11-H), 4.40 (1 H, d, J 11.2 Hz, OC*H*₂Ar), 4.31 (1 H, d, J 11.2 Hz, OC*H*₂Ar), 3.97 (2 H, s, 13-H and 13-H), 3.31 (3 H, s, ArOC*H*₃), 3.18 (1 H, dt, J 8.4, 4.2 Hz, 9-H), 2.65–2.70 (1 H, m, 10-H), 2.36 (1 H, ddd, J 14.7, 8.3 and 6.3 Hz, 7-H), 2.25–2.29 (1 H, m, 7-H), 1.72–1.82 (2 H, m, 8-H and 8-H), 1.60 (3 H, s, 12-C*H*₃), 0.98–0.99 [12 H, m, 10-C*H*₃ and SiC(C*H*₃)₃], 0.07 (3 H, s, SiC*H*₃), 0.07 (3 H, s, SiC*H*₃); $\delta_{\rm C}$ (125 MHz, C₆D₆) 180.2, 159.7, 135.2, 131.4, 129.5, 127.2, 114.0, 81.4, 71.9, 68.9, 54.7, 35.2, 30.8, 26.5, 26.1, 18.6, 16.1, 13.8, -5.0, -5.1; HRMS (ES⁻) *m*/*z* calc. for C₂₄H₃₉O₅Si ([M – H]⁻): 435.2572, found 435.2567.

Methyl ester 38

To a stirred suspension of carboxylic acid **37** (4.50 g, 10.3 mmol) and powdered K₂CO₃ (3.55 g, 25.8 mmol) in dry acetone (50 mL) was added MeI (2.50 mL, 40.8 mmol) in one portion at room temperature. After stirring for 16 h, the reaction mixture was concentrated under reduced pressure, and was then partitioned between sat. aq. NH₄Cl (75 mL) and Et₂O (50 mL). The layers were separated, and the aqueous layer was extracted with Et₂O $(3 \times 50 \text{ mL})$. The combined organic layers were washed with sat. aq. NaHCO₃ (1 \times 75 mL), brine (1 \times 75 mL), dried (MgSO₄), filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (10% Et₂O in hexanes) to give **38** (4.51 g, 97%) as a colourless oil. $R_{\rm f} = 0.58$ (silica gel, 1 : 1 hexanes–Et₂O); $[a]_{D}^{25}$ –14.9° (c 1.00 in CH₂Cl₂); v_{max} /cm⁻¹ (film) 2955, 2919, 1735, 1511, 1461, 1247, 1037, 887; $\delta_{\rm H}\,(500\,{\rm MHz},{\rm C_6D_6})$ 7.22 (2 H, d, J 8.4 Hz, ArH), 6.79 (2 H, d, J 8.4 Hz, ArH), 5.45 (1 H, d, J 9.5 Hz, 11-H), 4.41 (1 H, d, J 11.2 Hz, OCH₂Ar), 4.32 (1 H, d, J 11.2 Hz, OCH₂Ar), 3.96 (2 H, s, 13-H and 13-H), $3.33 (3 H, s, CO_2CH_3), 3.31 (3 H, s, ArOCH_3), 3.20 (1 H, dt,$ J 8.5, 4.3 Hz, 9-H), 2.66-2.70 (1 H, m, 10-H), 2.33-2.40 (1 H, m, 7-H), 2.24–2.30 (1 H, m, 7-H), 1.78–1.92 (2 H, m, 8-H and 8-H), 1.60 (3 H, s, 12-CH₃), 0.99 (3 H, d, J 8.5 Hz, 10-CH₃), 0.97 [9 H, s, SiC(CH₃)₃], 0.06 (3 H, s, SiCH₃), 0.06 (3 H, s, SiCH₃); $\delta_{\rm C}$ (125 MHz, C₆D₆) 173.7, 159.8, 135.3, 131.7, 129.7, 127.6, 114.2, 81.8, 72.0, 69.2, 54.9, 51.2, 35.4, 31.0, 27.0, 26.3, 18.8, 16.4, 14.0, -4.8, -4.9; HRMS (ES⁻) m/z calc. for C₂₅H₄₁O₅Si ([M - H]⁻): 449.2729, found: 449.2725.

a-Hydroxy ester 40

To a stirred solution of methyl ester **38** (3.61 g, 8.0 mmol) in THF (60 mL) was added KHMDS (32 mL, 0.5 M in toluene, 16.0 mmol) dropwise at -78 °C. After 30 min, a solution of the Davis oxaziridine **39**¹³ (6.61 g, 24.0 mmol) in THF (20 mL) was added and the solution was stirred at -78 °C for an additional 1 h. The reaction was then quenched by the addition of sat. aq. NH₄Cl (150 mL), warmed to room temperature, and extracted with Et₂O (3 × 60 mL). The combined organic layers were washed with sat. aq. NaHCO₃ (1 × 150 mL), brine (1 × 150 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient: 15–30% Et₂O in hexanes) to give **40** (3.59 g, 96%) as a colourless oil and as a 3 : 1 mixture of diastereomers at the C7 position (determined

by ¹H-NMR analysis). Full characterisation of the major (7S)-diastereomer is given below (49).

t-Butyldimethylsilyl ether 42

TBSCl (2.86 g, 19.0 mmol) was added in one portion to a stirred solution of alcohol **40** (3.58 g, 7.60 mmol) and imidazole (2.58 g, 38.0 mmol) in CH₂Cl₂ (40 mL). After 16 h, the reaction was quenched by the addition of water (100 mL), and was extracted with Et₂O (3×50 mL). The combined organic layers were then washed with sat. aq. NaHCO₃ (1×100 mL), brine (1×100 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (7.5% Et₂O in hexanes) to give **42** (3.87 g, 88%) as a light yellow oil and as a 3 : 1 mixture of diastereomers at the C7 position (determined by ¹H-NMR analysis). Full characterisation of the major (7*S*)-diastereomer is given below (**50**).

β-Ketophosphonate 44

To a stirred solution of dimethyl methylphosphonate (2.22 mL, 20.5 mmol) in THF (50 mL) was added *n*-BuLi (12.8 mL, 1.55 M in hexanes, 19.8 mmol) dropwise at -78 °C. After 30 min a solution of ester **42** (3.83 g, 6.6 mmol) in THF (20 mL) was added dropwise. After stirring for 1 h at -78 °C, the reaction was quenched by the addition of sat. aq. NH₄Cl (100 mL), warmed to room temperature, and extracted with EtOAc (4 × 60 mL). The combined organic layers were washed with brine (1 × 100 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (50% EtOAc in hexanes) to give **44** (4.26 g, 96%) as a highly viscous colourless oil and as a 3 : 1 mixture of diastereomers at the C7 position (determined by ¹H-NMR analysis). Full characterisation of the major (7*S*)-diastereomer is given below (**51**).

N-Acyl-oxazolidinone 45

To a stirred solution of carboxylic acid 37 (3.20 g, 7.33 mmol) in THF (20 mL) were added Et₃N (1.12 mL, 8.06 mmol) and freshly distilled pivaloyl chloride (0.99 mL, 8.06 mmol) dropwise at -78 °C, and the mixture was stirred for 1 h. In a separate flask, n-BuLi (3.5 mL, 2.5 M in hexanes, 8.80 mmol) was added dropwise to a stirred solution of (S)-4-benzyl-2-oxazolidinone (1.56 g, 8.80 mmol) in THF (20 mL) at -78 °C. After 1 h, the solution of oxazolidinone anion 47 was transferred by cannula into the solution of mixed anhydride 46, and the resulting mixture allowed to stir at -78 °C for 3 h. The reaction was then quenched with sat. aq. NH₄Cl (80 mL), and extracted with Et₂O (2 \times 40 mL). The combined organic layers were washed with sat. aq. NaHCO₃ (1 \times 80 mL), brine (1 \times 80 mL), dried (MgSO₄), filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (gradient: 10-30% EtOAc in hexanes) to give 45 (1.902 g, 44%) as a colourless oil. $R_{\rm f} = 0.21$ (silica gel, 4 : 1 hexanes–Et₂O); $[a]_{D}^{25}$ +12.0° (c 1.20 in CH₂Cl₂); v_{max} /cm⁻¹ (film) 2936, 1783, 1697, 1513, 1384, 1174, 834; $\delta_{\rm H}$ (600 MHz, C₆D₆) 7.27 (2 H, d, J 8.5 Hz, ArH), 7.05-7.08 (2 H, m, ArH), 7.00-7.03 (1 H, m, ArH), 6.89-6.90 (2 H, m, ArH), 6.77 (2 H, d, J 8.5 Hz, ArH), 5.47 (1 H, dd, J 9.5, 0.8 Hz, 11-H), 4.48 (1 H, d, J 11.2 Hz, OCH₂Ar), 4.37 (1 H, d, J 11.2 Hz, OCH₂Ar), 4.14–4.18 (1 H, m, OCH₂CHN), 3.96 (2 H, s, 13-H and 13-H), 3.53 (1 H, dd, J 8.9, 2.8 Hz, OCH₂CHN), 3.34 (3 H, s, ArOCH₃), 3.29–3.33 (2 H, m, 9-H and OCH₂CHN), 3.13 (1 H, ddd, *J* 17.3, 8.6 and 6.0 Hz, 7-H), 3.00 (1 H, ddd, *J* 17.3, 8.6 and 6.0 Hz, 7-H), 2.94 (1 H, dd, *J* 13.3, 3.2 Hz, CH₂Ph), 2.75–2.81 (1 H, m, 10-H), 2.34 (1 H, dd, *J* 13.3, 9.4 Hz, CH₂Ph), 1.91–2.02 (2 H, m, 8-H and 8-H), 1.62 (3 H, s, 12-CH₃), 1.04 (3 H, d, *J* 6.8 Hz, 10-CH₃), 0.93 [9 H, s, SiC(CH₃)₃], 0.04 (3 H, s, SiCH₃), 0.03 (3 H, s, SiCH₃); $\delta_{\rm C}$ (150 MHz, C₆D₆) 172.9, 159.5, 153.4, 136.0, 135.2, 131.5, 129.6, 129.6, 128.9, 127.4, 127.2, 113.9, 81.7, 71.8, 68.9, 65.7, 55.0, 54.8, 37.8, 35.2, 32.6, 26.1, 26.0, 18.5, 16.1, 13.9, -5.1, -5.1; HRMS (ES⁺) *m*/*z* calc. for C₃₄H₄₉NO₆SiNa ([MNa]⁺): 618.3221, found: 618.3204.

a-Hydroxy ester 49

A solution of oxazolidinone 45 (1.85 g, 3.10 mmol) in THF (5 mL) was added dropwise to a stirred solution of NaHMDS (3.73 mL, 1.0 M in THF, 3.73 mmol) in THF (8 mL) at -78 C. After 5 min, a solution of the Davis oxaziradine 39¹³ (1.28 g, 4.66 mmol) in THF (4 mL) was added, and stirring continued for 5 min before the rapid addition of a solution of AcOH (1 mL) in THF (3 mL). The mixture was then poured into sat. aq. NaHCO₃ (50 mL), and extracted with EtOAc (3×30 mL). The combined organic layers were washed with sat. aq. NaHCO₃ (1×50 mL), brine ($1 \times$ 50 mL), dried (MgSO₄), filtered and concentrated in vacuo. The residue was filtered through silica gel with 20% EtOAc in hexanes, and the filtrate was concentrated under reduced pressure to give 1.30 g of a residue (68) that was used without further purification in the next step. The crude alcohol 48 (0.500 g, 0.817 mmol) was then taken up in MeOH (4 mL) and added to a stirred solution of Mg(OMe)₂ (1.36 mL, 1.2 M in MeOH, 1.64 mmol) in MeOH (8 mL) at 0 °C. After 30 min, the reaction mixture was poured into sat. aq. NH₄Cl (25 mL), and then extracted with EtOAc (3 \times 20 mL). The combined organic layers were washed with brine (1 \times 25 mL), dried (MgSO₄), filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (30%) Et_2O in hexanes) to give 49 (0.313 g, 56% from 45) as a colourless paste. $R_{\rm f} = 0.32$ (silica gel, 1 : 1 hexanes-Et₂O); $[a]_{\rm D}^{25} - 36.7^{\circ}$ (c 0.09 in CH₂Cl₂); v_{max}/cm⁻¹ (film) 3468, 2955, 1738, 1514, 1361, 1174, 939; δ_H (600 MHz, C₆D₆) 7.28 (2 H, d, J 8.6 Hz, ArH), 6.77 (2 H, d, J 8.6 Hz, ArH), 5.39 (1 H, d, J 10.5 Hz, 11-H), 4.56 (1 H, d, J 10.8, Hz, OCH₂Ar), 4.51 (1 H, d, J 10.8 Hz, OCH₂Ar), 4.47–4.49 (1 H, m, 7-H), 3.92 (2 H, s, 13-H and 13-H), 3.72–3.75 (1 H, m, 9-H), 3.39 (1 H, br s, OH), 3.34 (3 H, s, CO₂CH₃), 3.29 (3 H, s, ArOCH₃), 2.67-2.73 (1 H, m, 10-H), 2.04 (1 H, ddd, J 14.0, 10.6 and 2.7 Hz, 8-H), 1.65 (1 H, ddd, J 14.0, 10.2 and 2.4 Hz, 8-H), 1.56 (3 H, s, 12-CH₃), 0.99 (3 H, d, J 6.8 Hz, 10-CH₃), 0.93 [9 H, s, SiC(CH₃)₃], $0.02 (6 \text{ H}, \text{ s}, \text{SiC}H_3 \text{ and SiC}H_3); \delta_{\text{C}} (150 \text{ MHz}, \text{C}_6\text{D}_6) 176.2, 159.6,$ 135.4, 131.5, 129.6, 127.0, 114.0, 79.3, 72.9, 68.9, 68.3, 54.8, 51.8, 37.0, 35.8, 26.1, 18.5, 16.0, 13.8, -5.1; HRMS (ES⁺) m/z calc. for C₂₅H₄₂O₆SiNa ([MNa]⁺): 489.2643, found: 489.2649.

t-Butyldimethylsilyl ether 50

TBSCl (436 mg, 2.89 mmol) was added in one portion to a stirred solution of alcohol **49** (450 mg, 0.964 mmol), imidazole (394 mg, 5.79 mmol) and a catalytic amount of 4-DMAP in CH₂Cl₂ (8 mL) at room temperature. After 16 h the reaction was quenched by the addition of water (25 mL), and then extracted with CH₂Cl₂ (3 × 15 mL). The combined organic layers were dried (MgSO₄), filtered

and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (gradient: 8-12% Et₂O in hexanes) to give 50 (484 mg, 86%) as a light yellow oil. $R_{\rm f} = 0.67$ (silica gel, 1 : 1 hexanes–Et₂O); $[a]_{D}^{25}$ –20.4° (c 1.67 in CH₂Cl₂); v_{max} /cm⁻¹ (film) 2957, 2856, 1751, 1583, 1359, 1146, 777; δ_H (500 MHz, C₆D₆) 7.25 (2 H, d, J 8.6 Hz, ArH), 6.77 (2 H, d, J 8.6 Hz, ArH), 5.35 (1 H, d, J 9.3 Hz, 11-H), 4.53-4.57 (2 H, m, 7-H and OCH₂Ar), 4.39 (1 H, d, J 11.0 Hz, OCH₂Ar), 3.94 (1 H, d, J 12.3 Hz, 13-H), 3.93 (1 H, d, J 12.3 Hz, 13-H), 3.64 (1 H, ddd, J 9.5, 3.9 and 2.4 Hz, 9-H), 3.36 (3 H, s, CO₂CH₃), 3.32 (3 H, s, ArOCH₃), 2.83-2.91 (1 H, dqd, J 9.3, 6.8 and 3.9 Hz, 10-H), 2.06 (1 H, ddd, J 13.9, 9.5 and 3.1 Hz, 8-H), 1.85 (1 H, ddd, J 13.9, 9.6 and 2.4 Hz, 8-H), 1.60 (3 H, s, 12-CH₃), 0.98 (3 H, d, J 6.8 Hz, 10-CH₃), 0.96 [9 H, s, SiC(CH₃)₃], 0.95 [9 H, s, SiC(CH₃)₃], 0.11 (3 H, s, SiCH₃), 0.04 (6 H, s, SiCH₃ and SiCH₃), 0.03 (3 H, s, SiCH₃); $\delta_{\rm C}$ (125 MHz, C₆D₆) 174.0, 159.6, 135.5, 131.5, 129.1, 126.9, 114.0, 78.8, 71.2, 70.3, 68.7, 54.8, 51.2, 37.3, 34.3, 26.2, 26.1, 18.6, 18.5, 15.1, 13.8, -4.4, -5.0; HRMS (ES⁺) m/z calc. for C₃₁H₅₆O₆Si₂Na ([MNa]⁺): 603.3507, found: 603.3510.

β-Ketophosphonate 51

To a stirred solution of dimethyl methylphosphonate (276 μ L, 2.55 mmol) in THF (8 mL) was added n-BuLi (1.0 mL, 2.5 M in hexanes, 2.5 mmol) dropwise at -78 °C. After 30 min a solution of ester 50 (470 mg, 0.823 mmol) in THF (4 mL) was added dropwise. After stirring for a further 1 h at -78 °C, the reaction was quenched by the addition of sat. aq. NH₄Cl (20 mL), warmed to room temperature, and extracted with EtOAc (4×10 mL). The combined organic layers were washed with brine $(1 \times 20 \text{ mL})$, dried (MgSO₄), filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (50% EtOAc in hexanes) to give 51 (507 mg, 92%) as a highly viscous colourless oil. $R_{\rm f} = 0.25$ (silica gel, 1 : 1 hexanes–EtOAc); $[a]_{\rm D}^{25} + 3.4^{\circ}$ (c 1.00 in CH₂Cl₂); v_{max}/cm⁻¹ (film) 2935, 1725, 1513, 1360, 1249, 1094, 777; δ_H (500 MHz, C₆D₆) 7.31 (2 H, d, J 8.6 Hz, ArH), 6.81 (2 H, d, J 8.6 Hz, ArH), 5.38 (1 H, d, J 9.2 Hz, 11-H), 4.50-4.53 (2 H, m, 7-H and OCH₂Ar), 4.38 (1 H, d, J 10.9 Hz, OCH₂Ar), 3.55–3.58 (1 H, m, 9-H), 3.43 (3 H, d, J 11.2 Hz, POCH₃), 3.40 (3 H, d, J 11.1 Hz, POCH₃), 3.35 (3 H, s, ArOCH₃), 3.12 (1 H, dd, J 22.1, 14.5 Hz, 5-H), 2.94 (1 H, dd, J 21.7, 14.5 Hz, 5-H), 2.86-2.91 (1 H, m, 10-H), 1.94 (1 H, ddd, J 14.1, 9.2 and 4.3 Hz, 8-H), 1.70 (1 H, ddd, J 14.1, 8.5 and 2.7 Hz, 8-H), 1.60 (3 H, s, 12-CH₃), 0.99 (3 H, d, J 6.8 Hz, 10-CH₃), 0.95 [9 H, s, SiC(CH₃)₃], 0.94 [9 H, s, SiC(CH₃)₃], 0.12 (3 H, s, SiCH₃), 0.05 (3 H, s, SiCH₃), 0.04 (6 H, s, SiCH₃ and SiCH₃); $\delta_{\rm C}$ (125 MHz, C₆D₆) 202.7 (d, ²J_{31P-13C} 6.2 Hz), 159.6, 135.6, 131.3, 129.5, 126.5, 114.0, 78.9, 77.1, 71.2, 68.6, 54.8, 52.4 (d, ${}^{2}J_{31}_{P-13}$ 6.3 Hz), 52.3 (d, ${}^{2}J_{31}_{P-13}$ 6.0 Hz), 36.1, 35.8 (d, ${}^{1}J_{31_{P}-13_{C}}$ 131.1 Hz), 34.1, 26.1, 26.1, 18.5, 18.4, 15.1, 13.8, -4.4, -5.0, -5.1, -5.1; HRMS (ES⁺) m/z calc. for C₃₃H₆₁O₈PSi₂Na ([MNa⁺]): 695.3535, found: 695.3537.

α , β -Unsaturated ketone 52

A solution of phosphonate **44** (8.08 g, 12.0 mmol) in acetonitrile (10 mL) was added to a stirred suspension of flame-dried LiCl (0.763 g, 18.0 mmol) in acetonitrile (100 mL) in a round-bottomed flask at room temperature. After 10 min, i-Pr₂NEt (3.10 mL, 18.0 mmol) was added and the mixture stirred for a further 10 min before the addition of a solution of aldehyde **14** (3.562 g,

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13.7 mmol) in acetonitrile (10 mL). The mixture was then allowed to stir for 48 h at room temperature, before being quenched by the addition of water (250 mL). The mixture was then extracted with Et_2O (3 × 100 mL), and the combined organic layers were washed with brine (1 × 150 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient: 5–15% Et_2O in hexanes) to give **52** (8.93 g, 92%) as a colourless oil and as a 3 : 1 mixture of diastereomers at the C7 position (determined by ¹H-NMR analysis). Full characterisation of the major (7*S*)-diastereomer is given below (**57**).

Diene 53

Methyltriphenylphosphonium bromide (6.29 g, 17.6 mmol) was dried under high vacuum (0.1 mmHg) for 16 h at room temperature, and was then suspended in THF (60 mL). KHMDS (33.0 mL, 0.5 M in toluene, 16.5 mmol) was then added dropwise to the stirred suspension. After 45 min, the bright yellow-orange solution was cooled to -78 °C, where a solution of ketone 52 (8.88 g, 11.0 mmol) in THF (15 mL) was added dropwise. After stirring for 1 h, the mixture was warmed to room temperature and then quenched by the addition of sat. aq. NH₄Cl (150 mL). The mixture was then extracted with Et_2O (3 × 100 mL), and the combined organic layers were washed with brine $(1 \times 150 \text{ mL})$, dried (MgSO₄), filtered and concentrated in vacuo. The residue was triturated with 9 : 1 hexanes-Et₂O, and the precipitated Ph₃PO was then removed by filtration. The filtrate was concentrated under reduced pressure, and then the residue was purified by flash chromatography on silica gel (10% Et₂O in hexanes) to give 53 (8.51 g, 95%) as a colourless oil and as a 3 : 1 mixture of diastereomers at the C7 position (determined by ¹H-NMR analysis). Full characterisation of the major (7S)-diastereomer is given below (58).

Allylic alcohols 54 and 55

Method A – from 53 (diastereomeric mixture). PPTS (0.146 g, 0.58 mmol) was added in one portion to a stirred solution of diene 53 (7.78 g, 9.66 mmol) in EtOH (390 mL) at room temperature, and the solution was then heated to 45 °C for 16 h. After cooling to room temperature, the reaction was quenched by the careful addition of sat. aq. NaHCO₃ (500 mL), and was then concentrated under reduced pressure to remove most of the EtOH. The mixture was then diluted with water (150 mL) and extracted with EtOAc (3×400 mL). The combined organic layers were then washed with brine (1×500 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient: 10–20% hexanes–Et₂O) to give 54 (3.74 g, 56%) followed by 55 (0.937 g, 14%), both as viscous, colourless oils.

Method B – from 58 (single diastereomer). PPTS (8.3 mg, 0.033 mmol) was added in one portion to a stirred solution of diene 58 (0.440 g, 0.546 mmol) in EtOH (22 mL) at room temperature, and the solution was then heated to 45 °C for 20 h. After cooling to room temperature, the mixture was concentrated under reduced pressure. The residue was then partitioned between sat. aq. NaHCO₃ (30 mL) and EtOAc (30 mL), the layers were separated, and the aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic layers were then washed with brine (1 × 30 mL), dried (MgSO₄), filtered and concentrated *in vacuo*.

The residue was purified by flash chromatography on silica gel (50% Et_2O in hexanes) to give **54** (0.329 g, 87%) as a viscous, colourless oil.

Data for alcohol 54. $R_f = 0.24$ (silica gel, 14 : 11 hexanes-Et₂O); $[a]_{D}^{25}$ +17.1° (c 1.14 in CH₂Cl₂); v_{max} /cm⁻¹ (film) 3441, 2952, 2862, 1738, 1614, 1514, 1462, 1247, 1096; $\delta_{\rm H}$ (600 MHz, CDCl₃) 7.25 (2 H, d, J 8.7 Hz, ArH), 6.86 (2 H, d, J 8.7 Hz, ArH), 6.07 (1 H, d, J 16.1 Hz, 5-H), 5.68 (1 H, dd, J 16.1, 7.0 Hz, 4-H), 5.48 (1 H, dd, J 9.4, 1.2 Hz, 11-H), 5.05 (1 H, s, 6-CH₂), 5.03 (1 H, s, 6-CH₂), 4.45 (1 H, d, J 11.3 Hz, OCH₂Ar), 4.38 (1 H, d, J 11.3 Hz, OCH₂Ar), 4.31 (1 H, dd, J 8.0, 4.9 Hz, 7-H), 4.27 (1 H, app t, J 7.0 Hz, 3-H), 4.00 (2 H, br dd, J 3.2, 0.8 Hz, 13-H and 13-H), 3.79 (3 H, s, CO₂CH₃), 3.59 (3 H, s, ArOCH₃), 3.40–3.44 (1 H, m, 9-H), 2.68–2.74 (1 H, m, 10-H), 2.49 (1 H, app qn, J 7.0 Hz, 2-H), 1.91 (1 H, br s, OH), 1.75-1.79 (1 H, m, 8-H), 1.69 (3 H, s, 12-CH₃), 1.62–1.66 (1 H, m, 8-H), 1.16 (3 H, d, J 7.0 Hz, 2-CH₃), 1.00 (3 H, d, J 6.9 Hz, 10-CH₃), 0.89 [9 H, s, SiC(CH₃)₃], 0.87 $[9 \text{ H}, \text{ s}, \text{SiC}(CH_3)_3], 0.03 (6 \text{ H}, \text{ s}, \text{SiC}H_3 \text{ and } \text{SiC}H_3), 0.00 (3 \text{ H}, \text{ s}, \text{ s})$ $SiCH_3$, -0.04 (3 H, s, $SiCH_3$); δ_C (150 MHz, $CDCl_3$) 174.8, 158.9, 148.3, 135.4, 131.2, 130.7, 129.6, 129.1, 127.1, 114.5, 113.6, 78.9, 75.6, 70.8, 70.8, 68.7, 55.2, 51.6, 47.4, 39.4, 34.4, 25.9, 25.7, 18.1, 18.1, 17.0, 13.8, 12.6, -4.1, -4.5, -5.1, -5.1; HRMS (ES⁺) m/z calc. for C₃₈H₆₆O₇Si₂Na ([MNa]⁺): 713.4239, found 713.4233.

Data for alcohol 55. $R_{\rm f} = 0.15$ (silica gel, 1 : 1 hexanes–Et₂O); $[a]_{D}^{25}$ -42.8° (c 1.91 in CHCl₃); v_{max} /cm⁻¹ (film) 3471, 2949, 2852, 1740, 1458, 1246, 832; *δ*_H (600 MHz, C₆D₆) 7.32 (2 H, d, *J* 8.5 Hz, ArH), 6.87 (2 H, d, J 8.5 Hz, ArH), 6.18 (1 H, d, J 16.2 Hz, H-5), 6.05 (1 H, dd, J 16.2, 6.7 Hz, H-4), 5.34 (1 H, d, J 8.7 Hz, H-11), 5.31 (1 H, s, 6=CH₂), 5.00 (1 H, s, 6=CH₂), 4.75 (1 H, d, J 9.3 Hz, H-7), 4.64 (1 H, d, J 10.8 Hz, OCH₂Ar), 4.43 (1 H, dd, J 6.7, 5.8 Hz, H-3), 4.41 (1 H, d, J 10.8 Hz, OCH₂Ar), 3.89 (2 H, s, H-13 and H-13), 3.69 (1 H, ddd, J 10.0, 3.7 and 1.3 Hz, H-9), 3.39 (3 H, s, CO₂CH₃), 3.39 (3 H, s, ArOCH₃), 2.93–2.98 (1 H, m, H-10), 2.44 (1 H, qd, J 7.0, 5.8 Hz, H-2), 2.08 (1 H, br s, OH), 1.87 (1 H, dd, J 13.3, 10.0 Hz, H-8), 1.74 (1 H, ddd, J 13.3, 9.3 and 1.3 Hz, H-8), 1.68 (3 H, s, 12-CH₃), 1.17 (3 H, d, J 7.0 Hz, 2-CH₃), 1.04 (3 H, d, J 6.8 Hz, 10-CH₃), 0.96 [9 H, s, SiC(CH₃)₃], 0.93 [9 H, s, SiC(CH₃)₃], 0.08 (3 H, s, SiCH₃), 0.04 (3 H, s, SiCH₃), 0.02 (6 H, s, SiCH₃ and SiCH₃); $\delta_{\rm C}$ (150 MHz, C₆D₆) 174.2, 159.6, 149.7, 136.2, 131.6, 131.5, 130.3, 129.1, 127.7, 114.6, 114.1, 80.1, 75.5, 71.1, 70.2, 68.5, 54.8, 51.2, 47.3, 40.6, 33.7, 26.1, 26.0, 18.4, 18.3, 14.6, 14.1, 12.0, -3.9, -4.0, -4.9, -5.0; HRMS (ES⁺) m/zcalc. for C38H66O7Si2Na ([MNa]+): 713.4239, found: 713.4230.

Bromide 56

To a stirred solution of allylic alcohol **54** (1.01 g, 1.45 mmol) in THF (30 mL) were added Et₃N (0.81 mL, 5.80 mmol) and MsCl (0.23 mL, 2.90 mmol) dropwise at 0 °C. After 1 h, the mixture was warmed to room temperature and LiBr (1.26 g, 14.5 mmol) was added in one portion. Stirring was continued for an additional 30 min before the reaction was quenched with water (60 mL) and extracted with Et₂O (3 × 30 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (5% Et₂O in hexanes) to give 1.04 g **56** (1.38 mmol, 95%) as a light yellow oil. $R_{\rm f} = 0.60$ (silica gel, 1 : 1 hexanes–Et₂O); $[a]_{\rm D}^{\rm 25} - 34.7^{\circ}$ (*c* 1.35 in CHCl₃); $v_{\rm max}/\rm cm^{-1}$ (film) 2958, 1738, 1511, 1361, 1096,

836; *δ*_H (600 MHz, C₆D₆) 7.27 (2 H, d, *J* 8.6 Hz, Ar*H*), 6.84 (2 H, d, J 8.6 Hz, ArH), 6.16 (1 H, d, J 16.2 Hz, H-5), 5.96 (1 H, dd, J 16.2, 6.7 Hz, H-4), 5.27–5.29 (2 H, m, H-11 and $6=CH_2$), 4.99 (1 H, s, 6=CH₂), 4.68 (1 H, dd, J 9.1, 1.5 Hz, H-7), 4.53 (1 H, d, J 10.8 Hz, OCH₂Ar), 4.43 (1 H, dd, J 6.7, 5.6 Hz, H-3), 4.33 (1 H, d, J 10.8 Hz, OCH₂Ar), 3.64 (1 H, d, J 9.8 Hz, H-13), 3.63 (1 H, d, J 9.8 Hz, H-13), 3.58 (1 H, ddd, J 9.7, 4.0 and 1.8 Hz, 9-H), 3.39 (3 H, s, CO₂CH₃), 3.38 (3 H, s, ArOCH₃), 2.75 (1 H, dqd, J 9.8, 6.8 and 4.0 Hz, H-10), 2.40 (1 H, qd, J 7.0, 5.6 Hz, H-2), 1.79 (1 H, ddd, J 14.2, 9.7 and 1.5 Hz, H-8), 1.68 (3 H, d, J 1.6 Hz, 12-CH₃), 1.58 (1 H, ddd, J 14.2, 9.3 and 1.8 Hz, H-8), 1.15 (3 H, d, J 7.0 Hz, 2-CH₃), 0.95 [9 H, s, SiC(CH₃)₃], 0.91 [9 H, s, SiC(CH₃)₃], 0.89 (3 H, d, J 6.8 Hz, 10-CH₃), 0.04 (3 H, s, SiCH₃), 0.01 (3 H, s, SiCH₃), 0.01 (3 H, s, SiCH₃), 0.00 (3 H, s, SiC H_3); δ_C (150 MHz, C₆D₆) 173.8, 159.6, 149.6, 133.5, 132.8, 131.6, 131.4, 130.1, 129.1, 114.5, 114.1, 79.6, 75.4, 71.2, 69.9, 54.8, 51.1, 47.2, 41.0, 40.8, 34.7, 26.2, 26.0, 18.4, 18.3, 15.0, 14.1, 11.8, -3.9, -4.0, -4.9, -4.9; HRMS (ES⁺) m/z calc. for C₃₈H₆₅⁷⁹BrO₆Si₂Na ([MNa]⁺): 775.3395, found: 775.3395.

α,β-Unsaturated ketone 57

A solution of phosphonate 51 (0.404 g, 0.60 mmol) in acetonitrile (4 mL) was added to flame-dried LiCl (0.038 g, 0.90 mmol) in a round-bottomed flask at room temperature. After stirring for 10 min, *i*-Pr₂NEt (0.16 mL, 0.90 mmol) was added, and stirring continued for a further 10 min before the addition of a solution of aldehyde 14 (0.180 g, 0.69 mmol) in acetonitrile (2 mL). The mixture was then allowed to stir for 36 h at room temperature, before being quenched by the addition of water (15 mL). The mixture was then extracted with Et_2O (3 \times 10 mL), and the combined organic layers were washed with brine $(1 \times 15 \text{ mL})$, dried (MgSO₄), filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (7.5% Et₂O in hexanes) to give 57 (0.476 g, 97%) as a colourless oil. $R_{\rm f}$ = 0.31 (silica gel, 4 : 1 hexanes-Et₂O); $[a]_{D}^{25} + 3.0^{\circ}$ (c 1.32 in CHCl₃); $v_{\rm max}$ /cm⁻¹ (film) 2954, 1741, 1697, 1616, 1450, 1362, 1075, 837; $\delta_{\rm H}$ (600 MHz, C₆D₆) 7.32 (2 H, d, J 8.4 Hz, ArH), 7.00 (1 H, dd, J 15.7, 4.6 Hz, 4-H), 6.84 (2 H, d, J 8.4 Hz, ArH), 6.71 (1 H, d, J 15.7 Hz, 5-H), 5.43 (1 H, d, J 9.0 Hz, 11-H), 4.70 (1 H, dd, J 8.5, 4.1 Hz, 7-H), 4.66 (1 H, dd, J 4.6, 3.8 Hz, 3-H), 4.57 (1 H, d, J 10.9 Hz, OCH₂Ar), 4.43 (1 H, d, J 10.9 Hz, OCH₂Ar), 4.02 (1 H, d, J 12.8 Hz, 13-H), 3.99 (1 H, d, J 12.8 Hz, 13-H), 3.66-3.70 (1 H, m, 9-H), 3.33 (6 H, s, ArOCH₃ and CO₂CH₃), 2.91–2.96 (1 H, m, 10-H), 2.32 (1 H, qd, J 7.0, 3.8 Hz, 2-H), 2.04 (1 H, ddd, J 13.9, 9.4 and 4.1 Hz, 8-H), 1.82 (1 H, ddd, J 13.9, 8.5 and 2.1 Hz, 8-H), 1.66 (3 H, s, 12-CH₃), 1.10 (3 H, d, J 7.0 Hz, 2-CH₃), 1.03 (3 H, d, J 6.5 Hz, 10-CH₃), 1.01 [9 H, s, SiC(CH₃)₃], 1.00 [9 H, s, $SiC(CH_3)_3$, 0.95 [9 H, s, $SiC(CH_3)_3$], 0.18 (3 H, s, $SiCH_3$), 0.10 (9 H, s, SiCH₃, SiCH₃ and SiCH₃), 0.03 (3 H, s, SiCH₃), 0.00 (3 H, s, SiCH₃); δ_C (150 MHz, C₆D₆) 198.9, 173.4, 159.7, 147.3, 135.8, 131.4, 129.4, 126.7, 125.4, 114.1, 79.2, 76.5, 73.2, 71.4, 68.8, 54.8, 51.2, 45.6, 36.9, 34.3, 26.2, 26.0, 26.0, 18.6, 18.3, 15.0, 13.9, 10.7, -4.0, -4.1, -4.8, -5.0, -5.1, -5.1; HRMS (ES⁺) m/z calc. for C₄₃H₇₈O₈Si₃Na ([MNa]⁺): 829.4896, found: 829.4894.

Diene 58

Methyltriphenylphosphonium bromide (0.343 g, 0.96 mmol) was dried under high vacuum (0.1 mmHg) for 16 h at room temperature, and was then suspended in THF (6 mL). KHMDS (1.80 mL, 0.5 M in toluene, 0.90 mmol) was then added dropwise to the stirred suspension at room temperature. After 30 min, the bright yellow-orange solution was cooled to -78 °C, where a solution of ketone 57 (0.480 g, 0.60 mmol) in THF (2 mL) was added dropwise. After stirring for 1 h, the mixture was warmed to room temperature and then quenched by the addition of sat. aq. NH₄Cl (15 mL). The mixture was then extracted with Et₂O (3 \times 10 mL), and the combined organic layers were washed with brine $(1 \times 15 \text{ mL})$, dried (MgSO₄), filtered and concentrated in vacuo. The residue was triturated with 9:1 hexanes-Et₂O, and the precipitated Ph₃PO was then removed by filtration. The filtrate was concentrated under reduced pressure, and then the residue was purified by flash chromatography on silica gel (10% Et₂O in hexanes) to give 58 (0.560 g, 94%) as a colourless oil. $R_{\rm f} = 0.51$ (silica gel, 4 : 1 hexanes–Et₂O); $[a]_{D}^{25}$ –34.7° (c 0.91 in CHCl₃); v_{max} /cm⁻¹ (film) 2956, 1741, 1616, 1459, 1362, 1098, 837; δ_H (600 MHz, C₆D₆) 7.38 (2 H, d, J 8.4 Hz, ArH), 6.92 (2 H, d, J 8.4 Hz, ArH), 6.26 (1 H, d, J 16.2 Hz, 5-H), 6.08 (1 H, dd, J 16.2, 6.4 Hz, 4-H), 5.45 (1 H, d, J 8.9 Hz, 11-H, 5.40 (1 H, s, 6=CH₂), 5.06 (1 H, s, 6=CH₂), 4.83 (1 H, d, J 9.1 Hz, 7-H), 4.69 (1 H, d, J 10.8 Hz, OCH₂Ar), 4.56 (1 H, dd, J 6.4, 5.7 Hz, 3-H), 4.45 (1 H, d, J 10.8 Hz, OCH₂Ar), 4.04 (1 H, d, J 12.7 Hz, 13-H), 4.00 (1 H, d, J 12.7 Hz, 13-H), 3.75 (1 H, dd, J 9.6, 2.5 Hz, 9-H), 3.40 (3 H, s, CO₂CH₃), 3.37 (3 H, s, ArOCH₃), 3.00–3.05 (1 H, m, 10-H), 2.49 (1 H, qd, J 7.0, 5.7 Hz, 2-H), 1.96 (1 H, dd, J 13.7, 9.6 Hz, 8-H), 1.79 (1 H, dd, J 13.7, 9.1 Hz, 8-H), 1.71 (3 H, s, 12-CH₃), 1.25 (3 H, d, J 7.0 Hz, 2-CH₃), 1.08 (3 H, d, J 6.8 Hz, 10-CH₃), 1.02 [9 H, s, SiC(CH₃)₃], 1.01 [9 H, s, SiC(CH₃)₃], 0.97 [9 H, s, SiC(CH₃)₃], 0.13 (3 H, s, SiCH₃), 0.11 (6 H, s, SiCH₃ and SiCH₃), 0.08 (3 H, s, SiCH₃), 0.08 (3 H, s, SiCH₃), 0.07 (3 H, s, SiCH₃); δ_C (150 MHz, C₆D₆) 174.0, 159.7, 149.9, 135.4, 131.8, 131.5, 130.3, 129.0, 127.2, 114.4, 114.1, 80.0, 75.4, 71.0, 69.9, 68.8, 54.7, 51.1, 47.3, 40.6, 33.6, 26.2, 26.2, 26.0, 18.6, 18.4, 18.3, 14.4, 13.9, 11.7, -3.8, -4.0, -4.9, -4.9, -5.0, -5.0; HRMS (ES⁺) m/z calc. for C₄₄H₈₀O₇Si₃Na ([MNa]⁺): 827.5104, found: 827.5104.

Triol 60

TsOH·H₂O (0.140 g, 0.737 mmol) was added in one portion to a stirred solution of alcohol 54 (0.511 g, 0.737 mmol) in MeOH (14 mL) at room temperature. After 16 h, the mixture was concentrated to half its original volume under reduced pressure, and sat. aq. NaHCO₃ (30 mL) was added. The mixture was then extracted with EtOAc (4 \times 20 mL), and the combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (30% hexanes in EtOAc) to give 60 (0.268 g, 79%) as a white powder that crystallised from benzene as colourless plates. $R_{\rm f} = 0.44$ (silica gel, EtOAc); mp = 102 °C; $[a]_{D}^{25}$ -32.4° (c 1.02 in CH₂Cl₂); v_{max}/cm^{-1} (film) 3388, 2957, 2873, 1731, 1717, 1456, 1418, 1248, 1068, 903; $\delta_{\rm H}$ (500 MHz, CDCl₃) 7.26 (2 H, d, J 8.6 Hz, ArH), 6.86 (2 H, d, J 8.6 Hz, ArH), 6.18 (1 H, d, J 16.2 Hz, H-5), 5.64 (1 H, dd, J 16.2, 6.4 Hz, H-4), 5.26 (1 H, s, 6=CH₂), 5.19 (1 H, d, J 8.9 Hz, H-11), $5.11 (1 \text{ H}, \text{s}, 6=CH_2), 4.59 (1 \text{ H}, \text{d}, J 10.8 \text{ Hz}, OCH_2\text{Ar}), 4.55-4.57$ (1 H, m, H-7), 4.37 (1 H, d, J 10.8 Hz, OCH₂Ar), 4.28–4.30 (1 H, m, H-3), 3.90 (2 H, s, H-13 and H-13), 3.78 (3 H, s, CO₂CH₃), 3.64 (3 H, s, ArOCH₃), 3.58 (1 H, ddd, J 9.8, 3.7 and 1.3 Hz, H-9), 3.31 (3 H, br s, OH, OH and OH), 2.84–2.88 (1 H, m, H-10), 2.53 (1 H,

in vacuo. The residue was purified by flash chromatography on

silica gel (gradient: 20-33% EtOAc in hexanes) to give 62 (16 mg,

31%, 65% based on recovered starting material) as a colourless

oil. $R_{\rm f} = 0.22$ (silica gel, 1 : 1 hexanes–EtOAc); $[a]_{\rm D}^{25} - 14.3^{\circ}$ (c

1.36 in CH₂Cl₂); ν_{max} /cm⁻¹ (film) 3467, 3071, 2956, 1738, 1513, 1248, 1097, 823; $\delta_{\rm H}$ (500 MHz, C₆D₆) 7.80–7.82 (4 H, m, SiAr*H*),

7.29 (2 H, d, J 8.6 Hz, ArH), 7.23-7.27 (6 H, m, SiArH), 6.82

(2 H, d, J 8.6 Hz, ArH), 5.56 (1 H, d, J 9.5 Hz, 11-H), 5.24 (1 H, s, 6=CH₂), 5.18 (1 H, s, 6=CH₂), 4.57 (1 H, d, J 11.0 Hz,

OCH₂Ar), 4.45–4.49 (2 H, m, 7-H and OCH₂Ar), 4.12 (2 H, s,

13-H and 13-H), 3.80-3.84 (m, 1 H, 3-H), 3.70-3.73 (1 H, m, 9-

H), 3.52 (1 H, d, J 2.0 Hz, 5-H), 3.32 (3 H, s, CO₂CH₃), 3.28

(3 H, s, ArOCH₃), 3.00 (1 H, dd, J 3.4, 2.0 Hz, 4-H), 2.81–2.86

(1 H, m, 10-H), 2.55 (1 H, qd, J 7.1, 4.9 Hz, 2-H), 2.39 (1 H, d,

J 4.2 Hz, OH), 2.30 (1 H, d, J 3.9 Hz, OH), 1.86–1.89 (2 H, m,

8-H and 8-H), 1.61 (3 H, s, 12-CH₃), 1.17-1.19 [12 H, m, 2-CH₃

and SiC(CH₃)₃], 1.05 (3 H, d, J 6.5 Hz, 10-CH₃); $\delta_{\rm C}$ (125 MHz,

 C_6D_6) 174.8, 159.8, 148.8, 136.0, 134.8, 134.3, 131.5, 129.9, 129.7,

129.6, 127.4, 114.1, 80.1, 72.6, 72.5, 70.9, 70.0, 69.4, 61.1, 55.4,

54.8, 51.4, 43.0, 37.6, 35.5, 27.1, 19.6, 16.1, 13.9, 11.7; HRMS

(ES⁺) *m/z* calc. for C₄₂H₅₈O₈SiNa ([MNa]⁺): 739.3636, found:

To a stirred solution of diene 61 (50 mg, 71.3 μ mol) and VO(acac)₂

(5 mg, 14.3 µmol) in CH₂Cl₂ (2 mL) was added tert-butyl

hydroperoxide (0.29 mL, 0.55 M in 1 : 9 decane-CH₂Cl₂, 159.5

µmol) at 0 °C. After 40 min at 0 °C the reaction was quenched

by the addition of 5% aq. Na₂SO₃ (5 mL). The mixture was

partitioned between CH₂Cl₂ (20 mL) and 5% aq. Na₂SO₃ (20 mL),

and the layers were separated. The aqueous layer was extracted

with CH_2Cl_2 (2 × 15 mL), and the combined organic layers

were washed with brine (1 \times 20 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash

chromatography on silica gel (gradient: 20-33% EtOAc in hexanes)

to give 63 (28.5 mg, 56%) as a colourless oil and as a 9 : 1 mixture

of epoxide diastereoisomers (determined by ¹H-NMR). $R_f = 0.28$ (silica gel, 1 : 1 hexanes–EtOAc); $[a]_{D}^{25} - 21.6^{\circ}$ (*c* 1.30 in CH₂Cl₂);

 v_{max} /cm⁻¹ (film) 3476, 2956, 2856, 2280, 1738, 1514, 1248, 1111, 812; δ_{H} (600 MHz, C₆D₆) – major diastereomer only – 7.80–7.81 (4 H, m, SiAr*H*), 7.28 (2 H, d, *J* 8.5 Hz, Ar*H*), 7.23–7.26 (6 H,

m, SiArH), 6.82 (2 H, d, J 8.5 Hz, ArH), 6.01 (1 H, dd, J 15.7,

1.5 Hz, 5-H), 5.92 (1 H, dd, J 15.7, 4.9 Hz, 4-H), 5.59 (1 H, d,

J 9.5 Hz, 11-H), 4.58 (1 H, d, J 11.0 Hz, OCH₂Ar), 4.49 (1 H,

d, J 11.0 Hz, OCH₂Ar), 4.28-4.30 (1 H, m, 3-H), 4.08-4.13 (3 H,

m, 7-H, 13-H and 13-H), 3.77 (1 H, ddd, J 9.4, 4.7 and 2.6 Hz,

9-H), 3.32 (3 H, s, CO₂CH₃), 3.27 (3 H, s, ArOCH₃), 2.81–2.87

52.4, 51.3, 45.0, 35.7, 35.5, 27.1, 19.6, 16.1, 13.9, 11.4; HRMS

(ES⁺) *m/z* calc. for C₄₂H₅₆O₈SiNa ([MNa]⁺): 739.3636, found:

739.3625.

739.3625.

Allylic epoxide 63

qd, J 7.1, 5.2 Hz, H-2), 1.82–1.86 (1 H, m, H-8), 1.63–1.67 (1 H, m, H-8), 1.62 (3 H, s, 12-CH₃), 1.12 (3 H, d, J 7.1 Hz, 2-CH₃), 0.98 (3 H, d, J 6.8 Hz, 10-CH₃); $\delta_{\rm C}$ (125 MHz, CDCl₃) 175.4, 159.1, 147.8, 135.5, 130.7, 130.4, 129.4, 129.0, 127.1, 114.4, 113.7, 79.4, 73.3, 71.1, 69.0, 68.0, 55.1, 51.7, 45.1, 35.5, 33.2, 14.3, 13.9, 11.6; HRMS (ES⁺) *m/z* calc. for C₂₆H₃₈O₇Na ([MNa]⁺): 485.2510, found: 485.2491.

Diol 61

TBDPSCI (120 µL, 0.45 mmol) was added to a stirred solution of triol 60 (190 mg, 0.41 mmol), Et₃N (90 µL, 0.62 mmol), and 4-DMAP (5 mg, 0.04 mmol) in CH₂Cl₂ (2 mL) at room temperature. Ater 16 h the reaction was quenched with sat. aq. NH₄Cl (15 mL), and the mixture was extracted with EtOAc (3 \times 10 mL). The combined organic layers were washed with brine $(1 \times 15 \text{ mL})$, dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (25% EtOAc in hexanes) to give 61 (221 mg, 77%) as a highly viscous, yellow oil. $R_{\rm f} = 0.51$ (silica gel, 1 : 1 hexanes-EtOAc); $[a]_{\rm D}^{25} - 10.6^{\circ}$ (c 1.24 in CHCl₃); v_{max}/cm⁻¹ (film) 3447, 3414, 2956, 1734, 1718, 1512, 1301, 1168, 823; $\delta_{\rm H}$ (500 MHz, C₆D₆) 7.78–7.81 (4 H, m, SiArH), 7.29 (2 H, d, J 8.6 Hz, ArH), 7.24–7.25 (6 H, m, SiArH), 6.83 (2 H, d, J 8.6 Hz, ArH), 6.39 (1 H, d, J 16.1 Hz, H-5), 5.88 (1 H, dd, J 16.1, 5.5 Hz, H-4), 5.49 (1 H, d, J 9.4 Hz, H-11), 5.41 (1 H, s, 6=CH₂), 5.09 (1 H, s, 6=CH₂), 4.72 (1 H, dd, J 9.0, 1.7 Hz, H-7), 4.58 (1 H, d, J 10.9 Hz, OCH₂Ar), 4.43 (1 H, d, J 10.9 Hz, OCH₂Ar), 4.36–4.40 (1 H, m, H-3), 4.10 (2 H, s, H-13 and H-13), 3.72 (1 H, ddd, J 9.8, 4.7 and 2.2 Hz, H-9), 3.34 (3 H, s, CO₂CH₃), 3.31 (3 H, s, ArOCH₃), 2.80–2.87 (1 H, dqd, J 9.4, 6.8 and 4.7 Hz, H-10), 2.62 (1 H, br s, OH), 2.42 (1 H, qd, J 7.1, 4.6 Hz, H-2), 2.19 (1 H, br s, OH), 1.96 (1 H, ddd, J 14.3, 9.8 and 1.7 Hz, H-8), 1.70 (1 H, ddd, J 14.3, 9.0 and 2.2 Hz, H-8), 1.60 (3 H, s, 12-CH₃), 1.18 [9 H, s, SiC(CH₃)₃], 1.14 (3 H, d, J 7.1 Hz, 2-CH₃), 1.03 (3 H, d, J 6.8 Hz, 10-CH₃); $\delta_{\rm C}$ (125 MHz, C₆D₆) 175.3, 159.7, 149.7, 136.0, 134.7, 134.2, 131.5, 130.6, 130.1, 129.9, 129.6, 128.1, 127.5, 114.1, 113.6, 80.3, 73.0, 72.4, 69.4, 68.7, 54.8, 51.3, 45.5, 38.7, 35.3, 27.1, 19.5, 15.8, 13.9, 11.6; HRMS (ES⁺) m/z calc. for C₄₂H₅₆O₇SiNa ([MNa⁺]): 723.3687, found: 723.3676.

Allylic epoxide 62

To a stirred suspension of powdered, activated 4 Å molecular sieves (50 mg) in CH₂Cl₂ (1 mL) was added (–)-diisopropyl D-tartrate (0.642 mL, 0.5 M in CH₂Cl₂, 0.321 mmol) at room temperature. The mixture was cooled to -25 °C, and was maintained at this temperature until the work-up. Freshly distilled Ti(Oi-Pr)₄ (0.571 mL, 0.5 M in CH₂Cl₂, 0.285 mmol) was then added dropwise. After 30 min tert-butyl hydroperoxide (0.973 mL, 0.55 M in 1:9 decane-CH₂Cl₂, 0.535 mmol) was added dropwise. After a further 30 min, a solution of diene 61 (50 mg, 71.3 µmol) in CH₂Cl₂ (1 mL) was added dropwise, and stirring was continued for a further 75 min, before the addition of NaOH (5 ml, 1 M in brine) and stirring for another 5 min. The mixture was then partitioned between water (20 mL) and CH₂Cl₂ (20 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with brine $(1 \times 20 \text{ mL})$, dried (MgSO₄), filtered and concentrated

(1 H, m, 10-H), 2.80 [1 H, d, *J* 5.6 Hz, 6-(O)*CH*₂], 2.47 (1 H, br d, *J* 5.0 Hz, O*H*), 2.38 [1 H, d, *J* 5.6 Hz, 6-(O)*CH*₂], 2.36 (1 H, br s, O*H*), 2.32 (1 H, qd, *J* 7.2, 4.4 Hz, 2-H), 1.94 (1 H, dd, *J* 13.6, 10.0 Hz, 8-H), 1.59–1.61 (1 H, m, 8-H), 1.59 (3 H, s, 12-*CH*₃), 1.19 [9 H, s, SiC(*CH*₃)₃], 1.09 (3 H, d, *J* 7.2 Hz, 2-*CH*₃), 1.06 (3 H, d, *J* 6.9, 10-*CH*₃); $\delta_{\rm C}$ (150 MHz, C₆D₆) – major diastereomer only – 175.2, 159.7, 136.0, 134.7, 134.3, 133.5, 131.6, 129.9, 129.6, 127.8, 127.6, 127.3, 114.0, 79.9, 72.7, 72.1, 69.3, 68.1, 60.5, 54.8,

A solution of hydrazone 11⁶ (0.703 g, 2.9 mmol) in THF (10 mL) was added dropwise to a stirred solution of freshly prepared LDA (3.48 mmol) in THF (20 mL) at -78 °C. After 1.75 h, a solution of iodide 65 (2.056 g, 3.48 mmol) in THF (10 mL) was added dropwise over 15 min, and the reaction was stirred at -78 °C for an additional 45 min before being quenched by the addition of aqueous pH 7.0 buffer (50 mL) and warmed to room temperature. The reaction mixture was extracted with Et₂O (3 \times 30 mL), and the combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo. The residue was purified by flash chromatography (33% Et₂O in hexanes with 1.5% Et₃N) to give 66 (1.797 g, 88%) as a viscous, colourless oil. $R_{\rm f} = 0.31$ (silica gel, 3 : 2 hexanes–Et₂O + 2% Et₃N); $[a]_D^{25}$ –59.1° (c 0.64 in CH₂Cl₂); v_{max}/cm⁻¹ (film) 2947, 1614, 1463, 1373, 1247, 905, 835; $\delta_{\rm H}$ (600 MHz, C₆D₆) 7.37 (2 H, J 8.6 Hz, ArH), 6.85 (2 H, J 8.6 Hz, ArH), 4.83 (1 H, d, J 11.3 Hz, OCH2Ar), 4.58-4.61 (2 H, m, 16-H and OCH₂Ar), 4.50 (1 H, dd, J 12.5, 1.5 Hz, 14-H), 4.24–4.28 (1 H, m, 19-H), 4.19 (1 H, d, J 12.5 Hz, 14-H), 4.06– 4.11 (1 H, m, 21-H), 3.93 (1 H, app q, J 7.0 Hz, 24-H), 3.67 (1 H, dd, J 8.9, 4.1 Hz, NCHCH₂OCH₃), 3.60 (1 H, qd, J 7.6, 4.1 Hz, NCHCH₂OCH₃), 3.31 (3 H, s, ArOCH₃), 3.31-3.34 (2 H, m, 25-H and NCHCH₂OCH₃), 3.21 (3 H, s, CH₂OCH₃), 3.05–3.09 (1 H, m, NCH₂CH₂CH₂), 2.29–2.37 (2 H, m, 17-H and NCH₂CH₂CH₂), 1.95–2.05 (2 H, m, 17-H and NCHCH₂CH₂), 1.79–1.88 (2 H, m, 18-H and 18-H), 1.47-1.86 (11 H, m, 20-H, 20-H, 22-H, 22-H, 23-H, 26-H, 26-H, 27-H, NCHCH2CH2, NCH2CH2CH2 and NCHCH₂CH₂), 1.41 [3 H, s, O₂C(CH₃)₂], 1.36 [3 H, s, O₂C(CH₃)₂], 1.25-1.43 (4 H, m, 23-H, 27-H, 28-H and 28-H), 1.07 [9 H, s, SiC(CH₃)₃], 0.90 (3 H, t, J 7.3 Hz, 28-CH₃), 0.27 (3 H, s, SiCH₃), 0.21 (3 H, s, SiCH₃); δ_c (125 MHz, C₆D₆) 159.6, 158.4, 132.2, 129.5, 113.9, 99.8, 82.3, 81.4, 76.6, 76.1, 72.7, 71.8, 69.9, 67.3, 64.4, 59.0, 54.7, 53.4, 43.7, 34.0, 31.8, 31.3, 28.3, 27.9, 27.7, 27.1, 26.3, 24.6, 23.3, 23.3, 23.1, 18.5, 14.3, -4.1, -4.4; HRMS (ES⁺) m/z calc. for C₃₉H₆₉N₂O₇Si ([MH]⁺): 705.4868, found 705.4858.

Ketone 68

A solution of hydrazone 66 (0.815 g, 1.15 mmol) in THF (5 mL) was added dropwise to a stirred solution of freshly prepared LDA (1.38 mmol) in THF (5 mL) at $-78 \degree$ C. After 1 h a solution of allylic bromide 56 (1.04 g, 1.38 mmol) in THF (5 mL) was added dropwise over 15 min. After stirring for an additional 1 h at -78 °C, the reaction was quenched by the addition of an aqueous pH 7.0 buffer solution (25 mL) and warmed to room temperature. The mixture was extracted with Et₂O (3×20 mL), and the combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo. Rapid flash chromatography (10% Et₂O in hexanes with 2% Et₃N) separated the excess bromide starting material and afforded the crude bis-alkylated hydrazone 67, which was taken up in a mixture of Et₂O (15 mL) and sat. aq. (CO₂H)₂ (15 mL) and stirred vigorously at room temperature for 48 h. The mixture was then diluted with water (30 mL) and extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine $(1 \times 30 \text{ mL})$, dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient: 5-10% Et₂O in hexanes) to give **68** (0.710 g, 49% from **66**) as a viscous,

light yellow syrup. $R_{\rm f} = 0.49$ (silica gel, 7 : 3 hexanes–Et₂O); $[a]_{\rm D}^{25}$ $+13.5^{\circ}$ (c 1.00 in CH₂Cl₂); v_{max} /cm⁻¹ (film) 2951, 2856, 1744, 1612, 1470, 1442, 1301, 1171, 1005, 869; δ_H (500 MHz, C₆D₆) 7.37 (4 H, d, J 8.6 Hz, ArH), 6.92 (2 H, d, J 8.6 Hz, ArH), 6.85 (2 H, d, J 8.6 Hz, ArH), 6.26 (1 H, d, J 16.1 Hz, 5-H), 6.07 (1 H, dd, J 16.1, 6.7 Hz, 4-H), 5.41 (1 H, s, 6=CH₂), 5.31 (1 H, d, J 8.8 Hz, 11-H), 5.07 (1 H, s, 6=CH₂), 4.85 (1 H, d, J 9.2 Hz, 7-H), 4.82 (1 H, d, J 11.3 Hz, OCH₂Ar), 4.68 (1 H, d, J 10.9 Hz, OCH₂Ar), 4.62 (1 H, d, J 11.3 Hz, OCH₂Ar), 4.54–4.56 (1 H, m, 3-H), 4.44 (1 H, d, J 10.9 Hz, OCH₂Ar), 4.28–4.31 (1 H, m, 14-H), 4.16– 4.20 (1 H, m, 16-H), 4.10-4.12 (1 H, m, 19-H), 4.06-4.09 (1 H, m, 21-H), 3.91-3.95 (1 H, m, 9-H), 3.74-3.76 (1 H, m, 24-H), 3.41 (3 H, s, CO₂CH₃), 3.37 (3 H, s, ArOCH₃), 3.33 (3 H, s, ArOCH₃), 3.32-3.33 (1 H, m, 25-H), 2.96-3.00 (1 H, m, 10-H), 2.83 (1 H, dd, J 15.3, 1.7 Hz, 13-H), 2.46-2.51 (1 H, m, 2-H), 2.29 (1 H, dd, J 15.3, 9.7 Hz, 13-H), 2.14-2.21 (1 H, m, 17-H), 1.94-1.98 (1 H, m, 8-H), 1.70 (3 H, s, 12-CH₃), 1.37 [3 H, s, O₂C(CH₃)₂], 1.32 [3 H, s, O₂C(CH₃)₂], 1.26–1.87 (16 H, m, 8-H, 17-H, 18-H, 18-H, 20-H, 20-H, 22-H, 22-H, 23-H, 23-H, 26-H, 26-H, 27-H, 27-H, 28-H and 28-H), 1.24 (3 H, d, J 7.0 Hz, 2-CH₃) 1.04-1.08 [12 H, m, 10-CH₃ and SiC(CH₃)₃], 1.01 [9 H, s, SiC(CH₃)₃], 0.98 [9 H, s, SiC(CH₃)₃], 0.91 (3 H, t, J 7.3 Hz, 28-CH₃), 0.25 (3 H, s, SiCH₃), 0.21 (3 H, s, SiCH₃), 0.12 (3 H, s, SiCH₃), 0.09 (3 H, s, SiCH₃), 0.07 (3 H, s, SiCH₃), 0.06 (3 H, s, SiCH₃); $\delta_{\rm C}$ (125 MHz, C₆D₆) 210.1, 174.0, 159.6, 159.5, 150.0, 132.2, 131.7, 131.5, 130.3, 129.5, 129.4, 129.0, 128.5, 114.4, 114.1, 113.9, 101.0, 82.4, 81.4, 80.0, 76.1, 75.4, 74.7, 74.4, 72.7, 71.0, 69.9, 69.8, 54.1, 51.1, 47.3, 43.9, 40.8, 38.4, 34.4, 34.1, 31.7, 31.4, 28.3, 27.9, 26.3, 26.2, 26.0, 24.7, 24.2, 24.1, 23.3, 18.4, 18.3, 17.3, 14.9, 14.4, 11.8, -3.8, -4.0, -4.2, -4.4, -4.9, -5.0; HRMS (ES⁺) m/z calc. for C₇₁H₁₂₀O₁₃Si₃Na ([MNa]⁺): 1287.7929, found: 1287.7927.

Hydrazone 69

A solution of hydrazone 11⁶ (0.420 g, 1.73 mmol) in THF (10 mL) was added dropwise to a stirred solution of freshly prepared LDA (2.07 mmol) in THF (15 mL) at -78 °C. After 2.5 h, a solution of iodide 64 (1.73 g, 2.07 mmol) in THF (10 mL) was added dropwise over 15 min, and the reaction was stirred at -78 °C for an additional hour before being quenched by the addition of aqueous pH 7.0 buffer (50 mL) and warmed to room temperature. The mixture was extracted with Et_2O (3 × 30 mL), and the combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (15% Et₂O in hexanes with 1% Et₃N) to give **69** (1.53 g, 93%) as a viscous, colourless oil. $R_f = 0.35$ (silica gel, 3 : 2 hexanes-Et₂O + 2% Et₃N); $[a]_{D}^{25}$ -7.6° (c 1.09 in CH₂Cl₂); v_{max} /cm⁻¹ (film) 2955, 2857, 1616, 1472, 1301, 1172, 937; $\delta_{\rm H}$ (500 MHz, C₆D₆) 7.29 (2 H, d, J 8.6 Hz, ArH), 6.85 (2 H, d, J 8.6 Hz, ArH), 4.59 (1 H, d, J 6.4 Hz, 16-H), 4.55 (1 H, d, J 11.5 Hz, OCH₂Ar), 4.47–4.50 (2 H, m, 14-H and OCH₂Ar), 4.19 (1 H, d, J 12.6 Hz, 14-H), 4.00-4.08 (2 H, m, 21-H and 19-H), 3.88–3.90 (1 H, m, 24-H), 3.69 (1 H, dd, J 8.8, 4.1 Hz, CH₂OCH₃), 3.58–3.64 (1 H, m, NCHCH₂OCH₃), 3.42–3.45 (1 H, m, 25-H), 3.36 (1 H, dd, J 8.8, 8.2 Hz, CH₂OCH₃), 3.33 (3 H, s, ArOCH₃), 3.27 (3 H, s, CH₂OCH₃), 3.06–3.10 (1 H, m, NCH₂CH₂), 2.26–2.36 (2 H, m, NCH₂CH₂ and NCH₂CH₂), 1.77– 2.17 (9 H, m, 17-H, 18-H, 20-H, 20-H, 22-H, 23-H, NCH₂CH₂, NCH₂CH₂CH₂ and NCH₂CH₂CH₂), 1.51-1.70 (7 H, m, 17-H, 22-H, 23-H, 26-H, 26-H, 27-H and 27-H), 1.42 [3 H, s, O₂C(CH₃)₂],

1.37 [3 H, s, $O_2C(CH_3)_2$], 1.30–1.46 (3 H, m, 18-H, 28-H and 28-H), 1.05 [9 H, s, $SiC(CH_3)_3$], 1.04 [9 H, s, $SiC(CH_3)_3$], 1.02 [9 H, s, $SiC(CH_3)_3$], 0.92 (3 H, t, *J* 7.3 Hz, 28-CH₃), 0.22 (3 H, s, $SiCH_3$), 0.20 (9 H, s, $SiCH_3$, $SiCH_3$ and $SiCH_3$), 0.14 (3 H, s, $SiCH_3$), 0.10 (3 H, s, $SiCH_3$); δ_C (150 MHz, C_6D_6) 159.7, 158.6, 131.7, 129.4, 114.0, 99.8, 82.2, 76.7, 73.6, 72.2, 71.7, 70.2, 70.1, 67.2, 64.2, 59.0, 54.7, 53.3, 45.3, 34.5, 33.0, 29.0, 28.9, 27.8, 27.5, 27.0, 26.2, 26.1, 24.5, 24.0, 23.2, 23.1, 18.3, 18.3, 14.3, -3.9, -4.0, -4.1, -4.1, -4.2; HRMS (ES⁺) m/z calc. for $C_{51}H_{99}N_2O_8Si_3$ ([MH]⁺): 951.6703, found: 951.6700.

Ketone 71

A solution of hydrazone 69 (1.66 g, 1.75 mmol) in THF (10 mL) was added dropwise to a stirred solution of freshly prepared LDA (1.92 mmol) in THF (10 mL) at -78 °C. After 1 h, a solution of allylic bromide 56 (1.45 g, 1.92 mmol) in THF (10 mL) was added dropwise over 15 min. After stirring for an additional hour at -78 °C, the reaction was quenched by the addition of an aqueous pH 7.0 buffer solution (25 mL) and warmed to room temperature. The mixture was extracted with Et_2O (3 × 20 mL), and the combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo. Rapid flash chromatography (10% Et₂O in hexanes with 2% Et₃N) separated the excess bromide starting material and afforded the crude bis-alkylated hydrazone 70, which was taken up in a mixture of Et_2O (30 mL) and sat. aq. (CO_2H)₂ (30 mL) and stirred vigorously at room temperature for 48 h. The mixture was then diluted with water (60 mL), and extracted with $Et_2O(3 \times 30 \text{ mL})$. The combined organic layers were washed with brine (1 \times 60 mL), dried (MgSO₄), filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (gradient: 2–7% Et₂O in hexanes) to give **71** (1.56 g, 59% from **69**) as a viscous, light yellow syrup. $R_{\rm f} = 0.45$ (silica gel, 4 : 1 hexanes–Et₂O); $[a]_{D}^{25}$ + 32.2° (c 1.71 in CH₂Cl₂); v_{max} /cm⁻¹ (film) 2953, 1743, 1610, 1457, 1361, 1171, 1004, 835; $\delta_{\rm H}$ (500 MHz, C₆D₆) 7.37 (2 H, d, J 8.7 Hz, ArH), 7.30 (2 H, d, J 8.7 Hz, ArH), 6.92 (2 H, d, J 8.7 Hz, ArH), 6.85 (2 H, d, J 8.7 Hz, ArH), 6.27 (1 H, d, J 16.1 Hz, 5-H), 6.08 (1 H, dd, J 16.1, 6.7 Hz, 4-H), 5.41 (1 H, s, 6=CH₂), 5.31 (1 H, d, J 8.3 Hz, 11-H), 5.07 (1 H, s, 6=CH₂), 4.85 (1 H, d, J 9.0 Hz, 7-H), 4.69 (1 H, d, J 10.8 Hz, OCH₂Ar), 4.54-4.57 (2 H, m, 3-H and OCH₂Ar), 4.49 (1 H, d, J 11.5 Hz, OCH₂Ar), 4.45 (1 H, d, J 10.8 Hz, OCH₂Ar), 4.30 (1 H, dd, J 7.7, 1.7 Hz, 14-H), 4.13 (1 H, dd, J 7.5, 4.2 Hz, 16-H), 3.98–4.05 (2 H, m, 19-H and 21-H), 3.88-3.92 (1 H, m, 24-H), 3.75 (1 H, ddd, J 9.7, 4.0 and 1.8 Hz, 9-H), 3.41 (3 H, s, CO₂CH₃), 3.41–3.45 (1 H, m, 25-H), 3.38 (3 H, s, ArOCH₃), 3.35 (3 H, s, ArOCH₃), 2.95-3.02 (1 H, m, 10-H), 2.83 (1 H, dd, J 15.2, 1.7 Hz, 13-H), 2.49 (1 H, qd, J 7.0, 5.5 Hz, 2-H), 2.28 (1 H, dd, J 15.2, 7.7 Hz, 13-H), 2.05–2.16 (2 H, m, 17-H and 23-H), 1.90–2.01 (4 H, m, 8-H, 17-H, 18-H and 26-H), 1.75-1.87 (4 H, m, 8-H, 20-H, 20-H and 26-H), 1.71 (3 H, s, 12-CH₃), 1.55-1.66 (4 H, 18-H, 22-H, 22-H and 23-H), 1.38 [3 H, s, O₂C(CH₃)₂], 1.34 [3 H, s, O₂C(CH₃)₂], 1.25 (3 H, d, J 7.0 Hz, 2-CH₃), 1.23-1.45 (4 H, 27-H, 27-H, 28-H and 28-H), 1.07 (3 H, d, J 6.8 Hz, 10-CH₃), 1.05 [9 H, s, SiC(CH₃)₃], 1.04 [9 H, s, SiC(CH₃)₃], 1.03 [9 H, s, SiC(CH₃)₃], 1.02 [9 H, s, SiC(CH₃)₃], 0.98 [9 H, s, SiC(CH₃)₃], 0.92 (3 H, t, J 9.3 Hz, 28- CH_3), 0.22 (3 H, s, SiCH₃), 0.21 (3 H, s, SiCH₃), 0.20 (3 H, s, SiCH₃), 0.19 (3 H, s, SiCH₃), 0.14 (3 H, s, SiCH₃), 0.13 (3 H, s, SiCH₃), 0.10 (3 H, s, SiCH₃), 0.09 (3 H, s, SiCH₃), 0.08 (3 H, s,

$$\begin{split} & \text{SiC}H_3), \ 0.06 \ (3 \ \text{H}, \ \text{s}, \ \text{SiC}H_3); \ \delta_{\mathbb{C}} \ (125 \ \text{MHz}, \ \mathbb{C}_6\mathbb{D}_6) \ 210.0, \ 173.9, \\ & 159.7, \ 159.6, \ 149.9, \ 132.2, \ 131.7, \ 131.5, \ 130.3, \ 129.4, \ 129.3, \ 129.0, \\ & 128.5, \ 114.3, \ 114.1, \ 114.0, \ 101.0, \ 82.2, \ 80.0, \ 75.4, \ 74.6, \ 74.5, \ 73.5, \\ & 72.2, \ 71.0, \ 70.1, \ 70.0, \ 69.9, \ 54.8, \ 54.7, \ 51.1, \ 47.3, \ 45.4, \ 40.8, \ 38.4, \\ & 34.4, \ 33.2, \ 29.1, \ 29.0, \ 27.6, \ 26.2, \ 26.1, \ 26.0, \ 25.2, \ 24.2, \ 24.1, \ 23.2, \\ & 18.4, \ 18.3, \ 17.2, \ 14.8, \ 14.3, \ 11.8, \ -3.8, \ -4.0, \ -4.1, \ -4.2, \\ & -4.8, \ -4.9; \ \text{HRMS} \ (\text{ES}^+) \ m/z \ \text{calc. for} \ \mathbb{C}_{83} \mathbb{H}_{150} \mathbb{O}_{14} \mathbb{S}_{15} \mathbb{Na} \ ([\text{MNa}]^+): \\ & 1533.9764, \ \text{found:} \ 1533.9775. \end{split}$$

Diol 72

To a vigorously stirred solution of ketone 68 (314 mg, 0.248 mmol) in 15 : 1 CH₂Cl₂-sat. aq. NaHCO₃ (5.5 mL) was added DDQ (170 mg, 0.75 mmol) in one portion at 0 °C. After 1 h at 0 °C the reaction mixture was partitioned between sat. aq. NaHCO₃ (15 mL) and CH_2Cl_2 (15 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were washed with brine $(1 \times 20 \text{ mL})$, dried (MgSO₄), filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (gradient: 10-20% Et₂O in hexanes) to give 72 (179 mg, 70%) as a colourless oil. $R_{\rm f} = 0.31$ (silica gel, 2 : 1 hexanes-Et₂O); $[a]_{\rm D}^{25} + 38.8^{\circ}$ (c 1.03 in CH₂Cl₂); v_{max} /cm⁻¹ (film) 3511, 2954, 2855, 1745, 1461, 1383, 1252, 1196, 1082, 976; $\delta_{\rm H}$ (500 MHz, C₆D₆) 6.27 (1 H, d, J 16.1 Hz, 5-H), 6.08 (1 H, dd, J 16.1, 6.8 Hz, 4-H), 5.46 (1 H, s, $6=CH_2$), 5.09 (1 H, s, 6=CH₂), 5.01–5.06 (2 H, m, 7-H and 11-H), 4.53 (1 H, app t, J 6.2 Hz, 3-H), 4.17 (1 H, dd, J 10.8, 3.1 Hz, 14-H), 4.06-4.08 (1 H, m, 16-H), 4.00-4.04 (1 H, m, 19-H), 3.91-3.97 (1 H, m, 21-H), 3.56–3.61 (2 H, m, 9-H and 24-H), 3.42 (3 H, s, CO₂CH₃), 3.32-3.38 (1 H, m, 25-H), 2.67 (1 H, dd, J 13.9, 3.1 Hz, 13-H), 2.56 (1 H, br s, OH), 2.49-2.54 (1 H, m, 2-H), 2.44 (1 H, br s, OH), 2.37–2.34 (1 H, m, 10-H), 2.22 (1 H, dd, J 13.9 Hz, 10.8 Hz, 13-H), 2.11-2.17 (1 H, m, 17-H), 1.90 (1 H, dd, J 13.2, 9.6 Hz, 8-H), 1.50 (3 H, s, 12-CH₃), 1.39 [3 H, s, O₂C(CH₃)₂], 1.37 [3 H, s, O₂C(CH₃)₂], 1.25 (3 H, d, J 7.0 Hz, 2-CH₃), 1.23–1.83 (16 H, m, 8-H, 17-H, 18-H, 18-H, 20-H, 20-H, 22-H, 22-H, 23-H, 23-H, 26-H, 26-H, 27-H, 27-H, 28-H and 28-H), 1.05 [9 H, s, SiC(CH₃)₃], 1.02 [9 H, s, SiC(CH₃)₃], 0.98 [9 H, s, SiC(CH₃)₃], 0.90–0.94 (6 H, m, 10-CH₃ and 28-CH₃), 0.24 (3 H, s, SiCH₃), 0.16 (6 H, s, SiCH₃) and SiCH₃), 0.15 (3 H, s, SiCH₃) 0.09 (3 H, s, SiCH₃), 0.07 (3 H, s, SiCH₃); δ_C (125 MHz, C₆D₆) 210.1, 173.9, 149.9, 133.5, 131.4, 131.3, 130.4, 114.3, 101.4, 82.8, 76.2, 75.5, 74.8, 74.4, 72.1, 72.1, 69.9, 69.8, 51.1, 47.4, 43.7, 43.3, 40.2, 39.7, 34.1, 33.8, 32.3, 28.3, 27.7, 26.2, 26.0, 24.2, 23.9, 23.8, 23.2, 18.5, 18.4, 18.3, 16.7, 16.2, 14.3, 11.9, -3.9, -4.2, -4.4, -4.5, -4.9; HRMS (ES⁺) m/z calc. for C₅₅H₁₀₄O₁₁Si₃Na ([MNa]⁺): 1047.6778, found: 1047.6761.

Acid 73

Methyl ester **72** (0.380 g, 0.370 mmol) was dissolved in 1,2dichloroethane (4 mL) in a 25 mL round-bottomed flask and Me₃SnOH (0.670 g, 3.70 mmol) was added. The reaction vessel was then sealed under argon and the stirred mixture was heated to 80 °C. Additional portions of Me₃SnOH (0.670 g, 3.70 mmol) were added every 24 h over a period of three days. Twenty-four hours after the final addition, the reaction mixture was cooled to room temperature, diluted with EtOAc, filtered through a pad of Celite[®], and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient: 10–20% EtOAc in hexanes) to give 73 (0.254 g, 68%) as a highly viscous, light yellow oil. $R_{\rm f} = 0.51$ (silica gel, 2 : 1 hexanes-EtOAc); $[a]_{\rm D}^{25} + 30.1^{\circ}$ (c 0.25 in CH₂Cl₂); v_{max}/cm^{-1} (film) 3510, 2956, 2857, 1744, 1713, 1472, 1382, 1173, 976; $\delta_{\rm H}$ (500 MHz, C₆D₆) 6.30 (1 H, d, J 16.1 Hz, 5-H), 6.10 (1 H, dd, J 16.1 Hz and 6.5 Hz, 4-H), 5.47 (1 H, s, 6=CH₂), 5.11 (1 H, s, 6=CH₂), 5.08 (1 H, d, J 10.0 Hz, 7-H), 5.02 (1 H, d, J 9.1 Hz, 11-H), 4.63 (1 H, app t, J 5.5 Hz, 3-H), 4.20 (1 H, dd, J 10.7, 2.7 Hz, 14-H), 4.08–4.10 (1 H, m, 16-H), 4.01–4.05 (1 H, m, 19-H), 3.93-3.98 (1 H, m, 21-H), 3.58-3.63 (2 H, m, 9-H and 24-H), 3.36-3.39 (1 H, m, 25-H), 2.69 (1 H, dd, J 14.1, 2.7 Hz, 13-H), 2.50-2.55 (1 H, m, 2-H), 2.30-2.37 (1 H, m, 10-H), 2.24 (1 H, dd, J 14.1, 10.7 Hz, 13-H), 2.12–2.17 (1 H, m, 17-H), 1.92 (1 H, dd, J 12.6, 9.5 Hz, 8-H), 1.52 (s, 3 H, 12-CH₃), 1.41 [3 H, s, O₂C(CH₃)₂], 1.39 [3 H, s, O₂C(CH₃)₂], 1.25 (3 H, d, J 7.0 Hz, 2-CH₃), 1.20–1.85 (18 H, m, OH, OH, 8-H, 17-H, 18-H, 18-H, 20-H, 20-H, 22-H, 22-H, 23-H, 23-H, 26-H, 26-H, 27-H, 27-H, 28-H and 28-H), 1.06 [9 H, s, SiC(CH_3)₃], 1.02 [9 H, s, SiC(CH_3)₃], 1.00 [9 H, s, SiC(CH₃)₃], 0.93 (6 H, m, 10-CH₃ and 28-CH₃), 0.25 (3 H, s, SiCH₃), 0.16 (9 H, s, SiCH₃, SiCH₃ and SiCH₃), 0.14 $(3 \text{ H}, \text{ s}, \text{SiC}H_3), 0.11 (3 \text{ H}, \text{ s}, \text{SiC}H_3); \delta_{\text{C}} (125 \text{ MHz}, \text{C}_6\text{D}_6) 210.2,$ 179.2, 149.7, 133.5, 131.1, 131.0, 130.5, 114.4, 101.4, 82.7, 76.3, 75.0, 74.8, 74.4, 72.3, 72.2, 70.0, 69.9, 47.2, 43.6, 43.4, 40.1, 39.6, 34.0, 33.8, 32.3, 28.3, 27.7, 26.2, 26.1, 24.2, 24.0, 23.9, 23.2, 18.5, 18.4, 16.8, 16.3, 14.3, 11.2, -3.9, -4.2, -4.4, -4.5, -4.9, -5.0;HRMS (ES⁺) m/z calc. for C₅₄H₁₀₂O₁₁Si₃Na ([MNa]⁺): 1033.6622, found: 1033.6611.

Macrolactone 75

To a stirred solution of carboxylic acid 73 (250 mg, 0.25 mmol) and Et₃N (1.38 mL, 9.85 mmol) in toluene (15 mL) was added 2,4,6trichlorobenzoylchloride 74 (1.16 mL, 7.41 mmol) at room temperature. After 16 h, the solution was diluted with an additional portion of toluene (15 mL) and then added dropwise via syringe pump to a stirred solution of 4-DMAP (906 mg, 7.41 mmol) in toluene (400 mL) over 6 h. After stirring for a further 16 h at room temperature, the reaction was quenched by the addition of 0.01 M aq. KHSO₄ (400 mL), and the mixture was extracted with EtOAc $(3 \times 300 \text{ mL})$. The combined organic layers were washed with brine (1 \times 200 mL), dried (MgSO₄), filtered and concentrated *in* vacuo. The residue was purified by flash chromatography on silica gel (gradient: 5–10% Et_2O in hexanes) to give 75 (197 mg, 80%) as a colourless foam. $R_f = 0.37$ (silica gel, 4 : 1 hexanes-Et₂O); $[a]_{D}^{25}$ +35.3° (c 0.53 in CH₂Cl₂); v_{max} /cm⁻¹ (film) 3443, 2951, 2854, 1742, 1731, 1472, 1251, 1091, 834; $\delta_{\rm H}$ (500 MHz, C₆D₆) 6.38 (1 H, d, J 16.1 Hz, 5-H), 6.14 (1 H, dd, J 16.1 5.7 Hz, 4-H), 5.38 (1 H, s, 6=CH₂), 5.29 (1 H, d, J 9.9 Hz, 11-H), 5.15 (1 H, s, 6=CH₂), 4.86-4.89 (2 H, m, 7-H and 25-H), 4.57 (1 H, app t, J 5.7 Hz, 3-H), 4.24-4.28 (1 H, m, 14-H), 4.04-4.16 (3 H, m, 16-H, 19-H and 21-H), 3.77-3.83 (2 H, m, 9-H and 24-H), 2.61 (1 H, app qn, J 6.9 Hz, 2-H), 2.51 (1 H, dd, J 14.1 3.1 Hz, 13-H), 2.35-2.42 (2 H, m, 10-H and 13-H), 2.02–2.11 (2 H, m, 17-H and OH), 1.65-1.89 (9 H, m, 8-H, 8-H, 17-H, 18-H, 18-H, 22-H, 23-H, 26-H and 26-H), 1.60 (3 H, s, 12-CH₃), 1.45–1.56 (3 H, m, 23-H, 27-H and 27-H), 1.25-1.40 [14 H, m, 20-H, 20-H, 22-H, 28-H, 28-H, 2-CH₃, O₂C(CH₃)₂ and O₂C(CH₃)₂], 0.99–1.03 [21 H, m, 10-CH₃, $SiC(CH_3)_3$ and $SiC(CH_3)_3$, 1.00 [9 H, s, $SiC(CH_3)_3$], 0.92 (3 H, t, J 7.0 Hz, 28-CH₃), 0.23 (3 H, s, SiCH₃), 0.20 (3 H, s, SiCH₃), 0.19 (3 H, s, SiCH₃), 0.14 (3 H, s, SiCH₃), 0.12 (3 H, s, SiCH₃), 0.11

 $\begin{array}{l} (3 \ H, \ s, \ SiCH_3); \ \delta_{\rm C} \ (125 \ MHz, \ C_6D_6) \ 210.6, \ 174.0, \ 149.2, \ 132.3, \\ 131.1, \ 129.9, \ 129.6, \ 113.5, \ 101.0, \ 79.0, \ 75.9, \ 74.9, \ 74.8, \ 74.6, \ 74.3, \\ 72.6, \ 71.0, \ 69.7, \ 47.7, \ 43.9, \ 43.4, \ 39.5, \ 39.1, \ 35.0, \ 32.0, \ 31.7, \ 27.9, \\ 27.3, \ 26.3, \ 26.2, \ 26.1, \ 24.9, \ 24.2, \ 24.1, \ 23.1, \ 18.5, \ 18.4, \ 17.6, \ 17.4, \\ 14.3, \ 14.0, \ -3.8, \ -4.0, \ -4.1, \ -4.4, \ -4.6, \ -4.8; \ HRMS \ (ES^+) \ m/z \\ {\rm calc. \ for \ C_{54}H_{100}O_{10}Si_3Na \ ([MNa]^+): \ 1015.6516, \ found: \ 1015.6512. \end{array}$

Macrocycle diketone 77

To a stirred suspension of alcohol 75 (30.1 mg, 30 µmol) and powdered, activated 4 Å molecular sieves (ca. 30 mg) in CH₂Cl₂ (1.5 mL) were added TPAP (5.5 mg, 15 µmol) and NMO (14.2 mg, 121 µmol) at room temperature. After 2 h the reaction was filtered through a pad of Celite[®], washing thoroughly with CH₂Cl₂, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (7% Et₂O in hexanes) to give 77 (27.7 mg, 92%) as a colourless foam. $R_{\rm f} = 0.52$ (silica gel, 4 : 1 hexanes–Et₂O); $[a]_{D}^{25}$ +51.0° (c 1.07 in CH₂Cl₂); $v_{\rm max}/{\rm cm}^{-1}$ (film) 2956, 2856, 1742, 1717, 1456, 1252, 1092, 908; $\delta_{\rm H}$ (600 MHz, C₆D₆) 6.41 (1 H, d, J 16.1 Hz, 5-H), 6.15 (1 H, dd, J 16.1 4.6 Hz, 4-H), 5.31 (1 H, s, 6=CH₂), 5.19 (1 H, d, J 9.4 Hz, 7-H), 5.16 (1 H, s, 6=CH₂), 5.10 (1 H, d, J 10.2 Hz, 11-H), 4.90 (1 H, td, J 6.6 3.6 Hz, 25-H), 4.59 (1 H, app t, J 4.9 Hz, 3-H), 4.21 (1 H, dd, J 8.0, 3.6 Hz, 14-H), 4.06–4.12 (2 H, m, 16-H and 19-H), 3.98–4.02 (1 H, m, 21-H), 3.76 (1 H, td, J 7.3, 3.6 Hz, 24-H), 3.35 (1 H, dq, J 10.2, 6.5 Hz, 10-H), 2.82 (1 H, dd, J 16.1, 9.4 Hz, 8-H), 2.47-2.57 (3 H, m, 2-H, 8-H and 13-H), 2.31 (1 H, dd, J 14.9, 8.0 Hz, 13-H), 2.02–2.04 (1 H, m, 17-H), 1.62 (3 H, s, 12-CH₃), 1.61-1.85 (7 H, m, 17-H, 18-H, 18-H, 22-H, 23-H, 26-H and 26-H), 1.44-1.54 (3 H, m, 23-H, 27-H and 27-H), 1.25-1.38 [14 H, m, 20-H, 20-H, 22-H, 28-H, 28-H, 2-CH₃, O₂C(CH₃)₂ and O₂C(CH₃)₂], 1.22 (3 H, d, J 6.5 Hz, 10-CH₃), 1.03 [9 H, s, SiC(CH₃)₃], 1.01 [9 H, s, SiC(CH₃)₃], 0.98 [9 H, s, SiC(CH₃)₃], 0.92 (3 H, t, J 6.7 Hz, 28-CH₃), 0.20 (3 H, s, SiCH₃), 0.18 (6 H, s, SiCH₃ and SiCH₃), 0.12 (6 H, s, SiCH₃ and SiCH₃), 0.11 (3 H, s, SiCH₃); $\delta_{\rm C}$ (150 MHz, C₆D₆) 209.7, 208.0, 173.6, 148.6, 134.7, 131.6, 128.2, 126.6, 112.9, 100.9, 78.9, 75.8, 74.8, 74.6, 73.6, 73.4, 70.5, 69.7, 49.6, 48.6, 47.8, 43.2, 38.3, 34.9, 32.0, 31.6, 27.8, 27.3, 26.2, 26.1, 25.0, 24.1, 24.0, 23.1, 18.5, 18.4, 17.4, 15.1, 14.2, 13.9, -3.9, -4.0, -4.3, -4.4, -4.6, -5.0; HRMS (ES⁺) m/z calc. for C₅₄H₉₈O₁₀Si₃Na ([MNa]⁺): 1013.6360, found: 1013.6359.

Hemiacetal 78

Ketone 77 (125 mg, 0.126 mmol) was dissolved in 9 : 1 acetonitrile– CH₂Cl₂ (20 mL) in a plastic vial and cooled to 0 °C, where 48% aq. HF (2 mL) was carefully added dropwise. The reaction mixture was slowly warmed to room temperature over 2 h, then stirred for a further 3 h at that temperature. The reaction was then quenched by adding the solution dropwise to sat. aq. NaHCO₃ (50 mL) at 0 °C. Upon completion of the addition, solid NaHCO₃ was added slowly until the pH of the mixture was greater than 8.0. The mixture was then extracted with EtOAc (5 × 20 mL), and the combined organic layers were dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient: 50–70% EtOAc in hexanes) to give **78** (49.7 mg, 65%) as an amorphous, colourless solid and as a 6 : 1 mixture of α - : β -anomers (determined by ¹H-NMR). $R_f = 0.48$ (silica gel, EtOAc); $[a]_D^{25} - 136.5^\circ$ (*c* 1.48 in CH₂Cl₂);

 $v_{\rm max}/{\rm cm}^{-1}$ (film) 3400, 2933, 1709, 1458, 1351, 1193, 1074, 901; $\delta_{\rm H}$ $(500 \text{ MHz}, C_6 D_6)$ – major anomer only – 6.08 (1 H, d, J 16.2 Hz, 5-H), 5.73 (1 H, s, 6=CH₂), 5.69 (1 H, dd, J 16.2, 7.2 Hz, 4-H), 5.24 (1 H, d, J 9.9 Hz, 11-H), 5.14 (1 H, s, 6=CH₂), 5.05 (1 H, d, J 9.3 Hz, 7-H), 4.91–4.96 (1 H, m, 25-H), 4.67 (1 H, br d, J 4.4 Hz, 3-OH), 4.58-4.61 (1 H, m, 3-H), 4.53 (1 H, br s, 14-OH), 4.00-4.06 (3 H, m, 16-H, 19-H and 21-H), 3.88 (1 H, br s, 16-OH), 3.77 (1 H, ddd, J 7.1, 6.1 and 2.7 Hz, 14-H), 3.52–3.55 (1 H, m, 24-H), 3.49–3.51 (2 H, m, 7-OH and 15-OH), 3.26 (1 H, dd, J 18.5, 2.7 Hz, 8-H), 2.80 (1 H, dq, J 9.9, 6.7 Hz, 10-H), 2.62 (1 H, qd, J 7.1, 2.2 Hz, 2-H), 2.58 (1 H, dd, J 14.4, 6.1 Hz, 13-H), 2.48 (1 H, dd, J 14.4, 7.1 Hz, 13-H), 2.29 (1 H, dd, J 18.5, 9.3 Hz, 8-H), 2.06-2.12 (1 H, m, 17-H), 1.80-1.87 (2 H, m, 17-H and 18-H), 1.53 (3 H, s, 12-CH₃), 1.15–1.63 (11 H, m, 20-H, 20-H, 22-H, 22-H, 23-H, 26-H, 26-H, 27-H, 27-H, 28-H and 28-H), 1.11 (3 H, d, J 6.7 Hz, 10-CH₃), 1.08 (3 H, d, J 7.1 Hz, 2-CH₃), 1.03–1.12 (2 H, m, 18-H and 23-H), 0.86 (3 H, t, J 6.8 Hz, 28-CH₃); $\delta_{\rm C}$ (125 MHz, C_6D_6 – major anomer only – 212.0 (C9), 173.6 (C1), 147.2 (C6), 136.7 (C12), 131.2 (C5), 128.5 (C4), 125.2 (C11), 114.5 (6=CH₂), 96.1 (C15), 81.6 (C24), 77.2 (C25), 76.8 (C14), 75.1 (C21), 75.0 (C3), 67.2 (C7), 66.7 (C16), 66.5 (C19), 48.2 (C2), 47.7 (C8), 47.3 (C10), 42.5 (C20), 41.4 (C13), 31.9 (C22), 31.0 (C26), 27.5 (C27), 27.4 (C23), 26.5 (C17), 25.6 (C18), 22.8 (C28), 17.3 (12-CH₃), 14.9 (10-CH₃), 14.1 (2-CH₃), 9.4 (28-CH₃); HRMS (ES⁺) m/z calc. for $C_{33}H_{52}O_{10}Na$ ([MNa]⁺): 631.3452, found: 631.3459.

Diol 79

To a vigorously stirred solution of ketone 71 (1.45 g, 0.96 mmol) in 2 : 1 CH₂Cl₂-aqueous pH 7.0 buffer (15 mL) was added DDQ (0.68 g, 3.0 mmol) in one portion at 0 °C. After 20 min the reaction was quenched by the addition of sat. aq. NaHCO₃ (15 mL), and extracted with Et₂O (3 \times 20 mL). The combined organic layers were washed with sat. aq. NaHCO₃ ($1 \times 20 \text{ mL}$), brine ($1 \times 20 \text{ mL}$), dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient: 5-15% Et₂O in hexanes) to give 79 (0.96 g, 78%) as a viscous, yellow oil. $R_{\rm f} = 0.19$ (silica gel, 4 : 1 hexanes-Et₂O); $[a]_{\rm D}^{25} + 36.5^{\circ}$ (c 1.41 in CH₂Cl₂); v_{max}/cm⁻¹ (film) 3510, 2956, 2859, 1746, 1738, 1382, 1172, 939; $\delta_{\rm H}$ (500 MHz, C₆D₆) 6.29 (1 H, d, J 16.2 Hz, H-5), 6.11 (1 H, dd, J 16.2, 6.8 Hz, H-4), 5.48 (1 H, s, 6=CH₂), 5.11 (1 H, s, 6=CH₂), 5.03–5.07 (2 H, m, H-7 and H-11), 4.55 (1 H, dd, J 6.8, 5.3 Hz, H-3), 4.16 (1 H, dd, J 11.0, 2.5 Hz, H-14), 4.10 (1 H, dd, J 6.8, 4.1 Hz, H-16), 3.97-4.03 (2 H, m, H-19 and H-21), 3.53-3.63 (3 H, m, H-9, H-24 and H-25), 3.43 (3 H, s, CO₂CH₃), 2.68 (1 H, dd, J 13.9, 2.5 Hz, H-13), 2.51-2.57 (2 H, m, H-2 and OH), 2.28–2.37 (1 H, m, H-10), 2.24 (1 H, dd, J 13.9, 11.0 Hz, H-13), 2.10-2.17 (1 H, m, H-17), 1.89-1.98 (4 H, m, H-8, H-17, H-23 and OH), 1.68–1.84 (5 H, m, H-8, H-18, H-20, H-26 and H-26), 1.55-1.67 (4 H, m, H-18, H-20, H-22 and H-23), 1.50 (3 H, s, 12-CH₃), 1.41 [3 H, s, O₂C(CH₃)₂], 1.36 [3 H, s, O₂C(CH₃)₂], 1.27 (3 H, d, J 7.0 Hz, 2-CH₃), 1.32–1.53 (5 H, m, H-22, H-27, H-27, H-28 and H-28), 1.07 [9 H, s, SiC(CH₃)₃], 1.04 [9 H, s, SiC(CH₃)₃], 1.03 [9 H, s, SiC(CH₃)₃], 0.99 [9 H, s, SiC(CH₃)₃], 0.96 [9 H, s, SiC(CH₃)₃], 0.91–0.94 (6 H, m, 10-CH₃ and 28-CH₃), 0.26 (3 H, s, SiCH₃), 0.20 (3 H, s, SiCH₃), 0.19 (3 H, s, SiCH₃), 0.19 (3 H, s, SiCH₃), 0.18 (3 H, s, SiCH₃), 0.16 (3 H, s, SiCH₃), 0.14 (3 H, s, SiCH₃), 0.10 (3 H, s, SiCH₃), 0.09 (3 H, s, SiCH₃), 0.08 (3 H, s, SiCH₃); δ_c (150 MHz, C₆D₆) 209.9, 173.9, 149.8, 133.5,

131.4, 130.4, 131.2, 114.3, 101.3, 76.2, 75.5, 74.7, 73.1, 72.2, 72.1, 69.9, 69.8, 69.7, 51.1, 47.4, 44.9, 43.7, 40.2, 39.7, 33.9, 33.1, 32.6, 29.2, 28.6, 26.1, 26.1, 26.1, 26.0, 25.0, 23.9, 23.2, 18.5, 18.4, 18.3, 18.3, 16.7, 16.1, 14.3, 11.9, -3.8, -4.0, -4.0, -4.1, -4.1, -4.3, -4.4, -4.9; HRMS (ES⁺) *m/z* calc. for C₆₇H₁₃₄O₁₂Si₅Na ([MNa]⁺): 1293.8613, found: 1293.8600.

Acid 80

Methyl ester 79 (0.83 g, 0.650 mmol) was dissolved in 1,2dichloroethane (20 mL) in a 50 mL round-bottomed flask and Me₃SnOH (1.18 g, 6.50 mmol) was added. The reaction vessel was then sealed under argon, and the stirred mixture was heated to 80 °C. Additional portions of Me₃SnOH (1.18 g, 6.50 mmol) were added every 12 h over a period of two days. Twelve hours after the final addition, the reaction was cooled to room temperature, diluted with EtOAc, filtered through a pad of Celite[®], and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography on silica gel (15% EtOAc in hexanes) to give 80 (0.365 g, 45%, 66% based on recovered starting material **79**) as a highly viscous, light yellow oil. $R_{\rm f} = 0.36$ (silica gel, 3 : 2 hexanes–Et₂O); $[a]_{D}^{25}$ +33.8° (c 7.70 in CH₂Cl₂); v_{max} /cm⁻¹ (film) $3493, 2955, 2890, 1745, 1711, 1471, 1361, 1092, 835; \delta_{\rm H}$ (500 MHz, C₆D₆) 6.30 (1 H, d, J 16.1 Hz, 5-H), 6.10 (1 H, dd, J 16.1, 6.4 Hz, 4-H), 5.48 (1 H, s, $6=CH_2$), 5.12 (1 H, s, $6=CH_2$), 5.06 (1 H, d, J 9.9 Hz, 11-H), 5.02 (1 H, d, J 9.0 Hz, 7-H), 4.63 (1 H, app t, J 5.0 Hz, 3-H), 4.16 (1 H, d, J 10.0 Hz, 14-H), 4.07–4.11 (1 H, 16-H), 3.96–4.01 (2 H, m, 19-H and 21-H), 3.60 (1 H, app t, J 9.1 Hz, 9-H), 3.52–3.57 (2 H, m, 24-H and 25-H), 2.67 (1 H, d, J 13.1 Hz, 13-H), 2.49-2.54 (1 H, m, 2-H), 2.30-2.37 (1 H, m, 10-H), 2.21-2.25 (1 H, m, 13-H), 2.06-2.16 (1 H, m, 17-H), 1.87-1.97 (4 H, m, 8-H, 17-H, 18-H and 22-H), 1.56–1.81 (9 H, m, 8-H, 18-H, 20-H, 20-H, 22-H, 23-H, 26-H, OH and OH), 1.51 (3 H, s, 12-CH₃), 1.47–1.53 (2 H, m, 26-H and 27-H), 1.41 [3 H, s, O₂C(CH₃)₂], 1.37 [3 H, s, O₂C(CH₃)₂], 1.30–1.44 (4 H, m, 23-H, 27-H, 28-H and 28-H), 1.25 (3 H, d, J 6.9 Hz, 2-CH₃), 1.06 [9 H, s, SiC(CH₃)₃], 1.04 [9 H, s, SiC(CH₃)₃], 1.03 [9 H, s, SiC(CH₃)₃], 1.01 [9 H, s, SiC(CH₃)₃], 0.96 [9 H, s, SiC(CH₃)₃], 0.91–0.94 (6 H, m, 10-CH₃) and 28-CH₃), 0.25 (3 H, s, SiCH₃), 0.19 (3 H, s, SiCH₃), 0.19 (3 H, s, SiCH₃), 0.18 (3 H, s, SiCH₃), 0.18 (3 H, s, SiCH₃), 0.17 (3 H, s, SiCH₃), 0.14 (3 H, s, SiCH₃), 0.13 (3 H, s, SiCH₃), 0.11 $(3 \text{ H}, \text{ s}, \text{SiC}H_3), 0.09 (3 \text{ H}, \text{ s}, \text{SiC}H_3); \delta_{\text{C}} (125 \text{ MHz}, \text{C}_6\text{D}_6) 210.0,$ 179.3, 149.7, 133.5, 131.2, 130.9, 128.5, 114.4, 101.3, 76.1, 75.0, 74.7, 73.1, 72.2, 72.1, 69.9, 69.8, 47.2, 44.9, 43.6, 40.1, 39.6, 33.8, 33.1, 32.5, 29.1, 28.5, 26.2, 26.2, 26.1, 26.1, 26.0, 24.9, 23.9, 23.9, 23.2, 18.5, 18.4, 18.3, 18.3, 16.7, 16.2, 14.3, 11.1, -3.8, -3.9, -4.0,-4.0, -4.1, -4.1, -4.3, -4.4, -4.8, -4.9; HRMS (ES⁺) m/z calc. for C₆₆H₁₃₂O₁₂Si₅Na ([MNa]⁺): 1279.8479, found: 1279.8474.

Macrolactone 81

To a stirred solution of carboxylic acid **80** (0.160 g, 0.127 mmol) and Et_3N (0.71 mL, 5.08 mmol) in toluene (8 mL) was added 2,4,6-trichlorobenzoyl chloride **74** (0.60 mL, 3.81 mmol) at room temperature. After stirring for 16 h, the solution was diluted with an additional portion of toluene (10 mL) and then added dropwise *via* syringe pump to a stirred solution of 4-DMAP (0.480 g, 3.81 mmol) in toluene (200 mL) over 6 h. After stirring for a further 16 h at room temperature, the reaction was quenched by

the addition of 0.01 M aq. KHSO₄ (200 mL), and the mixture was extracted with EtOAc (2×150 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo. The residue was purified by flash chromatography (10% Et₂O in hexanes) to give 81 (0.1032 g, 65%) as a colourless foam. $R_f = 0.52$ (silica gel, 4 : 1 hexanes– Et_2O); $[a]_D^{25}$ +59.6° (c 0.70 in CH₂Cl₂); $v_{\rm max}/{\rm cm}^{-1}$ (film) 3389, 2955, 1744, 1718, 1472, 1382, 1082, 835; δ_H (600 MHz, C₆D₆) 6.39 (1 H, d, J 16.0 Hz, 5-H), 6.23 (1 H, d, J 16.0 Hz, 4-H), 5.56 (1 H, s, 6=CH₂), 5.26 (1 H, d, J 9.9 Hz, 11-H), 5.17 (1 H, s, 6=CH₂), 5.11-5.14 (1 H, m, 25-H), 5.05 (1 H, d, J 7.5 Hz, 7-H), 4.58–4.61 (1 H, m, 3-H), 4.41 (1 H, d, J 9.8 Hz, 14-H), 4.10-4.13 (1 H, m, 16-H), 4.04-4.07 (1 H, m, 19-H), 3.96-4.01 (2 H, m, 21-H and 24-H), 3.75-3.79 (1 H, m, 9-H), 2.71 (1 H, d, J 14.1 Hz, 13-H), 2.63-2.67 (1 H, m, 2-H), 2.48 (1 H, br s, OH), 2.38–2.42 (1 H, m, 10-H), 2.21 (1 H, dd, J 14.1, 9.8 Hz, 13-H), 2.04–2.10 (1 H, m, 17-H), 1.98–2.02 (1 H, m, 20-H), 1.71– 1.91 (9 H, m, 8-H, 8-H, 17-H, 18-H, 20-H, 22-H, 22-H, 26-H and 27-H), 1.55–1.91 (3 H, m, 18-H, 23-H and 26-H), 1.52 (3 H, s, 12-CH₃), 1.47 [3 H, s, O₂C(CH₃)₂], 1.42 [3 H, s, O₂C(CH₃)₂], 1.32 (3 H, d, J 7.1 Hz, 2-CH₃) 1.29–1.49 (4 H, m, 23-H, 27-H, 28-H and 28-H), 1.05–1.06 [12 H, m, 10-CH₃ and SiC(CH₃)₃], 1.04 [9 H, s, SiC(CH₃)₃], 1.03 [9 H, s, SiC(CH₃)₃], 1.02 [9 H, s, SiC(CH₃)₃], 1.01 [9 H, s, SiC(CH₃)₃], 0.94 (3 H, t, J 7.1 Hz, 28-CH₃), 0.30 (3 H, s, SiCH₃), 0.26 (3 H, s, SiCH₃), 0.25 (3 H, s, SiCH₃), 0.20 (3 H, s, $SiCH_{3}$, 0.18 (6 H, s, $SiCH_{3}$ and $SiCH_{3}$), 0.16 (9 H, s, $SiCH_{3}$, SiCH₃ and SiCH₃), 0.14 (3 H, s, SiCH₃); $\delta_{\rm C}$ (150 MHz, C₆D₆) 210.1, 173.7, 149.7, 133.1, 131.0, 130.4, 128.8, 144.1, 101.3, 76.2, 75.9, 74.9, 73.1, 72.6, 72.3, 70.0, 69.7, 69.5, 47.7, 44.3, 44.2, 39.3, 38.6, 33.4, 32.9, 28.7, 28.5, 28.4, 26.3, 26.2, 26.2, 26.1, 24.7, 24.3, 24.1, 23.1, 18.6, 18.5, 18.3, 18.3, 17.5, 17.1, 14.3, 13.1, -3.6, -3.8, -4.0, -4.1, -4.2, -4.2, -4.4, -5.0; HRMS (ES⁺) m/z calc. for C₆₆H₁₂₈O₁₁Si₅Na ([MNa]⁺): 1261.8351, found 1261.8335.

Macrocyclic diketone 82

To a stirred suspension of alcohol 81 (98.3 mg, 79 µmol) and powdered, activated 4 Å molecular sieves (ca. 100 mg) in CH₂Cl₂ (3 mL) was added TPAP (5.5 mg, 15 µmol) and NMO (28 mg, 240 µmol) at room temperature. After 2 h, the reaction was filtered through a pad of Celite[®], washing thoroughly with CH₂Cl₂, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (5% Et₂O in hexanes) to give 82 (78 mg, 80%) as a colourless foam. $R_{\rm f}$ = 0.66 (silica gel, 4 : 1 hexanes-Et₂O); $[a]_{D}^{25}$ -19.0° (c 3.90 in CH₂Cl₂); *v*_{max}/cm⁻¹ (film) 2955, 2857, 1745, 1719, 1462, 1255, 979; δ_H (600 MHz, C₆D₆) 6.28 (1 H, d, J 16.1 Hz, H-5), 6.00 (1 H, dd, J 16.1, 5.5 Hz, H-4), 5.38 (1 H, s, 6=CH₂), 5.13–5.17 (3 H, m, H-7, H-11 and H-25), 5.09 (1 H, s, 6=CH₂), 4.83 (1 H, app t, J 3.9 Hz, H-3), 4.22–4.23 (1 H, m, H-14), 4.08–4.09 (1 H, m, H-16), 4.01-4.05 (2 H, m, H-19 and H-21), 3.93-3.95 (1 H, m, H-24), 3.34 (1 H, dq, J 10.1, 6.6 Hz, H-10), 2.83 (1 H, dd, J 15.7, 9.5 Hz, H-8), 2.50 (1 H, d, J 15.7 Hz, H-8), 2.43–2.46 (2 H, m, H-2 and H-13), 2.36 (1 H, dd, J 14.8, 7.2 Hz, H-13), 2.00-2.05 (1 H, m, H-17), 1.79–1.98 (7 H, m, H-17, H-18, H-20, H-20, H-22, H-23 and H-26), 1.63 (3 H, s, 12-CH₃), 1.62–1.77 (4 H, m, H-18, H-22, H-23 and H-26), 1.34 (3 H, d, J 7.0 Hz, 2-CH₃), 1.33 $[3 H, s, O_2C(CH_3)_2], 1.30 [3 H, s, O_2C(CH_3)_2], 1.30-1.45 (4 H, m, m)$ H-27, H-27, H-28 and H-28), 1.12 (3 H, d, J 6.5 Hz, 10-CH₃), 1.02 [9 H, s, SiC(CH₃)₃], 1.01 [9 H, s, SiC(CH₃)₃], 1.01 [9 H, s,

SiC(*CH*₃)₃], 1.00 [9 H, s, SiC(*CH*₃)₃], 0.99 [9 H, s, SiC(*CH*₃)₃], 0.91 (3 H, t, *J* 7.1 Hz, 28-*CH*₃), 0.24 (3 H, s, Si*CH*₃), 0.22 (3 H, s, Si*CH*₃), 0.21 (3 H, s, Si*CH*₃), 0.19 (6 H, s, Si*CH*₃ and Si*CH*₃), 0.18 (3 H, s, Si*CH*₃), 0.16 (3 H, s, Si*CH*₃), 0.16 (3 H, s, Si*CH*₃), 0.15(3 H, s, Si*CH*₃), 0.12 (3 H, s, Si*CH*₃); δ_c (150 MHz, C₆D₆) 209.6, 208.1, 173.0, 149.0, 134.9, 132.5, 129.1, 127.0, 113.7, 100.9, 76.0, 74.6, 74.0, 73.5, 73.1, 70.3, 70.0, 69.6, 49.7, 48.6, 47.2, 44.5, 38.0, 33.3, 32.9, 28.6, 28.3, 27.9, 26.2, 26.2, 26.1, 26.1, 25.0, 24.2, 24.1, 23.0, 18.5, 18.4, 18.3, 18.3, 18.3, 15.2, 14.2, 10.8, -3.8, -4.0, -4.1, -4.1, -4.2, -4.3, -4.4, -4.4, -4.5, -5.0; HRMS *m*/*z* calc. for C₆₆H₁₂₈O₁₁Si₅Na ([MNa]⁺): 1259.8195, found: 1295.8165.

Hemiacetal 83 and bicyclic acetal 84

Ketone 82 (0.105 g, 0.085 mmol) was dissolved in 4:1 acetonitrile-CH₂Cl₂ (20 mL) in a plastic vial and cooled to 0 °C, where 48% aq. HF (2 mL) was carefully added dropwise. The reaction mixture was slowly warmed to room temperature over 2 h, then stirred for a further 5 h at that temperature. The reaction was then quenched by adding the solution dropwise to sat. aq. NaHCO₃ (50 mL) at 0 °C. Upon completion of the addition, solid NaHCO3 was added slowly until the pH of the mixture was greater than 8.0. The mixture was then extracted with EtOAc (5 \times 20 mL), and the combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (gradient: 70-100% EtOAc in hexanes) to give 51 mg (94%) of a colourless foam. ¹H-NMR analysis indicated the presence of a 1 : 1.6 mixture of products 83 : 84, which could be separated via careful flash chromatography on silica gel (gradient: 50-100% EtOAc in hexanes).

Data for hemiacetal 83. $R_{\rm f} = 0.18$ (silica gel, EtOAc); $[a]_{\rm D}^{25}$ -116.0° (c 0.51 in CH₂Cl₂); v_{max} /cm⁻¹ (film) 3414, 2932, 1721, 1707, 1442, 1351, 1185, 1071, 902; $\delta_{\rm H}$ (500 MHz, $\rm C_6D_6)$ 6.24 (1 H, d, J 16.1 Hz, 5-H), 5.85 (1 H, dd, J 16.1, 4.7 Hz, 4-H), 5.58 (1 H, s, 6=CH₂), 5.22 (1 H, d, J 10.0 Hz, 11-H), 5.20 (1 H, s, 6=CH₂), 4.95–5.01 (2 H, m, 7-H and 25-H), 4.43 (1 H, br d, J 4.3 Hz, OH), 4.32-4.36 (1 H, m, 3-H), 4.04 (1 H, br s, OH), 3.78-3.87 (5 H, m, 14-H, 16-H, 19-H, 12-H and OH), 3.61 (2 H, br s, OH and OH), 3.54-3.57 (1 H, m, 24-H), 3.21 (1 H, dq, J 10.0, 6.6 Hz, 10-H), 3.08 (1 H, dd, J 17.4, 1.8 Hz, 8-H), 2.74 (1 H, qd, J 7.2, 4.0 Hz, 2-H), 2.49 (1 H, dd, J 17.4, 10.1 Hz, 8-H), 2.43 (1 H, d, J 13.1 Hz, 13-H), 2.28 (1 H, dd, J 13.1, 11.4 Hz, 13-H), 1.99-2.09 (2 H, m, 17-H and 26-H), 1.72–1.76 (2 H, m, 17-H and OH), 1.63 (3 H, s, 12-CH₃), 1.44–1.63 (7 H, m, 18-H, 20-H, 22-H, 22-H, 23-H, 26-H and 27-H), 1.26-1.39 (4 H, m, 23-H, 27-H, 28-H and 28-H), 1.15 (3 H, d, J 6.6 Hz, 10-CH₃), 1.06–1.12 (1 H, m, 20-H), 1.06 (3 H, d, J 7.2 Hz, 2-CH₃), 0.99 (1 H, d, J 13.8 Hz, 18-H), 0.93 $(3 \text{ H}, \text{t}, J 7.1 \text{ Hz}, 28\text{-}CH_3); \delta_{C} (125 \text{ MHz}, C_6H_6) 211.7 (C9), 174.5$ (C1), 147.6 (C6), 135.8 (C12), 129.7 (C5), 129.1 (C4), 127.2 (C11), $113.0 (6=CH_2), 97.2 (C15), 76.0 (C25), 73.9 (C14), 73.4 (C3), 72.1$ (C24), 69.3 (C16), 68.6 (C7), 66.3 (C21), 63.7 (C19), 47.9 (C10), 47.2 (C8), 46.3 (C2), 41.5 (C13), 34.7 (C20), 33.7 (C22), 30.1 (C23), 29.9 (C18), 28.4 (C27), 25.2 (C26), 23.6 (C17), 23.1 (C28), 16.9 (12-CH₃), 15.6 (10-CH₃), 14.4 (28-CH₃), 11.8 (2-CH₃); HRMS (ES⁺) m/z calc. for C₃₃H₅₃O₁₀ ([M - OH]⁺): 609.3633, found: 609.3641.

Data for bicyclic acetal 84. $R_{\rm f} = 0.28$ (silica gel, EtOAc); $[a]_{\rm D}^{25}$ -143.2° (*c* 1.16 in CH₂Cl₂); $v_{\rm max}/{\rm cm}^{-1}$ (film) 3409, 2931, 1721, 1706, 1485, 1346, 1185, 1023, 902; $\delta_{\rm H}$ (500 MHz, C₆D₆) 6.05 (1 H, d, J 16.2 Hz, 5-H), 5.73 (1 H, dd, J 16.2, 6.2 Hz, 4-H), 5.66 (1 H, s, 6=CH₂), 5.14 (1 H, s, 6=CH₂), 5.09 (1 H, ddd, J 8.5, 5.1 and 3.8 Hz, 25-H), 5.02 (1 H, d, J 9.9 Hz, 11-H), 4.93 (1 H, d, J 8.8 Hz, 7-H), 4.77-4.80 (1 H, m, 3-H), 4.70 (1 H, br s, 3-OH), 4.13-4.16 (2 H, m, 14-OH and 7-OH), 3.95-4.00 (1 H, m, 21-H), 3.80-3.86 (2 H, m, 14-H and 19-H), 3.66-3.73 (2 H, m, 16-H and 24-H), 3.59 (1 H, br s, 16-OH), 3.16 (1 H, br s, 24-OH), 3.11 (1 H, dq, J 9.9, 6.6 Hz, 10-H), 3.04 (1 H, dd, J 17.9, 2.5 Hz, 8-H), 2.56 (1 H, qd, J 7.1, 3.6 Hz, 2-H), 2.42–2.48 (2 H, m, 8-H and 13-H), 2.19 (1 H, dd, J 13.0, 11.9 Hz, 13-H), 1.88-1.96 (1 H, m, 17-H), 1.72-1.84 (3 H, m, 23-H, 23-H and 26-H), 1.60-1.70 (2 H, m, 17-H and 22-H), 1.57 (3 H, s, 12-CH₃), 1.23-1.58 (8 H, m, 18-H, 20-H, 22-H, 26-H, 27-H, 27-H, 28-H and 28-H), 1.17 (3 H, d, J 7.1 Hz, 2-CH₃), 1.10 (3 H, d, J 6.6 Hz, 10-CH₃), 1.07-1.10 (1 H, m, 20-H), 0.95–1.00 (1 H, m, 18-H), 0.90 (3 H, t, J 7.1 Hz, 28-CH₃); δ_c (125 MHz, C₆D₆) 212.1 (C9), 173.8 (C1), 147.2 (C6), 135.9 (C12), 130.8 (C4), 130.0 (C5), 127.5 (C11), 113.6 ($6=CH_2$), 96.9 (C15), 77.0 (C25), 73.8 (C24), 73.7 (C14), 73.5 (C3), 69.5 (C16), 68.1 (C7), 66.1 (C19), 65.8 (C21), 47.2 (C10), 46.9 (C8), 45.4 (C2), 43.3 (C13), 36.0 (C20), 33.7 (C22), 30.0 (C26), 30.0 (C18), 29.4 (C23), 28.4 (C27), 24.0 (C17), 23.0 (C28), 16.0 (12-CH₃), 15.3 (10- CH_3), 14.3 (28- CH_3), 10.0 (2- CH_3); HRMS (ES⁺) m/z calc. for C₃₃H₅₂O₁₀Na ([MNa]⁺): 631.3452, found: 631.3447.

Allylic epoxide 89

To a stirred solution of diene 84 (7.5 mg, 12.3 μ mol) in CH₂Cl₂ (1.5 mL), was added freshly prepared DMDO²⁶ (336 µL, 0.052 M in acetone, 17.5 µmol) dropwise at 0 °C. After 40 min at 0 °C, the reaction was quenched by the addition of Me₂S (1 drop) and was then concentrated in vacuo. The residue was purified by preparative thin-layer chromatography on silica gel (EtOAc) to give 89 (2.4 mg, 31%) as a colourless oil. $R_{\rm f} = 0.24$ (silica gel, EtOAc); $[a]_{D}^{25} - 70.8^{\circ}$ (c 0.24 in CH₂Cl₂); v_{max} /cm⁻¹ (film) 3412, 2928, 2856, 1726, 1714, 1664, 1458, 1386, 1264, 1192, 1097, 743; δ_H (600 MHz, C₆D₆) 5.83 (1 H, d, J 15.5 Hz, 5-H), 5.79 (1 H, dd, J 15.5, 3.7 Hz, 4-H), 5.02–5.05 (1 H, m, 25-H), 4.93 (1 H, d, J 10.1 Hz, 11-H), 4.80-4.82 (1 H, m, 3-H), 4.35 (1 H, br s, 3-OH), 4.21 (1 H, dd, J 9.9, 2.3 Hz, 7-H), 4.19 (1 H, br s, 14-OH), 3.84–3.91 (3 H, m, 14-H, 21-H and 24-OH), 3.76–3.79 (2 H, m, 19-H, 16-OH), 3.74 (1 H, br s, 7-OH), 3.66-3.72 (2 H, m, 16-H and 24-H), 3.29 [1 H, d, J 6.4 Hz, 6(O)CH₂], 3.09 (1 H, dq, J 10.1, 6.5 Hz, 10-H), 2.95 (1 H, dd, J 17.4, 2.3 Hz, 8-H), 2.54 (1 H, dd, J 17.4, 9.9 Hz, 8-H), 2.46 (1 H, d, J 13.6 Hz, 13-H), 2.37 (1 H, m, 2-H), 2.34 [1 H, d, J 6.4 Hz, 6(O)CH₂], 2.13 (1 H, dd, J 13.6, 11.8 Hz, 13-H), 1.82-1.87 (2 H, m, 17-H and 23-H), 1.66-1.77 (4 H, m, 17-H, 22-H, 23-H and 26-H), 1.55 (3 H, s, 12-CH₃), 1.35-1.62 (3 H, m, 18-H, 20-H, 22-H), 1.20-1.34 (5 H, m, 26-H, 27-H, 27-H, 28-H and 28-H), 1.08 (3 H, d, J 6.5 Hz, 10-CH₃), 1.07 (3 H, J 7.1 Hz, 2-CH₃), 0.97–1.05 (2 H, m, 18-H and 20-H), 0.90 (3 H, t, J 7.1 Hz, 28-CH₃); δ_c (150 MHz, C₆D₆) 211.9 (C9), 173.5 (C1), 136.0 (C12), 132.4 (C5), 127.5 (C11), 127.0 (C4), 97.0 (C15), 76.5 (C25), 74.0 (C21), 73.2 (C24), 71.9 (C3), 69.4 (C16), 68.3 (C7), 66.1 (C19), 65.8 (C14), 61.0 (C6), 53.8 [6(O)CH₂], 47.3 (C10), 44.4 (C2), 43.2 (C13), 42.6 (C8), 35.8 (C20), 33.1 (C22), 30.4 (C26), 29.9 (C18), 29.3, (C23), 28.4 (C27), 23.9 (C17), 23.0 (C28), 15.7 (12-CH₃), 15.0 (10-CH₃), 14.2 (28-CH₃), 9.3 (2-CH₃); HRMS (ES⁺) m/z calc. for C₃₃H₅₂O₁₁Na ([MNa]⁺): 647.3402, found: 647.3402.

Diol 91

To a vigorously stirred solution of ketone 90 (0.621 g, 0.57 mmol) in 4 : 1 CH₂Cl₂-aqueous pH 7.0 buffer (10 mL) was added DDQ (0.388 g, 1.71 mmol) in one portion at 0 °C. After 20 min the reaction was quenched by the addition of sat. aq. NaHCO₃ (25 mL), and warmed to room temperature. The layers were separated, and the aqueous layer was extracted with Et_2O (3 \times 20 mL). The combined organic layers were washed with sat. aq. NaHCO₃ (1×25 mL), brine (1×25 mL), dried (MgSO₄), filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (gradient: 10-20% Et₂O in hexanes) to give 91 (0.441 g, 91%) as a highly viscous, colourless oil. $R_{\rm f} =$ 0.41 (silica gel, 1 : 1 hexanes– Et_2O); $[a]_D^{25}$ +47.1° (c 1.20 in CH₂Cl₂); $v_{\rm max}/{\rm cm}^{-1}$ (film) 3510, 2956, 1745, 1461, 1382, 1094, 938, 837; $\delta_{\rm H}$ $(600 \text{ MHz}, C_6 D_6) 5.72 (1 \text{ H}, \text{ s}, 6=CH_2), 5.37 (1 \text{ H}, \text{ s}, 6=CH_2),$ 5.02 (1 H, d, J 10.1 Hz, 11-H), 4.72 (1 H, d, J 8.6 Hz, 7-H), 4.16 (1 H, dd, J 10.6, 2.8 Hz, 14-H), 4.08 (1 H, dd, J 7.0, 3.7 Hz, 16-H), 4.01-4.05 (1 H, m, 19-H), 3.92-3.97 (1 H, m, 21-H), 3.60 (1 H, q, J 7.0 Hz, 24-H), 3.54 (1 H, app t, J 9.0 Hz, 9-H), 3.34–3.38 (1 H, m, 25-H), 2.66 (1 H, dd, J 13.9, 2.8 Hz, 13-H), 2.48 (1 H, br s, OH), 2.38 (1 H, br s, OH), 2.20–2.28 (2 H, m, 10-H and 13-H), 2.13-2.17 (1 H, m, 17-H), 2.01 (1 H, dd, J 12.8, 10.2 Hz, 8-H), 1.66-1.97 (8 H, m, 8-H, 17-H, 18-H, 20-H, 20-H, 22-H, 23-H and 27-H), 1.45 (3 H, s, 12-CH₃), 1.39 [3 H, s, O₂C(CH₃)₂], 1.35 [3 H, s, O₂C(CH₃)₂], 1.22–1.64 (8 H, m, 18-H, 22-H, 23-H, 26-H, 26-H, 27-H, 28-H and 28-H), 1.03 [18 H, s, SiC(CH₃)₃ and SiC(CH₃)₃], 0.92 (3 H, t, J 7.3 Hz, 28-CH₃), 0.86 (3 H, d, J 6.6 Hz, 10-CH₃), 0.20 (3 H, s, SiCH₃), 0.16 (6 H, s, SiCH₃ and SiCH₃), 0.15 (3 H, s, SiCH₃); δ_c (150 MHz, C₆D₆) 210.2, 139.3, 133.6, 131.0, 115.8, 101.3, 82.8, 76.2, 74.8, 74.4, 74.1, 72.2, 71.4, 69.9, 43.4, 42.1, 40.0, 39.7, 34.1, 33.8, 32.3, 28.3, 27.7, 26.2, 26.0, 24.2, 23.9, 23.2, 18.4, 18.4, 16.8, 16.2, 14.3, -4.2, -4.5, -4.5, -4.9; HRMS (ES⁺) m/z calc. for $C_{42}H_{80}^{79}BrO_8Si_2$ ([MH]⁺): 847.4569, found: 847.4558.

Hemiacetal 92

To a stirred solution of diol 91 (150 mg, 0.177 mmol) in acetonitrile (5 mL) in a plastic vial was added 48% aq. HF (0.25 mL) dropwise at 0 °C. After 30 min, the mixture was warmed to room temperature and stirred for an additional 7 h. The reaction was then quenched by pouring the mixture slowly into sat. aq. NaHCO₃ (50 mL) at 0 °C. After stirring for a further 30 min, the mixture was warmed to room temperature and extracted with EtOAc (6 \times 20 mL). The combined organic layers were then dried (MgSO₄), filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (80% EtOAc in hexanes) to give 92 (56.3 mg, 56%) as a colourless foam and as a 10 : 1 mixture of α - : β -anomers (determined by ¹H-NMR). $R_{\rm f} =$ 0.28 (silica gel, EtOAc); $[a]_{D}^{25}$ -32.6° (c 1.12 in CH₂Cl₂); v_{max} /cm⁻¹ (film) 3385, 2955, 1628, 1446, 1266, 1092, 895; *δ*_H (600 MHz, C₆D₆, 343 K, major anomer only) 6.06 (1 H, s, $6=CH_2$), 5.52 (1 H, s, 6=CH₂), 5.23 (d, J 9.3 Hz, 11-H), 4.58–4.62 (1 H, m, 7-H), 4.17– 4.23 (2 H, m, 19-H and 21-H), 4.02–4.05 (1 H, m, 14-H), 3.93–3.96 (1 H, m, 17-H), 3.66–3.70 (2 H, m, 9-H and 24-H), 3.32–3.35 (1 H, m, 25-H), 2.59-2.63 (1 H, m, 13-H), 2.44-2.48 (1 H, m, 10-H), 2.37-2.42 (1 H, m, 13-H), 2.14-2.20 (1 H, m, 20-H), 2.04-2.07 (1 H, m, 8-H), 1.87–1.92 (1 H, m, 8-H), 1.75 (3 H, s, 12-CH₃), 1.72-1.80 (2 H, m, 20-H and 18-H), 1.47-1.68 (5 H, m, 17-H,

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17-H, 22-H, 22-H and 26-H), 1.20–1.45 (8 H, m, 18-H, 23-H, 23-H, 26-H, 27-H, 27-H, 28-H and 28-H), 0.90–0.95 (6 H, m, 10- CH_3 and 28- CH_3); δ_C (150 MHz, C_6D_6 , 343 K, major anomer only) 137.6 (C6), 135.0 (C12), 131.0 (C11), 116.1 (6= CH_2), 97.7 (C15), 83.4 (C24), 76.4 (C21), 75.0 (C25), 74.1 (C7), 74.0 (C9), 73.3 (C14), 68.0 (C19), 66.2 (C21), 43.0 (C20), 41.0 (C13), 39.6 (C10), 39.0 (C8), 34.0 (C23), 32.1 (C22), 28.2 (C26), 28.1 (C27), 26.9 (C17), 25.8 (C18), 23.1 (C28), 17.1 (12- CH_3), 16.8 (10- CH_3) 14.1 (28- CH_3); HRMS (ES⁺) m/z calc. for $C_{27}H_{47}^{79}BrO_8Na$ ([MNa]⁺): 601.2346, found: 601.2340.

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References

- 1 K. C. Nicolaou, W. E. Brenzovich, P. G. Bulger and T. M. Francis, Org. Biomol. Chem., 2006, DOI: 10.1039/b602020h.
- 2 M. Ishibashi, N. Yamaguchi, T. Sasaki and J. Kobayashi, J. Chem. Soc., Chem. Commun., 1994, 1455–1456.
- 3 I. Bauer, L. Maranda, K. A. Young, Y. Shimizu, C. Fairchild, L. Cornell, J. MacBeth and S. Huang, J. Org. Chem., 1995, 60, 1084–1086.
- 4 S. T. Diver and A. J. Giessert, *Synthesis*, 2004, 466–471; R. Stragies, M. Schuster and S. Blechert, *Angew. Chem., Int. Ed. Engl.*, 1997, 36, 2518–2520; C. Hansen and D. Lee, *J. Am. Chem. Soc.*, 2004, 126, 15 074–15 080; E. C. Hansen and D. Lee, *J. Am. Chem. Soc.*, 2003, 125, 9582–9583; K. C. Nicolaou, P. G. Bulger and D. Sarlah, *Angew. Chem., Int. Ed.*, 2005, 44, 4490–4527.
- 5 Metal-Catalyzed Cross-Coupling Reactions, ed. F. Diederich and P. J. Stang, Wiley-VCH, Weinheim, 2nd edn., 2004, p. 938; K. C. Nicolaou, P. G. Bulger and D. Sarlah, Angew. Chem., Int. Ed., 2005, 44, 4442–4489.
- 6 D. Enders, M. Voith and A. Lenzen, *Angew. Chem., Int. Ed.*, 2005, 44, 1304–1325; D. Enders, M. Voith and S. J. Ince, *Synthesis*, 2002, 1775–1779; A. Job, C. F. Janeck, W. Bettray, R. Peters and D. Enders, *Tetrahedron*, 2002, 58, 2253–2329.
- 7 G. Shapiro, D. Buechler and S. Hennet, *Tetrahedron Lett.*, 1990, **31**, 5733–5736.

- 8 M. A. Blanchette, W. Choy, J. T. Davis, A. P. Essenfeld, S. Masamune, W. R. Roush and T. Sakai, *Tetrahedron Lett.*, 1984, **25**, 2183–2186.
- 9 P. Li, J. Wang and K. Zhao, J. Org. Chem., 1998, 63, 3151-3152.
- 10 H. C. Brown and K. S. Bhat, J. Am. Chem. Soc., 1986, 108, 5919–5923.
- 11 J. A. Dale, D. L. Dull and H. S. Mosher, J. Org. Chem., 1969, 34, 2543–2549; J. A. Dale and H. S. Mosher, J. Am. Chem. Soc., 1973, 95, 512–519.
- 12 G. Zhong, Angew. Chem., Int. Ed., 2003, 42, 4247–4250; S. P. Brown, M. P. Brochu, C. J. Sinz and D. W. C. MacMillan, J. Am. Chem. Soc., 2003, 125, 10 808–10 809; Y. Hayashi, J. Yamaguchi, K. Hibino and M. Shoji, Tetrahedron Lett., 2003, 44, 8293–8296.
- 13 F. A. Davis, L. C. Vishwakarma, J. M. Billmers and J. Finn, J. Org. Chem., 1984, 49, 3241–3243; F. A. Davis and B.-C. Chen, Chem. Rev., 1992, 92, 919–934.
- 14 F. A. Davis and M. C. Weismiller, J. Org. Chem., 1990, 55, 3715-3717.
- 15 D. A. Evans, M. M. Morrissey and R. L. Dorow, J. Am. Chem. Soc., 1985, 107, 4346–4348.
- 16 T. D. Nelson and D. R. Crouch, Synthesis, 1996, 1031–1069.
- 17 T. Katsuki and K. B. Sharpless, J. Am. Chem. Soc., 1980, 102, 5974; T. Katsuki and V. S. Martin, Org. React., 1996, 48, 1–299.
- R. M. Hanson and K. B. Sharpless, *J. Org. Chem.*, 1986, **51**, 1922–1925;
 Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune and K. B. Sharpless, *J. Am. Chem. Soc.*, 1987, **109**, 5765–5780.
- 19 K. B. Sharpless and R. C. Michaelson, J. Am. Chem. Soc., 1973, 95, 6136–6137.
- 20 V. S. Martin, S. S. Woodard, T. Katsuki, Y. Yamada, M. Ikeda and K. B. Sharpless, *J. Am. Chem. Soc.*, 1981, **103**, 6237–6240.
- 21 D. Enders, T. Hundertmark and R. Lazny, Synlett, 1998, 721-722.
- 22 D. A. Evans, T. C. Britton and J. A. Ellman, *Tetrahedron Lett.*, 1987, 28, 6141–6144.
- 23 D. Liotta, U. Sunay, H. Santiesteban and W. Markiewicz, J. Org. Chem., 1981, 46, 2605–2610.
- 24 J. C. Sheehan and G. Doyle Daves, J. Org. Chem., 1964, 29, 2006–2008.
- 25 C. J. Salomon, E. G. Mata and O. A. Mascaretti, *Tetrahedron Lett.*, 1991, **32**, 4239–4242.
- 26 L. R. Reddy, P. Saravanan and E. J. Corey, J. Am. Chem. Soc., 2004, 126, 6230–6231; B. V. Subba Reddy, L. R. Reddy and E. J. Corey, *Tetrahedron Lett.*, 2005, 46, 4589–4593.
- 27 K. C. Nicolaou, A. A. Estrada, M. Zak, S. H. Lee and B. S. Safina, *Angew. Chem.*, *Int. Ed.*, 2005, 44, 1378–1382.
- 28 R. L. E. Furlán, E. G. Mata and O. A. Mascaretti, J. Chem. Soc., Perkin Trans. 1, 1998, 355–358; R. L. E. Furlán, E. G. Mata and O. A. Mascaretti, *Tetrahedron*, 1998, 54, 13 023–13 034; R. L. E. Furlán, E. G. Mata and O. A. Mascaretti, *Tetrahedron Lett.*, 1996, 37, 5229– 5232.
- 29 J. Inanaga, K. Hirata, H. Saeki, T. Katsuki and M. Yamaguchi, Bull. Chem. Soc. Jpn., 1979, 52, 1989–1993.
- 30 S. V. Ley, J. Norman, W. P. Griffith and S. P. Marsden, *Synthesis*, 1994, 639–666; W. P. Griffith, S. V. Ley, G. P. Whitcombe and A. D. White, *J. Chem. Soc., Chem. Commun.*, 1987, 1625–1627.
- 31 W. Adam, J. Bialas and L. Hadjiarapoglou, Chem. Ber., 1991, 124, 2377.