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 Me_3SnOH, 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

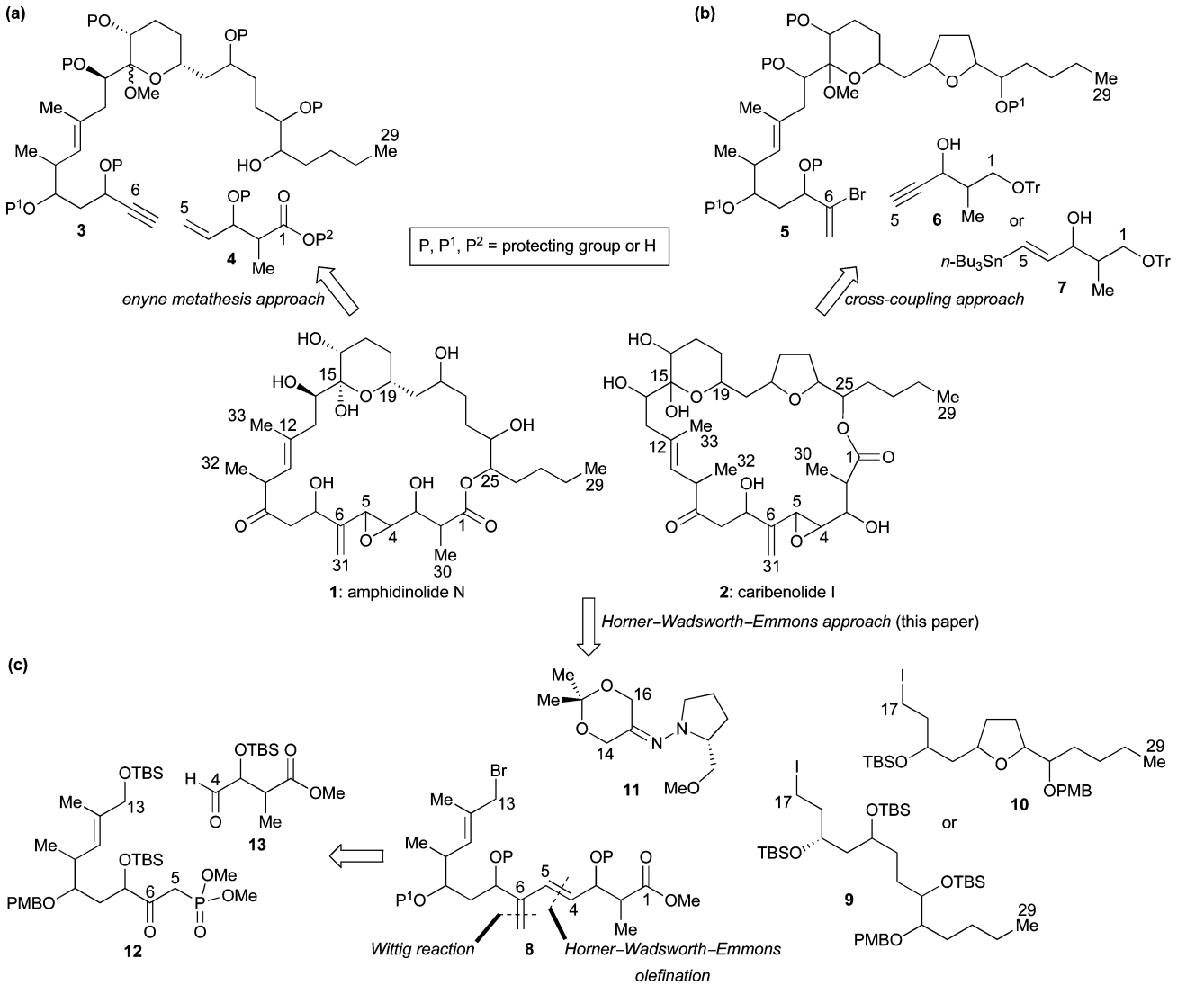
In the preceding paper in this issue,[1] we described studies on two synthetic approaches to the macrocyclic frameworks of the marine-derived antitumour agents amphidinolide N[2] (**1**) and caribenolide I[3] (**2**, Scheme 1). The primary goal of this work was to establish a flexible and convergent 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 cross-coupling reactions[5] could be enlisted to generate the C5–C6 bond that was ultimately required to reach **1** or **2**. A route to C6-vinyl 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 methodology[6] 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.

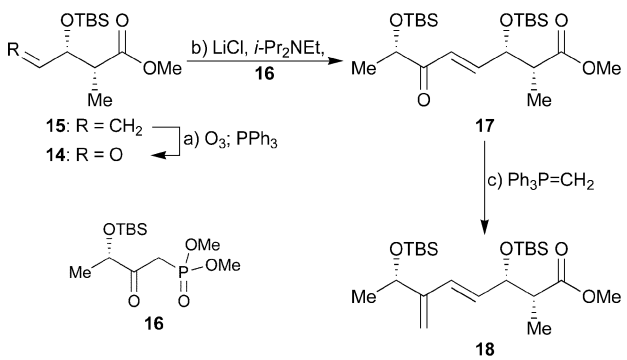
[a]*Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, USA. E-mail: kcn@scripps.edu; Fax: 858-784-2469; Tel: 858-784-2400*
[b]*Department of Chemistry and Biochemistry, University of California San Diego, 9500 Gilman Drive, La Jolla, California 92093, USA*



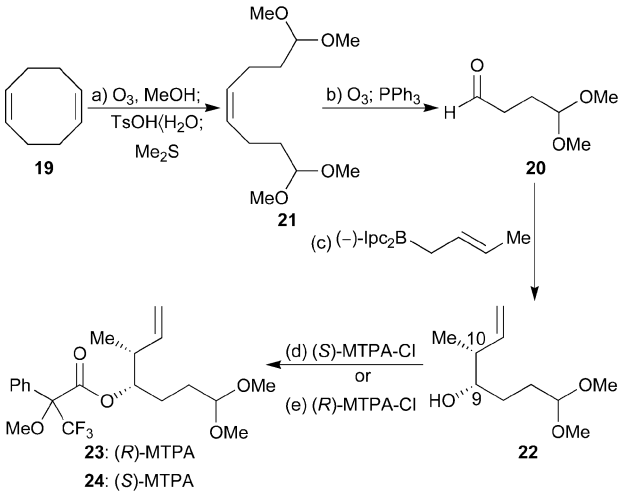
Scheme 1 Structures of amphidinolide N (**1**), caribenolide I (**2**) and retrosynthetic analysis: (a) enyne metathesis approach, (b) cross-coupling approach and (c) Horner–Wadsworth–Emmons approach.

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*-Pr_2NEt, 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



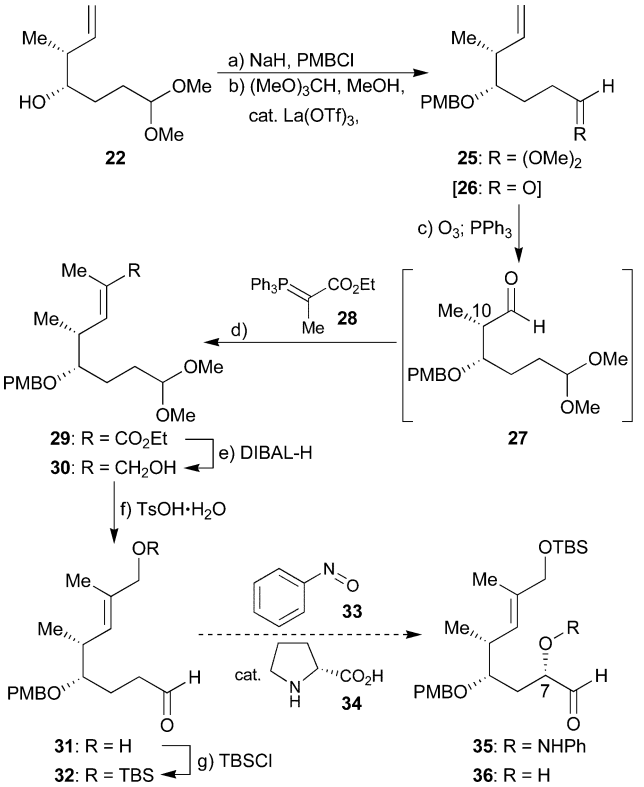
Scheme 2 Synthesis of model diene **18**. *Reagents and conditions*: a) O_3, CH_2Cl_2, −78 °C, then PPh_3 (1.5 equiv.), −78 → 25 °C, 1 h, 88%; b) **16** (1.0 equiv.), LiCl (1.5 equiv.), MeCN, 25 °C, 10 min, then *i*-Pr_2NEt (1.5 equiv.), 25 °C, 10 min, then **14** (1.2 equiv.), 25 °C, 36 h, 93%; c) Ph_3PCH_3Br (1.6 equiv.), KHMDS (1.5 equiv.), THF, 25 °C, 30 min, then **17**, −78 → 25 °C, 1 h, 94%. KHMDS = potassium bis(trimethylsilyl)amide.



Scheme 3 Synthesis of alcohol **22**. *Reagents and conditions*: a) O_3, $MeOH/CH_2Cl_2$ (1 : 1), −78 °C, then $TsOH{\cdot}H_2O$ (0.08 equiv.), −78 → 25 °C, 2 h, then Me_2S, 25 °C, 18 h, 50%; b) O_3, CH_2Cl_2, −78 °C, then PPh_3 (1.5 equiv.), −78 → 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 (+)-Ipc_2BOMe (1.6 equiv.), −78 °C, 1 h, then $BF_3{\cdot}OEt_2$ (1.6 equiv.), −78 °C, 30 min, then **20**, −78 °C, 4 h, 69%; d) (*S*)-MTPA-Cl (1.5 equiv.), Et_3N (3.0 equiv.), 4-DMAP (1.0 equiv.), CH_2Cl_2, 25 °C, 2 h, 97%; e) (*R*)-MTPA-Cl (1.5 equiv.), Et_3N (3.0 equiv.), 4-DMAP (1.0 equiv.), CH_2Cl_2, 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 reaction[10] 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]

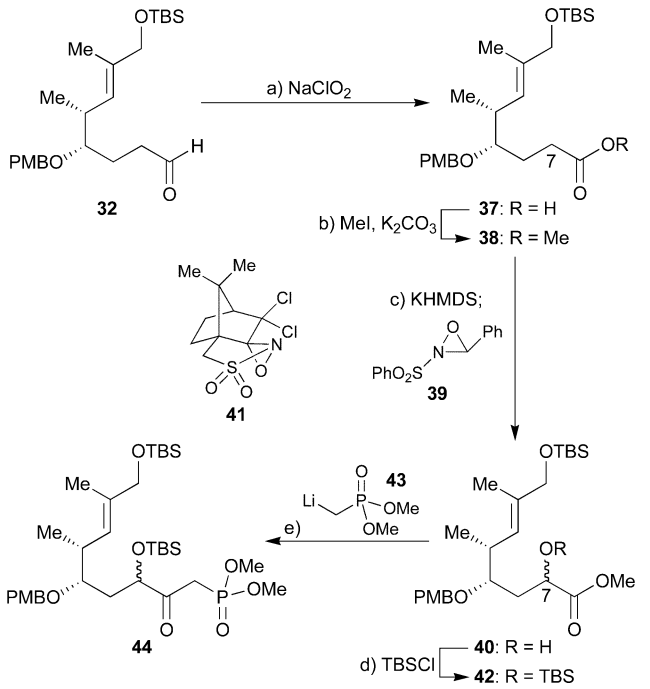
Alcohol **22** was then protected as the corresponding PMB ether **25** under basic conditions (Scheme 4). Unexpectedly, a significant degree of hydrolysis of the dimethyl acetal group occurred during this step, which yielded a 4 : 1 mixture of the dimethyl acetal **25** and aldehyde **26**. Therefore, 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** → **30**), acetal hydrolysis (**30** → **31**) and TBS ether formation (**31** → **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



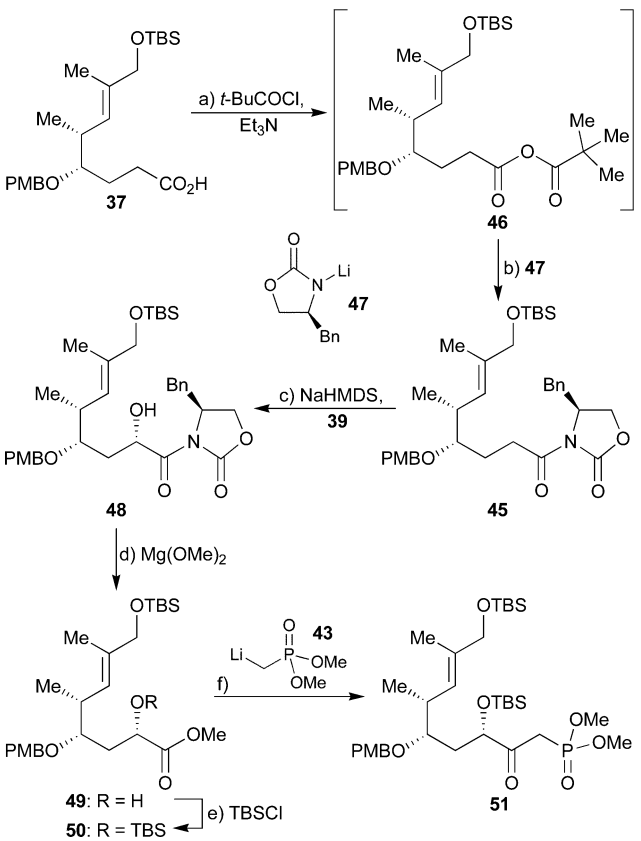
Scheme 4 Elaboration of alkene **22** to give aldehyde **32**, and attempted organocatalytic α-oxygenation. *Reagents and conditions*: a) NaH (1.6 equiv.), THF, 0 °C, 30 min, then PMBCl (1.6 equiv.), 70 °C, 16 h; b) $La(OTf)_3$ (0.02 equiv.), $HC(OMe)_3$, MeOH, 0 → 25 °C, 16 h, 96% (two steps); c) O_3, CH_2Cl_2, −78 °C, then PPh_3 (1.5 equiv.), −78 → 25 °C, 1 h; d) **28** (1.6 equiv.), C_6H_6, 70 °C, 32 h, 78% (two steps); e) DIBAL-H (3.0 equiv.), THF, −78 °C, 2.5 h, 96%; f) $TsOH{\cdot}H_2O$ (0.15 equiv.), acetone–H_2O (4 :1), 25 °C, 3 h; g) TBSCl (1.7 equiv.), imidazole (2.6 equiv.), 4-DMAP (cat.), CH_2Cl_2, 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** ($NaClO_2$, 78%) and its subsequent esterification (MeI, K_2CO_3, 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) $NaClO_2$ (1.8 equiv.), NaH_2PO_4 (3.5 equiv.), 2-methyl-2-butene (20.0 equiv.), *t*-BuOH–H_2O (4 : 1), 25 °C, 2 h, 78%; b) MeI (4.0 equiv.), K_2CO_3 (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.), CH_2Cl_2, 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.



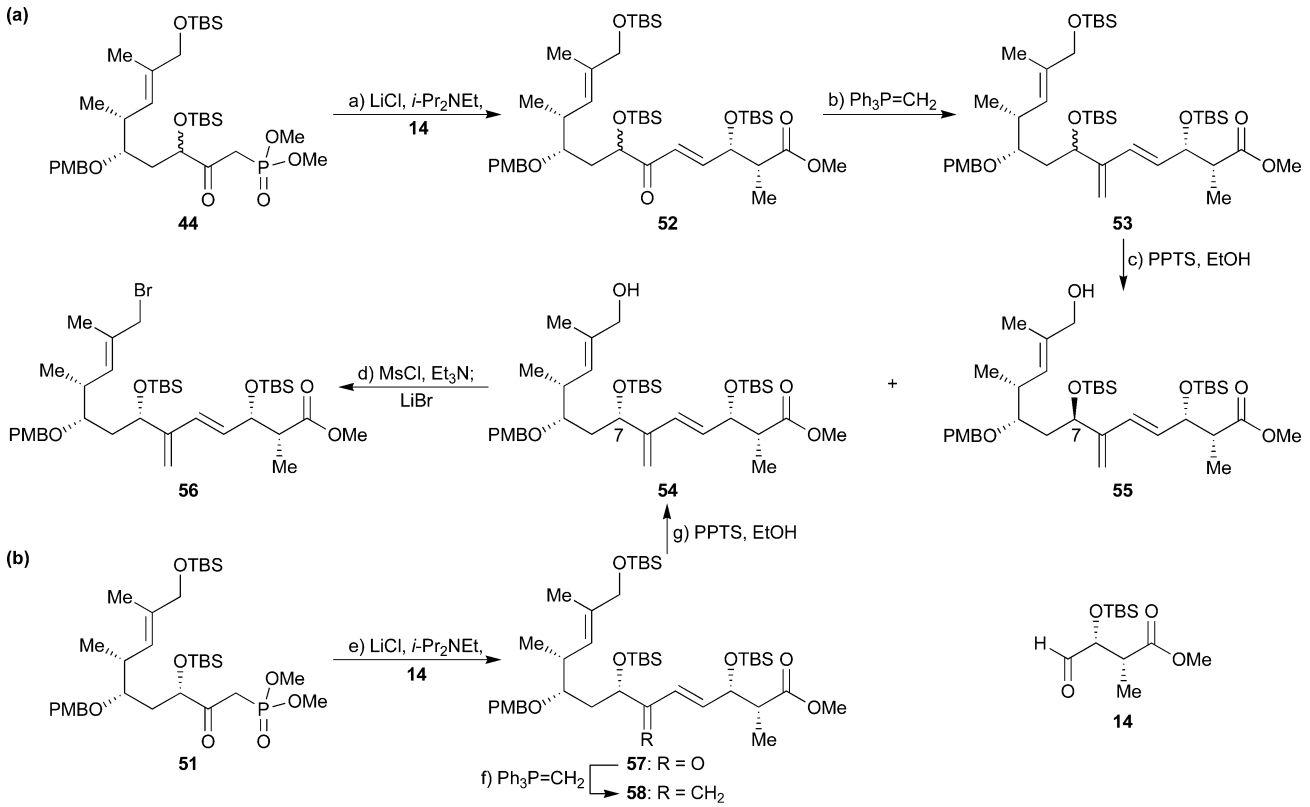
Scheme 6 Conversion of acid **37** to enantiomerically pure β-ketophosphonate **51**. *Reagents and conditions*: a) *t*-BuCOCl (1.1 equiv.), Et_3N (1.1 equiv.), THF, −78 °C, 1 h; b) **47** (1.2 equiv.), −78 °C, 3 h, 44%; c) NaHMDS (1.2 equiv.), THF, −78 °C, 5 min, then **39** (1.5 equiv.), −78 °C, 5 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.), CH_2Cl_2, 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.

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 cleavage[15] 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 removal[16] 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, 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 *m*CPBA 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

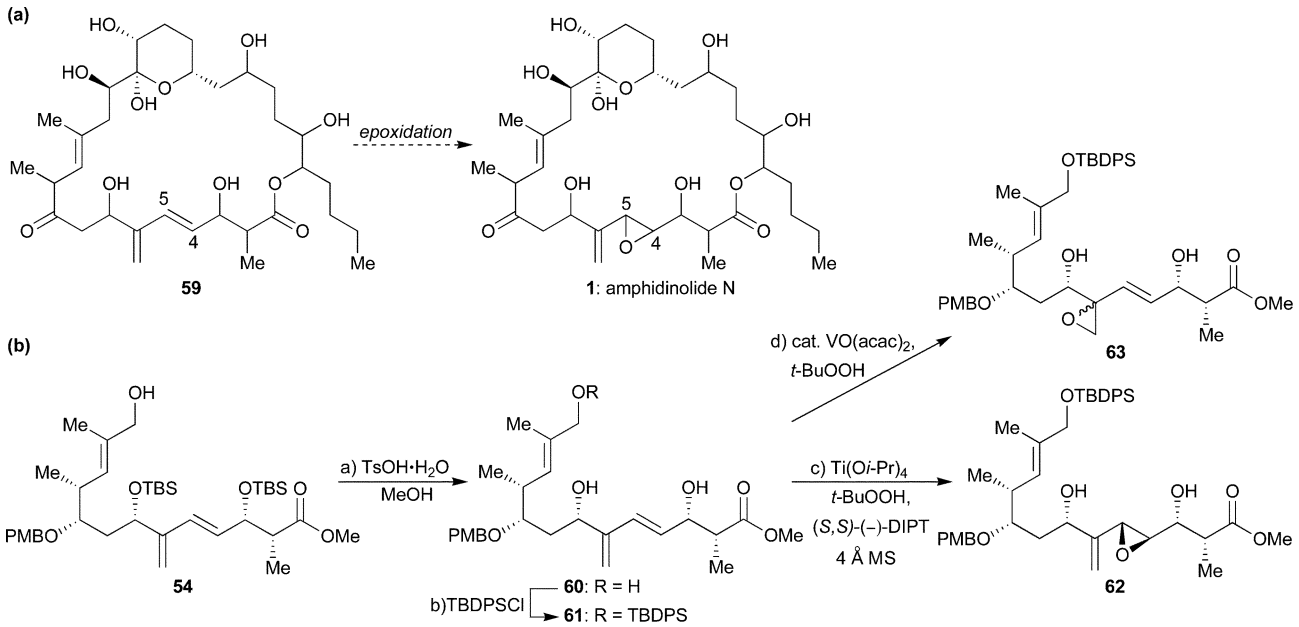


Scheme 7 Completion of the synthesis of C1–C13 allylic bromide coupling partner from either (a) β-ketophosphonate **44**, or (b) β-ketophosphonate **51**. *Reagents and conditions*: a) **44** (1.0 equiv.), LiCl (1.5 equiv.), MeCN, 25 °C, 10 min, then *i*-Pr_2NEt (1.5 equiv.), 25 °C, 10 min, then **14** (1.15 equiv.), 25 °C, 48 h, 92%; b) Ph_3PCH_3Br (1.6 equiv.), KHMDS (1.5 equiv.), THF, 25 °C, 45 min, then **52**, −78 → 25 °C, 1 h, 95%; c) PPTS (0.06 equiv.), EtOH, 45 °C, 16 h, 56% **54** + 14% **55**; d) MsCl (2.0 equiv.), Et_3N (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*-Pr_2NEt (1.5 equiv.), 25 °C, 10 min, then **14** (1.15 equiv.), 25 °C, 36 h, 97%; f) Ph_3PCH_3Br (1.6 equiv.), KHMDS (1.5 equiv.), THF, 25 °C, 30 min, then **57**, −78 → 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.

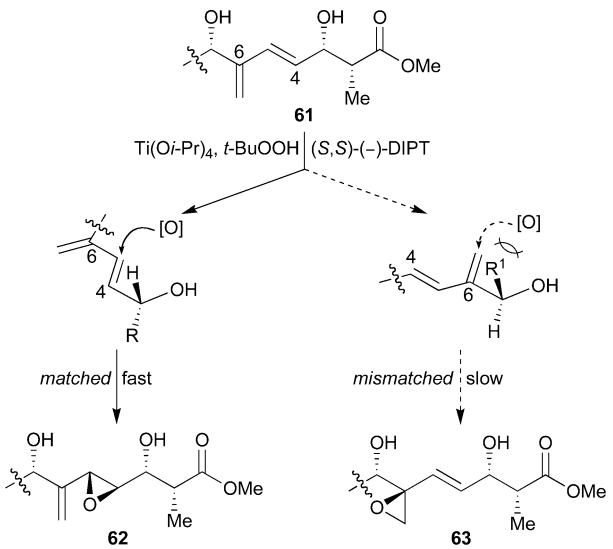
epoxidation[17] of diene **61** indeed resulted in selective epoxidation of the desired C4–C5 alkene. Using $Ti(Oi\text{-}Pr)_4$ (4.0 equiv.), (*S*,*S*)-(−)-diisopropyl tartrate (4.5 equiv.) and *t*-BuOOH (7.5 equiv.) in CH_2Cl_2 at −25 °C for 75 min, the product **62** could be isolated in 31% yield, 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 reagents[18] 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), or the 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 CH_2Cl_2 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



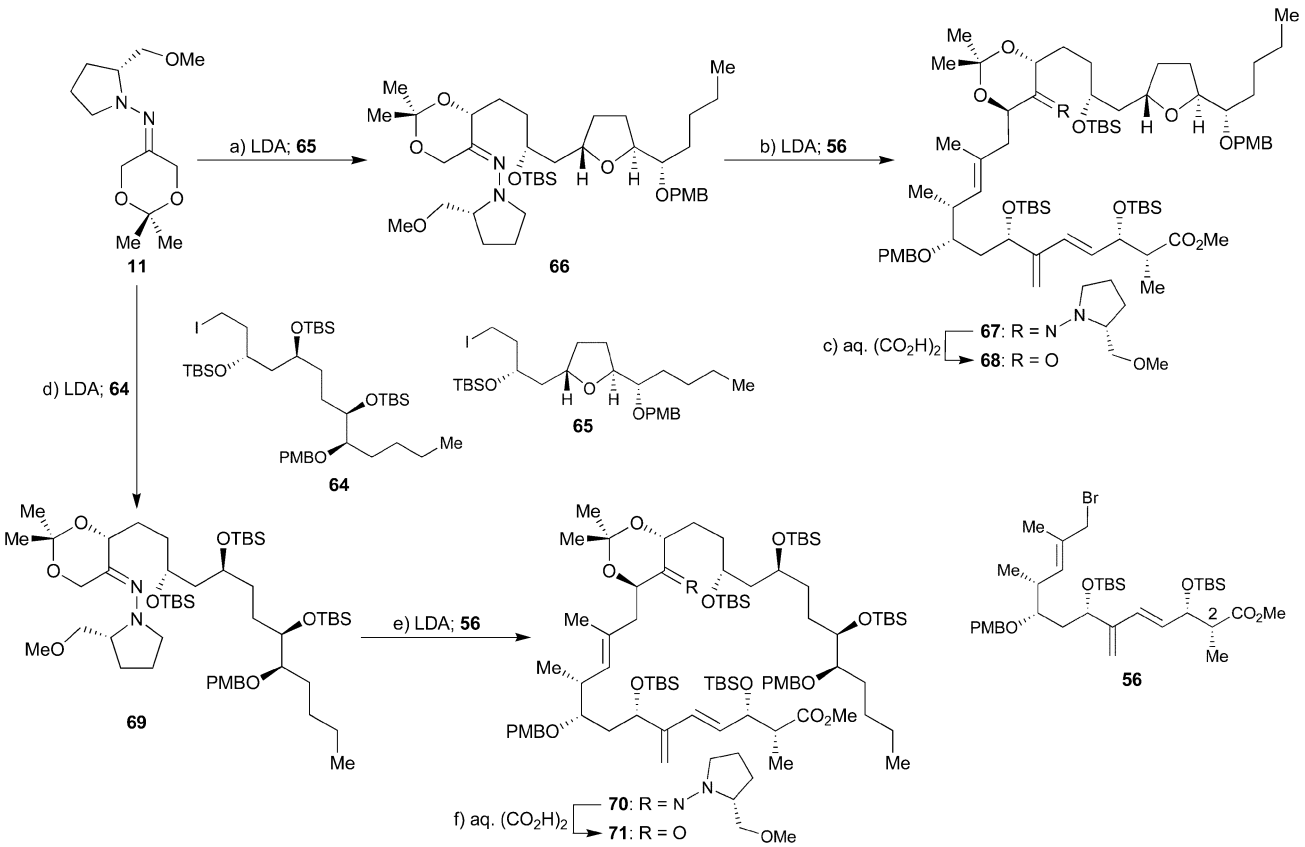
Scheme 8 (a) Proposed epoxidation of amphidinolide N precursor diene **59**, (b) regioselective epoxidation of model diene **61** to give either of allylic epoxides **62** or **63**. *Reagents and conditions*: a) TsOH·H_2O (1.0 equiv.), MeOH, 25 °C, 16 h, 79%; b) TBDPSCl (1.1 equiv.), Et_3N (1.4 equiv.), 4-DMAP (0.1 equiv.), CH_2Cl_2, 25 °C, 16 h, 77%; c) (*S*,*S*)-(−)-DIPT (4.5 equiv.), Ti(O*i*-Pr)$_4$ (4.0 equiv.), 4 Å MS, CH_2Cl_2, −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.), CH_2Cl_2, 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.

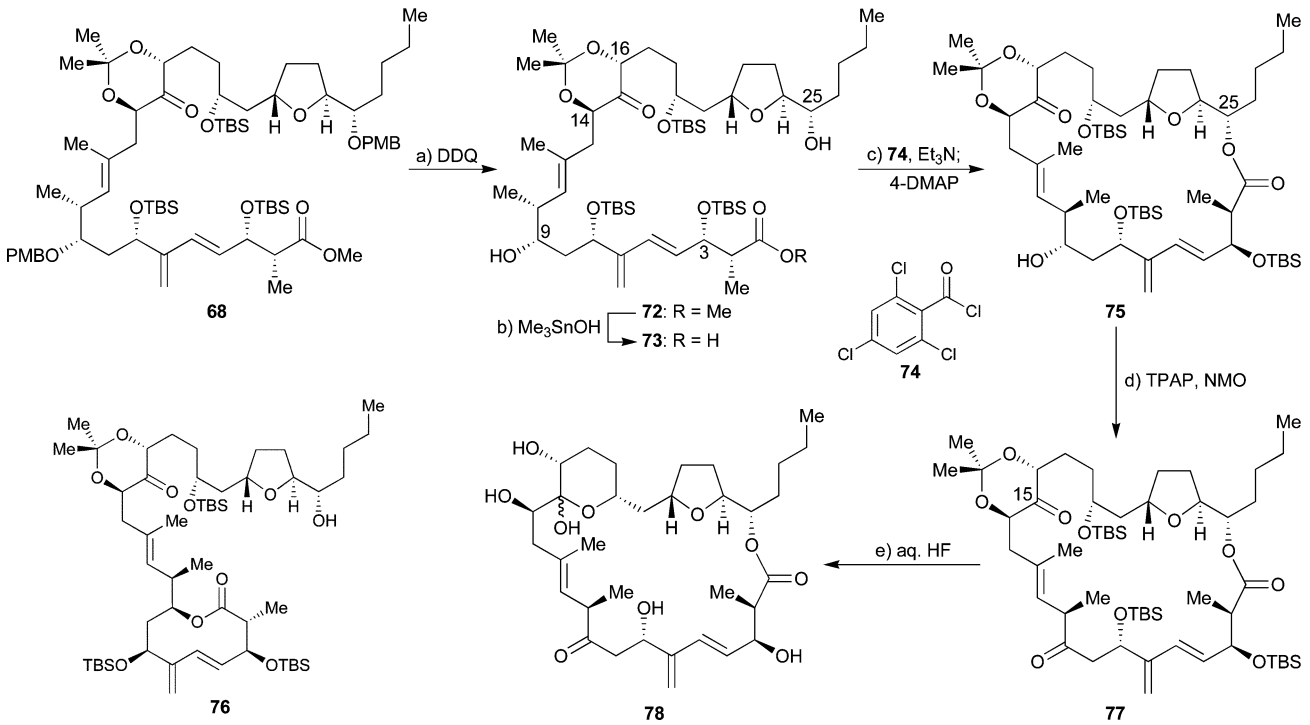
From ketones **68** or **71**, relatively few manipulations were required to reach the fully deprotected core structures of amphidinolide N (**1**) or caribenolide I (**2**), respectively, again taking advantage of some of the end-game chemistry developed during the unsuccessful first-generation enyne 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*-$Bu_3Sn)_2O$/PhMe[25] and $(Me_2AlTeMe)_2$/PhMe.[26] Fortunately, our recently developed protocol[27] for the mild and selective hydrolysis of esters using Me_3SnOH[28] provided a timely solution to this



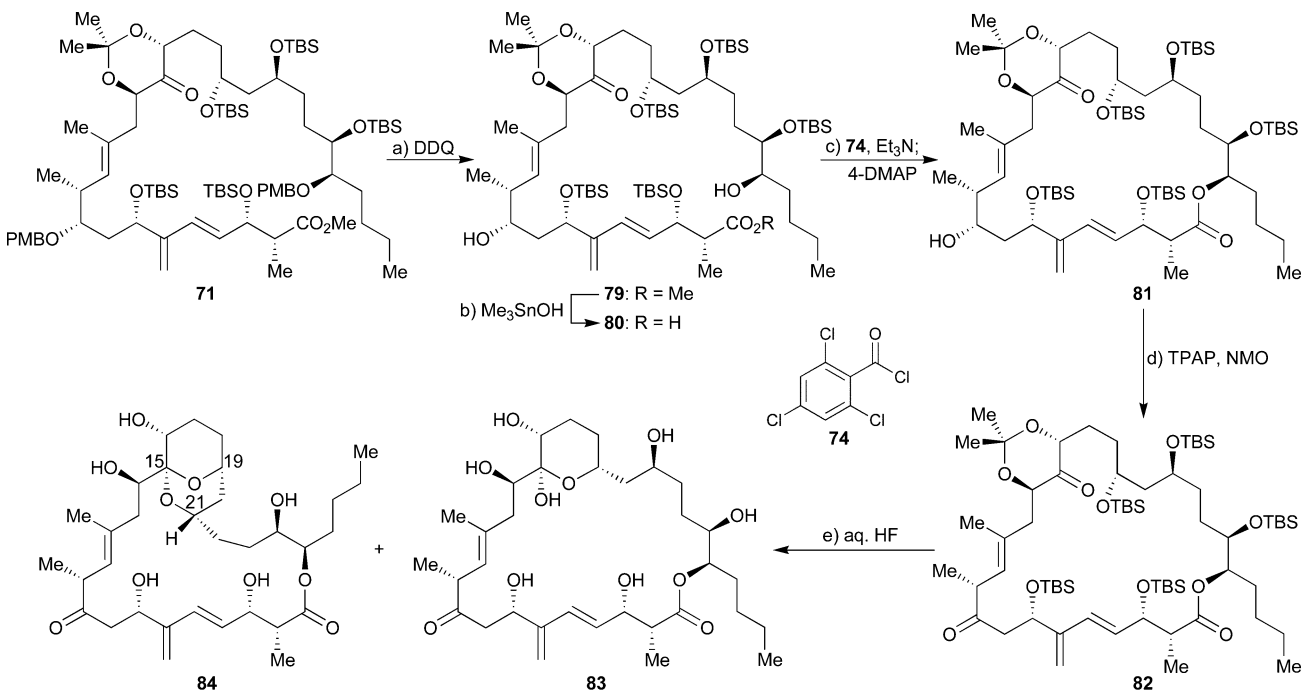
Scheme 10 Assembly of the complete caribenolide I and amphidinolide N carbon frameworks in ketones **68** and **71**, respectively, through hydrazone alkylation fragment coupling reactions. *Reagents and conditions*: a) LDA (1.2 equiv.), THF, −78 °C, 1.75 h, then **65** (1.2 equiv.), −78 °C, 45 min, 88%; b) LDA (1.2 equiv.), THF, −78 °C, 1 h, then **56** (1.2 equiv.), −78 °C, 1 h; c) sat. aq. $(CO_2H)_2$, Et_2O, 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; f) sat. aq. $(CO_2H)_2$, Et_2O, 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 conditions[29] 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 site-selective, 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 site-selectivity 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/NMO[30] (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 Me_3SnOH (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–CH_2Cl_2 (4 : 1), 0 → 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.), CH_2Cl_2–sat. aq. $NaHCO_3$ (15 : 1), 0 °C, 1 h, 70%; b) Me_3SnOH (4 × 10 equiv.), 1,2-dichloroethane, 80 °C, 96 h, 68%; c) **74** (30.0 equiv.), Et_3N (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, CH_2Cl_2, 25 °C, 2 h, 92%; e) 48% aq. HF, MeCN–CH_2Cl_2 (9 : 1), 0 → 25 °C, 5 h, 65% (α : β, 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) Me_3SnOH (5 × 10 equiv.), 1,2-dichloroethane, 80 °C, 60 h, 45% **80** + 21% **79**; c) **74** (30.0 equiv.), Et_3N (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 → 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

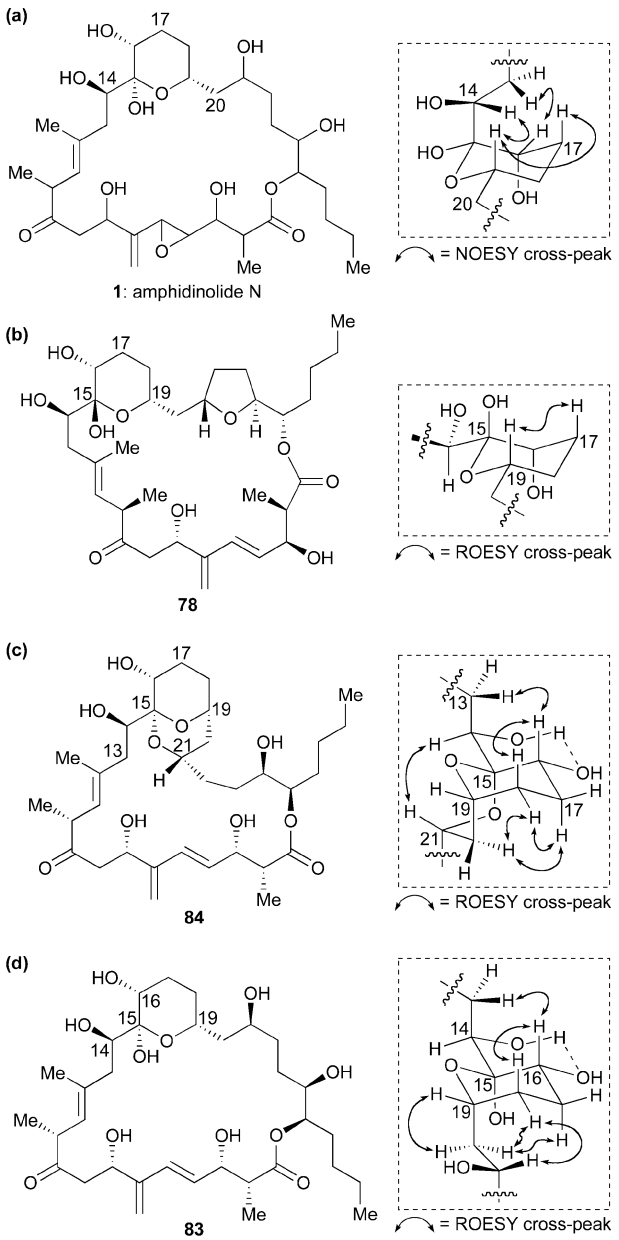
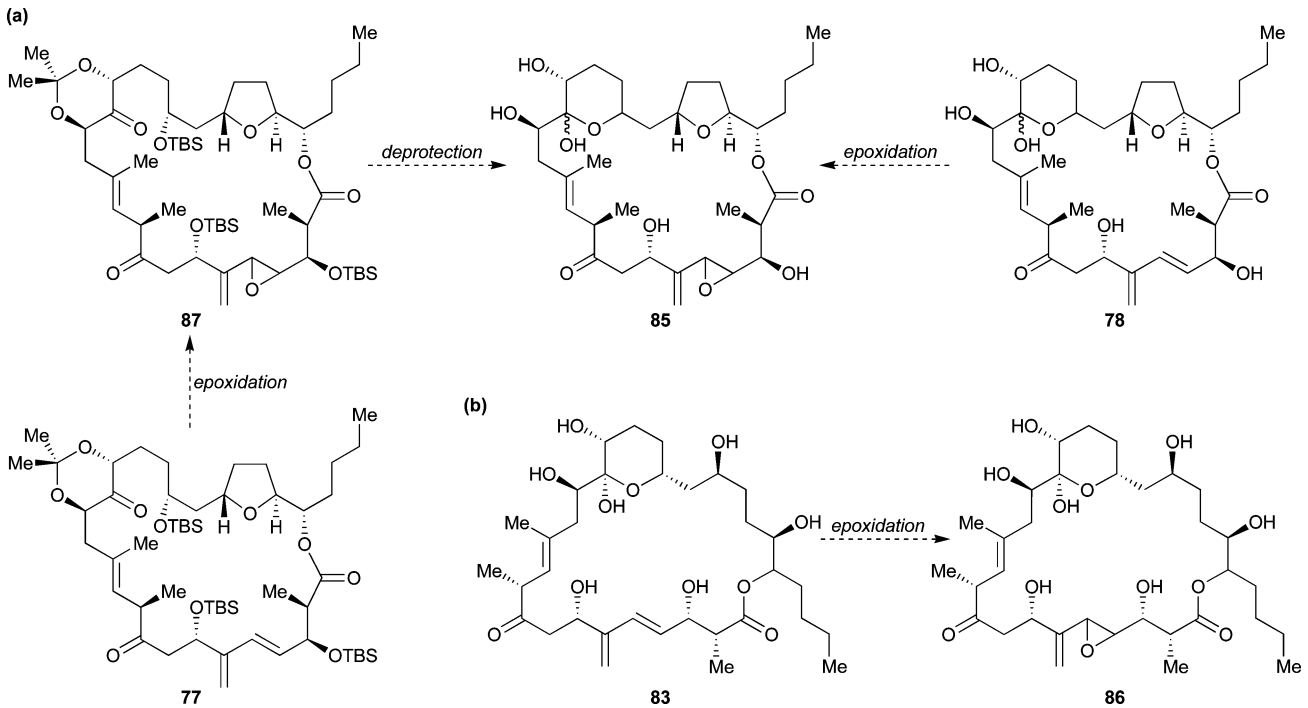


Fig. 1 Conformational analysis of the C13–C21 tetrahydropyran sectors of (a) amphidinolide N (**1**), (b) *des*-epoxy-caribenolide I stereoisomer **78**, (c) bicyclic acetal **84** and (d) *des*-epoxy-amphidinolide N stereoisomer **83**.

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 (21*R*), rather than (21*S*) 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

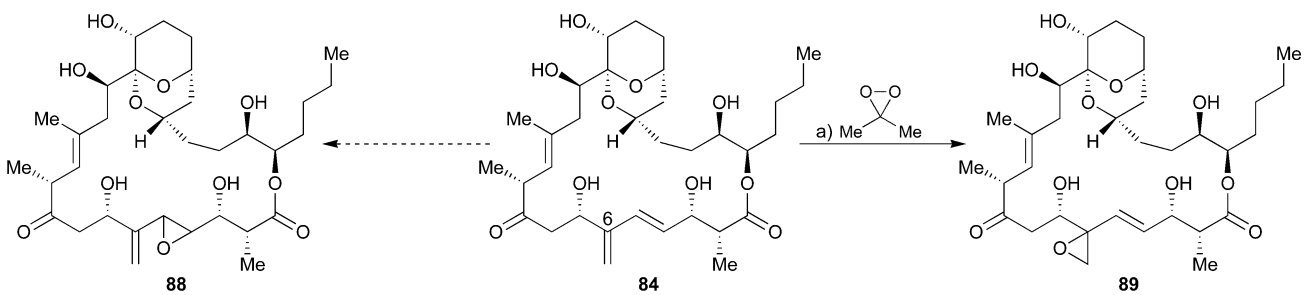


Scheme 13 (a) Attempted completion of the total synthesis of caribenolide I stereoisomer **85** through epoxidation of dienes **77** or **78**, (b) attempted completion of the total synthesis of amphidinolide N stereoisomer **86** through epoxidation of diene **83**.

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 DMDO[31] in CH_2Cl_2/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. Treatment 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 issue[1]) 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 μM. In comparison, caribenolide I (**2**) has an IC_{50} value of 1.6 nM against the HCT-116 cell line,[3] while amphidinolide N (**1**) has IC_{50} 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.

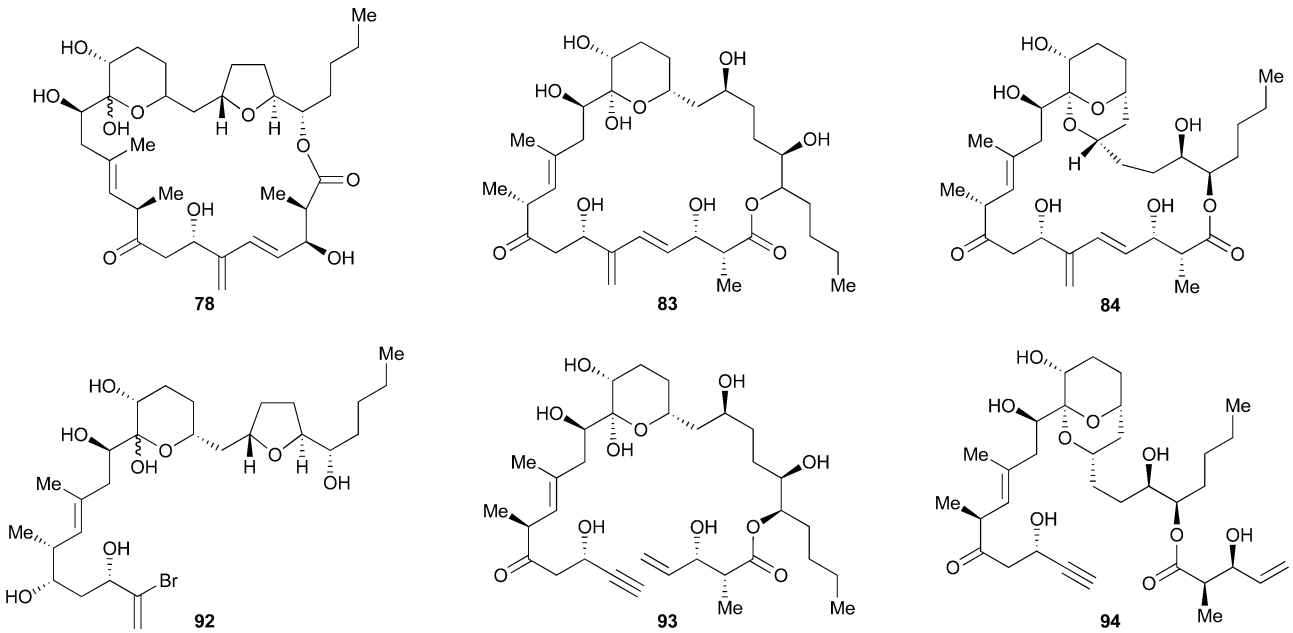
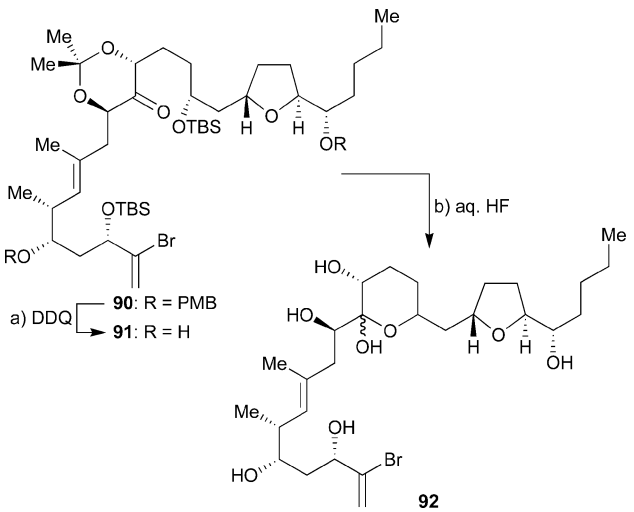


Fig. 2 Amphidinolide N and caribenolide I synthetic intermediates and analogues screened for cytotoxicity *in vitro*.



Scheme 15 Deprotection of ketone **90** to give hemiacetal **92**. *Reagents and conditions*: a) DDQ (3.0 equiv.), CH_2Cl_2–pH 7 aq. buffer (4 : 1), 0 °C, 20 min, 91%; b) 48% aq. HF, MeCN, 0 → 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 Me_3SnOH. 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 **15**[1] (4.00 g, 15.5 mmol) in CH_2Cl_2 (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. PPh_3 (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–Et_2O. The precipitated Ph_3PO 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% Et_2O in hexanes) to give **14** (3.563 g, 88%) as a colourless oil. $R_f = 0.12$ (silica gel, 23 : 2 hexanes–Et_2O); $[\alpha]_D^{25}$ +33.4° (*c* 1.31 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 2950, 2862, 1739, 1252, 1031, 836; δ_H (500 MHz, C_6D_6) 9.41 (1 H, s, H-4), 4.26 (1 H, d, *J* 3.6 Hz, H-3), 3.34 (3 H, s, CO_2CH_3), 2.72 (1 H, qd, *J* 7.0, 3.6 Hz, H-2), 1.05 (3 H, d, *J* 7.0 Hz, 2-CH_3), 0.86 [9 H, s, $SiC(CH_3)_3$], −0.03 (3 H, s, $SiCH_3$), −0.07 (3 H, s, $SiCH_3$); δ_C (125 MHz, C_6D_6) 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 $C_{12}H_{24}O_4SiNa$ ([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*-Pr_2NEt (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 Et_2O (3 × 20 mL), and the combined organic layers were washed with brine (1 × 35 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (5% Et_2O in hexanes) to give **17** (0.540 g, 93%) as a colourless oil. $R_f = 0.41$ (silica gel, 4 : 1 hexanes–Et_2O); $[\alpha]_D^{25}$ −3.8° (*c* 1.25 in $CHCl_3$); ν_{max}/cm^{-1} (film) 2954, 1746, 1698, 1634, 1435, 1362, 1081, 837; δ_H (600 MHz, $CDCl_3$) 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, CO_2CH_3), 2.57 (1 H, qd, *J* 7.0, 4.7 Hz, 2-H), 1.29 (3 H, d, *J* 6.7 Hz, 7-CH_3), 1.11 (3 H, d, *J* 7.0 Hz, 2-CH_3), 0.89 [9 H, s, $SiC(CH_3)_3$], 0.88 [9 H, s, $SiC(CH_3)_3$], 0.06 (3 H, s, $SiCH_3$), 0.06 (3 H, s, $SiCH_3$), 0.01 (3 H, s, $SiCH_3$), −0.01 (3 H, s, $SiCH_3$); δ_C (150 MHz, $CDCl_3$) 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 $C_{22}H_{45}O_5Si_2$ ([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 yellow-orange 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. NH_4Cl (15 mL). The mixture was then extracted with Et_2O (3 × 10 mL), and the combined organic layers were washed with brine (1 × 15 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was triturated with 9 : 1 hexanes–Et_2O, and the precipitated Ph_3PO 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. $R_f = 0.66$ (silica gel, 4 : 1 hexanes–Et_2O); $[\alpha]_D^{25}$ −18.7° (*c* 1.23 in $CHCl_3$); ν_{max}/cm^{-1} (film) 2955, 1742, 1433, 1361, 1094, 837; δ_H (600 MHz, $CDCl_3$) 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=CH_2), 5.00 (1 H, s, 6=CH_2), 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, CO_2CH_3), 2.54 (1 H, qd, *J* 7.0, 6.5 Hz, 2-H), 1.26 (3 H, d, *J* 6.3 Hz, 7-CH_3), 1.16 (3 H, d, *J* 7.0 Hz, 2-CH_3), 0.89 (9 H, s, $SiC(CH_3)_3$), 0.87 [9 H, s, $SiC(CH_3)_3$], 0.04 (3 H, s, $SiCH_3$), 0.03 (3 H, s, $SiCH_3$), 0.02 (3 H, s, $SiCH_3$), 0.00 (3 H, s, $SiCH_3$); δ_C (150 MHz, $CDCl_3$) 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 $C_{23}H_{47}O_4Si_2$ ([MH]$^+$): 443.3007, found: 443.3002.

4,4-Dimethoxybutanal 20[9]

A solution of alkene **21** (9.5 g, 40.9 mmol) was dissolved in CH_2Cl_2 (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. PPh_3 (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] $R_f = 0.16$ (silica gel, 4 : 1 hexanes–Et_2O); δ_H (400 MHz, $CDCl_3$) 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, $CH(OCH_3)_2$], 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).

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

1,5-Cyclooctadiene (40.0 g, 369.6 mmol) was dissolved in 1 : 1 CH_2Cl_2–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. $TsOH{\cdot}H_2O$ (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. Me_2S (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. $NaHCO_3$ (800 mL) and extracted with CH_2Cl_2 (3 × 500 mL). The combined organic layers were dried ($MgSO_4$), 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. $R_f = 0.24$ (silica gel, 2 : 1 hexanes–Et_2O); ν_{max}/cm^{-1} (film) 2943, 2829, 1447, 1365, 1124, 916; δ_H (500 MHz, $CDCl_3$) 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, $CH(OCH_3)_2$ and $CH(OCH_3)_2$], 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, $CDCl_3$) 129.2, 103.8, 52.5, 32.2, 22.2; HRMS (ES$^+$) m/z calc. for $C_{12}H_{24}O_4Na$ ([MNa]$^+$): 255.1567, found: 255.1574.

Alcohol 22

To a stirred solution of KO*t*-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 (+)-Ipc_2BOMe (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 $BF_3{\cdot}OEt_2$ (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. H_2O_2 (65 mL) was added dropwise over 30 min, and the solution was warmed to room temperature overnight, before being extracted with Et_2O (3 × 200 mL). The combined organic layers were washed with water (1 × 200 mL), brine (1 × 200 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient: 20–60% Et_2O in hexanes) to give **22** (7.79 g, 69%) as a light yellow oil. $R_f = 0.23$ (silica gel, 1 : 1 hexanes–Et_2O); $[\alpha]_D^{25}$ −2.4° (*c* 1.08 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 3459, 3073, 2952, 1455, 1369, 1126, 999; δ_H (500 MHz, C_6D_6) 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, $CH(OCH_3)_2$], 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, O*H*), 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-CH_3); δ_C (125 MHz, C_6D_6) 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 $C_{10}H_{20}O_3Na$ ($[MNa]^+$): 211.1305, found 211.1299.

(*R*)-Mosher's ester 23

To a stirred solution of alcohol **22** (35 mg, 0.186 mmol) in CH_2Cl_2 (2.5 mL) were added 4-DMAP (23 mg, 0.186 mmol), Et_3N (78 μL, 0.558 mmol) and (*S*)-(+)-methoxy-α-(triflurometh yl)phenylacetyl chloride (52 μL, 0.279 mmol) sequentially at room temperature. After 2 h the mixture was poured into sat. aq. $NaHCO_3$ (20 mL) and CH_2Cl_2 (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 × 20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient: 15–20% Et_2O in hexanes) to give **23** (73 mg, 97%) as a colourless oil. The ee of this material was determined to be 94% by ^{1}H- and ^{19}F-NMR studies. $R_f = 0.49$ (silica gel, 1 : 1 hexanes–Et_2O); $[\alpha]_D^{25}$ −16.4° (*c* 1.4 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 2950, 2831, 1744, 1641, 1451, 1262, 1169, 1125, 1081, 923, 720, 500; δ_H (500 MHz, C_6D_6) 7.71 (2 H, d, *J* 7.8 Hz, Ar*H*), 7.07–7.10 (2 H, m, Ar*H*), 7.01–7.05 (1 H, m, Ar*H*), 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, F_3CCOCH_3), 3.09 [3 H, s, $CH(OCH_3)_2$], 3.08 [3 H, s, $CH(OCH_3)_2$], 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-CH_3); δ_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, $^2J_{^{19}F-^{13}C}$ 27.5 Hz), 79.9, 55.4, 52.6, 52.4, 41.3, 28.9, 26.5, 15.8; δ_F (376 MHz, C_6D_6) −70.98 (major diasteroisomer), −70.95 (minor diastereoisomer); HRMS (ES^+) *m*/*z* calc. for $C_{20}H_{27}F_3O_5Na$ ($[MNa]^+$): 427.1703, found 427.1702.

(*S*)-Mosher's ester 24

To a stirred solution of alcohol **22** (41 mg, 0.218 mmol) in CH_2Cl_2 (3.5 mL) were added 4-DMAP (27 mg, 0.218 mmol), Et_3N (91 μL, 0.653 mmol) and (*R*)-(−)-methoxy-α-(triflurometh yl)phenylacetyl chloride (61 μL, 0.327 mmol) sequentially at room temperature. After 2 h the mixture was poured into sat. aq. $NaHCO_3$ (20 mL) and CH_2Cl_2 (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 × 20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient: 15–20% Et_2O in hexanes) to give **24** (84 mg, 95%) as a colourless oil. The ee of this material was determined to be 94% by ^{1}H- and ^{19}F-NMR studies. $R_f = 0.47$ (silica gel, 1 : 1 hexanes–Et_2O); $[\alpha]_D^{25}$ −35.3° (*c* 1.62 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 3075, 2954, 2832, 1746, 1643, 1452, 1259, 1122, 1017, 924, 720; δ_H (500 MHz, C_6D_6) 7.71 (2 H, d, *J* 7.7 Hz, Ar*H*), 7.07–7.11 (2 H, m, Ar*H*), 7.02–7.06 (1 H, m, Ar*H*), 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, F_3CCOCH_3), 3.05 [3 H, s, $CH(OCH_3)_2$], 3.03 [3 H, s, $CH(OCH_3)_2$], 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-CH_3); δ_C (125 MHz, C_6D_6) 166.5, 139.1, 133.0, 129.7, 128.5, 127.9, 124.4 (q, $^1J_{^{19}F-^{13}C}$ 288.3 Hz), 116.2, 104.1, 85.2 (q, $^2J_{^{19}F-^{13}C}$ 27.5 Hz), 55.5, 52.6, 52.1, 41.5, 28.5, 26.3, 16.0; δ_F (376 MHz, C_6D_6) −70.97 (major diasteroisomer), −71.00 (minor diastereoisomer); HRMS (ES^+) *m*/*z* calc. for $C_{20}H_{27}F_3O_5Na$ ($[MNa]^+$): 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, PMBCl (8.2 mL, 60.0 mmol) and *n*-Bu_4NI (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 × 150 mL), dried ($MgSO_4$), 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. $NaHCO_3$ (150 mL) was added. The mixture was extracted with Et_2O (3 × 150 mL), and the combined organic layers were washed with brine (1 × 150 mL), dried ($MgSO_4$), 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. $R_f = 0.53$ (silica gel, 1 : 1 hexanes–Et_2O); $[\alpha]_D^{25}$ −11.8° (*c* 1.00 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 2941, 2830, 1613, 1511, 1461, 1242, 1126, 958; δ_H (500 MHz, C_6D_6) 7.23 (2 H, d, *J* 8.6 Hz, Ar*H*), 6.79 (2 H, d, *J* 8.6 Hz, Ar*H*), 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 OCH_2Ar), 3.31 (3 H, s, $ArOCH_3$), 3.21 (1 H, dt, *J* 7.4, 4.3 Hz, 9-H), 3.15 [6 H, s, $CH(OCH_3)_2$], 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-CH_3); δ_C (125 MHz, C_6D_6) 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 $C_{18}H_{28}O_4Na$ ($[MNa]^+$): 331.1880, found: 331.1883.

α,β-Unsaturated ester 29

A solution of alkene **25** (29.0 g, 94.0 mmol) in CH_2Cl_2 (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. PPh_3 (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–Et_2O removed the excess PPh_3, 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–Et_2O, and the precipitated Ph_3PO was removed by filtration. The filtrate was concentrated under reduced pressure, and then purified by flash chromatography on silica gel (gradient: 9–20% Et_2O in hexanes) to give **29** (28.9 g, 78% from **25**) as a colourless oil. $R_f = 0.35$ (silica gel, 1 : 1 hexanes–Et_2O); $[\alpha]_D^{25}$ +1.1° (*c* 0.72 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 2953, 2928, 1707, 1647, 1510, 1450, 1364, 1068, 823; δ_H (500 MHz, C_6D_6) 7.20 (2 H, d, *J* 8.6 Hz, Ar*H*), 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, OCH_2Ar), 4.32 (1 H, d, *J* 11.3 Hz, OCH_2Ar), 4.24 (1 H, t, *J* 5.4 Hz, 6-H), 4.03 (2 H, app qd, *J* 7.1, 2.7 Hz, $CO_2CH_2CH_3$), 3.29 (3 H, s, ArOCH_3), 3.14–3.20 (1 H, m, 9-H), 3.13 [6 H, s, CH(OCH_3)$_2$], 2.66–2.70 (1 H, m, 10-H), 1.91 (3 H, d, *J* 1.4 Hz, 12-CH_3), 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, $CO_2CH_2CH_3$), 0.93 (3 H, d, *J* 6.8 Hz, 10-CH_3); δ_C (125 MHz, C_6D_6) 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 $C_{22}H_{34}O_6Na$ ([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 × 125 mL), and the combined organic layers were washed with brine (1 × 200 mL), dried ($MgSO_4$), 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. $R_f = 0.30$ (silica gel, 1 : 1 hexanes–EtOAc); $[\alpha]_D^{25}$ −18.0° (*c* 0.35 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 3433, 2932, 1611, 1455, 1370, 1176, 1067, 954; δ_H (500 MHz, C_6D_6) 7.25 (2 H, d, *J* 8.6 Hz, Ar*H*), 6.79 (2 H, d, *J* 8.6 Hz, Ar*H*), 5.44 (1 H, dq, *J* 9.5, 1.2 Hz, 11-H), 4.43 (1 H, d, *J* 11.3 Hz, OCH_2Ar), 4.39 (1 H, d, *J* 11.3 Hz, OCH_2Ar), 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, ArOCH_3), 3.21 (1 H, dt, *J* 7.5, 4.4 Hz, 9-H), 3.14 [6 H, s, CH(OCH_3)$_2$], 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-CH_3), 1.59–1.64 (1 H, m, 8-H), 1.42 (1 H, t, *J* 5.3 Hz, O*H*), 1.06 (3 H, d, *J* 6.8 Hz, 10-CH_3); δ_C (125 MHz, C_6D_6) 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 $C_{20}H_{32}O_5Na$ ([MNa]$^+$): 375.2142, found: 375.2142.

Aldehyde 32

$TsOH{\cdot}H_2O$ (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. $NaHCO_3$ (200 mL) and EtOAc (200 mL). The mixture was extracted with EtOAc (3 × 200 mL), the combined organic layers washed with brine (1 × 200 mL), dried ($MgSO_4$), 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 CH_2Cl_2 (300 mL), and imidazole (11.51 g, 169 mmol), a catalytic amount of 4-DMAP and TBSCl (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 Et_2O (3 × 200 mL). The combined organic layers were washed with brine (1 × 300 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient: 9–33% Et_2O in hexanes) to give **32** (25.84 g, 95% from **30**) as a colourless oil. $R_f = 0.52$ (silica gel, 1 : 1 hexanes–Et_2O); $[\alpha]_D^{25}$ −14.0° (*c* 1.00 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 2943, 2716, 1720, 1609, 1466, 1440, 1245, 1076, 775; δ_H (500 MHz, C_6D_6) 9.36 (1 H, dd, *J* 1.9, 1.1 Hz, 6-H), 7.22 (2 H, d, *J* 8.6 Hz, Ar*H*), 6.81 (2 H, d, *J* 8.6 Hz, Ar*H*), 5.42 (1 H, dd, *J* 9.5, 1.3 Hz, 11-H), 4.37 (1 H, d, *J* 11.1 Hz, OCH_2Ar), 4.24 (1 H, d, *J* 11.1 Hz, OCH_2Ar), 3.97 (2 H, s, 13-H and 13-H), 3.30 (3 H, s, ArOCH_3), 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-CH_3), 1.55–1.71 (2 H, m, 8-H and 8-H), 0.98 [12 H, m, 10-CH_3 and SiC(CH_3)$_3$], 0.06 (6 H, s, SiCH_3 and SiCH_3); δ_C (125 MHz, C_6D_6) 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 NaH_2PO_4 (3.99 g, 33.3 mmol) and $NaClO_2$ (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–H_2O (60 mL) at room temperature. After 2 h, the reaction was quenched by the addition of sat. aq. Na_2SO_3 (30 mL) and sat. aq. NH_4Cl (30 mL). The mixture was then acidified to a pH of 3.0 using 1 M aq. $KHSO_4$, and extracted with EtOAc (4 × 60 mL). The combined organic layers were washed with brine (1 × 100 mL), dried ($MgSO_4$), 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. $R_f = 0.47$ (silica gel, 1 : 1 hexanes–EtOAc); $[\alpha]_D^{25}$ −14.9° (*c* 0.61 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 3520, 2949, 2851, 1730, 1708, 1509, 1459, 1247, 1071, 936; δ_H (500 MHz, C_6D_6) 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, OCH_2Ar), 4.31 (1 H, d, *J* 11.2 Hz, OCH_2Ar), 3.97 (2 H, s, 13-H and 13-H), 3.31 (3 H, s, ArOCH_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-CH_3), 0.98–0.99 [12 H, m, 10-CH_3 and SiC(CH_3)$_3$], 0.07 (3 H, s, SiCH_3), 0.07 (3 H, s, SiCH_3); δ_C (125 MHz, C_6D_6) 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 $C_{24}H_{39}O_5Si$ ([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 K_2CO_3 (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. NH_4Cl (75 mL) and Et_2O (50 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (1 × 75 mL), brine (1 × 75 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (10% Et_2O in hexanes) to give **38** (4.51 g, 97%) as a colourless oil. $R_f = 0.58$ (silica gel, 1 : 1 hexanes–Et_2O); $[\alpha]_D^{25}$ −14.9° (*c* 1.00 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 2955, 2919, 1735, 1511, 1461, 1247, 1037, 887; δ_H (500 MHz, C_6D_6) 7.22 (2 H, d, *J* 8.4 Hz, Ar*H*), 6.79 (2 H, d, *J* 8.4 Hz, Ar*H*), 5.45 (1 H, d, *J* 9.5 Hz, 11-H), 4.41 (1 H, d, *J* 11.2 Hz, OCH_2Ar), 4.32 (1 H, d, *J* 11.2 Hz, OCH_2Ar), 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-CH_3), 0.99 (3 H, d, *J* 8.5 Hz, 10-CH_3), 0.97 [9 H, s, SiC(CH_3)$_3$], 0.06 (3 H, s, SiCH_3), 0.06 (3 H, s, SiCH_3); δ_C (125 MHz, C_6D_6) 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 $C_{25}H_{41}O_5Si$ ([M − H]$^-$): 449.2729, found: 449.2725.

α-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. NH_4Cl (150 mL), warmed to room temperature, and extracted with Et_2O (3 × 60 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (1 × 150 mL), brine (1 × 150 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient: 15–30% Et_2O 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 ^{1}H-NMR analysis). Full characterisation of the major (7*S*)-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 CH_2Cl_2 (40 mL). After 16 h, the reaction was quenched by the addition of water (100 mL), and was extracted with Et_2O (3 × 50 mL). The combined organic layers were then washed with sat. aq. $NaHCO_3$ (1 × 100 mL), brine (1 × 100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (7.5% Et_2O 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 ^{1}H-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. NH_4Cl (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 ($MgSO_4$), 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 ^{1}H-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 Et_3N (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. NH_4Cl (80 mL), and extracted with Et_2O (2 × 40 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (1 × 80 mL), brine (1 × 80 mL), dried ($MgSO_4$), 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. $R_f = 0.21$ (silica gel, 4 : 1 hexanes–Et_2O); $[\alpha]_D^{25}$ +12.0° (*c* 1.20 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 2936, 1783, 1697, 1513, 1384, 1174, 834; δ_H (600 MHz, C_6D_6) 7.27 (2 H, d, *J* 8.5 Hz, Ar*H*), 7.05–7.08 (2 H, m, Ar*H*), 7.00–7.03 (1 H, m, Ar*H*), 6.89–6.90 (2 H, m, Ar*H*), 6.77 (2 H, d, *J* 8.5 Hz, Ar*H*), 5.47 (1 H, dd, *J* 9.5, 0.8 Hz, 11-H), 4.48 (1 H, d, *J* 11.2 Hz, OCH_2Ar), 4.37 (1 H, d, *J* 11.2 Hz, OCH_2Ar), 4.14–4.18 (1 H, m, OCH$_2$C*H*N), 3.96 (2 H, s, 13-H and 13-H), 3.53 (1 H, dd, *J* 8.9,

2.8 Hz, OCH_2CHN), 3.34 (3 H, s, ArOCH_3), 3.29–3.33 (2 H, m, 9-H and OCH_2CHN), 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, CH_2Ph), 2.75–2.81 (1 H, m, 10-H), 2.34 (1 H, dd, *J* 13.3, 9.4 Hz, CH_2Ph), 1.91–2.02 (2 H, m, 8-H and 8-H), 1.62 (3 H, s, 12-CH_3), 1.04 (3 H, d, *J* 6.8 Hz, 10-CH_3), 0.93 [9 H, s, SiC(CH_3)$_3$], 0.04 (3 H, s, SiCH_3), 0.03 (3 H, s, SiCH_3); δ_C (150 MHz, C_6D_6) 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 $C_{34}H_{49}NO_6SiNa$ ([MNa]$^+$): 618.3221, found: 618.3204.

α-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 **39** [13] (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. $NaHCO_3$ (50 mL), and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (1 × 50 mL), brine (1 × 50 mL), dried ($MgSO_4$), 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. NH_4Cl (25 mL), and then extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (1 × 25 mL), dried ($MgSO_4$), 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. $R_f = 0.32$ (silica gel, 1 : 1 hexanes–Et_2O); $[\alpha]_D^{25}$ −36.7° (*c* 0.09 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 3468, 2955, 1738, 1514, 1361, 1174, 939; δ_H (600 MHz, C_6D_6) 7.28 (2 H, d, *J* 8.6 Hz, Ar*H*), 6.77 (2 H, d, *J* 8.6 Hz, Ar*H*), 5.39 (1 H, d, *J* 10.5 Hz, 11-H), 4.56 (1 H, d, *J* 10.8, Hz, OCH_2Ar), 4.51 (1 H, d, *J* 10.8 Hz, OCH_2Ar), 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, O*H*), 3.34 (3 H, s, CO_2CH_3), 3.29 (3 H, s, ArOCH_3), 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-CH_3), 0.99 (3 H, d, *J* 6.8 Hz, 10-CH_3), 0.93 [9 H, s, SiC(CH_3)$_3$], 0.02 (6 H, s, SiCH_3 and SiCH_3); δ_C (150 MHz, C_6D_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 $C_{25}H_{42}O_6SiNa$ ([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 CH_2Cl_2 (8 mL) at room temperature. After 16 h the reaction was quenched by the addition of water (25 mL), and then extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient: 8–12% Et_2O in hexanes) to give **50** (484 mg, 86%) as a light yellow oil. $R_f = 0.67$ (silica gel, 1 : 1 hexanes–Et_2O); $[\alpha]_D^{25}$ −20.4° (*c* 1.67 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 2957, 2856, 1751, 1583, 1359, 1146, 777; δ_H (500 MHz, C_6D_6) 7.25 (2 H, d, *J* 8.6 Hz, Ar*H*), 6.77 (2 H, d, *J* 8.6 Hz, Ar*H*), 5.35 (1 H, d, *J* 9.3 Hz, 11-H), 4.53–4.57 (2 H, m, 7-H and OCH_2Ar), 4.39 (1 H, d, *J* 11.0 Hz, OCH_2Ar), 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, CO_2CH_3), 3.32 (3 H, s, ArOCH_3), 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-CH_3), 0.98 (3 H, d, *J* 6.8 Hz, 10-CH_3), 0.96 [9 H, s, SiC(CH_3)$_3$], 0.95 [9 H, s, SiC(CH_3)$_3$], 0.11 (3 H, s, SiCH_3), 0.04 (6 H, s, SiCH_3 and SiCH_3), 0.03 (3 H, s, SiCH_3); δ_C (125 MHz, C_6D_6) 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 $C_{31}H_{56}O_6Si_2Na$ ([MNa]$^+$): 603.3507, found: 603.3510.

β-Ketophosphonate 51

To a stirred solution of dimethyl methylphosphonate (276 μL, 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. NH_4Cl (20 mL), warmed to room temperature, and extracted with EtOAc (4 × 10 mL). The combined organic layers were washed with brine (1 × 20 mL), dried ($MgSO_4$), 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. $R_f = 0.25$ (silica gel, 1 : 1 hexanes–EtOAc); $[\alpha]_D^{25}$ +3.4° (*c* 1.00 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 2935, 1725, 1513, 1360, 1249, 1094, 777; δ_H (500 MHz, C_6D_6) 7.31 (2 H, d, *J* 8.6 Hz, Ar*H*), 6.81 (2 H, d, *J* 8.6 Hz, Ar*H*), 5.38 (1 H, d, *J* 9.2 Hz, 11-H), 4.50–4.53 (2 H, m, 7-H and OCH_2Ar), 4.38 (1 H, d, *J* 10.9 Hz, OCH_2Ar), 3.55–3.58 (1 H, m, 9-H), 3.43 (3 H, d, *J* 11.2 Hz, POCH_3), 3.40 (3 H, d, *J* 11.1 Hz, POCH_3), 3.35 (3 H, s, ArOCH_3), 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-CH_3), 0.99 (3 H, d, *J* 6.8 Hz, 10-CH_3), 0.95 [9 H, s, SiC(CH_3)$_3$], 0.94 [9 H, s, SiC(CH_3)$_3$], 0.12 (3 H, s, SiCH_3), 0.05 (3 H, s, SiCH_3), 0.04 (6 H, s, SiCH_3 and SiCH_3); δ_C (125 MHz, C_6D_6) 202.7 (d, $^2J_{^{31}P-^{13}C}$ 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, $^2J_{^{31}P-^{13}C}$ 6.3 Hz), 52.3 (d, $^2J_{^{31}P-^{13}C}$ 6.0 Hz), 36.1, 35.8 (d, $^1J_{^{31}P-^{13}C}$ 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 $C_{33}H_{61}O_8PSi_2Na$ ([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*-Pr_2NEt (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,

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 ($MgSO_4$), 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 ^{1}H-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. NH_4Cl (150 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 ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was triturated with 9 : 1 hexanes–Et_2O, and the precipitated Ph_3PO 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% Et_2O 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 ^{1}H-NMR analysis). Full characterisation of the major (7*S*)-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. $NaHCO_3$ (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 ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient: 10–20% hexanes–Et_2O) 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. $NaHCO_3$ (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 ($MgSO_4$), 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–Et_2O); $[\alpha]_D^{25}$ +17.1° (*c* 1.14 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 3441, 2952, 2862, 1738, 1614, 1514, 1462, 1247, 1096; δ_H (600 MHz, $CDCl_3$) 7.25 (2 H, d, *J* 8.7 Hz, Ar*H*), 6.86 (2 H, d, *J* 8.7 Hz, Ar*H*), 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-CH_2), 5.03 (1 H, s, 6-CH_2), 4.45 (1 H, d, *J* 11.3 Hz, OCH_2Ar), 4.38 (1 H, d, *J* 11.3 Hz, OCH_2Ar), 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, CO_2CH_3), 3.59 (3 H, s, ArOCH_3), 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, O*H*), 1.75–1.79 (1 H, m, 8-H), 1.69 (3 H, s, 12-CH_3), 1.62–1.66 (1 H, m, 8-H), 1.16 (3 H, d, *J* 7.0 Hz, 2-CH_3), 1.00 (3 H, d, *J* 6.9 Hz, 10-CH_3), 0.89 [9 H, s, SiC(CH_3)$_3$], 0.87 [9 H, s, SiC(CH_3)$_3$], 0.03 (6 H, s, SiCH_3 and SiCH_3), 0.00 (3 H, 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 $C_{38}H_{66}O_7Si_2Na$ ([MNa]$^+$): 713.4239, found 713.4233.

Data for alcohol 55. R_f = 0.15 (silica gel, 1 : 1 hexanes–Et_2O); $[\alpha]_D^{25}$ −42.8° (*c* 1.91 in $CHCl_3$); ν_{max}/cm^{-1} (film) 3471, 2949, 2852, 1740, 1458, 1246, 832; δ_H (600 MHz, C_6D_6) 7.32 (2 H, d, *J* 8.5 Hz, Ar*H*), 6.87 (2 H, d, *J* 8.5 Hz, Ar*H*), 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=CH_2), 5.00 (1 H, s, 6=CH_2), 4.75 (1 H, d, *J* 9.3 Hz, H-7), 4.64 (1 H, d, *J* 10.8 Hz, OCH_2Ar), 4.43 (1 H, dd, *J* 6.7, 5.8 Hz, H-3), 4.41 (1 H, d, *J* 10.8 Hz, OCH_2Ar), 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, CO_2CH_3), 3.39 (3 H, s, ArOCH_3), 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, O*H*), 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-CH_3), 1.17 (3 H, d, *J* 7.0 Hz, 2-CH_3), 1.04 (3 H, d, *J* 6.8 Hz, 10-CH_3), 0.96 [9 H, s, SiC(CH_3)$_3$], 0.93 [9 H, s, SiC(CH_3)$_3$], 0.08 (3 H, s, SiCH_3), 0.04 (3 H, s, SiCH_3), 0.02 (6 H, s, SiCH_3 and SiCH_3); δ_C (150 MHz, C_6D_6) 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*/*z* calc. for $C_{38}H_{66}O_7Si_2Na$ ([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 Et_3N (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 Et_2O (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (5% Et_2O in hexanes) to give 1.04 g **56** (1.38 mmol, 95%) as a light yellow oil. R_f = 0.60 (silica gel, 1 : 1 hexanes–Et_2O); $[\alpha]_D^{25}$ −34.7° (*c* 1.35 in $CHCl_3$); ν_{max}/cm^{-1} (film) 2958, 1738, 1511, 1361, 1096,

836; δ_H (600 MHz, C_6D_6) 7.27 (2 H, d, *J* 8.6 Hz, Ar*H*), 6.84 (2 H, d, *J* 8.6 Hz, Ar*H*), 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=CH_2), 4.68 (1 H, dd, *J* 9.1, 1.5 Hz, H-7), 4.53 (1 H, d, *J* 10.8 Hz, OCH_2Ar), 4.43 (1 H, dd, *J* 6.7, 5.6 Hz, H-3), 4.33 (1 H, d, *J* 10.8 Hz, OCH_2Ar), 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, CO_2CH_3), 3.38 (3 H, s, ArOCH_3), 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-CH_3), 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-CH_3), 0.95 [9 H, s, SiC(CH_3)$_3$], 0.91 [9 H, s, SiC(CH_3)$_3$], 0.89 (3 H, d, *J* 6.8 Hz, 10-CH_3), 0.04 (3 H, s, SiCH_3), 0.01 (3 H, s, SiCH_3), 0.01 (3 H, s, SiCH_3), 0.00 (3 H, s, SiCH_3); δ_C (150 MHz, C_6D_6) 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 $C_{38}H_{65}{}^{79}BrO_6Si_2Na$ ([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*-Pr$_2$NEt (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$_2$O (3 × 10 mL), and the combined organic layers were washed with brine (1 × 15 mL), dried (MgSO$_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (7.5% Et$_2$O in hexanes) to give **57** (0.476 g, 97%) as a colourless oil. R_f = 0.31 (silica gel, 4 : 1 hexanes–Et$_2$O); $[\alpha]_D^{25}$ +3.0° (*c* 1.32 in CHCl$_3$); ν_{max}/cm^{-1} (film) 2954, 1741, 1697, 1616, 1450, 1362, 1075, 837; δ_H (600 MHz, C_6D_6) 7.32 (2 H, d, *J* 8.4 Hz, Ar*H*), 7.00 (1 H, dd, *J* 15.7, 4.6 Hz, 4-H), 6.84 (2 H, d, *J* 8.4 Hz, Ar*H*), 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, OCH_2Ar), 4.43 (1 H, d, *J* 10.9 Hz, OCH_2Ar), 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, ArOCH_3 and CO_2CH_3), 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-CH_3), 1.10 (3 H, d, *J* 7.0 Hz, 2-CH_3), 1.03 (3 H, d, *J* 6.5 Hz, 10-CH_3), 1.01 [9 H, s, SiC(CH_3)$_3$], 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, SiCH_3, SiCH_3 and SiCH_3), 0.03 (3 H, s, SiCH_3), 0.00 (3 H, s, SiCH_3); δ_C (150 MHz, C_6D_6) 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 $C_{43}H_{78}O_8Si_3Na$ ([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. NH$_4$Cl (15 mL). The mixture was then extracted with Et$_2$O (3 × 10 mL), and the combined organic layers were washed with brine (1 × 15 mL), dried (MgSO$_4$), filtered and concentrated *in vacuo*. The residue was triturated with 9 : 1 hexanes–Et$_2$O, and the precipitated Ph$_3$PO 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% Et$_2$O in hexanes) to give **58** (0.560 g, 94%) as a colourless oil. R_f = 0.51 (silica gel, 4 : 1 hexanes–Et$_2$O); $[\alpha]_D^{25}$ −34.7° (*c* 0.91 in CHCl$_3$); ν_{max}/cm^{-1} (film) 2956, 1741, 1616, 1459, 1362, 1098, 837; δ_H (600 MHz, C_6D_6) 7.38 (2 H, d, *J* 8.4 Hz, Ar*H*), 6.92 (2 H, d, *J* 8.4 Hz, Ar*H*), 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=CH_2), 5.06 (1 H, s, 6=CH_2), 4.83 (1 H, d, *J* 9.1 Hz, 7-H), 4.69 (1 H, d, *J* 10.8 Hz, OCH_2Ar), 4.56 (1 H, dd, *J* 6.4, 5.7 Hz, 3-H), 4.45 (1 H, d, *J* 10.8 Hz, OCH_2Ar), 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, CO_2CH_3), 3.37 (3 H, s, ArOCH_3), 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-CH_3), 1.25 (3 H, d, *J* 7.0 Hz, 2-CH_3), 1.08 (3 H, d, *J* 6.8 Hz, 10-CH_3), 1.02 [9 H, s, SiC(CH_3)$_3$], 1.01 [9 H, s, SiC(CH_3)$_3$], 0.97 [9 H, s, SiC(CH_3)$_3$], 0.13 (3 H, s, SiCH_3), 0.11 (6 H, s, SiCH_3 and SiCH_3), 0.08 (3 H, s, SiCH_3), 0.08 (3 H, s, SiCH_3), 0.07 (3 H, s, SiCH_3); δ_C (150 MHz, C_6D_6) 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 $C_{44}H_{80}O_7Si_3Na$ ([MNa]$^+$): 827.5104, found: 827.5104.

Triol 60

TsOH·H$_2$O (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. NaHCO$_3$ (30 mL) was added. The mixture was then extracted with EtOAc (4 × 20 mL), and the combined organic layers were dried (MgSO$_4$), 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_f = 0.44 (silica gel, EtOAc); mp = 102 °C; $[\alpha]_D^{25}$ −32.4° (*c* 1.02 in CH$_2$Cl$_2$); ν_{max}/cm^{-1} (film) 3388, 2957, 2873, 1731, 1717, 1456, 1418, 1248, 1068, 903; δ_H (500 MHz, CDCl$_3$) 7.26 (2 H, d, *J* 8.6 Hz, Ar*H*), 6.86 (2 H, d, *J* 8.6 Hz, Ar*H*), 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=CH_2), 5.19 (1 H, d, *J* 8.9 Hz, H-11), 5.11 (1 H, s, 6=CH_2), 4.59 (1 H, d, *J* 10.8 Hz, OCH_2Ar), 4.55–4.57 (1 H, m, H-7), 4.37 (1 H, d, *J* 10.8 Hz, OCH_2Ar), 4.28–4.30 (1 H, m, H-3), 3.90 (2 H, s, H-13 and H-13), 3.78 (3 H, s, CO_2CH_3), 3.64 (3 H, s, ArOCH_3), 3.58 (1 H, ddd, *J* 9.8, 3.7 and 1.3 Hz, H-9), 3.31 (3 H, br s, O*H*, O*H* and O*H*), 2.84–2.88 (1 H, m, H-10), 2.53 (1 H,

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-CH_3), 1.12 (3 H, d, *J* 7.1 Hz, 2-CH_3), 0.98 (3 H, d, *J* 6.8 Hz, 10-CH_3); δ_C (125 MHz, $CDCl_3$) 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 $C_{26}H_{38}O_7Na$ ([MNa]$^+$): 485.2510, found: 485.2491.

Diol 61

TBDPSCl (120 μL, 0.45 mmol) was added to a stirred solution of triol **60** (190 mg, 0.41 mmol), Et_3N (90 μL, 0.62 mmol), and 4-DMAP (5 mg, 0.04 mmol) in CH_2Cl_2 (2 mL) at room temperature. After 16 h the reaction was quenched with sat. aq. NH_4Cl (15 mL), and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (1 × 15 mL), dried ($MgSO_4$), 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_f = 0.51 (silica gel, 1 : 1 hexanes–EtOAc); $[\alpha]_D^{25}$ −10.6° (*c* 1.24 in $CHCl_3$); ν_{max}/cm^{-1} (film) 3447, 3414, 2956, 1734, 1718, 1512, 1301, 1168, 823; δ_H (500 MHz, C_6D_6) 7.78–7.81 (4 H, m, SiAr*H*), 7.29 (2 H, d, *J* 8.6 Hz, Ar*H*), 7.24–7.25 (6 H, m, SiAr*H*), 6.83 (2 H, d, *J* 8.6 Hz, Ar*H*), 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=CH_2), 5.09 (1 H, s, 6=CH_2), 4.72 (1 H, dd, *J* 9.0, 1.7 Hz, H-7), 4.58 (1 H, d, *J* 10.9 Hz, OCH_2Ar), 4.43 (1 H, d, *J* 10.9 Hz, OCH_2Ar), 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, CO_2CH_3), 3.31 (3 H, s, ArOCH_3), 2.80–2.87 (1 H, dqd, *J* 9.4, 6.8 and 4.7 Hz, H-10), 2.62 (1 H, br s, O*H*), 2.42 (1 H, qd, *J* 7.1, 4.6 Hz, H-2), 2.19 (1 H, br s, O*H*), 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-CH_3), 1.18 [9 H, s, SiC(CH_3)$_3$], 1.14 (3 H, d, *J* 7.1 Hz, 2-CH_3), 1.03 (3 H, d, *J* 6.8 Hz, 10-CH_3); δ_C (125 MHz, C_6D_6) 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 $C_{42}H_{56}O_7SiNa$ ([MNa$^+$]): 723.3687, found: 723.3676.

Allylic epoxide 62

To a stirred suspension of powdered, activated 4 Å molecular sieves (50 mg) in CH_2Cl_2 (1 mL) was added (−)-diisopropyl D-tartrate (0.642 mL, 0.5 M in CH_2Cl_2, 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(O*i*-Pr)$_4$ (0.571 mL, 0.5 M in CH_2Cl_2, 0.285 mmol) was then added dropwise. After 30 min *tert*-butyl hydroperoxide (0.973 mL, 0.55 M in 1 : 9 decane–CH_2Cl_2, 0.535 mmol) was added dropwise. After a further 30 min, a solution of diene **61** (50 mg, 71.3 μmol) in CH_2Cl_2 (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 CH_2Cl_2 (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 × 20 mL), dried ($MgSO_4$), filtered and concentrated *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_f = 0.22 (silica gel, 1 : 1 hexanes–EtOAc); $[\alpha]_D^{25}$ −14.3° (*c* 1.36 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 3467, 3071, 2956, 1738, 1513, 1248, 1097, 823; δ_H (500 MHz, C_6D_6) 7.80–7.82 (4 H, m, SiAr*H*), 7.29 (2 H, d, *J* 8.6 Hz, Ar*H*), 7.23–7.27 (6 H, m, SiAr*H*), 6.82 (2 H, d, *J* 8.6 Hz, Ar*H*), 5.56 (1 H, d, *J* 9.5 Hz, 11-H), 5.24 (1 H, s, 6=CH_2), 5.18 (1 H, s, 6=CH_2), 4.57 (1 H, d, *J* 11.0 Hz, OCH_2Ar), 4.45–4.49 (2 H, m, 7-H and OCH_2Ar), 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, CO_2CH_3), 3.28 (3 H, s, ArOCH_3), 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, O*H*), 2.30 (1 H, d, *J* 3.9 Hz, O*H*), 1.86–1.89 (2 H, m, 8-H and 8-H), 1.61 (3 H, s, 12-CH_3), 1.17–1.19 [12 H, m, 2-CH_3 and SiC(CH_3)$_3$], 1.05 (3 H, d, *J* 6.5 Hz, 10-CH_3); δ_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 $C_{42}H_{58}O_8SiNa$ ([MNa]$^+$): 739.3636, found: 739.3625.

Allylic epoxide 63

To a stirred solution of diene **61** (50 mg, 71.3 μmol) and VO(acac)$_2$ (5 mg, 14.3 μmol) in CH_2Cl_2 (2 mL) was added *tert*-butyl hydroperoxide (0.29 mL, 0.55 M in 1 : 9 decane–CH_2Cl_2, 159.5 μmol) at 0 °C. After 40 min at 0 °C the reaction was quenched by the addition of 5% aq. Na_2SO_3 (5 mL). The mixture was partitioned between CH_2Cl_2 (20 mL) and 5% aq. Na_2SO_3 (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 × 20 mL), dried ($MgSO_4$), 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 ^{1}H-NMR). R_f = 0.28 (silica gel, 1 : 1 hexanes–EtOAc); $[\alpha]_D^{25}$ −21.6° (*c* 1.30 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 3476, 2956, 2856, 2280, 1738, 1514, 1248, 1111, 812; δ_H (600 MHz, C_6D_6) – 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, SiAr*H*), 6.82 (2 H, d, *J* 8.5 Hz, Ar*H*), 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, OCH_2Ar), 4.49 (1 H, d, *J* 11.0 Hz, OCH_2Ar), 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, CO_2CH_3), 3.27 (3 H, s, ArOCH_3), 2.81–2.87 (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); δ_C (150 MHz, C_6D_6) – 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, 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 $C_{42}H_{56}O_8SiNa$ ([MNa]$^+$): 739.3636, found: 739.3625.

Hydrazone 66

A solution of hydrazone **11**[6] (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 Et_2O (3 × 30 mL), and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (33% Et_2O in hexanes with 1.5% Et_3N) to give **66** (1.797 g, 88%) as a viscous, colourless oil. $R_f = 0.31$ (silica gel, 3 : 2 hexanes–Et_2O + 2% Et_3N); $[a]_D^{25}$ −59.1° (*c* 0.64 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 2947, 1614, 1463, 1373, 1247, 905, 835; δ_H (600 MHz, C_6D_6) 7.37 (2 H, *J* 8.6 Hz, Ar*H*), 6.85 (2 H, *J* 8.6 Hz, Ar*H*), 4.83 (1 H, d, *J* 11.3 Hz, OCH_2Ar), 4.58–4.61 (2 H, m, 16-H and OCH_2Ar), 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, NCHCH_2OCH$_3$), 3.60 (1 H, qd, *J* 7.6, 4.1 Hz, NC*H*CH$_2$OCH$_3$), 3.31 (3 H, s, ArOCH_3), 3.31–3.34 (2 H, m, 25-H and NCHCH_2OCH$_3$), 3.21 (3 H, s, CH$_2$OCH_3), 3.05–3.09 (1 H, m, NCH_2CH$_2$CH$_2$), 2.29–2.37 (2 H, m, 17-H and NCH_2CH$_2$CH$_2$), 1.95–2.05 (2 H, m, 17-H and NCHCH_2CH$_2$), 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, NCHCH_2CH$_2$, NCH$_2$CH_2CH$_2$ and NCHCH_2CH$_2$), 1.41 [3 H, s, O$_2$C(CH_3)$_2$], 1.36 [3 H, s, O$_2$C(CH_3)$_2$], 1.25–1.43 (4 H, m, 23-H, 27-H, 28-H and 28-H), 1.07 [9 H, s, SiC(CH_3)$_3$], 0.90 (3 H, t, *J* 7.3 Hz, 28-CH_3), 0.27 (3 H, s, SiCH_3), 0.21 (3 H, s, SiCH_3); δ_C (125 MHz, C_6D_6) 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 $C_{39}H_{69}N_2O_7Si$ ([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 °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 Et_2O (3 × 20 mL), and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Rapid flash chromatography (10% Et_2O in hexanes with 2% Et_3N) separated the excess bromide starting material and afforded the crude bis-alkylated hydrazone **67**, which was taken up in a mixture of Et_2O (15 mL) and sat. aq. $(CO_2H)_2$ (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 × 30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient: 5–10% Et_2O in hexanes) to give **68** (0.710 g, 49% from **66**) as a viscous, light yellow syrup. $R_f = 0.49$ (silica gel, 7 : 3 hexanes–Et_2O); $[a]_D^{25}$ +13.5° (*c* 1.00 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 2951, 2856, 1744, 1612, 1470, 1442, 1301, 1171, 1005, 869; δ_H (500 MHz, C_6D_6) 7.37 (4 H, d, *J* 8.6 Hz, Ar*H*), 6.92 (2 H, d, *J* 8.6 Hz, Ar*H*), 6.85 (2 H, d, *J* 8.6 Hz, Ar*H*), 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=CH_2), 5.31 (1 H, d, *J* 8.8 Hz, 11-H), 5.07 (1 H, s, 6=CH_2), 4.85 (1 H, d, *J* 9.2 Hz, 7-H), 4.82 (1 H, d, *J* 11.3 Hz, OCH_2Ar), 4.68 (1 H, d, *J* 10.9 Hz, OCH_2Ar), 4.62 (1 H, d, *J* 11.3 Hz, OCH_2Ar), 4.54–4.56 (1 H, m, 3-H), 4.44 (1 H, d, *J* 10.9 Hz, OCH_2Ar), 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, CO$_2$CH_3), 3.37 (3 H, s, ArOCH_3), 3.33 (3 H, s, ArOCH_3), 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-CH_3), 1.37 [3 H, s, O$_2$C(CH_3)$_2$], 1.32 [3 H, s, O$_2$C(CH_3)$_2$], 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-CH_3) 1.04–1.08 [12 H, m, 10-CH_3 and SiC(CH_3)$_3$], 1.01 [9 H, s, SiC(CH_3)$_3$], 0.98 [9 H, s, SiC(CH_3)$_3$], 0.91 (3 H, t, *J* 7.3 Hz, 28-CH_3), 0.25 (3 H, s, SiCH_3), 0.21 (3 H, s, SiCH_3), 0.12 (3 H, s, SiCH_3), 0.09 (3 H, s, SiCH_3), 0.07 (3 H, s, SiCH_3), 0.06 (3 H, s, SiCH_3); δ_C (125 MHz, C_6D_6) 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 $C_{71}H_{120}O_{13}Si_3Na$ ([MNa]$^+$): 1287.7929, found: 1287.7927.

Hydrazone 69

A solution of hydrazone **11**[6] (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 ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (15% Et_2O in hexanes with 1% Et_3N) to give **69** (1.53 g, 93%) as a viscous, colourless oil. $R_f = 0.35$ (silica gel, 3 : 2 hexanes–Et_2O + 2% Et_3N); $[a]_D^{25}$ −7.6° (*c* 1.09 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 2955, 2857, 1616, 1472, 1301, 1172, 937; δ_H (500 MHz, C_6D_6) 7.29 (2 H, d, *J* 8.6 Hz, Ar*H*), 6.85 (2 H, d, *J* 8.6 Hz, Ar*H*), 4.59 (1 H, d, *J* 6.4 Hz, 16-H), 4.55 (1 H, d, *J* 11.5 Hz, OCH_2Ar), 4.47–4.50 (2 H, m, 14-H and OCH_2Ar), 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, CH_2OCH$_3$), 3.58–3.64 (1 H, m, NC*H*CH$_2$OCH$_3$), 3.42–3.45 (1 H, m, 25-H), 3.36 (1 H, dd, *J* 8.8, 8.2 Hz, CH_2OCH$_3$), 3.33 (3 H, s, ArOCH_3), 3.27 (3 H, s, CH$_2$OCH_3), 3.06–3.10 (1 H, m, NCH_2CH$_2$), 2.26–2.36 (2 H, m, NCH$_2$CH_2 and NCH_2CH$_2$), 1.77–2.17 (9 H, m, 17-H, 18-H, 20-H, 20-H, 22-H, 23-H, NCH$_2$CH_2, NCH$_2$CH$_2$CH_2 and NCH$_2$CH$_2$CH_2), 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, O$_2$C(CH_3)$_2$],

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-CH_3), 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 ($MgSO_4$), filtered and concentrated *in vacuo*. Rapid flash chromatography (10% Et_2O in hexanes with 2% Et_3N) 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 × 30 mL). The combined organic layers were washed with brine (1 × 60 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient: 2–7% Et_2O in hexanes) to give **71** (1.56 g, 59% from **69**) as a viscous, light yellow syrup. R_f = 0.45 (silica gel, 4 : 1 hexanes–Et_2O); $[a]_D^{25}$ + 32.2° (*c* 1.71 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 2953, 1743, 1610, 1457, 1361, 1171, 1004, 835; δ_H (500 MHz, C_6D_6) 7.37 (2 H, d, *J* 8.7 Hz, Ar*H*), 7.30 (2 H, d, *J* 8.7 Hz, Ar*H*), 6.92 (2 H, d, *J* 8.7 Hz, Ar*H*), 6.85 (2 H, d, *J* 8.7 Hz, Ar*H*), 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=CH_2), 5.31 (1 H, d, *J* 8.3 Hz, 11-H), 5.07 (1 H, s, 6=CH_2), 4.85 (1 H, d, *J* 9.0 Hz, 7-H), 4.69 (1 H, d, *J* 10.8 Hz, OCH_2Ar), 4.54–4.57 (2 H, m, 3-H and OCH_2Ar), 4.49 (1 H, d, *J* 11.5 Hz, OCH_2Ar), 4.45 (1 H, d, *J* 10.8 Hz, OCH_2Ar), 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, CO_2CH_3), 3.41–3.45 (1 H, m, 25-H), 3.38 (3 H, s, ArOCH_3), 3.35 (3 H, s, ArOCH_3), 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-CH_3), 1.55–1.66 (4 H, 18-H, 22-H, 22-H and 23-H), 1.38 [3 H, s, $O_2C(CH_3)_2$], 1.34 [3 H, s, $O_2C(CH_3)_2$], 1.25 (3 H, d, *J* 7.0 Hz, 2-CH_3), 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-CH_3), 1.05 [9 H, s, $SiC(CH_3)_3$], 1.04 [9 H, s, $SiC(CH_3)_3$], 1.03 [9 H, s, $SiC(CH_3)_3$], 1.02 [9 H, s, $SiC(CH_3)_3$], 0.98 [9 H, s, $SiC(CH_3)_3$], 0.92 (3 H, t, *J* 9.3 Hz, 28-CH_3), 0.22 (3 H, s, $SiCH_3$), 0.21 (3 H, s, $SiCH_3$), 0.20 (3 H, s, $SiCH_3$), 0.19 (3 H, s, $SiCH_3$), 0.14 (3 H, s, $SiCH_3$), 0.13 (3 H, s, $SiCH_3$), 0.10 (3 H, s, $SiCH_3$), 0.09 (3 H, s, $SiCH_3$), 0.08 (3 H, s, $SiCH_3$), 0.06 (3 H, s, $SiCH_3$); δ_C (125 MHz, C_6D_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, 18.4, 18.3, 17.2, 14.8, 14.3, 11.8, −3.8, −4.0, −4.1, −4.2, −4.8, −4.9; HRMS (ES^+) *m*/*z* calc. for $C_{83}H_{150}O_{14}Si_5Na$ ($[MNa]^+$): 1533.9764, found: 1533.9775.

Diol 72

To a vigorously stirred solution of ketone **68** (314 mg, 0.248 mmol) in 15 : 1 CH_2Cl_2–sat. aq. $NaHCO_3$ (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. $NaHCO_3$ (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 × 20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient: 10–20% Et_2O in hexanes) to give **72** (179 mg, 70%) as a colourless oil. R_f = 0.31 (silica gel, 2 : 1 hexanes–Et_2O); $[a]_D^{25}$ +38.8° (*c* 1.03 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 3511, 2954, 2855, 1745, 1461, 1383, 1252, 1196, 1082, 976; δ_H (500 MHz, C_6D_6) 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=CH_2), 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, CO_2CH_3), 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, O*H*), 2.49–2.54 (1 H, m, 2-H), 2.44 (1 H, br s, O*H*), 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-CH_3), 1.39 [3 H, s, $O_2C(CH_3)_2$], 1.37 [3 H, s, $O_2C(CH_3)_2$], 1.25 (3 H, d, *J* 7.0 Hz, 2-CH_3), 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, $SiC(CH_3)_3$], 1.02 [9 H, s, $SiC(CH_3)_3$], 0.98 [9 H, s, $SiC(CH_3)_3$], 0.90–0.94 (6 H, m, 10-CH_3 and 28-CH_3), 0.24 (3 H, s, $SiCH_3$), 0.16 (6 H, s, $SiCH_3$ and $SiCH_3$), 0.15 (3 H, s, $SiCH_3$) 0.09 (3 H, s, $SiCH_3$), 0.07 (3 H, s, $SiCH_3$); δ_C (125 MHz, C_6D_6) 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 $C_{55}H_{104}O_{11}Si_3Na$ ($[MNa]^+$): 1047.6778, found: 1047.6761.

Acid 73

Methyl ester **72** (0.380 g, 0.370 mmol) was dissolved in 1,2-dichloroethane (4 mL) in a 25 mL round-bottomed flask and Me_3SnOH (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 Me_3SnOH (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. $R_f = 0.51$ (silica gel, 2 : 1 hexanes–EtOAc); $[a]_D^{25}$ +30.1° (*c* 0.25 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 3510, 2956, 2857, 1744, 1713, 1472, 1382, 1173, 976; δ_H (500 MHz, C_6D_6) 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=CH_2), 5.11 (1 H, s, 6=CH_2), 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-CH_3), 1.41 [3 H, s, $O_2C(CH_3)_2$], 1.39 [3 H, s, $O_2C(CH_3)_2$], 1.25 (3 H, d, *J* 7.0 Hz, 2-CH_3), 1.20–1.85 (18 H, m, O*H*, O*H*, 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(CH_3)$_3$], 0.93 (6 H, m, 10-CH_3 and 28-CH_3), 0.25 (3 H, s, SiCH_3), 0.16 (9 H, s, SiCH_3, SiCH_3 and SiCH_3), 0.14 (3 H, s, SiCH_3), 0.11 (3 H, s, SiCH_3); δ_C (125 MHz, C_6D_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 $C_{54}H_{102}O_{11}Si_3Na$ ([MNa]$^+$): 1033.6622, found: 1033.6611.

Macrolactone 75

To a stirred solution of carboxylic acid **73** (250 mg, 0.25 mmol) and Et_3N (1.38 mL, 9.85 mmol) in toluene (15 mL) was added 2,4,6-trichlorobenzoylchloride **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. $KHSO_4$ (400 mL), and the mixture was extracted with EtOAc (3 × 300 mL). The combined organic layers were washed with brine (1 × 200 mL), dried ($MgSO_4$), 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–Et_2O); $[a]_D^{25}$ +35.3° (*c* 0.53 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 3443, 2951, 2854, 1742, 1731, 1472, 1251, 1091, 834; δ_H (500 MHz, C_6D_6) 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=CH_2), 5.29 (1 H, d, *J* 9.9 Hz, 11-H), 5.15 (1 H, s, 6=CH_2), 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 O*H*), 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-CH_3), 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-CH_3, $O_2C(CH_3)_2$ and $O_2C(CH_3)_2$], 0.99–1.03 [21 H, m, 10-CH_3, 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-CH_3), 0.23 (3 H, s, SiCH_3), 0.20 (3 H, s, SiCH_3), 0.19 (3 H, s, SiCH_3), 0.14 (3 H, s, SiCH_3), 0.12 (3 H, s, SiCH_3), 0.11 (3 H, s, SiCH_3); δ_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* calc. for $C_{54}H_{100}O_{10}Si_3Na$ ([MNa]$^+$): 1015.6516, found: 1015.6512.

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 CH_2Cl_2 (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 CH_2Cl_2, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (7% Et_2O in hexanes) to give **77** (27.7 mg, 92%) as a colourless foam. $R_f = 0.52$ (silica gel, 4 : 1 hexanes–Et_2O); $[a]_D^{25}$ +51.0° (*c* 1.07 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 2956, 2856, 1742, 1717, 1456, 1252, 1092, 908; δ_H (600 MHz, C_6D_6) 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=CH_2), 5.19 (1 H, d, *J* 9.4 Hz, 7-H), 5.16 (1 H, s, 6=CH_2), 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-CH_3), 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-CH_3, $O_2C(CH_3)_2$ and $O_2C(CH_3)_2$], 1.22 (3 H, d, *J* 6.5 Hz, 10-CH_3), 1.03 [9 H, s, SiC(CH_3)$_3$], 1.01 [9 H, s, SiC(CH_3)$_3$], 0.98 [9 H, s, SiC(CH_3)$_3$], 0.92 (3 H, t, *J* 6.7 Hz, 28-CH_3), 0.20 (3 H, s, SiCH_3), 0.18 (6 H, s, SiCH_3 and SiCH_3), 0.12 (6 H, s, SiCH_3 and SiCH_3), 0.11 (3 H, s, SiCH_3); δ_C (150 MHz, C_6D_6) 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 $C_{54}H_{98}O_{10}Si_3Na$ ([MNa]$^+$): 1013.6360, found: 1013.6359.

Hemiacetal 78

Ketone **77** (125 mg, 0.126 mmol) was dissolved in 9 : 1 acetonitrile–CH_2Cl_2 (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. $NaHCO_3$ (50 mL) at 0 °C. Upon completion of the addition, solid $NaHCO_3$ 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 ($MgSO_4$), 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 ^{1}H-NMR). $R_f = 0.48$ (silica gel, EtOAc); $[a]_D^{25}$ −136.5° (*c* 1.48 in CH_2Cl_2);

ν_{max}/cm^{-1} (film) 3400, 2933, 1709, 1458, 1351, 1193, 1074, 901; δ_H (500 MHz, C_6D_6) – major anomer only – 6.08 (1 H, d, *J* 16.2 Hz, 5-H), 5.73 (1 H, s, 6=C*H*$_2$), 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=C*H*$_2$), 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-O*H*), 4.58–4.61 (1 H, m, 3-H), 4.53 (1 H, br s, 14-O*H*), 4.00–4.06 (3 H, m, 16-H, 19-H and 21-H), 3.88 (1 H, br s, 16-O*H*), 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-O*H* and 15-O*H*), 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-C*H*$_3$), 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-C*H*$_3$), 1.08 (3 H, d, *J* 7.1 Hz, 2-C*H*$_3$), 1.03–1.12 (2 H, m, 18-H and 23-H), 0.86 (3 H, t, *J* 6.8 Hz, 28-C*H*$_3$); δ_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=*C*H$_2$), 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-*C*H$_3$), 14.9 (10-*C*H$_3$), 14.1 (2-*C*H$_3$), 9.4 (28-*C*H$_3$); 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 CH_2Cl_2–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. $NaHCO_3$ (15 mL), and extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (1 × 20 mL), brine (1 × 20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient: 5–15% Et_2O in hexanes) to give **79** (0.96 g, 78%) as a viscous, yellow oil. R_f = 0.19 (silica gel, 4 : 1 hexanes–Et_2O); $[\alpha]_D^{25}$ +36.5° (*c* 1.41 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 3510, 2956, 2859, 1746, 1738, 1382, 1172, 939; δ_H (500 MHz, C_6D_6) 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=C*H*$_2$), 5.11 (1 H, s, 6=C*H*$_2$), 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, CO_2CH_3), 2.68 (1 H, dd, *J* 13.9, 2.5 Hz, H-13), 2.51–2.57 (2 H, m, H-2 and O*H*), 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 O*H*), 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-C*H*$_3$), 1.41 [3 H, s, $O_2C(CH_3)_2$], 1.36 [3 H, s, $O_2C(CH_3)_2$], 1.27 (3 H, d, *J* 7.0 Hz, 2-C*H*$_3$), 1.32–1.53 (5 H, m, H-22, H-27, H-27, H-28 and H-28), 1.07 [9 H, s, $SiC(CH_3)_3$], 1.04 [9 H, s, $SiC(CH_3)_3$], 1.03 [9 H, s, $SiC(CH_3)_3$], 0.99 [9 H, s, $SiC(CH_3)_3$], 0.96 [9 H, s, $SiC(CH_3)_3$], 0.91–0.94 (6 H, m, 10-C*H*$_3$ and 28-C*H*$_3$), 0.26 (3 H, s, SiC*H*$_3$), 0.20 (3 H, s, SiC*H*$_3$), 0.19 (3 H, s, SiC*H*$_3$), 0.19 (3 H, s, SiC*H*$_3$), 0.18 (3 H, s, SiC*H*$_3$), 0.16 (3 H, s, SiC*H*$_3$), 0.14 (3 H, s, SiC*H*$_3$), 0.10 (3 H, s, SiC*H*$_3$), 0.09 (3 H, s, SiC*H*$_3$), 0.08 (3 H, s, SiC*H*$_3$); δ_C (150 MHz, C_6D_6) 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 $C_{67}H_{134}O_{12}Si_5Na$ ([MNa]$^+$): 1293.8613, found: 1293.8600.

Acid 80

Methyl ester **79** (0.83 g, 0.650 mmol) was dissolved in 1,2-dichloroethane (20 mL) in a 50 mL round-bottomed flask and Me_3SnOH (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 Me_3SnOH (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_f = 0.36 (silica gel, 3 : 2 hexanes–Et_2O); $[\alpha]_D^{25}$ +33.8° (*c* 7.70 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 3493, 2955, 2890, 1745, 1711, 1471, 1361, 1092, 835; δ_H (500 MHz, C_6D_6) 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=C*H*$_2$), 5.12 (1 H, s, 6=C*H*$_2$), 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, O*H* and O*H*), 1.51 (3 H, s, 12-C*H*$_3$), 1.47–1.53 (2 H, m, 26-H and 27-H), 1.41 [3 H, s, $O_2C(CH_3)_2$], 1.37 [3 H, s, $O_2C(CH_3)_2$], 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-C*H*$_3$), 1.06 [9 H, s, $SiC(CH_3)_3$], 1.04 [9 H, s, $SiC(CH_3)_3$], 1.03 [9 H, s, $SiC(CH_3)_3$], 1.01 [9 H, s, $SiC(CH_3)_3$], 0.96 [9 H, s, $SiC(CH_3)_3$], 0.91–0.94 (6 H, m, 10-C*H*$_3$ and 28-C*H*$_3$), 0.25 (3 H, s, SiC*H*$_3$), 0.19 (3 H, s, SiC*H*$_3$), 0.19 (3 H, s, SiC*H*$_3$), 0.18 (3 H, s, SiC*H*$_3$), 0.18 (3 H, s, SiC*H*$_3$), 0.17 (3 H, s, SiC*H*$_3$), 0.14 (3 H, s, SiC*H*$_3$), 0.13 (3 H, s, SiC*H*$_3$), 0.11 (3 H, s, SiC*H*$_3$), 0.09 (3 H, s, SiC*H*$_3$); δ_C (125 MHz, C_6D_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 $C_{66}H_{132}O_{12}Si_5Na$ ([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. $KHSO_4$ (200 mL), and the mixture was extracted with EtOAc (2 × 150 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (10% Et_2O 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 CH_2Cl_2); ν_{max}/cm^{-1} (film) 3389, 2955, 1744, 1718, 1472, 1382, 1082, 835; δ_H (600 MHz, C_6D_6) 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=CH_2), 5.26 (1 H, d, *J* 9.9 Hz, 11-H), 5.17 (1 H, s, 6=CH_2), 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, O*H*), 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-CH_3), 1.47 [3 H, s, $O_2C(CH_3)_2$], 1.42 [3 H, s, $O_2C(CH_3)_2$], 1.32 (3 H, d, *J* 7.1 Hz, 2-CH_3) 1.29–1.49 (4 H, m, 23-H, 27-H, 28-H and 28-H), 1.05–1.06 [12 H, m, 10-CH_3 and $SiC(CH_3)_3$], 1.04 [9 H, s, $SiC(CH_3)_3$], 1.03 [9 H, s, $SiC(CH_3)_3$], 1.02 [9 H, s, $SiC(CH_3)_3$], 1.01 [9 H, s, $SiC(CH_3)_3$], 0.94 (3 H, t, *J* 7.1 Hz, 28-CH_3), 0.30 (3 H, s, SiCH_3), 0.26 (3 H, s, SiCH_3), 0.25 (3 H, s, SiCH_3), 0.20 (3 H, s, SiCH_3), 0.18 (6 H, s, SiCH_3 and SiCH_3), 0.16 (9 H, s, SiCH_3, SiCH_3 and SiCH_3), 0.14 (3 H, s, SiCH_3); δ_C (150 MHz, C_6D_6) 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 $C_{66}H_{128}O_{11}Si_5Na$ ($[MNa]^+$): 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 CH_2Cl_2 (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 CH_2Cl_2, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (5% Et_2O in hexanes) to give **82** (78 mg, 80%) as a colourless foam. $R_f = 0.66$ (silica gel, 4 : 1 hexanes–Et_2O); $[a]_D^{25}$ −19.0° (*c* 3.90 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 2955, 2857, 1745, 1719, 1462, 1255, 979; δ_H (600 MHz, C_6D_6) 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=CH_2), 5.13–5.17 (3 H, m, H-7, H-11 and H-25), 5.09 (1 H, s, 6=CH_2), 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-CH_3), 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-CH_3), 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, H-27, H-27, H-28 and H-28), 1.12 (3 H, d, *J* 6.5 Hz, 10-CH_3), 1.02 [9 H, s, $SiC(CH_3)_3$], 1.01 [9 H, s, $SiC(CH_3)_3$], 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, SiCH_3), 0.22 (3 H, s, SiCH_3), 0.21 (3 H, s, SiCH_3), 0.19 (6 H, s, SiCH_3 and SiCH_3), 0.18 (3 H, s, SiCH_3), 0.16 (3 H, s, SiCH_3), 0.16 (3 H, s, SiCH_3), 0.15(3 H, s, SiCH_3), 0.12 (3 H, s, SiCH_3); δ_C (150 MHz, C_6D_6) 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 $C_{66}H_{128}O_{11}Si_5Na$ ($[MNa]^+$): 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–CH_2Cl_2 (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. $NaHCO_3$ (50 mL) at 0 °C. Upon completion of the addition, solid $NaHCO_3$ 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 ($MgSO_4$), 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. ^{1}H-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. $R_f = 0.18$ (silica gel, EtOAc); $[a]_D^{25}$ −116.0° (*c* 0.51 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 3414, 2932, 1721, 1707, 1442, 1351, 1185, 1071, 902; δ_H (500 MHz, 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=CH_2), 5.22 (1 H, d, *J* 10.0 Hz, 11-H), 5.20 (1 H, s, 6=CH_2), 4.95–5.01 (2 H, m, 7-H and 25-H), 4.43 (1 H, br d, *J* 4.3 Hz, O*H*), 4.32–4.36 (1 H, m, 3-H), 4.04 (1 H, br s, O*H*), 3.78–3.87 (5 H, m, 14-H, 16-H, 19-H, 12-H and O*H*), 3.61 (2 H, br s, O*H* and O*H*), 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 O*H*), 1.63 (3 H, s, 12-CH_3), 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-CH_3), 1.06–1.12 (1 H, m, 20-H), 1.06 (3 H, d, *J* 7.2 Hz, 2-CH_3), 0.99 (1 H, d, *J* 13.8 Hz, 18-H), 0.93 (3 H, t, *J* 7.1 Hz, 28-CH_3); δ_C (125 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-*C*H_3), 15.6 (10-*C*H_3), 14.4 (28-*C*H_3), 11.8 (2-*C*H_3); HRMS (ES^+) *m/z* calc. for $C_{33}H_{53}O_{10}$ ($[M - OH]^+$): 609.3633, found: 609.3641.

Data for bicyclic acetal 84. $R_f = 0.28$ (silica gel, EtOAc); $[a]_D^{25}$ −143.2° (*c* 1.16 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 3409, 2931, 1721, 1706, 1485, 1346, 1185, 1023, 902; δ_H (500 MHz, C_6D_6) 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=CH_2), 5.14 (1 H, s, 6=CH_2), 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-O*H*), 4.13–4.16 (2 H, m, 14-O*H* and 7-O*H*), 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-O*H*), 3.16 (1 H, br s, 24-O*H*), 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-CH_3), 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-CH_3), 1.10 (3 H, d, *J* 6.6 Hz, 10-CH_3), 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-CH_3); δ_C (125 MHz, C_6D_6) 212.1 (C9), 173.8 (C1), 147.2 (C6), 135.9 (C12), 130.8 (C4), 130.0 (C5), 127.5 (C11), 113.6 (6=*C*H_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-*C*H_3), 15.3 (10-*C*H_3), 14.3 (28-*C*H_3), 10.0 (2-*C*H_3); HRMS (ES^+) *m*/*z* calc. for $C_{33}H_{52}O_{10}Na$ ([MNa]$^+$): 631.3452, found: 631.3447.

Allylic epoxide 89

To a stirred solution of diene **84** (7.5 mg, 12.3 μmol) in CH_2Cl_2 (1.5 mL), was added freshly prepared DMDO[26] (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 Me_2S (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. $R_f = 0.24$ (silica gel, EtOAc); $[\alpha]_D^{25}$ −70.8° (*c* 0.24 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 3412, 2928, 2856, 1726, 1714, 1664, 1458, 1386, 1264, 1192, 1097, 743; δ_H (600 MHz, C_6D_6) 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-O*H*), 4.21 (1 H, dd, *J* 9.9, 2.3 Hz, 7-H), 4.19 (1 H, br s, 14-O*H*), 3.84–3.91 (3 H, m, 14-H, 21-H and 24-O*H*), 3.76–3.79 (2 H, m, 19-H, 16-O*H*), 3.74 (1 H, br s, 7-O*H*), 3.66–3.72 (2 H, m, 16-H and 24-H), 3.29 [1 H, d, *J* 6.4 Hz, 6(O)CH_2], 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)CH_2], 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-CH_3), 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-CH_3), 1.07 (3 H, *J* 7.1 Hz, 2-CH_3), 0.97–1.05 (2 H, m, 18-H and 20-H), 0.90 (3 H, t, *J* 7.1 Hz, 28-CH_3); δ_C (150 MHz, C_6D_6) 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)*C*H$_2$], 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-*C*H_3), 15.0 (10-*C*H_3), 14.2 (28-*C*H_3), 9.3 (2-*C*H_3); HRMS (ES^+) *m*/*z* calc. for $C_{33}H_{52}O_{11}Na$ ([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 CH_2Cl_2–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. $NaHCO_3$ (25 mL), and warmed to room temperature. The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (1 × 25 mL), brine (1 × 25 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient: 10–20% Et_2O in hexanes) to give **91** (0.441 g, 91%) as a highly viscous, colourless oil. R_f = 0.41 (silica gel, 1 : 1 hexanes–Et_2O); $[\alpha]_D^{25}$ +47.1° (*c* 1.20 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 3510, 2956, 1745, 1461, 1382, 1094, 938, 837; δ_H (600 MHz, C_6D_6) 5.72 (1 H, s, 6=CH_2), 5.37 (1 H, 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, O*H*), 2.38 (1 H, br s, O*H*), 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-CH_3), 1.39 [3 H, s, $O_2C(CH_3)_2$], 1.35 [3 H, s, $O_2C(CH_3)_2$], 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, $SiC(CH_3)_3$ and $SiC(CH_3)_3$], 0.92 (3 H, t, *J* 7.3 Hz, 28-CH_3), 0.86 (3 H, d, *J* 6.6 Hz, 10-CH_3), 0.20 (3 H, s, SiCH_3), 0.16 (6 H, s, SiCH_3 and SiCH_3), 0.15 (3 H, s, SiCH_3); δ_C (150 MHz, C_6D_6) 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. $NaHCO_3$ (50 mL) at 0 °C. After stirring for a further 30 min, the mixture was warmed to room temperature and extracted with EtOAc (6 × 20 mL). The combined organic layers were then dried ($MgSO_4$), 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 ^{1}H-NMR). R_f = 0.28 (silica gel, EtOAc); $[\alpha]_D^{25}$ −32.6° (*c* 1.12 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 3385, 2955, 1628, 1446, 1266, 1092, 895; δ_H (600 MHz, C_6D_6, 343 K, major anomer only) 6.06 (1 H, s, 6=CH_2), 5.52 (1 H, s, 6=CH_2), 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-CH_3), 1.72–1.80 (2 H, m, 20-H and 18-H), 1.47–1.68 (5 H, m, 17-H,

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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