Synthesis of *iso*-epoxy-amphidinolide N and *des*-epoxy-caribenolide I structures. Initial forays

K. C. Nicolaou,*[a,b] William E. Brenzovich,[a] Paul G. Bulger[a] and Tasha M. Francis[a]

Received (in Pittsburgh, PA, USA) 10 February 2006, Accepted 27th March 2006
First published as an Advance Article on the web 26th April 2006
DOI: 10.1039/b602020h

Two strategies for the projected total synthesis of the phenomenally potent antitumour macrolides amphidinolide N (**1**) and caribenolide I (**2**) are described. The title compounds are introduced as challenging and unique targets for chemical synthesis, and their retrosynthetic analysis is presented. The synthesis of the four defined key building blocks (**10**, **39**, **67** and **72**), required for the construction of amphidinolide N (**1**), in their enantiomerically pure forms, is described, followed by the coupling of **10**, **39** and **72** through hydrazone alkylation processes to generate the complete C6–C29 carbon framework of the target compound (**1**). Fusion of the remaining C1–C5 sector (**72**) onto the molecule by metathesis-based methods was unsuccessful, resulting in the adoption of a second-generation strategy which called for the employment of one of the array of palladium-catalysed cross-coupling reactions to generate the C5–C6 carbon–carbon bond. Vinyl bromide **125**, representing the C6–C29 skeleton of caribenolide I (**2**), was prepared through the sequential alkylation of hydrazone **10** with bromide **116** and iodide **55**, but failed to engage in the appropriate cross-coupling reaction with a variety of C1–C4 partners. Despite these setbacks, the information gleaned from these endeavours was to prove invaluable in laying the foundation for the eventual successful approach to the macrocyclic structures of amphidinolide N (**1**) and caribenolide I (**2**).

Introduction

In recent years, a remarkable array of structurally diverse and biologically active secondary metabolites has been isolated from a variety of marine organisms, such as fish, algal blooms and sponges.[1] It has been found that marine microorganisms, such as bacteria and dinoflagellates, are the true producers of many of these novel substances, through association in a symbiotic relationship with a larger host.[2] One such example of this phenomenon is the case of the amphidinolides, a class of macrolide natural products isolated from cultured extracts of *Amphidinium* sp., the latter being symbiotic dinoflagellates harvested from inside cells of marine acoel flatworms *Amphiscolops* sp. collected from coral reefs off the coast of Okinawa. Largely through the sterling efforts of the Kobayashi group, the number of identified members of this ever-expanding family of chemically unique macrolides, which possess a variety of backbone molecular architectures and macrocyclic ring-sizes (12–29-membered), currently stands at more than 30.[3] In addition to their unprecedented structures, most of the individual members of this natural product class have been shown to exhibit cytotoxicity against several mammalian cancer cell lines *in vitro*, with activities that can be loosely defined as ranging from good (IC_{50} < 10 μM) to excellent (IC_{50} < 1 nM). This combination of intriguing molecular structure and biological properties has prompted a flurry of activity directed towards the laboratory synthesis of these compounds, resulting in several total syntheses[4–9] and numerous partial syntheses[10] of various members of the amphidinolide family.

The isolation of amphidinolide N (**1**, Fig. 1) was reported by Kobayashi and co-workers in 1994.[11] Arguably the most structurally complex of this class of natural products (at least in terms of the number of stereocentres), amphidinolide N (**1**) was found to exhibit extraordinary cytotoxicity *in vitro*, with IC_{50} values of 0.08 and 0.09 nM against the murine lymphoma L1210 and human epidermoid carcinoma KB-31 cell lines, respectively. This level of activity is at least an order of magnitude greater than the next most potent members of the amphidinolide family, namely amphidinolides B (**3**, Fig. 1) and H (**4**). Indeed, amphidinolide N (**1**) is one of the most potent antitumour substances discovered to date, with activity levels rivalling those of the spongistatins.[12] Unfortunately, further studies into the efficacy of amphidinolide N (**1**) as a potential therapeutic agent have been precluded by the extremely limited amounts of material that could be isolated from the *Amphidinium* sp. cultures. The relative inaccessibility of the natural product has also hampered progress towards even a complete stereochemical assignment. Although the relative stereochemistry of the C14–C19 region of amphidinolide N (**1**) was tentatively assigned to be as shown in Fig. 1 on the basis of NOESY data,[11] the configurations of the remaining chiral centres, as well as the absolute configuration of the molecule, has so far not yet been determined.

In the year following the disclosure of amphidinolide N (**1**), the isolation of caribenolide I (**2**, Fig. 1) from cultured extracts of an *Amphidinium* sp. (which in this case was a free-swimming, rather than symbiont, dinoflagellate) was reported by Shimizu and co-workers.[13] Discovered during the course of screening for

[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*

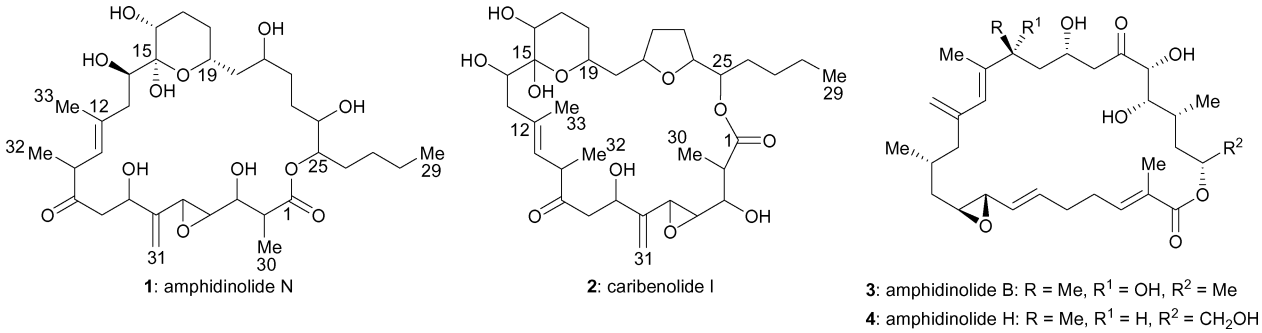


Fig. 1 Structures of amphidinolide N (**1**), caribenolide I (**2**), amphidinolide B (**3**) and amphidinolide H (**4**).

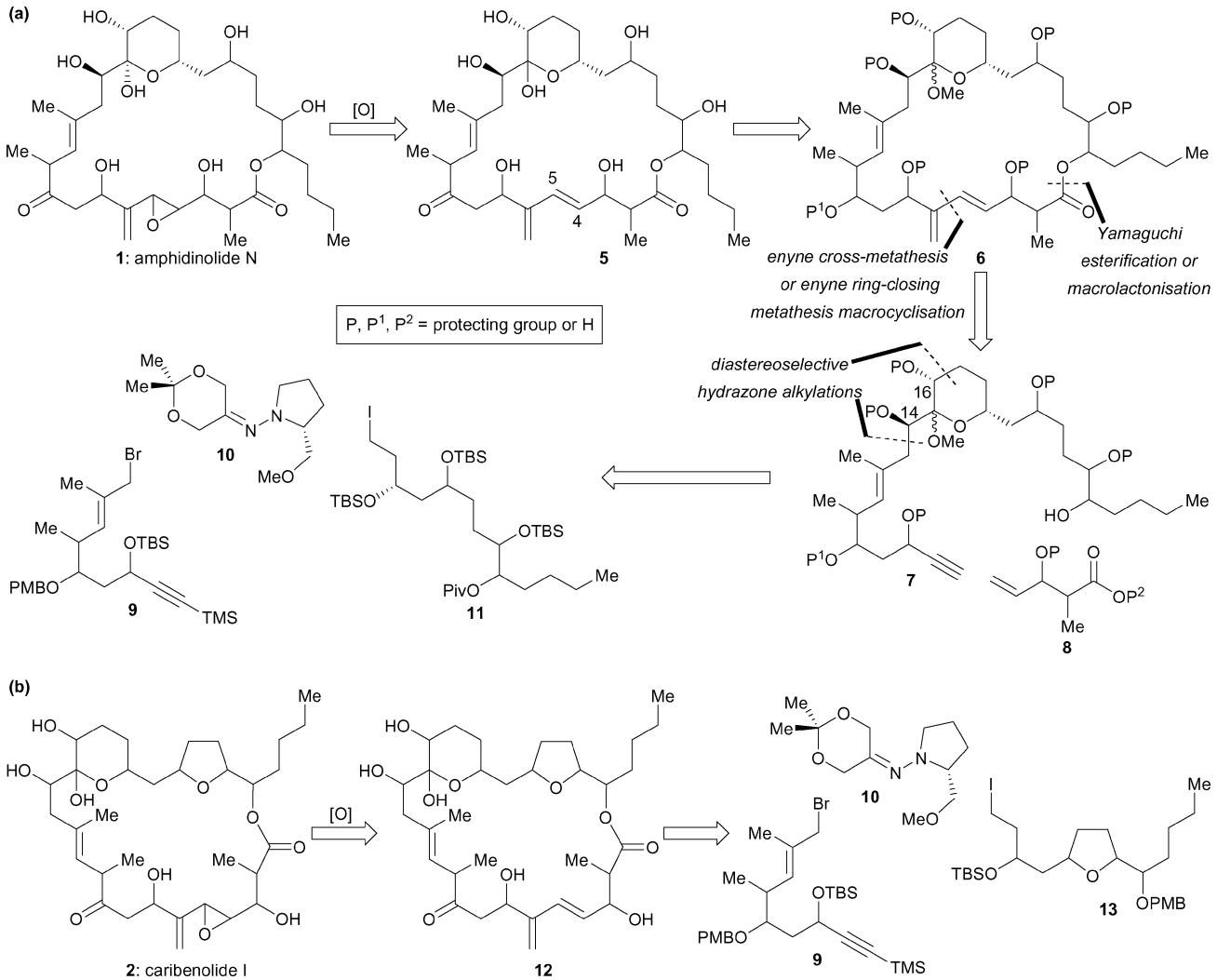
potent antineoplastic agents, caribenolide I (**2**) is clearly related biogenetically to amphidinolide N (**1**). Caribenolide I (**2**) and amphidinolide N (**1**) share an identical carbon–carbon connectivity, with the sole structural difference between the two molecules being the presence of a tetrahydrofuran ring (formally the result of an intramolecular dehydration between the C21 and C24 hydroxy groups) in the former. The biogenetic relationship and striking structural homology between caribenolide I (**2**) and amphidinolide N (**1**) suggests that the stereochemical relationships are conserved between the two molecules. However, since neither the relative nor absolute stereochemistry of caribenolide I (**2**) could be determined from the meagre amounts of material that could be procured from the producing organism, as was the case with amphidinolide N (**1**), this postulate remains unconfirmed. Caribenolide I (**2**) was found to show potent cytotoxic activity against the human colon cancer cell line HCT-116, with an IC_{50} value (1.6 nM) more than 100 times smaller than that of amphidinolide B (**3**). Importantly, this excellent activity was retained against the corresponding drug-resistant HCT-116/VM-46 cell line. Furthermore, caribenolide I (**2**) displayed activity *in vivo* against murine tumour P388 (T/C = 150 at a dose of 0.03 mg kg^{-1} body weight). Caribenolide I (**2**) would therefore also appear to be a promising anticancer therapeutic lead, but again the scarcity of material has prevented more detailed studies, a problem exacerbated by the fact that no more of the originally isolated sample remains, with it all having been consumed in the preliminary biological testing.[14]

Reports of synthetic studies on amphidinolide N (**1**) and caribenolide I (**2**) are notable only for their complete absence. We therefore embarked on a program to address the lack of information on these two remarkable targets with, initially, three main goals: (1) to develop practical synthetic routes to the core frameworks of both compounds **1** and **2**, (2) to obtain information regarding the identity of the relative and absolute stereochemistries of the natural products, and (3) to supply viable quantities of materials, both of the natural products themselves and also their analogues, for further biological investigations. In this article, and in the following paper in this issue,[15] we present a full account of our work in this area thus far.

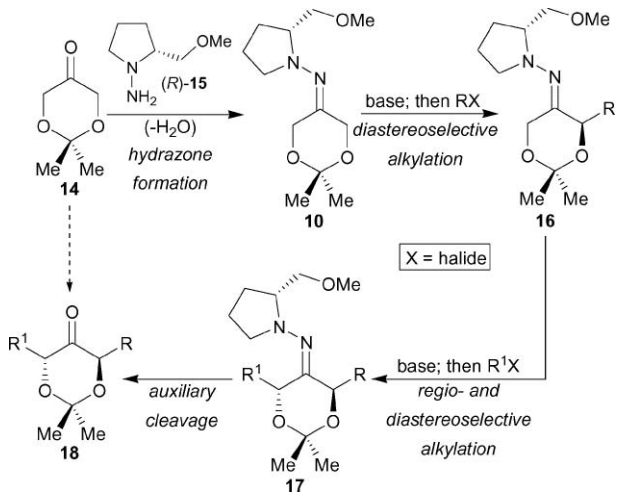
Results and discussion

From the outset, it was anticipated that the C4–C5 allylic epoxide unit present within both amphidinolide N (**1**) and caribenolide I (**2**) would prove to be the most delicate functionality contained within these molecules. In particular, the ability of this motif to survive standard global deprotection conditions was deemed to be questionable at best. It was therefore proposed to install the epoxide group in the final step of the synthesis, leading to, in the case of amphidinolide N (**1**), the protecting group-free diene **5** [Scheme 1(a)] as the direct precursor of the target molecule. Macrolide **5** would, in turn, be derived from compound **6**, which attracted our attention due to the possibility of exploiting either an enyne cross-metathesis[16] or an enyne ring-closing metathesis macrocyclisation[17] reaction to generate its 1,3-diene system. These reactions have been very much under-utilised in target-oriented synthesis compared to their more prestigious alkene-based siblings,[18] yet offer a potentially convenient access to the characteristic 1,3-disubstituted 1,3-diene system in compound **6**. Thus, **6** could be derived from alkyne **7** and alkene **8** either by enyne cross-metathesis followed by macrolactonisation, or by intermolecular esterification followed by an enyne ring-closing metathesis macrocyclisation. The C14–C16 subunit of alkyne **7** comprises a masked 1,3-dihydroxyketone derivative, allowing for two further points of disconnection as shown, to give bromide **9**, hydrazone **10** and iodide **11**. In the forward synthetic direction, these three fragments would be unified by sequential alkylation reactions of hydrazone **10**. If successful, this would represent the most advanced application to date of the protocol developed by the Enders group for the enantioselective synthesis of *anti*-disubstituted 1,3-dihydroxyacetone derivatives, the basic principles of which are illustrated in Scheme 2.[19] A similar retrosynthetic analysis for caribenolide I (**2**) then simply requires the replacement of iodide **11** with the corresponding tetrahydrofuran **13** [Scheme 1(b)]. The proposed routes to **1** and **2** were thus designed to have a high degree of flexibility and convergency. Given the uncertainties regarding the stereochemistry of the target compounds (**1** and **2**), it would be necessary that the routes to the individual fragments **9**, **11** and **13** be amenable to the production of any one of the possible stereoisomers.

In the absence of overwhelming evidence to favour any one particular stereoisomer of the natural products, the stereoselective routes to fragments **9**, **11** and **13** were designed, initially, based upon the perceived relative ease of synthesis. The synthesis of the amphidinolide N C17–C29 fragment **39** is illustrated in Scheme 3, and began with the protection of commercially available (*S*)-(−)-glycidol **19** as the corresponding trityl ether **20** (88%).[20] The copper(I)-catalysed opening of epoxide **20** using *n*-propylmagnesium bromide proceeded regioselectively[21] and in

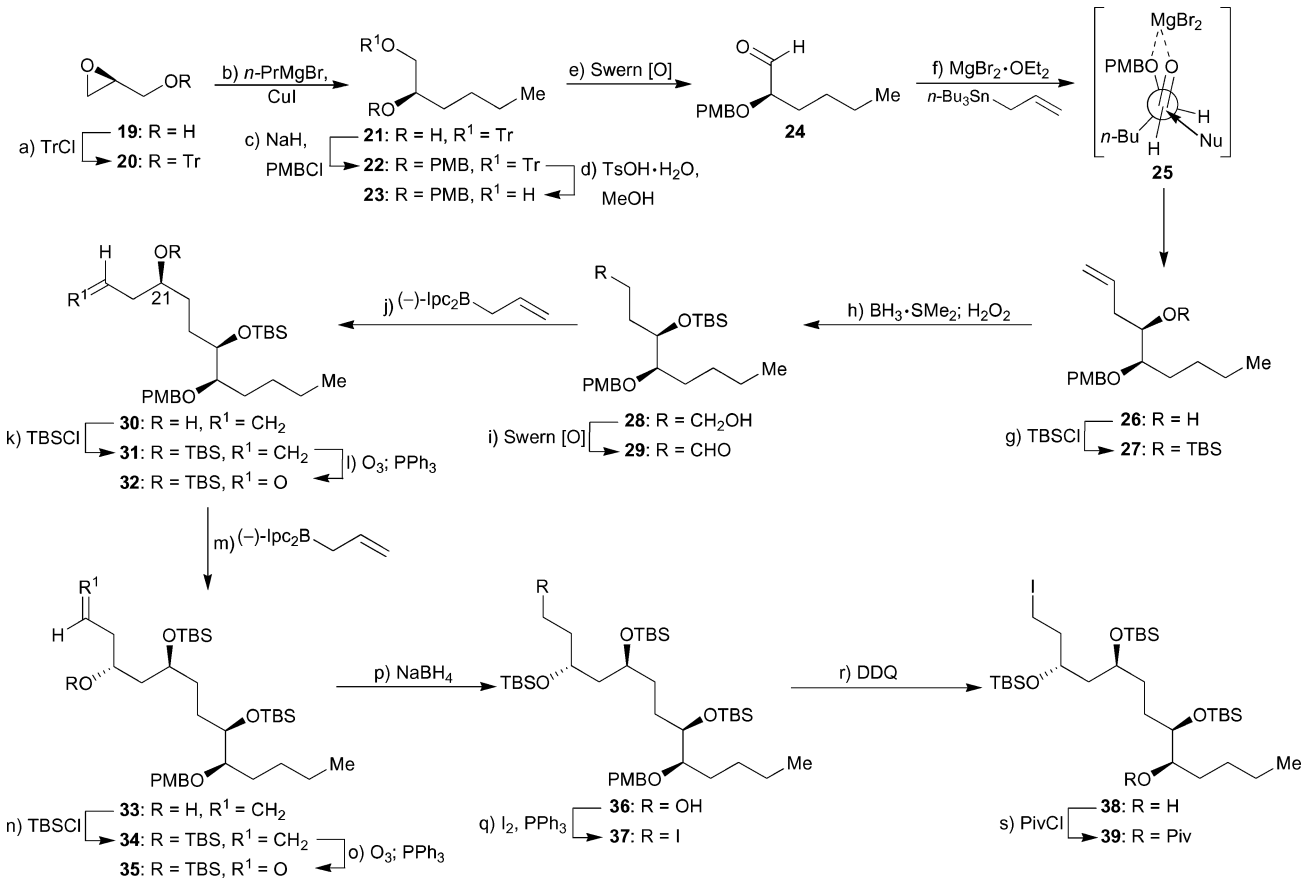


Scheme 1 Retrosynthetic analysis of (a) amphidinolide N (**1**) and (b) caribenolide I (**2**): enyne metathesis approach.



Scheme 2 The Enders hydrazone alkylation approach to the enantioselective synthesis of α,α′-disubstituted 1,3-dihydroxyketone derivatives (**18**).

excellent yield (97%) to afford secondary alcohol **21**. Conversion of alcohol **21** to the corresponding PMB ether (**22**) and subsequent unmasking of the primary hydroxy group to furnish **23** was followed by Swern oxidation to give aldehyde **24** (73% overall for the three-step sequence). Chelation-controlled allylation of aldehyde **24**, using conditions reported by Keck and Boden,[22] gave homoallylic alcohol **26** as the sole detectable stereoisomer (presumably as the result of the addition to the chelated aldehyde intermediate **25**) in nearly quantitative yield. It is important to note that the diastereofacial selectivity of this reaction could, if desired, be reversed by using THF as the solvent instead of Et_2O.[22] Protection of alcohol **26** as the corresponding TBS ether **27** was followed by regioselective hydroboration/oxidation to give primary alcohol **28** and subsequent oxidation to aldehyde **29**. Brown allylation[23] of aldehyde **29** proceeded with >95% diastereoselectivity to install the C21 stereocentre in alcohol **30** under reagent control. Silyl ether protection (**30** → **31**) and then ozonolysis of the terminal alkene provided aldehyde **32**, which was subjected to another three-step sequence of Brown allylation (**32** → **33**), protection (**33** → **34**) and ozonolysis to yield aldehyde **35**, with an average yield of 92% for the five-step sequence. Reduction of aldehyde **35** with $NaBH_4$ gave primary alcohol **36** (98%), which was converted into iodide **37** under standard conditions (I_2, PPh_3, imidazole, 98%). Completion of the synthesis

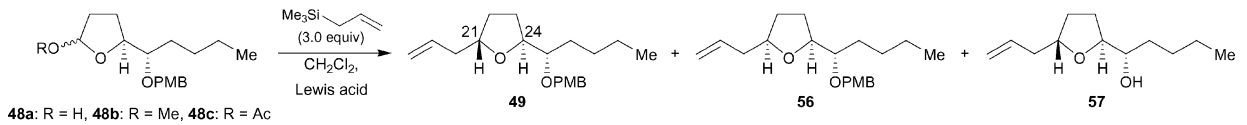


Scheme 3 Synthesis of amphidinolide N C17–C29 fragment **39**. *Reagents and conditions*: a) TrCl (1.1 equiv.), Et_3N (2.0 equiv.), CH_2Cl_2, 0 → 25 °C, 24 h, 88%; b) *n*-PrMgBr (2.0 equiv.), CuI (0.2 equiv.), THF, −45 °C, 80 min, 97%; c) NaH (1.5 equiv.), THF, 0 → 25 °C, 1 h, then PMBCl (1.5 equiv.), TBAI (0.02 equiv.), 45 → 55 °C, 36 h, 82%; d) $TsOH·H_2O$ (0.1 equiv.), MeOH, 25 °C, 20 min, 90%; e) DMSO (3.0 equiv.), $(COCl)_2$ (1.5 equiv.), CH_2Cl_2, −78 °C, 20 min, then **23**, −78 °C, 30 min, then Et_3N (6.0 equiv.), −78 → 25 °C, 1 h, 99%; f) allyltributyltin (1.7 equiv.), $MgBr_2·OEt_2$ (1.6 equiv.), Et_2O, 0 °C, 3 h, 99%; g) TBSCl (1.7 equiv.), imidazole (2.5 equiv.), 4-DMAP (cat.), CH_2Cl_2, 16 h, 95%; h) $BH_3·SMe_2$ (4.0 equiv.), THF, 0 → 25 °C, then 3 M aq. NaOH, H_2O_2 (35% in H_2O), 0 → 25 °C, 16 h, 85%; i) DMSO (2.8 equiv.), $(COCl)_2$ (1.4 equiv.), CH_2Cl_2, −78 °C, 20 min, then **28**, −78 °C, 30 min, then Et_3N (5.6 equiv.), −78 → 25 °C, 1 h, 93%; j) allylmagnesium bromide (2.1 equiv.), (+)-Ipc_2BOMe (2.1 equiv.), Et_2O, −78 → 25 °C, 75 min, then **29**, −78 → 0 °C, 3 h, then 3 M aq. NaOH, 35% aq. H_2O_2, 0 → 25 °C, 16 h, 90%; k) TBSCl (2.6 equiv.), imidazole (3.6 equiv.), 4-DMAP (cat.), CH_2Cl_2, 7 h, 89%; l) O_3, CH_2Cl_2, −78 °C, then PPh_3 (1.3 equiv.), −78 → 25 °C, 1 h, 92%; m) allylmagnesium bromide (2.1 equiv.), (+)-Ipc_2BOMe (2.1 equiv.), Et_2O, −78 → 25 °C, 75 min, then **32**, −78 → 0 °C, 3 h, then 3 M aq. NaOH, 35% aq. H_2O_2, 0 → 25 °C, 16 h, 95%; n) TBSCl (2.0 equiv.), imidazole (4.0 equiv.), 4-DMAP (cat.), CH_2Cl_2, 16 h, 95%; o) O_3, CH_2Cl_2, −78 °C, then PPh_3 (1.3 equiv.), −78 → 25 °C, 1 h, 90%; p) $NaBH_4$ (2.0 equiv.), MeOH, 0 °C, 10 min, 98%; q) I_2 (2.0 equiv.), PPh_3 (2.0 equiv.), imidazole (4.0 equiv.), C_6H_6, 0 → 25 °C, 30 min, 98%; r) DDQ (1.7 equiv.), CH_2Cl_2/pH 7 aq. buffer, 25 °C, 1 h, 90%; s) PivCl (12.0 equiv.), pyridine (12.0 equiv.), 4-DMAP (cat.), CH_2Cl_2, 0 → 25 °C, 22 h, 65%. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; 4-DMAP = 4-dimethylaminopyridine; Ipc = isopinocampheyl; Piv = pivaloyl; PMB = 4-methoxybenzyl; TBAI = tetra-*n*-butylammonium iodide; TBS = *tert*-butyldimethylsilyl; Tr = trityl; Ts = 4-toluenesulfonyl.

of fragment **39** was achieved by selective cleavage of the PMB group followed by reprotection of the resulting alcohol (**38**) as the corresponding pivalate (59% for the two steps).

Natural L-glutamic acid (**40**, Scheme 4) was the chosen starting material for the synthesis of the caribenolide I C17–C29 fragment **55**, and was converted in moderate yield (48%) into lactone **41** [24] (with retention of stereochemistry) *via* diazotisation/internal displacement. Formation of acid chloride **42** [25] was followed by the careful addition of *n*-butylmagnesium bromide at low temperature, resulting in chemoselective addition to yield ketone **43** (82% from **41**).[26] Reduction of the ketone group in compound **43** using K-Selectride® then furnished alcohol **45** as a single stereoisomer in 71% yield, presumably *via* a Felkin–Anh[27] mode of addition (*cf.* **44**);[26] protection of the resulting hydroxy group as the corresponding PMB ether (**46**) was best effected employing PMB-trichloroacetimidate (**47**) and a catalytic amount of $La(OTf)_3$ in toluene (91%).[28] Reduction of lactone **46** using DIBAL-H then gave lactol **48a**, which could be converted into either methyl furanoside **48b** (77% from **46**) or anomeric acetate **48c** (80% from **46**). The Lewis acid-catalysed allylation of **48a–c** to give the (21*S*)-tetrahydrofuran product **49** was then investigated (see Table 1). Initial studies were performed using allyltrimethylsilane and $BF_3·OEt_2$ in CH_2Cl_2 (Table 1, entries 1–4). With lactol **48a** as the substrate, allylation was accompanied by cleavage of the PMB group to give alcohol **57** as the isolated product in moderate yield, albeit as a single stereoisomer (entry 1). With methyl furanoside **48b**, a similar outcome was observed if the reaction was allowed to warm to ambient temperature (entry 2), but if it was maintained

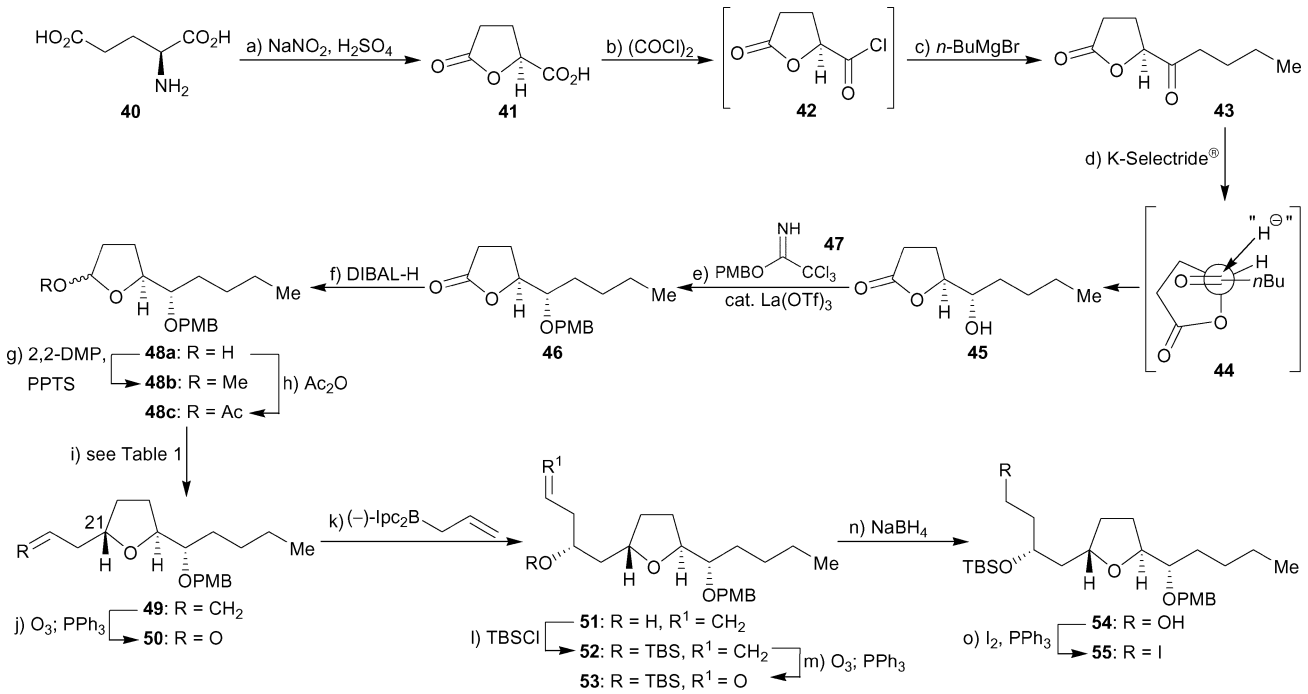
Table 1 Lewis acid-catalysed allylation of tetrahydrofuran substrates **48a**, **48b** and **48c** [a]



48a: R = H, **48b**: R = Me, **48c**: R = Ac

Entry	48	Lewis acid (equiv.)	Temperature/°C	Time	Yield (%)[b]	Diastereomeric ratio[c]
1	**a**	$BF_3{\cdot}OEt_2$ (3.0)	−78 → 25	3 h	40 (**57**)	—
2	**b**	$BF_3{\cdot}OEt_2$ (1.1)	−78 → 25	3 h	71 (**57**)	—
3	**b**	$BF_3{\cdot}OEt_2$ (1.1)	−78	6 h	68 (**49** + **56**)[d]	2.5 : 1
4	**c**	$BF_3{\cdot}OEt_2$ (1.1)	−78	45 min	72 (**49** + **56**)[d]	3 : 1
5	**c**	$MgBr_2$ (2.5)	0	4 h	60 (**48a**)	—
6	**c**	$ZnBr_2$ (2.5)	−20 → 25	48 h	—[e]	—
7	**c**	TMSOTf (0.1)	−78	30 min	96 (**49** + **56**)[d]	3.5 : 1
8	**c**	$La(OTf)_3$ (0.15)	−78	3 h	77 (**49** + **56**)[d]	3 : 1

[a] All reactions were performed using 3.0 equiv. of allylTMS and at a substrate concentration of 0.1 M in CH_2Cl_2. [b] Isolated yield after flash chromatography. [c] Ratio of **49** : **56**, determined from the ^{1}H-NMR spectrum of the crude reaction mixture. [d] Combined yield of **49** and **56**. [e] Reaction did not proceed to completion.

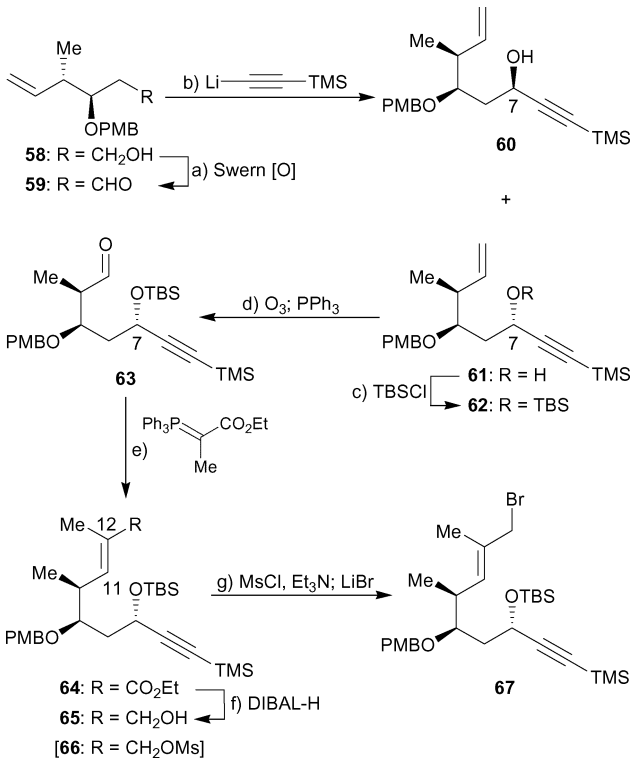


Scheme 4 Synthesis of caribenolide I C17–C29 fragment **55**. *Reagents and conditions*: a) $NaNO_2$ (1.2 equiv.), 2 N aq. H_2SO_4, H_2O, 25 °C, 21 h, 48%; b) $(COCl)_2$ (1.3 equiv.), DMF (cat.), CH_2Cl_2, 25 °C, 3 h; c) *n*-BuMgBr (0.95 equiv.), THF, −78 °C, 1.5 h, 82% (two steps); d) K-Selectride® (1.1 equiv.), THF, −78 → −10 °C, 3 h, 71%; e) **47** (1.6 equiv.), $La(OTf)_3$ (0.05 equiv.), toluene, 0 °C, 10 min, 91%; f) DIBAL-H (1.1 equiv.), toluene, −78 °C, 30 min, 89%; g) 2,2-DMP (1.5 equiv.), PPTS (0.1 equiv.), MeOH, 25 °C, 16 h, 87%; h) Ac_2O (1.4 equiv.), Et_3N (2.1 equiv.), 4-DMAP (0.03 equiv.), CH_2Cl_2, 25 °C, 90 min, 90%; i) (see Table 1); j) O_3, CH_2Cl_2, −78 °C, then PPh_3 (1.7 equiv.), −78 → 25 °C, 1 h, 90%; k) allylmagnesium bromide (2.3 equiv.), (+)-Ipc_2BOMe (2.3 equiv.), Et_2O, −78 → 25 °C, 1.5 h, then **50**, −78 °C, 3 h, then 3 M aq. NaOH, 35% aq. H_2O_2, 0 → 25 °C, 16 h, 69%; l) TBSCl (1.5 equiv.), imidazole (2.0 equiv.), CH_2Cl_2, 16 h, 90%; m) O_3, CH_2Cl_2, −78 °C, then PPh_3 (1.3 equiv.), −78 → 25 °C, 1 h, 89%; n) $NaBH_4$ (1.5 equiv.), MeOH, 0 °C, 15 min, 97%; q) I_2 (2.0 equiv.), PPh_3 (2.0 equiv.), imidazole (4.0 equiv.), C_6H_6, 25 °C, 30 min, 97%. DIBAL-H = diisobutylaluminium hydride; 4-DMAP = 4-dimethylaminopyridine; 2,2-DMP = 2,2-dimethoxypropane; Ipc = isopinocampheyl; K-Selectride® = potassium tri-*sec*-butylborohydride; PPTS = pyridinium *para*-toluenesulfonate; TBS = *tert*-butyldimethylsilyl.

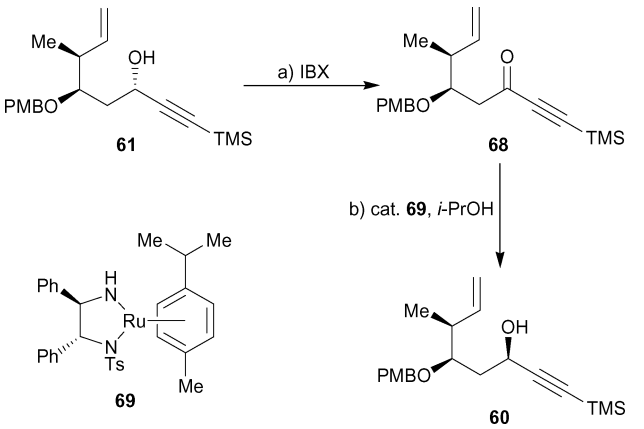
at −78 °C then the PMB group remained intact (entry 3), with a 2.5 : 1 mixture of **49** : **56** being formed in 68% overall yield. That the major product was indeed the C12–C24 *trans*-isomer (**49**) was confirmed by comparative nOe analysis of **49** and **56**, and is in accord with literature precedent for similar systems.[29] Acetate **48c** proved to be a superior substrate in this regard (entry 4), requiring a much shorter reaction time than the corresponding methoxy derivative. Having identified acetate **48c** as the best substrate for this reaction, a cursory examination of different Lewis acids (entries 5–8) led to the identification of TMSOTf as the reagent of choice (entry 7). Under these conditions, the desired (21*S*)-allylated product **49** could be isolated in 75% yield. The

diastereoselectivity of the allylation was relatively independent of both the Lewis acid (entries 4, 7 and 8) and the solvent used (results not shown). Alkene **49** was then elaborated to give iodide **55** (Scheme 4) through a sequence of six further transformations that proceeded through intermediates **50–55** in 47% overall yield.

The synthesis of allylic bromide fragment **67** (Scheme 5), common to both the amphidinolide N and caribenolide I proposed routes, began with known alcohol **58**, which was prepared by the method of Drouet and Theodorakis.[30] Swern oxidation of alcohol **58** to aldehyde **59** (96%) was followed by addition of the lithium anion of TMS-acetylene to give a 1 : 2.3 mixture of (7*R*)- : (7*S*)-epimers **60** : **61**, which were separable by flash chromatography, in a combined yield of 98%. The major (7*S*)-isomer (**61**) could be converted into the (7*R*)-isomer **60** *via* oxidation to the corresponding acetylenic ketone (**68**) using IBX (Swern or PCC oxidations proceeded in much lower yield) and subsequent Noyori asymmetric transfer hydrogenation employing ruthenium catalyst **69**,[31] as is illustrated in Scheme 6. This served to both confirm the identities of **60** and **61**, and provide more efficient access to



Scheme 5 Synthesis of amphidinolide N/caribenolide I C6–C13 coupling partner **67**: enyne metathesis approach. *Reagents and conditions*: a) DMSO (3.6 equiv.), $(COCl)_2$ (1.8 equiv.), CH_2Cl_2, −78 °C, 20 min, then **58**, −78 °C, 30 min, then Et_3N (7.2 equiv.), −78 → 25 °C, 1 h, 96%; b) *n*-BuLi (1.5 equiv.), trimethylsilylacetylene (1.5 equiv.), THF, −78 °C, 20 min, then **59**, THF, −78 → 0 °C, 2 h, 98% (**61** : **60**, 2.3 : 1); c) TBSCl (1.7 equiv.), imidazole (3.5 equiv.), 4-DMAP (cat.), CH_2Cl_2, 2 h, 93%; d) O_3, CH_2Cl_2, −78 °C, then PPh_3 (1.7 equiv.), −78 → 25 °C, 1 h, 98%; e) (carbethoxyethylidene)triphenylphosphorane (1.6 equiv.), C_6H_6, 70 °C, 16 h, 98%; f) DIBAL-H (2.0 equiv.), THF, 0 °C, 30 min, 99%; g) MsCl (3.0 equiv.), Et_3N (4.0 equiv.), THF, 0 → 25 °C, 1 h, then LiBr (10.0 equiv.), 45 min, 89%. DIBAL-H = diisobutylaluminium hydride; 4-DMAP = 4-dimethylaminopyridine; Ms = methanesulfonyl; TBS = *tert*-butyldimethylsilyl.

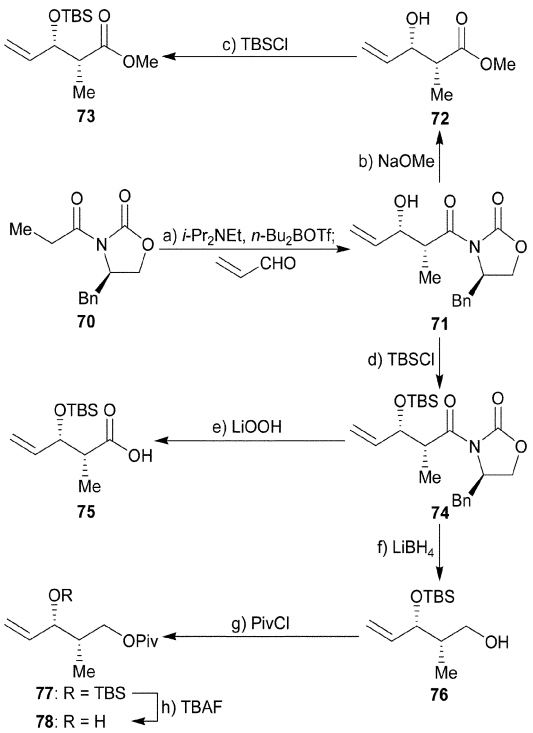


Scheme 6 Noyori asymmetric hydrogenation of acetylenic ketone **68**. *Reagents and conditions*: a) IBX (1.5 equiv.), DMSO, 25 °C, 2 h, 78%; b) **69** (0.01 equiv.), *i*-PrOH, 25 °C, 16 h, 84%. IBX = *ortho*-iodoxybenzoic acid.

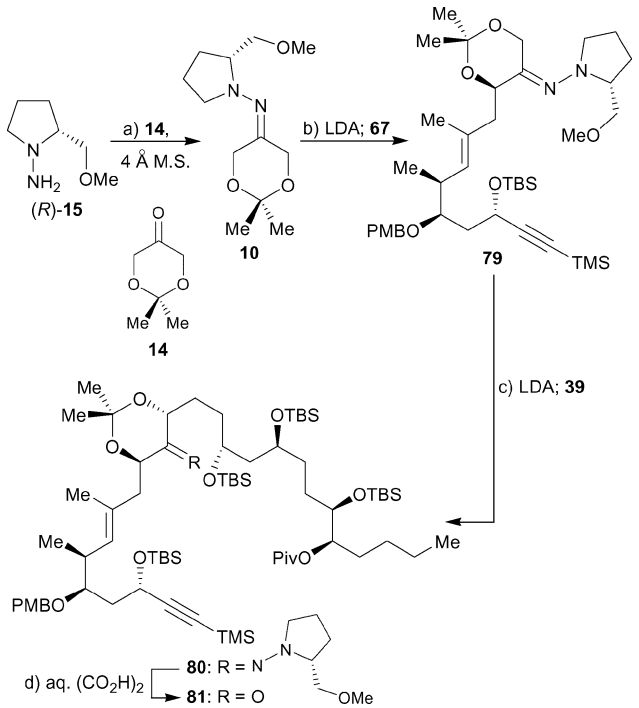
the (7*R*)-isomer **60**. Continuing with the synthesis of bromide **67** (Scheme 5), (7*S*)-alcohol **61** was elaborated through intermediates **62** and **63** to give ester **64**, with the C11–C12 trisubstituted alkene being installed through an *E*-selective Wittig reaction, in 89% overall yield. Reduction of the ester group in compound **64** using DIBAL-H then provided alcohol **65** in excellent yield (99%). The final step in the sequence required the conversion of the allylic primary hydroxy group into the corresponding bromide; of the many methods examined to effect this transformation, the most reliable and efficient involved the formation of a mesylate intermediate followed by displacement with bromide anion in a one-pot procedure (Scheme 5, **65** → **66** → **67**, 89%).[32]

To complete the assembly of the fragments required for the enyne metathesis-based approaches, an Evans aldol reaction of *N*-acyloxazolidinone **70** with acrolein afforded alcohol **71** (Scheme 7),[33] from which a number of potential C1–C4 alkene coupling partners (**72**–**78**) were prepared as shown.

The reported method for the synthesis of hydrazone **10** involves refluxing ketone **14** and hydrazine (*R*)-**15** together in benzene under Dean–Stark conditions for 20 h.[19] We have found that a more convenient procedure, particularly for small-scale applications, involves stirring the two components together in CH_2Cl_2 and in the presence of molecular sieves at ambient temperature for 2 h (Scheme 8). The sequential alkylation of hydrazone **10**, firstly with bromide **67** (see Scheme 5) to give compound **79** and then with amphidinolide N C17–C29 iodide fragment **39** (see Scheme 3), was followed by cleavage of the hydrazone auxiliary under mild conditions (aqueous oxalic acid)[34] to give ketone **81** in good overall yield (55% for the three steps). These key alkylation steps performed admirably, provided that the following modifications of literature protocols[19] were implemented: (1) LDA was used as the base (instead of *t*-BuLi); (2) the reactions were quenched soon after alkylation was judged to be complete (<1 h at −78 °C) by TLC analysis, rather than being allowed to warm to ambient temperature overnight; and (3) the first alkylated intermediate (**79**) was purified by flash column chromatography prior to the second step. These fragment coupling reactions allowed for the rapid assembly of the bulk of the carbon skeleton of amphidinolide N (**1**) in a concise and efficient manner. Each alkylation step was highly



Scheme 7 Synthesis of amphidinolide N/caribenolide I C1–C5 coupling partners: enyne metathesis approach. *Reagents and conditions*: a) *n*-Bu_2BOTf (1.2 equiv.), *i*-Pr_2NEt (1.4 equiv.), CH_2Cl_2, 0 °C, 10 min, then acrolein, −78 → 0 °C, 75 min, 93%; b) NaOMe (1.4 equiv.), MeOH, 0 °C, 40 min, 51%; c) TBSCl (2.0 equiv.), imidazole (4.0 equiv.), 4-DMAP (cat.), CH_2Cl_2, 16 h, 95%; d) TBSCl (3.0 equiv.), imidazole (6 equiv.), 4-DMAP (cat.), CH_2Cl_2, 16 h, 94%; e) LiOH (4.0 equiv.), 35% aq. H_2O_2 (8.0 equiv.), THF–H_2O (4 : 1), 0 °C, 5 h, 92%; f) $LiBH_4$ (3.0 equiv.), THF–MeOH (50? : 1), 0 → 25 °C, 16 h, 70%; g) PivCl (2.0 equiv.), pyridine (3.0 equiv.), 4-DMAP (cat.), CH_2Cl_2, 25 °C, 16 h, 90%; h) TBAF (2.1 equiv.), THF, 25 °C, 3.5 h, 89%. 4-DMAP = 4-dimethylaminopyridine; Piv = pivaloyl; TBAF = tetra-*n*-butylammonium fluoride; TBS = *tert*-butyldimethylsilyl; Tf = trifluoromethanesulfonyl.



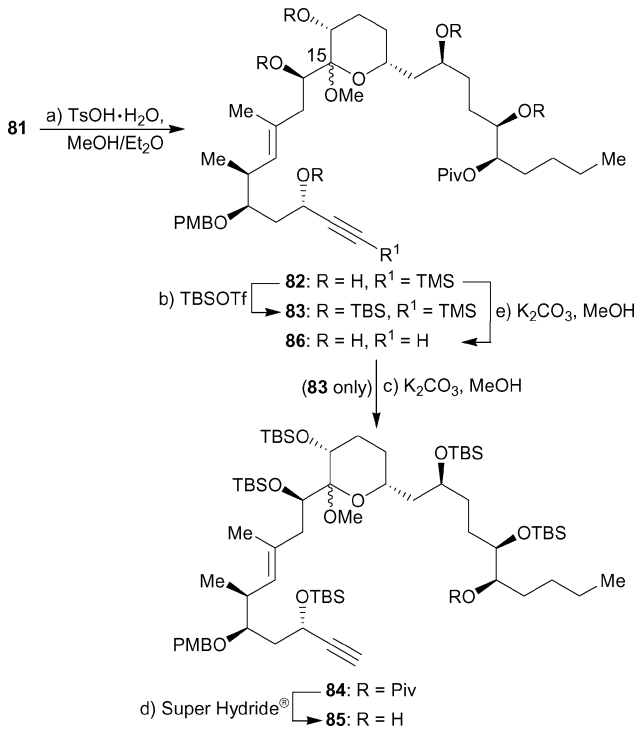
Scheme 8 Coupling of fragments **10**, **39** and **67**: enyne metathesis approach. *Reagents and conditions*: a) **14** (1.1 equiv.), 4 Å MS, CH_2Cl_2, 25 °C, 2 h, 98%; b) LDA (1.2 equiv.), THF, −78 °C, 1.5 h, then **67** (1.2 equiv.), −78 °C, 1 h, 84%; c) LDA (1.2 equiv.), THF, −78 °C, 2 h, then **39** (1.2 equiv.), −78 °C, 4 h; d) sat. aq. $(CO_2H)_2$, Et_2O, 25 °C, 40 h, 64% (two steps). LDA = lithium diisopropylamide; MS = molecular sieves.

stereoselective (dr > 95 : 5 as judged by ^{1}H-NMR spectroscopic analysis), with ketone **81** being isolated in stereochemically pure form after flash column chromatography.

From ketone **81**, protecting group adjustments were required before the enyne metathesis reactions could be attempted. Treatment of ketone **81** with TsOH in MeOH resulted in cleavage of the acetonide and the five TBS protecting groups, and subsequent ketalisation to give pyranose **82** as an inseparable 1.3 : 1 mixture of anomers in 64% yield (Scheme 9). Reprotection of the free hydroxy groups then gave pyranoside **83** (54%), from which the terminal alkyne was liberated by removal of the TMS group to give compound **84** (84%). Finally, the pivalate group was excised using Super Hydride®, yielding alcohol **85** (74%). An alternative alkyne coupling partner, compound **86**, was prepared directly from pyranose **82** by cleavage of the alkynyl TMS group in an unoptimised yield of 30%, to provide a substrate which lacks the steric congestion imposed by the five bulky TBS groups.

With alkynes **85** and **86** in hand, the stage was set for the enyne cross-metathesis reactions. Unfortunately, and despite numerous attempts and extensive variation of the reaction parameters, cross-metathesis between either **85** or **86** and any one of **72**, **73**, or **75**–**78** was never observed (Scheme 10). Eventually, it was found that, when alkyne **85** was exposed to second-generation ruthenium carbene **88** [35] in CH_2Cl_2 saturated with ethylene[36] under microwave irradiation,[37] cross-metathesis did occur cleanly, to give diene **91** in 80% yield. Disappointingly, however, and for reasons that are presently unclear, diene **91** proved to be resistant to alkene cross-metathesis with any of the C1–C4 terminal alkene coupling partners **72**, **73**, or **75**–**78**.

With cross-metathesis proving not to be a viable means to establish the 1,3-diene system, it was decided to reverse the order of the fragment coupling and ring-closure steps. Thus, as shown in Scheme 11, alcohol **85** underwent a rapid esterification with acid **75** under Yamaguchi conditions[38] to give enyne **94** (92%), which contains all of the carbon atoms required to reach the target natural product (**1**). However, a similar story unfolded with regard to the ring-closing metathesis macrocyclisation as was seen with the attempted cross-metathesis processes. Enyne **94** could not be cyclised directly to generate macrocyclic compound **95**, but was cleanly converted into diene **96** in 60% yield upon microwave irradiation in the presence of catalyst **88** under an ethylene atmosphere. Diene **96** was apparently all but inert to further productive metathesis events, failing either to cyclise to the corresponding macrocycle (**95**) or to undergo a significant degree of oligomerisation, despite prolonged exposure (under microwave irradiation or purely thermal conditions) to the ruthenium-based catalysts **87**–**89** or the highly active Schrock molybdenum-based catalyst **97**.[39]

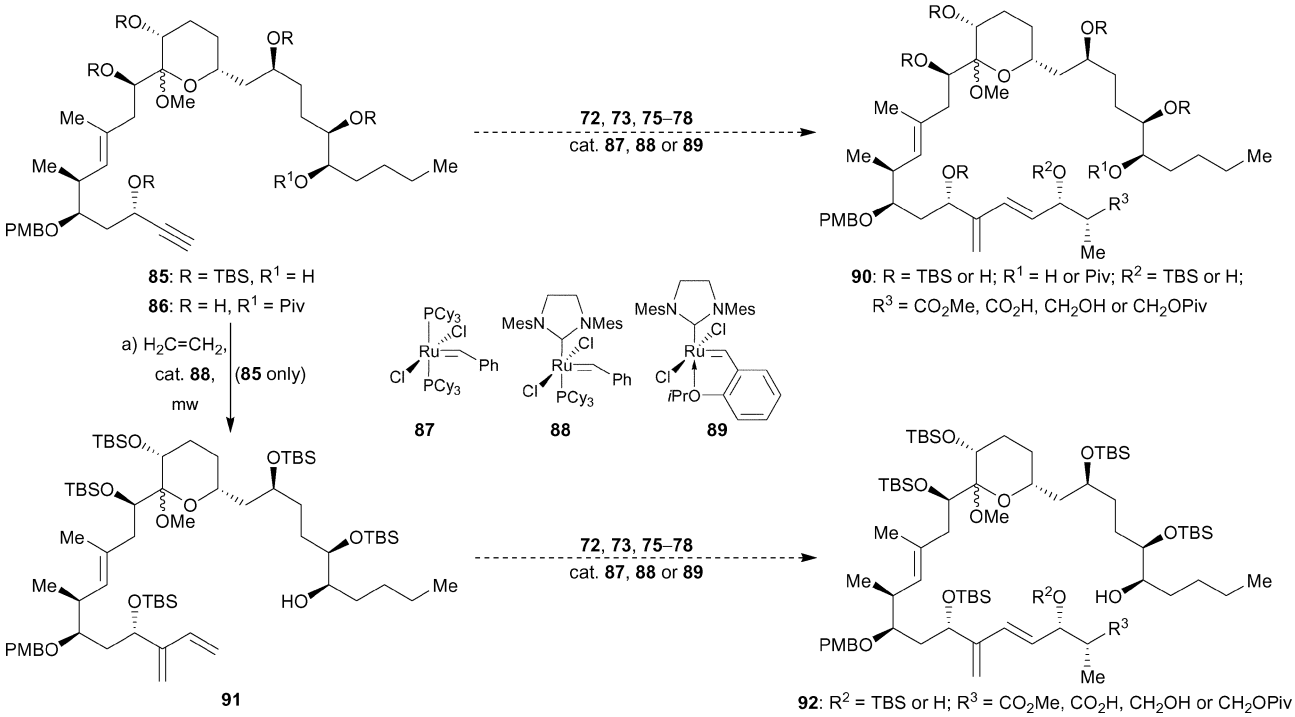


Scheme 9 Elaboration of ketone **81**. *Reagents and conditions*: a) TsOH·H_2O (2 × 0.5 equiv.), MeOH–CH_2Cl_2 (4 : 1), 25 °C, 20 h, 64%; b) TBSOTf (7.5 equiv.), 2,6-lutidine (15.0 equiv.), CH_2Cl_2, −78 → 0 °C, 1.5 h, 54%; c) K_2CO_3 (10.0 equiv.), MeOH–Et_2O (5 : 1), 25 °C, 4 h, 84%; d) Super Hydride® (4.0 equiv.), THF, 0 °C, 1.5 h, 74%; e) K_2CO_3 (10.0 equiv.), MeOH–Et_2O (4 : 1), 25 °C, 4 h, 30%. Super Hydride® = lithium triethylborohydride; Ts = 4-toluenesulfonyl.

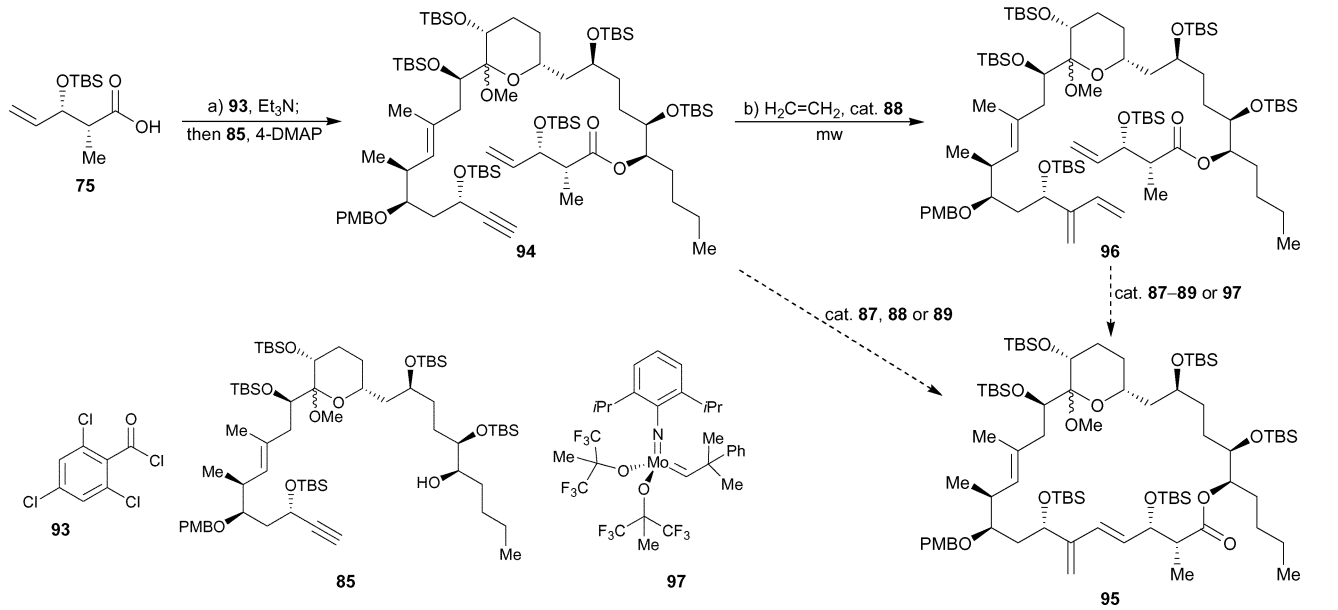
In the light of the reluctance of enyne **94** to undergo ring-closing metathesis macrocyclisation, it was proposed that a protecting group-free substrate could, potentially, adopt a more 'natural product-like' conformation that would be more amenable to ring-closure. Therefore, enyne **94** was treated with DDQ in a biphasic CH_2Cl_2/aqueous buffer solvent system to effect the selective cleavage of the PMB group in 89% yield (Scheme 12). Oxidation of the resulting alcohol (**98**) to the corresponding ketone (**99**) was most effectively carried out using the TPAP/NMO system[40] (76% yield), which avoided epimerisation of the sensitive C10 stereocentre. Global deprotection was then carried out by exposure of ketone **99** to 48% aq. HF in acetonitrile/CH_2Cl_2 at room temperature. Under these conditions, an inseparable 1 : 1 mixture of the desired hemiacetal **100** and the unexpected bicyclic acetal **101** was formed, a phenomenon which will be elaborated upon more fully in the following paper in this issue,[15] in 66% yield. To our dismay, however, the mixture of enynes **100** and **101** also failed to undergo ring-closing metathesis macrocyclisation, in this case to generate macrolide **102** (or the corresponding bicyclic acetal). This result was particularly galling in view of the fact that, had the ring-closure been successful, only one further step would have been required to complete the synthesis of the first stereoisomer of amphidinolide N (**1**).

At this point we began to consider alternative methods for the construction of the latent diene system contained within the C1–C13 sector of amphidinolide N (**1**) and caribenolide I (**2**), and reasoned that it could be accessed through a Stille coupling reaction[41] between a vinyl bromide of generic structure **103** (Scheme 13) and a C1–C5 vinyl stannane fragment **104**.

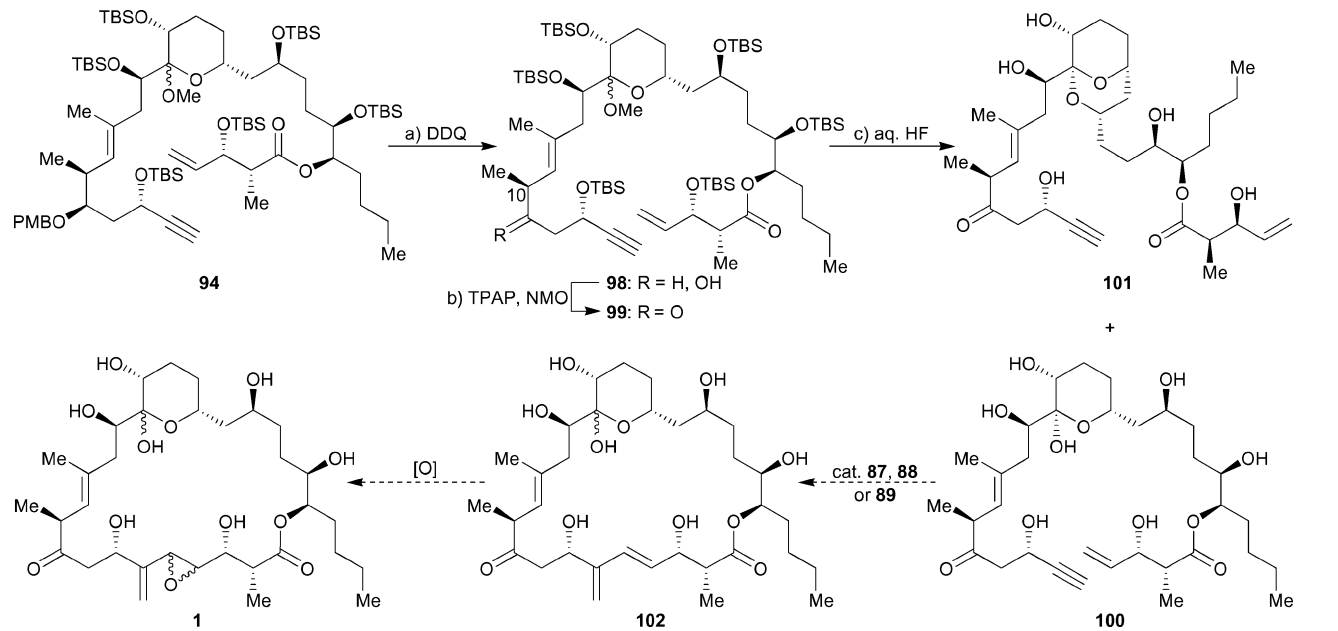
The synthesis of the vinyl bromide coupling partner began with the Evans aldol reaction of *N*-acyloxazolidinone **105** with



Scheme 10 Attempted enyne and alkene cross-metathesis fragment coupling processes. *Reagents and conditions*: a) **88** (2 × 0.05 equiv.), $CH_2{=}CH_2$ (1 atm), CH_2Cl_2, microwaves (100 W), 55 °C, 2 × 20 min and 1 × 50 min, 80%.

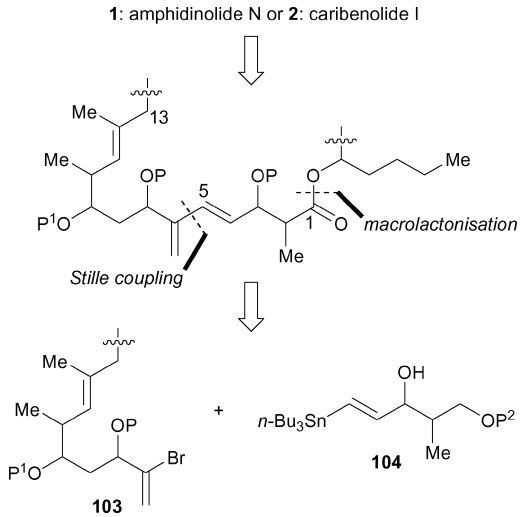


Scheme 11 Attempted enyne and alkene ring-closing metathesis macrocyclisation processes. *Reagents and conditions*: a) **75** (5.0 equiv.), Et_3N (10.0 equiv.), 2,4,6-trichlorobenzoyl chloride **93** (5.0 equiv.), toluene, 25 °C, 2 h, then **85** (1.0 equiv.), 4-DMAP (cat.), 25 °C, 45 min, 92%; b) **88** (2 × 0.05 equiv.), CH_2=CH_2 (1 atm), CH_2Cl_2, microwaves (100 W), 55 °C, 2 × 20 min and 1 × 50 min, 60%. 4-DMAP = 4-dimethylaminopyridine.

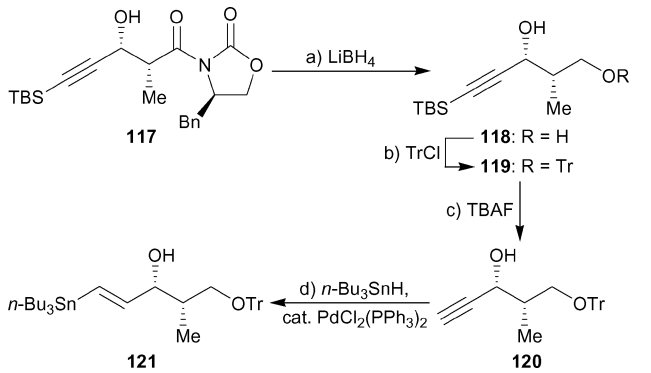


Scheme 12 Global deprotection of alkyne **94**, and attempted enyne ring-closing metathesis macrocyclisation. *Reagents and conditions*: a) DDQ (1.7 equiv.), CH_2Cl_2–pH 7 aq. buffer (2 : 1), 0 °C, 40 min, 89%; b) NMO (5.0 equiv.), 4 Å MS, CH_2Cl_2, 25 °C, 10 min, then TPAP (1.0 equiv.), 25 °C, 1.5 h, 76%; c) 48% aq. HF, MeCN–CH_2Cl_2 (8 : 1), 0 → 25 °C, 4 h, 66%. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; MS = molecular sieves; NMO = 4-methylmorpholine *N*-oxide; TPAP = tetra-*n*-propylammonium perruthenate.

2-bromoacrolein **106**,[42] to afford the *syn*-aldol adduct **107** as a single stereoisomer in 82% yield (Scheme 14). Following the procedure of Crich *et al.*,[43] treatment of compound **107** with zinc dust and solid ammonium chloride in methanol resulted in selective dechlorination to give the formal acetate aldol product **108** in 81% yield, with only a small amount (< 5%) of competing debromination. Silyl ether protection of the free hydroxy group in bromide **108** was followed by reductive cleavage of the oxazolidinone chiral auxiliary from compound **109**, and subsequent re-oxidation of the resulting primary alcohol (**110**) to the corresponding aldehyde (**111**, 72% from **108**).[44] A Brown crotylboration[45] of aldehyde **111** then installed the C9 and C10 vicinal stereocentres in good yield (84%) and with >98% diastereoselectivity. Trityl tetrafluoroborate (see Scheme 4) was the optimum acid catalyst for the conversion of the resulting alcohol (**112**) to PMB ether **113** using the trichloroacetimidate method,[46]



Scheme 13 Revised retrosynthetic analysis of the amphidinolide N (**1**) and caribenolide I (**2**) C1–C13 unit: cross-coupling approach.

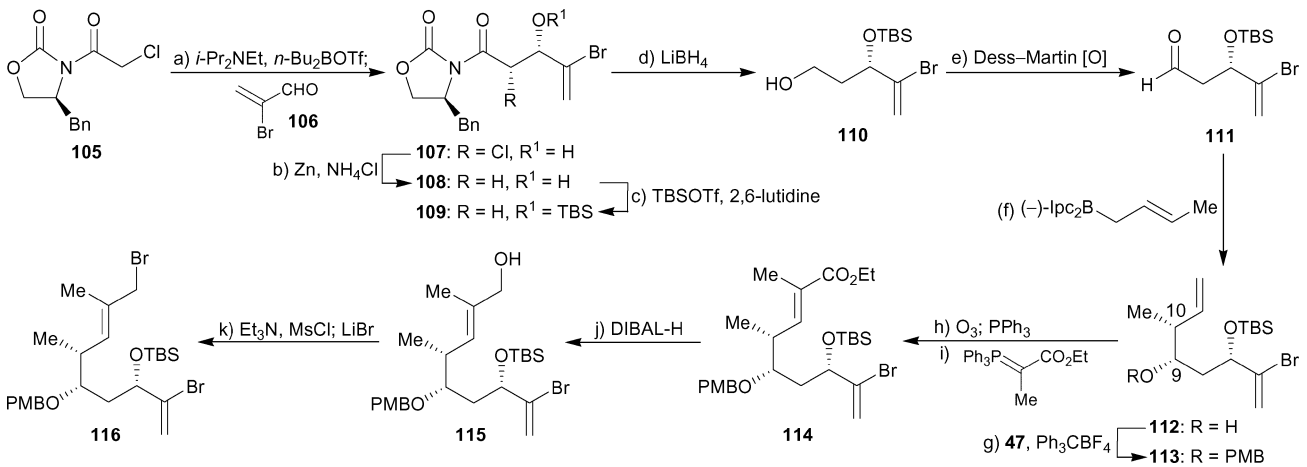


Scheme 15 Synthesis of vinyl stannane coupling partner **121**: cross-coupling approach. *Reagents and conditions*: a) $LiBH_4$ (2.5 equiv.), THF–MeOH (100 : 1), 0 → 25 °C, 3 h, 58%; b) TrCl (1.1 equiv.), Et_3N (1.6 equiv.), 4-DMAP (cat.), CH_2Cl_2, 25 °C, 8 h, 96%; c) TBAF (2.0 equiv.), THF, 25 °C, 2 h, 75%; d) $PdCl_2(PPh_3)_2$ (0.06 equiv.), *n*-Bu_3SnH (2.3 equiv.), THF, 25 °C, 61%. 4-DMAP = 4-dimethylaminopyridine; TBAF = tetra-*n*-butylammonium fluoride; Tr = triphenylmethyl.

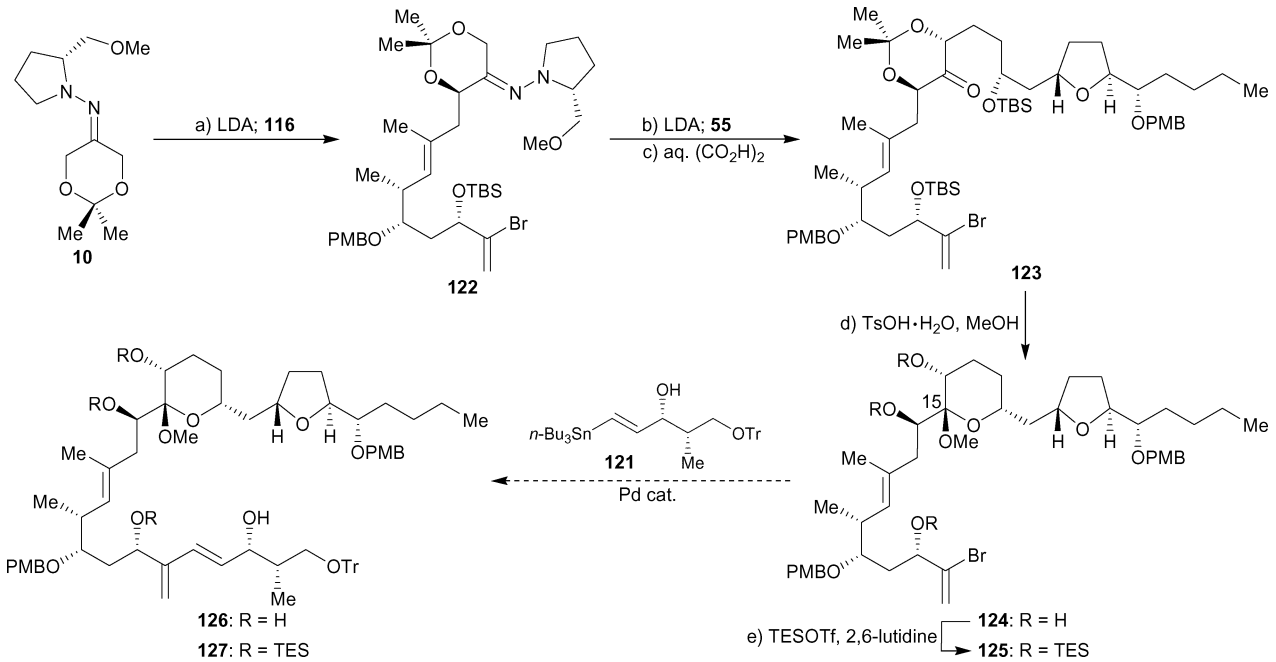
proving superior to either lanthanum triflate or PPTS. Selective ozonolysis of the terminal alkene in PMB ether **113** was followed by Wittig olefination of the crude aldehyde to give trisubstituted alkene **114** (58% for three steps from **112**). Reduction of the ester group (**114** → **115**, 87%) and subsequent bromination (92%) then completed the synthesis of C6–C13 vinyl bromide fragment **116**.

The C1–C4 vinyl stannane coupling partner **121** was prepared in four steps from alkyne **117**,[47] as shown in Scheme 15. Reductive cleavage of the oxazolidinone auxiliary gave diol **118** (58%), which was selectively tritylated at the primary hydroxy group to give secondary alcohol **119** in 96% yield. The latter was then treated with TBAF to effect the cleavage of the TBS group and afford alkyne **120** in 75% yield. Regioselective palladium-catalysed hydrostannylation[48] of terminal alkyne **120** then yielded stannane **121** (61%).

Following the alkylation protocols established earlier, hydrazone **10** was smoothly coupled with bromide **116** to give compound **122** in 91% yield (Scheme 16). This time, the second alkylation was performed using the caribenolide I C17–C29 iodide fragment **55** to give, following acidic hydrolysis of the crude reaction mixture to effect the cleavage of the hydrazone auxiliary, the highly functionalised ketone **123** in good overall yield (70%). Treatment of ketone **123** with TsOH in methanol led to the formation of triol **124** (57%), which could be silylated using TESOTf and 2,6-lutidine to give the fully protected substrate **125** in 87% yield. Pyranose **124** was isolated as a single stereoisomer, indicating



Scheme 14 Synthesis of amphidinolide N/caribenolide I C6–C13 coupling partner **116**: cross-coupling approach. *Reagents and conditions*: a) **105**, *i*-Pr_2NEt (1.25 equiv.), *n*-Bu_2BOTf (1.1 equiv.), CH_2Cl_2, −78 °C, 30 min, then **106** (3.0 equiv.), −78 → 25 °C, 21 h, 82%; b) Zn (4.0 equiv.), NH_4Cl (3.0 equiv.), MeOH, 25 °C, 6 h, 81%; c) TBSOTf (1.2 equiv.), 2,6-lutidine (1.3 equiv.), CH_2Cl_2, −78 → 25 °C, 2 h, 95%; d) $LiBH_4$ (2.5 equiv.), MeOH, −78 → 0 °C, 3 h, 85%; e) Dess–Martin periodinane (1.2 equiv.), $NaHCO_3$, CH_2Cl_2–DMSO (6 : 1), 25 °C, 1.5 h, 89%; f) KO*t*-Bu (1.5 equiv.), *trans*-2-butene (3.0 equiv.), *n*-BuLi (1.5 equiv.), THF, −45 °C, 30 min, then (+)-Ipc_2BOMe (1.5 equiv.), −78 °C, 1 h, then $BF_3{\cdot}OEt_2$ (1.1 equiv.), −78 °C, 30 min, then **111**, −78 °C, 3 h, then 3 M aq. NaOH, 35% aq. H_2O_2, 0 → 25 °C, 16 h, 84%; g) **47** (2.5 equiv.), Ph_3CBF_4 (0.03 equiv.), Et_2O, 25 °C, 18 h; h) O_3, CH_2Cl_2, −78 °C, then PPh_3 (4.4 equiv.), −78 → 25 °C, 1 h; i) (carbethoxyethylidene)triphenylphosphorane (1.3 equiv.), C_6H_6, 80 °C, 16 h, 58% (three steps); j) DIBAL-H (2.5 equiv.), toluene, 0 °C, 1 h, 87%; k) Et_3N (4.0 equiv.), MsCl (3.0 equiv.), THF, 0 °C, 1 h, then LiBr (10.0 equiv.), 0 → 25 °C, 30 min, 92%. DIBAL-H = diisobutylaluminum hydride; Ipc = isopinocampheyl; Ms = methanesulfonyl; TBS = *tert*-butyldimethylsilyl; Tf = trifluoromethanesulfonyl.



Scheme 16 Coupling of fragments **10**, **55** and **116**, and attempted Stille couplings. *Reagents and conditions*: a) **10** (1.15 equiv.), LDA (1.15 equiv.), THF, −78 °C, 2.5 h, then **116**, THF, −78 °C, 1 h, 91%; b) LDA (1.2 equiv.), THF, −78 °C, 1 h, then **55** (1.2 equiv.), THF, −78 °C, 1 h; c) sat. aq. $(CO_2H)_2$, Et_2O, 25 °C, 48 h, 70% (two steps); d) TsOH·H_2O (0.5 equiv.), MeOH–CH_2Cl_2 (5 : 1), 25 °C, 16 h, then Et_3N, 57%; e) TESOTf (5.0 equiv.), 2,6-lutidine (10.0 equiv.), CH_2Cl_2, −78 → −10 °C, 30 min, 87%. LDA = lithium diisopropylamide; TES = triethylsilyl; Tf = trifluoromethanesulfonyl; Ts = 4-toluenesulfonyl.

that only one anomer had been formed at the C15 position during the ketalisation step (**123b** → **124**). It was not possible to determine the configuration of this newly-formed chiral centre unambiguously, but we tentatively propose it to be the α-anomer, as depicted in Scheme 16. Thus, as is highlighted in Fig. 2(a), ROESY analysis of the TES-protected derivative **125** suggested

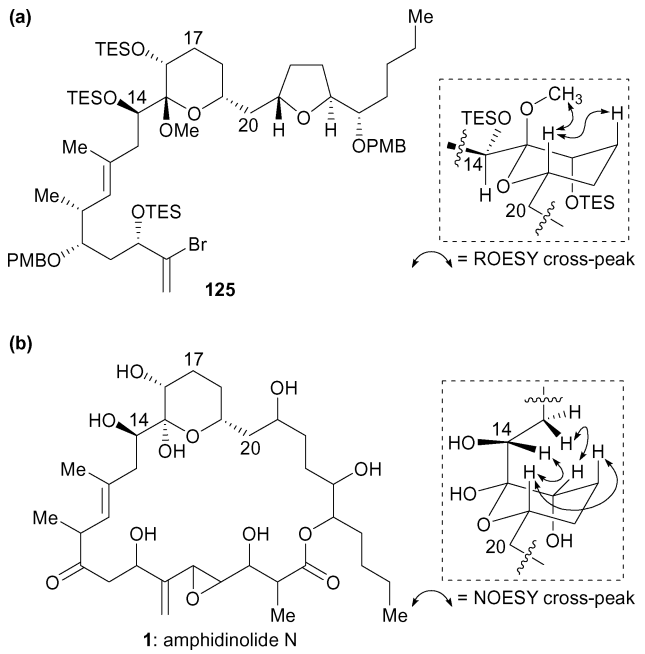
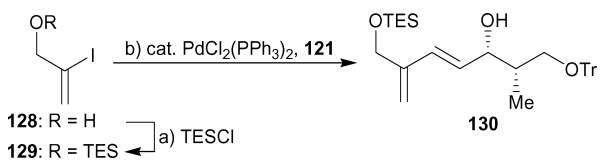


Fig. 2 Proposed stereochemistry of the C15–C19 tetrahydropyran system of (a) bromide **125**, (b) amphidinolide N (**1**).

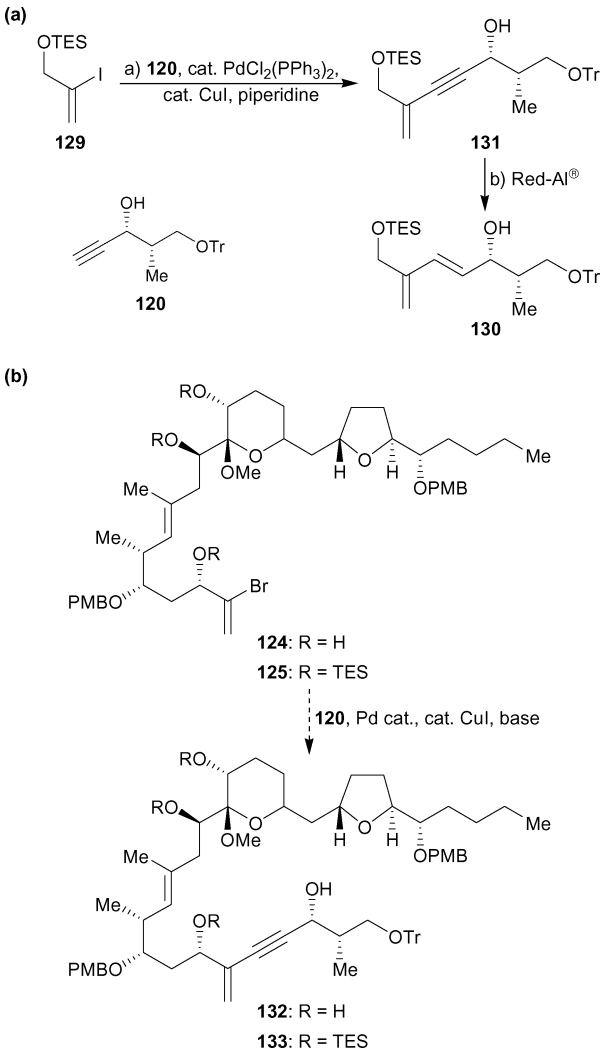
that the methoxy group occupies an axial position on the six-membered ring, stabilised by the anomeric effect, whilst the bulky C15 and C19 side chains reside in equatorial positions. This is in contrast to the conformation proposed for the C14–C19 subunit of amphidinolide N **1** [Fig. 2(b)], in which the side chain at the C15 position adopts an axial position, and which is presumably stabilised by intramolecular hydrogen-bonding.[11] Evidence for the conformation of **125** (and hence also that of **124**) being as shown in Fig. 2(a) is based largely on the following features of the ROESY spectrum of **125**: (1) an observable cross-peak between the C19 proton and the C15 methoxy group, and (2) the absence of observable cross-peaks between the C14 and C19 protons, and also between the C13 and C16 protons, with the latter two interactions both observed in the corresponding NOESY spectrum of amphidinolide N (**1**).[11]

Much to our chagrin, however, the coupling of vinyl stannane **121** and either of vinyl bromides **124** or **125** could not be effected under any one of a wide range of conditions (Scheme 16). The problem did not appear to lie with the vinyl stannane component (**121**) since, as shown in Scheme 17, this compound underwent cross-coupling with iodide **129** (prepared from the corresponding



Scheme 17 Stille coupling of iodide **129** with stannane **121**. *Reagents and conditions*: a) TESCl (1.2 equiv.), imidazole (2.5 equiv.), THF, 25 °C, 1.5 h, 45%; b) **121** (1.2 equiv.), $PdCl_2(PPh_3)_3$ (0.03 equiv.), THF, 25 → 60 °C, 24 h, 28%. TES = triethylsilyl.

alcohol **128**[49]) to give diene **130**, albeit in a low (unoptimised) yield of 28%. Furthermore, neither bromide **124** nor **125** could be induced to undergo cross-coupling with a variety of simpler, commercially available stannane reagents, such as tributyl(vinyl)tin.



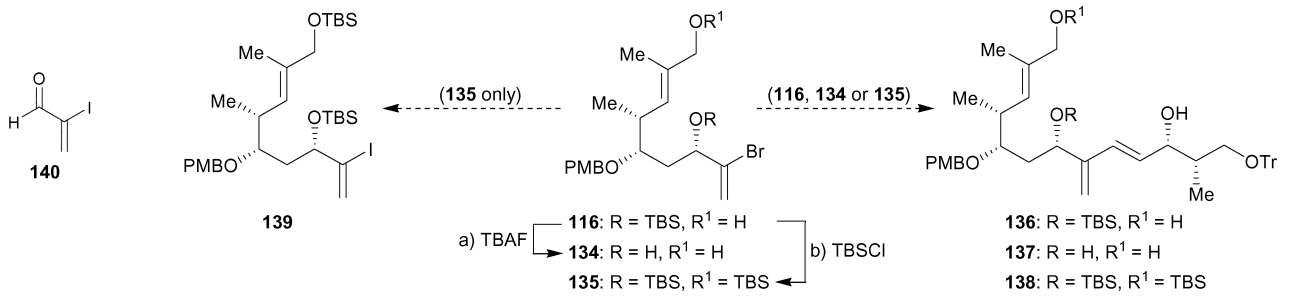
Scheme 18 (a) Sonogashira coupling/alkyne reduction route to diene **130**, (b) attempted Sonogashira couplings of bromides **124** or **125** with alkyne **120**. *Reagents and conditions*: a) **120** (0.77 equiv.), $PdCl_2(PPh_3)_2$ (0.04 equiv.), CuI (0.08 equiv.), Et_3N (7.7 equiv.), THF, 25 °C, 3.5 h, 64%; b) Red-Al® (4.0 equiv.), Et_2O, 0 °C, 1 h, 98%. Red-Al® = sodium bis(2-methoxyethoxy)aluminium hydride.

An alternative cross-coupling-based route to the diene system would involve a Sonogashira reaction[50] between bromides **124** or **125** and an appropriately substituted alkyne, followed by (*E*)-selective reduction of the triple bond in the resulting enyne system. In principle, this route seemed promising, as evidenced by the two-step conversion of iodide **129** to diene **130**, *via* alkyne **131**, in 63% yield [Scheme 18(a)]. In practice, when applied to the more elaborate bromides **124** or **125**, this method foundered on the recalcitrance of these substrates towards undergoing the required sp^2–sp^3 coupling with alkyne **120** [Scheme 18(b)].

Mindful that the steric bulk associated with the complete C6–C29 carbon framework in bromides **124** or **125** may have been impeding oxidative addition of palladium(0) complexes into the C6–Br bond, cross-couplings were attempted on the simpler bromides **116**, **134** and **135** (Scheme 19), but again to no avail. By now it was apparent that the intrinsic low reactivity of the C6–bromide towards oxidative addition, most likely due to the steric hindrance imposed by the adjacent C7 stereocentre, was going to preclude palladium-catalysed cross-couplings on this substrate from being a viable route to the diene system. It was therefore attempted to convert bromide **135** into the more reactive iodide species (**139**). Lithium–halogen exchange (with the intention of quenching the resulting lithiated species with an electrophilic iodine source) resulted in the rapid destruction of the starting material, whilst the direct Cu(I)-promoted conversion[51] of **135** to **139** was ineffectual. An alternative route to vinyl iodide **139** would have been to start from 2-iodoacrolein (**140**),[52] and elaborate as for the corresponding 2-bromo compound (*cf.* Scheme 14). Unfortunately, this was not possible due to the extreme instability of iodide **140** with respect to polymerisation, which prevented its isolation in a form pure enough for the subsequent Evans aldol reaction to be successful. At this point the cross-coupling routes to the 1,3-diene system were abandoned, since an alternative route that was concurrently under investigation was found to successfully provide access to the required diene system. This methodology could subsequently be applied to generate the complete macrocyclic frameworks of both amphidinolide N (**1**) and caribenolide I (**2**), and will be discussed in the following paper in this issue.[15]

Conclusion

Amphidinolide N (**1**) and caribenolide I (**2**) are structurally unique, marine-derived macrolide natural products which exhibit outstanding antitumour activity *in vitro*. With all of the originally



Scheme 19 Attempted cross-couplings of C6–C13 vinyl bromide derivatives. *Reagents and conditions*: a) TBAF (1.5 equiv.), THF, 0 → 25 °C, 1 h, 83%; b) TBSCl (2.0 equiv.), imidazole (3.0 equiv.), CH_2Cl_2, 25 °C, 1.5 h, 97%. TBAF = tetra-*n*-butylammonium fluoride; TBS = *tert*-butyldimethylsilyl.

isolated materials having been exhausted in preliminary assays, total synthesis currently represents the only viable means to access further quantities of these natural products, in order to allow both further biological investigation and also proof of structure and a complete stereochemical determination. We have developed stereoselective routes to fragments representing the entire carbon framework of both target compounds **1** and **2**. Construction of the 1,3-diene system embedded within key late-stage intermediates *en route* to both **1** and **2** has turned out to be a particularly challenging undertaking, with both metathesis- and cross-coupling-based procedures proving unsuccessful. Nevertheless, these synthetic forays have not only proven the enabling ability of the Enders hydrazone alkylation methodology to rapidly assemble the bulk of the molecular framework through fragment coupling reactions, but have also established potential end-game global deprotection manoeuvres. This intelligence gathering would prove to be invaluable in the revised strategy and final drive towards the macrocyclic frameworks of amphidinolide N (**1**) and caribenolide I (**2**), which is the subject of the following paper in this issue.[15]

Experimental

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions. Dry tetrahydrofuran (THF) and toluene were obtained by refluxing over sodium-benzophenone for one h, followed by distillation under argon. Dry methylene chloride (CH_2Cl_2), 1,2-dichloroethane, acetonitrile and diisopropylamine were obtained by refluxing over calcium hydride for one h, followed by distillation under argon. Benzene and diethyl ether (Et_2O) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Yields refer to chromatographically and spectroscopically (^{13}C-NMR) homogeneous materials, unless otherwise stated. Solvents were removed under reduced pressure using a Büchi R114 Rotavapor. Final traces of solvent were removed from samples using a Welch 1402 N high vacuum pump with pressures below 2 mmHg. Reactions were monitored by thin-layer chromatography (TLC) carried out on glass sheets pre-coated with silica (E. Merck silica gel 60 F_{254}), which were visualised by the quenching of UV fluorescence (λ_{max}254 nm) and/or by staining with 5% w/v phosphomolybdic acid in EtOH followed by heating. Flash chromatography was performed using E. Merck silica gel (60, particle size 40–60 μm). R_f values are quoted to ±0.01. Boiling points were obtained by short path distillation and are uncorrected. Melting points were obtained using a Thomas Hoover capillary melting point apparatus, and are uncorrected. Specific optical rotations were recorded on a Perkin-Elmer 343 polarimeter using the D-line of sodium at the specified temperature. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}; concentrations (c) are quoted in g 100 mL^{-1}. Infrared spectra were recorded as thin films between NaCl plates on a Perkin-Elmer 1600 series FT-IR spectrometer. Only significant absorption maxima (ν_{max}) are reported, and all absorptions are reported in wavenumbers (cm^{-1}). Proton magnetic resonance spectra (^{1}H-NMR) were recorded at 400, 500 or 600 MHz using Bruker AMX-400, DRX-500 and DRX-600 spectrometers. Chemical shifts (δ_H) are reported in parts per million (ppm), and are referenced to the residual protonated solvent peak. ^{1}H–^{1}H COSY, nOe or NOESY experiments were used in selected cases to aid assignment. The order of citation in parentheses is (1) number of equivalent nuclei (by integration), (2) multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet, br = broad), (3) coupling constant (J) quoted in Hertz (Hz) to the nearest 0.1 Hz, and (4) assignment. For clarity, the labelling of the protons corresponds to the numbering illustrated for the natural products (**1** and **2**) in Fig. 1. Carbon magnetic resonance spectra (^{13}C-NMR) were recorded at 125 or 150 MHz using Bruker DRX-500 and DRX-600 spectrometers. ^{1}H–^{13}C HSQC and HMBC experiments were used in selected cases to aid assignment. Chemical shifts (δ_C) are quoted in parts per million (ppm) and are referenced to the appropriate solvent peak. Fluorine magnetic resonance spectra (^{19}F-NMR) were recorded at 376 MHz using a Bruker AMX-400 spectrometer. Chemical shifts (δ_F) are quoted in parts per million (ppm). High resolution mass spectra (HRMS) were recorded on a VG ZAB-ZSE mass spectrometer using MALDI (matrix-assisted laser-desorption ionisation) or an Agilent ESI-TOF (electrospray time-of-flight) mass spectrometer at 4000 V emitter voltage.

Solutions of lithium diisopropylamide (LDA) were prepared by the dropwise addition of *n*-butyllithium (1.0 equiv.) a solution of diisopropylamine (1.0 equiv.) in the stated amount of THF at −78 °C and stirring for one h before the subsequent addition of the appropriate substrate. 4-Methoxybenzyl trichloroacetimidate (**47**) was prepared following the procedure of Organ and Wang.[53]

Hydrazone 10

To a stirred suspension of powdered, activated 4 Å molecular sieves (*ca.* 1.5 g) in CH_2Cl_2 (12 mL) were added ketone **14**[19] (1.1 g, 8.45 mmol) and (*R*)-(+)-1-amino-2-(methoxymethyl)pyrrolidine **15** (1.0 g, 7.68 mmol) at room temperature. After 2 h the mixture was diluted with Et_2O (20 mL) and filtered through a pad of Celite®, washing thoroughly with Et_2O. The filtrate was concentrated *in vacuo*, and the residue was purified by flash chromatography on silica gel (gradient: 25–40% Et_2O in hexanes with 2% Et_3N) to give **10** (1.82 g, 98%) as a colourless oil, the spectroscopic data of which were in agreement with those reported in the literature.[19] R_f = 0.20 (3 : 2 hexanes–Et_2O + 2% Et_3N); δ_H (400 MHz, $CDCl_3$) 4.54 (1 H, d, J 16.2 Hz, CH_2C=N), 4.31–4.35 (2 H, m, CH_2C=N and CH_2C=N), 4.24 (1 H, d, J 14.6 Hz, CH_2C=N), 3.39–3.43 (1 H, m, NCHCH$_2$OCH$_3$), 3.35 (3 H, s, CH$_2$OCH_3), 3.23–3.28 (2 H, m, CH_2OCH$_3$ and CH_2OCH$_3$), 3.04–3.09 (1 H, m, NCH_2CH$_2$), 2.46–2.52 (1 H, m, NCH_2CH$_2$), 1.96–2.03 (1 H, m, NCHCH_2), 1.79–1.88 (2 H, m, NCHCH_2 and NCH$_2$CH_2), 1.60–1.69 (1 H, m, NCH$_2$CH_2), 1.43 [3 H, s, O$_2$C(CH_3)$_2$], 1.40 [3 H, s, O$_2$C(CH_3)$_2$].

Epoxide 20[20]

To a stirred solution of TrCl (209.5 g, 754 mmol) in CH_2Cl_2 (900 mL) was added Et_3N (191 mL, 1.37 mol) at 0 °C, followed by a solution of (*S*)-(−)-glycidol (50.325 g, 679 mmol) in CH_2Cl_2 (100 mL) and a catalytic amount of 4-DMAP. The solution was allowed to warm to room temperature and stirred for 24 h, before the addition of sat. aq. NH_4Cl (1 L). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 500 mL). The organic layers were then dried ($MgSO_4$), filtered and concentrated

in vacuo. The residue was then partitioned between Et_2O (1 L) and water (500 mL). The layers were separated, and the organic layer was washed with brine (1 × 500 mL), dried ($MgSO_4$), and filtered through a pad of silica gel (10 cm × 10 cm), washing thoroughly with Et_2O. The filtrate was then concentrated *in vacuo* to give a yellow solid that was triturated from cold EtOH, and the product was collected by suction filtration and washed with cold EtOH to give **20** (186.7 g, 88%) as a white powder, the spectroscopic data of which were in agreement with those reported in the literature.[20] δ_H (500 MHz, $CDCl_3$) 7.47–7.50 (6 H, m, Ar*H*), 7.29–7.31 (6 H, m, Ar*H*), 7.22–7.25 (3 H, m, Ar*H*), 3.32–3.36 (1 H, m, 24-H), 3.12–3.17 (2 H, m, 24-H and 25-H), 2.75–2.77 (1 H, m, 26-H), 2.61–2.62 (1 H, m, 26-H); δ_C (125 MHz, $CDCl_3$) 143.8, 128.6, 127.8, 127.0, 86.7, 64.7, 51.0, 44.6.

Alcohol 21

Freshly prepared *n*-propylmagnesium bromide (500 mL, 2.36 M in THF, 1178 mmol) was added dropwise to a stirred suspension of CuI (22.47 g, 118 mmol) in THF (1 L) at −45 °C. After 30 min, a solution of epoxide **20** (186.4 g, 589 mmol) in THF (700 mL) was added dropwise over 1 h, and the resulting mixture was stirred for 20 min at −45 °C. The mixture was then carefully poured into a vigorously stirred solution of ice, water, and sat. aq. NH_4Cl (2 L). Et_2O (1 L) was added, and the mixture was stirred vigorously at room temperature for 10 min. Brine (500 mL) was added, the layers were separated, and the aqueous layer was extracted with Et_2O (2 × 1 L). The combined organic layers were dried ($MgSO_4$), filtered through Celite® and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient: 10–15% Et_2O in hexanes) to give **21** (206.7 g, 97%) as a colourless oil. R_f = 0.23 (silica gel, 21 : 4 hexanes–EtOAc); $[\alpha]_D^{25}$ −1.8° (*c* 1.88 in $CHCl_3$); ν_{max}/cm^{-1} (film) 3443, 3057, 2937, 1597, 1447, 1318, 1090, 762; δ_H (500 MHz, $CDCl_3$) 7.45–7.47 (6 H, m, Ar*H*), 7.29–7.33 (6 H, m, Ar*H*), 7.23–7.26 (3 H, m, Ar*H*), 3.75–3.81 (1 H, m, 25-H), 3.20 (1 H, dd, *J* 9.5, 3.3 Hz, 24-H), 3.06 (1 H, dd, *J* 9.5, 7.6 Hz, 24-H), 2.37 (1 H, br s, O*H*), 1.20–1.47 (6 H, m, 26-H, 26-H, 27-H, 27-H, 28-H and 28-H), 0.88 (3 H, t, *J* 7.1 Hz, 28-C*H*$_3$); δ_C (125 MHz, $CDCl_3$) 143.9, 128.6, 127.8, 127.0, 86.6, 70.9, 67.8, 33.0, 27.6, 22.6, 14.0; HRMS (ES^+) *m*/*z* calc. for $C_{25}H_{28}O_2Na$ ($[MNa]^+$): 383.1981, found: 383.1981.

p-Methoxybenzyl ether 22

A solution of alcohol **21** (205.5 g, 570 mmol) in THF (700 mL) was carefully added dropwise to a stirred suspension of NaH (34.2 g, 60% mineral oil dispersion, 855 mmol) in THF (1 L) at 0 °C, and the mixture stirred for 30 min at that temperature before warming to room temperature for 1 h. PMBCl (116 mL, 855 mmol) and tetra-*n*-butylammonium iodide (4.21 g, 11.4 mmol) were then added, and the solution was heated to 45 °C for 12 h, then to 55 °C for an additional 24 h. The reaction was then cooled to room temperature and cautiously quenched by the addition of sat. aq. NH_4Cl (1.5 L) and extracted with Et_2O (2 × 500 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 (gradient: 2–5% EtOAc in hexanes) to give **22** (224.2 g, 82%) as a pale orange oil. R_f = 0.39 (silica gel, 21 : 4 hexanes–EtOAc); $[\alpha]_D^{25}$ +19.0° (*c* 1.44 in $CHCl_3$); ν_{max}/cm^{-1} (film) 3058, 2869, 1613, 1448, 1248, 1091, 899; δ_H (500 MHz, $CDCl_3$) 7.52–7.54 (6 H, m, Ar*H*), 7.31–7.34 (8 H, m, Ar*H*), 7.24–7.26 (3 H, m, Ar*H*), 6.90 (2 H, d, *J* 8.6 Hz, Ar*H*), 4.69 (1 H, d, *J* 11.2 Hz, OC*H*$_2$Ar), 4.51 (1 H, d, *J* 11.2 Hz, OC*H*$_2$Ar), 3.81 (3 H, s, ArOC*H*$_3$), 3.55–3.59 (1 H, m, 25-H), 3.26 (1 H, dd, *J* 9.8, 5.8 Hz, 24-H), 3.17 (1 H, dd, *J* 9.8, 4.7 Hz, 24-H), 1.55–1.59 (2 H, m, 26-H and 26-H), 1.23–1.37 (4 H, m, 27-H, 27-H, 28-H and 28-H), 0.89 (3 H, t, *J* 7.1 Hz, 28-C*H*$_3$); δ_C (125 MHz, $CDCl_3$) 159.0, 144.2, 131.1, 129.4, 128.7, 127.7, 126.8, 113.7, 86.6, 78.2, 71.7, 66.2, 55.2, 31.8, 27.6, 22.7, 14.0; HRMS (ES^+) *m*/*z* calc. for $C_{33}H_{36}O_3Na$ ($[MNa]^+$): 503.2556, found: 503.2559.

Alcohol 23

To a suspension of protected diol **22** (145.1 g, 301 mmol) in MeOH (1.6 L) was added $TsOH{\cdot}H_2O$ (5.73 g, 30.1 mmol) in one portion at room temperature. After stirring for 20 min, Et_3N (14.3 mL) was added and the reaction mixture was concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (30% EtOAc in hexanes) to give **23** (64.88 g, 90%) as a pale yellow oil. R_f = 0.24 (silica gel, 3 : 2 hexanes–EtOAc); $[\alpha]_D^{25}$ −18.8° (*c* 0.86 in $CHCl_3$); ν_{max}/cm^{-1} (film) 3438, 2930, 1612, 1465, 1302, 1174, 822; δ_H (500 MHz, $CDCl_3$) 7.24 (2 H, d, *J* 8.7 Hz, Ar*H*), 6.85 (2 H, d, *J* 8.7 Hz, Ar*H*), 4.51 (1 H, d, *J* 11.2 Hz, OC*H*$_2$Ar), 4.44 (1 H, d, *J* 11.2 Hz, OC*H*$_2$Ar), 3.76 (3 H, s, ArOC*H*$_3$), 3.62 (1 H, dd, *J* 11.0, 2.9 Hz, 24-H), 3.42–3.49 (2 H, m, 24-H and 25-H), 2.22 (1 H, br s, O*H*), 1.54–1.60 (2 H, m, 26-H and 26-H), 1.26–1.32 (4 H, m, 27-H, 27-H, 28-H and 28-H), 0.87 (3 H, t, *J* 7.1 Hz, 28-C*H*$_3$); δ_C (125 MHz, $CDCl_3$) 159.1, 130.5, 129.3, 113.7, 79.4, 71.1, 64.1, 55.1, 30.5, 27.5, 22.8, 13.9; HRMS (MALDI-FTMS) *m*/*z* calc. for $C_{14}H_{22}O_3Na$ ($[MNa]^+$): 261.1461, found: 261.1463.

Aldehyde 24

A solution of DMSO (56.2 mL, 792 mmol) in CH_2Cl_2 (70 mL) was added dropwise over 20 min to a stirred solution of $(COCl)_2$ (34.5 mL, 396 mmol) in CH_2Cl_2 (1 L) at −78 °C. After 20 min, a solution of alcohol **23** (63.1 g, 264 mmol) in CH_2Cl_2 (400 mL) was added over 20 min, and the mixture was stirred for a further 30 min at −78 °C before the addition of Et_3N (221 mL, 1584 mmol) over 5 min. The mixture was allowed to warm to room temperature over 1 h, and was then poured into water (1 L). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 600 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: 10–15% EtOAc in hexanes) to give **24** (62.6 g, 99%) as a colourless oil. R_f = 0.49 (silica gel, 3 : 2 hexanes–EtOAc); $[\alpha]_D^{25}$ +59.0° (*c* 1.25 in $CHCl_3$); ν_{max}/cm^{-1} (film) 2959, 1732, 1514, 1378, 1249, 1094, 821; δ_H (500 MHz, $CDCl_3$) 9.58 (1 H, d, *J* 2.2 Hz, 24-H), 7.25 (2 H, d, *J* 8.7 Hz, Ar*H*), 6.86 (2 H, d, *J* 8.7 Hz, Ar*H*), 4.56 (1 H, d, *J* 11.4 Hz, OC*H*$_2$Ar), 4.45 (1 H, d, *J* 11.4 Hz, OC*H*$_2$Ar), 3.77 (3 H, s, ArOC*H*$_3$), 3.69 (1 H, td, *J* 6.5, 2.2 Hz, 25-H), 1.60–1.65 (2 H, m, 26-H and 26-H), 1.24–1.43 (4 H, m, 27-H, 27-H, 28-H and 28-H), 0.86 (3 H, t, *J* 7.2 Hz, 28-C*H*$_3$); δ_C (125 MHz, $CDCl_3$) 204.0, 159.4, 129.6, 129.4, 113.8, 83.1, 72.1, 55.2, 29.7, 26.8, 22.4, 13.8; HRMS (MALDI-FTMS) *m*/*z* calc. for $C_{14}H_{20}O_3Na$ ($[MNa]^+$): 259.1305, found: 259.1301.

Alcohol 26

A solution of aldehyde **24** (61.0 g, 258 mmol) in Et_2O (1.5 L) was cooled to 0 °C in a 5 L three-neck round-bottomed flask equipped with an addition funnel and a mechanical stirrer, then $MgBr_2{\cdot}OEt_2$ (106.7 g, 413 mmol) was added in one portion. After 10 min, allyltributyltin (136 mL, 439 mmol) was added dropwise over 10 min. After stirring for 3 h at 0 °C, the reaction was quenched by the addition of sat. aq. $NaHCO_3$ (1 L) and warmed to room temperature. The mixture was partitioned between Et_2O (1 L) and 5% aq. KF (1 L). The layers were separated and the organic layer was washed with brine (1 × 500 mL), and the combined aqueous layers were extracted with Et_2O (2 × 1 L). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient: 5–35% EtOAc in hexanes) to give **26** (70.95 g, 99%) as a colourless oil. $R_f = 0.20$ (silica gel, 4 : 1 hexanes–EtOAc); $[a]_D^{25}$ −17.2° (*c* 1.01 in $CHCl_3$); ν_{max}/cm^{-1} (film) 3451, 2932, 1613, 1465, 1249, 1088, 913; δ_H (500 MHz, $CDCl_3$) 7.24 (2 H, d, *J* 8.5 Hz, Ar*H*), 6.86 (2 H, d, *J* 8.5 Hz, Ar*H*), 5.83 (1 H, ddt, *J* 17.3, 10.3 and 7.0 Hz, 22-H), 5.05–5.09 (2 H, m, 21-H and 21-H), 4.56 (1 H, d, *J* 11.0 Hz, OCH_2Ar), 4.41 (1 H, d, *J* 11.0 Hz, OCH_2Ar), 3.77 (3 H, s, ArOCH_3), 3.52 (1 H, ddd, *J* 7.8, 5.5 and 4.8 Hz, 24-H), 3.28 (1 H, q, *J* 5.5 Hz, 25-H), 2.04–2.50 (3 H, m, 23-H, 23-H and O*H*), 1.58–1.65 (1 H, m, 26-H), 1.50–1.57 (1 H, m, 26-H), 1.26–1.36 (4 H, m, 27-H, 27-H, 28-H and 28-H), 0.89 (3 H, t, *J* 7.0 Hz, 28-CH_3); δ_C (125 MHz, $CDCl_3$) 159.2, 135.0, 130.5, 129.4, 117.1, 113.8, 81.0, 72.0, 72.0, 55.2, 38.1, 29.9, 27.4, 22.9, 14.0; HRMS (MALDI-FTMS) *m*/*z* calc. for $C_{17}H_{26}O_3Na$ ([MNa]$^+$): 301.1774, found: 301.1773.

t-Butyldimethylsilyl ether 27

TBSCl (64.43 g, 427.5 mmol) and a catalytic amount of 4-DMAP were added to a stirred solution of alcohol **26** (70.34 g, 252 mmol) and imidazole (42.8 g, 628.6 mmol) in CH_2Cl_2 (600 mL) at room temperature. After 16 h the reaction mixture was partitioned between brine (1 L) and CH_2Cl_2 (500 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 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: 2–4% EtOAc in hexanes) to give **27** (103.2 g, 95%) as a colourless oil. $R_f = 0.59$ (silica gel, 24 : 1 hexanes–EtOAc); $[a]_D^{25}$ +26.3° (*c* 1.52 in $CHCl_3$); ν_{max}/cm^{-1} (film) 2955, 2857, 1613, 1464, 1249, 1084, 1005, 836; δ_H (600 MHz, $CDCl_3$) 7.27 (2 H, d, *J* 8.6 Hz, Ar*H*), 6.88 (2 H, d, *J* 8.6 Hz, Ar*H*), 5.83 (1 H, ddt, *J* 17.2, 10.1 and 7.2 Hz, 22-H), 5.04 (1 H, d, *J* 17.2 Hz, 21-H), 5.02 (1 H, d, *J* 10.1 Hz, 21-H), 4.54 (1 H, d, *J* 11.4 Hz, OCH_2Ar), 4.47 (1 H, d, *J* 11.4 Hz, OCH_2Ar), 3.80 (3 H, s, ArOCH_3), 3.78–3.80 (1 H, m, 24-H), 3.30 (1 H, ddd, *J* 9.2, 4.3 and 2.9 Hz, 25-H), 2.37–2.41 (1 H, m, 23-H), 2.08–2.13 (1 H, m, 23-H), 1.60–1.66 (1 H, m, 26-H), 1.43–1.49 (1 H, m, 26-H), 1.36–1.42 (1 H, m, 27-H), 1.22–1.32 (3 H, m, 27-H, 28-H and 28-H), 0.89 (3 H, t, *J* 7.2 Hz, 28-CH_3), 0.88 [9 H, m, SiC(CH_3)$_3$], 0.03 (3 H, s, SiCH_3), 0.01 (3 H, s, SiCH_3); δ_C (150 MHz, $CDCl_3$) 159.1, 136.5, 131.1, 129.3, 116.4, 113.7, 81.6, 72.4, 72.0, 65.3, 36.3, 28.6, 28.4, 25.8, 22.8, 18.0, 14.1, −4.4; HRMS (ES$^+$) *m*/*z* calc. for $C_{23}H_{40}O_3SiNa$ ([MNa]$^+$): 415.2639, found: 415.2630.

Alcohol 28

$BH_3{\cdot}SMe_2$ (104 mL, 10.0 M, 1040 mmol) was added dropwise to a stirred solution of alkene **27** (102 g, 259.8 mmol) in THF (700 mL) at 0 °C. The solution was warmed to room temperature for 7 h, then was re-cooled to 0 °C before being quenched by the careful addition 3 M aq. NaOH (1.5 L) and Et_2O (500 mL), then the dropwise addition of 35% aq. H_2O_2 (700 mL) with vigorous stirring over 3 h. The solution was allowed to warm to room temperature overnight, then partitioned between brine (500 mL) and Et_2O (500 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (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: 15–25% EtOAc in hexanes) to give **28** (90.99 g, 85%) as a colourless oil. $R_f = 0.23$ (silica gel, 17 : 8 hexanes–EtOAc); $[a]_D^{25}$ +26.9° (*c* 1.57 in $CHCl_3$); ν_{max}/cm^{-1} (film) 3380, 2953, 1613, 1463, 1302, 1173, 893; δ_H (500 MHz, $CDCl_3$) 7.22 (2 H, d, *J* 8.6 Hz, Ar*H*), 6.84 (2 H, d, *J* 8.6 Hz, Ar*H*), 4.49 (1 H, d, *J* 11.4 Hz, OCH_2Ar), 4.43 (1 H, d, *J* 11.4 Hz, OCH_2Ar), 3.77 (3 H, s, ArOCH_3), 3.72–3.75 (1 H, m, 24-H), 3.57–3.60 (2 H, m, 21-H and 21-H), 3.28 (1 H, ddd, *J* 9.1, 4.6 and 2.7 Hz, 25-H), 1.88 (1 H, br s, O*H*), 1.53–1.71 (3 H, m, 22-H, 26-H and 26-H), 1.30–1.52 (4 H, m, 22-H, 23-H, 23-H and 27-H), 1.14–1.29 (3 H, m, 27-H, 28-H and 28-H), 0.83–0.86 [12 H, m, 28-CH_3 and SiC(CH_3)$_3$], 0.01 (3 H, s, SiCH_3), −0.02 (3 H, s, SiCH_3); δ_C (125 MHz, $CDCl_3$) 159.1, 131.0, 129.3, 113.7, 81.7, 72.4, 72.1, 63.1, 55.2, 29.5, 28.6, 28.4, 27.6, 25.8, 22.8, 18.0, 14.1, −4.4, −4.6; HRMS (ES$^+$) *m*/*z* calc. for $C_{23}H_{42}O_4SiNa$ ([MNa]$^+$): 433.2744, found: 433.2730.

Aldehyde 29

A solution of DMSO (43.5 mL, 613.6 mmol) in CH_2Cl_2 (60 mL) was added dropwise over 20 min to a stirred solution of $(COCl)_2$ (26.8 mL, 306.8 mmol) in CH_2Cl_2 (700 mL) at −78 °C. After 20 min, a solution of alcohol **28** (90.0 g, 219 mmol) in CH_2Cl_2 (300 mL) was added over 20 min, and the mixture stirred for 30 min at −78 °C before the addition of Et_3N (171 mL, 1227 mmol). The mixture was allowed to warm to room temperature over 1 h, and was then poured into water (1 L). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 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: 6–15% EtOAc in hexanes) to give **29** (83.53 g, 93%) as a colourless oil. $R_f = 0.24$ (silica gel, 8 : 1 hexanes–EtOAc); $[a]_D^{25}$ +27.0° (*c* 0.93 in $CHCl_3$); ν_{max}/cm^{-1} (film) 2955, 2715, 1727, 1513, 1361, 1173, 1005, 837; δ_H (600 MHz, $CDCl_3$) 9.75 (1 H, dd, *J* 1.7, 1.5 Hz, 21-H), 7.26 (2 H, d, *J* 8.6 Hz, Ar*H*), 6.87 (2 H, d, *J* 8.6 Hz, Ar*H*), 4.51 (1 H, d, *J* 11.3 Hz, OCH_2Ar), 4.44 (1 H, d, *J* 11.3 Hz, OCH_2Ar), 3.79 (3 H, s, ArOCH_3), 3.77–3.79 (1 H, m, 24-H), 3.29 (1 H, ddd, *J* 9.5, 4.4 and 2.6 Hz, 25-H), 2.51 (1 H, dddd, *J* 17.4, 8.6, 5.9 and 1.5 Hz, 22-H), 2.41 (1 H, dddd, *J* 17.4, 8.4, 6.7 and 1.7 Hz, 22-H), 1.96 (1 H, dddd, *J* 14.1, 8.6, 6.7 and 3.4 Hz, 23-H), 1.63–1.67 (1 H, m, 23-H), 1.58–1.62 (1 H, m, 26-H), 1.42–1.50 (1 H, m, 27-H), 1.34–1.40 (1 H, m, 26-H), 1.20–1.32 (3 H, m, 27-H, 28-H and 28-H), 0.88 (3 H, t, *J* 7.1 Hz, 28-CH_3), 0.86 [12 H, s, SiC(CH_3)$_3$], 0.01 (3 H, s, SiCH_3), 0.00 (3 H, s, SiCH_3); δ_C (150 MHz, $CDCl_3$) 202.7, 159.2, 130.9, 129.4, 113.7, 81.5, 72.0, 71.1, 55.3, 40.7, 28.7, 28.1,

25.8, 23.6, 22.7, 17.9, 14.1, −4.3, −4.7; HRMS (ES$^+$) m/z calc. for $C_{23}H_{40}O_4SiNa$ ([MNa]$^+$): 431.2588, found: 431.2570.

Alcohol 30

Allylmagnesium bromide (316 mL, 1.0 M in THF, 316 mmol) was added dropwise over 20 min to a stirred solution of (+)-Ipc_2BOMe (100 g, 316 mmol) in Et_2O (1.5 L) at −78 °C. After 15 min, the solution was warmed to room temperature for 1 h, then cooled to −78 °C, where a solution of aldehyde **29** (63.0 g, 154 mmol) in Et_2O (500 mL) was added over 20 min. After 3 h at −78 °C, the solution was warmed to 0 °C before the cautious addition of 3 M aq. NaOH (400 mL) over 90 min, followed by the dropwise addition of 35% aq. H_2O_2 (100 mL) over 1 h. After the addition of Et_2O (110 mL) and H_2O (700 mL), the mixture was allowed to stir overnight warming to room temperature. The layers were then separated, the aqueous layer was extracted with Et_2O (2 × 1 L), and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Most of the isopinocampheol by-product was removed by vacuum distillation (bath temperature 100–105 °C, 2 mmHg), and the residue was then purified by flash chromatography on silica gel (gradient: 10–25% Et_2O in hexanes) to give **30** (62.3 g, 90%) as a colourless oil. $R_f = 0.16$ (silica gel, 4 : 1 hexanes–EtOAc); $[a]_D^{25}$ +26.0° (*c* 0.55 in $CHCl_3$); ν_{max}/cm^{-1} (film) 3414, 2930, 1613, 1361, 1249, 1086, 836; δ_H (500 MHz, $CDCl_3$) 7.23 (2 H, d, *J* 8.5 Hz, Ar*H*), 6.84 (2 H, d, *J* 8.5 Hz, Ar*H*), 5.79 (1 H, dddd, *J* 17.2, 10.5, 7.5 and 7.0 Hz, 19-H), 5.07–5.11 (2 H, m, 18-H and 18-H), 4.49 (1 H, d, *J* 11.4 Hz, OCH_2Ar), 4.42 (1 H, d, *J* 11.4 Hz, OCH_2Ar), 3.77 (3 H, s, ArOCH_3), 3.71–3.74 (1 H, m, 24-H), 3.57–3.62 (1 H, m, 21-H), 3.28 (1 H, ddd, *J* 9.2, 4.6 and 2.7 Hz, 25-H), 2.23–2.28 (1 H, m, 20-H), 2.11–2.17 (1 H, m, 20-H), 1.90 (1 H, br s, O*H*), 1.55–1.57 (3 H, m, 22-H, 22-H and 23-H), 1.39–1.46 (1 H, m, 26-H), 1.33–1.38 (2 H, m, 26-H and 27-H), 1.21–1.28 (4 H, m, 23-H, 27-H, 28-H and 28-H), 0.85–0.89 [12 H, m, 28-CH_3 and SiC(CH_3)$_3$], 0.01 (3 H, s, SiCH_3), −0.02 (3 H, s, SiCH_3); δ_C (125 MHz, $CDCl_3$) 159.1, 134.9, 131.0, 129.3, 117.8, 113.7, 81.6, 72.6, 72.0, 71.1, 55.2, 41.8, 33.5, 28.5, 28.4, 27.5, 25.8, 22.8, 18.0, 14.1, −4.3, −4.6; HRMS (ES$^+$) m/z calc. for $C_{26}H_{46}O_4SiNa$ ([MNa]$^+$): 473.3057, found: 473.3060.

t-Butyldimethylsilyl ether 31

TBSCl (32.63 g, 216.5 mmol) and a catalytic amount of 4-DMAP were added to a stirred solution of alcohol **30** (61.1 g, 135 mmol) and imidazole (23.04 g, 338 mmol) in CH_2Cl_2 (600 mL) at room temperature. After 3 h, additional portions of TBSCl (20.0 g, 133 mmol) and imidazole (10.0 g, 147 mmol) were added. After an additional 4 h, the reaction mixture was partitioned between brine (1 L) and CH_2Cl_2 (500 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 400 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: 1–6% EtOAc in hexanes) to give **31** (68.0 g, 89%) as a colourless oil. $R_f = 0.67$ (silica gel, 4 : 1 hexanes–EtOAc); $[a]_D^{25}$ +20.0° (*c* 0.77 in $CHCl_3$); ν_{max}/cm^{-1} (film) 2923, 1613, 1463, 1361, 1172, 1041, 911; δ_H (500 MHz, $CDCl_3$) 7.25 (2 H, d, *J* 8.6 Hz, Ar*H*), 6.86 (2 H, d, *J* 8.6 Hz, Ar*H*), 5.80 (1 H, ddt, *J* 17.4, 10.3 and 7.2 Hz, 19-H), 5.01–5.05 (2 H, m, 18-H and 18-H), 4.52 (1 H, d, *J* 11.4 Hz, OCH_2Ar), 4.45 (1 H, d, *J* 11.4 Hz, OCH_2Ar), 3.79 (3 H, s, ArOCH_3), 3.66–3.72 (2 H, m, 21-H and 24-H), 3.27 (1 H, ddd, *J* 9.1, 4.5 and 2.7 Hz, 25-H), 2.20–2.23 (2 H, m, 20-H and 20-H), 1.59–1.72 (3 H, m, 22-H, 23-H and 26-H), 1.43–1.49 (1 H, m, 27-H), 1.21–1.41 (6 H, m, 22-H, 23-H, 26-H, 27-H, 28-H and 28-H), 0.90 [9 H, s, SiC(CH_3)$_3$], 0.87–0.89 [12 H, m, 28-CH_3 and SiC(CH_3)$_3$], 0.06 (6 H, s, SiCH_3 and SiCH_3), 0.03 (3 H, s, SiCH_3), 0.01 (3 H, s, SiCH_3); δ_C (125 MHz, $CDCl_3$) 159.0, 135.3, 131.2, 129.2, 116.6, 113.6, 81.9, 72.9, 72.3, 71.9, 55.2, 42.0, 33.7, 28.6, 28.5, 27.1, 25.9, 25.9, 22.8, 18.1, 18.0, 14.1, −4.3, −4.4, −4.5, −4.6; HRMS (ES$^+$) m/z calc. for $C_{32}H_{60}O_4Si_2Na$ ([MNa]$^+$): 587.3922, found: 587.3917.

Aldehyde 32

A solution of alkene **31** (57.0 g, 100.4 mmol) in CH_2Cl_2 (1 L) 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 (6.56 g, 25.0 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: 8–10% EtOAc in hexanes) to give **32** (52.1 g, 92%) as a colourless oil. $R_f = 0.26$ (silica gel, 8 : 1 hexanes–EtOAc); $[a]_D^{25}$ +27.3° (*c* 0.88 in $CHCl_3$); ν_{max}/cm^{-1} (film) 2956, 2712, 1727, 1513, 1361, 1172, 938; δ_H (500 MHz, $CDCl_3$) 9.76 (1 H, dd, *J* 2.7, 2.1 Hz, 19-H), 7.21 (2 H, d, *J* 8.6 Hz, Ar*H*), 6.83 (2 H, d, *J* 8.6 Hz, Ar*H*), 4.47 (1 H, d, *J* 11.4 Hz, OCH_2Ar), 4.44 (1 H, d, *J* 11.4 Hz, OCH_2Ar), 4.14–4.18 (1 H, m, 21-H), 3.75 (3 H, s, ArOCH_3), 3.66–3.69 (1 H, m, 24-H), 3.25 (1 H, ddd, *J* 9.1, 4.3 and 2.7 Hz, 25-H), 2.49 (1 H, ddd, *J* 15.6, 6.6 and 2.7 Hz, 20-H), 2.45 (1 H, ddd, *J* 15.6, 5.0 and 2.1 Hz, 20-H), 1.64–1.68 (2 H, m, 23-H and 26-H), 1.55–1.61 (1 H, m, 22-H), 1.42–1.47 (2 H, m, 22-H and 27-H), 1.20–1.37 (5 H, m, 23-H, 26-H, 27-H, 28-H and 28-H), 0.86 (3 H, t, *J* 7.1 Hz, 28-CH_3), 0.85 [9 H, s, SiC(CH_3)$_3$], 0.85 [9 H, s, SiC(CH_3)$_3$], 0.05 (3 H, s, SiCH_3), 0.03 (3 H, s, SiCH_3), −0.01 (3 H, s, SiCH_3), −0.02 (3 H, s, SiCH_3); δ_C (125 MHz, $CDCl_3$) 201.9, 159.1, 131.1, 129.2, 113.6, 81.8, 72.5, 72.0, 68.4, 55.1, 50.7, 34.5, 28.6, 28.4, 26.7, 25.8, 25.7, 22.7, 17.9, 17.9, 14.0, −4.4, −4.4, −4.6, −4.6; HRMS (ES$^+$) m/z calc. for $C_{31}H_{58}O_5Si_2Na$ ([MNa]$^+$): 589.3715, found: 589.3704.

Alcohol 33

Allylmagnesium bromide (215 mL, 1.0 M in THF, 215 mmol) was added dropwise over 20 min to a stirred solution of (+)-Ipc_2BOMe (68.1 g, 215 mmol) in Et_2O (1 L) at −78 °C. After 15 min, the solution was warmed to room temperature for 1 h, then cooled to −78 °C, where a solution of aldehyde **32** (58.6 g, 103 mmol) in Et_2O (350 mL) was added dropwise over 20 min. After 3 h at −78 °C, the solution was warmed to 0 °C before the cautious addition of 3 M aq. NaOH (300 mL) over 90 min, followed by the addition of 35% aq. H_2O_2 (75 mL) over 1 h. After the addition of Et_2O (100 mL) and H_2O (500 mL), the stirred mixture was allowed to warm to room temperature overnight. The layers were then separated, and the aqueous layer was extracted with Et_2O

(2 × 750 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Most of the isopinocampheol by-product was removed by vacuum distillation (bath temperature 100–105 °C, 2 mmHg), and the residue was then purified by flash chromatography on silica gel (gradient: 6–10% Et_2O in hexanes) to give **33** (59.79 g, 95%) as a colourless oil. $R_f = 0.39$ (silica gel, 3 : 1 hexanes–EtOAc); $[a]_D^{25}$ +32.4° (*c* 1.48 in $CHCl_3$); ν_{max}/cm^{-1} (film) 3474, 2955, 1613, 1463, 1302, 1172, 916, 774; δ_H (500 MHz, $CDCl_3$) 7.25 (2 H, d, *J* 8.6 Hz, Ar*H*), 6.87 (2 H, d, *J* 8.6 Hz, Ar*H*), 5.83 (1 H, ddt, *J* 17.3, 10.3 and 7.1 Hz, 17-H), 5.08–5.12 (2 H, m, 16-H and 16-H), 4.50 (1 H, d, *J* 11.4 Hz, OCH_2Ar), 4.47 (1 H, d, *J* 11.4 Hz, OCH_2Ar), 3.90–3.95 (1 H, m, 21-H), 3.79 (3 H, s, ArOCH_3), 3.77–3.81 (1 H, m, 19-H), 3.60–3.67 (1 H, m, 24-H), 3.28 (1 H, ddd, *J* 9.2, 4.4 and 2.7 Hz, 1H, 25-H), 3.07 (1 H, br s, O*H*), 2.22 (2 H, app t, *J* 6.8 Hz, 18-H and 18-H), 1.22–1.69 (12 H, m, 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), 0.88–0.90 [21 H, m, 28-CH_3, SiC(CH_3)$_3$ and SiC(CH_3)$_3$], 0.11 (3 H, s, SiCH_3), 0.11 (3 H, s, SiCH_3), 0.02 (3 H, s, SiCH_3), −0.01 (3 H, s, SiCH_3); δ_C (125 MHz, $CDCl_3$) 159.1, 134.9, 131.1, 129.2, 117.3, 113.7, 81.9, 73.2, 72.8, 72.0, 70.2, 55.2, 42.2, 42.1, 34.7, 28.6, 28.4, 26.1, 25.8, 25.8, 22.8, 18.0, 17.9, 14.0, −4.0, −4.4, −4.5, −4.7; HRMS (ES$^+$) *m*/*z* calc. for $C_{34}H_{64}O_5Si_2Na$ ([MNa]$^+$): 631.4184, found: 631.4159.

t-Butyldimethylsilyl ether 34

TBSCl (4.50 g, 29.9 mmol) and a catalytic amount of 4-DMAP were added to a stirred solution of alcohol **33** (9.13 g, 14.9 mmol) and imidazole (4.07 g, 59.8 mmol) in CH_2Cl_2 (70 mL) at room temperature. After 7 h, the reaction mixture was partitioned between brine (200 mL) and CH_2Cl_2 (100 mL). The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (2 × 100 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: 2–6% EtOAc in hexanes) to give **34** (10.22 g, 95%) as a colourless oil. $R_f = 0.33$ (silica gel, 24 : 1 hexanes–EtOAc); $[a]_D^{25}$ +14.9° (*c* 1.52 in $CHCl_3$); ν_{max}/cm^{-1} (film) 2955, 1612, 1463, 1252, 1091, 913; δ_H (500 MHz, $CDCl_3$) 7.27 (2 H, d, *J* 8.6 Hz, Ar*H*), 6.89 (2 H, d, *J* 8.6 Hz, Ar*H*), 5.84 (1 H, ddt, *J* 17.4, 9.7 and 7.1 Hz, 17-H), 5.05–5.07 (2 H, m, 16-H and 16-H), 4.54 (1 H, d, *J* 11.4 Hz, OCH_2Ar), 4.48 (1 H, d, *J* 11.4 Hz, OCH_2Ar), 3.81 (3 H, s, ArOCH_3), 3.77–3.82 (2 H, m, 19-H and 21-H), 3.72–3.75 (1 H, m, 24-H), 3.30 (1 H, ddd, *J* 8.9, 4.4 and 2.8 Hz, 25-H), 2.28–2.33 (1 H, m, 18-H), 2.16–2.20 (1 H, m, 18-H), 1.58–1.77 (5 H, m, 20-H, 20-H, 22-H, 23-H and 26-H), 1.45–1.52 (1 H, m, 27-H), 1.25–1.44 (6 H, m, 22-H, 23-H, 26-H, 27-H, 28-H and 28-H), 0.90–0.94 [30 H, m, 28-CH_3, SiC(CH_3)$_3$, SiC(CH_3)$_3$ and SiC(CH_3)$_3$], 0.07–0.09 (12 H, s, SiCH_3, SiCH_3, SiCH_3 and SiCH_3), 0.06 (3 H, s, SiCH_3), 0.04 (3 H, s, SiCH_3); δ_C (125 MHz, $CDCl_3$) 159.1, 135.0, 131.3, 129.2, 116.9, 113.7, 82.0, 72.9, 71.9, 69.7, 69.3, 55.2, 44.6, 42.0, 34.0, 28.7, 28.5, 26.9, 26.0, 25.9, 25.9, 22.8, 18.1, 18.1, 18.0, 14.1, −4.3, −4.3, −4.3, −4.4, −4.5, −4.5; HRMS (ES$^+$) *m*/*z* calc. for $C_{40}H_{78}O_5Si_3Na$ ([MNa]$^+$): 745.5049, found: 745.5050.

Aldehyde 35

A solution of alkene **34** (11.13 g, 15.4 mmol) in CH_2Cl_2 (100 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 (6.56 g, 25.0 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: 1–4% EtOAc in hexanes) to give **35** (10.07 g, 90%) as a colourless oil. $R_f = 0.29$ (silica gel, 8 : 1 hexanes–EtOAc); $[a]_D^{25}$ +24.8° (*c* 1.80 in $CHCl_3$); ν_{max}/cm^{-1} (film) 2956, 2715, 1728, 1613, 1386, 1251, 1006, 938; δ_H (500 MHz, $CDCl_3$) 9.80 (1 H, dd, *J* 3.0, 1.9 Hz, 17-H), 7.25 (2 H, d, *J* 8.6 Hz, Ar*H*), 6.87 (2 H, d, *J* 8.6 Hz, Ar*H*), 4.51 (1 H, d, *J* 11.4 Hz, OCH_2Ar), 4.47 (1 H, d, *J* 11.4 Hz, OCH_2Ar), 4.29–4.34 (1 H, m, 19-H), 3.79 (3 H, s, ArOCH_3), 3.69–3.74 (2 H, m, 21-H and 24-H), 3.28 (1 H, ddd, *J* 9.2, 4.4 and 2.7 Hz, 25-H), 2.60 (1 H, ddd, *J* 15.6, 4.4 and 1.9 Hz, 18-H), 2.48 (1 H, ddd, *J* 15.6, 6.7 and 3.0 Hz, 18-H), 1.78 (1 H, ddd, *J* 13.8, 7.1 and 5.6 Hz, 20-H), 1.56–1.68 (4 H, m, 20-H, 22-H, 23-H and 26-H), 1.43–1.50 (1 H, m, 27-H), 1.23–1.39 (6 H, m, 22-H, 23-H, 26-H, 27-H, 28-H and 28-H), 0.88–0.92 [30 H, m, 28-CH_3, SiC(CH_3)$_3$, SiC(CH_3)$_3$ and SiC(CH_3)$_3$], 0.08 (3 H, s, SiCH_3), 0.06 (6 H, s, SiCH_3 and SiCH_3), 0.05 (3 H, s, SiCH_3), 0.04 (3 H, s, SiCH_3), 0.02 (3 H, s, SiCH_3); δ_C (125 MHz, $CDCl_3$) 202.0, 159.1, 131.2, 129.2, 113.7, 81.9, 72.7, 72.0, 69.5, 65.7, 55.2, 50.8, 44.9, 34.1, 28.7, 28.4, 26.7, 25.9, 25.9, 25.7, 22.8, 18.0, 18.0, 17.9, 14.1, −4.2, −4.4, −4.4, −4.5, −4.5, −4.8; HRMS (ES$^+$) *m*/*z* calc. for $C_{39}H_{76}O_6Si_3Na$ ([MNa]$^+$): 747.4842, found: 747.4830.

Alcohol 36

$NaBH_4$ (1.04 g, 27.6 mmol) was added in one portion to a stirred solution of aldehyde **35** (10.0 g, 13.8 mmol) in MeOH (50 mL) at 0 °C. After 10 min, the reaction was quenched by the careful addition of sat. aq. NH_4Cl (50 mL) and was then concentrated under reduced pressure to remove most of the MeOH. The mixture was then diluted with water (100 mL) and extracted with EtOAc (3 × 75 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: 15–25% Et_2O in hexanes) to give **36** (9.86 g, 98%) as a viscous, colourless oil. $R_f = 0.31$ (silica gel, 4 : 1 hexanes–EtOAc); $[a]_D^{25}$ +6.0° (*c* 0.60 in $CHCl_3$); ν_{max}/cm^{-1} (film) 3454, 2955, 1612, 1471, 1360, 1251, 1092, 836; δ_H (500 MHz, $CDCl_3$) 7.25 (2 H, d, *J* 8.6 Hz, Ar*H*), 6.86 (2 H, d, *J* 8.6 Hz, Ar*H*), 4.51 (1 H, d, *J* 11.4 Hz, OCH_2Ar), 4.46 (1 H, d, *J* 11.4 Hz, OCH_2Ar), 4.04–4.09 (1 H, m, 19-H), 3.79 (3 H, s, ArOCH_3), 3.79–3.84 (1 H, m, 21-H), 3.68–3.72 (3 H, m, 17-H, 17-H and 24-H), 3.28 (1 H, ddd, *J* 9.2, 4.4 and 2.8 Hz, 25-H), 2.57 (1 H, br s, O*H*), 1.85–1.92 (1 H, m, 18-H), 1.58 (6 H, m, 18-H, 20-H, 20-H, 22-H, 23-H and 26-H), 1.43–1.49 (1 H, m, 27-H), 1.23–1.41 (6 H, m, 22-H, 23-H, 26-H, 27-H, 28-H and 28-H), 0.87–0.91 [30 H, m, 28-CH_3, SiC(CH_3)$_3$, SiC(CH_3)$_3$ and SiC(CH_3)$_3$], 0.10 (3 H, s, SiCH_3), 0.09 (3 H, s, SiCH_3), 0.05 (3 H, s, SiCH_3), 0.04 (3 H, s, SiCH_3), 0.03 (3 H, s, SiCH_3), 0.01 (3 H, s, SiCH_3); δ_C (125 MHz, $CDCl_3$) 159.1, 131.2, 129.2, 113.7, 81.9, 72.8, 72.0, 69.7, 69.4, 60.1, 55.2, 43.9, 37.6, 34.4, 28.7, 28.4, 26.5, 25.8, 25.8, 25.8, 22.8, 18.0, 18.0, 17.9, 14.1,

−4.2, −4.4, −4.4, −4.5, −4.5, −4.8; HRMS (ES$^+$) m/z calc. for $C_{39}H_{79}O_6Si_3$ ([MH]$^+$): 727.5179, found: 727.5184.

Iodide 37

To a stirred solution of alcohol **36** (9.85 g, 13.5 mmol) in benzene (90 mL) were added imidazole (3.76 g, 55.2 mmol), PPh_3 (7.24 g, 27.6 mmol), and I_2 (7.00 g, 27.6 mmol) sequentially at 0 °C. After warming to room temperature for 30 min, the reaction was quenched by the addition of sat. aq. $Na_2S_2O_3$ (100 mL), diluted with water (50 mL), and then extracted with Et_2O (3 × 75 mL). The combined organic layers were washed with sat. aq. $Na_2S_2O_3$ (1 × 100 mL), brine (1 × 100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was triturated with 4 : 1 hexanes–Et_2O, the precipitated Ph_3PO was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient: 1–2% Et_2O in hexanes) to give **37** (11.12 g, 98%) as a colourless oil. $R_f = 0.19$ (silica gel, 24 : 1 hexanes–EtOAc); $[a]_D^{25}$ +29.8° (*c* 0.45 in $CHCl_3$); ν_{max}/cm^{-1} (film) 2953, 1613, 1463, 1252, 1092, 909, 832; δ_H (500 MHz, $CDCl_3$) 7.23 (2 H, d, *J* 8.6 Hz, Ar*H*), 6.85 (2 H, d, *J* 8.6 Hz, Ar*H*), 4.49 (1 H, d, *J* 11.4 Hz, OCH_2Ar), 4.44 (1 H, d, *J* 11.4 Hz, OCH_2Ar), 3.78 (3 H, s, ArOCH_3), 3.78–3.81 (1 H, m, 19-H), 3.67–3.72 (2 H, m, 21-H and 24-H), 3.26 (1 H, ddd, *J* 9.2, 4.4 and 2.7 Hz, 25-H), 3.14–3.21 (2 H, m, 17-H and 17-H), 2.04–2.10 (1 H, m, 18-H), 1.88–1.95 (1 H, m, 18-H), 1.41–1.67 (6 H, m, 20-H, 20-H, 22-H, 23-H, 26-H and 27-H), 1.19–1.39 (6 H, m, 22-H, 23-H, 26-H, 27-H, 28-H and 28-H), 0.85–0.89 [30 H, m, 28-CH_3, SiC(CH_3)$_3$, SiC(CH_3)$_3$ and SiC(CH_3)$_3$], 0.07 (3 H, s, SiCH_3), 0.06 (3 H, s, SiCH_3), 0.05 (3 H, s, SiCH_3), 0.04 (3 H, s, SiCH_3), 0.02 (3 H, s, SiCH_3), −0.01 (3 H, s, SiCH_3); δ_C (125 MHz, $CDCl_3$) 159.0, 131.2, 129.2, 113.7, 81.9, 72.7, 71.9, 69.8, 69.5, 55.2, 44.4, 41.5, 34.2, 28.7, 28.4, 26.7, 25.9, 25.9, 25.8, 22.8, 18.0, 18.0, 18.0, 14.1, 2.3, −4.2, −4.2, −4.3, −4.3, −4.4, −4.4; HRMS (ES$^+$) m/z calc. for $C_{39}H_{77}IO_5Si_3Na$ ([MNa]$^+$): 859.4015, found: 859.3994.

Alcohol 38

DDQ (3.457 g, 15.2 mmol) was added in one portion to a vigorously stirred solution of **37** (7.52 g, 8.96 mmol) in CH_2Cl_2 (220 mL) and aqueous pH 7.0 buffer (75 mL) at room temperature. After 1 h, the reaction was quenched by the addition of sat. aq. $NaHCO_3$ (200 mL). The mixture was diluted with CH_2Cl_2 (100 mL), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 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: 2–4% EtOAc in hexanes) to give **38** (5.80 g, 90%) as a colourless oil. $R_f = 0.27$ (silica gel, 23 : 2 hexanes–EtOAc); $[a]_D^{25}$ +10.2° (*c* 0.99 in $CHCl_3$); ν_{max}/cm^{-1} (film) 3566, 2955, 1462, 1360, 1255, 1005, 938; δ_H (500 MHz, $CDCl_3$) 3.77–3.82 (1 H, m, 19-H), 3.69–3.74 (1 H, m, 21-H), 3.46–3.51 (1 H, m, 24-H), 3.37–3.41 (1 H, m, 25-H), 3.13–3.21 (2 H, m, 17-H and 17-H), 2.10 (1 H, br s, O*H*), 2.02–2.08 (1 H, m, 18-H), 1.88–1.95 (1 H, m, 18-H), 1.63–1.68 (2 H, m, 20-H, 23-H), 1.27–1.52 (10 H, m, 20-H, 22-H, 22-H, 23-H, 26-H, 26-H, 27-H, 27-H, 28-H and 28-H), 0.87–0.90 [30 H, m, 28-CH_3, SiC(CH_3)$_3$, SiC(CH_3)$_3$ and SiC(CH_3)$_3$], 0.08 (3 H, s, SiCH_3), 0.07 (3 H, s, SiCH_3), 0.06 (3 H, s, SiCH_3), 0.05 (3 H, s, SiCH_3), 0.05 (3 H, s, SiCH_3), 0.03 (3 H, s, SiCH_3); δ_H (125 MHz, $CDCl_3$) 75.3, 72.7, 69.7, 69.0, 44.1, 41.4, 33.6, 32.3, 28.7, 28.1, 25.9, 25.9, 25.8, 22.7, 18.0, 17.9, 17.9, 14.1, 2.0, −4.0, −4.2, −4.3, −4.4, −4.4, −4.7; HRMS (ES$^+$) m/z calc. for $C_{31}H_{70}IO_4Si_3$ ([MH]$^+$): 717.3621, found 717.3616.

Pivalate 39

Pyridine (1.43 mL, 17.6 mmol), freshly distilled PivCl (2.16 mL, 17.6 mmol), and a catalytic amount of 4-DMAP were added to a stirred solution of alcohol **38** (2.13 g, 2.93 mmol) in CH_2Cl_2 (15 mL) at 0 °C. After 2 h, the mixture was warmed to room temperature for 4 h before additional pyridine (1.43 mL, 17.6 mmol) and PivCl (2.16 mL, 17.6 mmol) were added. After a further 16 h, the reaction was then quenched by the addition of sat. aq. $NaHCO_3$ (50 mL), and extracted with CH_2Cl_2 (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 purified by flash chromatography on silica gel (gradient: 1–4% EtOAc in hexanes) to give **39** (1.537 g, 65%) as a colourless oil. $R_f = 0.48$ (silica gel, 23 : 2 hexanes–EtOAc); $[a]_D^{25}$ +26.9° (*c* 1.32 in $CHCl_3$); ν_{max}/cm^{-1} (film) 2955, 1728, 1428, 1256, 1093, 939, 837; δ_H (500 MHz, $CDCl_3$) 4.72 (1 H, dt, *J* 10.1, 3.2 Hz, 25-H), 3.78 (1 H, td, *J* 6.7, 4.6 Hz, 19-H), 3.71 (1 H, qn, *J* 5.6 Hz, 21-H), 3.56–3.60 (1 H, m, 24-H), 3.14 (2 H, t, *J* 7.3 Hz, 17-H and 17-H), 2.00–2.07 (1 H, m, 18-H), 1.87–1.94 (1 H, m, 18-H), 1.59–1.68 (3 H, m, 20-H, 22-H and 26-H), 1.43–1.54 (3 H, m, 20-H, 23-H and 26-H), 1.16 [9 H, s, $O_2CC(CH_3)_3$], 1.14–1.36 (6 H, m, 22-H, 23-H, 27-H, 27-H, 28-H, 28-H), 0.85–0.89 [30 H, m, 28-CH_3, SiC(CH_3)$_3$, SiC(CH_3)$_3$ and SiC(CH_3)$_3$], 0.09 (3 H, s, SiCH_3), 0.05 (3 H, s, SiCH_3), 0.04 (3 H, s, SiCH_3), 0.04 (3 H, s, SiCH_3), 0.03 (3 H, s, SiCH_3), 0.02 (3 H, s, SiCH_3); δ_C (125 MHz, $CDCl_3$) 177.8, 75.4, 72.2, 69.7, 69.1, 44.4, 41.5, 38.7, 33.8, 28.2, 27.3, 27.1, 27.0, 26.5, 25.9, 25.8, 25.8, 22.4, 18.0, 17.9, 17.9, 14.0, 1.8, −4.3, −4.3, −4.4, −4.4, −4.5, −4.5; HRMS (ES$^+$) m/z calc. for $C_{36}H_{78}IO_5Si_3$ ([MH]$^+$): 801.4196, found: 801.4191.

(2*S*)-5-Oxotetrahydrofuran-2-carboxylic acid 41 [24]

A solution of 2 N H_2SO_4 (600 mL) and a solution of $NaNO_2$ (82.8 g, 1.20 mol) in water (600 mL) were slowly added simultaneously to a vigorously stirred suspension of L-glutamic acid (147.13 g, 1.00 mol) in water (1 L) over 1 h (**CAUTION**: reaction is highly exothermic and involves the release of large quantities of NO_2 gas). Upon completion of the additions, the reaction was stirred at room temperature for a further 20 h, and then concentrated under reduced pressure, and azeotroped with toluene (2 × 250 mL). The residue was then triturated with boiling acetone (4 × 500 mL), the solids removed, and the filtrate was concentrated *in vacuo* to give a highly viscous, light yellow oil. The residue was dried under high vacuum (0.1 mmHg) for 1 h, then taken up in hot EtOAc (1 L), and stirred hot with $NaSO_4$ (100 g) for 1 h, before filtration to remove the solids, and concentration of the filtrate under reduced pressure. The residue was then stored at −20 °C overnight, where it solidified. The solid residue was triturated with cold $CHCl_3$, filtered, and washed with cold $CHCl_3$. The solid was collected and dried under vacuum (0.1 mmHg) to give **41** (62.4 g, 48%) as a colourless solid. The spectroscopic data were in accord with the literature.[24] δ_H (400 MHz, $CDCl_3$) 8.12 (1 H, s, CO_2H) 4.99–5.02 (1 H, s, 2-H), 2.55–2.70 (3 H, m, 3-H, 4-H and 4-H), 2.36–2.44 (1 H, m, 3-H).

Lactone 43 [25]

$(COCl)_2$ (8.72 mL, 100.0 mmol) was added dropwise to a stirred solution of acid **41** [24] (10.06 g, 77.0 mmol) in CH_2Cl_2 (100 mL) with a catalytic amount of DMF (0.1 mL) at room temperature in a round-bottomed flask equipped with a needle outlet to a gas bubbler. The solution was stirred until gas evolution ceased (*ca.* 3 h), and was then concentrated under reduced pressure, and the residue azeotroped with benzene (1 × 50 mL) to give a light pink residue that was dissolved in THF (250 mL) and cooled to −78 °C. Freshly prepared *n*-butylmagnesium bromide (73.5 mL, 1.0 M in THF, 73.5 mmol) was then added dropwise, and the solution was stirred for 1.5 h at −78 °C before being quenched by the addition of sat. aq. NH_4Cl (500 mL). After warming to room temperature, the mixture was extracted with EtOAc (3 × 200 mL), and the combined organic layers were washed with sat. aq. $NaHCO_3$ (1 × 400 mL), brine (1 × 400 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient: 33–50% EtOAc in hexanes) to give **43** (10.27 g, 82%) as a light yellow solid. R_f = 0.46 (silica gel, 1 : 1 hexanes–EtOAc); mp 36–37 °C; $[\alpha]_D^{25}$ −2.8° (*c* 1.07 in $CHCl_3$); ν_{max}/cm^{-1} (film) 2962, 2889, 1781, 1723, 1459, 1135, 1041; δ_H (600 MHz, $CDCl_3$) 4.80–4.82 (1 H, m, 24-H), 2.44–2.62 (5 H, m, 22-H, 22-H, 23-H, 26-H and 26-H), 2.16–2.23 (1 H, m, 23-H), 1.52–1.57 (2 H, m, 27-H and 27-H), 1.26–1.32 (2 H, m, 28-H and 28-H), 0.88 (3 H, t, *J* 7.4 Hz, 28-CH_3); δ_C (150 MHz, $CDCl_3$) 207.5, 176.0, 81.6, 38.4, 27.2, 24.8, 24.5, 22.1, 13.7; HRMS (ES^+) *m*/*z* calc. for $C_9H_{14}O_3Na$ ([MNa]$^+$): 193.0835, found: 193.0831.

Alcohol 44 [25]

K-Selectride® (66.0 mL, 1.0 M in THF, 66.0 mmol) was added dropwise to a stirred solution of ketone **43** (10.21 g, 60.0 mmol) in THF (240 mL) at −78 °C, and the resulting mixture was stirred at −78 °C for 1 h before warming to −10 °C for an additional 2 h. The reaction was then quenched by the careful addition of sat. aq. $NaHCO_3$ (500 mL) at −10 °C, and the mixture was warmed to room temperature before extraction with EtOAc (3 × 250 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (1 × 500 mL), brine (1 × 500 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient: 15–50% EtOAc in hexanes) to give **44** (7.43 g, 71%) as an oily solid. R_f = 0.34 (silica gel, 3 : 2 hexanes–EtOAc); $[\alpha]_D^{25}$ +25.9° (*c* 1.38 in $CHCl_3$); ν_{max}/cm^{-1} (film) 3460, 2931, 2861, 1766, 1461, 1184, 914; δ_H (500 MHz, $CDCl_3$) 4.39 (1 H, td, *J* 7.3, 4.3 Hz, 24-H), 3.50–3.53 (1 H, m, 25-H), 2.70 (1 H, br s, O*H*), 2.56 (1 H, ddd, *J* 17.7, 9.9 and 5.2 Hz, 22-H), 2.43–2.51 (1 H, m, 22-H), 2.16–2.23 (1 H, m, 23-H), 2.04–2.12 (1 H, m, 23-H), 1.40–1.53 (3 H, m, 26-H, 27-H and 27-H), 1.26–1.35 (3 H, m, 26-H, 28-H and 28-H), 0.86 (3 H, t, *J* 7.1 Hz, 28-CH_3); δ_C (125 MHz, $CDCl_3$) 177.6, 83.0, 73.3, 32.5, 28.6, 27.5, 23.9, 22.4, 13.8; HRMS (ES^+) *m*/*z* calc. for $C_9H_{16}O_3Na$ ([MNa$^+$]): 195.0992, found 195.0985.

p-Methoxybenzyl ether 46

$La(OTf)_3$ (0.851 g, 1.45 mmol) was added in one portion to a stirred solution of alcohol **44** (5.00 g, 29.0 mmol) and *p*-methoxybenzyl-2,2,2-trichloroacetimidate **47** (13.02 g, 46.5 mmol) in toluene (100 mL) at 0 °C. After 10 min the solution was concentrated *in vacuo*, and the residue was purified by flash chromatography on silica gel (gradient: 20–25% EtOAc in hexanes) to give **46** (7.69 g, 91%) as a light yellow oil. R_f = 0.47 (silica gel, 1 : 1 hexanes–EtOAc); $[\alpha]_D^{25}$ +4.8° (*c* 1.47 in $CHCl_3$); ν_{max}/cm^{-1} (film) 2928, 1774, 1726, 1586, 1358, 1177, 821; δ_H (600 MHz, $CDCl_3$) 7.24 (2 H, d, *J* 8.1 Hz, Ar*H*), 6.86 (2 H, d, *J* 8.1 Hz, Ar*H*), 4.49–4.57 (3 H, m, 24-H and OCH_2Ar), 3.78 (3 H, s, ArOCH_3), 3.36–3.39 (1 H, m, 25-H), 2.51–2.56 (1 H, m, 22-H), 2.40–2.46 (1 H, m, 22-H), 2.15–2.21 (1 H, m, 23-H), 1.91–1.97 (1 H, m, 23-H), 1.51–1.56 (2 H, m, 26-H and 26-H), 1.29–1.39 (4 H, m, 27-H, 27-H, 28-H and 28-H), 0.88 (3 H, t, *J* 7.0 Hz, 28-CH_3); δ_C (150 MHz, $CDCl_3$) 177.4, 159.1, 130.2, 129.4, 113.7, 81.9, 80.0, 72.2, 55.1, 29.4, 28.4, 27.4, 24.3, 22.6, 13.9; HRMS (ES^+) *m*/*z* calc. for $C_{17}H_{24}O_4Na$ ([MNa]$^+$): 315.1567, found: 315.1565.

Lactol 48a

A solution of DIBAL-H (3.3 mL, 1.0 M in toluene, 3.3 mmol) was added dropwise over 15 min to a stirred solution of lactone **46** (0.868 g, 3.0 mmol) in toluene (15.0 mL) at −78 °C. After stirring for an additional 30 min at −78 °C, the reaction was quenched by the addition of EtOAc (15 mL) and warmed to room temperature. The solution was then poured into a solution of sat. aq. Rochelle's salt (50 mL) and stirred vigorously at room temperature for 2 h. The mixture was then extracted with EtOAc (3 × 20 mL), and the combined organic layers were washed with brine (1 × 50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (20% EtOAc in hexanes) to give **48a** (0.786 g, 89%) as a light yellow oil and as an inseparable 1 : 1 mixture of anomers. R_f = 0.34 (silica gel, 1 : 1 hexanes–EtOAc); $[\alpha]_D^{25}$ −15.8° (*c* 1.09 in $CHCl_3$); ν_{max}/cm^{-1} (film) 3409, 2954, 1612, 1442, 1174, 982, 822. HRMS (ES^+) *m*/*z* calc. for $C_{17}H_{26}O_4Na$ ([MNa]$^+$): 317.1723, found: 317.1722.

Data for anomer (a). δ_H (500 MHz, C_6D_6) 7.30 (2 H, d, *J* 8.4 Hz, Ar*H*), 6.80 (2 H, d, *J* 8.4 Hz, Ar*H*), 5.56–5.58 (1 H, m, 21-H), 4.63 (1 H, d, *J* 11.3 Hz, OCH_2Ar), 4.51 (1 H, d, *J* 11.3 Hz, OCH_2Ar), 4.39 (1 H, app q, *J* 6.5 Hz, 24-H), 4.08 (1 H, d, *J* 2.6 Hz, O*H*), 3.29 (3 H, s, ArOCH_3), 3.23–3.26 (1 H, m, 25-H), 1.77–1.89 (3 H, m, 22-H, 23-H and 23-H), 1.54–1.64 (1 H, m, 26-H), 1.31–1.52 (4 H, m, 22-H, 26-H, 27-H and 27-H), 1.21–1.28 (2 H, m, 28-H and 28-H), 0.87 (3 H, t, *J* 7.3 Hz, 28-CH_3); δ_C (125 MHz, C_6D_6) 159.6, 131.8, 129.6, 113.9, 99.0, 81.2, 80.3, 72.4, 54.7, 33.4, 30.7, 28.1, 26.4, 23.3, 14.3.

Data for anomer (b). δ_H (500 MHz, C_6D_6) 7.26 (2 H, d, *J* 8.4 Hz, Ar*H*), 6.78 (2 H, d, *J* 8.4 Hz, Ar*H*), 5.50 (1 H, dd, *J* 7.0, 5.6 Hz, 21-H), 4.51 (1 H, d, *J* 11.1 Hz, OCH_2Ar), 4.47 (1 H, d, *J* 11.1 Hz, OCH_2Ar), 4.25 (1 H, d, *J* 7.0 Hz, O*H*), 4.02 (1 H, ddd, *J* 7.5, 7.2 and 4.6 Hz, 24-H) 3.31 (3 H, s, ArOCH_3), 3.14–3.17 (1 H, m, 25-H), 1.77–1.89 (1 H, m, 22-H), 1.70–1.77 (1 H, m, 23-H), 1.54–1.64 (2 H, m, 22-H and 26-H), 1.31–1.52 (4 H, m, 23-H, 26-H, 27-H and 27-H), 1.21–1.28 (2 H, m, 28-H and 28-H), 0.87 (3 H, t, *J* 7.3 Hz, 28-CH_3); δ_C (125 MHz, C_6D_6) 159.7, 131.0, 129.8, 114.1, 98.8, 81.8, 81.5, 72.4, 54.7, 34.7, 31.1, 28.1, 25.5, 23.3, 14.3.

Methyl furanoside 48b

PPTS (0.035 g, 0.14 mmol) was added in one portion to a stirred solution of lactol **48a** (0.400 g, 1.4 mmol) and 2,2-dimethoxypropane (0.26 mL, 2.1 mmol) in MeOH (5 mL) at room temperature. After 16 h the reaction was concentrated *in vacuo*, and then partitioned between brine (20 mL) and EtOAc (20 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 15 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 (10% EtOAc in hexanes) to give **48b** (0.375 g, 87%) as a light yellow oil. ^{1}H-NMR analysis revealed the compound to be a 1.2 : 1 mixture of anomers at C-21 which, for the purposes of characterisation, could be separated *via* careful flash chromatography on silica gel (10% Et_2O in hexanes).

Data for anomer (a). R_f = 0.75 (silica gel, 1 : 1 hexanes–EtOAc); $[\alpha]_D^{25}$ +47.3° (*c* 4.24 in $CHCl_3$); ν_{max}/cm^{-1} (film) 2954, 2833, 1612, 1459, 1202, 1040, 821; δ_H (500 MHz, C_6D_6) 7.29 (2 H, d, *J* 8.6 Hz, Ar*H*), 6.80 (2 H, d, *J* 8.6 Hz, Ar*H*), 4.95 (1 H, dd, *J* 3.9, 2.5 Hz, 21-H), 4.68 (1 H, d, *J* 11.3 Hz, OCH_2Ar), 4.53 (1 H, d, *J* 11.3 Hz, OCH_2Ar), 4.22–4.25 (1 H, m, 24-H), 3.32 (3 H, s, ArOCH_3), 3.28–3.32 (1 H, m, 25-H), 3.26 (3 H, s, OCH_3), 1.76–1.84 (3 H, m, 22-H, 23-H and 23-H), 1.31–1.51 (5 H, m, 22-H, 26-H, 26-H, 27-H and 27-H), 1.21–1.30 (2 H, m, 28-H and 28-H), 0.87 (3 H, t, *J* 7.3 Hz, 28-CH_3); δ_C (125 MHz, C_6D_6) 159.6, 132.1, 129.6, 113.9, 105.6, 81.0, 80.4, 77.6, 54.7, 54.5, 32.5, 30.9, 28.3, 26.2, 23.3, 14.3; HRMS (ES$^+$) *m*/*z* calc. for $C_{18}H_{28}O_4Na$ ([MNa]$^+$): 331.1880, found: 331.1870.

Data for anomer (b). R_f = 0.71 (silica gel, 1 : 1 hexanes–EtOAc); $[\alpha]_D^{25}$ −59.3° (*c* 5.03 in $CHCl_3$); ν_{max}/cm^{-1} (film) 2952, 2834, 1612, 1458, 1205, 1040, 821; δ_H (500 MHz, C_6D_6) 7.37 (2 H, d, *J* 8.5 Hz, Ar*H*), 6.70 (2 H, d, *J* 8.5 Hz, Ar*H*), 4.95 (1 H, d, *J* 11.2 Hz, OCH_2Ar), 4.86 (1 H, d, *J* 4.5 Hz, 21-H), 4.61 (1 H, d, *J* 11.2 Hz, OCH_2Ar), 4.04–4.08 (1 H, m, 24-H), 3.33 (3 H, s, ArOCH_3), 3.33–3.36 (1 H, m, 25-H), 3.25 (3 H, s, OCH_3), 1.81–1.84 (1 H, m, 22-H), 1.61–1.70 (1 H, m, 23-H), 1.44–1.54 (3 H, m, 22-H, 23-H and 26-H), 1.34–1.42 (3 H, m, 26-H, 27-H and 27-H), 1.18–1.29 (2 H, m, 28-H and 28-H), 0.86 (3 H, t, *J* 7.3 Hz, 28-CH_3); δ_C (125 MHz, C_6D_6) 159.5, 132.4, 129.5, 113.9, 105.3, 84.5, 83.2, 73.1, 54.8, 54.4, 33.2, 31.5, 28.1, 26.4, 23.2, 14.3; HRMS (ES$^+$) *m*/*z* calc. for $C_{18}H_{28}O_4Na$ ([MNa]$^+$): 331.1880, found: 331.1866.

Acetate 48c

Acetic anhydride (0.35 mL, 3.8 mmol) was added to stirred solution of lactol **48a** (0.786 g, 2.67 mmol), Et_3N (0.78 mL, 5.6 mmol) and 4-DMAP (0.0070 g, 0.08 mmol) in CH_2Cl_2 (13 mL) at room temperature. After 90 min, the mixture was concentrated *in vacuo*, and the residue was purified by flash chromatography on silica gel (25% EtOAc in hexanes) to give **48c** (0.807 g, 90%) as a colourless oil. ^{1}H-NMR analysis revealed the compound to be a 1 : 1 mixture of anomers which, for the purposes of characterisation, could be separated *via* careful flash chromatography on silica gel (10% Et_2O in hexanes).

Data for anomer (a). R_f = 0.42 (silica gel, 4 : 1 hexanes–Et_2O); $[\alpha]_D^{25}$ +34.2° (*c* 4.49 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 2954, 1741, 1612, 1466, 1302, 1086, 970, 823; δ_H (600 MHz, C_6D_6) 7.24 (2 H, d, *J* 8.3 Hz, Ar*H*), 6.78 (2 H, d, *J* 8.3 Hz, Ar*H*), 6.51 (1 H, d, *J* 5.1 Hz, 21-H), 4.55 (1 H, d, *J* 11.3 Hz, OCH_2Ar), 4.47 (1 H, d, *J* 11.3 Hz, OCH_2Ar), 4.28–4.31 (1 H, m, 24-H), 3.31 (3 H, s, ArOCH_3), 3.20 (1 H, app q, *J* 5.7 Hz, 25-H), 1.81–1.87 (1 H, m, 22-H), 1.67–1.74 (2 H, m, 22-H and 23-H), 1.66 (3 H, s, O_2CCH_3), 1.38–1.45 (4 H, m, 23-H, 26-H, 26-H, and 27-H), 1.26–1.32 (1 H, m, 27-H), 1.18–1.25 (2 H, m, 28-H and 28-H), 0.85 (3 H, t, *J* 7.3 Hz, 28-CH_3); δ_C (150 MHz, C_6D_6) 169.5, 159.6, 131.7, 129.6, 113.9, 99.3, 82.2, 80.5, 72.5, 54.7, 32.1, 30.5, 28.2, 25.4, 23.2, 21.0, 14.3; MS (ES$^+$) *m*/*z* calc. for $C_{19}H_{28}O_5Na$ ([MNa]$^+$): 359.18; found: 359.20.

Data for anomer (b). R_f = 0.33 (silica gel, 4 : 1 hexanes–Et_2O); $[\alpha]_D^{25}$ −36.1° (*c* 3.60 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 2955, 1736, 1612, 1466, 1302, 1082, 958, 849; δ_H (600 MHz, C_6D_6) 7.36 (2 H, d, *J* 8.4 Hz, Ar*H*), 6.80 (2 H, d, *J* 8.4 Hz, Ar*H*), 6.40 (1 H, d, *J* 3.7 Hz, 21-H), 4.86 (1 H, d, *J* 11.3 Hz, OCH_2Ar), 4.63 (1 H, d, *J* 11.3 Hz, OCH_2Ar), 4.00–4.03 (1 H, m, 24-H), 3.30 (3 H, s, ArOCH_3), 3.29–3.33 (1 H, m, 25-H), 1.69 (3 H, s, O_2CCH_3), 1.66–1.69 (1 H, m, 22-H), 1.39–1.52 (5 H, m, 22-H, 23-H, 23-H, 26-H and 27-H), 1.32–1.38 (2 H, m, 26-H and 27-H), 1.18–1.26 (2 H, m, 28-H and 28-H), 0.86 (3 H, t, *J* 7.2 Hz, 28-CH_3); δ_C (150 MHz, C_6D_6) 169.4, 159.6, 132.0, 129.8, 113.9, 98.8, 85.5, 81.8, 72.9, 54.7, 32.6, 31.3, 28.0, 25.6, 23.2, 21.1, 14.3; MS (ES$^+$) *m*/*z* calc. for $C_{19}H_{28}O_5Na$ ([MNa]$^+$): 359.18; found: 359.17.

***trans*-Allyltetrahydrofuran 49**

To a stirred solution of acetate **48c** (13.15 g, 39.1 mmol) and allyltrimethylsilane (15.5 mL, 97.5 mmol) in CH_2Cl_2 (200 mL) was added TMSOTf (0.71 mL, 3.9 mmol) dropwise at −78 °C. After 15 min, the reaction was quenched by the addition of sat. aq. $NaHCO_3$ (200 mL) and warmed to room temperature, before extraction with Et_2O (3 × 150 mL). The combined organic layers were washed with brine (1 × 150 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. ^{1}H-NMR analysis of the crude reaction mixture indicated the presence of a 3 : 1 mixture of diastereomers, based on the integration of the corresponding 21-H and 24-H protons. The major diastereomer was obtained in pure form after flash chromatography on silica gel (gradient: 2–10% Et_2O in hexanes) to give **49** (9.41 g, 75%) as a colourless oil. R_f = 0.32 (silica gel, 4 : 1 hexanes–Et_2O); $[\alpha]_D^{25}$ −16.9° (*c* 1.33 in $CHCl_3$); ν_{max}/cm^{-1} (film) 3072, 2942, 2860, 1608, 1461, 1173, 1038, 908; δ_H (500 MHz, C_6D_6) 7.35 (2 H, d, *J* 8.6 Hz, Ar*H*), 6.81 (2 H, d, *J* 8.6 Hz, Ar*H*), 5.89 (1 H, ddt, *J* 17.2, 10.2 and 7.0 Hz, 19-H), 5.02–5.09 (2 H, m, 18-H and 18-H), 4.82 (1 H, d, *J* 11.4 Hz, OCH_2Ar), 4.61 (1 H, d, *J* 11.4 Hz, OCH_2Ar), 3.92 (1 H, dt, *J* 7.8, 6.5 Hz, 24-H), 3.81 (1 H, app qn, *J* 6.5 Hz, 21-H), 3.31–3.36 (1 H, m, 25-H), 3.29 (3 H, s, ArOCH_3), 2.36 (1 H, ddd, *J* 13.6, 7.0 and 6.5 Hz, 20-H), 2.20 (1 H, ddd, *J* 13.6, 7.0 and 6.5 Hz, 20-H), 1.23–1.61 (10 H, m, 22-H, 22-H, 23-H, 23-H, 26-H, 26-H, 27-H, 27-H, 28-H and 28-H), 0.89 (3 H, t, *J* 7.3 Hz, 28-CH_3); δ_C (125 MHz, C_6D_6) 159.5, 135.7, 132.2, 129.7, 116.6, 113.9, 82.6, 81.4, 78.9, 72.8, 54.7, 40.8, 31.3, 30.6, 28.3, 27.9, 23.2, 14.3; HRMS (ES$^+$) *m*/*z* calc. for $C_{20}H_{30}O_3Na$ ([MNa]$^+$): 341.2087, found: 341.2096.

Aldehyde 50

A solution of alkene **49** (4.75 g, 15.0 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 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 (6.56 g, 25.0 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 (20% EtOAc in hexanes) to give **50** (4.33 g, 90%) as a colourless oil. $R_f = 0.16$ (silica gel, 4 : 1 hexanes–EtOAc); $[\alpha]_D^{25}$ −17.8° (*c* 1.12 in $CHCl_3$); ν_{max}/cm^{-1} (film) 2946, 2728, 1724, 1610, 1463, 1174, 818; δ_H (500 MHz, $CDCl_3$) 9.80 (1 H, dd, *J* 2.6, 1.9 Hz, 19-H), 7.26 (2 H, d, *J* 8.7 Hz, Ar*H*), 6.85 (2 H, d, *J* 8.7 Hz, Ar*H*), 4.60 (1 H, d, *J* 11.2 Hz, OCH_2Ar), 4.51 (1 H, d, 11.2 Hz, OCH_2Ar), 4.34 (1 H, dddd, *J* 7.4, 6.9, 6.5 and 5.3 Hz, 21-H), 3.94–3.98 (1 H, m, 24-H), 3.79 (3 H, s, ArOCH_3), 3.27–3.31 (1 H, m, 25-H), 2.68 (1 H, ddd, *J* 16.1, 7.4 and 2.6 Hz, 20-H), 2.59 (1 H, ddd, *J* 16.1, 5.3 and 1.9 Hz, 20-H), 2.08 (1 H, dddd, *J* 12.2, 8.5, 6.5 and 6.4 Hz, 22-H), 1.90 (1 H, dddd, *J* 12.4, 8.5, 7.0 and 5.7 Hz, 23-H), 1.66 (1 H, dddd, *J* 12.4, 9.4, 7.8 and 6.4 Hz, 23-H), 1.57 (1 H, dddd, *J* 12.2, 9.4, 6.9 and 5.7 Hz, 22-H), 1.39–1.47 (3 H, m, 26-H, 27-H and 27-H), 1.24–1.33 (3 H, m, 26-H, 28-H and 28-H), 0.88 (3 H, t, *J* 7.1 Hz, 28-CH_3); δ_C (125 MHz, $CDCl_3$) 201.5, 159.0, 131.1, 129.4, 113.6, 82.2, 80.9, 74.2, 72.4, 55.2, 49.6, 31.1, 30.6, 27.7, 27.5, 22.8, 14.0; HRMS (ES^+) *m*/*z* calc. for $C_{19}H_{28}O_4Na$ ([MNa]$^+$): 343.1880, found: 343.1882.

Alcohol 51

AllylMgBr (27.0 mL, 1.0 M in Et_2O, 27.0 mmol) was added to a stirred solution of (+)-Ipc_2BOMe (8.54 g, 27.0 mmol) in Et_2O (120 mL) at −78 °C. After 30 min, the mixture was warmed to room temperature for 1 h, then re-cooled to −78 °C, where a solution of aldehyde **50** (3.78 g, 11.8 mmol) in Et_2O (30 mL) was added dropwise, and the mixture stirred for 3 h at that temperature. The reaction was quenched by the addition of MeOH (10 mL) and warmed to 0 °C, where 3 M aq. NaOH (50 mL) was added, followed by the dropwise addition of 35% aq. H_2O_2 (11 mL) over 30 min. After warming to room temperature overnight, the mixture was extracted with Et_2O (3 × 50 mL), and 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: 10–35% Et_2O in hexanes) to give **51** (2.95 g, 69%) as a colourless oil. $R_f = 0.08$ (silica gel, 4 : 1 hexanes–EtOAc); $[\alpha]_D^{25}$ −13.9° (*c* 2.35 in $CHCl_3$); ν_{max}/cm^{-1} (film) 3447, 3067, 2924, 1609, 1461, 1243, 1076, 911; δ_H (500 MHz, $CDCl_3$) 7.27 (2 H, d, *J* 8.6 Hz, Ar*H*), 6.86 (2 H, d, *J* 8.6 Hz, Ar*H*), 5.82–5.86 (1 H, m, 17-H), 5.08–5.13 (2 H, m, 16-H and 16-H), 4.59 (1 H, d, *J* 11.1 Hz, OCH_2Ar), 4.53 (1 H, d, 11.1 Hz, OCH_2Ar), 4.16 (1 H, dtd, *J* 7.0, 6.8 and 4.0 Hz, 21-H), 3.91–3.95 (2 H, m, 19-H and 24-H), 3.80 (3 H, s, ArOCH_3), 3.30–3.32 (1 H, m, 25-H), 2.23–2.32 (2 H, m, 18-H and 18-H), 1.85–1.94 (2 H, m, 22-H and 23-H), 1.79 (1 H, ddd, *J* 14.3, 8.5 and 3.8 Hz, 20-H), 1.59–1.71 (3 H, m, 20-H, 22-H and 23-H), 1.46–1.51 (2 H, m, 27-H and 27-H), 1.23–1.44 (4 H, m, 26-H, 26-H, 28-H and 28-H), 0.88 (3 H, t, *J* 7.1 Hz, 28-CH_3); δ_C (125 MHz, $CDCl_3$) 159.0, 135.2, 131.0, 129.5, 117.3, 113.6, 81.8, 81.0, 77.3, 72.3, 68.3, 55.2, 41.9, 40.5, 30.7, 30.5, 27.8, 27.7, 22.8, 14.0; HRMS (ES^+) *m*/*z* calc. for $C_{22}H_{34}O_4Na$ ([MNa]$^+$): 385.2349, found: 385.2340.

t-Butyldimethylsilyl ether 52

Alcohol **51** (2.90 g, 8.0 mmol), imidazole (1.09 g, 16.0 mmol), and TBSCl (1.81 g, 12.0 mmol) were combined in CH_2Cl_2 (80 mL) at room temperature and the mixture was allowed to stir for 16 h. The reaction was then quenched by the addition of sat. aq. NH_4Cl (150 mL), and extracted with EtOAc (3 × 80 mL). The combined organic layers were 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 (10% EtOAc in hexanes) to give **52** (3.42 g, 90%) as a colourless oil. $R_f = 0.64$ (silica gel, 4 : 1 hexanes–EtOAc); $[\alpha]_D^{25}$ −45.4° (*c* 1.14 in $CHCl_3$); ν_{max}/cm^{-1} (film) 3447, 3067, 2924, 1609, 1461, 1243, 1076, 911; δ_H (500 MHz, $CDCl_3$) 7.29 (2 H, d, *J* 8.6 Hz, Ar*H*), 6.87 (2 H, d, *J* 8.6 Hz, Ar*H*), 5.83 (1 H, ddt, *J* 16.4, 10.8 and 7.2 Hz, 17-H), 5.03–5.06 (2 H, m, 16-H and 16-H), 4.73 (1 H, d, *J* 11.2 Hz, OCH_2Ar), 4.54 (1 H, d, *J* 11.2 Hz, OCH_2Ar), 3.91–4.01 (2 H, m, 19-H and 21-H), 3.85–3.87 (1 H, m, 24-H), 3.80 (3 H, s, ArOCH_3), 3.28–3.30 (1 H, m, 25-H), 2.20–2.31 (2 H, m, 18-H and 18-H), 1.93 (1 H, ddt, *J* 12.4, 8.7 and 6.4 Hz, 22-H), 1.82–1.84 (1 H, m, 23-H), 1.54–1.67 (3 H, m, 20-H, 20-H and 23-H), 1.41–1.48 (4 H, m, 22-H, 26-H, 27-H and 27-H), 1.24–1.35 (3 H, m, 26-H, 28-H and 28-H), 0.90 [9 H, s, SiC(CH_3)], 0.89 (3 H, t, *J* 7.3 Hz, 28-CH_3), 0.09 (3 H, s, SiCH_3), 0.08 (3 H, s, SiCH_3); δ_C (125 MHz, $CDCl_3$) 159.8, 135.0, 131.5, 129.5, 116.8, 113.6, 82.1, 81.4, 75.9, 72.5, 69.4, 55.2, 43.2, 42.9, 31.4, 30.9, 27.9, 27.7, 25.9, 22.8, 18.1, 14.1, −4.4, −4.7; HRMS (ES^+) *m*/*z* calc. for $C_{22}H_{34}O_4Na$ ([MNa]$^+$): 385.2349, found: 385.2340.

Aldehyde 53

A solution of alkene **52** (3.38 g, 7.1 mmol) in CH_2Cl_2 (70 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 (3.25 g, 12.4 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: 5–25% Et_2O in hexanes) to give **53** (3.02 g, 89%) as a colourless oil. $R_f = 0.56$ (silica gel, 3 : 1 hexanes–EtOAc); $[\alpha]_D^{25}$ −35.1° (*c* 1.53 in $CHCl_3$); ν_{max}/cm^{-1} (film) 2960, 2729, 1724, 1585, 1463, 1249, 1090, 837; δ_H (500 MHz, $CDCl_3$) 9.80 (1 H, dd, *J* 3.0, 2.2 Hz, 17-H), 7.29 (2 H, d, *J* 8.6 Hz, Ar*H*), 6.86 (2 H, d, *J* 8.6 Hz, Ar*H*), 4.66 (1 H, d, *J* 11.1 Hz, OCH_2Ar), 4.53 (1 H, d, *J* 11.1 Hz, OCH_2Ar), 4.37–4.39 (1 H, m, 19-H), 3.84–3.94 (2 H, m, 21-H and 24-H), 3.80 (3 H, s, ArOCH_3), 3.28–3.30 (1 H, m, 25-H), 2.64 (1 H, ddd, *J* 15.7, 5.4 and 2.2 Hz, 18-H), 2.51 (1 H, ddd, *J* 15.7, 5.5 and 3.0 Hz, 18-H), 1.95 (1 H, dddd, *J* 12.4, 8.7, 6.9 and 6.1 Hz, 22-H), 1.83 (1 H, dddd, *J* 12.4, 8.7, 6.9 and 5.9 Hz, 23-H), 1.75 (1 H, ddd, *J* 14.2, 8.1 and 3.4 Hz, 20-H), 1.70 (1 H, ddd, *J* 14.2, 8.9 and 4.9 Hz, 20-H), 1.61 (1 H, dddd, *J* 12.4, 9.8, 6.1 and 3.0 Hz, 23-H), 1.40–1.51 (4 H, m, 22-H, 26-H, 27-H and 27-H), 1.24–1.34 (3 H, m, 26-H, 28-H and 28-H), 0.88 (3 H, t, *J* 7.1 Hz, 28-CH_3), 0.87 [9 H, s, SiC(CH_3)$_3$], 0.10 (3 H, s, SiCH_3), 0.07 (3 H, s, SiCH_3); δ_C (125 MHz, $CDCl_3$) 202.3, 159.0, 131.3, 129.4, 113.6, 82.0, 81.2,

75.5, 72.4, 66.4, 55.2, 51.8, 44.2, 31.5, 30.9, 27.8, 27.5, 25.8, 22.8, 18.0, 14.1, −4.6, −4.7; HRMS (ES$^+$) m/z calc. for $C_{27}H_{46}O_5SiNa$ ([MNa]$^+$): 501.3007, found: 501.2986.

Alcohol 54

$NaBH_4$ (0.354 g, 9.38 mmol) was added in one portion to a stirred solution of aldehyde **53** (3.01 g, 6.25 mmol) in MeOH (30 mL) at 0 °C. After 15 min, the reaction was quenched by the careful addition of sat. aq. NH_4Cl (30 mL) and then concentrated under reduced pressure to remove most of the MeOH. The mixture was then diluted with water (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (1 × 50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient: 10–20% EtOAc in hexanes) to give **54** (2.92 g, 97%) as a colourless viscous oil. $R_f = 0.35$ (silica gel, 3 : 1 hexanes–EtOAc); $[\alpha]_D^{25}$ −28.2° (*c* 1.16 in $CHCl_3$); ν_{max}/cm^{-1} (film) 3441, 2949, 2854, 1611, 1467, 1301, 1075, 808; δ_H (500 MHz, $CDCl_3$) 7.27 (2 H, d, *J* 8.6 Hz, Ar*H*), 6.86 (2 H, d, *J* 8.6 Hz, Ar*H*), 4.66 (1 H, d, *J* 11.1 Hz, OC*H*$_2$Ar), 4.52 (1 H, d, *J* 11.1 Hz, OC*H*$_2$Ar), 4.12–4.13 (1 H, m, 19-H), 3.83–3.91 (3 H, m, 17-H, 21-H and 24-H), 3.80 (3 H, s, ArOC*H*$_3$), 3.69 (1 H, dt, *J* 10.8, 5.3 Hz, 17-H), 3.27–3.29 (1 H, m, 25-H), 2.38 (1 H, br s, O*H*), 1.79–1.98 (3 H, m, 20-H, 22-H and 23-H), 1.58–1.76 (4 H, m, 18-H, 18-H, 20-H and 23-H), 1.39–1.49 (4 H, m, 22-H, 26-H, 27-H and 27-H), 1.24–1.35 (3 H, m, 26-H, 28-H and 28-H), 0.86–0.89 [12 H, m, 28-C*H*$_3$ and SiC(C*H*$_3$)$_3$], 0.11 (3 H, s, SiC*H*$_3$), 0.10 (3 H, s, SiC*H*$_3$); δ_C (125 MHz, $CDCl_3$) 158.9, 131.2, 129.4, 113.5, 81.8, 81.1, 75.9, 72.4, 69.7, 59.8, 55.2, 42.8, 38.7, 31.5, 30.8, 27.8, 27.5, 25.8, 22.7, 17.9, 14.0, −4.6, −4.7; HRMS (ES$^+$) m/z calc. for $C_{27}H_{48}O_5SiNa$ ([MNa]$^+$): 503.3163, found: 503.3147.

Iodide 55

To a stirred solution of alcohol **54** (5.50 g, 11.4 mmol) in benzene (60 mL) were added imidazole (3.10 g, 45.6 mmol), PPh_3 (5.98 g, 22.8 mmol), and I_2 (5.79 g, 22.8 mmol) sequentially at room temperature. After 30 min, the reaction was quenched by the addition of sat. aq. $Na_2S_2O_3$ (60 mL), diluted with water (40 mL), and extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with sat. aq. $Na_2S_2O_3$ (1 × 50 mL), brine (1 × 50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was triturated with 4 : 1 hexanes–Et_2O, the precipitated Ph_3PO was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient: 2.5–5% Et_2O in hexanes) to give **55** (6.59 g, 97%) as a colourless oil. $R_f = 0.41$ (silica gel, 9 : 1 hexanes–Et_2O); $[\alpha]_D^{25}$ −15.5° (*c* 1.29 in $CHCl_3$); ν_{max}/cm^{-1} (film) 2954, 2856, 1612, 1468, 1301, 1068, 835; δ_H (500 MHz, $CDCl_3$) 7.30 (2 H, d, *J* 8.7 Hz, Ar*H*), 6.87 (2 H, d, *J* 8.7 Hz, Ar*H*), 4.72 (1 H, d, *J* 11.1 Hz, OC*H*$_2$Ar), 4.54 (1 H, d, *J* 11.1 Hz, OC*H*$_2$Ar), 3.84–3.94 (3 H, m, 19-H, 21-H and 24-H), 3.80 (3 H, s, ArOC*H*$_3$), 3.29–3.31 (1 H, m, 25-H), 3.20 (2 H, t, *J* 7.5 Hz, 17-H and 17-H), 2.07–2.10 (1 H, m, 18-H), 1.99–2.01 (1 H, m, 18-H), 1.92–1.95 (1 H, m, 23-H), 1.83 (1 H, dddd, *J* 12.5, 8.7, 6.9 and 5.9 Hz, 22-H), 1.57–1.69 (3 H, m, 20-H, 20-H and 23-H), 1.41–1.48 (4 H, m, 22-H, 26-H, 27-H and 27-H), 1.24–1.35 (3 H, m, 27-H, 28-H and 28-H), 0.90 [9 H, m, SiC(C*H*$_3$)$_3$], 0.89 (3 H, t, *J* 7.3 Hz, 28-C*H*$_3$), 0.10 (6 H, s, SiC*H*$_3$ and SiC*H*$_3$); δ_C (125 MHz, $CDCl_3$) 158.9, 131.4, 129.5, 113.6, 82.1, 81.3, 75.7, 72.6, 70.3, 55.2, 43.2, 42.2, 31.5, 30.9, 27.9, 27.7, 25.9, 22.8, 18.0, 14.1, 2.4, −4.4, −4.5; HRMS (ES$^+$) m/z calc. for $C_{27}H_{47}IO_4SiNa$ ([MNa]$^+$): 613.2180, found: 613.2175.

cis-Allyltetrahydrofuran 56

From the above procedure for the synthesis of **49**, the minor diasteromer, **56** (2.61 g, 21%) was also isolated as a colourless oil. $R_f = 0.34$ (silica gel, 4 : 1 hexanes–Et_2O); $[\alpha]_D^{25}$ −19.5° (*c* 1.11 in $CHCl_3$); ν_{max}/cm^{-1} (film) 3067, 2941, 2855, 1608, 1451, 1169, 1035, 909; δ_H (500 MHz, C_6D_6) 7.34 (2 H, d, *J* 8.4 Hz, Ar*H*), 6.81 (2 H, d, *J* 8.4 Hz, Ar*H*), 5.85–5.91 (1 H, m, 19-H), 5.03–5.09 (2 H, m, 18-H and 18-H), 4.79 (1 H, d, *J* 11.3 Hz, OC*H*$_2$Ar), 4.60 (1 H, d, *J* 11.3 Hz, OC*H*$_2$Ar), 4.07 (1 H, app q, *J* 6.9 Hz, 21-H), 3.94–3.98 (1 H, m, 24-H), 3.29 (3 H, s, OC*H*$_2$Ar) 3.24–3.28 (1 H, m, 25-H), 2.35 (1 H, ddd, *J* 13.5, 6.9 and 6.4 Hz, 20-H), 2.16 (1 H, ddd, *J* 13.5, 7.0 and 6.4 Hz, 20-H), 1.23–1.71 (10 H, m, 22-H, 22-H, 23-H, 23-H, 26-H, 26-H, 27-H, 27-H, 28-H and 28-H), 0.89 (3 H, t, *J* 7.3 Hz, 28-C*H*$_3$); δ_C (125 MHz, C_6D_6) 159.5, 135.7, 132.2, 129.6, 116.6, 113.9, 81.9, 81.5, 78.8, 72.7, 54.7, 40.8, 31.8, 31.1, 28.7, 28.4, 23.3, 14.3; HRMS (ES$^+$) m/z calc. for $C_{20}H_{30}O_3Na$ ([MNa]$^+$): 341.2087, found: 341.2096.

Alcohol 57

To a stirred solution of **48b** (150 mg, 0.49 mmol) and allyltrimethylsilane (0.16 mL, 0.98 mmol) in CH_2Cl_2 (2 mL) was added $BF_3{\cdot}OEt_2$ (68 μL, 0.54 mmol) at −78 °C. After stirring for 2 h at −78 °C, the solution was warmed to 0 °C for 1 h and then quenched by the addition of sat. aq. $NaHCO_3$ (5 mL) and warmed to room temperature. The mixture was extracted with EtOAc (3 × 5 mL), and the combined organic layers were washed with sat. aq. $NaHCO_3$ (1 × 10 mL), brine (1 × 10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (5% EtOAc in hexanes) to give **57** (71 mg, 71%) as a colourless oil. $R_f = 0.27$ (silica gel, 4 : 1 hexanes–Et_2O); $[\alpha]_D^{25}$ −8.5° (*c* 1.36 in $CHCl_3$); ν_{max}/cm^{-1} (film) 3448, 2931, 1465, 1247, 912; δ_H (600 MHz, C_6D_6) 5.73 (1 H, dddd, *J* 17.1, 10.2, 7.2 and 6.9 Hz, 19-H), 4.97–5.02 (2 H, m, 18-H and 18-H), 3.68–3.73 (1 H, m, 21-H), 3.56 (1 H, app q, *J* 6.8 Hz, 24-H), 3.29–3.33 (1 H, m, 25-H), 2.63 (1 H, br s, O*H*), 2.23 (1 H, ddd, *J* 13.2, 6.9 and 6.5 Hz, 20-H), 2.07 (1 H, ddd, *J* 13.2, 7.2 and 6.3 Hz, 20-H), 1.51–1.64 (2 H, m, 22-H and 23-H), 1.36–1.49 (4 H, m, 23-H, 26-H, 26-H and 27-H), 1.24–1.34 (4 H, m, 22-H, 27-H, 28-H and 28-H), 0.88 (3 H, t, *J* 7.3 Hz, 28-C*H*$_3$); δ_C (150 MHz, C_6D_6) 135.9, 117.5, 83.7, 79.4, 74.9, 41.1, 34.7, 31.5, 29.0, 28.4, 23.8, 15.0; HRMS (ES$^+$) m/z calc. for $C_{12}H_{22}O_2Na$ ([MNa]$^+$): 221.1512, found: 221.1505.

Aldehyde 59

A solution of DMSO (10.7 mL, 151 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a stirred solution of $(COCl)_2$ (6.59 mL, 75.5 mmol) in CH_2Cl_2 (150 mL) at −78 °C. After 20 min, a solution of alcohol **58** [30] (10.5 g, 41.9 mmol) in CH_2Cl_2 (20 mL) was added over 20 min, and the mixture stirred for 30 min at −78 °C before the addition of Et_3N (42.1 mL, 302 mmol) and warming to room temperature. After 1 h, the reaction mixture was poured

into water (250 mL), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 200 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: 10–20% EtOAc in hexanes) to give **59** (10.04 g, 96%) as a colourless oil. R_f = 0.49 (silica gel, 3 : 2 hexanes–EtOAc); $[\alpha]_D^{25}$ +14.2° (*c* 1.38 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 2967, 1728, 1613, 1302, 1173, 822; δ_H (600 MHz, $CDCl_3$) 9.68 (1 H, dd, *J* 3.4, 1.6 Hz, 7-H), 7.21 (2 H, d, *J* 8.6 Hz, Ar*H*), 6.83 (2 H, d, *J* 8.6 Hz, Ar*H*), 5.74 (1 H, ddd, *J* 16.9, 10.8 and 7.1 Hz, 11-H), 5.03–5.06 (2 H, m, 12-H and 12-H), 4.48 (1 H, d, *J* 11.1 Hz, OCH_2Ar), 4.41 (1 H, d, *J* 11.1 Hz, OCH_2Ar), 3.88–3.91 (1 H, m, 9-H), 3.72 (3 H, s, ArOCH_3), 2.52–2.57 (2 H, m, 8-H and 10-H), 2.40 (1 H, ddd, *J* 16.6, 3.4 and 1.6 Hz, 8-H), 1.02 (3 H, d, *J* 6.9 Hz, 10-CH_3); δ_C (150 MHz, $CDCl_3$) 201.2, 158.9, 139.4, 130.0, 129.0, 115.3, 113.4, 76.6, 71.0, 54.8, 44.8, 40.0, 13.7; HRMS (ES$^+$) *m*/*z* calc. for $C_{15}H_{20}O_3Na$ ([MNa]$^+$): 271.1305, found: 271.1296.

(7*R*)-Alcohol 60 and (7*S*)-alcohol 61

n-BuLi (43.0 mL, 1.6 M in hexanes, 68.2 mmol) was added dropwise to a stirred solution of (trimethylsilyl)acetylene (9.46 mL, 68.3 mmol) in THF (150 mL) at −78 °C. After 30 min, a solution of aldehyde **59** (11.3 g, 45.5 mmol) in THF (20 mL) was added dropwise. The mixture was stirred at −78 °C for 1 h, then at 0 °C for a further 1 h, before being quenched by the addition of sat. aq. NH_4Cl (250 mL). The mixture was extracted with Et_2O (3 × 150 mL), and the combined organic layers were washed with brine (1 × 250 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient: 10–20% EtOAc in hexanes) to give 15.265 g of a 3 : 1 mixture of diastereomeric products **60** and **61** (44.0 mmol, 98%) as a colourless oil. This mixture of diastereomers could be separated *via* careful flash chromatography on silica gel (gradient: 4–50% Et_2O in hexanes).

Data for compound 60. R_f = 0.26 (silica gel, 4 : 1 hexanes–Et_2O); $[\alpha]_D^{25}$ +63.7° (*c* 1.95 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 3420, 3074, 2962, 2171, 1614, 1463, 1250, 843; δ_H (600 MHz, $CDCl_3$) 7.30 (2 H, d, *J* 8.6 Hz, Ar*H*), 6.88 (2 H, d, *J* 8.6 Hz, Ar*H*), 5.78 (1 H, ddd, *J* 17.2, 10.6 and 6.8 Hz, 11-H), 5.07–5.11 (2 H, m, 12-H and 12-H), 4.60 (1 H, d, *J* 10.5 Hz, OCH_2Ar), 4.54 (1 H, dd, *J* 6.6, 2.5 Hz, 7-H), 4.47 (1 H, d, *J* 10.5 Hz, OCH_2Ar), 3.93–3.96 (1 H, m, 9-H), 3.80 (3 H, s, ArOCH_3), 3.02 (1 H, br s, O*H*), 2.65–2.70 (1 H, m, 10-H), 1.85–1.90 (1 H, m, 8-H), 1.71–1.75 (1 H, m, 8-H), 1.05 (3 H, d, *J* 6.9 Hz, 10-CH_3), 0.19 [9 H, s, Si(CH_3)$_3$]; δ_C (150 MHz, $CDCl_3$) 159.2, 140.1, 130.1, 129.6, 115.0, 113.8, 106.9, 89.2, 80.0, 71.6, 60.9, 55.2, 39.2, 36.6, 13.2, −0.1; HRMS (ES$^+$) *m*/*z* calc. for $C_{20}H_{30}O_3SiNa$ ([MNa]$^+$): 369.1856, found: 369.1850.

Data for compound 61. R_f = 0.20 (silica gel, 4 : 1 hexanes–Et_2O); $[\alpha]_D^{25}$ +61.7° (*c* 1.15 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 3416, 2959, 2171, 1613, 1463, 1244, 844; δ_H (600 MHz, $CDCl_3$) 7.25 (2 H, d, *J* 8.5 Hz, Ar*H*), 6.85 (2 H, d, *J* 8.5 Hz, Ar*H*), 5.75 (1 H, ddd, *J* 16.9, 10.9 and 6.8 Hz, 11-H), 5.06–5.09 (2 H, m, 12-H and 12-H), 4.57 (1 H, d, *J* 10.9 Hz, OCH_2Ar), 4.51 (1 H, dd, *J* 7.5, 6.3 Hz, 7-H), 4.38 (1 H, d, *J* 10.9 Hz, OCH_2Ar), 3.78 (3 H, s, ArOCH_3), 3.64 (1 H, ddd, *J* 10.1, 3.9 and 3.1 Hz, 9-H), 3.05 (1 H, br s, O*H*), 2.62–2.68 (1 H, m, 10-H), 1.96 (1 H, ddd, *J* 14.0, 10.1 and 7.5 Hz, 8-H), 1.73 (1 H, ddd, *J* 14.0, 6.3 and 3.1 Hz, 8-H), 1.03 (3 H, d, *J* 6.9 Hz, 10-CH_3), 0.16 [9 H, s, Si(CH_3)$_3$]; δ_C (150 MHz, $CDCl_3$) 159.2, 139.9, 129.4, 130.0, 115.1, 113.8, 106.4, 89.1, 79.7, 71.2, 61.9, 55.1, 39.2, 37.9, 13.1, −0.2; HRMS (ES$^+$) *m*/*z* calc. for $C_{20}H_{30}O_3SiNa$ ([MNa]$^+$): 369.1856, found: 369.1852.

t-Butyldimethylsilyl ether 62

Imidazole (6.12 g, 89.9 mmol), TBSCl (6.587 g, 43.7 mmol) and a catalytic amount of 4-DMAP were added sequentially to a stirred solution of alcohol **61** (8.91 g, 25.7 mmol) in CH_2Cl_2 (80 mL) at room temperature. After 2 h, the reaction was quenched by the addition of water (100 mL), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 75 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: 1–4% Et_2O in hexanes) to give **62** (10.945 g, 93%) as a colourless oil. R_f = 0.64 (silica gel, 3 : 2 hexanes–Et_2O); $[\alpha]_D^{25}$ +2.0° (*c* 2.46 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 2945, 2176, 1611, 1466, 1248, 843; δ_H (600 MHz, $CDCl_3$) 7.29 (2 H, d, *J* 8.2 Hz, Ar*H*), 6.89 (2 H, d, *J* 8.2 Hz, Ar*H*), 5.82 (1 H, ddd, *J* 16.9, 10.9 and 7.0 Hz, 11-H), 5.05–5.11 (2 H, m, 12-H and 12-H), 4.51–4.54 (2 H, m, 7-H and OCH_2Ar), 4.44 (1 H, d, *J* 11.0 Hz, OCH_2Ar), 3.81 (3 H, s, ArOCH_3), 3.61 (1 H, app dd, *J* 8.8, 3.8 Hz, 9-H), 2.52–2.58 (1 H, m, 10-H), 1.89 (1 H, ddd, *J* 13.5, 8.8 and 5.8 Hz, 8-H), 1.77 (1 H, ddd, *J* 13.5, 9.0 and 3.8 Hz, 8-H), 1.06 (3 H, d, *J* 6.9 Hz, 10-CH_3), 0.92 [9 H, s, SiC(CH_3)$_3$], 0.18 [9 H, s, Si(CH_3)$_3$], 0.15 (3 H, s, SiCH_3), 0.12 (3 H, s, SiCH_3); δ_C (150 MHz, $CDCl_3$) 159.1, 140.4, 131.0, 129.3, 114.8, 113.7, 107.5, 89.3, 79.6, 71.8, 61.6, 55.2, 40.3, 39.9, 25.8, 18.2, 14.6, −0.2, −4.5, −4.9; HRMS (ES$^+$) *m*/*z* calc. for $C_{25}H_{42}O_3Si_2Na$ ([MNa]$^+$): 485.2514; found: 485.2511.

Aldehyde 63

A solution of alkene **62** (10.0 g, 21.7 mmol) in CH_2Cl_2 (200 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 (8.54 g, 32.6 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: 2–20% Et_2O in hexanes) to give **63** (9.88 g, 98%) as a colourless oil. R_f = 0.26 (silica gel, 21 : 4 hexanes–Et_2O); $[\alpha]_D^{25}$ −10.0° (*c* 1.06 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 2955, 2171, 1724, 1613, 1462, 1246, 839; δ_H (600 MHz, $CDCl_3$) 9.76 (1 H, s, 11-H), 7.28 (2 H, d, *J* 8.5 Hz, Ar*H*), 6.91 (2 H, d, *J* 8.5 Hz, Ar*H*), 4.59–4.61 (1 H, m, 7-H), 4.55 (1 H, d, *J* 11.0 Hz, OCH_2Ar), 4.49 (1 H, d, *J* 11.0 Hz, OCH_2Ar), 3.98–4.01 (1 H, m, 9-H), 3.83 (3 H, s, ArOCH_3), 2.75–2.78 (1 H, m, 10-H), 2.05–2.10 (1 H, m, 8-H), 1.85–1.89 (1 H, m, 8-H), 1.15 (3 H, d, *J* 7.0 Hz, 10-CH_3), 0.93 [9 H, s, SiC(CH_3)$_3$], 0.21 [9 H, s, Si(CH_3)$_3$], 0.18 (3 H, s, SiCH_3), 0.15 (3 H, s, SiCH_3); δ_C (150 MHz, $CDCl_3$) 203.9, 159.2, 130.1, 129.4, 113.7, 106.8, 89.9, 76.6, 71.8, 60.9, 55.2, 49.8, 40.6, 25.7, 18.1, 10.0, −0.3, −4.5, −5.0; HRMS (ES$^+$) *m*/*z* calc. for $C_{25}H_{42}O_3Si_2Na$ ([MNa]$^+$): 485.2514, found: 485.2511.

α,β-Unsaturated ester 64

Aldehyde **63** (9.51 g, 20.5 mmol) and (carbethoxyethylidene)triphenylphosphorane (11.9 g, 32.8 mmol) were combined in benzene (100 mL) and heated to 70 °C overnight. The solution was then cooled to room temperature and concentrated under reduced pressure. The residue was triturated with 4 : 1 hexanes–Et_2O, and filtered to remove the solid Ph_3PO. The filtrate was the concentrated *in vacuo*, and the residue was purified by flash chromatography on silica gel (gradient: 4–15% Et_2O in hexanes) to give **64** (11.02 g, 98%) as a colourless oil. $R_f = 0.32$ (silica gel, 21 : 4 hexanes–Et_2O); $[\alpha]_D^{25}$ +2.9° (*c* 1.48 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 2959, 2169, 1710, 1614, 1462, 1249, 839; δ_H (600 MHz, $CDCl_3$) 7.25 (2 H, d, *J* 8.3 Hz, Ar*H*), 6.86 (2 H, d, *J* 8.3 Hz, Ar*H*), 6.67 (1 H, d, *J* 8.7 Hz, 11-H), 4.44–4.50 (3 H, m, 7-H, OCH_2Ar and OCH_2Ar), 4.16–4.20 (2 H, m, $CO_2CH_2CH_3$), 3.79 (3 H, s, $ArOCH_3$), 3.56–3.59 (1 H, m, 9-H), 2.79–2.82 (1 H, m, 10-H), 1.91 (1 H, ddd, *J* 13.5, 8.5 and 5.8 Hz, 8-H), 1.83 (3 H, s, 12-CH_3), 1.71 (1 H, ddd, *J* 13.5, 8.7 and 3.9 Hz, 8-H), 1.29 (3 H, t, *J* 7.1 Hz, $CO_2CH_2CH_3$), 1.04 (3 H, d, *J* 6.8 Hz, 10-CH_3), 0.89 [9 H, s, $SiC(CH_3)_3$], 0.14 [9 H, s, $Si(CH_3)_3$], 0.12 (3 H, s, $SiCH_3$), 0.09 (3 H, s, $SiCH_3$); δ_C (150 MHz, $CDCl_3$) 169.0, 160.0, 144.5, 131.6, 130.3, 128.9, 114.6, 108.1, 90.5, 79.9, 73.0, 62.3, 61.4, 56.1, 41.6, 37.6, 26.7, 19.1, 16.2, 15.2, 13.6, 0.7, −3.6, −4.0; HRMS (ES^+) *m/z* calc. for $C_{30}H_{50}O_5Si_2Na$ ($[MNa]^+$): 569.3089, found: 569.3081.

Allylic alcohol 65

DIBAL-H (14.8 mL, 1.0 M in toluene, 14.8 mmol) was added dropwise to a stirred solution of ester **64** (2.71 g, 4.93 mmol) in THF (30 mL) at 0 °C. After 30 min, the reaction was quenched by the addition of EtOAc (10 mL) and then MeOH (10 mL), and was then warmed to room temperature. The mixture was partitioned between EtOAc (50 mL) and sat. aq. Rochelle's salt (50 mL) and stirred vigorously for 3 h at room temperature. The layers were then separated, and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (1 × 50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient: 25–40% Et_2O in hexanes) to give **65** (2.469 g, 99%) as a colourless oil. $R_f = 0.51$ (silica gel, 1 : 1 hexanes–Et_2O); $[\alpha]_D^{25}$ −19.5° (*c* 1.66 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 3432, 2954, 2166, 1614, 1465, 1247, 912, 843; δ_H (600 MHz, $CDCl_3$) 7.27 (2 H, d, *J* 8.4 Hz, Ar*H*), 6.87 (2 H, d, *J* 8.4 Hz, Ar*H*), 5.33 (1 H, d, *J* 8.7 Hz, 11-H), 4.48–4.52 (2 H, m, 7-H and OCH_2Ar), 4.45 (1 H, d, *J* 11.1 Hz, OCH_2Ar), 3.98 (2 H, s, 13-H and 13-H), 3.80 (3 H, s, $ArOCH_3$), 3.54–3.56 (1 H, m, 9-H), 2.70–2.76 (1 H, m, 10-H), 1.89 (1 H, ddd, *J* 13.4, 8.8 and 6.1 Hz, 8-H), 1.69–1.73 (1 H, m, 8-H), 1.68 (1 H, br s, O*H*), 1.67 (3 H, s, 12-CH_3), 1.00 (3 H, d, *J* 6.6 Hz, 10-CH_3), 0.90 [9 H, s, $SiC(CH_3)_3$], 0.16 [9 H, s, $Si(CH_3)_3$], 0.14 (3 H, s, $SiCH_3$), 0.10 (3 H, s, $SiCH_3$); δ_C (150 MHz, $CDCl_3$) 159.0, 135.2, 131.0, 129.4, 128.0, 113.7, 105.7, 89.4, 79.6, 71.9, 68.8, 61.6, 55.2, 40.3, 35.0, 25.8, 18.2, 16.0, 13.9, −0.2, −4.5, −4.9; HRMS (ES^+) *m/z* calc. for $C_{28}H_{48}O_4Si_2Na$ ($[MNa]^+$): 527.2983, found: 527.2980.

Allylic bromide 67

MsCl (0.92 mL, 11.9 mmol) was added dropwise to a stirred solution of alcohol **65** (2.00 g, 3.98 mmol) and Et_3N (2.22 mL, 15.9 mmol) in THF (70 mL) at 0 °C. After 1 h the mixture was warmed to room temperature and LiBr (3.45 g, 39.8 mmol) was added in one portion. After a further 45 min at room temperature the reaction was quenched with water (150 mL) and extracted with Et_2O (3 × 60 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (2–4% Et_2O in hexanes) to give **67** (2.004 g, 89%) as a colourless oil. $R_f = 0.39$ (silica gel, 23 : 2 hexanes–Et_2O); $[\alpha]_D^{25}$ +13.3° (*c* 1.34 in CH_2Cl_2); δ_H (600 MHz, C_6D_6) 7.26 (2 H, d, *J* 8.6 Hz, Ar*H*), 6.80 (2 H, d, *J* 8.6 Hz, Ar*H*), 5.37 (1 H, d, *J* 9.4 Hz, 11-H), 4.75 (1 H, dd, *J* 8.4, 6.0 Hz, 7-H), 4.46 (2 H, s, OCH_2Ar and OCH_2Ar), 3.62–3.66 (1 H, m, 9-H), 3.57 (1 H, d, *J* 9.5 Hz, 13-H), 3.56 (1 H, d, *J* 9.5 Hz, 13-H), 3.31 (3 H, s, $ArOCH_3$), 2.54–2.60 (1 H, m, 10-H), 2.11 (1 H, ddd, *J* 13.5, 8.4 and 6.0 Hz, 8-H), 1.88 (1 H, ddd, *J* 13.5, 8.4 and 4.2 Hz, 8-H), 1.61 (3 H, s, 12-CH_3), 0.98 (3 H, d, *J* 6.9 Hz, 10-CH_3), 0.92 [9 H, s, $SiC(CH_3)_3$], 0.24 (3 H, s, $SiCH_3$), 0.16 [9 H, s, $Si(CH_3)_3$], 0.15 (3 H, s, $SiCH_3$); δ_C (150 MHz, C_6D_6) 159.7, 133.2, 132.7, 131.4, 129.7, 114.0, 108.4, 89.5, 79.5, 72.4, 62.0, 54.7, 41.2, 41.2, 36.3, 26.0, 18.4, 15.9, 14.9, −0.1, −4.1, −4.7; ν_{max}/cm^{-1} (film) 2951, 2166, 1615, 1465, 1250, 841; HRMS (ES^+) *m/z* calc. for $C_{28}H_{47}{}^{79}BrO_3Si_2Na$ ($[MNa]^+$): 589.2139, found: 589.2131.

Ketone 68

IBX (1.697 g, 6.06 mmol) was dissolved in DMSO (12 mL) at room temperature, then a solution of alcohol **61** (1.40 g, 4.04 mmol) in DMSO (4 mL) was added slowly and the mixture was stirred for 2 h. The reaction mixture was then poured into a vigorously stirred mixture of water (75 mL) and Et_2O (75 mL), and then filtered. The filtrate was diluted with Et_2O (300 mL), and the layers were separated. The organic layer was then washed with water (1 × 75 mL), brine (2 × 75 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (4% Et_2O in hexanes) to give **68** (1.083 g, 78%) as a colourless oil. $R_f = 0.22$ (silica gel, 22 : 3 hexanes–Et_2O); $[\alpha]_D^{25}$ −1.5° (*c* 1.30 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 3076, 2960, 2151, 2093, 1681, 1421, 1122, 847; δ_H (600 MHz, $CDCl_3$) 7.23 (2 H, d, *J* 8.5 Hz, Ar*H*), 6.84 (2 H, d, *J* 8.5 Hz, Ar*H*), 5.78 (1 H, ddd, *J* 16.7, 11.0 and 7.1 Hz, 11-H), 5.05–5.08 (2 H, m, 12-H and 12-H), 4.48 (2 H, s, OCH_2Ar), 4.01–4.04 (1 H, m, 9-H), 3.74 (3 H, s, $ArOCH_3$), 2.78 (1 H, dd, *J* 16.3, 8.5 Hz, 8-H), 2.60 (1 H, dd, *J* 16.3, 4.0 Hz, 8-H), 2.50–2.56 (1 H, m, 10-H), 1.04 (3 H, d, *J* 6.9 Hz, 10-CH_3), 0.23 [9 H, s, $Si(CH_3)_3$]; δ_C (150 MHz, $CDCl_3$) 185.5, 158.9, 139.4, 130.1, 129.0, 115.3, 113.4, 102.1, 97.5, 77.8, 71.5, 54.8, 46.9, 40.2, 14.1, −1.1; HRMS (ES^+) *m/z* calc. for $C_{20}H_{28}O_3SiNa$ ($[MNa]^+$): 367.1700, found: 367.1701.

Noyori reduction of 68 to 60

To a stirred solution of ketone **68** (1.35 g, 3.92 mmol) in 2-propanol (4 mL) was added ruthenium complex **69**[31] (24 mg, 0.04 mmol) in one portion at room temperature. After 16 h the mixture was concentrated *in vacuo*, and the residue was purified by flash chromatography on silica gel (gradient: 10–20% EtOAc in hexanes) to give **60** (1.315 g, 97%) as a colourless oil.

Oxazolidinone 71

To a stirred solution of oxazolidinone **70**[33] (4.665 g, 20.0 mmol) in CH_2Cl_2 (60 mL) were added *n*-Bu_2BOTf (24.0 mL, 1.0 M in

CH_2Cl_2, 24.0 mmol) and then *i*-Pr_2NEt (4.8 mL, 27.6 mmol) dropwise at 0 °C. After 10 min the mixture was cooled to −78 °C, and freshly distilled acrolein (7.0 mL, 104.8 mmol) was added dropwise over 5 min. The mixture was stirred at −78 °C for 45 min, then allowed to warm to 0 °C over 30 min, before a pH 7 aqueous buffer solution (30 mL) and MeOH (100 mL) were added. A 2 : 1 MeOH–35% aq. H_2O_2 mixture (100 mL) was then added dropwise over 20 min, and stirring continued at 0 °C for a further 20 min before the mixture was concentrated *in vacuo* to remove most of the CH_2Cl_2 and MeOH. The residue was partitioned between Et_2O (200 mL) and water (200 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 200 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: 25–33% EtOAc in hexanes) to give **71** (5.392 g, 93%) as white crystals. $R_f = 0.31$ (1 : 1 hexanes–EtOAc); mp 73–74 °C; $[a]_D^{25}$ −56.9° (*c* 1.06 in $CHCl_3$); ν_{max}/cm^{-1} (film) 3506, 2984, 2931, 1790, 1689, 1603, 1454, 1390, 1204, 1114; δ_H (600 MHz, $CDCl_3$) 7.32–7.34 (2 H, m, Ar*H*), 7.26–7.29 (1 H, m, Ar*H*), 7.20 (2 H, d, *J* 7.7 Hz, Ar*H*), 5.85 (1 H, ddd, *J* 17.2, 10.5 and 5.5 Hz, H-4), 5.35 (1 H, d, *J* 17.2 Hz, H-5), 5.22 (1 H, d, *J* 10.5 Hz, H-5), 4.29–4.72 (1 H, m, OCH_2CHN), 4.50–4.51 (1 H, m, H-3), 4.18–4.24 (2 H, m, OCH_2CHN and OCH_2CHN), 3.36–3.90 (1 H, m, H-2), 3.25 (1 H, dd, *J* 13.4, 3.0 Hz, CH_2Ph), 2.79 (1 H, dd, *J* 13.4, 9.5 Hz, CH_2Ph), 1.24 (3 H, d, *J* 7.0 Hz, 2-CH_3); δ_C (150 MHz, $CDCl_3$) 176.5, 153.1, 137.2, 134.9, 129.4, 128.9, 127.4, 116.3, 72.6, 66.2, 55.1, 42.4, 37.7, 10.9; HRMS (ES^+) *m*/*z* calc. for $C_{16}H_{19}NO_4Na$ ([MNa]$^+$): 312.1206, found 312.1206.

Methyl ester 72

To a stirred solution of oxazolidinone **71** (500 mg, 1.73 mmol) in MeOH (17 mL) was added NaOMe (130 mg, 2.41 mmol) in one portion at 0 °C. After 40 min at 0 °C, the reaction was quenched by the addition of sat. aq. NH_4Cl (20 mL), and mixture was concentrated under reduced pressure to remove most of the MeOH. The residue was paritioned between EtOAc (30 mL) and brine (20 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (20% EtOAc in hexanes) to give **72** (126 mg, 51%) as a colourless oil. $R_f = 0.54$ (1 : 1 hexanes–EtOAc); $[a]_D^{25}$ −19.4° (*c* 1.54 in $CHCl_3$); ν_{max}/cm^{-1} (film) 3489, 2996, 2953, 1733, 1648, 1459, 1436, 1151; δ_H (500 MHz, $CDCl_3$) 5.77 (1 H, ddd, *J* 17.2, 10.5 and 5.7 Hz, 4-H), 5.24 (1 H, app dt, *J* 17.2, 1.5 Hz, 5-H), 5.12 (1 H, app dt, *J* 10.5, 1.5 Hz, 5-H), 4.31–4.33 (1 H, m, 3-H), 3.63 (3 H, s, CO_2CH_3), 2.94 (1 H, br s, O*H*), 2.54–2.60 (1 H, m, 2-H), 1.11 (3 H, d, *J* 7.2 Hz, 2-CH_3); δ_C (125 MHz, $CDCl_3$) 175.5, 137.4, 116.0, 73.0, 51.6, 44.6, 11.2; HRMS (ES^+) *m*/*z* calc. for $C_7H_{12}O_3Na$ ([MNa]$^+$): 167.0679, found 167.0685.

t-Butyldimethylsilyl ether 73

To a stirred solution of alcohol **72** (2.40 g, 16.7 mmol) in CH_2Cl_2 (80 mL) were added imidazole (4.53 g, 66.6 mmol), TBSCl (5.02 g, 33.3 mmol) and a catalytic amount of 4-DMAP sequentially at room temperature. After 16 h the reaction was quenched with water (150 mL), and extracted with Et_2O (3 × 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: 2–4% Et_2O in hexanes) to give **73** (4.06 g, 95%) as a colourless oil. $R_f = 0.39$ (silica gel, 10 : 1 hexanes–Et_2O); $[a]_D^{25}$ −2.7° (*c* 1.17 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 2940, 2862, 1739, 1463, 1252, 1080, 770; δ_H (600 MHz, C_6D_6) 5.68–5.74 (1 H, m, H-4), 5.10 (1 H, dd, *J* 17.3, 1.2 Hz, H-5), 4.94 (1 H, dd, *J* 10.4, 0.8 Hz, H-5), 4.42–4.44 (1 H, m, H-3), 3.38 (3 H, s, CO_2CH_3), 2.38–2.42 (1 H, m, H-2), 1.13 (3 H, d, *J* 7.0 Hz, 2-CH_3), 0.90 [9 H, s, $SiC(CH_3)_3$], −0.01 (3 H, s, $SiCH_3$), −0.02 (3 H, s, $SiCH_3$); δ_C (150 MHz, C_6D_6) 173.8, 139.9, 115.3, 75.2, 51.0, 46.6, 26.0, 18.3, 11.3, −4.1, −5.0; HRMS (ES^+) *m*/*z* calc. for $C_{13}H_{26}O_3SiNa$ ([MNa]$^+$): 281.1543, found: 281.1540.

t-Butyldimethylsilyl ether 74

To a stirred solution of alcohol **71** (1.10 g, 3.8 mmol) in CH_2Cl_2 (20 mL) were added imidazole (1.55 g, 22.8 mmol), 4-DMAP (25 mg, 0.2 mmol) and TBSCl (1.72 g, 11.4 mmol) sequentially at room temperature. After 16 h the reaction was quenched by the addition of sat. aq. NH_4Cl (30 mL) and extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (1 × 30 mL), brine (1 × 30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (15% EtOAc in hexanes) to give **74** (1.44 g, 94%) as a white solid. $R_f = 0.48$ (4 : 1 hexanes–EtOAc); mp 54 °C; $[a]_D^{25}$ −67.8° (*c* 1.76 in $CHCl_3$); ν_{max}/cm^{-1} (film) 2957, 2856, 1783, 1700, 1383, 1209, 1099, 836; δ_H (600 MHz, $CDCl_3$) 7.32–7.34 (2 H, m, Ar*H*), 7.26–7.28 (1 H, m, Ar*H*), 7.22 (2 H, d, *J* 7.1 Hz, Ar*H*), 5.85 (1 H, ddd, *J* 17.2, 10.4 and 6.4 Hz, 4-H), 5.20 (1 H, d, *J* 17.2 Hz, 5-H), 5.11 (1 H, d, *J* 10.4 Hz, 5-H), 4.58–4.62 (1 H, m, OCH_2CHN), 4.33 (1 H, app t, *J* 6.4 Hz, 3-H), 4.12–4.17 (2 H, m, OCH_2CHN and OCH_2CHN), 3.98 (1 H, dq, *J* 6.4 Hz, 2-H), 3.28 (1 H, dd, *J* 13.4, 3.2 Hz, CH_2Ph), 2.77 (1 H, dd, *J* 13.4, 9.7 Hz, CH_2Ph), 1.21 (3 H, d, *J* 6.4 Hz, 2-CH_3), 0.89 [9 H, s, $Si(CH_3)_3$], 0.02 (3 H, s, $SiCH_3$), 0.01 (3 H, s, $SiCH_3$); δ_C (150 MHz, $CDCl_3$) 174.6, 153.1, 139.1, 135.3, 129.4, 128.8, 127.2, 115.6, 75.1, 65.9, 55.6, 44.0, 37.7, 25.7, 18.1, 12.4, −4.5, −5.2; HRMS (ES^+) *m*/*z* calc. for $C_{22}H_{33}NO_4SiNa$ ([MNa]$^+$): 426.2071, found 426.2071.

Carboxylic acid 75

To a stirred solution of oxazolidinone **74** (234 mg, 0.58 mmol) in 4 : 1 THF–water (4 mL) were added 35% aq. H_2O_2 (0.52 mL, 4.64 mmol) and a solution of $LiOH{\cdot}H_2O$ (97 mg, 2.32 mmol) in water (0.4 mL) sequentially at 0 °C. After 5 h, sat. aq. Na_2SO_3 (2 mL) was added, and stirring continued at 0 °C for a further 30 min. The mixture was then adjusted to pH 14 with 0.1 M aq. NaOH, and washed with Et_2O (1 × 20 mL). The aqueous layer was then adjusted to pH 3 using 0.1 M aq. $KHSO_4$, and extracted with EtOAc (3 × 30 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 (40% Et_2O in CH_2Cl_2) to give **75** (130 mg, 92%) as a colourless oil. $R_f = 0.61$ (1 : 1 CH_2Cl_2–Et_2O); $[a]_D^{25}$ −25.6° (*c* 1.28 in $CHCl_3$); ν_{max}/cm^{-1} (film) 3107, 2956, 2930, 1710, 1253, 1095, 837, 776; δ_H (500 MHz, C_6D_6) 5.68 (1 H, ddd, *J* 17.1, 10.4 and

6.2 Hz, H-4), 5.13 (1 H, d, *J* 17.1 Hz, H-5), 4.95 (1 H, d, *J* 10.4 Hz, H-5), 4.48–4.52 (1 H, m, H-3), 2.41 (1 H, qd, *J* 7.0, 4.8 Hz, 2-H), 1.15 (3 H, d, *J* 7.0 Hz, 2-CH_3), 0.96 [9 H, s, Si(CH_3)$_3$], 0.08 (3 H, s, SiCH_3), 0.02 (3 H, s, SiCH_3); δ_C (125 MHz, C_6D_6) 181.1, 139.3, 115.8, 74.9, 46.7, 26.0, 18.3, 10.9, −4.1, −5.0; HRMS (ES$^+$) *m*/*z* calc. for $C_{12}H_{24}O_3SiNa$ ([MNa]$^+$): 267.1387, found 267.1389.

Alcohol 76

To a stirred solution of oxazolidinone **74** (4.31 g, 10.7 mmol) in THF (50 mL) and MeOH (1.1 mL) was added $LiBH_4$ (16.0 mL, 2.0 M in THF, 32.0 mmol) dropwise at 0 °C. The mixture was allowed to warm to room temperature over 16 h, then recooled to 0 °C before being quenched by the cautious addition of 1 M aq. NaOH. After a further 10 min of stirring, the mixture was diluted with brine (50 mL) and extracted with EtOAc (3 × 40 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 (10% EtOAc in hexanes) to give **76** (1.73 g, 70%) as a colourless oil. $R_f = 0.53$ (4 : 1 hexanes–EtOAc); $[\alpha]_D^{25}$ −12.5° (*c* 2.02 in $CHCl_3$); ν_{max}/cm^{-1} (film) 3356, 2956, 2929, 1472, 1253, 1028, 837, 775; δ_H (500 MHz, C_6D_6) 5.75 (1 H, ddd, *J* 17.1, 10.4 and 6.2 Hz, H-4), 5.14 (1 H, d, *J* 17.1 Hz, H-5), 4.99 (1 H, d, *J* 10.4 Hz, H-5), 4.18–4.23 (1 H, m, H-3), 3.54–3.58 (1 H, m, H-1), 3.35–3.39 (1 H, m, H-1), 2.11 (1 H, br s, O*H*), 1.71–1.71 (1 H, m, 2-H), 0.96 [9 H, s, Si(CH_3)$_3$], 0.80 (3 H, d, *J* 7.0 Hz, 2-CH_3), 0.05 (3 H, s, SiCH_3), 0.04 (3 H, s, SiCH_3); δ_C (125 MHz, C_6D_6) 139.7, 115.0, 75.7, 65.1, 41.9, 26.0, 18.4, 11.6, −4.2, −5.0; HRMS (ES$^+$) *m*/*z* calc. for $C_{12}H_{26}O_2SiNa$ ([MNa]$^+$): 253.1594, found 253.1594.

Pivalate 77

To a stirred solution of alcohol **76** (365 mg, 1.58 mmol) in CH_2Cl_2 (10 mL) were added pyridine (0.39 mL, 4.75 mmol), 4-DMAP (10 mg, 0.08 mmol) and freshly distilled PivCl (0.39 mL, 3.16 mmol) sequentially at room temperature. After 16 h, the reaction was quenched by the addition of sat. aq. $NaHCO_3$ (30 mL), and extracted with Et_2O (3 × 30 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 (10% EtOAc in hexanes) to give **77** (444 mg, 90%) as a colourless oil. $R_f = 0.71$ (4 : 1 hexanes–EtOAc); $[\alpha]_D^{25}$ −5.4° (*c* 1.27 in $CHCl_3$); ν_{max}/cm^{-1} (film) 2958, 2854, 1732, 1474, 1283, 1153, 1032, 836, 776; δ_H (500 MHz, C_6D_6) 5.67 (1 H, ddd, *J* 17.2, 10.4 and 6.3 Hz, H-4), 5.10 (1 H, d, *J* 17.2 Hz, H-5), 4.95 (1 H, d, *J* 10.4 Hz, H-5), 4.11–4.13 (2 H, m, H-3 and H-1), 4.02 (1 H, dd, *J* 10.8, 6.2 Hz, H-1), 1.81–1.86 (1 H, m, 2-H), 1.18 [9 H, s, $O_2CC(CH_3)_3$], 0.96 [9 H, s, Si(CH_3)$_3$], 0.89 (3 H, d, *J* 6.9 Hz, 2-CH_3), 0.05 (3 H, s, SiCH_3), 0.04 (3 H, s, SiCH_3); δ_C (125 MHz, C_6D_6) 177.4, 140.2, 114.9, 74.3, 66.3, 39.6, 38.8, 27.4, 26.0, 18.4, 11.2, −4.0, −4.9; HRMS (ES$^+$) *m*/*z* calc. for $C_{17}H_{34}O_3SiNa$ ([MNa]$^+$): 337.2169, found 337.2171.

Alcohol 78

To a stirred solution of pivalate **77** (90 mg, 0.286 mmol) in THF (6 mL) was added TBAF (0.6 mL, 1.0 M in THF, 0.6 mmol) in one portion at room temperature. After 3.5 h, silica gel (*ca.* 1 g) was added, and the mixture was concentrated. The solid residue was loaded on to the top of a flash chromatography column, and the product eluted using a gradient of 20–25% Et_2O in hexanes, to give **78** (51 mg, 89%) as a colourless oil. $R_f = 0.41$ (1 : 1 hexanes–EtOAc); $[\alpha]_D^{25}$ −17.5° (*c* 2.35 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 3500, 2960, 2878, 1730, 1644, 1481, 1399, 1287, 1152, 990, 923; δ_H (600 MHz, C_6D_6) 5.62–5.68 (1 H, ddd, *J* 17.2, 10.5 and 5.3 Hz, H-4), 5.18 (1 H, dd, *J* 17.2, 1.7 Hz, H-5), 4.99 (1 H, dd, *J* 10.5, 1.7 Hz, H-5), 4.19 (1 H, dd, *J* 10.9, 6.8 Hz, H-1), 3.96–3.98 (1 H, m, H-3), 3.91 (1 H, dd, *J* 10.9, 6.3 Hz, H-1), 1.91 (1 H, br s, O*H*), 1.73–1.79 (1 H, m, H-2), 1.12 [9 H, s, $O_2CC(CH_3)_3$], 0.84 (3 H, d, *J* 7.0 Hz, 2-CH_3); δ_C (150 MHz, C_6D_6) 178.1, 139.7, 114.9, 73.0, 66.6, 38.8, 38.6, 27.3, 11.1; HRMS (ES$^+$) *m*/*z* calc. for $C_{11}H_{20}O_3Na$ ([MNa]$^+$): 223.1305, found 223.1306.

Hydrazone 79

A solution of hydrazone **10** (0.71 g, 2.94 mmol) in THF (10 mL) was added dropwise to a stirred solution of freshly prepared LDA (3.52 mmol) in THF (30 mL) at −78 °C. After 90 min a solution of bromide **67** (2.00 g, 3.52 mmol) in THF (15 mL) was added dropwise over 15 min. After a further 1 h at −78 °C the mixture was poured into aqueous pH 7.0 buffer solution (60 mL), and extracted with Et_2O (3 × 40 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: 25–40% Et_2O in hexanes with 1% Et_3N) to give **79** (1.81 g, 84%) as a pale yellow oil. $R_f = 0.25$ (silica gel, 3 : 2 hexanes–Et_2O + 1% Et_3N); $[\alpha]_D^{25}$ +24.9° (*c* 1.76 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 2961, 2166, 1615, 1465, 1302, 1172, 906, 671; δ_H (500 MHz, C_6D_6) 7.28 (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* 9.4 Hz, 11-H), 4.81 (1 H, dd, *J* 8.2, 6.5 Hz, 7-H), 4.72 (1 H, dd, *J* 7.0, 2.3 Hz, 14-H), 4.48–4.54 (3 H, m, 16-H and OCH_2Ar), 4.15 (1 H, d, *J* 12.3 Hz, 16-H), 3.77–3.80 (1 H, m, 9-H), 3.54–3.61 (2 H, m, NC*H*CH$_2$OCH$_3$ and NCHCH_2OCH$_3$), 3.32 (3 H, s, ArOCH_3), 3.25–3.28 (1 H, m, NCHCH_2OCH$_3$), 3.18 (4 H, m, NCH_2CH$_2$ and CH$_2$OCH_3), 3.07 (1 H, dd, *J* 14.4, 2.3 Hz, 13-H), 2.79–2.87 (1 H, m, 10-H), 2.41–2.46 (1 H, m, 13-H), 2.31–2.36 (1 H, m, NCH_2CH$_2$), 2.21–2.26 (1 H, m, 8-H), 2.04 (1 H, ddd, *J* 13.3, 8.2 and 4.6 Hz, 8-H), 1.85–1.91 (1 H, m, NCHCH_2CH$_2$), 1.82 (3 H, s, 12-CH_3), 1.50–1.68 (3 H, m, NCHCH_2CH$_2$, NCH$_2$CH_2CH$_2$ and NCH$_2$CH_2CH$_2$), 1.43 [3 H, s, $O_2C(CH_3)_2$], 1.40 [3 H, s, $O_2C(CH_3)_2$], 1.12 (3 H, d, *J* 6.9 Hz, 10-CH_3), 0.98 [9 H, s, SiC(CH_3)$_3$], 0.18 (3 H, s, SiCH_3), 0.16 [9 H, s, Si(CH_3)$_3$], 0.15 (3 H, s, SiCH_3); δ_C (125 MHz, C_6D_6) 159.7, 158.2, 132.9, 131.7, 129.6, 129.0, 114.0, 108.7, 99.9, 89.4, 79.9, 76.3, 72.2, 71.8, 67.4, 62.2, 58.9, 54.7, 53.4, 41.0, 37.2, 35.7, 27.5, 27.5, 27.3, 26.0, 24.6, 23.2, 18.4, 17.6, 16.6, 15.6, −0.1, −4.1, −4.7; HRMS (ES$^+$) *m*/*z* calc. for $C_{40}H_{69}N_2O_6Si_2$ ([MH]$^+$): 729.4688, found: 729.4681.

Ketone 81

A solution of hydrazone **79** (1.59 g, 2.18 mmol) in THF (8 mL) was added dropwise to a stirred solution of freshly prepared LDA (2.62 mmol) in THF (15 mL) at −78 °C. After 2 h, a solution of iodide **39** (2.10 g, 2.62 mmol) in THF (7 mL) was added dropwise over 15 min, and the mixture was stirred at −78 °C for before being poured into aqueous pH 7.0 buffer (60 mL). The layers were separated, and the aqueous layer was extracted with Et_2O

(3 × 25 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by filtration through silica gel with 10% Et_2O in hexanes with 1% Et_3N. This residue was then taken up in sat. aq. $(CO_2H)_2$ (17 mL) and Et_2O (17 mL) at room temperature, and was stirred vigorously for 16 h. Additional Et_2O (4 mL) and sat. aq. $(CO_2H)_2$ (4 mL) were then added, and the mixture was stirred for an additional 24 h. The mixture was then diluted with water (10 mL) and extracted with Et_2O (2 × 20 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: 2–15% Et_2O in hexanes) to give **81** (1.811 g, 64% from **79**) as a colourless foam. $R_f = 0.51$ (silica gel, 22 : 3 hexanes–Et_2O); $[\alpha]_D^{25}$ +52.5° (*c* 0.75 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 2955, 2171, 1746, 1613, 1472, 1250, 1096, 775; δ_H (600 MHz, C_6D_6) 7.22 (2 H, d, *J* 8.4 Hz, Ar*H*), 6.87 (2 H, d, *J* 8.4 Hz, Ar*H*), 5.27 (1 H, d, *J* 9.2 Hz, 11-H), 4.98 (1 H, dt, *J* 10.1, 3.1 Hz, 25-H), 4.68–4.70 (1 H, m, 7-H), 4.45 (2 H, s, OCH_2Ar), 4.17 (1 H, dd, *J* 9.8, 2.2 Hz, 14-H), 4.03 (1 H, dd, *J* 7.3, 4.2 Hz, 16-H), 3.87–3.92 (2 H, m, 19-H and 21-H), 3.73–3.76 (1 H, m, 24-H), 3.64–3.67 (1 H, m, 9-H), 3.34 (3 H, s, $ArOCH_3$), 2.65–2.71 (2 H, m, 10-H and 13-H), 2.08–2.17 (2 H, m, 8-H and 13-H), 1.96–2.02 (1 H, m, 17-H), 1.60–1.92 (11 H, m, 8-H, 17-H, 18-H, 18-H, 20-H, 20-H, 22-H, 23-H, 23-H, 26-H and 26-H), 1.56 (3 H, s, 12-CH_3), 1.23–1.42 (5 H, m, 22-H, 27-H, 27-H, 28-H and 28-H), 1.44 [3 H, s, $O_2C(CH_3)_2$], 1.39 [3 H, s, $O_2C(CH_3)_2$], 1.18 [9 H, s, $O_2CC(CH_3)_3$], 1.00 (3 H, d, *J* 6.8 Hz, 10-CH_3), 0.98 [9 H, s, $SiC(CH_3)_3$], 0.96 [9 H, s, $SiC(CH_3)_3$], 0.96 [9 H, s, $SiC(CH_3)_3$], 0.95 [9 H, s, $SiC(CH_3)_3$], 0.83 (3 H, t, *J* 6.8 Hz, 28-CH_3), 0.20 (3 H, s, $SiCH_3$), 0.18 (3 H, s, $SiCH_3$), 0.14 (3 H, s, $SiCH_3$), 0.13 [9 H, s, $Si(CH_3)_3$], 0.12 (3 H, s, $SiCH_3$), 0.12 (3 H, s, $SiCH_3$), 0.11 (3 H, s, $SiCH_3$), 0.09 (6 H, s, $SiCH_3$ and $SiCH_3$); δ_C (150 MHz, C_6D_6) 209.9, 177.3, 159.6, 131.6, 129.5, 129.0, 113.9, 108.6, 101.0, 89.2, 78.9, 75.4, 74.5, 74.1, 73.2, 72.2, 69.9, 69.9, 62.1, 54.7, 45.2, 41.0, 38.9, 38.4, 35.8, 34.0, 33.2, 28.7, 28.1, 27.8, 27.4, 26.2, 26.2, 26.1, 26.1, 25.0, 24.2, 24.1, 22.8, 18.4, 18.3, 18.3, 18.2, 17.3, 16.7, 14.2, 0.0, −4.1, −4.1, −4.2, −4.2, −4.3, −4.7; HRMS (ES^+) *m*/*z* calc. for $C_{70}H_{132}O_{11}Si_5Na$ ($[MNa]^+$): 1311.8508, found: 1311.8503.

Acetal 82

To a stirred solution of ketone **81** (1.80 g, 1.40 mmol) in 4 : 1 MeOH–CH_2Cl_2 (100 mL) was added $TsOH{\cdot}H_2O$ (133 mg, 0.698 mmol) in one portion at room temperature. After 16 h, another portion of $TsOH{\cdot}H_2O$ (133 mg, 0.698 mmol) was added, and stirring continued for a further 4 h. Et_3N (2 mL) was then added to the mixture, which was subsequently concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient: 50–66% EtOAc in hexanes) to give **82** (0.716 g, 64%) as a white foam. ^{1}H-NMR, ^{13}C-NMR and HSQC analysis revealed the product to be a 1.4 : 1 mixture of anomers at the C-15 position. $R_f = 0.31$ (1 : 2 hexanes–EtOAc); $[\alpha]_D^{25}$ +20.8° (*c* 1.06 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 3424, 2956, 2171, 1728, 1614, 1514, 1455, 1123; δ_H (600 MHz, C_6D_6) 7.27 [4 H, d, *J* 8.2 Hz, Ar*H* (anomers a and b)], 6.81 [4 H, d, *J* 8.2 Hz, Ar*H* (a and b)], 5.29 [2 H, d, *J* 7.1 Hz, 11-H (a and b)], 5.02–5.08 [2 H, m, 25-H (a and b)], 4.83 (1 H, br s, O*H*), 4.72–4.75 [2 H, m, 7-H (a and b)], 4.54 [2 H, d, *J* 11.0 Hz, OCH_2Ar (a and b)], 4.46 [2 H, d, *J* 11.0 Hz, OCH_2Ar (a and b)], 4.24 (1 H, br s, O*H*), 4.04–4.07 [1 H, m, 14-H (a and b)], 3.98–4.00 [2 H, m, 16-H (a and b)], 3.90–3.94 [2 H, m, 21-H (a and b)], 3.78–3.82 [1 H, m, 19-H (a)], 3.68–3.75 [5 H, m, 9-H (a and b), 19-H (b) and 24-H (a and b)], 3.37 [6 H, s, $ArOCH_3$ (a and b)], 3.14 [6 H, s, OCH_3 (a and b)], 2.82–2.87 [2 H, m, 10-H (a and b)], 2.33–2.43 [4 H, m, 13-H (a and b) and 13-H (a and b)], 2.14–2.20 [3 H, m, 8-H (a and b) and 17-H (a)], 1.91–2.00 [5 H, m, 8-H (a and b), 17-H (b) and 18-H (a and b)], 1.72 [6 H, s, 12-CH_3 (a and b)], 1.53–1.85 [15 H, m, 17-H (a and b), 20-H (a and b), 22-H (a and b), 22-H (a), 23-H (a and b), 23-H (a and b), 27-H (a and b) and 27-H (a and b)], 1.24 [9 H, s, $O_2CC(CH_3)_3$], 1.24 [9 H, s, $O_2CC(CH_3)_3$], 1.20–1.48 [6 H, m, 20-H (a and b), 22-H (b), 27-H (a and b), 27-H (a and b), 28-H (a and b) and 28-H (a and b)], 1.11–1.18 [2 H, m, 18-H (a and b)[, 1.08 p6 H, d, *J* 6.5 Hz, 10-CH_3 (a and b)], 0.88–0.93 [6 H, m, 28-CH_3 (a and b)]; δ_C (150 MHz, C_6D_6) 178.2, 159.6, 133.1, 133.0, 131.1, 129.7, 129.5, 129.4, 114.0, 108.5, 97.8, 88.8, 80.8, 76.6, 76.3, 72.7, 72.6, 72.4, 72.0, 72.0, 72.0, 71.9, 71.8, 71.7, 71.5, 71.0, 67.3, 61.7, 54.8, 47.7, 42.7, 40.9, 40.8, 39.8, 39.8, 39.1, 35.5, 34.2, 34.0, 33.1, 30.8, 30.1, 29.0, 28.5, 28.5, 28.2, 27.4, 27.4, 26.6, 26.5, 25.3, 23.1, 22.9, 17.0, 16.9, 15.9, 14.2, 0.1; HRMS (ES^+) *m*/*z* calc. for $C_{44}H_{74}O_{11}SiNa$ ($[MNa]^+$): 829.4892, found 829.4892.

t-Butyldimethylsilyl ether 83

To a stirred solution of alkyne **82** (539 mg, 0.668 mmol) and 2,6-lutidine (1.17 mL, 10.0 mmol) in CH_2Cl_2 (30 mL) was added TBSOTf (1.15 mL, 5.0 mmol) dropwise at −78 °C. The mixture was warmed to 0 °C and stirred for a further 90 min, before being partitioned between a 1 : 1 sat. aq. $NaHCO_3$–brine mixture (40 mL) and CH_2Cl_2 (20 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 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 (gradient: 2–3% Et_2O in hexanes) to give **83** (498 mg, 54%) as a pale yellow oil. ^{1}H-NMR, ^{13}C-NMR and HSQC analysis revealed the product to be a 1.4 : 1 mixture of anomers at the C-15 position. $R_f = 0.23$ (24 : 1 hexanes–Et_2O); $[\alpha]_D^{25}$ +3.3° (*c* 0.6 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 2953, 2857, 2171, 1728, 1614, 1514, 1462, 1250, 1123, 839; δ_H (500 MHz, C_6D_6, 343 K) 7.26 [4 H, d, *J* 8.5 Hz, Ar*H* (anomers a and b)], 6.79 [4 H, d, *J* 8.5 Hz, Ar*H* (a and b)], 5.38 [2 H, d, *J* 9.8 Hz, 11-H (a and b)], 4.99–5.02 [1 H, m, 25-H (a)], 4.97–5.00 [1 H, m, 25-H (b)], 4.76 [2 H, dd, *J* 8.6, 5.6 Hz, 7-H (a and b)], 4.56 [2 H, d, *J* 11.2 Hz, OCH_2Ar (a and b)], 4.51 [2 H, d, *J* 11.2 Hz, OCH_2Ar (a and b)], 4.32 [2 H, d, *J* 9.1 Hz, 14-H (a and b)], 3.93–3.97 [2 H, m, 19-H (a and b)], 3.81–3.86 [5 H, m, 16-H (a and b), 21-H (a and b) and 24-H (b)], 3.77–3.80 [1 H, m, 24-H (a)], 3.72–3.76 [2 H, m, 9-H (a and b)], 3.41 [6 H, s, $ArOCH_3$ (a and b)], 3.29 [3 H, s, OCH_3 (a)], 3.27 [3 H, s, OCH_3 (b)], 2.80–2.86 [2 H, m, 10-H (a and b)], 2.67 [2 H, d, *J* 13.9 Hz, 13-H (a and b)], 2.36–2.41 [2 H m, 13-H (a and b)], 2.09–2.16 [4 H, m, 8-H (a and b) and 17-H (a and b)], 1.94–2.03 [5 H, m, 8-H (a and b), 20-H (a and b) and 26-H (b)], 1.74 [6 H, s, 12-CH_3 (a and b)], 1.48–1.79 [16 H, m, 17-H (a and b), 18-H (a and b), 20-H (a and b), 22-H (a and b), 22-H (a and b), 23-H (a and b), 23-H (a and b), 26-H (a and b)], 1.24–1.44 [9 H, m, 18-H (a and b), 26-H (a), 27-H (a and b), 27-H (a and b), 28-H (a and b) and 28-H (a and b)], 1.20 [9 H, s, $O_2CC(CH_3)_3$], 1.19 [9 H, s, $O_2CC(CH_3)_3$], 1.15 [6 H, d, *J* 6.8 Hz, 10-CH_3 (a and b)], 1.01 [18 H, s, $SiC(CH_3)_3$ and $SiC(CH_3)_3$], 1.00 [18 H, s, $SiC(CH_3)_3$ and $SiC(CH_3)_3$], 0.99 [9 H, s, $SiC(CH_3)_3$], 0.98 [9 H, s, $SiC(CH_3)_3$], 0.98 [9 H, s, $SiC(CH_3)_3$], 0.97 [9 H, s, $SiC(CH_3)_3$], 0.96 [18 H, s, $SiC(CH_3)_3$ and $SiC(CH_3)_3$], 0.87

[3 H, t, *J* 7.2 Hz, 28-CH_3 (a)], 0.85]3 H, t, *J* 6.9 Hz, 28-CH_3 (b)], 0.26 (6 H, s, SiCH_3 and SiCH_3), 0.23 (6 H, s, SiCH_3 and SiCH_3), 0.20 (9 H, s, SiCH_3, SiCH_3 and SiCH_3), 0.18 (3 H, s, SiCH_3), 0.17 (6 H, s, SiCH_3 and SiCH_3), 0.16 [18 H, s, Si(CH_3)$_3$ (a and b)], 0.15 (3 H, s, SiCH_3), 0.15 (9 H, s, SiCH_3, SiCH_3 and SiCH_3), 0.13 (6 H, s, SiCH_3 and SiCH_3), 0.12 (3 H, s, SiCH_3), 0.11 (3 H, s, SiCH_3), 0.09 (6 H, s, SiCH_3 and SiCH_3); δ_C (125 MHz, C_6D_6, 343 K) 177.3, 159.8, 134.0, 132.0, 129.9, 129.4, 114.2, 109.0, 100.4, 89.4, 80.4, 76.3, 75.6, 73.6, 72.9, 72.3, 71.9, 69.7, 69.5, 69.0, 68.9, 67.9, 62.5, 54.9, 48.7, 44.3, 44.1, 43.2, 41.3, 39.0, 36.1, 34.5, 34.4, 32.1, 28.6, 28.5, 27.9, 27.7, 27.5, 27.5, 26.6, 26.5, 26.2, 26.1, 25.3, 24.2, 23.0, 22.8, 19.1, 18.5, 18.4, 18.3, 16.6, 16.3, 14.0, 0.0, −2.5, −3.5, −3.6, −3.8, −3.9, −3.9, −4.0, −4.1, −4.3, −4.5; HRMS (ES$^+$) *m*/*z* calc. for $C_{74}H_{144}O_{11}Si_6Na$ ([MNa]$^+$): 1399.9216, found 1392.9186.

Alkyne 84

To a stirred solution of alkyne **83** (390 mg, 0.283 mmol) in 4 : 1 MeOH–Et_2O (10 mL) was added finely powdered K_2CO_3 (391 mg, 2.829 mmol) in one portion at room temperature. After 4 h, the mixture was partitioned between Et_2O (30 mL) and water (30 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 20 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: 2–4% Et_2O in hexanes) to give **84** (309 mg, 84%) as a colourless syrup. ^{1}H-NMR, ^{13}C-NMR and HSQC analysis revealed the product to be a 1.4 : 1 mixture of anomers at the C-15 position. $R_f = 0.21$ (23 : 2 hexanes–Et_2O); $[\alpha]_D^{25}$ +5.3° (*c* 0.38 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 2955, 2857, 2280, 1727, 1614, 1514, 1463, 1250, 1123, 835; δ_H (600 MHz, C_6D_6, 343 K) 7.24 [4 H, d, *J* 8.5 Hz, Ar*H* (anomers a and b)], 6.78 [4 H, d, *J* 8.5 Hz, Ar*H* (a and b)], 5.35 [2 H, d, *J* 9.1 Hz, 11-H (a and b)], 4.99–5.01 [1 H, m, 25-H (a)], 4.96–4.99 [1 H, m, 25-H (b)], 4.71–4.73 [2 H, m, 7-H (a and b)], 4.54 [2 H, d, *J* 11.2 Hz, OCH_2Ar (a and b)], 4.46 [2 H, d, *J* 11.2 Hz, OCH_2Ar (a and b)], 4.32 [2 H, d, *J* 9.1 Hz, 14-H (a and b)], 3.95–3.99 [2 H, m, 19-H (a and b)], 3.81–3.85 [5 H, m, 16-H (a and b), 21-H (a and b) and 24-H (b)], 3.77–3.80 [1 H, m, 24-H (a)], 3.68–3.71 [2 H, m, 9-H (a and b)], 3.40 [6 H, s, ArOCH_3 (a and b)], 3.28 [3 H, s, OCH_3 (a)], 3.26 [3 H, s, OCH_3 (b)], 2.81–2.85 [2 H, m, 10-H (a and b)], 2.69 [2 H, d, *J* 13.9 Hz, 13-H (a and b)], 2.34–2.38 [2 H, m, 13-H (a and b)], 2.08–2.15 [4 H, m, 5-H (a and b) and 8-H (a and b)], 1.95–1.99 [5 H, m, 8-H (a and b), 20-H (a and b) and 26-H (b)], 1.72 [6 H, s, 12-CH_3 (a and b)], 1.46–1.80 [20 H, m, 17-H (a and b),17-H (a and b), 18-H (a and b), 18-H (a and b), 20-H (a and b), 22-H (a and b), 22-H (a and b), 23-H (a and b), 23-H (a and b) and 26-H (a and b)], 1.24–1.44 [7 H, m, 26-H (a), 27-H (a and b), 27-H (a and b), 28-H (a and b) and 28-H (a and b)], 1.20 [9 H, s, O_2CC(CH_3)$_3$], 1.18 [9 H, s, O_2CC(CH_3)$_3$], 1.13 [6 H, d, *J* 6.8 Hz, 10-CH_3 (a and b)], 1.00 [18 H, s, SiC(CH_3)$_3$ and SiC(CH_3)$_3$], 0.99 [18 H, s, SiC(CH_3)$_3$ and SiC(CH_3)$_3$], 0.98 [9 H, s, SiC(CH_3)$_3$], 0.98 [18 H, s, SiC(CH_3)$_3$ and SiC(CH_3)$_3$], 0.96 [9 H, s, SiC(CH_3)$_3$], 0.95 [18 H, s, SiC(CH_3)$_3$ and SiC(CH_3)$_3$], 0.87 [3 H, t, *J* 7.2 Hz, 28-CH_3 (a)], 0.85 [3 H, t, *J* 6.9 Hz, 28-CH_3 (b)], 0.24 (6 H, s, SiCH_3 and SiCH_3), 0.22 (6 H, s, SiCH_3 and SiCH_3), 0.19 (3 H, s, SiCH_3), 0.17 (9 H, s, SiCH_3, SiCH_3 and SiCH_3), 0.16 (6 H, s, SiCH_3 and SiCH_3), 0.15 (3 H, s, SiCH_3), 0.13 (3 H, s, SiCH_3), 0.12 (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), 0.10 (3 H, s, SiCH_3), 0.09 (6 H, s, SiCH_3 and SiCH_3); δ_C (150 MHz, C_6D_6, 343 K) 177.3, 159.8, 134.1, 131.9, 129.8, 129.4, 129.2, 114.2, 100.3, 86.2, 80.1, 76.3, 75.5, 73.6, 72.9, 72.9, 72.2, 71.9, 69.6, 69.4, 68.9, 68.8, 67.8, 61.8, 54.9, 44.3, 43.2, 41.2, 39.0, 35.9, 34.4, 34.3, 32.0, 28.6, 28.5, 27.9, 27.5, 27.4, 26.7, 26.6, 26.4, 26.2, 26.1, 26.1, 25.4, 23.0, 22.8, 19.0, 18.5, 18.4, 18.3, 16.5, 16.1, 14.0, −2.5, −3.5, −3.6, −3.7, −3.9, −3.9, −4.0, −4.1, −4.2, −4.3, −4.6; HRMS (ES$^+$) *m*/*z* calc. for $C_{71}H_{136}O_{11}Si_5Na$ ([MNa]$^+$): 1327.8821, found 1327.8835.

Alcohol 85

To a stirred solution of pivalate **84** (300 mg, 0.23 mmol) in THF (14 mL) was added Super Hydride® (0.92 mL, 1.0 M in THF, 0.92 mmol) dropwise at 0 °C. After 1.5 h the reaction was quenched by the cautious addition of water (5 mL). The mixture was partitioned between sat. aq. NH_4Cl (20 mL) and Et_2O (20 mL), and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 20 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: 4–8% Et_2O in hexanes) to give **85** (209 mg, 74%) as a colourless oil. ^{1}H-NMR, ^{13}C-NMR and HSQC analysis revealed the product to be a 1.4 : 1 mixture of anomers at the C-15 position. $R_f = 0.32$ (22 : 3 hexanes–Et_2O); $[\alpha]_D^{25}$ −10.8° (*c* 0.48 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 3459, 2957, 2856, 2280, 1615, 1514, 1472, 1251, 1122, 836; δ_H (600 MHz, C_6D_6, 343 K) 7.25 [4 H, d, *J* 8.4 Hz, Ar*H* (anomers a and b)], 6.79 [4 H, d, *J* 8.4 Hz, Ar*H* (a and b)], 5.37 [2 H, d, *J* 9.1 Hz, 11-H (a and b)], 4.73–4.75 [2 H, m, 7-H (a and b)], 4.55 [2 H, d, *J* 11.2 Hz, OCH_2Ar (a and b)], 4.47 [2 H, d, *J* 11.2 Hz, OCH_2Ar (a and b)], 4.34–4.37 [2 H, d, *J* 9.1 Hz, 14-H (a and b)], 4.01–4.03 [1 H, m, 19-H (a)], 3.94–3.97 [1 H, m, 19-H (b)], 3.83–3.87 [4 H, m, 16-H (a and b) and 21-H (a and b)], 3.70–3.73 [2 H, m, 9-H (a and b)], 3.52–2.55 [2 H, m, 25-H (a and b)], 3.47–3.49 [2 H, m, 24-H (a and b)], 3.40 [6 H, s, ArOCH_3 (a and b)], 3.30 [6 H, s, OCH_3 (a and b)], 2.82–2.86 [2 H, m, 10-H (a and b)], 2.71–2.74 [2 H, m, 13-H (a and b)], 2.36–2.40 [2 H, m, 13-H (a and b)], 2.10–2.14 [5 H, m, 5-H (a and b), 8-H (a and b) and 17-H (a)], 1.96–2.00 [4 H, m, 8-H (a and b) and 20-H (a and b)], 1.74 [6 H, s, 12-CH_3 (a and b)], 1.46–1.79 [17 H, m, 17-H (a and b), 18-H (a and b), 20-H (a and b), 22-H (a and b), 22-H (a and b), 23-H (a and b), 23-H (a and b), 26-H (a and b) and 26-H (b)], 1.25–1.40 [12 H, m, 17-H (b), 18-H (a and b), 26-H (a), 27-H (a and b), 27-H (a and b), 28-H (a and b) and 28-H (a and b)], 1.14 [6 H, d, *J* 6.8 Hz, 10-CH_3 (a and b)], 1.02 [18 H, s, SiC(CH_3)$_3$ and SiC(CH_3)$_3$], 1.00 [18 H, s, SiC(CH_3)$_3$ and SiC(CH_3)$_3$], 0.99 [9 H, s, SiC(CH_3)$_3$], 0.99 [9 H, s, SiC(CH_3)$_3$], 0.96 [18 H, s, SiC(CH_3)$_3$ and SiC(CH_3)$_3$], 0.93 [18 H, s, SiC(CH_3)$_3$ and SiC(CH_3)$_3$], 0.91 [3 H, t, *J* 7.3 Hz, 28-CH_3 (a)], 0.87 [3 H, t, *J* 7.1 Hz, 28-CH_3 (b)], 0.26 (6 H, s, SiCH_3 and SiCH_3), 0.24 (6 H, s, SiCH_3 and SiCH_3), 0.18 (6 H, s, SiCH_3 and SiCH_3), 0.17 (6 H, s, SiCH_3 and SiCH_3), 0.16 (3 H, s, SiCH_3), 0.14 (3 H, s, SiCH_3), 0.13 (3 H, s, SiCH_3), 0.13 (6 H, s, SiCH_3 and SiCH_3), 0.12 (3 H, s, SiCH_3), 0.10 (6 H, s, SiCH_3 and SiCH_3), 0.09 (6 H, s, SiCH_3 and SiCH_3), 0.07 (3 H, s, SiCH_3), 0.07 (3 H, s, SiCH_3); δ_C (150 MHz, C_6D_6, 343 K) 160.3, 134.6, 132.4, 130.3, 130.3, 129.9, 129.8, 114.7, 100.8, 86.7, 80.6, 77.1, 76.9, 74.4, 73.8, 73.4, 72.8, 72.4, 70.4, 70.3, 69.4, 68.4, 62.3, 55.4, 44.9, 44.8, 43.8, 41.8, 36.5, 36.4, 34.9, 34.5, 34.3, 33.5, 30.5, 30.0, 29.1, 28.3, 28.1, 27.2, 27.1, 27.0, 26.7, 26.7, 26.6, 25.9, 23.8, 23.6, 19.6, 19.1, 18.9, 18.8, 17.0, 16.6, 16.6, 14.7, 14.6, −2.0, −2.9,

−3.2, −3.3, −3.4, −3.5, −3.6, −3.6, −3.7, −3.7, −4.1; HRMS (ES$^+$) m/z calc. for $C_{66}H_{128}O_{10}Si_5Na$ ([MNa]$^+$): 1243.8246, found 1243.8277.

Alkyne 86

To a stirred solution of alkyne **82** (113 mg, 0.14 mmol) in 5 : 1 MeOH–Et_2O (7 mL) was added K_2CO_3 (193 mg, 1.4 mmol) in one portion at room temperature. After 4 h the mixture was diluted with Et_2O (20 mL), filtered through a pad of Celite®, washing thoroughly with Et_2O, and the filtrate was concentrated under reduced pressure. The residue was triturated with CH_2Cl_2, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient: 50–80% EtOAc in hexanes) to give **86** (31 mg, 30%) as a colourless paste. ^{1}H-NMR, ^{13}C-NMR and HSQC analysis revealed the product to be a 1.4 : 1 mixture of anomers at the C-15 position. R_f = 0.13 (1 : 2 hexanes–EtOAc); $[\alpha]_D^{25}$ +10.3° (*c* 1.31 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 3448, 2956, 2872, 2279, 1718, 1612, 1513, 1458, 1158, 1115, 740; δ_H (600 MHz, C_6D_6, 343 K) 7.23 [4 H, d, *J* 8.3 Hz, Ar*H* (anomers a and b)], 6.81 [4 H, d, *J* 8.3 Hz, Ar*H* (a and b)], 5.27 [2 H, d, *J* 9.0 Hz, 11-H (a and b)], 4.99–5.03 [2 H, m, 25-H (a and b)], 4.57–4.59 [2 H, m, 7-H (a and b)], 4.50 [2 H, d, *J* 11.1 Hz, OCH_2Ar (a and b)], 4.42 [1 H, d, *J* 11.1 Hz, OCH_2Ar (a and b)], 4.22 (2 H, br s, O*H* and O*H*), 3.99 [2 H, d, *J* 10.0 Hz, 14-H (a and b)], 3.89–3.92 [2 H, m, 16-H (a and b)], 3.83–3.86 [1 H, m, 21-H (a)], 3.74–3.78 [3 H, m, 19-H (a and b) and 21-H (b)], 3.62–3.68 [4 H, m, 9-H (a and b) and 24-H (a and b)], 3.39 [6 H, s, ArOCH_3 (a and b)], 3.13 [6 H, s, OCH_3 (a and b)], 2.78–2.82 [2 H, m, 10-H (a and b)], 2.42 [1 H, d, *J* 13.9 Hz, 13-H (a)], 2.22–2.28 [3 H, m, 13-H (a and b) and 13-H (b)], 2.06–2.11 [2 H, m, 8-H (a and b)], 1.85–1.95 [6 H, m, 8-H (a and b), 17-H (a and b) and 18-H (a and b)], 1.69 [6 H, s, 12-CH_3 (a and b)], 1.56–1.78 [15 H, m, 5-H (a and b), 17-H (a and b), 20-H (a and b), 22-H (a and b), 22-H (a and b), 23-H (a and b), 23-H (b) and 26-H (a and b)], 1.22–1.47 [13 H, m, 20-H (a and b), 23-H (a), 26-H (a and b), 27-H (a and b), 27-H (a and b), 28-H (a and b) and 28-H (a and b)], 1.21 [9 H, s, $O_2CC(CH_3)_3$], 1.21 [9 H, s, $O_2CC(CH_3)_3$], 1.10–1.14 [2 H, m, 18-H (a and b)], 1.04 [6 H, d, *J* 6.7 Hz, 10-CH_3 (a and b)], 0.87–0.90 [3 H, m, 28-CH_3 (a and b)]; δ_C (150 MHz, C_6D_6, 343 K) 178.0, 159.9, 133.7, 133.5, 131.4, 129.8, 129.7, 129.6, 129.5, 125.7, 114.3, 98.3, 86.0, 80.9, 76.8, 76.6, 73.5, 73.1, 72.9, 72.6, 72.1, 72.1, 72.0, 71.8, 71.1, 71.0, 67.1, 61.2, 54.9, 47.9, 43.4, 43.2, 40.9, 40.2, 40.2, 39.1, 35.8, 34.4, 34.1, 33.5, 30.5, 30.4, 30.1, 29.7, 28.3, 28.1, 27.4, 26.9, 26.6, 25.3, 25.3, 22.9, 22.8, 17.1, 17.1, 15.8, 14.0, 14.0; HRMS (ES$^+$) m/z calc. for $C_{41}H_{66}O_{11}Na$ ([MNa]$^+$): 757.4497, found 757.4496.

Diene 91

Alkyne **85** (65 mg, 53.2 μmol) and Grubbs second-generation catalyst **88** (2.3 mg, 2.7 μmol) were dissolved in CH_2Cl_2 (4 mL) in a microwave reactor tube (9.0 × 1.5 cm) equipped with a stirrer bar at room temperature. The solution was purged with ethylene (from a balloon) for 5 min, then sealed and microwaved (2 × 20 min, 100 W microwave power, 55 °C maximum temperature). After cooling to room temperature, the reactor tube was opened, another portion of catalyst **88** (2.3 mg, 2.7 μmol) was added, the mixture was purged with ethylene for 5 min, then the tube was sealed and microwaved again (1 × 50 min, 100 W microwave power, 55 °C maximum temperature). After cooling to room temperature, the reactor tube was opened and the mixture concentrated. The residue was purified by flash chromatography on silica gel (gradient: 2–6% Et_2O in hexanes) to give **91** (53 mg, 80%) as a colourless oil. ^{1}H-NMR, ^{13}C-NMR and HSQC analysis revealed the product to be a 1.4 : 1 mixture of anomers at the C-15 position. R_f = 0.38 (21 : 4 hexanes–Et_2O); $[\alpha]_D^{25}$ −2.2° (*c* 0.46 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 3546, 2955, 2861, 1614, 1514, 1472, 1252, 1123, 1095; δ_H (600 MHz, C_6D_6, 343 K) 7.30 [4 H, d, *J* 8.0 Hz, Ar*H* (anomers a and b)], 6.84 [4 H, d, *J* 8.0 Hz, Ar*H* (a and b)], 6.36 [2 H, dd, *J* 17.7, 11.1 Hz, 5-H (a and b)], 5.56 [2 H, d, *J* 17.7 Hz, 5=CH_2 (a and b)], 5.46 [2 H, d, *J* 9.2 Hz, 11-H (a and b)], 5.07–5.10 [6 H, m, 5=CH_2 (a and b), 6=CH_2 (a and b) and 6=CH_2 (a and b)], 4.62–4.65 [2 H, m, 7-H (a and b)], 4.55 [2 H, d, *J* 11.3 Hz, OCH_2Ar (a and b)], 4.47 [2 H, d, *J* 11.3 Hz, OCH_2Ar (a and b)], 4.37 [2 H, app d, *J* 8.7 Hz, 14-H (a and b)], 4.03–4.07 [1 H, m, 19-H (a)], 4.07 [1 H, m, 19-H (b)], 3.88–3.94 [4 H, m, 16-H (a and b) and 21-H (a and b)], 3.56–3.60 [2 H, m, 25-H (a and b)], 3.51–3.54 [4 H, m, 9-H (a and b) and 24-H (a and b)], 3.39 [6 H, s, ArOCH_3 (a and b)], 3.33 [3 H, s, OCH_3 (a)], 3.33 [3 H, s, OCH_3 (b)], 2.89–2.94 [2 H, m, 10-H (a and b)], 2.74 [2 H, d, *J* 13.7 Hz, 13-H (a and b)], 2.44–2.48 [2 H, m, 13-H (a and b)], 2.09–2.18 [2 H, 8-H (a and b)], 2.00–2.07 [4 H, m, 8-H (a and b) and 20-H (a and b)], 1.80 [6 H, s, 12-CH_3 (a and b)], 1.48–1.90 [20 H, m, 17-H (a and b), 17-H (a and b), 18-H (a and b), 20-H (a and b), 22-H (a and b), 22-H (a and b), 23-H (a and b), 23-H (a and b), 26-H (a and b) and 26-H (a and b)], 1.26–1.44 [10 H, m, 18-H (a and b), 27-H (a and b), 27-H (a and b), 28-H (a and b) and 28-H (a and b)], 1.24 [6 H, d, *J* 6.8 Hz, 10-CH_3 (a and b)], 1.06 [18 H, s, SiC(CH_3)$_3$ and SiC(CH_3)$_3$], 1.04 [18 H, s, SiC(CH_3)$_3$ and SiC(CH_3)$_3$], 1.03 [9 H, s, SiC(CH_3)$_3$], 1.02 [9 H, s, SiC(CH_3)$_3$], 0.99 [18 H, s, SiC(CH_3)$_3$ and SiC(CH_3)$_3$], 0.96 [18 H, s, SiC(CH_3)$_3$ and SiC(CH_3)$_3$], 0.93 (3 H, t, *J* 7.2 Hz, 28-CH_3), 0.90 [3 H, t, *J* 7.1 Hz, 28-CH_3 (b)], 0.32 [6 H, s, SiCH_3 and SiCH_3 (a)], 0.29 (6 H, s, SiCH_3 and SiCH_3), 0.22 (6 H, s, SiCH_3 and SiCH_3), 0.19 (3 H, s, SiCH_3), 0.17 (6 H, s, SiCH_3 and SiCH_3), 0.17 (3 H, s, SiCH_3), 0.15 (6 H, s, SiCH_3 and SiCH_3), 0.15 (3 H, s, SiCH_3), 0.13 (3 H, s, SiCH_3), 0.13 (6 H, s, SiCH_3 and SiCH_3), 0.12 (3 H, s, SiCH_3), 0.10 (3 H, s, SiCH_3), 0.10 (3 H, s, SiCH_3), 0.09 (3 H, s, SiCH_3); δ_C (150 MHz, C_6D_6, 343 K) 150.1, 136.0, 133.8, 132.2, 130.2, 130.2, 129.2, 129.0, 115.1, 114.2, 114.0, 100.4, 80.0, 76.6, 76.3, 73.9, 73.4, 73.0, 71.9, 71.3, 69.9, 69.8, 68.9, 67.9, 54.9, 44.4, 44.3, 43.3, 39.8, 35.6, 34.0, 33.8, 33.1, 30.5, 29.9, 29.5, 28.6, 27.7, 26.7, 26.6, 26.4, 26.1, 25.4, 23.3, 23.1, 19.1, 18.5, 18.4, 18.3, 18.3, 16.4, 16.3, 14.1, 14.0, −2.5, −2.5, −3.4, −3.6, −3.8, −3.8, −3.9, −3.9, −4.0, −4.1, −4.2, −4.3, −4.6; HRMS (ES$^+$) m/z calc. for $C_{68}H_{132}O_{10}Si_5Na$ ([MNa]$^+$): 1271.8559, found 1271.8869.

Ester 94

To a stirred solution of acid **75** (134 mg, 0.548 mmol) in toluene (6 mL) were added 2,4,6-trichlorobenzoyl chloride (86 μL, 0.548 mmol) and Et_3N (153 μL, 1.096 mmol) sequentially at room temperature. After 2 h, a solution of alcohol **85** (134 mg, 0.11 mmol) in toluene (6 mL) was added to the mixture, followed by a few crystals of 4-DMAP. After 45 min, the mixture was partitioned between sat. aq. NH_4Cl (30 mL) and Et_2O (30 mL). The layers were separated, and the aqueous layer was extracted

with Et_2O (3 × 20 mL). The combined organic layers were washed with a 1 : 1 sat. aq. $NaHCO_3$–brine mixture (1 × 30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient: 2–4% Et_2O in hexanes) to give **94** (146 mg, 92%) as a colourless oil. ^{1}H-NMR, ^{13}C-NMR and HSQC analysis revealed the product to be a 1.4 : 1 mixture of anomers at the C-15 position. $R_f = 0.17$ (25 : 1 hexanes–Et_2O); $[\alpha]_D^{25}$ −1.9° (*c* 0.48 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 2953, 2856, 2280, 1731, 1614, 1472, 1463, 1251, 1095, 837, 776; δ_H (600 MHz, C_6D_6, 343 K) 7.26 [4 H, d, *J* 8.6 Hz, Ar*H* (anomers a and b)], 6.80 [4 H, d, *J* 8.6 Hz, Ar*H* (a and b)], 5.92 [1 H, ddd, *J* 17.2, 10.4 and 6.8 Hz, 4-H (a)], 5.88 [1 H, ddd, *J* 17.2, 10.4 and 6.8 Hz, 4-H (b)], 5.38 [2 H, d, *J* 9.1 Hz, 11-H (a and b)], 5.22 [1 H, d, *J* 17.2 Hz, 4=CH_2 (a)], 5.19 [1 H, d, *J* 17.2 Hz, 4=CH_2 (b)], 5.03–5.08 [3 H, m, 4=CH_2 (a) and 25-H (a and b)], 5.01 [1 H, d, *J* 10.4 Hz, 4=CH_2 (b)], 4.74–4.77 [2 H, m, 7-H (a and b)], 4.57 [2 H, d, *J* 11.2 Hz, OCH_2Ar (a and b)], 4.49 [2 H, d, *J* 11.2 Hz, OCH_2Ar (a and b)], 4.46 [1 H, t, *J* 6.8 Hz, 3-H (a)], 4.42 [1 H, t, *J* 6.8 Hz, 3-H (b)], 4.35 [2 H, d, *J* 8.7 Hz, 14-H (a and b)], 3.97–4.02 [2 H, m, 19-H (a and b)], 3.86–3.89 [5 H, m, 16-H (a and b), 21-H (a and b) and 24-H (b)], 3.83–3.85 [1 H, m, 24-H (a)], 3.72–3.75 [2 H, m, 9-H (a and b)], 3.39 [6 H, s, ArOCH_3 (a and b)], 3.32 [3 H, s, OCH_3 (a)], 3.31 [3 H, s, OCH_3 (b)], 2.83–2.87 [2 H, m, 10-H (a and b)], 2.72 [2 H, d, *J* 13.9 Hz, 13-H (a and b)], 2.57 [2 H, qd, *J* 7.0, 6.8 Hz, 2-H (a and b)], 2.38–2.42 [2 H, m, 13-H (a and b)], 2.12–2.17 [6 H, m, 5-H (a and b), 8-H (a and b) and 17-H (a and b)], 1.98–2.05 [4 H, m, 8-H (a and b) and 20-H (a and b)], 1.75 [6 H, s, 12-CH_3 (a and b)], 1.70 [10 H, m, 17-H (a and b), 18-H (a and b), 20-H (a and b), 23-H (a and b) and 26-H (a and b)], 1.50–1.69 [8 H, m, 22-H (a and b), 22-H (a and b), 23-H (a and b) and 26-H (a and b)], 1.30–1.49 [10 H, m, 18-H (a and b), 27-H (a and b), 27-H (a and b), 28-H (a and b) and 28-H (a and b)], 1.29 [3 H, d, *J* 7.0 Hz, 2-CH_3 (a)], 1.28 [3 H, d, *J* 7.0 Hz, 2-CH_3 (b)], 1.17 [6 H, d, *J* 6.8 Hz, 10-CH_3 (a and b)], 1.03 [18 H, s, SiC(CH_3)$_3$ and SiC(CH_3)$_3$], 1.01 [18 H, s, SiC(CH_3)$_3$ and SiC(CH_3)$_3$], 1.01 [9 H, s, SiC(CH_3)$_3$], 1.00 [18 H, s, SiC(CH_3)$_3$ and SiC(CH_3)$_3$], 0.98 [9 H, s, SiC(CH_3)$_3$], 0.97 [18 H, s, SiC(CH_3)$_3$ and SiC(CH_3)$_3$], 0.96 [9 H, s, SiC(CH_3)$_3$], 0.96 [9 H, s, SiC(CH_3)$_3$], 0.90 [3 H, t, *J* 7.1 Hz, 28-CH_3 (b)], 0.88 [3 H, t, *J* 7.0 Hz, 28-CH_3 (a)], 0.28 (6 H, s, SiCH_3 and SiCH_3), 0.25 (6 H, s, SiCH_3 and SiCH_3), 0.23 (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), 0.18 (6 H, s, SiCH_3 and SiCH_3), 0.17 (3 H, s, SiCH_3), 0.16 (3 H, s, SiCH_3), 0.15 (3 H, s, SiCH_3), 0.14 (12 H, s, SiCH_3, SiCH_3, SiCH_3 and SiCH_3), 0.11 (3 H, s, SiCH_3), 0.10 (9 H, s, SiCH_3, SiCH_3 and SiCH_3), 0.08 (3 H, s, SiCH_3), 0.06 (3 H, s, SiCH_3); δ_C (150 MHz, C_6D_6, 343 K) 173.6, 173.5, 159.8, 140.4, 140.2, 134.1, 134.1, 131.9, 129.9, 129.8, 129.4, 129.3, 115.7, 114.2, 100.4, 86.2, 80.1, 76.7, 76.0, 75.8, 75.7, 73.4, 73.0, 72.9, 72.3, 71.9, 69.8, 69.4, 68.9, 68.9, 67.9, 61.9, 61.8, 54.9, 47.6, 44.5, 44.2, 43.3, 41.2, 36.0, 34.5, 34.5, 31.8, 30.6, 28.7, 28.6, 28.4, 27.9, 27.7, 26.7, 26.6, 26.4, 26.2, 26.1, 26.1, 25.4, 24.1, 23.1, 22.8, 19.1, 18.5, 18.4, 18.4, 18.3, 16.5, 16.1, 14.1, 14.0, 13.5, 13.2, −2.5, −3.5, −3.6, −3.7, −3.9, −4.0, −4.1, −4.2, −4.3, −4.5, −4.6; HRMS (ES$^+$) *m*/*z* calc. for $C_{78}H_{150}O_{12}Si_6Na$ ([MNa]$^+$): 1469.9635, found 1469.9624.

Diene 96

Alkyne **94** (130 mg, 90 μmol) and Grubbs second-generation catalyst **88** (3.8 mg, 4.5 μmol) were dissolved in CH_2Cl_2 (7 mL) in a microwave reactor tube (9.0 × 1.5 cm) equipped with a stirrer bar at room temperature. The solution was purged with ethylene (from a balloon) for 5 min, then sealed and microwaved (2 × 20 min, 100 W microwave power, 55 °C maximum temperature). After cooling to room temperature, the reactor tube was opened, another portion of catalyst **88** (3.8 mg, 4.5 μmol) was added, the mixture was purged with ethylene for 5 min, then the tube was sealed and microwaved again (1 × 50 min, 100 W microwave power, 55 °C maximum temperature). After cooling to room temperature, the reactor tube was opened and the mixture concentrated. The residue was purified by flash chromatography on silica gel (gradient: 2–2.5% Et_2O in hexanes) to give **96** (80 mg, 60%) as a colourless oil. ^{1}H-NMR, ^{13}C-NMR and HSQC analysis revealed the product to be a 1.4 : 1 mixture of anomers at the C-15 position. $R_f = 0.41$ (23 : 2 hexanes–Et_2O); $[\alpha]_D^{25}$ −10.5° (*c* 1.22 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 2956, 2860, 1732, 1615, 1514, 1471, 1250, 1123, 837; δ_H (600 MHz, C_6D_6, 343 K) 7.30 [4 H, d, *J* 8.4 Hz, Ar*H* (anomers a and b)], 6.84 [4 H, d, *J* 8.4 H, Ar*H* (a and b)], 6.36 [2 H, dd, *J* 17.7, 11.2 Hz, 5-H (a and b)], 5.94 [1 H, ddd, *J* 17.3, 10.5 and 6.9 Hz, 4-H (a)], 5.90 [1 H, ddd, *J* 17.2, 10.3 and 6.7 Hz, 4-H (b)], 5.55 [2 H, d, *J* 17.7 Hz, 5=CH_2 (a and b)], 5.45 [2 H, d, *J* 9.1 Hz, 11-H (a and b)], 5.23 [1 H, d, *J* 17.3 Hz, 4=CH_2 (a)], 5.20 [1 H, d, *J* 17.2 Hz, 4=CH_2 (b)], 5.02–5.11 [10 H, m, 4=CH_2 (a and b), 5=CH_2 (a and b), 6=CH_2 (a and b), 6=CH_2 (a and b) and 25-H (a and b)], 4.61–4.65 [2 H, m, 7-H (a and b)], 4.55 [2 H, d, *J* 11.3 Hz, OCH_2Ar (a and b)], 4.42 [4 H, m, 3-H (a and b) and OCH_2Ar (a and b)], 4.35 [2 H, d, *J* 8.7 Hz, 14-H (a and b)], 3.98–4.02 [2 H, m, 19-H (a and b)], 3.88–3.93 [5 H, m, 16-H (a and b), 21-H (a and b) and 24-H (b)], 3.86–3.88 [1 H, m, 24-H (a)], 3.50–3.53 [2 H, m, 9-H (a and b)], 3.40 [6 H, s, ArOCH_3 (a and b)], 3.33 [3 H, s, OCH_3 (a)], 3.32 [3 H, s, OCH_3 (b)], 2.89–2.94 [2 H, m, 10-H (a and b)], 2.71 [2 H, d, *J* 14.0 Hz, 13-H (a and b)], 2.58–2.63 [2 H, m, 2-H (a and b)], 2.43–2.47 [2 H, m, 13-H (a and b)], 1.99–2.19 [9 H, m, 8-H (a and b), 8-H (a and b), 17-H (a), 20-H (a and b) and 26-H (a and b)], 1.79 [6 H, s, 12-CH_3 (a and b)], 1.74–1.90 [9 H, m, 17-H (b), 18-H (a and b), 20-H (a and b), 22-H (a and b), 26-H (a and b)], 1.49–1.69 [8 H, m, 17-H (a and b), 22-H (a and b), 23-H (a and b) and 23-H (a and b)], 1.31–1.48 [10 H, m, 18-H (a and b), 27-H (a and b), 27-H (a and b), 28-H (a and b) and 28-H (a and b)], 1.31 [3 H, d, *J* 6.8 Hz, 2-CH_3 (b)], 1.30 [3 H, d, *J* 6.9 Hz, 2-CH_3 (a)], 1.23 [6 H, d, *J* 6.9 Hz, 10-CH_3 (a and b)], 1.06 [18 H, s, SiC(CH_3)$_3$ and SiC(CH_3)$_3$], 1.03 [18 H, s, SiC(CH_3)$_3$ and SiC(CH_3)$_3$], 1.03 [9 H, s, SiC(CH_3)$_3$], 1.02 [18 H, s, SiC(CH_3)$_3$ and SiC(CH_3)$_3$], 1.00 [18 H, s, SiC(CH_3)$_3$ and SiC(CH_3)$_3$], 0.99 [9 H, s, SiC(CH_3)$_3$], 0.98 [9 H, s, SiC(CH_3)$_3$], 0.97 [9 H, s, SiC(CH_3)$_3$], 0.92 [3 H, t, *J* 7.2 Hz, 28-CH_3 (b)], 0.90 [3 H, t, *J* 6.9 Hz, 28-CH_3 (a)], 0.31 (6 H, s, SiCH_3 and SiCH_3), 0.28 (6 H, s, SiCH_3 and SiCH_3), 0.25 (3 H, s, SiCH_3), 0.23 (3 H, s, SiCH_3), 0.21 (6 H, s, SiCH_3 and SiCH_3), 0.20 (3 H, s, SiCH_3), 0.19 (3 H, s, SiCH_3), 0.18 (3 H, s, SiCH_3), 0.17 (3 H, s, SiCH_3), 0.16 (3 H, s, SiCH_3), 0.16 (6 H, s, SiCH_3 and SiCH_3), 0.14 (6 H, s, SiCH_3 and SiCH_3), 0.13 (3 H, s, SiCH_3), 0.12 (3 H, s, SiCH_3), 0.11 (6 H, s, SiCH_3 and SiCH_3), 0.10 (3 H, s, SiCH_3), 0.09 (3 H, s, SiCH_3), 0.08 (3 H, s, SiCH_3); δ_C (150 MHz, C_6D_6, 343 K) 173.7, 173.6, 159.8, 150.1, 140.4, 140.2, 136.0, 133.7, 132.2, 130.3, 129.2, 129.0, 115.7, 115.1, 114.2, 114.0, 100.4, 80.0, 76.7, 76.1, 75.9, 75.7, 73.4, 73.0, 71.8, 71.3, 69.9, 69.5, 69.0, 69.0, 67.9, 54.9, 47.7, 44.4, 43.2, 39.8, 35.5, 34.6, 34.5, 31.8, 30.5, 30.1, 28.7, 28.7, 28.4, 27.9, 27.8, 26.7, 26.5, 26.2, 26.1, 25.4, 23.1, 22.9, 19.1, 18.6, 18.4, 18.3, 16.4, 16.2, 14.1, 14.0, 13.5, 13.3, −2.5, −3.5,

−3.6, −3.8, −3.8, −3.9, −4.0, −4.1, −4.2, −4.3, −4.3, −4.5, −4.6; HRMS (ES$^+$) *m/z* calc. for $C_{80}H_{154}O_{12}Si_6Na$ ([MNa]$^+$): 1497.9948, found 1497.9950.

Alcohol 98

To a vigorously stirred solution of alkyne **94** (200 mg, 0.138 mmol) in CH_2Cl_2 (7 mL) and aqueous pH 7 buffer (3.5 mL) was added DDQ (53.3 mg, 0.234 mmol) in one portion at 0 °C. After 40 min at this temperature, the mixture was partitioned between CH_2Cl_2 (30 mL) and sat. aq. $NaHCO_3$ (30 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 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: 2–3% Et_2O in hexanes) to give **98** (159 mg, 89%) as a colourless oil. ^{1}H-NMR, ^{13}C-NMR and HSQC analysis revealed the product to be a 1.4 : 1 mixture of anomers at the C-15 position. $R_f = 0.19$ (25 : 2 hexanes–Et_2O); $[\alpha]_D^{25}$ +3.1° (*c* 0.98 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 3501, 2957, 2857, 2280, 1730, 1617, 1462, 1255, 1123, 836, 776, 740; δ_H (500 MHz, C_6D_6, 343 K) 5.91 [1 H, ddd, *J* 17.3, 10.4 and 6.8 Hz, 4-H (anomer a)], 5.88 [1 H, ddd, *J* 17.5, 10.4 and 6.8 Hz, 4-H (anomer b)], 5.25 [2 H, d, *J* 9.6 Hz, 11-H (a and b)], 5.21 [1 H, d, *J* 17.3 Hz, 4=CH_2 (a)], 5.18 [1 H, d, *J* 17.5 Hz, 4=CH_2 (b)], 5.00–5.06 [4 H, m, 25-H (a and b) and 4=CH_2 (a and b)], 4.79–4.82 [2 H, m, 7-H (a and b)], 4.45 [1 H, t, *J* 6.8 Hz, 3-H (a)], 4.41 [1 H, t, *J* 6.8 Hz, 3-H (b)], 4.30–4.35 [2 H, m, 14-H (a and b)], 3.94–3.99 [2 H, m, 19-H (a and b)], 3.81–3.88 [6 H, m, 16-H (a and b), 21-H (a and b) and 24-H (a and b)], 3.77–3.80 [2 H, m, 9-H (a and b)], 3.30 [3 H, s, OCH_3 (b)], 3.30 [3 H, s, OCH_3 (a)], 2.77 [2 H, d, *J* 14.0 Hz, 13-H (a and b)], 2.55 [2 H, qd *J* 6.9, 6.8 Hz, 2-H (a and b)], 2.39–2.44 [2 H, m, 10-H (a and b)], 2.35 [2 H, dd, *J* 14.0, 8.6 Hz, 13-H (a and b)], 2.09–2.16 [4 H, m, 5-H (a and b) and 17-H (a and b)], 1.95–2.04 [4 H, m, 8-H (a and b) and 20-H (a and b)], 1.70 [3 H, s, 12-CH_3 (b)], 1.70 [3 H, s, 12-CH_3 (a)], 1.70–1.85 [10 H, m, 8-H (a and b), 17-H (a and b), 18-H (a and b), 20-H (a and b) and 23-H (a and b)], 1.45–1.67 [10 H, 22-H (a and b), 22-H (a and b), 23-H (a and b), 26-H (a and b) and 26-H (a and b)], 1.32–1.43 [10 H, m, 18-H (a and b), 27-H (a and b), 27-H (a and b), 28-H (a and b) and 28-H (a and b)], 1.28 [3 H, d, *J* 6.9 Hz, 2-CH_3 (b)], 1.27 [3 H, d, *J* 6.9 Hz, 2-CH_3 (a)], 1.03 [6 H, d, *J* 6.7 Hz, 10-CH_3 (a and b)], 1.01 [18 H, s, SiC(CH_3)$_3$ and SiC(CH_3)$_3$], 1.00 [18 H, s, SiC(CH_3)$_3$ and SiC(CH_3)$_3$], 0.99 [9 H, s, SiC(CH_3)$_3$], 0.99 [9 H, s, SiC(CH_3)$_3$], 0.99 [9 H, s, SiC(CH_3)$_3$], 0.98 [9 H, s, SiC(CH_3)$_3$], 0.98 [18 H, s, SiC(CH_3)$_3$ and SiC(CH_3)$_3$], 0.96 [9 H, s, SiC(CH_3)$_3$], 0.95 [9 H, s, SiC(CH_3)$_3$], 0.90 [3 H, t, *J* 7.1 Hz, 28-CH_3 (b)], 0.88 [3 H, t, *J* 7.1 Hz, 28-CH_3 (a)], 0.25 (6 H, s, SiCH_3 and SiCH_3), 0.22 (6 H, s, SiCH_3 and SiCH_3), 0.22 (9 H, s, SiCH_3, SiCH_3 and SiCH_3), 0.20 (6 H, s, SiCH_3 and SiCH_3), 0.18 (3 H, s, SiCH_3), 0.17 (3 H, s, SiCH_3), 0.17 (3 H, s, SiCH_3), 0.16 (6 H, s, SiCH_3 and SiCH_3), 0.16 (3 H, s, SiCH_3), 0.15 (6 H, s, SiCH_3 and SiCH_3), 0.13 (6 H, s, SiCH_3 and SiCH_3), 0.11 (9 H, s, SiCH_3, SiCH_3 and SiCH_3), 0.07 (3 H, s, SiCH_3), 0.06 (3 H, s, SiCH_3); δ_C (125 MHz, C_6D_6, 343 K) 173.8, 173.6, 140.5, 140.3, 135.6, 129.7, 115.7, 100.5, 86.4, 86.3, 76.8, 76.1, 75.9, 75.7, 73.5, 73.1, 72.5, 72.5, 72.0, 71.6, 69.9, 69.6, 69.1, 68.9, 67.9, 61.0, 47.8, 47.7, 44.5, 43.8, 43.7, 39.6, 39.5, 34.6, 31.9, 30.6, 28.8, 28.7, 28.5, 28.0, 27.8, 26.7, 26.7, 26.6, 26.5, 26.3, 26.2, 26.1, 25.4, 24.4, 23.2, 22.9, 19.1, 18.6, 18.5, 18.4, 18.4, 18.3, 16.9, 16.9, 16.8, 14.1, 14.0, 13.6, 13.3, −2.6, −2.6, −3.5, −3.5, −3.6, −3.8, −3.8, −3.9, −4.0, −4.1, −4.2, −4.3, −4.4, −4.8; HRMS (ES$^+$) *m/z* calc. for $C_{70}H_{142}O_{11}Si_6Na$ ([MNa]$^+$): 1349.9059, found 1349.9083.

Ketone 99

To a stirred suspension of alcohol **98** (140 mg, 0.105 mmol) and powdered, activated 4 Å molecular sieves (*ca.* 100 mg) in CH_2Cl_2 (6 mL) was added NMO (62 mg, 0.527 mmol) in one portion at room temperature. After 10 min, TPAP (37 mg, 0.105 mmol) was added in one portion, and stirring was continued for another 1.5 h, before the mixture was diluted with Et_2O (20 mL) and filtered through a pad of Celite®, washing thoroughly with Et_2O. The filtrate was washed with 5% aq. Na_2SO_3 (1 × 25 mL) and brine (1 × 25 mL). The combined aqueous layers were extracted with Et_2O (1 × 40 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: 1–2% Et_2O in hexanes) to give **99** (106 mg, 76%) as a colourless oil. ^{1}H-NMR, ^{13}C-NMR and HSQC analysis revealed the product to be a 1.4 : 1 mixture of anomers at the C-15 position. $R_f = 0.48$ (25 : 2 hexanes–Et_2O); $[\alpha]_D^{25}$ +33.1° (*c* 1.01 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 2955, 2865, 2281, 1731, 1722, 1618, 1472, 1257, 1123, 834, 776; δ_H (500 MHz, C_6D_6, 343 K) 5.94 [1 H, ddd, *J* 17.2, 10.4 and 6.8 Hz, 4-H (anomer a)], 5.90 [1 H, ddd, *J* 17.2, 10.4 and 6.8 Hz, 4-H (anomer b)], 5.18–5.25 [4 H, m, 11-H (a and b) and 4=CH_2 (a and b)], 5.01–5.11 [6 H, m, 7-H (a and b), 25-H (a and b) and 4=CH_2 (a and b)], 4.48 [1 H, t, *J* 6.8 Hz, 3-H (a)], 4.43 [1 H, t, *J* 6.8 Hz, 3-H (b)], 4.37 [2 H, app d, *J* 9.2 Hz, 14-H (a and b)], 3.98–4.03 [2 H, m, 19-H (a and b)], 3.84–3.90 [6 H, m, 16-H (a and b), 21-H (a and b) and 24-H (a and b)], 3.33 [3 H, s, OCH_3 (a)], 3.32 [3 H, s, OCH_3 (b)], 3.31–3.34 [2 H, m, 10-H) (a and b)], 2.99 [1 H, dd, *J* 16.2, 8.7 Hz, 8-H (b)], 2.98 [1 H, dd, *J* 16.2, 8.7 Hz, 8-H (a)], 2.73–2.76 [2 H, m, 13-H (a and b)], 2.65–2.70 [2 H, m, 8-H (a and b)], 2.59 [2 H, qd, *J* 7.0, 6.8 Hz, 2-H (a and b)], 2.36 [2 H, dd, *J* 14.2, 9.2 Hz, 13-H (a and b)], 2.11–2.19 [2 H, m, 17-H (a and b)], 2.08–2.09 [2 H, m, 5-H (a and b)], 1.99–2.07 [2 H, m, 20-H (a and b)], 1.73 [6 H, s, 12-CH_3 (a and b)], 1.71–1.89 [8 H, m, 18-H (a and b), 20-H (a and b), 23-H (a and b) and 26-H (a and b)], 1.45–1.69 [10 H, m, 17-H (a and b), 22-H (a and b), 22-H (a and b), 23-H (a and b) and 26-H (a and b)], 1.32–1.44 [10 H, m, 18-H (a and b), 27-H (a and b), 27-H (a and b), 28-H (a and b) and 28-H (a and b)], 1.31 [3 H, d, *J* 7.0 Hz, 2-CH_3 (b)], 1.30 [3 H, d, *J* 7.0 Hz, 2-CH_3 (a)], 1.22 [6 H, d, *J* 6.7 Hz, 10-CH_3 (a and b)], 1.02 [9 H, s, SiC(CH_3)$_3$], 1.02 [9 H, s, SiC(CH_3)$_3$], 1.01 [18 H, s, SiC(CH_3)$_3$ and SiC(CH_3)$_3$], 1.01 [9 H, s, SiC(CH_3)$_3$], 1.01 [9 H, s, SiC(CH_3)$_3$], 1.00 [18 H, s, SiC(CH_3)$_3$ and SiC(CH_3)$_3$], 0.98 [18 H, s, SiC(CH_3)$_3$ and SiC(CH_3)$_3$], 0.98 [9 H, s, SiC(CH_3)$_3$], 0.97 [9 H, s, SiC(CH_3)$_3$], 0.91 [3 H, t, *J* 7.1 Hz, 28-CH_3 (b)], 0.89 [3 H, t, *J* 7.1 Hz, 28-CH_3 (a)], 0.26 (6 H, s, SiCH_3 and SiCH_3), 0.24 (3 H, s, SiCH_3), 0.23 (6 H, s, SiCH_3 and 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), 0.18 (6 H, s, SiCH_3 and SiCH_3), 0.17 (9 H, s, SiCH_3, SiCH_3 and SiCH_3), 0.16 (3 H, s, SiCH_3), 0.15 (3 H, s, SiCH_3), 0.15 (3 H, s, SiCH_3), 0.12 (3 H, s, SiCH_3), 0.11 (3 H, s, SiCH_3), 0.10 (6 H, s, SiCH_3 and SiCH_3), 0.09 (3 H, s, SiCH_3), 0.07 (3 H, s, SiCH_3); δ_C (125 MHz, C_6D_6, 343 K) 206.2, 173.7, 173.6, 140.5, 140.3, 137.2, 137.2, 126.6, 115.8, 100.4, 85.7, 76.8, 76.1, 75.9, 75.8, 73.6, 73.1, 72.6, 71.9, 70.0, 69.6, 69.1, 69.0, 67.9, 59.7, 49.7, 49.1, 49.0, 47.8, 47.8, 44.6, 43.2, 34.6,

34.6, 32.0, 30.6, 28.8, 28.7, 28.6, 28.1, 27.7, 26.6, 26.5, 26.3, 26.2, 26.1, 26.1, 25.5, 23.2, 22.9, 19.1, 18.6, 18.5, 18.4, 18.4, 16.8, 16.1, 14.1, 14.0, 13.6, 13.3, −2.5, −3.4, −3.7, −3.7, −3.7, −3.8, −3.8, −3.9, −4.0, −4.0, −4.1, −4.2, −4.4, −4.8; HRMS (ES$^+$) m/z calc. for $C_{70}H_{140}O_{11}Si_6Na$ ([MNa]$^+$): 1347.8903, found 1347.8931.

Alkynes 100 and 101

To a stirred solution of alkyne **99** (95 mg, 71.6 μmol) in 8 : 1 MeCN–CH_2Cl_2 (15 mL) was added 48% aq. HF (1.4 mL) dropwise at 0 °C. The mixture was allowed to warm to room temperature and stirred for 4 h, before being poured carefully into ice-cold sat. aq. $NaHCO_3$ (30 mL). The mixture was diluted with EtOAc (30 mL), then solid $NaHCO_3$ was cautiously added with vigorous stirring until the pH of the mixture was 8. The layers were then separated, and the aqueous layer was extracted with EtOAc (5 × 20 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% hexanes in EtOAc-EtOAc) to give an inseparable 1 : 1 mixture (determined by ^{1}H-NMR) of bicyclic acetal **100** and hemiacetal **101** (29.6 mg, 66%) as a colourless oil. $R_f = 0.22$ (EtOAc); $[\alpha]_D^{25}$ +81.3° (c 1.38 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 3414, 2956, 2872, 2280, 1734, 1720, 1619, 1454, 1076, 813. HRMS (ES$^+$) m/z calc. for $C_{33}H_{53}O_{10}$ ([M − OH]$^+$): 609.3639, found 609.3633.

Data for acetal 100. δ_H (600 MHz, C_6D_6, 341 K) 5.84–5.90 (1 H, m, 4-H), 5.29–5.33 (1 H, m, 4=CH_2), 5.20–5.23 (1 H, m, 11-H), 5.06–5.11 (2 H, m, 25-H and 4=CH_2), 4.78–4.81 (1 H, m, 7-H), 4.54–4.56 (1 H, m, 3-H), 4.02 (1 H, dd, J 10.5, 2.3 Hz, 14-H), 3.87–3.94 (1 H, m, 19-H), 3.81–3.84 (1 H, m, 16-H), 3.70–3.74 (1 H, m, 21-H), 3.57–3.63 (1 H, m, 24-H), 3.21–3.26 (1 H, m, 10-H), 2.72–2.75 (2 H, m, 8-H and 8-H), 2.63–2.66 (1 H, m, 2-H), 2.51 (1 H, app d, J 14.3 Hz, 13-H), 2.25–2.29 (1 H, m, 13-H), 2.20 (1 H, s, 5-H), 1.80–1.91 (1 H, m, 17-H), 1.73 (3 H, s, 12-CH_3), 1.48–1.71 (8 H, m, 17-H, 18-H, 20-H, 22-H, 23-H, 23-H, 26-H and 26-H), 1.27–1.42 (5 H, m, 22-H. 27-H, 27-H, 28-H and 28-H), 1.18 (3 H, d, J 7.1 Hz, 2-CH_3), 1.09–1.12 (1 H, m, 20-H), 1.08 (3 H, d, J 6.9 Hz, 10-CH_3), 1.02–1.06 (1 H, m, 18-H), 0.88 (3 H, t, J 7.1 Hz, 28-CH_3); δ_C (150 MHz, C_6D_6, 341 K) 209.2 (C-9), 174.5 (C-1), 138.6 (C-4), 137.2 (C-12), 125.9 (C-11), 115.9 (4=CH$_2$), 98.3 (C-15), 85.0 (C-6), 76.7 (C-25), 73.8 (C-3), 73.8 (C-14), 73.0 (C-24), 72.7 (C-5), 68.5 (C-16), 67.0 (C-21), 66.3 (C-19), 58.8 (C-7), 47.8 (C-8), 47.4 (C-10), 45.4 (C-2), 41.0 (C-13), 35.2 (C-20), 31.5 (C-23), 30.8 (C-26), 30.2 (C-18), 29.9 (C-22), 28.1 (C-27), 24.0 (C-17), 22.9 (C-28), 17.4 (12-CH$_3$), 16.1 (10-CH$_3$), 14.1 (28-CH$_3$), 11.0 (2-CH$_3$).

Data for hemiacetal 101. δ_H (600 MHz, C_6D_6, 341 K) 5.78–5.85 (1 H, m, 4-H), 5.28–5.32 (1 H, m, 4=CH_2), 5.20–5.23 (2 H, m, 11-H and 25-H), 5.06–5.11 (1 H, m, 4=CH_2), 4.78–4.81 (1 H, m, 7-H), 4.47–4.49 (1 H, m, 3-H), 3.98 (1 H, dd, J 10.3, 2.3 Hz, 14-H), 3.87–3.94 (1 H, m, 19-H), 3.81–3.84 (1 H, m, 16-H), 3.74–3.77 (1 H, m, 21-H), 3.57–3.63 (1 H, m, 24-H), 3.21–3.26 (1 H, m, 10-H), 2.72–2.75 (2 H, m, 8-H and 8-H), 2.58–2.61 (1 H, m, 2-H), 2.51 (1 H, app d, J 14.3 Hz, 13-H), 2.24–2.28 (1 H, m, 13-H), 2.20 (1 H, s, 5-H), 1.80–1.91 (2 H, m, 17-H and 26-H), 1.73 (3 H, s, 12-CH_3), 1.48–1.71 (9 H, m, 17-H, 18-H, 20-H, 22-H, 22-H, 23-H, 23-H, 26-H and 27-H), 1.27–1.42 (3 H, m, 27-H, 28-H and 28-H), 1.20 (3 H, d, J 7.1 Hz, 2-CH_3), 1.09–1.12 (1 H, m, 20-H), 1.08 (3 H, d, J 6.9 Hz, 10-CH_3), 1.02–1.06 (1 H, m, 18-H), 0.92 (3 H, t, J 7.2 Hz, 28-CH_3); δ_C (150 MHz, C_6D_6, 341 K) 209.2 (C-9), 174.8 (C-1), 138.6 (C-4), 137.2 (C-12), 125.9 (C-11), 115.8 (4=CH$_2$), 98.5 (C-15), 85.1 (C-6), 77.1 (C-25), 73.5 (C-14), 73.4 (C-3), 72.8 (C-24), 72.8 (C-5), 68.5 (C-16), 66.6 (C-21), 66.3 (C-19), 58.8 (C-7), 47.8 (C-8), 47.4 (C-10), 45.8 (C-2), 41.0 (C-13), 35.0 (C-20), 33.3 (C-23), 30.8 (C-22), 30.1 (C-18), 28.3 (C-27), 27.4 (C-26), 24.0 (C-17), 23.0 (C-28), 17.4 (12-CH$_3$), 16.1 (10-CH$_3$), 14.1 (28-CH$_3$), 11.3 (2-CH$_3$).

2-Bromoacrolein 106 [42]

Br_2 (25.6 mL, 500 mmol) was added dropwise to a stirred solution of acrolein (33.4 mL, 500 mL) in CH_2Cl_2 (750 mL) at −78 °C over 10 min. After an additional 30 min at −78 °C, Et_3N (69.4 mL, 500 mmol) was added and the mixture was warmed to room temperature over 2 h. The reaction was then quenched by the addition of H_2O (600 mL), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (1 × 500 mL). The combined aqueous layers were washed with a 9 : 1 mixture of brine and 1 M HCl (500 mL), dried ($MgSO_4$), filtered and concentrated at room temperature and 300 torr. The residue was purified by vacuum distillation (bp 77–81 °C, 120 torr) to give 2-bromoacrolein **106** (46.05 g, 68%) as a light yellow oil, the spectroscopic data of which were in agreement with those reported in the literature.[42] δ_H (400 MHz, $CDCl_3$) 9.22 (1 H, s, 1-H), 6.88 (1 H, d, J 2.3 Hz, 3-H), 6.87 (1 H, d, J 2.3 Hz, 3-H). This material can be kept for several days when stored at 0 °C under an inert atmosphere, but for optimum results is best used directly following its preparation.

Oxazolidinone 107

A stirred solution of oxazolidinone **105** (23.08 g, 91 mmol) in CH_2Cl_2 (225 mL) was cooled to −78 °C, where n-Bu_2BOTf (100 mL, 1.0 M in CH_2Cl_2, 100 mmol) was added dropwise over 20 min, followed by the addition of freshly distilled i-Pr_2NEt (20.1 mL, 113 mmol). After stirring for 30 min at −78 °C, the solution was warmed to room temperature for 90 min, then re-cooled to −78 °C, where freshly prepared 2-bromoacrolein **106** (37.11 g, 275 mmol) was added dropwise. The solution was stirred at −78 °C for 5 h, then was allowed to warm to room temperature overnight. The solution was then cooled to 0 °C, and quenched by the addition of aqueous pH 7.0 buffer (250 mL) and MeOH (250 mL), followed by the slow dropwise addition of 35% aq. H_2O_2 (400 mL). After 1 h at 0 °C, the solution was extracted with CH_2Cl_2 (3 × 250 mL), and the combined organic layers were washed with sat. aq. $NaHCO_3$ (1 × 250 mL), brine (1 × 250 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The solid residue was purified by flash chromatography on silica gel (gradient: 35–75% Et_2O in hexanes) to give **107** (28.90 g, 82%) as white needles. R_f = 0.18 (silica gel, 1 : 1 hexanes–Et_2O); mp 105–106 °C; $[\alpha]_D^{25}$ +35.9° (c 1.73 in $CHCl_3$); ν_{max}/cm^{-1} (film) 3478, 3063, 2922, 1789, 1713, 1497, 1479, 1210, 1113, 995; δ_H (500 MHz, $CDCl_3$) 7.33–7.36 (2 H, m, ArH), 7.27–7.30 (1 H, m, ArH), 7.21–7.23 (2 H, m, ArH), 6.18 (1 H, dd, J 1.9, 1.4 Hz, 6=CH_2), 6.06 (1 H, d, J 4.1 Hz, 8-H), 5.78 (1 H, dd, J 1.9, 0.8 Hz, 6=CH_2), 4.76–4.78 (1 H, m, 7-H), 4.69–4.73 (1 H, m, OCH$_2$CHN), 4.28 (1 H, dd, J 9.2, 7.7 Hz, OCH_2CHN), 4.24 (1 H, dd, J 9.2, 3.1 Hz, OCH_2CHN), 3.44 (1 H,

d, *J* 5.6 Hz, O*H*), 3.28 (1 H, dd, *J* 13.6, 3.4 Hz, C*H*$_2$Ph), 2.85 (1 H, dd, *J* 13.6, 9.3 Hz, C*H*$_2$Ph); δ_C (125 MHz, $CDCl_3$) 167.7, 152.2, 134.4, 129.4, 129.0, 128.5, 127.5, 120.9, 74.7, 66.5, 56.5, 55.3, 37.0; HRMS (ES$^+$) *m*/*z* calc. for $C_{15}H_{16}{}^{79}Br^{35}ClNO_4$ ([MH]$^+$): 387.9946, found: 387.9938.

Oxazolidinone 108

Oxazolidinone **107** (28.90 g, 74.4 mmol), Zn dust (19.62 g, 300 mmol) and solid NH_4Cl (16.17 g, 300 mmol) were combined in MeOH (400 mL) and stirred vigorously at room temperature for 6 h. Et_2O (500 mL) was then added to the mixture, which was then filtered through a bed of Celite®, washing with Et_2O (2 × 100 mL), and the filtrate was concentrated under reduced pressure. The residue was then taken up in Et_2O (200 mL), filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (25% EtOAc in hexanes) to give **108** (21.42 g, 81%) as colourless needles. R_f = 0.18 (silica gel, 1 : 1 hexanes–Et_2O); $[\alpha]_D^{25}$ +30.0° (*c* 1.73 in $CHCl_3$); ν_{max}/cm^{-1} (film) 3481, 3063, 2921, 1780, 1700, 1498, 1478, 1289, 1072, 991; δ_H (500 MHz, $CDCl_3$) 7.32–7.35 (2 H, m, Ar*H*), 7.26–7.29 (1 H, m, Ar*H*), 7.20–7.21 (2 H, m, Ar*H*), 6.06 (1 H, dd, *J* 2.0, 1.1 Hz, 6=C*H*$_2$), 5.64 (1 H, d, *J* 2.0 Hz, 6=C*H*$_2$), 4.67–4.73 (2 H, m, 7-H and OCH$_2$C*H*N), 4.23 (1 H, dd, *J* 9.1, 7.6 Hz, OC*H*$_2$CHN), 4.19 (1 H, dd, *J* 9.1, 3.0 Hz, OC*H*$_2$CHN), 3.41–3.47 (2 H, m, O*H* and 8-H), 3.26–3.34 (2 H, m, 8-H and C*H*$_2$Ph), 2.82 (1 H, dd, *J* 13.5, 9.4 Hz, C*H*$_2$Ph); δ_C (125 MHz, $CDCl_3$) 171.2, 153.3, 134.8, 134.0, 129.4, 128.9, 127.4, 117.6, 72.1, 66.3, 55.0, 41.2, 37.6; HRMS (ES$^+$) *m*/*z* calc. for $C_{15}H_{16}{}^{79}BrNO_4Na$ ([MNa]$^+$): 376.0155, found: 376.0160.

t-Butyldimethylsilyl ether 109

To a stirred solution of alcohol **108** (21.21 g, 59.9 mmol) and 2,6-lutidine (9.1 mL, 78 mmol) in anhydrous CH_2Cl_2 (200 mL) was added TBSOTf (16.5 mL, 72.0 mmol) dropwise over 5 min at 0 °C. The mixture was allowed to warm to room temperature over 2 h, then EtOAc (600 mL) was added. The mixture was then washed with sat. aq. NH_4Cl (2 × 250 mL), brine (1 × 250 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (20% Et_2O in hexanes) to give **109** (26.54 g, 95%) as a colourless solid. R_f = 0.47 (silica gel, 1 : 1 hexanes–Et_2O); mp 55–56 °C; $[\alpha]_D^{25}$ +10.6° (*c* 1.05 in $CHCl_3$); ν_{max}/cm^{-1} (film) 3028, 2955, 2856, 1788, 1704, 1472, 1376, 1207, 1048, 900; δ_H (500 MHz, $CDCl_3$) 7.33–7.36 (2 H, m, Ar*H*), 7.27–7.30 (1 H, m, Ar*H*), 7.21–7.22 (2 H, m, Ar*H*), 5.99 (1 H, s, 6=C*H*$_2$), 5.58 (1 H, d, *J* 1.7 Hz, 6=C*H*$_2$), 4.82 (1 H, dd, *J* 8.0, 3.8 Hz, 7-H), 4.65–4.70 (1 H, m, OCH$_2$C*H*N), 4.15–4.21 (2 H, m, OC*H*$_2$CHN), 3.42 (1 H, dd, *J* 16.9, 8.0 Hz, 8-H), 3.30 (1 H, dd, *J* 13.4, 3.2 Hz, C*H*$_2$Ph), 3.24 (1 H, dd, *J* 16.9, 3.8 Hz, 8-H), 2.76 (1 H, dd, *J* 13.4, 9.6 Hz, C*H*$_2$Ph), 0.90 [9 H, s, SiC(C*H*$_3$)$_3$], 0.12 (3 H, s, SiC*H*$_3$), 0.11 (3 H, s, SiC*H*$_3$); δ_C (125 MHz, $CDCl_3$) 169.8, 153.3, 136.1, 135.1, 129.4, 129.0, 127.4, 117.3, 72.6, 66.1, 55.1, 43.0, 37.9, 25.7, 18.1, −4.7, −5.1; HRMS (ES$^+$) *m*/*z* calc. for $C_{21}H_{31}{}^{79}BrNO_4Si$ ([MH]$^+$): 468.1200, found: 468.1203.

Alcohol 110

A stirred solution of oxazolidinone **109** (26.44 g, 56.4 mmol) in THF (200 mL) and MeOH (9 mL) was cooled to −78 °C, where $LiBH_4$ (70.5 mL, 2.0 M in THF, 141 mmol) was added dropwise. After warming to 0 °C over 3 h, the reaction was quenched by the slow dropwise addition of sat. aq. NH_4Cl (350 mL). The mixture was extracted with Et_2O (3 × 200 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 (20% EtOAc in hexanes) to give **110** (14.20 g, 85%) as a colourless oil. R_f = 0.47 (silica gel, 1 : 1 hexanes–EtOAc); $[\alpha]_D^{25}$ −26.4° (*c* 1.01 in $CHCl_3$); ν_{max}/cm^{-1} (film) 3345, 2955, 2885, 1625, 1472, 1408, 1254, 1026, 868; δ_H (500 MHz, $CDCl_3$) 5.93 (1 H, dd, *J* 1.7, 1.2 Hz, 6=C*H*$_2$), 5.57 (1 H, d, *J* 1.7 Hz, 6=C*H*$_2$), 4.40 (1 H, app t, *J* 5.4 Hz, 7-H), 3.86 (1 H, dt, *J* 10.8, 6.2 Hz, 9-H), 3.77 (1 H, dt, *J* 10.8, 5.3 Hz, 9-H), 2.12 (1 H, br s, O*H*), 1.93 (2 H, app q, *J* 5.3 Hz, 8-H and 8-H), 0.91 [9 H, s, SiC(C*H*$_3$)$_3$], 0.10 (3 H, s, SiC*H*$_3$), 0.08 (3 H, s, SiC*H*$_3$); δ_C (125 MHz, $CDCl_3$) 136.0, 116.5, 65.2, 59.3, 37.6, 25.8, 18.1, −4.8, −5.3; HRMS (ES$^+$) *m*/*z* calc. for $C_{11}H_{23}{}^{79}BrO_2SiNa$ ([MNa]$^+$): 317.0543, found: 317.0535.

Aldehyde 111

To a stirred suspension of alcohol **110** (14.10 g, 47.7 mmol) and solid $NaHCO_3$ (9.67 g, 115 mmol) in CH_2Cl_2 (60 mL) was added a solution of the Dess–Martin periodinane (24.20 g, 57.2 mmol) in 3 : 1 CH_2Cl_2–DMSO (120 mL) slowly at room temperature. After 90 min the reaction was quenched by the addition of water (200 mL). The mixture was diluted with Et_2O (600 mL), washed with sat. aq. $Na_2S_2O_3$ (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 (10% EtOAc in hexanes) to give **111** (12.43 g, 89%) as a colourless oil. R_f = 0.54 (silica gel, 4 : 1 hexanes–EtOAc); $[\alpha]_D^{25}$ −32.0° (*c* 1.17 in $CHCl_3$); ν_{max}/cm^{-1} (film) 2957, 2858, 1728, 1473, 1255, 986; δ_H (500 MHz, $CDCl_3$) 9.76 (1 H, dd, *J* 2.4, 1.9 Hz, 9-H), 5.98 (1 H, dd, 1.8, 1.1 Hz, 6=C*H*$_2$), 5.58 (1 H, dd, *J* 1.8, 0.5 Hz, 6=C*H*$_2$), 4.67 (1 H, app dd, *J* 7.2, 4.1 Hz, 7-H), 2.78 (1 H, ddd, *J* 16.3, 7.2 and 2.4 Hz, 8-H), 2.67 (1 H, ddd, *J* 16.3, 4.1 and 1.9 Hz, 8-H), 0.88 [9 H, s, SiC(C*H*$_3$)$_3$], 0.08 (6 H, s, SiC*H*$_3$, SiC*H*$_3$); δ_C (125 MHz, $CDCl_3$) 200.1, 135.3, 117.1, 72.2, 49.6, 25.6, 18.0, −4.7, −5.2; HRMS (ES$^+$) *m*/*z* calc. for $C_{11}H_{21}{}^{79}BrO_2SiNa$ ([MNa]$^+$): 315.0386, found 315.0394.

Alkene 112

To a stirred suspension of KO*t*-Bu (0.639 g, 5.7 mmol) in THF (7 mL) at −45 °C was added *trans*-2-butene (1.1 mL, 11.4 mmol) followed by the dropwise addition of *n*-BuLi (2.30 mL, 2.5 M in hexanes, 5.7 mmol). After 30 min, the bright orange solution was cooled to −78 °C, where a solution of (+)-Ipc$_2$BOMe (1.80 g, 5.7 mmol) in THF (6 mL) was added, and the mixture stirred for 1 h before the addition of $BF_3{\cdot}OEt_2$ (0.77 mL, 6.1 mmol). After an additional 30 min at −78 °C, a solution of aldehyde **111** (1.13 g, 3.80 mmol) in THF (3 mL) was added to the mixture dropwise over 10 min. After a further 3 h at −78 °C, the reaction was quenched by the addition of MeOH (1 mL) and warmed to 0 °C. A solution of 3 N aq. NaOH (18 mL) was then added, followed by the dropwise addition of 35% aq. H_2O_2 (4 mL) over 30 min. The stirred mixture was then allowed to warm to room temperature overnight, and was then diluted with water (15 mL) and extracted with Et_2O (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 (5% Et_2O in hexanes) to give **112** (1.123 g, 84%) as a colourless oil. $R_f = 0.42$ (silica gel, 4 : 1 hexanes–EtOAc); $[\alpha]_D^{25}$ −18.5° (*c* 2.17 in $CHCl_3$); ν_{max}/cm^{-1} (film) 3529, 2957, 2858, 1618, 1458, 1258, 896; δ_H (500 MHz, $CDCl_3$) 5.96 (1 H, s, 6=CH_2), 5.77 (1 H, ddd, *J* 16.6, 10.9 and 8.0 Hz, 11-H), 5.57 (1 H, s, 6=CH_2), 5.06–5.09 (2 H, m, 12-H and 12-H), 4.49 (1 H, dd, *J* 6.3, 3.2 Hz, 7-H), 3.67 (1 H, ddd, *J* 10.3, 5.6 and 1.3 Hz, 9-H), 2.56 (1 H, br s, O*H*), 2.17–2.19 (1 H, dqd, *J* 8.0, 6.8, and 5.6 Hz, 10-H), 1.90 (1 H, ddd, *J* 14.3, 6.3 and 1.3 Hz, 8-H), 1.65 (1 H, ddd, *J* 14.3, 10.3 and 3.2 Hz, 8-H), 1.03 (3 H, d, *J* 6.8 Hz, 10-CH_3), 0.91 [9 H, s, SiC(CH_3)$_3$], 0.10 (3 H, s, SiCH_3), 0.08 (3 H, s, SiCH_3); δ_C (125 MHz, $CDCl_3$) 140.3, 135.6, 116.4, 115.6, 74.8, 70.8, 44.0, 38.9, 25.7, 18.0, 15.8, −4.9, −5.5; HRMS (ES^+) *m*/*z* calc. for $C_{15}H_{29}{}^{79}BrO_2SiNa$ ([MNa]$^+$): 371.1012, found: 371.1009.

Ethyl ester 114

Solid Ph_3CBF_4 (0.028 g, 0.085 mmol) was added in one portion to a stirred solution of alcohol **112** (0.99 g, 2.83 mmol) and *p*-methoxybenzyl-2,2,2-trichloroacetimidate **47** (1.97 g, 7.00 mmol) in Et_2O (15 mL) at room temperature. After 18 h the reaction was quenched by the addition of sat. aq. $NaHCO_3$ (40 mL), the layers were were separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (1 × 40 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (2.5% Et_2O in hexanes) to give 1.04 g of a colourless oil, which was dissolved in CH_2Cl_2 (70 mL) and cooled to −78 °C where a stream of ozone (*ca.* 10% in oxygen) was bubbled through the mixture until TLC analysis confirmed the complete consumption of starting material. Oxygen was bubbled through the solution for an additional 20 min to remove excess ozone. PPh_3 (3.25 g, 12.4 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, and the residue was taken up in benzene (10 mL). (Carbethoxyethylidene)triphenylphosphorane (1.32 g, 3.65 mmol) was added in one portion, and the solution was heated to reflux for 16 h. After cooling to room temperature the mixture was concentrated *in vacuo*. The residue was triturated with 5 : 1 hexanes–Et_2O, and the solid Ph_3PO was removed by filtration. The filtrate was then concentrated under reduced pressure, and purified by flash chromatography on silica gel (10% Et_2O in hexanes) to give **114** (0.908 g, 58% from **112**) as a colourless oil. $R_f = 0.42$ (silica gel, 4 : 1 heaxnes–EtOAc); $[\alpha]_D^{25}$ −6.8° (*c* 4.03 in $CHCl_3$); ν_{max}/cm^{-1} (film) 2957, 2857, 1710, 1464, 1299, 1095, 838; δ_H (600 MHz, $CDCl_3$) 7.29 (2 H, d, *J* 8.5 Hz, Ar*H*), 6.91 (2 H, d, *J* 8.5 Hz, Ar*H*), 6.71 (1 H, d, *J* 9.7 Hz, 11-H), 5.85 (1 H, s, 6=CH_2), 5.51 (1 H, s, 6=CH_2), 4.57 (1 H, d, *J* 11.0 Hz, OCH_2Ar), 4.48 (1 H, d, *J* 11.0 Hz, OCH_2Ar), 4.29 (1 H, dd, *J* 8.6, 2.9 Hz, 7-H), 4.21 (2 H, q, *J* 7.1 Hz, $CO_2CH_2CH_3$), 3.83 (3 H, s, ArOCH_3), 3.52–3.55 (1 H, m, 9-H), 2.87–2.93 (1 H, m, 10-H), 1.89 (3 H, s, 12-CH_3), 1.84 (1 H, ddd, *J* 14.1, 8.4 and 2.9 Hz, 8-H), 1.72 (1 H, ddd, *J* 14.1, 8.6 and 3.1 Hz, 8-H), 1.32 (3 H, t, *J* 7.1 Hz, $CO_2CH_2CH_3$), 1.07 (3 H, d, *J* 6.8 Hz, 10-CH_3), 0.91 [9 H, s, SiC(CH_3)$_3$], 0.07 (3 H, s, SiCH_3), 0.05 (3 H, s, SiCH_3); δ_C (150 MHz, $CDCl_3$) 168.0, 159.1, 143.4, 138.4, 130.8, 129.0, 128.1, 116.4, 113.7, 78.3, 73.9, 71.1, 60.4, 55.2, 39.4, 36.2, 25.7, 18.0, 14.8, 14.3, 12.7, −4.4, −5.1; HRMS (ES^+) *m*/*z* calc. for $C_{27}H_{43}{}^{79}BrO_5SiNa$ ([MNa]$^+$): 577.1955, found: 577.1941.

Allylic alcohol 115

To a stirred solution of ethyl ester **114** (0.890 g, 1.60 mmol) in toluene (8 mL) was added DIBAL-H (4.0 mL, 1.0 M in toluene, 4.0 mmol) dropwise at 0 °C. After 1 h, the reaction was quenched by the cautious addition of sat. aq. Rochelle's salt (20 mL) and allowed to warm to room temperature overnight. The mixture was diluted with water (20 mL) and extracted with EtOAc (3 × 25 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 (15% EtOAc in hexanes) to give **115** (0.711 g, 87%) as a viscous, colourless oil. $R_f = 0.31$ (silica gel, 1 : 1 hexanes–EtOAc); $[\alpha]_D^{25}$ −22.7° (*c* 4.0 in $CHCl_3$); ν_{max}/cm^{-1} (film) 3404, 2953, 2856, 1511, 1457, 1366, 1248, 1039, 894; δ_H (500 MHz, $CDCl_3$) 7.28 (2 H, d, *J* 8.5 Hz, Ar*H*), 6.88 (2 H, d, *J* 8.5 Hz, Ar*H*), 5.82 (1 H, s, 6=CH_2), 5.48 (1 H, d, *J* 1.6 Hz, 6=CH_2), 5.33 (1 H, d, *J* 9.3 Hz, 11-H), 4.57 (1 H, d, *J* 11.0 Hz, OCH_2Ar), 4.43 (1 H, d, *J* 11.0 Hz, OCH_2Ar), 4.28 (1 H, dd, *J* 8.7, 3.0 Hz, 7-H), 3.99 (2 H, s, 13-H and 13-H), 3.80 (3 H, s, ArOCH_3), 3.47–3.49 (1 H, m, 9-H), 2.81–2.85 (1 H, m, 10-H), 1.72 (3 H, s, 12-CH_3), 1.65–1.79 (2 H, m, 8-H and 8-H), 0.99 (3 H, d, *J* 6.8 Hz, 10-CH_3), 0.89 [9 H, s, SiC(CH_3)$_3$], 0.05 (3 H, s, SiCH_3), 0.04 (3 H, s, SiCH_3); δ_C (125 MHz, $CDCl_3$) 159.0, 138.6, 135.4, 131.1, 128.9, 128.1, 116.3, 113.7, 78.8, 73.9, 70.8, 68.9, 55.3, 38.8, 34.4, 25.7, 18.1, 15.2, 13.9, −4.4, −5.1; HRMS (ES^+) *m*/*z* calc. for $C_{25}H_{41}{}^{79}BrO_4SiNa$ ([MNa]$^+$): 535.1850, found: 535.1831.

Bromide 116

To a stirred solution of allylic alcohol **115** (2.80 g, 5.45 mmol) and Et_3N (3.03 mL, 21.81 mmol) in THF (50 mL) was added MsCl (1.27 mL, 16.36 mmol) dropwise at 0 °C. After 1 h the solution was warmed to room temperature and LiBr (4.73 g, 54.52 mmol) was added in one portion. After an additional 30 min at room temperature the reaction was quenched with water (80 mL) and extracted with Et_2O (3 × 60 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: 2–4% Et_2O in hexanes) to give **116** (2.888 g, 92%) as a light yellow oil. $R_f = 0.38$ (silica gel, 9 : 1 hexanes–Et_2O); $[\alpha]_D^{25}$ −17.9° (*c* 1.07 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 2955, 2856, 1613, 1461, 1302, 1096, 837; δ_H (600 MHz, $CDCl_3$) 7.28 (2 H, d, *J* 8.4 Hz, Ar*H*), 6.89 (2 H, d, *J* 8.4 Hz, Ar*H*), 5.83 (1 H, s, 6=CH_2), 5.53 (1 H, d, *J* 9.3 Hz, 11-H), 5.49 (1 H, s, 6=CH_2), 4.54 (1 H, d, *J* 10.9 Hz, OCH_2Ar), 4.43 (1 H, d, *J* 10.9 Hz, OCH_2Ar), 4.27 (1 H, dd, *J* 8.5 Hz, 2.8 Hz, 7-H), 3.98 (1 H, d, *J* 9.6 Hz, 13-H), 3.96 (1 H, d, *J* 9.6 Hz, 13-H), 3.81 (3 H, s, ArOCH_3), 3.45–3.49 (1 H, m, 9-H), 2.73–2.78 (1 H, m, 10-H), 1.79 (3 H, s, 12-CH_3), 1.71–1.79 (1 H, m, 8-H), 1.66 (1 H, ddd, *J* 14.1, 8.7 and 2.8 Hz, 8-H), 0.98 (3 H, d, *J* 6.8 Hz, 10-CH_3), 0.90 [9 H, s, SiC(CH_3)$_3$], 0.06 (3 H, s, SiCH_3), 0.04 (3 H, s, SiCH_3); δ_C (150 MHz, $CDCl_3$) 159.0, 138.5, 133.1, 132.4, 130.9, 129.0, 116.3, 113.7, 78.5, 73.8, 70.9, 55.3, 41.5,

38.9, 35.4, 25.8, 18.1, 15.1, 14.9, −4.4, −5.0; HRMS (ES^+) *m/z* calc. for $C_{25}H_{40}{}^{79}Br_2O_3SiNa$ ([MNa]$^+$): 597.1006, found: 597.1017.

Alkynyl diol 118

To a stirred solution of oxazolidinone **117**[47] (13.0 g, 32.37 mmol) in a mixture of THF (250 mL) and MeOH (2.8 mL) was added $LiBH_4$ (40 mL, 2.0 M in THF, 80.0 mmol) dropwise over 20 min at 0 °C. The mixture was allowed to warm to room temperature over 3 h, then quenched by the cautious addition of 1 M aq. NaOH (40 mL). The mixture was then partitioned between EtOAc (250 mL) and brine (250 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 250 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (50% EtOAc in hexanes) to give **118** (4.3 g, 58%) as a white powder. $R_f = 0.17$ (silica gel, 3 : 2 hexanes–EtOAc); mp 74–75 °C; $[\alpha]_D^{25}$ +3.6° (*c* 1.13 in $CHCl_3$); ν_{max}/cm^{-1} (film) 3480, 3020, 2858, 2168, 1413, 1022, 830; δ_H (400 MHz, $CDCl_3$) 4.50 (1 H, d, *J* 3.2 Hz, 3-H), 3.80–3.85 (2 H, m, 1-H and O*H*), 3.63 (1 H, dd, *J* 10.8, 4.0 Hz, 1-H), 3.21 (1 H, br s, O*H*), 2.02–2.11 (1 H, m, 2-H), 0.89–0.91 [12 H, m, 2-CH_3 and SiC(CH_3)$_3$], 0.09 (3 H, s, SiCH_3), 0.08 (3 H, s, SiCH_3); δ_C (100 MHz, $CDCl_3$) 105.2, 89.0, 66.7, 65.5, 40.1, 26.0, 16.4, 12.4, −4.7; HRMS (ES^-) *m/z* calc. for $C_{12}H_{24}O_2Si^{35}Cl$ ([MCl]$^-$): 263.1240, found: 263.1247.

Triphenylmethyl ether 119

To a stirred solution of diol **118** (300 mg, 1.31 mmol) in CH_2Cl_2 (5 mL) were added TrCl (400 mg, 1.44 mmol), Et_3N (0.29 mL) and 4-DMAP (a few crystals) at room temperature. After 8 h, the reaction was quenched by the addition of water (10 mL). The mixture was then partioned between CH_2Cl_2 (20 mL) and brine (20 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 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: 10–12% CH_2Cl_2 in hexanes) to give **119** (591 mg, 96%) as a colourless paste. $R_f = 0.34$ (silica gel, 22 : 3 hexanes–EtOAc); $[\alpha]_D^{25}$ +58.8° (*c* 1.17 in $CHCl_3$); ν_{max}/cm^{-1} (film) 3456, 3059, 2929, 2169, 1489, 1252, 1118, 836; δ_H (500 MHz, $CDCl_3$) 7.46 (6 H, d, *J* 7.5 Hz, Ar*H*), 7.29 (6 H, t, *J* 7.5 Hz, Ar*H*), 7.22 (3 H, t, *J* 7.3 Hz, Ar*H*), 4.53 (1 H, dd, *J* 7.3, 3.8 Hz, 3-H), 3.39–3.43 (2 H, m, 1-H and O*H*), 3.23 (1 H, dd, *J* 9.3, 4.9 Hz, 1-H), 2.17–2.25 (1 H, m, 2-H), 0.92–0.94 [12 H, m, 2-CH_3 and SiC(CH_3)$_3$], 0.10 (3 H, s, SiCH_3), 0.09 (3 H, s, SiCH_3); δ_C (125 MHz, $CDCl_3$) 143.6, 128.5, 127.7, 126.9, 105.7, 87.9, 87.3, 66.2, 66.1, 39.1, 26.0, 16.3, 12.7, −4.7; HRMS (MALDI-TOF) *m/z* calc. for $C_{31}H_{38}O_2SiNa$ ([MNa]$^+$): 493.2533, found: 493.2535.

Alkyne 120

To a stirred solution of alcohol **119** (580 mg, 1.23 mmol) in THF (4 mL) was added TBAF (2.46 mL, 1.0 M in THF, 2.46 mmol) in one portion at room temperature. After 2 h, the reaction was quenched by the addition of sat. aq. NH_4Cl (10 mL), before being partitioned between EtOAc (20 mL) and brine (20 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (20% EtOAc in hexanes) to give **120** (331 mg, 75%) as a colourless paste. $R_f = 0.22$ (silica gel, 4 : 1 hexanes–EtOAc); $[\alpha]_D^{25}$ +6.7° (*c* 1.25 in $CHCl_3$); ν_{max}/cm^{-1} (film) 3424, 3297, 3058, 2929, 2108, 1490, 1220, 1071, 901; δ_H (500 MHz, $CDCl_3$) 7.47 (6 H, d, *J* 7.4 Hz, Ar*H*), 7.29 (6 H, t, *J* 7.4 Hz, Ar*H*), 7.22 (3 H, t, *J* 7.3 Hz, 3 H, Ar*H*), 4.52 (1 H, ddd, *J* 7.6, 3.6 and 2.2 Hz, 3-H), 3.67 (1 H, br d, *J* 7.6 Hz, O*H*), 3.36 (1 H, t, *J* 9.2 Hz, 1-H), 3.27 (1 H, dd, *J* 9.2, 4.5 Hz, 1-H), 2.30 (1 H, d, *J* 2.2 Hz, 5-H), 2.19–2.24 (1 H, m, 2-H), 0.90 (3 H, d, *J* 7.0 Hz, 2-CH_3); δ_C (125 MHz, $CDCl_3$) 143.5, 128.5, 127.7, 126.9, 87.2, 83.0, 73.5, 66.0, 65.6, 38.8, 12.5; HRMS (MALDI-FTMS) *m/z* calc. for $C_{25}H_{24}O_2Na$ ([MNa]$^+$): 379.1668, found: 379.1674.

Tri-*n*-butyltin alkene 121

To a stirred solution of alkyne **120** (290 mg, 0.814 mmol) in THF (4 mL) was added $PdCl_2(PPh_3)_2$ (33 mg, 0.047 mmol) in one portion at RT. After 1 min, *n*-Bu_3SnH (0.5 mL, 1.859 mmol) was added dropwise over 3 min. TLC analysis (4 : 1, hexanes–EtOAc) of the reaction after a further 10 min indicated the complete consumption of alkyne starting material, and the mixture was concentrated. The residue was purified by flash chromatography on silica gel (6% EtOAc in hexanes) to give **121** (322 mg, 61%) as a colourless oil. $R_f = 0.26$ (silica gel, 47 : 3 hexanes–EtOAc); $[\alpha]_D^{25}$ −0.6° (*c* 1.04 in $CHCl_3$); ν_{max}/cm^{-1} (film) 3485, 2924, 1599, 1451, 1072, 908, 738; δ_H (500 MHz, $CDCl_3$) 7.46 (6 H, d, *J* 7.4 Hz, Ar*H*), 7.30 (6 H, t, *J* 7.4 Hz, Ar*H*), 7.22 (3 H, t, *J* 7.3 Hz, 3 H, Ar*H*), 6.17 (1 H, dd, *J* 19.2, 1.3 Hz, 5-H), 5.94 (1 H, dd, *J* 19.2, 5.0 Hz, 4-H), 4.26–4.30 (1 H, m, 3-H), 3.16–3.22 (2 H, m, 1-H and 1-H), 2.82 (1 H, d, *J* 5.4 Hz, O*H*), 2.03–2.08 (1 H, m, 2-H), 1.44–1.53 [6 H, m, Sn(CH_2CH$_2$CH$_2$CH$_3$)$_3$], 1.27–1.35 [6 H, m, Sn(CH$_2$CH_2CH$_2$CH$_3$)$_3$], 0.88–0.91 [18 H, m, 2-CH_3, Sn(CH$_2$CH$_2$CH_2CH$_3$)$_3$ and Sn(CH$_2$CH$_2$CH$_2$CH_3)$_3$]; δ_C (125 MHz, $CDCl_3$) 148.6, 143.8, 128.5, 127.8, 127.8, 126.9, 87.0, 66.7, 66.7, 38.6, 29.0, 27.2, 13.6, 11.5, 9.4; HRMS (MALDI-FTMS) *m/z* calc. for $C_{37}H_{52}O_2SnNa$ ([MNa]$^+$): 671.2881, found: 671.2905.

Hydrazone 122

A solution of hydrazone **10** (0.426 g, 1.76 mmol) in THF (10 mL) was added dropwise to a stirred solution of freshly prepared LDA (1.76 mmol) in THF (10 mL) at −78 °C. After 2.5 h, a solution of dibromide **116** (0.882 g, 1.53 mmol) in THF (10 mL) was added dropwise over 10 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 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 (15% Et_2O in hexanes with 1.5% Et_3N) to give **122** (1.03 g, 91%) as a viscous, colourless oil. $R_f = 0.24$ (silica gel, 3 : 2 hexanes–Et_2O + 2% Et_3N); $[\alpha]_D^{25}$ −55.4° (*c* 1.05 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 2929, 2856, 1614, 1371, 1248, 1097, 836; δ_H (600 MHz, C_6D_6) 7.36 (2 H, d, *J* 8.4 Hz, Ar*H*), 6.85 (2 H, d, *J* 8.4 Hz, Ar*H*), 5.57 (1 H, s, 6=CH_2), 5.43 (1 H, d, *J* 8.9 Hz, 11-H), 5.29 (1 H, s, 6=CH_2), 4.73 (1 H, d, *J* 6.9 Hz, 7-H), 4.67 (1 H, d, *J* 11.0 Hz, OCH_2Ar), 4.49–4.54 (3 H, m, 14-H,

16-H and OCH_2Ar), 4.24 (1 H, d, *J* 12.5 Hz, 16-H), 3.72–3.75 (1 H, m, 9-H), 3.63 (1 H, dd, *J* 8.8, 3.8 Hz, NCHCH_2OCH$_3$), 3.57–3.61 (1 H, m, NC*H*CH$_2$OCH$_3$), 3.31 (3 H, s, ArOCH_3), 3.30–3.34 (1 H, m, NCHCH_2OCH$_3$), 3.21 (3 H, s, CH$_2$OCH_3), 3.12–3.16 (1 H, m, NCH_2CH$_2$), 3.03 (1 H, d, *J* 14.1 Hz, 13-H), 2.93–2.98 (1 H, m, 10-H), 2.54 (1 H, dd, *J* 14.1, 7.6 Hz, 13-H), 2.32–2.36 (1 H, m, NCH_2CH$_2$), 1.98–2.06 (2 H, m, 8-H and 8-H), 1.92–1.95 (1 H, m, NCHCH_2CH$_2$), 1.87 (3 H, s, 12-CH_3), 1.60–1.68 (2 H, m, NCH$_2$CH_2CH$_2$ and NCHCH_2CH$_2$), 1.51–1.56 (1 H, m, NCH$_2$CH_2CH$_2$), 1.47 [3 H, s, O$_2$C(CH_3)$_2$], 1.41 [3 H, s, O$_2$C(CH_3)$_2$], 1.13 (3 H, d, *J* 6.8 Hz, 10-CH_3), 1.01 [9 H, s, SiC(CH_3)$_3$], 0.11 (3 H, s, SiCH_3), 0.10 (3 H, s, SiCH_3); δ_C (150 MHz, C$_6$D$_6$) 159.6, 158.6, 139.5, 132.9, 131.7, 129.9, 129.0, 116.3, 114.1, 99.9, 78.9, 76.2, 74.4, 71.4, 71.0, 67.4, 64.5, 58.9, 54.7, 53.3, 39.1, 37.4, 35.0, 27.5, 27.4, 26.1, 24.6, 23.2, 18.4, 17.6, 15.6, −4.2, −4.8; HRMS (ES$^+$) *m*/*z* calc. for C$_{37}$H$_{62}$^{79}BrN$_2$O$_6$Si ([MH]$^+$): 737.3555, found: 737.3550.

Ketone 123

A solution of hydrazone **122** (1.00 g, 1.35 mmol) in THF (8 mL) was added dropwise to a stirred solution of freshly prepared LDA (1.60 mmol) in THF (8 mL) at −78 °C. After 1 h a solution of iodide **55** (0.945 g, 1.60 mmol) in THF (8 mL) was added slowly over 10 min. After stirring for an additional hour at −78 °C, the reaction was quenched by the addition of aqueous pH 7.0 buffer solution (40 mL) and warmed to room temperature. The mixture was extracted with Et$_2$O (3 × 30 mL) and the combined organic layers were dried (MgSO$_4$), filtered and concentrated *in vacuo*. Rapid flash chromatography (5% Et$_2$O in hexanes with 2% Et$_3$N) separated the excess iodide starting material and afforded the crude bis-alkylated hydrazone, which was taken up in a mixture of Et$_2$O (15 mL) and sat. aq. (CO$_2$H)$_2$ (15 mL) and stirred vigorously at room temperature for two days before the addition of water (40 mL), and extraction with Et$_2$O (3 × 40 mL). The combined organic layers were washed with brine (1 × 40 mL), dried (MgSO$_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient: 5–10% Et$_2$O in hexanes) to give **123** (1.02 g, 70% from **122**) as a viscous, light yellow syrup. R_f = 0.34 (silica gel, 4 : 1 hexanes–Et$_2$O); $[\alpha]_D^{25}$ +26.4° (*c* 1.17 in CH$_2$Cl$_2$); ν_{max}/cm^{-1} (film) 2951, 2856, 1744, 1514, 1301, 1171, 836; δ_H (600 MHz, C$_6$D$_6$) 7.38 (2 H, d, *J* 8.4 Hz, Ar*H*), 7.33 (2 H, d, *J* 8.4 Hz, Ar*H*), 6.83–6.88 (4 H, m, Ar*H*), 5.57 (1 H, s, 6=CH_2), 5.63 (1 H, d, *J* 9.1 Hz, 11-H), 5.30 (1 H, s, 6=CH_2), 4.82 (1 H, d, *J* 11.3 Hz, OCH_2Ar), 4.61–4.63 (3 H, m, OCH_2Ar and OCH_2Ar), 4.46–4.49 (2 H, m, 7-H and OCH_2Ar), 4.28 (1 H, dd, 9.8, 1.5 Hz, 14-H), 4.16–4.20 (1 H, m, 19-H), 4.12 (1 H, dd, *J* 7.6, 3.4 Hz, 16-H), 4.05–4.10 (1 H, m, 21-H), 3.93 (1 H, q, *J* 6.9 Hz, 24-H), 3.66 (1 H, ddd, *J* 8.9, 8.6 and 3.0 Hz, 9-H), 3.33 (3 H, s, ArOCH_3), 3.31 (3 H, s, ArOCH_3), 3.31–3.33 (1 H, m, 25-H,), 2.81–2.87 (1 H, m, 10-H), 2.79 (1 H, d, *J* 14.2 Hz, 13-H), 2.30 (1 H, dd, *J* 15.1, 9.9 Hz, 13-H), 2.15–2.21 (1 H, m, 17-H), 2.03 (1 H, ddd, *J* 14.1, 8.9 and 2.8 Hz, 8-H), 1.94 (1 H, ddd, *J* 14.1, 9.1 and 3.0 Hz, 8-H), 1.64 (3 H, s, 12-CH_3), 1.62–1.89 (6 H, m, 17-H, 18-H, 18-H, 20-H, 20-H and 22-H), 1.47–1.61 (5 H, m, 23-H, 23-H, 26-H, 26-H and 27-H), 1.39 [3 H, s, O$_2$C(CH_3)$_2$], 1.34 [3 H, s, O$_2$C(CH_3)$_2$], 1.25–1.45 (4 H, m, 22-H, 27-H, 28-H and 28-H), 1.05–1.06 (3 H, m, 10-CH_3), 1.05 [9 H, s, SiC(CH_3)$_3$], 0.99 [9 H, s, SiC(CH_3)$_3$], 0.92 (3 H, t, *J* 7.3 Hz, 28-CH_3), 0.25 (3 H, s, SiCH_3), 0.21 (3 H, s, SiCH_3), 0.09 (3 H, s, SiCH_3), 0.07 (3 H, s, SiCH_3); δ_C (150 MHz, C$_6$D$_6$) 210.1, 159.6, 159.5, 139.5, 132.2, 132.1, 131.7, 129.5, 129.3, 129.0, 116.3, 114.1, 113.9, 101.1, 82.4, 81.4, 79.1, 76.1, 74.7, 74.5, 74.1, 72.7, 71.1, 69.9, 54.8, 54.7, 43.9, 39.4, 38.6, 35.2, 34.1, 31.7, 31.4, 28.3, 27.9, 26.3, 26.0, 24.7, 24.2, 24.1, 23.3, 18.4, 18.4, 17.0, 15.8, 14.4, −4.2, −4.2, −4.4, −4.8; HRMS (ES$^+$) *m*/*z* calc. for C$_{58}$H$_{95}$^{79}BrO$_{10}$Si$_2$Na ([MNa]$^+$): 1109.5539, found: 1109.5554.

Triol 124

TsOH·H$_2$O (26.1 mg, 0.138 mmol) was added in one portion to a stirred solution of ketone **123** (300 mg, 0.275 mmol) in 5 : 1 MeOH–CH$_2$Cl$_2$ (12 mL) at room temperature. After 16 h, Et$_3$N (0.50 mL) was added, and the reaction mixture was concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient: 15–30% EtOAc in hexanes) to give **124** (131 mg, 57%) as a colourless oil and as a single anomer. R_f = 0.30 (silica gel, 3 : 2 hexanes–EtOAc); $[\alpha]_D^{25}$ −74.7° (*c* 0.15 in CH$_2$Cl$_2$); ν_{max}/cm^{-1} (film) 3398, 2954, 1612, 1513, 1382, 1172, 974, 821; δ_H (500 MHz, C$_6$D$_6$) 7.31 (2 H, d, *J* 8.6 Hz, Ar*H*), 7.25 (2 H, d, *J* 8.6 Hz, Ar*H*), 6.81 (2 H, d, *J* 8.6 Hz, Ar*H*), 6.78 (2 H, d, *J* 8.6 Hz, Ar*H*), 5.86 (1 H, s, 6=CH_2), 5.41 (1 H, s, 6=CH_2), 5.21 (1 H, d, *J* 8.7 Hz, 11-H), 4.74 (1 H, d, *J* 11.2 Hz, OCH_2Ar), 4.63 (1 H, br s, O*H*), 4.56 (1 H, d, *J* 11.2 Hz, OCH_2Ar), 4.54 (1 H, d, *J* 11.2 Hz, OCH_2Ar), 4.38–4.42 (2 H, m, 7-H and OCH_2Ar), 4.19–4.24 (1 H, m, 21-H), 3.99–4.05 (3 H, m, 14-H, 19-H and O*H*), 3.91–3.95 (2 H, m, 16-H and 24-H), 3.68 (1 H, ddd, *J* 8.6, 4.6 and 2.4 Hz, 9-H), 3.34 (3 H, s, ArOCH_3), 3.33 (3 H, s, ArOCH_3), 3.26–3.30 (1 H, m, 25-H), 3.21 (3 H, s, OCH_3), 2.82–2.88 (1 H, m, 10-H), 2.33–2.46 (2 H, m, 13-H and 13-H), 1.99–2.05 (2 H, m, 8-H and 17-H), 1.86–1.95 (2 H, m, 8-H and 18-H), 1.66 (3 H, s, 12-CH_3), 1.45–1.83 (9 H, m, 17-H, 20-H, 20-H, 22-H, 23-H, 23-H, 26-H, 26-H and 27-H), 1.16–1.42 (6 H, m, 18-H, 22-H, 27-H, 28-H, 28-H and O*H*), 1.01 (3 H, d, *J* 6.8 Hz, 10-CH_3), 0.89 (3 H, t, *J* 7.1 Hz, 28-CH_3); δ_C (125 MHz, C$_6$D$_6$) 159.7, 159.6, 138.4, 133.0, 132.1, 131.2, 130.6, 129.6, 129.4, 115.9, 114.1, 114.0, 97.7, 82.5, 81.6, 79.5, 75.7, 73.9, 72.7, 72.5, 71.6, 68.8, 67.4, 54.8, 54.8, 47.7, 42.9, 41.2, 36.4, 34.9, 31.9, 28.3, 28.0, 27.2, 25.5, 23.3, 16.8, 15.1, 14.4; HRMS (ES$^+$) *m*/*z* calc. for C$_{44}$H$_{65}$BrO$_{10}$Na ([MNa]$^+$): 855.3653, found: 855.3645.

Triethylsilyl ether 125

To a stirred solution of triol **124** (74.3 mg, 89 μmol) and 2,6-lutidine (105 μL, 900 μmol) in CH$_2$Cl$_2$ (4 mL) at −78 °C was added TESOTf (102 μL, 450 μmol) dropwise at −78 °C. The mixture was then warmed to −10 °C and stirred for 30 min before being quenched by the slow addition of sat. aq. NaHCO$_3$ (10 mL) and warmed to room temperature. The layers were separated, and the aqueous layer was extracted with Et$_2$O (3 × 5 mL). The combined organic layers were washed with sat. aq. NH$_4$Cl (1 × 10 mL), brine (1 × 10 mL), dried (MgSO$_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (10% Et$_2$O in hexanes) to give **125** (91.2 mg, 87%) as a light yellow oil. R_f = 0.36 (silica gel, 4 : 1 hexanes–Et$_2$O); $[\alpha]_D^{25}$ −26.7° (*c* 4.35 in CH$_2$Cl$_2$); ν_{max}/cm^{-1} (film) 2954, 1616, 1419, 1302, 1171, 1049, 894; δ_H (600 MHz, C$_6$D$_6$) 7.33–7.36 (4 H, m, Ar*H*), 6.82–6.83 (4 H, m, Ar*H*), 5.64 (1 H, s, 6=CH_2), 5.45 (1 H, d, *J* 8.9 Hz, 11-H), 5.32 (1 H, s, 6=CH_2), 4.78 (1 H, d, *J* 11.3 Hz, OCH_2Ar), 4.65 (1 H,

d, *J* 11.2 Hz, OC*H*$_2$Ar), 4.59 (1 H, d, *J* 11.3 Hz, OC*H*$_2$Ar), 4.51–4.53 (2 H, m, 7-H and OC*H*$_2$Ar), 4.29–4.33 (2 H, m, 14-H and 21-H), 4.06 (1 H, app t, *J* 10.3 Hz, 19-H), 3.97 (1 H, q, *J* 6.9 Hz, 24-H), 3.88–3.90 (1 H, m, 16-H), 3.67–3.73 (1 H, m, 9-H), 3.37 (3 H, s, OC*H*$_3$), 3.31 (3 H, s, ArOC*H*$_3$), 3.31 (3 H, s, ArOC*H*$_3$), 3.31–3.33 (1 H, m, 25-H,), 2.95–3.00 (1 H, m, 10-H), 2.64–2.70 (1 H, m, 13-H), 2.37 (1 H, dd, *J* 13.7, 9.8 Hz, 13-H), 2.09–2.18 (2 H, m, 8-H and 17-H), 1.99 (1 H, ddd, *J* 13.4, 8.7 and 2.9 Hz, 8-H), 1.89 (3 H, s, 12-C*H*$_3$), 1.81–1.89 (3 H, m, 18-H, 20-H and 22-H), 1.60–1.66 (2 H, m, 20-H and 26-H), 1.49–1.57 (5 H, m, 17-H, 23-H, 23-H, 26-H and 27-H), 1.36–1.43 (2 H, m, 22-H and 27-H), 1.16–1.31 [12 H, m, 18-H, 28-H, 28-H and Si(CH$_2$C*H*$_3$)$_3$], 1.15 (3 H, d, *J* 6.8 Hz, 10-C*H*$_3$), 1.08 [9 H, t, *J* 7.9 Hz, Si(CH$_2$C*H*$_3$)$_3$], 1.01 [9 H, t, *J* 7.9 Hz, Si(CH$_2$C*H*$_3$)$_3$], 0.86–0.91 [9 H, m, 28-C*H*$_3$ and Si(C*H*$_2$CH$_3$)$_3$], 0.70 [6 H, q, *J* 7.9 Hz, Si(C*H*$_2$CH$_3$)$_3$], 0.62–0.66 [6 H, m, Si(C*H*$_2$CH$_3$)$_3$]; δ_C (150 MHz, C_6D_6) 159.6, 139.5, 135.6, 132.2, 131.8, 129.4, 129.1, 116.1, 114.0, 113.9, 99.8, 82.6, 79.1, 76.0, 74.5, 74.3, 72.7, 71.0, 69.1, 67.6, 54.7, 43.0, 39.1, 35.1, 31.8, 31.4, 28.3, 28.0, 25.9, 23.3, 18.3, 15.8, 14.3, 7.7, 7.5, 7.2, 6.2, 5.9, 5.3; HRMS (ES$^+$) *m*/*z* calc. for $C_{62}H_{107}{}^{79}BrO_{10}Si_3Na$ ([MNa$^+$]): 1197.6247, found 1197.6265.

Vinyl iodide 129

To a stirred solution of NaI (25.75 g, 171.8 mmol) in acetonitrile (200 mL) were added TMSCl (21.8 mL, 171.8 mmol) and water (1.86 mL, 103.1 mmol) sequentially at room temperature. After 10 min, propargyl alcohol (5.0 mL, 85.9 mmol) was added in one portion. After a further 90 min at room temperature, the mixture was diluted with water (500 mL), and then partitioned between Et_2O (500 mL) and 5% aq. $Na_2S_2O_3$ (500 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 500 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* (60 mmHg/25 °C), to give crude 2-iodoprop-2-en-1-ol (**128**)[49] as an orange oil. To a stirred solution of the crude alcohol in THF (100 mL) were added imidazole (14.62 g, 214.7 mmol) and TESCl (17.45 mL, 103.1 mmol) sequentially at room temperature. After a further 90 min, the mixture was quenched by the addition of water (100 mL). The mixture was then partitioned between Et_2O (400 mL) and 5% aq. $Na_2S_2O_3$ (400 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 300 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: 1–5% CH_2Cl_2 in hexanes) to give **129** (11.53 g, 45% for two steps) as a colourless oil. R_f = 0.24 (silica gel, 99 : 1 hexanes–CH_2Cl_2); ν_{max}/cm^{-1} (film) 2955, 2877, 1627, 1412, 1133, 1009, 898; δ_H (500 MHz, $CDCl_3$) 6.44 (1 H, app q, *J* 1.8 Hz, 6=C*H*$_2$), 5.80 (1 H, app q, *J* 1.6 Hz, 6=C*H*$_2$), 4.18 (2 H, dd, *J* 1.8, 1.6 Hz, 7-H and 7-H), 0.97 [9 H, t, *J* 7.9 Hz, Si(CH$_2$C*H*$_3$)$_3$], 0.63 [6 H, q, *J* 7.9 Hz, Si(C*H*$_2$CH$_3$)$_3$]; δ_C (125 MHz, $CDCl_3$) 122.8, 109.6, 70.7, 6.7, 4.4; MS (ES$^+$) *m*/*z* calc. for $C_9H_{20}IOSi$ ([MH]$^+$): 299.0, found: 299.1.

Diene 130

Method A – Stille coupling. To a stirred solution of iodide **129** (72 mg, 0.241 mmol) and $PdCl_2(PPh_3)_2$ (5.1 mg, 0.007 mmol) in THF (4 mL) was added a solution of stannane **121** (188 mg, 0.29 mmol) in THF (1 mL) in one portion at room temperature. The mixture was stirred for 6 h at room temperature, then warmed to 60 °C for a further 18 h. After cooling to room temperature, the mixture was diluted with Et_2O (50 mL), and washed with water (1 × 10 mL) and brine (1 × 10 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (15% EtOAc in hexanes) to give **130** (36 mg, 28%) as a colourless oil.

Method B – alkyne reduction. A solution of alkyne **131** (1.81 g, 3.44 mmol) in Et_2O (15 mL) was added dropwise over 10 min to a stirred solution of Red-Al® (4.13 mL, 3.33 M in toluene, 13.74 mmol) at 0 °C. After 50 min the reaction was quenched by the cautious addition of water (10 mL). The mixture was then diluted with Et_2O (50 mL) and sat. aq. Rochelle's salt (100 mL), and stirred vigorously at room temperature for 30 min. The mixture was then washed with brine (1 × 50 mL). The aqueous layer was extracted with EtOAc (3 × 50 mL), and the combined organic layers were washed with brine (1 × 50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient: 10–12% EtOAc in hexanes) to give **130** (1.78 g, 98%) as a colourless oil.

Data for compound 130. R_f = 0.13 (silica gel, 9 : 1 hexanes–EtOAc); $[\alpha]_D^{25}$ −5.9° (*c* 0.51 in $CHCl_3$); ν_{max}/cm^{-1} (film) 3460, 3028, 2956, 1604, 1451, 1238, 1014, 820; δ_H (500 MHz, $CDCl_3$) 7.43–7.44 (6 H, m, Ar*H*), 7.29–7.32 (6 H, m, Ar*H*), 7.22–7.25 (3 H, m, Ar*H*), 6.24 (1 H, d, *J* 16.2 Hz, 5-H), 5.54 (1 H, dd, *J* 16.2, 6.0 Hz, 4-H), 5.30 (1 H, s, 6=C*H*$_2$), 5.06 (1 H, s, 6=C*H*$_2$), 4.27–4.30 (1 H, m, 3-H), 4.24 (1 H, d, *J* 14.1 Hz, 7-H), 4.21 (1 H, d, *J* 14.1 Hz, 7-H), 3.18 (1 H, dd, *J* 9.2, 4.3 Hz, 1-H), 3.11 (1 H, dd, *J* 9.2, 7.4 Hz, 1-H), 2.83 (1 H, d, *J* 5.4 Hz, O*H*), 2.04–2.08 (1 H, m, 2-H), 0.97 [9 H, t, *J* 7.9 Hz, Si(CH$_2$C*H*$_3$)$_3$], 0.90 (3 H, d, *J* 7.0 Hz, 2-C*H*$_3$), 0.63 [6 H, q, *J* 7.9 Hz, Si(C*H*$_2$CH$_3$)$_3$]; δ_C (125 MHz, $CDCl_3$) 144.0, 143.7, 130.3, 128.8, 128.5, 127.9, 127.1, 114.2, 87.1, 75.2, 66.6, 62.4, 39.1, 12.0, 6.8, 4.4; HRMS (MALDI-FTMS) *m*/*z* calc. for $C_{34}H_{44}O_3SiNa$ ([MNa]$^+$): 551.2952, found: 551.2944.

Enyne 131

To a stirred solution of alkyne **120** (1.98 g, 5.55 mmol) and iodide **129** (2.15 g, 7.22 mmol) in THF (60 mL) were added Et_3N (7.74 mL, 55.5 mmol), $PdCl_2(PPh_3)_2$ (72 mg, 0.28 mmol) and CuI (106 mg, 0.56 mmol) sequentially at room temperature. After 3.5 h the mixture was partitioned between Et_2O (100 mL) and brine (100 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 100 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: 9–15% EtOAc in hexanes) to give **131** (1.87 g, 64%) as a colourless oil. R_f = 0.16 (silica gel, 9 : 1 hexanes–EtOAc); $[\alpha]_D^{25}$ +29.1° (*c* 1.86 in $CHCl_3$); ν_{max}/cm^{-1} (film) 3446, 3062, 2958, 2241, 1619, 1451, 1119, 815; δ_H (400 MHz, $CDCl_3$) 7.43–7.45 (6 H, m, Ar*H*), 7.29–7.33 (6 H, m, Ar*H*), 7.25–7.26 (3 H, m, Ar*H*), 5.61 (1 H, app q, *J* 2.0 Hz, 6=C*H*$_2$), 5.38 (1 H, app q, *J* 1.8 Hz, 6=C*H*$_2$), 4.62 (1 H, dd, *J* 7.9, 3.6 Hz, 3-H), 4.07 (2 H, dd, *J* 2.0, 1.8 Hz, 7-H and 7-H), 3.49 (1 H, d, *J* 7.9 Hz, O*H*), 3.31 (1 H, t, *J* 9.2 Hz, 1-H), 3.25 (1 H, dd, *J* 9.2, 4.4 Hz, 1-H), 2.24–2.31 (1 H, m, 2-H), 0.98 [9 H, t, *J* 7.9 Hz, Si(CH$_2$C*H*$_3$)$_3$], 0.90 (3 H, d, *J* 7.0 Hz, 2-C*H*$_3$), 0.64 [6 H, q, *J* 7.9 Hz, Si(C*H*$_2$CH$_3$)$_3$]; δ_C (100 MHz, $CDCl_3$)

143.6, 130.3, 128.6, 127.9, 127.1, 119.4, 89.2, 87.5, 83.7, 66.8, 66.6, 64.5, 39.1, 13.0, 6.8, 4.4; HRMS (MALDI-FTMS) *m/z* calc. for $C_{34}H_{42}O_3SiNa$ ([MNa]$^+$): 549.2795, found: 549.2799.

Diol 134

To a stirred solution of allylic alcohol **116** (0.232 g, 0.45 mmol) in THF (5 mL) was added TBAF (0.68 mL, 1.0 M in THF, 0.68 mmol) at 0 °C. The reaction was allowed to warm to room temperature over 1 h before being quenched by the addition of sat. aq. NH_4Cl (20 mL). The mixture was extracted with EtOAc (4 × 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 (60% Et_2O in hexanes) to give **134** (0.149 g, 83%) as a viscous, colourless oil. R_f = 0.05 (silica gel, 1 : 1 hexanes–EtOAc); $[a]_D^{25}$ −21.5° (*c* 4.8 in $CHCl_3$); ν_{max}/cm^{-1} (film) 3374, 2959, 2871, 1611, 1384, 1123, 821; δ_H (500 MHz, $CDCl_3$) 7.25 (2 H, d, *J* 8.4 Hz, Ar*H*), 6.87 (2 H, d, *J* 8.4 Hz, Ar*H*), 5.92 (1 H, s, 6=CH_2), 5.53 (1 H, s, 6=CH_2), 5.25 (1 H, d, *J* 9.0 Hz, 11-H), 4.58 (1 H, d, *J* 10.9 Hz, OCH_2Ar), 4.41 (1 H, d, *J* 10.9 Hz, OCH_2Ar), 4.32–4.33 (1 H, m, 7-H), 3.96 (2 H, s, 13-H and 13-H), 3.79 (3 H, s, ArOCH_3), 3.59–3.61 (1 H, m, 9-H), 2.83–2.92 (3 H, m, 10-H, O*H* and O*H*), 1.80–1.91 (2 H, m, 8-H and 8-H), 1.68 (3 H, s, 12-CH_3), 1.00 (3 H, d, *J* 6.8 Hz, 10-CH_3); δ_C (125 MHz, $CDCl_3$) 159.2, 136.7, 135.7, 130.2, 129.4, 127.5, 116.2, 113.8, 79.1, 73.4, 71.4, 68.4, 55.2, 34.9, 34.0, 14.9, 14.0; HRMS (ES$^+$) *m/z* calc. for $C_{19}H_{27}{}^{79}BrO_4Na$ ([MNa]$^+$): 421.0985, found: 421.0974.

Alkene 135

To a stirred solution of allylic alcohol **116** (0.175 g, 0.34 mmol) and imidazole (0.069 g, 1.0 mmol) in CH_2Cl_2 (6.0 mL) was added TBSCl (0.105 g, 0.68 mmol) in one portion at room temperature. After 1.5 h, the reaction was quenched by the addition of sat. aq. NH_4Cl (25 mL), and the mixture was extracted with Et_2O (3 × 15 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 (10% Et_2O in hexanes) to give **135** (0.207 g, 97%) as a colourless oil. R_f = 0.65 (silica gel, 4 : 1 hexanes–EtOAc); $[a]_D^{25}$ −16.8° (*c* 7.4 in $CHCl_3$); ν_{max}/cm^{-1} (film) 2947, 2853, 1615, 1387, 1248, 1081, 891; δ_H (500 MHz, $CDCl_3$) 7.29 (2 H, d, *J* 8.6 Hz, Ar*H*), 6.88 (2 H, d, *J* 6.8 Hz, Ar*H*), 5.82 (1 H, s, 6=CH_2), 5.47 (1 H, d, *J* 1.5 Hz, 6=CH_2), 5.31 (1 H, d, *J* 9.2 Hz, 11-H), 4.59 (1 H, d, *J* 11.0 Hz, OCH_2Ar), 4.41 (1 H, d, *J* 11.0 Hz, OCH_2Ar), 4.30 (1 H, dd, *J* 8.8, 3.1 Hz, 7-H), 4.02 (2 H, s, 13-H and 13-H), 3.81 (3 H, s, ArOCH_3), 3.50–3.52 (1 H, m, 9-H), 2.86–2.89 (1 H, m, 10-H), 1.75 (1 H, ddd, *J* 14.1, 8.8 and 3.2 Hz, 8-H), 1.69 (1 H, ddd, *J* 14.1, 8.4 and 3.1 Hz, 8-H), 1.64 (3 H, s, 12-CH_3), 0.98 (3 H, d, *J* 6.9 Hz, 10-CH_3), 0.97 [9 H, s, SiC(CH_3)$_3$], 0.92 [9 H, s, SiC(CH_3)$_3$], 0.08 (3 H, s, SiCH_3), 0.08 (3 H, s, SiCH_3), 0.06 (3 H, s, SiCH_3), 0.05 (3 H, s, SiCH_3); δ_C (125 MHz, $CDCl_3$) 159.0, 139.0, 134.9, 131.2, 128.9, 126.3, 116.1, 113.7, 78.7, 73.9, 70.6, 68.4, 55.3, 38.6, 33.8, 26.0, 25.8, 18.4, 18.1, 14.9, 13.6, −4.4, −5.0, −5.1, −5.2; HRMS (ES$^+$) *m/z* calc. for $C_{31}H_{55}{}^{79}BrO_4Si_2Na$ ([MNa]$^+$): 649.2714, found: 649.2721.

Acknowledgements

We thank Dr D. H. Huang and Dr G. Siuzdak for NMR spectroscopic and mass spectrometric assistance, respectively. Financial support for this work was provided by the National Institutes of Health (USA) and The Skaggs Institute for Chemical Biology, and a predoctoral fellowship from the National Science Foundation (USA) (to W. E. B.).

References

1 For reviews, see: J. W. Blunt, B. R. Copp, M. H. G. Munro, P. T. Northcote and M. R. Prinsep, *Nat. Prod. Rep.*, 2005, **22**, 15–61 and refs. cited therein.
2 Y. Shimizu, *Chem. Rev.*, 1993, **93**, 1685–1698; J. Kobayashi and M. Ishibashi, *Chem. Rev.*, 1993, **93**, 1753–1769.
3 J. Kobayashi and M. Tsuda, *Nat. Prod. Rep.*, 2004, **21**, 77–93; J. Kobayashi and M. Ishibashi, in *Comprehensive Natural Products Chemistry*, ed. K. Mori, Elsevier, New York, 1999, vol. 8, pp. 619–634; M. Ishibashi and J. Kobayashi, *Heterocycles*, 1997, **44**, 543–572.
4 Amphidinolide A: B. M. Trost, P. E. Harrington, J. D. Chisholm and S. T. Wrobleski, *J. Am. Chem. Soc.*, 2005, **127**, 13 598–13 610; B. M. Trost, S. T. Wrobleski, J. D. Chisholm, P. E. Harrington and M. Jung, *J. Am. Chem. Soc.*, 2005, **127**, 13 589–13 597; B. M. Trost and P. E. Harrington, *J. Am. Chem. Soc.*, 2004, **126**, 5028–5029; B. M. Trost, J. D. Chisholm, S. J. Wrobleski and M. Jung, *J. Am. Chem. Soc.*, 2002, **124**, 12 420–12 421; R. E. Maleczka, L. R. Terrell, F. Geng and J. S. Ward, *Org. Lett.*, 2002, **4**, 2841–2844; H. W. Lam and G. Pattenden, *Angew. Chem., Int. Ed.*, 2002, **41**, 508–511.
5 Amphidinolide J: D. R. Williams and W. S. Kissel, *J. Am. Chem. Soc.*, 1998, **120**, 11 198–11 199.
6 Amphidinolide K: D. R. Williams and K. G. Meyer, *J. Am. Chem. Soc.*, 2001, **123**, 765–766.
7 Amphidinolide P: B. M. Trost, J. P. N. Papillon and T. Nussbaumer, *J. Am. Chem. Soc.*, 2006, **127**, 17 921–17 937; B. M. Trost and J. P. N. Papillon, *J. Am. Chem. Soc.*, 2004, **126**, 13 618–13 619; D. R. Williams, B. J. Myers and L. Mi, *Org. Lett.*, 2000, **2**, 945–948.
8 Amphidinolide T: E. A. Colby, K. C. O'Brien and T. F. Jamison, *J. Am. Chem. Soc.*, 2005, **127**, 4297–4307; E. A. Colby, K. C. O'Brien and T. F. Jamison, *J. Am. Chem. Soc.*, 2004, **126**, 998–999; C. Aïssa, R. Riveiros, J. Ragot and A. Fürstner, *J. Am. Chem. Soc.*, 2003, **125**, 15 512–15 520; A. K. Ghosh and C. Liu, *J. Am. Chem. Soc.*, 2003, **125**, 2374–2375; A. Fürstner, C. Aïssa, R. Riveiros and J. Ragot, *Angew. Chem., Int. Ed.*, 2002, **41**, 4763–4766.
9 Amphidinolide W: A. K. Ghosh and G. Gong, *J. Am. Chem. Soc.*, 2004, **126**, 3704–3705.
10 J. A. Marshall, G. Schaaf and A. Nolting, *Org. Lett.*, 2005, **7**, 5331–5333; F. P. Liesener and M. Kalesse, *Synlett*, 2005, 2236–2238; T. Andreoa, A. M. Costa, L. Esteban, L. Gonzalez, G. Mas and J. Vilarrasa, *Org. Lett.*, 2005, **7**, 4083–4086; W. Zhang and R. G. Carter, *Org. Lett.*, 2005, **7**, 4209–4212; A. K. Mandal, J. S. Schneekloth and C. M. Crews, *Org. Lett.*, 2005, **7**, 3645–3648; K. C. O'Brien, E. A. Colby and T. F. Jamison, *Tetrahedron*, 2005, **61**, 6243–6248; M. K. Gurjar, S. Mohapatra, U. D. Phalgune, V. G. Puranik and D. K. Mohapatra, *Tetrahedron Lett.*, 2004, **45**, 7899–7902; B. J. Shotwell and W. R. Roush, *Org. Lett.*, 2004, **6**, 3865–3868; W. Zhang, R. G. Carter and A. F. T. Yokochi, *J. Org. Chem.*, 2004, **69**, 2569–2572; J.-H. Pang, Y.-J. Ham and D.-Y. Lee, *Bull. Korean Chem. Soc.*, 2003, **24**, 891–892; T. Kubota, M. Tsuda and J. Kobayashi, *Tetrahedron*, 2003, **59**, 1613–1625; J.-H. Pang and D.-H. Lee, *Bull. Korean Chem. Soc.*, 2002, **23**, 1173–1176; T. K. Chakraborty, *Tetrahedron Lett.*, 2001, **42**, 3387–3390; M. B. Cid and G. Pattenden, *Tetrahedron Lett.*, 2000, **41**, 7373–7378; D.-H. Lee and M.-D. Rho, *Tetrahedron Lett.*, 2000, **41**, 2573–2576; T. K. Chakraborty and S. Das, *Chem. Lett.*, 2000, 80–81; D. R. Williams and K. G. Meyer, *Org. Lett.*, 1999, **1**, 1303–1305; K. Ohi and S. Nishiyama, *Synlett*, 1999, 573–575; K. Ohi and S. Nishiyama, *Synlett*, 1999, 571–572; H. Ishiyama, T. Takemura, M. Tsuda and J. Kobayashi, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1163–1166; H. Ishiyama, T. Takemura, M. Tsuda and J. Kobayashi, *Tetrahedron*, 1999, **55**, 4583–4595; L. R. Terrell and J. S. Ward, *Tetrahedron Lett.*, 1999, **40**, 3097–3100; H. M. Eng and D. C. Myles, *Tetrahedron Lett.*, 1999, **40**, 2275–2278; H. M. Eng and D. C. Myles, *Tetrahedron Lett.*, 1999, **40**, 2279–2282; T. K.

Chakraborty and D. Thippeswamy, *Synlett*, 1999, 150–152; T. K. Chakraborty and V. R. Suresh, *Tetrahedron Lett.*, 1998, **39**, 9109–9112; T. K. Chakraborty and V. R. Suresh, *Tetrahedron Lett.*, 1998, **39**, 7775–7778; K. Ohi, K. Shima, K. Hamada, Y. Saito, N. Yamada, S. Ohba and S. Nishiyama, *Bull. Chem. Soc. Jpn.*, 1998, **71**, 2433–2440; B. M. Cid and G. Pattenden, *Synlett*, 1998, 540–542; D.-H. Lee and M.-D. Rho, *Bull. Korean Chem. Soc.*, 1998, **19**, 386–390; G. J. Hollingworth and G. Pattenden, *Tetrahedron Lett.*, 1998, **39**, 703–706; J. Kobayashi, A. Hatakeyama and M. Tsuda, *Tetrahedron*, 1998, **54**, 697–704; M. Tsuda, A. Hatakeyama and J. Kobayashi, *J. Chem. Soc., Perkin Trans. 1*, 1998, 149–156; D.-H. Lee and S.-K. Lee, *Tetrahedron Lett.*, 1997, 7909–7910; T. K. Chakraborty and V. R. Suresh, *Chem. Lett.*, 1997, 565–566; T. K. Chakraborty, D. Thippeswamy, V. R. Suresh and S. Jayaprakash, *Chem. Lett.*, 1997, 563–564; H. Ishiyama, M. Ishibashi and J. Kobayashi, *Chem. Pharm. Bull.*, 1996, **44**, 1819–1822; C. Boden and G. Pattenden, *Synlett*, 1994, 181–182; S. J. O'Conner and P. G. Williard, *Tetrahedron Lett.*, 1989, **30**, 4637–4640.

11 M. Ishibashi, N. Yamaguchi, T. Sasaki and J. Kobayashi, *J. Chem. Soc., Chem. Commun.*, 1994, 1455–1456.

12 J. Pietruszka, *Angew. Chem., Int. Ed.*, 1998, **37**, 2629–2636.

13 I. Bauer, L. Maranda, K. A. Young, Y. Shimizu, C. Fairchild, L. Cornell, J. MacBeth and S. Huang, *J. Org. Chem.*, 1995, **60**, 1084–1086.

14 Y. Shimizu, personal communication.

15 K. C. Nicolaou, P. G. Bulger and W. E. Brenzovich, *Org. Biomol. Chem.*, 2006, DOI: 10.1039/b602021f.

16 S. T. Diver and A. J. Giessert, *Synthesis*, 2004, 466–471; R. Stragies, M. Schuster and S. Blechert, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 2518–2520.

17 E. C. Hansen and D. Lee, *J. Am. Chem. Soc.*, 2004, **126**, 15 074–15 080; E. C. Hansen and D. Lee, *J. Am. Chem. Soc.*, 2003, **125**, 9582–9583.

18 K. C. Nicolaou, P. G. Bulger and D. Sarlah, *Angew. Chem., Int. Ed.*, 2005, **44**, 4490–4527.

19 D. Enders, M. Voith and A. Lenzen, *Angew. Chem., Int. Ed.*, 2005, **44**, 1304–1325; D. Enders, M. Voith and S. J. Ince, *Synthesis*, 2002, 1775–1779; A. Job, C. F. Janeck, W. Bettray, R. Peters and D. Enders, *Tetrahedron*, 2002, **58**, 2253–2329.

20 D. Xing, P. Chen, R. Keil, C. D. Kilts, B. Shi, V. M. Camp, G. Malveaux, T. Ely, M. J. Owens, J. Votaw, M. Davis, J. M. Hoffman, R. A. E. BaKay, T. Subramanian, R. L. Watts and M. M. Goodman, *J. Med. Chem.*, 2000, **43**, 639–648.

21 A. Ahmed, E. K. Hoegenauer, V. S. Enev, M. Hanbauer, H. Kaehlig, E. Öhler and J. Mulzer, *J. Org. Chem.*, 2003, **68**, 3026–3042.

22 G. E. Keck and E. P. Boden, *Tetrahedron Lett.*, 1984, **25**, 265–268.

23 H. C. Brown and P. K. Jadhav, *J. Am. Chem. Soc.*, 1983, **105**, 2092–2093.

24 O. H. Gringore and F. P. Rouessac, *Org. Synth.*, 1985, **63**, 121–126.

25 C. Eguchi and A. Kakuta, *Bull. Chem. Soc. Jpn.*, 1974, **47**, 1704–1708.

26 M. Larchevêque and J. Lalande, *J. Chem. Soc., Chem. Commun.*, 1985, 83–84.

27 M. Chérest, H. Felkin and N. Prudent, *Tetrahedron Lett.*, 1968, 2199–2204; N. T. Anh, *Top. Curr. Chem.*, 1980, **88**, 145–162.

28 A. N. Rai and A. Basu, *Tetrahedron Lett.*, 2003, **44**, 2267–2269.

29 C. H. Larsen, B. H. Ridgway, J. T. Shaw, D. M. Smith and K. A. Woerpel, *J. Am. Chem. Soc.*, 2005, **127**, 10 879–10 884; M. F. Buffet, D. J. Dizon, S. V. Ley, D. J. Reynolds and R. I. Storer, *Org. Biomol. Chem.*, 2004, **2**, 1145–1154.

30 K. E. Drouet and E. A. Theodorakis, *Chem.–Eur. J.*, 2000, **6**, 1987–2001.

31 K. Matsumura, S. Hashiguchi, T. Ikariya and R. Noyori, *J. Am. Chem. Soc.*, 1997, **119**, 8738–8739; K.-J. Haack, S. Hashiguchi, A. Fujii, T. Ikariya and R. Noyori, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 285–288; S. Hashiguchi, A. Fujii, K.-J. Haack, K. Matsumura, T. Ikariya and R. Noyori, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 288–290.

32 P. Soucy, A. L'Heureux, A. Toró and P. Deslongchamps, *J. Org. Chem.*, 2003, **68**, 9983–9987.

33 J. C. Anderson, B. P. McDermott and E. J. Griffin, *Tetrahedron*, 2000, **56**, 8747–8767.

34 D. Enders, T. Hundertmark and R. Lazny, *Synlett*, 1998, 721–722.

35 M. Scholl, S. Ding, C. W. Lee and R. H. Grubbs, *Org. Lett.*, 1999, **1**, 953–956.

36 M. Mori, N. Sakakibara and A. Kinoshita, *J. Org. Chem.*, 1998, **63**, 6082–6083.

37 S. S. Salim, R. K. Bellingham and R. C. D. Brown, *Eur. J. Org. Chem.*, 2004, 800–806.

38 J. Inanaga, K. Hirata, H. Saeki, T. Katsuki and M. Yamaguchi, *Bull. Chem. Soc. Jpn.*, 1979, **52**, 1989–1993.

39 R. R. Schrock, J. S. Murdzek, G. C. Bazan, J. Robbins, M. DiMare and M. O'Regan, *J. Am. Chem. Soc.*, 1990, **112**, 3875–3886.

40 S. V. Ley, J. Norman, W. P. Griffith and S. P. Marsden, *Synthesis*, 1994, 639–666; W. P. Griffith, S. V. Ley, G. P. Whitcombe and A. D. White, *J. Chem. Soc., Chem. Commun.*, 1987, 1625–1627.

41 V. Farina and V. Krishnamurthy, *Org. React.*, 1997, **50**, 1–652; J. K. Stille, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 508–524.

42 A. B. Smith, P. A. Levenberg, P. J. Jerris, R. M. Scarborough and P. M. Wovkulich, *J. Am. Chem. Soc.*, 1981, **103**, 1501–1513; R. H. Baker, S. W. Tinsley, D. Butler and B. Riegel, *J. Am. Chem. Soc.*, 1950, **72**, 393–395.

43 D. Crich, X.-Y. Jiao and M. Bruncko, *Tetrahedron*, 1997, **53**, 7127–7138.

44 K. Nagasawa, H. Ishihara, Y. Zako and I. Shimizu, *J. Org. Chem.*, 1993, **58**, 2523–2529.

45 H. C. Brown and K. S. Bhat, *J. Am. Chem. Soc.*, 1986, **108**, 5919–5923.

46 N. Nakajima, K. Horita, R. Abe and O. Yonemitsu, *Tetrahedron Lett.*, 1988, **29**, 4139–4142.

47 T. Bach and S. Heuser, *Chem.–Eur. J.*, 2002, **8**, 5585–5592.

48 H. X. Zhang, F. Guibé and G. Balavoine, *J. Org. Chem.*, 1990, **55**, 1857–1867; K. C. Nicolaou, K. C. Fylaktakidou, H. Monenschein, Y. Li, B. Weyershausen, H. J. Mitchell, H. Wei, P. Guntupalli, D. Hepworth and K. Sugita, *J. Am. Chem. Soc.*, 2003, **125**, 15 433–15 442.

49 N. Kamiya, Y. Chikami and Y. Ishii, *Synlett*, 1990, 675–676.

50 K. Sonogashira, Y. Tohda and N. Hagihara, *Tetrahedron Lett.*, 1975, 4467–4470; H. A. Dieck and F. R. Heck, *J. Organomet. Chem.*, 1975, **93**, 259–263; L. Cassar, *J. Organomet. Chem.*, 1975, **93**, 253–259.

51 H. Suzuki, M. Aihara, H. Yamamoto, Y. Takamoto and T. Ogawa, *Synthesis*, 1988, 236–238.

52 Y. Segall, E. C. Kimmel, D. R. Dohn and J. E. Casida, *Mutat. Res.*, 1985, **158**, 61–68.

53 M. G. Organ and J. Wang, *J. Org. Chem.*, 2003, **68**, 5568–5574.