Tetrahedron 66 (2010) 6534–6545

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Total synthesis of (−)-dictyostatin, a microtubule-stabilising anticancer macrolide of marine sponge origin

Ian Paterson *, Robert Britton, Oscar Delgado, Nicola M. Gardner, Arndt Meyer, Guy J. Naylor, Karine G. Poullennec

University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK

ARTICLE INFO

Article history:
Received 9 September 2009
Received in revised form 12 November 2009
Accepted 21 January 2010
Available online 1 February 2010

Dedicated to Professor Steven Ley on the occasion of his receipt of the Tetrahedron Prize

Keywords:
Macrolide
Cytotoxic
Tubulin
Aldol reaction
Olefination

ABSTRACT

An efficient convergent synthesis of the anticancer marine macrolide (−)-dictyostatin is described that proceeds in 4.6% yield over 27 steps. Most of the stereocentres were configured using substrate control, making use of a common building block to install the C12–C14 and C20–C22 stereotriads, with a lactate boron aldol reaction employed to construct a C4–C10 β-ketophosphonate as utilised in the pivotal Still–Gennari HWE coupling step with a fully elaborated C11–C26 aldehyde. Following introduction of the (2*Z*,4*E*)-dienoate, a modified Yamaguchi macrolactonisation and deprotection delivered the requisite 22-membered macrocyclic lactone.

1. Introduction

Marine organisms have proven to be a rich source of biologically active natural products.[1,2] Many of these novel chemotypes exhibit exceptional levels of biological activity, combined with unique modes of action, which may have value as lead structures for the development of new therapeutic agents. Dictyostatin (**1**, Fig. 1) is a potent cytotoxic marine macrolide, first isolated in 1994 by Pettit et al.[3] from the same Indian Ocean sponge as the spongistatins. Due to the low isolation yield (1.35 mg from 400 kg of wet sponge), relatively few biological assays were performed. However, these revealed dictyostatin to have promising antitumour properties, strongly inhibiting the growth of a selection of cancer cell lines. Almost a decade passed until Wright et al. reisolated dictyostatin in 2003 from a Caribbean sponge of the family *Corallistidae*, collected with a manned submersible at great depth off the coast of Jamaica.[4] Providing a somewhat more abundant source, this allowed more extensive biological evaluations, which demonstrated significant inhibition of cancer cell proliferation at low nanomolar concentrations. Significantly, this potent antimitotic activity was retained against multidrug-resistant cell lines and a characteristic Taxol-like mode of action was revealed, causing an accumulation of cells in the G2/M phase of the cell cycle, extensive microtubule bundling and cellular death via apoptosis. Complementing the benchmark of Taxol (**2**), this clinically proven microtubule-stabilising mechanism is shared with discodermolide (**3**)[5] and epothilone B (**4**),[6] as well as a number of other structurally distinct natural products that have emerged as important leads for anticancer drug discovery programmes.[7]

The planar structure of dictyostatin featuring a 26-carbon backbone with 11 stereogenic centres, a 22-membered macrolactone, an endocyclic (2*Z*,4*E*)-dienoate and a pendant (*Z*)-diene moiety was deduced by the Pettit group, primarily on the basis of 2D NMR spectroscopic data.[3] The elucidation of the complete stereostructure as in **1** was achieved in our laboratory in 2004,[8] based on the use of NOESY experiments and Murata's method of *J*-based configurational analysis. Recently, extensive NMR analysis, molecular modelling and docking studies were employed to propose a bound conformation for dictyostatin in the taxoid binding site on β-tubulin.[9] The results support a high degree of overlap between the bioactive conformations of dictyostatin and discodermolide,[10] stimulating the design and synthesis of hybrid molecules as novel microtubule-stabilising agents that retain potent antiproliferative activity.[11]

* Corresponding author. E-mail address: ip100@cam.ac.uk (I. Paterson).

0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.01.083

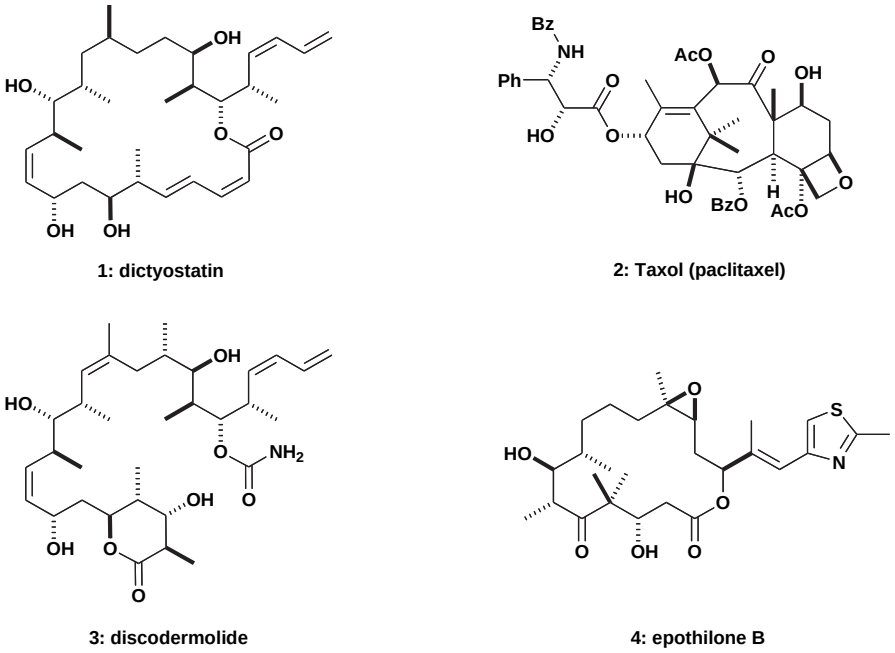


Figure 1. Natural products with a shared microtubule-stabilising mode of action.

The impressive biological profile of dictyostatin, coupled with its elaborate stereostructure and low natural abundance, have led to its widespread identification as an important synthetic target.[12–17] As well as providing a sustainable supply for preclinical evaluation, an efficient and flexible synthetic strategy should enable extensive SAR studies to help define the pharmacophore with a view to simplifying the structure whilst retaining functionality. As a conformationally constrained macrolide, dictyostatin represents an attractive template for the optimisation of a new structural class of microtubule-stabilising anticancer agent. Soon after the full stereostructure was disclosed by our laboratory, the first two total syntheses of (−)-dictyostatin were reported concurrently by ourselves[13] and the Curran group.[14] Subsequently, there have been two further completed total syntheses by the groups of Phillips[15] and Ramachandran,[16] as well as a growing number of fragment syntheses.[17] Additionally, the synthesis and biological activities of a range of structural analogues of dictyostatin have been reported independently by ourselves[18] and Curran and Day.[19] Notably, Eiseman and Curran have recently demonstrated the promising *in vivo* antitumour properties associated with 6-*epi*-dictyostatin in xenograft mouse studies.[20]

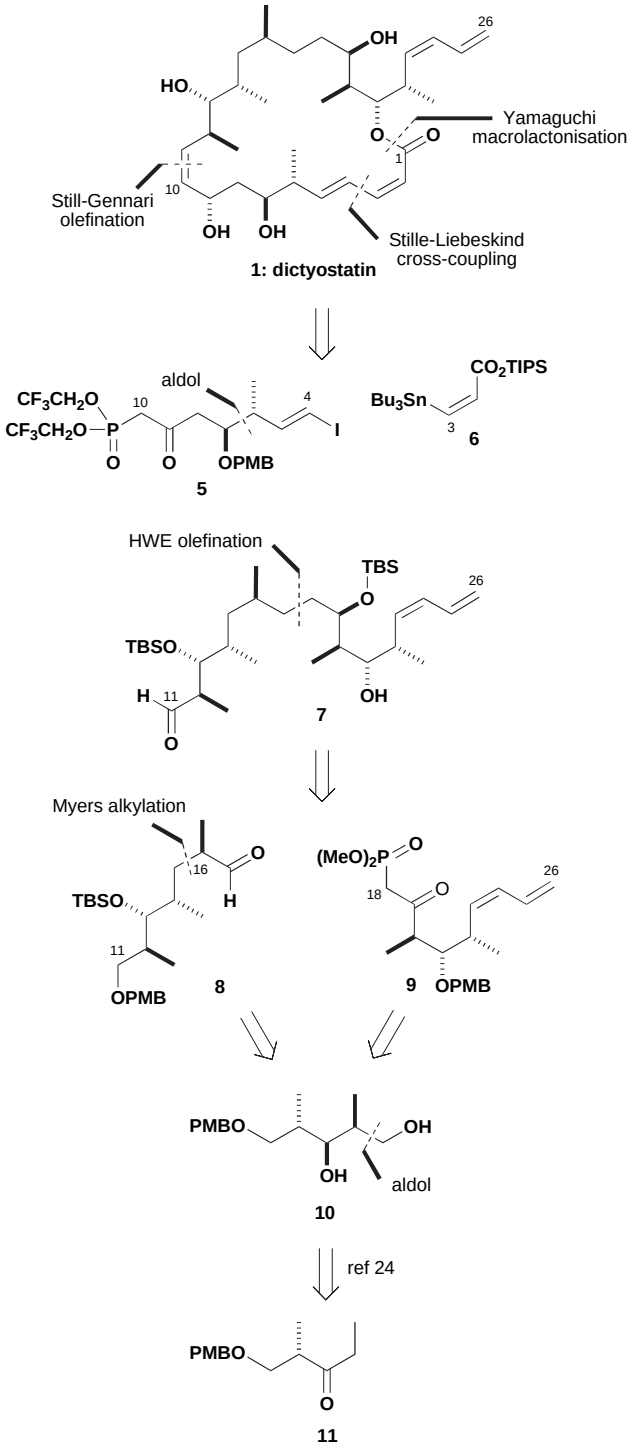
Despite these remarkable efforts, there remains a pressing need to develop a more practical and efficient route to dictyostatin itself. Herein, we report full details of an improved total synthesis of dictyostatin that evolved from our previously reported strategy[13] and parallel work on SAR studies.[18] Notably, this route has been used to prepare sufficient quantities of synthetic dictyostatin to facilitate further biological evaluation of this promising anticancer agent.

2. Retrosynthetic analysis and general synthetic strategy

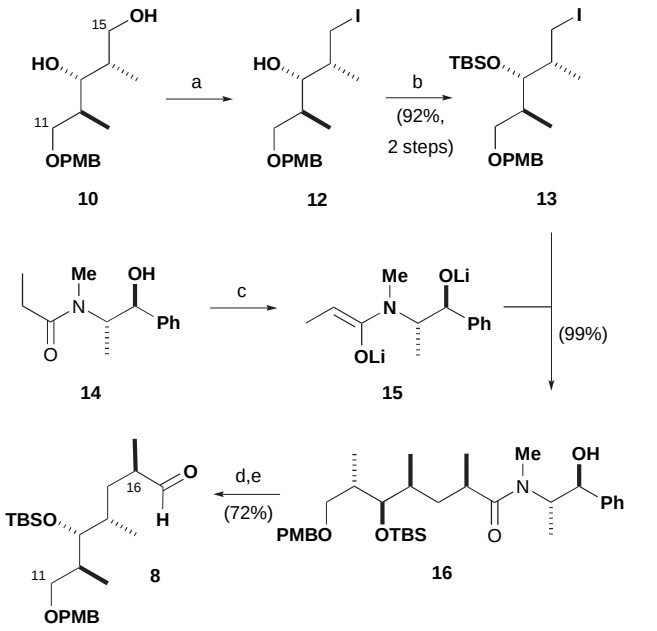
As devised originally, our modular synthetic strategy[13] for dictyostatin was designed to be highly convergent and readily amenable to analogue synthesis by late-stage diversification. As outlined in Scheme 1, we envisaged a late-stage Yamaguchi macrolactonisation preceded by a Stille–Liebeskind cross-coupling reaction[21] with vinyl stannane **6** to generate the (2*Z*,4*E*)-dienoate. The (10*Z*)-alkene would be installed via a complex Still–Gennari olefination[22,23] between β-ketophosphonate **5** and aldehyde **7**. In turn, the C11–C26 subunit **7** was planned to arise through a Horner–Wadsworth–Emmons (HWE) coupling of aldehyde **8** and phosphonate **9**. The shared stereochemical triad of these two intermediates indicated that they could both be accessed via a common intermediate **10**, which is readily available by boron-mediated aldol methodology developed in the context of our discodermolide work.[24] The isolated methyl-bearing stereocentre at C16 in aldehyde **8** would be configured by a Myers alkylation. While these disconnections are shared with our original route, we chose to revise the synthesis of the pivotal C4–C10 subunit **5** having the C7 hydroxyl now protected as a PMB ether,[11,18a] utilising our lactate aldol methodology[25] in preference to the Brown crotylation used previously. In addition, we elected to configure the C9 hydroxyl-bearing stereocentre after the Still–Gennari-type fragment coupling and before the macrolactonisation step. A judicious selection of protecting groups was expected to help further refine the synthesis.

3. Results and discussion

The synthesis of the C11–C26 fragment **7**, containing eight of the eleven stereocentres and the terminal diene of dictyostatin, required the efficient construction of the requisite HWE coupling partners **8** and **9** from the common precursor **10**. Using our boron aldol methodology, this valuable stereotriad building block can be prepared on a multi-gram scale from the ethyl ketone **11** derived from (*S*)-Roche ester (67%, five steps), as described previously.[24] Preparation of the C11–C17 aldehyde **7** began with selective iodination[26] of the primary hydroxyl in 1,3-diol **10**, followed by secondary hydroxyl protection of **12** with TBSOTf and 2,6-lutidine, to yield iodide **13** in 92% yield (Scheme 2). Myers' propionamide **14**[27] was then treated with LDA to generate the lithium enolate **15**, before addition of iodide **13** effected formation of the desired alkylation product **16**. This homologation sequence proceeded in high yield to configure the C16 methyl-bearing stereocentre with excellent diastereoselectivity (99%, >20:1 dr). Pleasingly, upon reductive cleavage of the amide in **16** with $BH_3 \cdot NH_3$, the pseudoephedrine auxiliary could be recovered by recrystallisation prior to chromatographic purification of the resulting primary alcohol



Scheme 1. Retrosynthetic analysis for dictyostatin leading to key building blocks.



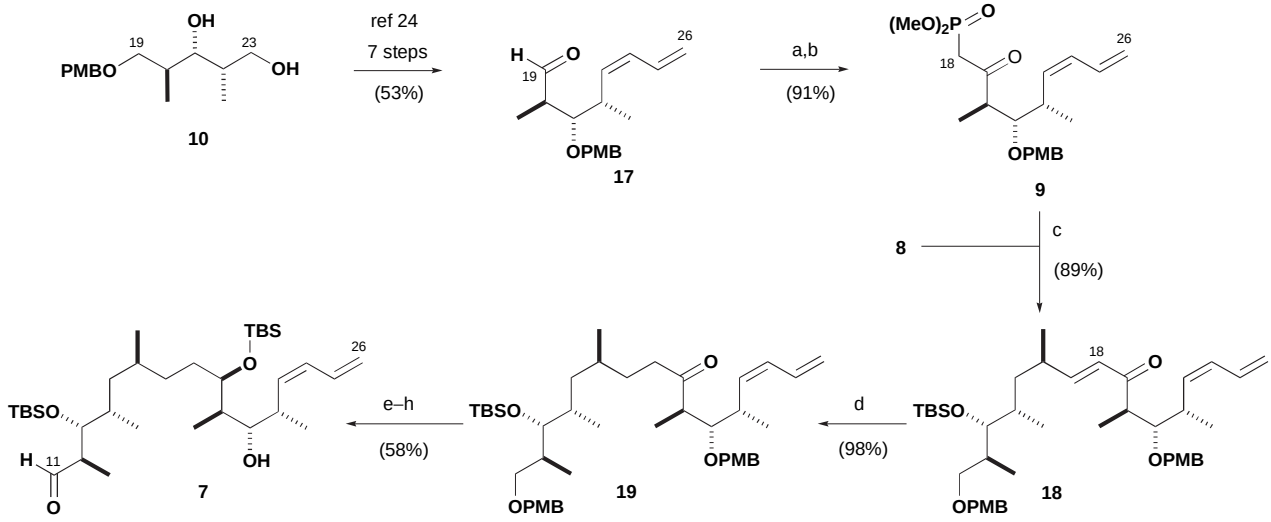
Scheme 2. (a) PPh_3, I_2, pyr, PhMe, 0 °C→rt, 16 h; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 2 h; (c) *i*-Pr_2NH, LiCl, *n*-BuLi, THF, −78 °C→0 °C→rt, 90 min; **13**, THF, 0 °C→rt, 16 h; (d) LDA, $BH_3{\cdot}NH_3$, THF, rt, 2 h; (e) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C, 2 h.

product. Oxidation of this alcohol with Dess–Martin periodinone provided the corresponding aldehyde **8** (72%, two steps),[28] set for the key HWE fragment union. In comparison, efforts to convert the alkylation product **16** directly to aldehyde **8**, by treatment with $LiAlH(OEt)_3$, led to poor yields, epimerisation and extensive by-product formation.

The β-ketophosphonate coupling partner **9** was also prepared from common intermediate **10** (Scheme 3), whereby a previously described[24] sequence afforded the (*Z*)-diene substituted aldehyde **17** (53%, seven steps), as used to great effect in our discodermolide work. Conversion of **17** into the desired phosphonate **9** was initiated by addition of $(MeO)_2P(O)CH_2Li$, before the resulting epimeric mixture of alcohols was then reoxidised with Dess–Martin periodinone (91%). Reaction between the aldehyde **8** and phosphonate **9** using HWE conditions developed in our group ($Ba(OH)_2$ in wet THF),[29] resulted in isolation of the enone **18** as exclusively the (*E*)-isomer in excellent yield (89%) when performed on a 5 g scale. The enone **18** then underwent a conjugate reduction with Stryker's reagent,[30] to yield the corresponding α,β-saturated ketone **19** in 98% yield. Interestingly, it was found that addition of traces of water significantly increased the rate of hydride transfer. However, attempts to utilise a catalytic amount of Stryker's reagent proved unrewarding,[31] leading to lower yields.

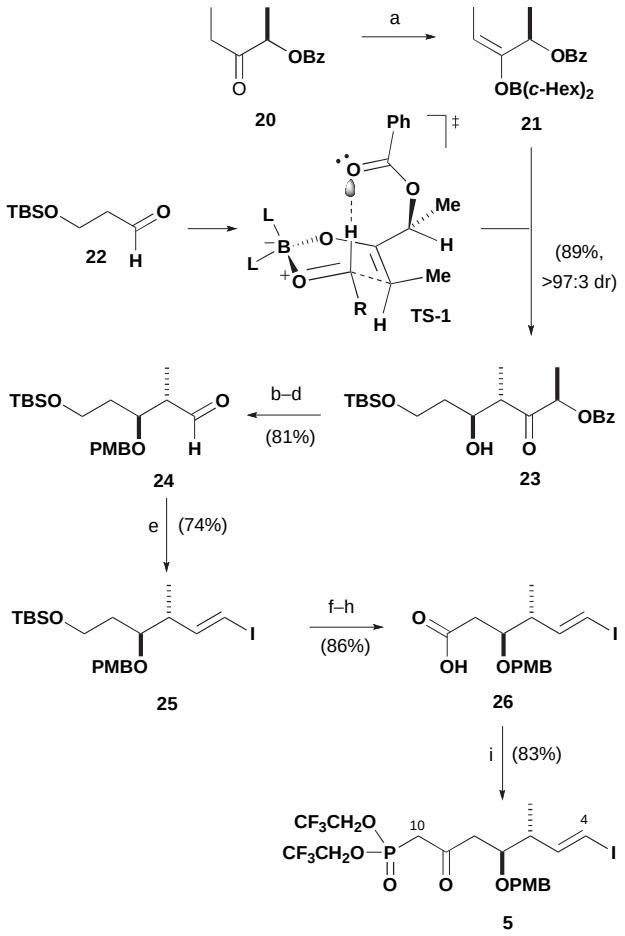
With the entire C11–C26 carbon backbone now in place, we next focused on achieving an efficient, stereoselective reduction of the C19 carbonyl group. Rather than proceed by cleavage of both PMB ethers and chelation-controlled reduction of the resulting β-hydroxyketone using $Zn(BH_4)_2$, followed by a two-step sequence to selectively introduce a TBS ether at C19 over C21 as implemented previously,[13] we elected to initially retain the PMB ethers to help streamline the synthesis. Gratifyingly, after screening a number of metal hydrides, it was found that $LiAlH(O^tBu)_3$[32] at low temperature (−30 °C, THF) reduced the ketone **19** smoothly to the requisite (19*R*)-alcohol in excellent diastereoselectivity (>20:1 dr) on a multi-gram scale. Subsequently, treatment with TBSOTf and 2,6-lutidine protected the C19 hydroxyl, before a bis-PMB deprotection via oxidative cleavage with DDQ, in a biphasic solution of DCM and pH 7 buffer, afforded the corresponding diol in 65% yield from ketone **19**. Selective oxidation[33a] of the primary over the secondary alcohol using the Piancatelli protocol (catalytic TEMPO and $PhI(OAc)_2$)[33b] resulted in formation of the α-chiral aldehyde **7** in 89% yield, without any epimerisation. This efficient and scaleable synthesis of the fully elaborated C11–C26 subunit **7** was completed in 20 steps and 16% overall yield along the longest linear sequence starting from (*S*)-Roche ester, in readiness for its Still–Gennari coupling with the complex phosphonate **5**.

Synthesis of the C4–C10 fragment **5** relied on a boron-mediated aldol reaction to configure the *anti*-related C6 and C7 stereocentres (Scheme 4). The ethyl ketone **20** was prepared in three steps and 65% yield from (*R*)-*iso*butyl lactate, as described previously.[25a] Selective



Scheme 3. (a) $(MeO)_2P(O)Me$, *n*-BuLi, THF, −78 °C, 20 min; (b) DMP, CH_2Cl_2, rt, 30 min; (c) **8**, $Ba(OH)_2$, THF/H_2O, rt, 90 min; (d) $[(Ph_3P)CuH]_6$, PhMe/H_2O, rt, 16 h; (e) $LiAlH(Ot\text{-}Bu)_3$, THF, −30 °C, 72 h; (f) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78→0 °C, 30 min; (g) DDQ, CH_2Cl_2/pH 7 buffer, 0 °C, 2 h; (h) $PhI(OAc)_2$, cat. TEMPO, CH_2Cl_2, 0 °C→rt, 16 h.

generation of the (*E*)-boron enolate **21** was achieved using our standard conditions of treatment with $(c\text{-Hex})_2BCl/Me_2NEt$ in Et_2O. Addition of aldehyde **22** at −78 °C, followed by oxidative work-up, afforded the expected 1,4-*syn*-1,3-*anti* adduct **23** in excellent yield and selectivity (89%, >97:3 dr). This aldol reaction is believed to proceed preferentially through the bicyclic boat-like transition state **TS-1**, stabilised by a formyl hydrogen bond between the benzoate carbonyl oxygen and the aldehyde with minimisation of A(1,3) strain between the α-stereocentre of the enolate and the methyl substituent.[25a,34] Consequently, the requisite stereocentres at C6 and C7 in dictyostatin could be installed in a facile and efficient manner on a multi-gram scale, where this procedure was found to be operationally simpler than the Brown crotylation protocol employed earlier,[13] involving significantly less effort in chromatographic purification and delivering improved levels of stereocontrol. We have since used this more convenient aldol-based route to synthesise a potent hybrid of dictyostatin and discodermolide.[11a]



Scheme 4. (a) *c*-Hex_2BCl, Me_2NEt, Et_2O, −78→0 °C, 1 h; **22**, −78→−20 °C, 19 h; H_2O_2, MeOH, pH 7 buffer, 0 °C→rt, 1 h; (b) PMBTCA, cat. $Sc(OTf)_3$, THF, 0 °C, 50 min; (c) $NaBH_4$, MeOH, 0 °C→rt, 45 min; K_2CO_3, 0 °C→rt, 16 h; (d) $NaIO_4$, MeOH/pH 7 buffer, 0 °C→rt, 35 min; (e) $CrCl_2$, CHI_3, dioxane/THF, 0 °C, 18 h; (f) TBAF, AcOH, THF, rt, 18 h; (g) DMP, pyr, CH_2Cl_2, 0 °C, 2 h; (h) $NaClO_2$, $Na_2H_2PO_4$, *t*-BuOH/2-methyl-2-butene, rt, 2 h; (i) 1-chloro-*N*,*N*-trimethylpropenyl-amine, CH_2Cl_2, rt, 1 h; LiHMDS, bis(2,2,2-trifluoroethyl)-2-methylphosphonate, THF, −98 °C, 90 min.

With both of the key coupling partners **5** and **7** in hand, the stage was set for the complex Still–Gennari-type HWE olefination which was modelled on the pivotal fragment coupling step employed in our third-generation discodermolide synthesis.[23] After extensive

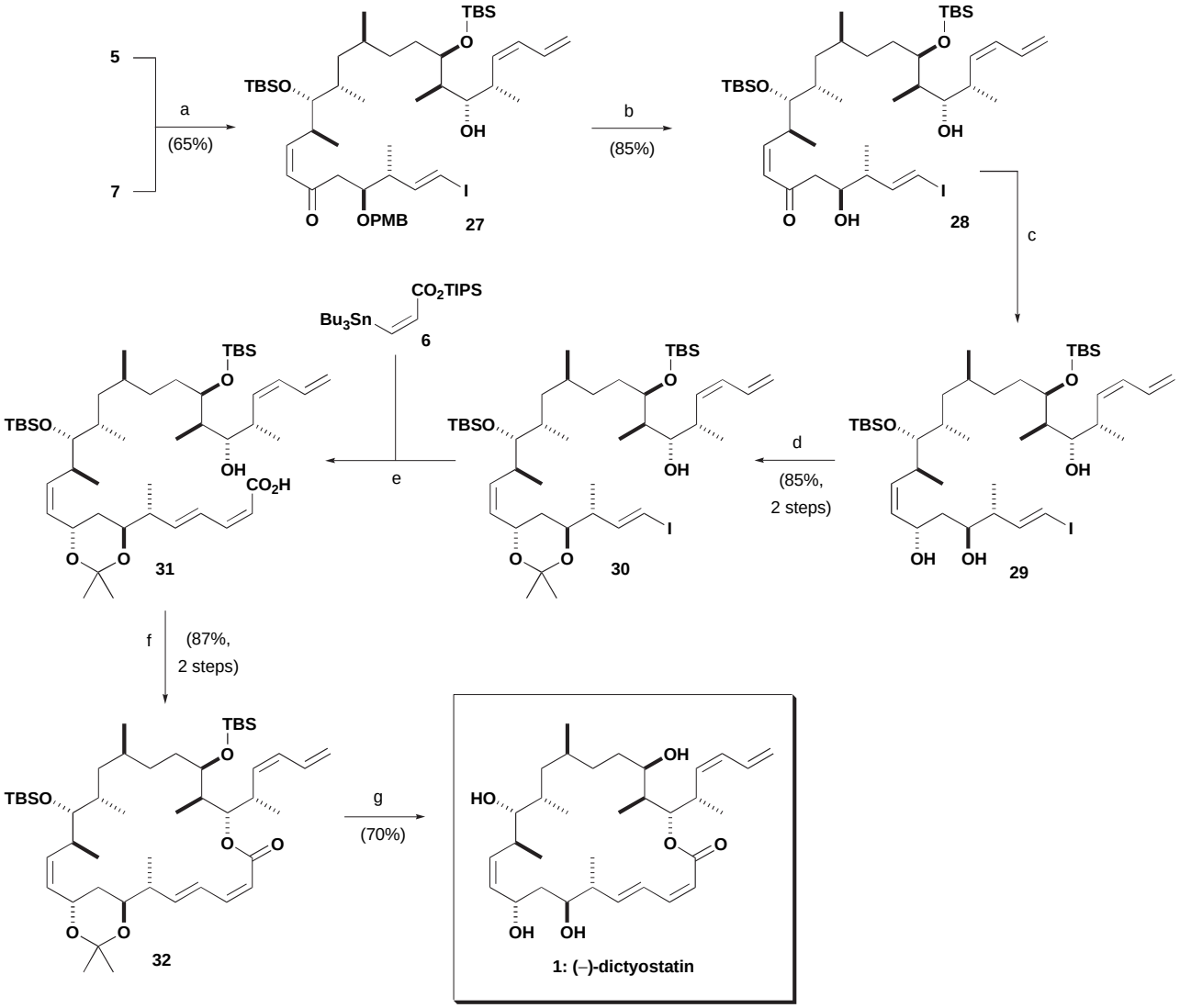
At this stage, we needed to introduce the bis-(2,2,2-trifluoroethyl)-methylphosphonate functionality in **5**, in readiness for the complex Still–Gennari olefination with the C11–C26 aldehyde **7**. Thus cleavage of the TBS ether in **25** was implemented by treatment with AcOH-buffered TBAF. The ensuing primary alcohol was then subjected to a two-step oxidation sequence (Dess–Martin periodinane then Pinnick oxidation[37]) to afford acid **26** on a multi-gram scale. This acid was then advanced directly onto the next step without purification. Treatment with Ghosez's reagent[38] provided the intermediate acid chloride cleanly under mild conditions, as found in our discodermolide work.[23] This was then added to a solution of lithiated bis-(2,2,2-trifluoroethyl)-methylphosphonate at −98 °C to yield β-ketophosphonate **5** in 71% yield from **25**. Overall, this readily scaleable synthesis of the C4–C10 subunit **5** was completed in 12 steps and 25% yield from (*R*)-*iso*-butyl lactate.

In addition of aldehyde **22** at −78 °C, followed by oxidative work-up,

screening of conditions, including base, solvent, concentration and temperature, we found that the optimal yield and selectivity were achieved by using an excess of phosphonate **5** (1.5 equiv) and treating this with K_2CO_3 and 18-crown-6 in the presence of aldehyde **7** in PhMe/HMPA (10:1) (Scheme 5). Good selectivity (6:1 *Z*:*E*) could then be realised for the desired (*Z*)-enone **27**, which was isolated in 65% yield.[39] This pivotal Still–Gennari-type fragment coupling strategy has figured prominently in our synthesis of a variety of dictyostatin analogues for SAR studies.[18]

Oxidative cleavage of the PMB ether occurred on exposure of adduct **27** to DDQ, affording the diol **28** cleanly (85%). This β-hydroxyketone was intended for use in a directed reduction of the enone moiety and our initial attempts focused on the Evans–Saksena protocol[40] using $NaBH(OAc)_3$ in MeCN/AcOH. However, this afforded a mixture of epimers at C9 (90% yield), formed in a modest 2:1 dr in favour of the 1,3-*anti* diol **29**. Similar results were obtained in our analogue work,[18b–d] indicating that such complex (*Z*)-enones are poor substrates for this particular hydroxyl-directed reduction method. In an attempt to improve the diastereoselectivity, the samarium (II) iodide mediated Evans–Tishchenko protocol[41] was next attempted, yielding the desired 1,3-*anti* diol relationship in an improved 5:1 dr (70%). Finally, the most successful and scaleable results were obtained using the (*R*)-CBS reagent[42] and $BH_3 \cdot THF$ at −30 °C, providing the 1,3-*anti* diol in 7:1 dr. Conversion to the corresponding acetonide **30**, with 2,2-dimethoxypropane and catalytic PPTS, then allowed for straightforward chromatographic purification, proceeding in 85% yield from **28**. At this stage, the 1,3-*anti* relationship between C7 and C9 was also confirmed by ^{13}C NMR acetonide analysis, utilising the Rychnovsky method.[43]

The endgame strategy commenced with the completion of the full dictyostatin backbone. Employing a copper-mediated Stille–Liebeskind cross-coupling protocol,[21] a mixture of vinyl iodide **30** and stannane **6**[44] was treated with CuTC in deoxygenated NMP to afford an acid-sensitive TIPS ester, which was immediately deprotected with KF in THF/MeOH to yield the seco-acid **31**,[45] in preparation for subjection to a modified Yamaguchi macrolactonisation protocol.[46] Thus, treatment of **31** with 2,4,6-trichlorobenzoylchloride, Et_3N and DMAP in PhMe at room temperature afforded the 22-membered macrocyclic lactone **32** in 87% yield from vinyl iodide **30**. An initial problem encountered with this step was the sensitive dienoate moiety partly isomerising to the more stable (2*E*,4*E*)-isomer under the reaction conditions. This is likely due to a reversible Michael addition of DMAP onto the C3 (or C5) position, where free rotation of the C2–C3 bond then allows formation of the thermodynamically favoured (2*E*,4*E*)-dienoate. Pleasingly, this



Scheme 5. (a) K_2CO_3, 18-crown-6, PhMe/HMPA, 0 °C, 6 d; (b) DDQ, CH_2Cl_2/pH 7 buffer, 0 °C, 1 h; (c) (*R*)-CBS·BH_3, THF, −40 °C, 16 h; (d) cat. PPTS, $(MeO)_2CMe_2/CH_2Cl_2$, 0 °C→rt, 16 h; (e) **6**, CuTC, NMP, rt, 16 h; KF, THF/MeOH, rt, 3 h; (f) 2,4,6-trichlorobenzoylchloride, Et_3N, PhMe, rt, 2 h; DMAP, PhMe, rt, 18 h; (g) HF·pyr, THF, 0 °C→rt, 96 h.

unwanted side reaction could be reduced to <5% by using the minimum possible equivalents of Yamaguchi reagent (1.8 equiv) and slow, portionwise addition of DMAP (0.5 equiv) to the solution of the preformed mixed anhydride. This result represents a useful improvement over our first-generation route,[13] where a different seco-acid was macrolactonised under conventional Yamaguchi conditions.

All that now remained to complete the total synthesis was the global deprotection of macrocycle **32**. On larger scale runs, removing the protecting groups with 3 M HCl/MeOH (1:3) caused a significant amount of translactonisation onto the C19 hydroxyl, to afford the isomeric 20-membered macrocycle. However, switching to a more dependable protocol[18c] using HF·pyridine converted **32** into (−)-dictyostatin (**1**), $[\alpha]_D^{20}$ −32.7 (*c* 0.22, MeOH),[47] in 70% yield with minimal ring contraction. This material was spectroscopically identical to an authentic sample. To date, we have used this modified synthetic route to prepare 40 mg batches of dictyostatin for further biological studies, as well as a series of structural analogues.

4. Conclusions

In summary, an improved synthesis of the anticancer macrolide (−)-dictyostatin (**1**) has been completed based on a highly convergent strategy. This proceeds in 4.6% yield over 27 steps in the longest linear sequence (from (*S*)-Roche ester), and has the potential to produce the larger quantities of dictyostatin required for further preclinical studies. Most of the stereocentres are configured using substrate control, making use of the common building block **10** to install the C12–C14 and C20–C22 stereotriads, with a lactate boron aldol reaction serving to construct the key β-ketophosphonate **5** required for the pivotal Still–Gennari fragment coupling step with the fully elaborated C11–C26 aldehyde **7**. The majority of the steps have been performed on a multi-gram scale, facilitating material throughput. This evolution of our original synthetic strategy should enable the preparation of substantial quantities of dictyostatin, as well as facilitate access to further structural analogues,[18,19] as required for further biological evaluation, particularly with regard to *in vivo* xenograft studies.[20]

5. Experimental

5.1. Data for compounds

*5.1.1. Iodide **12**.* To a solution of diol **10**[24] (4.00 g, 14.9 mmol, 1.0 equiv) in PhMe (200 mL) at 0 °C was added Ph_3P (5.68 g, 22.4 mmol, 1.5 equiv) and pyridine (3.74 mL, 46.2 mmol, 3.1 equiv). To this mixture was added a solution of I_2 (5.48 g, 20.9 mmol, 1.4 equiv) in PhMe (100 mL) over 1.5 h, before warming to rt and stirring for 16 h. Cold hexane (300 mL) was added, and after 30 min, the reaction mixture was filtered through Celite and concentrated in vacuo. Flash chromatography (10% EtOAc/hexane) afforded iodide **12** as a colourless oil, which was used directly in the next step: R_f 0.42 (20% EtOAc/hexane); $[\alpha]_D^{20}$ +46.9 (*c* 1.81, $CHCl_3$); IR (liquid film)/cm^{-1} 3482, 2963, 2932, 1613, 1586, 1513, 1462; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (2H, d, *J*=8.7 Hz, ArH), 6.87 (2H, d, *J*=8.7 Hz, ArH), 4.47 (1H, d, *J*=11.4 Hz, OCH_xH_yAr), 4.42 (1H, d, *J*=11.4 Hz, OCH_xH_yAr), 3.79 (3H, s, OMe), 3.69 (1H, s, OH), 3.63 (1H, d, *J*=8.8 Hz, H13), 3.57 (1H, dd, *J*=9.1, 3.9 Hz, H11a), 3.46 (1H, t, *J*=9.1 Hz, H11b), 3.35 (1H, dd, *J*=9.6, 7.7 Hz, H15a), 3.17 (1H, dd, *J*=9.5, 6.6 Hz, H15b), 1.90–1.97 (1H, m, H12), 1.82–1.90 (1H, m, H14), 0.99 (3H, d, *J*=6.9 Hz, Me14), 0.77 (3H, d, *J*=6.6 Hz, Me12); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 129.5, 129.4, 113.9, 78.1, 76.1, 73.2, 55.3, 38.8, 36.1, 13.3, 13.2, 12.9; HRMS (ESI$^+$) calcd for $C_{15}H_{27}INO_3$ $[M+NH_4]^+$: 396.1030, found: 396.1032.

*5.1.2. TBS ether **13**.* To a solution of iodide **12** (5.64 g, 14.9 mmol, 1.0 equiv) in CH_2Cl_2 (300 mL) at −78 °C was added 2,6-lutidine (7.00 mL, 59.7 mmol, 4.0 equiv) then TBSOTf (6.85 mL, 29.8 mmol, 2.0 equiv). The reaction mixture was warmed to 0 °C and stirred for 2 h before addition of satd aq NH_4Cl (250 mL). The phases were separated, the aqueous phase extracted with CH_2Cl_2 (3×200 mL), and the combined organic extracts dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (light petroleum → 10% EtOAc/light petroleum) afforded TBS ether **13** (6.78 g, 92% over two steps) as a colourless oil: R_f 0.72 (40% EtOAc/hexane); $[\alpha]_D^{20}$ +15.1 (*c* 1.04, CH_2Cl_2); IR (CH_2Cl_2)/cm^{-1} 2989, 1394, 1066; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (2H, d, *J*=8.7 Hz, ArH), 6.88 (2H, d, *J*=8.7 Hz, ArH), 4.42 (1H, d, *J*=11.3 Hz, OCH_xH_yAr), 4.38 (1H, d, *J*=11.3 Hz, OCH_xH_yAr), 3.81 (3H, s, OMe), 3.68 (1H, dd, *J*=5.9, 2.8 Hz, H13), 3.50 (1H, dd, *J*=9.2, 4.7 Hz, H11a), 3.19–3.26 (2H, m, H11b+H15a), 3.11 (1H, dd, *J*=9.4, 7.3 Hz, H15b), 1.86–1.99 (2H, m, H12+H14), 0.99 (3H, d, *J*=6.8 Hz, Me14), 0.94 (3H, d, *J*=6.8 Hz, Me12), 0.88 (9H, s, $SiC(CH_3)_3$), 0.07 (3H, s, $SiCH_3$), 0.05 (3H, s, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 130.7, 129.2, 113.8, 76.2, 72.7, 72.3, 55.3, 39.6, 38.1, 26.1, 18.8, 15.3, 14.9, 14.5, 3.7, −4.1; HRMS (+ESI) calcd for $C_{21}H_{41}INO_3Si$ $[M+NH_4]^+$: 510.1895, found: 510.1902.

*5.1.3. Amide **16**.* To a solution of *i*-Pr_2NH (8.00 mL, 57.2 mmol, 8.4 equiv) and LiCl (5.72 g, 136 mmol, 20 equiv) in THF (30 mL) at −78 °C was added *n*-BuLi (34.9 mL of a 1.6 M solution in hexanes, 55.9 mmol, 8.2 equiv). After 30 min at 0 °C, the solution was cooled to −78 °C and amide **14** (6.03 g, 27.3 mmol, 4.0 equiv) in THF (12 mL) was added. The reaction mixture was stirred for 1 h at −78 °C, 20 min at 0 °C and 5 min at rt before being re-cooled to 0 °C. To the resulting enolate solution was added iodide **13** (3.35 g, 6.81 mmol, 1.0 equiv) in THF (12 mL) pre-cooled to 0 °C. After stirring at rt for 16 h, satd aq NH_4Cl (60 mL) was added and the phases separated. The aqueous phase was extracted with EtOAc (3×60 mL) and the combined organic extracts dried ($MgSO_4$) and concentrated in vacuo. The excess amide **14** was recrystallised (PhMe) from the crude product, filtered and the crystals washed with cold PhMe. The filtrate was concentrated in vacuo and purified using flash chromatography (40% EtOAc/light petroleum) to give amide **16** (3.93 g, 99%) as a colourless oil: R_f 0.25 (10% EtOAc/hexane); IR (CH_2Cl_2)/cm^{-1} 2958, 2929, 2856, 1614, 1513, 1462, 1248; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.40 (5H, m, ArH), 7.27 (2H, d, *J*=8.8 Hz, ArH), 6.87 (2H, d, *J*=8.8 Hz, ArH), 4.59 (1H, d, *J*=7.6 Hz, OH), 4.38–4.45 (3H, m, OCH_2Ar+PhCH), 3.81 (3H, s, OMe), 3.55 (1H, dd, *J*=9.1, 4.7 Hz, H11a), 3.48 (1H, dd, *J*=6.3, 2.2 Hz, H13), 3.26 (1H, t, *J*=8.2 Hz, H11b), 2.84 (3H, s, NMe), 2.66–2.75 (1H, m, NCH), 1.90–1.99 (1H, m, H12), 1.73–1.81 (1H, m, H16), 1.54–1.62 (1H, m, H14), 1.19–1.27 (2H, m, H15a+H15b), 1.13 (3H, d, *J*=6.6 Hz, Me), 1.09 (3H, d, *J*=6.9 Hz, Me16), 0.96 (3H, d, *J*=6.9 Hz, Me12), 0.90 (9H, s, $SiC(CH_3)_3$), 0.78 (3H, d, *J*=Me14), 0.04 (3H, s, $SiCH_3$), 0.03 (3H, s, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.0, 159.0, 142.7, 130.9, 129.1, 128.7, 128.3, 127.5, 127.0, 126.3, 113.7, 77.8, 76.5, 72.9, 72.6, 55.3, 40.0, 38.4, 34.2, 33.4, 26.24, 26.18, 18.5, 18.3, 14.8, 14.4, 13.9, −3.6, −4.0; HRMS (+ESI) calcd for $C_{34}H_{56}NO_5Si$ $[M+H]^+$: 586.3922, found: 586.3916.

*5.1.4. Aldehyde **8**.* To a solution of *i*-Pr_2NH (2.80 mL, 20.1 mmol, 4.2 equiv) in THF (10 mL) at −78 °C was added *n*-BuLi (11.7 mL of a 1.6 M solution in hexanes, 18.2 mmol, 3.9 equiv). After 30 min at 0 °C, the preformed solution of LDA was added to a suspension of $BH_3·NH_3$ in THF (20 mL), stirred for 15 min at rt and re-cooled to 0 °C. To this solution was then added via cannula the amide **16** (2.81 g, 4.79 mmol, 1.0 equiv) in THF (30 mL). After 2 h at rt, the reaction mixture was cooled to 0 °C and quenched by the addition of 3 M HCl (50 mL). The phases were separated, the aqueous phase extracted with Et_2O (3×60 mL) and the combined organic extracts concentrated in vacuo. The resulting crude alcohol was used directly in the next step: R_f 0.50 (40% EtOAc/hexane); $[\alpha]_D^{20}$ −14.3 (*c* 0.45, CH_2Cl_2); IR (CH_2Cl_2)/cm^{-1} 3397, 2929, 1513, 1247, 1037; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (2H, d, *J*=8.5 Hz, ArH), 6.89 (2H, d, *J*=8.5 Hz,

ArH), 4.41 (1H, d, J=11.9 Hz, OCH_xH_yAr), 4.37 (1H, d, J=11.9 Hz, OCH_xH_yAr), 3.82 (3H, s, OMe), 3.55 (1H, dd, J=9.1, 5.3 Hz, H11a), 3.49–3.53 (1H, m, H17a), 3.46 (1H, dd, J=5.6, 2.8 Hz, H13), 3.36–3.41 (1H, m, H17b), 3.24 (1H, dd, J=9.1, 6.9 Hz, H11b), 2.00 (1H, sep, J=5.9 Hz, H12), 1.71–1.79 (1H, m, H14), 1.65–1.71 (1H, m, H16), 1.39 (1H, dt, J=13.5, 5.8 Hz, H15a), 0.96 (3H, d, J=6.9 Hz, Me12), 0.93–0.95 (1H, m, H15b), 0.94 (3H, d, J=6.6 Hz, Me16), 0.90 (9H, s, $SiC(CH_3)_3$), 0.88 (3H, d, J=6.4 Hz, Me14), 0.05 (3H, s, $SiCH_3$), 0.04 (3H, s, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 130.8, 129.2, 113.7, 77.4, 72.7, 67.3, 55.3, 38.2, 37.9, 33.5, 33.1, 26.2, 18.5, 17.8, 15.4, −3.6, −4.0; HRMS (+ESI) calcd for $C_{24}H_{44}NaO_4Si$ $[M+Na]^+$: 447.2907, found: 447.2935.

A suspension of the above alcohol (4.88 g, 11.5 mmol, 1.0 equiv) and $NaHCO_3$ (9.70 g, 115 mmol, 10 equiv) in CH_2Cl_2 (200 mL) at 0 °C was treated with Dess–Martin periodinane (5.80 g, 13.8 mmol, 1.2 equiv). After 2 h, the reaction mixture was concentrated in vacuo and purified by flash chromatography (20% EtOAc/light petroleum) to afford aldehyde **8** (3.50 g, 72% over two steps) as a colourless oil: R_f 0.30 (10% EtOAc/hexane); $[\alpha]_D^{20}$ −18.2 (*c* 0.44, CH_2Cl_2); IR $(CH_2Cl_2)/cm^{-1}$ 2930, 1726, 1513, 1247, 1037; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.53 (1H, d, J=2.4 Hz, H17), 7.24 (2H, d, J=8.7 Hz, ArH), 6.87 (2H, d, J=8.7 Hz, ArH), 4.41 (1H, d, J=11.5 Hz, OCH_xH_yAr), 4.37 (1H, d, J=11.5 Hz, OCH_xH_yAr), 3.80 (3H, s, OMe), 3.50 (1H, d, J=5.6 Hz, H11a), 3.49 (1H, dd, J=12.7, 5.6 Hz, H13), 3.25 (1H, dd, J=9.0, 7.5 Hz, H11b), 2.40 (1H, sex, J=6.6 Hz, H16), 1.94 (1H, sep, J=6.1 Hz, H12), 1.79 (1H, ddd, J=13.4, 8.0, 5.4 Hz, H15a), 1.62–1.73 (1H, m, H14), 1.19 (1H, ddd, J=14.4, 8.9, 5.7 Hz, H15b), 1.07 (3H, d, J=7.0 Hz, Me16), 0.94 (3H, d, J=7.0 Hz, Me12), 0.89 (9H, s, $SiC(CH_3)_3$), 0.87 (3H, d, J=7.0 Hz, Me14), 0.03 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.2, 159.1, 130.8, 129.1, 113.7, 77.0, 72.7, 55.2, 44.2, 38.0, 35.9, 33.7, 26.1, 18.4, 15.1, 14.5, 14.3, −3.7, −4.1; HRMS (+ESI) calcd for $C_{24}H_{42}NaO_4Si$ $[M+Na]^+$: 445.2750, found: 445.2750.

5.1.5. Phosphonate ***9***. To a solution of dimethyl methylphosphonate (6.43 mL, 59.3 mmol, 3.1 equiv) in THF (250 mL) at −78 °C was added dropwise *n*-BuLi (44.2 mL of 1.6 M solution in hexanes, 70.7 mmol, 3.7 equiv). The reaction mixture was stirred at −78 °C for 30 min before the addition via cannula of a solution of freshly prepared aldehyde **17**[24] (5.51 g, 19.1 mmol, 1.0 equiv) in THF (125 mL) pre-cooled to −78 °C. After stirring for 20 min at −78 °C, the reaction was quenched by the addition of brine (200 mL) and warmed to rt. The phases were separated and the aqueous layer extracted with EtOAc (3×150 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo and purified by flash chromatography (EtOAc) to give an epimeric mixture of β-hydroxyphosphonates (7.87 g, 98%) as a pale yellow oil: R_f 0.28 (EtOAc).

To a stirred solution of the above β-hydroxyphosphonates (6.73 g, 19.6 mmol, 1.0 equiv) in CH_2Cl_2 (250 mL) at rt was added Dess–Martin periodinane (8.31 g, 23.5 mmol, 1.2 equiv). The reaction mixture was stirred for 30 min and the resulting slurry concentrated in vacuo to a volume of ca. 5 mL and purified by flash chromatography (EtOAc) to give β-ketophosphonate **9** (6.22 g, 93%) as a pale yellow oil: R_f 0.42 (EtOAc); $[\alpha]_D^{20}$ −2.8 (*c* 1.7, $CHCl_3$); IR (liquid film)/cm^{-1} 2959, 1711, 1574, 1248; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (2H, d, J=8.5 Hz, ArH), 6.86 (2H, d, J=8.5 Hz, ArH), 6.49 (1H, dt, J=16.8, 10.7 Hz, H25), 6.02 (1H, t, J=11.0 Hz, H24), 5.50 (1H, t, J=10.3 Hz, H23), 5.20 (1H, d, J=16.8 Hz, H26a), 5.12 (1H, d, J=10.1 Hz, H26b), 4.55 (1H, d, J=10.8 Hz, OCH_xH_yAr), 4.51 (1H, d, J=10.8 Hz, OCH_xH_yAr), 3.79 (3H, s, OMe), 3.76 (3H, d, J=11.0 Hz, POMe), 3.74 (3H, d, J=11.3 Hz, POMe), 3.58 (1H, dd, J=6.3, 3.8 Hz, H21), 3.30 (1H, dd, J=22.0, 14.4 Hz, H18a), 2.91–3.02 (2H, m, H18b+H22), 2.76–2.84 (1H, m, H20), 1.19 (3H, d, J=7.0 Hz, Me20), 1.06 (3H, d, J=6.8 Hz, Me22); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.6 (d, J=3.8 Hz), 159.2, 133.5, 132.1, 130.4, 129.9, 129.4, 118.1, 113.7, 83.5, 74.2, 55.2, 52.9, 50.6, 41.3, 40.3, 35.8, 18.9, 12.7; HRMS (+ESI) calcd for $C_{21}H_{32}O_6P$ $[M+H]^+$: 411.1931, found: 411.1932.

5.1.6. Enone ***18***. To solid $Ba(OH)_2 \cdot 8H_2O$ (2.62 g, 8.29 mmol, 1.0 equiv; dried by heating under high vacuum) was added a solution of phosphonate **9** (3.40 g, 8.29 mmol, 1.0 equiv) in THF (130 mL) via cannula. After stirring for 1 h at rt, a solution of aldehyde **8** (3.50 g, 8.29 mmol, 1.0 equiv) in THF/water (40:1, 66.3 mL) was added via cannula. After 1.5 h, the reaction mixture was quenched by the addition of brine (200 mL) and the phases separated. The aqueous layer was extracted with CH_2Cl_2 (3×200 mL) and the combined organic extracts dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (15% EtOAc/hexane → EtOAc) afforded (*E*)-enone **18** (5.20 g, 89%) as a colourless oil: R_f 0.30 (10% EtOAc/hexane); $[\alpha]_D^{20}$ +16.1 (*c* 0.21, CH_2Cl_2); IR $(CH_2Cl_2)/cm^{-1}$ 2958, 1690, 1664, 1613, 1513, 1247, 1038; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (2H, d, J=8.7 Hz, ArH), 7.24 (2H, d, J=8.7 Hz, ArH), 6.87 (4H, d, J=8.7 Hz, ArH), 6.68 (1H, dd, J=15.3, 8.3 Hz, H17), 6.39 (1H, dt, J=16.7, 10.6 Hz, H25), 6.03 (1H, d, J=15.8 Hz, H18), 6.00 (1H, t, J=11.0 Hz, H24), 5.52 (1H, t, J=10.6 Hz, H23), 5.14 (1H, d, J=16.7 Hz, H26a), 5.00 (1H, d, J=10.3 Hz, H26b), 4.55 (1H, d, J=10.6 Hz, OCH_xH_yAr), 4.53 (1H, d, J=10.6 Hz, OCH_xH_yAr), 4.40 (1H, d, J=11.7 Hz, OCH_xH_yAr), 4.38 (1H, d, J=11.7 Hz, OCH_xH_yAr), 3.78 (6H, s, 2×OMe), 3.68 (1H, dd, J=8.2, 3.1 Hz, H21), 3.48 (1H, dd, J=9.0, 4.7 Hz, H11a), 3.43 (1H, dd, J=6.3, 2.3 Hz, H13), 3.23 (1H, t, J=8.5 Hz, H11b), 2.92 (1H, qn, J=7.8 Hz, H20), 2.72–2.81 (1H, m, H22), 2.33 (1H, sep, J=7.0 Hz, H16), 1.85–1.96 (1H, m, H12), 1.54–1.63 (1H, m, H14), 1.40 (1H, ddd, J=13.4, 8.9, 4.7 Hz, H15a), 1.20–1.28 (1H, m, H15b), 1.18 (3H, d, J=6.8 Hz, Me20), 1.08 (3H, d, J=6.8 Hz, Me22), 1.00 (3H, d, J=6.8 Hz, Me16), 0.92 (3H, d, J=6.8 Hz, Me12), 0.88 (9H, s, $SiC(CH_3)_3$), 0.82 (3H, d, J=6.8 Hz, Me14), 0.03 (3H, s, $SiCH_3$), 0.02 (3H, s, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.1, 159.1, 159.0, 152.8, 134.0, 132.4, 130.85, 130.83, 129.6, 129.3, 129.1, 127.9, 117.4, 113.7, 84.2, 77.4, 75.3, 72.7, 72.6, 55.2, 48.5, 41.1, 37.9, 36.4, 34.3, 33.8, 26.1, 20.2, 18.9, 18.4, 15.3, 14.4, 14.1, −3.6, −4.1; HRMS (+ESI) calcd for $C_{43}H_{67}O_6Si$ $[M+H]^+$: 707.4701, found: 707.4696.

5.1.7. Ketone ***19***. To a solution of enone **18** (1.00 g, 1.42 mmol, 1.0 equiv) in freeze-thaw deoxygenated PhMe/water (400:1, 20 mL) was added $[(Ph_3P)CuH]_6$ (1.11 g, 0.566 mmol, 0.4 equiv). After stirring for 16 h at rt, the reaction mixture was filtered through Celite, washed with EtOAc (60 mL) and concentrated in vacuo. Flash chromatography (light petroleum → 20% EtOAc/light petroleum) afforded the ketone **19** (985 mg, 98%) as a colourless oil: R_f 0.38 (10% EtOAc/hexane); $[\alpha]_D^{20}$ +1.2 (*c* 0.60, CH_2Cl_2); IR $(CH_2Cl_2)/cm^{-1}$ 2929, 1709, 1613, 1513, 1247, 1037; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (2H, d, J=8.5 Hz, ArH), 7.27 (2H, d, J=8.5 Hz, ArH), 6.89 (4H, d, J=8.5 Hz, ArH), 6.46 (1H, dt, J=17.0, 10.7 Hz, H25), 6.05 (1H, t, J=11.0 Hz, H24), 5.55 (1H, t, J=10.7 Hz, H23), 5.20 (1H, d, J=16.1 Hz, H26a), 5.09 (1H, d, J=10.4 Hz, H26b), 4.55 (1H, d, J=10.4 Hz, OCH_xH_yAr), 4.49 (1H, d, J=10.4 Hz, OCH_xH_yAr), 4.40 (1H, d, J=11.4 Hz, OCH_xH_yAr), 4.39 (1H, d, J=11.4 Hz, OCH_xH_yAr), 3.82 (6H, s, 2×OMe), 3.66 (1H, dd, J=8.2, 3.4 Hz, H21), 3.54 (1H, dd, J=9.1, 4.4 Hz, H11a), 3.46 (1H, dd, J=6.3, 2.5 Hz, H13), 3.26 (1H, t, J=8.5 Hz, H11b), 2.79 (1H, ddd, J=10.1, 6.9, 3.1 Hz, H20), 2.75 (1H, qn, J=7.6 Hz, H22), 2.37–2.44 (2H, m, H18a+H18b), 1.92–1.99 (1H, m, H12), 1.70–1.76 (1H, m, H14), 1.62–1.69 (1H, m, H17a), 1.37–1.46 (1H, m, H16), 1.23–1.30 (1H, m, H15a), 1.19 (3H, d, J=7.2 Hz, Me20), 1.18–1.20 (1H, m, H17b), 1.11 (3H, d, J=6.9 Hz, Me22), 1.00–1.08 (1H, m, H15b), 0.97 (3H, d, J=6.9 Hz, Me12), 0.90 (9H, s, $SiC(CH_3)_3$), 0.85 (3H, d, J=6.9 Hz, Me14), 0.82 (3H, d, J=6.6 Hz, Me16), 0.05 (3H, s, $SiCH_3$), 0.04 (3H, s, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.3, 159.1, 159.0, 134.0, 132.1, 130.9, 130.8, 129.6, 129.3, 129.1, 117.8, 113.7, 83.8, 75.3, 73.0, 72.7, 55.3, 50.4, 42.6, 40.3, 38.2, 36.2, 33.2, 29.77, 29.73, 26.2, 25.8, 20.0, 18.8, 18.5, 15.2, 14.7, 14.0, −3.6, −4.0; HRMS (+ESI) calcd for $C_{43}H_{68}NaO_6Si$ $[M+Na]^+$: 731.4677, found: 731.4665.

5.1.8. Alcohol ***19a***. To a solution of ketone **19** (1.90 g, 2.69 mmol, 1.0 equiv) in THF (20 mL) at −30 °C was added $LiAlH(O^tBu)_3$ (13.4 mL of a 1 M solution in THF, 13.4 mmol, 5.0 equiv) over 10 min.

After stirring for 72 h, the reaction mixture was quenched by the addition of satd aq NH_4Cl (20 mL) and warmed to rt. The phases were separated, the aqueous phase extracted with EtOAc (3×20 mL) and the combined organic extracts dried ($MgSO_4$) and concentrated in vacuo. The resulting alcohol (>95:5 dr at C19) could be used directly in the next step. Flash chromatography (20% EtOAc/hexane) provided a pure sample for characterisation: R_f 0.33 (20% EtOAc/hexane); $[\alpha]_D^{20}$ +15.2 (*c* 0.46, $CHCl_3$); IR (liquid film)/cm^{-1} 2957, 1513, 1249, 1037; ^1H NMR (500 MHz, $CDCl_3$) δ 7.28 (2H, d, *J*=8.5 Hz, ArH), 7.26 (2H, d, *J*=8.7 Hz, ArH), 6.89 (2H, d, *J*=8.7 Hz, ArH), 6.86 (2H, d, *J*=8.5 Hz, ArH), 6.69 (1H, dt, *J*=16.9, 10.4 Hz, H25), 6.09 (1H, t, *J*=11.0 Hz, H24), 5.52 (1H, t, *J*=10.4 Hz, H23), 5.25 (1H, d, *J*=15.9 Hz, H26a), 5.16 (1H, d, *J*=10.1 Hz, H26b), 4.71 (1H, d, *J*=10.3 Hz, OCH_xH_yAr), 4.40–4.47 (3H, d, *J*=10.3 Hz, OCH_xH_yAr+OCH_2Ar), 3.82 (3H, s, OMe), 3.80 (3H, s, OMe), 3.71 (1H, br t, *J*=6.2 Hz, H19), 3.54 (1H, dd, *J*=9.0, 4.5 Hz, H11a), 3.46 (1H, dd, *J*=6.1, 2.6 Hz, H13), 3.42 (1H, dd, *J*=6.7, 4.1 Hz, H21), 3.26 (1H, t, *J*=8.9 Hz, H11b), 3.08 (1H, dqn, *J*=9.9, 6.6 Hz, H22), 1.91–1.99 (1H, m, H12), 1.67–1.76 (2H, m, H14+H20), 1.41–1.51 (4H, m, H16+H17a+H18a+H18b), 1.25–1.32 (2H, m, H15a+H17b), 1.03–1.05 (1H, m, H15b), 1.04 (3H, d, *J*=6.8 Hz, Me22), 0.95–0.99 (6H, m, Me12+Me20), 0.90 (9H, s, $SiC(CH_3)_3$), 0.88 (3H, d, *J*=6.3 Hz, Me16), 0.84 (3H, d, *J*=6.7 Hz, Me14), 0.05 (3H, s, $SiCH_3$), 0.04 (3H, s, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 159.0, 135.3, 132.4, 131.0, 130.3, 129.7, 129.5, 129.1, 117.8, 113.8, 113.7, 87.7, 77.4, 75.3, 74.1, 73.0, 72.6, 55.3, 42.6, 38.9, 38.2, 35.6, 33.3, 32.7, 32.5, 30.3, 26.2, 20.3, 18.5, 18.1, 15.2, 14.7, 6.6, −3.6, −4.0; HRMS (+ESI) calcd for $C_{43}H_{71}O_6Si$ $[M+H]^+$: 711.5014, found: 711.5017.

5.1.9. TBS ether ***19b****.* To a solution of the foregoing alcohol (1.91 g, 2.69 mmol, 1.0 equiv) in CH_2Cl_2 (50 mL) at −78 °C was added 2,6-lutidine (562 μL, 4.82 mmol, 1.8 equiv) then TBSOTf (738 μL, 3.21 mmol, 1.2 equiv). The reaction mixture was warmed to 0 °C and stirred for 30 min before being quenched by the addition of satd aq NH_4Cl (50 mL). The phases were separated, the aqueous phase extracted with CH_2Cl_2 (3×50 mL) and the combined organic extracts dried ($MgSO_4$) and concentrated in vacuo. The resulting TBS ether could be used directly in the next step. Flash chromatography (20% EtOAc/hexane) provided a pure sample for characterisation: R_f 0.49 (20% EtOAc/hexane); $[\alpha]_D^{20}$ +5.4 (*c* 0.17, $CHCl_3$); IR (liquid film)/cm^{-1} 2956, 292, 2855, 1613, 1586, 1513, 1462; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 (2H, d, *J*=8.4 Hz, ArH), 7.28 (2H, d, *J*=8.4 Hz, ArH), 6.90 (4H, d, *J*=7.7 Hz, ArH), 6.62 (1H, dt, *J*=16.8, 10.7 Hz, H25), 6.04 (1H, t, *J*=11.0 Hz, H24), 5.61 (1H, t, *J*=10.6 Hz, H23), 5.21 (1H, d, *J*=16.7 Hz, H26a), 5.12 (1H, d, *J*=1.0 Hz, H26b), 4.59 (1H, d, *J*=10.6 Hz, OCH_xH_yAr), 4.53 (1H, d, *J*=10.6 Hz, OCH_xH_yAr), 4.45 (1H, d, *J*=12.1 Hz, OCH_xH_yAr), 4.43 (1H, d, *J*=12.1 Hz, OCH_xH_yAr), 3.83 (6H, s, 2×OMe), 3.63–3.68 (1H, m, H19), 3.55 (1H, dd, *J*=8.8, 4.5 Hz, H11a), 3.46 (1H, d, *J*=5.4 Hz, H13), 3.34–3.39 (1H, m, H21), 3.27 (1H, t, *J*=8.7 Hz, H11b), 2.98–3.06 (1H, m, H22), 1.99–2.01 (1H, m, H12), 1.64–1.73 (2H, m, H14+H20), 1.54–1.64 (1H, m, H18a), 1.29–1.45 (3H, m, H16+H17a+H18b), 1.20–1.27 (2H, m, H15a+H17b), 1.14 (3H, d, *J*=6.7 Hz, Me22), 1.01–1.08 (1H, m, H15b), 0.97–1.00 (6H, m, Me12+Me20), 0.89–0.94 (21H, m, 2×$SiC(CH_3)_3$+Me16), 0.84 (3H, d, *J*=6.5 Hz, Me14), 0.12 (3H, s, $SiCH_3$), 0.11 (3H, s, $SiCH_3$), 0.06 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 159.0, 134.6, 132.4, 132.3, 131.4, 131.0, 129.1, 128.9, 117.2, 113.69, 113.68, 84.4, 77.3, 75.1, 73.0, 72.8, 72.7, 55.2, 42.9, 40.5, 38.2, 35.2, 33.0, 32.4, 31.7, 30.3, 26.2, 26.0, 25.9, 20.1, 18.8, 18.5, 18.2, 18.1, 15.1, 14.4, 9.2, −3.57, −3.61, −4.0, −4.5; HRMS (+ESI) calcd for $C_{49}H_{88}NO_6Si_2$ $[M+NH_4]^+$: 842.6145, found: 842.6150.

5.1.10. Diol ***19c****.* To a solution of the foregoing TBS ether (2.22 g, 2.69 mmol, 1.0 equiv) in CH_2Cl_2/pH 7 buffer (10:1, 12.6 mL) at 0 °C was added DDQ (3.10 g, 13.5 mmol, 5 equiv). After stirring for 2 h, the reaction mixture was diluted with pH 7 buffer (12 mL) and the phases separated. The aqueous phase was extracted with CH_2Cl_2 (3×12 mL) and the combined organic extracts dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (light petroleum→10% Et_2O/1% CH_2Cl_2/light petroleum) afforded the corresponding diol (1.08 g, 65% over three steps) as a colourless oil: R_f 0.25 (10% EtOAc/light petroleum); $[\alpha]_D^{20}$ −11.5 (*c* 1.23, $CHCl_3$); IR (CH_2Cl_2)/cm^{-1} 3377, 2956, 2929, 2857, 1462; ^1H NMR (500 MHz, $CDCl_3$) δ 6.62 (1H, dt, *J*=16.9, 10.5 Hz, H25), 6.09 (1H, t, *J*=11.1 Hz, H24), 5.40 (1H, t, *J*=10.6 Hz, H23), 5.20 (1H, d, *J*=17.0 Hz, H26a), 5.11 (1H, d, *J*=10.3 Hz, H26b), 3.72–3.76 (1H, m, H19), 3.55–3.61 (2H, m, H11a+H11b), 3.44–3.48 (2H, m, H13+H21), 2.75–2.83 (1H, m, H22), 2.43 (1H, s, OH), 2.27 (1H, s, OH), 1.84 (1H, sep, *J*=6.9 Hz, H12), 1.66–1.74 (2H, m, H14+H20), 1.56–1.65 (2H, m, H17a+H18a), 1.36–1.46 (2H, m, H16+H18b), 1.24–1.35 (2H, m, H15a+H17b), 1.02–1.07 (1H, m, H15b), 0.95 (3H, d, *J*=6.6 Hz, Me22), 0.94 (3H, d, *J*=6.9 Hz, Me12), 0.90–0.91 (12H, m, $SiC(CH_3)_3$+Me20), 0.88 (9H, s, $SiC(CH_3)_3$), 0.87 (3H, d, *J*=6.8 Hz, Me16), 0.86 (3H, d, *J*=7.0 Hz, Me14), 0.10 (3H, s, $SiCH_3$), 0.07–0.08 (9H, m, $SiCH_3$+$Si(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 135.2, 132.3, 130.0, 117.7, 80.6, 77.3, 76.4, 66.1, 41.6, 38.3, 37.8, 36.1, 35.1, 31.9, 31.4, 30.5, 26.1, 25.9, 20.4, 18.3, 18.0, 17.7, 16.1, 15.2, 7.0, −3.79, −3.81, −4.0, −4.4; HRMS (+ESI) calcd for $C_{33}H_{68}NaO_4Si_2$ $[M+Na]^+$: 607.4554, found: 607.4561.

5.1.11. Aldehyde ***7****.* To a solution of the foregoing diol (851 mg, 1.46 mmol, 1.0 equiv) in CH_2Cl_2 (25 mL) at 0 °C was added $PhI(OAc)_2$ (938 mg, 2.91 mmol, 2.0 equiv) then TEMPO (91.0 mg, 0.582 mmol, 0.4 equiv). After warming slowly to rt, the reaction mixture was stirred for 16 h, then treated with satd aq $Na_2S_2O_3$ (25 mL) and stirred for an additional 30 min. The phases were separated, the aqueous phase extracted with CH_2Cl_2 (3×30 mL) and the combined organic extracts dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (5% EtOAc/light petroleum) afforded aldehyde **7** (755 mg, 89%) as a colourless oil: R_f 0.66 (20% EtOAc/hexane); $[\alpha]_D^{20}$ −28.3 (*c* 1.43, $CHCl_3$); IR (CH_2Cl_2)/cm^{-1} 2952, 2929, 2857, 1725; ^1H NMR (500 MHz, $CDCl_3$) δ 9.76 (1H, d, *J*=2.8 Hz, H11), 6.63 (1H, ddd, *J*=11.2, 10.1, 1.2 Hz, H25), 6.10 (1H, td, *J*=11.2, 0.7 Hz, H24), 5.41 (1H, t, *J*=10.6 Hz, H23), 5.21 (1H, dd, *J*=16.9, 2.1 Hz, H26a), 5.12 (1H, d, *J*=10.1 Hz, H26b), 3.76–3.77 (2H, m, H13+H19), 3.47 (1H, dt, *J*=7.6, 2.4 Hz, H21), 2.78–2.83 (1H, m, H22), 2.52–2.57 (1H, m, H12), 2.24 (1H, d, *J*=2.3 Hz, OH), 1.67–1.76 (2H, m, H14+H20), 1.59–1.65 (2H, m, H18a+H17a), 1.37–1.47 (2H, m, H16+H18b), 1.25–1.34 (1H, m, H15a+H17b), 1.07 (3H, d, *J*=7.1 Hz, Me12), 0.99–1.04 (1H, m, H15b), 0.96 (3H, d, *J*=6.8 Hz, Me22), 0.91 (3H, d, *J*=6.9 Hz, Me20), 0.89 (9H, s, $SiC(CH_3)_3$), 0.87–0.89 (6H, m, Me14+Me16), 0.88 (9H, s, $SiC(CH_3)_3$), 0.085 (3H, s, $SiCH_3$), 0.08 (3H, s, $SiCH_3$), 0.06 (3H, s, $SiCH_3$), 0.04 (3H, s, $SiCH_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 205.1, 135.3, 132.3, 130.0, 117.8, 78.0, 77.4, 76.4, 50.1, 41.2, 37.8, 36.1, 35.0, 31.9, 30.5, 26.0, 25.9, 20.4, 18.3, 18.1, 17.7, 15.1, 12.3, 7.0, −3.83, −3.78, −4.2, −4.4; HRMS (+ESI) calcd for $C_{33}H_{66}NaO_4Si_2$ $[M+Na]^+$: 605.4397, found: 605.4395.

5.1.12. Aldol adduct ***23****.* To a stirred solution of *c*-Hex_2BCl (6.11 mL, 27.9 mmol, 1.2 equiv) and Me_2NEt (2.77 mL, 25.6 mmol, 1.1 equiv) in Et_2O (60 mL) at −78 °C was added freshly azeotroped ketone **20**[25a] (5.75 g, 27.9 mmol, 1.2 equiv) in Et_2O (60 mL) via cannula. The reaction mixture was then warmed to 0 °C and stirred for 1 h. A white precipitate formed before the solution was re-cooled to −78 °C and aldehyde **22** (4.38 g, 23.3 mmol, 1.0 equiv) in Et_2O (85 mL) was added via cannula. The reaction mixture was stirred for 3 h, then maintained at −20 °C for 16 h, before the addition of MeOH (80 mL), pH 7 buffer (80 mL) and H_2O_2 (80 mL of 30 mol% solution) at rt. The mixture was stirred for 1 h, then water (250 mL) was added and the phases separated. The aqueous phase was extracted with CH_2Cl_2 (4×200 mL), before the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (50% Et_2O/light petroleum) afforded aldol adduct **23** (8.19 g, 89%, >97:3 dr) as a pale yellow oil: R_f 0.59 (50% Et_2O/light petroleum); $[\alpha]_D^{20}$ −9.8

(*c* 0.49, $CHCl_3$); IR (liquid film)/cm^{-1} 3503, 2930, 2857, 1719, 1602, 1452; ^1H NMR (500 MHz, $CDCl_3$) δ 8.08 (2H, dd, *J*=8.4, 1.1 Hz, ArH), 7.58 (1H, t, *J*=7.8 Hz, ArH), 7.45 (2H, t, *J*=7.8 Hz, ArH), 5.44 (1H, q, *J*=7.1 Hz, H4), 4.02 (1H, t, *J*=8.5 Hz, H7), 3.89 (1H, ddd, *J*=10.3, 5.8, 4.6 Hz, H9a), 3.81 (1H, ddd, *J*=10.1, 8.0, 3.9 Hz, H9b), 3.46 (1H, s, OH), 2.96 (1H, qn, *J*=7.3 Hz, H6), 1.74–1.81 (1H, m, H8a), 1.60–1.64 (1H, m, H8b), 1.57 (3H, d, *J*=6.9 Hz, Me4), 1.19 (3H, d, *J*=7.0 Hz, Me6), 0.88 (9H, s, $SiC(CH_3)_3$), 0.06 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.0, 166.0, 161.2, 133.4, 130.0, 128.6, 75.2, 73.4, 62.2, 48.5, 35.7, 26.0, 18.3, 15.8, 13.8, −5.4; HRMS (+ESI) calcd for $C_{21}H_{35}O_5Si$ $[M+H]^+$: 395.2248, found: 395.2254.

5.1.13. PMB ether ***23a****.* To a stirred solution of azeotroped alcohol **23** (5.90 g, 14.95 mmol, 1.0 equiv) and PMBTCA (6.34 g, 22.4 mmol, 1.5 equiv) in THF (250 mL) at 0 °C was added $Sc(OTf)_3$ (220 mg, 0.45 mmol, 0.03 equiv). After 50 min, satd aq $NaHCO_3$ (300 mL) was added and the phases separated. The aqueous phase was extracted with EtOAc (3×300 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (9% EtOAc/light petroleum) afforded the PMB ether as a pale yellow oil: R_f 0.50 (20% EtOAc/light petroleum); $[\alpha]_D^{20}$ +7.8 (*c* 1.54, $CHCl_3$); IR (liquid film)/cm^{-1} 2928, 2856, 1718, 1613, 1586, 1514, 1452; ^1H NMR (500 MHz, $CDCl_3$) δ 8.08 (2H, d, *J*=7.3 Hz, ArH), 7.57 (1H, t, *J*=7.4 Hz, ArH), 7.45 (2H, t, *J*=7.5 Hz, ArH), 7.16 (2H, d, *J*=8.8 Hz, ArH), 6.84 (2H, d, *J*=8.8 Hz, ArH), 5.38 (1H, q, *J*=7.0 Hz, H4), 4.40 (1H, d, *J*=10.7 Hz, OCH_xH_yAr), 4.33 (1H, d, *J*=10.7 Hz, OCH_xH_yAr), 3.91 (1H, ddd, *J*=8.7, 7.0, 3.2 Hz, H7), 3.79 (3H, s, ArOMe), 3.74 (2H, q, *J*=5.5 Hz, H9a+H9b), 3.16 (1H, dq, *J*=7.0, 5.8 Hz, H6), 1.82 (1H, dd, *J*=7.0, 3.5 Hz, H8a), 1.63–1.70 (1H, m, H8b), 1.47 (3H, d, *J*=7.0 Hz, Me4), 1.16 (3H, d, *J*=7.0 Hz, Me6), 0.89 (9H, s, $SiC(CH_3)_3$), 0.05 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.8, 165.9, 159.2, 133.3, 130.7, 129.9, 129.8, 129.3, 128.6, 113.9, 75.1, 72.6, 59.0, 55.3, 47.1, 34.2, 29.8, 26.0, 18.3, 15.4, 13.4, −5.2, −5.3; HRMS (+ESI) calcd for $C_{29}H_{46}NO_6Si$ $[M+NH_4]^+$: 532.3089, found: 532.3092.

5.1.14. Diol ***23b****.* To a stirred solution of the foregoing PMB ether (7.57 g, 14.95 mmol, 1.0 equiv) in MeOH (350 mL) at 0 °C was added $NaBH_4$ (1.131 g, 29.9 mmol, 2.0 equiv). The reaction mixture was warmed to rt and stirred for 45 min, before being re-cooled to 0 °C and K_2CO_3 (8.26 g, 59.8 mmol, 4.0 equiv) added. After warming to rt and stirring overnight, water (200 mL) and pH 7 buffer (200 mL) were added. The aqueous phase was extracted with CH_2Cl_2 (4×400 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (20% EtOAc/light petroleum→EtOAc) afforded the diol (5.60 g, 91% over two steps) as a colourless oil: R_f 0.10 (20% EtOAc/light petroleum); $[\alpha]_D^{20}$ −4.9 (*c* 1.45, $CHCl_3$); IR (liquid film)/cm^{-1} 3400, 2930, 2856, 1613, 1586, 1514, 1463; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 (2H, d, *J*=8.6 Hz, ArH), 6.87 (2H, d, *J*=8.6 Hz, ArH), 4.51 (1H, d, *J*=10.7 Hz, OCH_xH_yAr), 4.46 (1H, d, *J*=10.7 Hz, OCH_xH_yAr), 3.81–3.85 (1H, m, H9a), 3.80 (3H, s, ArOMe), 3.68–3.76 (3H, m, H4, H7, H9b), 3.56 (1H, dd, *J*=8.8, 3.6 Hz, H5), 3.32 (1H, s, OH), 2.46 (1H, s, OH), 1.84–1.92 (2H, m, H8a+H8b), 1.69–1.77 (1H, m, H6), 1.16 (3H, d, *J*=6.3 Hz, Me6), 0.90 (9H, s, $SiC(CH_3)_3$), 0.85 (3H, d, *J*=6.9 Hz, Me4), 0.06 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5, 130.5, 129.7, 114.1, 79.4, 71.6, 68.4, 60.2, 55.5, 38.5, 34.0, 26.1, 18.5, 16.3, 11.9, −5.1, −5.2; HRMS (+ESI) calcd for $C_{22}H_{44}NO_5Si$ $[M+NH_4]^+$: 430.2983, found: 430.2983.

5.1.15. Aldehyde ***24****.* To a stirred solution of the foregoing diol (2.00 g, 4.85 mmol, 1.0 equiv) in MeOH/pH 7 buffer (56 mL: 14 mL) at 0 °C was added $NaIO_4$ (4.15 g, 19.4 mmol, 4.0 equiv). After 5 min, the reaction mixture was warmed to rt and stirred for 30 min, before water (60 mL) was added. The aqueous phase was extracted with EtOAc (3×50 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (10% EtOAc/light petroleum) afforded aldehyde **24** (1.58 g, 89%) as a colourless oil: R_f 0.48 (20% EtOAc/hexane); $[\alpha]_D^{20}$ +3.8 (*c* 0.75, $CHCl_3$); IR (liquid film)/cm^{-1} 2953, 2929, 2857, 1708, 1613, 1514, 1463; ^1H NMR (500 MHz, $CDCl_3$) δ 9.73 (1H, d, *J*=2.5 Hz, H5), 7.26 (2H, d, *J*=8.5 Hz, ArH), 6.89 (2H, d, *J*=8.5 Hz, ArH), 4.53 (1H, d, *J*=11.5 Hz, OCH_xH_yAr), 4.47 (1H, d, *J*=11.5 Hz, OCH_xH_yAr), 3.94 (1H, ddd, *J*=7.0, 5.5, 4.0 Hz, H7), 3.82 (3H, s, OMe), 3.70–3.78 (2H, m, H9a+H9b), 2.69–2.75 (1H, m, H6), 1.77–1.85 (1H, m, H8a), 1.69–1.76 (1H, m, H8b), 1.12 (3H, d, *J*=7.0 Hz, Me6), 0.91 (9H, s, $SiC(CH_3)_3$), 0.075 (3H, s, $SiCH_3$), 0.07 (3H, s, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.2, 159.3, 130.3, 129.3, 113.8, 76.2, 71.7, 59.1, 55.3, 49.8, 34.7, 25.9, 18.2, 9.9, −5.34, −5.37; HRMS (+ESI) calcd for $C_{20}H_{34}O_4NaSi$ $[M+Na]^+$: 389.2124, found: 389.2146.

5.1.16. Vinyl iodide ***25****.* To a vigorously stirred suspension of $CrCl_2$ (13.6 g, 111 mmol, 8.0 equiv) in dioxane/THF (1:1, 75 mL) at 0 °C was added a solution of aldehyde **24** (5.08 g, 13.9 mmol, 1.0 equiv) in dioxane/THF (1:1, 30 mL). After 5 min, CHI_3 (19.1 g, 48.5 mmol, 3.5 equiv) was added to the reaction mixture. After 18 h at 0 °C, water (75 mL) and EtOAc (75 mL) were added and the phases separated. The aqueous layer was extracted with EtOAc (4×75 mL), and the combined organic extracts dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (hexane→3% EtOAc/hexane) afforded the (*E*)-vinyl iodide **25** (4.97 g, 74%) as a colourless oil: R_f 0.59 (20% EtOAc/hexane); $[\alpha]_D^{20}$ −8.7 (*c* 0.92, $CHCl_3$); IR (liquid film)/cm^{-1} 2954, 2928, 2856, 1612, 1513, 1462; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (2H, d, *J*=8.5 Hz, ArH), 6.86 (2H, d, *J*=8.5 Hz, ArH), 6.50 (1H, dd, *J*=14.5, 8.0 Hz, H5), 6.02 (1H, d, *J*=14.3 Hz, H4), 4.44 (2H, s, OCH_2Ar), 3.80 (3H, s, OMe), 3.67 (2H, t, *J*=6.5 Hz, H9a+H9b), 3.46 (1H, dt, *J*=7.0, 4.8 Hz, H7), 2.42–2.52 (1H, m, H6), 1.60–1.67 (2H, m, H8a+H8b), 1.02 (3H, d, *J*=6.8 Hz, Me6), 0.89 (9H, s, $SiC(CH_3)_3$), 0.03 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 148.6, 130.7, 129.6, 113.7, 78.3, 75.4, 72.1, 59.6, 55.3, 44.0, 34.6, 26.0, 18.5, 15.0, −5.2; HRMS (+ESI) calcd for $C_{21}H_{36}IO_3Si$ $[M+H]^+$: 491.1473, found: 491.1476.

5.1.17. Alcohol ***25a****.* To a stirred solution of TBS ether **25** (4.50 g, 9.17 mmol, 1.0 equiv) in THF (100 mL) at rt was added a pre-mixed solution of TBAF (18.4 mL of 1 M solution in THF, 18.4 mmol, 2.0 equiv) and AcOH (1.8 mL, 32.1 mmol, 3.5 equiv). After 18 h, satd aq $NaHCO_3$ (100 mL) was added and the phases separated. The aqueous layer was extracted with EtOAc (3×100 mL), and the combined organic extracts dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (10% EtOAc/hexane) afforded the corresponding alcohol (3.33 g, 95%) as a colourless oil: R_f 0.28 (40% EtOAc/hexane); $[\alpha]_D^{20}$ −3.4 (*c* 0.41, $CHCl_3$); IR (liquid film)/cm^{-1} 3404, 2963, 1612, 1514, 1461; ^1H NMR (500 MHz, $CDCl_3$) δ 7.27 (2H, d, *J*=8.7 Hz, ArH), 6.89 (2H, d, *J*=8.7 Hz, ArH), 6.50 (1H, dd, *J*=14.6, 7.9 Hz, H5), 6.09 (1H, dd, *J*=14.4, 0.9 Hz, H4), 4.54 (1H, d, *J*=11.0 Hz, OCH_xH_yAr), 4.44 (1H, d, *J*=11.0 Hz, OCH_xH_yAr), 3.91 (3H, s, OMe), 3.71–3.75 (2H, m, H9a+H9b), 3.54 (1H, qn, *J*=4.0 Hz, H7), 2.58 (1H, sex, *J*=5.3 Hz, H6), 1.64–1.74 (2H, m, H8a+H8b), 1.05 (3H, d, *J*=6.9 Hz, Me6); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 148.2, 130.1, 129.6, 113.9, 80.2, 75.6, 71.8, 60.4, 55.3, 43.3, 33.1, 21.0; HRMS (+ESI) calcd for $C_{15}H_{25}INO_3Si$ $[M+NH_4]^+$: 394.0874, found: 394.0878.

5.1.18. Aldehyde ***25b****.* To a stirred solution of the foregoing alcohol (1.90 g, 5.05 mmol, 1.0 equiv) and pyridine (1.23 mL, 15.2 mmol, 3.0 equiv) in CH_2Cl_2 (40 mL) at 0 °C was added Dess–Martin periodinane (3.21 g, 7.58 mmol, 1.5 equiv). After 2 h, satd aq $NaHCO_3$ (25 mL) and $Na_2S_2O_3$ (25 mL) were added and the phases separated. The aqueous layer was extracted with CH_2Cl_2 (3×50 mL), and the combined organic extracts dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (5% EtOAc/hexane) afforded the corresponding aldehyde (1.70 g, 90%) as a colourless oil: R_f 0.54 (40% EtOAc/hexane); $[\alpha]_D^{20}$ −7.1 (*c* 4.22, $CHCl_3$); IR (liquid film)/cm^{-1} 2929, 1723, 1612, 1586, 1514, 1463; ^1H NMR (500 MHz, $CDCl_3$) δ 9.78 (1H, d, *J*=1.5 Hz, H9), 7.25 (2H, d, *J*=8.5 Hz, ArH), 6.90 (2H, d,

J=8.5 Hz, ArH), 6.51 (1H, dd, J=14.5, 8.0 Hz, H5), 6.13 (1H, dd, J=14.5, 1.0 Hz, H4), 4.49 (2H, s, OCH_2Ar), 3.90 (1H, dt, J=8.0, 4.5 Hz, H7), 3.83 (3H, s, OMe), 2.67 (1H, ddd, J=17.0, 8.0, 2.5 Hz, H8a), 2.53–2.58 (1H, m, H6), 2.50 (1H, ddd, J=17.0, 4.0, 1.5 Hz, H8b), 1.08 (3H, d, J=7.0 Hz, Me6); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.0, 159.4, 147.3, 129.9, 129.5, 113.9, 76.4, 76.3, 72.0, 55.3, 45.8, 44.0, 14.7; HRMS (CI) calcd for $C_{15}H_{23}INO_3$ $[M+NH_4]^+$: 392.0717, found: 392.0722.

5.1.19. Acid ***26***. To a stirred solution of the foregoing aldehyde (2.00 g, 5.34 mmol, 1.0 equiv) in *t*-BuOH/2-methyl-2-butene (8:1, 17 mL) at rt was added a mixture of $NaClO_2$ (1.92 g, 21.4 mmol, 4.0 equiv) and $Na_2H_2PO_4$ (2.95 g, 21.4 mmol, 4.0 equiv) in water (15 mL). After 2 h, brine (25 mL) and EtOAc (25 mL) were added and the phases separated. The aqueous layer was extracted with CH_2Cl_2 (3×40 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo. Flash chromatography (40% EtOAc/hexane) afforded acid **26** (2.14 g, 99%) as a colourless oil: R_f 0.48 (40% EtOAc/hexane); $[\alpha]_D^{20}$ +5.7 (*c* 1.06, $CHCl_3$); IR (liquid film)/cm^{-1} 2965, 2932, 1706, 1612, 1513, 1456; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (2H, d, J=8.9 Hz, ArH), 6.89 (2H, d, J=8.9 Hz, ArH), 6.51 (1H, dd, J=14.5, 8.2 Hz, H5), 6.13 (1H, d, J=14.5 Hz, H4), 4.56 (1H, d, J=10.8 Hz, OCH_xH_yAr), 4.49 (1H, d, J=10.8 Hz, OCH_xH_yAr), 3.82 (4H, s, OMe+H7), 2.47–2.62 (3H, m, H6+H8a+H8b), 1.08 (3H, d, J=6.8 Hz, Me6); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.6, 159.4, 147.2, 129.9, 129.5, 113.9, 77.9, 76.5, 72.3, 55.3, 44.1, 36.8, 14.9; HRMS (+ESI) calcd for $C_{15}H_{23}INO_4$ $[M+NH_4]^+$: 408.0666, found: 408.0667.

5.1.20. Phosphonate ***5***. To a stirred solution of acid **26** (811 mg, 2.08 mmol, 1.0 equiv) in CH_2Cl_2 at rt was added 1-chloro-*N*,*N*-trimethylpropenyl-amine (550 μL, 4.16 mmol, 2.0 equiv). After 1 h, the volatiles were removed in vacuo and the crude acid chloride was dried for 2 h under high vacuum. A solution of $(Me_3Si)_2NH$ (1.43 mL, 6.85 mmol, 3.3 equiv) in THF (10 mL) at −78 °C was treated with *n*-BuLi (3.9 mL of 1.6 M solution in hexanes, 6.23 mmol, 3.0 equiv) and allowed to warm to 0 °C for 5 min. A solution of bis(2,2,2-trifluoroethyl)-2-methylphosphonate (1.62 g, 6.23 mmol, 3.0 equiv) in THF (10 mL), cooled to −98 °C (MeOH/liquid N_2) for 20 min, was treated (via syringe addition) first with the solution of LiHMDS (pre-cooled to −78 °C), then with the pre-formed acid chloride in THF (10 mL). After 1.5 h at −98 °C, satd aq NH_4Cl (20 mL) was added and the phases separated. The aqueous layer was extracted with Et_2O (2×50 mL), the combined organic extracts dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (20% EtOAc/hexane) afforded the phosphonate **5** (1.09 g, 83%) as an oil: R_f 0.42 (40% EtOAc/hexane); $[\alpha]_D^{20}$ +21.5 (*c* 1.52, $CHCl_3$); IR (liquid film)/cm^{-1} 2973, 1719, 1613, 1515, 1455; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (2H, d, J=8.8 Hz, ArH), 6.89 (2H, d, J=8.8 Hz, ArH), 6.49 (1H, dd, J=13.8, 8.3 Hz, H5), 6.13 (1H, dd, J=14.7, 1.0 Hz, H4), 4.37–4.51 (6H, m, $ArCH_2O$+2×CF_3CH_2O), 3.88 (1H, qn, J=4.1 Hz, H7), 3.82 (3H, s, OMe), 3.27 (2H, d, $^2J_{H,P}$=21.5 Hz, H10a+H10b), 2.81 (1H, dd, J=16.4, 8.2 Hz, H8a), 2.57 (1H, dd, J=16.6, 3.9 Hz, H8b), 2.48–2.55 (1H, m, H6), 1.07 (3H, d, J=6.9 Hz, Me6); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.8 (d, $^2J_{C,P}$=6.6 Hz), 159.4, 147.1, 129.9, 129.6, 113.9, 77.3, 76.5, 72.4, 62.3 (2C, m), 55.2, 46.3 (d, $^3J_{C,P}$=4.8 Hz), 43.8, 42.5 (d, $^1J_{C,P}$=137.4 Hz), 14.5; HRMS (CI) calcd for $C_{20}H_{28}F_6INO_6P$ $[M+NH_4]^+$: 650.0598, found: 650.0605.

5.1.21. Alcohol ***28***. To a solution of PMB ether **27**[18b,39] (160 mg, 0.168 mmol, 1.0 equiv) in CH_2Cl_2/pH 7 buffer (10:1, 400 mL) at 0 °C was added DDQ (191 mg, 0.840 mmol, 5.0 equiv). After stirring for 1 h, pH 7 buffer (500 mL) was added and the phases separated. The aqueous phase was extracted with CH_2Cl_2 (3×400 mL) and the combined organic extracts dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (light petroleum→10% EtOAc/light petroleum) afforded alcohol **28** (119 mg, 85%) as a colourless oil: R_f 0.40 (40% EtOAc/light petroleum); $[\alpha]_D^{20}$ +0.3 (*c* 1.76, $CHCl_3$); IR (liquid film)/cm^{-1} 3472, 2956, 2929, 2856, 1684, 1607, 1472, 1461, 1416; ^{1}H NMR (500 MHz, C_6D_6) δ 6.85 (1H, dt, J=16.9, 11.0 Hz, H25), 6.66 (1H, dd, J=14.5, 8.6 Hz, H5), 6.43 (1H, dd, J=11.6, 10.0 Hz, H11), 6.23 (1H, t, J=11.1 Hz, H24), 5.88 (1H, d, J=11.3 Hz, H10), 5.87 (1H, d, J=14.6 Hz, H4), 5.59 (1H, t, J=10.5 Hz, H23), 5.28 (1H, d, J=16.0 Hz, H26a), 5.19 (1H, d, J=10.0 Hz, H26b), 4.08–4.16 (1H, m, H12), 4.00 (1H, q, J=6.3 Hz, H19), 3.85–3.91 (1H, m, H7), 3.64–3.68 (1H, m, H21), 3.58–3.62 (1H, m, H13), 3.22 (1H, d, J=3.0 Hz, OH), 2.97–3.06 (1H, m, H22), 2.40 (1H, dd, J=17.6, 9.7 Hz, H8a), 2.15 (1H, dd, J=17.5, 2.6 Hz, H8b), 1.99–2.02 (1H, m, H6), 1.87–1.98 (2H, m, H18a+H20), 1.80–1.86 (1H, m, H14), 1.69–1.75 (1H, m, H18b), 1.55–1.66 (3H, m, H15a+H16+H17a), 1.24 (3H, d, J=6.7 Hz, Me12), 1.23 (3H, d, J=6.7 Hz, Me20), 1.16 (9H, s, $SiC(CH_3)_3$), 1.14 (9H, s, $SiC(CH_3)_3$), 1.07–1.13 (11H, m, H15b+H17b+Me14+Me16+Me22), 0.94 (3H, d, J=7.0 Hz, Me6), 0.27 (3H, s, $SiCH_3$), 0.26 (6H, s, $Si(CH_3)_2$), 0.23 (3H, s, $SiCH_3$); ^{13}C NMR (125 MHz, C_6D_6) δ 201.4, 151.7, 147.7, 135.0, 132.6, 130.4, 125.7, 117.7, 80.1, 75.9, 75.7, 75.3, 70.0, 48.0, 45.8, 41.8, 39.2, 36.8, 36.4, 36.1, 32.2, 31.6, 31.0, 26.2, 26.0, 20.7, 18.9, 18.5, 18.2, 17.7, 16.3, 15.6, 8.4, −3.6, −3.8, −4.5; HRMS (+ESI) calcd for $C_{41}H_{78}IO_5Si_2$ $[M+H]^+$: 833.4427, found: 833.4439.

5.1.22. Diol ***29***. To a stirred solution of (*R*)-methyl-oxazaborolidine (50 μL of a 1 M solution in PhMe) at 0 °C was added $BH_3\cdot DMS$ (50 μL of a 1 M solution in THF). After 1 h, the pre-formed reductant (50.4 μL of 0.5 M solution in THF/PhMe, 25.2 μmol, 1.5 equiv) was added dropwise to a solution of ketone **28** (14.0 mg, 16.8 μmol, 1.0 equiv) in THF (2.2 mL) at −40 °C. After 16 h, the reaction mixture was quenched by the slow addition of MeOH (2 mL) and warmed to rt. The crude product was azeotroped from MeOH five times and purified by flash chromatography (15% EtOAc/hexane) to afford the 1,3-*anti* diol **29** (12.1 mg, 86%) and the epimeric 1,3-*syn* diol (1.8 mg, 13%) as colourless oils: R_f 0.26 (20% EtOAc/hexane); $[\alpha]_D^{20}$ −44.8 (*c* 1.53, $CHCl_3$); IR (liquid film)/cm^{-1} 3422, 2957, 2929, 2857, 1462, 1378, 1253; ^{1}H NMR (500 MHz, C_6D_6) δ 6.72 (1H, dt, J=17.1, 10.8 Hz, H25), 6.51 (1H, dd, J=14.4, 8.5 Hz H5), 6.10 (1H, t, J=11.4 Hz, H24), 5.80 (1H, dd, J=14.1, 0.6 Hz, H4), 5.53 (1H, t, J=10.6 Hz, H11), 5.44 (1H, t, J=10.2 Hz, H23), 5.40 (1H, dd, J=11.0, 7.6 Hz, H10), 5.15 (1H, dd, J=16.9, 1.9 Hz, H26a), 5.06 (1H, br d, J=10.2 Hz, H26b), 4.66 (1H, dt, J=8.3, 3.4 Hz, H9), 3.87–3.90 (1H, m, H19), 3.61–3.65 (1H, m, H7), 3.53 (1H, br t, J=4.2 Hz, H21), 3.41 (1H, dd, J=5.3, 2.8 Hz, H13), 2.83–2.92 (2H, m, H12+H22), 2.04 (1H, br s, OH), 1.89–1.95 (1H, m, H6), 1.77–1.85 (3H, m, H14+H18a+H20), 1.72–1.77 (1H, m, H18b), 1.61–1.70 (2H, m, H8a+H8b), 1.40–1.61 (3H, m, H15a+H16+H17a), 1.10–1.18 (2H, m, H15b+H17b), 1.10 (3H, d, J=6.8 Hz, Me20), 1.04 (9H, s, $SiC(CH_3)_3$), 1.01–1.04 (3H, m, Me12), 1.01 (9H, s, $SiC(CH_3)_3$), 0.98–1.00 (6H, m, Me14+Me22), 0.98 (3H, d, J=6.8 Hz, Me16), 0.82 (3H, d, J=7.0 Hz, Me6), 0.16 (3H, s, $SiCH_3$), 0.15 (3H, s, $SiCH_3$), 0.14 (3H, s, $SiCH_3$), 0.12 (3H, s, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.0, 135.9, 135.4, 132.3, 130.5, 130.0, 118.0, 79.4, 77.7, 76.7, 76.1, 71.4, 66.7, 47.0, 41.9, 39.9, 37.4, 36.3, 36.0, 34.2, 31.9, 31.4, 30.3, 26.3, 26.0, 20.4, 19.7, 18.5, 18.1, 17.7, 16.0, 15.0, 6.8, −3.1, −3.67, −3.75, −4.3; HRMS (+ESI) calcd for $C_{41}H_{79}NaIO_4Si_2$ $[M+Na]^+$: 857.4403, found: 857.4390.

5.1.23. Iodide ***30***. To a solution of diol **29** (73 mg, 87.5 μmol, 1.0 equiv) in $(MeO)_2CMe_2/CH_2Cl_2$ (2:1, 9 mL) at 0 °C was added PPTS (1.0 mg, 1.75 μmol, 0.02 equiv). After stirring at rt for 16 h, satd aq $NaHCO_3$ (10 mL) was added and the phases separated. The aqueous phase was extracted with CH_2Cl_2 (3×10 mL) and the combined organic extracts dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (10% EtOAc/hexane) afforded iodide **30** (76 mg, 99%) as a colourless oil: R_f 0.71 (20% EtOAc/light petroleum); $[\alpha]_D^{20}$ −12.5 (*c* 1.28, $CHCl_3$); IR (liquid film)/cm^{-1} 2958, 2929, 2857, 1461, 1378, 1254, 1223, 1073; ^{1}H NMR (500 MHz, C_6D_6) δ 6.71 (1H, dt, J=16.6, 10.4 Hz, H25), 6.62 (1H, dd, J=14.3, 8.1 Hz, H5), 6.08 (1H, t, J=10.8 Hz, H24), 5.85 (1H, d, J=14.7 Hz, H4), 5.66 (1H, t, J=11.2 Hz, H11), 5.52 (1H, dd,

J=10.8, 8.1 Hz, H10), 5.43 (1H, t, J=10.8 Hz, H23), 5.15 (1H, br d, J=16.6 Hz, H26a), 5.05 (1H, br d, J=10.8 Hz, H26b), 4.71–4.78 (1H, m, H9), 3.87–3.91 (1H, m, H19), 3.55 (1H, dt, J=9.3, 5.8 Hz, H7), 3.52 (1H, dd, J=6.2, 3.5 Hz, H21), 3.42 (1H, dd, J=5.0, 3.1 Hz, H13), 2.80–2.92 (2H, m, H12+H22), 1.97–2.05 (1H, m, H6), 1.78–1.86 (3H, m, H14+H18a+H20), 1.75 (1H, ddd, J=13.2, 9.5, 5.8 Hz, H8a), 1.60–1.69 (2H, m, H15a+H18b), 1.45–1.58 (3H, m, H8b+H16+H17a), 1.39 (3H, s, CCH_3), 1.31 (3H, s, CCH_3), 1.12–1.18 (2H, m, H15b+H17b), 1.10 (3H, d, J=7.0 Hz, Me20), 1.08 (3H, d, J=7.0 Hz, Me12), 1.04 (9H, s, $SiC(CH_3)_3$), 1.01 (9H, s, $SiC(CH_3)_3$), 1.005 (3H, d, J=6.5 Hz, Me14), 0.99 (3H, d, J=6.5 Hz, Me16), 0.98 (3H, d, J=7.0 Hz, Me22), 0.83 (3H, d, J=7.0 Hz, Me6), 0.15 (6H, s, $Si(CH_3)_2$), 0.13 (3H, s, $SiCH_3$), 0.12 (3H, s, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.2, 136.9, 135.3, 132.3, 130.0, 128.5, 117.8, 100.5, 79.4, 77.5, 76.5, 75.2, 69.2, 63.4, 45.0, 42.1, 37.8, 36.8, 36.4, 36.1, 34.4, 32.0, 31.5, 30.4, 26.2, 26.0, 25.0, 24.4, 20.4, 19.1, 18.4, 18.1, 17.7, 15.3, 15.1, 7.0, −3.4, −3.66, −3.73, −4.4; HRMS (+ESI) calcd for $C_{44}H_{83}NaIO_5Si_2$ $[M+Na]^+$: 897.4716, found: 897.4714.

*5.1.24. Acid **31**.* To a solution of iodide **30** (42.2 mg, 48.2 μmol, 1.0 equiv) and stannane **6**[44] (50.0 mg, 96.2 μmol, 2.0 equiv) in freeze-thaw deoxygenated NMP (1800 μL) at rt was added CuTC[21] (46.0 mg, 241 μmol, 5.0 equiv). After stirring for 14 h, satd aq NH_4Cl (2 mL) was added and the phases separated. The aqueous phase was extracted with CH_2Cl_2 (3×2 mL) and the combined organic extracts dried ($MgSO_4$) and concentrated in vacuo (0.1 mmHg/0 °C to remove NMP). The crude silyl ester intermediate was re-dissolved in THF/MeOH (3:1, 2 mL) and to this solution at rt was added KF (28.0 mg, 482 μmol, 10 equiv). After 3 h, satd aq NH_4Cl (2 mL) was added and the phases separated. The aqueous phase was extracted with CH_2Cl_2 (3×2 mL) and the combined organic extracts dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (5% EtOAc/light petroleum→20% EtOAc/light petroleum) afforded acid **31** (40.6 mg, 99%) as a colourless oil contaminated with traces of tin residues,[45] which was used without further purification: R_f 0.22 (30% EtOAc/light petroleum); $[\alpha]_D^{20}$ −23.2 (*c* 1.61, $CHCl_3$); IR (liquid film)/cm^{-1} 2957, 2928, 2856, 1692, 1637, 1601, 1515, 1462; ^{1}H NMR (500 MHz, C_6D_6) δ 7.69 (1H, br t, J=13.0 Hz, H4), 6.71 (1H, dt, J=17.4, 10.6 Hz, H25), 6.31 (1H, br t, J=10.8 Hz, H3), 6.10 (1H, t, J=10.1 Hz, H24), 6.03 (1H, dd, J=16.2, 8.1 Hz, H5), 5.69 (1H, t, J=10.8 Hz, H11), 5.46–5.62 (2H, m, H2+H10), 5.46 (1H, t, J=10.1 Hz, H23), 5.15 (1H, d, J=17.5 Hz, H26a), 5.05 (1H, d, J=10.8 Hz, H26b), 4.76–4.82 (1H, m, H9), 3.85–3.91 (1H, m, H19), 3.71 (1H, ddd, J=11.1, 10.1, 5.7 Hz, H7), 3.58–3.62 (1H, m, H21), 3.44 (1H, br t, J=3.7 Hz, H13), 2.81–2.92 (2H, m, H12+H22), 2.21–2.28 (1H, m, H6), 1.79–1.89 (4H, m, H8a+H14+H18a+H20), 1.46–1.70 (4H, m, H8b+H16+H17a+H18b), 1.46 (3H, s, CCH_3), 1.22–1.39 (2H, m, H15a+H17b), 1.37 (3H, s, CCH_3), 1.10–1.15 (1H, m, H15b), 1.10 (3H, d, J=6.0 Hz, Me12), 1.08 (3H, d, J=6.9 Hz, Me20), 1.04 (9H, s, $SiC(CH_3)_3$), 1.03 (9H, s, $SiC(CH_3)_3$), 1.00–1.02 (3H, m, Me6), 0.99 (6H, d, J=6.5 Hz, Me14+Me16), 0.97 (3H, d, J=7.3 Hz, Me22), 0.17 (3H, s, $SiCH_3$), 0.15 (3H, s, $SiCH_3$), 0.14 (3H, s, $SiCH_3$), 0.12 (3H, s, $SiCH_3$); ^{13}C NMR (125 MHz, C_6D_6) δ 170.9, 147.7, 147.4, 135.7, 135.0, 132.6, 130.7, 130.1, 117.9, 115.9, 114.1, 100.5, 79.8, 76.1, 75.5, 69.9, 64.0, 42.3, 42.1, 29.5, 37.3, 37.0, 36.6, 34.7, 32.3, 31.9, 30.8, 26.4, 25.9, 25.3, 24.6, 20.7, 19.3, 18.7, 18.4, 17.9, 16.1, 15.7, 8.7, −3.1, −3.4, −3.6, −4.3; HRMS (+ESI) calcd for $C_{47}H_{90}NO_7Si_2$ $[M+NH_4]^+$: 836.6250, found: 836.6255.

*5.1.25. Macrolactone **32**.* To a solution of acid **31** (30.1 mg, 36.8 μmol, 1.0 equiv) in PhMe (2.5 mL) at rt was added Et_3N (13.8 μL, 99.3 μmol, 2.7 equiv) then 2,4,6-trichlorobenzoylchloride (10.3 μL, 66.2 μmol, 1.8 equiv). After stirring for 2 h, the reaction mixture was diluted with PhMe (50 mL) and DMAP (2.2 mg, 18.3 μmol, 0.5 equiv) was added. After 18 h, satd aq $NaHCO_3$ (50 mL) was added and the phases separated. The aqueous phase was extracted with CH_2Cl_2 (3×40 mL) and the combined organic extracts dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (20% hexane/toluene) afforded macrolactone **32** (25.9 mg, 88%) as a colourless oil: R_f 0.59 (10% EtOAc/light petroleum); $[\alpha]_D^{20}$ +2.6 (*c* 0.53, $CHCl_3$); IR (liquid film)/cm^{-1} 2957, 2930, 2856, 1716, 1645, 1581, 1516, 1461; ^{1}H NMR (500 MHz, C_6D_6) δ 7.65 (1H, dd, J=14.9, 11.3 Hz, H4), 6.72 (1H, dt, J=17.0, 10.6 Hz, H25), 6.25 (1H, t, J=11.3 Hz, H3), 6.02 (1H, t, J=11.3 Hz, H24), 5.76 (1H, t, J=11.3 Hz, H11), 5.68 (1H, dd, J=15.6, 6.4 Hz, H5), 5.63 (1H, d, J=11.3 Hz, H2), 5.58 (1H, t, J=9.9 Hz, H10), 5.51 (1H, d, J=8.5 Hz, H21), 5.44 (1H, t, J=11.3 Hz, H23), 5.13 (1H, d, J=16.3 Hz, H26a), 5.06 (1H, d, J=10.6 Hz, H26b), 4.73 (1H, ddd, J=14.9, 9.6, 6.0 Hz, H9), 3.89–3.94 (1H, m, H7), 3.44–3.50 (1H, m, H19), 3.38–3.41 (1H, m, H13), 2.99–3.08 (1H, m, H22), 2.86–2.94 (1H, m, H12), 2.52–2.59 (1H, m, H6), 1.95–2.02 (1H, m, H20), 1.83–1.92 (1H, m, H18a), 1.69–1.83 (3H, m, H8a+H14+H17a), 1.37–1.54 (2H, m, H8b+H16), 1.45 (3H, s, CCH_3), 1.40 (3H, s, CCH_3), 1.18–1.36 (2H, m, H15a+H18b), 1.25 (3H, d, J=6.9 Hz, Me6), 1.14 (3H, d, J=7.1 Hz, Me12), 1.10 (3H, d, J=7.1 Hz, Me20), 1.05 (9H, s, $SiC(CH_3)_3$), 1.03 (9H, s, $SiC(CH_3)_3$), 0.98 (6H, d, J=6.5 Hz, Me14+Me22), 0.96 (3H, d, J=6.7 Hz, Me16), 0.80–0.89 (2H, m, H15b+H17b), 0.14 (3H, s, $SiCH_3$), 0.12 (3H, s, $SiCH_3$), 0.11 (3H, s, $SiCH_3$), 0.10 (3H, s, $SiCH_3$); ^{13}C NMR (125 MHz, C_6D_6) δ 165.6, 144.2, 144.0, 137.0, 134.8, 133.9, 132.6, 130.2, 130.0, 117.7, 115.6, 100.5 79.4, 75.8, 74.5, 67.9, 64.0, 41.3, 41.2, 40.5, 36.6, 36.1, 34.8, 33.8, 33.0, 31.4, 30.9, 26.3, 26.2, 25.4, 24.6, 20.4, 19.5, 18.7, 18.3, 17.9, 16.6, 11.8, 11.1, −3.5, −3.6, −3.8, −3.9; HRMS (+ESI) calcd for $C_{47}H_{85}O_6Si_2$ $[M+H]^+$: 801.5879, found: 801.5868.

*5.1.26. (−)-Dictyostatin (**1**).* To a solution of macrolactone **32** (81.4 mg, 102 μmol, 1.0 equiv) in THF (11 mL) at 0 °C was added HF·pyr (400 μL) dropwise over 20 min. Over the course of the next four days, four aliquots of HF·pyr (300 μL) were added at rt to this stirred reaction mixture. The reaction mixture was then quenched by its careful addition to satd aq $NaHCO_3$ (50 mL) at 0 °C, warmed to rt and stirred for a further 30 min. The phases were separated, the aqueous phase was extracted with EtOAc (3×50 mL) and the combined organic extracts dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (30% hexane/EtOAc) afforded (−)-dictyostatin (**1**) (38.0 mg, 70%) as an amorphous white solid: R_f 0.47 (EtOAc); $[\alpha]_D^{20}$ −32.7 (*c* 0.22, MeOH);[47] IR (liquid film)/cm^{-1} 2955, 2930, 2858, 1716, 1462, 1257; ^{1}H NMR (700 MHz, CD_3OD) δ 7.21 (1H, dd, J=15.5, 11.4 Hz, H4), 6.70 (1H, dt, J=15.2, 10.4 Hz, H25), 6.65 (1H, t, J=11.4 Hz, H3), 6.18 (1H, dd, J=15.5, 6.7 Hz, H5), 6.06 (1H, t, J=11.1 Hz, H24), 5.55 (1H, d, J=11.4 Hz, H2), 5.55 (1H, t, J=10.0 Hz, H11), 5.41 (1H, dd, J=10.8, 8.9 Hz, H10), 5.33 (1H, dd, J=11.1, 10.6 Hz, H23), 5.24 (1H, dd, J=15.2, 1.7 Hz, H26a), 5.14 (1H, dd, J=10.4, 1.7 Hz, H26b), 5.13 (1H, dd, J=6.9, 5.1 Hz, H21), 4.65 (1H, dddd, J=10.1, 9.5, 2.9, 0.8 Hz, H9), 4.05 (1H, ddd, J=10.6, 4.0, 2.7 Hz, H7), 3.34 (1H, m, H19), 3.16 (1H, ddq, J=10.6, 6.9, 6.8 Hz, H22), 3.10 (1H, dd, J=8.1, 2.9 Hz, H13), 2.76 (1H, m, H12), 2.60 (1H, m, H6), 1.88 (1H, m, H20), 1.83 (1H, m, H18a), 1.59 (1H, m, H14), 1.57 (1H, m, H17a), 1.53 (1H, m, H16), 1.49 (1H, ddd, J=14.0, 10.6, 2.9 Hz, H8a), 1.42 (1H, ddd, J=14.0, 10.1, 2.7 Hz, H8b), 1.24 (1H, ddd, J=13.8, 10.3, 3.8 Hz, H15a), 1.15 (3H, d, J=6.9 Hz, Me27), 1.13 (3H, d, J=7.0 Hz, Me28), 1.10 (1H, m, H18b), 1.07 (3H, d, J=6.9 Hz, Me31), 1.01 (3H, d, J=6.8 Hz, Me32), 0.95 (3H, d, J=6.5 Hz, Me29), 0.93 (3H, d, J=6.6 Hz, Me30), 0.89 (1H, m, H15b), 0.69 (1H, m, H17b); ^{13}C NMR (125 MHz, CD_3OD) δ 168.0, 146.3, 144.8, 134.9, 134.5, 133.4, 131.3, 131.1, 128.5, 118.5, 118.0, 80.3, 78.6, 73.7, 70.3, 65.4, 44.0, 42.2, 40.8, 40.5, 35.8, 35.7, 35.3, 32.7, 32.5, 31.2, 21.8, 19.3, 18.0, 15.9, 13.6, 10.3; HRMS (+ESI) calcd for $C_{32}H_{52}NaO_6$ $[M+Na]^+$: 555.3662, found: 555.3663. This spectroscopic data was identical to that recorded for an authentic sample of dictyostatin.

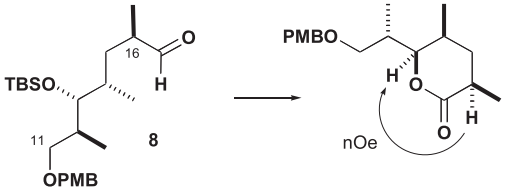
Acknowledgements

Financial support was provided by the EPSRC, the NSERC of Canada (R.B.), the Gobernio de Canarias, the Cambridge European Trust (O.D.), the EC (Network HPRN-CT-2000-18 and Marie Curie

Fellowship to K.G.P.) and AstraZeneca (N.M.G.). We thank Dr. Amy Wright (Harbour Branch Oceanographic Institution) for providing an authentic sample of dictyostatin, Professor John Leonard (AstraZeneca) for helpful discussions, Dr. Stuart Mickel (Novartis Pharma AG) for the gift of chemicals and the EPSRC National Mass Spectrometry Service (Swansea) for mass spectra.

References and notes

1. An annual review is dedicated to marine natural products: Blunt, J. W.; Copp, B. R.; Hu, W.-P.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2009**, *26*, 170.
2. (a) Koehn, F. E.; Carter, G. T. *Nat. Rev. Drug Discovery* **2005**, *4*, 206; (b) Butler, M. S. *Nat. Prod. Rep.* **2005**, *22*, 162; (c) Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2007**, *70*, 461; (d) Paterson, I.; Anderson, E. A. *Science* **2005**, *310*, 451.
3. Pettit, G. R.; Cichacz, Z. A.; Gao, F.; Boyd, M. R.; Schmidt, J. M. *J. Chem. Soc., Chem. Commun.* **1994**, 1111.
4. Isbrucker, R. A.; Cummins, J.; Pomponi, S. A.; Longley, R. E.; Wright, A. E. *Biochem. Pharmacol.* **2003**, *66*, 75.
5. Kowalski, R. J.; Giannakakou, P.; Gunesekera, S. P.; Longley, R. E.; Day, B. W.; Hamel, E. *Mol. Pharmacol.* **1997**, *52*, 613.
6. Bollag, D. M.; McQueney, P. A.; Zhu, J.; Hensens, O.; Koupal, L.; Liesch, J.; Goetz, M.; Lazarides, E.; Woods, C. M. *Cancer Res.* **1995**, *55*, 2325.
7. Altmann, K.-H.; Gertsch, J. *Nat. Prod. Rep.* **2007**, *24*, 327.
8. Paterson, I.; Britton, R.; Delgado, O.; Wright, A. E. *Chem. Commun.* **2004**, 632.
9. Canales, A.; Matesanz, R.; Gardner, N. M.; Andreu, J. M.; Paterson, I.; Díaz, J. F.; Jiménez-Barbero, J. *Chem.—Eur. J.* **2008**, *14*, 7557.
10. Sanchez-Pedregal, V. M.; Kubicek, K.; Meiler, J.; Lyothier, I.; Paterson, I.; Carlomagno, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 7388.
11. (a) Paterson, I.; Naylor, G. J.; Wright, A. E. *Chem. Commun.* **2008**, 4628; (b) Paterson, I.; Gardner, N. M. *Chem. Commun.* **2007**, 49; (c) Paterson, I.; Naylor, G. J.; Fujita, T.; Guzman, E.; Wright, A. E. *Chem. Commun.* **2010**, *46*, 261.
12. (a) Florence, G. J.; Gardner, N. M.; Paterson, I. *Nat. Prod. Rep.* **2008**, *25*, 342; (b) Paterson, I.; Yeung, K.-S. *Chem. Rev.* **2005**, *105*, 4237.
13. For a preliminary account of some of this work, see Paterson, I.; Britton, R.; Delgado, O.; Meyer, A.; Poullennec, K. G. *Angew. Chem., Int. Ed.* **2004**, *43*, 4629.
14. (a) Shin, Y.; Fournier, J.-H.; Fukui, Y.; Bruckner, A. M.; Curran, D. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 4634; (b) Shin, Y.; Fournier, J.-H.; Bruckner, A.; Madiraju, C.; Balachandran, R.; Raccor, B. S.; Edler, M. C.; Hamel, E.; Sikorski, R. P.; Vogt, A.; Day, B. W.; Curran, D. P. *Tetrahedron* **2007**, *63*, 8537.
15. O'Neil, G. W.; Phillips, A. J. *J. Am. Chem. Soc.* **2006**, *128*, 5340.
16. Ramachandran, P. V.; Srivastava, A.; Hazra, D. *Org. Lett.* **2007**, *9*, 157.
17. For fragment syntheses, see: (a) O'Neil, G. W.; Phillips, A. J. *Tetrahedron Lett.* **2004**, *45*, 4253; (b) Kangani, C. O.; Brückner, A. M.; Curran, D. P. *Org. Lett.* **2005**, *7*, 379; (c) Julia, J.; Maier, M. E. *Synlett* **2006**, 693; (d) Prusov, E.; Röhm, H.; Maier, M. E. *Org. Lett.* **2006**, *8*, 1025; (e) Baba, V. S.; Das, P.; Mukkanti, K.; Iqbal, J. *Tetrahedron Lett.* **2006**, *47*, 7927; (f) Dilger, A. K.; Gopalsamuthiram, V.; Burke, S. D. *J. Am. Chem. Soc.* **2007**, *129*, 16273; (g) Monti, C.; Sharon, O.; Gennari, C. *Chem. Commun.* **2007**, 4271; (h) Sharon, O.; Monti, C.; Gennari, C. *Tetrahedron* **2007**, *63*, 5873; (i) Gennari, C.; Castoldi, D.; Sharon, O. *Pure Appl. Chem.* **2007**, *79*, 173; (j) Saibaba, V.; Sampath, A.; Mukkanti, K.; Iqbal, J.; Das, P. *Synthesis* **2007**, 2797; (k) Curran, D. P.; Moura-Letts, G. *Org. Lett.* **2007**, *9*, 5; (l) Zanato, C.; Pignataro, L.; Hao, Z.; Gennari, C. *Synthesis* **2008**, 2158; (m) Dias, L. C.; Lima, D. J. P.; Goncalves, C. C. S.; Andricopulo, A. D. *Eur. J. Org. Chem.* **2009**, 1491; (n) Ramachandran, P. V.; Pratihar, D. *Org. Lett.* **2009**, *11*, 1467; (o) Shimp, H. L.; Micalizio, G. C. *Tetrahedron* **2009**, *65*, 5908.
18. (a) Paterson, I.; Gardner, N. M.; Poullennec, K. G.; Wright, A. E. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2443; (b) Paterson, I.; Gardner, N. M.; Poullennec, K. G.; Wright, A. E. *J. Nat. Prod.* **2008**, *71*, 364; (c) Paterson, I.; Gardner, N. M.; Guzman, E.; Wright, A. E. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6268; (d) Paterson, I.; Gardner, N. M.; Guzman, E.; Wright, A. E. *Bioorg. Med. Chem.* **2009**, *17*, 2282; (e) Paterson, I.; Gardner, N. M.; Naylor, G. J. *Pure Appl. Chem.* **2009**, *81*, 169.
19. (a) Shin, Y.; Fournier, J.-H.; Balachandran, R.; Madiraju, C.; Raccor, B. S.; Zhu, G.; Edler, M. C.; Hamel, E.; Day, B. W.; Curran, D. P. *Org. Lett.* **2005**, *7*, 2873; (b) Fukui, Y.; Bruckner, A. M.; Shin, Y.; Balachandran, R.; Day, B. W.; Curran, D. P. *Org. Lett.* **2006**, *8*, 301; (c) Jung, W.-H.; Harrison, C.; Shin, Y.; Fournier, J.-H.; Balachandran, R.; Raccor, B. S.; Sikorski, R. P.; Vogt, A.; Curran, D. P.; Day, B. W. *J. Med. Chem.* **2007**, *50*, 2951; (d) Raccor, B. S.; Vogt, A.; Sikorski, R. P.; Madiraju, C.; Balachandran, R.; Montgomery, K.; Shin, Y.; Fukui, Y.; Jung, W.-H.; Curran, D. P.; Day, B. W. *Mol. Pharmacol.* **2008**, *73*, 718.
20. Eiseman, J. L.; Bai, L.; Jung, W.-H.; Moura-Letts, G.; Day, B. W.; Curran, D. P. *J. Med. Chem.* **2008**, *51*, 6650.
21. Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748.
22. Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.
23. (a) Paterson, I.; Lyothier, I. *Org. Lett.* **2004**, *6*, 4933; (b) Paterson, I.; Lyothier, I. *J. Org. Chem.* **2005**, *70*, 5494.
24. (a) Paterson, I.; Delgado, O.; Florence, G. J.; Lyothier, I.; Scott, J. P.; Sereinig, N. *Org. Lett.* **2003**, *5*, 35; (b) Paterson, I.; Delgado, O.; Florence, G. J.; Lyothier, I.; O'Brien, M.; Scott, J. P.; Sereinig, N. *J. Org. Chem.* **2005**, *70*, 150.
25. (a) Paterson, I.; Wallace, D. J.; Cowden, C. J. *Synthesis* **1998**, 639; (b) Paterson, I.; Wallace, D. J.; Velazquez, S. M. *Tetrahedron Lett.* **1994**, *35*, 9083; (c) Paterson, I.; Wallace, D. J. *Tetrahedron Lett.* **1994**, *35*, 9087.
26. Garegg, P. J.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2866.
27. Myers, A. G.; Yang, B. Y.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496.
28. The 1,3-*syn* stereochemical relationship between the C14 and C16 methyl substituents was established by treatment of **8** with HCl in EtOH to cleave the TBS ether, followed by a TEMPO/PhI(OAc)$_2$ selective oxidation to give the corresponding δ-lactone. Analysis of the NOESY spectrum confirmed the desired stereochemistry.



29. Paterson, I.; Yeung, K.-S.; Smaill, J. B. *Synlett* **1993**, 774.
30. Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291.
31. Lipshutz, B. H.; Keith, J.; Papa, P.; Vivian, R. *Tetrahedron Lett.* **1998**, *39*, 4627.
32. Hung, D. T.; Nerenberg, J. B.; Schreiber, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 11054.
33. (a) Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P.; Sereinig, N. *J. Am. Chem. Soc.* **2001**, *123*, 9535; (b) De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974.
34. For DFT calculations on related aldol transition states, see: Paton, R. S.; Goodman, J. M. *J. Org. Chem.* **2008**, *73*, 1253.
35. Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.
36. Optimisation of a similar Takai reaction in the context of our elaiolide synthesis indicated that a 1:1 mixture of THF and dioxane gave the best compromise between selectivity and yield, and the same trend was also observed in this case Paterson, I.; Lombart, H.-G.; Allerton, C. *Org. Lett.* **1999**, *1*, 19.
37. Bal, B. S.; Childers, W. E.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.
38. Devos, A.; Remion, J.; Frisque-Hesbain, A.-M.; Colens, A.; Ghosez, L. *J. Chem. Soc., Chem. Commun.* **1979**, 1180.
39. Full experimental details for this step and characterisation data for enone **27** are reported in Ref. 18b.
40. Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.
41. Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447.
42. Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551.
43. Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511.
44. The vinyl stannane **6** was prepared from the corresponding acid which has been reported previously, see: (a) Critcher, D. J.; Pattenden, G. *Tetrahedron Lett.* **1996**, *37*, 9107; (b) Gomez, A. M.; Lopez, J. C.; Fraser-Reid, B. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1689.
45. Purification to remove all of the free acid by-product of stannane **6** proved difficult due to the similar R_f value of the compounds. However, this impurity had no apparent deleterious effect on the next step.
46. Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
47. In comparison, the specific rotation measured for a natural sample of dictyostatin was $[\alpha]_D^{20}$ −27.4 (*c* 0.16, MeOH) and that reported by Pettit et al. (Ref. 3) was −20 (*c* 0.12, MeOH). For copies of NMR spectra of dictyostatin, see the Supplementary data for Ref. 13.