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Phorboxazole B synthetic studies: construction of C(1–32) and C(33–46) subtargets†

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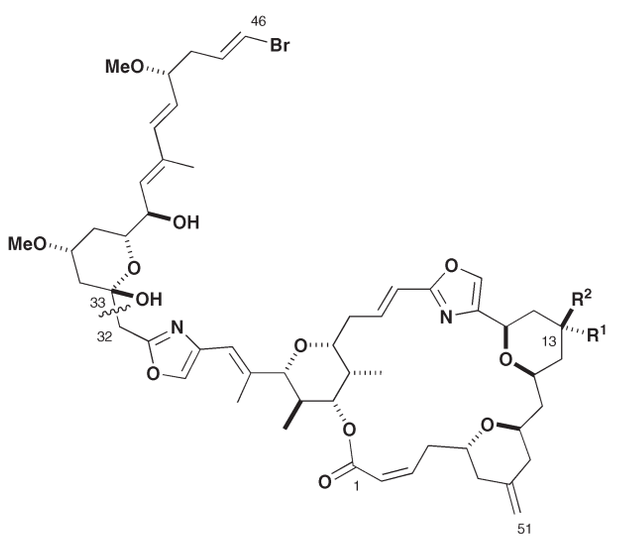
The convergent syntheses of the C(1–32) and C(33–46) domains of phorboxazole B are described. An iterative cyclocondensation strategy exploited the Jacobsen hetero-Diels–Alder (HDA) reaction as a platform for the synthesis of both the C(5–9) and C(11–15) tetrahydropyran rings. The use of 2-silyloxydiene coupling partners bearing an increasing resemblance to the phorboxazole skeleton was found to lead to a reduction in diastereoselectivity, however, in the case of the C(11–15) ring. The coupling of aldehyde **21** and 2-silyloxydiene **20** by this route provided a C(1–32) fragment which was elaborated to the macrolide core of phorboxazole B. The synthesis of the C(33–46) domain involved a Nozaki–Kishi coupling of aldehyde **31** and vinyl iodide **39**. The syntheses of **31** and **39** were highly diastereoselective: an Evans [Cu(Ph-pybox)]$(SbF_6)_2$-catalysed Mukaiyama aldol reaction formed the cornerstone of the synthesis of **31** whilst a Nagao–Fujita acetate aldol reaction provided a convenient means of installing the sole stereogenic centre of **39**.

Introduction

The isolation of phorboxazoles A and B (**1** and **2**, respectively, Fig. 1) from the Indian Ocean sponge *Phorbas* sp. was reported by Searle and Molinski in 1995.[1] Their characteristic 21-membered oxazole-*tris*-tetrahydropyran macrolide ring subtended by an oxazole-tetrahydropyran side-chain represents a novel chemotype. Both **1** and **2** display essentially the same profile in terms of biological activity, the antimitotic component of which (**1** displays a mean GI_{50} of 1.58 nM against the US NCI panel of 60 human cancer cell lines[2]) has rendered them premier medicinal targets. Whilst their precise mechanism of action is subject to ongoing investigations, their ability to induce S-phase cell cycle arrest in Burkitt lymphoma CA46 cells[3] complements the activity of antineoplastic agents which disrupt tubulin polymerisation or microtubule disassembly. In addition to their powerful biological activity, their scarcity and architectural complexity have captured the attention of a number of synthetic groups, culminating in five total syntheses to date,[4–9] and numerous fragment syntheses.[10,11]

Our strategy was envisaged as offering a highly convergent addition to the existing corpus, and targets the C(32–33) bond as the site of the ultimate carbon–carbon bond formation (Fig. 1). Herein, we report the synthesis of the C(1–32) and C(33–46) domains which may enable this end to be realised.



1 R^1 = OH, R^2 = H
2 R^1 = H, R^2 = OH

Fig. 1 Structures of phorboxazoles A and B, and targeted C(32–33) bond formation.

Results and discussion

Synthesis of a C(1–14) fragment

Our previous studies towards the synthesis of the phorboxazoles have led to the convergent synthesis of a pentacyclic C(4–32) unit.[11b] Whilst this work provided a sophisticated example of tetrahydropyranone assembly using Jacobsen's HDA methodology, there was no convenient provision for the appendage of a C(1–3) unit which would allow the completion of the macrolide core. Moreover, the installation of the native functionality of the C(5–9) ring lacked step-efficiency. We now report revised synthetic studies that tackle both of these issues.

In common with the work of Smith,[12] and Donaldson and Greer,[10a,13] 2,3-dihydro-γ-pyrone **3** was recognised as being a suitable building block around which a synthesis of a C(1–14) fragment could be fashioned (Scheme 1). Its enantioselective synthesis *via* an HDA reaction between Danishefsky's diene **4** and aldehyde **5** using Jacobsen's HDA catalyst **6a**[14] proceeded in 89% yield with an acceptable 90% ee.

Attention then turned to the conjugate addition of a suitable nucleophile, ideally corresponding to a propargylic synthon,[15] to dihydropyrone **3**.[16] A rapid screen of the reaction of dihydropyrone **7** (Scheme 2), a redundant compound from a previous synthetic route,[17] with allenylmagnesium bromide in the presence of various additives, revealed a pronounced bias towards carbonyl, rather than Michael, attack (Table 1, entries 1–3) with the result that alcohol **8** was the major product isolated. This unanticipated mode of reactivity led to allylmagnesium bromide being adopted as a surrogate nucleophile, with a view to effecting a formal oxidation of the allyl group to the coveted propargyl group at a later stage. Initial results with allylcopper nucleophiles also showed a proclivity for carbonyl attack

† Electronic supplementary information (ESI) available: general experimental information and procedures for the preparation of **6a**, **6b**, **17**, **18**, **21**, **28**, **36**, **32**, **40**, **42**. See http://www.rsc.org/suppdata/ob/b4/b407240e/

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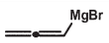
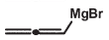
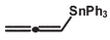
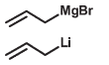
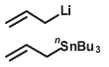
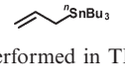
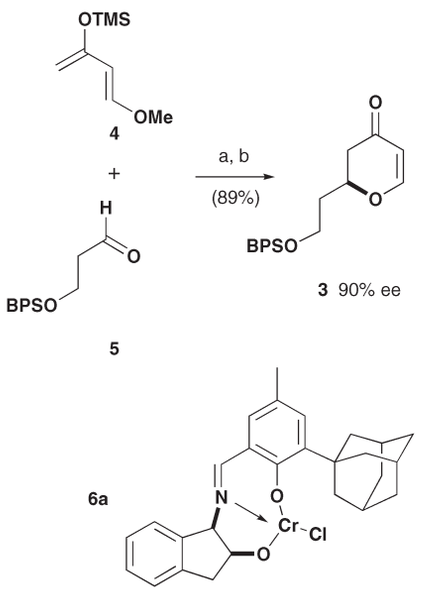
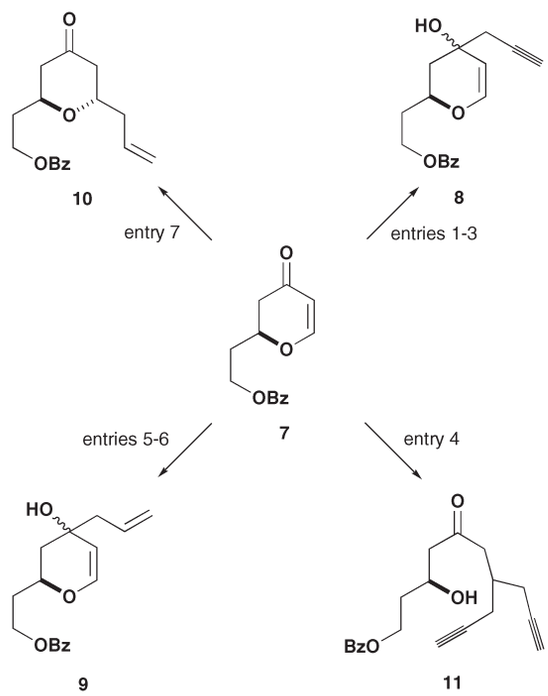
Table 1 Reactions of dihydropyrone **7** with allyl and allenyl metal reagents giving products **8**–**11** (see Scheme 2)

Entry	Nucleophile	Additives[a]	Temperature/°C	Yield (%)
1		CuI, TMSCl, DMPU	−78 → −50	94
2		CuBr·DMS (5 mol%), TMSCl, HMPA	−78 → −45	71
3		CuCl (5 mol%), $MnCl_4Li_2$	0	90
4		$TiCl_4$	0	51
5		CuI, DMPU, TMSCl	−78 → −45	16[b]
6		CuI, DMPU, TMSCl	−78	31[c]
7		TMSOTf	−78 → −50	86[d]

[a] Entries 1–3, 5 and 6 were performed in THF; entries 4 and 7 were performed in CH_2Cl_2. [b] The yield of alcohol **9** was 34% based on recovered dihydropyrone **7**. [c] The yield of alcohol **9** was 82% based on recovered dihydropyrone **7**. A small amount (4% based on recovered **7**) of tetrahydropyranone **10** was also isolated. [d] This yield referes to material isolated after treatment of the crude reaction mixture with TBAF (1 M THF)/AcOH.



Scheme 1 *Reagents and conditions*: a) **6a** (5 mol%), EtOAc, BaO; b) TFA, CH_2Cl_2.



Scheme 2 Reactions of dihydropyrone **7** with allyl and allenyl metal reagents (see Table 1).

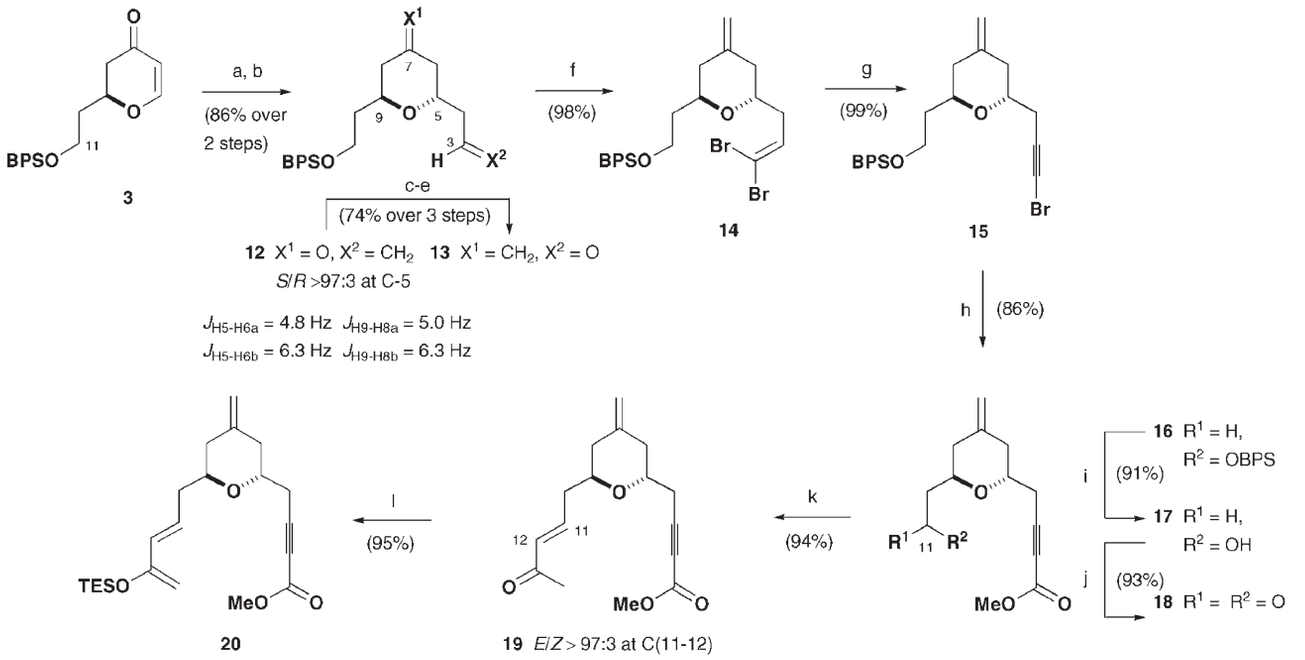
(Table 1, entries 5 and 6) and furnished alcohol **9** as the only product of any importance. The chemoselectivity displayed by these reactions was attributed to the ability of the ring oxygen atom to deactivate the enone moiety towards the single electron transfer (SET) processes which feature prominently in possible mechanisms for copper(I)-initiated Michael additions to α,β-unsaturated ketones.[18] The use of reaction conditions which failed to attenuate the excessive reactivity of allylic (and by possible analogy, allenyl/propargyl) copper(I)/cuprate reagents[19] may also have been at fault.

With these failures fresh in our minds, attention turned to a method more akin to the classical Sakurai–Hosomi method of conjugate addition.[20] Gratifyingly, the reaction of dihydropyrone **7** with allyl tributylstannane and TMSOTf, followed by treatment with TBAF (1 M THF)–AcOH (10 : 1, v/v) exclusively led to the formation of tetrahydropyranone **10** (entry 7). The trapping of the initially-formed adduct as the TMS enol ether was noteworthy as related experiments with a titanium enolate intermediate (albeit in the propargyl series) suffered from the elimination of the tetrahydropyran oxygen atom leading to the formation of the double Michael addition product, β-hydroxy ketone **11**, as the major product (entry 4).[16]

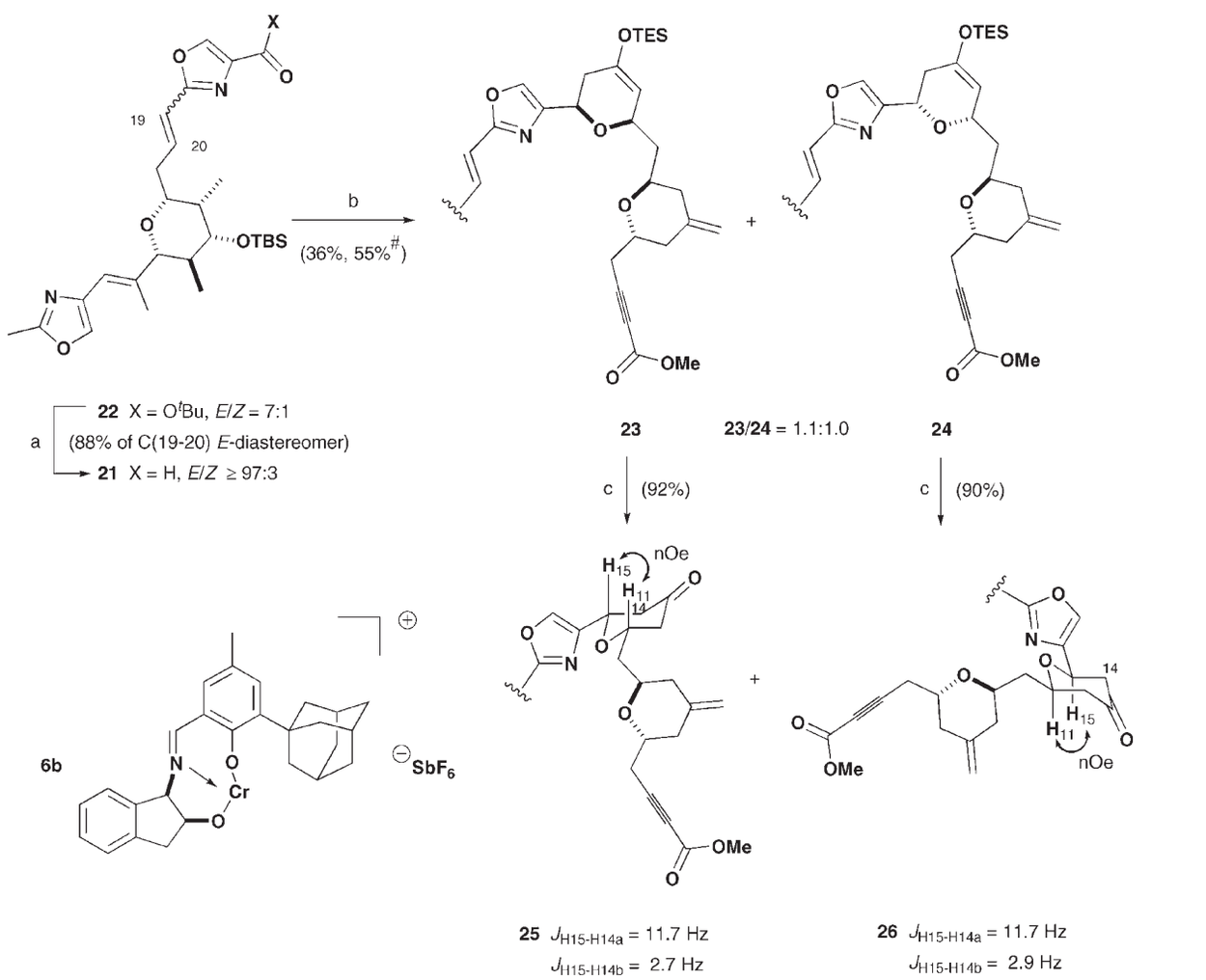
The transition to the series with *tert*-butyldiphenylsilyl (BPS) protection at C-11 proceeded without incident, allowing the gram-scale synthesis of the desired allyl adduct **12** (Scheme 3). That the desired *trans* stereochemistry at C-5 and C-9 had been installed was established *via* the extraction of the medium vicinal coupling constants shown. With a sound route to a basic C(5–9) tetrahydropyranone matrix now available, reliable methods were used for the elaboration of **12**. Thus the dihydroxylation of the terminal olefin, Wittig methylenation of the C-7 olefin and oxidative diol cleavage yielded aldehyde **13** in 74% yield over the three steps. The two-carbon homologation of aldehyde **13** was conveniently performed by subjecting the corresponding geminal dibromide **14** to the Grandjean *et al.* modification[21] of the Corey–Fuchs reaction. In this way, the dehydrobromination of **14** with NaHMDS gave alkynyl bromide **15**, whose C-2-lithiate was subsequently quenched with methyl chloroformate so as to afford methyl ynoate **16** in 86% yield. The elaboration of the C-11 terminus of **16** was now required. Thus the discharge of the BPS ether with HF·py was followed by the oxidation of the resulting alcohol **17** to aldehyde **18** and its two-carbon homologation to enone **19** using a $Ba(OH)_2{\cdot}xH_2O$-promoted Horner–Wadsworth–Emmons (HWE) reaction.[22] The derivatisation of the methyl ketone of **19** to the corresponding TES enol ether **20** proceeded in 95% yield.[23]

Jacobsen HDA coupling studies

The aldehyde heterodienophile **21** which was to be coupled with the C(1–14) domain was prepared by the DIBAl-H reduction of the corresponding *tert*-butyl ester **22**[11a] (Scheme 4). That minimal overreduction was observed was explained by the ability of the oxazole ester moiety to act as a Weinreb amide surrogate.



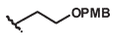
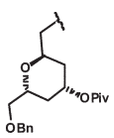
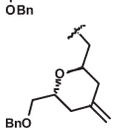
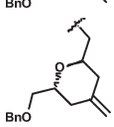
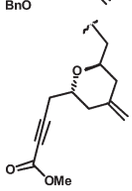
Scheme 3 *Reagents and conditions*: a) $H_2C{=}CHCH_2SnBu_3$, TMSOTf, CH_2Cl_2, −78 → −50 °C; b) TBAF (1 M THF)–AcOH (10 : 1, v/v), THF, 0 °C; c) OsO_4 (4 mol%), NMO, ^{t}BuOH–THF–H_2O (4 : 4 : 1); d) $Ph_3P{=}CH_2$, THF, −40 → −20 °C; e) $Pb(OAc)_4$, Na_2CO_3, CH_2Cl_2, 0 °C → RT; f) CBr_4, Ph_3P, CH_2Cl_2, −10 °C; g) NaHMDS, THF, −98 °C; h) (i) ^{n}BuLi, THF, −78 °C, (ii) MeOC(O)Cl, HMPA; i) HF·py, MeCN, 0 °C; j) DMP, CH_2Cl_2; k) $MeC(O)CH_2P(O)(OMe)_2$, $Ba(OH)_2{\cdot}xH_2O$, THF; l) TESOTf, Et_3N, Et_2O, 0 °C.



Scheme 4 *Reagents and conditions*: a) (i) DIBAl-H, CH_2Cl_2, −78 °C, (ii) chromatographic removal of C(19–20) *Z*-diastereomer; b) **20**, **6b** (10 mol%), 4 Å molecular sieves, acetone; c) TBAF–AcOH (1 : 2, mol/mol), THF, 0 °C. # = Yield based on recovered **20**.

In line with our previous studies, the construction of the C(11–15) ring of the phorboxazole skeleton using the Jacobsen HDA reaction between diene **20** and aldehyde **21** was targeted. The lower reactivity of our diene coupling partner, when compared to Danishefsky's diene, necessitated the use of the more reactive hexafluoroantimonate catalyst **6b**,[11b,14a] as

Table 2 Hetero-Diels–Alder reactions between 2-silyloxydienes and oxazole-containing aldehydes using catalyst **6b** (see Scheme 5)

Heterodienophile	R^2	Percentage yield (based on recovered diene)	dr [ee (%)][a]
		46 (95)	>97:3[b] [81]
		42 (95)	3.2:1.0
		41 (87)	1.5:1.0[b]
21		44 (90)	1.5:1.0
21		36 (55)	1.1:1.0

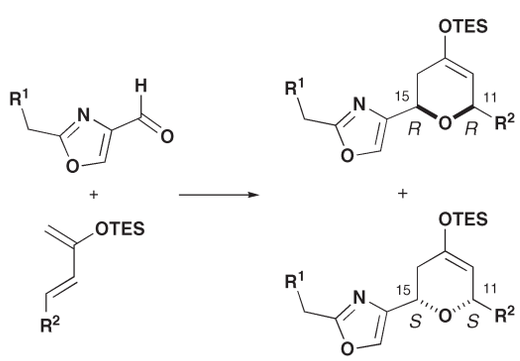
[a] The (11*R*,15*R*) stereoisomer predominated over the (11*S*,15*S*) stereoisomer in each case. [b] These diastereo- and enantio-selectivities refer to the tetrahydropyranone products resulting from silyl enol ether hydrolysis.

opposed to the chloride catalyst **6a** used previously in Scheme 1. A brief optimisation of the reaction allowed two diastereomeric silyloxydihydropyran products, **23** and **24**, to be isolated in a combined 36% yield and as a 1.1:1.0 mixture. Silyl enol ether hydrolysis afforded tetrahydropyranones **25** and **26**, whose *endo* topology was ascertained from the detection of NOE contacts at H-11/H-15. The comparison of their ^{1}H NMR data for H-10a/b with those of structurally-related compounds[11b] allowed the tentative assignment of the absolute configurations at C-11 and C-15 in **25** and **26**. The use of the enantiomeric catalyst failed to noticeably change the diastereomeric ratio (**25**/**26** = 1.0:1.3), indicating that a mismatched case of double diastereodifferentiation was unlikely to be in operation. Instead, it seemed likely that an indeterminate Lewis acid was promoting the reaction through a manifold in which any chiral information was not being effectively relayed to the transition state.

These results, when taken together with our earlier studies,[11b] indicate a pronounced fall off in the diastereoselectivity of the Jacobsen HDA reaction as more and more of the native phorboxazole functionality was built into the C-11 substituent of the diene coupling partner, as in the general transformation shown in Scheme 5. This is best exemplified by a comparison of the stereoselectivities for a series of examples, as tabulated in Table 2, which provide a sense of the terrain in which our investigations have been conducted. The modest conversions observed in these Jacobsen HDA reactions pointed to the apparent inhibition of the catalytic cycle by either one of the substrates and/or the silyloxydihydropyran product. A possible source of this inhibition may have been competitive ligation between the oxazole nitrogen atoms and the ligand heteroatoms for the chromium(III) atom of the catalyst.[24]

Synthesis of a C(1–32) macrocyclic domain

Despite its limitations in terms of yield and diastereoselectivity, the convergency of our stratagem allowed the manipulation of **25** to produce a macrocyclic fragment. In order to do this, the issue of installing the C-13 stereogenic centre was addressed. Given the epimeric nature of **1** and **2** at this position, a diastereomerically clean reduction at this stage was of more importance than the absolute stereochemistry realised (Scheme 6). The



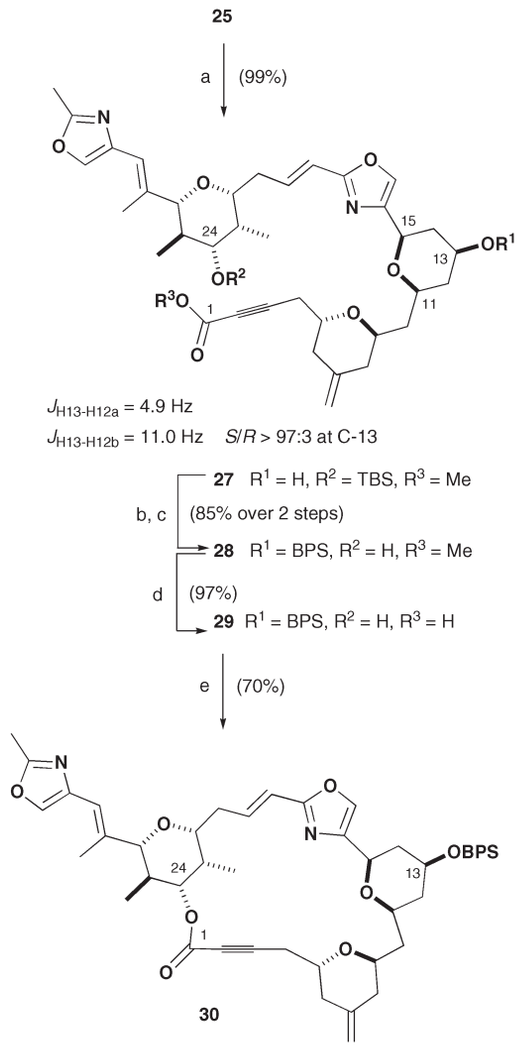
Scheme 5 *Reagents and conditions*: **6b**, 4 Å molecular sieves, acetone (see Table 2).

$LiAl(O^tBu)_3H$ reduction of the newly-fashioned tetrahydropyranone ring of **25** gave alcohol **27** with the C-13 configuration of phorboxazole B. This stereochemical assignment rested securely on the detection of NOE contacts at H-13/H-11 and H-13/H-15, and the extraction of an axial–axial $J_{H13–H12b}$ value and an axial–equatorial $J_{H13–H12a}$ value from the ^{1}H NMR signal for H-13, which implied axial hydride delivery so as to give an equatorial alcohol.[25,26]

In order to permit the differential manipulation of the oxygenated functionality at C-13 and C-24, the C-13 hydroxyl group was protected as its BPS ether. This was treated in its crude form with methanolic HCl so as to afford alcohol **28** (85% over two steps from **27**). The saponification of the methyl ester of **28** at C-1 to give carboxylic acid **29** was accomplished, with the removal of a minimal amount of the C-13 BPS ether, using LiOH in THF/water. The completion of the C(1–32) macrolactone ring of **30** was achieved, as with the Evans synthesis,[5] using a room temperature Yamaguchi macrolactonisation reaction.[27,28]

Synthesis of a C(33–38) fragment

Contemporaneous to these attempts to establish a convergent entry into the macrolactone ring was our work directed towards a synthesis of the corresponding C(33–46) fragment of the phorboxazoles. Our approach was reliant on the preparation and union of suitable C(33–38) and C(39–46) fragments

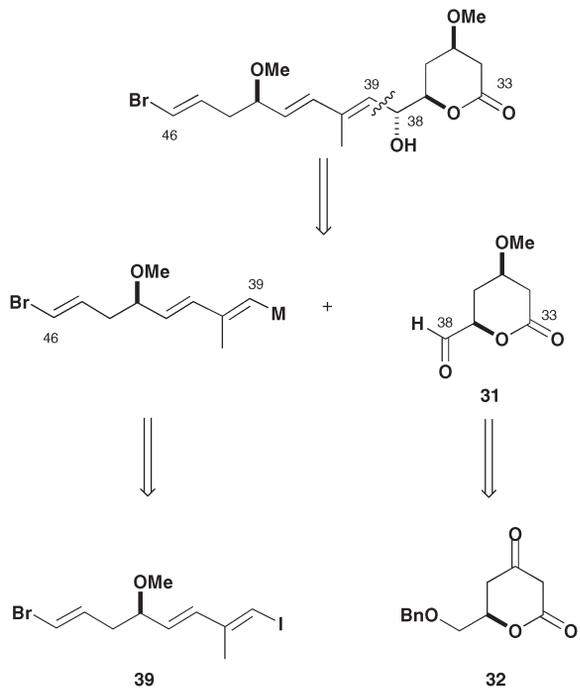


Scheme 6 *Reagents and conditions*: a) $LiAl(O^tBu)_3H$, THF, −78 → −10 °C; b) BPSCl, ImH, DMF; c) conc. HCl (1%), MeOH; d) $LiOH{\cdot}H_2O$, THF, H_2O; e) (i) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, (ii) DMAP, PhMe.

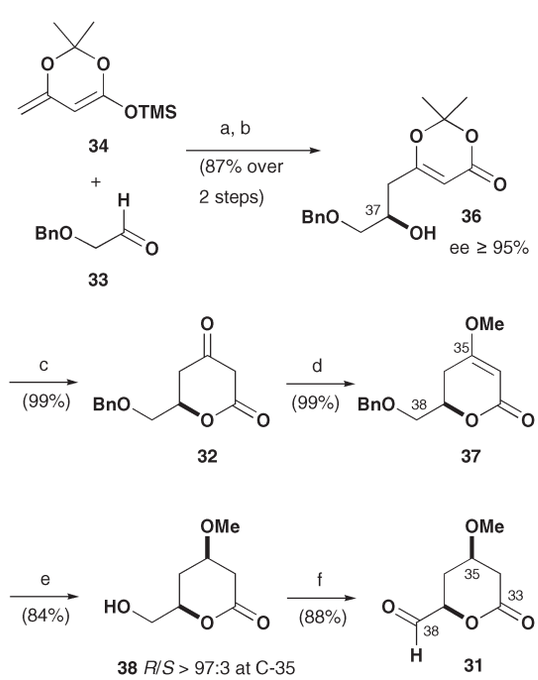
(Scheme 7). The former, as exemplified by aldehyde **31**, was envisaged as being accessible from ketolactone **32**.

As with, though independent of, the work of the Evans group,[5,29] we were keen to exploit their copper(II)-pybox-catalysed Mukaiyama aldol coupling studies for the enantioselective installation of the C-37 stereogenic centre. In our case (Scheme 8), this involved a Mukaiyama aldol reaction between (benzyloxy)acetaldehyde **33** and dienolate **34** which was catalysed by [Cu((*R*,*R*)-Ph-pybox)]$(SbF_6)_2$ (**35**). This provided multigram quantities of alcohol **36** (≥95% ee according to Kakisawa–Mosher analysis[30]). Its base-promoted cyclisation, using the protocol of Sato *et al.*,[31] formed ketolactone **32** in almost quantitative yield. The installation of the C-35 stereogenic centre was readily accomplished in a highly diastereoselective fashion (*R*/*S* > 97 : 3 at C-35) by hydrogenating **37**, the corresponding methyl enol ether of **32**. This step also served to unmask the C-38 hydroxyl group so as to give alcohol **38**, which was subsequently oxidised to the fragile aldehyde **31**, in anticipation for our C(38–39) coupling studies.

With regard to a C(39–46) fragment with which aldehyde **31** could be coupled, we were drawn to the possibilities offered by triene **39** (Scheme 7) with its native C-43 methoxy group and terminal *E*-vinyl bromide in place. Triene **39** also featured in the Evans synthesis where it was obtained from *R*-trityl glycidol.[5b] Our phorboxazole retrosynthetic search, by contrast, was coloured by a desire to avoid the chiral pool, and led us to investigate the possibility of subjecting dienal **40** to an asymmetric acetate-type aldol reaction.

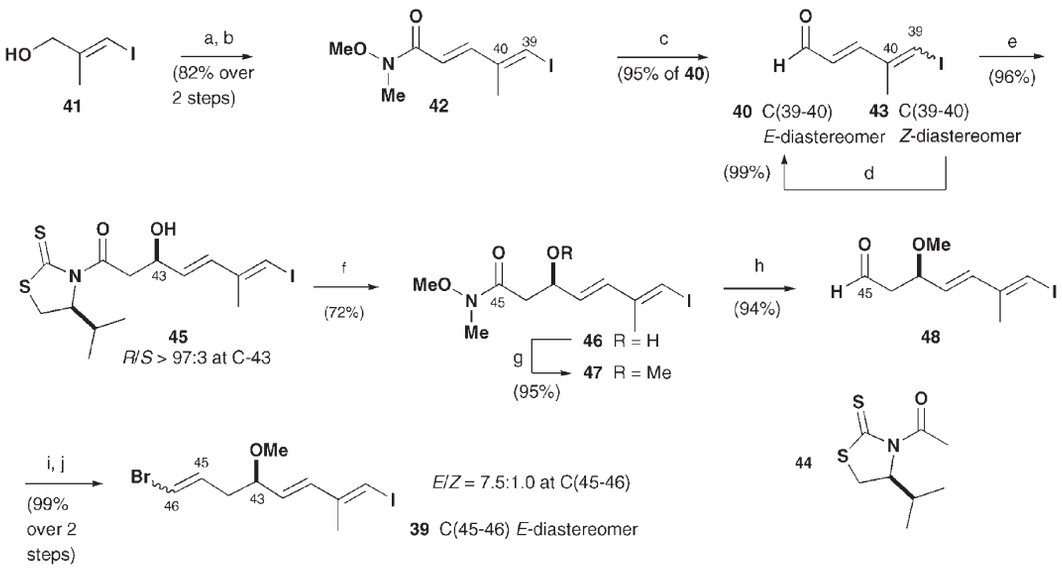


Scheme 7 Retrosynthetic analysis of C(33–46) fragment.



Scheme 8 *Reagents and conditions*: a) [Cu((*R*,*R*)-Ph-pybox)]-$(SbF_6)_2$ **35** (8 mol%), CH_2Cl_2, −98 °C → −78 °C; b) PPTs, MeOH; c) K_2CO_3, MeOH; d) $(MeO)_2SO_2$, K_2CO_3, acetone; e) H_2, Pd–C, EtOAc; f) Swern [O].

The synthesis of triene **39** was initiated by the MnO_2-mediated oxidation of the known alcohol **41**[32] and a Masamune–Roush-type HWE homologation (Scheme 9).[33] The DIBAl-H reduction of **42**, the Weinreb amide product of this sequence, ineluctably gave the desired aldehyde **40** together with small but variable amounts of the corresponding C(39–40) *Z*-diastereomer **43**. An iodine-mediated isomerisation step was sufficient to convert **43** to **40**, increasing the efficiency of the transformation. An auxiliary which is known to promote the diastereocontrolled aldol reaction between itself and α,β-unsaturated aldehydes is the 4(*S*)-isopropyl-1,3-thiazolidine-2-thione [4(*S*)-IPTT] of the groups of Nagao and Fujita.[34] The use of the tin(II) enolate of *N*-acetyl-4(*S*)-IPTT **44** resulted in the virtually exclusive formation of the desired diastereomer **45**. The use of the titanium(IV)

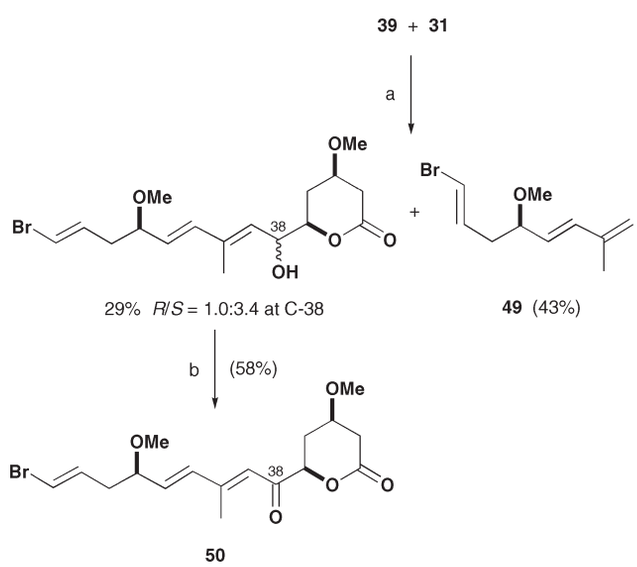


Scheme 9 *Reagents and conditions*: a) MnO_2, CH_2Cl_2; b) MeON(Me)C(O)CH_2P(O)$(OEt)_2$, LiCl, DBU, MeCN–CH_2Cl_2 (3 : 1); c) DIBAl-H, THF, −78 °C; d) I_2, CH_2Cl_2; e) (i) **44**, $Sn(OTf)_2$, *N*-ethylpiperidine, CH_2Cl_2, −40 °C, (ii) **40**, −98 → −78 °C; f) MeNHOMe·HCl, ImH, CH_2Cl_2; g) MeI, Ag_2O, Et_2O, reflux; h) DIBAl-H, THF, −78 °C; i) $^nBu_3SnCHI_2$, $CrCl_2$, DMF; j) NBS, MeCN, 0 °C.

enolate, by contrast, as recommended by Urpí, Vilarrasa and co-workers,[35] proved less diastereoselective [**45** : (*epi*-C-43)-**45** = 5.5 : 1.0]. The manipulation of aldol adduct **45** involved the initial conversion to Weinreb amide **46**. A subsequent *O*-methylation at C-43 so as to give methyl ether **47** was followed by a DIBAl-H reduction. This sequence furnished aldehyde **48** in 64% yield over the three steps from **45**. The conversion of aldehyde **48** to the corresponding *E*-vinyl bromide **39** was conveniently achieved *via* the corresponding vinyl stannane, using the Hodgson variant[36] of the Takai–Utimoto reaction.[37] A comparison of the optical rotation of this material with that of the Evans group verified that the correct C-43 stereochemistry had been installed, as expected, during the Nagao–Fujita aldol reaction.

Synthesis of the C(33–46) domain

With quantities of both vinyl iodide **39** and aldehyde **31** available, the stage was set for examining their union. An analysis of the functionality present in the coupling partners made the choice of chemoselective coupling conditions a prerequisite. The vinyl iodide of **39** was to be functionalised whilst leaving the vinyl bromide moiety intact, and the resulting vinylmetal species reacted with the C-38 aldehyde functionality of **31** in the presence of the C-33 lactone. There was also a need to minimise any elimination of the base-sensitive methoxy groups at C-35 and C-43. Attention quickly turned to the Nozaki–Kishi reaction.[38] A rapid survey of possible reaction conditions, which included varying the solvent composition, the relative stoichiometry of **31** and **39**, and the amounts and ratio of $CrCl_2$/$NiCl_2$ used was briefly performed. 4-*tert*-Butylpyridine was used as an additive on occasions, in line with the recommendations of Kishi and co-workers.[39] Whilst the yields for this process were modest (≤29%, Scheme 10) and dependent on the reaction conditions, the diastereoselectivity consistently showed a modest preference for the undesired C-38 epimer (*R*/*S* ≈ 1 : 3 at C-38).[40] The formation of a significant quantity (*ca.* 40%) of **49**, the desiodo analogue of vinyl iodide **39**, would indicate that an oxidative insertion into the C–I bond of **39** had taken place, despite its steric encumbrance, but that the resulting vinylchromium(III) nucleophile had been quenched prior to the coupling. Since the allyl alcohol products of the reaction were inseparable at this stage, and with a view to correcting the C-38 stereochemistry in the future *via* a diastereoselective ketone reduction protocol, the mixture was oxidised to the corresponding ketone **50** using the Griffith–Ley protocol.[41]



Scheme 10 *Reagents and conditions*: a) $NiCl_2$–$CrCl_2$ (10 : 1), $^tBuC_5H_4N$, THF; b) TPAP, 4 Å molecular sieves, CH_2Cl_2.

Outlook

Whilst the viability of the implied retrosynthetic dissection in Fig. 1 remains to be demonstrated if our synthetic studies of phorboxazole B are to reach a successful conclusion, the synthesis of **30** and **50**, our most advanced fragments to date, have made the venture a rewarding one thus far. Compounds **30** and **50** have been synthesised in 19 linear steps (4.0% from dihydropyrone **3**) and 11 linear steps (7.1% from allylic alcohol **41**) respectively. Their successful elaboration and union are presently under study and may allow one of the phorboxazoles to be procured *via* a longest linear sequence which is comparable to, or better than, those reported to date.[5,6]

Experimental

Dihydropyrone 3

A mixture of Jacobsen Schiff base chloride catalyst **6a**[14c] (7.6 mg, 16 μmol), BaO (63 mg, dried overnight at 150 °C and at 1 mm Hg prior to use) and dry EtOAc (100 μL) were pre-stirred (60 min) at RT and in the absence of light. Aldehyde **5** (117 mg, 0.374 mmol) in dry EtOAc (200 μL, including washings) was

subsequently added prior to cooling to 0 °C. Some of the extra EtOAc was removed *in vacuo* over 10 min, so as to return the solvent volume to *ca.* 0.2 mL, before Danishefsky's diene **4** (60.7 μL, 0.312 mmol) was added. Once the reaction mixture had been stirred at 0 °C and in the dark for 24 h, CH_2Cl_2 (1.0 mL) and then TFA (1 pipette drop) were added. A period of warming to RT over 10 min was followed by the washing of the reaction mixture through a short pad of silica gel atop a short pad of Celite® with copious Et_2O, before the combined filtrates were concentrated *in vacuo*. The purification of the residue by flash column chromatography on silica gel (light petroleum–EtOAc–MeOH gradient, 80 : 10 : 1 → 40 : 10 : 1) gave recovered aldehyde **5** (30.1 mg), dihydropyrone **3** (106 mg, 89%) as a yellow oil and then a small amount of 4-methoxy-3-but-(*E*)-en-2-one. The following data pertain solely to dihydropyrone **3** whose enantiomeric ratio was 95.1 : 4.9 according to chiral HPLC analysis [light petroleum–^{i}PrOH (249 : 1); R_t = 26 min (**3**: 95.1%), R_t = 28 min (*ent*-**3**: 4.9%); detection at λ = 250 nm]. R_f 0.21 (light petroleum–EtOAc, 3 : 1); $[\alpha]_D^{20}$ −55 (*c* = 0.44, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2930 (s), 1681 (s, C=O), 1596 (s, C=C), 1273 (m), 1111 (s), 702 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.65 (4H, d, *J* = 7.8 Hz, ArH), 7.46–7.37 (6H, m, ArH), 7.29 (1H, d, *J* = 5.9, H-5), 5.40 (1H, d, *J* = 5.9, H-6), 4.68 (1H, dddd, *J* = 12.5, 8.5, 4.4, 4.4, H-9), 3.86 (1H, ddd, *J* = 10.6, 4.7, 4.7, H-11a), 3.78 (1H, ddd, *J* = 10.6, 5.4, 5.4, H-11b), 2.54 (1H, dd, *J* = 16.8, 12.5, H-8a), 2.46 (1H, dd, *J* = 16.8, 4.4, H-8b), 2.06–1.98 (1H, m, H-10a), 1.92–1.84 (1H, m, H-10b) 1.05 [9H, s, $SiC(CH_3)_3$]; ^{13}C NMR (62.9 MHz, $CDCl_3$) δ_C 192.5, 163.0, 135.5 (2C), 133.5 (2C), 129.7 (2C), 127.7 (2C), 107.1, 76.5, 59.2, 42.0, 37.2, 26.8, 19.2; HRMS (+ESI) calc. for $C_{23}H_{28}O_3SiNa$ (MNa^+) 403.1705, found 403.1715.

Tetrahydropyranone 12

To a cold (−78 °C), stirred solution of dihydropyrone **3** (1.76 g, 4.61 mmol) in dry CH_2Cl_2 (20 mL) was added neat TMSOTf (0.919 mL, 5.08 mmol) over 2 min. After a further 5 min, neat allyl tributylstannane (3.15 mL, 10.2 mmol) was added over 5 min. After 2 h at −78 °C, the orange solution was allowed to warm to −50 °C over a further 60 min. The quenching of the reaction with MeOH–pH 7 buffer solution (8 mL of 3 : 1) and rapid stirring for 5 min was followed by rapid warming to 0 °C, its dilution with pH 7 buffer solution (20 mL) and subsequent warming to RT. The partitioning of the reaction mixture between Et_2O (100 mL) and water (100 mL), and then brine (100 mL), was followed by drying ($MgSO_4$) and concentration *in vacuo* so as to give the crude trimethylsilyl enol ether intermediate. This was diluted with THF (30 mL) and cooled to 0 °C prior to the addition of TBAF (1 M in THF)–AcOH (10.14 mL of 10 : 1, v/v). A period of stirring without argon protection for 40 min was followed by the partitioning of the reaction mixture between Et_2O (200 mL) and water (200 mL), and then brine (200 mL). The organic phase was dried (Na_2SO_4) and concentrated *in vacuo* before being diluted with Et_2O (30 mL) and vigorously stirred with KF on Celite®[42] (7.14 g of 1 : 1, w/w). After 60 min the suspension was filtered, washing through with copious Et_2O and then EtOAc, before being concentrated *in vacuo*. Analysis by 500 MHz NMR revealed *S*/*R* > 97 : 3 at C-5. Flash column chromatography on silica gel (light petroleum–EtOAc, 20 : 1) furnished tetrahydropyranone **12** (1.68 g, 86%) as a colourless oil. R_f 0.59 (light petroleum–EtOAc, 10 : 1); $[\alpha]_D^{20}$ −14 (*c* = 5.3, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2931 (m), 2858 (m), 1720 (s, C=O), 1428 (m), 1112 (s), 823 (m), 739 (m), 703 (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.68–7.63 (4H, m, ArH), 7.45–7.35 (6H, m, ArH), 5.73 (1H, dddd, *J* = 17.1, 10.0, 7.0, 7.0 Hz, H-3), 5.10–5.03 (2H, m, H-2a & H-2b), 4.40 (1H, dddd, *J* = 8.8, 6.3, 5.0, 5.0, H-9), 4.00 (1H, dddd, *J* = 7.3, 7.3, 6.3, 4.8, H-5), 3.79 (1H, ddd, *J* = 10.5, 8.0, 5.5, H-11a), 3.69 (1H, ddd, *J* = 10.5, 6.3, 5.5, H-11b), 2.57 (1H, dd, *J* = 14.3, 5.0, H-8a), 2.46 (1H, dd, *J* = 14.3, 4.8, H-6a), 2.38–2.18 (4H, m, H-6b, H-8b, H-4a & H-4b), 1.86 (1H, dddd, *J* = 14.1, 8.8, 5.5, 5.5, H-10a), 1.68 (1H, dddd, 14.1, 8.0, 6.3, 5.0, H-10b), 1.04 [9H, s, $SiC(CH_3)_3$]; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 207.4, 135.5, 135.5, 133.6, 133.6, 133.4, 129.6, 129.6, 127.7, 127.6, 117.9, 71.4, 69.2, 59.9, 46.7, 46.3, 39.0, 36.8, 26.8, 19.1; HRMS (+ESI) calc. for $C_{26}H_{34}O_3SiNa$ (MNa^+) 445.2175, found 445.2190.

Aldehyde 13

To a solution of tetrahydropyranone **12** (7.79 g, 18.4 mmol) and NMO (2.59 g, 22.1 mmol) in ^{t}BuOH–THF–water (225 mL, 4 : 4 : 1) at RT was added OsO_4 in ^{t}BuOH (3.75 g of 5%, w/w, 0.74 mmol). A period of stirring for 24 h without argon protection was followed by the addition of $Na_2S_2O_3$ solution (100 mL) and stirring for 45 min, over which time the initial yellow colour of the reaction mixture darkened. The partitioning of the reaction mixture between CH_2Cl_2 (4 × 100 mL) and water (100 mL) was followed by the drying (Na_2SO_4) of the combined organic extracts and concentration *in vacuo*. This furnished a 1.0 : 1.0 mixture C-3 diol epimers (8.38 g) which was purified by flash column chromatography on silica gel (CH_2Cl_2–MeOH gradient, 100 : 1 → 20 : 1).

To a chilled (0 °C), stirred suspension of dry triphenylphosphonium bromide (53.4 g, 149 mmol) in dry THF (150 mL) was added PhLi in 70 : 30 cyclohexane–Et_2O (77.7 mL, 1.80 M, 140 mmol) *via* syringe pump (2 mL min^{-1}). Once 2 h had elapsed from the start of the addition, the almost homogeneous orange solution was cooled from 0 to −40 °C. A solution of the diol mixture (8.38 g, 18.4 mmol) in dry THF (46 mL, including washings) was subsequently added and the resulting mixture allowed to warm slowly to −20 °C over 3 h. The reaction mixture was subsequently quenched with pH 7 buffer solution (40 mL), rapidly warmed to RT, diluted with water (200 mL) and extracted with Et_2O–CH_2Cl_2 (4 × 200 mL of 10 : 1). The combined organic extracts were washed with brine (200 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography on silica gel, loading and eluting with Et_2O–CH_2Cl_2–light petroleum (3 : 1 : 1) gave a mixture of methylenated ketones (7.61 g) which were epimeric at C-3. To a chilled (0 °C) mixture of this material (7.61 g, 16.7 mmol) and Na_2CO_3 (3.91 g, 36.9 mmol) in dry CH_2Cl_2 (80 mL) was added $Pb(OAc)_4$ (8.99 g, 20.3 mmol) in a portionwise fashion over 5 min. After 30 min stirring at 0 °C, the flask was removed from the cooling bath. After a further 60 min, the reaction mixture was washed through a pad of Celite® with copious Et_2O. The filtrate was washed with water (2 × 100 mL), and then brine (100 mL), before being dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography on silica gel (light petroleum–EtOAc, 15 : 1 and then 7 : 1) gave aldehyde **13** (5.73 g, 74% from tetrahydropyranone **12**) as a colourless oil. R_f 0.32 (light petroleum–EtOAc, 5 : 1); $[\alpha]_D^{20}$ −25 (*c* = 0.21, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3072 (w), 2932 (m), 2857 (m), 1726 (s, C=O), 1428 (m), 1111 (s), 1090 (s), 739 (m), 702 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.66 (1H, dd, *J* = 2.5, 1.8 Hz, H-3), 7.67–7.64 (4H, m, ArH), 7.44–7.35 (6H, m, ArH), 4.79–4.78 (2H, m, H-51a & H-51b), 4.21 (1H, dddd, *J* = 7.8, 7.5, 5.5, 4.0, H-5), 4.06 (1H, dddd, *J* = 8.5, 5.3, 5.0, 4.8, H-9), 3.75 (1H, ddd, *J* = 10.3, 7.8, 5.8, H-11a), 3.67 (1H, ddd, *J* = 10.3, 6.5, 5.8, H-11b), 2.63 (1H, ddd, *J* = 16.3, 7.8, 2.5, H-4a), 2.44 (1H, ddd, *J* = 16.3, 5.5, 1.8, H-4b), 2.38 (1H, dddd, *J* = 13.3, 4.8, 1.3, 1.3, H-8a), 2.36 (1H, dd, *J* = 13.3, 4.0, H-6a), 2.04–1.99 (2H, m, H-6b & H-8b), 1.88 (1H, dddd, *J* = 14.1, 8.5, 5.8, 5.8, H-10a), 1.65 (1H, dddd, *J* = 14.1, 7.8, 6.5, 5.3, H-10b), 1.04 [9H, s, $SiC(CH_3)_3$]; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 200.9, 141.1, 135.6 (2C), 133.9 (2C), 129.6 (2C), 127.6 (2C), 111.1, 69.7, 67.2, 60.4, 47.6, 39.6, 39.2, 35.6, 26.9, 19.2; HRMS (+ESI) calc. for $C_{26}H_{34}O_3SiNa$ (MNa^+) 445.2175, found 445.2179.

Geminal dibromide 14

To a chilled (−10 °C), stirred solution of CBr_4 (16.2 g, 48.8 mmol) in dry CH_2Cl_2 (20 mL) was added a pre-chilled (−10 °C) solution of Ph_3P (25.6 g, 97.4 mmol) in dry CH_2Cl_2 (35 mL, including

washings) over 20 min. After a further 10 min, a pre-chilled (−10 °C) solution of aldehyde **13** (5.15 g, 12.2 mmol) in dry CH_2Cl_2 (25 mL, including washings) was added to the now orange solution. The reaction was quenched after 30 min with $NaHCO_3$ solution (50 mL) before being rapidly warmed to RT and washed through a Celite® pad with copious Et_2O. The phases of the filtrate were separated and the organic phase washed with water (150 mL) and then brine (150 mL) before being dried (Na_2SO_4). Flash column chromatography on silica gel (light petroleum–EtOAc gradient, light petroleum → 10 : 1) after dry-loading onto silica gel, gave geminal dibromide **14** (6.91 g, 98%) as a colourless oil. R_f 0.37 (light petroleum–EtOAc, 10 : 1); $[\alpha]_D^{20}$ −35 (c = 2.1, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2932 (m), 2857 (m), 1472 (w), 1428 (m), 1111 (s), 892 (w), 823 (m), 787 (w), 740 (m), 702 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.68 (2H, dd, J = 5.4, 1.6 Hz, ArH), 7.66 (2H, dd, J = 5.4, 1.9, ArH), 7.44–7.35 (6H, m, ArH), 6.39 (1H, dd, J = 7.5, 6.4, H-3), 4.78 (1H, m, H-51a), 4.77 (1H, m, H-51b), 4.02 (1H, dddd, J = 9.8, 5.4, 5.1, 4.9, H-9), 3.80–3.65 (3H, m, H-11a, H-11b & H-5), 2.38–2.29 (3H, m, H-4a, H-6a & H-8a), 2.19 (1H, ddd, J = 15.3, 7.5, 5.4, H-4b), 2.02–1.96 (2H, m, H-6b & H-8b), 1.86 (1H, dddd, J = 14.0, 8.4, 6.1, 5.4, H-10a), 1.62 (1H, dddd, J = 14.0, 7.7, 6.8, 5.1, H-10b), 1.05 [9H, s, $SiC(CH_3)_3$]; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 141.5, 135.6, 135.6, 135.1, 133.9, 133.8, 129.6 (2C), 127.6, 127.6, 110.8, 89.8, 70.1, 69.4, 60.5, 39.4, 39.3, 37.2, 35.9, 26.9, 19.2; HRMS (+ESI) calc. for $C_{27}H_{34}Br_2O_2SiNa$ (MNa^+) 601.0597, found 601.0602.

Alkynyl bromide 15

To a cold (−98 °C), stirred solution of geminal dibromide **14** (6.80 g, 11.8 mmol) in dry THF (117 mL) was added NaHMDS in THF (13.0 mL of 1.00 M, 13.0 mmol) dropwise over 3 min to leave a yellow solution. After stirring for a further 60 min, the reaction was quenched with AcOH in THF (20 mL in 1 : 9, v/v), before being rapidly warmed to RT. Its partitioning between Et_2O (3 × 200 mL) and pH 7 buffer solution (100 mL) was followed by the drying ($MgSO_4$) of the organic phase and concentration *in vacuo*. Flash column chromatography on silica gel (light petroleum and then light petroleum–EtOAc, 20 : 1) gave alkynyl bromide **15** as a colourless oil (5.79 g, 99%). R_f 0.47 (light petroleum–EtOAc, 7 : 1); $[\alpha]_D^{20}$ −16 (c = 14, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3071 (w, =C–H), 2932 (w), 2857 (w), 1428 (m), 1106 (s), 1085 (s), 823 (m), 738 (m), 700 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.71–7.69 (4H, m, ArH), 7.44–7.38 (6H, m, ArH), 4.83 (1H, m, H-51a), 4.80 (1H, m, H-51b), 4.04 (1H, dddd, J = 10.1, 5.8, 5.8, 5.4 Hz, H-9), 3.84–3.70 (3H, m, H-11a, H-11b & H-5), 2.41–2.37 (4H, m, H-4a, H-4b, H-6a & H-8a), 2.12 (1H, dd, J = 13.2, 6.8, H-6b), 2.01 (1H, dd, J = 13.2, 5.8, H-8b), 1.91 (1H, dddd, J = 14.3, 8.7, 5.8, 5.8, H-10a), 1.66 (1H, dddd, J = 14.3, 7.3, 7.3, 5.4, H-10b), 1.08 [9H, s, $SiC(CH_3)_3$]; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 141.3, 135.6, 135.5, 133.9, 133.8, 129.5, 129.5, 127.6, 127.6, 110.9, 76.7, 70.0, 69.7, 60.5, 39.7, 39.2, 38.6, 35.8, 26.9, 24.8, 19.2; HRMS (+ESI) calc. for $C_{27}H_{33}BrO_2SiNa$ (MNa^+) 519.1331, found 519.1325.

Methyl ester 16

To a cold (−78 °C), stirred solution of alkynyl bromide **15** (5.85 g, 10.1 mmol) in dry THF (100 mL) was added ^{n}BuLi in hexanes (7.87 mL of 1.54 M, 12.1 mmol) in a dropwise fashion. After 30 min, methyl chloroformate (2.34 mL, 30.3 mL) and then HMPA (5.27 mL, 30.3 mmol) were added to the pale yellow solution of the lithium acetylide. A period of vigorous stirring for a further 30 min was followed by careful quenching with AcOH in THF (2 mL of 1 : 9, v/v). After rapid warming to RT, the reaction mixture was partitioned between Et_2O (3 × 200 mL) and pH 7 buffer solution (100 mL). The combined organic fractions were subsequently washed with brine (200 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography on silica gel (light petroleum–EtOAc gradient, light petroleum → 10 : 1) gave methyl ester **16** (4.82 g, 86%) as a colourless oil. R_f 0.30 (light petroleum–EtOAc, 6 : 1); $[\alpha]_D^{20}$ −23 (c = 0.67, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2947 (m), 1717 (s, C=O), 1428 (m), 1256 (s), 1112 (s), 1082 (s), 740 (m), 703 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.68 (2H, dd, J = 5.4, 1.6 Hz, ArH), 7.66 (2H, dd, J = 5.4, 1.9, ArH), 7.44–7.35 (6H, m, ArH), 4.78 (1H, m, H-51a), 4.77 (1H, m, H-51b), 4.02 (1H, dddd, J = 9.8, 5.4, 5.1, 4.9, H-9), 3.80–3.65 (3H, m, H-11a, H-11b & H-5), 3.72 (3H, s, CO_2CH_3), 2.38–2.29 (3H, m, H-4a, H-6a & H-8a), 2.19 (1H, ddd, J = 15.3, 7.5, 5.4, H-4b), 2.02–1.96 (2H, m, H-6b & H-8b), 1.86 (1H, dddd, J = 14.0, 8.4, 6.1, 5.4, H-10a), 1.62 (1H, dddd, J = 14.0, 7.7, 6.8, 5.1, H-10b), 1.05 [9H, s, $SiC(CH_3)_3$]; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 154.0, 140.8, 135.6, 135.6, 133.9, 133.8, 129.6, 129.6, 127.6 (2C), 111.3, 86.0, 74.5, 69.8, 69.7, 60.4, 52.5, 39.2, 38.6, 35.8, 26.9, 23.8, 19.2; HRMS (+ESI) calc. for $C_{29}H_{36}O_4SiNa$ (MNa^+) 499.2281, found 499.2271.

Enone 19

A sample of $Ba(OH)_2{\cdot}8H_2O$ (*ca.* 500 mg) was dried by heating at 140 °C (oil bath temperature) for 3 h at <1 mm Hg. Dimethyl (2-oxopropyl)phosphonate (416 mg, 2.51 mmol) in dry THF (20 mL) was added to an accurately-weighed sample of the dried $Ba(OH)_2{\cdot}xH_2O$ (215 mg, <1.25 mmol, glovebox), forming an emulsion. After vigorous stirring for 30 min, aldehyde **18** (493 mg, 2.09 mmol) in THF–water (41 mL of 40 : 1, including washings) was added. A period of stirring for 105 min was followed by the pouring of the reaction mixture into chilled (0 °C) NH_4Cl solution (20 mL), the separation of the phases and the back-extraction of the aqueous phase with Et_2O (2 × 30 mL). The combined organic fractions were washed with brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo*. An analysis of this material by 400 MHz ^{1}H NMR revealed a single C(11–12) alkene diastereomer (E/Z > 97 : 3). Flash column chromatography on silica gel (light petroleum–EtOAc gradient, 8 : 1 → 2 : 1) gave enone **19** (543 mg, 94%) as a colourless oil. R_f 0.24 (light petroleum–EtOAc, 2 : 1); $[\alpha]_D^{20}$ −59 (c = 3.6, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2949 (w), 2239 (w, C≡C), 1714 (s, C=O), 1674 (m), 1435 (w), 1255 (s), 1076 (m), 979 (w); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 6.79 (1H, ddd, J = 16.1, 7.3, 7.0 Hz, H-11), 6.11 (1H, d, J = 16.1, H-12), 4.86 (1H, m, H-51a), 4.85 (1H, m, H-51b), 4.05 (1H, dddd, J = 6.8, 6.8, 6.0, 4.5, H-5), 3.92 (1H, dddd, J = 7.0, 6.8, 6.0, 4.5, H-9), 3.75 (3H, s, CO_2CH_3), 2.62 (1H, dd, J = 17.2, 6.8, H-4a), 2.59–2.51 (1H, m, H-10a), 2.51 (1H, dd, J = 17.2, 6.8, H-4b), 2.45 (1H, dd, J = 13.6, 4.5, H-6a), 2.37 (1H, dd, J = 13.2, 4.5, H-8a), 2.33 (1H, ddd, J = 12.6, 7.3, 6.8, H-10b), 2.25 (3H, s, H-14), 2.13 (1H, dd, J = 13.6, 6.0, H-6b), 2.04 (1H, dd, J = 13.2, 6.0, H-8b); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 198.4, 153.9, 143.7, 139.9, 133.3, 112.0, 85.6, 74.4, 71.4, 70.1, 52.5, 39.0, 38.4, 36.5, 26.6, 23.4; HRMS (+ESI) calc. for $C_{16}H_{20}O_4Na$ (MNa^+) 299.1259, found 299.1270.

Silyl enol ether 20

To a chilled (0 °C), stirred solution of enone **19** (430 mg, 1.56 mmol) and Et_3N (0.651 mL, 4.67 mmol) in dry Et_2O (20 mL) was added TESOTf (0.528 mL, 2.33 mmol). After 60 min, the reaction mixture was washed through a short plug of deactivated, neutral alumina with copious Et_2O. The concentration of the filtrate *in vacuo* was followed by gravity column chromatography on deactivated, neutral alumina (Et_2O) so as to furnish silyl enol ether **20** (576 mg, 95%) as a colourless oil. R_f 0.63 (light petroleum–EtOAc, 3 : 1); $[\alpha]_D^{20}$ −28 (c = 2.0, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2954 (w), 2240 (w, C≡C), 1717 (s, C=O), 1251 (s), 1074 (s), 1017 (s), 965 (m), 749 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.94–5.92 (2H, m, H-12 & H-13), 4.86–4.84 (1H, m, H-51a), 4.82–4.81 (1H, m, H-51b), 4.26–4.25 (1H, m, H-14a), 4.23–4.22 (1H, m, H-14b), 4.07–4.01 (1H, m, H-5), 3.79 (1H, dddd, J = 10.8, 6.6, 6.4, 6.4, H-9), 3.76 (3H, s, CO_2CH_3), 2.62–2.51 (2H, m, H-4a & H-4b), 2.45 (1H, dd, J = 13.2, 4.2, H-6a), 2.42–2.32 (1H, m, H-8a), 2.36–2.27 (1H, m, H-10a), 2.29–2.20 (1H, m, H-8b), 2.17 (1H,

dd, J = 13.2, 6.3, H-6b), 2.03 (1H, dd, J = 13.4, 6.6, H-10b), 0.99 (9H, t, J = 7.8, $SiCH_2CH_3$), 0.71 (6H, q, J = 7.8, $SiCH_2CH_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 154.8, 154.0, 140.6, 130.3, 126.6, 111.6, 94.4, 85.9, 74.5, 72.4, 70.2, 52.6, 38.6, 38.3, 36.1, 23.6, 6.8, 4.9; HRMS (+ESI) calc. for $C_{22}H_{34}O_4SiNa$ (MNa^+) 413.2124, found 413.2134.

Silyloxydihydropyran 23

To a mixture of aldehyde **21** (78.0 mg, 0.156 mmol) and activated, crushed 4 Å molecular sieves (102 mg) was added Jacobsen Schiff base hexafluoroantimonate catalyst **6b**[14a] in dry acetone (100 μL of 0.156 M, 15.6 μmol). The vial was wrapped in aluminium foil and the mixture left to pre-stir at RT for 3 h. Silyl enol ether **20** (60.8 mg, 0.156 mmol) was then added in dry acetone (0.3 mL, including washings) and the solvent volume reduced to *ca.* 0.1 mL under a positive stream of argon. After being stirred for 40 h in the absence of light, the reaction mixture was washed through a cotton wool plug with copious Et_2O and concentrated *in vacuo*. Gravity column chromatography on deactivated, neutral alumina (light petroleum–EtOAc gradient, light petroleum → 2 : 1) gave residual silyl enol ether **20** (20.1 mg, 33%), a mixture of silyloxydihydropyrans **23**–**24** (50.1 mg, 36%, **23**–**24** = 1.1 : 1.0) and then residual aldehyde **21** (27.0 mg, 35%). After purification by HPLC [light petroleum–EtOAc (2.8 : 1.0); R_t = 20 min (**24**: 48.5%), R_t = 24 min (**23**: 51.5%); detection at λ = 254 nm], silyl enol ether **23** (26.2 mg, 19%) was isolated as a colourless oil. R_f 0.18 (light petroleum–EtOAc, 1 : 3); $[\alpha]_D^{20}$ +36 (c = 0.34, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2955 (s), 2929 (s), 2855 (m), 2241 (s, C≡C), 1717 (s, C=O), 1253 (s), 1075 (s), 835 (s), 749 (m); ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.49 (1H, s, H-30), 7.47 (1H, s, H-17), 6.66 (1H, ddd, J = 15.8, 8.5, 6.6, H-20), 6.32 (1H, d, J = 15.8, H-19), 6.18 (1H, s, H-28), 4.88 (1H, dd, J = 1.7, 1.7, H-12), 4.84–4.82 (1H, m, H-51a), 4.81–4.79 (1H, m, H-51b), 4.61 (1H, dd, J = 10.9, 3.2, H-15), 4.41 (1H, ddd, J = 7.3, 6.1, 1.7, H-11), 4.02 (1H, dddd, J = 6.8, 6.3, 6.1, 4.3, H-5), 4.01–3.97 (1H, m, H-9), 3.75 (3H, s, CO_2CH_3), 3.54 (1H, ddd, J = 7.9, 6.0, 1.9, H-22), 3.45 (1H, d, J = 10.1, H-26), 3.42 (1H, dd, J = 9.9, 5.7, H-24), 2.58–2.52 (1H, m, H-21a), 2.58–2.53 (1H, m, H-4a), 2.49–2.43 (4H, m, H-4b, H-6a, H-8a & H-14a), 2.44 (3H, s, H-32), 2.34–2.28 (1H, m, H-21b), 2.28 (1H, dd, J = 15.9, 3.2, H-14b), 2.13 (1H, dd, J = 12.9, 6.8, H-8b), 2.05 (1H, dd, J = 12.2, 6.1, H-6b), 2.01 (1H, ddd, J = 13.4, 7.3, 7.3, H-10a), 1.92 (3H, s, H-48), 1.79 (1H, qdd, J = 5.7, 5.7, 1.9, H-23), 1.73 (1H, ddq, J = 10.1, 9.9, 6.6, H-25), 1.58 (1H, ddd, J = 13.4, 7.3, 6.1, H-10b), 0.98 (9H, t, J = 8.0, $SiCH_2CH_3$), 0.98 (3H, d, J = 5.7, H-50), 0.91 [9H, s, $SiC(CH_3)_3$], 0.75 (3H, d, J = 6.6, H-49), 0.68 (6H, q, J = 8.0, $SiCH_2CH_3$), 0.06 [3H, s, $Si(CH_3)_aMe$], 0.05 [3H, s, $SiMe(CH_3)_b$]; ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 161.1, 160.6, 154.0, 148.4, 142.2, 140.6, 138.1, 137.8, 136.4, 135.5, 134.1, 118.6, 118.3, 111.6, 105.0, 88.8, 85.9, 77.4, 77.4, 74.5, 71.5, 69.9, 69.8, 69.7, 52.6, 39.4, 39.1, 39.1, 38.6, 36.4, 35.0, 34.8, 25.8, 23.8, 18.1, 14.3, 13.9, 13.8, 6.7, 5.9, 5.0, −4.1, −4.8; HRMS (+ESI) calc. for $C_{49}H_{74}N_2O_9Si_2Na$ (MNa^+) 913.4831, found 913.4815.

Tetrahydropyranone 25

To a chilled (0 °C) solution of silyloxydihydropyran **23** (26.2 mg, 29.4 μmol) in THF (2.5 mL) was added AcOH in THF (58.8 μL of 1.00 M, 58.8 μmol) and then TBAF in THF (29.4 μL of 1.00 M, 29.4 μmol). After stirring for 60 min, the reaction mixture was poured into water (10 mL) and extracted with CH_2Cl_2 (4 × 10 mL). The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The purification of the residue by silica gel PTLC (light petroleum–EtOAc, 2 : 3), gave tetrahydropyranone **25** (21.0 mg, 92%) as a colourless oil. R_f 0.47 (light petroleum–EtOAc, 2 : 3); $[\alpha]_D^{20}$ +23 (c = 0.12, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2928 (s), 2240 (w, C≡C), 1717 (s, C=O), 1257 (s), 1076 (s), 835 (m), 776 (m); ^1H NMR (700 MHz, $CDCl_3$) δ_H 7.51 (1H, s, H-17), 7.49 (1H, s, H-30), 6.69 (1H, ddd, J = 16.2, 8.3, 6.3, H-20), 6.32 (1H, d, J = 16.2, H-19), 6.18 (1H, s, H-28), 4.83–4.82 (1H, m, H-51a), 4.81–4.80 (1H, m, H-51b), 4.71 (1H, dd, J = 11.7, 2.7, H-15), 4.02 (1H, dddd, J = 6.7, 6.3, 6.1, 4.0, H-5), 3.99–3.93 (2H, m, H-9 & H-11), 3.75 (3H, s, CO_2CH_3), 3.54 (1H, ddd, J = 7.9, 5.0, 2.1, H-22), 3.44 (1H, d, J = 10.3, H-26), 3.43 (1H, dd, J = 9.9, 4.8, H-24), 2.79 (1H, dd, J = 14.8, 11.7, H-14a), 2.61 (1H, dd, J = 14.8, 2.7, H-14b), 2.60–2.53 (3H, m, H-4a, H-12a & H-21a), 2.45 (1H, dd, J = 17.1, 6.1, H-4b), 2.44 (3H, s, H-32), 2.42–2.36 (3H, m, H-6a, H-8a & H-12b), 2.31 (1H, ddd, J = 7.9, 6.3, 5.0, H-21b), 2.24 (1H, ddd, J = 14.3, 9.8, 5.1, H-10a), 2.17 (3H, s, H-48), 2.08 (1H, dd, J = 13.5, 6.7, H-6b), 2.02 (1H, dd, J = 13.3, 6.1, H-8b), 1.79 (1H, qdd, J = 6.9, 4.8, 2.1, H-23), 1.73 (1H, ddq, J = 10.3, 9.9, 6.4, H-25), 1.62 (1H, ddd, J = 14.3, 7.7, 4.3, H-10b), 0.98 (3H, d, J = 6.9, H-50), 0.91 [9H, s, $SiC(CH_3)_3$], 0.75 (3H, d, J = 6.4, H-49), 0.06 [3H, s, $Si(CH_3)_aMe$], 0.05 [3H, s, $SiMe(CH_3)_b$]; ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 205.7, 161.5, 160.6, 153.9, 140.8, 140.2, 138.1, 137.8, 137.1, 135.6, 134.5, 118.6, 118.0, 111.9, 88.8, 85.9, 74.4, 74.1, 71.6, 69.9, 68.8, 52.6, 46.9, 46.1, 39.3, 39.2, 39.2, 38.7, 36.5, 34.8, 25.8, 23.7, 18.1, 14.3, 13.9, 13.8, 5.9, −4.1, −4.8 (two signals missing due to coincidence); HRMS (+ESI) calc. for $C_{43}H_{60}N_2O_9SiNa$ (MNa^+) 799.3966, found 799.3976.

The data for tetrahydropyranone **26**, which was prepared using the analogous deprotection of silyl enol ether **24**, were as follows: R_f 0.51 (light petroleum–EtOAc, 2 : 3); $[\alpha]_D^{20}$ +29 (c = 2.0, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2928 (m), 2238 (w, C≡C), 1716 (s, C=O), 1256 (s), 1107 (m), 1075 (s), 1029 (m), 887 (m), 835 (m), 775 (m); ^1H NMR (700 MHz, $CDCl_3$) δ_H 7.56 (1H, s, H-17), 7.49 (1H, s, H-30), 6.69 (1H, ddd, J = 16.2, 7.2, 6.9 Hz, H-20), 6.33 (1H, d, J = 16.2, H-19), 6.17 (1H, s, H-28), 4.81–4.80 (1H, m, H-51a), 4.80–4.79 (1H, m, H-51b), 4.73 (1H, dd, J = 11.7, 2.9, H-15), 4.06–4.01 (3H, m, H-5, H-9 & H-11), 3.74 (3H, s, CO_2CH_3), 3.54 (1H, ddd, J = 7.9, 7.9, 5.6, H-22), 3.44 (1H, d, J = 10.3, H-26), 3.43 (1H, dd, J = 9.9, 4.8, H-24), 2.86 (1H, dd, J = 14.9, 11.7, H-14a), 2.70–2.63 (1H, m, H-12a), 2.67 (1H, dd, J = 17.2, 8.3, H-12b), 2.58–2.53 (1H, m, H-21a), 2.55 (1H, dd, J = 14.9, 2.9, H-14b), 2.46–2.42 (1H, m, H-6a), 2.45–2.36 (2H, m, H-4a & H-4b), 2.44 (3H, s, H-32), 2.34–2.28 (1H, m, H-21b), 2.30 (1H, dd, J = 13.5, 4.2, H-8a), 2.08 (1H, dd, J = 13.6, 5.1, H-6b), 1.97 (1H, dd, J = 13.5, 7.5, H-8b), 1.92 (3H, s, H-47), 1.80–1.76 (1H, m, H-10a), 1.79 (1H, qdd, J = 6.9, 5.6, 4.8, H-23), 1.74–1.71 (1H, m, H-10b), 1.73 (1H, ddq, J = 10.3, 9.9, 6.4, H-25), 0.98 (3H, d, J = 6.9, H-50), 0.91 [9H, s, $SiC(CH_3)_3$], 0.75 (3H, d, J = 6.4, H-49), 0.07 [3H, s, $Si(CH_3)_aMe$], 0.05 [3H, s, $SiMe(CH_3)_b$]; ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 206.0, 161.5, 160.6, 153.9, 140.8, 140.5, 138.1, 137.9, 136.9, 135.5, 134.7, 118.5, 118.1, 111.6, 88.9, 86.3, 77.5, 77.4, 74.1, 73.7, 71.4, 70.5, 68.2, 52.5, 48.0, 46.2, 40.5, 39.8, 39.3, 38.6, 36.4, 34.9, 25.8, 23.0, 18.1, 14.3, 13.9, 13.7, 5.9, −4.1, −4.8; HRMS (+ESI) calc. for $C_{43}H_{60}N_2O_9SiNa$ (MNa^+) 799.3966, found 799.3951.

Alcohol 27

To a cold (−78 °C), stirred solution of tetrahydropyranone **25** (14.0 mg, 18.0 μmol) in dry THF (0.60 mL) was added $LiAl(O^tBu)_3H$ in THF (0.180 mL of 1.00 M, 0.180 mmol). The warming of the reaction to −20 °C over 30 min was followed by its stirring at between −20 and −10 °C for a further 90 min. The careful addition of NH_4Cl solution (5.0 mL) was followed by rapid warming to RT and extraction with Et_2O–EtOAc (3 × 10 mL of 9 : 1). The combined extracts were washed with brine (25 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Analysis by 500 MHz ^1H NMR revealed an S/R ratio of >97 : 3 at C-13. Purification by silica gel PTLC (light petroleum–EtOAc, 4 : 1) gave alcohol **27** (13.9 mg, 99%) as a colourless oil. R_f 0.49 (EtOAc); $[\alpha]_D^{20}$ +17 (c = 0.85, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3377 (br, O–H), 2926 (m), 2240 (w, C≡C), 1715 (m, C=O), 1255 (s), 1075 (s), 1030 (m), 835 (m), 775 (m), 753 (m); ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.48 (1H, s, H-30), 7.44 (1H, s, H-17), 6.65 (1H, ddd, J = 15.9, 8.0, 6.0, H-20), 6.31 (1H, d, J = 15.9, H-19), 6.17 (1H, s, H-28), 4.81–4.78 (2H, m, H-51a & H-51b), 4.40 (1H, dd, J = 11.8, 2.4, H-15), 4.08 (1H, dddd, J = 8.4, 5.0,

5.0, 5.0, H-5), 3.96–3.89 (1H, m, H-9), 3.92 (1H, dddd, *J* = 11.0, 11.0, 6.1, 4.9, H-13), 3.76 (3H, s, CO_2CH_3), 3.71–3.67 (1H, m, H-11), 3.53 (1H, ddd, *J* = 8.8, 6.8, 2.2, H-22), 3.44 (1H, d, *J* = 10.4, H-26), 3.42 (1H, dd, *J* = 10.1, 4.6, H-24), 2.69 (1H, dd, *J* = 17.3, 8.4, H-4a), 2.54 (1H, ddd, *J* = 14.1, 6.8, 6.0, H-21a), 2.46–2.39 (2H, m, H-6a & H-8a), 2.44 (3H, s, H-32), 2.43–2.37 (1H, m, H-4b), 2.37–2.25 (1H, m, H-21b), 2.25 (1H, ddd, *J* = 12.2, 6.1, 2.4, H-14a), 2.23–2.18 (1H, m, H-12a), 2.13–2.09 (1H, m, H-10a), 2.09–2.01 (1H, m, H-6b), 2.00 (1H, dd, *J* = 13.2, 5.5, H-8b), 1.91 (3H, s, H-48), 1.78 (1H, qdd, *J* = 6.9, 4.6, 2.2, H-23), 1.76–1.69 (1H, m, H-25), 1.60 (1H, ddd, *J* = 12.2, 11.8, 11.0, H-14b), 1.54 (1H, ddd, *J* = 13.9, 7.6, 5.3, H-10b), 1.28 (1H, ddd, *J* = 12.2, 12.2, 11.0, H-12b), 0.97 (3H, d, *J* = 6.9, H-50), 0.90 [9H, s, $SiC(CH_3)_3$], 0.74 (3H, d, *J* = 6.5, H-49), 0.06 [3H, s, $Si(CH_3)_aMe$], 0.05 [3H, s, $SiMe(CH_3)_b$] (OH signal missing); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 161.1, 160.6, 154.2, 142.2, 140.4, 138.1, 137.8, 136.3, 135.5, 134.0, 118.5, 118.3, 111.6, 88.8, 86.7, 77.4, 77.4, 74.1, 72.9, 71.2, 70.0, 68.6, 67.8, 52.8, 40.2, 39.8, 39.5, 39.4, 39.1, 38.9, 36.4, 34.8, 25.8, 23.2, 18.1, 14.3, 13.9, 13.8, 5.8, −4.1, −4.8; HRMS (+ESI) calc. for $C_{43}H_{62}N_2O_9SiNa$ (MNa^+) 801.4122, found 801.4095.

Seco-acid 29

A solution of methyl ester **28** (4.6 mg, 5.1 μmol) and $LiOH{\cdot}H_2O$ (1.1 mg, 26 μmol) in THF (1.7 mL) and water (0.34 mL) was vigorously stirred at RT, and without argon protection, for 2 h. It was subsequently partitioned between CH_2Cl_2–^{i}PrOH (5 × 10 mL of 9 : 1, v/v) and HCl solution (10 mL of 0.15 M) before the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The purification of the residue by silica gel PTLC (EtOAc–^{i}PrOH–AcOH, 90 : 10 : 1) gave *seco*-acid **29** (4.4 mg, 97%) as a white solid. R_f 0.11 (EtOAc–^{i}PrOH–AcOH, 90 : 10 : 1); $[\alpha]_D^{20}$ +10.3 (*c* = 0.89, MeOH); ν_{max} (thin film)/cm^{-1} 3355 (br m, O–H), 2927 (m), 2857 (m), 2235 (w, C≡C), 1655 (m), 1582 (s), 1363 (s), 1105 (s), 1027 (s), 735 (s); ^{1}H NMR (500 MHz, CD_3OD) δ_H 7.77 (1H, s, H-30), 7.69–7.65 (4H, m, ArH), 7.61 (1H, s, H-17), 7.47–7.36 (6H, m, ArH), 6.73 (1H ddd, *J* = 16.1, 7.9, 6.3, H-20), 6.32 (1H, d, *J* = 16.1, H-19), 6.17 (1H, s, H-28), 4.82–4.78 (1H, m, H-51a), 4.77–4.72 (1H, m, H-51b), 4.20 (1H, dd, *J* = 11.7, 1.6, H-15), 3.96 (1H, dddd, *J* = 10.4, 10.4, 4.4, 4.4, H-13), 3.85 (1H, dddd, *J* = 9.8, 5.0, 5.0, 5.0, H-5), 3.77–3.72 (1H, m, H-9), 3.68–3.58 (1H, m, H-22), 3.52 (1H, d, *J* = 10.4, H-26), 3.46 (1H, dd, *J* = 10.1, 4.7, H-24), 3.39–3.34 (1H, m, H-11), 2.54 (1H, ddd, *J* = 13.9, 6.6, 6.3, H-21a), 2.48–2.35 (2H, m, H-4a & H-6a), 2.42 (3H, s, H-32), 2.41–2.30 (1H, m, H-21b), 2.31–2.22 (1H, m, H-8a), 2.26–2.14 (2H, m, H-4b & H-6b), 2.13–2.09 (1H, m, H-14a), 1.97–1.88 (1H, m, H-8b), 1.95–1.84 (1H, m, H-23), 1.90 (3H, s, H-48), 1.89–1.79 (2H, m, H-10a & H-12a), 1.76–1.65 (1H, m, H-25), 1.71–1.58 (1H, m, H-14b), 1.43 (1H, ddd, *J* = 13.6, 6.3, 6.0, H-10b), 1.36–1.23 (1H, m, H-12b), 1.04 [9H, s, $SiC(CH_3)_3$], 0.99 (3H, d, *J* = 6.6, H-50), 0.83 (3H, d, *J* = 6.6, H-49) (OH and COOH signals missing); ^{13}C NMR (125.7 MHz, CD_3OD) δ_C 162.8, 162.7, 143.3, 142.7, 140.0, 138.9, 138.5, 137.6, 136.9, 136.9, 136.0, 135.4, 135.3, 131.0, 131.0, 128.8 (2C), 119.2, 118.6, 111.6, 90.2, 79.0, 77.2, 74.1, 72.1, 71.9, 70.7, 70.6, 40.3, 40.1, 40.0, 39.1, 37.2, 35.4, 30.8, 27.5, 24.3, 23.7, 19.9, 14.6, 13.8, 13.4, 6.1 (C-1, C-2 and C-3 signals missing due to signal broadening); HRMS (+ESI) calc. for $C_{52}H_{64}N_2O_9SiNa$ (MNa^+) 911.4279, found 911.4253.

Macrolactone 30

To a sample of *seco*-acid **29** (3.5 mg, 3.9 μmol) was added a dry THF solution (738 μL) of 2,4,6-trichlorobenzoyl chloride (64.0×10^{-3} M, 47.2 μmol) and Et_3N (0.128 M, 94.4 μmol). The resulting solution was stirred at RT for 45 min before the volatiles were removed *in vacuo* using a needle inserted through the septum. The vigour with which volatiles were removed at this stage was controlled using occasional ice bath cooling. A solution of the residue in dry PhME (1.0 mL) was added *via* syringe pump over 8 h to a solution of DMAP (4.8 mg, 39 μmol) in dry PhME (8.5 mL) which was being stirred at RT. At the end of the addition, the transfer was quantified with more dry PhME (0.50 mL) before the cloudy solution was left to stir for a further 12 h. The reaction mixture was subsequently diluted with EtOAc (10 mL) and sequentially washed with citric acid solution (10 mL), $NaHCO_3$ solution (10 mL) and brine (10 mL). The drying (Na_2SO_4) of the organic fraction and its concentration *in vacuo* was followed by the purification of the residue by silica gel PTLC (light petroleum–EtOAc, 1 : 1). This furnished macrolactone **30** (2.4 mg, 70%) as a colourless oil. R_f 0.40 (light petroleum–EtOAc, 1 : 1); $[\alpha]_D^{20}$ +17 (*c* = 0.13, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2924 (s), 2852 (s), 2229 (w), 1713 (s, C=O), 1112 (s), 1094 (s), 704 (m); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.68–7.66 (4H, m, ArH), 7.50 (1H, s, H-30), 7.45–7.35 (6H, m, ArH), 7.37 (1H, s, H-17), 6.69 (1H, ddd, *J* = 15.9, 9.0, 6.3 Hz, H-20), 6.29 (1H, d, *J* = 15.9, H-19), 6.24 (1H, s, H-28), 4.78–4.77 (1H, m, H-51a), 4.73–4.72 (1H, m, H-51b), 4.40 (1H, dd, *J* = 10.9, 4.6, H-24), 4.12–4.05 (1H, m, H-9), 4.09 (1H, dd, *J* = 10.3, 1.9, H-15), 3.95–3.86 (1H, m, H-11), 3.87 (1H, dddd, *J* = 9.8, 5.7, 4.9, 2.4, H-5), 3.59 (1H, d, *J* = 10.3, H-26), 3.46–3.40 (1H, m, H-22), 3.46 (1H, app. dd, *J* = 11.0, 9.8, H-13), 2.96 (1H, dd, *J* = 17.3, 5.7, H-4a), 2.66 (1H, ddq, *J* = 10.9, 10.3, 6.3, H-25), 2.53–2.48 (2H, m, H-21a & H-21b), 2.45 (1H, dd, *J* = 13.4, 4.9, H-8a), 2.44 (3H, s, H-32), 2.34 (1H, dd, *J* = 13.4, 9.8, H-6a), 2.23 (1H, dd, *J* = 17.3, 4.9, H-4b), 2.12 (1H, dd, *J* = 13.4, 2.4, H-6b), 2.08–2.00 (1H, m, H-23), 2.01–1.94 (1H, m, H-14a), 2.00–1.96 (1H, m, H-10a), 1.96 (3H, s, H-48), 1.93 (1H, dd, *J* = 13.4, 4.9, H-8b), 1.76–1.69 (1H, m, H-10b), 1.75–1.66 (1H, m, H-12a), 1.75 (1H, ddd, *J* = 12.2, 11.0, 10.3, H-14b), 1.49 (1H, ddd, *J* = 12.2, 12.2, 11.0, H-12b), 1.06 [9H, s, $SiC(CH_3)_3$], 1.03 (3H, d, *J* = 6.8, H-50), 0.84 (3H, d, *J* = 6.3, H-49); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 160.9, 160.7, 153.6, 141.9, 141.5, 137.5, 136.6, 135.7 (2C), 135.7, 134.4, 134.2, 134.2, 129.8, 129.7, 127.6 (2C), 125.5, 119.7, 118.9, 110.8, 92.7, 89.4, 84.7, 78.3, 75.4, 72.9, 70.0, 69.2, 67.6, 65.9, 42.2, 39.1, 38.2, 38.0, 37.7, 34.2, 30.3, 29.7, 26.9, 23.8, 19.1, 14.1, 13.8, 13.5, 5.5; HRMS (+ESI) calc. for $C_{52}H_{62}N_2O_8SiNa$ (MNa^+) 893.4173, found 893.4156.

Methyl enol ether 37

To a solution of ketolactone **32** (599 mg, 2.56 mmol) in dry acetone (20 mL) was added $(MeO)_2SO_2$ (254 μL, 2.68 mmol). Solid K_2CO_3 (371 mg, 2.68 mmol) was added portionwise over 6 h. A period of stirring for a further 48 h at RT led to the almost complete consumption of **32**. The reaction mixture was diluted with Et_2O (100 mL), washed with water (2 × 100 mL) and then brine (100 mL), before being dried ($MgSO_4$) and concentrated *in vacuo*. The purification of the residue by flash column chromatography on silica gel (light petroleum–EtOAc, 2 : 3) gave methyl enol ether **37** (626 mg, 99%) as a colourless oil. R_f 0.22 (light petroleum–EtOAc, 2 : 3); $[\alpha]_D^{20}$ = +62 (*c* = 0.43, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2918 (s), 1704 (m, C=O), 1621 (m, C=C), 1223 (m), 1094 (m), 1051 (m), 819 (w); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.37–7.30 (5H, m, ArH), 5.14 (1H, d, *J* = 1.4, H-34), 4.60 (2H, s, $ArCH_aH_b$ & $ArCH_aH_b$), 4.58–4.54 (1H, m, H-37), 3.74 (3H, s, OCH_3), 3.71–3.69 (2H, m, H-38a & H-38b), 2.72 (1H, ddd, *J* = 17.2, 11.8, 1.4, H-36a), 2.40 (1H, dd, *J* = 17.2, 4.1, H-36b); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 172.7, 166.6, 137.7, 128.5, 127.9, 127.7, 90.2, 74.6, 73.7, 70.6, 56.0, 29.8; HRMS (+ESI) calc. for $C_{14}H_{17}O_4$ (MH^+) 249.1127, found 249.1125.

Alcohol 38

To a solution of benzyl ether **37** (626 mg, 2.52 mmol) in undried EtOAc (20 mL, winchester grade) was carefully added Pd–C (980 mg of 10%, w/w). The solution was subsequently placed under a hydrogen atmosphere (balloon pressure) and the headspace purged. After 12 h of stirring at RT, the hydrogen atmosphere was replaced with nitrogen. The washing of the reaction mixture through a short Celite® pad, under a nitrogen

stream and with copious EtOAc–MeOH (20 : 1), was followed by its concentration *in vacuo*. Analysis by 400 MHz ^{1}H NMR revealed a single C-35 epimer (*R*/*S* > 97 : 3). Flash column chromatography on silica gel (EtOAc–MeOH, 20 : 1) gave recovered benzyl ether **37** (21 mg, 3%), and alcohol **38** (339 mg, 84%) as a colourless oil which solidified to a white solid on standing. R_f 0.24 (EtOAc–MeOH, 20 : 1); mp 38–40 °C (from CH_2Cl_2); $[\alpha]_D^{20}$ = −29 (*c* = 1.2, $CHCl_3$); IR (thin film)/cm^{-1} 3417 (br, O–H), 2922 (s), 1729 (s, C=O), 1257 (s), 1090 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.34 (1H, dddd, *J* = 11.6, 5.5, 3.1, 3.1, H-37), 3.83–3.77 (2H, m, H-38a & H-35), 3.73–3.67 (1H, m, H-38b), 3.35 (3H, s, OCH_3), 2.86 (1H, dd, *J* = 17.2, 5.6, H-34a), 2.63 (1H, dd, *J* = 6.7, 6.6, OH), 2.55 (1H, dd, *J* = 17.2, 7.2, H-34b), 2.24 (1H, ddd, *J* = 13.7, 5.5, 4.2, H-36a), 1.72 (1H, ddd, *J* = 13.7, 11.6, 8.5, H-36b); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 170.1, 77.7, 72.1, 64.5, 56.0, 36.2, 30.3; HRMS (+ESI) calc. for $C_7H_{13}O_4$ (MH^+) 161.0814, found 161.0812.

Aldehyde 31

To a cold (−78 °C), stirred solution of $(COCl)_2$ (0.149 mL, 1.71 mmol) in dry CH_2Cl_2 (4.0 mL) was added a solution of DMSO in dry CH_2Cl_2 (1.21 mL of 2.82 M, 3.41 mmol) over 3 min. After 10 min stirring, alcohol **38** (91.0 mg, 0.568 mmol) in dry CH_2Cl_2 (2.0 mL, including washings) was added dropwise over 3 min. After a further 75 min at −78 °C, Et_3N (0.792 mL, 5.68 mmol) was added dropwise so as to produce a slightly cloudy solution. After 15 min, the solution was allowed to warm to −20 °C over 30 min. After 10 min at −20 °C, light petroleum–PhMe (10 mL of 3 : 1) was added and the reaction mixture was rapidly warmed to RT. It was subsequently washed through a short Celite® plug with copious light petroleum–PhMe (3 : 1) before the filtrate was concentrated *in vacuo*. The purification of the residue by flash column chromatography on silica gel (EtOAc) gave aldehyde **31** (79.2 mg, 88%) as a colourless oil. R_f 0.20 (EtOAc); $[\alpha]_D^{20}$ = −42 (*c* = 0.95, $CHCl_3$); IR ($CHCl_3$ solution)/cm^{-1} 3012 (m), 2934 (m), 2835 (m), 1736 (s, C=O), 1357 (m), 1236 (m), 1097 (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 9.71 (1H, s, H-38), 4.73 (1H, dd, *J* = 6.7, 2.8, H-37), 3.79–3.77 (1H, m, H-35), 3.21 (3H, s, OCH_3), 2.84 (1H, dd, *J* = 17.9, 2.8, H-34a), 2.65 (1H, dd, *J* = 17.9, 3.9, H-34b), 2.49 (1H, ddd, *J* = 14.4, 2.8, 2.0, H-36a), 2.19 (1H, app. dd, *J* = 14.4, 6.7, H-36b); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 199.4, 167.3, 80.1, 71.1, 56.1, 36.7, 29.0; HRMS (+EI) calc. for $C_6H_9O_3$ ([M–CHO]$^+$) 129.0552, found 129.0548.

Aldol adduct 45

An excess of $Sn(OTf)_2$ (*ca.* 3.0 g) was pre-washed with dry Et_2O (3 × 5 mL) and dried *in vacuo* (1 mm Hg) in order to remove traces of CF_3SO_3H. To a cold (−55 °C), stirred suspension of an accurately-weighed amount of this material (1.72 g, 4.12 mmol, glovebox) in dry CH_2Cl_2 (6.0 mL), was added *N*-ethylpiperidine (0.566 mL, 4.12 mmol) in a dropwise fashion. After 15 min, the solution was slightly yellow in colour. A solution of *N*-acetyl-4(*S*)-IPTT **44** (698 mg, 3.43 mmol, azeotropically dried 3 × with PhMe) in dry CH_2Cl_2 (4 mL, including washings) was added dropwise. The mixture was vigorously stirred at between −50 and −40 °C for 3 h and then between −40 and −38 °C for 90 min before it was cooled to −98 °C. After the dropwise addition of dienal **40** (915 mg, 4.12 mmol) in dry CH_2Cl_2 (6.6 mL, including washings), the temperature was allowed to slowly rise to −78 °C. The solution was vigorously stirred at this temperature until 150 min after the end of the addition of **40**, at which point a pH 7 buffer–MeOH mixture (6 mL of 2 : 1) was added dropwise. The mixture was rapidly warmed to RT and washed through a short Celite® plug with copious Et_2O. The partitioning of the filtrate between Et_2O (200 mL) and water (200 mL), and then brine (200 mL), was followed by drying ($MgSO_4$) and concentration *in vacuo*. An analysis of the residue by 500 MHz ^{1}H NMR showed no sign of (*epi*-C-43)-**45**. Its purification by flash column chromatography on silica gel (light petroleum–EtOAc, 20 : 1 and then 4 : 1) gave recovered dienal **40** (182 mg), and then aldol adduct **45** [1.40 g, 96% based on *N*-acetyl-4(*S*)-IPTT **44**] as a yellow solid. R_f 0.41 (light petroleum–EtOAc, 1 : 1); mp 81–83 °C (from Et_2O); $[\alpha]_D^{20}$ = +135 (*c* = 5.3, $CHCl_3$); IR (CH_2Cl_2 solution)/cm^{-1} 3592 (w, O–H), 3016 (m), 2986 (s), 2968 (s), 1682 (s, C=O), 1470 (m), 1364 (s), 1314 (s), 1168 (s), 1094 (s), 1043 (s), 965 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.42 (1H, d, *J* = 15.6 Hz, H-41), 6.39 (1H, s, H-39), 5.81 (1H, dd, *J* = 15.6, 5.8, H-42), 5.16 (1H, ddd, *J* = 7.9, 6.3, 1.0, CH^{i}Pr), 4.72 (1H, dddd, *J* = 8.7, 5.8, 4.1, 3.0, H-43), 3.70 (1H, dd, *J* = 17.5, 3.0, H-44a), 3.52 (1H, dd, *J* = 11.5, 7.9, CH_aH$_b$S), 3.33 (1H, dd, *J* = 17.5, 8.7, H-44b), 3.04 (1H, dd, *J* = 11.5, 1.0, CH$_a$$H_b$S), 2.92 (1H, d, *J* = 4.1, OH), 2.41–2.32 (1H, m, $CHMe_2$), 1.97 (3H, s, H-47), 1.07 [3H, d, *J* = 6.8, CH(CH_3)$_a$Me], 0.99 [3H, d, *J* = 6.8, CHMe(CH_3)$_b$]; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 203.0, 172.3, 144.4, 131.6, 130.3, 84.5, 71.4, 68.4, 45.1, 30.8, 30.7, 20.1, 19.1, 17.8; HRMS (+ESI) calc. for $C_{14}H_{20}INO_2S_2Na$ (MNa^+) 447.9878, found 447.9885.

Weinreb amide 46

A solution of aldol adduct **45** (290 mg, 0.682 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride (166 mg, 1.70 mmol) and imidazole (232 mg, 3.41 mmol) in dry CH_2Cl_2 (3.6 mL) was stirred at RT for 24 h before being poured into chilled (0 °C) NH_4Cl solution (10 mL). Extractions with Et_2O (4 × 10 mL) were followed by the washing of the combined organic fractions with brine (40 mL), drying (Na_2SO_4) and concentration *in vacuo* to a yellow oil. Flash column chromatography on silica gel (light petroleum–EtOAc gradient, 3 : 1 → 2 : 1) gave 4(*S*)-IPTT and then Weinreb amide **46** (160 mg, 72%) as a yellow oil. R_f 0.38 (EtOAc); $[\alpha]_D^{20}$ = +13 (*c* = 2.8, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3409 (w, O–H), 2918 (w), 1636 (s, C=O), 1424 (m), 1386 (s), 1296 (m), 998 (m), 964 (s), 763 (w); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 6.41 (1H, dq, *J* = 15.8, 0.6, H-41), 6.36 (1H, s, H-39), 5.79 (1H, dd, *J* = 15.8, 6.0, H-42), 4.59 (1H, dddd, *J* = 8.8, 6.0, 3.8, 2.9, H-43), 3.97 (1H, d, *J* = 3.8, OH), 3.68 (3H, s, OCH_3), 3.19 (3H, s, NCH_3), 2.72 (1H, dd, *J* = 17.3, 2.9, H-44a), 2.60 (1H, dd, *J* = 17.3, 8.8, H-44b), 1.95 (3H, d, *J* = 0.6, H-47); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 169.7, 142.2, 129.3, 129.0, 83.8, 68.6, 61.8, 39.5, 33.4, 21.9; HRMS (+ESI) calc. for $C_{10}H_{16}INO_3Na$ (MNa^+) 348.0073, found 348.0081.

Methyl ether 47

To a stirred mixture of alcohol **46** (26.9 mg, 82.7 μmol) and Ag_2O (192 mg, 0.829 mmol, glovebox) was added MeI in dry Et_2O (2.06 mL of 1 : 3). After being refluxed for 3 h, the reaction mixture was cooled to RT and washed through a short plug of silica gel with copious Et_2O. Concentration *in vacuo* gave methyl ether **47** (26.6 mg, 95%) as a colourless oil. R_f 0.33 (light petroleum–EtOAc, 1 : 1); $[\alpha]_D^{20}$ = +37 (*c* = 0.89, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2935 (w), 1658 (s, C=O), 1385 (m), 1092 (s), 998 (m), 966 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.39 (1H, s, H-39), 6.37 (1H, dq, *J* = 15.8, 1.0, H-41), 5.67 (1H, dd, *J* = 15.8, 7.5, H-42), 4.17 (1H, ddd, *J* = 8.3, 7.5, 5.0, H-43), 3.68 (3H, s, $NOCH_3$), 3.28 [3H, s, C-43(OCH_3)], 3.18 (3H, s, NCH_3), 2.88 (1H, dd, *J* = 15.6, 8.3, H-44a), 2.48 (1H, dd, *J* = 15.6, 5.0, H-44b), 1.97 (3H, d, *J* = 1.0, H-47); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 171.3, 144.4, 133.2, 129.4, 84.5, 78.2, 61.3, 56.7, 38.2, 32.0, 20.1; HRMS (+ESI) calc. for $C_{11}H_{18}INO_3Na$ (MNa^+) 362.0229, found 362.0221.

Aldehyde 48

DIBAl-H in CH_2Cl_2 (1.67 mL of 1.00 M, 1.67 mmol) was added in a dropwise fashion to a cold (−78 °C), stirred solution of Weinreb amide **47** (390 mg, 1.39 mmol) in dry THF (10 mL). A period of stirring for 30 min was followed by the dropwise addition of MeOH (0.50 mL). After 5 min, the reaction mixture was cannulated into a vigorously stirred, biphasic mixture of Et_2O (100 mL) and Rochelle's salt solution (100 mL)

which was being held at −15 °C. The transfer was quantified with more Et_2O. The rapid warming of the reaction mixture to RT and stirring for 30 min was followed by a phase separation and the back-extraction of the aqueous phase with Et_2O (2 × 25 mL). The combined organic fractions were washed with brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography on silica gel (light petroleum–EtOAc, 10 : 1 → 2 : 1) gave aldehyde **48** (303 mg, 94%) as a colourless oil. R_f 0.57 (light petroleum–EtOAc, 1 : 1); $[\alpha]_D^{20}$ = +33 (*c* = 0.94, $CHCl_3$); IR (CH_2Cl_2 solution)/cm^{-1} 3062 (m), 2981 (s), 2962 (s), 2930 (s), 2827 (m), 2732 (w), 1725 (s, C=O), 1682 (s), 1298 (s), 1160 (m), 1116 (s), 1099 (s), 966 (s), 896 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.76 (1H, dd, *J* = 2.2, 1.9, H-45), 6.44 (1H, s, H-39), 6.37 (1H, d, *J* = 15.6, H-41), 5.63 (1H, dd, *J* = 15.6, 7.7, H-42), 4.15 (1H, ddd, *J* = 7.9, 7.7, 4.8, H-43), 3.29 (3H, s, OCH_3), 2.73 (1H, ddd, *J* = 16.4, 7.9, 2.2, H-44a), 2.56 (1H, ddd, *J* = 16.4, 4.8, 1.9, H-44b), 1.97 (3H, s, H-47); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 200.2, 144.1, 133.9, 128.4, 85.2 (2C), 56.5, 49.3, 20.0; HRMS (+ESI) calc. for $C_9H_{13}IO_2Na$ (MNa^+) 302.9858, found 302.9859.

Triene 39

The DMF used in this reaction had been degassed prior to use using three freeze–pump–thaw cycles. $CrCl_2$ (930 mg, 7.57 mmol, glovebox), which was being stirred under vacuum, was gently dried with a heat gun. The $CrCl_2$ was placed under argon on cooling to RT, and the flask was wrapped in aluminium foil before being cooled to 0 °C. Dry DMF (13.0 mL) was added and the flask was removed from the cooling bath. After 15 min, a solution of aldehyde **48** (212 mg, 0.757 mmol) and ^{n}Bu$_3$SnCHI$_2$ [43] (843 mg, 1.51 mmol) in dry DMF (4.4 mL, including washings) was added to the green suspension. A period of vigorous stirring for 60 min was followed by cooling to 0 °C and quenching with pH 7 buffer solution (5.0 mL). The mixture was poured into water (50 mL) and extracted with EtOAc (3 × 50 mL). The combined extracts were washed with water (3 × 100 mL) and then brine (100 mL) before being dried ($MgSO_4$) and concentrated *in vacuo*. An Et_2O solution of the residue was washed through a short plug of neutral, deactivated alumina. The concentration of the filtrate *in vacuo* produced the crude stannane (695 mg) as an ochre oil which consisted of a chromatographically separable 8.2 : 1.0 mixture of *E*/*Z* diastereomers at C(45–46). For convenience, the bulk sample was not purified at this stage. The crude stannane mixture was dissolved in dry MeCN (18 mL) and cooled to 0 °C. A solution of NBS (240 mg, 1.35 mmol) in dry MeCN (4.0 mL) was added dropwise and the resulting solution was stirred for a further 30 min before $Na_2S_2O_3$ solution–$NaHCO_3$ solution (10 mL of 1 : 1) was slowly added. The solution was removed from the cooling bath, vigorously stirred for 10 min and poured into water (50 mL). Extractions with Et_2O (3 × 50 mL) were followed by the washing of the combined extracts with water (2 × 100 mL) and then brine (100 mL), drying ($MgSO_4$) and concentration *in vacuo*. An analysis of the residue by 400 MHz ^{1}H NMR gave an *E*/*Z* alkene ratio at C(45–46) of 7.5 : 1.0. Flash column chromatography on silica gel doped with 10% w/w $AgNO_3$ (light petroleum and then light petroleum–EtOAc, 45 : 1) gave triene **39** and its C(45–46) *Z*-diastereomer (268 mg, 99% over two steps from aldehyde **48**) as a colourless oil which was devoid of tributyltin residues. After the preparative HPLC purification {light petroleum–Et_3N (1%); R_t = 24.6 min [C(45–46) *Z*-diastereomer: 11.8%], R_t = 26.7 min (**39**: 88.2%); detection at λ = 254 nm} of the sample, the spectral data of triene **39** were found to be in agreement with those of Evans *et al.*,[5b] though there was a discrepancy in the magnitude of the optical rotation. R_f 0.14 (light petroleum–EtOAc, 50 : 1); $[\alpha]_D^{20}$ = +6.6 (*c* = 0.62, CH_2Cl_2) [lit.:[5b] +11.2 (*c* = 7.7, CH_2Cl_2)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.41 (1H, s, H-39), 6.30 (1H, d, *J* = 15.6, H-41), 6.16 (1H, ddd, *J* = 13.7, 7.0, 7.0, H-45), 6.10 (1H, d, *J* = 13.7, H-46), 5.57 (1H, dd, *J* = 15.6, 7.8, H-42), 3.63 (1H, ddd, *J* = 7.8, 6.1, 6.1, H-43), 3.26 (3H, s, OCH_3), 2.37–2.23 (2H, m, H-44a & H-44b), 1.97 (3H, s, H-47).

Ketone 50

A stirred mixture of $CrCl_2$ (55.1 mg, 0.448 mmol) and $NiCl_2$ (5.8 mg, 45 μmol) was gently heated under vacuum with a heat gun for 3 min. On cooling to RT, the flask was back-filled with argon. A degassed solution (three freeze–pump–thaw cycles) of triene **39** (20.0 mg, 56.0 μmol) in dry THF/4-*tert*-butylpyridine (1.4 mL of 6 : 1, including washings) was added so as to produce a homogeneous green solution. A solution of aldehyde **31** in dry DMSO (0.830 mL of 0.135 M, 0.112 mmol) was subsequently added dropwise before the flask was wrapped in aluminium foil. A period of stirring for 9 h was followed by the addition of light petroleum–EtOAc (10 mL of 1 : 1) and sodium serinate solution (10 mL of 1 M, 10 mmol). The vigorous stirring of the biphasic mixture for 40 min without argon protection was followed by pouring into water (20 mL). The phases were separated and the aqueous phase back-extracted with EtOAc (2 × 20 mL). The combined organic phases were washed with water (50 mL) and then brine (50 mL) before being dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography on a silica gel-filled pipette column (light petroleum–EtOAc gradient, 15 : 1 → 3 : 1 → EtOAc) gave the desiodo triene **49** (5.6 mg) and then an inseparable mixture of C-38 allylic alcohols (6.4 mg, 29%, *R*/*S* = 1.0 : 3.4 by 400 MHz ^{1}H NMR). To a solution of this mixture (3.1 mg, 8.0 μmol) in dry CH_2Cl_2 (1.0 mL) and activated, crushed 4 Å molecular sieves (30 mg) was added a dry CH_2Cl_2 solution (80.0 μL) of TPAP (0.010 M, 0.80 μmol) and NMO (0.149 M, 11.9 μmol). Complete conversion was achieved after 2 h stirring at RT. The purification of the mixture using a silica gel-filled pipette column (light petroleum–EtOAc gradient, 1 : 1 → 3 : 1) gave ketone **50** (1.8 mg, 58%) as a colourless oil. R_f 0.18 (light petroleum–EtOAc, 1 : 1); $[\alpha]_D^{20}$ = −4.0 (*c* = 0.13, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2918 (s), 1743 (s, OC=O), 1676 (m, C=O), 1582 (s, C=C), 1438 (w), 1352 (w), 1216 (w), 1157 (w), 1094 (s), 971 (w); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 6.57 (1H, s, H-39), 6.34 (1H, d, *J* = 15.7, H-41), 6.19 (1H, ddd, *J* = 13.6, 7.2, 7.2, H-45), 6.12 (1H, d, *J* = 13.6, H-46), 6.04 (1H, dd, *J* = 15.7, 7.4, H-42), 4.70 (1H, dd, *J* = 7.2, 5.4, H-37), 3.78 (1H, dddd, *J* = 9.2, 5.4, 5.0, 3.8, H-35), 3.74 (1H, ddd, *J* = 7.4, 6.7, 6.7, H-43), 3.29 (3H, s, OCH_3), 3.27 (3H, s, OCH_3), 2.79 (1H, dd, *J* = 17.5, 5.0, H-34a), 2.68 (1H, dd, *J* = 17.5, 5.4, H-34b), 2.38–2.28 (3H, m, H-44a, H-44b & H-36a), 2.28 (3H, s, H-47), 2.24 (1H, ddd, *J* = 13.5, 9.2, 7.2, H-36b); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 197.0, 168.3, 153.4, 137.4, 136.5, 133.2, 121.6, 106.8, 80.8, 80.6, 71.8, 56.8, 56.2, 38.8, 36.8, 30.9, 14.7; HRMS (+ESI) calc. for $C_{17}H_{23}BrO_5Na$ (MNa^+) 409.0627, found 409.0635.

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References

1 P. A. Searle and T. F. Molinski, *J. Am. Chem. Soc.*, 1995, **117**, 8126–8131.
2 P. A. Searle, T. F. Molinski, L. J. Brzezinski and J. W. Leahy, *J. Am. Chem. Soc.*, 1996, **118**, 9422–9423.
3 T. F. Molinski, *Tetrahedron Lett.*, 1996, **37**, 7879–7880.
4 C. J. Forsyth, F. Ahmed, R. D. Cink and C. S. Lee, *J. Am. Chem. Soc.*, 1998, **120**, 5597–5598.
5 (*a*) D. A. Evans and D. M. Fitch, *Angew. Chem., Int. Ed.*, 2000, **39**, 2536–2540; (*b*) D. A. Evans, D. M. Fitch, T. E. Smith and V. J. Cee, *J. Am. Chem. Soc.*, 2000, **122**, 10033–10046.
6 A. B. Smith III, P. R. Verhoest, K. P. Minbiole and M. Schelhaas, *J. Am. Chem. Soc.*, 2001, **123**, 4834–4836; A. B. Smith III, K. P. Minbiole, P. R. Verhoest and M. Schelhaas, *J. Am. Chem. Soc.*, 2001, **123**, 10942–10953.

7 M. A. González and G. Pattenden, *Angew. Chem., Int. Ed.*, 2003, **42**, 1255–1258; G. Pattenden, M. A. González, P. B. Little, D. S. Millan, A. T. Plowright, J. A. Tornos and T. Ye, *Org. Biomol. Chem.*, 2003, **1**, 4173–4208.

8 D. R. Williams, A. A. Kiryanov, U. Emde, M. P. Clark, M. A. Berliner and J. T. Reeves, *Angew. Chem., Int. Ed.*, 2003, **42**, 1258–1262.

9 For a review of the total synthesis of the phorboxazoles, see: L. O. Haustedt, I. V. Hartung and H. M. R. Hoffmann, *Angew. Chem., Int. Ed.*, 2003, **42**, 2711–2716.

10 (*a*) P. B. Greer and W. A. Donaldson, *Tetrahedron*, 2002, **58**, 6009–6018, and refs. cited therein; (*b*) B. Liu and W.-S. Zhou, *Tetrahedron Lett.*, 2003, **44**, 4933–4935; (*c*) D. R. Li, Y. Q. Tu, G.-Q. Lin and W.-S. Zhou, *Tetrahedron Lett.*, 2003, **44**, 8729–8732; (*d*) T. M. Hansen, M. M. Engler and C. J. Forsyth, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 2127–2130; (*e*) J. S. Yadav and G. Rajaiah, *Synlett*, 2004, 1537–1539; (*f*) B. S. Lucas, L. M. Luther and S. D. Burke, *Org. Lett.*, 2004, **6**, 2965–2968.

11 For our previous synthetic studies, see: (*a*) I. Paterson and E. A. Arnott, *Tetrahedron Lett.*, 1998, **39**, 7185–7188; (*b*) I. Paterson and C. A. Luckhurst, *Tetrahedron Lett.*, 2003, **44**, 3749–3754.

12 A. B. Smith III, P. R. Verhoest, K. P. Minbiole and J. J. Lim, *Org. Lett.*, 1999, **1**, 909–912.

13 P. B. Greer and W. A. Donaldson, *Tetrahedron Lett.*, 2000, **41**, 3801–3803.

14 (*a*) A. G. Dossetter, T. F. Jamison and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 1999, **38**, 2398–2400; (*b*) G. D. Joly and E. N. Jacobsen, *Org. Lett.*, 2002, **4**, 1795–1798; (*c*) K. Gademann, D. E. Chavez and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2002, **41**, 3059–3061.

15 For a rare example of conjugate propargyl delivery using an organolithium, see: E. J. Corey and C. Rücker, *Tetrahedron Lett.*, 1982, **23**, 719–722.

16 For examples of this behaviour with dihydropyrones, see: P. J. Kocienski, P. Raubo, C. Smith and F. T. Boyle, *Synthesis*, 1999, 2087; P. Kocienski, R. Narquizian, P. Raubo, C. Smith, L. J. Farrugia, K. Muir and F. T. Boyle, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2357.

17 Unpublished results from C. A. L.

18 H. O. House, *Acc. Chem. Res.*, 1976, **9**, 59–67.

19 B. H. Lipshutz, E. L. Ellsworth, S. H. Dimock and R. A. J. Smith, *J. Org. Chem.*, 1989, **54**, 4977–4979; B. H. Lipshutz, E. L. Ellsworth, S. H. Dimock and R. A. J. Smith, *J. Am. Chem. Soc.*, 1990, **112**, 4404–4410.

20 A. Hosomi and H. Sakurai, *J. Am. Chem. Soc.*, 1977, **99**, 1673–1675.

21 D. Grandjean, P. Pale and J. Chuche, *Tetrahedron Lett.*, 1994, **35**, 3529–3530.

22 I. Paterson, K.-S. Yeung and J. B. Smaill, *Synlett.*, 1993, 774–776.

23 H. Emde, D. Domsch, H. Feger, U. Frick, A. Götz, H. H. Hergott, K. Hofmann, W. Kober, K. Krägeloh, T. Oesterle, W. Steppan, W. West and G. Simchen, *Synthesis*, 1982, 1–26.

24 However, Schiff base chromium(III) complexes, with similar structures to **6a** and **6b**, have been used for hetero-ene reactions, in conjunction with sub-stoichiometric amounts of the nitrogen-containing Hünig's base, with no apparent deleterious effect on the reaction: R. T. Ruck and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2003, **42**, 4771–4774.

25 Kakisawa–Mosher analysis of the Mosher ester derivatives of the equatorial alcohol resulting from the $NaBH_4$-mediated reduction of the undesired tetrahydropyranone **26** confirmed the configurational assignment of this material and hence that of the desired tetrahydropyranone **25**. See ref. 30.

26 The global minimum conformer of tetrahydropyranone **25**, as established by molecular mechanics (MM2* forcefield, MacroModel version 8.0), failed to explain the seeming preference that the sterically bulky $LiAl(O^tBu)_3H$ reducing agent showed for axial attack.

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

28 After the completion of this manuscript, the Lindlar reduction of the C(2–3) triple bond of macrolactone **30** also proved possible.

29 D. A. Evans, J. A. Murry and M. C. Kozlowski, *J. Am. Chem. Soc.*, 1996, **118**, 5814–5815; D. A. Evans, V. J. Cee, T. E. Smith, D. M. Fitch and P. S. Cho, *Angew. Chem., Int. Ed.*, 2000, **39**, 2533–2536; D. A. Evans, M. C. Kozlowski, J. A. Murry, C. S. Burgey, K. R. Campos, B. T. Connell and R. J. Staples, *J. Am. Chem. Soc.*, 1999, **121**, 669–685.

30 I. Ohtani, T. Kusumi, Y. Kashman and H. Kakisawa, *J. Am. Chem. Soc.*, 1991, **113**, 4092–4096.

31 M. Sato, J. Sakaki, Y. Sugita, S. Yasuda, H. Sakoda and C. Kaneko, *Tetrahedron*, 1991, **47**, 5689–5708.

32 R. Baker and J. L. Castro, *J. Chem. Soc., Perkin Trans. 1*, 1990, 47–65.

33 M. A. Blanchette, W. Choy, J. T. Davis, A. P. Essenfeld, S. Masamune, W. R. Roush and T. Sakai, *Tetrahedron Lett.*, 1984, **25**, 2183–2186.

34 Y. Nagao, Y. Hagiwara, T. Kumagai, M. Ochiai, T. Inoue, K. Hashimoto and E. Fujita, *J. Org. Chem.*, 1986, **51**, 2391–2393.

35 A. González, J. Aiguadé, F. Urpí and J. Vilarrasa, *Tetrahedron Lett.*, 1996, **37**, 8949–8952.

36 D. M. Hodgson, A. M. Foley and P. J. Lovell, *Tetrahedron Lett.*, 1998, **39**, 6419–6420.

37 K. Takai, K. Nitta and K. Utimoto, *J. Am. Chem. Soc.*, 1986, **108**, 7408–7410.

38 For a comprehensive review, see: A. Fürstner, *Chem. Rev.*, 1999, **99**, 991–1045.

39 D. P. Stamos, X. C. Sheng, S. S. Chen and Y. Kishi, *Tetrahedron Lett.*, 1997, **38**, 6355–6358.

40 The absolute configuration at C-38 was apparent by a comparison of the ^1H NMR spectrum of the allylic alcohol mixture with that of compounds of known absolute configuration at this position.

41 S. V. Ley, J. Norman, W. P. Griffith and S. P. Marsden, *Synthesis*, 1994, 639–666.

42 T. Ando and J. Yamawaki, *Chem. Lett.*, 1979, 45–46.

43 The $^nBu_3SnCHI_2$ reagent was prepared in almost quantitative yield from the analogous dibromo compound under Finkelstein conditions (LiI, acetone). The dibromo compound was prepared in 89% yield using the procedure of Hodgson and co-workers: D. M. Hodgson, L. T. Boulton and G. N. Maw, *Tetrahedron*, 1995, **51**, 3713–3724.