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Synthesis of a tetraoxy-bis-nortaxadiene, en route to taxol, using a cascade radical cyclisation sequence

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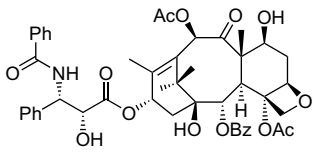
ABSTRACT

Concise syntheses of the substituted enynediones **28a**, **33b** and **36** starting from the cyclohexenealdehyde **18**, corresponding to ring A in the taxanes, and the vinylstannane **24**, are described. Treatment of **36** with Bu_3SnH–AIBN did not lead to the oxy-substituted taxadiene **37** expected from a tandem radical macrocyclisation–radical transannulation sequence; instead, a mixture of unidentified products resulted. When the PMB ether **33b** corresponding to the alcohol **36** was treated with Bu_3SnH–AIBN under similar conditions, *p*-anisaldehyde was isolated, as a major by-product, but no evidence for the formation of a taxadiene could be observed. In contrast, the iododienynedione **41**, i.e., deoxy **36**, underwent a tandem radical macrocyclisation–transannulation sequence, when treated with Bu_3SnH–AIBN, leading to the tetraoxy-bis-nortaxadiene **42** in 44% yield. Attempts to synthesise the alcohol **28b** from the silyl ether **28a** en route to the iodide **28c** instead gave the substituted tetrahydrofuran **29** via an intramolecular oxy-Michael reaction.

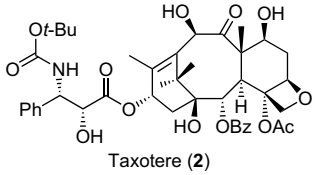
1. Introduction

The natural product taxol (paclitaxel or Taxol™) **1**, isolated from the Pacific yew tree *Taxus brevifolia*,[1] has been the focus of intense interest amongst chemists and biologists ever since its pronounced anti-cancer properties were revealed some 30 years ago.[2] After a further period of research studying its mode of action, followed by chemical trials, Taxol and its semi-synthetic analogue Taxotere **2** entered the clinic in the early 1990s as drugs for the treatment of ovarian and breast cancer.[3] With its availability from natural sources very limited, taxol became one of the most challenging targets for total synthesis throughout the late 1980s and the early 1990s. These efforts culminated in two independent syntheses of taxol, published simultaneously by the research groups led by Holton[4] and by Nicolaou[5] in 1994, closely followed by distinctly different total syntheses by Danishefsky et al. (1996),[6] Wender et al. (1997),[7] Kuwajima et al. (1998)[8] and by Mukaiyama et al. (1999).[9] Needless to say, however, over the past 20 years, a wide range of ingenious synthetic designs towards the unique tricyclic ring system in taxol have emerged, some of which may also yet lead to further total syntheses.[10,11]

Nature elaborates the 6,8,6-tricyclic ring system in taxanes using a sequence of electrophilic macrocyclisation followed by two transannular cyclisations from geranylgeranylpyrophosphate (GGPP) **3**.[12] A series of cytochrome P450-mediated oxidations then enter the arena to decorate the taxadiene hydrocarbon **5** with its oxygenation pattern.[13] In 1984, and before taxol became such a revered compound, we synthesised the 6,12-bicyclic hydrocarbon **4**, known as verticillene, which was a purported biosynthetic intermediate between GGPP and taxadiene.[14] We also examined electrophilic transannular cyclisations from verticillene **4** but, unfortunately, we were not able to convert it into the 6,8,6-tricyclic taxadiene **5**. Interestingly, Croteau et al.[15] were also unable to obtain taxadiene **5** when verticillene **4** was added to incubations containing the taxadiene synthase enzyme.[16]



Taxol (**1**)



Taxotere (**2**)

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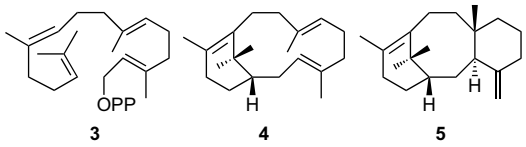
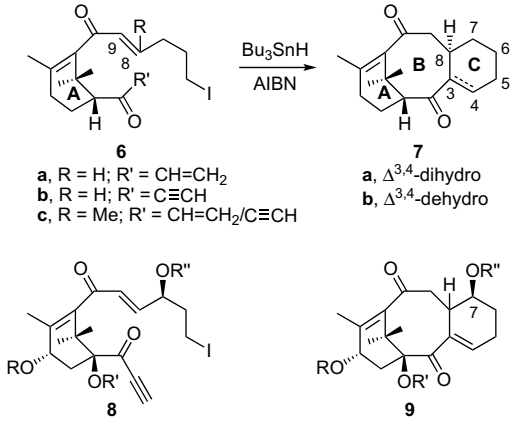


3 4 5

Over the past decade and more, our research group has examined a range of carbon-centred radical-mediated cascade cyclisations to access a variety of ring-fused systems found in natural products.[17] These studies also included a synthetic approach to the taxane ring system,[18] which distinguished itself from all other approaches, whereby the 8,6-(BC) fused ring system in the natural product was elaborated in a single step via a tandem radical cascade sequence from a substituted A-ring precursor, viz. **6**→**7**.[19] We have now investigated this approach to taxanes using a more oxygen-substituted ring A precursor, i.e., **8**, with the aim of producing an advanced taxadiene, viz. **9**, towards taxol itself.

2. Results and discussion

An important limitation in the radical cascade sequence, **6**→**7**, to the tricyclic ring system in the taxanes was found when precursors carrying methyl group substitutions at C8 on their C8–C9 alkene bonds were used, i.e., **6c**. In these instances, only the products **11** resulting from intramolecular 1,5-H abstraction involving the first-formed alkyl radical centre and the vinyl methyl group, via **10**, were isolated, rather than the anticipated angular methyl substituted tricycles **12**.[19] Accordingly, our synthesis design towards taxol necessitated that we introduce the (angular) *C*8-methyl group after elaborating any oxygenated taxane tricycle.



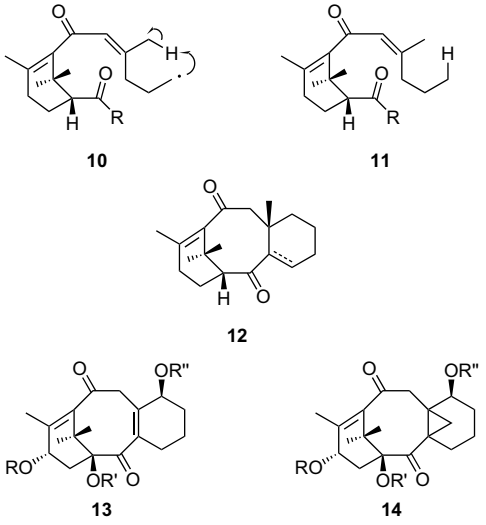
6
a, R = H; R' = CH=CH$_2$
b, R = H; R' = C≡CH
c, R = Me; R' = CH=CH$_2$/C≡CH

7
a, $\Delta^{3,4}$-dihydro
b, $\Delta^{3,4}$-dehydro

8 **9**

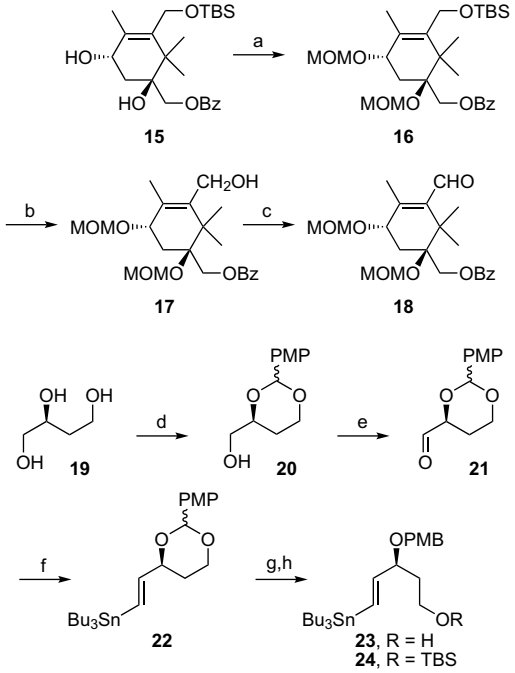
A number of sequences were considered, however, whereby an angular methyl group could be introduced at C8 in an appropriately oxygenated taxadiene intermediate, i.e., **9**. These included using a C–H insertion reaction at C8 from a diazo ester intermediate associated with the C7 hydroxy group in **9**,[20] or by Michael addition of an appropriate methylcuprate to the conjugated enone **13** derived from **9**,[21] and/or via cleavage of the cyclopropane ring in a cyclopropyl ketone intermediate viz. **14**.[22] In spite of all these plausible considerations, however, we first needed to prepare the oxygenated taxadiene **9** from the radical cascade precursor **8**!

To achieve the aforementioned objective, we began by synthesising the fully oxygen-substituted chiral A-ring compound **15**, starting from 2,2-dimethyl-cyclohexan-1,3-dione using a sequence we had already developed and published in full.[11a,23] Protection of the secondary and tertiary hydroxyl groups in **15** as their MOM ethers, followed by deprotection of the silyl ether group in the product **16** first gave the primary alcohol **17** (Scheme 1). Oxidation of **17** next gave the corresponding aldehyde **18** in readiness for coupling to the substituted vinylstannane **24**. The vinylstannane **24** was prepared in five steps from commercial (*S*)-1,2,4-butanetriol **19**. Thus, protection of the triol **19** as its *p*-methoxybenzylidene acetal followed by oxidation of the primary alcohol group in **20** using Swern conditions, first gave the aldehyde **21**. A modified Takai olefination reaction[24] next gave the *E*-vinylstannane **22**, which was then reduced, using DIBAL, leading to the primary alcohol **23**. Finally, treatment of **23** with TBS chloride gave the differentially protected 1,3-diol substituted vinylstannane **24**.



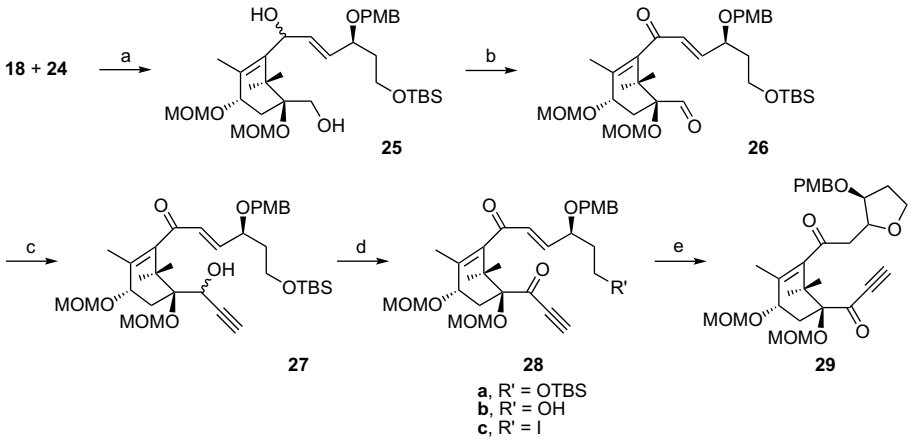
10 **11** **12** **13** **14**

Addition of the cyclohexenealdehyde **18** to the vinyllithium species produced from the stannane **24**, using *n*-BuLi, followed by an aqueous work-up, gave a mixture of diastereoisomers of the adduct **25**, resulting from simultaneous removal of the benzoate group in **18** (Scheme 2). Oxidation of the primary and secondary hydroxyl groups in **25** next led to the ketoaldehyde **26**, which reacted



15 **16** **17** **18** **19** **20** **21** **22** **23**, R = H **24**, R = TBS

Scheme 1. Reagents and conditions: (a) TBAI, DIPEA, MOMCl, CH_2Cl_2, 83%; (b) TBAF, THF, 60%; (c) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 82%; (d) *p*-methoxybenzaldehyde dimethyl acetal, CH_2Cl_2, 40 °C, 77%; (e) $(COCl)_2$, DMSO, then NEt_3, CH_2Cl_2, −78 °C, 82%; (f) $CrCl_2$, DMF, $Bu_3SnCHBr_2$, LiI, THF, 48%; (g) DIBAL, CH_2Cl_2, 67%; (h) NEt_3, DMAP, TBSCl, 95%.



Scheme 2. Reagents and conditions: (a) **24**, *n*-BuLi, THF, −78 °C, then **18**, 92%; (b) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 85%; (c) HCCMgBr, THF, 0 °C; (d) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 98% (over two steps); (e) TBAF, THF, 55%.

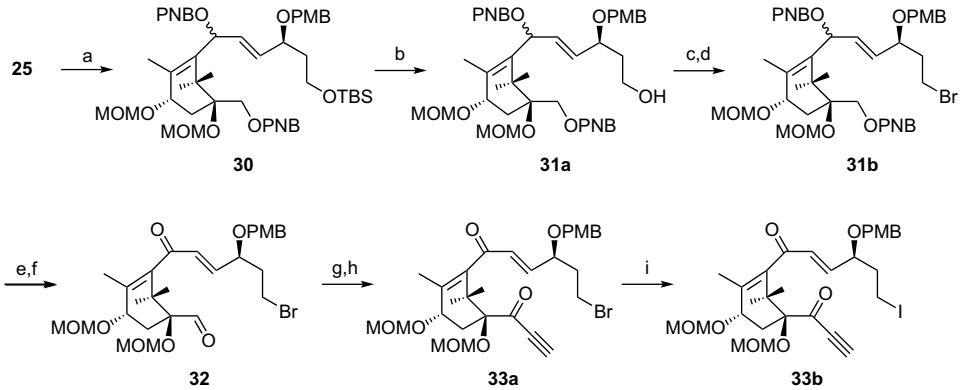
selectively with acetylenemagnesium bromide producing the propargylic alcohol **27**. Oxidation of **27**, using Dess–Martin periodinane, then gave the ynone **28a** in 98% yield over two steps. Our plan now was to remove the silyl ether protecting group in **28a** and then convert the resulting alcohol **28b** into the corresponding iodide **28c**, in readiness for the proposed radical cascade to a taxane, viz. **9**. Unfortunately, when the silyl ether **28a** was treated with TBAF, the resulting alcohol **28b** underwent immediate intramolecular oxy-Michael cyclisation producing the tetrahydrofuran **29** instead.

To overcome the above problem, we first converted the diol **25** into its bis-*p*-nitrobenzyl derivative **30** and then removed the TBS protection producing the alcohol **31a** (Scheme 3). The alcohol **31a** was next converted into the bromide **31b**, via its mesylate. The ester groups in **31b** were saponified and the resulting diol was then oxidised to the ketoaldehyde **32**. Finally, the ketoaldehyde **32** was converted into the enynone **33a** using procedures described earlier in the conversion of **26** into **28**. Interchange of bromide for iodide in **33a**, using Finkelstein conditions, then gave the radical precursor **33b**. Much to our chagrin, when the iodide **33b** was treated with Bu_3SnH–AIBN, the only 'product' isolated was *p*-anisaldehyde. We believe the *p*-anisaldehyde originates from cleavage of the benzyl ether group at C7 in **33b** via a process involving 1,5-H abstraction by the alkyl radical intermediate **34**, leading to the benzyl radical **35**, which then undergoes a precedented fragmentation as shown in Scheme 4.[25] Unfortunately, no products, resulting from the anticipated radical cascade, were isolated.

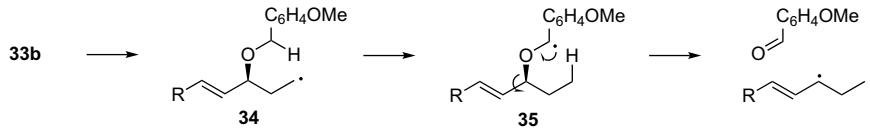
Almost as a last resort we then attempted to carry out a radical cascade from the substrate **36a** containing no protecting group associated with the C7 hydroxy group. This alcohol was easily produced from the PMB ether **33b** after treatment with DDQ in CH_2Cl_2–H_2O at 0 °C (Scheme 5). Subsequent treatment of the iodide **36a** with Bu_3SnH–AIBN led to a mixture of products, but we were baffled to find that not only did none of them correspond to the substituted taxane ring system **37**, but also none of them contained any alkene unsaturation on analysis of their NMR spectroscopic data! A similar fate was met by the corresponding TBS ether (**36b**).

At this point in time in our studies, we asked ourselves whether it was simply the oxy-substitution at C7, which was affecting the attempted radical cascade reactions from the iodides **33b** and **36**, or perhaps it had something to do with the oxy-substitutions in the A-rings of the same precursors. To answer this question we decided to examine a radical cascade from the substituted iodide **41**, which lacked any oxy-functionality at C7, but contained a fully oxy-substituted A-ring. The iodoenynedione **41** was produced from the aldehyde **18** and the vinylstannane **38** derived from pent-4-yn-1-ol[26] using procedures and reagents, which were identical to those used previously in the syntheses of the analogous compounds **28**, **33** and **36** from **18** (Scheme 6).

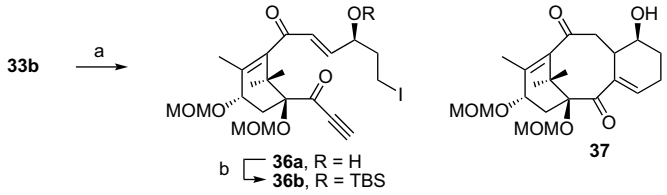
We were gratified to find that when the iodide **41** was treated with Bu_3SnH–AIBN, it underwent alkyl radical formation, followed by a tandem 12-*endo*-*dig* macrocyclisation and 6-*exo*-*trig* cyclisation leading to the 6,8,6-tricyclic dienedione **42**, in 44% yield after purification by chromatography. The structure and stereochemistry of the tricycle **42** followed from analysis of its ^1H–^1H COSY NMR spectroscopic data together with comparison of its spectroscopic data with those of the analogue **7a** devoid of oxy-substitution in the A-ring, prepared by us in early work.[19]



Scheme 3. Reagents and conditions: (a) PNBCl, NEt_3, DMAP, CH_2Cl_2, 97%; (b) HF·Py, Py, 84%; (c) MsCl, NEt_3, CH_2Cl_2; (d) LiBr, THF, 56 °C, 73% (over two steps); (e) K_2CO_3, MeOH, 86%; (f) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2; (g) HCCMgBr, THF, 0 °C; (h) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 67% (over three steps); (i) NaI, butan-2-one, 80 °C, 95%.



Scheme 4. Fragmentation of the alkyl radical centre produced from the iodide **33b**, leading to *p*-anisaldehyde.



Scheme 5. Reagents and conditions: (a) DDQ, CH_2Cl_2–H_2O, 87%; (b) TBSOTf, 2,6-lutidene, CH_2Cl_2, 56%.

The successful outcome of the cascade cyclisation from **41** to **42** demonstrated that the oxy-substituents in the A-ring of the precursor **41** had no effect on the outcome of the cascade. With the benefit of hindsight, the failure of the C7 oxy-substituted enynediones **36** to undergo the anticipated cascade radical sequence, leading to **37**, could be due to an unforeseen, competitive, H-radical abstraction process involving the C7–H centre. Thus, the alkyl radical centre **44** produced from **36** would be expected to undergo a 12-*endo*-*dig* cyclisation leading to the vinylic radical species **45** (Scheme 7). Instead of undergoing the expected 6-*exo*-*trig* cyclisation, leading to **37**, the vinylic radical **45** could then undergo 1,5-H abstraction leading to the new radical centre **46**, which is stabilised by both the neighbouring oxy-centre and the conjugated enone unit. The radical centre **46** could then undergo fragmentation, producing a new carbonyl group at C7, i.e., **48**, or it could take part in a variety of alternative cyclisation and/or H-abstraction processes from the delocalised radical species **47**, leading to a plethora of products. Interesting as these suggestions may be, we have no experimental evidence to support them and they must therefore remain as speculation for the time being.

Our synthesis of the tetraoxy-bis-nortaxadiene **42** is distinguished from other approaches to the taxane ring system, in that the B and C rings are produced in a single step from a substituted A-ring precursor. In the syntheses of taxol **1** developed by Holton[4] and Wender[7] and their respective colleagues, the A,B-ring system was produced first, to which the C-ring was later annulated. By contrast, the research groups led by Nicolaou,[5] Danishefsky,[6] and Kuwajima[8] all prepared ring A and ring C precursors as a prelude to making the eight-membered B-ring. Finally, Mukaiyama et al.[9] synthesised their taxol, by first preparing the B-ring and then annulating the C (first) and the A-ring. Although our own synthetic approach to taxol was eventually thwarted by the lack of sufficient quantities of the taxadiene **42** to continue with, it is gratifying to note that **42** is at the same oxidation level, and of similar constitution, to the advanced intermediate **43** used by Kuwajima et al.[8] in their synthesis of taxol. Thus, a synthetic sequence involving 1,2-carbonyl group transposition, i.e., C10 to C9, and oxidative dehydrogenation of the C7 to C8 bond in **42**, as key steps, could have provided access to the compound **43** from **42**.

3. Conclusions

The approach to complex polycyclic structures involving cascades of radical cyclisations is a powerful strategy, which is now widely applied in contemporary organic synthesis. Protagonists of the applications of this novel radical chemistry will emphasise its special benefits when compared with corresponding ionic reactions. For our own part, we have shown here, and elsewhere, how powerful radical cascade reactions can be in accessing a variety of complex ring-fused systems, not just taxanes, but steroids and a multitude of polycyclic terpenoids.[17] We would also emphasise that when these same radical cascades do not proceed according to plan, they can always be relied upon to produce new chemistry and interesting new chemical structures.

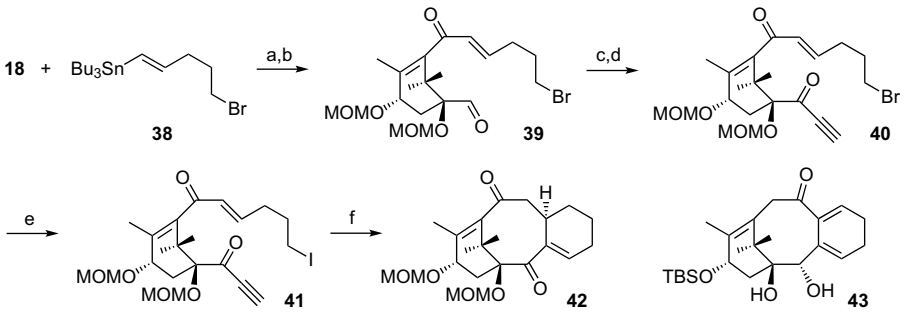
4. Experimental

4.1. General details

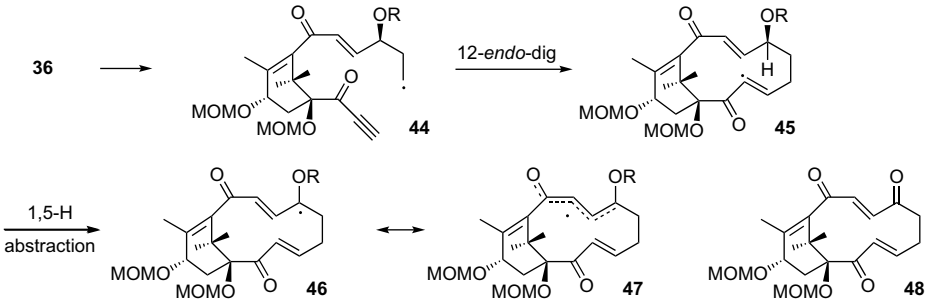
For general experimental details see Ref. 27.

*4.1.1. [(S)-2-(4-Methoxy-phenyl)-[1,3]dioxan-4-yl]-methanol (**20**)*

4-Methoxybenzaldehyde dimethyl acetal (2.00 mL, 11.7 mmol) was added dropwise over 5 min to a stirred solution of (*S*)-1,2,4-butanetriol **19** (1.01 g, 9.5 mmol) in dichloromethane (30 mL) at room temperature. *p*-Toluenesulfonic acid (0.13 g, 0.60 mmol) was added in one portion and the mixture was then heated at 40 °C for 20 h under a nitrogen atmosphere. The mixture was cooled and then concentrated in vacuo. The residue was purified by flash column chromatography on silica, using 40% ethyl acetate in petroleum ether as eluent, to give the *alcohol* (1.64 g, 77%) as a colourless oil; $[\alpha]_D^{23}$ +7.2 (*c* 1.3, $CHCl_3$); ν_{max} (film)/cm^{-1} 3595, 3491, 2936 and 2865; δ_H (360 MHz, $CDCl_3$) 1.38 (1H, br d, *J* 13.2, OCH_2CHHCH), 1.76–1.90 (1H, m, OCH_2CHHCH), 2.76 (1H, br s, O*H*), 3.59 (2H, br d, *J* 5.4, $CHOCH_2OH$), 3.78 (3H, s, $ArOCH_3$), 3.87–3.96 (2H, m, CH_2CHO), 4.24 (1H, ddd, *J* 1.0, 5.0 and 11.3, CH_2CHO), 5.46 (1H, s, C*H*Ar), 6.89 (2H, d, *J* 8.8, 2×Ar*H*), 7.42 (2H, d, *J* 8.8, 2×Ar*H*); δ_C (90 MHz, $CDCl_3$) 26.7 (t),



Scheme 6. Reagents and conditions: (a) **38**, *n*-BuLi, THF, −78 °C, then **18**; (b) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 86% (over two steps); (c) HCCMgBr, THF, 0 °C; (d) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 64% (over two steps); (e) NaI, butan-2-one, 80 °C, 58%; (f) Bu_3SnH, AIBN, PhH, 80 °C, 44%.



Scheme 7. Possible 1,5-H abstraction from the vinylic radical **45**.

55.2 (q), 65.4 (t), 66.5 (t), 77.5 (d), 101.0 (d), 113.5 (2×d), 127.4 (2×d), 130.9 (s), 159.9 (s); *m*/*z* (ES) 247.0931 (M^++Na, 100%, $C_{12}H_{16}NaO_4$ requires 247.0946).

*4.1.2. (S)-2-(4-Methoxy-phenyl)-[1,3]dioxane-4-carbaldehyde (**21**)*

A solution of DMSO (0.9 mL, 12.6 mmol) in dichloromethane (10 mL) was added dropwise over 15 min to a stirred solution of oxalyl chloride (0.62 mL, 7.13 mmol) in dichloromethane (10 mL) at −78 °C under a nitrogen atmosphere. The solution was stirred at −78 °C for 20 min and then a solution of the alcohol **20** (1.01 g, 4.50 mmol) in dichloromethane (10 mL) was added dropwise over 15 min. The solution was stirred at −78 °C for 25 min, then triethylamine (2.00 mL, 27.7 mmol) was added dropwise over 5 min and the mixture was allowed to warm to room temperature over 1 h. Water (20 mL) was added and the separated aqueous phase was then extracted with dichloromethane (2×20 mL). The combined organic extracts were washed with brine (20 mL), then dried over magnesium sulfate and concentrated in vacuo. The residue was purified by flash column chromatography on silica, using 40% ethyl acetate in petroleum ether as eluent, to give the *aldehyde* (0.817 g, 82%) as a colourless oil; ν_{max} (film)/cm^{-1} 2934, 2860 and 1738; δ_H (360 MHz, $CDCl_3$) 1.78 (1H, dtd, *J* 1.5, 2.7 and 13.4, OCH_2CHHCH), 1.95 (1H, dtd, *J* 5.0, 11.9 and 13.4, OCH_2CHHCH), 3.78–3.80 (1H, m, CH_2CHO), 3.81 (3H, s, $ArOCH_3$), 3.99 (1H, ddd, *J* 2.7, 11.7 and 11.9, CH_2CHO), 4.28–4.37 (1H, m, CH_2CHO), 5.56 (1H, s, CHAr), 6.93 (2H, d, *J* 8.7, 2×ArH), 7.46 (2H, d, *J* 8.7, 2×ArH), 9.71 (1H, s, CHO); δ_C (90 MHz, $CDCl_3$) 25.9 (t), 55.3 (q), 66.4 (t), 80.3 (d), 101.1 (d), 113.7 (2×d), 127.4 (2×d), 130.2 (s), 160.2 (s), 200.6 (d), *m*/*z* (ES) 277.1069 (M^++MeOH+Na, 100%, $C_{13}H_{18}NaO_5$ requires 277.1052).

*4.1.3. Tributyl-{(E)-2-[(S)-2-(4-methoxy-phenyl)-[1,3]dioxan-4-yl]-vinyl}-stannane (**22**)*

N,*N*-Dimethylformamide (3 mL) was added dropwise to a stirred solution of chromium(II) chloride (2.5 g, 20 mmol, weighed out in a glove bag under an argon atmosphere) in THF (60 mL) at room temperature under an argon atmosphere. The solution was stirred at room temperature for 20 min and then a solution of $Bu_3SnCHBr_2$ (3.6 g, 7.8 mmol) and the aldehyde **21** (0.46 g, 2.0 mmol) in THF (30 mL) was added dropwise over 10 min via cannula. The reaction flask was covered with aluminium foil and then a solution of lithium iodide (2.26 g, 16.9 mmol) in THF (30 mL) was added dropwise via cannula over 10 min. The mixture was stirred at room temperature for 17 h, then water (50 mL) was added and the aqueous layer was extracted with diethyl ether (2×50 mL). The combined organic extracts were dried over magnesium sulfate and then concentrated in vacuo. The residue was purified by flash column chromatography on silica, using 10% diethyl ether in petroleum ether (bp 40–60 °C) as eluent, to give the *stannane* (0.5 g, 48%) as a colourless oil; $[\alpha]_D^{23}$ −5.7 (*c* 0.98, $CDCl_3$). (Found: C, 58.7; H, 8.3. $C_{25}H_{42}O_3Sn$ requires C, 58.8; H, 8.3%.) ν_{max} (film)/cm^{-1} 2937, 2851, 1615 and 1518; δ_H (360 MHz, $CDCl_3$) 0.83–1.04 (15H, m, 3×CH_2CH_3, 3×CH_2CH_3), 1.26–1.40 (6H, m, 3×$CH_2CH_2CH_3$), 1.45–1.59 (6H, m, 3×$SnCH_2$), 1.63 (1H, br dd, *J* 1.3 and 13.0, CHHCHO), 1.94 (1H, dtd, *J* 5.0, 11.7 and 130, CHHCHO), 3.81 (3H, s, $ArOCH_3$), 4.00 (1H, dt, *J* 2.5 and 11.5, CH_2CHO), 4.29 (1H, ddd, *J* 0.9, 5.0 and 11.5, CH_2CHO), 4.32–4.39 (1H, m, CH_2CHO), 5.55 (1H, s, CHAr), 6.12 (1H, dd, *J* 4.9 and 19.3, CH=CHSn), 6.29 (1H, dd, *J* 1.2 and 19.3, CH=CHSn), 6.92 (2H, d, *J* 8.8, 2×ArH), 7.48 (2H, d, *J* 8.8, 2×ArH); δ_C (90 MHz, $CDCl_3$) 7.6 (3×t), 13.7 (3×q), 27.3 (3×t), 29.1 (3×t), 31.3 (t), 55.2 (q), 67.0 (t), 79.9 (d), 101.1 (d), 113.6 (2×d), 127.5 (2×d), 129.1 (d), 131.1 (s), 147.5 (d), 159.9 (s); *m*/*z* (ES) 511.2252 (M^++H, 20%, $C_{25}H_{43}O_3Sn$ requires 511.2234).

*4.1.4. (E)-(S)-3-(4-Methoxy-benzyloxy)-5-tributylstannanyl-pent-4-en-1-ol (**23**)*

A solution of DIBAL (1.0 M) in hexanes (2.10 mL, 2.10 mmol) was added dropwise over 5 min to a stirred solution of the stannane **22** (0.53 g, 1.04 mmol) in dichloromethane (20 mL) at 0 °C under a nitrogen atmosphere. The solution was stirred at room temperature for 1 h and then a saturated solution of aqueous Rochelle's salt (5 mL) was added at 0 °C. The mixture was warmed to room temperature over 20 min and then extracted with diethyl ether (3×20 mL). The combined organic extracts were dried over magnesium sulfate and then concentrated in vacuo. The residue was purified by flash column chromatography on silica, using 20% ethyl acetate in petroleum ether (bp 40–60 °C) as eluent, to give the *alcohol* (0.36 g, 67%) as a colourless oil; ν_{max} (film)/cm^{-1} 3626, 3507, 2929, 1613 and 1514; δ_H (360 MHz, $CDCl_3$) 0.83–0.97 (15H, m, 3×CH_2CH_3, 3×CH_2CH_3), 1.24–1.39 (6H, m, 3×$CH_2CH_2CH_3$), 1.46–1.58 (6H, m, 3×$SnCH_2$), 1.72–1.93 (2H, m, $CH_2CHOPMB$), 2.57 (1H, br s, OH), 3.68–3.85 (2H, m, CH_2OH), 3.81 (3H, s, $ArOCH_3$), 3.96 (1H, dt, *J* 4.6 and 7.4, $CH_2CHOPMB$), 4.30 (1H, d, *J* 11.4, OCHHAr), 4.50 (1H, d, *J* 11.4, OCHHAr), 5.91 (1H, dd, *J* 7.4 and 19.1, CH=CHSn), 6.20 (1H, dd, *J* 0.7 and 19.1, CH=CHSn), 6.88 (2H, d, *J* 8.7, 2×ArH), 7.24 (2H, d, *J* 8.7, 2×ArH); δ_C (90 MHz, $CDCl_3$) 9.6 (3×t), 13.8 (3×q), 27.3 (3×t), 29.2 (3×t), 37.8 (t), 55.3 (t), 61.0 (q), 70.0 (t), 82.8 (d), 113.9 (2×d), 129.5 (2×d), 130.5 (s), 132.0 (d), 148.1 (d), 159.3 (s); *m*/*z* (ES) 513.2441 (M^++H, 100%, $C_{25}H_{44}O_3Sn$ requires 513.2391).

*4.1.5. tert-Butyl-[(E)-(S)-3-(4-methoxy-benzyloxy)-5-tributyl-stannanyl-pent-4-enyloxy]-dimethyl-silane (**24**)*

N,*N*-Dimethylaminopyridine (6.6 mg, 0.054 mmol) was added in one portion to a stirred solution of the alcohol **23** (0.25 g, 0.48 mmol), triethylamine (0.15 mL, 1.08 mmol) and *tert*-butyldimethylsilyl chloride (0.12 g, 0.76 mmol) in dichloromethane (1.5 mL) at room temperature. The solution was stirred at room temperature for 4 h and then a saturated solution of aqueous sodium hydrogencarbonate (5 mL) was added. The separated aqueous phase was extracted with dichloromethane (3×5 mL) and the combined organic extracts were then dried over magnesium sulfate and concentrated in vacuo. The residue was purified by flash column chromatography on silica using 10% diethyl ether in petroleum ether (bp 40–60 °C) as eluent to give the *silyl ether* (0.29 g, 95%) as

a colourless oil; $[\alpha]_D^{23}$ −30.3 (*c* 1.15, $CHCl_3$). (Found: C, 59.6; H, 9.4. $C_{31}H_{58}O_3SnSi$ requires C, 59.4; H, 9.3%.) ν_{max} (film)/cm^{-1} 2931, 2856, 1613 and 1514; δ_H (360 MHz, $CDCl_3$) 0.04 (6H, s, 2×SiC*H*$_3$), 0.84–0.95 (24H, m, 3×C*H*$_2$CH$_3$, 3×CH$_2$C*H*$_3$, 3×SiC(C*H*$_3$)$_3$), 1.47–1.58 (6H, m, 3×C*H*$_2$CH$_2$CH$_3$), 1.33 (6H, ttd, *J* 7.3, 7.3 and 7.3, 3×SnC*H*$_2$), 1.70 (1H, tdd, *J* 6.5, 12.3 and 13.4, C*H*HCH$_2$OTBS), 1.86 (1H, tdd, *J* 6.2, 7.2 and 12.3, C*H*HCH$_2$OTBS), 3.64 (1H, td *J* 6.2 and 10.1, C*H*HOTBS), 3.72 (1H, td, *J* 6.5 and 10.1, C*H*HOTBS), 3.81 (3H, s, ArOC*H*$_3$), 3.87 (1H, dd, *J* 7.2 and 13.4, CH$_2$C*H*OPMB), 4.28 (1H, d, *J* 11.3, OC*H*HAr), 4.52 (1H, d, *J* 11.3, OC*H*HAr), 5.86 (1H, dd, *J* 7.2 and 19.1, C*H*=CHSn), 6.14 (1H, dd, *J* 0.7 and 19.1, CH=C*H*Sn), 6.87 (2H, d, *J* 8.7, 2×Ar*H*), 7.25 (2H, d, *J* 8.7, 2×Ar*H*); δ_C (90 MHz, $CDCl_3$) −5.2 (2×q), 9.6 (3×t), 13.8 (3×q), 18.4 (s), 26.0 (3×q), 27.3 (3×t), 29.2 (3×t), 38.7 (t), 55.3 (q), 59.6 (t), 69.9 (t), 80.1 (d), 113.8 (2×d), 129.4 (2×d), 131.1 (d), 131.3 (s), 149.0 (d), 159.0 (s); *m*/*z* (ES) 627.3294 (M^++H, 95%, $C_{31}H_{58}O_3SnSi$ requires 627.3287), 649.3107 (M^++Na, 100%, $C_{31}H_{58}NaO_3SiSn$ requires 649.3075).

4.1.6. Benzoic acid (S)-3-(tert-butyl-dimethyl-silanyloxymethyl)-1,5-bis-methoxymethoxy-2,2,4-trimethyl-cyclohex-3-enyl ester (**16**)

Tetrabutylammonium iodide (0.83 g, 2.26 mmol) was added in one portion to a stirred solution of the diol **15** (0.30 g, 0.64 mmol)[23] in dry dichloromethane (10 mL) at room temperature. Diisopropylethylamine (5.5 mL, 31.6 mmol) was added dropwise over 2 min and then methyloxymethyl chloride (1.8 mL, 23.7 mmol) was added over 2 s at room temperature. The mixture was stirred at room temperature for 17 h and then more tetrabutylammonium iodide (0.52 g, 1.41 mmol), diisopropylethylamine (3.6 mL, 20.7 mmol) and methyloxymethyl chloride (1.2 mL, 14.7 mmol) were added. The mixture was then stirred at room temperature for a further 4 h. Water (5 mL) was added and the separated aqueous phase was then extracted with dichloromethane (2×5 mL). The combined organic extracts were dried over magnesium sulfate and then concentrated in vacuo. The residue was purified by flash column chromatography on silica, using 20% ethyl acetate in petroleum ether (bp 40–60 °C) as eluent, to give the *protected diol* (0.28 g, 83%); $[\alpha]_D^{23}$ −3.4 (*c* 1.1, $CHCl_3$); ν_{max} (film)/cm^{-1} 2954 and 1716; δ_H (360 MHz, $CDCl_3$) 0.09 (6H, s, 2×SiC*H*$_3$), 0.91 (9H, s, 3×SiC(C*H*$_3$)$_3$), 1.19 (6H, s, 2×C(C*H*$_3$)$_2$), 1.80 (3H, s, C=C(C*H*$_3$)), 2.15 (1H, dd, *J* 5.6 and 14.3, OCHC*H*H), 2.52 (1H, dd, *J* 2.9 and 14.3, OCHC*H*H), 3.27 (3H, s, OC*H*$_3$), 3.35 (3H, s, OC*H*$_3$), 4.06 (1H, dd, *J* 2.9 and 5.6, OC*H*CH$_2$), 4.17 (2H, s, C*H*$_2$OSi), 4.20 (1H, d, *J* 7.1, OC*H*HO), 4.40 (1H, d, *J* 11.9, C*H*HOBz), 4.56 (1H, d, *J* 11.9, C*H*HOBz), 4.71 (1H, d, *J* 7.1, OC*H*HO), 4.87 (1H, d, *J* 7.4, OC*H*HO), 5.00 (1H, d, *J* 7.4, OC*H*HO), 7.43 (2H, t, *J* 7.6, 2×Ar*H*), 7.54 (1H, t, *J* 7.4, Ar*H*), 8.05 (2H, d, *J* 7.1, 2×Ar*H*); δ_C (90 MHz, $CDCl_3$) −5.4 (2×q), 16.6 (q), 18.3 (s), 20.9 (q), 23.9 (q), 25.8 (3×q), 27.7 (t), 42.6 (s), 55.6 (q), 55.8 (q), 59.3 (t), 68.4 (t), 73.2 (d), 78.5 (s), 91.7 (t), 94.5 (t), 128.5 (2×d), 129.5 (2×d), 130.2 (s), 130.5 (s), 132.8 (d), 139.3 (s), 166.1 (s); *m*/*z* (ES) 545.2878 (M^++Na, 100%, $C_{28}H_{46}NaO_7Si$ requires 545.2911).

4.1.7. Benzoic acid (S)-3-hydroxymethyl-1,5-bis-methoxymethoxy-2,2,4-trimethyl-cyclohex-3-enyl ester (**17**)

Tetrabutylammonium fluoride (0.411 g, 0.613 mmol) was added in one portion to a stirred solution of the silyl ether **16** (0.320 g, 0.613 mmol) in dry THF (10 mL) at room temperature, and the mixture was then stirred at room temperature for 2 h. A saturated solution of aqueous ammonium chloride (10 mL) followed by diethyl ether (10 mL) were added, and the separated aqueous phase was then extracted with diethyl ether (2×10 mL). The combined organic extracts were dried over magnesium sulfate and then concentrated in vacuo. The residue was purified by flash column chromatography on silica, using 50% ethyl acetate in petroleum ether (bp 40–60 °C) as eluent, to give the *alcohol* (0.15 g, 60%) as a colourless oil; ν_{max} (film)/cm^{-1} 3614, 3501 (br), 2952 and 1716; δ_H (360 MHz, $CDCl_3$) 1.16 (3H, s, C(C*H*$_3$)$_2$), 1.21 (3H, s, C(C*H*$_3$)$_2$), 1.85 (3H, s, C=C(C*H*$_3$)), 2.14 (1H, dd, *J* 5.5 and 14.3, OCHC*H*H), 2.46 (1H, dd, *J* 3.5 and 14.3, OCHC*H*H), 3.27 (3H, s, OC*H*$_3$), 3.34 (3H, s, OC*H*$_3$), 4.04 (1H, dd, *J* 3.5 and 5.5, OC*H*CH$_2$), 4.14 (1H, d, *J* 11.7, C*H*HOH), 4.21 (1H, d, *J* 7.1, OC*H*HO), 4.21 (1H, d, *J* 11.7, C*H*HOH), 4.38 (1H, d, *J* 11.9, C*H*HOBz), 4.56 (1H, d, *J* 11.9, C*H*HOBz), 4.69 (1H, d, *J* 7.1, OC*H*HO), 4.88 (1H, d, *J* 7.4, OC*H*HO), 4.97 (1H, d, *J* 7.4, OC*H*HO), 7.42 (2H, t, *J* 7.6, 2×Ar*H*), 7.54 (1H, t, *J* 7.4, Ar*H*), 8.03 (2H, d, *J* 8.5, 2×Ar*H*); δ_C (90 MHz, $CDCl_3$) 16.4 (q), 21.2 (q), 23.6 (q), 27.9 (t), 41.6 (s), 55.6 (q), 55.8 (q), 58.9 (t), 68.2 (t), 73.0 (d), 78.3 (s), 91.7 (t), 94.7 (t), 128.5 (2×d), 129.4 (2×d), 130.3 (s), 131.6 (s), 132.9 (d), 140.0 (s), 166.1 (s); *m*/*z* (ES) 431.2065 (M^++Na, 100%, $C_{22}H_{32}NaO_7$ requires 431.2046).

4.1.8. Benzoic acid (1S,5S)-3-formyl-1,5-bis-methoxymethoxy-2,2,4-trimethyl-cyclohex-3-enylmethyl ester (**18**)

Sodium hydrogencarbonate (150 mg, 1.79 mmol) and Dess–Martin periodinane (148 mg, 0.35 mmol) were added to a stirred solution of the alcohol **17** (65.8 mg, 0.161 mmol) in dichloromethane (10 mL) at room temperature. The mixture was stirred at room temperature for 1 h, and then saturated solutions of aqueous sodium hydrogencarbonate (5 mL) and aqueous sodium thiosulfate (5 mL) were added. The biphasic mixture was stirred at room temperature for 5 min, and then diethyl ether (10 mL) was added. The separated aqueous phase was extracted with diethyl ether (2×10 mL) then the combined organic extracts were then dried over magnesium sulfate and concentrated in vacuo. The residue was purified by flash column chromatography on silica, using 40% ethyl acetate in petroleum ether (bp 40–60 °C) as eluent, to give the *aldehyde* (54 mg, 82%) as a colourless oil; $[\alpha]_D^{23}$ +2.3 (*c* 1.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 2952, 1719 and 1682; δ_H (360 MHz, $CDCl_3$) 1.35 (3H, s, C(C*H*$_3$)$_2$), 1.38 (3H, s, C(C*H*$_3$)$_2$), 2.13 (3H, s, C=C(C*H*$_3$)), 2.26 (1H, dd, *J* 5.6 and 14.4, OCHC*H*H), 2.38 (1H, dd, *J* 5.6 and 14.4, OCHC*H*H), 3.34 (3H, s, OC*H*$_3$), 3.37 (3H, s, OC*H*$_3$), 4.16 (1H, t, *J* 5.6, OC*H*CH$_2$), 4.36 (1H, d, *J* 7.1, OC*H*HO), 4.42 (1H, d, *J* 12.2, C*H*HOBz), 4.46 (1H, d, *J* 12.2, C*H*HOBz), 4.74 (1H, d, *J* 7.1, OC*H*HO), 4.92 (1H, d, *J* 7.4, OC*H*HO), 4.95 (1H, d, *J* 7.4, OC*H*HO), 7.43–7.49 (2H, m, 2×Ar*H*), 7.55–7.61 (1H, m, Ar*H*), 8.03–8.07 (2H, m, 2×Ar*H*), 10.20 (1H, s, C*H*O); δ_C (90 MHz, $CDCl_3$) 15.6 (q), 22.1 (q), 22.5 (q), 28.3 (t), 41.7 (s), 55.9 (q), 56.1 (q), 67.4 (t), 73.8 (d), 78.8 (s), 91.7 (t), 95.5 (t), 128.6 (2×d), 129.5 (2×d), 130.1 (s), 133.1 (d), 140.5 (s), 148.5 (s), 166.1 (s), 193.7 (d); *m*/*z* (ES) 429.1991 (M^++Na, 100%, $C_{22}H_{30}NaO_7$ requires 429.1889).

4.1.9. (E)-(S)-6-(tert-Butyl-dimethyl-silanyloxy)-1-((3S,5S)-5-hydroxymethyl-3,5-bis-methoxymethoxy-2,6,6-trimethyl-cyclohex-1-enyl)-4-(4-methoxy-benzyloxy)-hex-2-en-1-ol (**25**)

A solution of *n*-BuLi (2.5 M) in hexanes (1.6 mL, 2.5 mmol) was added dropwise over 2 min to a stirred solution of the vinylstannane **24** (1.7 g, 2.7 mmol) in dry THF (4 mL) at −78 °C. The solution was stirred at −78 °C for 1 h and then a solution of the aldehyde **18** (290 mg, 0.71 mmol) in dry THF (10 mL) was added dropwise over 2 min at −78 °C. The mixture was warmed to room temperature over 17 h, and then water (30 mL) and diethyl ether (30 mL) were added. The separated aqueous phase was extracted with diethyl ether (3×30 mL) and the combined organic extracts were dried then over magnesium sulfate and concentrated in vacuo. The residue was purified by flash column chromatography on silica, using 20% ethyl acetate in petroleum ether (bp 40–60 °C) as eluent, to give: (i) *diastereoisomer A* (177 mg, 39%); (eluted first) ν_{max} (film)/cm^{-1} 3609, 2954, 1612 and 1514; δ_H (360 MHz, $CDCl_3$) 0.04 (6H, s, 2×SiC*H*$_3$), 0.89 (9H, s, 3×SiC(C*H*$_3$)$_3$), 1.03 (3H, s, C(C*H*$_3$)$_2$), 1.20 (3H, s, C(C*H*$_3$)$_2$), 1.62–1.73 (2H, m, C*H*$_2$CH$_2$OTBS), 1.93 (3H, s, C=C(C*H*$_3$)), 2.04 (1H, dd, *J* 5.3 and 14.5, OCHC*H*H), 2.34 (1H, d, *J* 14.5, OCHC*H*H), 3.43 (3H, s, OC*H*$_3$), 3.44 (3H, s, OC*H*$_3$), 3.60–3.75 (4H, m, CH$_2$C*H*$_2$OTBS and C*H*$_2$OH), 3.80 (3H, s, ArOC*H*$_3$), 3.89–3.95 (1H, m, OC*H*CH$_2$), 3.99 (1H, dd, *J* 7.9 and 13.1, C*H*OPMB), 4.29 (1H, d, *J* 11.2, OC*H*HArOMe), 4.50 (1H, d, *J* 11.2, OC*H*HArOMe), 4.68 (1H, d, *J* 6.8, OC*H*HO), 4.83 (1H, d, *J* 6.8, OC*H*HO), 4.90 (1H, s, C=

CC*H*(O)CH=CH), 4.91 (1H, d, *J* 7.2, OC*H*HO), 4.96 (1H, d, *J* 7.2, OC*H*HO), 5.64 (1H, ddd, *J* 1.0, 7.9 and 15.7, CH=C*H*CH(OPMB)), 5.88 (1H, dd, *J* 4.7 and 15.7, C*H*=CHCH(OPMB)), 6.87 (2H, d, *J* 8.5, 2×Ar*H*), 7.24 (2H, d, *J* 8.5, 2×Ar*H*); δ_C (90 MHz, $CDCl_3$) −5.3 (2×q), 17.7 (q), 18.3 (s), 23.3 (q), 26.0 (3×q), 28.6 (t), 29.8 (q), 39.0 (t), 42.9 (s), 55.3 (q), 55.5 (q), 56.4 (q), 59.4 (t), 65.9 (t), 69.8 (d), 70.2 (t), 75.6 (d), 76.0 (d), 80.0 (s), 91.6 (t), 96.8 (t), 113.8 (2×d), 129.4 (2×d), 130.8 (s), 131.0 (s), 131.6 (d), 134.0 (d), 142.2 (s), 159.1 (s); *m*/*z* (ES) 661.3727 (M^++Na, 100%, $C_{34}H_{58}NaO_9Si$ requires 661.3748); and (ii) *diastereoisomer B* (208 mg, 46%); (eluted second) ν_{max} (film)/cm^{-1} 3607, 2955, 1602 and 1514; δ_H (360 MHz, $CDCl_3$) 0.04 (2×3H, s, 2×SiC*H*$_3$), 0.89 (9H, s, 3×SiC(C*H*$_3$)$_3$), 1.12 (3H, s, C(C*H*$_3$)$_2$), 1.19 (3H, s, C(C*H*$_3$)$_2$), 1.75–1.81 (1H, m, C*H*HCH$_2$OTBS), 1.89–2.02 (1H, m, C*H*HCH$_2$OTBS), 1.89 (3H, s, C=C(C*H*$_3$)), 2.10 (1H, dd, *J* 5.8 and 14.6, OCHC*H*H), 2.23 (1H, dd, *J* 5.8 and 14.6, OCHC*H*H), 3.43 (3H, s, OC*H*$_3$), 3.44 (3H, s, OC*H*$_3$), 3.75–3.83 (4H, m, CH$_2$C*H*$_2$OTBS and C*H*$_2$OH), 3.80 (3H, s, ArOC*H*$_3$), 3.91 (1H, t, *J* 5.8, OC*H*CH$_2$), 3.97–4.03 (1H, m, C*H*OPMB), 4.28 (1H, d, *J* 11.2, OC*H*HArOMe), 4.50 (1H, d, *J* 11.2, OC*H*HArOMe), 4.68 (1H, d, *J* 6.9, OC*H*HO), 4.82 (1H, d, *J* 6.9, OC*H*HO), 4.83 (1H, d, *J* 7.4, OC*H*HO), 4.94 (1H, d, *J* 7.4, OC*H*HO), 4.96 (1H, br d, *J* 4.2, C=CC*H*(O)CH=CH), 5.63 (1H, ddd, *J* 1.7, 8.0 and 15.6, CH=C*H*CH(OPMB)), 5.89 (1H, dd, *J* 4.2 and 15.6, C*H*=CHCH(OPMB)), 6.86 (2H, d, *J* 8.7, 2×Ar*H*), 7.23 (2H, d, *J* 8.7, 2×Ar*H*); δ_C (90 MHz, $CDCl_3$) −5.3 (2×q), 17.6 (q), 18.3 (s), 22.7 (q), 26.0 (3×q), 28.5 (t), 30.4 (q), 39.0 (t), 42.9 (s), 55.3 (q), 55.5 (q), 56.2 (q), 59.4 (t), 65.6 (t), 69.9 (d), 70.0 (t), 75.6 (d), 76.1 (d), 80.7 (s), 91.3 (t), 96.6 (t), 113.8 (2×d), 129.4 (2×d), 130.8 (s), 131.2 (d), 131.4 (s), 134.6 (d), 142.2 (s), 159.1 (s); *m*/*z* (ES) 661.3798 (M^++Na, 100%, $C_{34}H_{58}NaO_9Si$ requires 661.3748).

*4.1.10. (1S,5S)-3-[(E)-(S)-6-(tert-Butyl-dimethyl-silanyloxy)-4-(4-methoxy-benzyloxy)-hex-2-enoyl]-1,5-bis-methoxymethoxy-2,2,4-trimethyl-cyclohex-3-enecarbaldehyde (**26**)*

Sodium hydrogencarbonate (95.4 mg, 1.14 mmol) and Dess–Martin periodinane (153 mg, 0.36 mmol) were added in one portion to a stirred solution of a mixture of diastereoisomers of the alcohol **25** (72.0 mg, 0.113 mmol) in dichloromethane (4 mL) at room temperature. The mixture was stirred at room temperature for 2 h, and then saturated solutions of aqueous sodium hydrogencarbonate (5 mL) and aqueous sodium thiosulfate (5 mL) were added. The biphasic mixture was stirred at room temperature for 5 min and then diethyl ether (10 mL) was added. The separated aqueous phase was extracted with diethyl ether (3×10 mL), and the combined organic extracts were then dried over magnesium sulfate and concentrated in vacuo. The residue was purified by flash column chromatography on silica, using 20% ethyl acetate in petroleum ether (bp 40–60 °C) as eluent, to give the *ketoaldehyde* (60.7 mg, 85%) as a colourless oil; δ_H (360 MHz, $CDCl_3$) 0.04 (6H, s, 2×SiC*H*$_3$), 0.88 (9H, s, 3×SiC(C*H*$_3$)$_3$), 1.16 (3H, br s, C(C*H*$_3$)$_2$), 1.19 (3H, br s, C(C*H*$_3$)$_2$), 1.66 (3H, s, C=C(C*H*$_3$)), 1.98–2.09 (1H, m, C*H*HCH$_2$OTBS), 2.09–2.21 (1H, m, C*H*HCH$_2$OTBS), 2.23–2.27 (1H, m, OCHC*H*H), 2.40–2.47 (1H, m, OCHC*H*H), 3.41 (3H, s, OC*H*$_3$), 3.42 (3H, s, OC*H*$_3$), 3.79 (3H, s, ArOC*H*$_3$), 3.82 (2H, m, CH$_2$C*H*$_2$OTBS), 4.04–4.08 (1H, m, OC*H*CH$_2$), 4.21–4.29 (1H, m, C*H*OPMB), 4.36 (1H, d, *J* 11.4, OC*H*HArOMe), 4.52 (1H, d, *J* 11.4, OC*H*HArOMe), 4.64 (1H, d, *J* 6.8, OC*H*HO), 4.72 (1H, d, *J* 7.4, OC*H*HO), 4.75 (1H, d, *J* 6.8, OC*H*HO), 4.89 (1H, d, *J* 7.4, OC*H*HO), 6.33 (1H, d, *J* 15.9, C*H*=CHCH(OPMB)), 6.77 (1H, dd, *J* 6.5 and 15.9, CH=C*H*CH(OPMB)), 6.90 (2H, d, *J* 8.7, 2×Ar*H*), 7.22 (2H, d, *J* 8.7, 2×Ar*H*), 9.77 (1H, s, C*H*O).

*4.1.11. (E)-(S)-1-((3S,5S)-3,5-Bis-methoxymethoxy-2,6,6-trimethyl-5-propynoyl-cyclohex-1-enyl)-6-(tert-butyl-dimethyl-silanyloxy)-4-(4-methoxy-benzyloxy)-hex-2-en-1-one (**28a**)*

A solution of ethynylmagnesium bromide (0.5 M) in THF (1 mL, 0.50 mmol) was added dropwise over 5 min to a stirred solution of the aldehyde **26** (21.8 mg, 0.034 mmol) in dry THF (1.5 mL) at 0 °C. The mixture was warmed to room temperature over 17 h and then water (5 mL) and diethyl ether (10 mL) were added. The separated aqueous phase was extracted with diethyl ether (3×10 mL) and the combined organic extracts were then dried over magnesium sulfate and concentrated in vacuo to leave the propargyl alcohol **27** as an oil. Sodium hydrogencarbonate (21.9 mg, 0.261 mmol) and Dess–Martin periodinane (13.2 mg, 0.0311 mmol) were added in one portion to a stirred solution of **27** in dichloromethane (4 mL) at room temperature. The mixture was stirred at room temperature for 3.5 h, and then saturated solutions of aqueous sodium hydrogencarbonate (5 mL) and aqueous sodium thiosulfate (5 mL) were added. The biphasic mixture was stirred at room temperature for 5 min and then diethyl ether (10 mL) was added. The separated aqueous phase was extracted with diethyl ether (2×10 mL), and the combined organic extracts were then dried over magnesium sulfate and concentrated in vacuo. The residue was purified by flash column chromatography on silica, using 20% ethyl acetate in petroleum ether (bp 40–60 °C) as eluent, to give the *ynone* (13.3 mg, 98%) as a colourless oil; δ_H (360 MHz, $CDCl_3$) 0.04 (6H, s, 2×SiC*H*$_3$), 0.89 (9H, s, 3×SiC(C*H*$_3$)$_3$), 1.17 (3H, br s, C(C*H*$_3$)$_2$), 1.20 (3H, br s, C(C*H*$_3$)$_2$), 1.67 (3H, s, C=C(C*H*$_3$)), 1.97–2.08 (1H, m, C*H*HCH$_2$OTBS), 2.09–2.19 (1H, m, C*H*HCH$_2$OTBS), 2.22–2.27 (1H, m, OCHC*H*H), 2.41–2.48 (1H, m, OCHC*H*H), 3.40 (3H, s, OC*H*$_3$), 3.44 (3H, s, OC*H*$_3$), 3.48 (1H, s, C≡C*H*), 3.81 (3H, s, ArOC*H*$_3$), 3.83 (2H, m, CH$_2$C*H*$_2$OTBS), 4.02–4.08 (1H, m, OC*H*CH$_2$), 4.20–4.29 (1H, m, C*H*OPMB), 4.34 (1H, d, *J* 11.2, OC*H*HArOMe), 4.48 (1H, d, *J* 11.2, OC*H*HArOMe), 4.64 (1H, d, *J* 6.9, OC*H*HO), 4.71 (1H, d, *J* 7.2, OC*H*HO), 4.76 (1H, d, *J* 6.9, OC*H*HO), 4.90 (1H, d, *J* 7.2, OC*H*HO), 6.32 (1H, d, *J* 16.1, C*H*=CHCH(OPMB)), 6.78 (1H, dd, *J* 6.8 and 16.1, CH=C*H*CH(OPMB)), 6.89 (2H, d, *J* 8.9, 2×Ar*H*), 7.23 (2H, d, *J* 8.9, 2×Ar*H*).

*4.1.12. 1-((1S,5S)-3-{2-[(S)-3-(4-Methoxy-benzyloxy)-tetrahydrofuran-2-yl]-acetyl}-1,5-bis-methoxymethoxy-2,2,4-trimethyl-cyclohex-3-enyl)-propynone (**29**)*

Tetrabutylammonium fluoride (15 mg, 0.05 mmol) was added in one portion to a stirred solution of the silyl ether **28a** (13.3 mg, 0.02 mmol) in dry THF (2 mL) at room temperature. The mixture was stirred at room temperature for 1 h and then water (5 mL) and diethyl ether (10 mL) were added. The separated aqueous phase was extracted with diethyl ether (3×10 mL) and the combined organic extracts were then dried over magnesium sulfate and concentrated in vacuo. The residue was purified by flash column chromatography on silica, using 10% ethyl acetate in petroleum ether (bp 40–60 °C) as eluent, to give the substituted *tetrahydrofuran* (6.0 mg, 55%) as a colourless oil; δ_H (360 MHz, $CDCl_3$) 1.16 (3H, br s, C(C*H*$_3$)$_2$), 1.19 (3H, br s, C(C*H*$_3$)$_2$), 1.68 (3H, s, C=C(C*H*$_3$)), 1.86–2.22 (4H, m, (C=O)C*H*$_2$CH and CH(OPMB)C*H*$_2$CH$_2$), 2.23–2.27 (1H, m, OCHC*H*H), 2.40–2.46 (1H, m, OCHC*H*H), 3.39 (3H, s, OC*H*$_3$), 3.42 (1H, s, C≡C*H*), 3.48 (3H, s, OC*H*$_3$), 3.70–3.76 (1H, m, (C=O)CH$_2$-C*H*OCH$_2$), 3.74 (3H, s, ArOC*H*$_3$), 3.97–4.09 (3H, m, OC*H*CH$_2$ and CH(OPMB)CH$_2$C*H*$_2$OCH), 4.14–4.19 (1H, m, C*H*OPMB), 4.33 (1H, d, *J* 11.6, OC*H*HArOMe), 4.52 (1H, d, *J* 11.6, OC*H*HArOMe), 4.63 (1H, d, *J* 6.4, OC*H*HO), 4.69 (1H, d, *J* 7.1, OC*H*HO), 4.74 (1H, d, *J* 6.4, OC*H*HO), 4.89 (1H, d, *J* 7.1, OC*H*HO), 6.88 (2H, d, *J* 9.0, 2×Ar*H*), 7.21 (2H, d, *J* 9.0, 2×Ar*H*).

*4.1.13. [(E)-(S)-6-[(3S,5S)-3,5-Bis-methoxymethoxy-2,6,6-trimethyl-5-(4-nitrophenoxymethyl)-cyclohex-1-enyl]-3-(4-methoxy-benzyloxy)-6-(4-nitrophenoxy)-hex-4-enyloxy]-tert-butyl-dimethyl-silane (**30**)*

Triethylamine (0.31 mL, 2.22 mmol) and *N*,*N*-dimethylaminopyridine (13 mg, 0.11 mmol) were added to a stirred solution of diastereoisomer A of the diol **25** (142.6 mg, 0.224 mmol) in dry dichloromethane (10 mL) at room temperature. *para*-Nitrobenzoyl chloride (266 mg, 1.43 mmol) was added, in one portion, and the

mixture was then stirred at room temperature for 1.5 h. Water (10 mL) was added and the separated aqueous phase was then extracted with dichloromethane (2×10 mL). The combined organic extracts were dried over magnesium sulfate and then concentrated in vacuo. The residue was purified by flash column chromatography on silica, using 30% ethyl acetate in petroleum ether (bp 40–60 °C) as eluent, to give the bis-*benzoate* (203 mg, 97%) as a colourless oil; ν_{max} (film)/cm^{-1} 2955, 1725, 1610 and 1531; δ_H (360 MHz, $CDCl_3$) 0.01–0.04 (6H, m, 2×SiCH_3), 0.87 (9H, s, 3×SiC(CH_3)$_3$), 1.26 (6H, s, 2×C(CH_3)$_2$), 1.69 (1H, td, *J* 6.1 and 13.4, C*H*HCH$_2$OTBS), 1.84 (1H, td, *J* 5.7 and 13.4, C*H*HCH$_2$OTBS), 2.05 (3H, s, C=C(CH_3)), 2.31 (1H, br d, *J* 6.3, OCHC*H*H), 2.58 (1H, br d, *J* 14.3, OCHC*H*H), 3.32 (3H, s, OCH_3), 3.34 (3H, s, OCH_3), 3.63 (1H, td, *J* 5.3 and 9.1, CH$_2$C*H*HOTBS), 3.69–3.76 (1H, m, CH$_2$C*H*HOTBS), 3.79 (3H, s, ArOCH_3), 4.02–4.09 (2H, m, OC*H*CH$_2$ and C*H*OPMB), 4.24 (1H, d, *J* 6.9, C*H*HOBz*p*NO$_2$), 4.31 (1H, d, *J* 11.5, OC*H*HArOMe), 4.47–4.53 (1H, m, OC*H*HO), 4.50 (2H, d, *J* 11.5, OC*H*HArOMe), 4.58–4.63 (1H, m, C*H*HOBz*p*NO$_2$), 4.73 (1H, d, *J* 6.9, OC*H*HO), 4.91 (2H, s, OC*H*HO), 5.74 (1H, ddd, *J* 1.2, 7.5 and 15.6, C*H*=CHCH(OPMB)), 5.92 (1H, dd, *J* 4.0 and 15.6, CH=C*H*CH(OPMB)), 6.43 (1H, d, *J* 4.0, C=CC*H*(O)CH=CH), 6.85 (2H, d, *J* 8.7, 2×Ar*H*), 7.23 (2H, d, *J* 8.7, 2×Ar*H*), 8.20–8.25 (4H, m, Ar*H*), 8.28–8.34 (4H, m, Ar*H*); δ_C (90 MHz, $CDCl_3$) −5.4 (2×q), 14.1 (q), 18.2 (q), 18.4 (s), 23.3 (q), 25.9 (3×q), 29.6 (t), 38.7 (t), 43.5 (s), 55.3 (q), 55.8 (q), 56.1 (q), 59.2 (t), 68.8 (t), 70.4 (t), 72.2 (d), 72.7 (d), 75.6 (d), 78.1 (s), 91.2 (t), 94.7 (t), 113.8 (2×d), 123.7 (4×d), 123.8 (4×d), 129.4 (2×d), 130.2 (s), 130.5 (d), 130.8 (d), 135.7 (2×s), 135.8 (s), 137.3 (s), 150.5 (s), 150.6 (s), 159.1 (s), 163.5 (s), 164.1 (s); *m*/*z* (ES) 960.4101 (M^++H+Na, 100%, $C_{48}H_{65}N_2NaO_{15}Si$ requires 960.4101).

The *diastereoisomer B* of the diol **25** (224 mg, 0.35 mmol) was treated under the same conditions to give the corresponding diastereomeric *bis-benzoate* (314 mg, 95%) as a colourless oil; ν_{max} (film)/cm^{-1} 2930, 1726, 1610 and 1531; δ_H (360 MHz, $CDCl_3$) 0.02 (3H, s, SiCH_3), 0.03 (3H, s, SiCH_3), 0.87 (9H, s, 3×SiC(CH_3)$_3$), 1.26 (6H, s, 2×C(CH_3)$_2$), 1.69 (1H, td, *J* 5.9 and 13.6, C*H*HCH$_2$OTBS), 1.84 (1H, td, *J* 5.9 and 13.6, C*H*HCH$_2$OTBS), 2.04 (3H, s, C=C(CH_3)), 2.32 (2H, br d, *J* 5.5, OCHCH_2), 3.34 (3H, s, OCH_3), 3.35 (3H, s, OCH_3), 3.62 (1H, td, *J* 5.9 and 10.0, CH$_2$C*H*HOTBS), 3.73 (1H, td, *J* 5.9 and 10.0, CH$_2$C*H*HOTBS), 3.78 (3H, s, ArOCH_3), 4.01–4.09 (2H, m, OC*H*CH$_2$ and C*H*OPMB), 4.31 (1H, d, *J* 11.7, OC*H*HArOMe), 4.41 (1H, d, *J* 7.0, OC*H*HO), 4.50 (1H, d, *J* 11.7, C*H*HOBz*p*NO$_2$), 4.51 (1H, d, *J* 11.7, C*H*HOBz*p*NO$_2$), 4.61 (1H, d, *J* 11.7, OC*H*HArOMe), 4.74 (1H, d, *J* 7.0, OC*H*HO), 4.86 (1H, d, *J* 7.6, OC*H*HO), 4.94 (1H, d, *J* 7.6, OC*H*HO), 5.75 (1H, ddd, *J* 1.2, 7.5 and 15.6, C*H*=CHCH(OPMB)), 5.94 (1H, dd, *J* 4.5 and 15.6, CH=C*H*CH(OPMB)), 6.44 (1H, d, *J* 4.5, C=CC*H*(O)CH=CH), 6.85 (2H, d, *J* 8.7, 2×Ar*H*), 7.23 (2H, d, *J* 8.7, 2×Ar*H*), 8.21 (2H, d, *J* 6.6, 2×Ar*H*), 8.23 (2H, d, *J* 6.6, 2×Ar*H*), 8.30 (2H, d, *J* 5.5, 2×Ar*H*), 8.32 (2H, d, *J* 5.5, 2×Ar*H*); δ_C (90 MHz, $CDCl_3$) −5.3 (2×q), 14.2 (q), 18.3 (s), 18.6 (q), 23.5 (q), 26.0 (3×q), 29.8 (t), 38.8 (t), 43.5 (s), 55.3 (q), 55.9 (q), 56.1 (q), 59.2 (t), 68.4 (t), 70.5 (t), 72.9 (d), 74.3 (d), 75.8 (d), 79.0 (s), 91.7 (t), 95.6 (t), 113.9 (2×d), 123.7 (4×d), 123.8 (4×d), 129.4 (2×d), 129.7 (s), 130.5 (d), 130.9 (d), 135.6 (2×s), 135.7 (s), 137.0 (s), 150.6 (2×s), 159.2 (s), 163.6 (s), 164.3 (s); *m*/*z* (ES) 959.3951 (M^++Na, 100%, $C_{48}H_{64}N_2NaO_{15}Si$ requires 959.3974).

*4.1.14. (E)-(S)-6-[(3S,5S)-3,5-Bis-methoxymethoxy-2,6,6-trimethyl-5-(4-nitrophenoxymethyl)-cyclohex-1-enyl]-3-(4-methoxy-benzyloxy)-6-(4-nitrophenoxy)-hex-4-en-1-ol (**31a**)*

A solution of hydrogen fluoride (70% solution) in pyridine (0.1 mL) was added dropwise over 1 min to a stirred solution of diastereoisomer A of the silyl ether **30** (15.3 mg, 0.016 mmol) in pyridine (0.5 mL, 6.2 mmol) at 0 °C. The solution was stirred at room temperature for 1.5 h and then poured onto a saturated solution of aqueous sodium hydrogencarbonate (20 mL). The resulting biphasic mixture was extracted with ethyl acetate (3×15 mL), and the combined organic extracts were then washed with a saturated solution of aqueous copper(II) sulfate (15 mL). The organic layer was dried over magnesium sulfate and then concentrated in vacuo to leave the *alcohol* (11.3 mg, 84%) as a colourless oil, which was used without further purification; ν_{max} (film)/cm^{-1} 3606, 2931, 1724, 1610 and 1531; δ_H (360 MHz, $CDCl_3$) 1.23 (3H, s, C(CH_3)$_2$), 1.25 (3H, s, C(CH_3)$_2$), 1.72–1.95 (2H, m, CH_2CH$_2$OH), 2.04 (3H, s, C=C(CH_3)), 2.25–2.40 (1H, m, OCHC*H*H), 2.59 (1H, br d, *J* 6.3, OCHC*H*H), 3.00 (3H, s OCH_3), 3.35 (3H, s, OCH_3), 3.71–3.80 (2H, m, CH$_2$CH_2OH), 3.78 (3H, s, ArOCH_3), 4.05–4.13 (2H, m, OC*H*CH$_2$ and C*H*OPMB), 4.20 (1H, d, *J* 6.9, OC*H*HO), 4.32 (1H, d, *J* 11.3, OC*H*HArOMe), 4.45 (1H, d, *J* 11.8, C*H*HOBz*p*NO$_2$), 4.53 (1H, d, *J* 11.3, OC*H*HArOMe), 4.63 (1H, d, *J* 11.8, C*H*HOBz*p*NO$_2$), 4.71 (1H, d, *J* 6.9, OC*H*HO), 4.90 (1H, d, *J* 7.7, OC*H*HO), 4.93 (1H, d, *J* 7.7, OC*H*HO), 5.79 (1H, app dddd, *J* 1.1, 3.5, 7.4 and 15.6, C*H*=CHCH(OPMB)), 5.96 (1H, dd, *J* 5.2 and 15.6, CH=C*H*CH(OPMB)), 6.41 (1H, d, *J* 4.9, C=CC*H*(O)CH=CH), 6.85 (2H, d, *J* 8.7, 2×Ar*H*), 7.22 (2H, d, *J* 8.7, 2×Ar*H*), 8.22 (2H, d, *J* 9.0, 2×Ar*H*), 8.23 (2H, d, *J* 9.0, 2×Ar*H*), 8.30 (2H, d, *J* 9.0, 2×Ar*H*), 8.31 (2H, d, *J* 9.0, 2×Ar*H*); δ_C (90 MHz, $CDCl_3$) 14.2 (q), 18.6 (q), 23.6 (q), 29.8 (t), 37.8 (t), 43.5 (s), 55.3 (q), 55.9 (q), 56.2 (q), 60.4 (t), 68.9 (t), 70.4 (t), 72.3 (d), 72.8 (d), 78.1 (s), 77.9 (d), 91.9 (t), 94.8 (t), 114.0 (2×d), 123.7 (4×d), 123.8 (4×d), 129.5 (2×d), 130.0 (s), 130.5 (d), 130.8 (d), 134.5 (s), 135.7 (2×s), 137.4 (s), 150.6 (s), 150.7 (s), 159.4 (s), 163.6 (s), 164.3 (s); *m*/*z* (ES) 845.3076 (M^++Na, 100%, $C_{42}H_{50}N_2NaO_{15}$ requires 845.3109).

The *diastereoisomer B* of the silyl ether **30** (380 mg, 0.41 mmol) was treated under the same conditions to give the corresponding diastereomeric *alcohol* (324 mg, 97%) as a colourless oil; ν_{max} (film)/cm^{-1} 3519, 2936, 1724, 1610 and 1531; δ_H (360 MHz, $CDCl_3$) 1.26 (6H, s, 2×C(CH_3)$_2$), 1.72–1.89 (2H, m, CH_2CH$_2$OH), 2.05 (3H, s, C=C(CH_3)), 2.28–3.36 (2H, m, OCHCH_2), 3.35 (6H, s, 2×OCH_3), 3.69–3.75 (2H, m, CH$_2$CH_2OH), 3.80 (3H, s, ArOCH_3), 4.08–4.15 (2H, m, OC*H*CH$_2$ and C*H*OPMB), 4.32 (1H, d, *J* 11.3, OC*H*HArOMe), 4.39 (1H, d, *J* 7.0, OC*H*HO), 4.50 (1H, d, *J* 12.2, C*H*HOBz*p*NO$_2$), 4.54 (1H, d, *J* 11.3, OC*H*HArOMe), 4.61 (1H, d, *J* 12.2, C*H*HOBz*p*NO$_2$), 4.73 (1H, d, *J* 7.0, OC*H*HO), 4.87 (1H, d, *J* 7.6, OC*H*HO), 4.94 (1H, d, *J* 7.6, OC*H*HO), 5.77 (1H, ddd, *J* 1.4, 7.5 and 15.7, C*H*=CHCH(OPMB)), 5.97 (1H, dd, *J* 4.4 and 15.7, CH=C*H*CH(OPMB)), 6.46 (1H, d, *J* 4.4, C=CC*H*(O)CH=CH), 6.87 (2H, d, *J* 8.7, 2×Ar*H*), 7.73 (2H, d, *J* 8.7, 2×Ar*H*), 8.21 (2H, d, *J* 8.9, 2×Ar*H*), 8.24 (2H, d, *J* 8.9, 2×Ar*H*), 8.31 (2H, d, *J* 7.6, 2×Ar*H*), 8.33 (2H, d, *J* 7.6, 2×Ar*H*); δ_C (90 MHz, $CDCl_3$) 14.2 (q), 18.6 (q), 22.9 (q), 29.8 (t), 37.9 (t), 43.5 (s), 55.3 (q), 55.8 (q), 56.0 (q), 60.3 (t), 68.3 (t), 70.4 (t), 72.7 (d), 74.1 (d), 78.0 (d), 78.8 (s), 91.6 (t), 95.4 (t), 114.0 (2×d), 123.8 (4×d), 123.9 (4×d), 129.5 (2×d), 130.1 (s), 130.5 (d), 130.8 (d), 133.8 (s), 135.5 (2×s), 136.8 (s), 150.7 (2×s), 159.4 (s), 163.7 (s), 164.3 (s); *m*/*z* (ES) 845.3155 (M^++Na, 100%, $C_{42}H_{50}N_2NaO_{15}$ requires 845.3109).

*4.1.15. (E)-(S)-6-[(3S,5S)-3,5-Bis-methoxymethoxy-2,6,6-trimethyl-5-(4-nitrophenoxymethyl)-cyclohex-1-enyl]-1-bromo-3-(4-methoxy-benzyloxy)-6-(4-nitrophenoxy)-hex-4-ene (**31b**)*

Triethylamine (7 μL, 0.05 mmol) was added dropwise to a stirred solution of diastereoisomer A of the alcohol **31a** (29.8 mg, 0.04 mmol) in dry dichloromethane (4 mL) at −20 °C. Methanesulfonyl chloride (3 μL, 0.04 mmol) was added dropwise and the mixture was then stirred at room temperature for 1 h. A solution of lithium bromide (31.3 mg, 0.36 mmol) in THF (2 mL) was added dropwise via cannula over 1 min, and the mixture was heated to 56 °C for 17 h and then cooled to room temperature. A saturated solution of aqueous sodium hydrogencarbonate (10 mL) and ethyl acetate (10 mL) were added, and the separated aqueous phase was then extracted with ethyl acetate (3×15 mL). The combined organic extracts were dried over magnesium sulfate and then concentrated in vacuo. The residue was purified by flash column chromatography on silica, using 50% ethyl acetate in petroleum ether (bp 40–60 °C) as eluent, to give the *bromide* (23.4 mg, 73%) as

a colourless oil; ν_{max} (film)/cm^{-1} 2934, 1725, 1610 and 1631; δ_H (360 MHz, $CDCl_3$) 1.26 (6H, br s, 2×C(CH_3)$_2$), 2.01–2.21 (2H, m, CH_2CH_2Br), 2.06 (3H, s, C=C(CH_3)), 2.29–2.35 (1H, m, OCHCH*H*), 2.58 (1H, br d, *J* 13.7, OCHCH*H*), 3.32 (3H, s, OCH_3), 3.36 (3H, s, OCH_3), 3.41–3.48 (1H, m, CH_2CHHBr), 3.49–3.57 (1H, m, CH_2CHHBr), 3.80 (3H, s, ArOCH_3), 4.05–4.11 (2H, m, OCH_2 and C*H*OPMB), 4.23 (1H, d, *J* 6.9, O*CH*HO), 4.33 (1H, d, *J* 11.1, C*H*HOBz*p*NO$_2$), 4.45 (1H, d, *J* 11.7, O*CH*HArOMe), 4.52 (1H, d, *J* 11.1, C*H*HOBz*p*NO$_2$), 4.63 (1H, d, *J* 11.7 °C*H*HArOMe), 4.72 (1H, d, *J* 6.9, O*CH*HO), 4.91 (1H, s, O*CH*HO), 4.92 (1H, s, O*CH*HO), 5.73 (1H, ddd, *J* 1.5, 7.5 and 15.4, C*H*=CHCH(OPMB)), 5.99 (1H, dd, *J* 5.0 and 15.4, CH=C*H*CH(OPMB)), 6.43 (1H, d, *J* 4.2, C=CC*H*(O)CH=CH), 6.87 (2H, d, *J* 8.7, 2×Ar*H*), 7.24 (2H, d, *J* 8.7, 2×Ar*H*), 8.23 (2H, d, *J* 9.0, 2×Ar*H*), 8.24 (2H, d, *J* 9.0, 2×Ar*H*), 8.32 (2H, d, *J* 9.0, 2×Ar*H*), 8.33 (2H, d, *J* 9.0, 2×Ar*H*); δ_C (90 MHz, $CDCl_3$) 14.2 (q), 18.6 (q), 28.4 (t), 29.7 (t), 31.6 (q), 37.9 (t), 43.4 (s), 55.3 (q), 55.9 (q), 56.0 (q), 68.3 (t), 70.3 (t), 72.8 (d), 74.1 (d), 77.9 (d), 78.9 (s), 91.7 (t), 95.5 (t), 113.9 (2×d), 123.7 (8×d), 129.4 (2×d), 130.1 (s), 130.5 (d), 130.9 (d), 133.6 (s), 135.5 (2×s), 136.8 (s), 150.6 (s), 150.7 (s), 159.3 (s), 163.6 (s), 164.3 (s); *m*/*z* (ES) 907.2247 (M^++Na, 100%, $C_{42}H_{49}BrN_2NaO_{14}$ requires 907.2247).

The *diastereoisomer B* of the alcohol **31a** (14.4 mg, 0.02 mmol) was treated under the same conditions to give the corresponding diastereomeric *bromide* (13.2 mg, 83%) as a colourless oil; δ_H (360 MHz, $CDCl_3$) 1.26 (6H, br s, 2×C(CH_3)$_2$), 1.98–2.02 (1H, m, C*H*HCH$_2$Br), 2.03 (3H, s, C=C(CH_3)), 2.11–2.20 (1H, m, C*H*HCH$_2$Br), 2.32 (2H, br s, OCHCH_2), 3.35 (6H, s, 2×OCH_3), 3.44 (1H, td, *J* 6.2 and 10.0, CH_2CHHBr), 3.54 (1H, td, *J* 6.0 and 10.0, CH_2CHHBr), 3.81 (3H, s, ArOCH_3), 4.06–4.14 (2H, m, 2H, m, OCH_2 and C*H*OPMB), 4.33 (1H, d, *J* 11.6, O*CH*HArOMe), 4.40 (1H, d, *J* 7.1, O*CH*HO), 4.50 (1H, d, *J* 6.6, C*H*HOBz*p*NO$_2$), 4.53 (1H, d, *J* 6.6, C*H*HOBz*p*NO$_2$), 4.62 (1H, d, *J* 11.6, O*CH*HArOMe), 4.73 (1H, d, *J* 7.1, O*CH*HO), 4.86 (1H, d, *J* 7.6, O*CH*HO), 4.94 (1H, d, *J* 7.6, O*CH*HO), 5.73 (1H, ddd, *J* 1.6, 7.6 and 15.7, C*H*=CHCH(OPMB)), 6.01 (1H, dd, *J* 4.5 and 15.7, CH=C*H*CH(OPMB)), 6.45 (1H, d, *J* 4.5, C=CC*H*(O)CH=CH), 6.87 (2H, d, *J* 8.7, 2×Ar*H*), 7.24 (2H, d, *J* 8.7, 2×Ar*H*), 8.22 (2H, d, *J* 9.0, 2×Ar*H*), 8.24 (2H, d, *J* 9.0, 2×Ar*H*), 8.32 (2H, d, *J* 9.0, 2×Ar*H*), 8.34 (2H, d, *J* 9.0, 2×Ar*H*); δ_C (90 MHz, $CDCl_3$) 14.2 (q), 18.6 (q), 28.5 (t), 29.7 (t), 30.3 (q), 38.5 (t), 43.5 (s), 55.3 (q), 55.9 (q), 56.0 (q), 68.3 (t), 70.7 (t), 72.7 (d), 74.2 (d), 76.7 (d), 78.9 (s), 91.6 (t), 95.5 (t), 113.9 (2×d), 123.7 (8×d), 129.4 (2×d), 130.0 (s), 130.5 (d), 130.9 (d), 133.5 (s), 135.5 (s), 135.6 (s), 136.8 (s), 150.6 (s), 150.7 (s), 159.3 (s), 163.6 (s), 164.2 (s).

*4.1.16. (1S,5S)-3-[(E)-(S)-6-Bromo-4-(4-methoxy-benzyloxy)-hex-2-enoyl]-1,5-bis-methoxymethoxy-2,2,4-trimethyl-cyclohex-3-enecarbaldehyde (**32**)*

Potassium carbonate (104 mg, 0.75 mmol) was added in one portion to a stirred solution of diastereoisomer A of the bis-benzoate **31b** (11.2 mg, 0.13 mmol) in methanol (2 mL) at room temperature. The mixture was stirred at room temperature for 1 h and then concentrated in vacuo. Water (5 mL) and ethyl acetate (5 mL) were added to the residue and the separated aqueous phase was then extracted with ethyl acetate (3×10 mL). The combined organic extracts were dried over magnesium sulfate and then concentrated in vacuo. The residue was purified by flash column chromatography on silica, using 70% ethyl acetate in petroleum ether (bp 40–60 °C) as eluent, to give the corresponding *diol* (6.4 mg, 86%) as a colourless oil; ν_{max} (film)/cm^{-1} 3606, 2954, 1612 and 1514; δ_H (360 MHz, $CDCl_3$) 1.02 (3H, br s, C(CH_3)$_2$), 1.16 (3H, br s, C(CH_3)$_2$), 1.92 (3H, s, C=C(CH_3)), 1.86–2.06 (2H, m, CH_2CH_2Br), 2.09–2.20 (1H, m, OCHC*H*H), 2.47 (1H, d, *J* 14.3, OCHC*H*H), 3.38–3.56 (2H, m, CH_2CH_2Br), 3.44 (3H, s, OCH_3), 3.49 (3H, s, OCH_3), 3.69–3.77 (2H, m, CH_2OH), 3.79 (3H, s, ArOCH_3), 3.88–3.96 (1H, m, OC*H*CH_2), 4.01 (1H, dt, *J* 4.5 and 8.0, C*H*OPMB), 4.30 (1H, d, *J* 11.1, O*CH*HArOMe), 4.50 (1H, d, *J* 11.1, O*CH*HArOMe), 4.72 (1H, d, *J* 6.8, O*CH*HO), 4.77 (1H, d, *J* 7.6, O*CH*HO), 4.87 (1H, d, *J* 6.8, O*CH*HO), 4.91 (1H, br d, *J* 3.3, C=CC*H*(O)CH=CH), 5.15 (1H, d, *J* 7.6, O*CH*HO), 5.63 (1H, ddd, *J* 1.5, 7.8 and 15.5, C*H*=CHCH(OPMB)), 5.90 (1H, dd, *J* 4.5 and 15.5, CH=C*H*CH(OPMB)), 6.87 (2H, d, *J* 8.6, 2×Ar*H*), 7.23 (2H, d, *J* 8.6, 2×Ar*H*); δ_C (90 MHz, $CDCl_3$) 17.7 (q), 23.3 (q), 28.1 (t), 29.9 (t), 30.3 (q), 38.7 (t), 42.9 (s), 55.3 (q), 55.8 (q), 56.5 (q), 65.9 (t), 69.5 (d), 70.4 (t), 75.8 (d), 77.0 (d), 79.8 (s), 91.3 (t), 97.2 (t), 113.9 (2×d), 125.5 (s), 129.5 (2×d), 130.3 (d), 131.0 (s), 134.8 (d), 142.1 (s), 159.3 (s); *m*/*z* (ES) 609.2018 (M^++Na, 100%, $C_{28}H_{43}BrNaO_8$ requires 609.2039).

The *diastereoisomer B* of the bis-benzoate **31b** (97.4 mg, 0.11 mmol) was treated under the same conditions to give the corresponding diastereomeric *diol* (61.4 mg, 95%); δ_H (360 MHz, $CDCl_3$) 1.13 (3H, br s, C(CH_3)$_2$), 1.20 (3H, br s, C(CH_3)$_2$), 1.88 (3H, s, C=C(CH_3)), 1.96–2.06 (2H, m, CH_2CH_2Br), 2.11–2.25 (2H, m, OCHCH_2), 3.43 (3H, s, OCH_3), 3.45 (3H, s, OCH_3), 3.40–3.49 (1H, m, CH_2CHHBr), 3.50–3.59 (1H, m, CH_2CHHBr), 3.64–3.72 (1H, m, C*H*HOH), 3.76–3.83 (1H, m, C*H*HOH), 3.81 (3H, s, ArOCH_3), 3.89–3.93 (1H, m, OC*H*CH_2), 4.04 (1H, dt, *J* 4.4 and 8.0, C*H*OPMB), 4.30 (1H, d, *J* 11.2, O*CH*HArOMe), 4.52 (1H, d, *J* 11.2, O*CH*HArOMe), 4.68 (1H, d, *J* 6.9, O*CH*HO), 4.82 (1H, d, *J* 6.9, O*CH*HO), 4.83 (1H, d, *J* 7.4, O*CH*HO), 4.94 (1H, d, *J* 7.4, O*CH*HO), 4.96–4.99 (1H, m, C=CC*H*(O)CH=CH), 5.65 (1H, ddd, *J* 1.8, 8.0 and 15.5, C*H*=CHCH(OPMB)), 5.95 (1H, dd, *J* 4.3 and 15.5, CH=C*H*CH(OPMB)), 6.88 (2H, d, *J* 8.6, 2×Ar*H*), 7.24 (2H, d, *J* 8.6, 2×Ar*H*); δ_C (90 MHz, $CDCl_3$) 17.5 (q), 22.7 (q), 28.5 (t), 30.0 (t), 30.3 (q), 38.8 (t), 42.9 (s), 55.3 (q), 55.6 (q), 56.2 (q), 65.5 (t), 69.7 (d), 70.2 (t), 75.6 (d), 77.1 (d), 80.6 (s), 91.2 (t), 96.6 (t), 113.9 (2×d), 129.3 (s), 129.5 (2×d), 129.9 (s), 130.3 (d), 135.6 (d), 142.1 (s), 159.2 (s).

Sodium hydrogencarbonate (29 mg, 0.34 mmol) and Dess–Martin periodinane (31.4 mg, 0.074 mmol) were added in one portion to a stirred solution of diastereoisomer A of the above diol (13.8 mg, 0.023 mmol) in dichloromethane (2.3 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min and then allowed to warm to room temperature over 5 h. Saturated solutions of aqueous sodium hydrogencarbonate (1 mL) and aqueous sodium thiosulfate (1 mL) were added to the mixture, which was stirred at room temperature for 5 min and then diethyl ether (5 mL) was added. The separated aqueous phase was extracted with diethyl ether (3×5 mL), and the combined organic extracts were then dried over sodium sulfate and concentrated in vacuo. The residue was purified by flash column chromatography on silica, using 30% ethyl acetate in pentane as eluent, to give the *ketoaldehyde* (11.3 mg, 84%) as a colourless oil; ν_{max} (film)/cm^{-1} 2937, 1727, 1613 and 1514; δ_H (360 MHz, $CDCl_3$) 1.15 (3H, br s, C(CH_3)$_2$), 1.20 (3H, br s, C(CH_3)$_2$), 1.65 (3H, s, C=C(CH_3)), 1.98–2.09 (1H, m, C*H*HCH$_2$Br), 2.09–2.20 (1H, m, C*H*HCH$_2$Br), 2.26 (1H, dd, *J* 6.8 and 15.0, OCHC*H*H), 2.43 (1H, dd, *J* 6.4 and 15.0, OCHC*H*H), 3.38–3.49 (1H, m, CH_2CHHBr), 3.40 (3H, s, OCH_3), 3.43 (3H, s, OCH_3), 3.54 (1H, ddd, *J* 5.9, 8.8 and 10.1, CH_2CHHBr), 3.81 (3H, s, ArOCH_3), 4.06–4.12 (1H, m, OC*H*CH_2), 4.21–4.29 (1H, m, C*H*OPMB), 4.35 (1H, d, *J* 11.0, O*CH*HArOMe), 4.52 (1H, d, *J* 11.0, O*CH*HArOMe), 4.66 (1H, d, *J* 7.0, O*CH*HO), 4.73 (1H, d, *J* 7.4, O*CH*HO), 4.77 (1H, d, *J* 7.0, O*CH*HO), 4.84 (1H, d, *J* 7.4, O*CH*HO), 6.35 (1H, d, *J* 16.0, C*H*=CHCH(OPMB)), 6.75 (1H, dd, *J* 6.5 and 16.0, CH=C*H*CH(OPMB)), 6.89 (2H, d, *J* 8.6, 2×Ar*H*), 7.24 (2H, d, *J* 8.6, 2×Ar*H*), 9.79 (1H, s, C*H*O); δ_C (90 MHz, $CDCl_3$) 17.3 (q), 21.9 (q), 25.4 (q), 27.9 (t), 29.1 (t), 37.9 (t), 40.6 (s), 55.3 (q), 56.0 (q), 56.1 (q), 71.5 (t), 73.2 (d), 75.8 (d), 85.1 (s), 92.6 (t), 96.3 (t), 114.0 (2×d), 129.5 (s), 129.6 (2×d), 130.6 (s), 132.8 (d), 140.6 (s), 149.3 (d), 159.5 (s), 199.1 (s), 202.5 (d); *m*/*z* (ES) 605.1736 (M^++Na, 100%, $C_{28}H_{39}BrNaO_8$ requires 605.1726).

*4.1.17. (E)-(S)-1-((3S,5S)-3,5-Bis-methoxymethoxy-2,6,6-trimethyl-5-propynoyl-cyclohex-1-enyl)-6-bromo-4-(4-methoxy-benzyl-oxy)-hex-2-en-1-one (**33a**)*

A solution of ethynylmagnesium bromide (0.5 M) in THF (2.8 mL, 1.4 mmol) was added dropwise over 5 min to a stirred solution of the ketoaldehyde **32** (61 mg, 0.09 mmol) in dry THF (2 mL) at 0 °C, and the mixture was then warmed to room temperature over 17 h. Water (2 mL) and 2 M hydrochloric acid (2 mL)

were added and the separated aqueous phase was then extracted with diethyl ether (3×15 mL). The combined organic extracts were dried over magnesium sulfate and concentrated in vacuo. Sodium hydrogencarbonate (142 mg, 1.69 mmol) and Dess–Martin periodinane (108 mg, 0.254 mmol) were added in one portion to a stirred solution of the residue in dichloromethane (2 mL) at room temperature. The mixture was stirred at room temperature for 1 h, and then saturated solutions of aqueous sodium hydrogencarbonate (2 mL) and aqueous sodium thiosulphate (2 mL) were added. The biphasic mixture was stirred at room temperature for 5 min and then diethyl ether (5 mL) was added. The separated aqueous phase was extracted with diethyl ether (3×15 mL), and the combined organic extracts were then dried over sodium sulfate and concentrated in vacuo. The residue was purified by flash column chromatography on silica, using 30% ethyl acetate in petroleum ether (bp 40–60 °C) as eluent, to give the *ynone* (69 mg, 67%) as a colourless oil; ν_{max} (film)/cm^{-1} 3297, 2936, 2097, 1645, 1613 and 1514; δ_H (360 MHz, $CDCl_3$) 1.17 (3H, br s, C(C*H*$_3$)$_2$), 1.24 (3H, br s, C(C*H*$_3$)$_2$), 1.64 (3H, s, C=C(C*H*$_3$)), 1.99–2.07 (1H, m, C*H*HCH$_2$Br), 2.12–2.20 (1H, m, C*H*HCH$_2$Br), 2.54 (2H, t, *J* 7.2, OCHC*H*$_2$), 3.41 (3H, s, OC*H*$_3$), 3.38–3.45 (1H, m, CH$_2$C*H*HBr), 3.43 (3H, s, OC*H*$_3$), 3.47 (1H, s, C≡C*H*), 3.50–3.57 (1H, m, CH$_2$C*H*HBr), 3.81 (3H, s, ArOC*H*$_3$), 4.22–4.29 (2H, m, OC*H*CH$_2$ and C*H*OPMB), 4.43 (1H, d, *J* 11.0, OC*H*HArOMe), 4.42 (1H, d, *J* 11.0, OC*H*HArOMe), 4.67 (1H, d, *J* 7.2, OC*H*HO), 4.76 (1H, d, *J* 5.7, OC*H*HO), 4.78 (1H, d, *J* 5.7, OC*H*HO), 4.83 (1H, d, *J* 7.2, OC*H*HO), 6.34 (1H, d, *J* 16.0, C*H*=CHCH(OPMB)), 6.83 (1H, dd, *J* 6.6 and 16.0, CH=C*H*CH(OPMB)), 6.89 (2H, d, *J* 8.7, 2×Ar*H*), 7.23 (2H, d, *J* 8.7, 2×Ar*H*); δ_C (90 MHz, $CDCl_3$) 17.3 (q), 21.8 (q), 26.6 (q), 29.2 (t), 30.8 (t), 38.0 (t), 41.3 (s), 55.4 (q), 56.0 (q), 56.6 (q), 71.5 (t), 73.5 (d), 75.8 (d), 81.9 (d), 82.6 (s), 88.7 (s), 94.0 (t), 96.5 (t), 114.0 (2×d), 129.4 (s), 129.6 (2×d), 130.5 (s), 132.0 (d), 140.7 (s), 149.6 (d), 159.5 (s), 189.0 (s), 199.5 (s); *m*/*z* (ES) 629.1721 (M^++Na, 100%, $C_{30}H_{39}BrNaO_8$ requires 629.1726).

4.1.18. (E)-(S)-1-((3S,5S)-3,5-Bis-methoxymethoxy-2,6,6-trimethyl-5-propynoyl-cyclohex-1-enyl)-6-iodo-4-(4-methoxy-benzyloxy)-hex-2-en-1-one (**33b**)

Sodium iodide (26 mg, 0.17 mmol) was added in one portion to a stirred solution of the bromide **33a** (69 mg, 0.113 mmol) in butan-2-one (2 mL) at room temperature and the mixture was then heated under reflux for 16 h. The mixture was allowed to cool to room temperature and then water (2 mL) and diethyl ether (2 mL) were added. The separated aqueous phase was extracted with diethyl ether (2×5 mL), and the combined organic extracts were then dried over sodium sulfate and concentrated in vacuo. The residue was purified by flash column chromatography on silica, using 30% ethyl acetate in petroleum ether (bp 40–60 °C) as eluent, to give the *iodide* (70 mg, 95%) as a colourless oil; $[\alpha]_D^{23}$ −17.4 (*c* 0.84, $CHCl_3$); ν_{max} (film)/cm^{-1} 3298, 2935, 2096, 1726, 1613 and 1515; δ_H (360 MHz, $CDCl_3$) 1.26 (6H, s, 2×C(C*H*$_3$)$_2$), 1.65 (3H, s, C=C(C*H*$_3$)), 1.98–2.13 (2H, m, C*H*$_2$CH$_2$I), 2.52 (1H, d, *J* 7.9, OCHC*H*H), 2.54 (1H, d, *J* 7.9, OCHC*H*H), 3.21–3.31 (2H, m, CH$_2$C*H*$_2$I), 3.42 (3H, s, OC*H*$_3$), 3.43 (3H, s, OCH$_3$), 3.46 (1H, s, C≡C*H*), 3.82 (3H, s, ArOC*H*$_3$), 4.21–4.19 (1H, m, C*H*OPMB), 4.25 (1H, dd, *J* 7.9 and 7.9, OC*H*CH$_2$), 4.34 (1H, d, *J* 11.0, OC*H*HArOMe), 4.52 (1H, d, *J* 11.0, OC*H*HArOMe), 4.68 (1H, d, *J* 7.2, OC*H*HO), 4.77 (1H, d, *J* 5.7, OC*H*HO), 4.79 (1H, d, *J* 5.7, OC*H*HO), 4.83 (1H, d, *J* 7.2, OC*H*HO), 6.34 (1H, d, *J* 16.0, C*H*=CHCH(OPMB)), 6.83 (1H, dd, *J* 6.6 and 16.0, CH=C*H*CH(OPMB)), 6.89 (2H, d, *J* 8.7, 2×Ar*H*), 7.24 (2H, d, *J* 8.7, 2×Ar*H*); δ_C (90 MHz, $CDCl_3$) 1.5 (t), 17.3 (q), 21.8 (q), 26.7 (q), 30.8 (t), 38.7 (t), 41.3 (s), 55.4 (q), 56.0 (q), 56.7 (q), 71.4 (t), 73.5 (d), 77.7 (d), 81.9 (d), 82.6 (s), 88.7 (s), 94.0 (t), 96.5 (t), 114.0 (2×d), 129.5 (s), 129.6 (2×d), 130.5 (s), 133.1 (d), 140.7 (s), 149.4 (d), 159.5 (s), 189.0 (s), 199.5 (s); *m*/*z* (ES) 677.1530 (M^++Na, 100%, $C_{30}H_{39}INaO_8$ requires 677.1587).

4.1.19. (E)-(S)-1-((3S,5S)-3,5-Bis-methoxymethoxy-2,6,6-trimethyl-5-propynoyl-cyclohex-1-enyl)-4-hydroxy-6-iodo-hex-2-en-1-one (**36a**)

2,3-Dichloro-5,6-dicyanobenzoquinone (DDQ) (25.0 mg, 0.11 mmol) was added in one portion to a stirred solution of the iodide **33b** (36.6 mg, 0.06 mmol) in dichloromethane (3.5 mL) and water (0.5 mL) at room temperature. The mixture was stirred at room temperature for 2 h and then an extra portion of DDQ (25.0 mg, 0.11 mmol) was added in one portion at room temperature. The mixture was stirred at room temperature for a further 2 h, and then a saturated solution of aqueous sodium hydrogencarbonate (5 mL) was added. The separated aqueous phase was extracted with dichloromethane (4×5 mL) and the combined organic extracts were dried over sodium sulfate and then concentrated in vacuo. The residue was purified by flash column chromatography on silica, using 30% ethyl acetate in petroleum ether (bp 40–60 °C) as eluent, to give the *alcohol* (25.8 mg, 87%) as a colourless oil; $[\alpha]_D^{23}$ −1.0 (*c* 0.24, $CHCl_3$); ν_{max} (film)/cm^{-1} 3604, 3297, 2935, 2096, 1725 and 1675; δ_H (360 MHz, $CDCl_3$) 1.15 (3H, s, C(C*H*$_3$)$_2$), 1.22 (3H, s, C(C*H*$_3$)$_2$), 1.61 (3H, s, C=C(C*H*$_3$)), 1.98–2.10 (2H, m, C*H*$_2$CH$_2$I), 2.51 (2H, t, *J* 7.5, OCHC*H*$_2$), 3.26–3.36 (2H, m, CH$_2$C*H*$_2$I), 3.42 (3H, s, OC*H*$_3$), 3.43 (3H, s, OCH$_3$), 3.47 (1H, s, C≡C*H*), 4.23 (1H, t, *J* 7.5, OC*H*CH$_2$), 4.49–4.57 (1H, m, C*H*OH), 4.66 (1H, d, *J* 7.4, OC*H*HO), 4.76 (1H, d, *J* 6.8, OC*H*HO), 4.77 (1H, d, *J* 6.8, OC*H*HO), 4.83 (1H, d, *J* 7.4, OC*H*HO), 6.36 (1H, d, *J* 15.9, C*H*=CHCH(OH)), 6.89 (1H, dd, *J* 4.9 and 15.9, CH=C*H*CH(OH)); δ_C (90 MHz, $CDCl_3$) 1.5 (t), 17.3 (q), 21.8 (q), 26.6 (q), 30.8 (t), 39.6 (t), 41.3 (s), 56.0 (q), 56.6 (q), 71.0 (d), 73.5 (d), 81.9 (d), 82.5 (s), 88.6 (s), 93.9 (t), 96.5 (t), 130.4 (s), 130.9 (d), 140.8 (s), 151.0 (d), 189.0 (s), 199.6 (s); *m*/*z* (ES) 573.0775 (M^++K, 100%, $C_{22}H_{31}IKO_7$ requires 573.0752).

4.1.20. (E)-(S)-1-((3S,5S)-3,5-Bis-methoxymethoxy-2,6,6-trimethyl-5-propynoyl-cyclohex-1-enyl)-4-(tert-butyl-dimethyl-silanyloxy)-6-iodo-hex-2-en-1-one (**36b**)

tert-Butyl-dimethylsilyl triflate (50 μL, 0.22 mmol) was added dropwise over 10 s to a stirred solution of the alcohol **36a** (18.1 mg, 0.034 mmol) and 2,6-lutidine (40 μL, 0.34 mmol) in dry dichloromethane (2 mL) at −20 °C. The mixture was warmed to room temperature over 17 h and then water (5 mL) was added. The separated aqueous phase was extracted with dichloromethane (3×5 mL) and the combined organic extracts were then dried over magnesium sulfate and concentrated in vacuo. The residue was purified by flash column chromatography on silica using 20% ethyl acetate in petroleum ether (bp 40–60 °C) as eluent to give the *silyl ether* (12.3 mg, 56%); $[\alpha]_D^{23}$ +3.7 (*c* 0.60, $CHCl_3$); ν_{max} (film)/cm^{-1} 3297, 2931, 2096, 1711 and 1676; δ_H (360 MHz, $CDCl_3$) 0.04 (3H, s, SiC*H*$_3$), 0.12 (3H, s, SiC*H*$_3$), 0.90 (9H, s, 3×SiC(C*H*$_3$)$_3$), 1.14 (3H, s, C(C*H*$_3$)$_2$), 1.22 (3H, s, C(C*H*$_3$)$_2$), 1.61 (3H, s, C=C(C*H*$_3$)), 1.97–2.10 (2H, m, C*H*$_2$CH$_2$I), 2.39–2.47 (2H, m, OCHC*H*$_2$), 3.13–3.25 (2H, m, CH$_2$C*H*$_2$I), 3.42 (3H, s, OC*H*$_3$), 3.43 (3H, s, OCH$_3$), 3.46 (1H, s, C≡C*H*), 4.13–4.20 (1H, m, OC*H*CH$_2$), 4.39–4.47 (1H, m, C*H*OTBS), 4.66 (1H, d, *J* 6.8, OC*H*HO), 4.76 (1H, d, *J* 7.2, OC*H*HO), 4.77 (1H, d, *J* 6.8, OC*H*HO), 4.83 (1H, d, *J* 7.2, OC*H*HO), 6.28 (1H, d, *J* 15.8, C*H*=CHCH(OTBS)), 6.86 (1H, dd, *J* 5.7 and 15.8, CH=C*H*CH(OTBS)); δ_C (90 MHz, $CDCl_3$) −4.3 (q) −4.6 (q), 1.2 (t), 17.3 (q), 18.2 (s), 21.8 (q), 25.9 (3×q), 26.7 (q), 30.8 (t), 40.6 (t), 41.3 (s), 56.0 (q), 56.6 (q), 71.8 (d), 73.5 (d), 81.9 (d), 82.6 (s), 88.8 (s), 94.0 (t), 96.5 (t), 130.3 (s), 131.0 (d), 140.9 (s), 151.6 (d), 189.1 (s), 199.6 (s); *m*/*z* (ES) 671.1889 (M^++Na, 60%, $C_{28}H_{45}INaO_7Si$ requires 671.1877).

4.1.21. (1S,5S)-3-((E)-6-Bromo-hex-2-enoyl)-1,5-bis-methoxymethoxy-2,2,4-trimethyl-cyclohex-3-enecarbaldehyde (**39**)

A solution of *n*-BuLi (2.5 M) in hexanes (0.65 mL, 1.6 mmol) was added dropwise over 2 min to a stirred solution of the vinylstannane **38** (715 mg, 1.63 mmol)[19] in dry THF (10 mL) at −78 °C. The mixture was stirred at −78 °C for 1 h and then a solution of the

aldehyde **18** (132 mg, 0.32 mmol) in dry THF (5 mL) at −78 °C was added dropwise over 2 min. The mixture was warmed to room temperature over 17 h, and then water (10 mL) and diethyl ether (10 mL) were added. The separated aqueous phase was extracted with diethyl ether (3×10 mL), and the combined organic extracts were then dried over magnesium sulfate and concentrated in vacuo. The residue was purified by flash column chromatography on silica, using 30% ethyl acetate in petroleum ether (bp 40–60 °C) as eluent, to give the corresponding *diol* analogue of **25** (79.6 mg, 53%) as a mixture of diastereoisomers. Sodium hydrogencarbonate (142 mg, 1.69 mmol) and Dess–Martin periodinane (146 mg, 0.344 mmol) were added to a stirred solution of the diol in dichloromethane (10 mL) at room temperature. The mixture was stirred at room temperature for 2 h, and then a saturated solution of aqueous sodium thiosulfate (5 mL) was added. The biphasic mixture was stirred at room temperature for 5 min and then diethyl ether (5 mL) was added. The separated aqueous phase was extracted with diethyl ether (3×10 mL), and the combined organic extracts were then dried over sodium sulfate and concentrated in vacuo. The residue was purified by flash column chromatography on silica, using 30% ethyl acetate in petroleum ether (bp 40–60 °C) as eluent, to give the *ketoaldehyde* (67.5 mg, 86%) as a colourless oil; $[\alpha]_D^{23}$ +8.0 (*c* 1.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 2953 and 1726; δ_H (360 MHz, $CDCl_3$) 1.12 (3H, br s, $C(CH_3)_2$), 1.29 (3H, br s, $C(CH_3)_2$), 1.62 (3H, s, C=C(CH_3)), 1.99–2.09 (2H, m, CH_2CH_2Br), 2.25 (1H, dd, *J* 7.5 and 15.0, OCHC*H*H), 2.36–2.49 (3H, m, OCHC*H*H and C=CCH_2CH_2), 3.40–3.44 (2H, m, CH_2CH_2Br), 3.41 (3H, s, OCH_3), 3.43 (3H, s, OCH_3), 4.08 (1H, t, *J* 7.5, O*CH*CH_2), 4.66 (1H, d, *J* 7.1, O*CH*HO), 4.74 (1H, d, *J* 7.4, O*CH*HO), 4.77 (1H, d, *J* 7.1, O*CH*HO), 4.84 (1H, d, *J* 7.4, O*CH*HO), 6.19 (1H, dt, *J* 1.3 and 15.9, (C=O)C*H*=CHCH$_2$), 6.83 (1H, dt, *J* 7.0 and 15.9, (C=O)CH=C*H*CH$_2$), 9.79 (1H, s, CHO); δ_C (90 MHz, $CDCl_3$) 17.3 (q), 22.0 (q), 25.3 (q), 28.0 (t), 30.8 (t), 30.9 (t), 32.5 (t), 40.5 (s), 56.0 (q), 56.1 (q), 73.4 (d), 85.1 (s), 92.6 (t), 96.4 (t), 130.3 (s), 133.5 (d), 140.9 (s), 149.5 (d), 199.4 (s), 202.8 (d); *m*/*z* (ES) 469.1169 (M^++Na, 100%, $C_{20}H_{31}BrNaO_6$ requires 496.1202).

4.1.22. *(E)-1-((3S,5S)-3,5-Bis-methoxymethoxy-2,6,6-trimethyl-5-propynoyl-cyclohex-1-enyl)-6-bromo-hex-2-en-1-one (**40**)*

A solution of ethynylmagnesium bromide (0.5 M) in THF (1.5 mL, 0.75 mmol) was added dropwise over 5 min to a stirred solution of the aldehyde **39** (67.5 mg, 0.15 mmol) in dry THF (3 mL) at 0 °C. The mixture was warmed to room temperature over 17 h and then water (5 mL) and 2 M hydrochloric acid (0.5 mL) were added. The separated aqueous phase was extracted with diethyl ether (3×10 mL), and the combined organic extracts were then dried over sodium sulfate and concentrated in vacuo. Sodium hydrogencarbonate (123 mg, 1.46 mmol) and Dess–Martin periodinane (124 mg, 0.29 mmol) were added to a stirred solution of the residue in dichloromethane (5 mL) at room temperature. The mixture was stirred at room temperature for 2 h and then a saturated solution of aqueous sodium thiosulfate (2 mL) was added. The biphasic mixture was stirred at room temperature for 5 min and then diethyl ether (5 mL) was added. The separated aqueous phase was extracted with diethyl ether (3×15 mL), and the combined organic extracts were then dried over sodium sulfate and concentrated in vacuo. The residue was purified by flash column chromatography on silica, using 30% ethyl acetate in petroleum ether (bp 40–60 °C) as eluent, to give the *ynone* (44.9 mg, 64%) as a colourless oil; $[\alpha]_D^{23}$ +3.4 (*c* 1.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 3296, 2945, 2096, 1704, 1674, 1651 and 1616; δ_H (360 MHz, $CDCl_3$) 1.14 (3H, br s, $C(CH_3)_2$), 1.21 (3H, br s, $C(CH_3)_2$), 1.60 (3H, s, C=C(CH_3)), 1.98–2.07 (2H, m, CH_2CH_2I), 2.40–2.47 (2H, m, C=CCH_2), 2.51 (2H, t, *J* 7.9, OCHCH_2), 3.38–3.44 (2H, m, CH_2CH_2I), 3.42 (3H, s, OCH_3), 3.43 (3H, s, OCH_3), 3.47 (1H, s, C≡C*H*), 4.23 (1H, t, *J* 7.9, O*CH*CH_2), 4.66 (1H, d, *J* 6.9, O*CH*HO), 4.76 (1H, d, *J* 7.3, O*CH*HO), 4.77 (1H, d, *J* 6.9, O*CH*HO), 4.82 (1H, d, *J* 7.3, O*CH*HO), 6.17 (1H, dt, *J* 1.2 and 15.8, (C=O)C*H*=CHCH$_2$), 6.89 (1H, dt, *J* 7.0 and 15.8, (C=O)CH=C*H*CH$_2$); δ_C (90 MHz, $CDCl_3$) 17.2 (q), 21.8 (q), 26.6 (q), 30.7 (t), 30.9 (2×t), 32.5 (t), 41.2 (s), 56.5 (q), 56.0 (q), 73.6 (d), 82.0 (d), 82.6 (s), 88.6 (s), 93.9 (t), 96.4 (t), 130.1 (s), 133.6 (d), 140.8 (s), 149.7 (d), 189.0 (s), 199.8 (s); *m*/*z* (ES) 493.1210 (M^++Na, 100%, $C_{22}H_{31}BrNaO_6$ requires 493.1202).

4.1.23. *(E)-1-((3S,5S)-3,5-Bis-methoxymethoxy-2,6,6-trimethyl-5-propynoyl-cyclohex-1-enyl)-6-iodo-hex-2-en-1-one (**41**)*

Sodium iodide (66 mg, 0.43 mmol) was added in one portion to a stirred solution of the bromide **40** (45.0 mg, 0.093 mmol) in butan-2-one (3 mL) at room temperature. The mixture was heated under reflux for 16 h and then allowed to cool to room temperature. Water (2 mL) and diethyl ether (2 mL) were added and the separated aqueous phase was extracted with diethyl ether (3×5 mL). The combined organic extracts were dried over sodium sulfate and concentrated in vacuo to leave a residue, which was purified by flash column chromatography on silica, using 30% ethyl acetate in petroleum ether (bp 40–60 °C) as eluent, to give the *iodide* (29 mg, 58%) as a colourless oil; $[\alpha]_D^{23}$ +5.6 (*c* 1.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 3295, 2938, 2096, 1728, 1675 and 1644; δ_H (400 MHz, $CDCl_3$) 1.15 (3H, br s, $C(CH_3)_2$), 1.22 (3H, br s, $C(CH_3)_2$), 1.61 (3H, s, C=C(CH_3)), 1.95–2.03 (2H, m, CH_2CH_2I), 2.36–2.43 (2H, m, C=CCH_2), 2.51 (2H, app. dd, *J* 7.9 and 9.6, OCHCH_2), 3.20 (2H, t, *J* 6.8, CH_2CH_2I), 3.42 (3H, s, OCH_3), 3.43 (3H, s, OCH_3), 3.43 (1H, s, C≡C*H*), 4.23 (1H, t, *J* 7.9, O*CH*CH_2), 4.66 (1H, d, *J* 7.2, O*CH*HO), 4.76 (1H, d, *J* 3.3, O*CH*HO), 4.77 (1H, d, *J* 3.3, O*CH*HO), 4.83 (1H, d, *J* 7.2, O*CH*HO), 6.18 (1H, dt, *J* 1.4 and 15.8, (C=O)C*H*=CHCH$_2$), 6.87 (1H, dt, *J* 7.0 and 15.8, (C=O)CH=C*H*CH$_2$); δ_C (100 MHz, $CDCl_3$) 5.2 (t), 17.2 (q), 21.8 (q), 26.7 (q), 30.8 (t), 31.6 (t), 33.2 (t), 41.3 (s), 56.6 (q), 56.0 (q), 73.5 (d), 82.0 (d), 82.5 (s), 88.6 (s), 93.9 (t), 96.5 (t), 130.1 (s), 133.6 (d), 140.9 (s), 149.3 (d), 189.1 (s), 199.6 (s); *m*/*z* (ES) 541.1076 (M^++Na, 100%, $C_{22}H_{31}INaO_6$ requires 541.1063).

4.1.24. *(1S,8R,13S)-1,13-Bis-methoxymethoxy-12,15,15-trimethyltricyclo[9.3.1.0^{3,8}]pentadeca-3,11-diene-2,10-dione (**42**)*

A solution of tributyltin hydride (20 μL, 0.074 mmol) and AIBN (0.5 mg) in dry, degassed benzene (5 mL) was added dropwise over 4 h to a solution of the iodide **41** (28.6 mg, 0.055 mmol) and 2,2-azo-bis-isobutyronitrile (0.5 mg) in dry, degassed benzene (18 mL) at 80 °C under an argon atmosphere. The mixture was stirred at 80 °C for 3 h and then allowed to cool to room temperature. The mixture was concentrated in vacuo and the residue was purified by flash column chromatography on silica, using 30% ethyl acetate in petroleum ether (bp 40–60 °C) as eluent, to give the *tricycle* (9.6 mg, 44%) as a colourless oil; $[\alpha]_D^{23}$ −9.2 (*c* 0.5, $CHCl_3$); ν_{max} (film)/cm^{-1} 2931, 1694 (br); δ_H (500 MHz, $CDCl_3$) 1.17 (3H, s, $C(CH_3)_2$), 1.40 (3H, s, $C(CH_3)_2$), 1.65 (3H, br s, C=C(CH_3)), 1.67–1.72 (3H, m, C=CCH$_2$CH_2 and C=OCH$_2$CHCH*H*), 2.13–2.19 (3H, m, C=CCH_2 and C=OCH$_2$CHCH*H*), 2.44 (1H, dd, *J* 9.3 and 13.7, OCHCH*H*), 2.47–2.51 (1H, m, C=CC*H*), 2.54 (1H, dd, *J* 3.4 and 19.1, (C=O)CH*H*α), 2.85 (1H, dd, *J* 12.9 and 19.1, (C=O)CH*H*β), 2.99 (1H, dd, *J* 1.9 and 13.7, OCHCH*H*), 3.40 (3H, s, OCH_3), 3.44 (3H, s, OCH_3), 4.38 (1H, d, *J* 9.3, O*CH*CH_2), 4.62 (1H, d, *J* 6.8, O*CH*HO), 4.65 (1H, d, *J* 7.1, O*CH*HO), 4.85 (1H, d, *J* 6.8, O*CH*HO), 4.85 (1H, d, *J* 7.1, O*CH*HO), 5.69 (1H, t, *J* 3.6, C=C*H*); δ_C (125 MHz, $CDCl_3$) 16.3 (q), 21.6 (q), 24.4 (t), 26.4 (q), 29.6 (t), 33.0 (t), 33.4 (d), 34.1 (t), 38.3 (s), 50.6 (t), 56.0 (q), 56.1 (q), 70.8 (d), 85.0 (s), 92.7 (t), 95.6 (t), 128.8 (d), 135.8 (s), 142.2 (s), 144.7 (s), 206.6 (s), 209.0 (s); *m*/*z* (ES) 415.2107 (M^++Na, 100%, $C_{22}H_{32}NaO_6$ requires 415.2097).

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