

A two-directional synthesis of the C₅₈–C₇₁ fragment of palytoxin

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A two directional approach, in which asymmetric dihydroxylation and reduction reactions were used to control absolute configuration, was exploited in the preparation of a C₂-symmetrical dipyrane. The homotopic dihydropyran (DHP) rings of this precursor were differentiated statistically using by a Prévost reaction and further functionalisation. A second Prévost reaction was used to functionalise the other DHP; global deprotection and peracetylation gave a protected version of the C₅₈–C₇₁ fragment of palytoxin. Methods which might be of value in future synthetic work were developed for the stereoselective functionalisation of THP rings similar to those found in this fragment.

Introduction

Palytoxin, **1**, was isolated from marine soft corals of the genus *Palythoa*.¹ Palytoxin acts by interacting with sodium-potassium-activated APTase² and its toxicity is rivalled only by a few naturally occurring proteins.¹ The connectivity of palytoxin was determined in 1981,³ and its complete structure elucidated a year later.⁴ A total synthesis of palytoxin was reported in 1989.⁵ Palytoxin remains one of the most complex molecules to have succumbed to total synthesis, both in terms of its molecular size and its structural and stereochemical complexity.

Our goals were more modest. The C₅₈–C₇₁ fragment (**2**) of palytoxin is tantalizingly close to being C₂-symmetric. The only features which break its symmetry are (a) the absence of a hydroxyl group from C₅₉, and (b) different (2,6) relative configurations of the two tetrahydropyran rings. We sought to exploit this hidden symmetry for the first time in a two-directional synthesis of the fragment **2**. We have previously described some methods for the synthesis of diastereomeric polyhydroxylated tetrahydropyrans (THPs).⁶ Some of these methods might be used to differentiate between the termini of a C₂-symmetric template and to control the configuration of the two THP rings of **2**.

Our synthetic plan is outlined in Scheme 1. It was envisaged that a C₂-symmetric template, **3**, would be prepared using a two-directional⁷ approach. At this stage, the dihydropyran rings of **3** would be functionalised stereoselectively and the C₅₉ hydroxyl group removed (→**4**).

Having differentiated between the homotopic termini of **3**, this information would be exploited in the stepwise and stereoselective introduction of the C₅₈ and C₇₁ side chains. The C₅₈ acetal does not have a neighbouring deactivating substituent;⁸ reaction at C₅₈ was, therefore, expected to occur first and to allow the introduction of an axial side chain. In contrast, the acyloxy substituent on C₇₀ was expected to act as both a deactivating⁸ and a participating group:⁹ subsequent substitution would, therefore, introduce an equatorial side chain at C₇₁.

Two-directional synthesis of a C₂-symmetrical template

The reaction of the enediamide¹⁰ **5**, prepared from *trans*-β-hydroxybutyric acid, with commercially available AD-mix¹¹ β was extremely slow. However, addition of 1 mol% potassium osmate and 5 mol% hydroquinidine 1,4-phthalazinediyl diether (DHQD₂-PHAL) enabled efficient dihydroxylation; the resulting diol was, however, rather water soluble, and was, therefore, silylated *in situ* to give the corresponding silyl diether **6** in 67% overall yield (Scheme 2). Addition of 2-lithio furan to the diamide **6** gave the diketone **7** in >95% yield.¹⁰

Table 1 Deprotection of the bis silyl ether **7**

Entry	Conditions	Product	Yield ^a (%)
1	TBAF, THF, 20 °C	^b	—
2	NH ₄ F, MeOH, 60 °C	^c	—
3	AcOH–H ₂ O, 20 °C	^c	—
4	TBAF, AcOH, 20 °C	12	43
5	HF·pyridine, 20 °C	12	20

^a Yield of purified product. ^b Analysis of the crude reaction mixture by 300 MHz ¹H NMR spectroscopy indicated that elimination had occurred.

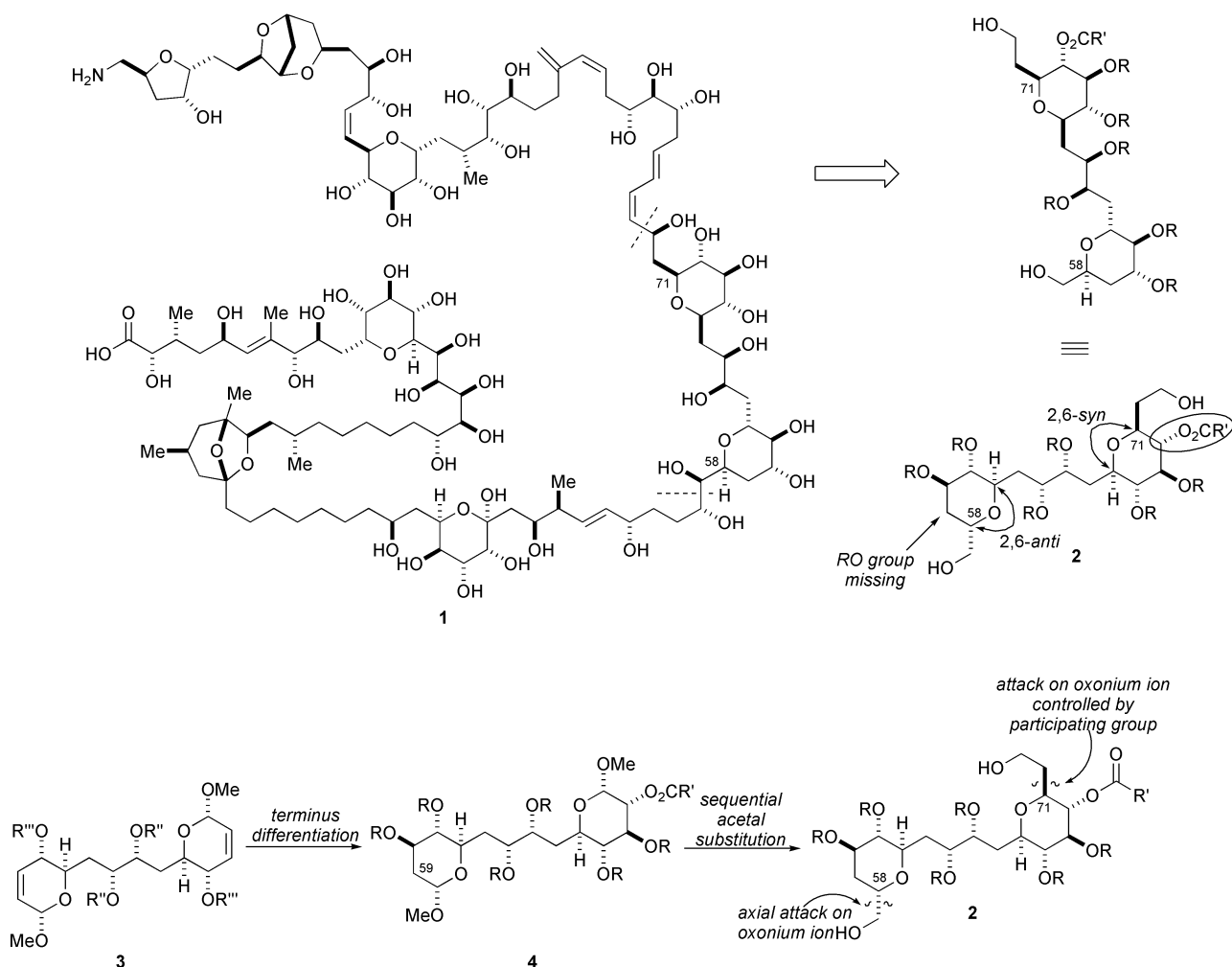
^c No reaction.

The dilactone¹² **8a** and the diester **8b** were investigated as alternative acylating reagents: these compounds were prepared as racemates from the sodium salt of *trans*-β-hydroxybutyric acid, either by treatment of the corresponding silver salt with iodine (→**8a**),¹² or by Upjohn dihydroxylation followed by acid-catalysed reaction with 2,2-dimethoxypropane (→**8b**). The acylating agents **8** were treated with 2-lithio furan in THF at –78 °C; analysis of the crude reaction mixtures by 300 MHz ¹H NMR spectroscopy revealed, however, complex mixtures of products.

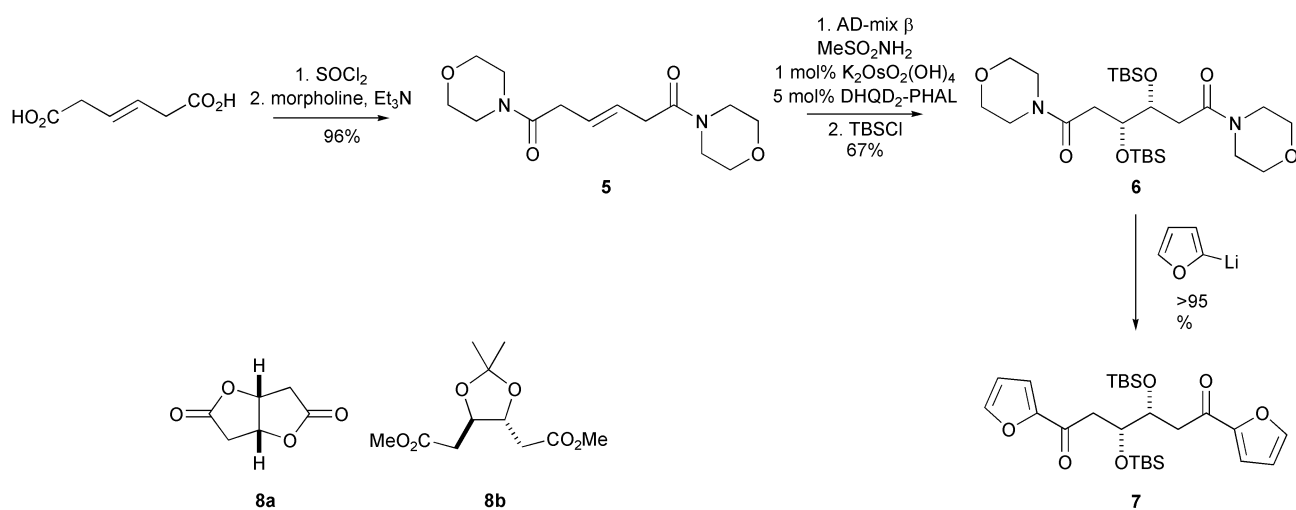
We have previously investigated the substrate-controlled reduction of a racemic sample of the diketone **7** with a range of reagents.¹⁰ However, these reactions were either unselective or were ^{1,3}*syn*-diastereoselective. In an attempt to develop an ^{1,3}*anti*-selective method, we investigated the addition of 2-lithio furan to a 3-silyloxy aldehyde (Scheme 3). Hence, reduction of the diamide **9** with DIBAL gave the aldehyde **10** in 64% yield. Unfortunately, addition of 2-lithio furan to **10** was not diastereoselective, and gave the hydroxy ketone **11** as a 50 : 50 mixture of diastereoisomers.

An alternative approach involved delivery of a reducing agent to the carbonyl groups. The deprotection of **7**, however, proved problematic (Scheme 4). Treatment of **7** with TBAF in THF resulted in elimination (entry 1, Table 1), and the use of milder reagents¹³ resulted in no reaction at all (entries 2–3). The use of a buffered fluoride source resulted in less competing elimination,¹⁴ and low yields of the diol **12** could be obtained (entries 4–5).¹⁵ Treatment of the diol **12** with tetramethylammonium triacetoxyborohydride¹⁶ in acetic acid resulted only in decomposition of the starting material. The diol **12** was, therefore, treated with chlorodisopropylsilane, pyridine and catalytic DMAP, and the bis silyl ether **13** was obtained in 34% yield. In view of the low yield of **13**, Lewis acid-¹⁷ and base-¹⁸ mediated intramolecular hydride delivery was not studied in detail.

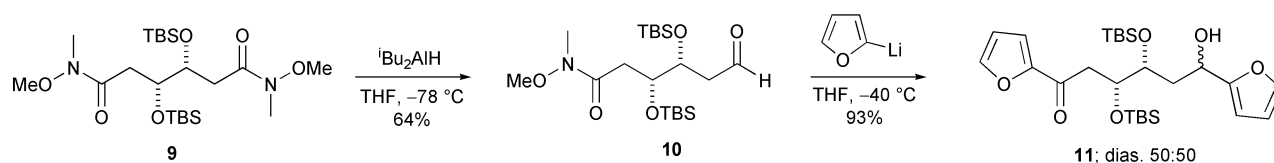
Our failure to identify substrate-controlled methods for the ^{1,3}*anti*-selective synthesis of diketones such as **7** lead us to



Scheme 1



Scheme 2



Scheme 3

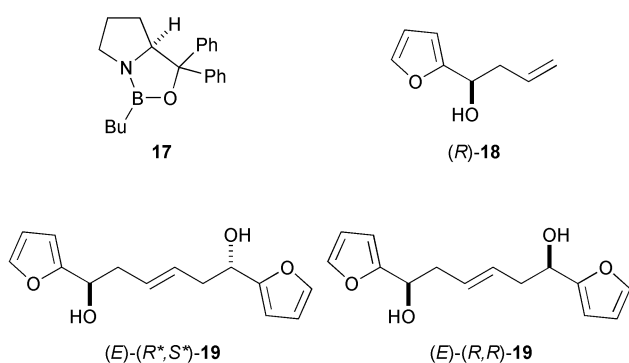
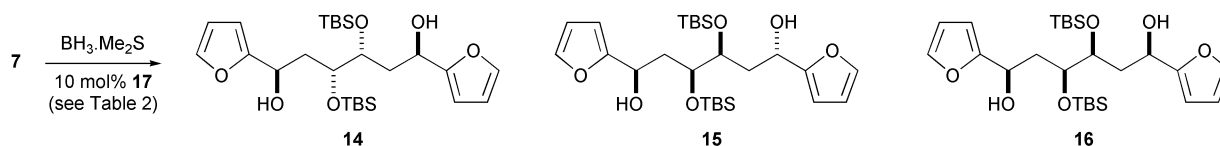
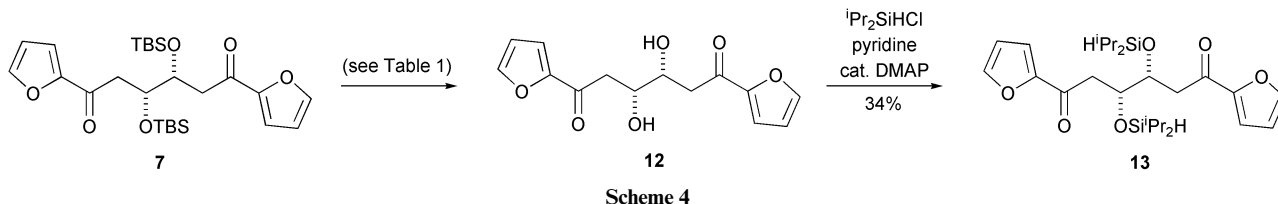
investigate reagent-controlled methods instead (Scheme 5). Treatment of the diketone (*R,R*)-7 with 10 mol% of the CBS reagent¹⁹ 17 gave a 90 : 10 mixture of the diols 14 and 16

(entry 1, Table 2). There was no trace of the unsymmetrical diastereoisomer 15. The diols 14 and 16, whose relative configuration had previously been determined, were readily

Table 2 Asymmetric reduction of the diketone 7

Entry	Starting material	Ratio of products ^a 14 : 15 : 16	Yield 14 ^b (%)	ee 14 ^c (%)	Yield 16 ^b (%)
1	7 ^d	90 : 0 : 10	82	>98	7
2	<i>rac</i> - 7	49.7 : 0.6 : 49.7	41	>98	42

^a Determined by analytical HPLC. ^b Yield of purified diastereoisomer. ^c Determined by chiral analytical HPLC. ^d Synthesised from enantiomerically enriched **6**, prepared by asymmetric dihydroxylation of the diamide **5**.



separable by column chromatography.¹⁰ Analysis of the diol **14** by chiral analytical HPLC revealed it to have >98% ee.

Given these favourable results, we probed the asymmetric reduction reaction further. Thus, asymmetric reduction of a racemic sample of the diketone **7** under the same conditions gave a 49.7 : 0.6 : 49.7 mixture of the diols **14–16** (entry 2, Table 2). Separation of the diols **14** and **16** by column chromatography, and analysis by chiral HPLC, revealed that the diol **14** had >98% ee. In the light of this result, we propose that the asymmetric dihydroxylation of **5** was only moderately enantioselective, and gave, after silylation, the diamide **6** with *ca.* 80% ee. The asymmetric reduction of **7** was, however, highly enantioselective: a *ca.* 90 : 10 mixture of the enantiomeric diketones **7** was, therefore, converted into a 90 : 10 mixture of diastereomeric diols **14** and **16**.

An alternative approach was to control the 'outside' stereogenic centres before dihydroxylating a central double bond. Homo-metathesis of the allylic alcohol **18**, prepared by Barbier-type coupling of allyl bromide with furfural, gave the diol **19** as a mixture of isomers, from which the centrosymmetric (*E*)-(*R**,*S**) isomer could be recrystallised in 19% yield. Having established that a metathesis approach was viable, the allylic alcohol (*R*)-**18** was prepared by Sharpless kinetic resolution;^{21,22} homo-metathesis of (*R*)-**18** gave **19** as a 4 : 1 mixture of *E* and *Z* geometric isomers from which the required *C*₂-symmetric isomer (*E*)-(*R,R*)-**19** could be isolated in 63% yield by column chromatography. This approach was not pursued further.

Double oxidative ring expansion^{23,24} of the difuryl diol **14** using *tert*-butyl hydroperoxide and catalytic vanadyl(v) acetylacetonate, was followed by protection as the corresponding bis methyl acetal. The dipyranone **20** was isolated by filtration of

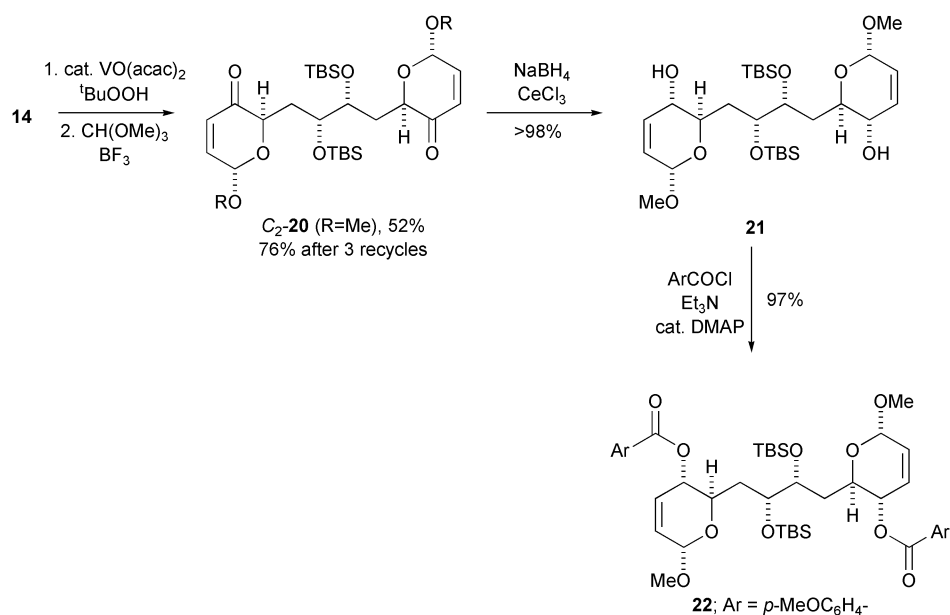
the reaction mixture in >98% yield as a 63 : 37 mixture of *C*₂-symmetrical and unsymmetrical anomers (Scheme 6). Careful purification by flash chromatography gave the required *C*₂-symmetrical dipyranone **20** in 52% yield. It was possible to re-equilibrate the mixture of diastereoisomers isolated from the mother liquors by treatment with trimethyl orthoformate and boron trifluoride: the *C*₂-symmetrical dipyranone **20** was obtained in 76% yield after three recycles.

Stereoselective Luche²⁵ reduction of the *meso* dipyranone **20** was highly stereoselective, and gave the diol **21** as a >95 : 5 mixture of diastereoisomers. The selectivity of the reaction **20**→**21** is remarkable, and reflects >97 : 3 stereo- and regio-selectivity for each of the individual reduction steps. The configuration of the diol **21** was assigned by analysis of the vicinal coupling constant (8.7 Hz) between the protons at C-2 and C-3. Similar stereoselective Luche reductions of dihydropyrans have been exploited by us^{6,10,26,27} and others;²⁸ the fundamental preference for axial attack on six-membered ketones (in the absence of strong steric effects) has previously been rationalized theoretically.²⁹ The diol **21** was converted into the corresponding *p*-methoxybenzoyl diester **22**.

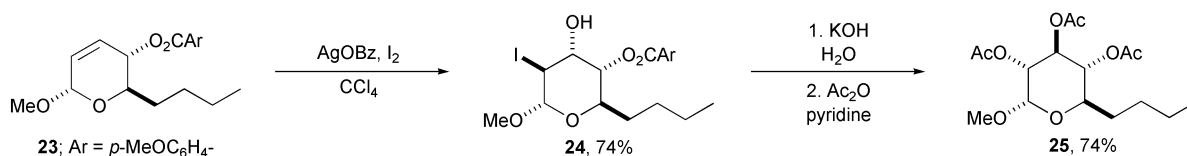
Development of methods for the stereoselective functionalisation of tetrahydropyran rings

Efficient methods were required for the functionalisation of the two tetrahydropyran rings of the di-THP **22**. In view of the complexity of this compound, we decided to develop the required methods using a model system (see Schemes 7–9). Previously, we have investigated the use of a Prévost reaction in the stereoselective functionalisation of compounds such as **23**.⁶ Treatment of the allylic *p*-methoxybenzoate **23** with iodine and silver benzoate in rigorously dry carbon tetrachloride gave a *ca.* 4 : 1 mixture of stereoisomers from which the hydroxy iodide **24** could be obtained in 74% yield⁶ (Scheme 7). Hydrolysis of the hydroxy iodide **24** with aqueous potassium hydroxide solution, and peracetylation, gave the triacetate **25** in 74% yield. The triacetate **25** has the relative configuration found in one of the THPs (*C*₆₇–*C*₇₁) of the required fragment **2**.

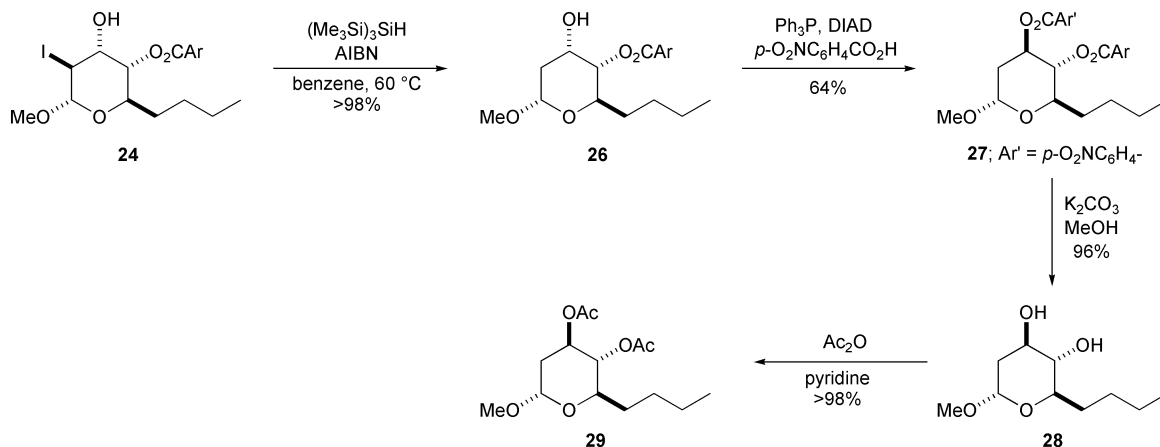
The other THP (*C*₅₈–*C*₆₂) in the fragment **22** lacks a hydroxyl group at *C*₅₉. The model compound **24** was, therefore, treated with tributyltin hydride³⁰ and AIBN in refluxing benzene for one hour (Scheme 8). Unfortunately, a 50 : 50 mixture of the regioisomeric hydroxy esters **26** and **30** was obtained, whose configuration was determined by careful analysis of their ¹H NMR spectra (for **26**, 3-H had *J* = 10.1 and 3.0 Hz). Given that



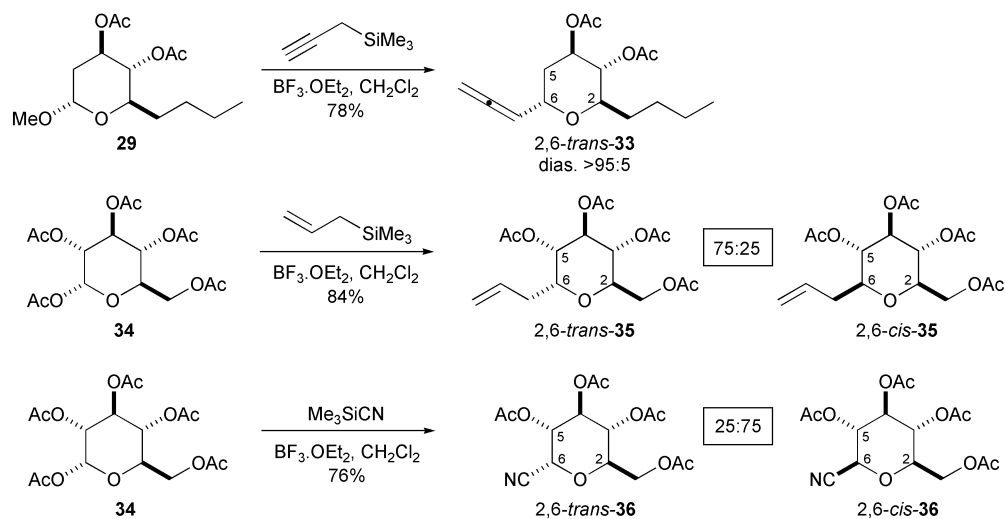
Scheme 6



Scheme 7



Scheme 8



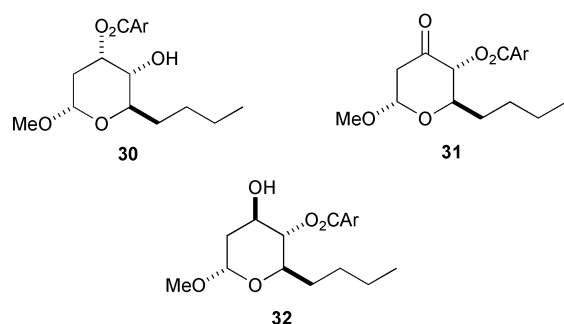
Scheme 9

Table 3 Diastereoselective acetal substitution reactions involving carbon nucleophiles

Entry	Starting material	Reagents	Product	Yield ^a (%)	Dias. ^b 2,6- <i>trans</i> : <i>cis</i>	<i>J</i> (H ⁵ H ⁶) 2,6- <i>trans</i>	<i>J</i> (H ⁵ H ⁶) 2,6- <i>cis</i>
1	29	propargyl-SiMe ₃ , BF ₃ ·OEt ₂ , CH ₂ Cl ₂	33	78 ^c	>95 : 5	5.6, 1.8	—
2a	37	propargyl-SiMe ₃ , BF ₃ ·OEt ₂ , CH ₂ Cl ₂	—	^d	—	—	—
2b	37	allyl-SiMe ₃ , BF ₃ ·OEt ₂ , CH ₂ Cl ₂	—	^d	—	—	—
3a	34	allyl-SiMe ₃ , BF ₃ ·OEt ₂ , CH ₂ Cl ₂	35	84	75 : 25	5.8	—
3b	34	Me ₃ SiCN, BF ₃ ·OEt ₂ , MeNO ₂	36	76	25 : 75	3.4	9.8

^a Yield of mixture of diastereoisomers. ^b Determined by analysis of the 300 MHz ¹H NMR spectrum of the crude reaction mixture. ^c Yield of single diastereoisomer. ^d No reaction.

much shorter reaction times did not prevent the intramolecular transfer of the *p*-methoxybenzoyl group, it is likely that a thermodynamic mixture of the esters **26** and **30** had been obtained. The susceptibility of the initial product **26** to rearrangement was thought to stem from the Lewis acidity of the tributyltin iodide by-product. The use of tris(trimethylsilyl)silane³¹ gave superior results, and the required alcohol **26** was obtained as a single regioisomer in >98% yield provided that the reaction was quenched after ten minutes.† It has been previously been shown that (Me₃Si)₃SiI is less Lewis acidic than tributyltin iodide.³²

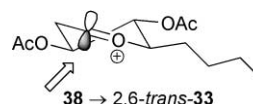


Unsurprisingly, subjection of the iodo alcohol **24** to Mitsunobu's reaction conditions³³ resulted only in reversion to the allylic ester **23**. However, treatment of the alcohol **26** with triphenylphosphine, *p*-nitrobenzoic acid and diisopropyl azodicarboxylate (DIAD) gave the required diester **27** in 64% yield, as well as the elimination product **23** (12% yield). Methanolysis of the diester **27** gave the diol **28** which, after acetylation, provided the diacetate **29** in 96% yield over the two steps.

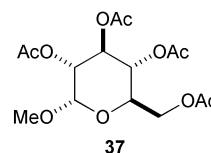
An alternative approach for inverting the configuration of the alcohol **26** would involve oxidation to the corresponding ketone **31**, followed by stereoselective reduction. Treatment of the alcohol **26** with pyridinium chlorochromate³⁴ buffered with sodium acetate gave the ketone **31** in 89% yield. Unfortunately, reduction of the ketone **31** with sodium borohydride (→ 80 : 20 **26** : **32**) and K-selectride (→ >95 : 5 **26** : **32**) resulted in mainly equatorial attack of the reagent; this trajectory avoids an unfavourable 1,3-diaxial interaction with the axial methoxy group.²³ In addition, both of these reactions were further complicated by migration²³ of the acyl group of **26** to give its regioisomer **30**.

Methods were developed for the diastereoselective reaction of six-membered acetals using carbon nucleophiles (see Scheme 9 and Table 3). Treatment of the methyl acetal **29** with propargyl trimethylsilane³⁵ and boron trifluoride etherate in dichloromethane was highly diastereoselective, and gave the allene **33** in 78% yield as a >95 : 5 mixture of diastereoisomers. The 2,6-*trans* configuration of the product was determined by careful analysis of its 300 MHz ¹H NMR spectrum (entry 1, Table 3). The highly stereoselective reaction of **29** is believed to stem from axial attack of the propargyl silane on the

intermediate oxonium ion **38** (Fig. 1).³⁶ The THP 2,6-*trans*-**33** has the same relative configuration as the C₅₈–C₆₂ THP of palytoxin.

**Fig. 1**

In contrast, no reaction was observed when the methyl acetal **37** was treated with either propargyl trimethylsilane or allyl trimethylsilane under similar conditions (entries 2a–b, Table 3).‡ This difference in reactivity is synthetically useful since selective reaction of one of the acetals of **4** would be required in our approach to the palytoxin fragment **2**; however, the reactivity difference is not surprising since neighbouring electron withdrawing acyloxy substituents are well known to destabilise oxonium ions strongly.⁸ However, the acetal of **37** was easily activated by transformation into the corresponding anomeric acetate:³⁷ treatment of **37** with catalytic sulfuric acid in acetic anhydride gave the pentacetate **34** in >98% yield as a 7 : 3 mixture of anomers.



The reaction of the pentacetate **34** with carbon nucleophiles was straightforward (entries 3a–b, Table 3). Treatment of **34** with allyl trimethylsilane and boron trifluoride etherate gave the THP³⁸ **35** as a 75 : 25 mixture of 2,6-*trans* and 2,6-*cis* diastereoisomers **35**. In contrast, reaction of **34** with trimethylsilyl cyanide and boron trifluoride etherate in nitromethane proceeded in the opposite diastereoselective sense: a 75 : 25 mixture of 2,6-*cis* and 2,6-*trans* tetrahydropyrans³⁹ **36** was obtained. In each case, the ratio and configurations of the products were determined by careful analysis of the 300 MHz ¹H NMR spectra of the crude reaction mixtures (see Table 3).

The complementary reactions of the pentacetate **34** (→**35** or **36**) are remarkable and deserve further comment. Activation of **34** must initially give the oxonium ion **39** which may close to give the dioxolenium ion **40** (Fig. 2). It appears that carbon nucleophiles strike a more delicate balance between reaction⁴⁰ with the dioxolenium ion **40** (with clean inversion of configuration) and direct attack on the less stable oxonium ion **39** (with axial attack). The sp²-hybridised nucleophile—allyl trimethylsilane—is believed to have attacked the oxonium ion **39** preferentially, leading to a 75 : 25 mixture of diastereoisomers in favour of the THP 2,6-*trans*-**35**. In contrast, the trimethylsilyl cyanide may have undergone preferential reaction with **40** to

† After four hours, the alcohols **26** and **30** were isolated as an 80 : 20 mixture of regioisomers.

‡ Perbenzylated methyl glycosides are much more reactive and undergo clean reaction with propargyl trimethylsilane in the presence of trimethylsilyl trifluoromethanesulfonate (ref. 35).

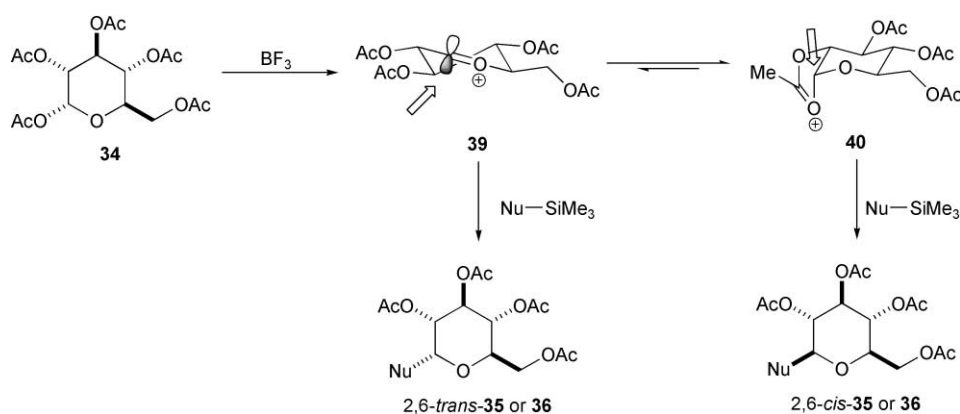
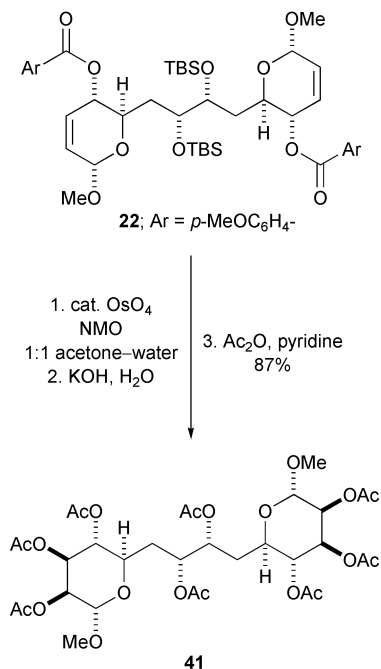


Fig. 2

give mainly the THP 2,6-*cis*-**36**. Alternatively, it is possible that the configuration of the cyanide-substituted THPs **36** was thermodynamically controlled.

Synthesis of a protected version of the C_{58} – C_{71} fragment of palytoxin

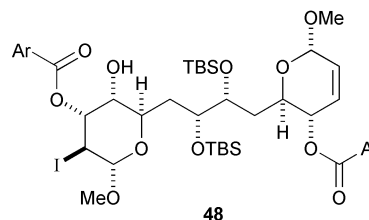
The C_2 -symmetrical intermediate **22** is a highly functionalised template for further functionalisation (Schemes 10 and 11). Hence, treatment of **22** with catalytic osmium tetroxide and NMO in acetone–water was followed by hydrolysis with aqueous potassium hydroxide solution and peracetylation: the octaacetate **41** was obtained in 87% yield as a single diastereoisomer (Scheme 10). The level of stereoselectivity observed in the two-directional functionalisation **22**→**41** is remarkable, and we have previously exploited this approach in the synthesis of some C-linked disaccharide mimetics.^{26,41} However, despite the stereochemical complexity of the octaacetate **41**, this approach does not directly tackle the critical issue of differentiation between the homotopic termini of **22**: considerable functional group manipulation would be required to convert **41** into the protected fragment **2**.



Scheme 10

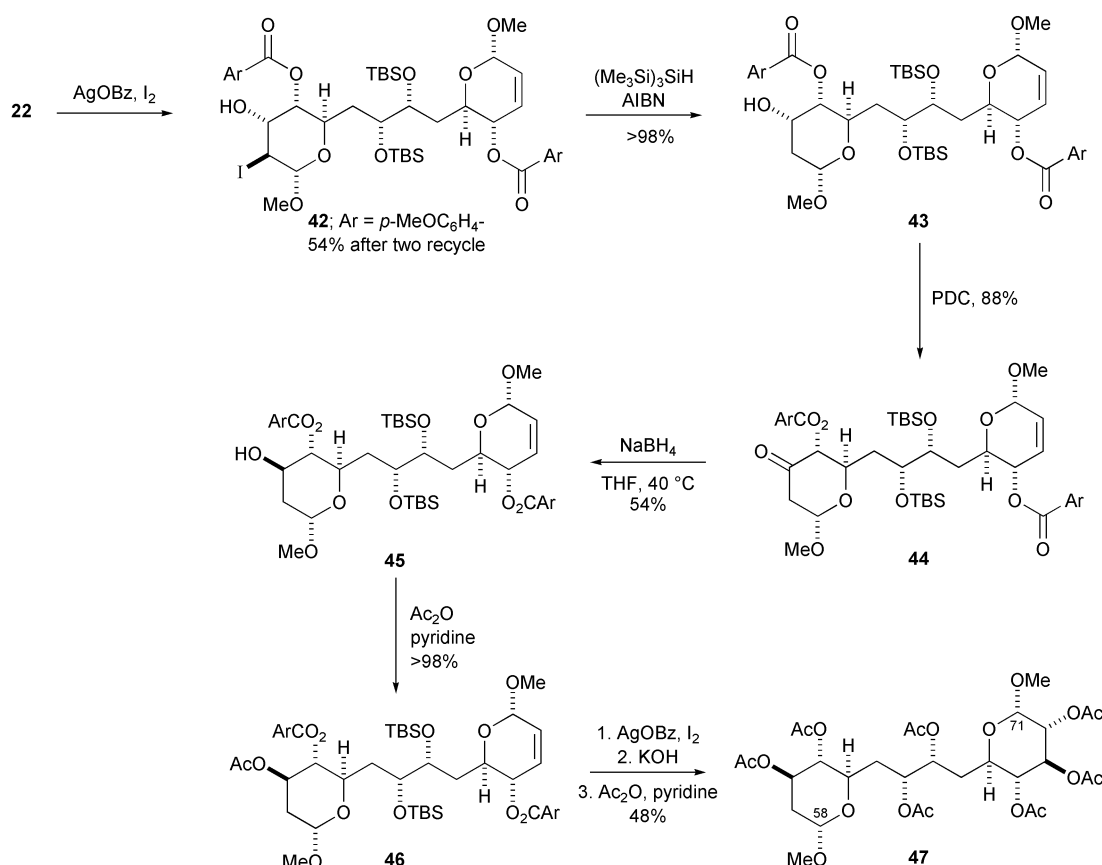
We investigated the use of a Prévost reaction to differentiate between the homotopic termini of **22** (Scheme 11). The two dihydropyran rings of **22** are sufficiently remote that an essentially statistical functionalisation was expected. Furthermore,

our model studies have shown that similar Prévost reactions are only moderately (*ca.* 80 : 20) regioselective.⁶ Treatment of the template **22** with one equivalent of both iodine and silver benzoate in dry carbon tetrachloride gave a mixture of the regioisomeric hydroxy esters **42** and **48**, together with recovered starting material. Separation, and two successive recycles of the recovered starting material, gave the required hydroxy esters **42** in 54% overall yield.



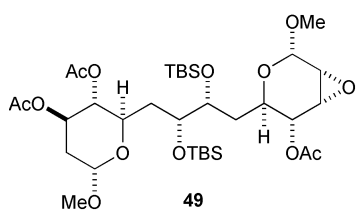
The iodo alcohol **42** was treated with tris(trimethylsilyl)silane and AIBN in benzene at 60 °C, and the required hydroxy ester **43** was obtained in >98% yield. There was no trace of the regioisomeric hydroxy ester which would have resulted from Lewis acid-catalysed migration of the acyl substituent. Unfortunately, attempted Mitsunobu inversion of the alcohol of **43** resulted only in elimination to return the template **22**. Alternative reaction conditions, including reversing the order of reagent addition and using DIAD in place of DEAD, did not suppress the elimination. The presence of a proton which is anti-periplanar to the leaving group may well promote the unwanted elimination pathway; however, in view of the similarity between **43** and the model alcohol **26**, in which only substituents which are remote from the reacting THP rings are different, this result was highly surprising.

Despite having found this approach fruitless in a model system, we explored the use of an oxidation, followed by a stereoselective reduction, to correct the configuration of the alcohol of **43**. Oxidation of the alcohol **43** with pyridinium chlorochromate, in the presence of sodium acetate, gave the corresponding ketone **44**. As we had observed with the ketone **31**, however, reduction with sodium borohydride in ethanol gave mainly the equatorial alcohol: analysis of the crude reaction mixture by 300 MHz ^1H NMR spectroscopy revealed a 90 : 10 mixture of the alcohols **43** and **45**, together with significant quantities of the rearrangement product in which the neighbouring *p*-methoxybenzoyl group had migrated to the alcohol of **43**. Remarkably, the sense of induction was reversed by treating the ketone **44** with sodium borohydride in THF at 50 °C. Under these conditions, the required alcohol **45** was obtained in 54% yield. Careful analysis of the 500 MHz ^1H NMR spectra of **43** and **45** revealed the hydroxyl group to be axial [$^3J(\text{H}^3\text{H}^4)$: 2.8 Hz] and equatorial [$^3J(\text{H}^3\text{H}^4)$: 10.0 Hz] respectively. The alcohol **45** was acetylated to give **46** in >98% yield.



Scheme 11

The Prévost reaction of **46** provided a valuable means for functionalising the remaining THP ring. Reaction of the allylic *p*-methoxybenzoate **46** with iodine and silver benzoate in rigorously dry carbon tetrachloride gave a crude product which was treated with potassium hydroxide in water–THF and peracetylated. Under these conditions, the epoxide **49** was obtained as a single diastereoisomer in 74% yield. Although we had expected that ring-opening of the epoxide by hydroxide ion would have occurred under these conditions, the isolation of the epoxide **49** did, at least, provide direct evidence for a mechanism proposed for the transformation **24**→**25**.⁶ Furthermore, in view of the hydrolysis of the *tert*-butyldimethylsilyl ethers of **22** (→**41**) under remarkably similar conditions, the survival of the silyl ethers in **49** was surprising. It appears that the use of THF as a co-solvent in hydrolysis of the Prévost product is important: under biphasic conditions, the substrate may remain in the organic layer and, therefore, be physically separated from the aqueous base.



Indeed, treatment of the crude Prévost product with refluxing aqueous potassium hydroxide in the *absence* of THF, and peracetylation, provided the required intermediate **47**; the relative configuration of **47** was established by comparison of its ¹H NMR spectrum with those of the model compounds **25**⁶ and **29**. We have previously shown, in related systems, that similar epoxides are also opened to give *trans*-diequatorial products; this unusual⁴² observation has been rationalized elsewhere.⁶ The heptaacetate **47** is a protected version of the C₅₈–C₇₁ fragment of palytoxin.

Summary

We have shown that the Prévost reaction is a reliable reaction for the functionalisation of allylic *p*-methoxybenzoates. This reaction was used to functionalise both of the THP rings of the di-THP **47**. In the first instance, treatment of the C₂-symmetrical template **22** with iodine and silver benzoate gave the iodo alcohol **42** in which the homotopic termini had been differentiated. The participation of the neighbouring *p*-methoxybenzoyloxy group ensured that the iodine atom was introduced to (and could subsequently be removed from) the atom (C₅₉) of palytoxin which lacks a hydroxyl group. At a later stage, a Prévost reaction was used once more to functionalise the other THP ring; after hydrolysis, and peracetylation, a protected C₅₈–C₇₁ fragment, **47**, of palytoxin was isolated.

Using a model system, methods have been developed for the reaction of the two acetals of **47** with carbon nucleophiles. However, due to a lack of material, the fragment **47** was not further functionalised. We have shown that the C₅₈ acetal of **47** is likely to be the more reactive, and reaction of this acetal with carbon nucleophiles would probably lead to a 2,6-*anti* THP, as required. The C₇₁ acetal has a neighbouring participating group, and in a model system, this feature could be exploited in the synthesis of a 2,6-*syn* THP ring.

In summary, a two-directional synthetic strategy has been applied in the synthesis of a protected version of the C₅₈–C₇₁ fragment of palytoxin. This fragment is almost C₂-symmetrical, and this hidden symmetry was exploited in the synthesis of the C₂-symmetrical template **22**. Further stereoselective functionalisation gave the required fragment **47**.

Experimental

General experimental methods have been previously described.⁶ All non-aqueous reactions were performed under an atmosphere of nitrogen. Analytical HPLC was conducted on a Gynkotek HPLC system with diode array detection; unless

otherwise stated, the column oven was set at 24 °C. An Econosil column (silica particle size: 10 µm) was used for analytical (4.6 × 250 mm) work, and a Chiracel OD column (4.6 × 250 mm) was used for chiral analytical HPLC; samples were calibrated against external standard samples dissolved in methanol. Semi-preparative HPLC was conducted with a Waters 2525 binary gradient pump with detection by a Micro-mass ZQ mass spectrometer; an XTerra® preparative HPLC column (19 × 50 mm) was used. Microanalyses were carried out by staff of the Department of Chemistry using a Carlo Erba 1106 automatic analyser.

(3R,4R)-3,4-Di-(*tert*-butyl-dimethyl-silyloxy)-1,6-di-morpholin-4-yl-hexane-1,6-dione 6

The amide **5** (300 mg, 1.056 mmol) was added to a stirred suspension of AD-mix β (1.479 g, 1.4 g per mmol), methanesulfonamide (100 mg, 1.056 mmol), potassium osmate dihydrate (4 mg, 1 mol%) and ligand DHQD₂-PHAL (41 mg, 5 mol%) in 1 : 1 *t*-butanol-water (3 ml) at 0 °C. This solution was stirred vigorously for 48 h before quenching with a saturated aqueous solution of sodium sulfite (3 ml). After stirring for a further 30 min the solution was evaporated to dryness and the thoroughly dried residue stirred in dry DMF (5 ml). The solution was filtered and the residue washed with a further portion of DMF (1.0 ml). The solution was stirred for 24 h at room temperature under N₂ after the addition of imidazole (433 mg, 6.37 mmol) and *t*-butyl-dimethylsilyl chloride (637 mg, 4.22 mmol). The solvent was removed by evaporation under reduced pressure at 80 °C and the residue partitioned between EtOAc (10 ml) and saturated aqueous sodium bicarbonate (5 ml). The organic layer was washed with water (2 × 5 ml) and brine (5 ml) before drying (MgSO₄). Solvent was removed under reduced pressure to give the silyl diether **10** **6** (386 mg, 67%) as a colourless oil.

(4R*,5R*)-Di-(5-methoxycarbonylmethyl)-2,2-dimethyl-[1,3]-dioxolane 8b

trans-Hydromuconic acid (1.00 g, 6.94 mmol) was added slowly in small portions to a stirred solution of potassium carbonate (958 mg, 6.94 mmol) in water (5 ml). *N*-methylmorpholine-*N*-oxide (1.62 g, 13.88 mmol) and osmium tetroxide (10 mg, catalytic) were added and the solution stirred at room temperature for 4 h. The solution was acidified to pH 1 with *p*-toluenesulfonic acid and evaporated to dryness under reduced pressure. The residue was dissolved in a 1 : 1 mixture of acetone–2,2-dimethoxypropane (15 ml) and stirred at room temperature for a further 12 h. The solution was neutralized with triethylamine (2 ml) and the solvent removed under reduced pressure. The residue was partitioned between EtOAc (20 ml) and water (20 ml) and the aqueous layer extracted with a further portion of EtOAc (10 ml). The combined extracts were dried (MgSO₄) and the solvent removed under reduced pressure to give the diester **8b** (634 mg, 35%) as a colourless oil, $\nu_{\max}/\text{cm}^{-1}$ (CHCl₃ solution) 2989 (C–H), 2955, 1741 (C=O), 1439, 1382, 1204, 1172 and 1061; δ_{H} (300 MHz; CDCl₃) 4.17 (2H, t, *J* 4.0), 3.71 (6H, s, CH₃), 2.67 (4H, d, *J* 5.0) and 1.40 (6H, s, CH₃); δ_{C} (75 MHz; CDCl₃) 171.4 (C=O), 109.6, 77.1, 52.2, 38.0 and 27.5.

(3R*,4R*)-3,4-Bis-(*tert*-butyl-dimethyl-silyloxy)-6-oxo-6-[methoxy(methyl)amino]hexan-1-al 10

DIBAL (2.95 ml, 2.95 mmol, as a 1 M solution in toluene) was added to a stirred solution of the Weinreb diamide **10** **9** (363 mg, 0.738 mmol) in dry THF (10 ml) at –78 °C. The solution was stirred for a further 6 h and quenched with methanol (0.5 ml). The solution was allowed to warm to room temperature, saturated aqueous sodium potassium tartrate solution added (10 ml), stirred vigorously until the two layers separated and the aqueous layer extracted with EtOAc (2 × 10 ml). The combined organic layers were dried (MgSO₄), pre-absorbed on silica gel

and purified by flash chromatograph, eluting with EtOAc, to give the aldehyde **10** (205 mg, 64%) as a colourless oil, *R*_f 0.19 (EtOAc); (Found: MNa⁺ 456.2577; C₂₀H₄₃NO₅Si₂ requires MNa, 456.2577); $\nu_{\max}/\text{cm}^{-1}$ (CHCl₃ solution) 3447, 2939 (C–H), 2857, 1715, 1664, 1472, 1413, 1388, 1256 and 1096; δ_{H} (300 MHz; CDCl₃) 9.72 (1H, dd, *J* 2.9 and 1.7, HC=O), 4.32–4.14 (2H, m, 3-H and 4-H), 3.62 (3H, s, OCH₃), 3.11 (3H, s, NCH₃), 2.65–2.43 (4H, m, CH₂), 0.79 (9H, s, ^{*t*}Bu), 0.77 (9H, s, ^{*t*}Bu), 0.05 (3H, s, SiCH₃), 0.03 (3H, s, SiCH₃), 0.00 (3H, s, SiCH₃) and –0.04 (3H, s, SiCH₃); δ_{C} (75 MHz; CDCl₃) 201.9 (C=O), 71.5, 70.1, 61.7, 46.2, 33.3, 32.4, 26.1, 26.1, 18.3, –4.1, –4.5 and –4.5; *m/z* (ES) 456.2 (100%, MNa⁺).

Addition of 2-lithio furan to the aldehyde 10

Butyllithium (535 µl of a 1.52 M solution in hexanes, 0.813 mmol) was added slowly to a stirred solution of furan (64 µl, 0.890 mmol) in dry tetrahydrofuran (3 ml) at –78 °C. The solution was allowed to warm to 0 °C, stirred for a further 30 min, rapidly cooled to –40 °C and the aldehyde **10** (74 mg, 0.171 mmol) added as a solution in THF (0.5 ml). The solution was stirred for a further 6 h, quenched by addition of a saturated aqueous solution of ammonium chloride (5 ml), warmed to room temperature and the aqueous layer extracted with EtOAc (3 × 50 ml). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure to give the alcohol **11** (81 mg, 93%) as a colourless oil. Analysis of the crude reaction mixture by 300 MHz ¹H NMR revealed a 1 : 1 mixture of diastereoisomers.

(3R*,4R*)-1,6-Di-furan-2-yl-3,4-dihydroxy-hexane-1,6-dione 12

A solution of hydrogen fluoride–pyridine complex was prepared by dissolving commercial HF pyridine complex (3.8 ml) and pyridine (14 ml) in tetrahydrofuran (40 ml). The diketone **7** (1.35 g, 2.66 mmol) was dissolved in 10 ml of this solution and stirred at room temperature under N₂ for 4 days before the solution was cautiously dropped into a saturated aqueous solution of sodium bicarbonate (20 ml). The aqueous layer was extracted with EtOAc (4 × 20 ml) and the combined extracts dried (MgSO₄), solvent was removed under reduced pressure and the residue pre-absorbed on silica gel. Purification by flash chromatography, eluting with 6 : 4 EtOAc–petrol, gave the difuryl diol **12** (148 mg, 20%) as colourless prisms, mp 127.4–128.7 °C; *R*_f 0.12 (6 : 4 EtOAc–petrol); (Found: MNa⁺ 301.0678; C₁₄H₁₄O₆ requires MNa, 301.0688); $\nu_{\max}/\text{cm}^{-1}$ (CHCl₃ solution) 3307 (O–H), 3115, 1664 (C=O), 1563, 1469, 1398, 1282, 1162, 1051 and 1024; δ_{H} (300 MHz; DMSO-*d*₆) 8.03 (2H, dd, *J* 1.5 and 0.6, furyl 5-H), 7.50 (2H, dd, *J* 2.9 and 0.6, furyl 4-H), 6.76 (2H, dd, *J* 2.9 and 1.5, furyl 3-H), 4.95 (2H, d, *J* 5.5), 4.09 (2H, broad s, 3-H and 4-H), 3.46 (2H, s, OH), 3.05 (2H, dd, *J* 15.4 and 9.0, CH_aH_b), 2.92 (2H, dd, *J* 15.4 and 2.6, CH_aH_b); δ_{C} (75 MHz; DMSO-*d*₆) 187.9 (C=O), 152.8 (furyl 2-C), 147.9 (furyl 5-C), 119.0 (furyl), 112.8 (furyl), 70.2 (C–O) and 41.4 (CH₂); *m/z* (ES) 301.1 (100%, MNa⁺).

(1R,3R,4R,6R)-3,4-Di-(*tert*-butyl-dimethyl-silyloxy)-1,6-di-furan-2-yl-hexane-1,6-diol 14

A stock solution of the CBS reagent (0.2 M solution) was freshly prepared by stirring a solution of (*S*)-diphenylprolinol (506 mg, 2 mmol) and *n*-butylboronic acid (204 mg, 2 mmol) in sodium dried toluene (10 ml) over 4 Å molecular sieves for 2 h. An aliquot of the stock solution of the CBS reagent (197 µl, 39.4 µmol, 10 mol%) was added to a stirred solution of the diketone **7** (200 mg, 0.39 mmol) in toluene (3.2 ml) at room temperature under N₂. To the stirred solution borane dimethyl sulfide complex (0.39 ml, 0.78 mmol, 2 M solution in THF) was added slowly over 1 h. The solution was stirred for a further 5 h and then quenched with a saturated aqueous solution of ammonium chloride (3 ml). The organic layer was dried

(MgSO₄) and solvent removed by evaporation under reduced pressure to give a crude product. Analysis by analytical HPLC (gradient elution: 99 : 1 → 98 : 2 hexane : IPA over 30 min, with detection at 220 nm) revealed a 90 : 10 mixture of the diastereoisomers **14** and **16**. The crude product was pre-absorbed onto silica gel and separated by flash chromatography to give the difuryl diol **14** (165.6 mg, 82%) as colourless needles, mp 105–106 °C; $[\alpha]_D = +31.7$ ($c = 1.69$, CHCl₃). Analysis of the diol **14** by chiral analytical HPLC revealed it to have >98% ee and >99% purity (gradient elution: 99.6 : 0.4 → 97.5 : 2.5 hexane–isopropanol over 30 min; flow: 1.0 ml min⁻¹; observation at λ_{\max} 219 nm; retention times, 24.4 and 26.2 min).

Also obtained was the difuryl diol **16** (13.9 mg, 7%) as colourless needles, mp 95–96 °C; $[\alpha]_D = -19.6$ ($c = 1.43$, CHCl₃).

Asymmetric reduction of the racemic diketone **7**

By the same general method, the racemic diketone **7** (200 mg, 0.39 mmol) gave a crude product. Analysis by analytical HPLC revealed a 49.7 : 0.6 : 49.7 mixture of the diols **14**, **15** and **16**. Pre-absorption of the crude mixture onto silica gel and separation by flash chromatography gave the diol **14** (82 mg, 41%), mp 105–106 °C, $[\alpha]_D = +29.4$ ($c = 0.14$, CHCl₃), and the diol **16** (83 mg, 42%), mp 95–97 °C, $[\alpha]_D = -18.2$ ($c = 0.11$, CHCl₃). Analysis of the diol **14** by chiral analytical HPLC revealed it to have >98% ee.

(*E*)-(1*R*,6*R*)-1,6-Difuran-2-yl-hex-3-ene-1,6-diol **19**

The furyl alcohol **21** (*R*)-**18** (1.00 g, 7.30 mmol) and bis(tricyclohexylphosphine)benzylideneruthenium(IV) dichloride (300 mg, 0.36 mmol, 5 mol%) in dichloromethane (4 ml) were refluxed under N₂ for 4 days. The solvent was evaporated under reduced pressure to give a crude product. Analysis by 300 MHz ¹H NMR spectroscopy revealed a 4 : 1 ratio of *E* : *Z* isomers. Flash chromatography (gradient elution: 2 : 8 → 1 : 1 EtOAc–petrol) gave the alkene (*E*)-(1*R*,6*R*)-**19** (570 mg, 63%) as a colourless oil, R_f 0.09 (2 : 8 EtOAc–petrol); $\nu_{\max}/\text{cm}^{-1}$ (CHCl₃ solution) 3255, 2917, 1504, 1437, 1353, 1298, 1228, 1216, 1151, 1009 and 907; δ_H (300 MHz; CDCl₃) 7.11 (2H, dd, J 1.8 and 0.9, furyl 5-H), 6.15 (2H, dd, J 3.0 and 1.8, furyl 3-H), 6.04 (2H, dd, J 3.0 and 0.9, furyl 4-H), 5.36 (2H, br s, $HC=C$), 4.50 (2H, t, J 6.3, $HC-O$), 2.60 (2H, broad s, OH) and 2.38 (4H, broad, CH₂); δ_C (75 MHz; CDCl₃) 156.5 (furyl 2-C), 142.3 (furyl 5-C), 129.8, 110.5 (furyl), 106.4 (furyl), 67.3 (C–O) and 39.4 (CH₂); m/z (ES) 270.8 (100%, MNa⁺).

(*E*)-(1*R**,6*S**)-1,6-Difuran-2-yl-hex-3-ene-1,6-diol **19**

By the same general method, the racemic alcohol **18** (1.00 g, 7.30 mmol) and bis(tricyclohexylphosphine)benzylideneruthenium(IV) dichloride (300 mg, 0.36 mmol, 5 mol%) in dichloromethane (4 ml), gave a crude product. Analysis by 300 MHz ¹H NMR spectroscopy revealed a 4 : 1 mixture of *E* : *Z* isomers. Recrystallization from chloroform gave the alkene (*E*)-(1*R**,6*S**)-**19** (171 mg, 19%) as colourless needles, mp 112.7–114.2 °C; R_f 0.12 (2 : 8 EtOAc–petrol); $\nu_{\max}/\text{cm}^{-1}$ (CHCl₃ solution) 3255 (O–H), 2917, 1504, 1437, 1353, 1298, 1228, 1216, 1151, 1009 and 907; δ_H (300 MHz; CDCl₃) 7.53 (2H, dd, J 1.6 and 0.7, furyl 5-H), 6.35 (2H, dd, J 3.0 and 1.6, furyl 3-H), 6.04 (2H, dd, J 3.0 and 0.7, furyl 4-H), 5.40 (2H, dd, J 7.3 and 3.7, $HC=C$), 5.25 (2H, d, J 5.3), 4.44 (2H, m), 3.36 (2H, s, OH) and 2.50–2.34 (4H, broad, CH₂); δ_C (75 MHz; CDCl₃) 157.9 (furyl 2-C), 141.9 (furyl 5-C), 128.8, 110.4 (furyl), 105.8 (furyl), 66.5 (C–O) and 39.4 (CH₂); m/z (ES) 270.8 (100%, MNa⁺).

(*R*)-2-[(2*R*,3*R*)-2,3-Bis-(*tert*-butyl-dimethyl-silanyloxy)-4-((*R*)-3-oxo-6-hydroxy-3,6-dihydro-2*H*-pyran-2-yl)-butyl]-6-hydroxy-6*H*-pyran-3-one **20** (*R* = H)

t-Butyl hydroperoxide (570 μ l, 2.85 mmol, 5 M solution in decanes) was added to a stirred solution of the diol **14** (586 mg,

1.14 mmol) and vanadyl acetylacetonate (5 mg) in dichloromethane (4 ml) at room temperature under N₂. The solution was stirred for 6 h before the solution was evaporated to half its original volume with a steady stream of nitrogen. The flocculent white needles were filtered and washed with petrol ether (2 ml). A second crop was procured by evaporating under reduced pressure at room temperature, trituration with petrol (4 ml) and filtration. The dipyrnone **20** (*R* = H; 594 mg, 96%; 65 : 35 mixture of anomers) was obtained as flocculent colourless needles, $[\alpha]_D = +24.2$ ($c = 0.57$, MeOH); R_f 0.34 (1 : 1 EtOAc–petrol); (Found: MNa⁺, 565.2622; C₂₆H₄₆O₈Si₂ requires MNa, 565.2629); $\nu_{\max}/\text{cm}^{-1}$ (thin film) 3341, 2927, 2853, 1684, 1470, 1259, 1204, 1091 and 1044; δ_H (300 MHz; DMSO-*d*₆) 7.14 (2H, d, J 8.5, O–H^{min}), 6.97 (2H, dd, J 10.2 and 3.6, 5-H^{maj}), 6.93 (2H, d, J 10.2, 5-H^{min}), 6.84 (2H, d, J 7.4, O–H^{maj}), 6.00 (2H, d, J 10.2, 4-H^{min}), 5.93 (2H, d, J 10.2, 4-H^{maj}), 5.38 (2H, d, J 8.5, 6-H^{min}), 5.33 (2H, dd, J 7.4 and 3.6, 6-H^{maj}), 4.38 (2H, d, J 11.0, 2-H^{maj}), 3.93 (2H, d, J 10.2, 2-H^{min}), 3.84 (2H, m, 2-H' and 3-H'), 1.80–1.50 (4H, m, CH₂^{maj+min}), 0.74 (18H, s, 'Bu, H^{maj+min}) and 0.00 (12H, s, SiCH₃, H^{maj+min}); δ_C (75 MHz; DMSO-*d*₆) 197.9 (3-C^{maj}), 197.4 (3-C^{min}), 148.4 (5-C^{maj+min}), 127.9 (4-C^{min}), 125.8 (4-C^{maj}), 91.0 (6-C^{min}), 86.7 (6-C^{maj}), 74.5 (C^{min}), 70.4 (C^{maj}), 69.6 (C^{maj}), 69.2 (C^{min}), 26.1 ('Bu), 18.0, –4.3, –4.4 and –4.5; m/z (ES) 565.9 (100%, MNa⁺).

(*R*)-2-[(2*R*,3*R*)-2,3-Bis-(*tert*-butyl-dimethyl-silanyloxy)-4-((*R*)-3-oxo-6-methoxy-3,6-dihydro-2*H*-pyran-2-yl)-butyl]-6-methoxy-6*H*-pyran-3-one **20** (*R* = Me)

Boron trifluoride diethyl etherate complex (5 μ l, 39 μ mmol) was added to a stirred solution of (*R*)-2-[(2*R*,3*R*)-2,3-bis-(*tert*-butyl-dimethyl-silanyloxy)-4-((*R*)-3-oxo-6-hydroxy-3,6-dihydro-2*H*-pyran-2-yl)-butyl]-6-hydroxy-6*H*-pyran-3-one **20** (*R* = H) (427 mg, 0.78 mmol) and trimethyl orthoformate (258 μ l, 2.35 mmol) in dichloromethane (5 ml) at room temperature under N₂. Stirring was continued for a further 30 min before the solution was quenched with saturated aqueous sodium bicarbonate (10 ml). The aqueous layer was extracted with dichloromethane (2 \times 5 ml) and the combined organic extracts dried (MgSO₄). Solvent was removed under reduced pressure to give the acetal **20** (*R* = Me; 446 mg, >98%; 63 : 37 mixture of anomers), a colourless oil, R_f 0.28 (2 : 8 EtOAc–petrol); (Found: MNH₄⁺, 588.3384. C₂₈H₅₀Si₂O₈ requires MNH₄ 588.3388); $\nu_{\max}/\text{cm}^{-1}$ (CHCl₃ solution) 2957 (C–H), 2931 2859, 1699 (C=O), 1472, 1390, 1259, 1101 and 1053; δ_H (300 MHz; CDCl₃) 6.77 (2H, d, J 10.3, 5-H^{min}), 6.71 (2H, dd, J 10.2 and 3.3, 5-H^{maj}), 6.07 (2H, d, J 10.3, 4-H^{min}), 6.00 (2H, d, J 10.2, 4-H^{maj}), 5.18 (2H, s, 6-H^{min}), 4.97 (2H, d, J 3.3, 6-H^{maj}), 4.39 (2H, dd, J 10.5 and 1.8, 2-H^{maj}), 4.05 (2H, d, J 11.0, 2-H^{min}), 3.92 (2H, t, J 11.0, 2,3-H^{min}), 3.56 (6H, s, OMe^{maj+min}), 2.08 (2H, d, J 12.0 CH₂H_b^{maj}), 1.96 (2H, d, J 12.0, CH₂H_b^{min}), 1.85 (2H, d, J 13.8, CH₂H_b^{min}), 1.78 (2H, d, J 13.8, CH₂H_b^{min}), 0.77 (18H, s, 'Bu, H^{min}), 0.77 (18H, s, 'Bu, H^{maj}), 0.03 (6H, s, SiCH₃, H^{min}), 0.02 (6H, s, SiCH₃, H^{maj}), 0.00 (6H, s, SiCH₃, H^{min}), –0.03 (6H, s, SiCH₃, H^{maj}); δ_C (75 MHz; CDCl₃) 195.5 (3-C^{maj}), 195.4 (3-C^{min}), 146.3 (5-C^{min}), 141.9 (5-C^{maj}), 128.5 (4-C^{min}), 126.6 (4-C^{maj}), 96.0 (6-C^{min}), 93.3 (6-C^{maj}), 74.0 (C^{min}), 70.9 (C^{maj}), 69.8 (C^{maj}), 69.6 (C^{min}), 55.9 (OMe^{maj}), 54.8 (OMe^{min}), 30.2 (CH₂^{maj}), 29.4 (CH₂^{min}), 24.7 ('Bu^{maj+min}), 17.0, –4.8 (SiMe), –4.9 (SiMe), –5.9 (SiMe) and –5.7 (SiMe); m/z (ES) 593.7 (100%, MNa⁺).

In a separate experiment, the dipyrnone C₂-**20** (*R* = Me), spectroscopically identical to the major isomer obtained previously, was isolated in 52% yield by careful flash column chromatography (eluting with 2 : 8 EtOAc–petrol).

(2*R*,3*R*,6*R*)-2-[(2*R*,3*R*)-2,3-Bis-(*tert*-butyl-dimethyl-silanyloxy)-4-((2*R*,3*R*,6*R*)-3-hydroxy-6-methoxy-3,6-dihydro-2*H*-pyran-2-yl)-butyl]-6-methoxy-3,6-dihydro-2*H*-pyran-3-ol **21**

The diacetal **20** (421 mg, 0.736 mmol; 63 : 37 mixture of anomers) and cerium chloride heptahydrate (686 mg, 1.84

mmol) were stirred under nitrogen at $-40\text{ }^{\circ}\text{C}$ in ethanol (5 ml) while sodium borohydride (62 mg, 1.62 mmol) was added slowly in small portions. The solution was stirred for 6 h, quenched with water (1.0 ml) and evaporated under reduced pressure to give a crude product which was pre-absorbed onto silica gel and purified by careful flash chromatography (gradient elution: 15 : 85 \rightarrow 25 : 75 EtOAc–petrol) to give the *diol* **21** (173 mg, 41%) as a colourless oil, $[a]_{\text{D}} = +19.4$ ($c = 0.12$, CHCl_3); R_f 0.32 (3 : 7 EtOAc–petrol); (Found: MNH_4^+ , 592.3707. $\text{C}_{28}\text{H}_{54}\text{Si}_2\text{O}_8$ requires MNH_4^+ 592.3701); $\nu_{\text{max}}/\text{cm}^{-1}$ (CHCl_3 solution) 3436, 2956, 2929, 2856, 1472, 1260, 1054 835; δ_{H} (500 MHz; CDCl_3) 5.85 (2H, d, J 10.2, 5-H), 5.60 (2H, dt, J 10.2 and 1.8, 4-H), 4.65 (2H, s, 6-H), 3.72 (2H, br m, 3-H), 3.46 (2H, td, J 8.7 and 1.8, 2-H), 3.32 (6H, s, OMe), 1.80–1.50 (4H, m, CH_2), 0.77 (18H, s, tBu), 0.01 (6H, s, SiCH_3) and 0.00 (6H, s, SiCH_3); δ_{C} (125 MHz; CDCl_3) 134.1, 126.7, 96.0, 71.7, 69.8, 68.5, 56.9, 34.0, 26.3, 18.4, -3.6 and -4.2 ; m/z (ES) 574.3 (100%, MNH_4^+).

In a separate experiment, the *dipyranone* **C₂-20** was reduced under identical conditions to give the *diol* **21** in >98% yield.

4-Methoxybenzoic acid (2*R,3*R*,6*R*)-2-[(2*R**,3*R*)-2,3-bis-(*tert*-butyl-dimethyl-silanyloxy)-4-((2*R**,3*R*,6*R*)-6-methoxy-3-(4-methoxybenzoyloxy)-3,6-dihydro-2*H*-pyran-2-yl)-butyl]-6-methoxy-3,6-dihydro-2*H*-pyran-3-yl ester **22****

The *diol* **21** (273 mg, 0.474 mmol) and triethylamine (237 μl , 1.71 mmol) were stirred at room temperature under nitrogen in dichloromethane (5 ml, 0.095 M in the *diol*) while *p*-anisoyl chloride (142 μl , 1.04 mmol) was added by syringe. The resulting solution was treated with DMAP (2.9 mg, 23.7 μmol) and stirred for 18 hours. The solution was quenched with saturated aqueous sodium bicarbonate (5 ml) and diluted with chloroform (10 ml). The organic layer was separated and washed with saturated aqueous sodium bicarbonate (2×5 ml) and brine (5 ml) and was dried (MgSO_4) and evaporated under reduced pressure to give a crude product which was purified by flash chromatography, after pre-absorption onto silica gel (gradient elution: 1 : 9 \rightarrow 2 : 8 EtOAc–petrol) to give the *diester* **22** (389 mg, 97%) as a colourless crystalline solid, mp 191–192 $^{\circ}\text{C}$; $[a]_{\text{D}} = +17.3$ ($c = 0.31$, CHCl_3); R_f 0.32 (15 : 85 EtOAc–petrol); (Found: MNa^+ , 865.3394. $\text{C}_{44}\text{H}_{66}\text{Si}_2\text{O}_{12}$ requires MNa 865.3991); $\nu_{\text{max}}/\text{cm}^{-1}$ (CHCl_3 solution) 2931 (C–H), 2857, 1718 (C=O), 1604, 1512, 1464, 1325, 1257, 1105, 1051; δ_{H} (300 MHz; CDCl_3) 7.75 (4H, d, J 8.7, Ar), 6.69 (4H, d, J 8.7, Ar), 5.80 (2H, d, J 10.3, 5-H), 5.61 (2H, dt, J 10.3 and 1.8, 4-H), 4.93 (2H, dd, J 9.5 and 1.8, 3-H), 4.64 (2H, s, 6-H), 3.86 (2H, t, J 9.5, 2-H), 3.70 (2H, dd, J 9.5 and 7.2, 2-H' and 3-H'), 3.68 (6H, s, OMe), 3.29 (6H, s, OMe), 1.61 (2H, dd, J 13.8 and 9.5, CH_2H_b), 1.26 (2H, dd, J 13.8 and 7.2, CH_2H_b), 0.76 (18H, s, tBu), 0.00 (6H, s, SiCH_3) and -0.03 (6H, s, SiCH_3); δ_{C} (75 MHz; CDCl_3) 164.0, 132.2, 130.6, 127.8, 122.7, 114.0, 96.1, 71.6, 69.9, 66.7, 57.1, 55.9, 34.2, 26.2, 18.4, -3.6 and -4.2 ; m/z (ES) 883.4 (100%, MNa^+).

4-Methoxybenzoic acid (2*R,3*S**,4*S**,6*S**)-2-butyl-4-hydroxy-6-methoxy-tetrahydropyran-3-yl ester **26****

A solution of iodo alcohol **24** (104 mg, 0.224 mmol) in benzene (3.0 ml) was deoxygenated by bubbling through a steady stream of nitrogen for 30 seconds. Tris-(trimethylsilyl)silane (150 μl) was added while the solution was stirred under nitrogen at 65 $^{\circ}\text{C}$, and azobisisobutyronitrile (5 mg) was added. The reaction was stirred at 65 $^{\circ}\text{C}$ for a further 30 min or until TLC indicated completion, cooled in an ice bath and loaded directly without pre-absorption or concentration onto a short column of silica. Elution first with 1 : 9 EtOAc–petrol and then 4 : 6 EtOAc–petrol gave the *hydroxy ester* **26** (74.9 mg, >98%; **26** : **30** >98 : 2) as a colourless oil, R_f 0.36 (3 : 7 EtOAc–petrol); (Found: MH^+ , 339.1804. $\text{C}_{18}\text{H}_{26}\text{O}_6$ requires MH 339.1807); $\nu_{\text{max}}/\text{cm}^{-1}$ (CHCl_3 solution) 3522, 2955, 1713, 1606, 1512, 1257,

1168, 1090 and 1026; δ_{H} (500 MHz; CDCl_3) 7.90 (2H, d, J 9.0, Ar), 6.79 (2H, d, J 9.0, Ar), 4.72 (1H, d, J 3.0, 6-H), 4.67 (1H, dd, J 10.1 and 3.0, 3-H), 4.11 (1H, br, td, J 3.5 and 3.0, 4-H), 4.02 (1H, td, J 10.1 and 2.6, 2-H), 3.73 (3H, s, OMe), 3.37 (1H, d, J 9.4, OH), 3.28 (3H, s, OMe), 2.03 (1H, dd, J 14.8 and 3.0, CH_2H_b), 1.90 (1H, td, J 14.8 and 3.0, CH_2H_b), 1.75–1.20 (6H, m, butyl CH_2) and 0.87 (3H, t, J 7.4, CH_3); δ_{C} (75 MHz; CDCl_3) 166.4 (C=O), 162.5 (Ar), 130.8 (Ar), 121.2 (Ar), 112.6 (Ar), 97.4 (6-H), 72.6, 64.9, 63.9, 54.2, 31.4, 28.0, 22.8 and 14.4; m/z (ES) 360.8 (100%, MNa^+).

4-Methoxy-benzoic acid (2*R,3*S**,4*R**,6*S**)-2-butyl-4-(4-nitrobenzoyl)-6-methoxy-tetrahydro pyran-3-yl ester **27****

Diisopropyl azodicarboxylate (108 mg, 103 μl , 0.534 mmol) was added slowly to a stirred solution of triphenylphosphine (140.0 mg, 0.534 mmol) in THF (3 ml) at 0 $^{\circ}\text{C}$ under nitrogen. The resulting slurry was stirred for a further 20 min, the hydroxy ester **26** (93 mg, 0.276 mmol) was added as a solution in THF (1.2 ml), *p*-nitrobenzoic acid (89.2 mg, 0.534 mmol) added immediately and the solution was allowed to warm to room temperature and stirred for a further 48 h before solvent was removed and the residue pre-absorbed onto silica. Purification by flash chromatography, eluting with 15 : 85 EtOAc–petrol gave the *diester* **27** (85.8 mg, 64%), a colourless crystalline solid, mp 180–181 $^{\circ}\text{C}$; R_f 0.24 (1 : 9 EtOAc–petrol); $\nu_{\text{max}}/\text{cm}^{-1}$ (CHCl_3 solution) 2932, 1721, 1712, 1606, 1526, 1263, 1172, 1119, 1049; δ_{H} (300 MHz; CDCl_3) 8.20 (2H, d, J 9.0, Ar), 8.08 (2H, d, J 9.0, Ar), 7.92 (2H, d, J 9.0, Ar), 6.85 (2H, d, J 9.0, Ar), 5.62 (1H, ddd, J 12.9, 9.6 and 5.4, 4-H), 5.22 (1H, t, J 9.6, 3-H), 4.90 (1H, d, J 3.4, 6-H), 3.92 (1H, td, J 9.6 and 2.3, 2-H), 3.82 (3H, s, OMe), 3.42 (3H, s, OMe), 2.47 (1H, dd, J 12.9 and 5.4, CH_2H_b), 1.95 (1H, td, J 12.9 and 3.4, CH_2H_b), 1.80–1.10 (6H, m, butyl CH_2) and 0.87 (3H, t, J 7.4, CH_3); δ_{C} (75 MHz; CDCl_3) 165.9, 164.4, 164.1, 150.9, 135.6, 132.2, 131.2, 123.9, 122.0, 114.1, 98.2, 73.5, 72.0, 69.7, 55.9, 55.3, 35.7, 31.5, 27.9, 23.0 and 14.4; m/z (ES) 509.7 (100%, MNa^+).

Also obtained was allylic *p*-methoxybenzoate **23** (10.6 mg, 12%).

(2*R,3*S**,4*R**,6*S**)-2-Butyl-6-methoxy-tetrahydro-pyran-3,4-diol **28****

Potassium carbonate (144.5 mg, 1.047 mmol) was added to a stirred solution of the *diester* **27** (102 mg, 0.209 mmol) in methanol (2 ml), at room temperature under nitrogen. The solution was stirred for 3 days, the solvent was removed under reduced pressure and the residue pre-absorbed onto silica. Purification by flash chromatography (gradient elution: 4 : 6 \rightarrow 8 : 2 EtOAc–petrol) gave the *diol* **28** (41.0 mg, 96%), as a colourless oil, R_f 0.21 (1 : 1 EtOAc–petrol); (Found: MNH_4^+ , 222.1704. $\text{C}_{10}\text{H}_{24}\text{NO}_4$ requires MNH_4 222.1705); $\nu_{\text{max}}/\text{cm}^{-1}$ (CHCl_3 solution) 3400 (O–H), 2933 (C–H), 1443, 1209, 1128, 1050, 951, 900; δ_{H} (300 MHz; CDCl_3) 4.75 (1H, d, J 3.2, 6-H), 3.87 (1H, ddd, J 11.6, 9.2 and 5.0, 4-H), 3.55 (2H, br, OH), 3.44 (1H, td, J 9.2 and 2.0, 2-H), 3.31 (3H, s, OMe), 3.13 (1H, t, J 9.2, 3-H), 2.11 (1H, ddd, J 12.7, 5.0 and 0.9, CH_2H_b), 1.65 (1H, ddd, J 12.7, 11.6 and 3.2, CH_2H_b), 1.55–1.25 (6H, m, CH_2) and 0.92 (3H, t, J 6.8, CH_3); δ_{C} (75 MHz; CDCl_3) 98.6, 76.7, 71.5, 69.9, 54.9, 38.0, 31.6, 28.1, 23.2 and 14.5; m/z (ES) 222.1 (100%, MNH_4^+).

Acetic acid (2*R,3*S**,4*R**,6*S**)-3-acetoxy-2-butyl-6-methoxy-tetrahydropyran-4-yl ester **29****

The *diol* **28** (54.6 mg, 0.268 mmol) was stirred in a mixture of acetic anhydride (2 ml) and pyridine (1 ml) at room temperature under nitrogen for 12 h. Solvent was removed under reduced pressure and the residue dissolved in chloroform (5 ml) and washed with a saturated aqueous sodium bicarbonate solution (2 ml) and brine (2 ml), dried (MgSO_4) and evaporated under

reduced pressure to give the *diacetate* **29** (76.9 mg, >98%) as a colorless oil, R_f 0.34 (3 : 7 EtOAc–petrol); (Found: MNH_4^+ , 306.1917. $C_{14}H_{28}NO_6$ requires MNH_4 306.1917); ν_{max}/cm^{-1} (CHCl₃ solution) 2955 (C–H), 1443, 1369, 1244, 1226, 1128, 1092, 1048; δ_H (300 MHz; CDCl₃) 5.24 (1H, ddd, J 11.7, 9.4 and 5.4, 4-H), 4.78 (1H, dd, J 3.7 and 1.2, 6-H), 4.77 (1H, t, J 9.4, 3-H), 3.69 (1H, td, J 9.4 and 2.8, 2-H), 3.33 (3H, s, OMe), 2.22 (1H, ddd, J 12.8, 5.4 and 1.2, CH_aH_b), 2.05 (3H, s, OAc), 2.01 (3H, s, OAc), 1.77 (1H, ddd, J 12.8, 11.7 and 3.7, CH_aH_b), 1.55–1.15 (6H, m, CH_2) and 0.90 (3H, t, J 7.4, CH_3); δ_C (75 MHz; CDCl₃) 170.7, 170.7, 98.0, 73.7, 69.8, 69.4, 55.1, 35.5, 31.4, 27.8, 23.0, 21.4, 21.3, 14.4; m/z (ES) 306.2 (100%, MNH_4^+).

4-Methoxybenzoic acid (2*R**,3*S**,6*S**)-2-butyl-4-oxo-6-methoxy-tetrahydropyran-3-yl ester **31**

A solution of the alcohol **26** (24.2 mg, 71.6 μ mol) in dichloromethane (4 ml) was added to a stirred suspension of anhydrous sodium acetate (59 mg, 0.72 mmol), pyridinium chlorochromate (62 mg, 0.288 mmol) and powdered 3 Å molecular sieves (50 mg) in dichloromethane (16 ml). The solution was stirred at 0 °C for 6 h, filtered through a plug of celite and the filtrate was washed with saturated aqueous sodium bicarbonate (2 × 5 ml) and water (5 ml), dried (MgSO₄) and evaporated under reduced pressure. The crude product was pre-absorbed on silica and purified by flash chromatography, eluting with 15 : 85 EtOAc–petrol to give the *ketone* **31** (21.5 mg, 89%) as a colourless oil, R_f 0.27 (15 : 85 EtOAc–petrol); (Found: MNa^+ , 359.1470. $C_{18}H_{24}O_6$ requires MNa 359.1471); ν_{max}/cm^{-1} (CHCl₃ solution) 2924 (C–H), 2854, 1745 (C=O), 1720 (C=O), 1606, 1512, 1257, 1169, 1104, 1044; δ_H (300 MHz; CDCl₃) 7.96 (2H, d, J 9.0, Ar), 6.87 (2H, d, J 9.0, Ar), 5.14 (1H, d, J 10.2, 3-H), 5.07 (1H, dd, J 3.2 and 1.0, 6-H), 4.06 (1H, ddd, J 10.2, 8.6 and 2.6, 2-H), 3.80 (3H, s, OMe), 3.32 (3H, s, OMe), 2.80 (1H, dd, J 14.1 and 3.2, CH_aH_b), 2.61 (1H, dd, J 14.1 and 1.0, CH_aH_b), 1.80–1.10 (6H, m, butyl CH_2) and 0.84 (3H, t, J 7.4, CH_3); δ_C (75 MHz; CDCl₃) 199.1 (C=O), 165.4, 164.2, 132.5, 122.0, 114.1, 99.9 (6-C), 77.7, 71.7, 55.9, 55.3, 49.8, 32.6, 30.1, 27.7, 23.0 and 14.4; m/z (ES) 359.1 (100%, MNa^+).

Acetic acid (2*R**,3*R**,4*R**,6*S**)-3-acetoxy-2-butyl-6-propa-1,2-dienyl-tetrahydro-pyran-4-yl ester 2,6-*trans*-**33**

A solution of boron trifluoride diethyl etherate complex (3.2 μ l, 25.6 μ mol) in dry dichloromethane (100 μ l) was added slowly to a stirred solution of *diacetate* **29** (36.8 mg, 127.8 μ mol) and propargyl trimethylsilane (48 μ l, 0.639 mmol) in dry dichloromethane (1.2 ml) at 0 °C under nitrogen. The solution was allowed to warm to room temperature and stirred for a further 16 h, diluted with dichloromethane (5 ml), quenched with saturated aqueous sodium bicarbonate solution (2 ml). The aqueous layer was further extracted with chloroform (2 × 3 ml) and the combined organic extracts were dried (MgSO₄). The solvent was removed under reduced pressure and the residue pre-absorbed onto silica. Purification by flash chromatography (gradient elution: 1 : 9 → 3 : 7 EtOAc–petrol) gave the *allene* 2,6-*trans*-**33** (29.5 mg, 78%; >95 : 5 mixture of diastereoisomers) as a colourless oil, R_f 0.37 (4 : 6 EtOAc–petrol); (Found: MNa^+ , 309.1521. $C_{16}H_{24}O_5$ requires MNa 309.1521); ν_{max}/cm^{-1} (CHCl₃ solution) 2957 (C–H), 2872, 1957, 1749, 1368, 1243, 1225, 1049; δ_H (300 MHz; CDCl₃) 5.19 (1H, dd, J 5.6 and 3.6), 5.16 (1H, ddd, J 11.1, 9.2 and 5.1, 4-H), 4.97 (2H, m), 4.77 (1H, t, J 9.2, 3-H), 4.69 (1H, m, 6-H), 3.66 (3H, td, J 9.2 and 3.1, 2-H), 2.25 (1H, ddd, J 13.1, 5.1 and 1.8, CH_aH_b), 2.05 (3H, s, OAc), 2.03 (3H, s, OAc), 1.89 (1H, dddd, J 13.1, 11.1, 5.6 and 0.8, CH_aH_b), 1.45–1.20 (6H, m, butyl CH_2) and 0.89 (3H, t, J 6.8, CH_3); δ_C (75 MHz; CDCl₃) 208.2, 170.8, 170.6, 91.3, 78.3, 74.0, 72.1, 70.0, 69.8, 32.7, 31.4, 27.8, 23.0, 21.5, 21.4 and 14.4; m/z (ES) 309.1 (100%, MNa^+).

Acetic acid (2*R**,3*R**,4*R**,5*S**,6*R**)-3,5-diacetoxy-2-acetoxymethyl-6-allyl-tetrahydro-pyran-4-yl ester 2,6-*cis*-**35**

Boron trifluoride diethyl etherate complex (100 μ l, 0.769 mmol) was added slowly to a stirred solution of glucose pentaacetate **34** (100 mg, 0.256 mmol) and allyl trimethylsilane (400 μ l, 2.56 mmol) in dry nitromethane (2.0 ml) at 0 °C. The solution was allowed to warm to room temperature and stirred for 3 days, diluted with dichloromethane (5 ml) and quenched with saturated aqueous sodium bicarbonate solution (4 ml). The aqueous layer was extracted with chloroform (2 × 3 ml) and the combined organic extracts were dried (MgSO₄). The solvent was removed under reduced pressure and the residue pre-absorbed onto silica. Purification by flash chromatography (gradient elution: 3 : 7 → 1 : 1 EtOAc–petrol) gave the THP **35** (80.0 mg, 84%; 75 : 25 2,6-*cis* : *trans*) as a colourless oil, δ_H (500 MHz; CDCl₃) 5.78 (1H, dddd, J 17.1, 10.0, 7.5 and 6.0, allyl), 5.34 (1H, t, J 9.0, 4-H), 5.17 (1H, dq, J 17.1 and 1.0, allyl), 5.12 (1H, dq, J 10.0 and 1.0, allyl), 5.09 (1H, dd, J 9.0 and 5.8, 5-H), 4.98 (1H, t, J 9.0, 3-H), 4.28 (1H, ddd, J 10.5, 5.8 and 4.8, 6-H), 4.21 (1H, dd, J 12.0 and 5.2, CH_aH_b OAc), 4.08 (1H, dd, J 12.0 and 2.8, CH_aH_b OAc), 3.87 (1H, ddd, J 9.0, 5.2 and 2.8, 2-H), 2.56 (1H, dddd, J_{HH} 15.5, J 10.5 and 7.5, $^4J_{HH}$ 1.0), 2.33 (1H, dddd, J_{HH} 15.5, J 6.0 and 4.8, $^4J_{HH}$ 1.0), 2.08 (3H, s, OAc), 2.05 (3H, s, OAc), 2.04 (3H, s, OAc) and 2.03 (3H, s, OAc) (data for major isomer only); δ_C (125 MHz; CDCl₃) 171.1 (C=O), 170.6 (C=O), 170.1 (C=O), 170.0 (C=O), 133.4 (C=C), 118.3 (C=C), 77.6, 76.0, 74.8, 72.3, 72.0, 70.7, 70.6, 69.2, 62.6, 30.9 and 21.1 (data for major isomer only).

Acetic acid (2*R**,3*R**,4*R**,5*S**,6*S**)-3,5-diacetoxy-2-acetoxymethyl-6-cyano-tetrahydro-pyran-4-yl ester 2,6-*trans*-**36**

Boron trifluoride diethyl etherate complex (100 μ l, 0.769 mmol) was added slowly to a stirred solution of glucose pentaacetate **34** (100 mg, 0.256 mmol) and trimethylsilyl cyanide (170 μ l, 1.28 mmol) in dry nitromethane (2.0 ml) at 0 °C under nitrogen. The solution was allowed to warm to room temperature, stirred for 3 days, diluted with dichloromethane (5 ml) and quenched with a saturated aqueous solution of sodium bicarbonate (4 ml). The aqueous layer was further extracted with chloroform (2 × 3 ml) and the combined organic extracts dried (MgSO₄). The solvent was removed under reduced pressure and the residue pre-absorbed onto silica. Purification by flash chromatography, (gradient elution: 2 : 8 → 4 : 6 EtOAc–petrol) gave the cyanide **36** (69.6 mg, 76%; 75 : 25 2,6-*trans* : *cis*) as a colourless oil, δ_H (500 MHz; CDCl₃) 5.41 (1H, t, J 9.6, 4- H^{min}), 5.24 (1H, t, J 9.6, 4- H^{maj}), 5.11 (1H, t, J 9.6, 3- H^{maj}), 5.03 (1H, t, J 9.6, 5- H^{min}), 5.00 (1H, t, J 9.6, 3- H^{min}), 4.89 (1H, d, J 3.4, 6- H^{min}), 4.83 (1H, dd, J 9.6 and 3.4, 5- H^{min}), 4.26 (1H, dd, J 9.6, 6- H^{maj}), 4.19 (1H, dd, J 12.8 and 4.7, CH_aH_b OAc min), 4.17 (1H, dd, J 12.8 and 5.1, CH_aH_b OAc maj), 4.07 (1H, dd, J 12.8 and 2.1, CH_aH_b OAc maj), 4.05 (1H, dd, J 12.8 and 2.1, CH_aH_b OAc min), 3.92 (1H, ddd, J 9.6, 4.7 and 2.1, 2- H^{min}), 3.65 (1H, ddd, J 9.6, 5.1 and 2.1, 2- H^{maj}), 2.04 (6H, s, OAc maj), 2.03 (3H, s, OAc min), 2.01 (3H, s, OAc min), 1.97 (3H, s, OAc maj), 1.96 (3H, s, OAc min), 1.95 (3H, s, OAc maj) and 1.94 (3H, s, OAc min); δ_C (125 MHz; CDCl₃) 170.5 (C=O), 170.1 (C=O), 169.6 (C=O), 169.2 (C=O), 114.6 (CN), 97.2 (6-C), 73.2, 69.3, 67.6, 66.8, 61.8, 21.2 (Me), 21.1 (Me), 20.9 (Me) and 20.8 (Me) (data for 2,6-*trans*-**36** only).

Acetic acid (2*R*,3*R*,4*R*,5*S*,6*R*)-3,5-diacetoxy-2-[(2*R*,3*R*)-2,3-diacetoxy-4-[(2*R*,3*R*,4*R*,5*S*,6*R*)-3,4,5-triacetoxy-6-methoxy-tetrahydro-pyran-2-yl]-butyl]-6-methoxy-tetrahydro-pyran-4-yl ester **41**

Osmium tetroxide (1 mg, catalytic) was added to a stirred solution of the diester **22** (10.2 mg, 12.1 μ mmol) and NMO (14 mg, 120 μ mol) in 1 : 1 acetone–water (1.5 ml). The solution was stirred for a further 2 days before the solvent was removed under reduced pressure. A solution of potassium hydroxide (100 mg) in water (1 ml) was added to the residue and the solution refluxed under nitrogen for 2 days. The solvent was

removed under reduced pressure and the residue stirred in a mixture of acetic anhydride (4 ml) and pyridine (2 ml) for 4 hours. The solvent was removed under reduced pressure and the residue partitioned between chloroform (5 ml) and water (5 ml). The organic layer was washed with saturated aqueous sodium bicarbonate solution (2 × 3 ml) and brine (3 ml). The organic layer was dried (MgSO₄) and evaporated under reduced pressure to give a crude product which was pre-absorbed onto silica gel and purified by flash chromatography (gradient elution: 3 : 7 → 4 : 7 EtOAc–petrol) to give the *octaacetate* **41** (7.9 mg, 87%) as a colourless oil, *R*_f 0.36 (3 : 7 EtOAc–petrol); (Found: MNa⁺, 773.2481. C₃₂H₄₆O₂₀ requires *MNa* 773.2480); $\nu_{\max}/\text{cm}^{-1}$ (CHCl₃ solution) 2925, 1748 (C=O), 1371, 1222, 1162, 1131, 1085, 1046; δ_{H} (500 MHz; CDCl₃) 5.29 (2H, dd, *J* 10.2 and 3.4, 4-H), 5.26 (2H, br, d, *J* 8.6, CH₂OAc), 5.20 (2H, dd, *J* 3.4 and 1.7, 5-H), 5.06 (2H, t, *J* 10.2, 3-H), 4.60 (2H, d, *J* 1.7, 6-H), 3.70 (2H, td, *J* 9.8 and 2.1, 2-H), 3.35 (6H, s, OMe), 2.16 (6H, s, OAc), 2.08 (6H, s, OAc), 2.07 (6H, s, OAc), 1.99 (6H, s, OAc), 1.73 (4H, m, CH₂); *m/z* (ES) 773.0 (100%, MNa⁺).

(2*R*,3*R*,4*S*,5*R*,6*R*)-2-[(2*R*,3*R*)-2,3-Bis-(*tert*-butyl-dimethyl-silanyloxy)-4-((2*R'*,3*R'*,6*R'*)-6'-methoxy-3'-(4-methoxybenzoyloxy)-3,6-dihydro-2*H*-pyran-2-yl)-butyl]-5-iodo-6-methoxy-3-(4-methoxybenzoyloxy)-tetrahydro-pyran-4-ol **42**

A mixture of the diester **22** (105 mg, 0.124 mmol) and freshly prepared silver benzoate (28.5 mg, 0.124 mmol, 1.0 mol eq) were dried azeotropically using toluene and the residue dissolved in dry CCl₄ (2.7 ml). Iodine (31.5 mg, 0.124 mmol, 1.0 mol eq) was added to the stirred suspension and the mixture stirred for a 24 days with protection from light. The suspension was diluted with chloroform (10 ml) and the silver salts removed by centrifugation. The organic filtrate was washed with 10% aqueous sodium sulfite solution (2 × 2 ml) and saturated sodium bicarbonate (2 × 2 ml), dried (MgSO₄) and evaporated under reduced pressure. The crude residue was purified by flash chromatography after pre-absorption onto silica gel (gradient elution: 1 : 9 → 25 : 75 EtOAc : petrol) to give the *iodo alcohol* **42** (48.2 mg, 39%, >98 : 2 mixture of regioisomers) as a colourless oil, *R*_f 0.24 (15 : 85 EtOAc–petrol); (Found: MNH₄⁺, 1004.3515. C₄₄H₆₇I-Si₂O₁₃ requires *MNH*₄⁺, 1004.3509); $\nu_{\max}/\text{cm}^{-1}$ (CHCl₃ solution) 3422 (O–H), 2955 (C–H), 2930, 2856, 1717 (C=O), 1607, 1512, 1257, 1168, 1103, 1053; δ_{H} (500 MHz; CDCl₃) 7.84 (2H, d, *J* 9.0, Ar), 7.83 (2H, d, *J* 9.0, Ar), 6.78 (2H, d, *J* 9.0, Ar), 6.76 (2H, d, *J* 9.0, Ar), 5.86 (1H, d, *J* 10.5, 5-H'), 5.68 (1H, dt, *J* 10.5 and 2.3, 4-H'), 5.16 (1H, dd, *J* 9.4 and 2.3, 3-H), 5.03 (1H, dd, *J* 9.2 and 1.5, 3-H'), 4.78 (1H, d, *J* 2.8, 6-H), 4.72 (1H, s, 6-H'), 4.15 (3H, m, 5-H, 4-H and 2-H), 3.98 (1H, td, *J* 7.2 and 3.6, CHOTBS), 3.91 (1H, t, *J* 9.2, 2-H'), 3.79 (1H, m, CHOTBS), 3.74 (3H, s, OMe), 3.73 (3H, s, OMe), 3.37 (3H, s, OMe), 3.36 (3H, s, OMe), 3.02 (1H, br, OH), 1.84 (1H, ddd, *J* 13.8, 10.5 and 4.1, CH₂H_b), 1.69 (1H, dd, *J* 13.8 and 10.5, CH₂H_b), 1.34 (2H, dd, *J* 14.1 and 9.7, CH₂H_b), 0.83 (9H, s, 'Bu), 0.81 (9H, s, 'Bu), 0.07 (3H, s, SiMe), 0.02 (3H, s, SiMe), 0.01 (3H, s, SiMe) and 0.00 (3H, s, SiMe); δ_{C} (125 MHz; CDCl₃) 166.2, 166.0, 164.0, 164.0, 132.4, 132.3, 130.6, 128.9, 127.8, 122.6, 122.4, 114.1, 102.7, 96.1, 71.6, 71.4, 71.1, 70.9, 69.9, 66.6, 66.5, 57.2, 57.0, 55.9, 34.1, 32.7, 31.4, 30.1, 27.1, 26.3, 26.2, 18.5, 18.4, –3.5, –3.5, –4.1 and –4.2; *m/z* (ES) 1009.6 (100%, MNa⁺).

Also obtained was recovered starting material (24 mg, 23%). The recovered starting material was recycled twice to give an overall 54% yield of **42**.

(2*R*,3*R*,4*S*,6*R*)-2-[(2*R*,3*R*)-2,3-Bis-(*tert*-butyl-dimethyl-silanyloxy)-4-((2*R'*,3*R'*,6*R'*)-6'-methoxy-3'-(4-methoxybenzoyloxy)-3,6-dihydro-2*H*-pyran-2-yl)-butyl]-6-methoxy-3-(4-methoxybenzoyloxy)-tetrahydro-pyran-4-ol **43**

A solution of *iodo alcohol* **42** (95.6 mg, 96.8 μmol) in benzene (3.5 ml) was deoxygenated by a steady stream of nitrogen for 30 seconds. Tris-(trimethylsilyl)silane (0.484 mmol) was added

and the solution was stirred under nitrogen at 70 °C and azobisisobutyronitrile (10 mg) added. The reaction was stirred at 70 °C for 30 min, cooled and loaded directly without pre-absorption or concentration onto a short column of silica. Elution with 1 : 9 EtOAc–petrol and then 4 : 6 EtOAc–petrol gave the *alcohol* **43** (83 mg, >98%) as a colourless oil, *R*_f 0.34 (4 : 6 EtOAc–petrol); (Found: MNa⁺, 883.4095. C₄₄H₆₈O₁₃Si₂ requires *MNa*, 883.4096); $\nu_{\max}/\text{cm}^{-1}$ (CHCl₃ solution) 3535 (O–H), 2930, 2856, 1716 (C=O), 1607, 1512, 1257, 1168, 1108, 1051, 1031; δ_{H} (300 MHz; CDCl₃) 7.83 (2H, d, *J* 9.0, Ar), 7.78 (2H, d, *J* 9.0, Ar), 6.71 (2H, d, *J* 9.0, Ar), 6.69 (2H, d, *J* 9.0, Ar), 5.82 (1H, d, *J* 10.2, 5-H'), 5.62 (1H, dt, *J* 10.2 and 2.1, 4-H'), 4.93 (1H, dd, *J* 9.5 and 2.1, 3-H'), 4.68 (1H, s, 6-H'), 4.56 (1H, d, *J* 3.3, 6-H), 4.44 (1H, dd, *J* 10.0 and 2.8, 3-H), 4.08 (1H, t, *J* 10.0, 2-H), 4.08 (1H, m, 4-H), 3.86 (1H, t, *J* 9.5, 2-H'), 3.73 (2H, m, CHOTBS), 3.69 (3H, s, OMe), 3.69 (3H, s, OMe), 3.32 (3H, s, OMe), 3.27 (3H, s, OMe), 3.11 (1H, d, *J* 9.5, OH), 1.97 (1H, dd, *J* 14.8 and 3.3, 5-H_aH_b), 1.81 (1H, dt, *J* 14.8 and 3.3, 5-H_aH_b), 1.59 (2H, dd, *J* 14.1 and 10.2, CH₂H_b), 1.30 (2H, m, CH₂H_b), 0.80 (9H, s, 'Bu), 0.76 (9H, s, 'Bu), 0.01 (3H, s, SiMe), 0.00 (3H, s, SiMe), –0.02 (3H, s, SiMe) and –0.04 (3H, s, SiMe); δ_{C} (75 MHz; CDCl₃) 166.1, 163.9, 163.9, 132.4, 132.2, 130.6, 127.8, 122.7, 114.0, 114.0, 99.0, 96.0, 77.6, 73.9, 72.4, 71.7, 69.9, 66.8, 65.7, 63.6, 57.1, 56.4, 55.9, 55.8, 35.6, 33.9, 33.7, 30.1, 26.2, 18.5, 18.4, –3.5, –3.5, –3.9 and –4.2; *m/z* (ES) 883.4 (100%, MNa⁺).

(2*R*,3*R*,6*R*)-2-[(2*R*,3*R*)-2,3-Bis-(*tert*-butyl-dimethyl-silanyloxy)-4-((2*R'*,3*R'*,6*R'*)-3'-(4-methoxybenzoyloxy)-6'-methoxy-3,6-dihydro-2*H*-pyran-2-yl)-butyl]-6-methoxy-3-(4-methoxybenzoyloxy)-tetrahydro-pyran-4-one **44**

A solution of the alcohol **43** (12.3 mg, 14.3 μmol) in dichloromethane (1.2 ml) was added to a stirred suspension of anhydrous sodium acetate (11.8 mg, 143 μmol), pyridinium chlorochromate (12.3 mg, 57.2 μmol, 4 mol%) and powdered 3 Å molecular sieves (50 mg) in dichloromethane (5 ml). The solution was stirred under nitrogen and the temperature maintained at 0 °C for 2 h. The reaction mixture was filtered through a plug of celite, washed with saturated aqueous sodium bicarbonate solution (2 × 3 ml) and water (3 ml), and the organic layer dried (MgSO₄) and evaporated under reduced pressure. The crude product was pre-absorbed onto silica gel and purified by flash chromatography, eluting with 2 : 8 EtOAc–petrol, to give the *ketone* **44** (10.8 mg, 88%) as a colourless oil, *R*_f 0.42 (3 : 7 EtOAc–petrol); (Found: MNa⁺, 881.3940. C₄₄H₆₆O₁₃Si₂ requires *MNa*, 881.3940); $\nu_{\max}/\text{cm}^{-1}$ (CHCl₃ solution) 2928, 2856, 1721 (C=O), 1606, 1512, 1463, 1259, 1168, 1104, 1051; δ_{H} (500 MHz; CDCl₃) 7.83 (2H, d, *J* 9.0, Ar), 7.79 (2H, d, *J* 9.0, Ar), 6.74 (2H, d, *J* 9.0, Ar), 6.73 (2H, d, *J* 9.0, Ar), 5.83 (1H, d, *J* 10.2, 5-H'), 5.65 (1H, dt, *J* 10.2 and 2.1, 4-H'), 4.98 (1H, dd, *J* 9.4 and 2.1, 3-H'), 4.89 (1H, d, *J* 4.3, 6-H), 4.89 (1H, d, *J* 9.8, 3-H), 4.69 (1H, s, 6-H'), 4.08 (1H, t, *J* 9.4, 2-H'), 3.90 (1H, t, *J* 9.8, 2-H), 3.78 (1H, dd, *J* 7.7 and 4.3, CHOTBS), 3.77 (1H, dd, *J* 7.7 and 4.3, CHOTBS), 3.71 (6H, s, OMe), 3.34 (3H, s, OMe), 3.26 (3H, s, OMe), 2.69 (1H, dd, *J* 13.7 and 4.3, 5-H_aH_b), 2.50 (1H, d, *J* 13.7, 5-H_aH_b), 1.85 (1H, dd, *J* 14.1 and 9.8, CH₂H_b), 1.64 (1H, dd, *J* 14.1 and 10.3), 1.43 (1H, dd, *J* 14.1 and 9.4), 1.31 (1H, dd, *J* 14.1 and 9.8), 0.81 (9H, s, 'Bu), 0.79 (9H, s, 'Bu), 0.05 (3H, s, SiMe), 0.00 (3H, s, SiMe), 0.00 (3H, s, SiMe) and –0.02 (3H, s, SiMe); δ_{C} (75 MHz; CDCl₃) 133.4, 133.0, 131.3, 128.6, 123.5, 123.1, 115.6, 114.7, 100.9, 96.7, 72.7, 72.0, 71.0, 70.6, 67.0, 57.5, 56.5, 56.2, 54.0, 47.0, 35.5, 34.2, 26.4, 26.3, 18.5, –3.4, –3.4, –4.1 and –4.2; *m/z* (ES) 881.4 (100%, MNa⁺).

(2*R*,3*R*,4*R*,6*R*)-2-[(2*R*,3*R*)-2,3-Bis-(*tert*-butyl-dimethyl-silanyloxy)-4-((2*R'*,3*R'*,6*R'*)-3'-(4-methoxybenzoyloxy)-6'-methoxy-3,6-dihydro-2*H*-pyran-2-yl)-butyl]-6-methoxy-3-(4-methoxybenzoyloxy)-tetrahydro-pyran-4-ol **45**

Sodium borohydride (30 mg, 0.789 mmol) was added to a stirred solution of the ketone **44** (12.4 mg, 14.5 μmol) in THF

(1.5 ml) at 50 °C. The solution was stirred for 30 min, cooled to room temperature and quenched with water (0.2 ml). The solvent was evaporated under reduced pressure and the residue pre-absorbed onto silica gel, purified by flash chromatography (gradient elution: 15 : 85 → 4 : 6 EtOAc–petrol) to give the *alcohol* **45** (6.6 mg, 54%) as a colourless oil, R_f 0.46 (3 : 7 EtOAc–petrol); (Found: MNa^+ , 883.4095. $C_{44}H_{68}O_{13}Si_2$ requires MNa , 883.4096); ν_{max}/cm^{-1} (CHCl₃ solution) 3468 (O–H), 2928, 2855, 1716 (C=O), 1606, 1512, 1463, 1258, 1168, 1104, 1051; δ_H (300 MHz; CDCl₃) 7.84 (2H, d, J 9.0, Ar), 7.81 (2H, d, J 9.0, Ar), 6.75 (2H, d, J 9.0, Ar), 6.75 (2H, d, J 9.0, Ar), 6.02 (1H, d, J 10.2, 5-H'), 5.82 (1H, dd, J 10.2 and 2.1, 4-H'), 5.26 (1H, m, 3-H), 5.22 (1H, dd, J 9.5 and 2.1, 3-H'), 4.86 (1H, s, 6-H'), 4.71 (1H, d, J 3.0, 6-H), 4.07 (1H, t, J 9.5, 2-H'), 3.91 (2H, m, CHOTBS), 3.87 (3H, s, OMe), 3.86 (3H, s, OMe), 3.69 (1H, td, J 10.0 and 2.8, 4-H), 3.49 (3H, s, OMe), 3.36 (3H, s, OMe), 3.36 (1H, t, J 9.3, 2-H), 2.26 (1H, dd, J 14.0 and 5.4, 5- H_aH_b), 1.87 (1H, ddd, J 14.0, 10.0 and 3.0, 5- H_aH_b), 1.82–1.73 (3H, m, CH₂), 1.65 (1H, dd, J 13.8 and 8.7, CH₂ H_b), 0.81 (9H, s, 'Bu), 0.78 (9H, s, 'Bu), 0.05 (3H, s, SiMe), 0.01 (3H, s, SiMe), 0.00 (3H, s, SiMe) and –0.01 (3H, s, SiMe); m/z (ES) 883.4 (100%, MNa^+).

(2R,3R,4R,6R)-2-[(2R,3R)-2,3-Bis-(tert-butyl-dimethyl-silanyloxy)-4-((2R',3R',6R')-3'-(4-methoxybenzoyloxy)-6'-methoxy-3,6-dihydro-2H-pyran-2-yl)-butyl]-4-acetoxy-6-methoxy-3-(4-methoxybenzoyloxy)-tetrahydropyran **46**

The alcohol **45** (10.2 mg, 11.7 μ mol) was dissolved in a mixture of acetic anhydride (2 ml) and pyridine (1 ml). The mixture was stirred under nitrogen at room temperature for 2 hours before the solvent was removed under reduced pressure. The solid residue was dissolved in chloroform (5 ml), washed with saturated aqueous sodium bicarbonate solution (2 \times 3 ml) and water (3 ml), dried (MgSO₄) and evaporated under reduced pressure to give the *acetate* **46** (10.4 mg, >98%) as a colourless oil, R_f 0.37 (2 : 8 EtOAc–petrol); (Found: MNa^+ , 925.4200. $C_{46}H_{70}O_{14}Si_2$ requires MNa , 925.4202); ν_{max}/cm^{-1} (CHCl₃ solution) 2928, 2856, 1746, (C=O), 1718 (C=O), 1606, 1512, 1464, 1257, 1168, 1103, 1049; δ_H (500 MHz; CDCl₃) 7.98 (2H, d, J 9.0, Ar), 7.91 (2H, d, J 9.0, Ar), 6.90 (2H, d, J 9.0, Ar), 6.88 (2H, d, J 9.0, Ar), 6.02 (1H, d, J 10.3, 3-H'), 5.82 (1H, dt, J 10.3 and 2.1, 4-H'), 5.33 (1H, ddd, J 11.5, 9.4 and 5.1, 4-H), 5.20 (1H, dd, J 9.4 and 2.1, 3-H'), 4.88 (1H, t, J 9.4, 3-H), 4.85 (1H, s, 6-H'), 4.71 (1H, dd, J 3.0 and 1.2, 6-H), 4.06 (1H, t, J 9.8), 3.88 (1H, dd, J 9.8 and 4.7), 3.87 (3H, s, OMe), 3.84 (1H, td, J 9.8 and 5.1), 3.83 (3H, s, OMe), 3.49 (3H, s, OMe), 3.38 (3H, s, OMe), 2.38 (1H, ddd, J 12.7, 5.1 and 1.2, 5- H_aH_b), 2.12–1.76 (5H, m, 5- H_aH_b , 1-H and 4-H'), 0.94 (9H, s, 'Bu), 0.91 (9H, s, 'Bu), 0.18 (3H, s, SiMe), 0.13 (3H, s, SiMe), 0.12 (3H, s, SiMe) and 0.12 (3H, s, SiMe); m/z (ES) 925.1 (100%, MNa^+).

(2R,3R,4R,6R)-2-[(2R,3R)-2,3-Bis-(tert-butyl-dimethyl-silanyloxy)-4-((2R',3R',4S',5R',6R')-3'-acetoxy-4',5'-epoxy-6'-methoxy-tetrahydro-pyran)-butyl]-3,4-diacetoxy-6-methoxy-tetrahydropyran **49**

The allylic ester **46** (8.9 mg, 9.8 μ mol) was dried azeotropically from toluene and dissolved in dry carbon tetrachloride (1.5 ml). To the stirred solution under N₂ freshly prepared and azeotropically dried silver benzoate (30.7 mg, 96.0 μ mol) was added, followed by iodine (25.0 mg, 96.0 μ mol). The suspension was stirred at room temperature with protection from light for 4 days. The suspension was diluted with chloroform (5 ml) and the silver residues removed by centrifugation. The residue was washed with chloroform (3 ml) and the combined organic extracts were washed with saturated aqueous sodium bicarbonate solution (2 \times 3 ml), 10% aqueous sodium sulfite solution (2 \times 3 ml) and brine (3 ml). The organic layer was dried (MgSO₄) and the solvent removed under reduced pressure. The residue was dissolved in THF (1.2 ml), aqueous potassium

hydroxide solution (2.0 M, 1.5 ml) added, and the reaction mixture was stirred at room temperature for 2 h and refluxed for 2 days, evaporated under reduced pressure and the residue dissolved in 2 : 1 acetic anhydride–pyridine (3 ml). The reaction was stirred for 6 h and evaporated under reduced pressure to give a crude product which was dissolved in chloroform (5 ml), washed with saturated aqueous sodium bicarbonate solution (1.0 M, 2 \times 3 ml) and brine (3 ml), dried (MgSO₄) and evaporated under reduced pressure to give the *epoxide* **49** (6.5 mg, 90%) as a colourless oil, R_f 0.42 (3 : 7 EtOAc–petrol); (Found: MNH_4^+ , 752.4073. $C_{33}H_{66}O_{13}Si_2$ requires MNH_4 , 752.4073); ν_{max}/cm^{-1} (CHCl₃ solution) 2926, 2855, 1743, 1654, 1463, 1371, 1259, 1072, 1047; δ_H (500 MHz; C₆D₆) 5.45 (1H, ddd, J 11.7, 9.4 and 4.9, 4-H), 4.93 (1H, t, J 9.4, 3-H), 4.70 (1H, dd, J 9.4 and 1.6, 3-H'), 4.27 (1H, d, J 2.6, 6-H'), 4.21 (1H, d, J 2.6, 6-H), 4.17 (1H, t, J 9.4, 2-H), 3.95 (1H, dd, J 9.5 and 7.7, CHOTBS), 3.90 (1H, dd, J 9.5 and 4.3, CHOTBS), 3.84 (1H, td, J 9.4 and 3.0, 2-H'), 3.19 (3H, s, OMe), 3.08 (3H, s, OMe), 3.02 (1H, dd, J 4.3 and 1.6, 4-H'), 2.73 (1H, dd, J 4.3 and 2.6, 5-H'), 2.12–1.98 (5H, m, CH₂ and 5- H_aH_b), 1.80 (1H, ddd, J 14.1, 11.7 and 2.6, 5- H_aH_b), 1.52 (3H, s, OAc), 1.45 (3H, s, OAc), 1.42 (3H, s, OAc), 0.95 (9H, s, 'Bu), 0.93 (9H, s, 'Bu), 0.20 (3H, s, SiMe), 0.14 (3H, s, SiMe), 0.12 (3H, s, SiMe) and 0.09 (3H, s, SiMe); m/z (ES) 752.2 (100%, MNH_4^+).

Acetic acid (1R,2R)-2-acetoxy-3-((2''R,3''R,4''R,6''S)-3'',4''-diacetoxy-6''-methoxy-tetrahydro-pyran-2-yl)-1-((2'R,3'R,4'S,5'R,6'S)-3',4',5'-triacetoxy-6'-methoxy-tetrahydro-pyran-2'-ylmethyl)-propyl ester **47**

By the same general method, using aqueous potassium hydroxide solution (2.0 M, 1.5 ml) as the solvent in the hydrolysis step, the allylic ester **46** (4.0 mg, 4.4 μ mol) gave a crude product which was purified by semi-preparative HPLC-MS (20 : 80 MeCN–water for 1 min, then ramp to 35 : 65 MeCN–water over 30 s, then ramp to 65 : 35 MeCN–water over 4 min, then ramp to 95 : 5 MeCN–water over 30 s, then 95 : 5 MeCN–water over 3 min, 24 °C) to give the *heptaacetate* **47** (1.5 mg, 48%) as a colourless viscous oil, retention time 4.6 min, $[a]_D = -10$ ($c = 0.1$, CHCl₃); R_f 0.2 (3 : 7 EtOAc–petrol); (Found: 715.2421; $C_{30}H_{44}O_{18}$ requires MNa , 715.2426); ν_{max}/cm^{-1} 2940, 1750 (C=O), 1442, 1371, 1246, 1224, 1043; δ_H (500 MHz; CDCl₃) 5.43 (1H, t, J 9.5, 4''-H), 5.26–5.22 (3H, m, 1-, 2- and 4'-H), 4.88 (1H, d, J 9.5, 5''-H), 4.87 (1H, s, 6''-H), 4.85 (1H, t, J 9.5, 3''-H), 4.78–4.75 (2H, m, 3'- and 6'-H), 3.73–3.68 (2H, m, 2' and 2''-H), 3.35 (3H, s, OCH₃), 3.28 (3H, s, OMe), 2.2–1.8 (2H, m, 5'-H₂), 2.08 (3H, s, OAc), 2.05 (6H, s, OAc \times 2), 2.01 (3H, s, OAc), 2.00 (3H, s, OAc), 1.6–1.2 (4H, m, CH₂ \times 2); m/z (ES) 715 (100, MNa^+).

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References

- 1 Y. Hirata, D. Uemura and Y. Ohizumi, in *Handbook of Natural Toxins*, A. T. Tu, Editor, 1988, Marcel Dekker, New York, p. 241.
- 2 E. Habermann, *Toxicon*, 1989, **27**, 1171.
- 3 D. Uemura, K. Ueda, Y. Hirata, H. Naoki and T. Iwashita, *Tetrahedron Lett.*, 1981, **22**, 2781; R. E. Moore and G. Bartolini, *J. Am. Chem. Soc.*, 1981, **103**, 2491.
- 4 J. K. Cha, W. J. Christ, J. M. Finan, H. Fujioka, L. L. K. Y. Kishi, S. S. Ko, J. Leder, W. W. M. Jr., K.-P. Pfaff, M. Yonaga, D. Uemura and Y. Hirata, *J. Am. Chem. Soc.*, 1982, **104**, 7369; R. E. Moore,

- G. Bartolini, J. Barchi, A. A. Bothner-By, J. Dadok and J. Ford, *J. Am. Chem. Soc.*, 1982, **104**, 3776.
- 5 R. W. Armstrong, J.-M. Beau, S. H. Cheon, W. J. Christ, H. Fujioka, W.-H. Ham, L. D. Hawkins, H. Jin, S. H. Kang, Y. Kishi, M. J. Martinelli, W. W. M. Jr., M. Mizuno, M. Nakata, A. E. Stutz, F. X. Talamas, M. Taniguchi, J. A. Tino, K. Ueda, J. Uenishi, J. B. White and M. Yonaga, *J. Am. Chem. Soc.*, 1989, **111**, 7525; R. W. Armstrong, J.-M. Beau, S. H. Cheon, W. J. Christ, H. Fujioka, W.-H. Ham, L. D. Hawkins, H. Jin, S. H. Kang, Y. Kishi, M. J. Martinelli, W. W. M. Jr., M. Mizuno, M. Nakata, A. E. Stutz, F. X. Talamas, M. Taniguchi, J. A. Tino, K. Ueda, J. Uenishi, J. B. White and M. Yonaga, *J. Am. Chem. Soc.*, 1989, **111**, 7530.
 - 6 R. Hodgson, T. Majid and A. Nelson, *J. Chem. Soc., Perkin Trans. 1*, 2002, 1444.
 - 7 S. L. Schreiber and C. S. Poss, *Acc. Chem. Res.*, 1994, **27**, 9.
 - 8 N. L. Douglas, S. V. Ley, U. Lucking and S. Warriner, *J. Chem. Soc., Perkin Trans. 1*, 1998, 51; Z. Zhang, I. R. Ollmann, X.-S. Ye, R. Wischnat, T. Baasov and C.-H. Wong, *J. Am. Chem. Soc.*, 1999, **121**, 734.
 - 9 T. B. Grindley, in *Modern Methods in Carbohydrate Synthesis*, S. H. Khan and R. A. O'Neill, Editors, 1996, Harwood, New York; T. Ziegler, in *Carbohydrate Chemistry*, G. J. Boons, Editor, 1998, Blackie, Glasgow.
 - 10 M. Harding, R. Hodgson and A. Nelson, *J. Chem. Soc., Perkin Trans. 1*, 2002, 2403.
 - 11 H. C. Kolb, M. S. VanNieuwenhze and K. B. Sharpless, *Chem. Rev.*, 1994, **94**, 2483.
 - 12 M. Hizuka, N. Hayashi, T. Kamishita, H. Suemune and K. Saki, *Chem. Pharm. Bull.*, 1988, **36**, 1550.
 - 13 J. A. Marshall and R. Sedrani, *J. Org. Chem.*, 1991, **56**, 5496; W. Zhang and M. J. Robins, *Tetrahedron Lett.*, 1992, **33**, 1177.
 - 14 T. Toshima, K. Tatsuta and M. Kinoshita, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 2369.
 - 15 J. Otera, Y. Niibo and H. Nozaki, *Tetrahedron Lett.*, 1992, **33**, 3655.
 - 16 D. A. Evans, K. T. Chapman and E. M. Carreira, *J. Am. Chem. Soc.*, 1988, **110**, 3560.
 - 17 S. Anwar, G. Bradley and A. P. Davis, *J. Chem. Soc., Perkin Trans. 1*, 1991, 1383–1389.
 - 18 M. Fujita and T. Hiyama, *J. Org. Chem.*, 1988, **53**, 5405–5415.
 - 19 E. J. Corey, R. K. Bakshi, S. Shibata, C. P. Chen and V. K. Singh, *J. Am. Chem. Soc.*, 1987, **109**, 7925.
 - 20 C.-J. Li, T. Meng, X.-H. Yi, M. Jidai and T.-H. Chan, *J. Org. Chem.*, 1997, **62**, 8632.
 - 21 T. Kametani, M. Tsubuki, Y. Tatsuzaki and T. Honda, *J. Chem. Soc., Perkin Trans. 1*, 1990, 639.
 - 22 M. Kusakabe, Y. Kitano, Y. Kobayashi and F. Sato, *J. Org. Chem.*, 1989, **54**, 2085.
 - 23 S. Koeppe and J. Thiem, *J. Carbohydr. Chem.*, 1987, **6**, 57–85.
 - 24 S. F. Martin and P. W. Zinke, *J. Am. Chem. Soc.*, 1989, **111**, 2311.
 - 25 J.-L. Luche, *J. Am. Chem. Soc.*, 1978, **100**, 2226.
 - 26 M. Harding, R. Hodgson, T. Majid, K. J. McDowall and A. Nelson, *Org. Biomol. Chem.*, 2003, 338.
 - 27 R. Hodgson, T. Majid and A. Nelson, *J. Chem. Soc., Perkin Trans. 1*, 2002, 1631.
 - 28 J. M. Harris, M. D. Keranen, H. Nguyen, V. G. Young and G. A. O'Doherty, *Carbohydr. Res.*, 2000, **328**, 17–36; B. Szechner and O. Achmatowicz, *J. Carbohydr. Chem.*, 1992, **11**, 401–406.
 - 29 G. Frenking, K. F. Koehler and M. T. Reetz, *Angew. Chem.*, 1991, **103**, 1167–1170; J. Huet, Y. Maroni-Barnaud, A. Nguyen Trong and J. Seyden-Penne, *Tetrahedron Lett.*, 1976, 159–162; R. T. Luibbrand, I. R. Taigounov and A. A. Taigounov, *J. Org. Chem.*, **66**, 7254–7262.
 - 30 W. P. Neuman, *Synthesis*, 1987, 665.
 - 31 C. Chatgililoglu, *Acc. Chem. Res.*, 1992, **25**, 188.
 - 32 I. E. Marko, S. L. Warriner and B. Augustyns, *Org. Lett.*, 2000, **2**, 3123.
 - 33 D. L. Hughes, in *Organic Reactions*, 1992, Wiley, New York, p. 335.
 - 34 E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 1975, 2647.
 - 35 W. R. Kobertz, C. R. Bertozzi and M. D. Bednarski, *Tetrahedron Lett.*, 1992, **33**, 737–740.
 - 36 O. Gaertzen, A. M. Misske, P. Wolbers and H. M. R. Hoffmann, *Synlett*, 1999, 1041.
 - 37 G. J. P. H. Boons, G. A. V. d. Marel, J. T. Poolman and J. H. V. Boom, *Recl. Trav. Chim. Pays-Bas*, 1989, **108**, 339.
 - 38 D. Horton and T. Mikaye, *Carbohydr. Res.*, 1988, **184**, 221.
 - 39 P. Köll and A. Förtsch, *Carbohydr. Res.*, 1987, **171**, 301.
 - 40 H. C. Kolb and K. B. Sharpless, *Tetrahedron*, 1992, **48**, 10515.
 - 41 M. Harding and A. Nelson, *Chem. Commun.*, 2001, 695; R. Hodgson, T. Majid and A. Nelson, *Chem. Commun.*, 2001, 2076.
 - 42 J. C. Leffingwell and E. E. Rayals, *Tetrahedron Lett.*, 1965, 3829.