A titanium naphtholate approach for the synthesis of analogues of griseusin A †

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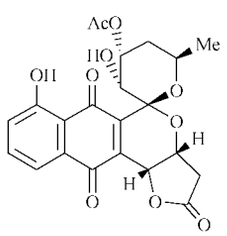
The synthesis of analogues of the spiroketal-containing pyranonaphthoquinone antibiotic griseusin A **1** is described. The key disconnection focused on hydroxyalkylation of naphthol **21** with aldehyde **12**. Aldehyde **12** was prepared from oxazolidinone **5** and (*R*)-aldehyde **6**. Aldol condensation of oxazolidinone **5** with aldehyde **6** using tin(II) triflate and tetramethylethylenediamine afforded adduct **8** with the required 2′,3′-*anti* 3′,5′-*syn* stereochemistry as the major product. Aldol adduct **8** was then converted into aldehyde **12**. The titanium naphtholate generated from naphthol **21** using $TiCl_3O^iPr$ then afforded alcohol **26** upon addition of aldehyde **12**. Oxidation of alcohol **26** afforded ketone **29** which underwent acetylation to acetate **31**. Conversion of naphthol acetate **31** into naphthoquinone **33** followed by addition of 2-(trimethylsilyloxy)furan effected furofuran annulation to a 1 : 1 inseparable mixture of adducts **34**. Ceric ammonium nitrate oxidative rearrangement of this mixture of adducts produced lactol **35** which underwent cyclization to a 3.2 : 1 mixture of spiroketals **36a** and **36b** wherein epimerization at C-3′ had occurred.

Griseusins A **1** and griseusin B **2** were isolated from a soil sample collected in Peru which had been inoculated with *Streptomyces griseus* K-63.[1] They are unique members of the pyranonaphthoquinone family of antibiotics[2] in that they contain a 1,7-dioxaspiro[5.5]undecane ring system fused to a juglone ring system and have aroused interest due to their inhibitory activity against gram-positive bacteria, pathogenic fungi and yeasts[1] together with their proposed bioreductive alkylating properties.[3] The absolute configuration of griseusin A **1** has been confirmed by X-ray analysis of a 6,8-dibromo derivative[4] and only one total synthesis of griseusin A **1** has been reported to date.[5]



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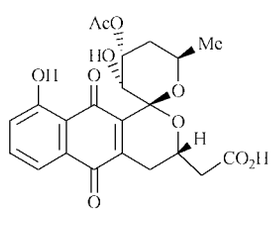

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Yoshii and co-workers[5] assembled the spiroacetal portion of the griseusins *via* cyclization of a δ,δ′-dihydroxy ketone in which the oxygenated substituents of the spiroketal ring system were derived from a carbohydrate precursor. Functionalization of the initial carbohydrate involved a lengthy process.

Results and discussion

Our initial synthetic approach to griseusin A **1** focused on assembly of the basic pentacyclic framework of the griseusin A molecule with introduction of the oxygenated substituents of the spiroketal ring system *via* hydroxylation of an unsaturated spiroketal.[6] In this case the final hydroxylation occurred on the C-5a–C-11a naphthoquinone double bond, necessitating a rethink of our synthetic strategy. We herein report[7] our synthetic studies towards griseusin A **1** wherein the spiroketal oxygenated substituents are assembled onto an acyclic naphthalene precursor at an early stage in the synthesis. The basic griseusin A **1** framework is assembled *via* oxidative rearrangement of a furo[3,2-*b*]naphtho[2,1-*d*]furan **34** which in turn is assembled by addition of 2-(trimethylsilyloxy)furan to a 2-acylated 1,4-naphthoquinone **33**. In turn, the oxygenated substituents on the side chain of this key naphthoquinone **33** were assembled using a stereoselective aldol condensation.

Naphthoquinone **33** was assembled from naphthol **21** and aldehyde **12**. Construction of aldehyde **12** with the desired 2′,3′-*anti* 3′,5′-*syn* stereochemistry was based on a key *anti* aldol condensation of acyloxazolidinone **5** with aldehyde **6** (Scheme 1). Acyloxazolidinone **5** was itself prepared by the low-temperature N-alkylation of the lithiate of 4-benzyloxazolidinone **4** with benzyloxyacetyl chloride (Scheme 1). In turn, the oxazolidinone **4** was prepared by heating (*R*)-phenylalaninol **3** [obtained *via* reduction of (*R*)-phenylalanine[8]] with diethyl carbonate.

Aldehyde **6** was synthesized in three steps from commercially available ethyl (*R*)-(−)-3-hydroxybutyrate **13** (Scheme 2). Reduction of silyl ether **14** with $LiBH_4$ in diethyl ether afforded alcohol **15** in 89% yield. Treatment of **15** with tetrapropylammonium perruthenate (TPAP) with 4-methylmorpholine *N*-oxide as co-oxidant then afforded aldehyde **6** in 81% yield. Further purification of the crude aldehyde **6** by flash chromatography resulted in considerable loss of material due to its ready oxidation by air.[9] Aldehyde **6** was therefore prepared immediately before use in the subsequent aldol reaction. The optical rotation recorded for **6** produced using TPAP ($[\alpha]_D$ −17.90§) was slightly higher than that obtained when using pyridinium chlorochromate ($[\alpha]_D$ −14.4),[10] suggesting that the latter reagent effected partial racemization of aldehyde **6**.

With the oxazolidinone **5** and aldehyde **6** in hand, attention

† Experimental details for conversion of alcohol **11** to acetonide **20** are available as supplementary data. For direct electronic access see http://www.rsc.org/suppdata/p1/a9/a909243i

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§ $[\alpha]_D$-values are given in units of 10^{-1} deg cm^2 g^{-1} throughout.

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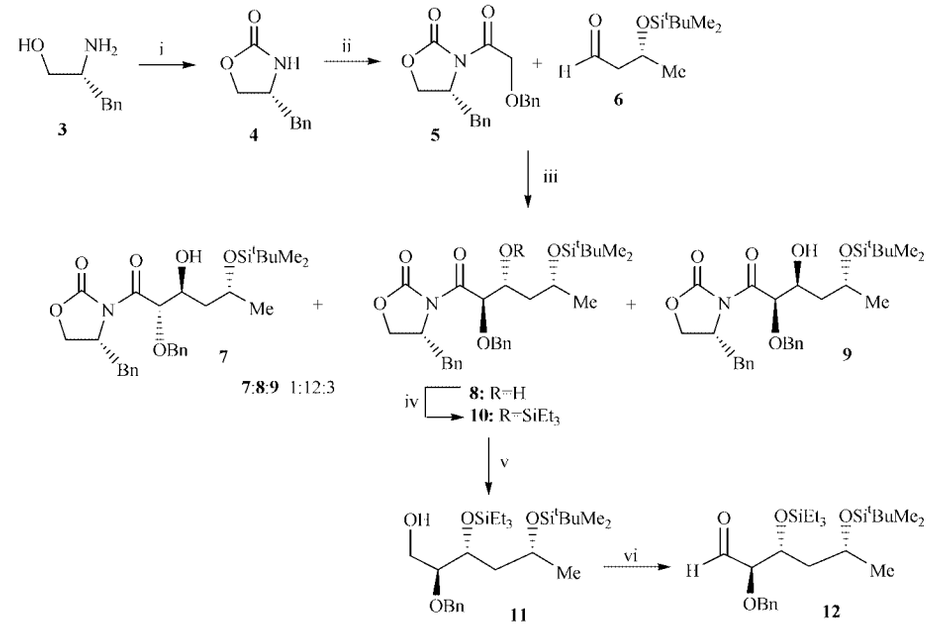
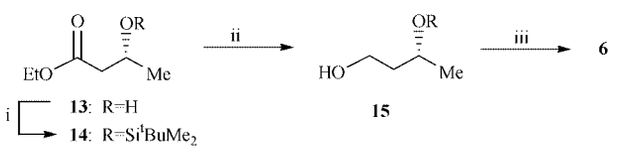


Scheme 1 *Reagents, conditions and yields*: (i) $(EtO)_2CO$, K_2CO_3, 135 °C (80%); (ii) ^{n}BuLi, THF, −78 °C, 2 h; then $BnOCH_2COCl$ (84%); (iii) $Sn(OTf)_2$, CH_2Cl_2, Et_3N, −78 °C; then **6**, TMEDA: **7** (5%), **8** (60%), **9** (15%); (iv) Et_3SiCl, imidazole, DMF (84%); (v) $LiBH_4$, THF, 0 °C (82%); (vi) TPAP, NMO, CH_2Cl_2 (80%).



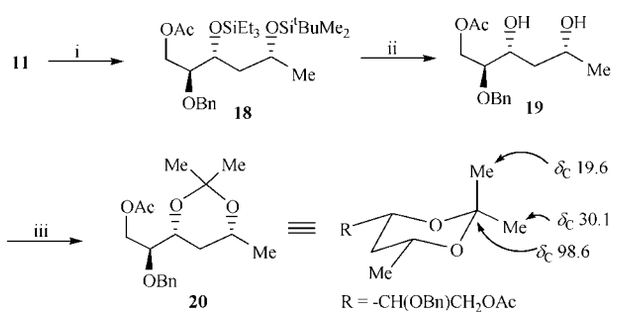
Scheme 2 *Reagents, conditions and yields*: (i) Si^tBuMe_2, imidazole, DMF, 0 °C to room temp. (87%); (ii) $LiBH_4$, Et_2O (89%); (iii) TPAP, NMO, CH_2Cl_2 (81%).

then focused on the subsequent aldol coupling reaction. Evans *et al.*[11] reported that the addition of isobutyraldehyde to the tin(II) enolate of benzyloxyoxazolidinone **5** resulted in 63% yield of the *anti* aldol product **16**. With this in mind, the stannous enolate of oxazolidinone **5** was generated with 1.5 mol equiv. of $Sn(OTf)_2$ and Et_3N at −78 °C. After stirring of the reaction mixture at −78 °C for 1 h, addition of tetramethylethylenediamine (1.5 equiv.) followed by the addition of aldehyde **6** and stirring for 2 h at −78 °C afforded an 80% yield of aldol products **7**, **8** and **9** in 1 : 12 : 3 proportions (Scheme 1).

The *anti* configuration of the major aldol product **8** was assigned based on literature precedent[11,12] and was supported by the magnitude of the 2′,3′ vicinal coupling constant, which was similar to the coupling constant observed for analogous protons in related *anti* aldol products **16**, **17** (Table 1). Assignment of proton and carbon NMR spectra was supported by COSY and DEPT experiments.

H-2′ of the major aldol adduct **8** resonated as a doublet at δ 5.31 with coupling constant J 7.7 Hz, thus the chemical shift and coupling constant were similar to the analogous protons in **16**[11] and **17**[12] (Table 1) which were formed under essentially the same reaction conditions. This analysis, however, did not establish whether the major *anti* aldol product was **7** or **8**. It was therefore necessary to show whether H-3′ was *syn* or *anti* to H-5′.

The major aldol adduct **8** was converted into triethylsilyl ether **10** using triethylsilyl chloride and imidazole in view of the fact that use of trimethylsilyl trifluoromethanesulfonate and 2,6-lutidine resulted in epimerization at C-2. Reductive removal of the oxazolidinone using lithium borohydride afforded alcohol **11** in 82% yield, which was converted into acetate **18** under standard conditions (Scheme 3). Deprotection of both silyl ethers using pyridinium toluene-*p*-sulfonate in ethanol afforded



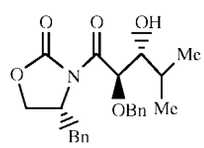
Scheme 3 *Reagents and conditions*: (i) Ac_2O, Et_3N, DMAP (cat.); (ii) pyridinium toluene-*p*-sulfonate (cat.), EtOH; (iii) *p*-TsOH, acetone, room temp.

diol **19**, which was converted into acetonide **20** using acetone and toluene-*p*-sulfonic acid (*p*-TsOH). The ^{13}C NMR spectrum for **20** featured methyl carbons at δ_C 19.6 and δ_C 30.1 and a ketal carbon at δ_C 98.6, which was consistent with a *syn*-diol-derived acetonide. It was therefore established that H-3 and H-5 were *syn* to each other in adduct **8** and, given that the configuration at C-5′ in **8** was *R*, the absolute stereochemistry at C-3′ was established to be *R*. The magnitude of the vicinal 2′,3′ coupling constant suggested that the relationship between H-2′ and H-3′ is *anti* and allowed assignment of the configuration at C-2′ in **8** as *R*.

The second most abundant product from the aldol reaction was assigned as the 2′,3′-*syn* isomer **9** based largely on the chemical shift (δ 5.17) and coupling constant (J 2.9 Hz) observed for for H-2′ (Table 1). In the least polar minor isomer **7**, H-2′ resonated at δ 5.28 with coupling constant J 5.9 Hz, which was similar to **8** and quite different from **9**, suggesting 2′,3′-*anti* and 3′,5′-*anti* stereochemistry.

The *anti* product **8** is formed as a major product over the normal Evans' *syn* product **9**. Based on the suggestion[13] that there may be a change in the co-ordination pattern of the divalent tin(II) enolate upon addition of tetramethylethylenediamine to the reaction mixture, together with literature precedent on *anti* aldol reactions[14,15] and the knowledge of tin(II) co-ordination patterns,[16,17] it is proposed that this aldol reaction proceeds *via* a boat-like transition state **B** (Fig. 1). Thus, **8** is produced from boat-like transition state **B** as the

Table 1 Comparison of chemical shifts (δ) and coupling constants (J/Hz) for aldol adducts **7**–**9**, **16**, **17**



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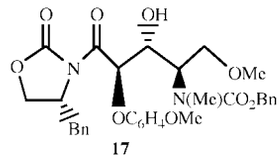

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Product	**8**[a]	**16**[b]	**17**[c]	**7**[a]	**9**[a]
$SiMe_2$	0.08, s			0.08, s 0.10, s	0.05, s
^{t}Bu	0.86, s			0.90, s	0.87, s
Me	1.18, d, 6.2		2.86, s (NMe)	1.21, d, 6.2	1.19, d, 6.2
H-4′^{A}	1.67, ddd, 14.3, 9.7, 9.7	2.12, m	4.34, m	1.68–1.86, m	1.58, ddd, 14.3, 7.1, 2.2
H-4′^{B}	1.94, ddd, 14.3, 3.8, 1.6				1.78–1.94, m
CH^APh	2.60, dd, 13.6, 9.9	2.62, dd, 13.4, 9.9	2.94, dd, 13.9, 8.1	2.65, dd, 13.2, 9.9	2.72, dd, 13.6, 9.9
CH^BPh	3.15, dd, 13.6, 3.3	3.22, dd, 13.5, 3.2	3.11, dd, 13.9, 3.7	3.31, dd, 13.2, 3.3	3.27, dd, 13.6, 3.3
3′-OH	3.54, d, 2.2	1.92, d, 9.3	not listed	3.23, d, 4.5	2.83, d, 6.2
H-3′	3.94–4.01, m	3.70, m	4.02, dd, 6.9, 5.2	4.14–4.34, m	
H-5	4.01–4.17, m	4.17, m	4.19, dd, 8.9, 3.3	4.00–4.14, m	4.09–4.28, m
H-5′		0.88, d, 6.8	4.28, dd, 8.9, 8.0 A: 3.62, dd, 10.9, 4.6	4.14–4.34, m	
		1.00, d, 7.0	B: 3.68, dd, 10.9, 8.6		
OCH^AAr	4.61, s	4.52, d, 11.5	4.42, d, 11.4 (C_6H_4OMe) 5.07, d, 12.9 (Ph)	4.61, s	4.54, d, 11.7
OCH^BAr		4.55, d, 11.5	4.46, d, 11.4 (C_6H_4OMe) 5.09, d, 12.9 (Ph)		4.75, d, 11.7
H-4	4.53–4.69, m	4.70, m	4.64, m	4.48–4.66, m	4.63–4.78, m
H-2′	5.31, d, 7.7	5.36, d, 8.5	5.35, d, 6.9	5.28, d, 5.9	5.17, d, 2.9
ArH	7.17–7.41, m	7.10–7.40, m	6.87, m 7.21–7.36, m	7.21–7.40, m	7.19–7.42, m
OMe			3.22, 3.76, s		

[a] Data recorded at 200 Hz in $CDCl_3$ and listed as δ, multiplicity and J-values(s) (Hz). [b] Recorded at 500 MHz in $CDCl_3$.[11] [c] Recorded at 500 MHz in D_6-DMSO at 125 °C.[12] [d] See H-5′ signals.

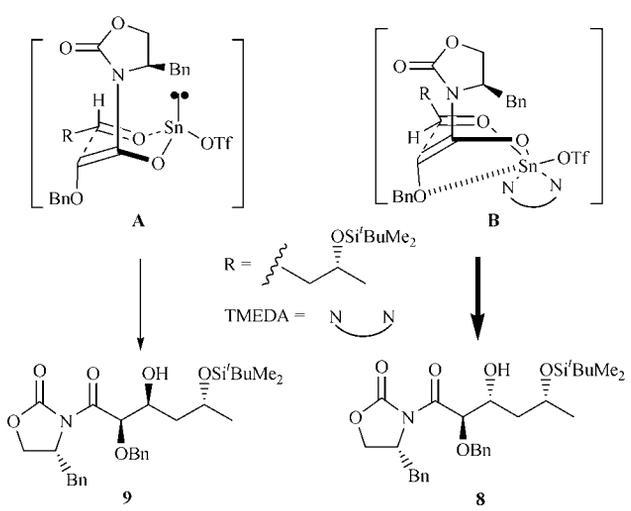
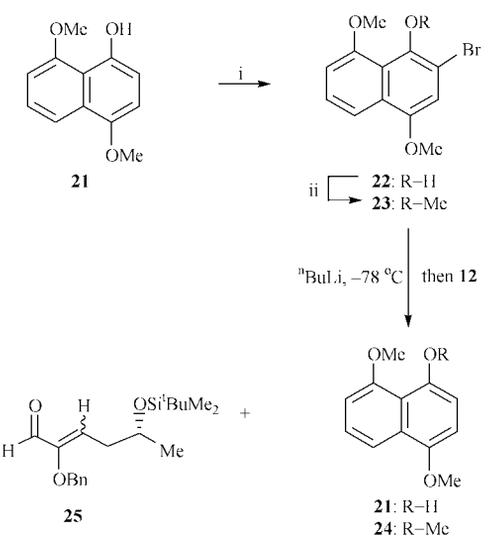


Fig. 1

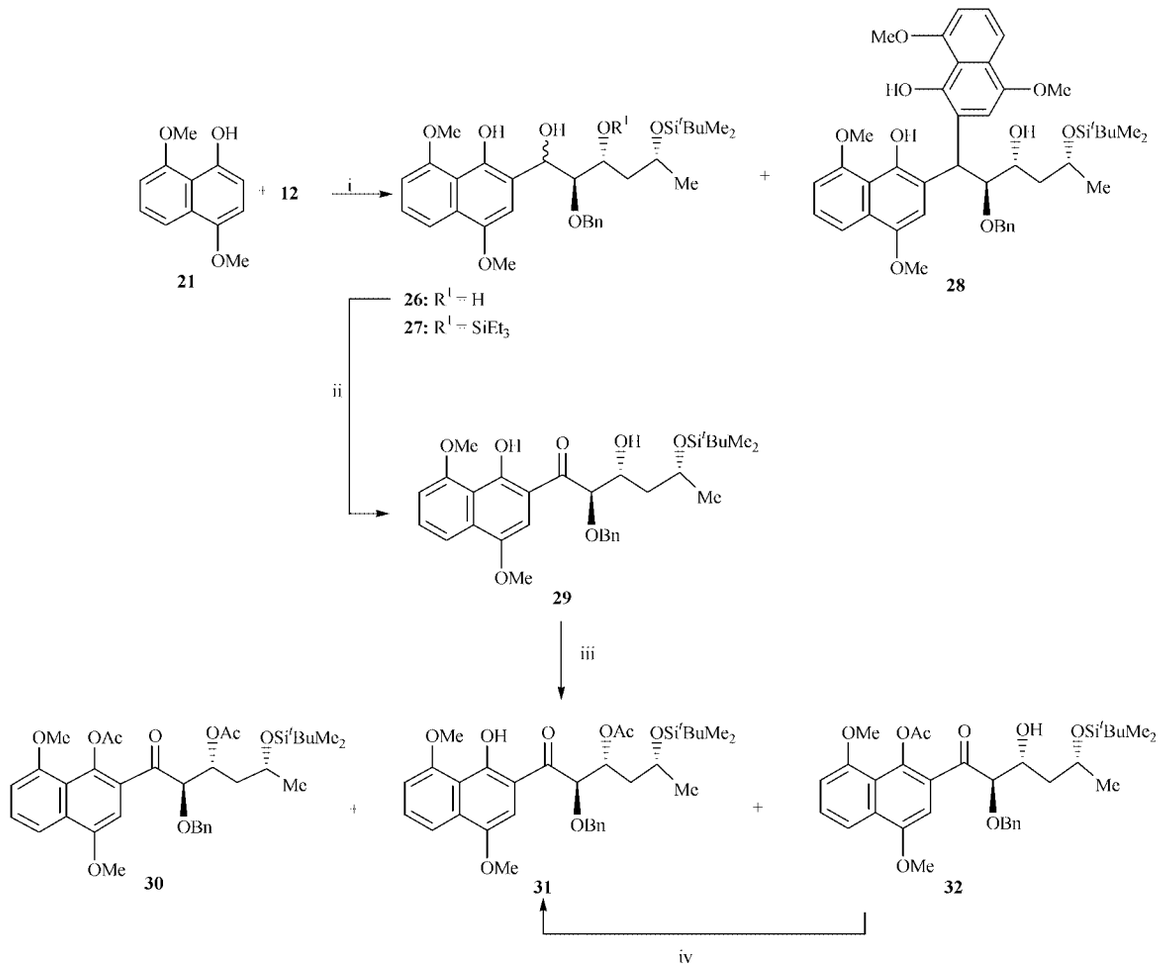
major isomer over **9** which is formed from the chair-like transition state **A**.

Oxidation of alcohol **11** to aldehyde **12** was effected without epimerization using TPAP and *N*-methylmorpholine *N*-oxide (NMO). With aldehyde **12** in hand, our attention focused on its union with a suitable oxygenated naphthalene fragment *en route* to the key naphthoquinone **32**. Selective bromination of naphthol **21** at C-3 afforded bromonaphthalene **22** in 72% yield, which underwent methylation with potassium hydroxide and dimethyl sulfate to give trimethoxynaphthalene **23** in 68% yield (Scheme 4). Initial efforts to combine naphthalene **23** and aldehyde **12** focused on generation of an organolithium reagent



Scheme 4 *Reagents, conditions and yields*: (i) Br_2, CCl_4, room temp. (72%); (ii) Me_2SO_4, THF–DMSO, 0 °C; then aq. KOH, 0 °C to room temp. (68%); (iii) **22**, ^{n}BuLi (2.0 equiv.), THF, −78 °C; then **12**: **21** (73%), **25** (24%).

from bromide **23** followed by the addition of aldehyde **12**. Disappointingly, only 1,4,5-trimethoxynaphthalene **24** was recovered from the reaction. Attempts to reduce the basicity of the naphthyl anion by transmetallation to a softer organomagnesium or organocerium species also proved ineffective. Generation of the dianion from bromonaphthol **22** with *n*-butyllithium (2.0 equiv.) followed by addition of aldehyde **12** resulted in formation of unsaturated aldehyde **25**. The three oxygenated



Scheme 5 *Reagents, conditions and yields*: (i) $TiCl_3(O^iPr)$, CH_2Cl_2, 0 °C, 9 min: **26** (44%), **27** (9%), **28** (6%); (ii) MnO_2, CH_2Cl_2 (62%); (iii) Ac_2O, CH_2Cl_2, Et_3N: **30** (25%), **31** (41%), **32** (20%); (iv) guanidine, $KOBu^t$, EtOH, 5 min, room temp. (47%).

substituents on the naphthalene ring resulted in a marked increase in the basic character of the naphthyl anion[18] such that protonation of anionic species by the aldehyde **12** is occurring.

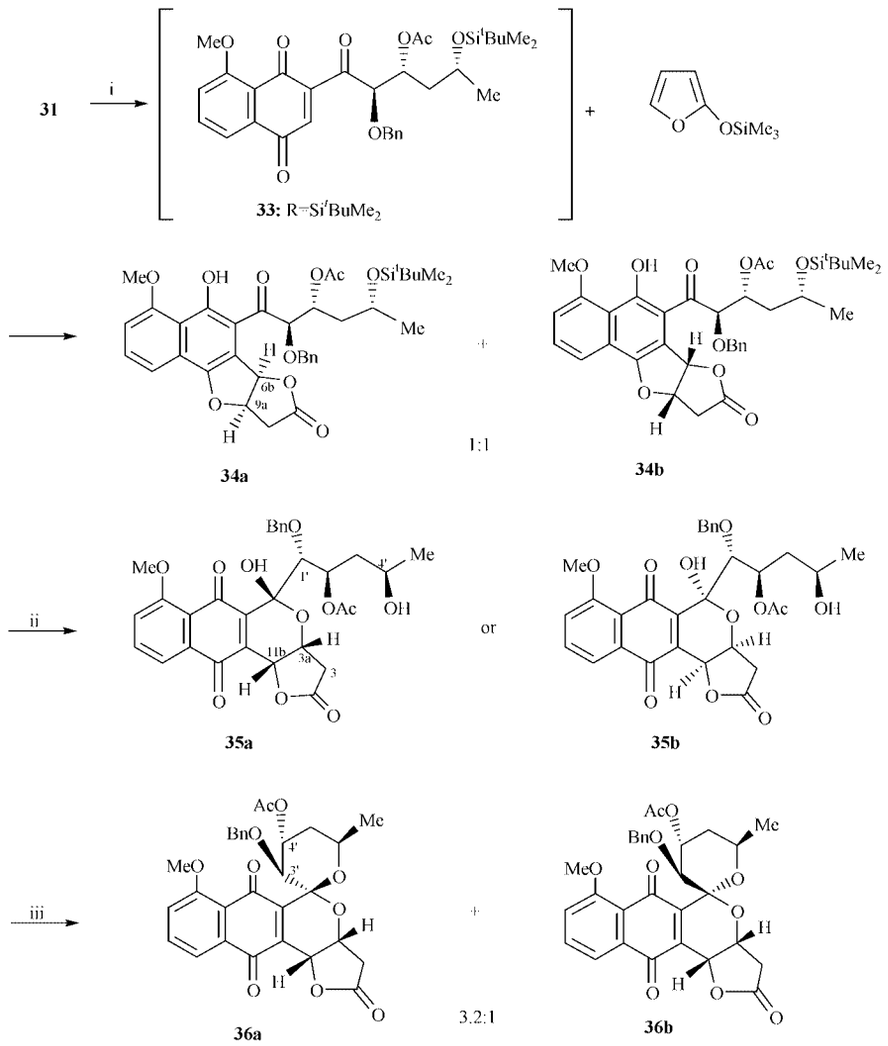
In light of the difficulties experienced with the above approach, we next decided to effect C-arylation of aldehyde **12** using a titanium naphtholate generated from naphthol **21**. This strategy was based on work by Bigi and co-workers.[19] and Casiraghi *et al.*[20] who have effected regiospecific *ortho*-arylation of α-alkoxy and α-amino carbonyl compounds. In the present work the desired benzylic alcohols **26** were prepared in moderate yield by addition of a titanium naphtholate generated from naphthol **21** to aldehyde **12** (Scheme 5).

Use of $TiCl(O^iPr)_3$ and $TiCl_2(O^iPr)_2$ to generate the titanium naphtholate species afforded only recovered starting material whereas use of the more Lewis acidic $TiCl_3(O^iPr)$ did effect union of naphthol **21** with aldehyde **12**. Precise reaction conditions were developed for this step in order to minimize formation of biarylmethane **28**.[21] A cooled solution (0 °C) of naphthol **21** in dichloromethane was added to a solution of $TiCl_3(O^iPr)$ in dichloromethane at 0 °C. The resultant titanium naphtholate was then transferred to a solution of aldehyde **12** in dichloromethane and the reaction mixture stirred at 0 °C for 9 min. Purification by flash chromatography afforded benzylic alcohols **26** in 44% yield along with triethylsilyl ethers **27** and biarylmethane **28** in 9% and 6% yield, respectively. The order of addition described and the short reaction time was crucial in order to minimize formation of the undesired biarylmethane **28**.

Formation of biarylmethane **28** as a by-product was confirmed by elemental analysis which established the molecular formula $C_{43}O_{54}O_9Si$. The ^1H NMR spectrum displayed all the features consistent with the biarylmethane structure including four singlets at δ 3.62, 3.74, 3.83 and 3.90 assigned to the methoxy groups, and two singlets at δ 9.35 and 9.43 assigned to the two hydroxy groups. A doublet at δ 5.42 with coupling constant $J_{1',2'}$ 7.6 Hz was assigned to H-1′.

With alcohols **26** in hand, oxidation with manganese dioxide provided ketone **29** (62%), which afforded acetates **31** (41%), **32** (20%) and diacetate **30** (25%) upon treatment with acetic anhydride and triethylamine. Acetylation of alcohol **29** using acetic anhydride and triethylamine in the presence of a catalytic quantity of 4-(dimethylamino)pyridine (DMAP) afforded solely diacetate **30** in 69% yield. Naphthyl acetate **32** underwent conversion into alkyl acetate **31** upon treatment with guanidine in ethanol[22] thereby providing more of the desired acetate **31**. The high-field ^1H and ^{13}C NMR spectra for acetate **31** confirmed that epimerization of the stereocentre α to the carbonyl group had not occurred at this stage of the synthesis.

The key naphthol **31** underwent oxidative demethylation to unstable naphthoquinone **33** upon treatment with aq. ceric [cerium(IV)] ammonium nitrate (CAN) in acetonitrile (Scheme 6). Immediate addition of 2-(trimethylsilyloxy)furan to the naphthoquinone **33** then afforded a 1 : 1 inseparable mixture of furonaphthofurans **34a/b** in 42% yield. Formation of adduct **34** was confirmed by spectroscopic analysis. High-resolution mass spectrometry established the molecular formula $C_{36}H_{44}O_{10}Si$. The IR spectrum featured three bands at 1778, 1741 and 1668 cm^{-1} due to the carbonyl groups of the γ-lactone, ester and ketone, respectively, whilst a broad band at 3320 cm^{-1} was characteristic of the hydroxy group. The ^1H NMR spectrum exhibited a multiplet at δ 5.36–5.56 assigned to the bridgehead proton H-9a and H-3′, whilst two doublets at δ 6.36 and 6.69



Scheme 6 *Reagents, conditions and yields*: (i) CAN, CH_3CN, H_2O; then 2-(trimethylsilyloxy)furan (42%); (ii) CAN, CH_3CN, H_2O; then 5% HF (48%); (iii) CSA, CH_2Cl_2, reflux (52%).

(both with coupling constant $J_{6b,9a}$ 5.9 Hz) were assigned to H-6b. These protons resonated at similar chemical shifts to those reported for analogous furo[3,2-*b*]naphthofurans[23] and was consistent with *cis* fusion of the two furan rings. The chemical shifts of the protons in the side chain of adduct **34** were similar to the corresponding protons in naphthalene-acetate **31**. The ^{13}C NMR spectrum was also consistent with the proposed structure with two methine carbons at δ_C 81.4 and 81.9 being assigned to the bridgehead carbon C-9a in the two diastereomers and resonances at δ_C 85.2 and 85.4 being assigned to C-6b of the individual diastereomers. It was disappointing that the bulky benzyloxy substituent at C-2′ on naphthoquinone **33** failed to influence any stereocontrol in the ensuing annulation.

With furonaphthofurans **34** in hand, oxidative rearrangement of this tetracyclic system to the pyranonaphthoquinone ring system present in griseusin A **1** was then investigated. The 1:1 mixture of furonaphthofurans **34a** and **34b** were treated with an excess of CAN (8 equiv.) in acetonitrile at room temperature under nitrogen. After stirring of the mixture for 10 min, formation of baseline material was observed upon analysis by TLC and attempts to purify the crude product by flash chromatography resulted in decomposition.

It was therefore next decided to effect deprotection of the silyl group and oxidative rearrangement in one step. Towards this end, 5% hydrofluoric acid was added dropwise to the reaction mixture 45 s after adducts **34a** and **34b** were treated with CAN (3.0 equiv.) in acetonitrile. Before the addition of 5% hydrofluoric acid, TLC analysis indicated the formation of a complex mixture of products. However, after the addition of 5% hydrofluoric acid and stirring for 2 h at room temperature, one major product was observed by TLC, together with a substantial quantity of baseline material. Careful purification by flash chromatography afforded lactol **35a** or **35b** in 48% yield.

The ^1H and ^{13}C NMR spectra of the lactol isolated, together with analysis by HPLC, indicated that only one diastereomer of the lactol (either **35a** or **35b**) was formed from the 1:1 mixture of adducts **34a** and **34b**. Definitive assignment of the exact structure of the lactol obtained however, proved difficult. It transpired that subsequent cyclization to a spiroketal allowed a more detailed analysis of the stereochemistry (*vide infra*).

High-resolution mass spectrometry established the molecular formula $C_{30}H_{30}O_{11}$ for lactol **35**. The IR spectrum featured a hydroxy band at 3446 cm^{-1} and bands at 1783 and 1664 cm^{-1} due to the carbonyl groups of the γ-lactone and quinone, respectively. The ^1H NMR spectrum showed an upfield shift in the resonances of the bridgehead protons H-3a and H-11b relative to the bridgehead protons H-6b and H-9a in the initial adducts **34a** and **34b**. The coupling constant between the bridgehead protons was notably reduced from 5.9 Hz to 2.4 Hz, reflecting the 5,6 ring fusion now in place. The coupling constant, $J_{3a,11b}$ 2.4 Hz, was similar to that reported for the analogous protons in griseusin A **1**[1], supporting the presence of a *cis*-fused furonaphthopyran ring system.

A doublet resonating at δ 2.68 with a large geminal coupling J_{gem} 17.6 Hz was assigned to H-3^A, whilst a doublet of doublets at δ 2.99 with a geminal coupling J_{gem} 17.6 Hz and an additional coupling to H-3a, $J_{3B,3a}$ 5.0 Hz was assigned to H-3^B. The sharp resonance for the phenolic protons in adducts **34a** and **34b** were

Table 2 Comparison of chemical shifts (δ) and coupling constants (J/Hz) for spiroketals **36a**, **36b** and griseusin A **1**

	1 [a]	**36a** [b]	**36b** [b]
H-3^{A}	2.72, d, 17	2.74, d, 17.6	2.68, d, 17.6
H-3^{B}	3.07, dd, 17, 5	3.00, dd, 17.6, 4.9	3.00, dd, 17.6, 4.9
H-3a	4.81, dd, 5, 3	4.68–4.70	4.94–4.96
H-8	7.10–7.80	7.30–7.36	7.30–7.36
H-9	7.10–7.80	7.47, t, 8.0, 8.0	7.47, t, 8.0, 8.0
H-10	7.10–7.80	7.75, d, 8.0	7.75, d, 8.0
H-11b	5.31, d, 3	5.31, d, 2.8	5.27, d, 2.8
H-3′	4.95, dd, 12, 4	3.47, d, 9.8	3.52, d, 9.8
H-4′	5.29, q, 4	4.21–4.28	4.21–4.28
H-5′^{A}	1.91, td, 11, 4	2.00–2.03	2.00–2.03
H-5′^{B}	2.10, ddd, 11, 4	2.10–2.13	2.10–2.13
C*H*Me	4.18, dqd, 11, 6, 2	5.20–5.25	5.20–5.25
$COCH_3$	2.08	2.00	2.03
OCH^{A}Ph		4.67, d, 11.3	4.74, d, 11.1
OCH^{B}Ph		4.92, d, 11.3	4.95, d, 11.1
Ph		7.30–7.36	7.30–7.36
Me	1.22, d, 6	1.42, d, 6.1	1.37, d, 5.8
OMe		3.98	4.00
3′-OH	2.90		
7-OH	11.80		

[a] Data recorded at 60 MHz in $CDCl_3$ and listed as δ_H, multiplicity and J-value(s) (Hz).[1] [b] Recorded at 400 MHz in $CDCl_3$.

replaced by two broad resonances at δ 4.35 and δ 5.03 due to hydroxy groups. The ^{13}C NMR spectrum reflected the loss of the carbonyl group at δ_C 198.5 and the presence of an additional resonance at δ_C 91.1 was consistent with a lactol carbon, C-5. Two quaternary carbonyl carbons at δ 182.1 and δ 188.3 were assigned to C-11 and C-6 respectively. The vicinal coupling constant $J_{3a,11b}$ 2.4 Hz established that the relative stereochemistry of the bridgehead protons at C-3a and C-11b was *cis*. The position of the hydroxy group at C-5, however, was assigned as axial and *cis* with respect to the bridgehead protons H-3a and H-11b based on anomeric and steric effects. Similar assignments were made in related work focused on the synthesis of kalafungin [23] and model ring systems for griseusin A **1**.[6]

Having synthesized lactol **35**, our final step to construct the spiroketal ring of griseusin A **1** involved an acid-catalysed cyclization. Lactol **35** was heated under gentle reflux with a catalytic quantity of camphor-10-sulfonic acid in dichloromethane for two days affording a 3.2:1 mixture of epimerized spiroketals **36a** and **36b** in 52% yield after purification by flash chromatography.

The two spiroketals **36a** and **36b** were inseparable by flash chromatography, therefore the product ratio was established by the integration of the ^1H NMR spectrum. The ^1H NMR spectrum exhibited two doublets at δ 1.37 and 1.42 assigned to 6′-Me of the minor and major spiroketals, respectively, whilst the singlets resonating at δ 3.98 and 4.00 were assigned to the methoxy group of the major and minor isomers, respectively (Table 2). Two doublets at δ 2.68 (minor) and 2.74 (major) with coupling constant J_{gem} 17.6 Hz were assigned to H-3^{A}. In the major isomer **36a**, H-3^{A} exhibited a similar chemical shift and coupling constant to that observed for the same proton in griseusin A **1** (δ 2.72, J 17 Hz). Two doublets resonating at δ 5.27 (minor) and 5.31 (major) with coupling constant $J_{11b,3a}$ 2.8 Hz, were assigned to H-11b. The chemical shift of H-11b in the major isomer **36a** was similar to the analogous proton in griseusin A **1** (δ 5.31), whilst H-11b in the minor isomer **36b** (δ 5.27) appeared further upfield compared with griseusin A **1** since H-11b in the minor isomer **36b** is not *syn* to O-1′. Two doublets at δ 3.47 (major) and 3.52 (minor) with coupling constant $J_{3',4'}$ 9.8 Hz were assigned to H-3′. A multiplet resonating at δ 2.00–2.03 (major and minor) was assigned to H-5′^{A}, whilst a multiplet at δ 2.10–2.13 (major and minor) was assigned to H-5′^{B}. The chemical shift of H-5′ in the major **36a** and minor **36b** isomers was similar to the analogous protons in griseusin A **1**.

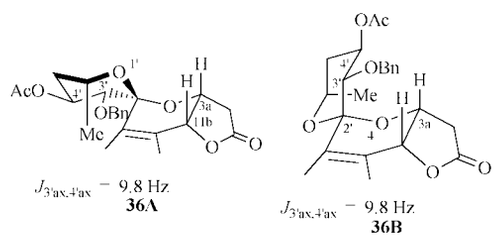


Fig. 2

In the present work, the coupling constant between H-3′ and H-4′ observed for both the major and minor isomers of the isolated spiroketals, was $J_{3',4'}$ 9.8 Hz. Cyclization of lactol **35** with the stereochemistry of the side chain as depicted (benzyloxy and acetate groups *anti*) would not afford a spiroketal with a large vicinal coupling constant $J_{4',3'}$. The possibility that epimerization at C-3′ on the spiroketal ring had taken place was therefore examined.

The most favoured conformation of the two C-3′ epimers of the spiroketal ring system of griseusin A are represented in Fig. 2. The C-3′ epimerized spiroketals **36a** and **36b** exhibit conformations wherein the two bulky substituents at C-3′ and C-4′ adopt more favourable equatorial positions. Spiroketals **36a** and **36b** wherein the methylene group of the fused γ-lactone occupies a pseudoequatorial position at C-3a are also preferred in that unfavourable steric interactions between the methylene group of the γ-lactone ring with either the oxygen atom O-1′ or C-3′ on the spiroketal ring are alleviated.

Based on these considerations, it was assumed that the two spiroketals isolated from the spirocyclization of lactol **35** were spiroketals **36a** and **36b**. The thermodynamically more stable major spiroketal was assigned as **36a** where the benzyloxy group at C-3′ is directed away from the bridgehead protons, H-3a and H-11b. In the minor isomer **36b** the benzyloxy group is in close proximity to H-3a and H-11b, thereby exhibiting unfavourable steric interactions.

The stereochemistry assigned to the two spiroketals **36a** and **36b** was confirmed by examination of the ^1H NMR spectrum. The magnitude of the vicinal coupling constant between H-3′ and H-4′ ($J_{3',4'}$ 9.8 Hz) for the major **36a** and minor **36b** isomers was consistent with the benzyloxy and acetate groups being equatorial. In the major isomer **36a**, H-3^{A} is in close proximity to the benzyloxy group, hence it is deshielded, appearing further downfield at δ 2.74 relative to the equivalent proton in the minor isomer **36b** where H-3^{A} resonates at δ 2.68. H-11b in

the major isomer **36a** is *syn* to O-1′, therefore it is deshielded, appearing further downfield at δ 5.31 compared with δ 5.27 for H-11b in the minor isomer **36b**. In the minor isomer **36b**, H-3′ resonated as a doublet at δ 3.52, whilst in the major isomer **36a**, H-3′ resonated as a doublet at δ 3.47. Thus, H-3′ is more deshielded in isomer **36b** where the BnOC–H bond is antiperiplanar to the C-5–O-4 bond.

The stereochemistry of the major isomer **36a** was further established by NOE experiments wherein enhancement of the C*H*OAc signal was observed when the 6′-Me resonance was irradiated. Irradiation of OC*H*Ph in the minor isomer **36b** resulted in enhancement of H-11b signal, indicating that H-11b and OC*H*Ph are in close proximity. Given that H-11b and OC*H*Ph in the major isomer **36a** are well removed from each other, further evidence is provided for assignment of the minor isomer as spiroketal **36b**.

Variation of the reaction conditions to effect cyclization of lactol **35** to spiroketals **36a** and **36b** was also investigated. When acetonitrile or toluene was used as the solvent, formation of baseline material resulted, and this material decomposed upon attempted purification by flash chromatography. Employing anhydrous magnesium sulfate to remove water generated from the reaction also led to decomposition. Use of alternative acid catalysts did not offer any improvement. Efforts to prevent epimerization in the final cyclization step also met with little success.

In summary, a synthesis of pyranonaphthoquinone spiroketals (**36a** and **36b**) which are closely related to griseusin A **1** has been presented. The synthetic work described herein provides a non-carbohydrate-based approach to the synthesis of analogues of this natural product. The epimerization observed in the final spirocyclization step demonstrates that subtle stereoelectronic effects provide the driving force for the stereochemistry observed in the final spiroketals.

Experimental

Mps were determined using a Kofler hot-stage apparatus and are uncorrected. IR spectra were recorded using a Perkin-Elmer 1600 Fourier Transform IR spectrophotometer as Nujol mulls, thin films or solutions in the solvent specified. Absorption maxima are expressed in wavenumbers (cm^{-1}) with the following abbreviations: vs = very strong, s = strong, m = medium, w = weak and br = broad. ^{1}H NMR spectra were recorded on a Bruker AC 200 (200 MHz) or a Bruker AM 400 (400 MHz) spectrometer at ambient temperature. All *J*-values are given in Hz. Chemical shifts are expressed in parts per million downfield shift from tetramethylsilane as an internal standard, and reported as position (δ_H), relative integral, multiplicity (s = singlet, br s = broad singlet, d = doublet, dd = double doublet, ddd = double double doublet, t = triplet, dt = doublet of triplets, q = quartet, qd = quartet doublet, m = multiplet), coupling constant (*J*/Hz) and assignment. ^{13}C NMR spectra were recorded on a Bruker AC 200 (50.3 MHz) or a Bruker AM 400 (100.6 MHz) spectrometer at ambient temperature with complete proton decoupling. Data are expressed in parts per million downfield shift from tetramethylsilane as an internal standard and reported as position (δ_C), multiplicity (aided by DEPT135, COSY and HETCOR experiments) and assignment. Some peaks may be coincidental. Low-resolution mass spectra were recorded on a VG70-250S, a VG70-SD or a AEI model MS902 double-focusing magnetic sector mass spectrometer operating with an ionization potential of 70 eV (EI, CI). High-resolution mass spectra were recorded at nominal resolution of 5000 or 10 000 as appropriate. LSIMS spectra were recorded between 200–550 Da. Major fragments are given as percentages relative to the base peak and assigned where possible. Ionization methods employed were (i) electron impact (EI), (ii) chemical ionization with ammonia as reagent gas (CI), (iii) fast-atom bombardment (FAB), (iv) liquid secondary-ion mass spectrometry (LSIMS) using caesium(I) ions as the primary beam (10 kV) and *m*-nitrobenzyl alcohol (NBA) and a 5:1 mix (v/v) of dithiothreitol–dithioerythritol (DTDE) as a matrix. Optical rotations were recorded on an Optical Activity POLAAR 2001 polarimeter using a 5 dm^{-3} cell. Samples were prepared at the concentration (measured in g/100 cm^3) in the solvent indicated. Thin-layer chromatography (TLC) was performed using 0.2 mm thick precoated silica gel plates (Merck Kieselgel 60 F_{254} or Riedel-de Haen Kieselgel S F_{254}). Compounds were visualized by UV fluorescence or by staining with iodine or vanillin in methanolic sulfuric acid. Flash chromatography was performed using Merck Kieselgel 60 or Riedel-de Haen Kieselgel S silica gel (both 230–400 mesh) with the indicated solvents. Concentration '*in vacuo*' or 'at reduced pressure' refers to concentration using a rotary evaporator connected to a water aspirator. Removal of residual solvent or volatile reagents where desired was achieved by evacuation (0.1–0.01 mmHg) with a high-stage oil vacuum pump. Ether refers to diethyl ether, hexane refers to light petroleum with distillation range 40–60 °C.

(4*R*)-4-(Phenylmethyl)oxazolidin-2-one 4

A mixture of (2*R*)-2-amino-3-phenylpropan-1-ol **3**[8] (5.81 g, 38.4 mmol), potassium carbonate (0.53 g, 3.84 mmol) and diethyl carbonate (8.84 ml, 73.0 mmol) was carefully heated to 135–140 °C, and ethanol was allowed to distil as it was formed. After 6 h, the light brown slurry was cooled to room temperature, diluted with dichloromethane (400 ml), and filtered through a Celite pad to remove potassium carbonate. The organic layer was washed with aq. sodium hydrogen carbonate (2 × 100 ml; 10% w/v), dried over magnesium sulfate and the solvent was removed under reduced pressure to afford a pale yellow crystalline solid. Recrystallization from hexane–ethyl acetate (4:1) gave the title compound **4** (5.45 g, 80%) as colourless needles, mp 86.5–88.5 °C {lit.,[8] 87.0–88.5 °C [(4*S*)-enantiomer]}; $[\alpha]_D$ −4.90 (*c* 2.262, EtOH) {lit.,[8] $[\alpha]_D$ +4.9 (*c* 1.10, EtOH) [(4*S*)-enantiomer]}. The ^{1}H NMR spectrum was in agreement with that reported in the literature.[8]

(4*R*)-3-[2-(Phenylmethoxy)acetyl]-4-(phenylmethyl)oxazolidin-2-one 5

To a solution of (4*R*)-4-(phenylmethyl)oxazolidin-2-one **4** (4.54 g, 25.6 mmol) in dry tetrahydrofuran (THF) (68 ml) cooled to −78 °C under an atmosphere of nitrogen was added *n*-butyllithium (1.60 M; 17.6 ml, 28.2 mmol). The temperature was raised to −20 °C over 1.5 h lowered back to −78 °C and benzyloxyacetyl chloride (5.20 g, 28.2 mmol) as a solution in dry THF (5 ml) added slowly. The solution was stirred for a further 0.5 h before being quenched by the addition of saturated aq. ammonium chloride (16 ml). Following extraction with dichloromethane (73 ml), the organic layer was washed successively with aq. sodium hydroxide (24 ml; 1 M), water (24 ml) and brine (24 ml) before being dried over sodium sulfate. The solvent was removed under reduced pressure to afford a pale yellow oil, which upon purification by flash chromatography using hexane–ethyl acetate (7:3) as eluent gave the *title compound* **5** (7.00 g, 84%) as a colourless crystalline solid (Found: C, 69.9; H, 5.7; N, 4.2. $C_{19}H_{19}NO_4$ requires C, 70.1; H, 5.9; N, 4.3%); $[\alpha]_D$ −69.57 (*c* 1.638, CH_2Cl_2); ν_{max} (Nujol)/cm^{-1} 1765s (O*C*=*O*N) and 1703s (N*C*=*O*C); δ_H (200 MHz; $CDCl_3$) 2.80 (1H, dd, J_{gem} 13.4 and *J* 9.3, CHC*H*^{A}Ph), 3.29 (1H, dd, J_{gem} 13.4 and *J* 3.1, CHC*H*^{B}Ph), 4.09–4.29 (2H, m, H_2-5), 4.57–4.75 (5H, m, H-4, O*C*H_2Ph, H-2′) and 7.13–7.49 (10H, m, Ph); δ_C (50 MHz; $CDCl_3$) 37.6 (CH_2, CH*C*H_2Ph), 54.6 (CH, C-4), 67.1 (CH_2, C-2′), 69.5 (CH_2, C-5), 73.3 (CH_2, O*C*H_2Ph), 127.3, 127.9(2), 128.4, 128.9, 129.3 [CH, 2 × Ph (last 4 peaks coincidental)], 134.8 (quat, CHCH_2*Ph*), 137.1 (quat, OCH_2*Ph*), 153.2 (quat, C-2) and 170.0 (quat, C-1′); *m*/*z* (EI) 326 (MH^+, 0.5%), 234 (M − CH_2Ph, 3), 219 (MH − OCH_2Ph, 27), 176

(MH − OCH_2Ph − CH_3CO, 3), 128 (MH − OCH_2Ph − CH_3-CO − CH_2Ph, 14), 91 (CH_2Ph, 100) and 65 (10).

Ethyl-(3*R*) 3-(*tert*-butyldimethylsilyloxy)butanoate 14

To a solution of ethyl-(3*R*) 3-hydroxybutanoate **13** (2.36 g, 17.9 mmol) and *N*,*N*-dimethylformamide (DMF) (12.2 ml) at 0 °C under an atmosphere of nitrogen was added *tert*-butyldimethylsilyl chloride (2.85 g, 18.8 mmol) and imidazole (3.04 g, 44.7 mmol). After 2 h, the reaction mixture was left to warm to room temperature and was stirred for a further 20 h. The solution was poured into ether (87 ml), washed successively with water (3 × 14 ml) and brine (14 ml), then dried over sodium sulfate. Removal of the solvent under reduced pressure gave a clear liquid which upon distillation afforded the title compound **14** (3.82 g, 87%) as a colourless liquid, bp 110–111 °C/13 mmHg (lit.,[24] 87–88 °C/5 mmHg); $[a]_D$ −26.15 (*c* 4.148, $CHCl_3$) {lit.,[24] $[a]_D$ −25.5 (*c* 1.16, $CHCl_3$)}. The ^1H NMR spectrum was in agreement with that reported in the literature.[24]

(3*R*)-3-(*tert*-Butyldimethylsilyloxy)butan-1-ol 15

To a stirred suspension of lithium borohydride (319 mg, 14.7 mmol) in dry ether (22 ml) under an atmosphere of nitrogen was added a solution of ethyl-(3*R*) 3-(*tert*-butyldimethylsilyloxy)butanoate **14** (2.41 g, 9.78 mmol) and methanol (0.57 ml) in dry ether (4.85 ml) over a period of 1 h. The reaction mixture was heated under reflux for 5 h, then cooled in ice and quenched by the addition of sodium hydroxide (12.9 ml; 2 M). After 20 min, the mixture was poured into ether (58 ml) at room temperature. The layers were separated and the aqueous phase extracted with ether (3 × 40 ml). The combined organic extracts were washed with brine (32 ml), dried over sodium sulfate, and the solvent removed under reduced pressure. The clear liquid obtained was distilled to give the title compound **15** (1.77 g, 89%) as a colourless liquid, bp 62–63 °C/0.1 mmHg (lit.,[24] 74–80 °C/4 mmHg); $[a]_D$ −30.18 (*c* 0.280, $CHCl_3$) {lit.,[24] $[a]_D$ −30.4 (*c* 1.09, $CHCl_3$)}. The ^1H NMR spectrum was in agreement with that reported in the literature.[24]

(3*R*)-3-(*tert*-Butyldimethylsilyloxy)butanal 6

To a solution of (3*R*)-3-(*tert*-butyldimethylsilyloxy)butan-1-ol **15** (2.82 g, 13.8 mmol) in dichloromethane (57 ml) under an atmosphere of nitrogen were added NMO (2.43 g, 20.7 mmol) and powdered 4 Å molecular sieves (5.20 g). After 5 min, TPAP (170 mg, 3.5 mol%) was added and the reaction mixture stirred at room temperature for 4 h. Filtration of the reaction mixture through a silica gel pad, followed by removal of the solvent under reduced pressure gave the title compound **6** (2.24 g, 81%) as a clear liquid (Found: MH^+, 203.1467. Calc. for $C_{10}H_{22}OSi$: MH^+, 203.1430); $[a]_D$ −17.90 (*c* 0.354, $CHCl_3$) {lit.,[10] $[a]_D$ −14.4 (*c* 1.05, $CHCl_3$)}; ν_{max} (film)/cm^{-1} 2723w (*H*–C=O), 1734s (C=O), 1134m and 1092m (C–O); δ_C (50 MHz; $CDCl_3$) −5.0, −4.4 (CH_3, $SiMe_2$), 17.9 (C, *C*Me_3), 24.1 (CH_3, C-4), 25.7 (CH_3, C*Me*$_3$), 52.9 (CH_2, C-2), 64.5 (CH, C-3) and 202.1 (CH, C-1); *m*/*z* (LSIMS, NBA matrix) 203 (MH^+, 7%), 187 (16), 159 (MH − CH_2CHOH, 81), 145 ($C_7H_{17}OSi$, 26), 115 ($C_6H_{15}Si$, 38), 103 (23), 89 ($C_4H_9O_2$, 22), 75 ($C_3H_7O_2$, 24) and 73 ($C_3H_5O_2$, 100). The ^1H NMR spectrum was in agreement with that reported in the literature.[10] The crude material was used in the next step without further purification.

Tin(II) trifluoromethanesulfonate

The title compound was prepared by an adaptation of the method of Mukaiyama *et al*.[25] After addition of the trifluoromethanesulfonic acid (18.7 ml, 0.21 mol) to anhydrous tin(II) chloride (12.72 g, 0.067 mol) under an atmosphere of nitrogen, the mixture was heated for 21 h, then extra acid was added (5 ml, 0.056 mol) and the mixture heated for a further 4 h. The excess of acid and volatiles was removed *in vacuo* and the solid washed thoroughly with sodium-dried ether (6 × 40 ml). The product, tin(II) trifluoromethanesulfonate (20.5 g, 73%), was dried under reduced pressure at 50 °C for 8 h, then stored under argon in a desiccator until required (Found: C, 5.8; F, 27.05; S, 15.3. Calc. for $C_2F_6O_6S_2Sn$: C, 5.8; F, 27.35; S, 15.4%).

3-[5-(*tert*-Butyldimethylsilyloxy)-3-hydroxy-2-(phenylmethoxy)-hexanoyl]-4-(phenylmethyl)oxazolidin-2-one 7–9

To a suspension of stannous [tin(II)] trifluoromethanesulfonate (6.90 g, 16.6 mmol) in dry dichloromethane (53.5 ml) under an atmosphere of nitrogen was added triethylamine (2.31 ml, 16.6 mmol) and the resultant yellow suspension was immediately cooled to −78 °C. After 5 min, a solution of oxazolidinone **5** (3.59 g, 11.0 mmol) in dry dichloromethane (17.9 ml) was added and the resultant mixture was stirred at −78 °C for 1 h. *N*,*N*,*N*′,*N*′-Tetramethylethylenediamine (TMEDA) (2.50 ml, 16.6 mmol) was then added, followed after 5 min by a solution of aldehyde **6** (2.23 g, 11.0 mmol) in dry dichloromethane (3.3 ml). The reaction mixture was stirred at −78 °C for 2 h, then poured into a vigorously stirred, ice-cooled mixture of 1 M aq. sodium hydrogen sulfate–dichloromethane (1:1; 1.43 l). After stirring for 5 min, the layers were separated and the aqueous layer extracted with dichloromethane (360 ml). The combined organic fractions were washed successively with saturated aq. sodium hydrogen carbonate (540 ml) and brine (540 ml), dried over sodium sulfate, and the solvent removed under reduced pressure. Purification of the pale yellow oil by flash chromatography using hexane–ethyl acetate (4:1) as eluent gave:

(i) *(4R,2′S,3′S,5′R)-aldol adduct* **7** (291 mg, 5%); R_f 0.63 [hexane–ethyl acetate (7:3)] as a colourless oil (Found: C, 65.9; H, 7.55; N, 2.70. $C_{29}H_{41}NO_6Si$ requires C, 66.0; H, 7.80; N, 2.65%); $[a]_D$ −50.10 (*c* 1.562, $CHCl_3$); ν_{max} (film)/cm^{-1} 3629–3363br (m, OH), 1777s (O*C*=*O*N), 1703s (N*C*=*O*C), 1395m, 1387m (C–N) and 1111br m (C–O); δ_H (200 MHz; $CDCl_3$) 0.08, 0.10 (6H, s, $SiMe_2$), 0.90 (9H, s, Bu^t), 1.21 (3H, d, *J* 6.2, H_3-6′), 1.68–1.86 (2H, m, H_2-4′), 2.65 (1H, dd, J_{gem} 13.2 and *J* 9.9, CHC*H*^{A}Ph), 3.23 (1H, d, *J* 4.5, OH), 3.31 (1H, dd, J_{gem} 13.2 and *J* 3.3, CHC*H*^{B}Ph), 4.00–4.14 (2H, m, H_2-5), 4.14–4.34 (2H, m, H-3′, -5′), 4.48–4.66 (1H, m, H-4), 4.61 (2H, s, O*C*H_2Ph), 5.28 (1H, d, $J_{2',3'}$ 5.9, H-2′) and 7.21–7.40 (10H, m, Ph); δ_C (50 MHz; $CDCl_3$) −5.1, −4.5 (CH_3, $SiMe_2$), 17.9 (quat, *C*Me_3), 23.3 (CH_3, C-6′), 25.8 (CH_3, C*Me*$_3$), 37.6 (CH_2, CH*C*H_2Ph), 40.8 (CH_2, C-4′), 55.1 (CH, C-4), 66.4 (CH_2, C-5), 66.6 (CH, C-5′), 69.9 (CH, C-3′), 73.2 (CH_2, O*C*H_2Ph), 79.8 (CH, C-2′), 127.2, 127.9, 128.3, 128.5, 128.9, 129.4 [CH, 2 × Ph (last 4 peaks coincidental)], 135.3 (quat, $CHCH_2$*Ph*), 137.4 (quat, OCH_2*Ph*), 153.2 (quat, C-2) and 172.0 (quat, C-1′); *m*/*z* (LSIMS, NBA matrix) 528 (MH^+, 17%), 396 (M − $C_6H_{16}OSi$, 11), 304 (11), 286 (17), 178 ($C_{10}H_{12}NO_2$, 13), 91 (CH_2Ph, 100), 75 [$(CH_3)_2SiOH$, 14] and 73 (23).

(ii) *(4R,2′R,3′R,5′R)-aldol adduct* **8** (3.48 g, 60%); R_f 0.56 [hexane–ethyl acetate (7:3)] as a colourless oil (Found: C, 66.0; H, 7.4; N, 2.6%); $[a]_D$ −56.11 (*c* 1.788, $CHCl_3$); ν_{max} (film)/cm^{-1} 3589–3280m (OH), 1784s (O*C*=*O*N), 1703s (N*C*=*O*C), 1389m (C–N) and 1105m (C–O); δ_H (200 MHz; $CDCl_3$) 0.08 (6H, s, $SiMe_2$), 0.86 (9H, s, Bu^t), 1.18 (3H, d, $J_{6',5'}$ 6.2, H_3-6′), 1.67 (1H, ddd, J_{gem} 14.3, $J_{4'A,3'}$ 9.7 and $J_{4'A,5'}$ 9.7, H-4′^{A}), 1.94 (1H, ddd, J_{gem} 14.3, $J_{4'B,3'}$ 3.8 or 1.6 and $J_{4'B,5'}$ 1.6 or 3.8, H-4′^{B}), 2.60 (1H, dd, J_{gem} 13.6 and *J* 9.9, CHC*H*^{A}Ph), 3.15 (1H, dd, J_{gem} 13.6 and *J* 3.3, CHC*H*^{B}Ph), 3.54 (1H, d, *J* 2.2, OH), 3.94–4.01 (1H, m, H-3′), 4.01–4.17 (3H, m, H-5, -5′), 4.53–4.69 (1H, m, H-4), 4.61 (2H, s, O*C*H_2Ph), 5.31 (1H, d, $J_{2',3'}$ 7.7, H-2′) and 7.17–7.41 (10H, m, Ph); δ_C (50 MHz; $CDCl_3$) −5.0, −4.2 (CH_3, $SiMe_2$), 17.6 (quat, *C*Me_3), 24.2 (CH_3, C-6′), 25.6 (CH_3, C*Me*$_3$), 37.7 (CH_2, CH*C*H_2Ph), 42.2 (CH_2, C-4′), 55.2 (CH, C-4), 66.2 (CH_2, C-5), 69.6 (CH, C-5′), 72.6 (CH, C-3′), 72.8 (CH_2, O*C*H_2Ph), 78.8 (CH, C-2′), 127.0, 127.8, 128.1, 128.2, 128.6, 129.2 [CH, 2 × Ph (last 4 peaks coincidental)], 135.1 (quat, $CHCH_2$*Ph*), 137.1 (quat, OCH_2*Ph*), 153.3 (quat, C-2) and 172.1

(quat, C-1′); *m/z* (LSIMS, NBA matrix) 528 (MH^+, 18%), 396 (M − $C_6H_{16}OSi$, 16), 304 (6), 286 (8), 268 (11), 178 ($C_{10}H_{12}NO_2$, 11), 159 ($C_8H_{19}OSi$, 8), 117 (8), 91 (CH_2Ph, 100), 75 [$(CH_3)_2SiOH$, 9], 73 (16), 55 (9) and 43 (CH_3CO, 8).

(iii) *(4R,2′R,3′S,5′R)-aldol adduct* **9** (872 mg, 15%); R_f 0.48 [hexane–ethyl acetate (7:3)] as a colourless oil (Found: C, 65.7; H, 7.6; N, 2.6%); $[\alpha]_D$ −16.91 (*c* 5.348, $CHCl_3$); ν_{max} (film)/cm^{-1} 3624–3278m (OH), 1782s (O*C*=*O*N), 1710s (N*C*=*O*C), 1390m (C–N) and 1105br m (C–O); δ_H (200 MHz; $CDCl_3$) 0.05 (6H, s, $SiMe_2$), 0.87 (9H, s, Bu^t), 1.19 (3H, d, $J_{6',5'}$ 6.2, H_3-6′), 1.58 (1H, ddd, J_{gem} 14.3, $J_{4'A,3'}$ 7.1 or 2.2 and $J_{4'A,5'}$ 2.2 or 7.1, H-4′^{A}), 1.78–1.94 (1H, m, H-4′^{B}), 2.72 (1H, dd, J_{gem} 13.6 and *J* 9.9, CHCH^APh), 2.83 (1H, d, *J* 6.2, OH), 3.27 (1H, dd, J_{gem} 13.6 and *J* 3.3, CHCH^BPh), 4.09–4.28 (4H, m, H_2-5, H-3′, -5′), 4.54 (1H, d, J_{gem} 11.7, OCH^APh), 4.63–4.78 (1H, m, H-4), 4.75 (1H, d, J_{gem} 11.7, OCH^BPh), 5.17 (1H, d, $J_{2',3'}$ 2.9, H-2′) and 7.19–7.42 (10H, m, Ph); δ_C (50 MHz; $CDCl_3$) −5.2, −4.5 (CH_3, $SiMe_2$), 17.9 (quat, *C*Me$_3$), 23.4 (CH_3, C-6′), 25.7 (CH_3, C*Me*$_3$), 37.5 (CH_2, CH*C*H_2Ph), 42.0 (CH_2, C-4′), 55.6 (CH, C-4), 65.9 (CH, C-5′), 66.7 (CH_2, C-5), 69.1 (CH, C-3′), 72.9 (CH_2, O*C*H_2Ph), 79.9 (CH, C-2′), 127.3, 128.0, 128.3(2), 128.9, 129.3 [CH, 2 × Ph (last 4 peaks coincidental)], 135.1 (quat, $CHCH_2$-*Ph*), 137.1 (quat, OCH_2*Ph*), 153.2 (quat, C-2) and 170.6 (quat, C-1′); *m/z* (LSIMS, NBA matrix) 528 (MH^+, 19%), 470 (M − C_4H_9, 5), 396 (M − $C_6H_{16}OSi$, 15), 286 (13), 268 (8), 178 ($C_{10}H_{12}NO_2$, 11), 159 ($C_8H_{19}OSi$, 7), 117 (9), 91 (CH_2Ph, 100), 75 [$(CH_3)_2SiOH$, 13] and 73 (21). Upon prolonged refrigeration at approximately 2 °C the oil formed a white solid (needles), mp 68.0–71.0 °C.

(4*R*,2′*R*,3′*R*,5′*R*)-3-[5-(*tert*-Butyldimethylsilyloxy)-2-(phenylmethoxy)-3-(triethylsilyloxy)hexanoyl]-4-(phenylmethyl)oxazolidin-2-one 10

To a solution of alcohol **8** (2.71 g, 5.15 mmol) in dry DMF (5.55 ml) at 0 °C under an atmosphere of nitrogen were added imidazole (1.40 g, 20.6 mmol) and triethylsilyl chloride (1.30 ml, 7.72 mmol). The resultant solution was allowed to reach room temperature and was stirred overnight. The reaction mixture was poured into ether (200 ml), washed successively with water (3 × 50 ml) and brine (50 ml), then dried over sodium sulfate. Removal of the solvent at reduced pressure afforded a pale yellow oil that was purified by flash chromatography using hexane–ethyl acetate (4:1) as eluent to give the *title compound* **10** (2.74 g, 84%) as a colourless oil (Found: C, 65.4; H, 8.4; N, 2.1. $C_{35}H_{55}NO_6Si_2$ requires C, 65.5; H, 8.6; N, 2.2%); $[\alpha]_D$ −43.75 (*c* 1.408, $CHCl_3$); ν_{max} (film)/cm^{-1} 1784s (O*C*=*O*N), 1709s (N*C*=*O*C), 1388br s (C–N) and 1116br s (C–O); δ_H (200 MHz; $CDCl_3$) 0.01, 0.06 (6H, s, $SiMe_2$), 0.58 [6H, q, *J* 7.9, Si(CH_2CH$_3$)$_3$], 0.88 (9H, s, Bu^t), 0.92 [9H, t, *J* 7.9, Si(CH_2-CH_3)$_3$], 1.13 (3H, d, $J_{6',5'}$ 5.9, H_3-6′), 1.71–1.93 (2H, m, H_2-4′), 2.55 (1H, dd, J_{gem} 13.4 and *J* 9.9, CHCH^APh), 3.13 (1H, dd, J_{gem} 13.4 and *J* 3.3, CHCH^BPh), 4.00–4.16 (4H, m, H_2-5, H-3′, -5′), 4.51–4.67 (3H, m, H-4, OCH_2Ph), 5.40 (1H, d, $J_{2',3'}$ 7.0, H-2′) and 7.16–7.43 (10H, m, Ph); δ_C (50 MHz; $CDCl_3$) −4.6, −4.5 (CH_3, $SiMe_2$), 5.0 (CH_2, CH_3CH_2Si), 6.8 (CH_3, *C*H$_3$-CH_2Si), 18.1 (quat, *C*Me$_3$), 23.5 (CH_3, C-6′), 25.9 (CH_3, C*Me*$_3$), 37.9 (CH_2, CH*C*H_2Ph), 46.0 (CH_2, C-4′), 55.6 (CH, C-4), 65.7 (CH, C-5′), 66.1 (CH_2, C-5), 70.9 (CH, C-3′), 73.2 (CH_2, O*C*H_2Ph), 80.9 (CH, C-2′), 127.3, 127.9, 128.3, 128.5, 129.0, 129.4 [CH, 2 × Ph (last 4 peaks coincidental)], 135.3 (quat, $CHCH_2$*Ph*), 137.5 (quat, OCH_2*Ph*), 153.2 (quat, C-2) and 172.2 (quat, C-1′); *m/z* (LSIMS, NBA matrix) 642 (M^+, 4%), 612 (7), 584 (M − C_4H_{10}, 5), 510 (M − $C_6H_{16}OSi$, 9), 418 (5), 286 (6), 268 (8), 185 (7), 159 ($C_8H_{19}OSi$, 35), 115 (22), 91 (CH_2Ph, 100), 73 (47) and 59 (13).

(2*S*,3*R*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-2-(phenylmethoxy)-3-(triethylsilyloxy)hexan-1-ol 11

To a solution of oxazolidinone **10** (2.96 g, 4.67 mmol) in dry THF (185 ml) at 0 °C under an atmosphere of nitrogen was added portionwise, over a period of 2 min, lithium borohydride (216 mg, 9.82 mmol). The solution was allowed to reach room temperature and was stirred for 5 h, then quenched by the addition of water (10 ml). After 10 min the reaction mixture was poured into ether (346 ml), washed successively with water (103 ml) and brine (103 ml), and dried over sodium sulfate. Removal of the solvent at reduced pressure gave a clear oil that upon purification by flash chromatography, using hexane–ethyl acetate (4:1) as eluent, gave the *title compound* **11** (1.79 g, 82%) as a colourless oil (Found: C, 63.8; H, 10.35. $C_{25}H_{48}O_4Si_2$ requires C, 64.05; H, 10.3%); $[\alpha]_D$ −10.53 (*c* 1.906, $CHCl_3$); ν_{max} (film)/cm^{-1} 3659–3167m (OH) and 1087br s (C–O); δ_H (200 MHz; $CDCl_3$) 0.06 (6H, s, $SiMe_2$), 0.65 [6H, q, *J* 7.7, Si(CH_2-CH_3)$_3$], 0.90 (9H, s, Bu^t), 0.98 [9H, t, *J* 7.7, Si(CH_2CH_3)$_3$], 1.15 (3H, d, $J_{6,5}$ 6.1, H_3-6), 1.58–1.86 (2H, m, H_2-4), 2.51–2.69 (1H, br s, OH), 3.44–3.50 (1H, m, H-2), 3.80 (2H, br s, H-1), 3.89–4.04 (1H, m, H-5), 4.04–4.19 (1H, m, H-3), 4.62 (1H, d, J_{gem} 11.5, OCH^APh), 4.70 (1H, d, J_{gem} 11.5, OCH^BPh) and 7.26–7.46 (5H, m, Ph); δ_C (50 MHz; $CDCl_3$) −4.6, −4.4 (CH_3, $SiMe_2$), 4.9 (CH_2, CH_3CH_2Si), 6.9 (CH_3, *C*H$_3$CH$_2$Si), 18.0 (quat, *C*Me$_3$), 23.9 (CH_3, C-6), 25.9 (CH_3, C*Me*$_3$), 44.6 (CH_2, C-4), 61.1 (CH_2, C-1), 65.7 (CH, C-5), 71.0 (CH, C-3), 71.8 (CH_2, O*C*H_2Ph), 81.6 (CH, C-2), 127.6, 127.8, 128.3 [CH, Ph (last 2 peaks coincidental)] and 138.4 (quat, OCH_2*Ph*); *m/z* (LSIMS, NBA matrix) 469 (MH^+, 6%), 411 (M − C_4H_9, 2), 337 (MH − $C_8H_{19}OSi$, 9), 245 (11), 159 ($C_8H_{19}OSi$, 30), 115 (13), 91 (CH_2Ph, 100), 73 (31) and 59 (9).

Auxiliary **4** (621 mg, 75%) was also recovered from the reaction.

(2*R*,3*R*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-2-(phenylmethoxy)-3-(triethylsilyloxy)hexanal 12

To a mixture of alcohol **11** (95.7 mg, 0.20 mmol), NMO (35.9 mg, 0.31 mmol) and powdered 4 Å molecular sieves (110 mg) in dichloromethane (0.54 ml) at 0 °C under an atmosphere of nitrogen was added TPAP (3.60 mg, 5 mol%). The reaction mixture was allowed to warm to room temperature and stirred for 4 h. Filtration of the reaction mixture through a silica gel pad and removal of the solvent at reduced pressure afforded a clear oil. Purification by flash chromatography using hexane–ethyl acetate (4:1) as eluent gave the *title compound* **12** (76.1 mg, 80%) as a colourless oil (Found: C, 64.4; H, 9.7. $C_{25}H_{46}O_4Si_2$ requires C, 64.3; H, 9.9%); $[\alpha]_D$ +14.64 (*c* 1.152, $CHCl_3$); ν_{max} (film)/cm^{-1} 2737w, 2703w (*H*–*C*=O), 1736s (C=O) and 1109br s (C–O); δ_H (200 MHz; $CDCl_3$) 0.02, 0.03 (6H, s, $SiMe_2$), 0.60 [6H, q, *J* 7.9, Si(CH_2CH$_3$)$_3$], 0.87 (9H, s, Bu^t), 0.94 [9H, t, *J* 7.9, Si(CH_2CH_3)$_3$], 1.12 (3H, d, $J_{6,5}$ 6.2, H_3-6), 1.58–1.85 (2H, m, H_4-4), 3.73 (1H, dd, $J_{2,1}$ 2.6 and $J_{2,3}$ 2.6, H-2), 3.86–4.01 (1H, m, H-5), 4.13–4.24 (1H, m, H-3), 4.59 (1H, d, J_{gem} 11.6, OCH^APh), 4.65 (1H, d, J_{gem} 11.6, OCH^BPh), 7.27–7.39 (5H, m, Ph) and 9.69 (1H, d, $J_{1,2}$ 2.6, H-1); δ_C (50 MHz; $CDCl_3$) −4.7, −4.4 (CH_3, $SiMe_2$), 4.9 (CH_2, CH_3CH_2Si), 6.8 (CH_3, *C*H$_3$CH$_2$Si), 18.0 (quat, *C*Me$_3$), 23.9 (CH_3, C-6), 25.8 (CH_3, C*Me*$_3$), 44.1 (CH_2, C-4), 65.5 (CH, C-5), 71.5 (CH, C-3), 72.7 (CH_2, O*C*H_2Ph), 86.2 (CH, C-2), 127.9, 128.4 [CH, Ph (2 and 3 peaks coincidental respectively)], 137.4 (quat, OCH_2*Ph*) and 204.0 (CH, C-1); *m/z* (CI) 484 ($MH^+ + NH_3$, 1%), 467 (MH^+, 11), 335 (MH − $C_6H_{16}OSi$, 100), 235 (15), 215 (11), 203 (24), 159 ($C_8H_{19}OSi$, 75), 132 ($C_6H_{16}OSi$, 63), 120 (13), 108 (20), 91 (CH_2Ph, 80) and 74 (12).

2-Bromo-4,8-dimethoxy-1-naphthol 22

A solution of bromine (191 mg, 1.20 mmol) in tetrachloromethane (3.7 ml) was added dropwise to a solution of 4,8-dimethoxy-1-naphthol **21**[23] (243 mg, 1.19 mmol) in tetrachloromethane (10.1 ml). After 30 min, aq. sodium thiosulfate (12.7 ml; 10% w/v) was added and the resultant mixture stirred for 10 min. The reaction mixture was then poured into aq.

sodium thiosulfate (38 ml; 10% w/v) and extracted with dichloromethane (3 × 25 ml). The combined organic fractions were washed successively with aq. sodium thiosulfate (25 ml; 10% w/v), water (2 × 50 ml) and brine (50 ml), dried over sodium sulfate, and the solvent removed under reduced pressure. Purification by flash chromatography using hexane–ethyl acetate (8:2) as eluent afforded the title compound **22** (243 mg, 72%) as colourless needles, mp 141.0–143.0 °C (decomp.) [lit.,[26] 141–142 °C (decomp.)].

2-Bromo-1,4,8-trimethoxynaphthalene 23

To 2-bromo-1,4,8-dimethoxy-1-naphthol **22** (300 mg, 1.06 mmol), dimethyl sulfoxide (DMSO) (0.5 ml) and THF (1.0 ml) at 0 °C was added, with stirring, dimethyl sulfate (0.15 ml, 2.12 mmol). After 10 min, aq. potassium hydroxide (238 mg, 4.24 mmol in 0.3 ml) was added dropwise and the resultant purple solution stirred for 1 h at 0 °C, then stirred for a further 2 h upon reaching room temperature. The mixture was poured into ethyl acetate (20 ml), washed with water (3 × 4 ml) and dried over sodium sulfate. Removal of the solvent under reduced pressure and purification of the residue by flash chromatography, using hexane–ethyl acetate (95:5) as eluent, gave the title compound **23** (214 mg, 68%) as a white crystalline solid, mp 84.0–85.5 °C (lit.,[27] 85–87 °C); ν_{max} ($CHCl_3$)/cm^{-1} 1074s (C–O); δ_C (50 MHz; $CDCl_3$) 56.0, 56.1 (CH_3, 1-, 4- or 8-OMe), 61.4 (CH_3, 4- or 1-OMe), 107.7, 108.7 (CH, C-3, -7), 113.9 (quat, C-2), 114.7 (CH, C-5), 120.9 (quat, C-8a), 125.8 (CH, C-6), 127.9 (quat, C-4a), 146.4, 151.5 (quat, C-1, C-4) and 156.1 (quat, C-8); *m/z* (EI) 298 [M^+(^{81}Br), 100%], 296 [M^+(^{79}Br), 100], 283 [M^+(^{81}Br) − CH_3, 34], 281 [M^+(^{79}Br) − CH_3, 34], 202 (92 and 187 (51). The ^{1}H NMR spectrum was in agreement with that reported in the literature.[28]

Dianion reaction of naphthol 22 with aldehyde 12

To 2-bromo-4,8-dimethoxy-1-naphthol **22** (6.5 mg, 0.0231 mmol) as a solution in dry THF (0.25 ml) at −78 °C under nitrogen was added *n*-butyllithium (2.45 M; 22 μl, 0.0462 mmol). After precisely 85 s, a solution of aldehyde **12** (10.8 mg, 0.0231 mmol) in THF (0.1 ml) was added and the solution stirred at −78 °C for 15 min. The reaction mixture was allowed to warm to room temperature and was stirred for 72 h, then quenched by the addition of saturated aq. ammonium chloride (0.5 ml) and ether (2 ml). The mixture was poured into ether (20 ml) and washed with water (5 ml). The aqueous phase was extracted with ether (2 × 10 ml) and the combined extracts were washed with brine (10 ml) and dried over sodium sulfate. Evaporation of the solution under reduced pressure gave a yellow oil that was purified by flash chromatography, using hexane–ethyl acetate (4:1) as eluent to afford:

(i) 4,8-dimethoxy-1-naphthol **21** (3.4 mg, 73%).

(ii) aldehyde **25** (2.6 mg, 24%) as a clear oil; ν_{max} (film)/cm^{-1} 3013–3106br w (Ar–H), 2739, 2718w (*H*–*C*=O), 1691s (C=O) and 1631m (C=C); δ_H (200 MHz; $CDCl_3$) 0.01, 0.02 (each 3H, s, $SiMe_2$), 0.87 (9H, s, Bu^t), 1.08 (3H, d, *J* 6.1, Me), 2.31–2.42 (2H, m, H_3-4), 3.69–3.86 (1H, m, H-5), 5.05 (2H, s, OCH_2Ph), 6.10 (1H, dd, $J_{3,4A}$ 7.3 and $J_{3,4B}$ 7.3, H-3), 7.23–7.42 (5H, m, Ph) and 9.26 (1H, s, H-1); *m/z* (EI) 159 [–CH(Me)(OTBDMS), 29%], 149 [=C(CHO)(OCH$_2$Ph)H, 30], 91 (CH_2Ph, 100), 57 (Bu^t, 80) and 43 (CH_3CO, 83).

Trichlorotitanium isopropoxide[29]

A solution of isopropyl alcohol (1.09 g, 18.2 mmol) in dichloromethane (30 ml) was added to a solution of titanium tetrachloride (3.45 g, 18.2 mmol) in dichloromethane (40 ml) at 0 °C under an atmosphere of nitrogen and the reaction mixture was stirred for 5 min. The solvent was removed under reduced pressure and the residue sublimed to yield trichlorotitanium isopropoxide (2.76 g, 71%) as a highly hygroscopic yellow solid.

Titanium nachtholate coupling

A solution of 4,8-dimethoxy-1-naphthol **21** (0.39 g, 1.89 mmol) in dichloromethane (4.7 ml) was added to a solution of trichlorotitanium isopropoxide (0.60 g, 2.83 mmol) in dichloromethane (3.9 ml) at 0 °C under an atmosphere of nitrogen. After 5 min, the resultant solution was added to a solution of aldehyde **12** (0.88 g, 1.89 mmol) in dichloromethane (4.2 ml) at 0 °C. The reaction mixture was stirred for 9 min, then quenched with aq. sodium dihydrogen phosphate (5.5 ml; 10%) and partitioned between dichloromethane (110 ml) and water (50 ml). The aqueous layer was extracted with dichloromethane (2 × 110 ml). The combined organic layers were dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue purified by flash chromatography using hexane–ethyl acetate (7:3) as eluent to yield:

(i) *(2′S,3′R,5′R)-2-[5-(tert-butyldimethylsilyloxy)-1-hydroxy-2-(phenylmethoxy)-3-(triethylsilyloxy)hexyl]-4,8-dimethoxy-1-naphthol* **27** (114 mg, 9%) as a yellow oil (Found: M^+, 670.3721. $C_{37}H_{58}O_7Si_2$ requires *M*, 670.3720); $[\alpha]_D$ −5.817 (*c* 1.090, $CHCl_3$); ν_{max} (film)/cm^{-1} 3399br w (OH), 2954s (C–H), 1609m (C=C) and 1070s (C–O); δ_H (400 MHz; $CDCl_3$) 0.11, 0.12 (6H, s, $SiMe_2$), 0.60 [6H, q, *J* 8.0, Si(CH_2CH_3)$_3$], 0.91 (9H, s, Bu^t), 0.94 [9H, t, *J* 8.0, Si(CH_2CH_3)$_3$], 1.20 (3H, d, $J_{6′,5′}$ 6.0, H_3-6′), 1.92–2.02 (2H, m, H_2-4′), 3.83 (1H, dd, $J_{2′,1′}$ 4.0 and $J_{2′,3′}$ 2.5, H-2′), 3.93 (3H, s, OMe), 3.99 (1H, br s, OH), 4.04 (3H, s, OMe), 4.07–4.12 (2H, m, H-3′, -5′), 4.21 (1H, d, J_{gem} 11.0, H-1″^{A}), 4.66 (1H, d, J_{gem} 11.0, H-1″^{B}), 5.47 (1H, d, $J_{1′,2′}$ 4.0, H-1′), 6.84 (1H, dd, $J_{6,7}$ 7.7 and J_5 0.6, H-7), 7.19–7.38 (6H, m, H-3, Ph), 7.32 (1H, dd, $J_{6,5}$ 8.5 and $J_{7,6}$ 7.7, H-6), 7.88 (1H, dd, $J_{5,6}$ 8.5 and $J_{5,7}$ 0.6, H-5) and 9.20 (1H, s, OH); δ_C (100 MHz; $CDCl_3$) −3.9, −3.5 (CH_3, $SiMe_2$), 5.6 (CH_2, CH_3CH_2Si), 7.5 (CH_3, CH_3CH_2Si), 18.8 (quat, CMe_3), 24.6 (CH_3, C-6′), 26.6 (CH_3, CMe_3), 44.7 (CH_2, C-4′), 56.5, 56.8 (CH_3, 2 × OMe), 66.6, 68.2 (CH, C-1′, -5′), 72.7 (CH, C-3′), 74.6 (CH_2, C-1″), 84.4 (CH, C-2′), 105.8 (CH, C-3), 106.3 (CH, C-7), 115.8 (quat, C-2), 116.7 (CH, C-5), 122.4 (quat, C-8a), 125.3 (CH, C-6), 128.0 (quat, C-4a), 128.5, 128.6, 128.8 [CH, Ph (last 2 peaks coincidental)], 139.2 (quat, OCH_2Ph) and 144.4, 148.6, 156.7 (quat, C-1, -4, -8); *m/z* (EI) 670 (M^+, 10%), 652 (M − H_2O, 2), 540 ($C_{31}H_{44}O_6Si$, 25), 520 (M − $C_6H_{18}O_2Si$, 5), 336 ($C_{21}H_{20}O_4$, 9), 317 ($C_{16}H_{37}O_2Si_2$, 15), 275 ($C_{16}H_{19}O_4$, 10), 245 ($C_{14}H_{13}O_4$, 8), 232 ($C_{13}H_{12}O_4$, 48), 159 ($C_8H_{19}OSi$, 24), 145 ($CH_2OSiMe_2Bu^t$, 9) and 91 (CH_2Ph, 100).

(ii) *(2′S,3′R,5′R)-2-[5-(tert-Butyldimethylsilyloxy)-1,3-dihydroxy-2-(phenylmethoxy)hexyl]-4,8-dimethoxy-1-naphthol* **26** (463 mg, 44%) as a yellow oil (Found: C, 66.6; H, 8.0. $C_{31}H_{44}O_7Si$ requires C, 66.8; H, 8.0%); $[\alpha]_D$ −79.17 (*c* 0.192, $CHCl_3$); ν_{max} (film)/cm^{-1} 3396br m (OH), 2952m (C–H), 1606m (C=C) and 1068br s (C–O); δ_H (400 MHz; $CDCl_3$) 0.08, 0.10 (6H, s, $SiMe_2$), 0.89 (9H, s, Bu^t), 1.22 (3H, d, $J_{6′,5′}$ 6.0, H_3-6′), 1.79–1.86 (1H, m, H-4′^{A}), 1.87–2.01 (1H, m, H-4′^{B}), 3.71 (1H, dd, $J_{2′,1′}$ 3.9 and $J_{2′,3′}$ 3.9, H-2′), 3.86 (1H, br s, 1′-OH), 3.89, 3.97 (6H, s, 2 × OMe), 4.00–4.18 (3H, m, H-3′, H-5′, 3′-OH), 4.28 (1H, d, J_{gem} 11.3, H-1″^{A}), 4.52 (1H, d, J_{gem} 11.3, H-1″^{B}), 5.51 (1H, d, $J_{1′,2′}$ 3.9, H-1′), 6.80 (1H, dd, $J_{6,7}$ 7.7 and $J_{6,5}$ 0.7 Hz, H-7), 7.08–7.18 (6H, m, H-3, Ph), 7.27 (1H, dd, $J_{6,5}$ 8.6 and $J_{7,6}$ 7.7, H-6), 7.82 (1H, dd, $J_{5,6}$ 8.6 and $J_{5,7}$ 0.7, H-5) and 9.21 (1H, s, OH); δ_C (100 MHz; $CDCl_3$) −4.9, −4.1 (CH_3, $SiMe_2$), 17.8 (quat, CMe_3), 24.4 (CH_3, C-6′), 25.7 (CH_3, CMe_3), 41.7 (CH_2, C-4′), 55.7, 55.9 (CH_3, 2 × OMe), 67.2, 69.9, 72.3 (CH, C-1′, -5′, -3′), 74.1 (CH_2, C-1″), 83.6 (CH, C-2′), 104.7, 105.1 (CH, C-3, -7), 115.0 (quat, C-2), 115.8 (CH, C-5), 121.5 (quat, C-8a), 124.6 (CH, C-6), 127.1 (quat, C-4a), 127.4, 127.9, 128.0 [CH, Ph (last 2 peaks coincidental)], 138.1 (quat, OCH_2Ph) and 143.4, 147.8, 155.8 (quat, C-1, -4, -8); *m/z* (EI) 556 (M^+, 4%), 538 (M − H_2O, 4), 424 (M − $HOSiC_6H_{15}$, 47), 336 ($C_{21}H_{20}O_4$, 15), 245 (M − C_7H_8O − $C_{10}H_{23}O_2Si$, 50), 232 (M − $C_{18}H_{32}O_3Si$, 58), 217 ($C_{13}H_{13}O_3$, 31), 205 ($C_{12}H_{13}O_3$, 13), 131 ($OSiMe_2Bu^t$, 5) and 91 (CH_2Ph, 100).

(iii) *(2′S,3′R,5′R)-2,2″-[5-(tert-Butyldimethylsilyloxy)-3-hydroxy-2-(phenylmethoxy)hexane-1,1-diyl]bis-(4,8-dimethoxy-1-naphthol)* **28** (42 mg, 6%) as a pale brown solid (Found: C, 69.3; H, 7.4. $C_{43}H_{-54}O_9Si$ requires C, 69.5; H, 7.3%); $[a]_D$ −14.29 (*c* 0.364, $CHCl_3$); ν_{max} (film)/cm^{-1} 3395br s (OH), 2952, 2930, 2855s (C–H), 1608s (C=C), 1070br s (C–O); δ_H (400 MHz; $CDCl_3$) −0.18, −0.09 (6H, s, $SiMe_2$), 0.71 (9H, s, Bu′), 1.02 (3H, d, $J_{6',5'}$ 6.0, H_3-6′), 1.67–1.73 (1H, m, H-4′^{A}), 2.11–2.21 (1H, m, H-4′^{B}), 3.62, 3.74, 3.83, 3.90 (12H, s, 4 × OMe), 3.84–3.87 (1H, m, H-3′), 3.88 (1H, br s, OH), 3.91–3.94 (1H, m, H5′), 4.29 (1H, d, J_{gem} 11.6, OC*H*^{A}Ph), 4.39–4.42 (1H, m, H-2′), 4.69 (1H, d, J_{gem} 11.6, OC*H*^{B}Ph), 5.42 (1H, d, $J_{1',2'}$ 7.6, H-1′), 6.66, 6.68 (2H, d, $J_{6,7}$ 8.0 and $J_{6'',7''}$ 8.0, H-7, H-7″), 6.95 (1H, s, H-3 or H-3″), 6.96–7.17 (5H, m, Ph), 7.13–7.16 (2H, m, H-6 or H-6″), 7.40 (1H, s, H-3″ or -3), 7.65, 7.70 (2H, d, $J_{5,6}$ 8.6 and $J_{5'',6''}$ 8.6, H-5, H-5″) and 9.35, 9.43 (2H, s, 2 × OH); δ_C (100 MHz; $CDCl_3$) −5.0, −4.3 (CH_3, $SiMe_2$), 17.9 (quat, *C*Me$_3$), 24.2 (CH_3, C-6), 25.8 (CH_3, C*Me*$_3$), 38.4 (CH, C-1′), 41.3 (CH_2, C-4′), 55.7, 55.8, 55.9, 56.0 (CH_3, 4 × OMe), 65.8 (CH, C-5′), 73.2 (CH, C-3′), 74.4 (CH_2, O*C*H$_2$Ph), 85.3 (CH, C-2′), 104.8, 104.9 (CH, C-7, -7″), 108.2, 108.9 (CH, C-3, -3″), 115.5, 115.6 (quat, C-2, -2″), 115.7, 115.8 (CH, C-5, -5″), 122.0, 122.4 (quat, C-8a, -8a″), 124.4, 124.5 (CH, C-6, -6″), 126.7, 126.8 (quat, C-4a, -4a″), 126.9, 127.3, 127.8 [CH, Ph (last 2 peaks coincidental)], 139.3 (quat, OCH$_2$*Ph*), 144.6, 145.5 (quat, C-4, -4″), 147.3, 147.6 (quat, C-1, -1″) and 155.8 (quat, C-8, -8″); *m*/*z* (EI) 742 (M$^+$, 17%), 710 (M − CH_3OH, 2), 634 (M − HOC_7H_7, 2), 538 (M − $C_{12}H_{12}O_3$, 2), 419 ($C_{25}H_{23}O_6$, 100), 387 ($C_{24}H_{19}O_5$, 10), 159 ($C_8H_{19}OSi$, 6), 145 (CH_2OSiMe_2Bu', 5) and 91 (CH_2Ph, 29).

(2′*R*,3′*R*,5′*R*)-2-[5-(*tert*-Butyldimethylsilyloxy)-3-hydroxy-2-(phenylmethoxy)hexanoyl]-4,8-dimethoxy-1-naphthol 29

Manganese dioxide (130 mg, 1.50 mmol) was added to a solution of alcohol **26** (167 mg, 0.30 mmol) in dichloromethane (3 ml) and the reaction mixture was stirred for 5 h at room temperature under an atmosphere of nitrogen. The reaction mixture was filtered through Celite and the solvent removed under reduced pressure. The residue was purified by flash chromatography using hexane–ethyl acetate (8:2) as eluent to yield the *title compound* **29** (103 mg, 62%) as a bright yellow oil (Found: C, 66.8; H, 7.6. $C_{31}H_{42}O_7Si$ requires C, 67.1; H, 7.6%); $[a]_D$ +21.19 (*c* 0.800, $CHCl_3$); ν_{max} (film)/cm^{-1} 3494br w (OH), 2952, 2850m (C–H), 1616m (C=O), 1600m (C=C) and 1074s (C–O); δ_H (400 MHz; $CDCl_3$) 0.02, 0.04 (6H, s, $SiMe_2$), 0.83 (9H, s, Bu′), 1.15 (3H, d, $J_{6',5'}$ 6.0, H_3-6′), 1.78–1.80 (2H, m, H_2-4′), 3.90, 4.06 (6H, s, 2 × OMe), 4.00–4.05 (2H, m, H-5′, OH), 4.28–4.32 (1H, m, H-3′), 4.56 (1H, d, J_{gem} 11.7, H-1″^{A}), 4.75 (1H, d, J_{gem} 11.7, H-1″^{B}), 5.04 (1H, d, $J_{2',3'}$ 4.5, H-2′), 6.95 (1H, d, $J_{6,7}$ 8.0, H-7), 7.22 (1H, s, H-3), 7.24–7.38 (5H, m, Ph), 7.54 (1H, dd, $J_{7,6}$ 8.0 and $J_{6,5}$ 8.0, H-6), 7.83 (1H, dd, $J_{5,6}$ 8.0 and $J_{5,7}$ 0.7, H-5) and 12.90 (1H, br s, 1-OH); δ_C (100 MHz; $CDCl_3$) −5.0, −4.2 (CH_3, $SiMe_2$), 17.7 (quat, *C*Me$_3$), 24.2 (CH_3, C-6′), 25.7 (CH_3, C*Me*$_3$), 40.9 (CH_2, C-4′), 55.6, 56.2 (CH_3, 2 × OMe), 69.4, 72.1 (CH, C-5′, -3′), 72.4 (CH_2, C-1″), 85.7, 102.5, 107.0 (CH, C-2′, -3, -7), 114.4 (quat, C-2), 115.0 (CH, C-5), 116.1 (quat, C-8a), 127.6, 127.9, 128.2 [CH, Ph (last 2 peaks coincidental)], 129.8 (CH, C-6), 132.2, 137.7 (quat, C-4a, OCH$_2$*Ph*), 147.0, 156.9, 158.6 (quat, C-1, -4, -8) and 201.1 (quat, C-1′); *m*/*z* (EI) 554 (M$^+$, 3%), 445 (M − C_7H_9O, 2), 406 (M − $C_6H_{16}O_2Si$, 3), 352 ($C_{21}H_{20}O_5$, 24), 261 ($C_{14}H_{13}O_5$, 23), 246 ($C_{14}H_{14}O_4$, 11), 231 ($C_{13}H_{11}O_4$, 100), 205 ($C_{12}H_{13}O_3$, 11), 160 ($C_8H_{20}OSi$, 14), 145 (CH_2OSiMe_2Bu', 57), 131 ($C_6H_{15}OSi$, 9) and 91 (CH_2Ph, 89).

Acetylation of diol 29

Without using DMAP as a catalyst. To a solution of diol **29** (79 mg, 0.14 mmol) in dichloromethane (2.8 ml) was added acetic anhydride (0.067 ml, 0.71 mmol) followed by triethylamine (0.1 ml, 0.71 mmol) and the mixture was stirred at room temperature for 6 h. The solvent was removed at reduced pressure and the residue purified by flash chromatography, using hexane–ethyl acetate (9:1) then (4:1) as eluent to afford:

(i) *(2′R,3′R,5′R)-2-[3-Acetoxy-5-(tert-butyldimethylsilyloxy)-2-(phenylmethoxy)hexanoyl]-4,8-dimethoxy-1-naphthol* **31** (37 mg, 41%) as a fluorescent yellow oil (Found: C, 66.5; H, 7.5. $C_{33}H_{44}O_8Si$ requires C, 66.4; H, 7.4%); $[a]_D$ −14.10 (*c* 0.156, $CHCl_3$); ν_{max} (film)/cm^{-1} 3327br w (OH), 2955, 2855m (C–H), 1732s (C=O, acetate), 1626s (C=O), 1244br s (C–O, acetate) and 1074s (C–O); δ_H (200 MHz; $CDCl_3$) −0.20, −0.09 (6H, s, $SiMe_2$), 0.68 (9H, s, Bu′), 1.01 (3H, d, $J_{6',5'}$ 12.5, H_3-6′), 1.79 (1H, ddd, J_{gem} 14.7, $J_{4'A,5'}$ 6.2 and $J_{4'A,3'}$ 2.8, H-4′^{A}), 2.00 (3H, s, $OCOCH_3$), 2.03 (1H, ddd, J_{gem} 14.7, $J_{4'B,3'}$ 9.2 and $J_{4'B,5'}$ 2.8, H-4′^{B}), 3.78–3.81 (1H, m, H-5′), 3.98, 4.05 (6H, s, 2 × OMe), 4.38 (1H, d, J_{gem} 12.3, H-1″^{A}), 4.84 (1H, d, J_{gem} 12.3, H-1″^{B}), 5.21 (1H, d, $J_{2',3'}$ 2.8, H-2′), 5.40 (1H, ddd, $J_{3',4'B}$ 9.2, $J_{3',2'}$ 2.8 and $J_{3',4'A}$ 2.8, H-3′), 6.97 (1H, dd, $J_{6,7}$ 8.1 and $J_{7,5}$ 0.8, H-7), 7.30–7.36 (6H, m, H-3, Ph), 7.57 (1H, dd, $J_{7,6}$ 8.1 and $J_{6,5}$ 8.1, H-6), 7.82 (1H, dd, $J_{5,6}$ 8.1 and $J_{5,7}$ 0.8, H-5) and 14.20 (1H, s, OH); δ_C (50 MHz; $CDCl_3$) −5.2, −4.7 (CH_3, $SiMe_2$), 17.8 (quat, *C*Me$_3$), 21.1 (CH_3, CO*C*H$_3$), 23.1 (CH_3, C-6′), 25.5 (CH_3, C*Me*$_3$), 37.4 (CH_2, C-4′), 56.1, 56.3 (CH_3, 2 × OMe), 65.6 (CH, C-5′), 71.8 (CH, C-3′), 72.2 (CH_2, C-1″), 81.2 (CH, C-2′), 101.1 (CH, C-3), 107.5 (CH, C-7), 112.0 (quat, C-2), 114.7 (CH, C-5), 116.6 (quat, C-8a), 127.9, 128.0, 128.3 [CH, Ph (last 2 peaks coincidental)], 130.8 (CH, C-6), 133.1 (quat, C-4a), 137.5 (quat, OCH$_2$*Ph*), 147.2 (quat, C-4), 159.6, 160.0 (quat, C-1, -8), 170.7 (quat, C=O) and 200.3 (quat, C-1′); *m*/*z* (CI) 597 (MH$^+$, 3%), 566 (MH − $HOCH_3$, 1), 537 (MH − $HOCOCH_3$, 2), 465 (MH − $HOSiMe_2Bu'$, 2), 431 (MH − $C_9H_{10}O_3$, 5), 404 (M − $HOCOCH_3$ − $HOSiMe_2Bu'$, 4), 378 ($C_{23}H_{21}O_5$, 61), 300 (43), 279 (100), 219 ($C_{13}H_{15}O_3$, 30) and 205 ($C_{12}H_{13}O_3$, 32).

(ii) *(2′R,3′R,5′R)-2-[3-Acetoxy-5-(tert-butyldimethylsilyloxy)-2-(phenylmethoxy)hexanoyl]-4,8-dimethoxy-1-naphthyl acetate* **30** (23 mg, 25%) as a pale yellow oil (Found: M$^+$, 638.2928. $C_{35}H_{46}O_9Si$ requires M$^+$, 638.2911); $[a]_D$ −12.75 (*c* 1.992, $CHCl_3$); ν_{max} (film)/cm^{-1} 2930, 2856m (C–H), 1740s (C=O, acetate), 1618s (C=O), 1243, 1215br s (C–O, acetate) and 1073s (C–O); δ_H (400 MHz; $CDCl_3$) −0.08, −0.02 (6H, s, $SiMe_2$), 0.79 (9H, s, Bu′), 1.05 (3H, d, $J_{6',5'}$ 6.1 Hz, H_3-6′), 1.70–1.77 (1H, m, H-4′^{A}), 1.98 (3H, s, 3′-OCOCH$_3$), 2.01–2.08 (1H, m, H-4′^{B}), 2.35 (3H, s, 1-OCOCH$_3$), 3.80–3.82 (1H, m, H-5′), 3.97, 4.01 (6H, s, 2 × OMe), 4.50 (1H, d, J_{gem} 12.3, H-1″^{A}), 4.85 (1H, d, J_{gem} 12.3, H-1″^{B}), 5.00 (1H, d, $J_{2',3'}$ 3.2, H-2′), 5.20–5.27 (1H, m, H-3′), 6.95 (1H, dd, $J_{6,7}$ 8.0 and $J_{5,5}$ 0.7, H-7), 7.14 (1H, s, H-3), 7.31–7.38 (5H, m, Ph), 7.51 (1H, dd, $J_{7,6}$ 8.0 and $J_{6,5}$ 8.0, H-6) and 7.90 (1H, dd, $J_{5,6}$ 8.0 and $J_{5,7}$ 0.7, H-5); δ_C (50 MHz; $CDCl_3$) −5.2, −4.9 (CH_3, $SiMe_2$), 17.8 (quat, *C*Me$_3$), 20.1, 20.9 (CH_3, 2 × CO*C*H$_3$), 23.0 (CH_3, C-6′), 25.6 (CH_3, C*Me*$_3$), 38.4 (CH_2, C-4′), 55.8, 56.1 (CH_3, 2 × OMe), 65.6 (CH, C-5′), 71.5 (CH, C-3′), 72.3 (CH_2, C-1″), 81.5 (CH, C-2′), 102.4 (CH, C-3), 107.7 (CH, C-7), 114.7 (CH, C-5), 119.6 (quat, C-2), 125.4 (quat, C-8a), 127.8 (quat, C-4a), 128.0, 128.3, 128.4 [CH, Ph (last 2 peaks coincidental)], 130.2 (CH, C-6), 137.3 (quat, OCH$_2$*Ph*), 139.8 (quat, C-4), 152.8, 156.7 (quat, C-1, -8), 170.1, 170.3 (quat, 2 × C=O) and 197.2 (quat, C-1′); *m*/*z* (CI) 639 (MH$^+$, 19%), 507 (MH − $C_6H_{16}OSi$, 23), 337 ($C_{19}H_{33}O_3Si$, 6), 273 ($C_{16}H_{19}O_4$, 55), 231 ($C_{13}H_{11}O_4$, 15), 159 (C_8H_9OSi, 28), 143 ($C_7H_{15}OSi$, 66) and 107 (C_7H_7O, 100).

(iii) *(2′R,3′R,5′R)-2-[5-(tert-Butyldimethylsilyloxy)-3-hydroxy-2-(phenylmethoxy)hexanoyl]-4,8-dimethoxy-1-naphthyl acetate* **32** (18 mg, 20%) as a pale yellow oil (Found: M$^+$, 596.2821. $C_{33}H_{44}O_8Si$ requires *M*, 596.2805); $[a]_D$ −13.28 (*c* 0.256, $CHCl_3$); ν_{max} (film)/cm^{-1} 3496br w (OH), 2930, 2855m (C–H), 1766m (C=O, acetate), 1600m (C=O), 1265br s (C–O, acetate) and 1071s (C–O); δ_H (400 MHz; $CDCl_3$) 0.02, 0.04 (6H,

s, $SiMe_2$), 0.85 (9H, s, Bu^t), 1.13 (3H, d, $J_{6',5'}$ 5.9, H-6′), 1.11–1.73 (2H, m, H_2-4′), 2.28 (3H, s, $OCOCH_3$), 3.46 (1H, s, OH), 3.90, 3.91 (6H, s, 2 × OMe), 4.00–4.05 (1H, m, H-5′), 4.15–4.18 (1H, m, H-3′), 4.56 (1H, d, J_{gem} 11.8, H-1″^{A}), 4.70 (1H, d, $J_{2',3'}$ 4.6, H-2′), 4.73 (1H, d, J_{gem} 11.8, H-1″^{B}), 6.91 (1H, d, $J_{6,7}$ 8.0, H-7), 7.04 (1H, s, H-3), 7.23–7.32 (5H, m, Ph), 7.46 (1H, dd, $J_{7,6}$ 8.0 and $J_{6,5}$ 8.0, H-6) and 7.86 (1H, d, $J_{5,6}$ 8.0, H-5); δ_C (50 MHz; $CDCl_3$) −4.9, −4.0 (CH_3, $SiMe_2$), 17.9 (quat, *C*Me$_3$), 21.0 (CH_3, CO*C*H$_3$), 24.3 (CH_3, C-6′), 25.8 (CH_3, C*Me$_3$*), 40.7 (CH_2, C-4′), 55.8, 56.1 (CH_3, 2 × OMe), 69.5 (CH, C-5′), 71.9 (CH, C-3′), 72.6 (CH_2, C-1″), 85.9 (CH, C-2′), 102.8 (CH, C-3), 107.7 (CH, C-7), 114.9 (CH, C-5), 119.5 (quat, C-2), 127.3 (quat, C-4a, -8a), 127.8, 128.1, 128.4 [CH, Ph (last 2 peaks coincidental)], 130.1 (CH, C-6), 137.6 (quat, OCH$_2$*Ph*), 139.5 (quat, C-4), 152.7, 156.4 (quat, C-1, -8), 170.1 (quat, C=O) and 200.2 (quat, C-1′); *m*/*z* (EI) 596 (M^+, 2%), 554 ($C_{31}H_{42}O_7Si$, 1), 445 (M − HOC_7H_7 − $COCH_3$, 2), 352 ($C_{21}H_{20}O_5$, 3), 337 ($C_{19}H_{33}O_3Si$, 3), 273 ($C_{16}H_{17}O_4$, 10), 261 ($C_{14}H_{13}O_5$, 35), 248 ($C_{14}H_{16}O_4$, 18), 231 ($C_{13}H_{11}O_4$, 100), 217 ($C_{13}H_{13}O_3$, 10), 205 ($C_{12}H_{13}O_3$, 9), 159 ($C_8H_{19}OSi$, 19), 145 ($CH_2OSiMe_2Bu^t$, 54) and 91 (CH_2Ph, 72) and 57 (C_4H_9, 35).

Using DMAP as a catalyst. To a solution of diol **29** (11.5 mg, 0.021 mmol) in dichloromethane (0.42 ml) were added acetic anhydride (4.1 μl, 0.044 mmol), triethylamine (6.1 μl, 0.044 mmol) and a catalytic quantity of DMAP and the reaction mixture was stirred at room temperature for 5 min. Removal of the solvent under reduced pressure afforded a brown oil, which was purified by flash chromatography using hexane–ethyl acetate (4:1) as eluent to yield diacetate **30** (9.1 mg, 69%) as a pale yellow oil for which the ^{1}H NMR data were consistent with those reported above.

Deacetylation of acetate 32

To a suspension of guanidine hydrochloride (2.8 mg, 0.029 mmol) in dry ethanol (0.095 ml) was added potassium *tert*-butoxide (2.7 mg, 0.024 mmol) and the solution was stirred for 5 min at room temperature. To the mixture was added a solution of acetate **32** (14.3 mg, 0.024 mmol) in dichloromethane (0.2 ml). After 5 min, the reaction mixture was partitioned between water (5 ml) and dichloromethane (5 ml). The aqueous layer was extracted with dichloromethane (2 × 5 ml), and the combined organic layers washed with water (2 × 5 ml) and dried over sodium sulfate. Removal of the solvent under reduced pressure afforded a yellow oil, which was purified by flash chromatography using hexane–ethyl acetate (8:2) as eluent to afford acetate **31** (5.8 mg, 47%) as a fluorescent yellow oil for which the ^{1}H NMR spectrum was in agreement with that reported above.

(6b*R*,9a*R*,2′*R*,3′*R*,5′*R*)- and (6b*S*,9a*S*,2′*R*,3′*R*,5′*R*)-6-[3-Acetoxy-5-(*tert*-butyldimethylsilyloxy)-2-(phenylmethoxy)-hexanoyl]-9,9a-dihydro-5-hydroxy-4-methoxyfuro[3,2-*b*]-naphtho[2,1-*d*]furan-8(6b*H*)-one 34

A solution of CAN nitrate (161 mg, 0.29 mmol) in water (1.0 ml) was added dropwise to a vigorously stirred solution of naphthalene acetate **31** (70 mg, 0.12 mmol) in acetonitrile (7.4 ml) at room temperature and the mixture was stirred for exactly 1 min. Anhydrous magnesium sulfate was added and the resultant suspension was immediately cooled to 0 °C. After 1 min, a solution of 2-(trimethylsilyloxy)furan (0.039 ml, 0.23 mmol) in acetonitrile (1.2 ml) was added dropwise and the mixture was stirred at 0 °C for 15 min, diluted with dichloromethane (30 ml), washed with water (2 × 15 ml) and dried over magnesium sulfate. The solvent was removed under reduced pressure to give an orange oil, which was purified by flash chromatography using hexane–ethyl acetate (4:1) as eluent to afford the *title compound* (33 mg, 42%) as a yellow semi-solid and as a 1:1 (**34a**:**34b**) mixture of stereoisomers (^{1}H NMR) (Found: MH^+, 665.2756. $C_{36}H_{44}O_{10}Si$ requires *M*H, 665.2782); ν_{max} (film)/cm^{-1} 3320br w (OH), 2954, 2923m (C–H), 1778s (C=O, γ-lactone), 1741s (C=OCH$_3$) and 1668m (*C*=*O*CHOBn); δ_H (400 MHz; $CDCl_3$) −0.19, −0.08, −0.06*, −0.02* (6H, s, $SiMe_2$), 0.70, 0.78* (9H, s, Bu^t), 1.02, 1.05* (3H, d, $J_{6',5'}$ 6.1, H_3-6′), 1.72, 1.87* (1H, m, H-4′^{A}), 1.89, 1.98* (3H, s, $OCOCH_3$), 2.04–2.09 (1H, m, H-4′^{B}), 3.04–3.11 (2H, m, H_2-9), 3.71–3.77 (1H, m, H-5′), 4.11 (3H, s, OMe), 4.52, 4.58* (1H, d, J_{gem} 7.7, OC*H^A*Ph), 4.83, 4.90* (1H, d, J_{gem} 7.7, OC*H^B*Ph), 5.33, 5.45* (1H, d, $J_{2',3'}$ 4.0, H-2′), 5.36–5.56 (2H, m, H-3′, H-9a), 6.36, 6.69* (1H, d, $J_{6b,9a}$ 5.9, H-6b), 6.95–7.00 (1H, m, H-3), 7.26–7.52 (7H, m, H-1, -2, Ph) and 10.14, 10.31* (1H, s, OH); δ_C (50 MHz; $CDCl_3$) −4.9, −4.7, −4.6, −3.6 (CH_3, $SiMe_2$), 15.2, 18.0 (quat, *C*Me$_3$), 21.1, 21.2 (CH_3, CO*C*H$_3$), 23.1, 23.4 (CH_3, C-6′), 25.7 (CH_3, C*Me$_3$*), 35.7 (CH_2, C-9), 38.5, 39.8 (CH_2, C-4′), 56.7 (CH_3, OMe), 65.9, 66.1 (CH, C-5′), 71.1, 71.7 (CH, C-3′), 72.4, 72.7 (CH_2, O*C*H$_2$Ph), 81.4, 81.9 (CH, C-9a), 84.5, 84.8 (CH, C-2′), 85.2, 85.4 (CH, C-6b), 107.6 (quat, C-6), 107.7 (quat, C-6a), 116.2 (CH, C-3), 116.5 (CH, C-1), 124.9 (quat, C-4a), 127.5, 127.8, 128.2 [CH, Ph (last 2 peaks coincidental)], 128.4 (quat, C-10b), 129.4 (CH, C-2), 138.3 (quat, OCH$_2$*Ph*), 150.9 (quat, C-10a), 152.4, 152.6 (quat, C-5), 157.4, 157.9 (quat, C-4), 170.0, 170.1 (quat, *C*OCH$_3$), 174.2 (quat, C-8) and 198.5 (quat, C-1′); *m*/*z* (LSIMS, NBA matrix) 665 (MH^+, 33%), 619 (MH − CH_2O_2, 13), 533 (M − $C_6H_{15}OSi$, 12), 473 (M − $C_8H_{19}O_3Si$, 9), 389 (M − $C_{12}H_{23}O_5Si$, 15), 299 (MH − $C_{20}H_{34}O_4Si$, 100) and 255 (M − $C_{21}H_{33}O_6Si$, 18).

(3a*R*,5*R*,11b*R*,1′*R*,2′*R*,4′*R*)- or (3a*S*,5*S*,11b*S*,1′*R*,2′*R*,4′*R*)-5-[2-Acetoxy-4-hydroxy-1-(phenylmethoxy)pentyl]-3,3a,5,11b-tetrahydro-5-hydroxy-7-methoxyfuro[3,2-*b*]naphtho[2,3-*d*]-pyran-2,6,11-trione 35

A solution of CAN nitrate (39 mg, 0.070 mmol) in water (0.073 ml) was added dropwise to a solution of furonaphthofuran **34** (16 mg, 0.023 mmol) in acetonitrile (1.3 ml) at room temperature and the mixture was stirred for 45 s. Hydrofluoric acid (0.07 ml; 5% w/w) was then added dropwise and the mixture was stirred for 2 h. The reaction mixture was poured into ethyl acetate (5 ml), washed with water (2 × 3 ml) and dried over sodium sulfate. Removal of the solvent under reduced pressure gave a yellow oil, which was purified by flash chromatography using hexane–ethyl acetate (75:25) as eluent to give the *title compound* **35** (6.5 mg, 48%) as a yellow oil (Found: MH^+, 567.1854. $C_{30}H_{30}O_{11}$ requires *M*H, 567.1866); ν_{max} (film)/cm^{-1} 3446br w (OH), 2957–2924m (C–H), 1783s (C=O, γ-lactone), 1739s ($COCH_3$) and 1664m (C=O, quinone); δ_H (400 MHz; $CDCl_3$) 1.37 (3H, d, $J_{5',4'}$ 6.2, H-5′), 1.71–1.78 (1H, m, H-3′^{A}), 1.92–2.03 (1H, m, H-3′^{B}), 1.99 (3H, s, $OCOCH_3$), 2.68 (1H, d, J_{gem} 17.6, H-3^A), 2.99 (1H, dd, J_{gem} 17.6 and $J_{3B,3a}$ 5.0, H-3^B), 3.52 (1H, d, $J_{1',2'}$ 10.2, H-1′), 3.99 (3H, s, OMe), 4.22 (1H, ddd, $J_{2',3'A}$, 10.4, $J_{2',1'}$ 10.2 and $J_{2',3'B}$ 2.4, H-2′), 4.35 (1H, br s, OH), 4.73 (1H, d, J_{gem} 11.1, H-1″^{A}), 4.94 (1H, dd, $J_{3a,3B}$ 5.0 and $J_{3a,11b}$ 2.4, H-3a), 4.95 (1H, d, J_{gem} 11.1, H-1″^{B}), 5.03 (1H, br s, OH), 5.17–5.20 (1H, m, H-4′), 5.27 (1H, d, $J_{11b,3a}$ 2.4, H-11b), 7.24 (1H, d, $J_{8,9}$ 8.0, H-8), 7.33–7.39 (5H, m, Ph), 7.49 (1H, dd, $J_{9,8}$ 8.0 and $J_{9,10}$ 8.0, H-9) and 7.77 (1H, dd, $J_{10,9}$ 8.0 and $J_{10,8}$ 0.7, H-10); δ_C (100 MHz; $CDCl_3$) 14.8 (CH_3, C-5′), 19.4 (CH_3, CO*C*H$_3$), 37.4 (CH_2, C-3), 37.9 (CH_2, C-3′), 56.9 (CH_3, OMe), 66.0 (CH, C-2′), 67.9 (CH, C-3a), 68.7 (CH, C-4′), 69.9 (CH, C-11b), 76.7 (CH_2, C-1″), 83.8 (CH, C-1′), 91.1 (quat, C-5), 94.4 (quat, C-6a), 117.6 (CH, C-8), 119.8 (CH, C-10), 129.0 (quat, C-10a), 129.0, 129.1, 129.3 [CH, Ph (last 2 peaks coincidental)], 130.3 (quat, C-11a), 131.1 (CH, C-9), 137.5 (quat, OCH$_2$*Ph*), 147.3 (quat, C-5a), 157.4 (quat, C-7), 171.1 (quat, *C*OCH$_3$) and 175.0, 182.1, 188.3 (quat, C-2, -11, -6); *m*/*z* (CI) 584 ($MH^+ + NH_3$, 62%), 567 (MH^+, 16), 549 (M+NH_3 − OH − OH, 15), 524 (MH+NH_3 − $HOCOCH_3$, 3), 479 (M+NH_3 − $C_4H_8O_3$, 9), 296 (44) and 148 (100).

(3a*R*,5*R*,11b*R*,3′*S*,4′*R*,6′*R*)- and (3a*R*,5*S*,11b*R*,3′*S*,4′*R*,6′*R*)-4′-Acetoxy-3a,11b,3′,4′,5′,6′-hexahydro-7-methoxy-3′-(phenylmethoxy)-6′-methylspiro{5*H*-furo[3,2-*b*]naphtho[2,3-*d*]pyran-5,2′-[2*H*-pyran}-2,6,11(3*H*)-trione 36a and 36b

To a solution of furonaphthopyrantrione **35** (3.4 mg, 6.0 μmol) in dichloromethane (1 ml) was added a catalytic quantity of camphor-10-sulfonic acid (*ca.* 0.12 mg). The mixture was heated gently under reflux for 2 days. Removal of the solvent under reduced pressure gave a yellow oil, which was purified by flash chromatography using hexane–ethyl acetate (6:4) as eluent to give the *title compound* (1.7 mg, 52%) as a yellow oil and as a 3.2:1 (**36a**:**36b**¶) mixture of stereoisomers (^{1}H NMR) (Found: MH^+, 549.1747. $C_{30}H_{28}O_{10}$ requires *M*H, 549.1761); δ_H (400 MHz; $CDCl_3$) 1.37* (0.7H, d, *J* 5.8, Me), 1.42 (2.3H, d, (Found: MH^+, 549.1747. $C_{30}H_{28}O_{10}$ requires *M*H, 549.1761); δ_H (400 MHz; $CDCl_3$) 1.37* (0.7H, d, *J* 5.8, Me), 1.42 (2.3H, d, *J* 6.1, Me), 2.00, 2.03* (3H, s, $COCH_3$), 2.00–2.03 (1H, m, H-5′^{A}), 2.10–2.13 (1H, m, H-5′^{B}), 2.68* (0.24H, d, J_{gem} 17.6, H-3^A), 2.74 (0.76H d, J_{gem} 17.6, H-3^A), 3.00 (1H, dd, J_{gem} 17.6 and $J_{3B,3a}$ 4.9, H-3^B), 3.47 (0.76H, d, $J_{3',4'}$ 9.8, H-3′), 3.52* (0.24H, d, $J_{3',4'}$ 9.8, H-3′), 3.98, 4.00* (3H, s, OMe), 4.21–4.28 (1H, m, H-4′), 4.67 (0.76H, d, J_{gem} 11.3, OC*H*^{A}Ph), 4.68–4.70 (0.76H, m, H-3a), 4.74* (0.24H, d, J_{gem} 11.1, OC*H*^{A}Ph), 4.92 (0.76H, d, J_{gem} 11.3, OC*H*^{B}Ph), 4.94–4.96* (0.24H, m, H-3a), 4.95* (0.24H, d, J_{gem} 11.1, OC*H*^{B}Ph), 5.20–5.25 (1H, m, H-6′), 5.27* (0.24H, d, $J_{11b,3a}$ 2.8, H-11b), 5.31 (0.76H, d, $J_{11b,3a}$ 2.8, H-11b), 7.30–7.36 (6H, m, H-8, Ph), 7.47 (1H, t, $J_{9,8}$ 8.0 and $J_{9,10}$ 8.0, H-9) and 7.75 (1H, d, $J_{10,9}$ 8.0, H-10); *m/z* (FAB, NBA matrix) 549 (MH^+, 2%), 521 (MH − CO, 2), 489 (MH − $HOCOCH_3$, 2), 419 (9), 155 (73), 138 (100), 91 (CH_2Ph, 79), 78 (33).

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¶ The asterisk denotes resonances assigned to the minor isomer.

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