Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 63 (2007) 12123–12130

The synthesis of (−)-varitriol and (−)-3′-*epi*-varitriol via a Ramberg–Bäcklund route

Graeme D. McAllister, James E. Robinson and Richard J. K. Taylor*

Department of Chemistry, University of York, Heslington, York YO10 5DD, UK

Received 28 August 2007; revised 24 September 2007; accepted 25 September 2007

Abstract—A concise route to the anti-tumour natural product (−)-varitriol, together with its novel isomer (−)-3′-*epi*-varitriol, is described using a Horner–Wadsworth–Emmons (HWE)/conjugate addition/Ramberg–Bäcklund sequence as the cornerstone. The flexibility of the synthetic route has been demonstrated by the preparation of novel varitriol analogues.
© 2007 Elsevier Ltd. All rights reserved.

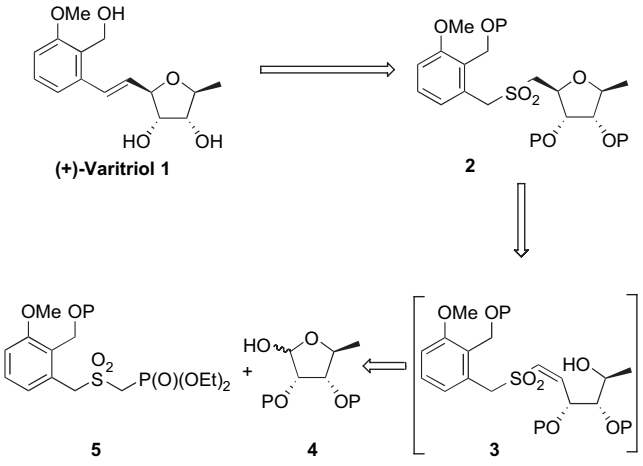
1. Introduction

(+)-Varitriol **1** was isolated from a marine-derived strain of the fungus *Emericella variecolor* and its structure reported by Malmstrøm et al. in 2002.[1] (+)-Varitriol **1** exhibits significant activity against a variety of tumours, most notably with selected renal, CNS and breast cancer cell lines, although its mode of action remains to be elucidated.[1,2]

In 2006 Jennings and Clemens reported the total synthesis of (−)-varitriol in approximately 14 steps from D-(−)-ribose utilising alkene metathesis to link together the carbohydrate and aromatic portions of the molecule.[3] This synthesis provided structural confirmation and established the absolute configuration of (+)-varitriol **1**.

2. Results and discussion

The combination of potent biological properties and a relatively straightforward molecular structure make the development of synthetic routes to varitriol and its analogues an enticing prospect with SAR studies in mind. We have an interest in the application of the Ramberg–Bäcklund reaction to the synthesis of biologically active compounds[4–6] and have recently reported its use for the preparation of stilbenoid anticancer agents such as combretastatin A-4, DMU-212 and novel synthetic analogues.[5] Given that we have also developed a Horner–Wadsworth–Emmons (HWE)/conjugate addition/Ramberg–Bäcklund sequence to prepare styrenyl *C*-glycosides,[6] it was hoped that this novel methodology could be applied to the synthesis of (+)-varitriol **1** as shown in Scheme 1.



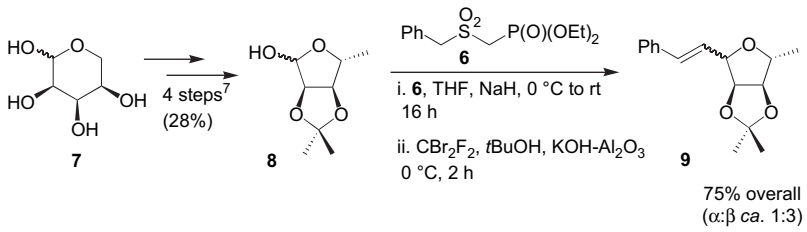
Scheme 1.

Thus, it was envisaged that HWE reaction between benzylsulfonyl phosphonate **5** and lactol **4** would transiently produce vinyl sulfone **3** which would give sulfone **2** after re-cyclisation. Ramberg–Bäcklund reaction of sulfone **2** should then lead to (+)-varitriol **1**. Indeed, the earlier studies had shown that in some cases it was possible to combine the Horner–Wadsworth–Emmons (HWE)/conjugate addition/Ramberg–Bäcklund sequence in a one-pot operation. Lactol **4** is accessible from L-(+)-ribose[7] but in view of its prohibitive cost the following studies utilised D-(−)-ribose, ultimately producing (−)-varitriol **1** (the same financial rationale was followed in the earlier[3] study).

This analysis prompted us to investigate the feasibility of the approach in a model study using the readily available benzylsulfonyl reagent **6**[6] (Scheme 2). The known lactol **8** was easily prepared from D-(−)-ribose **7** using a published[7]

* Corresponding author. Tel.: +44 1904 432606; e-mail: rjkt1@york.ac.uk

0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.09.057



Scheme 2.

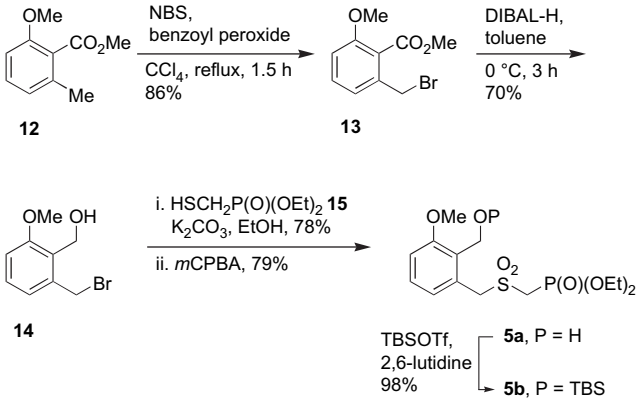
procedure involving acetonide formation, tosylation, iodide displacement and hydrogenolysis (28% overall yield, 32% in lit.[7]).

With the key components **6** and **8** in hand, the one-pot HWE/conjugate addition/Ramberg–Bäcklund reaction was carried out. Thus, sodium hydride was employed to generate the anionic HWE reagent from phosphonate **6** and then lactol **8** was added. After completion of the HWE/conjugate addition phase (16 h), the tandem halogenation/Ramberg–Bäcklund sequence was carried out in situ using the conditions devised by Chan et al.[8] (CF_2Br_2, ^{t}BuOH, KOH–Al_2O_3). We were delighted to observe that this one-pot procedure produced the desired styryl *C*-glycoside **9** cleanly in 75% yield as a separable mixture (**9α**:**9β** ca. 1:3) of α- and β-isomers [in this paper the α/β descriptors are employed to indicate the lower face (α) and the upper face (β) with the molecules drawn as illustrated—this is clearly seen in structures **11α** and **11β**]. The *trans*-alkene structure was confirmed by ^{1}H NMR spectroscopy (**9α**, *J* 15.9 Hz; **9β**, *J* 16.1 Hz). This approach had therefore furnished the non-natural β-styrenyl isomer as the major product. The thermodynamic preference for the 1,2-*cis*-relationship in 2,3-*O*-isopropylidene derivatives of furanosyl *C*-glycosides is well precedented.[6,9]

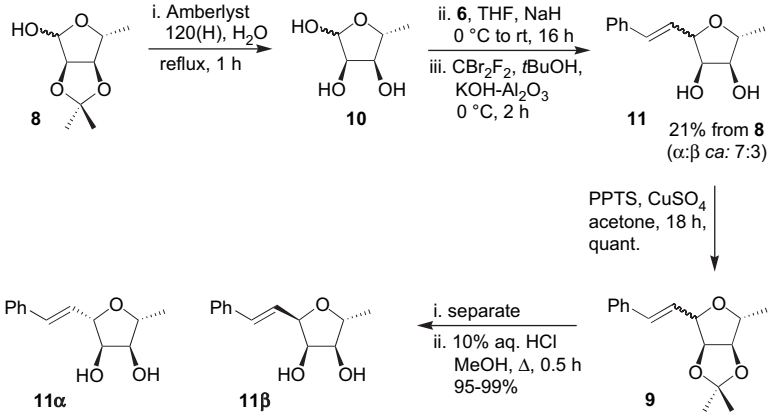
In an attempt to enhance the selectivity of the reaction for the required α-styrenyl substituent, the isopropylidene protecting group of lactol **8** was removed using Amberlyst 120(H) resin in water to give the corresponding diol lactol **10** (Scheme 3). Without purification, lactol **10** was subjected to the HWE/conjugate addition/Ramberg–Bäcklund sequence. The desired diols **11** were obtained as an inseparable mixture in an unoptimised 21% yield over the sequence of steps from acetonide **8**, gratifyingly with the required α-styrenyl derivative **11α** predominating (α:β ca. 7:3).

As **11α** and **11β** were inseparable, and as the NOE studies were inconclusive, the ratio was determined by conversion back to the corresponding isopropylidene derivatives **9** (Scheme 3). The isomers of **9** could be separated by chromatography and pure samples of **11α** and **11β** obtained by deprotection using dilute hydrochloric acid in methanol.

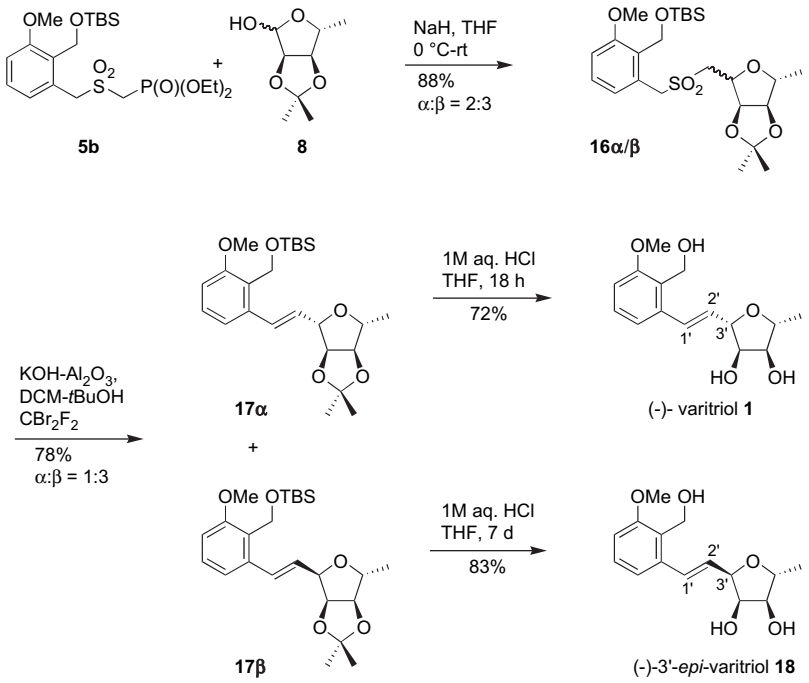
Having established the viability of the Ramberg–Bäcklund approach to prepare novel varitriol analogues, the next objective was to prepare the functionalised benzylsulfonyl reagent **5** needed for the synthesis of varitriol itself. Eventually, the route shown in Scheme 4 proved successful. Thus, the known[10] benzoate **12** was brominated under radical conditions and the product **13** was reduced to give bromo alcohol **14**. Treatment of compound **14** with phosphonylmethane thiol **15**,[11] followed by oxidation, gave the requisite HWE reagent **5a** in good yield (Scheme 4). This could easily be silylated to produce phosphonate **5b** in essentially quantitative yield.



Scheme 4.



Scheme 3.



Scheme 5.

The key one-pot HWE/RBR sequence was first carried out using unprotected phosphonate **5a** and lactol **8**. Unfortunately, this reaction proved to be capricious and furnished upon work-up a complex mixture of products none of which resembled by ^{1}H NMR spectroscopy the desired (−)-varitriol **1**. We therefore next investigated the sequential procedure using the silylated phosphonate **5b** (Scheme 5). Thus, reaction of compound **5b** and lactol **8** under standard HWE/conjugate addition conditions gave an inseparable mixture of sulfones **16α** and **16β** (α:β ca. 2:3). Ramberg–Bäcklund reaction of this mixture of sulfones gave an excellent yield of *trans*-alkene products **17α** and **17β** (α:β ca. 1:3) (Scheme 5). Fortunately, the two epimers could be separated by careful chromatography on silica. Global deprotection of each isomer using the published conditions[3,12] gave (−)-varitriol **1** and its 3′-epimer **18** in excellent yield. It is interesting to note that, while deprotection of **17α** was complete in 18 h, deprotection of its epimer **17β** took much longer to achieve completion (7 days).

We then went on to establish that the HWE/conjugate addition/Ramberg–Bäcklund sequence could be carried out as a one-pot operation with the protected phosphonate **5b** and lactol **8** (Scheme 6). However, despite producing alkenes **17** directly in reasonable overall yield, the stereo-control was again disappointing (α:β ca. 1:1.3).

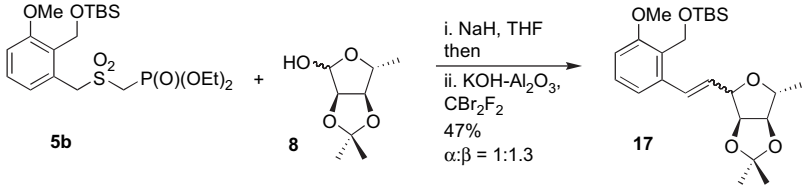
(−)-Varitriol **1** and (−)-3′-*epi*-varitriol **18** were fully characterised and were easily distinguishable by ^{1}H and ^{13}C NMR spectroscopy (Table 1).

Table 1. Key ^{1}H and ^{13}C NMR data comparison[a]

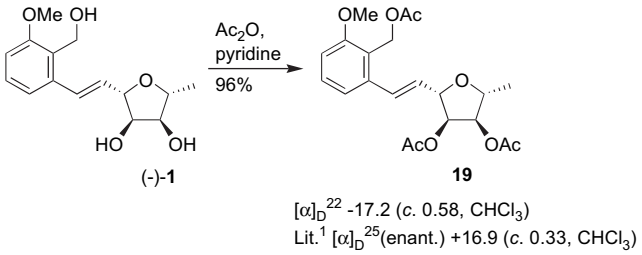
	Natural (+)-**1**[1]	Synthetic (−)-**1**	(−)-3′-*epi*-**18**
H-1′	δ 7.14 (d, *J* 15.8)	δ 7.12 (d, *J* 15.5)	δ 7.05 (d, *J* 15.5)
H-2′	δ 6.19 (dd, *J* 6.7, 15.8)	δ 6.20 (dd, *J* 6.8, 15.5)	δ 6.32 (dd, *J* 7.5, 15.5)
C-2′	δ 132.3	δ 132.4	δ 130.8
C-3′	δ 85.2	δ 85.3	δ 82.1

[a] All spectra were recorded in acetone-d_6. The spectra of natural (+)-**1** were obtained at 300 MHz (^{1}H) and 100 MHz (^{13}C).[1] The NMR data for synthetic (−)-**1** and **18** were obtained at 500 MHz (^{1}H) and 125 MHz (^{13}C).

The spectroscopic data for (−)-varitriol **1** closely matched those in the literature.[1,3] However, somewhat surprisingly, the measured $[\alpha]_D$ value for (−)-varitriol **1** was markedly different from those published {$[\alpha]_D$ −40.6 (*c* 1.6, MeOH), cf. lit.[1] (enant.) +18.5 (*c* 2.3, MeOH), lit.[3] −18.2 (*c* 3.3, MeOH)}. In order to clarify this issue, the known triacetate **19**, previously reported by Malmstrøm et al.,[1] was prepared (Scheme 7). We were delighted to observe that the specific rotation value for our peracetylated product agreed with that reported, thereby providing final confirmation for the authenticity of synthetic (−)-varitriol **1**.[13]



Scheme 6.



Scheme 7.

In summary, the Ramberg–Bäcklund reaction has been utilised as part of a short and flexible route to the anti-cancer natural product (−)-varitriol **1** and its novel 3′-epimer **18**. This route is operationally straightforward, and is considerably shorter (seven steps, 14% from D-ribose; three steps, 49% from lactol **8**) than the one previously reported.[3] We have also shown that this approach can be used in the synthesis of novel varitriol analogues. The low α/β-stereoselectivity observed is disappointing—but it does ensure rapid access to both 'anomeric' series, and this is useful in structure–activity studies.

3. Experimental

3.1. General details

All reagents were purchased from commercial sources and used without further purification. All reactions were carried out in oven-dried or flame-dried glassware under a nitrogen or argon atmosphere using standard syringe and septum techniques unless otherwise stated. Diethyl ether and THF were freshly distilled from sodium/benzophenone. Dichloromethane and dimethylformamide were dried using an MBraun Solvent Purification System. Thin layer chromatography was performed on precoated 0.2 mm Merck Kieselgel 60 F_{254} silica plates and compounds were visualised under 245 nm ultraviolet irradiation followed by staining in either alkaline potassium permanganate or ethanolic vanillin solution. Flash column chromatography was performed using Fluka Kieselgel 60 F (220–440 mesh) with the indicated solvents. Petroleum ether refers to the fractions with boiling range 40–60 °C.

Melting points were determined on a Gallenkamp melting point apparatus. Optical rotations were measured using a Jasco DIP 370 Digital Polarimeter at λ=598 nm and are given in 10^{-1} deg cm^2 g^{-1}. Infrared spectra were recorded with a ThermoNicolet IR100 spectrophotometer as thin films between sodium chloride plates. Absorption maxima are expressed in wavenumbers (cm^{-1}).

^{1}H and ^{13}C NMR spectra were obtained using either a JEOL 400 MHz spectrophotometer operating at either 400 MHz or 100 MHz or a Bruker AMX 500 spectrometer operating at 500 MHz or 125 MHz, respectively. Data are expressed in parts per million downfield shift from tetramethylsilane as an internal standard or relative to $CDCl_3$. All *J* values are given in hertz. Assignments are made with the aid of DEPT 135, COSY and HSQC experiments.

Mass spectra were recorded using a Fisons Analytical VG-Autospec spectrometer operating in chemical ionisation (CI), electron ionisation (EI) or fast atom bombardment (FAB) mode or on a Bruker Daltronics microTOF spectrometer operating in electrospray ionisation (ESI) mode.

Diethyl benzylsulfonylmethylphosphonate **6**,[6] lactol **8**,[7] benzoate **12**[10] and thiol **15**[11] were prepared by published methods.

3.1.1. (*E*)-2′-(4′,5′-*O*-Isopropylidene-7′-deoxy-D-ribofuranosyl)styrene 9. A solution of phosphonate **6**[6] (224 mg, 0.73 mmol) in THF (2.5 mL) was added to a stirred suspension of sodium hydride (19 mg, 0.80 mmol) in THF (2.5 mL) at 0 °C under an atmosphere of argon. After stirring for 15 min a solution of lactol **8**[7] (127 mg, 0.73 mmol) in THF (2.5 mL) was added and the mixture allowed to warm to rt. The mixture was stirred for 20 h before the addition of *tert*-butanol (2.92 mL). Potassium hydroxide on alumina[8] (1.46 g) was added and the suspension cooled to 0 °C before the addition of CBr_2F_2 (0.27 mL, 2.92 mmol). After stirring for 3 h, water (10 mL) was added and the aqueous layer extracted with diethyl ether (3×20 mL). The combined organic extracts were dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. The resultant residue was purified by careful flash column chromatography using pet. ether–EtOAc (9:1) to give *styrenes* **9α** (31 mg, 18% over two steps) and **9β** (109 mg, 57% over two steps) as colourless oils.

3.1.1.1. Minor (3′,4′)-*trans* isomer 9α (less polar isomer). R_f (7:3 pet. ether–EtOAc) 0.69; $[\alpha]_D^{20}$ −21.5 (*c* 0.89, $CHCl_3$); ν_{max}(film)/cm^{-1} 2980, 2931, 1599, 1493, 1450, 1375, 1210, 1157, 1078, 967, 863 and 746; δ_H (400 MHz, $CDCl_3$) 1.28 (3H, s, Me), 1.31 (3H, d, *J* 6.4, H7′), 1.51 (3H, s, Me), 3.97 (1H, qd, *J* 6.4 and 4.9, H6′), 4.27 (1H, dd, *J* 7.0 and 4.9, H5′), 4.37 (1H, app. t, *J* 6.4, H3′), 4.47 (1H, dd, *J* 7.0 and 4.9, H4′), 6.17 (1H, dd, *J* 15.9 and 6.7, H2′), 6.64 (1H, d, *J* 15.9, H1′), 7.16 (1H, t, *J* 7.1, H4), 7.24 (2H, t, *J* 7.1, H3) and 7.32 (2H, d, *J* 7.1, H2); δ_C (100 MHz, $CDCl_3$) 19.0 (C7′), 25.4 (C*Me*$_2$), 27.3 (C*Me*$_2$), 80.2 (C6′), 84.8 (C3′), 85.6 (C4′), 86.2 (C5′), 115.1 (*C*Me$_2$), 126.6 (C3), 127.0 (C2′), 127.8 (C4), 128.5 (C2), 132.5 (C1′) and 136.4 (C1); *m*/*z* (ESI): 261 (MH$^+$, 98%) and 203; HRMS (ESI): found MH$^+$, 261.1484. $C_{16}H_{21}O_3$ requires, 261.1485.

3.1.1.2. Major (3′,4′)-*cis* isomer 9β (more polar isomer). R_f (7:3 pet. ether–EtOAc) 0.57; $[\alpha]_D^{20}$ −21.5 (*c* 0.55, $CHCl_3$); ν_{max}(film)/cm^{-1} 2981, 2934, 1451, 1375, 1266, 1209, 1163, 1108, 1068, 969, 902, 862, 752 and 693; δ_H (400 MHz, $CDCl_3$) 1.12 (3H, d, *J* 7.0, H7′), 1.25 (3H, s, Me), 1.46 (3H, s, Me), 4.24 (1H, q, *J* 7.0, H4′), 4.39 (1H, dd, *J* 7.5 and 4.0, H3′), 4.44 (1H, dd, *J* 6.1 and 0.9, H5′), 4.66 (1H, dd, *J* 6.1 and 4.0, H4′), 6.28 (1H, dd, *J* 16.1 and 7.5, H2′), 6.62 (1H, d, *J* 16.1, H1′), 7.15 (1H, t, *J* 7.3, H4), 7.22 (2H, d, *J* 7.3, H3) and 7.34 (2H, *J* 7.3, H2); δ_C (100 MHz, $CDCl_3$) 17.0 (C7′), 24.9 (C*Me*$_2$), 26.2 (C*Me*$_2$), 79.5 (C6′), 80.3 (C3′), 82.8 (C4′), 86.5 (C5′), 112.4 (*C*Me$_2$), 124.0 (C2′), 126.7 (C3), 127.7 (C4), 128.4 (C2), 133.6 (C1′) and 136.6 (C1); *m*/*z* (ESI): 261 (MH$^+$, 36%), 259 and 203; HRMS (ESI): found MH$^+$, 261.1485. $C_{16}H_{21}O_3$ requires, 261.1485.

3.1.2. (*E*)-2′-(4′,5′-*O*-Isopropylidene-7′-deoxy-D-ribofuranosyl)styrene 11. (a) A mixture of lactol **8** (106 mg, 0.61 mmol) and Amberlyst 120(H) resin (catalytic amount)

in H_2O (2 mL) was heated to reflux for 1 h then cooled to rt. The reaction was filtered and the resin washed with H_2O (3×5 mL), then the solvent evaporated in vacuo and the residue dried by azeotrope with EtOH (3×10 mL). After drying under high vacuum for 4 h, crude lactol **10** (80 mg, 0.60 mmol, 98%) was obtained as colourless oil. This was used in the next step without further purification. A solution of phosphonate **6** (183 mg, 0.60 mmol) in *N*,*N*-dimethylformamide (3 mL) was added to a stirred suspension of sodium hydride (29 mg, 0.72 mmol) in *N*,*N*-dimethylformamide (4 mL) at 0 °C under an atmosphere of argon. After stirring for 0.5 h, a solution of diol lactol **10** (80 mg, 0.60 mmol) in *N*,*N*-dimethylformamide (3 mL) was added and the mixture allowed to warm to rt. The mixture was stirred for 16 h before the addition of *tert*-butanol (1.20 mL). Potassium hydroxide on alumina (1.20 g) was added and the suspension cooled to 0 °C before the addition of CBr_2F_2 (0.22 mL, 2.39 mmol). After stirring for 12 h, aqueous hydrochloric acid (10 mL, 10%) was added followed by CH_2Cl_2 (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3×20 mL) and the combined organic extracts dried over magnesium sulfate. Filtration and removal of the solvent under reduced pressure gave a residue that was purified by careful flash column chromatography using pet. ether–EtOAc (9:1–1:9) to give an inseparable mixture of isomers of *styrenes* **11** (28 mg, 21% over two steps) as a yellow oil; R_f (9:1 CH_2Cl_2–MeOH) 0.32; ν_{max}(film)/cm^{-1} 3368 (br) (OH), 2970, 2924, 1493, 1449, 1376, 1089s, 967, 898, 746 and 691; *m*/*z* (ESI): 243 (M+Na$^+$, 73%), 221 (MH, 100) and 177; HRMS (ESI): found MH$^+$, 221.1175. $C_{13}H_{17}O_3$ requires, 221.1172.

(b) Pure samples of the separated isomers **11α** and **11β** were obtained by separate hydrolyses of **9α** and **9β**.

3.1.2.1. Major (3′,4′)-*trans* isomer 11α. δ_H (400 MHz, $CDCl_3$) 1.29 (3H, d, *J* 6.4, H7′), 2.53 (1H, d, *J* 4.9, OH), 2.58 (1H, d, *J* 5.2, OH), 3.71 (1H, br q, *J* 4.9, H5′), 3.85 (1H, app. p, *J* 6.4, H6′), 3.89 (1H, br q, *J* 5.8, H4′), 4.24 (1H, ddd, *J* 6.1, 6.1 and 0.6, H3′), 6.14 (1H, dd, *J* 15.9 and 7.0, H2′), 6.63 (1H, d, *J* 15.9, H1′), 7.15–7.19 (1H, m, H4), 7.24 (2H, t, *J* 7.6, H2) and 7.30–7.35 (2H, m, H3); δ_C (100 MHz, $CDCl_3$) 19.0 (C7′), 75.5 (C4′), 76.1 (C5′), 79.7 (C6′), 84.1 (C3′), 126.6 (C3), 127.4 (C2′), 127.9 (C4), 128.5 (C2), 132.6 (C1′) and 136.3 (C1).

3.1.2.2. Minor (3′,4′)-*cis* isomer 11β. δ_H (400 MHz, $CDCl_3$) 1.27 (3H, d, *J* 6.4, H7′), 3.77–3.81 (1H, m, H5′), 3.94 (1H, dq, *J* 6.4 and 6.4, H6′), 4.12 (1H, br t, *J* 4.3, H4′), 4.62 (1H, ddd, *J* 6.7, 4.3 and 1.2, H3′), 6.25 (1H, dd, *J* 16.1 and 6.7, H2′), 6.62 (1H, d, *J* 16.1, H1′), 7.15–7.19 (1H, m, H4), 7.24 (2H, t, *J* 7.6, H2) and 7.30–7.35 (2H, m, H3); δ_C (100 MHz, $CDCl_3$) 18.8 (C7′), 73.4 (C4′), 77.9 (C6′), 78.6 (C5′), 80.7 (C3′), 124.6 (C2′), 126.7 (C2), 128.0 (C4), 128.6 (C3), 133.5 (C1′) and 136.2 (C1).

3.1.3. Methyl 2-(bromomethyl)-6-methoxybenzoate 13. A degassed mixture of benzoate **12**[10] (3.75 g, 20.81 mmol), *N*-bromosuccinimide (4.07 g, 22.89 mmol) and benzoyl peroxide (0.36 g, 1.04 mmol) in carbon tetrachloride (50 mL) was heated under reflux for 1.5 h. The mixture was allowed to cool to rt and saturated aqueous sodium hydrogen carbonate (30 mL) was added. The organic layer was washed with saturated aqueous sodium hydrogen carbonate (2×30 mL) and brine (2×30 mL), and dried over magnesium sulfate. Filtration and removal of the solvent under reduced pressure furnished a crude orange residue that was purified by flash column chromatography using pet. ether–diethyl ether (8:2) as the eluent to give *bromide* **13** (4.65 g, 86%) as an orange oil; R_f (1:1 pet. ether–Et_2O) 0.50; ν_{max}(film)/cm^{-1} 3006, 2949, 2840, 1728s (CO), 1588, 1471, 1435, 1272s, 1115, 1071, 959, 936 and 742; δ_H (400 MHz, $CDCl_3$) 3.82 (3H, s, OMe), 3.94 (3H, s, OMe), 4.48 (2H, s, CH_2Br), 6.88 (1H, dd, *J* 8.1 and 0.7, H3), 6.99 (1H, dd, *J* 8.1 and 0.7, H5) and 7.32 (1H, td, *J* 8.1 and 0.7, H4); δ_C (100 MHz, $CDCl_3$) 30.0 (CH_2Br), 52.5 (OMe), 56.1 (OMe), 111.5 (C5), 122.2 (C3), 123.1 (C1), 131.1 (C4), 136.5 (C2), 156.8 (C6) and 167.5 (CO_2Me); *m*/*z* (ESI): 281 (M[^{79}Br]+Na$^+$, 66%), 259 (MH, 100), 227 and 179; HRMS (ESI): found M[^{79}Br]H$^+$, 258.9966. $C_{10}H_{12}BrO_3$ requires, 258.9964.

3.1.4. 2-(Bromomethyl)-6-methoxybenzyl alcohol 14. To a stirred solution of ester **13** (4.65 g, 17.93 mmol) in toluene (45 mL) at 0 °C under an atmosphere of argon was added dropwise diisobutylaluminum hydride (1 M in toluene, 39.45 mL, 39.45 mmol). After stirring for 3 h, aqueous hydrochloric acid (10%) was cautiously added and the mixture allowed to warm to rt. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The combined organic extracts were dried over magnesium sulfate and the solvent removed under reduced pressure. Purification of the resultant residue by flash column chromatography using pet. ether–diethyl ether (7:3–1:1) as the eluent afforded *alcohol* **14** (2.92 g, 70%) as a colourless solid; mp 69–71 °C; R_f (1:1 pet. ether–Et_2O) 0.29; ν_{max}(film)/cm^{-1} 3364 (br) (OH), 2931, 2838, 1587, 1468, 1267, 1070, 1003 and 747; δ_H (400 MHz, $CDCl_3$) 3.81 (3H, s, OMe), 4.54 (2H, s, CH_2Br), 4.78 (2H, br s, CH_2O), 6.83 (1H, d, *J* 8.1, H3), 6.91 (1H, dd, *J* 8.1 and 0.9, H5) and 7.19 (1H, t, *J* 8.1, H4); δ_C (100 MHz, $CDCl_3$) 31.0 (CH_2Br), 55.7 (OMe), 56.6 (OMe), 111.3 (C5), 122.7 (C3), 127.7 (C1), 129.3 (C4), 137.4 (C2) and 158.4 (C6); *m*/*z* (ESI): 253 (M[^{79}Br]+Na$^+$, 12%), 230 and 213 (M-OH, 100); HRMS (ESI): found M[^{79}Br]+Na$^+$, 252.9840. $C_9H_{11}BrO_2Na$ requires, 252.9835.

3.1.5. Diethyl [(2-hydroxymethyl)-3-methoxybenzylsulfonyl]methylphosphonate 5a. (a) A solution of thiol **15**[11] (1.87 g, 10.14 mmol) in degassed ethanol (20 mL) was added dropwise to a stirred suspension of K_2CO_3 (1.54 g, 11.15 mmol) in degassed ethanol (10 mL) at 0 °C under an atmosphere of argon. To this mixture was added dropwise a solution of bromide **14** (2.34 g, 10.14 mmol) in degassed ethanol (20 mL). After stirring for 24 h the solvent was removed and the residue taken up in CH_2Cl_2 (50 mL). The mixture was acidified with dilute aqueous hydrochloric acid (10%) and the aqueous layer extracted with CH_2Cl_2 (4×50 mL). The combined organic extracts were dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. Purification of the resultant residue by flash column chromatography using pet. ether–EtOAc–MeOH (9:10:1) gave the *sulfide* (2.63 g, 78%) as a viscous colourless oil; R_f (4.5:5:1 pet. ether–EtOAc–MeOH) 0.25; ν_{max}(film)/cm^{-1} 3395 (br) (OH), 2982, 1586, 1468, 1265s, 1051, 1024s, 968, 826 and 731; δ_H (400 MHz, $CDCl_3$)

1.26 (6H, t, *J* 7.0, OCH_2CH_3), 2.51 (2H, d, *J* 12.5, SCH_2P), 3.78 (3H, s, OMe), 3.99 (2H, d, *J* 0.6, CH_2SCH_2P), 4.08 (2H, q, *J* 7.0, OCH_2CH_3), 4.10 (2H, q, *J* 7.0, OCH_2CH_3), 4.72 (2H, s, CH_2O), 6.77 (1H, d, *J* 7.9, H4), 6.89 (1H, dd, *J* 7.9 and 0.6, H6) and 7.15 (1H, t, *J* 7.9, H5); δ_C (100 MHz, $CDCl_3$) 16.3 (OCH_2CH_3), 16.3 (OCH_2CH_3), 22.7 (SCH_2P), 24.2 (SCH_2P), 33.8 (CH_2SCH_2P), 33.8 (CH_2SCH_2P), 55.5 (OMe), 55.6 (CH_2O), 62.6 (OCH_2CH_3), 62.7 (OCH_2CH_3), 110.0 (C4), 122.7 (C6), 128.1 (C2), 128.5 (C5), 136.5 (C1) and 158.4 (C3); *m*/*z* (ESI): 357 ($M+Na^+$, 13%), 335 (MH, 10) and 317; HRMS (ESI): found $M+Na^+$, 357.0893. $C_{14}H_{23}O_5PSNa$ requires, 357.0896. (b) To a solution of this sulfide (2.63 g, 7.86 mmol) in CH_2Cl_2 (100 mL) at 0 °C, was added sodium hydrogen carbonate (1.98 g, 23.58 mmol) under a stream of nitrogen. This was followed by *m*-chloroperoxybenzoic acid (4.84 g, 19.65 mmol, ca. 70%). After stirring for 20 h, saturated aqueous sodium hydrogen carbonate (50 mL) was added and the aqueous layer extracted with CH_2Cl_2 (4×100 mL). The combined organic extracts were dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. Purification of the resultant residue using pet. ether–EtOAc–MeOH (4:5:1) afforded *sulfone* **5a** (2.27 g, 79%) as a colourless solid; mp 86–88 °C; R_f (4:5:1 pet. ether–EtOAc–MeOH) 0.16; ν_{max}(film)/cm^{-1} 3431 (br) (OH), 2982, 2913, 1588, 1470, 1319 (SO_2), 1267, 1151 (SO_2), 1020, 833, 804 and 733; δ_H (400 MHz, $CDCl_3$) 1.29 (6H, t, *J* 7.0, OCH_2CH_3), 3.55 (2H, d, *J* 16.2, SO_2CH_2P), 3.79 (3H, s, OMe), 4.17 (2H, q, *J* 7.0, OCH_2CH_3), 4.19 (2H, q, *J* 7.0, OCH_2CH_3), 4.73 (2H, s, CH_2O), 4.75 (2H, s, $CH_2SO_2CH_2P$), 6.88 (1H, d, *J* 7.9, H4), 7.04 (1H, dd, *J* 7.9 and 0.6, H6) and 7.23 (1H, t, *J* 7.9, H5); δ_C (100 MHz, $CDCl_3$) 16.1 (OCH_2CH_3), 16.2 (OCH_2CH_3), 48.2 (SO_2CH_2P), 49.6 (SO_2CH_2P), 55.7 (OMe), 56.0 (CH_2O), 57.3 ($CH_2SO_2CH_2P$), 63.7 (OCH_2CH_3), 63.7 (OCH_2CH_3), 111.6 (C4), 124.3 (C6), 127.0 (C2), 129.1 (C5), 129.8 (C1) and 158.6 (C3); *m*/*z* (ESI): 389 ($M+Na^+$, 30%), 367 (MH, 6) and 349; HRMS (ESI): found $M+Na^+$, 389.0781. $C_{14}H_{23}O_7PSNa$ requires, 389.0794.

3.1.6. Diethyl {[2-(*tert*-butyldimethylsilyloxy)methyl]-3-methoxybenzylsulfonyl}methylphosphonate 5b. To a stirred solution of sulfone **5a** (0.30 g, 0.89 mmol) in dry CH_2Cl_2 (5 mL) at −78 °C under an atmosphere of nitrogen was added dropwise 2,6-lutidine (0.11 mL, 0.98 mmol), followed by *tert*-butyldimethylsilyl trifluoromethane–sulfonate (0.21 mL, 0.90 mmol). The solution was allowed to warm to rt over 1 h before the addition of ammonium chloride (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3×10 mL) and the combined organic extracts dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. Purification of the resultant oil by flash column chromatography using pet. ether–EtOAc–MeOH (4:5:1) as the eluent afforded *sulfone* **5b** (0.38 g, 98%) as a colourless oil; R_f (4:5:1 pet. ether–EtOAc–MeOH) 0.53; ν_{max}(film)/cm^{-1} 2930, 2856, 1589, 1468, 1322 (SO_2), 1255, 1053s (SO_2), 975, 836 and 732; δ_H (400 MHz, $CDCl_3$) 0.00 (3H, s, $SiMe_2$), 0.00 (3H, s, $SiMe_2$), 0.82 (9H, s, Si^tBu), 1.31 (6H, td, *J* 7.0 and 0.9, OCH_2CH_3), 3.49 (2H, d, *J* 16.5, SO_2CH_2P), 3.76 (3H, s, OMe), 4.19 (2H, qd, *J* 7.0 and 1.5, OCH_2CH_3), 4.21 (2H, q, *J* 7.0 and 1.5, OCH_2CH_3), 4.84 (2H, s, CH_2O or $CH_2SO_2CH_2P$), 4.92 (2H, s, $CH_2SO_2CH_2P$ or CH_2O), 6.84 (1H, d, *J* 7.8, H4), 7.10 (1H, d, *J* 7.8, H6) and 7.22 (1H, td, *J* 7.9 and 1.5, H5); δ_C (100 MHz, $CDCl_3$) −5.5 ($SiMe_2$), 16.1 (OCH_2CH_3), 16.2 (OCH_2CH_3), 18.1 (Si^tBu), 25.7 (Si^tBu), 47.9 (SO_2CH_2P), 49.3 (SO_2CH_2P), 55.3 (OMe), 55.8 (CH_2O), 57.3 ($CH_2SO_2CH_2P$), 63.4 (OCH_2CH_3), 63.4 (OCH_2CH_3), 111.4 (C4), 123.9 (C6), 128.8 (C5), 129.0 (C2), 129.6 (C1) and 157.4 (C3); *m*/*z* (ESI): 595 ($MH+C_6H_{15}Si^+$, 15%), 498 ($M+NH_4$, 44), 481 (MH, 31) and 349; HRMS (ESI): found $M+NH_4^+$, 498.2104. $C_{20}H_{41}NO_7PSSi$ requires, 498.2105.

3.1.7. {[2-(*tert*-Butyldimethylsilyloxy)methyl]-3-methoxybenzylsulfonyl}methyl-4′,5′-*O*-isopropylidene-7′-deoxy-D-ribofuranose 16. To a stirred suspension of sodium hydride (20 mg, 0.50 mmol, 60%) in THF (1 mL) at 0 °C under an atmosphere of argon was added a solution of phosphonate **5b** (0.20 g, 0.42 mmol) in THF (2 mL). The mixture was allowed to warm to rt and was stirred for 0.5 h. The solution was cooled back to 0 °C and a solution of lactol **8** (0.07 g, 0.42 mmol) in THF (2 mL) added dropwise. After stirring for 24 h, brine (5 mL) was added and the aqueous layer extracted with diethyl ether (3×10 mL). The combined organic extracts were dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. Purification of the resultant oil by flash column chromatography using pet. ether–EtOAc (7:3) as the eluent afforded a 42:58 inseparable mixture of *sulfones* **16** (0.16 g, 79%) as a colourless oil; R_f (7:3 pet. ether–EtOAc) 0.35; ν_{max}(film)/cm^{-1} 2932, 2856, 1588, 1467, 1378, 1310 (SO_2), 1253, 1115, 1061s, 1006 (SO_2), 837 and 776; *m*/*z* (ESI): 523 ($M+Na^+$, 85%), 501 (MH, 42) and 369; HRMS (ESI): found MH^+, 501.2339. $C_{24}H_{41}O_7SSi$ requires, 501.2337.

3.1.7.1. Minor (3′,4′)-*trans* isomer 16α. δ_H (400 MHz, $CDCl_3$) 0.01 (3H, s, $SiMe_2$), 0.03 (3H, s, $SiMe_2$), 0.85 (9H, s, Si^tBu), 1.32 (3H, s, Me), 1.36 (3H, d, *J* 6.4, H7′), 1.53 (3H, s, Me), 3.25–3.27 (2H, m, H2′), 3.80 (3H, s, OMe), 4.05 (1H, qd, *J* 6.4 and 4.8, H6′), 4.28–4.35 (2H, m, H3′ and H5′), 4.55 (1H, dd, *J* 7.1 and 5.7, H4′), 4.60 (1H, d, *J* 14.2, H1′), 4.78 (1H, d, *J* 14.2, H1′), 4.98 (2H, s, CH_2O), 6.86 (1H, d, *J* 8.0, H6), 7.06 (1H, dd, *J* 8.0 and 0.9, H5) and 7.23 (1H, t, *J* 8.0, H4); δ_C (100 MHz, $CDCl_3$) −5.4 ($SiMe_2$), 18.2 (Si^tBu), 18.8 (C7′), 25.5 (CMe_2), 25.9 (Si^tBu), 27.3 (CMe_2), 54.9 (C2′), 55.5 (OMe), 55.9 (CH_2O), 57.4 (C1′), 78.7 (C3′), 80.9 (C6′), 84.0 (C4′), 85.6 (C5′), 111.3 (C3), 115.6 (CMe_2), 124.2 (C5), 128.6 (C4), 129.0 (C1 or C6), 129.8 (C6 or C1) and 157.5 (C2).

3.1.7.2. Major (3′,4′)-*cis* isomer 16β. δ_H (400 MHz, $CDCl_3$) −0.01 (3H, s, $SiMe_2$), 0.04 (3H, s, $SiMe_2$), 0.85 (9H, s, Si^tBu), 1.17 (3H, d, *J* 7.2, H7′), 1.29 (3H, s, Me), 1.46 (3H, s, Me), 3.11 (1H, ddd, *J* 15.2, 3.2 and 1.2, H2′), 3.50 (1H, dd, *J* 15.2 and 9.1, H2′), 3.79 (3H, s, OMe), 4.28–4.36 (1H, m, H6′), 4.39 (1H, dt, *J* 9.1 and 3.2, H3′), 4.50 (1H, d, *J* 6.1, H5′), 4.64 (1H, d, *J* 14.1, H1′), 4.72 (1H, dd, *J* 5.8 and 4.0, H4′), 4.84 (1H, dd, *J* 14.1 and 1.2, H1′), 4.95 (2H, s, CH_2O), 6.86 (1H, d, *J* 8.0, H6), 7.12 (1H, dd, *J* 8.0 and 1.1, H5) and 7.23 (1H, t, *J* 8.0, H4); δ_C (100 MHz, $CDCl_3$) −5.4 ($SiMe_2$), 16.6 (C7′), 18.2 (Si^tBu), 24.6 (CMe_2), 25.8 (Si^tBu), 26.0 (CMe_2), 52.0 (C3′), 55.5 (OMe), 55.9 (CH_2O), 57.0 (C1′), 73.8 (C3′), 80.1 (C6′), 81.5 (C4′), 85.8 (C5′), 111.2 (C3), 112.7 (CMe_2), 124.4 (C5), 128.5 (C4), 129.3 (C1 or C6), 129.9 (C6 or C1) and 157.4 (C2).

3.1.8. 2-[(*E*)-2-(2-*tert*-Butyldimethylsilyloxymethyl-3-methoxyphenyl)-styryl]-4′,5′-*O*-isopropylidene-7′-deoxy-D-ribofuranose 17. (a) Sulfones **16** (500 mg, 1.00 mmol) were dissolved in CH_2Cl_2 (15 mL) and *tert*-BuOH (2 mL) and cooled to 0 °C under argon. Potassium hydroxide on alumina (2.00 g) was added, followed by CBr_2F_2 (0.46 mL, 5.00 mmol). The reaction was allowed to warm to rt and stirred overnight. The mixture was filtered through a plug of Celite©, and the plug washed with CH_2Cl_2 (2×30 mL). Concentration in vacuo, followed by chromatography on silica eluting with pet. ether–EtOAc (9:1) gave the two *styrene* products **17α**[3] (82 mg, 0.19 mmol, 19%) and **17β** (256 mg, 0.59 mmol, 59%) as colourless oils. **17α**: R_f (9:1 pet. ether–EtOAc) 0.53; $[\alpha]_D^{20}$ −25.7 (*c* 0.8, $CHCl_3$); ν_{max}(film)/cm^{-1} 2930, 2856, 1579, 1471, 1380, 1252 and 1079; δ_H (400 MHz, acetone-d_6) 0.14 (6H, s, Si*Me*$_2$), 0.98 (9H, s, Si*t*-*Bu*), 1.43 (3H, s, Me), 1.44 (3H, d, *J* 6.5, H7′), 1.65 (3H, s, Me), 3.89 (3H, s, OMe), 4.13 (1H, q, *J* 6.5, H6′), 4.41 (1H, dd, *J* 4.5 and 7.0, H3′), 4.55 (1H, app. t, *J* 6.0, H5′), 4.62 (1H, dd, *J* 5.5 and 6.5, H4′), 4.89 (2H, s, CH_2OSi), 6.28 (1H, dd, *J* 6.5 and 16.0, H2′), 6.86 (1H, d, *J* 8.0, H6), 7.18 (1H, d, *J* 8.0, H5), 7.24 (1H, d, *J* 16.0, H1′) and 7.27 (1H, app. t, *J* 8.0, H4); δ_C (100 MHz, acetone-d_6) −5.3 (Si*Me*$_2$), 18.4 (Si*t*-*Bu*), 19.1 (C7′), 25.5 (Si*t*-*Bu*), 26.0 (C*Me*$_2$), 27.4 (C*Me*$_2$), 55.6 (OMe), 55.9 (CH_2O), 80.2 (C4′), 84.8 (C5′), 85.7 (C6′), 86.3 (C3′), 110.0 (C3), 114.8 (*C*Me$_2$), 118.7 (C5), 126.6 (C1), 128.5 (C4), 129.4 (C1′), 130.1 (C2′), 138.5 (C6) and 157.4 (C2); *m*/*z* (ESI): 457 [(M+Na)$^+$, 100%], 303, 245, 227, 199 and 159; found (M+Na)$^+$, 457.2387. $C_{24}H_{38}O_5SiNa$ requires, 457.2381. **17β**: R_f 9:1 pet. ether–EtOAc) 0.44; $[\alpha]_D^{20}$ −95.7 (*c* 1.1, $CHCl_3$); ν_{max}(film)/cm^{-1} 2931, 2856, 1579, 1471, 1374, 1256 and 1067; δ_H (400 MHz, acetone-d_6) 0.11 (3H, s, Si*Me*$_2$), 0.12 (3H, s, Si*Me*$_2$), 0.96 (9H, s, Si*t*-*Bu*), 1.27 (3H, d, *J* 7.0, H7′), 1.40 (3H, s, Me), 1.60 (3H, s, Me), 3.88 (3H, s, OMe), 4.38 (1H, q, *J* 7.0, H6′), 4.55 (1H, dd, *J* 4.0 and 7.5, H3′), 4.58 (1H, d, *J* 6.0, H5′), 4.81 (1H, dd, *J* 4.0 and 6.0, H4′), 4.90 (2H, AB q, *J* 11.5, CH_2OSi), 6.34 (1H, dd, *J* 8.0 and 16.0, H2′), 6.84 (1H, dd, *J* 2.5 and 7.0, H6) and 7.23–7.33 (3H, m, H1′,4,5); δ_C (100 MHz, acetone-d_6) −5.2 (Si*Me*$_2$), 17.2 (C7′), 18.4 (Si*t*-*Bu*), 25.0 (Si*t*-*Bu*), 26.0 (two signals), 26.4, 55.6 (OMe), 56.0 (CH_2O), 79.7 (C4′), 80.7 (C5′), 83.1 (C6′), 86.7 (C3′), 110.0 (C3), 112.5 (*C*Me$_2$), 119.1 (C5), 126.3 (C1), 126.5 (C4), 128.5 (C1′), 131.8 (C2′), 138.7 (C6) and 157.3 (C2); *m*/*z* (ESI): 457 [(M+Na)$^+$, 100%], 303, 245, 227, 189 and 159; found (M+Na)$^+$, 457.2394. $C_{24}H_{38}O_5SiNa$ requires, 457.2381.

(b) One-pot route to styrenes **17**. A solution of phosphonate **5b** (160 mg, 0.33 mmol) in THF (2.5 mL) was added to a stirred suspension of sodium hydride (16 mg, 0.40 mmol, 60%) in THF (1.5 mL) at 0 °C under an atmosphere of argon. After stirring for 15 min a solution of lactol **8** (58 mg, 0.33 mmol) in THF (1.5 mL) was added and the mixture allowed to warm to rt. The reaction was stirred for 20 h before the addition of potassium hydroxide on alumina (663 mg). The suspension was cooled to 0 °C before the addition of CBr_2F_2 (155 μL, 1.70 mmol). After stirring for 18 h, the reaction was filtered through Celite© washing with CH_2Cl_2 (25 mL). The solvent was removed under reduced pressure, and the resultant residue was purified by careful flash column chromatography using pet. ether–EtOAc (9:1) to give the *styrenes* **9α** and **9β** as a 1:1.3 mixture (68 mg, 47% over two steps) as colourless oils. Data matched those reported above.

3.1.9. (−)-Varitriol 1. A solution of styrene **17α** (70 mg, 0.16 mmol) in THF (6 mL) and aqueous HCl (1 M, 3 mL) was stirred at rt for 18 h. The reaction was neutralised by the addition of saturated aqueous sodium bicarbonate (5 mL) and extracted into CH_2Cl_2 (3×20 mL). The combined organic extracts were dried over magnesium sulfate, filtered and concentrated under reduced pressure. Chromatography on silica eluting with CH_2Cl_2–acetone (3:2) gave (−)-varitriol **1** (32 mg, 0.12 mmol, 72%) as a colourless oil; R_f (3:2 CH_2Cl_2–acetone) 0.30; $[\alpha]_D^{20}$ −40.6 (*c* 1.6, MeOH) [lit.[1] $[\alpha]_D^{25}$ (enant.) +18.5 (*c* 2.3, MeOH)]; ν_{max}-(film)/cm^{-1} 3321, 2897, 1576 and 1472; δ_H (500 MHz, acetone-d_6) 1.27 (3H, d, *J* 6.5, H7′), 2.92 (1H, br s, OH), 3.65 (1H, br s, OH), 3.69 (1H, app. t, *J* 5.5, H5′), 3.82 (3H, s, OMe), 3.84 (1H, app. t, *J* 6.5, H6′), 3.91 (1H, app. t, *J* 5.5, H4′), 4.05 (1H, br s, OH), 4.29 (1H, app. t, *J* 6.0, H3′), 4.72 (2H, s, OCH_2), 6.20 (1H, dd, *J* 6.8 and 15.5, H2′), 6.89 (1H, d, *J* 8.0, H6), 7.12 (1H, d, *J* 15.5, H1′), 7.13 (1H, d, *J* 8.0, H5) and 7.22 (1H, app. t, *J* 8.0, H4); δ_C (125 MHz, acetone-d_6) 19.5 (C7′), 55.4 (OCH_2), 56.0 (OMe), 76.4 (C4′), 77.1 (C5′), 80.0 (C6′), 85.3 (C3′), 110.6 (C3), 119.3 (C5), 127.9 (C1), 129.2 (C4), 129.3 (C1′), 132.4 (C2′), 139.0 (C6) and 158.9 (C2); *m*/*z* (ESI): 303 [(M+Na)$^+$, 100%]; found (M+Na)$^+$, 303.1213. $C_{15}H_{20}O_5Na$ requires, 303.1203. These data were in broad accord with those published in the literature (see text).[1,3]

3.1.10. (−)-3′-*epi*-Varitriol 18. A solution of styrene **17β** (104 mg, 0.24 mmol) in THF (9 mL) and aqueous HCl (1 M, 4.5 mL) was stirred at rt for 7 days. The reaction was neutralised by the addition of saturated aqueous sodium bicarbonate (10 mL) and extracted into CH_2Cl_2 (3×50 mL). The combined organic extracts were dried over magnesium sulfate, filtered and concentrated under reduced pressure. Chromatography on silica eluting with CH_2Cl_2–acetone (3:2) gave (−)-3′-*epi*-varitriol **18** (56 mg, 0.20 mmol, 83%) as a colourless oil; R_f (3:2 CH_2Cl_2–acetone) 0.30; $[\alpha]_D^{20}$ −9.7 (*c* 2.25, MeOH); ν_{max}(film)/cm^{-1} 3356, 2966, 1696, 1575 and 1470; δ_H (500 MHz, acetone-d_6) 1.24 (3H, d, *J* 6.0, H7′), 2.95 (1H, br s, OH), 3.82 (3H, s, OMe), 3.79–3.85 (2H, m, H5′, OH), 3.94 (1H, dd, *J* 7.5 and 6.0, H6′), 4.05 (1H, br s, OH), 4.16 (1H, app. t, *J* 4.5, H4′), 4.63 (1H, dd, *J* 6.5 and 4.0, H3′), 4.72 (2H, s, OCH_2), 6.32 (1H, dd, *J* 15.5 and 7.5, H2′), 6.88 (1H, d, *J* 8.0, H6), 7.05 (1H, d, *J* 15.5, H1′), 7.14 (1H, d, *J* 8.0, H5) and 7.22 (1H, app. t, *J* 8.0, H4); δ_C (125 MHz, acetone-d_6) 19.3 (C7′), 55.4 (OCH_2), 56.0 (OMe), 74.7 (C4′), 78.1 (C5′), 79.3 (C6′), 82.1 (C3′), 110.5 (C3), 119.5 (C5), 127.9 (C1), 129.3 (C4), 129.9 (C1′), 130.8 (C2′), 139.3 (C6) and 158.8 (C2); *m*/*z* (ESI): 303 [(M+Na)$^+$, 100%], 189 and 159; found (M+Na)$^+$, 303.1199. $C_{15}H_{20}O_5Na$ requires, 303.1203.

3.1.11. Triacetylvaritriol 19. (−)-Varitriol **1** (28 mg, 0.10 mmol) was dissolved in pyridine (0.7 mL) and Ac_2O (60 μL, 0.60 mmol) added. After stirring at rt for 4 h, the reaction was diluted with CH_2Cl_2 (10 mL) and washed with aqueous HCl (1 M, 5 mL), saturated aqueous sodium bicarbonate (5 mL) and brine (5 mL). The organic solution was dried over magnesium sulfate, filtered and concentrated in vacuo. Chromatography on silica eluting with pet. ether–

EtOAc (4:1) gave triacetate **19** (39 mg, 0.096 mmol, 96%) as a colourless oil; R_f (4:1 pet. ether–EtOAc) 0.18; $[\alpha]_D^{20}$ −17.2 (*c* 0.58, $CHCl_3$) [lit.[1] $[\alpha]_D^{25}$ (enant.) +16.9 (*c* 0.33, $CHCl_3$)]; δ_H (400 MHz, $CDCl_3$) 1.37 (3H, d, *J* 6.4, H7′), 2.05, 2.08 and 2.09 (3×3H, 3×s, 3×OAc), 3.82 (3H, s, OMe), 4.12 (1H, quintet, *J* 6.4, H6′), 4.52 (1H, app. t, *J* 6.7, H3′), 4.92 (1H, app. t, *J* 5.8, H5′), 5.07 (1H, app. t, *J* 5.8, H4′), 5.24 (2H, AB q, *J* 11.6, OCH_2), 6.12 (1H, dd, *J* 6.7 and 15.6, H2′), 6.84 (1H, d, *J* 8.0, H6), 6.97 (1H, d, *J* 15.6, H1′), 7.12 (1H, d, *J* 8.0, H5) and 7.29 (1H, app. t, *J* 8.0, H4); δ_C (100 MHz, $CDCl_3$) 19.0 (C7′), 20.6 (Me), 20.7 (Me), 21.0 (Me), 55.8 (OMe), 57.6 (CH_2O), 74.7 (C4′), 75.6 (C5′), 77.5 (C6′), 81.4 (C3′), 110.2 (C3), 118.8 (C5), 129.7 (C4), 119.8 (C1′), 129.9 (C2′), 130.0 (C1), 138.3 (C6), 158.4 (C2), 169.9 (CO), 169.9 (CO) and 171.2 (CO). These data were in agreement with those reported in the literature.[1]

Acknowledgements

The University of York (G.D.M.), the EPSRC and the MOD (J.E.R.) are thanked for financial assistance.

References and notes

1. Malmstrøm, J.; Christophersen, C.; Barrero, A. F.; Oltra, J. E.; Justicia, J.; Rosales, A. *J. Nat. Prod.* **2002**, *65*, 364–367.
2. Mayer, A. M. S.; Gustafson, K. R. *Eur. J. Cancer* **2004**, *40*, 2676–2704.
3. Clemens, R. T.; Jennings, M. P. *Chem. Commun.* **2006**, 2720–2721.
4. For recent reviews on the Ramberg–Bäcklund reaction, see: Taylor, R. J. K.; McAllister, G. D.; Franck, R. W. *Carbohydr. Res.* **2006**, *341*, 1298–1311; Taylor, R. J. K.; Casy, G. *Org. React.* **2003**, *62*, 357–475.
5. Robinson, J. E.; Taylor, R. J. K. *Chem. Commun.* **2007**, 1617–1619 and references therein.
6. (a) McAllister, G. D.; Paterson, D. E.; Taylor, R. J. K. *Angew. Chem., Int. Ed.* **2003**, *42*, 1387–1391; (b) Jeanmart, S.; Taylor, R. J. K. *Tetrahedron Lett.* **2005**, *46*, 9043–9048.
7. (a) Hughes, N. A.; Speakman, P. R. H. *Carbohydr. Res.* **1965**, *1*, 171–175; (b) Jensen, H. H.; Jensen, A.; Hazell, R. G.; Bols, M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1190–1198.
8. Chan, T.-L.; Fong, S.; Li, Y.; Man, T.-O.; Poon, C.-D. *J. Chem. Soc., Chem. Commun.* **1994**, 1771–1772.
9. (a) Davidson, A. H.; Hughes, L. R.; Qureshi, S. S.; Wright, B. *Tetrahedron Lett.* **1988**, *29*, 693–696; (b) Ohrui, H.; Jones, G. H.; Moffatt, J. G.; Maddox, M. L.; Christensen, A. T.; Byram, S. K. *J. Am. Chem. Soc.* **1975**, *97*, 4602–4613 and references therein.
10. Ronald, R. C.; Winkle, M. R. *Tetrahedron* **1983**, *39*, 2031–2042.
11. Mikolajczyk, M.; Grzejszczak, S.; Chefczynska, A.; Zatorski, A. *J. Org. Chem.* **1979**, *44*, 2967–2972.
12. Clemens and Jennings reported the synthesis of **17α** (Ref. 3). However, no physical data were given.
13. Saponification of **19** cleanly regenerated (−)-varitriol **1** (67%) and the measured rotation was consistent with the value obtained earlier in our study $[\alpha]_D$ −41.2 (*c* 1.8, MeOH). This finding indicates a possible error in the $[\alpha]_D$ values originally reported in the literature (Refs. 1 and 3).