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Total synthesis of (±)-luminacin D

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Abstract—A 15-step synthesis of (±)-luminacin D from ethyl pent-2-ynoate is reported. The pivotal step involves the formation of the central C-2′/C-3′ bond of the natural product by condensation of the titanium enolate derived from aromatic ketone **1** with aldehyde **2a**. A remote asymmetric centre in aldehyde **2a** exerts control over the stereochemical course of this reaction, with the major adduct (**3a**, 54% yield) possessing the required (2′*S**,3′*R**,5′*R**)-stereochemistry. This assignment was unambiguously established by X-ray crystallography of late stage synthetic intermediate, **17**. Further manipulation of **3a** (six steps) yielded synthetic (±)-luminacin D spectroscopically identical to material isolated from *Streptomyces* sp. Mer-VD1207 by Naruse et al.

1. Introduction

Angiogenesis, the sprouting of new blood vessels from pre-existing ones, is essential during tissue repair, foetal development and the female reproductive cycle.[1] Moreover, it is of fundamental importance to the development of cancers, with tumour growth limited to about 1–2 mm in diameter in the absence of new capillary development.[2] Currently, there is enormous interest in the identification and use of angiogenesis inhibitors for the control and treatment of cancer and other diseases.[3] Recently, 14 members of a family of anti-angiogenic natural product called the luminacins were isolated from the culture broths of *Streptomyces* sp. Mer-VD1207.[4] These compounds contain a functionalised 1,5-dioxaspiro[2.5]octane ring system linked to a polysubstituted aromatic nucleus. The chemical structures of two of the more potent inhibitors namely luminacin C_2 and D are depicted (Fig. 1). Different members of the luminacin family show variation in the oxidation level at C-1″, and have small variations in the substituents at C-1, C-2′ and C-8′. The luminacins inhibit the initial stages of capillary tube formation and operate by a unique mode of action.[5] Studies using luminacin C_2[6] have revealed that it is an inhibitor of Src signal transduction, acting by disruption of proline-rich ligand mediated protein–protein interactions (PLPIs), rather than by direct inhibition of Src kinase activity.[7–9] Preliminary SAR studies reveal that an aldehyde group at C-1 is important for this anti-angiogenic activity.[5] Further studies by Davies et al., have shown that simplified analogues devoid of the epoxide ring retain the ability to inhibit VEGF stimulated angiogenesis.[10] Moreover, Oneyama et al., have established that synthetic analogues totally devoid of the 1,5-dioxaspiro[2.5]octane ring system can inhibit certain PLPIs.[9]

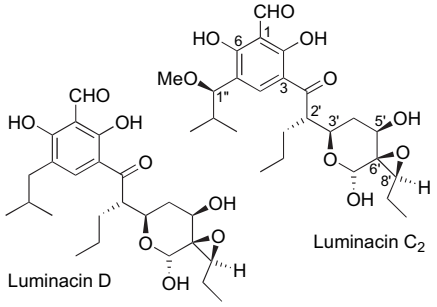

Figure 1. Structures of luminacin C_2 and D.

Motivated by their important biological properties, several groups have embarked on the synthesis of various members of the luminacin family. The total synthesis of *ent*-luminacin C_1 and C_2 was first reported in 2001 by Tatsuta et al.[11] In addition, elegant racemic syntheses of luminacin D have been reported by Wood et al.,[12] and by the Eisai company.[13] In 2006, the asymmetric synthesis of the natural (−)-enantiomer of luminacin D was achieved by Jogireddy and Maier.[14] In this article, we disclose our own efforts directed towards the total synthesis of luminacin D, which has culminated in the development of new, concise route to this compound class.

Our highly convergent approach is based on employing a *syn*-selective aldol to make the C-2′/C-3′ bond by reaction of aromatic ketone **1** with a β-alkoxy substituted aldehyde **2** (Scheme 1). In this manner, we hoped to produce β-hydroxy ketone **3** containing the complete carbon skeleton of

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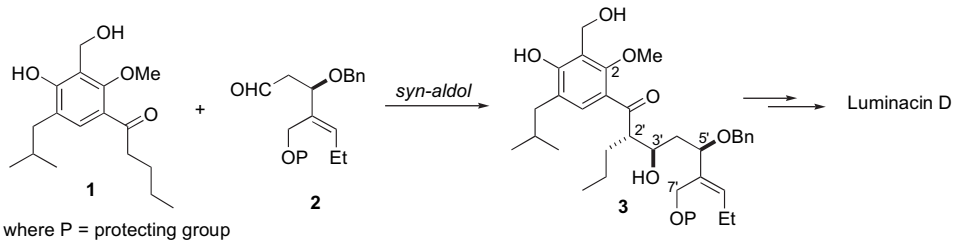
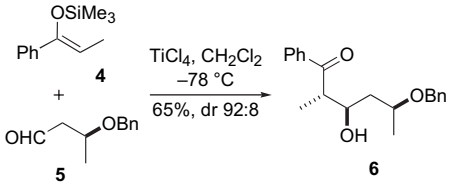


Scheme 1. Proposed diastereocontrolled aldol approach to luminacin D.

luminacin D with the correct relative stereochemistry at C-2′, C-3′ and C-5′. Crucially, we hoped that the β-benzyloxy group of aldehyde **2** might exert some remote stereochemical bias in this aldol reaction such that the required (2′*S**,3′*R**,5′*R**)-diastereomer would be produced. In this regard, we were encouraged by a report by Reetz who had demonstrated that (*Z*)-trimethylsilyl ether **4**, derived from phenylethylketone, reacts with (3-benzyloxy)butanal (**5**) to give β-hydroxy ketone **6** as essentially a single diastereomer under chelation control (Scheme 2).[15]



Scheme 2. Precedent for aldol diastereoselection from the work of Reetz.[15]

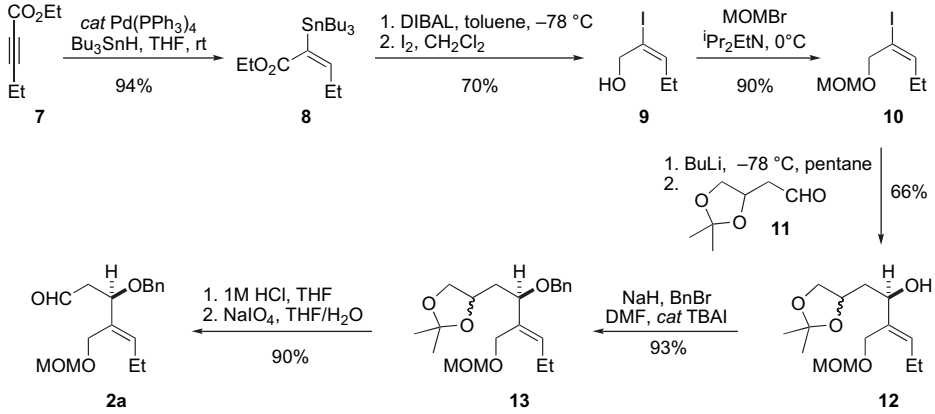
The selection of **1** as the ketone component for the aldol condensation was based on our earlier work in which we had established that this compound undergoes highly diastereoselective *syn*-aldol reactions with simple aldehydes (e.g., 5-hexenal), and can be transformed into 'luminacin-like' structures by smooth demethylation at C-2 and oxidation of the hydroxymethyl group at C-1.[10] For aldehyde **2**, we selected a benzyl ether for the C-5′ hydroxyl group (luminacin numbering) in accordance with the work of Reetz (Scheme 2).[15] The choice of the protecting group for the C-7′ was not specified at the outset of this work.

Completion of the synthesis of luminacin D from **3** was anticipated to involve: (i) deprotection of the C-2 and C-7′ hydroxyl groups; (ii) chemoselective oxidation of the allylic and benzylic alcohol groups (with concomitant formation of the pyran ring); and (iii) diasterocontrolled epoxidation of the alkene double bond. In this way, we hoped to develop a short, stereocontrolled approach to luminacin D that might also be suitable for the synthesis of analogues with which to further probe the origin of the anti-angiogenic activity in this compound class.

2. Results and discussion

2.1. Synthesis of aldehyde 2a (P=MOM)

Aldehyde **2a** (P=MOM) for the aldol condensation was made in eight steps from ethyl pent-2-ynoate **7** (Scheme 3). Regio- and stereocontrolled hydrostannylation of **8** with tributyltin hydride in the presence of tetrakis-(triphenylphosphine)-palladium(0) (2 mol %) afforded (*E*)-vinyl stannane **8** in 94% yield.[16–18] Reduction of **8** with DIBAL (2.0 equiv) and subsequent conversion to vinyl iodide **9** was achieved by tin–iodine exchange using molecular iodine. Protection of the hydroxyl group of **9** as a MOM ether proceeded uneventfully to give **10** in 90% yield. Next, we needed to undertake a three carbon homologation at C-6′ (luminacin numbering) to complete the synthesis of **2a**. For this purpose, we employed aldehyde **11**, made in two steps from 1,2,4-butanetriol,[19,20] as a masked equivalent of malondialdehyde. Lithium–iodine exchange performed on **10** using *n*-butyllithium in pentane generated the corresponding organolithium, which was reacted with aldehyde **11** to give **12** in an acceptable 66% yield. Alcohol **12** was produced as an inseparable 64:36 mixture of diastereomers as a result of the creation of a new stereogenic centre. This is inconsequential as the second asymmetric centre is ultimately removed. Crucially, no loss of stereochemical integrity with respect to the



Scheme 3. Synthesis of aldehyde **2a**.

olefin geometry was seen in this coupling reaction. It is worth noting that we were concerned about advancing the synthesis with the C-7′ MOM group, for fear it may ultimately prove difficult to remove. Indeed, we were able to prepare the corresponding vinyl iodide in which the MOM group of **10** was replaced by TBDPS, however efforts to conduct the lithiation–alkylation sequence using this derivative were unsuccessful. Hence, we were forced to proceed towards luminacin D using MOM protected **12**. Benzylation of the secondary hydroxyl group of this compound gave ether **13** in 93% yield. To complete the synthesis of aldehyde **2a**, the acetonide was hydrolysed using aqueous hydrochloric acid and the resultant 1,2-diol cleaved using sodium periodate. In this manner, aldehyde (±)-**2a** could be made on a multi-gram scale in eight steps and 33% overall yield. At this juncture, the (*E*)-stereochemistry about the trisubstituted double bond was established using NOE difference experiments.[21] This assignment was later confirmed by X-ray crystallography of an advanced synthetic intermediate (vide infra).

2.2. Aldol condensation

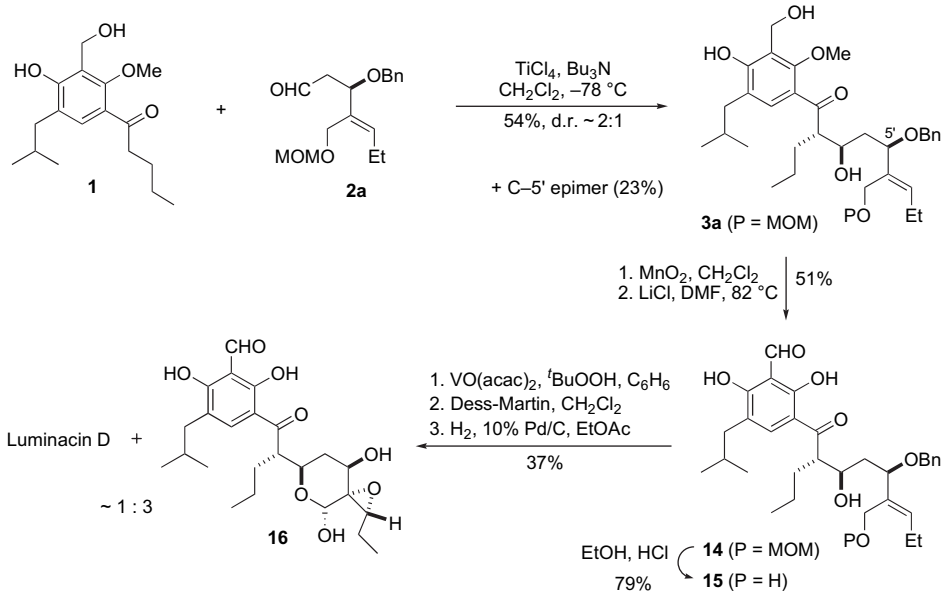
The synthesis of ketone **1** was accomplished in eight steps and 33% overall yield from 2,4-dimethoxybenzaldehyde in accordance to our published method.[10] Based on our earlier model studies, we were encouraged to explore the use of the titanium enolate derived from **1** for the aldol condensation. Generation of the tetrachlorotitanium enolate was achieved using the Evans protocol,[22] by treatment of **1** with titanium tetrachloride (2.3 equiv) and tributylamine (2.75 equiv). Subsequent addition of aldehyde **2a** (1.4 equiv) produced just two of the four possible diastereomers in ca. 2:1 as judged by HPLC analysis of the crude reaction mixture.[23] Careful chromatographic purification enabled the isolation of **3a** (P=MOM) bearing the correct luminacin D stereochemistry in a 54% yield (Scheme 4). The (2′*S**,3′*R**,5′*R**,6′*E*)-stereochemistry of **3a** was unambiguously established by X-ray crystallography at a later stage in the synthetic sequence (vide infra). A second diastereomer was also isolated in 23% yield after the chromatography. Since aldol reactions of **1** using simple achiral aldehydes give good levels of preference for the *syn*-adducts (≥74% de), we tentatively suggest that this minor (but significant) diastereomer is the C-5′ epimer of **3a** and not one of the possible *anti*-aldol diastereomers.

The stereochemical outcome of the aldol condensation is consistent with the work of Reetz on simple model substrates (Scheme 2).[15] These workers proposed a chelation-controlled model to account for the observed stereoinduction. That said, the levels of diastereoselectivity observed in the formation of **3a**, whilst synthetically useful, were markedly lower (dr ~2:1 cf. 92:8) in our case. The rather different reaction conditions may account for the observed erosion in stereoselectivity. Unfortunately, application of the seemingly more selective Mukaiyama-type aldol conditions used by Reetz was not possible as efforts to produce (*Z*)-trimethylsilylenol ethers derived from **1** and related ketone substrates were unsuccessful.

Despite the modest levels of diastereoselectivity observed in the formation of **3a**, this transformation proved operationally reliable. Sufficient material could be prepared to progress the synthesis and so no further efforts were undertaken to optimise this step.

2.3. Completion of the synthesis

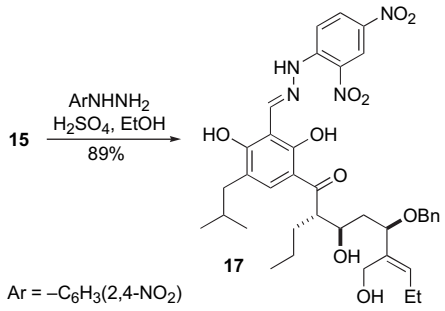
Advancing aldol **3a** to luminacin D required six additional synthetic steps (Scheme 4). Selective oxidation of the benzylic alcohol group to the corresponding aldehyde was achieved in near quantitative yield (98%) using manganese dioxide. Removal of the methyl group at C-2 proved more problematic. The best conditions identified for this reaction were those used in our earlier model studies,[10] namely LiCl in DMF at 82 °C.[24] Considerable care was required for performing this reaction and it was found to be essential not to



Scheme 4. Completion of the synthesis of (±)-luminacin D.

push the reaction to completion to prevent extensive product degradation. By close monitoring by TLC, bisphenol **14** could be isolated in an acceptable 52% yield along with recovered starting material (22%), which could be recycled. Fortuitously, the anticipated problems with deprotection of the MOM group did not materialise, and liberation of the C-7′ hydroxyl group proceeded uneventfully to provide tetraol **15** in 79% yield.

At this juncture, it was still not known whether the aldol reaction had proceeded to give the correct diastereomer. Gratifyingly, derivatisation of **15** by treatment with 2,4-dinitrophenylhydrazine provided crystalline hydrazone derivative **17** in 89% yield (Scheme 5). Using a single crystal of **17** grown from EtOH/H_2O, it was hence possible to deduce the solid-state structure of this hydrazone by X-ray crystallography. An ORTEP depiction of this structure is provided in Figure 2. Since **17** possesses the required (2′*S**,3′*R**,5′*R**,6′*E*)-stereochemistry, we can deduce that **3a**, **14** and **15** from which it is derived, have the same stereochemical configurations.



Scheme 5. Derivatisation of **15** for single crystal X-ray diffraction.

With the knowledge that the correct diastereomer of **15** had been produced, the completion of the synthesis was close. Epoxidation of the double bond of **15** was achieved using $VO(acac)_2$ and *tert*-butyl hydroperoxide in benzene. This produced two epoxide diastereomers (dr ~3:1), which were not readily separable. This mixture was directly treated with Dess–Martin periodinane (1.0 equiv) in CH_2Cl_2 for 20 min, which enabled chemoselective oxidation of the primary C-7′ hydroxyl group and concomitant lactol formation. Other oxidations examined (cat TEMPO, TCCA; cat TPAP, NMO) proved less useful for this step. At this juncture, the epoxide diastereomers could be separated and partially purified. They were then independently subjected to catalytic hydrogenation to facilitate debenzylation providing (±)-luminacin D and 6′,8′-*epi*-luminacin D (**16**) in a combined 37% yield over the three steps.

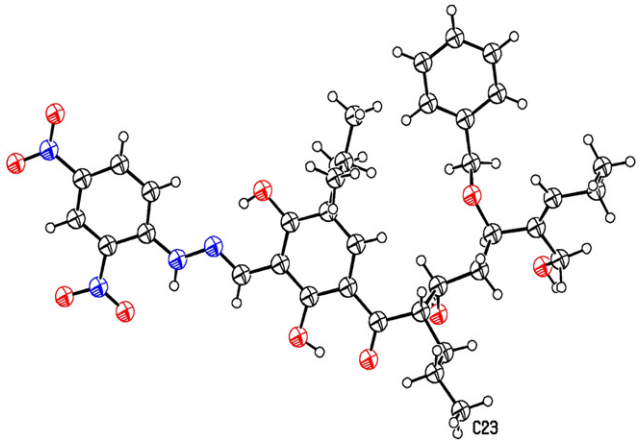


Figure 2. X-ray crystal structure of **17** (thermal ellipsoids at 50% probability) with disordered side chains and solvent removed for clarity.

Gratifyingly, the ^1H and ^{13}C NMR spectra of one of these compounds closely matched with those reported for (−)-luminacin D isolated by Naruse et al.[4] The other diastereomer showed significant differences in the ^{13}C chemical shifts of some resonances in the region of the epoxide (C-6′: $\Delta\delta$=3.2 ppm; C-7′: $\Delta\delta$=1.7 ppm) consistent with the proposal that it was 6′,8′-*epi*-luminacin D. However, rather disappointingly, the minor product (9% over the three steps) formed in this sequence was luminacin D, with the major product being 6′,8′-*epi*-luminacin D (28% over 3 steps) indicating that epoxidation of **15** proceeds predominately from the wrong face.

To try and rectify this problem, other epoxidation conditions were examined (*m*-CPBA, $NaHCO_3$, CH_2Cl_2, CH_3COCF_3 and oxone®). Unfortunately, these led to extensive decomposition. Whilst Sharpless asymmetric epoxidation conditions with the appropriate tartrate enantiomer might overide the natural facial preference of the substrate, a single enantiomer of **15** is ideally required for these experiments to prevent complications associated with kinetic resolution of the substrate. Hence, these studies have not been conducted at this point in time. Additional model studies suggested that adjusting the protecting groups at C-5′ and/or C-7′ was unlikely to overturn the facial selectivity of this epoxidation.[25]

Attempts to change the order of the last few steps of the synthesis were also not fruitful. Dess–Martin periodinane oxidation of the C-7′ hydroxyl group of a substrate closely related to **15** (bearing a MeO– rather than an HO– group at C-2) lead to scrambling of the olefin geometry. Thus, formation of the pyran ring prior to the epoxidation was not practical. Similar problems of alkene isomerisation were noted previously by Wood attempting a closely related transformation.[12] Unfortunately, limited supplies of **15** prevented us from pursuing other possible solutions to this problem, and the issue of controlling the stereoselectivity of the epoxidation step remains unsolved.

3. Conclusions

A short synthesis of (±)-luminacin D from ethyl pent-2-ynoate has been achieved in which the key step involves diastereocontrolled construction of the central C-2′/C-3′ bond by use of substrate control. In comparison to other syntheses of luminacin D, this approach is highly competitive in terms of brevity. The longest linear sequence being just 15 steps [cf. 13 steps (Wood et al.),[12] 20 steps (Maier and Jogireddy)[14] and 21 steps (Eisai)[13]]. The overall yield for the approach is disappointing (ca. 0.64%), although this is largely a result of the poor diastereofacial selectivity in epoxidation step. It is notable that other approaches to luminacin D have failed to achieve control with respect to introduction of this

functional group.[12,14] This limitation aside, its high convergency should mean that it will be highly suitable for the synthesis of analogues, and work in this direction is ongoing in our laboratory. Moreover, by producing aldehyde **2a** as a single enantiomer, it will be possible to develop an asymmetric synthesis of this natural product in which all the stereochemical information is programmed from the C-5′ stereocentre.

4. Experimental

4.1. General

Full details concerning the synthesis of ketone **1** are provided in the supporting information of Ref. 10. Anhydrous solvents were purchased in Sure/Seal™ bottles from Sigma–Aldrich Co., or dried prior to use by distillation. All other solvents and reagents were used as received or purified by standard protocols. All experiments were performed under an inert atmosphere in oven-dried glassware. Column chromatography was carried out using Matrex silica 60 unless otherwise stated. Optical rotations were determined using an Optical Activity Ltd. AA1000 Polarimeter. Infrared spectra were recorded on a Nicolet MAGNA 550 or Perkin–Elmer 'Spectrum One' FTIR spectrometer with internal calibration. ^{1}H and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz, respectively on a Bruker ACF-300 or AM-300; at 400 MHz and 100 MHz, respectively on a Bruker DRX-400, DPX-400 or AV-400 spectrometer; or at 500 MHz and 125 MHz, respectively on a Bruker DRX-500. Low resolution mass spectra were recorded on a Kratos Profile HV3 or Micromass Quattro II mass spectrometer fitted with an electron ionisation source, or an Esquire 2000 platform with electrospray ionisation. High resolution mass spectra were obtained using a Finnigan MAT 95XP, Finnigan MAT 900XLT, Micromass 70-VSEQ or VG-7070E instrument. Elemental analyses were carried out on a Perkin–Elmer 2400 CHN or Carlo Erba 1160 elemental analyser.

4.1.1. (*E*)-Ethyl 2-(tributylstannyl)pent-2-enoate (8). To a stirred solution of ethyl pent-2-ynoate (10.0 g, 79.3 mmol) and $Pd(PPh_3)_4$ (1.98 g, 1.72 mmol) in THF (100 mL), was added dropwise via cannula a degassed solution of tributyltin hydride (23.2 mL, 86.2 mmol) in THF (100 mL). The resulting orange solution was stirred for 5 h and then concentrated in vacuo. The resulting oil was diluted with hexane, left to stand for 24 h, then filtered through a pad of Celite® and the filtrate concentrated. Column chromatography (2% Et_2O in petroleum ether) provided **8** (31.0 g, 94%) as a colourless oil. This product was contaminated with ethyl 3-(tributylstannyl)pent-2-enoate (ca. 10% as judged by ^{1}H NMR). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.03 (1H, t, J=7.0 Hz), 4.14 (2H, q, J=7.0 Hz), 2.47–2.37 (2H, m), 1.60–1.40 (6H, m), 1.36–1.25 (9H, m), 1.03 (3H, t, J=7.5 Hz), 1.00–0.85 (15H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2 (C), 154.9 (CH), 134.9 (C), 59.9 (CH_2), 28.9 (CH_2), 27.3 (CH_2), 25.5 (CH_2), 14.4 (CH_3), 12.0 (CH_3), 11.9 (CH_3), 10.2 (CH_2); IR (neat) 2959, 1695 cm^{-1}; MS (CI) m/z 436 (M+NH_4^+; ^{120}Sn), 419 (MH^+; ^{120}Sn), 378, 361, 308. Anal. Calcd for $C_{19}H_{38}O_2Sn$: C, 54.70; H, 9.18%. Found: C, 54.71; H, 9.21%.

4.1.2. (*E*)-2-(Tributylstannyl)pent-2-en-1-ol (18). To a stirred solution of ester **8** (5.0 g, 12.0 mmol) in toluene (150 mL) at −78 °C, was added dropwise a solution of DIBAL (1.5 M in toluene, 16.0 mL, 24.0 mmol). During this addition, the internal temperature was maintained below −70 °C. The reaction was stirred at −78 °C for 4 h then quenched by the cautious addition of methanol (25 mL). The solution was allowed to warm to room temperature and poured onto a rapidly stirred aqueous solution of sodium potassium tartrate (250 mL) and stirred vigorously for 18 h. The resulting mixture was extracted with diethyl ether (3×125 mL), and the combined organic phases were dried over Na_2SO_4, filtered and concentrated in vacuo. Column chromatography (Al_2O_3 (Activity II); 30% Et_2O in pentane) gave **18** (3.90 g, 87%) as a colourless oil. This product contained an impurity tentatively assigned as 3-(tributylstannyl)pent-2-en-1-ol (ca. 5% as judged by ^{1}H NMR). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.55 (1H, tt, J=6.8, 2.0 Hz), 4.42–4.28 (2H, m), 2.14–2.02 (2H, m), 1.60–1.39 (6H, m), 1.37–1.26 (6H, m), 0.97 (3H, t, J=7.5 Hz), 0.94–0.80 (15H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7 (C), 142.1 (CH), 63.5 (CH_2), 29.2 (CH_2), 27.4 (CH_2), 22.7 (CH_2), 14.2 (CH_3), 13.7 (CH_3), 10.0 (CH_2); IR (neat) 3409, 2956, 2871, 1611, 1457 cm^{-1}; MS (ES^-) m/z 375 ($M-H^+$; ^{120}Sn); Anal. Calcd for $C_{17}H_{36}OSn$: C, 54.42; H, 9.67%. Found: C, 54.59; H, 9.62%.

4.1.3. (*E*)-2-Iodopent-2-en-1-ol (9). To a stirred solution of **18** (6.5 g, 17.3 mmol) in dichloromethane (150 mL), was added dropwise a solution of iodine (4.30 g, 16.9 mmol) in dichloromethane (150 mL). The resultant solution was stirred for 5 h and then concentrated in vacuo. The residue was dissolved in diethyl ether (25 mL), potassium fluoride (50% w/w; 25 mL) was added and the resulting mixture stirred for 12 h. The mixture was then extracted with diethyl ether (3×25 mL) and the combined organic phases were washed with saturated sodium thiosulfate solution (2× 25 mL) and brine (2×10 mL), then dried over $MgSO_4$, filtered and concentrated in vacuo. Column chromatography (5% Et_2O in petroleum ether) gave **9** (2.91 g, 81%) as a colourless oil, which darkened on standing. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.30 (1H, t, J=7.5 Hz), 4.19 (2H, s), 2.14 (3H, m), 0.98 (3H, t, J=7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2 (CH), 102.1 (C), 64.8 (CH_2), 25.7 (CH_2), 13.8 (CH_3); IR (neat) 3335, 2967, 2933, 1643 cm^{-1}; MS (EI^+) m/z, 212 (M^+), 195, 109; HRMS (EI^+): calcd for C_5H_9IO 211.9698; found 211.9695.

4.1.4. (*E*)-2-Iodo-1-(methoxymethoxy)pent-2-ene (10). To a solution of **9** (3.10 g, 14.6 mmol) in dichloromethane (20 mL) at 0 °C was added diisopropylethylamine (5.0 mL, 28.9 mmol). After stirring for 2 h, bromomethyl methyl ether (2.4 mL, 28.9 mmol) was added and the solution allowed to warm to room temperature and stirred for 18 h. The resulting mixture was washed with saturated sodium hydrogen carbonate solution (3×20 mL) and then with brine (2×15 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated in vacuo. Column chromatography (CH_2Cl_2) gave **10** (3.36 g, 90%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.44 (1H, t, J=7.6 Hz), 4.64 (2H, s), 4.23 (2H, s), 3.41 (3H, s), 2.16 (2H, app. quin, J=7.6 Hz), 1.00 (3H, t, J=7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.4 (CH), 96.5 (C), 94.7 (CH_2), 68.2 (CH_2),

55.6 (CH_3), 24.6 (CH_2), 13.8 (CH_3); IR (neat) 2933, 1630, 1457 cm^{-1}; MS (ES^+) *m/z* 274 ($M+NH_4^+$); Anal. Calcd for $C_7H_{13}O_2I$: C, 32.83; H, 5.12%. Found: C, 33.00; H, 5.12%.

4.1.5. (*E*)-3-[(Methoxymethoxy)methyl]-1-(2,2-dimethyl-1,3-dioxolan-4-yl)hex-3-en-2-ol (12). To a stirred solution of **10** (500 mg, 1.95 mmol) in pentane (15 mL) at −78 °C was added *n*-butyllithium (1.6 M in hexane; 1.7 mL, 2.72 mmol). The mixture was stirred for 20 min then **11**[20] (562 mg, 3.90 mmol) in pentane (2 mL) was added. After stirring for a further 40 min, the reaction was quenched by the addition of saturated ammonium chloride solution (3 mL). The solution was allowed to warm to room temperature and extracted with diethyl ether (3×40 mL). The combined organic phases were washed with saturated sodium hydrogen carbonate solution (2×40 mL) and then with brine (2×40 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. Column chromatography (30% EtOAc in CH_2Cl_2) gave **12** (352 mg, 66%) as a colourless oil and as a 64:36 mixture of diastereomers; ^1H NMR (300 MHz, $CDCl_3$) δ 5.73–5.65 (1H, m), 4.59 (2H, s), 4.33–4.02 (5H, m), 3.59–3.50 (1H, m), 3.35 (3H, s), 3.15 (0.64H, d, *J*=2.8 Hz), 2.78 (0.36H, d, *J*=5.1 Hz), 2.18–2.05 (2H, m), 1.92–1.74 (2H, m), 1.39 and 1.38 (3H, s), 1.32 (3H, s), 0.96 (3H, t, *J*=7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.6 (C), 136.2 (C), 134.6 (CH), 133.9 (CH), 109.5 (C), 109.0 (C), 96.3 (CH_2), 96.2 (CH_2), 75.5 (CH), 74.5 (CH), 74.1 (CH), 73.0 (CH), 70.1 (CH_2), 70.0 (CH_2), 63.2 (CH_2), 62.7 (CH_2), 55.82 (CH_3), 55.78 (CH_3), 40.2 (CH_2), 39.9 (CH_2), 27.3 (CH_3), 26.2 (CH_3), 21.3 (CH_2), 14.6 (CH_3); IR (neat) 3461, 2935, 2876, 1456, 1369 cm^{-1}; MS (CI^+) *m/z* 292 ($M+NH_4^+$), 275 (MH^+), 257; Anal. Calcd for $C_{14}H_{26}O_5$: C, 61.29; H, 9.55%. Found: C, 61.14; H, 9.44%.

4.1.6. 4-(*E*)-2-Benzyloxy-3-[(methoxymethoxy)methyl]-hex-3-enyl-2,2-dimethyl-1,3-dioxolane (13). To a stirred suspension of sodium hydride (60% dispersion in mineral oil, 285 mg, 4.35 mmol) in DMF (4.2 mL) at 0 °C was added a solution of **12** (796 mg, 2.90 mmol) in DMF (1.6 mL). After 10 min, benzyl bromide (370 mL, 3.12 mmol) and tetrabutylammonium iodide (107 mg, 0.29 mmol) were added and the mixture allowed to stir overnight. The reaction mixture was then diluted with aqueous NH_4Cl (30 mL) and extracted with diethyl ether (3×25 mL). The combined organic phases were washed with water and then with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Column chromatography (50% diethyl ether in light petroleum ether) gave **13** (982 mg, 93%) as a colourless oil and as a 66:34 mixture of diastereomers. ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.29 (5H, m), 5.73 (0.34H, t, *J*=7.5 Hz), 5.72 (0.66H, t, *J*=7.5 Hz), 4.64 (2H, m), 4.49 (0.66H, d, *J*=11.8 Hz), 4.49 (0.34H, d, *J*=11.5 Hz), 4.29–3.86 (6H, m), 3.56–3.48 (1H, m), 3.38 (1.02H, s), 3.37 (1.98H, s), 2.28–2.15 (2H, m), 2.12–2.05 (0.66H, m), 1.88–1.74 (1.34H, m), 1.38 (3H, s), 1.34 and 1.33 (3H, s), 1.03 (1.98H, t, *J*=7.5 Hz), 1.02 (1.02H, t, *J*=7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7 (C), 138.6 (C), 137.2 (CH), 136.1 (CH), 134.1 (C), 133.3 (C), 128.3 (CH), 127.8 (CH), 127.5 (CH), 127.0 (CH), 108.4 (C), 108.3 (C), 96.1 (CH_2), 95.9 (CH_2), 80.1 (CH), 80.0 (CH), 73.9 (CH), 73.4 (CH), 70.2 (CH_2), 70.1 (CH_2), 69.9 (CH_2), 69.3 (CH_2), 61.7 (CH_2), 61.5 (CH_2), 55.3 (CH_2), 39.8 (CH_2), 38.3 (CH_2), 27.0 (CH_3), 25.9 (CH_3), 21.1 (CH_2), 21.0 (CH_2), 14.4 (CH_3); IR (neat) 2984, 2874, 1454, 1378, 1028 cm^{-1}; MS (ES^+) *m/z* 382 ($M+NH_4^+$), 365 (MH^+), 333, 257; HRMS (ES^+): calcd for $C_{21}H_{36}NO_5$ ($M+NH_4^+$) 382.2588; found 382.2587.

4.1.7. (*E*)-4-Benzyloxy-5-[(methoxymethoxy)methyl]oct-5-ene-1,2-diol (19). To a stirred solution of **13** (1.50 g, 4.12 mmol) in THF (21 mL) was added a solution of 1 M HCl (21 mL). After 4 h, the mixture was diluted with ethyl acetate (50 mL) and washed with saturated sodium hydrogen carbonate solution (3×35 mL) and brine (2×25 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated in vacuo. Column chromatography (diethyl ether) gave **19** (1.30 g, 97%) as a colourless oil and as a 66:34 mixture of diastereomers. ^1H NMR (400 MHz, $CDCl_3$) δ 7.41–7.28 (5H, m), 5.81 (0.34H, t, *J*=7.5 Hz), 5.79 (0.66H, t, *J*=7.5 Hz), 4.66 (2H, s), 4.57 (0.66H, d, *J*=11.3 Hz), 4.55 (0.34H, d, *J*=11.6 Hz), 4.32 (0.66H, d, *J*=11.3 Hz), 4.29 (0.34H, d, *J*=11.6 Hz), 4.19–4.02 (3H, m), 3.95–3.87 (1H, m), 3.63–3.57 (1H, m), 3.51–3.45 (1H, m), 3.41 (3H, s), 2.71 (2H, br s), 2.32–2.19 (2H, m), 1.99–1.66 (2H, m), 1.07 (1.02H, t, *J*=7.5 Hz), 1.06 (1.98H, t, *J*=7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2 (C), 137.8 (C), 137.1 (CH), 136.8 (CH), 133.4 (C), 133.3 (C), 128.6 (CH), 128.5 (CH), 128.0 (CH), 127.95 (CH), 127.9 (CH), 127.8 (CH), 96.0 (CH_2), 83.0 (CH), 79.9 (CH), 71.7 (CH), 70.2 (CH_2), 70.1 (CH_2), 69.3 (CH), 66.9 (CH_2), 66.7 (CH_2), 61.7 (CH_2), 61.6 (CH_2), 55.5 (CH_3), 55.4 (CH_3), 38.3 (CH_2), 38.1 (CH_2), 21.1 (CH_2), 14.3 (CH_3), 14.2 (CH_3); IR (neat) 3432, 2932, 2875, 1454, 1148 cm^{-1}; MS (FAB) *m/z* 325 $(M+H)^+$; Anal. Calcd for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70%. Found C, 66.85; H, 8.69%.

4.1.8. (*E*)-3-Benzyloxy-4-[(methoxymethoxy)methyl]-hept-4-enal (2a). To a stirred solution of **19** (1.94 g, 5.98 mmol) in tetrahydrofuran (50 mL) and H_2O (16 mL) was added $NaIO_4$ (2.47 g, 11.55 mmol). After 40 min, the mixture was diluted with ethyl acetate (50 mL) and washed with H_2O (3×40 mL). The organic phase was separated, dried over $MgSO_4$, filtered and concentrated in vacuo. Column chromatography (60% diethyl ether in light petroleum ether) gave **2a** (1.62 g, 93%) as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 9.72 (1H, t, *J*=1.4 Hz), 7.37–7.26 (5H, m), 5.78 (1H, t, *J*=7.4 Hz), 4.61 (2H, s), 4.51 (1H, d, *J*=11.5 Hz), 4.37–4.32 (1H, m), 4.30 (1H, d, *J*=11.5 Hz), 4.16 (1H, d, *J*=10.9 Hz), 4.04 (1H, d, *J*=10.9 Hz), 3.37 (3H, s), 2.81 (1H, ddd, *J*=16.0, 9.0, 2.8 Hz), 2.61 (1H, ddd, *J*=16.3, 4.5, 1.8 Hz), 2.28–2.15 (2H, m), 1.03 (3H, t, *J*=7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.5 (CH), 138.1 (C), 137.3 (CH), 132.6 (C), 128.4 (CH), 127.9 (CH), 127.7 (CH), 95.9 (CH_2), 77.61 (CH), 70.2 (CH_2), 61.4 (CH_2), 55.4 (CH_3), 48.8 (CH_2), 21.0 (CH_2), 14.3 (CH_3); IR (neat) 2962, 2823, 1724 cm^{-1}; MS (CI^+) *m/z* 293 (MH^+); Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27%. Found C, 70.01; H, 8.14%.

4.1.9. (2*S,3*R**,5*R**,6*E*)-5-Benzyloxy-3-hydroxy-1-(4-hydroxy-3-hydroxymethyl-5-isobutyl-2-methoxy-phenyl)-6-[(methoxymethoxy)methyl]-2-propyl-non-6-en-1-one (3a).** To a solution of **1** (400 mg, 1.39 mmol) in dichloromethane (15 mL) at −78 °C was added $TiCl_4$ (1 M in dichloromethane, 3.2 mL, 3.2 mmol). After 10 min, tributylamine (905 μL, 3.81 mmol) was added and the solution was stirred

for an additional 2 h. Aldehyde **2a** (560 mg, 1.92 mmol) in dichloromethane (2 mL) was added and the reaction mixture was stirred for a further 2 h at −78 °C, and then quenched by the addition of H_2O (8 mL) and allowed to warm to room temperature. The mixture was diluted with dichloromethane (25 mL) and washed with saturated sodium hydrogen carbonate solution (3×30 mL) and then with brine (2×25 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated in vacuo. HPLC analysis of the mixture [Spherisorb S10 ODS2 column; 95% MeCN:5% KH_2PO_4 buffer; 1 mL/min, 280 nm, 10.05 min (major); 11.05 min (minor)] indicated that two diastereomers were produced in ca. 2:1 ratio. Repeated column chromatography (30% Et_2O in petrol then 15% EtOAc in CH_2Cl_2) provided **3a** (438 mg, 54%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (1H, s), 7.23–7.14 (6H, m), 5.63 (1H, t, J=7.6 Hz), 4.84 (2H, s), 4.51 (1H, d, J=6.5 Hz), 4.47 (1H, d, J=6.5 Hz), 4.39 (1H, d, J=11.6 Hz), 4.15 (1H, d, J=11.6 Hz), 4.05 (1H, d, J=11.0 Hz), 4.08–3.95 (3H, m), 3.83 (1H, d, J=11.0 Hz), 3.52 (3H, s), 3.39–3.29 (2H, m), 3.25 (3H, s), 2.41–2.29 (2H, m), 2.16–2.04 (2H, m), 1.89–1.63 (4H, m), 1.55–1.44 (1H, m), 1.28–1.04 (2H, m), 0.92 (3H, t, J=7.5 Hz), 0.82 (3H, d, J=6.8 Hz), 0.80 (3H, d, J=6.5 Hz), 0.76 (3H, t, J=7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.2 (C), 160.0 (C), 155.6 (C), 138.4 (C), 136.4 (CH), 133.4 (C), 131.9 (CH), 128.4 (CH), 127.8 (CH), 127.6 (CH), 125.3 (C), 124.5 (C), 117.9 (C), 95.7 (CH_2), 80.1 (CH), 70.1 (CH_2), 69.5 (CH), 63.2 (CH_3), 61.7 (CH_2), 58.6 (CH_2), 55.4 (CH), 54.2 (CH_3), 39.9 (CH_2), 38.7 (CH_2), 29.6 (CH_2), 28.4 (CH), 22.5 (CH_3), 22.4 (CH_3), 21.2 (CH_2), 21.0 (CH_2), 14.5 (CH_3), 14.3 (CH_3); IR (neat) 3284, 2956, 1661, 1585 cm^{-1}; MS (ES$^+$) m/z 609 (M+Na$^+$), 587 (MH$^+$), 479; Anal. Calcd for $C_{34}H_{50}O_8$: C, 69.60; H, 8.59%. Found: C, 69.53; H, 8.52%. A second, less polar component (185 mg, 23%) tentatively assigned as the C-5′ epimer of **3a** was also isolated. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (1H, s), 7.24–7.16 (6H, m), 5.63 (1H, t, J=7.5 Hz), 4.87 (2H, s), 4.47 (2H, m), 4.41 (1H, d, J=11.6 Hz), 4.17 (1H, d, J=11.6 Hz), 4.00 (1H, d, J=10.8 Hz), 3.98–3.90 (2H, m), 3.89 (1H, d, J=10.8 Hz), 3.54 (3H, s), 3.45–3.38 (1H, m), 3.26 (3H, s), 2.41–2.32 (2H, m), 2.18–2.00 (2H, m), 1.89–1.70 (3H, m), 1.64 (1H, ddd, J=14.3, 4.5, 2.2 Hz), 1.54–1.44 (1H, m), 1.32–1.02 (2H, m), 0.92 (3H, t, J=7.5 Hz), 0.82 (3H, d, J=6.8 Hz), 0.81 (3H, d, J=6.5 Hz), 0.78 (3H, t, J=7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.0 (C), 159.6 (C), 155.4 (C), 137.9 (C), 137.3 (CH), 133.2 (C), 132.1 (CH), 128.5 (CH), 127.8 (CH), 127.7 (CH), 125.2 (C), 124.8 (C), 117.8 (C), 95.9 (CH_2), 83.5 (CH), 72.1 (CH), 70.1 (CH_2), 63.3 (CH_3), 61.5 (CH_2), 58.6 (CH_2), 55.3 (CH), 54.8 (CH_3), 39.8 (CH_2), 38.7 (CH_2), 29.9 (CH_2), 28.4 (CH), 22.5 (CH_3), 21.0 (CH_2), 20.9 (CH_2), 14.5 (CH_3), 14.3 (CH_3); IR (neat) 3319, 2956, 2871, 1661, 1585, 1454 cm^{-1}; MS (ES$^+$) m/z 609 (M+Na$^+$), 587 (MH$^+$), 479; Anal. Calcd for $C_{34}H_{50}O_8$: C, 69.60; H, 8.59%. Found C, 69.59; H, 8.65%.

4.1.10. 3-[(2*S,3*R**,5*R**,6*E*)-5-Benzyloxy-3-hydroxy-6-[(methoxymethoxy)methyl]-2-propyl-non-6-enoyl]-6-hydroxy-5-isobutyl-2-methoxy-benzaldehyde (20).** To a stirred solution of **3a** (477 mg, 0.813 mmol) in dichloromethane (40 mL) was added MnO_2 (1.12 g, 13.2 mmol). After 4 h, the mixture was filtered through a pad of silica with ethyl acetate (200 mL) then the filtrate concentrated in vacuo. Column chromatography (5% diethyl ether in CH_2Cl_2) gave **20** (465 mg, 98%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.35 (1H, s), 10.26 (1H, s), 7.60 (1H, s), 7.31–7.23 (5H, m), 5.71 (1H, t, J=7.3 Hz), 4.63–4.58 (2H, m), 4.48 (1H, d, J=11.8 Hz), 4.24 (1H, d, J=11.8 Hz), 4.14 (1H, d, J=10.8 Hz), 4.18–4.02 (2H, m), 3.98 (1H, d, J=10.8 Hz), 3.86 (3H, s), 3.50–3.44 (1H, m), 3.37 (3H, s), 3.08 (1H, br s), 2.48 (2H, d, J=7.3 Hz), 2.25–2.15 (2H, m), 1.98–1.75 (4H, m), 1.61–1.52 (1H, m), 1.36–1.15 (2H, m), 1.01 (3H, t, J=7.5 Hz), 0.90 (6H, 2×d, J=6.8 Hz), 0.86 (3H, t, J=7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.7 (C), 194.9 (CH), 164.4 (C), 162.0 (C), 139.6 (CH), 138.5 (C), 136.4 (CH), 133.4 (C), 128.4 (CH), 127.9 (CH), 127.6 (CH), 126.5 (C), 123.9 (C), 113.7 (C), 95.9 (CH_2), 80.2 (CH), 70.3 (CH_2), 69.0 (CH), 66.1 (CH_3), 61.6 (CH_2), 55.4 (CH_3), 54.8 (CH), 39.8 (CH_2), 37.9 (CH_2), 29.4 (CH_2), 28.2 (CH), 22.4 (CH_3), 21.2 (CH_2), 21.0 (CH_2), 14.4 (CH_3), 14.3 (CH_3); IR (neat) 3448, 2891, 2876, 1632 cm^{-1}; MS (ES$^+$) m/z 607 (M+Na$^+$), 602 (M+NH$_4^+$), 585 (MH$^+$), 477; Anal. Calcd for $C_{34}H_{48}O_8$: C, 69.84; H, 8.27%. Found C, 69.90; H, 8.38%.

4.1.11. 3-[(2*S,3*R**,5*R**,6*E*)-5-Benzyloxy-3-hydroxy-6-[(methoxymethoxy)methyl]-2-propyl-non-6-enoyl]-2,6-dihydroxy-5-isobutyl-benzaldehyde (14).** To a solution of **20** (348 mg, 0.60 mmol) in degassed DMF (35 mL) was added lithium chloride (254 mg, 5.99 mmol). The resulting solution was heated at 82 °C for 27 h. On cooling, the mixture was extracted with diethyl ether (3×25 mL), and the combined organic phases were washed with Na_2CO_3 solution, water and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Column chromatography (50% Et_2O in petroleum ether) gave **14** (178 mg, 52% {67% based upon recovered starting material}) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.15 (1H, s), 12.88 (1H, s), 10.32 (1H, s), 7.60 (1H, s), 7.27–7.15 (5H, m), 5.64 (1H, t, J=7.5 Hz), 4.48 (2H, s), 4.43 (1H, d, J=11.8 Hz), 4.18 (1H, d, J=11.8 Hz), 4.02 (1H, d, J=10.8 Hz), 4.06–3.94 (2H, m), 3.88 (1H, d, J=10.8 Hz), 3.36–3.33 (1H, m), 3.25 (3H, s), 3.21 (1H, br s), 2.39 (1H, dd, J=13.4, 7.0 Hz), 2.27 (1H, dd, J=13.4, 7.3 Hz), 2.17–2.07 (2H, m), 1.87–1.58 (5H, m), 1.28–1.08 (2H, m), 0.94 (3H, t, J=7.5 Hz), 0.84 (3H, d, J=6.5 Hz), 0.81 (3H, d, J=6.5 Hz), 0.78 (3H, t, J=7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.6 (C), 194.3 (CH), 167.8 (C), 167.5 (C), 139.8 (CH), 138.2 (C), 136.6 (CH), 132.9 (C), 128.5 (CH), 127.8 (CH), 127.7 (CH), 120.8 (C), 112.3 (C), 109.3 (C), 95.9 (CH_2), 80.2 (CH), 70.2 (CH_2), 70.1 (CH), 61.8 (CH_2), 55.4 (CH), 50.6 (CH_3), 39.0 (CH_2), 37.9 (CH_2), 31.3 (CH_2), 28.3 (CH), 22.4 (CH_3), 22.2 (CH_3), 21.0 (CH_2), 20.9 (CH_2), 14.3 (CH_3); IR (neat) 3433, 2957, 2871, 1738, 1628, 1587 cm^{-1}; MS (ES$^+$) m/z 593 (M+Na$^+$); HRMS (ES$^+$): calcd for $C_{33}H_{50}NO_8$ (M+NH$_4^+$) 588.3531; found 588.3538.

4.1.12. (2*S,3*R**,5*R**,6*E*)-3-(5-Benzyloxy-3-hydroxy-6-hydroxymethyl-2-propyl-non-6-enoyl)-2,6-dihydroxy-5-isobutyl-benzaldehyde (15).** To a stirred solution of **14** (150 mg, 0.26 mmol) in ethanol (6 mL) at 40 °C was added 37% HCl (129 μL, 1.55 mmol). The solution was stirred at 40 °C for 7 h and then extracted with ethyl acetate (3×6 mL). The organic fraction was washed with saturated sodium hydrogen carbonate solution (3×5 mL) and brine (7 mL), dried over $MgSO_4$, filtered and concentrated in

vacuo. Column chromatography (30% EtOAc in CH_2Cl_2) gave **15** (109 mg, 79%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.02 (1H, s), 12.90 (1H, s), 10.31 (1H, s), 7.58 (1H, s), 7.25–7.18 (5H, m), 5.52 (1H, t, J=7.3 Hz), 4.45 (1H, d, J=11.8 Hz), 4.22 (1H, d, J=11.8 Hz), 4.11 (2H, m), 4.04–4.00 (1H, m), 3.97 (1H, dd, J=7.8, 4.8 Hz), 3.35–3.28 (1H, m), 2.50 (2H, br s), 2.40 (1H, dd, J=13.6, 7.0 Hz), 2.26 (1H, dd, J=13.6, 7.0 Hz), 2.21–2.02 (2H, m), 1.91–1.58 (4H, m), 1.26–1.07 (3H, m), 0.94 (3H, t, J=7.6 Hz), 0.83 (3H, d, J=6.6 Hz), 0.81 (3H, d, J=6.8 Hz), 0.80 (3H, t, J=7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.3 (C), 194.7 (CH), 168.4 (C), 167.9 (C), 139.9 (CH), 138.4 (C), 136.1 (CH), 135.8 (C), 128.9 (CH), 128.4 (CH), 128.2 (CH), 121.5 (C), 112.4 (C), 109.8 (C), 81.7 (CH), 70.6 (CH_2), 70.0 (CH), 57.9 (CH_2), 50.7 (CH), 39.7 (CH_2), 38.3 (CH_2), 31.4 (CH_2), 28.7 (CH), 28.5 (CH_3), 22.8 (CH_3), 22.6 (CH_3), 21.4 (CH_2), 21.3 (CH_2), 14.8 (CH_3); IR (neat) 3372, 2958, 2870, 1625, 1453, 1385 cm^{-1}; MS (ES$^+$) m/z 549 (M+Na$^+$), 527 (M+H$^+$), 419; HRMS (ES$^+$): calcd for $C_{31}H_{46}NO_7$ (M+NH$_4^+$) 544.3269; found 544.3265.

4.1.13. (2*S,3*R**,5*R**,6*E*)-5-Benzyloxy-1-[3-[(2,4-dinitrophenyl)-hydrazonomethyl]-2,4-dihydroxy-5-isobutyl-phenyl]-3-hydroxy-6-hydroxymethyl-2-propyl-non-6-en-1-one (17).** To a solution of **15** (50 mg, 0.095 mmol) in ethanol (400 μL) were added a freshly prepared solution of 2,4-dinitrophenylhydrazine (20 mg, 0.101 mmol) and sulfuric acid (50 μL) in ethanol (360 μL). This solution was stirred for 2 min, then diluted with ethyl acetate (5 mL) and washed with saturated sodium hydrogen carbonate solution (3×5 mL), water (3×5 mL) and then with brine (2×5 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated in vacuo. Column chromatography (8% diethyl ether in dichloromethane) gave **17** (60 mg, 89%) as a bright yellow solid (mp 76.5–78.5 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.84 (1H, s), 11.52 (1H, s), 11.28 (1H, s), 9.10 (1H, d, J=2.5 Hz), 8.75 (1H, s), 8.34 (1H, dd, J=9.4, 2.5 Hz), 7.53 (1H, d, J=9.4 Hz), 7.48 (1H, s), 7.26–7.18 (5H, m), 5.53 (1H, t, J=7.2 Hz), 4.46 (1H, d, J=11.9 Hz), 4.22 (1H, d, J=11.9 Hz), 4.16–4.10 (2H, m), 4.07–4.03 (1H, m), 3.98 (1H, dd, J=7.9, 4.7 Hz), 3.39–3.34 (1H, m), 2.48 (1H, dd, J=13.8, 6.9 Hz), 2.34 (1H, dd, J=13.8, 6.9 Hz), 2.21–2.04 (2H, m), 1.98–1.62 (6H, m), 1.69–1.64 (3H, m), 0.95 (3H, t, J=7.5 Hz), 0.87 (3H, d, J=6.6 Hz), 0.85 (3H, d, J=6.6 Hz), 0.81 (3H, t, J=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.1 (C), 162.5 (C), 145.9 (CH), 142.2 (C), 137.6 (C), 136.9 (C), 134.8 (CH), 134.6 (CH), 134.4 (C), 129.5 (CH), 128.9 (C), 128.7 (C), 127.5 (CH), 126.9 (CH), 126.8 (CH), 122.7 (CH), 119.9 (C), 114.1 (CH), 111.6 (C), 104.6 (C), 80.3 (CH), 69.4 (CH_2), 68.6 (CH), 56.5 (CH_2), 49.3 (CH), 38.4 (CH_2), 37.6 (CH_2), 29.7 (CH_2), 28.7 (CH), 28.3 (CH_3), 21.5 (CH_3), 21.3 (CH_3), 20.1 (CH_2), 19.8 (CH_2), 13.4 (CH_3); IR (neat) 3282, 2957, 2871, 1606, 1517 cm^{-1}; MS (ES$^+$) m/z 729 (M+Na$^+$), 707 (MH$^+$), 599; HRMS (ES$^+$): calcd for $C_{37}H_{50}N_5O_{10}$ (M+NH$_4^+$) 724.3552; found 724.3559.

Crystal data for **17**: $C_{37}H_{46}N_4O_{10}\cdot C_2H_5OH$, M=752.85, yellow block, 0.55×0.22×0.18 mm, triclinic, P-1 (No 2), α=83.471(2)°, β=71.588(2)°, γ=84.489(2)°, a=12.3738(11), b=13.1676(12), c=13.2414(12) Å, T=220 K, U=2029.6(3) Å^3, Z 2, D_{cal}=1.232 g cm^{-3}, μ(Mo Kα)=0.090 mm^{-1}, 24 711 reflections measured, 9513 unique [R_{int}=0.0386], R [$I>2\sigma(I)$]=0.0555, wR [$I>2\sigma(I)$]=0.1749 (all data), $GooF$=0.998. Crystallographic data (excluding structural factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 631511. Copies can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or email: deposit@ccdc.cam.ac.uk).

4.1.14. Luminacin D and 6′,8′-*epi*-luminacin D (16). To a stirred solution of **15** (200 mg, 0.38 mmol) in benzene (6 mL) was added vanadyl acetylacetonate (10 mg, 0.038 mmol) and a solution of *tert*-butyl hydroperoxide (5 M in decane; 114 μL, 0.57 mmol). The reaction mixture turned brown and the reaction progress was monitored by thin layer chromatography until judged complete. The reaction mixture was diluted with ethyl acetate (5 mL) and washed with saturated sodium hydrogen carbonate solution (3×10 mL) and brine (3×10 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. Column chromatography (2% Et_2O in CH_2Cl_2) yielded a partially purified mixture of epoxide diastereomers that were used directly in the next step. To the mixture of epoxides (148 mg, 0.27 mmol) in dichloromethane (8 mL) was added Dess–Martin periodinane (114.5 mg, 0.27 mmol). After stirring for 20 min, the reaction mixture was poured onto a rapidly stirred solution of sodium sulfite (50% w/w; 10 mL). After 20 min, the mixture was extracted with dichloromethane (4×10 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. Column chromatography allowed partial purification of 5′-benzyl-luminacin D (32 mg) and 5′-benzyl-6′,8′-*epi*-luminacin D (60 mg), which were separately subjected to debenzylation. To 5′-benzyl-luminacin D (32 mg, 0.059 mmol) in ethyl acetate (3 mL) was added 10% Pd/C (20 mg) and the mixture stirred vigorously under a hydrogen atmosphere for 10 min. The mixture was filtered through a pad of Celite® then the filtrate concentrated in vacuo. Preparative thin layer chromatography (30% EtOAc in hexanes) gave (±)-luminacin D (15 mg, 9% over three steps) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 14.15 (1H, s), 12.98 (1H, s), 10.40 (1H, s), 7.73 (1H, s), 4.99 (1H, br s), 4.38 (1H, dd, J=10.0, 8.4 Hz), 4.23–4.15 (1H, m), 3.55 (1H, dt, J=9.0, 4.0 Hz), 3.29 (1H, t, J=7.0 Hz), 2.61 (1H, d, J=2.8 Hz), 2.47 (1H, dd, J=13.5, 7.0 Hz), 2.42 (1H, dd, J=13.5, 7.0 Hz), 2.02 (1H, ddd, J=12.5, 5.0, 1.5 Hz), 1.95–1.74 (3H, m), 1.68–1.56 (2H, m), 1.51 (1H, d, J=11.8 Hz), 1.42 (1H, q, J=11.9 Hz), 1.29–1.18 (2H, m), 1.08 (3H, t, J=7.5 Hz), 0.91 (3H, d, J=6.6 Hz), 0.90 (3H, d, J=6.6 Hz), 0.87 (3H, t, J=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.7 (C), 194.3 (CH), 168.0 (C), 167.5 (C), 139.5 (CH), 121.0 (C), 112.6 (C), 109.4 (C), 94.5 (CH), 69.8 (CH), 62.4 (CH), 61.8 (C), 59.9 (CH) 49.4 (CH), 38.0 (CH_2), 37.3 (CH_2), 32.1 (CH_2), 28.3 (CH), 22.4 (CH_3), 22.3 (CH_3), 20.7 (CH_2), 20.6 (CH_2), 14.3 (CH_3), 10.6 (CH_3); IR (neat) 3396, 2958, 2871, 1624, 1458, 1383 cm^{-1}; MS (ES$^+$) m/z 473 (M+Na$^+$), 451 (MH$^+$), 253; HRMS (ES$^+$): calcd for $C_{24}H_{38}NO_8$ (M+NH$_4^+$) 468.2592; found 468.2588. Similarly, to 5′-benzyl-6′,8′-*epi*-luminacin D (60 mg, 0.11 mmol) in ethyl acetate (4 mL) was added 10% Pd/C (30 mg) and the reaction mixture stirred vigorously under a hydrogen atmosphere for 10 min. The mixture was filtered through a pad of Celite® then the filtrate concentrated in vacuo. Column

chromatography (30% ethyl acetate in hexane) gave **16** (48 mg, 28% over 3 steps) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.15 (1H, s), 12.96 (1H, s), 10.39 (1H, s), 7.74 (1H, s), 4.96 (1H, d, J=2.0 Hz), 4.45 (1H, ddd, J=11.8, 7.0, 2.0 Hz), 4.38 (1H, dd, J=11.8, 5.0 Hz), 3.59–3.53 (1H, m), 3.27 (1H, t, J=6.8 Hz), 3.14 (1H, d, J=3.0 Hz), 2.45 (2H, d, J=7.3 Hz), 2.12 (1H, ddd, J=12.5, 4.8, 2.2 Hz), 2.05 (1H, br s), 1.92–1.80 (3H, m), 1.72–1.60 (3H, m), 1.50 (1H, q, J=11.8 Hz), 1.46–1.39 (1H, m), 1.25 (3H, t, J=7.2 Hz), 0.91 (3H, d, J=6.6 Hz), 0.89 (3H, d, J=6.8 Hz), 0.88 (3H, t, J=7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.0 (C), 194.7 (CH), 168.4 (C), 167.8 (C), 140.2 (CH), 121.2 (C), 113.0 (C), 109.7 (C), 92.8 (CH), 70.2 (CH), 65.0 (C), 63.2 (CH), 59.9 (CH), 49.4 (CH), 38.3 (CH_2), 37.0 (CH_2), 32.1 (CH_2), 28.6 (CH), 22.7 (2×CH_3), 21.6 (CH_2), 21.0 (CH_2), 14.6 (CH_3), 10.4 (CH_3); IR (neat) 3411, 2958, 2871, 1624, 1455, 1384 cm^{-1}; MS (ES$^+$) m/z 473 (M+Na$^+$), 451 (MH$^+$), 253; HRMS (ES$^+$): calcd for $C_{24}H_{38}NO_8$ (M+NH_4^+) 468.2592; found 468.2596.

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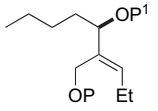

21 (P = H; P^1 = Bn);
22 (P = H; P^1 = H);
23 (P = TBDMS; P^1 = Bn).