Total Synthesis of (−)-Luminacin D

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Abstract—A second generation synthesis of (−)-luminacin D based on an early stage introduction of the trisubstituted epoxide group is reported, allowing access to the natural product in an improved yield and a reduced number of steps (5.4%, 17 steps vs 2.6%, 19 steps). A full account of the optimization work is provided, with the reversal of stereoselection in the formation of the C4 alcohol in equally excellent diastereoselectivity as the key improvement.

1. Introduction
Angiogenesis is defined as the formation of new blood vessels from the pre-existing vascular network.1 Through its involvement in numerous pathologies, including tumor growth and metastasis, angiogenesis and its associated regulation mechanisms have emerged as promising targets in drug
discovery. In particular, remarkable efforts have been directed towards the identification of angiogenic modulators among the natural products.\textsuperscript{2,3}

The luminacin family of natural products, originally isolated from bacterial fermentation, contains numerous members that have been shown to exhibit potent antiangiogenic activity in several assays. Wakabayashi et al. notably demonstrated that luminacins operate by blocking the initial stages of the capillary tube formation \textit{in vitro}, with luminacin D 1a (Chart 1) being the most active among the 12 members tested.\textsuperscript{4} Later on, additional \textit{in vivo} studies using luminacin C2 1b revealed that this molecule effectively inhibited the phosphorylation activity of Src tyrosine kinases, and was found to exert its unique mode of action by disrupting Src mediated protein-protein interactions.\textsuperscript{5,6} Src tyrosine kinases play key roles in the regulation of numerous processes associated to angiogenesis, including growth, differentiation, migration and survival.\textsuperscript{7} In addition, luminacin C2 was also found to inhibit breast cancer cell invasion and metastasis \textit{in vitro} by disrupting the AMAP1-cortactin binding (protein-protein interactions).\textsuperscript{8} The recent isolation of two cancer cell migration inhibitors of similar structure (migracins A and B, 1c, 1d), highlighted once more the therapeutic potential of these molecules.\textsuperscript{9}

\begin{center}
Chart 1. Structure of luminacins
\end{center}

Despite its promising anti-angiogenic activity as revealed by the original work of Wakabayashi, luminacin D has been less extensively studied in comparison with some other members of its family, and little information can be found regarding its mode of action and biological functions. To obtain
further material to enable further biological investigations, chemical synthesis is the most efficient way given the modest yield from extraction (and the fact that a new extraction campaign would be required).

Apart from our recent contribution, so far there have been four reported syntheses of luminacin derivatives, each presenting shortcomings in term of length or selectivity. In particular, the efficiency of three from these four syntheses was dramatically compromised by the low or undesired stereoselectivity associated with the epoxidation step which, in addition, in each case took place at a late stage of the synthesis. In this context, we achieved a highly diastereoselective synthesis of (−)-luminacin D in 19 steps. As shown in Scheme 1, our synthetic approach relied on the stereoselective introduction of the epoxide moiety at an early stage of the synthesis starting from the enantiopure sulfoxide, and subsequently to utilize the chirality of the epoxide group in 4 for the diastereoselective completion of the aliphatic fragment. This was achieved via a chelation-controlled allylation procedure of the enantiopure α-epoxy aldehyde, which proceeded in excellent yield and diastereoselectivity. Unfortunately, the reaction led to the formation of the undesired diastereoisomer, and thus an inversion of the obtained alcohol stereocentre was required to complete the synthesis. As further shown in the retrosynthetic analysis, the formation of Luminacin D was realized via arylation of the fully functionalized fragment, whose construction was envisaged via spontaneous hemiacetal formation and syn-aldol reaction from the key compound. A full account of the different approaches for the formation of the cyclic hemiacetal moiety, and further optimizations of several other steps are disclosed here. In particular, this includes our efforts towards the development of methodology that resulted in direct access to the key intermediate from 4.
Scheme 1. Retrosynthetic analysis and new diastereoselective methodologies developed

**Results and discussion**

**Synthesis of the epoxide precursor (ester-sulfoxide 9)**

Starting from the $\alpha$-sulfoxy-esters 5, we initially investigated the one-pot Knoevenagel procedure described by Tanikaga et al.\textsuperscript{16} in order to access to the desired (E)-alkenes $8_{\text{Tol}}$ and $8_{\text{Ph}}$. This method proved unsuccessful when applied to our substrates (recovery of starting material). Hence, as described in our previous communication,\textsuperscript{10} the formation of racemic and enantiopure $\alpha,\beta$-unsaturated (E)-alkenes ($\pm$)-$8_{\text{Ph}}$ and $8_{\text{Tol}}$ was then accomplished in 2 steps from the corresponding $\beta$-sulfoxy-ester, as shown in Scheme 2. At first, following a known procedure,\textsuperscript{17} an aldol-type condensation of 5 with propanal led to the $\beta$-hydroxy ester 7 as an impure mixture of diastereoisomers. It was found that treatment of this mixture with MsCl in pyridine afforded alkenes 8 in excellent yield and
stereoselectivity. Further to Tanikaga’s stereochemical assignment by chemical shift differences, the \( E \) configuration of \( 8 \) is now further confirmed by NOE analysis (see SI).

Scheme 2. Synthesis of \((E)\)-alkenes \( 8 \)

The subsequent epoxidation step had been achieved in a diastereoselective manner in our previous synthesis, using a procedure that was adapted from De La Pradilla’s vinyl sulfoxide methodology (Table 1, entries 1 and 2). The reaction proceeded in excellent yield and diastereoselectivity with the phenyl derivative \( 8_{\text{Ph}} \) (90\%, \( dr \) 94:6), while the same reaction conditions applied with tolyl derivative \( 8_{\text{Tol}} \) led to lower yield and diastereoselectivity (77\%, \( dr \) 88:12). In addition, the product \( 12 \) was obtained in 19\% yield as mixture of diastereoisomers (Table 1). The latter was thought to arise from the nucleophilic attack of \( n \)-BuLi onto the Michael intermediate \( 11 \), since an excess of \( n \)-BuLi was used compared to \( t \)-BuOOH (5 vs 4 equiv., respectively).

We then decided to investigate modified conditions for the epoxidation reaction. The first experiment was carried out with \( 8_{\text{Tol}} \) by using an excess of \( t \)-BuOOH compared to \( n \)-BuLi (Entry 3). Although the reaction proceeded without any formation of \( 12 \), the formation of undesired by-products could be observed by \(^1H\) NMR, alongside with the expected \( \text{trans} \)-epoxides \( \text{syn-9}_{\text{Tol}} \) and \( \text{anti-9}_{\text{Tol}} \). After column
chromatography, the epoxides were isolated as a mixture of diastereoisomers in moderate yield (60%, \(dr \text{ syn-}9_{\text{Tol}}/\text{anti-}9_{\text{Tol}} 95:5\)). A mixture of two unexpected products was also isolated in 16% yield, which allowed their assignment as the cis-epoxide isomers \(\text{syn-}10_{\text{Tol}}\) and \(\text{anti-}10_{\text{Tol}}\). Following this, it was found that using a 1:1 ratio of \(t\)-BuOOH and \(n\)-BuLi, and reducing the reaction time allowed to minimize the formation of the cis-epoxides \(10_{\text{Tol}}\) (Entry 4). The trans-epoxide \(9_{\text{Tol}}\) was isolated in both excellent yield and diastereoselectivity in these conditions (82%, \(dr \text{ syn-}9_{\text{Tol}}/\text{anti-}9_{\text{Tol}} 91:9\)). Interestingly, the replacement of \(n\)-BuLi by NaH as base with the racemic derivative \((\pm)-8_{\text{ph}}\) resulted in promoting the formation of cis-isomers \(10_{\text{ph}}\), with a good selectivity towards the syn-epoxide \((\pm)-\text{syn-}10_{\text{ph}}\) (Entry 5). The same outcome was observed when an excess of NaH compared to \(t\)-BuOOH was used with the tolyl derivative \(8_{\text{Tol}}\) (Entry 6). The epoxidation reaction was carried out on 3 g scale (10 mmol) with the tolyl derivative \(8_{\text{Tol}}\) using the optimised conditions, and enabled isolation of the expected trans-epoxides \(9_{\text{Tol}}\) in a slightly improved yield and diastereoselectivity compared to our earlier procedure (Entry 7, 82%, \(dr \text{ syn/anti} 92:8 \text{ vs } 77\% \text{ dr syn/anti} 88:12\)). A minor quantity of the cis-epoxides \(10_{\text{Tol}}\) was also obtained after separation (<2% yield).
Table 1. Optimisation of the epoxidation reaction. Prefixes *syn/anti* refer to the relative position of the sulfoxide aryl group compared to the epoxide function. Prefixes *trans/cis* (as used in the discussion) refer to the relative arrangement of the epoxide substituents.

| Entry | Ar. | Base (equiv.) | t-BuOOH (equiv.) | t (h) | *dr syn-9/anti-9/ syn-10/anti-10* | Overall Yield (%)<sup>b</sup> | Yield 9 (%)<sup>b</sup> | Yield 10 (%)<sup>b</sup> |
|-------|-----|---------------|-----------------|-------|-------------------------------|---------------------------|----------------|------------------|
| 1<sup>c</sup> | Ph  | *n*-BuLi (5)  | 4<sup>d</sup> | 0.4  | 94:6<sup>c,e</sup> | 89 | 89 | f |
| 2<sup>c</sup> | Tol | *n*-BuLi (5)  | 4<sup>d</sup> | 0.4  | 88:12<sup>c,e</sup> | 77 | 77 | f |
| 3      | Tol | *n*-BuLi (4)  | 4.9 – 6<sup>g</sup> | 1.5  | 72 : 4 : 16 : 8 | 91 | 60 | 16 |
| 4      | Tol | *n*-BuLi (3)  | 3<sup>d</sup> | 0.4  | 81 : 8 : 6 : 6 | 88 | 82 | h |
| 5      | Ph  | NaH (2.5)     | 3.2 – 3.9<sup>f</sup> | 0.4  | 35 : 4 : 54 : 7 | 78 | 23 | 53 |
| 6      | Tol | NaH (3.2)     | 3<sup>d</sup> | 0.4  | 45 : 2 : 50 : 3 | 78 | h | 25 |
| 7<sup>c</sup> | Tol | *n*-BuLi (3)  | 3<sup>d</sup> | 0.4  | 86 : 7 : 4 : 3 | 88 | 82 | <2 |

<sup>a</sup>syn-9<sub>Tol</sub>, anti-9<sub>Tol</sub>, syn-10<sub>Tol</sub>, anti-10<sub>Tol</sub>

<sup>b</sup>Overall Yield, Yield 9, and Yield 10 are expressed as percentage.

<sup>c</sup>Conditions: THF, -78 °C

<sup>d</sup>Reaction time in hours.

<sup>e</sup>Dr. syn/anti.

<sup>f</sup>Overall yield.

<sup>g</sup>Base: *n*-BuLi (5) to *n*-BuLi (3).

<sup>h</sup>Yield 9 and Yield 10.
The assignment of configuration of all the epoxide stereomers was achieved by a combination of X-ray crystallographic analysis and a chemical correlation experiment. The configuration of the crystalline C3 (“pseudo”-) epimers syn-9<sub>Tol</sub> and (±)-syn-10<sub>Ph</sub> was established by X-ray analysis (see supporting information), as the syn-isomers for both 9 and 10 crystallized as pure diastereomers. The stereochemical relationship between the syn- and anti-epoxides was established by the oxidation (Scheme 3) of a mixture of isomers syn-10<sub>Tol</sub> and anti-10<sub>Tol</sub> (dr ~1:1), which led to a single sulfone 13 (as observed by 1H NMR), which allowed unambiguous assignment of anti-10<sub>Tol</sub> as the cis-anti-epoxide (and by inference, also that of anti-10<sub>Ph</sub>).

Scheme 3. Sulfone formation

**Synthesis of the intermediate 3: the diastereoselective reduction approach**

As already mentioned, we previously reported the development of chelation-controlled allylation methodology, which, when applied to aldehydes possessing an α-oxygenated center, proceeded with excellent diastereoselectivity. The selectivity outcome was found consistent with the formation of a 1,3-chelated transition state, in which facial selectivity is dictated by a Cornforth-Evans (CE) type
model. With the aim of developing a complementary approach to the aforementioned allylation step, our investigations were directed towards a chelation-mediated reduction involving 1,3-keto esters such as 4b, in which the stereoselection would be equally predicted by the CE model. Hence, by invoking 14, hydride attack of the least congested Si-face would directly lead to the key intermediate 3 (Scheme 4). We were encouraged in this approach by the work of Castle et al. regarding the selective addition of various nucleophiles to a 1,3-alkoxy ketone containing an α-OTBS substituent, which was found to operate via a 1,3-chelation controlled transition state combined with CE-type stabilization. Furthermore, a number of methodologies for the metal-mediated diastereoselective reduction of β-keto esters, β-hydroxy ketones and α-epoxy ketones have been described, leading in general to excellent facial selectivity.

### Scheme 4. Proposed reduction approach

In order to simplify the optimization studies, we first focused on the synthesis of the β-propyl keto ester 4c, whose formation was envisaged via acylation reaction of the sulfoxide 9\textsubscript{Tol} (Table 2). This was achieved in moderate yield, via treatment of 9\textsubscript{Tol} with t-BuLi and subsequent trapping of the resulting oxiranyl anion with methyl butyrate, under Barbier conditions. As these reactions were carried out on the 92:8 syn/anti mixture, an 84% product enantiopurity was obtained. Unfortunately, the selective crystallization procedure of 9 as explained above was only achieved after carrying out the experiments given in Table 2, but would give access to enantiopure material. As shown in table 2, several trials...
involving a Lewis acid to induce chelation-control during the reduction reaction were undertaken. As a first experiment, treatment of 4c with NaBH₄ and MgBr₂, in a mixture of THF/DCM gave no expected product. Instead, these conditions resulted in the formation of the bromohydrin 17 as major product (48% isolated yield), alongside with the reduced bromohydrin 18 as a mixture of diastereoisomers. The anti-product 18a was isolated in 9% yield. The epoxide opening issue was overcome by performing the reaction at 0 °C in MeOH, leading to the exclusive formation of products 16. To our surprise, the undesired anti-diastereoisomer 16a was obtained as major product (dr 16a/16b 71:29, Entry 2), which is not consistent with reaction via the transition state 14 (cf. Scheme 4). Replacing MgBr₂ by CaCl₂ as chelating metal resulted in a similar outcome, with 15a obtained in good isolated yield and excellent diastereoselectivity (70%, dr 16a/16b 97:3, Entry 3). Following this, the use of Et³SiH or L-selectride as reducing agents with MgBr₂ was also attempted at -78 °C, though both conditions led to the exclusive formation of the bromohydrin 17 (Entry 4 and 5). Since the involvement of MgBr₂/CaCl₂ led to undesired diastereoselectivity or unexpected reactivity, the reduction of the ketone 4c was attempted using L-selectride only (Entry 6). This time, the reaction proceeded in good yield and excellent diastereoselectivity towards the desired syn-product 16b (Entry 6, 90%, dr 16a/16b 1:9). Interestingly, employing the more hindered LS-selectride led to a drop of conversion and selectivity.
Table 2. Acylation and attempted conditions for the reduction reaction

| Entry | Conditions | Yield | Yield | Yield |
|-------|------------|-------|-------|-------|
|       |            | 16 (%) (dr) | 17 (%) | 18 (%) (dr) |
| 1     | NaBH₄ (1.05 equiv.), MgBr₂, (1.6 equiv.), DCM/THF 2:1, -78 °C to rt, 3 h | a | 78⁷⁺ (48)⁷⁺⁺ | 22⁷⁺ (9)⁷⁺⁺ (dr 18a/18b 93:7)⁷⁺⁺⁺ |
| 2     | NaBH₄ (1.2 equiv.), MgBr₂ (2 equiv.), MeOH, 0 °C, 30 min. | 100⁷⁺⁺⁺ | a | a |
| 3     | NaBH₄ (0.6 equiv.), CaCl₂ (2 equiv.), MeOH, 0 °C, 30 min | 100⁷⁺⁺⁺⁺ (72)⁷⁺⁺⁺⁺ (dr 16a/16b 97:3)⁷⁺⁺⁺⁺ |
| 4     | Et₃SiH (1.05 equiv.), MgBr₂ (1.6 equiv), DCM, -78 °C, 2 h | a | 83⁷⁺⁺⁺⁺⁺ (64)⁷⁺⁺⁺⁺⁺ | a |
| 5     | L-selectride (1.05 equiv.), MgBr₂, (1.6 equiv), DCM, -78 °C, 2 h | a | 100⁷⁺⁺⁺⁺⁺ | a |
| 6     | L-selectride (1.05 equiv.), THF, -78 °C, 30 min. | 100⁷⁺⁺⁺⁺⁺ (90)⁷⁺⁺⁺⁺⁺ | a | a |
| 7     | LS-selectride (1.3 equiv.), THF, -78 °C, 45 min. | 48⁷⁺⁺⁺⁺ | a | a |

⁷⁺ Not formed; ⁷⁺⁺ Determined by ¹H NMR; ⁷⁺⁺⁺ Isolated yield.

As shown in Figure 1, the selectivity observed when NaBH₄/CaCl₂ and MgBr₂ were used could be explained by the 1,2-chelated transition state 19, assuming that the metal salt catalyzes the formation
formation of alkoxyborohydrides $\text{NaBH}_4\cdot n(\text{OMe})_n$ in MeOH. The coordination between a $\text{Ca}^{2+}$ and the methoxy group of the borohydride species would therefore direct the hydride attack to the $\text{Re}$-face, leading to the $\text{anti}$-compound $16\text{a}$. On the other hand, the models $20$ and $21$ are consistent with the selectivity observed when $\text{L}$ or $\text{LS}$-selectride are employed, assuming that the $\text{Li}$ cation is able to chelate between the carbonyl groups (model $20$) or between the carbonyl group and the epoxide (model $21$). Hydride attack from the least hindered Si-face in both cases would lead to the observed formation of the $\text{syn}$-compound $16\text{b}$.

![Figure 1](image.png)

**Figure 1.** Possible rationalization of the selectivity outcome

The relative configuration of $16\text{a}$ and $16\text{b}$ was assigned by NMR comparison with the $\text{anti}$-alcohol, which was obtained after reduction of the double bond of previously synthesized $3$ (Scheme 5). The regioselectivity of bromide mediated epoxide opening on $4\text{c}$, and the relative configuration of the resulting $18\text{a}$, were determined thanks to X-ray crystallographic analysis (See SI).

**Scheme 5. Hydrogenation of 3 to allow assignment of the relative stereochemistry**

![Scheme 5](image.png)
Motivated by these results, the acylation/diastereoselective reduction procedure was then applied towards the luminacin D synthesis, using methyl but-3-eneoate $22^{27}$ and L-selectride (Scheme 6). Since the intermediate $4b$ proved unstable to purification on silica gel (with double bond isomerization occurring during silica gel chromatography, not shown), the reduction reaction was attempted on the crude material, immediately after work-up. A first experiment was conducted on small scale with the racemic epoxide $(\pm)-9_{Ph}$ and L-selectride as reducing agent. The syn-$\alpha$-epoxy alcohol $(\pm)-3$ was obtained as major product in an encouraging yield (19 % over 2 steps), together with a minor quantity of the anti-diastereoisomer $(\pm)-7$ (1% over 2 steps, separation achieved by column chromatography). Unfortunately, the reaction proved less efficient on 1 g scale, resulting in a drop of yield (14% for $(\pm)-3$ over 2 steps). Several parameters, including the volatility of intermediate $4b$ and the purification issues induced by the formation of numerous by-products over the 2 steps, made the process cumbersome.

Scheme 6. Formation of 3 and 7 via the reduction approach

Synthesis of the intermediate 3: the allylation approach

Given the moderate yield obtained with the previous approach, the original strategy involving an allylation reaction was reconsidered, with the aim of developing new conditions allowing access to the opposite selectivity outcome compared to the MgBr$_2$-promoted allylation procedure. Given the
unexpected stereochemical outcome of the reduction process using CaCl₂ as explained above, this additive was now used in a reinvestigation of the allylation of 4a. Hence, the aldehyde 4a (and (±)-4a) was re-synthesized through formylation of the epoxide precursors 9, applying similar conditions as used for the acylation procedure (Table 3). Pleasingly, the reaction proceeded in an improved yield compared to our previous procedure,¹⁰ and is generally more efficient as it can be conducted at -78 °C (instead of -120 °C) without the need of CeCl₃, which had to be dried under vacuum prior to the reaction and made the work up difficult.

We then examined the use of a modified procedure for the allylation reaction (Table 3). The conditions of the reported procedure (Entry 1), but with CaCl₂ instead of MgBr₂, were investigated first (Entry 2). Despite the poor conversion obtained, we were pleased to notice that only the desired syn-diastereoisomer 3 was formed during the reaction, as observed by ¹H NMR of the reaction mixture before chromatography. Increasing the temperature, concentration and reaction time resulted in a better conversion, with 3 obtained in a very good diastereoselectivity (Entry 3, dr 3/7 92:8). Based on these results, it was envisaged that CaCl₂ might not be involved in a chelated transition state, but would only act as a weak activator of the reaction. To confirm this hypothesis, investigations were directed towards the use of non-chelating conditions for the allylation reaction. A first experiment involving the reaction of 4a with allyltrimethylsilane and a sub-stoichiometric amount of TBAF led to the recovery of the starting material (Entry 4).²⁸ However, the allylation of 4a occurred using the more reactive pinacolyl allylboronate 23 in DCM, by raising the temperature from -78 °C to rt overnight (entry 5).²⁹ As predicted, the non-chelation control promoted the formation of the desired syn-diastereoisomer 3, in an excellent diastereoselectivity and isolated yield. This result mirrors the work of Mulzer and Prantz, who recently demonstrated that the selectivity of the allylation of 2,2-dialkyl-3-oxopropionates could be reverted by switching from chelation (TiCl₄) to non-chelation (BF₃•OEt₂) mediated allylation.³⁰ It should be noted that both these Lewis acids are not compatible with the epoxide-containing substrate 4.
The optimised two-steps procedure was then carried out on 1.5 g (5 mmol) scale of sulfoxide 9_{tol} (dr 92:8)(Entry 6). The slow addition of t-BuLi to the mixture via syringe pump over a period of 1 h was found to give the best results for the formylation reaction. After column chromatography, the aldehyde 4a was obtained in a mixture with minor impurities. Subsequent treatment with the pinacolyl allylboronate 23 using the optimised conditions enabled isolation of the syn-alcohol 3 as major product in 33 % yield over 2 steps, together with the minor anti-diastereoisomer 7, isolated in 1% yield. Although an accurate dr determination was not possible by ^1H NMR due to the presence of impurities, the ratio of isolated yields of 7 and 3 is consistent with that observed on small scale. Similar results were obtained when the racemic phenyl epoxide (±)-9_{ph} was used as starting material (Entry 7).

Table 3. Formylation and attempted conditions for the allylation reaction

| Entry | Ar | M    | Conditions                                      | Conversion (%)^a | dr 7/3 | Yield 7 (%)^b | Yield 3 (%)^b |
|-------|----|------|------------------------------------------------|------------------|-------|---------------|---------------|
| 1c    | Tol| SnBu₃| MgBr₂ (1.6 equiv.), DCM (0.2 M), -78 °C, 2 h   | > 95.5^a         |       | 87            |               |
| 2     | Ph | SnBu₃| CaCl₂ (1.6 equiv.), DCM (0.2 M), -78 °C, 2h    | 4                | n.d   | 4             |               |
| 3     | Ph | SnBu₃| CaCl₂ (1 equiv.), DCM (0.7M), rt, 30h          | 35               | 8:92^a| 28            | <1            |
| 4     | Ph | TMS  | TBAF (0.1 equiv.), MS 4Å, DCM (0.05 M), rt, 48h| s.m recovered    |       |               |               |
In the context of the luminacin D synthesis, this new procedure represents a significant improvement compared to the previous route reported by our laboratory, which required two extra steps for the formation of 3, in a lower overall yield (24% over 4 steps). The excellent substrate control of this allylation reaction under non-chelating conditions can be rationalized (Figure 2) by invoking the classic Cornforth-Evans (24) or polar Felkin-Anh (25) models, assuming that the C-O bond of the epoxide acts as the “polar substituent” in preference to the ester.

Figure 2. Cornforth-Evans (24) and polar Felkin-Anh (25) models to explain the observed diastereoselectivity.

Completion of the aliphatic fragment: aldol reaction and attempted lactonization.

With access to the pure intermediate 3 (and (±)-3), the synthesis was pursued towards the formation of aldehyde 26 (and (±)-26), which was accomplished in two steps, following the reported procedure
The β-chiral silyl ether center on 26 offered the possibility for remote stereocontrol, which had been exploited in the luminacin D synthesis by Shipman et al. However, the use of a titanium enolate derived from an aromatic ketone (already containing the luminacin D aliphatic moiety) only led to modest stereocontrol ($dr \sim 2:1$, in favor of the desired isomer). Interestingly, while this type of remote stereocontrol has been mainly investigated for Mukaiyama aldol reactions, we found no related investigations of the extent of remote stereocontrol for aldol reactions involving classic $N$-acyl oxazolidinone boron enolate reagents. Hence, at this juncture, it was decided to investigate this process using simplified model compounds in order to evaluate its potential usefulness in the luminacin D synthesis (Table 4). Aldehydes (±)-27 and (±)-28 were prepared according to standard procedures and subjected to aldol reactions with the boron enolate of 29. For the reaction between the ethyl oxazolidinone 28a and (±)-26, a low stereocontrol was obtained (Entry 1). As predicted from the Evans model, the major isomer contained the desired relative stereochemistry for our purposes (see SI for the determination of the product relative stereochemistry). Increasing the size of the protecting group (as in (±)-28) led to a slight increase of the desired selectivity (Entry 2). A further increase of the steric bulk by using 29b, the reagent required for the luminacin D synthesis, did give a reasonable 5:1 ratio (Entry 3).

**Scheme 7. Synthesis of aldehyde 26**

(Scheme 7).
Table 4. Investigation of remote stereocontrol for the aldol reaction

| Entry | dr 30/31 | R  | P     |
|-------|----------|----|-------|
| 1     | 2:1      | Me | Bn    |
| 2     | 3:1      | Me | TBDPS |
| 3     | 5:1      | Pr | TBDPS |

* Determined by $^1$H NMR.

With this level of selectivity obtained, this diastereoselective aldol reaction was then performed on the racemic natural product intermediate (±)-32 with a TBDPS protecting group (Scheme 8). Unfortunately, a slightly diminished level of selectivity (4:1) was obtained for the desired aldol diastereomer (±)-33.

Scheme 8. Translation of the diastereoselective aldol reaction to the natural product system
Given the modest diastereoselectivity favoured the desired stereomer, a matched double diastereodifferentiation process using a chiral oxazolidinone based auxiliary was then investigated. This approach has also been used in the luminacin D synthesis by Maier et al.\textsuperscript{14} Hence, the enantiopure oxazolidinone 35\textsuperscript{33} was required (Scheme 9). For atom economy reasons, it was decided to use a TES protecting group as opposed to a TBDPS group. Initially, the racemic aldehyde (±)-26 was engaged in Evans-aldol reaction with the acyl chiral oxazolidinone, which led to the formation of two (among the four possible) aldol adducts (\textsuperscript{1}H NMR analysis) in a 1:1 \textit{dr}. The two isomers could be separated by preparative HPLC after TES protection of the formed alcohol, allowing isolation of the expected aldol product 38\textsuperscript{10} as well as the isomer 39, the latter resulting from the aldol reaction of the oxazolidinone 35 with the enantiomer of 26, since racemic starting material was employed. Given the low remote stereocontrol exerted by the alcohol chiral centre as shown above, it is thought that the auxiliary dominates the stereoselection, leading to the C2’,C3’-syn-C3’,C5’-syn diastereoisomer 37. With enantioenriched aldehyde 26 (\textit{er} 92:8), exclusive formation of the aldol products 36 and 37 in a 91:9 \textit{dr} was observed. From that mixture, alcohol protection and HPLC separation allowed isolation of 38 and 39 in 86 and 6\% yields, respectively. As mentioned above, applying the selective crystallization procedure of 9 would avoid this separation issue, as in this case only aldol product 36 would be formed.
Cyclization of the aliphatic fragment: first approach

It was envisaged that the synthesis of the aliphatic fragment could be completed at this stage by acid-catalyzed t-Bu deprotection, which would initiate lactone formation that then could be reduced to the luminacin D lactol ring. The lactone formation was first investigated using the racemic aldol product 33 was used as model substrate (Scheme 10). To our surprise, heating with CSA in toluene led to a product with the t-Bu ester intact, but in which cyclization towards the epoxide group had occurred, leading to 41 in excellent yield (81%). When TFA in DCM was used, the desired lactone formation did occur, but only 11% of the 43 was isolated. Under these conditions, the same alternative cyclization leading to a tetrahydropyran group occurred, even if the resulting product 44 was isolated as the carboxylic acid. Presumably the slow t-butyl ester deprotection promoted tetrahydropyran over lactone formation, and the COOH deprotection leading to 44 could have occurred after the ring formation.
Assignment of the different cyclisation products was achieved by HMBC and NOE analyses (see supporting information).

Scheme 10. Deprotection and unexpected cyclisation of the aldol product 33

Cyclization under basic conditions was also unsuccessful (Scheme 11). Treatment of the aldol product 33 with sodium hydride resulted in the formation of a product 45 in low yield, in which both elimination and oxazolidinone ring opening had occurred. Interestingly, when 33 was subjected to lithium ethylthiolate (see next section), the same elimination product was obtained in quantitative yield. A mechanism of formation for this product 45 is proposed: deprotonation of the hydroxyl group initiates cyclization to the carbamate group, expelling the primary alkoxide 48, which could then be involved in carbon dioxide elimination to give 49, possibly via an intramolecular deprotonation pathway as shown. Finally, amide anion protonation, either by reaction with 33, or in the workup, leads to 45. The fact that no elimination/oxazolidinone opening product such as 45 was formed with lithium
ethylthiolate when the alcohol group was protected (see next section) is consistent with the proposed mechanism.

**Scheme 11. Base catalysed elimination of aldol product 33**

**Cyclization of the aliphatic fragment: second approach**

Given the unsuccessful lactone formation, it was envisaged to postpone this step until after the introduction of the aryl fragment (Scheme 12). Hence, oxazolidinone removal was attempted via thioester formation. At high reagent concentration, the product 52, resulting from oxazolidinone opening with lithium ethyl thiolate was sometimes observed, alongside with the expected thioester 50. Nevertheless, a fully chemoselective conversion of TES-protected aldol product 38 to the thioester 50 was achieved in excellent yield using dilute [EtSLi] conditions. The subsequent palladium-mediated reduction reaction produced the final aldehyde fragment 51. The yield of the reduction was significantly increased by adding the reagents at 0 °C rather than rt as reported in the previous procedure (96% vs 66-75%).
Completion of the synthesis

With the aliphatic fragment in hand, we pursued our efforts towards the synthesis of the bromoaryl derivatives 55 and 58, as potential substrates for the coupling reaction. As depicted in Scheme 13, these two compounds could be synthesized from the same intermediate 53, and only differ from the choice of protecting groups. In the first case, O-lithiation of 53 and treatment with BOMCl enabled introduction of the benzyloxy moiety in moderate yield. The obtained 54 was then brominated with NBS to yield the desired bromoaryl 55. For 58, an O-formylation reaction was followed by aldehyde reduction, silylation and finally bromination.

Scheme 13. Synthesis of aromatic fragments
The coupling reaction was then carried out in the presence of \textit{t-}BuLi and an excess of the bromoaryl derivative (Scheme 14), leading in each case to the desired product 59 as a mixture of benzylic alcohol epimers in excellent yield. Pleasingly, the excess of aromatic compound could be easily recovered by column chromatography as an inseparable mixture of 57 and 58, and treatment with NBS allowed complete recycling of 58. The mixture of epimers 59a and 59b was then subjected to DIBAL-H reduction in order to convert the \textit{t-}butyl ester to the corresponding aldehydes 60a-b (Scheme 14). Surprisingly, the minor benzylic alcohol epimer was found to be unreactive towards reduction, and aldehydes 60a and 60b were obtained as a single diastereoisomer, together with the remaining isomerically pure starting material 59a-b (the alcohol configuration at C1’ could not be determined). Aldehyde 60b could separated from 59b by preparative HPLC, and was subsequently converted to the hemiacetal 61b after treatment with TBAF and spontaneous cyclisation. In the case of 60a, separation from its starting material was not possible, and the TBAF treatment was thus applied to the mixture. This led to the formation of the desired hemiacetal derivative 61a, together with the residual starting material 62a, with separation now achieved by column chromatography.
Assuming that the lack of reactivity observed for the minor epimer 59a (and 59b) was due to conformational restrictions imposed by the alcohol configuration at C1’, a sequential oxidation/reduction process towards the formation of 60a was attempted (Scheme 26). Thus, the benzylic alcohol was oxidised using Dess-Martin periodinane (DMP) in 73% yield, and the resulting ketone 63 was then treated with an excess of DIBAL-H. Although the benzylic ketone in C1’ was effectively reduced, only trace amount of the aldehyde 60a could be observed by NMR. Instead, the compound 59a was obtained as a single epimer, whose configuration unfortunately corresponds to that of the previously observed unreactive isomer. Following this, no further investigation was attempted on this sequence, and the synthesis was pursued on the major epimer 61a.
Completion of the luminacin D synthesis was achieved in 2 further steps from the intermediate 61a (Scheme 16). At first, the treatment of 61a using DMP in the presence of NaHCO₃ enabled oxidation of the benzylic alcohols to give 64 in moderate yield. The oxidation step proved cumbersome, with the best yield (56%) obtained after termination of the reaction prior to completion (5 min), separation of the product from the starting material, and re-subjecting the remaining starting material to DMP. A longer reaction time (10 min or 1.5 h) led to a drop in yield (43% in each case). Finally, subsequent deprotection provided (−)-luminacin D 1a in 92% yield after column chromatography, and in 80% after HPLC purification.
The final sequence was then investigated with the tri-benzylated 61b, as simultaneous deprotection of the benzyl ethers would enable to complete the synthesis with only bis-benzylic oxidation left to do (Scheme 17). However, the hydrogenolysis attempts were associated with numerous selectivity issues, and 65 was never obtained in a meaningful yield. It was found that the primary benzylic alcohol could easily be fully reduced to a methyl group, while the secondary benzyl alcohol was also found to be labile.

Scheme 17. Attempted hydrogenolysis of the tribenzylated 61b

In view of these unexpected results, deprotection conditions were investigated on a simple model substrate 66 (Scheme 18), resulting from the coupling reaction between 55 and propionaldehyde (not shown). It was envisioned that DDQ oxidation of the electron rich aromatic ring, similar to $p$-methoxy benzyl cleavage, would directly lead to the corresponding C1 aldehyde 68, alongside with BnOH.\textsuperscript{36,37} However, despite considerable experimentation, this was not achieved. Surprisingly, this process did yield the ketone 67, which, though potentially useful for our purposes, was judged too low-yielding for application on the luminacin D system. Hence, the hydrogenolysis approach was reinvestigated, using the same model system.
Given its perceived instability, the secondary benzylic alcohol group was first oxidized to the ketone 69 (Scheme 19). Manganese dioxide was found ineffective at this transformation on small scale. The full debenzylolation was now achieved under acidic conditions previously as used by Tatsuda\textsuperscript{11} to give the triol 70 in excellent yield. In this reaction, control of the reaction time was required, as over-reduction to 71 occurred with longer reaction times, a side-reaction not reported by Tatsuda.\textsuperscript{11}
Finally, these successful reactions were applied to 61b (Scheme 20). Pleasingly, the initial oxidation to ketone 72 proceeded in quantitative yield, as did the subsequent debenzylation reaction to triol 73. Luminacin D 1a was then obtained by a second Dess-Martin oxidation.

Scheme 20. Completion of the synthesis from the second protecting group strategy

Conclusions

A successful second generation synthesis of enantiopure (−)-luminacin D is reported in full. The synthetic strategy relies on a conventional key disconnection to give an aromatic and aliphatic fragment. The synthesis of the chiral aliphatic fragment relies on the diastereoselective introduction of the trisubstituted epoxide subunit, which is achieved by modified de la Pradilla sulfoxide methodology, with the sulfoxide then becoming a reactive handle for introduction of a formyl group. A key step is the subsequent diastereoselective allylation of this formyl group. Initial methodology relying on chelation control achieved this allylation in very high diastereoselectivity, but with the wrong relative
stereochemistry. Subsequently, different allylation conditions under non-chelation control were found that achieved this process with the correct relative stereochemistry, in equally excellent de. As a complementary approach, we also showed that high levels of diastereoselectivity could be achieved through the reduction of β-keto ester containing an α-quartenary epoxide center, although this approach was hampered by the low-yielding acylation reaction of the sulfoxide derivative.

Completion of the aliphatic fragment was achieved by aldol reaction involving acyl-oxazolidinones. A first approach solely relying on remote stereocontrol induced by a β-OSiR$_3$ center was moderately successful (4:1 de), but the diastereoselection could be amplified by the use of a ‘matched’ chiral oxazolidinone. Installation of the cyclic hemiacetal group proved not possible at this stage, but was achieved after coupling with the aromatic fragment. Elaborate final deprotection investigations using two different protecting groups for the primary benzylic alcohol were required to arrive at a successful luminacin D synthesis. In spite of the extra oxidation step required to achieve the synthesis, the second aromatic protecting strategy described was found more satisfactory in term of yield than the first route described (40% over 6 steps vs 22% yield over 5 steps for the first route). The successful enantioselective formation of the trisubstituted epoxide and the diastereoselective installation of an adjacent chiral alcohol group will be of general applicability. To the best of our knowledge, remote stereocontrol by a β-OSiR$_3$ center of an achiral oxazolidinone based boron enol ether mediated aldol reaction had not been described before. Overall, this second generation synthesis enabled access to the natural product in an improved yield and a reduced number of steps compared to our previous approach (5.4%, 17 steps vs 2.6%, 19 steps).

**Experimental Section**

General methods: see SI. For atom numbering in the NMR data, see corresponding figures in the SI.
Two-step procedure to give alkenes \(8_{\text{Tol}}\) and \(\pm 8_{\text{Ph}}\): To a solution of \(t\)-BuMgCl (1.7 M in THF, 66 mL, 112.8 mmol, 1.5 equiv) in THF (150 mL) at -78 °C was added \(5_{\text{Tol}}\) (19.13 g, 75.2 mmol, 1 equiv) in THF (350 mL) via dropping funnel. The mixture was then stirred at -78 °C for 1 h before propionaldehyde (97%, 17.2 mL, 233.2 mmol, 3.1 equiv) was added dropwise. The reaction was then stirred for a further 1.5 h at -78 °C. The reaction mixture was then allowed to warm up to 0 °C before quenching with a saturated solution of \(\text{NH}_4\text{Cl}\) (200 mL) and \(\text{H}_2\text{O}\) (100 mL). The layers were separated and the aqueous phase was extracted with Et\(_2\)O (3×250 mL). Organic phases were combined, dried over MgSO\(_4\) and concentrated \textit{in vacuo}. Purification \textit{via} column chromatography (petroleum ether/EtOAC 8:2 to 5:5) afforded 24.5 g of the impure addition product \(7_{\text{Tol}}\) as mixture of diastereoisomers and as a white solid, which was directly used in the next step. The addition product \(7_{\text{Tol}}\) (24.5 g) was dissolved in pyridine (250 mL), and MsCl (17.5 mL, 225.7 mmol, 3 equiv.) was added dropwise, by keeping the temperature between -10 and 0 °C for 40 min. The reaction mixture was stirred for 16 h without removing the ice bath (T=10 °C after 16 h), before quenching with a solution of HCl (1M, 500 mL) dropwise at 0 °C. The mixture was extracted with Et\(_2\)O (3×600 mL). Organic phases were combined, dried over MgSO\(_4\) and concentrated \textit{in vacuo}. Purification \textit{via} column chromatography (petroleum ether/EtOAc 8:2) afforded compound \(8_{\text{Tol}}\) as a yellow oil (19.6 g, 88% over 2 steps).

The same procedure was applied with \(\pm 5_{\text{Ph}}\) (25.7 g, 107.1 mmol, 1 equiv) to afford \(\pm 8_{\text{Ph}}\) as a yellow oil (22.4 g, 75% over 2 steps) after column chromatography (petroleum ether/EtOAc 8:2). Data for \(8_{\text{Tol}}\) and \(\pm 8_{\text{Ph}}\) matched those previously reported.\(^{10}\)

Epoxidation of the enantiopure alkene \(8_{\text{Tol}}\) using \(t\)-BuOOH/\(n\)-BuLi: To a solution of \(t\)-BuOOH (5.5M in decane, dried over MS 4Å, 5.4 mL, 29.8 mmol, 3 equiv.) in THF (290 mL) at -78 °C was added \(n\)-BuLi (2.45 M in hexane, 12.1 mL, 29.8 mmol, 3 equiv.) dropwise \textit{via} cannula. The resulting
solution was stirred at the same temperature for 20 min, before adding a solution of \(8_{\text{Tol}}\) (2.92 g, 9.91 mmol, 1 equiv.) in THF (80 mL) dropwise via cannula. The reaction mixture was then stirred at -78 \(^\circ\)C for a further 25 min, and was quenched at this temperature with a saturated solution of \(\text{Na}_2\text{S}_2\text{O}_3\) (200 mL). The mixture was allowed to warm up to 0 \(^\circ\)C, and was extracted at this temperature with EtOAc (3×200 mL). Organic phases were combined, dried over \(\text{Na}_2\text{SO}_4\) and concentrated \textit{in vacuo}, yielding a mixture of crude epoxides \(9_{\text{Tol}}\) and \(10_{\text{Tol}}\) (\(\text{dr}\) syn-\(9_{\text{Tol}}\)/anti-\(9_{\text{Tol}}\)/syn-\(10_{\text{Tol}}\)/anti-\(10_{\text{Tol}}\) 86: 7 : 4 : 3). Purification \textit{via} column chromatography (pentane/Et\(_2\)O 8:2 to 6:4) afforded \textit{trans}-epoxides \(9_{\text{Tol}}\) as a white solid (2.52 g, 82%) and the impure \textit{cis}-epoxides \(10_{\text{Tol}}\) as colourless oil (68 mg, isolated with minor impurity, <2%). An analytical mixture of \(9_{\text{Tol}}\) was recrystallized from hot pentane (few drops of Et\(_2\)O added) to give the pure epoxide syn-\(9_{\text{Tol}}\). Analytically pure samples of syn-\(10_{\text{Tol}}\) and anti-\(10_{\text{Tol}}\) were obtained on small scale for characterization purposes.

Data for \(9_{\text{Tol}}\) (mixture of diastereoisomers) matched those previously reported.\(^{10}\)

\textit{Data for the pure syn-9\(_{\text{Tol}}\):} \([\alpha]_D^0 +49.2\) (c 1.4, CHCl\(_3\), 23 \(^\circ\)C); mp: 54 – 56 \(^\circ\)C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.60 (2H, d, \(^3J_{HH}\) 8.1 Hz, \(H_9\), \(H_{13}\)), 7.32 (2H, d, \(^3J_{HH}\) 8.1 Hz, \(H_{10}\), \(H_{12}\)), 3.54 (1H, t, \(^3J_{HH}\) 6.4 Hz, \(H_3\)), 2.41 (3H, s, \(H_{14}\)), 1.81 – 1.60 (4H, m, \(H_4\)), 1.34 (9H, m, \(H_7\)), 1.03 (3H, t, \(^3J_{HH}\) 7.5 Hz, \(H_5\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 162.4 (C\(_1\)), 142.5 (C\(_8\) or C\(_{11}\)), 137.1 (C\(_{11}\) or C\(_8\)), 129.7 (C\(_9\) and C\(_{13}\)), 125.6 (C\(_{10}\) and C\(_{12}\)), 84.4 (C\(_6\)), 75.3 (C\(_3\)), 61.1 (C\(_3\)), 27.8 (C\(_7\)), 21.7 (C\(_2\)), 21.5 (C\(_{14}\)) 10.0 (C\(_3\)) ppm.

\textit{Data for 10\(_{\text{Tol}}\):} IR (neat) 2971 (w, br.), 1743 (m), 1716 (m), 1251 (m), 1096 (s), 1062 (s) cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.73 (2H, d, \(^3J_{HH}\) 7.8 Hz, \(H_9\), \(H_{13}\), \(\text{anti}\)), 7.62 (2H, d, \(^3J_{HH}\) 8.6 Hz, \(H_9\), \(H_{13}\), \(\text{syn}\)), 7.38 – 7.28 (4H, m, \(H_{10}\), \(H_{12}\), \(\text{syn and anti}\)), 3.45 (1H, dd, \(^3J_{HH}\) 7.3 Hz, \(^3J_{HH}\) 5.5 Hz, \(H_3\), \(\text{syn}\)), 3.26 (1H, dd, \(^3J_{HH}\) 7.5 Hz, \(^3J_{HH}\) 5.1 Hz, \(H_3\), \(\text{anti}\)), 2.42 (3H, s, \(H_{14}\), \(\text{syn}\)), 2.41 (3H, s, \(H_{14}\), \(\text{anti}\)), 2.32 – 2.00 (4H, m, \(H_4\), \(\text{syn and anti}\)), 1.27 (9H, s, \(\text{syn}\)), 1.244 (9H, s, \(H_7\), \(\text{anti}\)), 1.236 (3H, t, \(^3J_{HH}\) 7.3 Hz, \(H_5\), \(\text{syn}\)), 1.17 (3H, t, \(^3J_{HH}\) 7.5 Hz, \(H_5\), \(\text{anti}\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 164.7 (C\(_5\), \(\text{anti}\)), 163.2 (C\(_5\), \(\text{syn}\)), 142.9 (C\(_8\))
or C₁₁, syn or anti), 141.5 (C₈ or C₁₁, syn or anti), 138.3 (C₈ or C₁₁, syn or anti), 136.9 (C₈ or C₁₁, syn or anti), 129.7 (C₁₀ and C₁₂, syn or anti), 129.6 (C₁₀ and C₁₂, syn or anti), 127.3 (C₁₀ and C₁₂, syn or anti), 124.7 (C₉ and C₁₃, syn), 84.4 (C₆, anti), 84.1 (C₆, syn), 74.3 (C₂, anti), 73.0 (C₂, syn), 65.9 (C₃, anti), 65.4 (C₃, syn), 27.64 (C₇, syn), 27.59 (C₇, anti), 21.5 (C₁₄, anti), 21.4 (C₁₄, syn), 19.5 (C₄, anti), 10.9 (C₅, anti), 10.6 (C₅, syn) ppm; MS (ESI⁺) (m/z) (peak 1) 311 [M+H]⁺, 255 [M - tBu + 2H]⁺; (peak 2) 311 [M+H]⁺, 255 [M-tBu+2H]⁺; HRMS (ESI⁺) for C₁₆H₂₂O₄S [M+Na]⁺ calcd. 333.1131, found. 333.1136.

Epoxidation of the alkene (±)-8ₚₕ using NaH/t-BuOOH: To a solution of t-BuOOH (5-6 M in decane, 480 µL, 2.4 – 2.9 mmol, 3.2 – 3.9 equiv.) in THF (12 mL) at -78 °C was added NaH (60 % dispersion in mineral oil, 75.2 mg, 1.88 mmol, 2.5 equiv.) portionwise. The resulting suspension was allowed to warm up to rt and stirred at this temperature for 20 min. The suspension was then cooled to -78 °C before adding a solution of (±)-8ₚₕ (211 mg, 0.75 mmol, 1 equiv.) in THF (8 mL) via cannula. The reaction mixture was then stirred at -78 °C for 20 min, and was quenched at this temperature with a saturated solution of Na₂S₂O₃ (10 mL). The mixture was allowed to warm up to 0 °C, and was extracted at this temperature with Et₂O (2×10 mL). Organic phases were combined, dried over Na₂SO₄ and concentrated in vacuo, yielding the crude epoxides 9ₚₕ and 10ₚₕ (dr syn-9ₚₕ/anti-9ₚₕ/syn-10ₚₕ/anti-10ₚₕ 35: 4: 54: 7). Purification via column chromatography (pentane/Et₂O 9:1 to 5:5) and preparative HPLC (pentane/Et₂O 7:3) afforded the trans-epoxides 9ₚₕ as a viscous oil (52 mg, 23%), as well as the cis-epoxides 10ₚₕ as a white solid (117 mg, 53%). An analytical sample of 10ₚₕ was recrystallized from hot pentane (few drops of Et₂O added) to give the pure epoxide (±)-syn-10ₚₕ.

Data for (±)-(syn+anti)-9ₚₕ matched those previously reported.¹⁰

Data for (±)-(syn+anti)-10ₚₕ: IR (neat) 3080 (w), 2983 (w, br.), 1737 (m), 1373 (m), 1158 (s), 1088 (s); ¹H NMR (400 MHz, CDCl₃) δ 7.92 – 7.80 (2H, m, Hₐr, anti), 7.79 – 7.67 (2H, m, Hₐr, syn), 7.60 – 7.44
(6H, m, H₆, syn and anti), 3.47 (1H, dd, 3JHH 7.3 Hz, 3JHH 5.4 Hz, H₃, syn), 3.29 (1H, dd, 3JHH 7.6 Hz, 3JHH 5.2 Hz, H₃, anti), 2.33 – 2.07 (4H, m, H₄, syn and anti), 1.247 (3H, t, 3JHH 7.3 Hz, H₅, syn), 1.240 (9H, s, H₇, syn), 1.235 (9H, s, H₇, anti), 1.19 (3H, t, 3JHH 7.5 Hz, H₅, anti); ¹³C NMR (100 MHz, CDCl₃) δ 164.7 (C₁, anti), 163.2 (C₁, syn), 141.5 (CqAr, anti), 140.3 (CqAr, syn), 132.3 (CHAr, anti), 131.1 (CHAr, syn), 129.1 (2C, CHAr, anti), 128.9 (2C, CHAr, syn), 127.3 (2C, CHAr, anti), 124.7 (2C, CHAr, syn), 84.5 (C₆, anti), 84.2 (C₆, syn), 74.4 (C₂, anti), 73.0 (C₂, syn), 65.9 (C₃, anti), 65.3 (C₃, syn), 27.6 (C₇, syn and anti), 21.3 (C₄, anti), 19.5 (C₄, syn), 11.0 (C₅, anti), 10.6 (C₅, syn) ppm.

Oxidation of sulfoxide derivatives 10ₚₙ to give 13: To a solution of sulfoxides 10ₚₙ (dr syn-10ₚₙ/anti-10ₚₙ ~1:1, 243 mg, 0.78 mmol, 1 equiv.) in DCM (5 mL) at rt was added portionwise m-CPBA (77%, 192 mg, 0.86 mmol, 1.1 equiv.). The resulting suspension was stirred at this temperature for 4 h, before quenching with saturated solution of Na₂S₂O₅ (5 mL). The layers were separated, and the aqueous phases were extracted with Et₂O (3×5 mL). Organic phases were combined, dried over Na₂SO₄ and concentrated in vacuo. Purification via column chromatography (pentane/EA 8:2) afforded sulfone 13 as a viscous oil (192 mg, 75%). IR (neat) 2978 (w, br.), 1736 (m), 1331 (m), 1253 (m), 1140 (s, br.) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.87 (2H, d, 3JHH 8.3 Hz, H₉ and H₁₃), 7.37 (2H, d, 3JHH 8.0 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.87 (2H, d, 3JHH 8.3 Hz, H₉ and H₁₃), 7.37 (2H, d, 3JHH 8.0
Hz, H₁₀ and H₁₂), 3.28 (1H, dd, ³J_HH 7.5 Hz, ³J_HH 5.2 Hz, H₇), 2.46 (3H, s, H₁₄), 2.33 – 2.11 (2H, m, H₉), 1.28 (9H, s, H₅), 1.19 (3H, t, ³J_HH 7.5 Hz, H₃); ¹³C NMR (100 MHz, CDCl₃) δ 162.7 (C₁), 145.4 (C₈ or C₁₁), 135.9 (C₈ or C₁₁), 129.6 (C₁₀ and C₁₂), 128.9 (C₉ and C₁₃), 84.9 (C₆), 74.3 (C₂), 66.3 (C₃), 27.5 (C₇), 21.7 (C₁₄), 20.4 (C₄), 10.9 (C₅) ppm; MS (ESI⁺) (m/z) 344 [M+NH₄]⁺, 349 [M+Na]⁺; HRMS (ESI⁺) for C₁₆H₂₂O₅S [M+Na]⁺ calcd. 349.1080, found. 349.1079.

Acylation reaction: synthesis of model substrate 4c: To compound 9_{tot} (dr 92:8, 217 mg, 0.70 mmol, 1 equiv.) dissolved in Et₂O (4.7 mL), was added methyl butanoate 15 (95 µL, 0.84 mmol, 1.2 equiv.) at rt. The mixture was cooled to -78 °C and stirred for 10 min, before adding a solution of t-BuLi (1.9 M in pentane, 880 µL, 1.69 mmol, 2.4 equiv.) dropwise for 5 min. The resulting mixture was stirred at this temperature for 20 min, and was quenched at -78 °C with a saturated solution of NH₄Cl (2 mL). The mixture was then extracted with Et₂O (3×5 mL). Organic phases were combined, dried over Na₂SO₄ and concentrated under reduced pressure (30 °C, < 500 mbar) to minimize losses through compound evaporation. Purification via column chromatography (pentane/Et₂O 95:5 to 9:1) afforded the compound 4c as a colourless oil (67 mg, 91% purity with 9% Et₂O, 65 mg calculated, 38%, ee ~84%). IR (neat) 2972 (w, br.), 1743 (s), 1716 (s), 1369 (m), 1253 (m), 1163 (m), 1136 (s) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.24 (1H, t, ³J_HH 6.1 Hz, H₃), 2.58 (1H, dt, ²J_HH 17.9 Hz, ³J_HH 7.1 Hz, H₆), 2.40 (1H, dt, ²J_HH 17.4 Hz, ³J_HH 6.8 Hz, H₉), 1.71 - 1.56 (4H, m, H₄, H₁₀), 1.53 (9H, s, H₅), 1.10 (3H, t, ³J_HH 7.5 Hz, H₅ or H₁₁), 0.92 (3H, t, ³J_HH 7.5 Hz, H₁₁ or H₉); ¹³C NMR (100 MHz, CDCl₃) δ 203.0 (C₈), 164.6 (C₁), 83.5 (C₆), 65.9 (C₂), 63.1 (C₉), 39.5 (C₃), 28.0 (C₆), 22.7 (C₄ or C₁₀), 16.7 (C₁₀ or C₄), 13.6 (C₅ or C₁₁), 10.1 (C₁₁ or C₃) ppm; MS (ESI⁺) (m/z) 265 [M+Na]⁺, 260 [M+NH₄]⁺, 187 [M-tBu+2H]⁺; HRMS (ESI⁺) for C₁₆H₂₂O₄ [M+Na]⁺ calcd. 265.1416, found. 265.1410.
Diastereoselective reduction using L-selectride (syn-selective): To a solution of 4c (129 mg, 0.53 mmol, 1 equiv.) in THF (4 mL) at -78 °C was added L-selectride (1M solution in THF, 560 µL, 0.56 mmol, 1.05 equiv.) dropwise. The mixture was stirred for 30 min at -78 °C, before quenching with a saturated solution of NH₄Cl (2 mL). The layers were separated and the aqueous phase was extracted with Et₂O (3×5 mL). Organic phases were combined, dried over Na₂SO₄ and concentrated in vacuo, yielding the crude alcohol 16 as a mixture of diastereoisomers (dr 16a/16b 1:9). Purification via column chromatography (petroleum ether/EtOAc 8:2 to 7:3) allowed isolation of the anti-α-epoxy alcohol 16a (10 mg, 8%) as well as the syn-α-epoxy alcohol 16b (78 mg, 60%). A mixture of both diastereoisomers 16 was also obtained (28 mg, 22%, dr 16a/16b 15:85). Overall yield for 16: 116 mg, 90%.

Data for the anti-product 16a: IR (neat) 3519 (w, br.), 2975 (w, br.), 1735 (s, br.), 1376 (m), 1266 (s), 1142 (s) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.56 (1H, td, 3J_HH 8.1 Hz, 3J_HH 3.9 Hz, H₈), 3.07 (1H, t, 3J_HH 6.5 Hz, H₃), 2.46 (1H, d, 3J_HH 7.8 Hz, OH-8), 1.83 – 1.31 (6H, m, H₄, H₉, H₁₀), 1.53 (9H, s, H₇), 1.07 (3 H, t, 3J_HH 7.3 Hz, H₅ or H₁₁), 0.95 (3 H, t, 3J_HH 7.1 Hz, H₁₁ or H₅); ¹³C NMR (100 MHz, CDCl₃) δ 168.2 (C₁), 83.3 (C₆), 72.5 (C₈), 64.6 (C₂), 62.4 (C₃), 35.7 (C₄ or C₉ or C₁₀), 28.1 (C₇), 21.6 (C₄ or C₉ or C₁₀), 18.7 (C₄ or C₉ or C₁₀), 14.0 (C₅ or C₁₁), 10.2 (C₁₁ or C₅) ppm; MS (ESI⁺) (m/z) 511 [2M+Na]⁺, 267 [M+Na]⁺, 189 [M-tBu+2H]⁺; HRMS (ESI⁺) for C₁₃H₂₄O₄ [M+Na]⁺ calcd. 267.1567, found. 267.1573.

Data for the syn-product 16b: IR (neat) 3455 (w, br.), 2968 (m, br.), 1746 (s), 1372 (s), 1244 (s), 1134 (s) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.16 – 3.90 (1H, m, H₈), 3.19 (1H, t, 3J_HH 6.4 Hz, H₃), 1.69 – 1.52 (6H, m, H₄, H₉, H₁₀), 1.50 (9H, s, H₇), 1.05 (3 H, t, 3J_HH 7.5 Hz, H₅ or H₁₁), 0.95 (3 H, t, 3J_HH 7.0 Hz, H₁₁ or H₅); ¹³C NMR (100 MHz, CDCl₃) δ 167.5 (C₁), 82.6 (C₆), 69.6 (C₈), 66.0 (C₂), 60.5 (C₃), 35.8 (C₄ or C₉ or C₁₀), 28.0 (C₇), 21.4 (C₄ or C₉ or C₁₀), 18.6 (C₄ or C₉ or C₁₀), 13.9 (C₅ or C₁₁), 10.2 (C₁₁, 10.2 (C₁₁.
or C$_3$ ppm; MS (ESI$^+$) (m/z) 511 [2M+Na]$^+$, 267 [M+Na]$^+$, 189 [M − t-Bu + 2H]$^+$; HRMS (ESI$^+$) for C$_{13}$H$_{24}$O$_4$ [M+Na]$^+$ calcd. 267.1567, found. 267.1565.

**Diastereoselective reduction using NaBH$_4$/CaCl$_2$ (anti-selective):** To a solution of 4c (120 mg, 0.50 mmol, 1 equiv.) in MeOH (4 mL) at rt was added CaCl$_2$ (111 mg, 1 mmol, 2 equiv.). The mixture was stirred at this temperature for 5 min (dissolution of CaCl$_2$), and was cooled down to 0 °C. NaBH$_4$ (11 mg, 0.3 mmol, 0.6 equiv.) was then added, and the resulting solution was stirred at this temperature for 20 min, before quenching with a saturated solution of NH$_4$Cl (3 mL). The mixture was extracted with Et$_2$O (3×20 mL). Organic phases were combined, dried over Na$_2$SO$_4$ and concentrated *in vacuo*, yielding the crude alcohol 16 as a mixture of diastereoisomers (dr 16a/16b 97:3). Purification *via* column chromatography (petroleum ether/EtOAc 8:2 to 7:3) afforded the *anti*-product 16a (87 mg, 72%). *Data for the anti-product 16a:* see above.

**Synthesis of bromohydrin 17 using Et$_3$SiH/MgBr$_2$:** To a suspension of magnesium granules (20 mg, 0.85 mmol, 1.6 equiv) in Et$_2$O (2 mL) at rt was added 1,2-dibromoethane (73 µL, 0.85 mmol, 1.6 equiv). The mixture started to spontaneously reflux and was stirred for approximately 2 h until complete dissolution of the magnesium. Et$_2$O was then evacuated from the flask under vacuum to yield a white solid which was dissolved in DCM (3 mL). Separately, a flask containing compound 4c (128 mg, 0.53 mmol, 1 equiv.) in DCM (2 mL) was prepared and added to MgBr$_2$ suspension *via* syringe. In another flask, Et$_3$SiH (88 µL, 0.55 mmol, 1.05 equiv.) was dissolved in DCM (2 mL). All flasks were then cooled down at -78 °C and stirred for 10 min, after which the solution of Et$_3$SiH was then transferred *via* syringe followed by stirring for 2 h at -78 °C. The mixture was then quenched with a saturated solution of NaHCO$_3$ (2 mL) and diluted with H$_2$O (10 mL). The layers were separated and the aqueous phase was extracted with DCM (3×10 mL). Organic phases were combined, dried over
Na₂SO₄ and concentrated in vacuo. Purification via column chromatography (pentane/Et₂O 97:3) afforded the bromohydrin 17 as white solid (109 mg, 64%).

Data for 17: IR (neat) 3478 (w, br.), 2956 (w, br.), 1716 (s, br.), 1376 (m), 1281 (m), 1259 (m), 1153 (s), 1123 (s) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.68 (1H, dd, ³JHH 10.8 Hz, ⁴JHH 2.2 Hz, H₃), 4.19 (1H, s, OH-2, disappeared upon D₂O exchange), 2.72 (1H, dt, ²JHH 18.2 Hz, ³JHH 6.9 Hz, H₉), 2.45 (1H, dt, ²JHH 18.2 Hz, ³JHH 7.3 Hz, H₉'), 1.85 – 1.70 (1H, m, H₄), 1.69 – 1.53 (3H, m, H₄', H₁₀), 1.57 (9H, s, H₇), 1.07 (3H, t, ³JHH 7.2 Hz, H₅), 0.89 (3H, t, ³JHH 7.3 Hz, H₁₁); ¹³C NMR (100 MHz, CDCl₃) δ 205.3 (C₈), 167.9 (C₁), 87.3 (C₂ or C₆), 85.2 (C₂ or C₂), 61.3 (C₃), 40.3 (C₆), 27.7 (C₇), 26.7 (C₄), 16.7 (C₁₀), 13.5 (C₁₁), 12.8 (C₅) ppm; MS (ESI⁺) (m/z) 347 [M⁺(¹¹Br)+Na]⁺, 345 [M⁺(⁷⁹Br)+Na]⁺; HRMS (ESI⁺) for C₁₃H₂₃⁷⁹BrO₄ [M+Na]⁺ calcd. 345.0672, found. 345.0669.

Synthesis of bromohydrins 17 and 18 using NaBH₄/MgBr₂: To a suspension of magnesium granules (23 mg, 0.94 mmol, 1.6 equiv) in Et₂O (2 mL) was added 1,2-dibromoethane (80 µL, 0.94 mmol, 1.6 equiv) at rt. The mixture started to spontaneously reflux and was stirred for approximately 2 h until complete dissolution of the magnesium. Et₂O was then evacuated from the flask under vacuum to yield a white solid which was dissolved in DCM (3 mL). Separately, a flask containing 4c (142 mg, 0.59 mmol, 1 equiv.) in DCM (2 mL) was prepared and added to MgBr₂ suspension via syringe. In another flask, NaBH₄ (23 mg, 0.62 mmol, 1.05 equiv.) was dissolved in THF (2 mL). All flasks were then cooled down at -78 °C and stirred for 10 min, after which the solution of NaBH₄ was then transferred via syringe, followed by stirring at this temperature for 1 h. The reaction mixture was then allowed to warm up to rt, and stirring was continued for 1 h, before quenching with NaHCO₃ (2 mL), and diluting with H₂O (10 mL). The layers were separated and the aqueous phase was extracted with DCM (3×10 mL). Organic phases were combined, dried over Na₂SO₄ and concentrated in vacuo, yielding the crude bromohydrin 17 and the reduced bromohydrin 18 as a mixture of diastereoisomers.
Purification via column chromatography (pentane/Et₂O 97:3 to 8:2) afforded the bromohydrin 17 as a white solid (91 mg, 48%) and the anti-diol 18a as a white solid (18 mg, 9%), which was recrystallized was recrystallized from hot pentane (few drops of Et₂O added) for characterization purpose.

**Data for 18a:** mp: 99 – 102 °C; IR (neat) 3561 (w), 3402 (w, br.), 2964 (w, br.), 1739 (s), 1372 (m), 1153 (s), 1130 (s) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.47 (1H, dd, 3JHH 11.3 Hz, 3JHH 2.5 Hz, H₃), 3.74 (1H, ddd, 3JHH 12.0 Hz, 3JHH 10.5 Hz, 3JHH 2.0 Hz, H₈), 3.53 (1H, s, OH-2), 2.09 (1H, dqd, 2JHH 14.5 Hz, 3JHH 7.2 Hz, 3JHH 2.3 Hz, H₄), 1.94 (1H, d, 3JHH 12.0 Hz, OH-8), 1.85 – 1.70 (2H, m, H₄', H₉), 1.69 – 1.59 (1H, m, H₁₀), 1.56 (9H, s, H₇), 1.48 – 1.33 (1H, m, H₁₀'), 1.16 – 1.01 (1H, m, H₉), 1.11 (3H, t, 3JHH 7.2 Hz, H₃), 0.94 (3H, t, 3JHH 7.3 Hz, H₁₁); ¹³C NMR (100 MHz, CDCl₃) δ 172.0 (C₁), 84.8 (C₂ or C₆), 81.2 (C₆ or C₂), 73.6 (C₈), 63.3 (C₃), 34.8 (C₉), 28.0 (C₇), 24.9 (C₄), 19.5 (C₁₀), 13.9 (C₁₁), 12.8 (C₃) ppm; MS (ESI⁺) (m/z) 349 [M(br)+Na]⁺, 347 [M(br)+Na]⁺; HRMS (ESI⁺) for C₁₅H₂₅₇⁹BrO₄ [M+Na]⁺ calcd. 347.0828, found. 347.0836.

Two-step procedure (acylation/diastereoselective reduction) to give the α-epoxy alcohols (±)-3 and (±)-7: To a solution of (±)-9ₚₚ (265 mg, 0.89 mmol, 1 equiv.) in Et₂O (6.0 mL) at rt was added methyl but-3-enoate 22 (dried over molecular sieves 4Å, 21% pentane, 163 mg, 1.43 mmol, 1.6 equiv.). The mixture was cooled down at -78 °C and stirred for 10 min, before adding dropwise a solution of t-BuLi (1.8 M in pentane, 1.2 mL, 2.13 mmol, 2.4 equiv.) for 5 min. The resulting mixture was stirred -78 °C for 20 min, and was quenched at this temperature with a saturated solution of NH₄Cl (5 mL). The mixture was then extracted with Et₂O (3×10 mL). Organic phases were combined, dried over Na₂SO₄ and concentrated under reduced pressure (30 °C, < 500 mbar) to give the crude β-keto ester (±)-4b. The crude product (±)-4b was then dissolved in THF (3 mL), and L-selectride (1M solution in THF, 0.36 mmol, 360 µL, 0.4 equiv.) was added to the mixture dropwise at -78 °C. The resulting solution was
stirred at this temperature for 10 min, before quenching with a saturated solution of NH₄Cl (3 mL). The mixture was extracted with Et₂O (3×10 mL), dried over Na₂SO₄ and concentrated under reduced pressure, giving the crude α-epoxy allylic alcohols (±)-3 and (±)-7 as a mixture of diastereoisomers (dr n.d. due to complexity of the crude mixture, but only the syn-alcohol (±)-3 was observed by ¹H NMR, see SI). Purification via column chromatography (pentane/Et₂O 9:1 to 6:4) afforded the anti-α-epoxy alcohol (±)-7 as a colourless oil (2 mg, isolated with unknown impurities, ~1% over 2 steps) and the syn-α-epoxy alcohol (±)-3 as a colourless oil (41 mg, 19% over 2 steps). Data for the syn-product 3 and the anti-product 7 correspond to those previously reported.¹⁰

**Hydrogenation of the syn α-epoxy alcohol (±)-3 to give (±)-16b:** Compound (±)-3 (60 mg, 0.25 mmol, 1 equiv.) was dissolved in EtOAc (4 mL). Pd/C (10% wt, 26 mg, 26 µmol, 10 mol%) was added and the resulting mixture was flushed with H₂. Stirring under an atmosphere of H₂ at rt was continued for 24 h, before the mixture was filtered through a pad of silica and concentrated in vacuo, yielding the syn-alcohol (±)-16b as a colourless oil (58 mg, 96%). *Data for (±)-16b:* see acylation procedure.

**Formylation of (±)-9ₚₜ to give the α-epoxy aldehyde (±)-4a (small scale, optimized conditions):**
To compound (±)-9ₚₜ (410 mg, 1.38 mmol, 1 equiv.), dissolved in Et₂O (9 mL) was added DMF (dried over molecular sieves 4Å, 160 µL, 2.07 mmol, 1.5 equiv.) at rt. The mixture was cooled down at -78 °C and stirred for 10 min, before adding a solution of t-BuLi (1.7 M in pentane, 2.3 mL, 3.86 mmol, 2.8 equiv.) dropwise for 15 min. The resulting mixture was stirred for further 20 min at -78 °C and was quenched with a saturated solution of NH₄Cl (5 mL). The mixture was then extracted with Et₂O (3×10 mL). Organic phases were combined, dried over Na₂SO₄ and concentrated under reduced pressure (30 °C, <500 mbar). Purification via column chromatography (pentane/Et₂O 8:2 to 7:3) afforded the α-epoxy aldehyde (±)-4a as a colourless oil (133 mg, 94% purity with 6% Et₂O, 130 mg calculated, 47%). *Data for (±)-4a* matched those previously reported.¹⁰
**Allylation of (±)-4a to give the α-epoxy alcohols (±)-3 and (±)-7 (small scale):** Aldehyde (±)-4a (129 mg, 0.64 mmol, 1 equiv.) was dissolved in DCM (2.1 mL) at rt. The solution was cooled to -78 °C, after which allylboronic acid pinacol ester (97%, 135 µL, 0.70 mmol, 1.1 equiv.) was added dropwise at -78 °C. The reaction was allowed to warm up for 14 h (without removing the dry ice bath, T = 10 °C after 14 h). The mixture was then quenched at rt with H₂O (5 mL) and stirring was continued for 5 min. The layers were separated, and the aqueous phase was extracted with Et₂O (3×10 mL). Organic phases were combined, dried over Na₂SO₄ and concentrated in vacuo to give the crude α-epoxy alcohol as a mixture of diastereoisomers (dr 3/7 >95:5). Purification via column chromatography (pentane/Et₂O 8:2 to 7:3) afforded the anti α-epoxy alcohol (±)-7 as a colourless oil (3 mg, 2%) and the syn-α-epoxy alcohol (±)-3 as a colourless oil (125 mg, 80 %). Data for the syn-product (±)-3 and the anti-product (±)-7 correspond to those previously reported.

**Two-step procedure (Formylation/allylation) to give the α-epoxy alcohols 3 and 7 (large scale):** To compound 9_Tol (dr 92:8, 1.58 g, 5.1 mmol, 1 equiv.), dissolved in Et₂O (33 mL) was added DMF (dried over molecular sieves 4Å, 588 µL, 7.6 mmol, 1.5 equiv.). The mixture was cooled down at -78 °C and stirred for 10 min, before adding a solution of t-BuLi (1.9 M in pentane, 6 mL, 12.0 mmol, 2.4 equiv.) dropwise via syringe pump for 1 h. The resulting mixture was stirred at -78 °C for 20 min and was quenched at this temperature with a saturated solution of NH₄Cl (25 mL). The mixture was then extracted with Et₂O (3×30 mL). The organic phases were combined, dried over Na₂SO₄ and concentrated under reduced pressure (30 °C, <500 mbar). Purification via column chromatography (pentane/Et₂O 8:2 to 7:3) afforded the impure α-epoxy aldehyde 4a as a colourless oil (483 mg, isolated with ca. 30% of Et₂O, ee ~84%), which was used in the next step without further purification. The mixture was dissolved in DCM (8 mL) and cooled down at -78 °C, after which allylboronic acid pinacol ester (475 µL, 2.53 mmol, 0.5 equiv.) was added dropwise. The reaction was then allowed to warm up for 16 h (without removing the dry ice bath, T ~ 15 °C after 16 h). The mixture was then...
quenched at rt with H₂O (8 mL), and stirring was continued for 5 min. The layers were separated, and the aqueous phase was extracted with Et₂O (3×20 mL). Organic phases were combined, dried over Na₂SO₄ and concentrated in vacuo to give the crude α-epoxy alcohol 3 and 7 as a mixture of diastereoisomers (dr n.d due to complexity of the crude mixture, see copy of ¹H NMR spectrum in SI). Purification via column chromatography (pentane/Et₂O 8:2 to 7:3) afforded the anti α-epoxy alcohol 7 as a colourless oil (11 mg, 1% over 2 steps), and the syn α-epoxy alcohol 3 as a colourless oil (400 mg, 33% over 2 steps). The same procedure was carried out with the phenyl derivative (±)-9ₜₒ₉ (1.67 g, 5.63 mmol, 1 equiv.), giving syn-α-epoxy alcohol (±)-3 as a colourless oil (454 mg, 33% over 2 steps). Data for the syn-product 3 and the anti-product 7 correspond to those previously reported.¹⁰

**Synthesis of aldehyde 26 (2 steps):** Compound 3 (465 mg, 26 mmol, 1 equiv.) was dissolved in DCM (19 mL) at rt. The resulting solution was cooled to 0 °C, after which imidazole (326 mg, 4.79 mmol, 2.5 equiv.) was added in one portion, followed by chlorotriethylsilane (645 µL, 3.84 mmol, 2 equiv.) dropwise. The reaction was then stirred at rt for 16 h, before quenching with a saturated solution of NH₄Cl (20 mL). The layers were separated, and the aqueous phase was extracted with Et₂O (3×20 mL). Organic phases were combined, dried over Na₂SO₄ and concentrated under reduced pressure. Purification via column chromatography (pentane/Et₂O 96:4) afforded the impure protected allyl alcohol (811 mg, 83% purity with 17% of TESOH), which was engaged in the next step without further purification. Ozone was bubbled through a solution of impure protected allyl alcohol (811 mg) in DCM (61 mL) at -78 °C until the solution became blue (ca. 15 min). The excess of ozone was purged from the solution by bubbling oxygen through for 20 min. Triphenylphosphine (587 mg, 2.1 mmol, 1.1 equiv.) was then added dropwise, and stirring was continued for 1h at -78 °C, before allowing to warm up to rt over 1h. The resulting mixture was then concentrated under vacuum. Purification via column chromatography (crude loaded in DCM; pentane/Et₂O 85:15 to 80:20) afforded TES protected aldehyde 3 as a colourless oil (593 mg, 86% over 2 steps). The same procedure was carried out with
(±)-3 (720 g, 2.97 mmol, 1 equiv.), giving aldehyde (±)-26 as a colourless oil (930 mg, 85% over 2 steps). Data for compound 26 correspond to those previously reported.\textsuperscript{10}

**Evans-aldol reaction using the racemic aldehyde (±)-26:** To a solution of (S)-4-benzyl-3-pentanoyloxazolidin-2-one (S)-1.93 (1.34 g, 5.12 mmol, 2 equiv) in DCM (4.6 mL) at 0 °C was added Bu\textsubscript{2}BOTf (1M in DCM, 5.10 mL, 5.12 mmol, 2 equiv) dropwise to give an orange solution. The mixture was stirred for 5 min, then DIPEA (890 µL, 5.12 mmol, 2 equiv.) was added dropwise and the solution became yellow. After another 5 min stirring at this temperature, the mixture was cooled down to -78 °C and transferred via cannula to a solution of aldehyde (±)-26 (918 mg, 2.56 mmol, 1 equiv.) in DCM (5.6 mL) at -78 °C. The resulting mixture was stirred at this temperature for 3.5 h, then allowed to warm up at 0 °C and stirred for further 1.5 h. The reaction mixture was quenched at 0 °C with a mixture of H\textsubscript{2}O\textsubscript{2}/phosphate buffer pH 7 (1:1, 30 mL) and was extracted with DCM (3×20mL). Organic layers were combined, dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated under pressure to give the crude mixture of aldol products 36 and 37 (dr 36/37 1:1). Purification via column chromatography (pentane/Et\textsubscript{2}O 8:2 to 5:5) afforded the mixture of aldol adducts as colourless viscous oil (1.3 g, 80% purity with 20% Et\textsubscript{2}O, 1.26 g calculated, 78%, dr 36/37 36:64). A fraction of the diastereoisomer 37 was also obtained (208 mg, 86% purity with 14 % Et\textsubscript{2}O, 203 mg calculated, 13%, trace amount of 36 was detected by \textsuperscript{1}H NMR).

**Evans-aldol reaction using the enantioenriched aldehyde 26:** The same procedure was applied with 26 (er 92:8, 593 mg, 1.65 mmol, 1 equiv.) to give a mixture of aldol adducts 36 and 37 as a colourless viscous oil (943 mg, 88% purity with 12% Et\textsubscript{2}O, 927 mg calculated, 91%, dr 36/37 92:8). Data for the mixture of 36 and 37 correspond to those previously reported.\textsuperscript{10}

**Synthesis of the protected aldol adducts 38 and 39:**
- From the evans aldol using the racemic aldehyde: To a solution of aldols 36 and 37 (dr 36:64, 1.23 g, 1.98 mmol, 1 equiv.) in DCM (20 mL) at 0 °C was added imidazole (336 mg, 3.77 mmol, 2.5 equiv.) in one portion, followed by the dropwise addition of chlorotriethylsilane (670 µL, 3.02 mmol, 2 equiv.). The reaction was then stirred for 16 h at rt before quenching with a saturated solution of NH₄Cl (20 mL). The layers were separated, and the aqueous phase was extracted with Et₂O (3×20 mL). Organic phases were combined, dried over Na₂SO₄ and concentrated under reduced pressure. Purification via column chromatography (petroleum ether/EtOAC 96:4) followed by HPLC purifications (hexane/EtOAc 93:7) afforded 38 (566 mg, 39%), and 39 (728 mg, 50%) as colourless viscous oils. The same procedure was applied with 37 only (198 mg, 0.32 mmol). Purification via column chromatography (pentane/EtOAC 96:4) afforded the protected 39 as a colourless resin (233 mg, 99%). Cumulated yield of the two fractions: 38 (728 mg, 43%) and 39 (799 mg, 48%).

- From the evans aldol using the enantioenriched aldehyde: The same procedure was applied to a solution of aldol adducts 36 and 37 (dr 36/37 92:8, 935 mg, 1.51 mmol, 1 equiv.). Purification via column chromatography (petroleum ether/EtOAC 96:4) followed by HPLC (hexane/EtOAc 93:7) afforded 38 (950 mg, 86%), and 39 (66 mg, 6%) as colourless viscous oils. Data for 38 correspond to those previously reported.¹⁰ Data for 39: [α]D +25.7 (c 0.88, CHCl₃, 23 °C); IR (neat) 2966 (w, br.), 1772 (m), 1749 (s), 1737 (s), 1697 (s), 1455 (s), 1387 (s), 1205 (m), 1092 (m, br.) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.39 – 7.19 (5H, m, H₅Ar), 4.73 – 4.61 (1H, m, H₁₄), 4.21 – 4.12 (3H, m, H₂, H₁₅, H₁₅'), 4.05 – 3.99 (1H, m, H₃), 3.76 (1H, dd, ³JHH 8.6 Hz, ³JHH 4.1 Hz, H₅), 3.37 (1H, dd, ²JHH 13.2 Hz, ³JHH 2.9 Hz, CHHPh), 2.96 (1H, t, ³JHH 6.4 Hz, H₇), 2.73 (1H, dd, ²JHH 13.2 Hz, ³JHH 10.1 Hz, CHHPh), 2.19 (1H, ddd, ²JHH 14.8 Hz, ³JHH 7.4 Hz, ³JHH 4.1 Hz, H₄), 1.99 (1H, ddd, ²JHH 14.7 Hz, ³JHH 8.7 Hz, ³JHH 4.0 Hz, H₅), 1.89 – 1.77 (1H, m, H₁₂), 1.71 – 1.57 (2H, m, H₆, H₁₁), 1.50 (9H, s, C(CH₃)₃), 1.53 – 1.42 (1H, m, H₉), 1.41 – 1.33 (2H, m, H₁₂, H₁₂'), 1.06 (3H, t, ³JHH 7.5 Hz, H₉), 1.02 – 0.91 (21H, m, H₁₃, CH₃TES, CH₃', TES), 0.73 – 0.58 (12H, m, CH₂TES, CH₂', TES); ¹³C NMR (100 MHz, CDCl₃) δ 174.8 (C₁), 166.9

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(C_{10}), 153.1 (C_{10}), 135.6 (C_{qAr}), 129.4 (2C, CH_{Ar}), 128.9 (2C, CH_{Ar}), 127.3 (CH_{Ar}), 82.2 (CMe_{3}), 72.3 (C_{3}), 70.6 (C_{3}), 67.0 (C_{3}), 65.8 (C_{13}), 61.1 (C_{1}), 56.1 (C_{14}), 48.3 (C_{2}), 41.8 (C_{4}), 37.9 (CH_{2}Ph), 30.8 (C_{11}), 28.1 (C(CH_{3})_{3}), 21.9 (C_{6}), 20.8 (C_{12}), 14.3 (C_{13}), 10.2 (C_{5}), 6.95 (CH_{3}TES), 6.92 (CH_{3}^{'}TES), 5.0 (CH_{2}TES), 4.9 (CH_{2}^{'}TES) ppm; MS (ESI^+) (m/z) 756.5 [M+Na]^+; HRMS (ESI^+) for C_{39}H_{57}NO_{8}Si_{2} [M+Na]^+ caledd 756.4297; found 756.4287.

Treatment of 33 (as a mixture with 34) with CSA to give the tetrahydropyran derivative 41: To a solution of 33 (and 34, dr 33/34 4:1, 70 mg, 0.107 mmol, 1 equiv) in toluene (5 mL) was added CSA (2.5 mg, 10.7 µmol, 0.1 equiv) portionwise. The solution was then stirred and heated to 80 ºC for 16 h before the solvent was evaporated under reduced pressure. Purification by column chromatography (petroleum ether/EtOAc 80/20) afforded 41 as a colourless oil (56 mg, 81%), contaminated with traces of the tetrahydropyran derivative resulting from the cyclisation of 34).

Data for 41: \(^1H\) NMR (400MHz, CDCl\(_3\)) \(\delta\) 7.90 – 7.62 (4H,m, H_{Ar-TBDPS}), 7.54 – 7.31 (6H, m, H_{Ar-TBDSP}), 4.32 (1H, td, \(^2J_{HH}\), \(^3J_{HH}\) 8.8 Hz, \(^3J_{HH}\) 7.1 Hz, H_{14}), 4.22 (1H, td, \(^2J_{HH}\), \(^3J_{HH}\) 9.0 Hz, \(^3J_{HH}\) 6.8 Hz, H_{14'}), 4.07 (1H, td, \(^3J_{HH}\) 8.2 Hz, \(^3J_{HH}\) 5.3 Hz, H_{2}), 3.96 – 3.95 (1H, br. s, OH), 3.91 (1H, ddd, \(^2J_{HH}\) 11.0 Hz, \(^3J_{HH}\) 9.6 Hz, \(^3J_{HH}\) 7.1 Hz, H_{13}), 3.82 (1H, dd, \(^3J_{HH}\) 11.6 Hz, \(^3J_{HH}\) 5.6 Hz, H_{5}), 3.69 (1H, ddd, \(^2J_{HH}\) 11.0 Hz, \(^3J_{HH}\) 9.1 Hz, \(^3J_{HH}\) 6.6 Hz, H_{13'}), 3.28 (1H, ddd, \(^3J_{HH}\) 11.4 Hz, \(^3J_{HH}\) 8.3 Hz, \(^3J_{HH}\) 1.5 Hz, H_{5}), 2.95 (1H, dd, \(^3J_{HH}\) 10.6 Hz, \(^3J_{HH}\) 1.5 Hz, H_{7}), 2.14 (1H, app. q, J 11.6 Hz, H_{4}), 1.78 – 1.63 (3H, m, H_{8}, H_{10}), 1.61 (9H, s, C(CH_{3})_{3ester}), 1.34 (1H, ddd, \(^2J_{HH}\) 12.1 Hz, \(^3J_{HH}\) 5.6 Hz, \(^3J_{HH}\) 2.0 Hz, H_{4'}), 1.24 – 1.13 (3H, m, H_{8'}, H_{11}), 1.02 (9H, s, C(CH_{3})_{3TBDPS}), 0.93 (3H, t, \(^3J_{HH}\) 7.6 Hz, H_{9}), 0.86 (3H, t, \(^3J_{HH}\) 7.3 Hz, H_{12}); \(^13C\) NMR (100 MHz, CDCl\(_3\)) \(\delta\) 177.4 (COOrBu), 172.0 (C_{1}), 152.9 (C_{15}), 136.0 (2C, CH_{Ar-TBDPS}), 135.8 (2C, CH_{Ar-TBDPS}), 134.7 (C_{qAr-TBDPS}), 132.7 (C_{qAr-TBDPS}), 129.8 (CH_{Ar-TBDPS}), 129.4 (CH_{Ar-TBDPS}), 127.6 (2C, CH_{Ar-TBDPS}), 127.3 (2C, CH_{Ar-TBDPS}), 83.3 ((CH_{3})_{3C_{ester}}, 82.0 (C_{7}), 78.0 (C_{6}), 76.2 (C_{5}), 75.9 (C_{7}), 61.4 (C_{14}), 47.0 (C_{2}), 42.6 (C_{13}), 35.7 (C_{4}), 31.1 (C_{10}), 28.3 (C(CH_{3})_{3ester}), 26.8 (C(CH_{3})_{3TBDPS}), 45
22.2 (C₈), 20.3 (C₁₁), 19.3 ((CH₃)₂C-TBDPS), 14.1 (C₁₂), 11.1 (C₉) ppm; MS (ESI⁺) (m/z) 620.4 [M-rBu+2H]⁺, 676.5 [M+Na]⁺; HRMS (ESI⁺) for C₉₈H₅₁NO₈Si [M+Na]⁺ calcd. 676.3276, found. 676.3279.

**Treatment of 33** (as a mixture with 34) with TFA to give the tetrahydropyran derivative 44 and the lactone 43: To a solution of 33 (and 34, dr 33/34 4:1, 38 mg, 58.1 µmol, 1 equiv.) in DCM (700 µL) was added TFA (300 µL, excess) dropwise at 0 ºC. The solution was allowed to warm to rt before stirring for 4 h. The reaction solvent was then evaporated under reduced pressure, removing TFA traces by azeotropically distilling with portions of toluene (2×5 mL). Purification by column chromatography (hexane/EtOAc 60/40) followed by HPLC (hexane/EtOAc 60/40) afforded 44 (23.2 mg, 67%) as a colourless oil, alongside with a mixture of 43 and 44 (3.8 mg, 11%, ratio 43/44 ~5:1, contaminated with traces of the tetrahydropyran derivative resulting from the cyclisation of the minor 34) as colourless oils.

Data for 44: IR (neat) 3480, 2960, 2859, 1779, 1699, 1108 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.76 – 7.64 (4H, m, Hₘₐₜ-TBDPS), 7.49 – 7.34 (6H, m, Hₘₐₜ-TBDPS), 4.41 – 4.26 (2H, m, H₁₄, H₁₄'), 4.16 (1H, td, ³Jₜₜ 8.0 Hz, ³Jₜₜ 5.3 Hz, H₂), 3.98 – 3.91 (2H, m, H₃, H₁₃), 3.87 – 3.79 (1H, m, H₁₃'), 3.46 (1H, ddd, ³Jₜₜ 11.9 Hz, 7.3 Hz, ³Jₜₜ 2.0 Hz, H₃), 3.14 (1H, dd, ³Jₜₜ 10.6 Hz, ³Jₜₜ 2.0 Hz, H₇), 2.37 (1H, s, OH), 2.06 (1H, dt, ³Jₜₜ 13.6 Hz, ³Jₜₜ 11.6 Hz, H₄), 1.91 – 1.74 (1H, m, H₉), 1.70 – 1.56 (1H, m, H₁₀), 1.54 – 1.39 (1H, m, H₁₀'), 1.50 (1H, ddd, ³Jₜₜ 13.6 Hz, ³Jₜₜ 5.8 Hz, ³Jₜₜ 2.0 Hz, H₄'), 1.35 – 1.22 (2H, m, H₈'), 1.22 – 1.11 (2H, m, H₁₁), 1.04 (9H, s, C(CH₃)₃estyryl), 0.95 (3H, t, ³Jₜₜ 7.3 Hz, H₉), 0.85 (3H, t, ³Jₜₜ 7.3 Hz, H₁₂); ¹³C NMR (100 MHz, CDCl₃) δ 173.9 (COOH), 173.8 (C₁), 153.0 (C₁₅), 136.0 (2C, CHₐr-TBDPS), 135.9 (2C, CHₐr-TBDPS), 134.2 (C₃Ar-TBDPS), 132.7 (C₉Ar-TBDPS), 129.9 (CHₐr-TBDPS), 129.6 (CHₐr-TBDPS), 127.7 (2C, CHₐr-TBDPS), 127.6 (2C, CHₐr-TBDPS), 82.2 (C₇), 78.3 (C₈), 76.3 (C₉), 75.8 (C₅), 61.7 (C₁₄), 46.0 (C₂), 42.7 (C₁₃), 34.6 (C₄), 30.7 (C₁₀), 26.7 (C(CH₃)₃TBDS), 22.3 (C₈), 20.1 (C₁₁), 19.3 (C₉₈H₅₁NO₈Si [M+Na]⁺ calcd. 676.3276, found. 676.3279; MS (ESI⁺) (m/z) 620.4 [M-rBu+2H]⁺, 676.5 [M+Na]⁺; HRMS (ESI⁺) for C₉₈H₅₁NO₈Si [M+Na]⁺ calcd. 676.3276, found. 676.3279.)
(CH₃)₅C₈TBDPS), 14.0 (C₁₂), 10.6 (C₈) ppm; MS (ESI) (m/z) 596.3 [M-H]; HRMS (ESI⁺) for C₃₂H₄₃NO₈Si [M+Na]⁺ calcd. 620.2650, found. 620.2651.

Data for 43 (isolated in a mixture with 44): ¹H NMR (400MHz, CDCl₃) δ 7.81 – 7.59 (4H, m, HA-TBDPS), 7.54 – 7.33 (6H, m, HA-TBDPS), 5.20 (1H, ddd, ³JHH 11.6 Hz, ³JHH 6.7 Hz, ³JHH 3.5 Hz, H₃), 4.40 (2H, m, H₁₄), 4.36 – 4.29 (1H, m, H₂), 4.06 – 3.89 (1H, m, H₁₅), 3.89 – 3.81 (1H, m, H₁₆), 3.74 (1H, d, ³JHH 3.2 Hz, H₇), 2.81 (1H, t, ³JHH 6.3 Hz, H₈), 2.20 (1H, t, ²JHH 12.9 Hz, H₄), 1.90 – 1.72 (3H, m, H₉, H₁₀, H₁₁), 1.70 – 1.40 (2H, m, H₉, H₁₁), 1.38 – 1.21 (2H, m, H₁₂), 1.09 (9H, s, C(CH₃)₃-TBDPS), 0.96 (3H, t, ³JHH 7.6 Hz, H₁₀), 0.91 (3H, t, ³JHH 7.3 Hz, H₁₃). ¹³C NMR (100 MHz, CDCl₃) δ 173.1 (C₁), 167.5 (C₇), 136.1 (2C, CH₃-Ar-TBDPS), 135.8 (2C, CH₃-Ar-TBDPS), 133.4 (CqAr-TBDPS), 132.1 (CqAr-TBDPS), 130.0 (CH₃-Ar-TBDPS), 129.9 (CH₃-Ar-TBDPS), 127.8 (2C, CH₃-Ar-TBDPS), 127.7 (2C, CH₃-Ar-TBDPS), 77.2 (C₂), 71.6 (C₃), 64.6 (C₈), 62.3 (C₆), 61.8 (C₁₃), 45.8 (C₂), 42.7 (C₁₄), 33.5 (C₄), 30.2 (C₁₁), 26.8 (C(CH₃)₃-esters), 20.3 (C₁₁), 19.9 (C₈), 19.3 (C(CH₃)₃TBDPS), 14.0 (C₁₃), 10.1 (C₁₀) ppm; MS (ESI⁺) (m/z) 602.3 [M+Na]⁺, 643.3 [M+Na+MeCN]⁺, 1181.7 [2M+Na]⁺; HRMS (ESI⁺) for C₃₂H₄₃NO₈Si [M+Na]⁺ calcd. 602.2545, found. 602.2548.

Data for 44: see above

Treatment of 33 with NaH to give the elimination product 45: To a solution of 33 and 34 (dr 33/34 4:1, 24 mg, 36.1 µmol, 1 equiv) in THF (1 mL) at -78 °C was added NaH (60% dispersion in mineral oil, 1.5 mg, 36.1 µmol, 1 equiv). The reaction was stirred for 1 h at -78 °C before warming to 0 °C during 1 h and stirring for a further h at the same temperature. The reaction was then quenched with H₂O (3 mL) before extracting with Et₂O (3×3 mL). The combined organic extracts were then washed with brine (2 mL), dried over NaSO₄, filtered and solvent evaporated under reduced pressure. Purification by column chromatography (petroleum ether/EtOAc 60/40 to 40/60) afforded 45 as a colourless oil (5.1 mg, 23%).
Data for 45: IR (neat): 3397.2, 3071.3, 2961.7, 2931.4, 2858.7, 1745.8, 1724.4 cm\(^{-1}\); \(^1\)H NMR (400MHz, CDCl\(_3\)) \(\delta\): 7.75 – 7.65 (4H, m, H\(_{Ar-TBDPS}\)), 7.49 – 7.36 (4H, m, H\(_{Ar-TBDPS}\)), 5.92 – 5.85 (1H, m, NH), 5.88 (4H, t, \(^3\)J\(_{HH}\) 7.6 Hz, H\(_3\)), 3.97 (1H, t, \(^3\)J\(_{HH}\) 7.1 Hz, H\(_2\)), 3.65 (1H, t, \(^3\)J\(_{HH}\) 5.1 Hz, H\(_{13}\)), 3.35 (1H, ddd, \(^2\)J\(_{HH}\) 14.2 Hz, \(^3\)J\(_{HH}\) 10.1 Hz, \(^3\)J\(_{HH}\) 4.6 Hz, H\(_{14}\)), 3.30 (3H, ddd, \(^2\)J\(_{HH}\) 14.2 Hz, \(^3\)J\(_{HH}\) 10.1 Hz, \(^3\)J\(_{HH}\) 4.5 Hz, H\(_{14'}\)), 3.14 (1H, t, \(^3\)J\(_{HH}\) 6.3 Hz, H\(_7\)), 2.50 (1H, dt, \(^2\)J\(_{HH}\) 14.1 Hz, \(^3\)J\(_{HH}\) 7.1 Hz, H\(_4\)), 2.45 (1H, dt, \(^2\)J\(_{HH}\) 14.1 Hz, \(^3\)J\(_{HH}\) 7.5 Hz, H\(_4'\)), 2.08 – 1.86 (2H, m, H\(_{11}, H_{11'}\)), 1.72 – 1.52 (1H, m, H\(_8\)), 1.48 (9H, s, C(CH\(_3\))\(_3\)ester), 1.44 – 1.35 (1H, m, H\(_8\)), 1.29 – 1.14 (2H, m, H\(_{12}\)), 1.09 (9H, s, C(CH\(_3\))\(_3\)TBDPS), 1.02 (3H, t, \(^3\)J\(_{HH}\) 7.6 Hz, H\(_9\)), 0.76 (3H, t, \(^3\)J\(_{HH}\) 7.3 Hz, H\(_{13}\)), \(^{13}\)C NMR (100MHz, CDCl\(_3\)) \(\delta\): 171.2 (C\(_1\)), 167.7 (C\(_{10}\)), 139.2 (C\(_2\)), 136.0 (CH\(_{Ar-TBDPS}\)), 135.9 (CH\(_{Ar-TBDPS}\)), 133.8 (C\(_{qAr-TBDPS}\)), 132.4 (C\(_{qAr-TBDPS}\)), 130.1 (CH\(_{Ar-TBDPS}\)), 129.9 (CH\(_{Ar-TBDPS}\)), 129.1 (C\(_3\)), 127.8 (CH\(_{Ar-TBDPS}\)), 127.7 (CH\(_{Ar-TBDPS}\)), 82.9 ((CH\(_3\))\(_3\)C\(_{ester}\)), 73.9 (C\(_5\)), 66.8 (C\(_6\)), 63.0 (C\(_{15}\)), 61.9 (C\(_7\)), 43.0 (C\(_{14}\)), 33.9 (C\(_4\)), 29.0 (C\(_{11}\)), 28.1 (C(CH\(_3\))\(_3\)ester), 26.9 (C(CH\(_3\))\(_3\)TBDPS), 22.0 (C\(_{12}\)), 21.7 (C\(_8\)), 19.5 ((CH\(_3\))\(_3\)C\(_{TBDPS}\)), 13.9 (C\(_9\)), 10.1 (C\(_{13}\)) ppm; MS (ESI\(^+\)) (m/z): 554.4 [M-tBu+2H]\(^+\), 610.5 [M+H]\(^+\), 632.5 [M+Na]\(^+\); HRMS (ESI\(^+\)) for C\(_{35}H\(_{31}\)NO\(_6\)Si [M+Na]\(^+\) calcd. 632.3378, found. 632.3372.

Synthesis of thioester 50: see ref 10. Data for byproducts 52 (obtained using non-optimized conditions, traces of impurity observed): IR (neat) 3369 (w), 2955 (s), 2876 (m), 1747 (m), 1712 (s), 1486 (w). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 3.04 – 2.89 (4H, m, H\(_{3,5}\)), 3.52 (1H, t, \(^3\)J\(_{HH}\) 7.6 Hz, H\(_7\)), 3.34 (1H, t, \(^3\)J\(_{HH}\) 7.1 Hz, H\(_2\)), 3.17 (1H, ddd, \(^2\)J\(_{HH}\) 14.2 Hz, \(^3\)J\(_{HH}\) 10.1 Hz, \(^3\)J\(_{HH}\) 4.5 Hz, H\(_{14}\)), 3.00 (1H, m, H\(_4\)), 2.12 (1H, dddd, \(^2\)J\(_{HH}\) 14.1 Hz, \(^3\)J\(_{HH}\) 7.1 Hz, H\(_4\)), 2.02 – 1.79 (2H, m, H\(_{11}, H_{11'}\)), 1.70 – 1.62 (1H, m, H\(_8\)), 1.54 (9H, s, C(CH\(_3\))\(_3\)ester), 1.39 – 1.26 (1H, m, H\(_8\)), 1.14 – 0.92 (2H, m, H\(_{12}\)), 0.77 (3H, t, \(^3\)J\(_{HH}\) 7.3 Hz, H\(_9\)), 0.71 (3H, t, \(^3\)J\(_{HH}\) 7.3 Hz, H\(_{13}\)), 136.8 (C\(_2\)), 133.8 (C\(_{qAr-TBDPS}\)), 132.4 (C\(_{qAr-TBDPS}\)), 131.1 (C\(_{Ar-TBDPS}\)), 129.9 (CH\(_{Ar-TBDPS}\)), 129.1 (C\(_3\)), 127.8 (CH\(_{Ar-TBDPS}\)), 127.7 (CH\(_{Ar-TBDPS}\)), 82.9 ((CH\(_3\))\(_3\)C\(_{ester}\)), 73.9 (C\(_5\)), 66.8 (C\(_6\)), 63.0 (C\(_{15}\)), 61.9 (C\(_7\)), 43.0 (C\(_{14}\)), 33.9 (C\(_4\)), 29.0 (C\(_{11}\)), 28.1 (C(CH\(_3\))\(_3\)ester), 26.9 (C(CH\(_3\))\(_3\)TBDPS), 22.0 (C\(_{12}\)), 21.7 (C\(_8\)), 19.5 ((CH\(_3\))\(_3\)C\(_{TBDPS}\)), 13.9 (C\(_9\)), 10.1 (C\(_{13}\)) ppm; MS (ESI\(^+\)) (m/z): 554.4 [M-tBu+2H]\(^+\), 610.5 [M+H]\(^+\), 632.5 [M+Na]\(^+\); HRMS (ESI\(^+\)) for C\(_{35}H\(_{31}\)NO\(_6\)Si [M+Na]\(^+\) calcd. 632.3378, found. 632.3372.
C(CH₃)₃, 1.42 – 1.17 (4H, m, H₈', H₁₁', H₁₂), 1.38 (3H, t, 3J_HH 7.3 Hz, H₉ or H₁₃ or H₁₈), 1.08 – 0.97 (21H, m, CH₂TES, CH₂'TES, H₉ or H₁₃ or H₁₈), 0.93 (3H, t, 3J_HH 7.1 Hz, H₉ or H₁₃ or H₁₈), 0.80 – 0.61 (12H, m, CH₂TES, CH₂'TES) ppm; ¹³C NMR (100 MHz, CDCl₃) δ ppm 172.3 (C₁), 170.9 (C₁₆ or C₁₀), 166.4 (C₁₆ or C₁₀), 137.3 (CₙAr), 129.2 (2C, CH₆Ar), 128.5 (2C, CH₆Ar), 126.6 (CH₆Ar), 82.4 (C(CH₃)₃), 74.2 (C₅), 71.3 (C₃), 67.20 (C₁₅), 67.17 (C₆), 61.4 (C₇), 52.1 (C₂), 48.8 (C₁₄), 40.4 (C₄), 37.4 (CH₂Bn), 29.7 (C₈ or C₁₁ or C₁₂), 28.1 (C(CH₃)₃), 25.4 (C₁₇), 21.9 (C₈ or C₁₁ or C₁₂), 21.2 (C₈ or C₁₁ or C₁₂), 14.9 (C₉ or C₁₃ or C₁₈), 14.2 (C₉ or C₁₃ or C₁₈), 10.1 (C₉ or C₁₃ or C₁₈), 7.0 (CH₃TES), 6.9 (CH₃'TES), 5.3 (CH₂TES), 5.1 (CH₂'TES) ppm; MS (ESI⁺) (m/z) 818.4 [M+Na]⁺; HRMS (ESI⁺) for C₄₃H₇₃NO₈SSi₂ [M+Na]⁺ calcd 818.4501, found 818.4482.

Reduction of the thioester 50 to give aldehyde 51: To a solution of thioester 50 (170 mg, 0.27 mmol, 1 equiv.) in DCM (1.5 mL) at 0 °C was added Et₃SiH (129 µL, 0.81 mmol, 3 equiv.) and Pd/C (10% wt, 57 mg, 54 µmol, 20 mol%) in one portion. The mixture was then stirred for 20 min at rt, before adding DCM (0.75 mL). The suspension was stirred for further 18 h, before filtering through celite®, washing with DCM (15 mL), and concentrating under reduced pressure. Purification via column chromatography (pentane/Et₂O 98:2 to 95:5) afforded compound 51 as a colourless oil (145 mg, 96%). Data for 51 correspond to those previously reported.¹⁰

Formylation of 53 to give aldehyde 56: To a solution of 53 (3.0 g, 8.2 mmol, 1 equiv.) in Et₂O (25 mL) at rt was added TMEDA (1.9 mL, 13.0 mmol, 1.58 equiv.) and the solution was cooled to 0 °C. Following this, n-BuLi (1.6 M in hexanes, 8.1 mL, 13.0 mmol, 1.58 equiv.) was added dropwise and the mixture was stirred at 0 °C for 15 min. DMF (1.50 mL, 19.0 mmol, 2.3 equiv.) was then added dropwise at 0 °C and the reaction mixture was stirred for a further h. The reaction mixture was allowed to warm to rt slowly and was quenched with H₂O (20 mL). The mixture was extracted with ether (2×20 mL). The combined organic phases were washed with brine (20 mL), dried over MgSO₄ and
concentrated \textit{in vacuo}. Purification \textit{via} column chromatography (hexane/Et₂O 90:10) afforded compound \textbf{56} as a white solid (1.33 g, 43%).

Data for \textbf{56}: IR (neat) 3032, 2954, 2866, 1685, 1591 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 10.59 (1H, s, \(H_{12}\)), 7.54 – 7.29 (11H, m, \(H_{Ar}\), \(H_3\), \(H_6\)), 6.80 (1H, d, \(^3\)\(J_{HH}\) 8.6 Hz, \(H_4\)), 5.18 (2H, s, \(H_{10}\) or \(H_{11}\)), 4.94 (2H, s, \(H_{10}\) or \(H_{11}\)), 2.41 (2H, d, \(^3\)\(J_{HH}\) 7.2 Hz, \(H_7\)), 1.90 (1H, tspt, \(^3\)\(J_{HH}\) 7.2 Hz, \(^3\)\(J_{HH}\) 6.6 Hz, \(H_8\)), 0.86 (6H, d, \(^3\)\(J_{HH}\) 6.6 Hz, \(H_9\), \(H_9'\)) ppm; \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 189.6 (C\(_{12}\)), 160.0 (C\(_1\) or C\(_5\)), 158.8 (C\(_1\) or C\(_5\)), 137.13 (C\(_3\)), 137.09 (C\(_{qAr}\)), 136.3 (C\(_{qAr}\)), 128.7 (2C, CH\(_{Ar}\)), 128.51 (C\(_2\)), 128.48 (2C, CH\(_{Ar}\)), 128.2 (2C, CH\(_{Ar}\)), 128.1 (2C, CH\(_{Ar}\)), 127.2 (2C, CH\(_{Ar}\)), 119.4 (C\(_6\)), 108.5 (C\(_4\)), 77.3 (C\(_{10}\) or C\(_{11}\) (DEPT 135)), 70.9 (C\(_{10}\) or C\(_{11}\)), 38.6 (C\(_7\)), 29.1 (C\(_8\)), 22.4 (C\(_9\) and C\(_{9'}\)) ppm; MS (EI) (m/z) 90.9 [Bn]+ (100%), 257.0 [M-Bn+2H-CO]+ (2%), 347.0 [M-CO+H]+ (4%); HRMS (ESI\(^{+}\)) for C\(_{25}\)H\(_{26}\)O\(_3\) [M+Na]\(^{+}\) calcd. 397.1774, found. 397.1771.

\textit{Reduction of aldehyde} \textbf{56} \textit{and TBS-protection to give} \textbf{57}: To a solution of aldehyde 5.4 (1.0 g, 2.7 mmol, 1 equiv.) in THF (20 mL) at rt was added NaBH\(_4\) (220 mg, 5.9 mmol, 2.2 equiv.) in one portion. The reaction mixture was stirred for 1.5 h at this temperature, before quenching with H\(_2\)O (10 mL), followed by dropwise addition of HCl (0.5 M, 5 mL). The mixture was diluted with Et\(_2\)O (10 mL) and the phases were separated. The aqueous phase was re-extracted with Et\(_2\)O (2x25 mL) and the combined organic phases were washed with a saturated solution of NH\(_4\)Cl (20 mL). The combined organic phases were dried over Na\(_2\)SO\(_4\) and concentrated \textit{in vacuo}, to give the corresponding alcohol as a pale oil which was used without further purification.

The crude alcohol (1.0 g, 2.7 mmol, 1 equiv.) was then dissolved in DMF (25 mL) at rt, after which TBSCl (0.48 g, 3.2 mmol, 1.2 equiv.) was added dropwise, followed by imidazole (0.43 g, 6.4 mmol, 2.4 equiv.) in one portion. The reaction mixture was stirred for 1 h before quenching with H\(_2\)O (20 mL), and stirred for additional 15 min. The mixture was extracted with Et\(_2\)O (3x25 mL), the combined
organic phases were washed with brine (20 mL) dried over Na$_2$SO$_4$ and concentrated in vacuo. Purification via column chromatography (hexane/Et$_2$O 80:20) afforded compound 57 as a yellow oil (1.18 g, 90% over 2 steps).

IR (neat) 3031 (w), 2952 (m), 2866 (m), 1600 (m), 1483 (m), 1347 (m) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.53 – 7.30 (10H, m, H$_{Ar}$), 7.05 (1H, d, $^3$J$_{HH}$ 8.4 Hz, H$_3$), 6.70 (1H, d, $^3$J$_{HH}$ 8.4 Hz, H$_4$), 5.09 (2H, s, H$_{11}$ or H$_{10}$), 5.05 (2H, s, H$_{11}$ or H$_{10}$), 4.84 (2H, s, H$_{12}$), 2.46 (2H, d, $^3$J$_{HH}$ 7.2 Hz, H$_7$), 1.93 (1H, tspt, $^3$J$_{HH}$ 7.2 Hz, $^3$J$_{HH}$ 6.6 Hz H$_8$), 0.89 (6H, d, $^3$J$_{HH}$ 6.7 Hz, H$_9$, H$_9'$), 0.84 (9H, s, H$_{15}$), -0.01 (6H, s, H$_{13}$, H$_{13}'$); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 157.4 (C$_1$ or C$_5$), 156.7 (C$_5$ or C$_1$), 138.2 (C$_q$Ar), 137.3 (C$_q$Ar), 130.5 (C$_3$), 128.4 (3 or 4C, CH$_{Ar}$), 127.8 (CH$_{Ar}$), 127.7 (2 or 3C, CH$_{Ar}$), 127.44 (C$_2$ or C$_8$), 127.41 (2C, CH$_{Ar}$), 122.9 (C$_6$ or C$_2$), 107.9 (C$_4$), 76.8 (C$_{10}$ or C$_{11}$), 70.5 (C$_{10}$ or C$_{11}$), 55.2 (C$_{12}$), 39.2 (C$_8$), 29.3 (C$_7$), 26.0 (C$_{15}$), 22.6 (C$_9$ and C$_9'$), 18.4 (C$_{14}$), -5.4 (C$_{13}$ and C$_{13'}$) ppm; MS (ESI$^+$) (m/z) 513 [M+Na]$^+$; HRMS (ESI$^+$) for C$_{31}$H$_{42}$O$_3$Si [M+Na]$^+$ calcd. 513.2975; found. 513.2976.

Bromination to yield the aromatic derivative 58: To a solution of protected triol 57 (998 mg, 2.0 mmol, 1 equiv.) in dry CHCl$_3$ (20 mL) at rt was added NBS (724 mg, 4.0 mmol, 2 equiv.) and the reaction mixture was stirred overnight in the dark. At completion the reaction mixture was concentrated in vacuo and extracted with Et$_2$O (30 mL) and H$_2$O (30 mL). The aqueous layer was re-extracted with ether (30 mL) and the combined organic phases were dried over Na$_2$SO$_4$ and concentrated in vacuo. Purification via column chromatography (hexane/Et$_2$O 97:3) afforded compound 58 as a yellow solid (1.11 g, 96%).

IR (neat) 2954 (s), 2928 (m), 2856 (w), 1497 (w), 1448 (m) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.60 – 7.53 (2H, m with the presence of $^3$J$_{HH}$ 7.0 Hz, H$_{Ar}$ and/or H$_3$), 7.49 – 7.31 (9H, m, H$_{Ar}$ and/or H$_3$), 5.13 (2H, s, H$_{11}$ or H$_{10}$), 5.00 (2H, s, H$_{11}$ or H$_{10}$), 4.77 (2H, s, H$_{12}$), 2.45 (2H, d, $^3$J$_{HH}$ 7.2 Hz, H$_7$), 1.94 (1H,
Coupling reaction between 51 and 58: To a solution of bromoaryl 58 (427 mg, 0.75 mmol, 3 equiv.) in THF (2.5 mL) at -78 °C was added t-BuLi (1.86 M in pentane, 400 µL, 0.75 mmol, 3 equiv.) dropwise. The mixture was stirred at this temperature for 10 min, after which a solution of aldehyde 51 (142 mg, 0.25 mmol, 1 equiv.) in THF (9 mL) was added at -78 °C, and the flask was washed with THF (2 mL). The resulting solution was stirred at -78 °C for 45 min, before quenching at this temperature with H₂O (10 mL). The mixture was then allowed to warm up to rt before extracting with Et₂O (3×20 mL). The organic layers were combined, dried over Na₂SO₄ and concentrated under reduced pressure. Purification via column chromatography (pentane/Et₂O 9:1) gave the coupling product 59a as a mixture of epimers (245 mg, 92%, dr 63:37), alongside with an inseparable mixture of aromatic derivatives 57 and 58 (206 mg, 57/58 70:30). A preparative HPLC (pentane/EtOAc 98:2) was then performed on an analytical mixture of the pure 59a (80 mg) which allowed separation of the major epimer of 58a (52 mg) and the minor epimer of 58a (27 mg) for characterisation purpose (major isomer eluted first). The configuration at C1 was not determined.

Data for 58a (major isomer): [α]D +18.6 (c 1.26, CHCl₃, 22°C); ¹H NMR (400 MHz, CDCl₃) δ 7.52 - 7.29 (11H, m, H₄), 5.22 – 5.17 (2H, m, H₁, CH₂Ph), 5.15 – 5.09 (2H, m, CH₂Ph), 5.00 – 4.93 (1H, m, CH₂Ph), 4.83 – 4.72 (2H, m, H₁₇), 4.07 – 3.99 (1H, m, H₃), 3.43 (1H, d, 3JHH 1.3 Hz, OH-1), 3.32 (1 H,
dd, $^3J_{HH}$ 7.0 Hz, $^3J_{HI}$ 5.1 Hz, H$_2$), 2.71 (1H, t, $^3J_{HI}$ 6.4 Hz, H$_3$), 2.55 (1H, dd, $^3J_{HI}$ 13.3 Hz, $^3J_{HH}$ 7.4 Hz, H$_{1d}$), 2.39 (1H, dd, $^3J_{HH}$ 13.4 Hz, $^3J_{HI}$ 7.1 Hz, H$_{1d}$), 2.23 (1H, dt, $^2J_{HH}$ 14.7 Hz, $^3J_{HH}$ 7.4 Hz, H$_4$), 2.09 – 1.95 (2H, m, H$_8$, H$_{15}$), 1.83 – 1.75 (1H, m, H$_2$), 1.63 – 1.40 (2H, m, H$_8$, H$_{11}$), 1.48 (9H, s, C(CH$_3$)$_3$ ester), 1.39 – 1.16 (4H, m, H$_8$, H$_{11}$, H$_{12}$, H$_{12'}$), 1.00 – 0.85 (27H, m, H$_9$, H$_{16}$, H$_{16'}$, CH$_3$TES), 0.80 (9H, s, C(CH$_3$)$_3$TES), 0.73 (3H, t, $^3J_{HH}$ 6.6 Hz, H$_{13}$), 0.69 – 0.55 (12H, m, CH$_3$TES), -0.03 (3H, s, CH$_3$TES), -0.06 (3H, s, CH$_3$TES); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 166.4 (C$_{10}$), 156.4 (COBn), 154.1 (COBn), 138.1 (C$_{qAr}$), 137.7 (C$_{qAr}$), 132.6 (C$_{qAr}$), 129.0 (CH$_3$), 128.4 (2C, CH$_{Ar}$), 128.3 (2C, CH$_{Ar}$), 127.7 (CH$_{Ar}$), 127.5 (CH$_{Ar}$), 127.2 (2C, CH$_{Ar}$), 127.1 (C$_{qAr}$), 126.9 (2C, CH$_{Ar}$), 82.1 ((CH$_3$)$_3$ ester), 77.3 (CH$_2$Ph (DEPT 135)), 76.6 (CH$_2$Ph), 75.9 (C$_3$), 74.9 (C$_3$), 71.4 (C$_1$), 67.0 (C$_6$), 61.1 (C$_7$), 55.4 (C$_{12'}$), 47.3 (C$_2$), 41.3 (C$_4$), 39.3 (C$_{14}$), 29.5 (C$_{15}$), 28.0 (C(CH$_3$)$_3$ ester), 25.8 (C(CH$_3$)$_3$TES), 24.7 (C$_{11}$), 23.0 (C$_{12}$), 22.6 (C$_{16}$ or C$_{16'}$), 22.4 (C$_{16}$ or C$_{16'}$), 20.9 (C$_8$), 18.0 ((CH$_3$)$_3$C$_{TES}$), 14.6 (C$_{13}$), 10.1 (C$_9$), 6.9 (CH$_3$TES, CH$_3'$TES), 5.36 (CH$_3$TES), 4.88 (CH$_2'$TES), -5.5 (CH$_3$TES), -5.7 (CH$_3'$TES) ppm; MS (ESI$^+$) (m/z) 1071.65 [M+Na]$^+$. 

Data for 58a (minor isomer): $[\alpha]_D$ +13.6 (c 0.69, CHCl$_3$, 22°C); IR (neat) 3477 (w, br.), 2958 (s, br.).
(CH$_{Ar}$), 127.3 (C$_4$Ar), 127.2 (2C, CH$_{Ar}$), 126.9 (2C, CH$_{Ar}$), 82.1 ((CH$_3$)$_3$C$_{ester}$), 77.7 (CH$_2$Ph), 76.5 (CH$_2$Ph), 74.5 (C$_3$ or C$_5$), 73.6 (C$_3$ or C$_5$), 70.1 (br. s, C$_7$), 67.2 (C$_6$), 61.4 (C$_7$), 55.4 (C$_{17}$), 49.2 (C$_2$), 39.4 (C$_4$ or C$_{14}$), 39.2 (C$_4$ or C$_{14}$), 29.8 (C$_{12}$ or C$_{11}$), 29.2 (C$_{13}$), 27.9 (C(CH$_3$)$_3$est$_{ester}$), 25.8 (C(CH$_3$)$_3$TBS), 22.6 (C$_{16}$ or C$_{16'}$), 22.5 (C$_{16}$ or C$_{16'}$), 21.7 (C$_8$), 21.0 (C$_{11}$ or C$_{12}$), 17.9 ((CH$_3$)$_3$est$_{TBS}$), 14.1 (C$_{13}$), 10.2 (C$_9$), 6.9 (CH$_3$ TES, CH$_3$TES), 5.4 (CH$_2$TES), 5.1 (CH$_2$TES), -5.5 (CH$_3$TBS), -5.6 (CH$_3$TBS) ppm; MS (ESI$^+$) (m/z) 1071.66 [M+Na]$^+$.  

**Reduction/Deprotection leading to hemiacetal 61a, and deprotected ester 62a:** To a solution of 5.7 (107 mg, 0.10 mmol, dr 67:33, 1 equiv.) in toluene (3.2 mL) at -78 °C was added DIBAL-H (1M in heptane, 400 µL, 0.40 mmol, 4 equiv.) dropwise. The resulting mixture was stirred for 1 h at this temperature, before quenching with MeOH (3 mL) at -78 °C. The solution was allowed to warm up to 0 °C after which H$_2$O (3 mL) was added and the resulting mixture was stirred for further 1 h at 0 °C. The mixture was filtered through a pad of celite®, washed with EtOAc (24 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (5 mL). The combined organic layers were dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure. Purification via column chromatography (pentane/Et$_2$O 95:5 to 9:1) followed by preparative HPLC (hexane/Et$_2$O 9:1) gave a mixture of aldehyde 60a and starting material 59a (86 mg), which was used in the next step without further purification.

The mixture (86 mg) was then dissolved in THF (3 mL), and TBAF (1M in THF, 520 µL, 0.52 mmol, 5.2 equiv.) was added dropwise at 0 °C. The resulting solution was stirred for 1 h at 0 °C, then the mixture was allowed to warm up to rt, and stirring was continued for 2.5 h at this temperature, before evaporating under reduced pressure. Purification via column chromatography (pentane/acetone 8:2 to 7:3) gave the hemiacetal 61a as a single epimer and as a colourless oil (35 mg, isolated with 5% of 62a, 54% over 2 steps), as well as an impure mixture of deprotected ester 62a, which was repurified by
preparative HPLC (hexane/acetone 7:3) to give the pure 62a as a colourless oil (10.9 mg, 15% over 2 steps, dr 85:15).

Data for 61a: [α]_D +31.8 (c 0.23, CHCl₃, 21 °C); IR (neat) 3408 (m, br.), 2955 (s, br.), 2353 (m, br.), 21 °C); IR (neat) 3395 (m, br.), 2966 (s, br.), 1724 (m), 1457 (m), 1370 (m), 1247 (m), 1098 (s) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.53 – 7.35 (10H, m, HAr), 7.32 (1H, s, HAr), 5.11 (1H, d, 3J_HH 5.8 Hz, H1), 5.05 (1H, d, 2J_HH 10.9 Hz, CHHPh), 5.00 – 4.92 (3H, m, CHHPh, CH₂Ph), 4.84 (1H, s, HAr), 4.73 (2H, app. d, 3J_HH 4.9 Hz, H17), 4.02 (1H, td, 3J_HH 11.3 Hz, 3J_HH 7.3 Hz, H14), 2.29 (1H, t, 7.5 Hz, H5), 2.60 (1H, dd, 2J_HH 13.2 Hz, 3J_HH 7.1 Hz, H14), 2.52 (1H, dd, 2J_HH 13.3 Hz, 3J_HH 7.3 Hz, H14), 1.94 (1H, m, OH-1), 0.91 (3H, d, 3J_HH 7.3 Hz, H14); ¹³C NMR (100 MHz, CDCl₃) δ 156.1 (COBn), 152.8 (COBn), 137.2 (CqAr), 136.6 (CqAr), 133.0 (CqAr), 131.9 (CqAr), 129.1 (CHAr), 128.7 (4C, CHAr), 128.6 (CHAr), 128.4 (2C, CHAr), 128.2 (CHAr), 127.7 (2C, CHAr), 127.4 (CqAr), 94.3 (C₂), 77.7 (CH₂Bn), 76.5 (CH₂Bn), 71.1 (C₁), 69.8 (C₃ or C₄), 63.0 (C₃ or C₄), 61.8 (C₆), 59.6 (C₈), 56.3 (C₁₇), 49.0 (C₂), 39.4 (C₁₄), 37.3 (C₄), 29.3 (C₁₅), 26.6 (C₁₁), 23.3 (C₁₂), 22.6 (C₁₆ or C₁₇), 22.4 (C₁₆ or C₁₇), 20.6 (C₉), 14.5 (C₁₃), 10.6 (C₁₀); MS (ESI⁺) (m/z) 657 [M+Na]⁺; HRMS (ESI⁺) for C₃₈H₆₀O₆ [M+Na]⁺ calc 657.3398, found 657.3385.

Data for 62a (mixture of diastereoisomers): IR (neat) 3395 (m, br.), 2966 (s, br.), 1724 (m), 1457 (m), 1370 (m), 1247 (m), 1098 (s) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.53 – 7.33 (20H, m, HAr, major and minor), 7.32 (1H, s, HAr, minor), 7.26 (1H, s, HAr, major), 5.11 – 5.08 (1H, m, H₁, minor), 5.04 (2H, d, 2J_HH 11.1 Hz, CHHPh, major and minor), 5.00 – 4.92 (6H, m, CH₂Ph, CHHPh, major and minor), 4.75 (2H, app. d, 3J_HH 5.9 Hz, H₁₇, major), 4.41 (1H, ddd, 3J_HH 9.1 Hz, 3J_HH 6.5 Hz, 3J_HH 3.0 Hz, H₃ or H₅, major), 4.31 – 4.20 (2H, m, H₃ or H₅, major and minor), 4.17 – 4.09 (1H, m, H₃ or H₅, minor), 3.73 –
3.65 (1H, m, OH-3 or OH-5, major), 3.27 (1H, t, $^3J_{HH}$ 6.4 Hz, H$_7$, major and minor), 3.14 – 3.08 (1H, m, OH, minor), 3.04 – 2.97 (1H, d, $^3J_{HH}$ 8.8 Hz, OH-5 or OH-3, major), 2.86 (1H, br. d, $^3J_{HH}$ 9.5 Hz, OH, minor), 2.66 – 2.42 (3H, m, H$_{14}$, H$_{14}'$, OH-17, major), 2.06 – 1.89 (3H, m, H$_2$, H$_4$, H$_{15}$, major), 1.69 – 1.51 (3H, m, H$_6$, H$_8$, OH-1, major), 1.48 (9H, s, (CH$_3$)$_3$C, major), 1.44 (9H, s, (CH$_3$)$_3$C, minor), 1.32 – 1.10 (2H, m, H$_{12}$), 1.09 – 0.98 (2H, m, H$_{11}$), 1.06 (3H, t, $^3J_{HH}$ 7.7 Hz, H$_9$, major), 0.908 (3H, d, $^3J_{HH}$ 6.3 Hz, H$_{16}$ or H$_{16}'$, major), 0.904 (3H, d, $^3J_{HH}$ 6.2 Hz, H$_{16}$ or H$_{16}'$, major), 0.73 (3H, t, $^3J_{HH}$ 7.1 Hz, H$_9$, major); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 167.8 (C$_{10}$), 156.4 (C$_{OBn}$), 153.3 (C$_{OBn}$), 137.1 (C$_{qAr}$), 136.6 (C$_{qAr}$), 132.4 (C$_{qAr}$), 131.7 (C$_{qAr}$), 129.3 (CH$_{Ar}$), 128.72 (CH$_{Ar}$), 128.66 (br. s, CH$_{Ar}$), 128.60 (CH$_{Ar}$) 128.53 (CH$_{Ar}$), 128.48 (CH$_{Ar}$), 128.3 (CH$_{Ar}$), 128.1 (CH$_{Ar}$), 127.8 (CH$_{Ar}$), 127.7 (CH$_{Ar}$), 127.6 (C$_{qAr}$), 82.6 ((CH$_3$)$_3$C), 77.6 (CH$_2$Bn), 76.4 (CH$_2$Bn), 72.6 (C$_1$ or C$_3$ or C$_5$, minor), 72.4 (C$_1$ or C$_3$ or C$_5$, minor), 71.0 (C$_1$), 70.4 (C$_3$), 67.4 (C$_5$), 65.9 (C$_6$), 59.8 (C$_7$), 56.5 (C$_{17}$), 48.1 (C$_2$), 39.3 (C$_{14}$), 34.6 (C$_4$), 29.2 (C$_{13}$), 29.1 (C$_{11}$), 28.0 (C(CH$_3$)$_3$), 27.9 (C(CH$_3$)$_3$, minor), 22.6 (C$_{16}$), 22.5 (C$_{16'}$), 21.4 (C$_8$), 20.7 (C$_{12}$), 14.1 (C$_{13}$), 10.3 (C$_9$) ppm; MS (ESI$^+$) (m/z) (peak 1) 729 [M+Na]$^+$, (peak 2) 729 [M+Na]$^+$; HRMS (ESI$^+$) for C$_{42}$H$_{58}$O$_9$[M+Na]$^+$ calcd 729.3973; found 729.3964.

_Bis-benzylic oxidation of 61a to give 64:_ To a solution of 61a (18.5 mg, 29.1 µmol, 1 equiv.) in DCM (2 mL) at 0 °C were successively added NaHCO$_3$ (24.4 mg, 29.1 µmol, 10 equiv.) and Dess-Martin periodinane (25.3 mg, 59.7 µmol, 2.05 equiv.). The mixture was stirred at rt for 5 min, before filtering through a pad of silica (pentane/Et$_2$O 5:5) to give 8 mg of impure keto aldehyde 64. A mixture of mono-oxidised product and starting material 61a (9.1 mg, ca. 2:1 respectively) was also isolated. The mixture of starting material 61a and mono-oxidised product (9.1 mg) was redissolved in DCM (1 mL), and NaHCO$_3$ (13 mg) was added at 0 °C, followed by Dess-Martin periodinane (8 mg). The resulting suspension was then stirred at rt for 8 min, before filtering through a pad of silica (pentane/Et$_2$O 5:5) to give 3 mg of impure keto aldehyde, which was combined with the first fraction
and purified via column chromatography (pentane/Et2O 5:5) to give the pure benzyl protected luminacin D 64 (10.3 mg, 56%) as a colourless oil.

Data for 64: IR (neat) cm⁻¹ 3432 (br., m), 2957 (m, br.), 1690 (s), 1556 (m), 1094 (s, br.); ¹H NMR (400 MHz, CDCl₃) δ 10.33 (1H, s, H₁₇), 7.52 – 7.33 (11H, m, H₄₋₉), 5.07 (1H, d, JHH 10.3 Hz, CH₃Ph), 5.04 (1H, d, JHH 10.1 Hz, CH₃Ph), 4.98 (1H, d, JHH 11.5 Hz, CH₃Ph), 4.95 (1H, d, JHH 11.3 Hz, CH₃Ph), 4.66 (1H, d, JHH 2.3 Hz, H₇), 4.39 (1H, ddd, JHH 11.7 Hz, JHH 4.8 Hz, JHH 4.8 Hz, JHH 1.3 Hz, H₃), 3.36 (1H, dt, JHH 8.7 Hz, JHH 4.3 Hz, H₂), 3.22 (1H, t, JHH 6.5 Hz, H₈), 2.49 (2H, d, JHH 7.2 Hz, H₁₄), 2.47 (1H, d, JHH 2.8 Hz, OH⁻7), 2.01 – 1.85 (3H, m, H₄, H₇, H₈), 1.59 – 1.45 (4H, m, H₄, H₉, H₉, H₁₁), 1.44 – 1.29 (1H, m, H₁₂), 1.29 – 1.15 (1H, m, H₁₂), 1.03 (3H, t, JHH 7.5 Hz, H₁₀), 0.92 – 0.85 (9H, m, H₁₃, H₁₆, H₁₆); ¹³C NMR (100 MHz, CDCl₃) δ 203.6 (C₁₇), 189.1 (C₁), 161.3 (COBn), 156.7 (COBn), 136.1 (C₉Ar), 135.81 (C₉Ar), 135.77 (CHAr), 132.7 (C₉Ar), 132.4 (C₉Ar), 128.9 (2C, CH₆), 128.68 (CH₆), 128.65 (2C, CH₆), 128.60 (2C, CH₆), 128.5 (CH₆), 128.2 (2C, CH₆), 124.3 (C₉Ar), 94.3 (C₇), 80.2 (CH₂Bn), 78.2 (CH₂Bn), 67.5 (C₃), 62.8 (C₅), 61.5 (C₆), 59.5 (C₇), 54.9 (C₂), 38.7 (C₁₄), 36.8 (C₈), 29.1 (C₁₃), 28.1 (C₁₁), 22.5 (C₁₆ or C₁₆), 22.3 (C₁₆ or C₁₆), 20.9 (C₈), 20.5 (C₁₂), 14.3 (C₁₃), 10.5 (C₁₀) ppm; MS (ESI⁺) (m/z) 653 [M+Na]⁺; HRMS (ESI⁺) for C₃₈H₄₆O₈ [M+Na]⁺ calcd 653.3085; found 653.3091.

**Hydrogenolysis of 64 to give (−)-luminacin D 1a:** The benzyl protected luminacin D 1a (12.6 mg, 20.5 µmol, 1 equiv.) was dissolved in EtOAc (8 mL). Pd/C (10% wt, 5 mg, 21 µmol, 10 mol%) was added and the resultant mixture was flushed with H₂. Stirring under an atmosphere of H₂ was continued at rt for 24 h, before the mixture was filtered through a pad of silica and concentrated in vacuo. Purification by column chromatography (hexane/EtOAc 70:30) followed by preparative HPLC
(hexane/EtOAc 65:35) afforded (−)-Luminacin D 1.1 as a pale yellow residue (7.2 mg, 80%). Data for 1a correspond to those previously reported.10,38

DDQ-oxidation of 66 to give compound 67: To a solution of 66 (55 mg, 0.11 mmol, 1 equiv) in DCM/H2O (9:1, 5 mL) was added DDQ (119 mg, 0.524 mmol, 5 equiv) The reaction was then heated to reflux for 24 h, after which the reaction was portioned between a saturated solution of NaHCO3 (5 mL) and DCM (5 mL), the separated aqueous phase was then extracted with a further portion of DCM (5 mL). The combined organic extracts were then scrubbed with brine (5 mL), dried over Na2SO4, filtered and the solvent was evaporated under reduced pressure. The crude was purified by column chromatography (petroleum ether/Et2O 80:20) to give 67 as a colourless oil (22 mg, 48%). The product was further purified by HPLC (hexane/acetone 90:10) to give 9.8 mg (22%) of pure product.

Data for 67: 1H NMR (400 MHz, CD3CN) δ 7.57 – 7.32 (11 H, m, HAr, H3), 4.99 (2H, s, CH2Ph), 4.95 (2H, s, CH2Ph), 4.67 (2H, d, 3JHH 4.9 Hz, H13), 3.08 (1H, t, 3JHH 5.1 Hz, OH), 2.96 (2H, q, 3JHH 7.3 Hz, H11), 2.54 (2H, d, 3JHH 7.2 Hz, H7), 2.01 – 1.85 (1H, m, H8), 1.08 (3H, m, H12), 0.88 (6H, d, 3JHH 6.8 Hz, H9, H9′) ppm; 13C NMR (100MHz, CDCl3) δ 204.5 (C10), 161.1 (COBn), 157.0 (COBn), 139.0 (CqAr), 138.6 (CqAr), 132.8 (C2), 132.5 (C3), 131.7 (C6), 130.6 (C4), 130.0 (CHAr), 129.9 (CHAr), 129.7 (CHAr), 129.6 (CHAr), 129.6 (CHAr), 129.4 (CHAr), 79.7 (CH2Bn), 78.1 (CH2Bn), 55.7 (C13), 40.2 (C7), 36.9 (C11), 30.4 (C8), 23.1 (C9 and C9′), 9.1 (C12) ppm; MS (ESI+) (m/z) 455 [M+Na]+, 496.3 [M+Na+MeCN]+.

DMP-oxidation of 66 to give compound 69: To a solution of 66 (70 mg, 0.133 mmol, 1 equiv) in DCM (5 mL) was sequentially added NaHCO3 (56 mg, 0.67 mmol, 5 equiv) and Dess-Martin periodane (68 mg, 0.160 mmol, 1.2 equiv). The mixture was stirred at rt for 1 h before quenching with a saturated solution of Na2SO3 (3 mL) and water (5 mL). The mixture was then extracted with portions of DCM (3×10 mL) and the combined extracts washed with NaHCO3 (3×7.5 mL), dried over Na2SO4,
filtered and the solvent evaporated under reduced pressure. The crude residue was then purified by column chromatography (petroleum ether/Et₂O 80:20) to yield 69 as a colourless oil (64 mg, 92%).

Data for 69: IR (neat) 3031, 2955, 2869, 1680, 1588 cm⁻¹; ¹H NMR (400MHz, CDCl₃) δ 7.51 – 7.32 (15H, m, H₂Ar), 7.28 (1H, t, H₃, overlapped with the solvent peak), 5.04 (2H, s, CHPh), 5.02 (2H, s, CH₂Ph), 4.68 (2H, s, CH₂Ph), 4.56 (2H, s, CH₂Ph), 3.00 (2H, q, ³JHH 7.4 Hz, H₁₁), 2.54 (2H, d, ³JHH 7.1 Hz, H₉), 1.99 (1H, t, δJHH 7.1 Hz, δJHH 6.6 Hz, H₉), 1.15 (3H, t, ³JHH 7.1 Hz, H₁₂), 0.92 (6H, d, ³JHH 6.6 Hz, H₉, H₉) ppm; ¹³C NMR (100MHz, CDCl₃) δ 203.8 (C₁₀), 160.6 (C₂OBn), 156.4 (C₂OBn), 137.9 (C₂Ar), 137.5 (C₂Ar), 137.0 (C₂Ar), 131.8 (C₃), 131.5 (C₄), 130.2 (C₂), 128.7 (C₂Ar), 128.7 (C₂Ar), 128.5 (C₂Ar), 128.4 (C₂Ar), 128.0 (C₂Ar), 127.9 (C₂Ar), 127.7 (C₂Ar), 127.6 (C₂Ar), 127.3 (C₂Ar), 126.2 (C₃), 78.8 (C₂Bn), 77.0 (C₂Bn), 73.3 (C₂Bn), 62.7 (C₁₃), 39.1 (C₇), 35.9 (C₁₁), 29.2 (Cₙ), 22.5 (Cₙ and Cₙ), 8.5 (C₁₂) ppm; MS (ESI⁺) (m/z) 545 [M+Na]+; HRMS (ESI⁺) for C₃₅H₉₀O₄ [M+Na]+ calcd. 545.2662, found. 545.2667.

Hydrogenolysis of 69 (short reaction time): To a solution of 69 (95 mg, 0.182 mmol, 1 equiv) in THF (285 µL) was added Pd/C in one portion under N₂, followed by acetic acid dropwise (15 µL). The reaction was then purged with H₂ by bubbling through the suspension, adding THF periodically to combat evaporation. After 2.5 h under H₂ the mixture was filtered through celite® and washing with THF (3×3 mL), the solvent was then evaporated and the crude purified by column chromatography (petroleum ether/Et₂O 80:20) to yield the triol 70 as a colourless oil (36 mg, 78%).

Data for 70: IR (neat) 3403, 3213, 2964, 2914, 1606 cm⁻¹; ¹H NMR (400MHz, CDCl₃) δ 13.02 (1H, s, OH), 9.00 (1H, s, OH), 7.40 (1H, s, H₃), 5.09 (1H, d, ³JHH 5.1 Hz, H₁₁), 2.95 (1H, q, ³JHH 7.1 Hz, H₉), 2.43 (2H, d, ³JHH 7.1 Hz, H₉), 2.33 (1H, t, ³JHH 5.3 Hz, OH₁₃), 1.92 (1H, t, δJHH 7.1 Hz, δJHH 6.6 Hz, H₉), 1.23 (3H, t, ³JHH 7.3 Hz, H₁₂), 0.93 (6H, d, ³JHH 6.6 Hz, H₉, H₉) ppm; ¹³C NMR (100MHz, CDCl₃) δ 205.7 (C₁₀), 162.1 (COH), 159.7 (COH), 131.4 (C₃), 120.6 (C₂), 111.9 (Cₖ), 110.4 (C₄), 58.8 (C₁₃), ...
38.8 (C₁₁), 31.1 (C₇), 28.5 (C₈), 22.4 (C₉ and C₉'), 8.7 (C₁₂) ppm; MS (ESI⁺) (m/z) 316. [M+Na+MeCN]⁺, 527. [2M+Na]⁺; HRMS (ESI) for C₁₄H₂₀O₄ [M-H]⁻: calcd 251.1289, found 251.1285.

_Hydrogenolysis of 69 (extended reaction time):_ To a solution of 69 (60 mg, 0.115 mmol, 1 equiv) in THF (0.95 mL) was added Pd/C in one portion under N₂, followed by acetic acid dropwise (50µL). The reaction was then purged with H₂ by bubbling through the suspension, adding THF periodically to combat evaporation. After 20 h under H₂ the mixture was filtered through celite® and washed with THF (3×3 mL), the solvent was then evaporated to yield a mixture of 71 and 70 (28 mg, > 99%, 71/70 98:2).

Data for 71: IR (neat) 3457, 2955, 2869, 1624, 1464 cm⁻¹; ¹H NMR (400MHz, CDCl₃) δ 12.97 (1H, s, OH), 7.36 (1H, s, H₃), 5.35 (1H, br. s., OH), 2.97 (2H, q, ³J_HH 7.2 Hz, H₁₁), 2.44 (2H, d, ³J_HH 7.1 Hz, H₇), 2.14 (3H, s, H₁₃), 1.89 (CH₂CHMe₂, tspt, ³J_HH 7.1 Hz, ³J_HH 6.8 Hz, H₃), 1.24 (3H, t, ³J_HH 7.2 Hz, H₁₂), 0.94 (6H, d, ³J_HH 6.8 Hz, H₉, H₉') ppm; ¹³C NMR (100MHz, CDCl₃) δ 205.7 (C₁₀), 161.1 (COH), 158.4 (COH), 129.5 (C₃), 118.3 (C₂), 112.7 (C₆), 110.3 (C₄), 39.2 (C₇), 31.2 (C₁₁), 28.7 (C₈), 22.4 (C₉ and C₉'), 8.7 (C₁₃), 7.5 (C₁₂) ppm; MS (ESI⁻) (m/z) 235 [M-H]⁻, HRMS (ESI⁺) for C₁₄H₂₀O₃ [M+H]⁺ calcd. 237.1485, found. 237.1490.

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**Supporting Information:** Characterization data for known compounds, copies of ¹H, ¹³C, spectra of all novel compounds, dr determinations, copies of chiral HPLC chromatograms and crystallographic data (CIF files) for compounds _syn-9₁₀₅_, (±)_syn-1₀₉₆_ and _1₇₆_. This material is available free of charge via the Internet at [http://pubs.acs.org](http://pubs.acs.org/).
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