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Total Synthesis of (−)-Luminacin D

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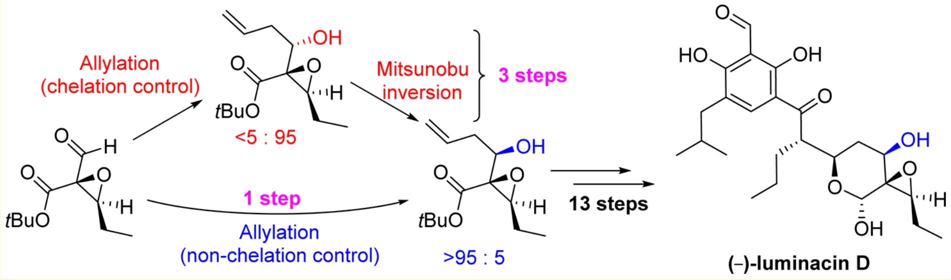
S Supporting Information



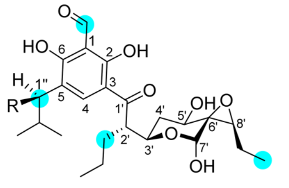
ABSTRACT: A second-generation synthesis of (−)-luminacin D based on an early stage introduction of the trisubstituted epoxide group is reported, allowing access to the natural product in an improved yield and a reduced number of steps (5.4%, 17 steps vs 2.6%, 19 steps). A full account of the optimization 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 toward the identification of angiogenic modulators among the natural products.[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 in vitro, with luminacin D **1a** (Chart 1) being the most active among the 12 members tested.[4] Later on, additional 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.[5,6] Src tyrosine kinases play key roles in the regulation of numerous processes associated with angiogenesis, including growth, differentiation, migration, and survival.[7] In addition, luminacin C2 was also found to inhibit breast cancer cell invasion and metastasis in vitro by disrupting the AMAP1-cortactin binding (protein−protein interactions).[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.[9]

Chart 1. Structure of Luminacins



R = H Luminacin D **1a** ● Structural variations
R = OMe Luminacin C2 **1b**
R = OEt Migracin B **1c** (Migracin A **1d** = C1'' epimer)

Despite its promising antiangiogenic 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,[10] so far there have been four reported syntheses of luminacin derivatives,[11−15] each presenting shortcomings in terms 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.[10] As shown in Scheme 1, our

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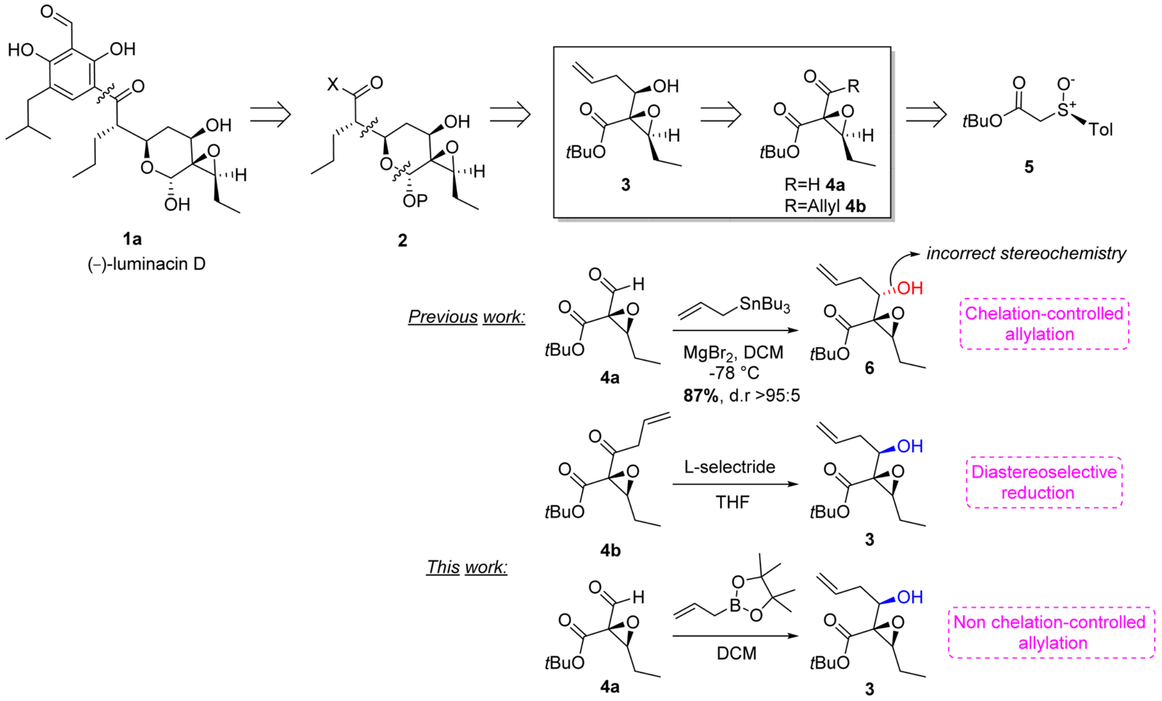
Scheme 1. Retrosynthetic Analysis and New Diastereoselective Methodologies Developed

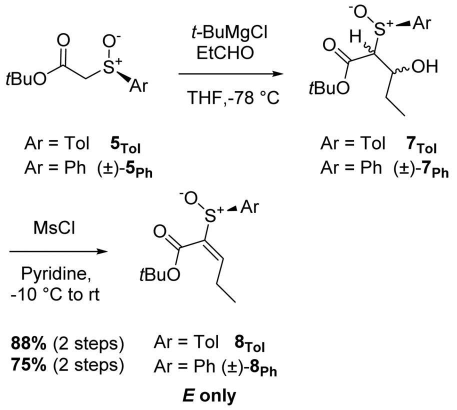


synthetic approach relied on the stereoselective introduction of the epoxide moiety at an early stage of the synthesis starting from the enantiopure sulfoxide **5**, and subsequently to utilize the chirality of the epoxide group in **4** for the diastereoselective completion of the aliphatic fragment. This was achieved via a chelation-controlled allylation procedure of the enantiopure α-epoxy aldehyde **4a**, which proceeded in excellent yield and diastereoselectivity. Unfortunately, the reaction led to the formation of the undesired diastereoisomer **6**, and thus an inversion of the obtained alcohol stereocenter was required to complete the synthesis. As further shown in the retrosynthetic analysis, the formation of Luminacin D **1a** was realized via arylation of the fully functionalized fragment **2**, whose construction was envisaged via spontaneous hemiacetal formation and *syn*-aldol reaction from the key compound **3**. 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 toward the development of a methodology that resulted in direct access to the key intermediate **3** from **4**.

2. RESULTS AND DISCUSSION

Synthesis of the Epoxide Precursor (Ester-sulfoxide 9). Starting from the α-sulfoxy-esters **5**, we initially investigated the one-pot Knoevenagel procedure described by Tanikaga et al.[16] in order to access to the desired (*E*)-alkenes **8**$_{\mathrm{Tol}}$ and ($\pm$)-**8**$_{\mathrm{Ph}}$. This method proved unsuccessful when applied to our substrates (recovery of starting material). Hence, as described in our previous communication,[10] the formation of racemic and enantiopure α,β-unsaturated (*E*)-alkenes ($\pm$)-**8**$_{\mathrm{Ph}}$ and **8**$_{\mathrm{Tol}}$ was then accomplished in 2 steps from the corresponding β-sulfoxy-ester, as shown in Scheme 2. At first, following a known procedure,[17] an aldol-type condensation of **5** with propanal led to the β-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 the Supporting Information).

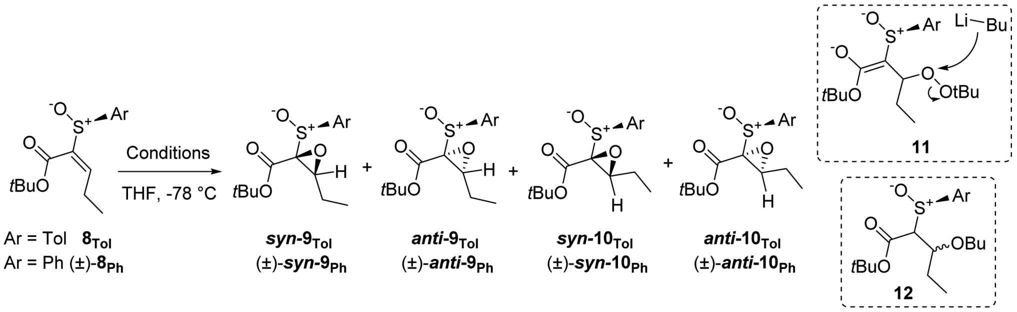
Scheme 2. Synthesis of (*E*)-Alkenes 8



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).[18] The reaction proceeded in excellent yield and diastereoselectivity with the phenyl derivative **8**$_{\mathrm{Ph}}$ (90%, *dr* 94:6), while the same reaction conditions applied with tolyl derivative **8**$_{\mathrm{Tol}}$ led to lower yield and diastereoselectivity (77%, *dr* 88:12). In addition, the product **12** was obtained in 19% yield as a 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**$_{\mathrm{Tol}}$ by using an excess of *t*-BuOOH compared to *n*-BuLi (entry

Table 1. Optimization of the Epoxidation Reaction[i]



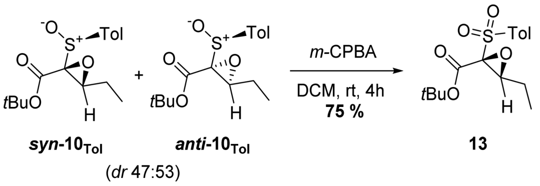
entry	Ar.	base (equiv)	*t*-BuOOH (equiv)	*t* (h)	*dr* ***syn*-9/*anti*-9/*syn*-10/*anti*-10**[a]	overall yield (%)[b]	yield **9** (%)[b]	yield **10** (%)[b]
1[c]	Ph	*n*-BuLi (5)	4[d]	0.4	94:6:[e]:[e]	89	89	[f]
2[c]	Tol	*n*-BuLi (5)	4[d]	0.4	88:12:[e]:[e]	77	77	[f]
3	Tol	*n*-BuLi (4)	4.9–6[g]	1.5	72:4:16:8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

[a] Determined by ^1H NMR. [b] Isolated yield. [c] Reaction carried out on 3–6 g (10–20 mmol) scale. [d] A commercial solution of *t*-BuOOH in decane (5.5 M) was used. [e] Not detected. [f] Traces were observed in ^1H NMR. [g] A commercial solution of *t*-BuOOH in decane (5–6 M) was used. [h] Not isolated. [i] 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 Results and Discussion) refer to the relative arrangement of the epoxide substituents.

3). Although the reaction proceeded without any formation of **12**, the formation of undesired byproducts could be observed by ^1H NMR, alongside with the expected *trans*-epoxides ***syn*-9_{Tol}** and ***anti*-9_{Tol}**. After column chromatography, the epoxides were isolated as a mixture of diastereoisomers in moderate yield (60%, *dr* ***syn*-9_{Tol}/*anti*-9_{Tol}** 95:5). A mixture of two unexpected products was also isolated in 16% yield, which allowed their assignment as the *cis*-epoxide isomers ***syn*-10_{Tol}** and ***anti*-10_{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_{Tol}** (entry 4). The *trans*-epoxide **9_{Tol}** was isolated in both excellent yield and diastereoselectivity in these conditions (82%, *dr* ***syn*-9_{Tol}/*anti*-9_{Tol}** 91:9). Interestingly, the replacement of *n*-BuLi by NaH as base with the racemic derivative (±)-**8_{ph}** resulted in promoting the formation of *cis*-isomers **10_{ph}**, with a good selectivity toward the *syn*-epoxide (±)-***syn*-10_{ph}** (entry 5). The same outcome was observed when an excess of NaH compared to *t*-BuOOH was used with the tolyl derivative **8_{Tol}** (entry 6). The epoxidation reaction was carried out on a 3 g scale (10 mmol) with the tolyl derivative **8_{Tol}** using the optimized conditions, and enabled isolation of the expected *trans*-epoxides **9_{Tol}** in a slightly improved yield and diastereoselectivity compared to our earlier procedure (entry 7, 82%, *dr* ***syn*/*anti*** 92:8 vs 77% *dr* ***syn*/*anti*** 88:12). A minor quantity of the *cis*-epoxides **10_{Tol}** was also obtained after separation (<2% yield).

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_{Tol}** and (±)-***syn*-10_{Ph}** was established by X-ray analysis (see the 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_{Tol}** and ***anti*-10_{Tol}** (*dr* ∼ 1:1), which led to a single sulfone **13** (as observed by ^1H NMR), which allowed unambiguous assignment of ***anti*-10_{Tol}** as the *cis*-*anti*-epoxide (and by inference, also that of ***anti*-10_{Ph}**).

Scheme 3. Sulfone Formation



Synthesis of the Intermediate 3: The Diastereoselective Reduction Approach. As already mentioned, we previously reported the development of a chelation-controlled allylation methodology, which, when applied to aldehydes possessing an *α*-oxygenated center, proceeded with excellent diastereoselectivity.[10] 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 toward 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).

Scheme 4. Proposed Reduction Approach

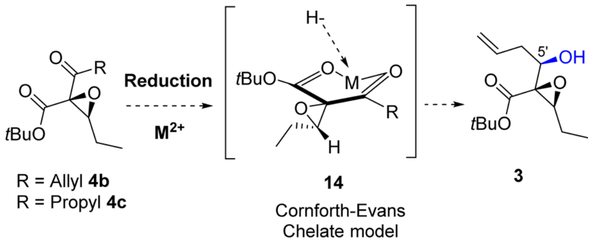


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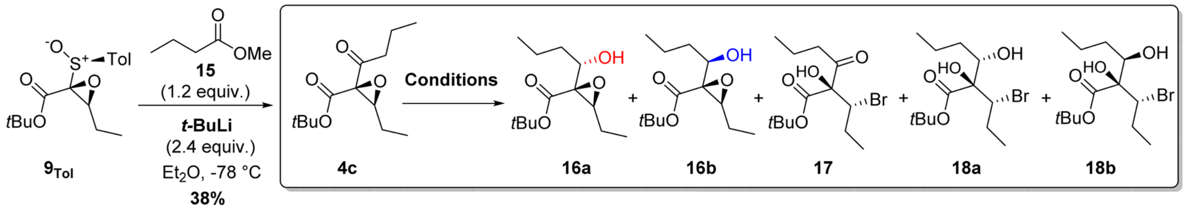
Table 2. Acylation and Attempted Conditions for the Reduction Reaction



entry	conditions	yield **16** (%) (*dr*)	yield **17** (%)	yield **18** (%) (*dr*)
1	$NaBH_4$ (1.05 equiv), $MgBr_2$ (1.6 equiv), DCM/THF 2:1, −78 °C to rt, 3 h	[a]	78[b] (48)[c]	22[b] (9)[c] (*dr* **18a**/**18b** 93:7)[a]
2	$NaBH_4$ (1.2 equiv), $MgBr_2$ (2 equiv), MeOH, 0 °C, 30 min	100[b] (*dr* **16a**/**16b** 71:29)[b]	[a]	[a]
3	$NaBH_4$ (0.6 equiv), $CaCl_2$ (2 equiv), MeOH, 0 °C, 30 min	100[b] (72)[c] (*dr* **16a**/**16b** 97:3)[b]	[a]	[a]
4	Et_3SiH (1.05 equiv), $MgBr_2$ (1.6 equiv), DCM, −78 °C, 2 h	[a]	83[b] (64)[c]	[a]
5	L-selectride (1.05 equiv), $MgBr_2$, (1.6 equiv), DCM, −78 °C, 2 h	[a]	100[b]	[a]
6	L-selectride (1.05 equiv), THF, −78 °C, 30 min	100[b] (90)[c] (*dr* **16a**/**16b** 1:9)[b]	[a]	[a]
7	LS-selectride (1.3 equiv), THF, −78 °C, 45 min	48[b] (*dr* **16a**/**16b** 33:67)[b]	[a]	[a]

[a] Not formed. [b] Determined by ^1H NMR. [c] Isolated yield.

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.[19] 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.[20−26]

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 $\mathbf{9_{Tol}}$ (Table 2). This was achieved in moderate yield, via treatment of $\mathbf{9_{Tol}}$ 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.[19] As a first experiment, treatment of **4c** with $NaBH_4$ and $MgBr_2$, 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 diasteroisomers. 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 $MgBr_2$ by $CaCl_2$ as chelating metal[21,22] 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 Et_3SiH or L-selectride as reducing agents with $MgBr_2$ was also attempted at −78 °C, though both conditions led to the exclusive formation of the bromohydrin **17** (entries 4 and 5). Since the involvement of $MgBr_2$/$CaCl_2$ 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 toward 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.

As shown in Figure 1, the selectivity observed when $NaBH_4$/$CaCl_2$ and $MgBr_2$ were used could be explained by the 1,2-chelated transition state **19**, assuming that the metal salt catalyzes the formation formation of alkoxyborohydrides $NaBH_{4}$-n(OMe)n in MeOH.[26] The coordination between a Ca^{2+} and the methoxy group of the borohydride species would, therefore, direct the hydride attack to the *Re*-face, leading to the *anti*-compound **16a**. On the other hand, the models **20** and **21** are consistent with the selectivity observed when L- or LS-selectride are employed, assuming that the 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 *syn*-compound **16b**.

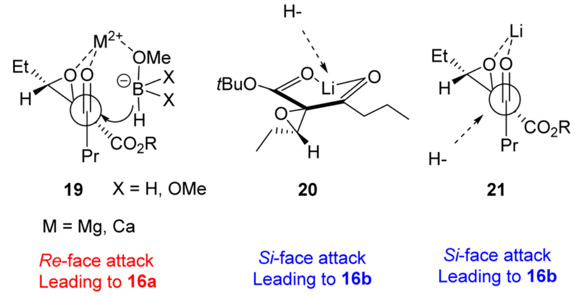


Figure 1. Possible rationalization of the selectivity outcome.

The relative configuration of **16a** and **16b** was assigned by NMR comparison with the *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 **4c**, and the relative configuration of the resulting **18a**, were determined thanks to X-ray crystallographic analysis (see the Supporting Information).

Motivated by these results, the acylation/diastereoselective reduction procedure was then applied toward the luminacin D

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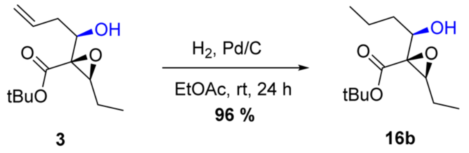
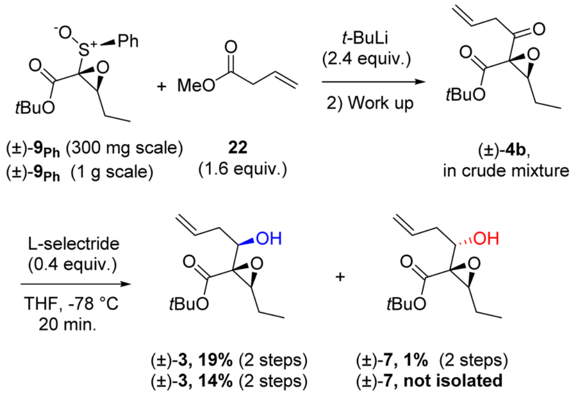
Scheme 5. Hydrogenation of 3 To Allow Assignment of the Relative Stereochemistry



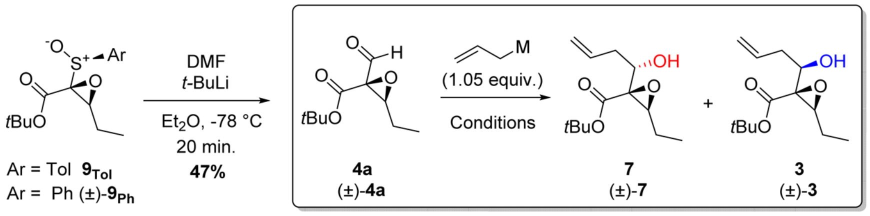
synthesis, using methyl but-3-eneoate **22**[27] and L-selectride (Scheme 6). Since the intermediate **4b** proved unstable to purification on silica gel (with double bond isomerization occurring during silica gel chromatography, not shown), the reduction reaction was attempted on the crude material,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

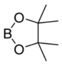
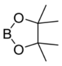
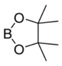
Scheme 6. Formation of 3 and 7 via the Reduction Approach



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 CaCl$_2$ as explained above, this additive was now used in a reinvestigation of the allylation of **4a**. Hence, the aldehyde **4a** (and (±)-**4a**) was resynthesized through formylation of the epoxide precursors **9**, applying similar

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]
1[c]	Tol	SnBu$_3$	MgBr$_2$ (1.6 equiv.), DCM (0.2 M), -78 °C, 2 h	[d]	> 95:5[a]	87	[e]
2	Ph	SnBu$_3$	CaCl$_2$ (1.6 equiv.), DCM (0.2 M), - -78 °C, 2h	4	n.d	4	[e]
3	Ph	SnBu$_3$	CaCl$_2$ (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	[f]	[f]	[f]
5	Ph	 **23**	DCM (0.3 M), -78 °C to rt, 16 h	100	< 5:95 [a]	2	80
6[g]	Tol	 **23**	DCM (0.3 M), -78 °C to rt, 16 h	100	<5:95[d]	1 (2 steps)	33 (2 steps)
7[g]	Ph	 **23**	DCM (0.3 M), -78 °C to rt, 16 h	100	<5:95[d]	[e]	33 (2 steps)

[a] Determined by ^{1}H NMR. [b] Isolated yield. [c] Reaction carried out on 3 mmol of **4a**. [d] Based on isolated yields. [e] Not isolated. [f] Not detected. [g] Reaction carried out on 5 mmol of **8** (2 steps procedure).

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 CeCl$_3$, 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 CaCl$_2$ instead of MgBr$_2$, 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 ^{1}H 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). On the basis of these results, it was envisaged that CaCl$_2$ 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 toward the use of nonchelating conditions for the allylation reaction. A first experiment involving the reaction of **4a** with allyltrimethylsilane and a substoichiometric 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 nonchelation 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 (TiCl$_4$) to nonchelation (BF$_3$·OEt$_2$) mediated allylation.[30] It should be noted that both of these Lewis acids are not compatible with the epoxide-containing substrate **4**. The optimized two-step procedure was then carried out on a 1.5 g (5 mmol) scale of sulfoxide **9$_{\mathbf{Tol}}$** (*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 optimized 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 ^{1}H NMR due to the presence of impurities, the ratio of isolated yields of **7** and **3** is consistent with that observed on a small scale. Similar results were obtained when the racemic phenyl epoxide (±)-**9$_{\mathbf{Ph}}$** was used as starting material (entry 7).

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 nonchelating 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.

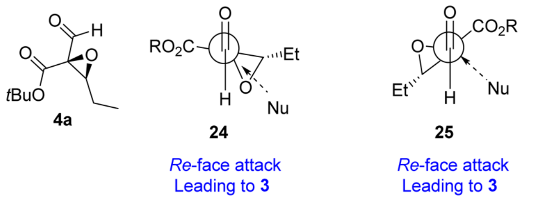


Figure 2. Cornforth−Evans (**24**) and polar Felkin−Anh (**25**) models to explain the observed diastereoselectivity.

Completion of the Aliphatic Fragment: Aldol Reaction and Attempted Lactonization. With access to the pure intermediate **3** (and (±)-**3**), the synthesis was pursued toward the formation of aldehyde **26** (and (±)-**26**), which was accomplished in two steps, following the reported procedure (Scheme 7). 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.[15] 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* ∼ 2:1, in favor of the desired isomer). Interestingly, while this type of remote stereocontrol has been mainly investigated for Mukaiyama aldol reactions,[31] 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, we 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**[32] and (±)-**28**[32] 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

Scheme 7. Synthesis of Aldehyde 26

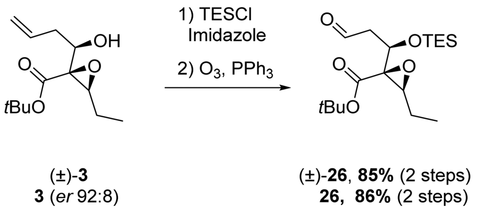
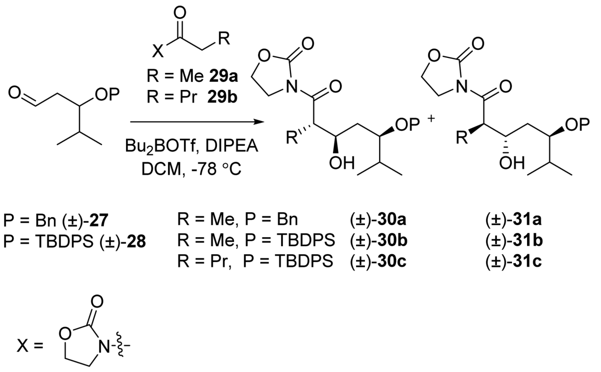


Table 4. Investigation of Remote Stereocontrol for the Aldol Reaction



entry	*dr* **30**/**31**[a]	R	P
1	2:1	Me	Bn
2	3:1	Me	TBDPS
3	5:1	Pr	TBDPS

[a] Determined by ^{1}H NMR.

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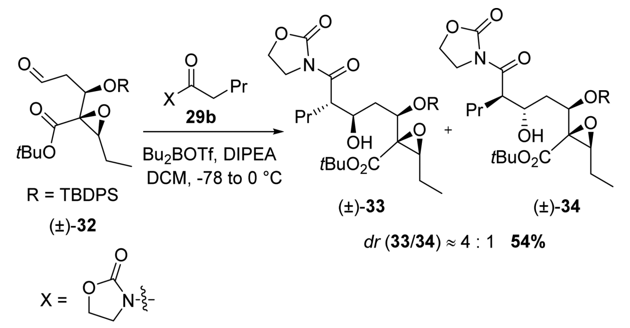
the Evans model, the major isomer contained the desired relative stereochemistry for our purposes (see the Supporting Information for the determination of the product relative stereochemistry). Increasing the size of the protecting group (as in (±)-**28**) led to a slight increase of the desired selectivity (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).

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

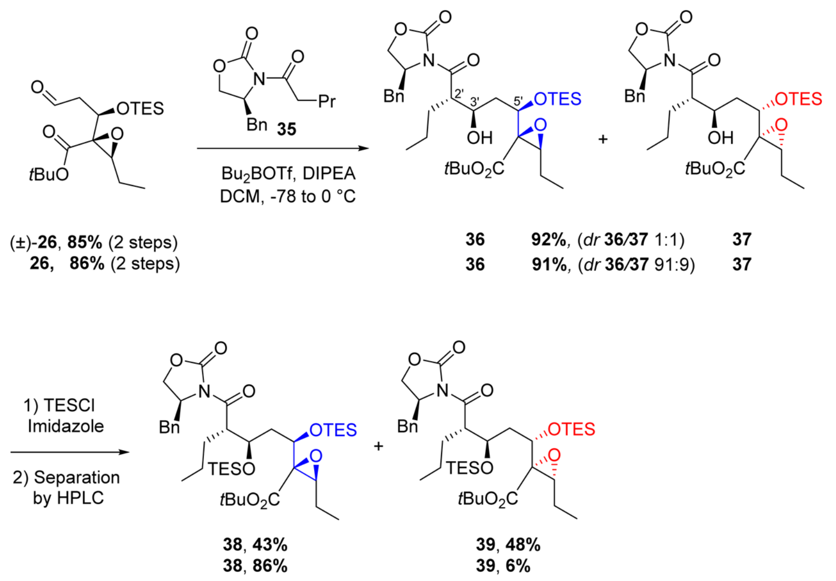


Given that the modest diastereoselectivity favored the desired stereomer, a matched double diastereodifferentiation process using a chiral oxazolidinone based auxiliary was then investigated. This approach has also been used in the luminacin D synthesis by Maier et al.[14] Hence, the enantiopure oxazolidinone **35**[33] was required (Scheme 9). For atom economy reasons, we 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 (^{1}H NMR analysis) in a 1:1 *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**[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 center 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** (*er* 92:8), exclusive formation of the aldol products **36** and **37** in a 91:9 *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.

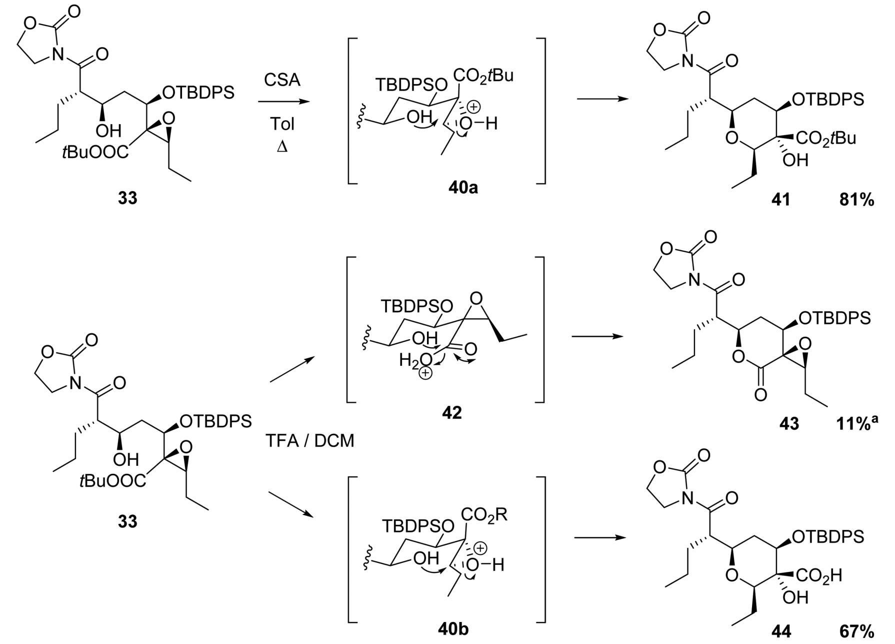
Cyclization of the Aliphatic Fragment: First Approach. It was envisaged that the synthesis of the aliphatic fragment could be completed at this stage by acid-catalyzed *t*-Bu deprotection, which would initiate lactone formation that then could be reduced to the luminacin D lactol ring. The lactone formation was first investigated using the racemic aldol product **33** 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 toward 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 cyclization products was achieved by HMBC and NOE analyses (see the Supporting Information).

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,

Scheme 9. Evans-Aldol Reaction and Subsequent Separation of the Diastereoisomers

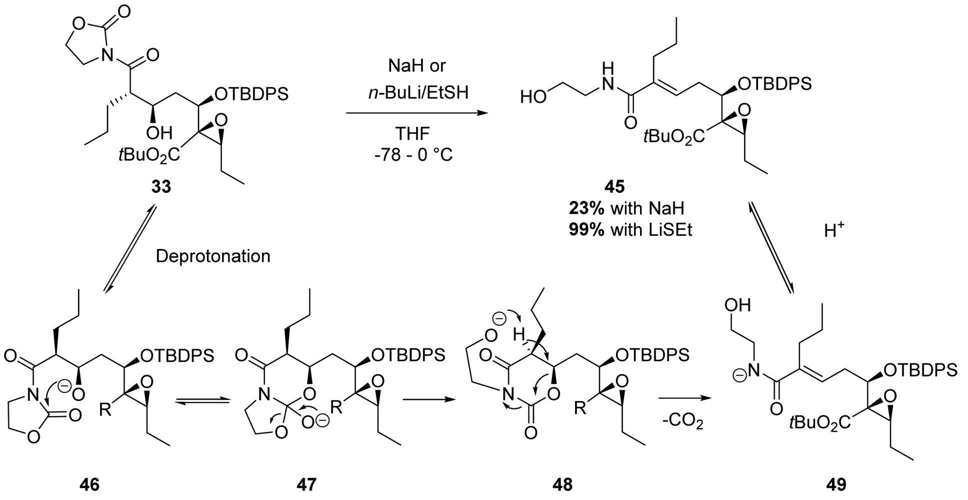


Scheme 10. Deprotection and Unexpected Cyclization of the Aldol Product 33

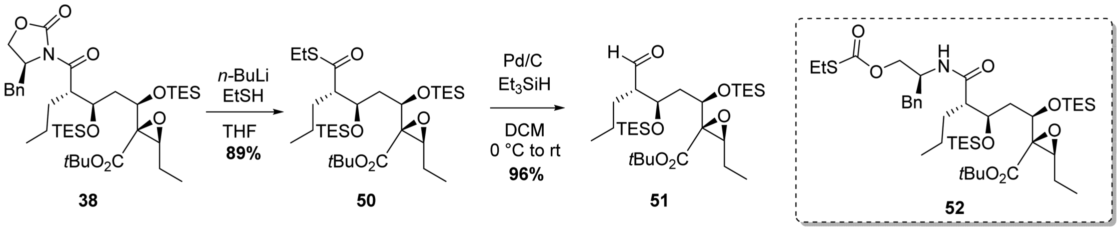


[a]Isolated in a mixture with **44** (see the Experimental Section).

Scheme 11. Base-Catalyzed Elimination of Aldol Product 33

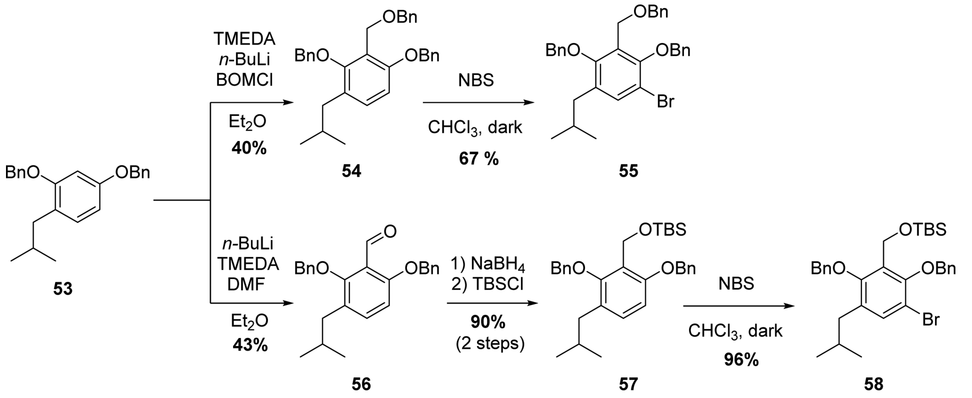


Scheme 12. Completion of the Aliphatic Fragment Synthesis

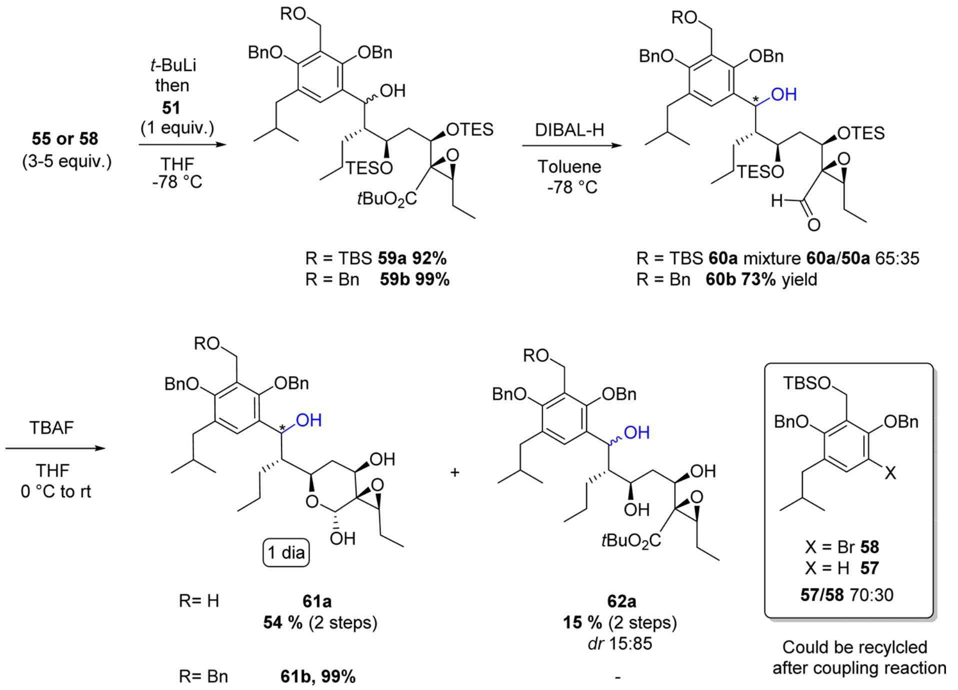


in which both elimination and oxazolidinone ring-opening had occurred. Interestingly, when **33** was subjected to lithium ethylthiolate (see next section), the same elimination product was obtained in quantitative yield. A mechanism of formation for this product **45** is proposed: deprotonation of 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 13. Synthesis of Aromatic Fragments



Scheme 14. Formation of Hemiacetals 61

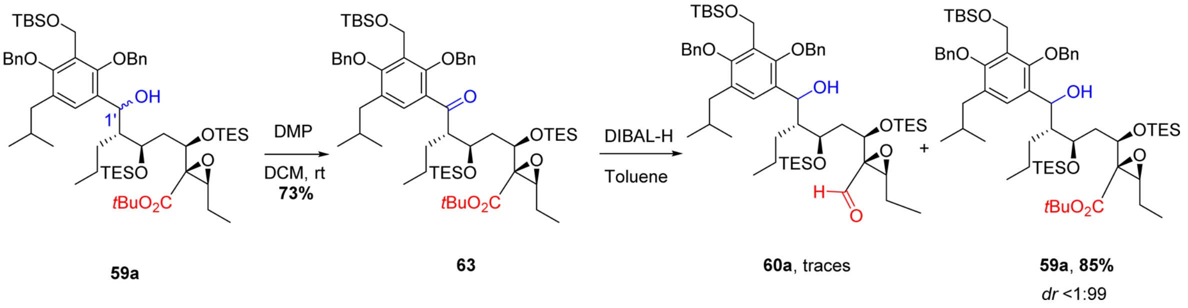


Cyclization of the Aliphatic Fragment: Second Approach. Given the unsuccessful lactone formation, it was envisaged to postpone this step until after the introduction of the aryl fragment (Scheme 12). Hence, oxazolidinone removal was attempted via thioester formation. At high reagent concentration, the 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%).

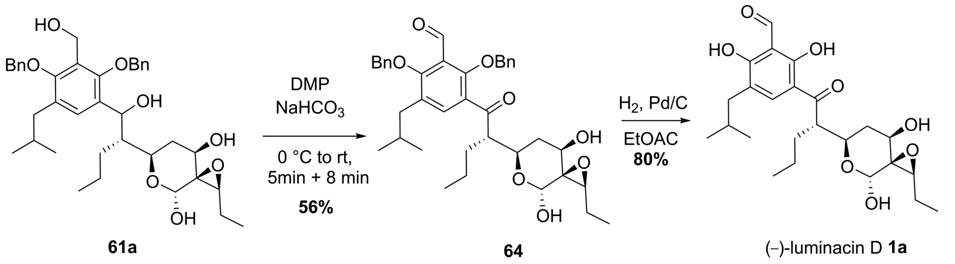
Completion of the Synthesis. With the aliphatic fragment in hand, we pursued our efforts toward the synthesis of the bromoaryl derivatives **55** and **58**, as potential substrates for the coupling reaction. As depicted in Scheme 13, these two compounds could be synthesized from the same intermediate **53**,[10,34,35] 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.[10] 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.

The coupling reaction was then carried out in the presence of *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 *t*-butyl ester to the corresponding aldehydes **60a−b** (Scheme 14). Surprisingly, the minor benzylic alcohol epimer was found to be unreactive toward 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

Scheme 15. Attempted Sequential Oxidation/Reduction Process



Scheme 16. Completion of the Synthesis from the First Protecting Group Strategy



[α]^D -12.6 (c 0.10, $CHCl_3$, 20 °C)
lit. -13.0 (c 0.10, $CHCl_3$, 23° C)[38]

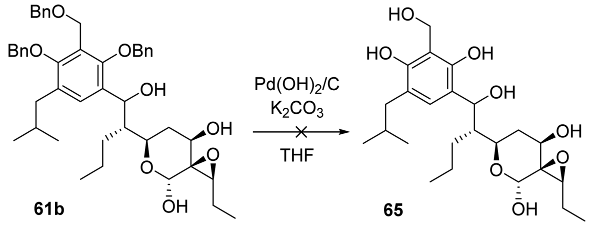
from **59b** by preparative HPLC, and was subsequently converted to the hemiacetal **61b** after treatment with TBAF and spontaneous cyclization. In the case of **60a**, separation from its starting material was not possible, and the TBAF treatment was thus applied to the mixture. This led to the formation 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 toward the formation of **60a** was attempted (Scheme 15). Thus, the benzylic alcohol was oxidized 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 a 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 $NaHCO_3$ 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 resubjecting 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.

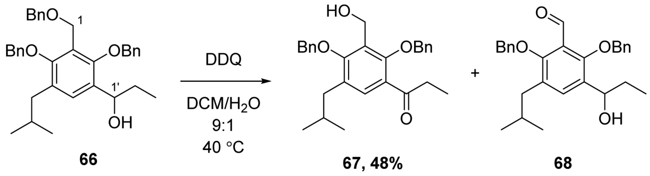
The final sequence was then investigated with the tribenzylated **61b**, as simultaneous deprotection of the benzyl ethers would enable to complete the synthesis with only bis-benzylic oxidation left to do (Scheme 17). However, the hydrogenolysis attempts were associated with numerous selectivity issues, 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

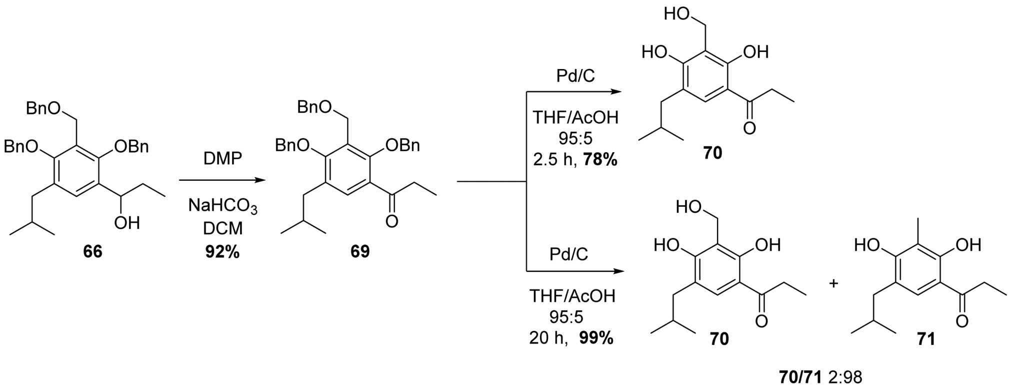


In view of these unexpected results, deprotection conditions were investigated on a simple model substrate **66** (Scheme 18), resulting from the coupling reaction between **55** and propionaldehyde (not shown). It was envisioned that DDQ

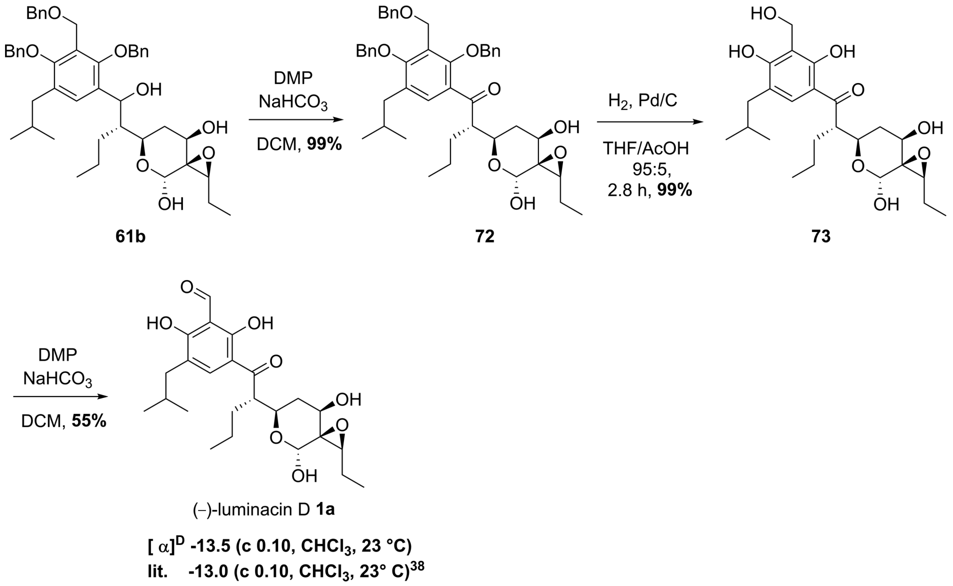
Scheme 18. DDQ Promoted Debenzylation/Oxidation of the Secondary Benzyl Alcohol



Scheme 19. Oxidation/Reduction Sequence



Scheme 20. Completion of the Synthesis from the Second Protecting Group Strategy



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.[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 a small scale. The full debenzylation was now achieved under acidic conditions previously as used by Tatsuda[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.[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.

3. 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 a 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 nonchelation 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 terms 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).

4. EXPERIMENTAL SECTION

General Methods. See the Supporting Information. For atom numbering in the NMR data, see the corresponding figures in the Supporting Information.

Two-Step Procedure to Give Alkenes ***8***$_{\textit{Tol}}$ *(and (±)-****8***$_{\textit{Ph}}$*).* 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 NH_4Cl (200 mL) and H_2O (100 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (3 × 250 mL). Organic phases were combined, dried over $MgSO_4$, and concentrated in vacuo. Purification via column chromatography (petroleum ether/EtOAC 8:2 to 5:5) afforded 24.5 g of the impure addition product **7**$_{\text{Tol}}$ as a 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_2O (3 × 600 mL). Organic phases were combined, dried over $MgSO_4$, and concentrated in vacuo. Purification 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 (±)-**5**$_{\text{Ph}}$ (25.7 g, 107.1 mmol, 1 equiv) to afford (±)-**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 (±)-**8**$_{\text{Ph}}$ matched those previously reported.[10]

Epoxidation of the Enantiopure Alkene ***8***$_{\textit{Tol}}$ *Using t-BuOOH/n-BuLi.* To a solution of *t*-BuOOH (5.5 M in decane, dried over MS 4 Å, 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 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 °C for a further 25 min and was quenched at this temperature with a saturated solution of $Na_2S_2O_3$ (200 mL). The mixture was allowed to warm up to 0 °C and was extracted at this temperature with EtOAc (3 × 200 mL). Organic phases were combined, dried over Na_2SO_4, and concentrated in vacuo, yielding a mixture of crude epoxides **9**$_{\text{Tol}}$ and **10**$_{\text{Tol}}$ (*dr* ***syn*****-9**$_{\text{Tol}}$/***anti*****-9**$_{\text{Tol}}$/***syn*****-10**$_{\text{Tol}}$/***anti*****-10**$_{\text{Tol}}$ 86:7:4:3). Purification via column chromatography (pentane/Et_2O 8:2 to 6:4) afforded *trans*-epoxides **9**$_{\text{Tol}}$ as a white solid (2.52 g, 82%) and the impure *cis*-epoxides **10**$_{\text{Tol}}$ as a colorless oil (68 mg, isolated with minor impurity, <2%). An analytical mixture of **9**$_{\text{Tol}}$ was recrystallized from hot pentane (few drops of Et_2O 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 a small scale for characterization purposes.

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

Data for the Pure ***syn-9***$_{\textit{Tol}}$*.* $[\alpha]_D$ +49.2 (c 1.4, $CHCl_3$, 23 °C); mp: 54−56 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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_2), 61.1 (C_3), 27.8 (C_7), 21.7 (C_4), 21.5 (C_{14}) 10.0 (C_5) ppm.

Data for ***10***$_{\textit{Tol}}$*.* IR (neat) 2971 (w, br.), 1743 (m), 1716 (m), 1251 (m), 1096 (s), 1062 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (2H, d, $^3J_{HH}$ 7.8 Hz, H_9, H_{13}, *anti*), 7.62 (2H, d, $^3J_{HH}$ 8.6 Hz, H_9, H_{13}, *syn*), 7.38−7.28 (4H, m, H_{10}, H_{12}, *syn and anti*), 3.45 (1H, dd, $^3J_{HH}$ 7.3 Hz, $^3J_{HH}$ 5.5 Hz, H_3, *syn*), 3.26 (1H, dd, $^3J_{HH}$ 7.5 Hz, $^3J_{HH}$ 5.1 Hz, H_3, *anti*), 2.42 (3H, s, H_{14}, *syn*), 2.41 (3H, s, H_{14}, *anti*), 2.32−2.00 (4H, m, H_4, *syn and anti*), 1.27 (9H, s, *syn*), 1.244 (9H, s, H_7, *anti*), 1.236 (3H, t, $^3J_{HH}$ 7.3 Hz, H_5, *syn*), 1.17 (3H, t, $^3J_{HH}$ 7.5 Hz, H_5, *anti*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7 (C_5, *anti*), 163.2 (C_5, *syn*), 142.9 (C_8 or C_{11}, *syn or anti*), 141.5 (C_8 or C_{11}, *syn or anti*), 138.3 (C_8 or C_{11}, *syn or anti*), 136.9 (C_8 or C_{11}, *syn or anti*), 129.7 (C_{10} and C_{12}, *syn or anti*), 129.6 (C_{10} and C_{12}, *syn or anti*), 127.3 (C_9 and C_{13}, *anti*), 124.7 (C_9 and C_{13}, *syn*), 84.4 (C_6, *anti*), 84.1 (C_6, *syn*), 74.3 (C_2, *anti*), 73.0 (C_2, *syn*), 65.9 (C_3, *anti*), 65.4 (C_3, *syn*), 27.64 (C_7, *syn*), 27.59 (C_7, *anti*), 21.5 (C_{14}, *anti*), 21.4 (C_{14}, *syn*), 21.3 (C_4, *syn*), 19.5 (C_4, *anti*), 10.9 (C_5, *anti*), 10.6 (C_5, *syn*) ppm; MS (ESI$^+$) (m/z) (peak 1) 311 [M + H]$^+$, 255 [M − *t*Bu + 2H]$^+$; (peak 2) 311 [M + H]$^+$, 255 [M − *t*Bu + 2H]$^+$; HRMS (ESI$^+$) for $C_{16}H_{22}O_4S$ [M + Na]$^+$ calcd. 333.1131, found. 333.1136.

*Epoxidation of the Alkene (±)-****8***$_{\textit{Ph}}$ *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 (±)-**8**$_{\text{Ph}}$ (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 $Na_2S_2O_3$ (10 mL). The mixture was allowed to warm up to 0 °C and was extracted at this temperature with Et_2O (2 × 10 mL). Organic phases were combined, dried over Na_2SO_4, and concentrated in vacuo, yielding the crude epoxides **9**$_{\text{Ph}}$ and **10**$_{\text{Ph}}$ (*dr* ***syn*****-9**$_{\text{Ph}}$/***anti*****-9**$_{\text{Ph}}$/***syn*****-10**$_{\text{Ph}}$/***anti*****-10**$_{\text{Ph}}$ 35:4:54:7). Purification via column chromatography (pentane/Et_2O 9:1 to 5:5) and preparative HPLC (pentane/Et_2O 7:3) afforded the *trans*-epoxides **9**$_{\text{Ph}}$ as a viscous oil (52 mg, 23%), as well as the *cis*-epoxides **10**$_{\text{Ph}}$ as a white solid (117 mg, 53%). An analytical sample of **10**$_{\text{Ph}}$ was recrystallized from hot pentane (few drops of Et_2O added) to give the pure epoxide (±)-***syn*****-10**$_{\text{Ph}}$.

Data for (±)-(***syn+anti***)-**9**$_{\text{Ph}}$ matched those previously reported.[10]

*Data for (±)-(syn+anti)-****10***$_{\textit{Ph}}$*.* IR (neat) 3080 (w), 2983 (w, br.), 1737 (m), 1373 (m), 1158 (s), 1088 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 7.92−7.80 (2H, m, H_{Ar}, *anti*), 7.79−7.67 (2H, m, H_{Ar}, *syn*), 7.60−7.44 (6H, m, H_{Ar}, *syn and anti*), 3.47 (1H, dd, $^3J_{HH}$ 7.3 Hz, $^3J_{HH}$ 5.4 Hz, H_3, *syn*), 3.29 (1H, dd, $^3J_{HH}$ 7.6 Hz, $^3J_{HH}$ 5.2 Hz, H_3, *anti*), 2.33−2.07 (4H, m, H_4, *syn and anti*), 1.247 (3H, t, $^3J_{HH}$ 7.3 Hz, H_5, *syn*), 1.240 (9H, s, H_7, *syn*), 1.235 (9H, s, H_7, *anti*), 1.19 (3H, t, $^3J_{HH}$ 7.5 Hz, H_5, *anti*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7 (C_1, *anti*), 163.2 (C_1, *syn*), 141.5 (C_{qAr}, *anti*), 140.3 (C_{qAr}, *syn*), 132.3 (CH_{Ar}, *anti*), 131.1 (CH_{Ar}, *syn*), 129.1 (2C, CH_{Ar}, *anti*), 128.9 (2C, CH_{Ar}, *syn*), 127.3 (2C, CH_{Ar}, *anti*), 124.7 (2C, CH_{Ar}, *syn*), 84.5 (C_6, *anti*), 84.2 (C_6, *syn*), 74.4 (C_2, *anti*), 73.0 (C_2, *syn*), 65.9 (C_3, *anti*), 65.3 (C_3, *syn*), 27.6 (C_7, *syn and anti*), 21.3 (C_4, *anti*), 19.5 (C_4, *syn*), 11.0 (C_5, *anti*), 10.6 (C_5, *syn*) ppm. MS (ESI$^+$) (*m*/*z*) (peak 1) 241 [M − *t*Bu + 2H]$^+$; (peak 2) 241 [M − *t*Bu + 2H]$^+$;HRMS (ESI$^+$) for $C_{15}H_{20}O_4S$ [M + Na]$^+$ calcd. 319.0975, found. 319.0979.

*Data for (±)-**syn-10**$_{Ph}$.* mp 105−108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79−7.67 (2H, m, H_{Ar}), 7.60−7.44 (3H, m, H_{Ar}), 3.47 (1H, dd, $^3J_{HH}$ 7.2 Hz, $^3J_{HH}$ 5.4 Hz, H_3), 2.25−2.07 (2H, m, H_4), 1.247 (3H, t, $^3J_{HH}$ 7.3 Hz, H_5), 1.242 (9H, s, H_7); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2 (C_1), 140.4 (C_{qAr}), 131.1 (CH_{Ar}), 128.9 (2C, CH_{Ar}), 124.7 (2C, CH_{Ar}), 84.2 (C_6), 73.0 (C_2), 65.4 (C_3), 27.6 (C_7), 21.4 (C_4), 10.6 (C_5) ppm.

*Oxidation of Sulfoxide Derivatives **10**$_{Tol}$ To Give **13**.* To a solution of sulfoxides **10**$_{Ph}$ (*dr* ***syn*-10**$_{Ph}$/***anti*-10**$_{Ph}$ ~ 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 a saturated solution of $Na_2S_2O_3$ (5 mL). The layers were separated, and the aqueous phases were extracted with Et_2O (3 × 5 mL). Organic phases were combined, dried over Na_2SO_4, and concentrated in vacuo. Purification via column chromatography (pentane/Et_2O 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}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (2H, d, $^3J_{HH}$ 8.3 Hz, H_9 and H_{13}), 7.37 (2H, d, $^3J_{HH}$ 8.0 Hz, H_{10} and H_{12}), 3.28 (1H, dd, $^3J_{HH}$ 7.5 Hz, $^3J_{HH}$ 5.2 Hz, H_3), 2.46 (3H, s, H_{14}), 2.33−2.11 (2H, m, H_4), 1.28 (9H, s, H_7), 1.19 (3H, t, $^3J_{HH}$ 7.5 Hz, H_5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7 (C_1), 145.4 (C_8 or C_{11}), 135.9 (C_8 or C_{11}), 129.6 (C_{10} and C_{12}), 128.9 (C_9 and C_{13}), 84.9 (C_6), 74.3 (C_2), 66.3 (C_3), 27.5 (C_7), 21.7 (C_{14}), 20.4 (C_4), 10.9 (C_5) ppm; MS (ESI$^+$) (*m*/*z*) 344 [M + NH_4]$^+$, 349 [M + Na]$^+$; HRMS (ESI$^+$) for $C_{16}H_{22}O_5S$ [M + Na]$^+$ calcd. 349.1080, found. 349.1079.

*Acylation Reaction: Synthesis of Model Substrate **4c**.* To compound **9**$_{Tol}$ (*dr* 92:8, 217 mg, 0.70 mmol, 1 equiv), dissolved in Et_2O (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 NH_4Cl (2 mL). The mixture was then extracted with Et_2O (3 × 5 mL). Organic phases were combined, dried over Na_2SO_4, and concentrated under reduced pressure (30 °C, <500 mbar) to minimize losses through compound evaporation. Purification via column chromatography (pentane/Et_2O 95:5 to 9:1) afforded the compound **4c** as a colorless oil (67 mg, 91% purity with 9% Et_2O, 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}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.24 (1H, t, $^3J_{HH}$ 6.1 Hz, H_3), 2.58 (1H, dt, $^2J_{HH}$ 17.9 Hz, $^3J_{HH}$ 7.1 Hz, H_9), 2.40 (1 H, dt, $^2J_{HH}$ 17.4 Hz, $^3J_{HH}$ 6.8 Hz, $H_{9'}$), 1.71−1.56 (4H, m, H_4, H_{10}), 1.53 (9H, s, H_7), 1.10 (3 H, t, $^3J_{HH}$ 7.5 Hz, H_5 or H_{11}), 0.92 (3 H, t, $^3J_{HH}$ 7.5 Hz, H_{11} or H_5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.0 (C_8), 164.6 (C_1), 83.5 (C_6), 65.9 (C_2), 63.1 (C_3), 39.5 (C_9), 28.0 (C_6), 22.7 (C_4 or C_{10}), 16.7 (C_{10} or C_4), 13.6 (C_5 or C_{11}), 10.1 (C_{11} or C_5) ppm; MS (ESI$^+$) (*m*/*z*) 265 [M + Na]$^+$, 260 [M + NH_4]$^+$, 187 [M − *t*Bu + 2H]$^+$; HRMS (ESI$^+$) for $C_{13}H_{22}O_4$ [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 (1 M 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 NH_4Cl (2 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (3 × 5 mL). Organic phases were combined, dried over Na_2SO_4, 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}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.56 (1H, td, $^3J_{HH}$ 8.1 Hz, $^3J_{HH}$ 3.9 Hz, H_8), 3.07 (1H, t, $^3J_{HH}$ 6.5 Hz, H_3), 2.46 (1H, d, $^3J_{HH}$ 7.8 Hz, O$\underline{H}$-8), 1.83−1.31 (6H, m, H_4, H_9, H_{10}), 1.53 (9H, s, H_7), 1.07 (3 H, t, $^3J_{HH}$ 7.3 Hz, H_5 or H_{11}), 0.95 (3 H, t, $^3J_{HH}$ 7.1 Hz, H_{11} or H_5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2 (C_1), 83.3 (C_6), 72.5 (C_8), 64.6 (C_2), 62.4 (C_3), 35.7 (C_4 or C_9 or C_{10}), 28.1 (C_7), 21.6 (C_4 or C_9 or C_{10}), 18.7 (C_4 or C_9 or C_{10}), 14.0 (C_5 or C_{11}), 10.2 (C_{11} or C_5) 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. 267.1573.

*Data for the syn-Product **16b**.* IR (neat) 3455 (w, br.), 2968 (m, br.), 1746 (s), 1372 (s), 1244 (s), 1134 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.16−3.90 (1H, m, H_8), 3.19 (1H, t, $^3J_{HH}$ 6.4 Hz, H_3), 1.69−1.52 (6H, m, H_4, H_9, H_{10}), 1.50 (9H, s, H_7), 1.05 (3 H, t, $^3J_{HH}$ 7.5 Hz, H_5 or H_{11}), 0.95 (3 H, t, $^3J_{HH}$ 7.0 Hz, H_{11} or H_5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5 (C_1), 82.6 (C_6), 69.6 (C_8), 66.0 (C_2), 60.5 (C_3), 35.8 (C_4 or C_9 or C_{10}), 28.0 (C_7), 21.4 (C_4 or C_9 or C_{10}), 18.6 (C_4 or C_9 or C_{10}), 13.9 (C_5 or C_{11}), 10.2 (C_{11} or C_5) 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_4Cl (3 mL). The mixture was extracted with Et_2O (3 × 20 mL). Organic phases were combined, dried over Na_2SO_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_3SiH/$MgBr_2$.* To a suspension of magnesium granules (20 mg, 0.85 mmol, 1.6 equiv) in Et_2O (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_2O 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 a $MgBr_2$ suspension via syringe. In another flask, Et_3SiH (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_3SiH 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_2O (10 mL). The layers were separated, and the aqueous phase was extracted with DCM (3 × 10 mL). Organic phases were combined, dried over Na_2SO_4, and concentrated in vacuo. Purification via column chromatography (pentane/Et_2O 97:3) afforded the bromohydrin **17** as a 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}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.68 (1H, dd, $^3J_{HH}$ 10.8 Hz, $^3J_{HH}$ 2.2 Hz, H_3), 4.19 (1H, s, O$\underline{H}$-2, disappeared upon D_2O exchange), 2.72 (1H, dt, $^2J_{HH}$ 18.2 Hz, $^3J_{HH}$ 6.9 Hz, H_9), 2.45 (1H, dt, $^2J_{HH}$ 18.2 Hz, $^3J_{HH}$ 7.3 Hz, $H_{9'}$), 1.85−1.70 (1H, m, H_4), 1.69−1.53 (3H, m, $H_{4'}$, H_{10}), 1.57 (9H, s, H_7), 1.07 (3 H, t, $^3J_{HH}$ 7.2 Hz, H_5), 0.89 (3 H, t, $^3J_{HH}$ 7.3 Hz, H_{11}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.3 (C_8), 167.9 (C_1), 87.3 (C_2 or C_6), 85.2 (C_6 or C_2), 61.3 (C_3), 40.3 (C_6), 27.7 (C_7), 26.7 (C_4), 16.7 (C_{10}), 13.5 (C_{11}), 12.8 (C_5) ppm; MS (ESI$^+$) (*m*/*z*) 347 [M(^{81}Br) + Na]$^+$, 345 [M(^{79}Br) + Na]$^+$; HRMS (ESI$^+$) for $C_{13}H_{23}{}^{79}BrO_4$ [M + Na]$^+$ calcd. 345.0672, found. 345.0669.

*Synthesis of Bromohydrins **17** and **18** Using $NaBH_4$/$MgBr_2$.* To a suspension of magnesium granules (23 mg, 0.94 mmol, 1.6 equiv) in Et_2O (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. Et_2O 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 a $MgBr_2$ suspension via syringe. In another flask, $NaBH_4$ (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 $NaBH_4$ 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 $NaHCO_3$ (2 mL), and diluting with H_2O (10 mL). The layers were separated, and the aqueous phase was extracted with DCM (3 × 10 mL). Organic phases were combined, dried over Na_2SO_4, and concentrated in vacuo, yielding the crude bromohydrin **17** and the reduced bromohydrin **18** as a mixture of diastereoisomers (*dr* **18a**/**18b** 93:7). Purification via column chromatography (pentane/Et_2O 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 from hot pentane (few drops of Et_2O added) for characterization purposes.

*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, $CDCl_3$) δ 4.47 (1H, dd, $^3J_{HH}$ 11.3 Hz, $^3J_{HH}$ 2.5 Hz, H_3), 3.74 (1H, ddd, $^3J_{HH}$ 12.0 Hz, $^3J_{HH}$ 10.5 Hz, $^3J_{HH}$ 2.0 Hz, H_8), 3.53 (1H, s, $O\underline{H}$-2), 2.09 (1H, dqd, $^2J_{HH}$ 14.5 Hz, $^3J_{HH}$ 7.2 Hz, $^3J_{HH}$ 2.3 Hz, H_4), 1.94 (1H, d, $^3J_{HH}$ 12.0 Hz, $O\underline{H}$-8), 1.85−1.70 (2H, m, $H_{4'}$, H_9), 1.69−1.59 (1H, m, H_{10}), 1.56 (9H, s, H_7), 1.48−1.33 (1H, m, $H_{10'}$), 1.16−1.01 (1H, m, $H_{9'}$), 1.11 (3H, t, $^3J_{HH}$ 7.2 Hz, H_5), 0.94 (3H, t, $^3J_{HH}$ 7.3 Hz, H_{11}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0 (C_1), 84.8 (C_2 or C_6), 81.2 (C_6 or C_2), 73.6 (C_8), 63.3 (C_3), 34.8 (C_9), 28.0 (C_7), 24.9 (C_4), 19.5 (C_{10}), 13.9 (C_{11}), 12.8 (C_5) ppm; MS (ESI$^+$) (*m*/*z*) 349 $[M(^{81}Br) + Na]^+$, 347 $[M(^{79}Br) + Na]^+$; HRMS (ESI$^+$) for $C_{13}H_{25}{}^{79}BrO_4$ $[M + Na]^+$ 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 (±)-$\mathbf{9_{Ph}}$ (265 mg, 0.89 mmol, 1 equiv) in Et_2O (6.0 mL) at rt was added methyl but-3-enoate **22** (dried over molecular sieves 4 Å, 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 NH_4Cl (5 mL). The mixture was then extracted with Et_2O (3 × 10 mL). Organic phases were combined, dried over Na_2SO_4, 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 (1 M solution in THF, 0.36 mmol, 360 *μ*L, 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 NH_4Cl (3 mL). The mixture was extracted with Et_2O (3 × 10 mL), dried over Na_2SO_4, 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 the Supporting Information). Purification via column chromatography (pentane/Et_2O 9:1 to 6:4) afforded the *anti*-*α*-epoxy alcohol (±)-**7** as a colorless oil (2 mg, isolated with unknown impurities, ∼1% over 2 steps) and the *syn*-*α*-epoxy alcohol (±)-**3** as a colorless 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 *μ*mol, 10 mol %) was added, and the resulting mixture was flushed with H_2. Stirring under an atmosphere of H_2 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 colorless oil (58 mg, 96%). *Data for* (±)-**16b**: see acylation procedure.

*Formylation of (±)-$\mathbf{9_{Ph}}$ To Give the α-Epoxy Aldehyde (±)-**4a** (Small Scale, Optimized Conditions).* To compound (±)-$\mathbf{9_{Ph}}$ (410 mg, 1.38 mmol, 1 equiv), dissolved in Et_2O (9 mL), was added DMF (dried over molecular sieves 4 Å, 160 *μ*L, 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 a further 20 min at −78 °C and was quenched with a saturated solution of NH_4Cl (5 mL). The mixture was then extracted with Et_2O (3 × 10 mL). Organic phases were combined, dried over Na_2SO_4, and concentrated under reduced pressure (30 °C, <500 mbar). Purification via column chromatography (pentane/Et_2O 8:2 to 7:3) afforded the *α*-epoxy aldehyde (±)-**4a** as a colorless oil (133 mg, 94% purity with 6% Et_2O, 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 *μ*L, 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 H_2O (5 mL), and stirring was continued for 5 min. The layers were separated, and the aqueous phase was extracted with Et_2O (3 × 10 mL). Organic phases were combined, dried over Na_2SO_4, and concentrated in vacuo to give the crude *α*-epoxy alcohol as a mixture of diatereoisomers (*dr* **3**/**7** > 95:5). Purification via column chromatography (pentane/Et_2O 8:2 to 7:3) afforded the *anti*-*α*-epoxy alcohol (±)-**7** as a colorless oil (3 mg, 2%) and the *syn*-*α*-epoxy alcohol (±)-**3** as a colorless oil (125 mg, 80%). Data for the *syn*-product (±)-**3** and the *anti*-product (±)-**7** correspond to those previously reported.[10]

*Two-Step Procedure (Formylation/Allylation) To Give the α-Epoxy Alcohols **3** and **7** (Large Scale).* To compound $\mathbf{9_{Tol}}$ (*dr* 92:8, 1.58 g, 5.1 mmol, 1 equiv), dissolved in Et_2O (33 mL), was added DMF (dried over molecular sieves 4 Å, 588 *μ*L, 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 NH_4Cl (25 mL). The mixture was then extracted with Et_2O (3 × 30 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated under reduced pressure (30 °C, <500 mbar). Purification via column chromatography (pentane/Et_2O 8:2 to 7:3) afforded the impure *α*-epoxy aldehyde **4a** as a colorless oil (483 mg, isolated with ca. 30% of Et_2O, *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 *μ*L, 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 H_2O (8 mL), and stirring was continued for 5 min. The layers were separated, and the aqueous phase was extracted with Et_2O (3 × 20 mL). Organic phases were combined, dried over Na_2SO_4, and concentrated in vacuo to give the crude *α*-epoxy alcohols **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 the Supporting Information). Purification via column chromatography (pentane/Et_2O 8:2 to 7:3) afforded the *anti*-*α*-epoxy alcohol **7** as a colorless oil (11 mg, 1% over 2 steps), and the *syn*-*α*-epoxy alcohol **3** as a colorless oil (400 mg, 33% over 2 steps). The same procedure was carried out with the phenyl derivative (±)-$\mathbf{9_{Tol}}$ (1.67 g, 5.63 mmol, 1 equiv), giving *syn*-*α*-epoxy alcohol (±)-**3** as a colorless 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 *μ*L, 3.84 mmol, 2 equiv) dropwise. The reaction was then stirred at rt for 16 h, before quenching with a saturated solution of NH_4Cl (20 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (3 × 20 mL). Organic phases were combined, dried over Na_2SO_4, and concentrated under reduced pressure. Purification via column chromatography (pentane/Et_2O 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 1 h at −78 °C, before allowing to warm up to rt over 1 h. The resulting mixture was then concentrated under vacuum. Purification via column chromatography (crude loaded in DCM; pentane/Et_2O 85:15 to 80:20) afforded TES protected aldehyde **3** as a colorless 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 colorless oil (930 mg, 85% over 2 steps). Data for compound **26** correspond to those previously reported.[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_2BOTf (1 M 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 a further 1.5 h. The reaction mixture was quenched at 0 °C with a mixture of H_2O_2/phosphate buffer pH 7 (1:1, 30 mL) and was extracted with DCM (3 × 20 mL). Organic layers were combined, dried over Na_2SO_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_2O 8:2 to 5:5) afforded the mixture of aldol adducts as a colorless viscous oil (1.3 g, 80% purity with 20% Et_2O, 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_2O, 203 mg calculated, 13%, trace amount of **36** was detected by ^1H 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 colorless viscous oil (943 mg, 88% purity with 12% Et_2O, 927 mg calculated, 91%, *dr* 36/37 92:8). Data for the mixture of **36** and **37** correspond to those previously reported.[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 NH_4Cl (20 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (3 × 20 mL). Organic phases were combined, dried over Na_2SO_4, 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 colorless 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 colorless 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 colorless viscous oils. Data for **38** correspond to those previously reported.[10] Data for **39**: $[\alpha]_D$ +25.7 (c 0.88, $CHCl_3$, 23 °C); IR (neat) 2966 (w, br.), 1772 (m), 1749 (s), 1697 (s), 1455 (s), 1387 (s), 1205 (m), 1092 (m, br.) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39−7.19 (5H, m, H_{Ar}), 4.73−4.61 (1H, m, H_{14}), 4.21−4.12 (3H, m, H_2, H_{15}, $H_{15'}$), 4.05−3.99 (1H, m, H_3), 3.76 (1H, dd, $^3J_{HH}$ 8.6 Hz, $^3J_{HH}$ 4.1 Hz, H_5), 3.37 (1H, dd, $^2J_{HH}$ 13.2 Hz, $^3J_{HH}$ 2.9 Hz, $C\underline{H}HPh$), 2.96 (1H, t, $^3J_{HH}$ 6.4 Hz, H_7), 2.73 (1H, dd, $^2J_{HH}$ 13.2 Hz, $^3J_{HH}$ 10.1 Hz, $CH\underline{H}Ph$), 2.19 (1H, ddd, $^2J_{HH}$ 14.8 Hz, $^3J_{HH}$ 7.4 Hz, $^3J_{HH}$ 4.1 Hz, H_4), 1.99 (1H, ddd, $^2J_{HH}$ 14.7 Hz, $^3J_{HH}$ 8.7 Hz, $^3J_{HH}$ 4.0 Hz, $H_{4'}$), 1.89−1.77 (1 H, m, H_{11}), 1.71−1.57 (2H, m, H_8, $H_{11'}$), 1.50 (9H, s, $C(C\underline{H}_3)_3$), 1.53−1.42 (1H, m, $H_{8'}$), 1.41−1.33 (2H, m, H_{12}, $H_{12'}$), 1.06 (3H, t, $^3J_{HH}$ 7.5 Hz, H_9), 1.02−0.91 (21H, m, H_{13}, $C\underline{H}_{3TES}$, $C\underline{H}_3{'}_{TES}$), 0.73−0.58 (12H, m, $C\underline{H}_{2TES}$, $C\underline{H}_2{'}_{TES}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8 (C_1), 166.9 (C_{10}), 153.1 (C_{16}), 135.6 (C_{qAr}), 129.4 (2C, CH_{Ar}), 128.9 (2C, CH_{Ar}), 127.3 (CH_{Ar}), 82.2 ($\underline{C}Me_3$), 72.3 (C_5), 70.6 (C_3), 67.0 (C_6), 65.8 (C_{15}), 61.1 (C_7), 56.1 (C_{14}), 48.3 (C_2), 41.8 (C_4), 37.9 ($\underline{C}H_2Ph$), 30.8 (C_{11}), 28.1 ($C(\underline{C}H_3)_3$), 21.9 (C_8), 20.8 (C_{12}), 14.3 (C_{13}), 10.2 (C_9), 6.95 ($\underline{C}H_{3\ TES}$), 6.92 ($\underline{C}H_3{'}_{TES}$), 5.0 ($\underline{C}H_{2TES}$), 4.9 ($\underline{C}H_2{'}_{TES}$) ppm; MS ($ESI^+$) (*m*/*z*) 756.5 $[M + Na]^+$; HRMS (ESI^+) for $C_{39}H_{67}NO_8Si_2$ $[M + Na]^+$ calcd. 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 °C for 16 h before the solvent was evaporated under reduced pressure. Purification by column chromatography (petroleum ether/EtOAc 80/20) afforded **41** as a colorless oil (56 mg, 81%, contaminated with traces of the tetrahydropyran derivative resulting from the cyclization of **34**).

*Data for **41**.* ^1H NMR (400 MHz, $CDCl_3$) δ 7.90−7.62 (4H,m, $H_{Ar\text{-}TBDPS}$), 7.54−7.31 (6H, m, $H_{Ar\text{-}TBDSP}$), 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, $O\underline{H}$), 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_3), 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, $C(C\underline{H}_3)_{3ester}$), 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, $C(C\underline{H}_3)_{3TBDPS}$), 0.93 (3H, t, $^3J_{HH}$ 7.6 Hz, H_9), 0.86 (3H, t, $^3J_{HH}$ 7.3 Hz, H_{12}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4 ($\underline{C}OO$*t*Bu), 172.0 (C_1), 152.9 (C_{15}), 136.0 (2C, $CH_{Ar\text{-}TBDPS}$), 135.8 (2C, $CH_{Ar\text{-}TBDPS}$), 134.7 ($C_{qAr\text{-}TBDPS}$), 132.7 ($C_{qAr\text{-}TBDPS}$), 129.8 ($CH_{Ar\text{-}TBDPS}$), 129.4 ($CH_{Ar\text{-}TBDPS}$), 127.6 (2C, $CH_{Ar\text{-}TBDPS}$), 127.3 (2C, $CH_{Ar\text{-}TBDPS}$), 83.3 ($(CH_3)_3\underline{C}_{ester}$), 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 ($C(\underline{C}H_3)_{3ester}$), 26.8 ($C(\underline{C}H_3)_{3TBDPS}$), 22.2 ($C_8$), 20.3 ($C_{11}$), 19.3 ($(CH_3)_3\underline{C}_{TBDPS}$), 14.1 ($C_{12}$), 11.1 ($C_9$) ppm; MS ($ESI^+$) (*m*/*z*) 620.4 [M − *t*Bu + 2H]$^+$, 676.5 $[M + Na]^+$; HRMS (ESI^+) for $C_{36}H_{51}NO_8Si$ $[M + Na]^+$ 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 °C. 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 colorless oil, alongside with a mixture of **43** and **44** (3.8 mg, 11%, ratio **43**/**44** ∼ 5:1, contaminated with traces of the tetrahydropyrane derivative resulting from the cyclization of the minor **34**) as colorless oils.

*Data for **44**.* IR (neat) 3480, 2960, 2859, 1779, 1699, 1108 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76−7.64 (4H, m, $H_{Ar\text{-}TBDPS}$), 7.49−7.34 (6H, m, $H_{Ar\text{-}TBDPS}$), 4.41−4.26 (2H, m, H_{14}, $H_{14'}$), 4.16 (1H, td, $^3J_{HH}$ 8.0 Hz, $^3J_{HH}$ 5.3 Hz, H_2), 3.98−3.91 (2H, m, H_5, H_{13}), 3.87−3.79 (1H, m, $H_{13'}$), 3.46 (1H, ddd, $^3J_{HH}$ 11.9 Hz, 7.3 Hz, $^3J_{HH}$ 2.0 Hz, H_3), 3.14 (1H, dd, $^3J_{HH}$ 10.6 Hz, $^3J_{HH}$ 2.0 Hz, H_7), 2.37 (1H, s, $O\underline{H}$), 2.06 (1H, dt, $^2J_{HH}$ 13.6 Hz, $^3J_{HH}$ 11.6 Hz, H_4), 1.91−1.74 (1H, m, H_8), 1.70−1.56 (1H, m, H_{10}), 1.54−1.39 (1H, m, $H_{10'}$), 1.50 (1H, ddd, $^2J_{HH}$ 13.6 Hz, $^3J_{HH}$ 5.8 Hz, $^3J_{HH}$ 2.0 Hz, $H_{4'}$), 1.35−1.22 (2H, m, $H_{8'}$), 1.22−1.11 (2H, m, H_{11}), 1.04 (9H, s, $C(C\underline{H}_3)_{3ester}$), 0.95 (3H, t, $^3J_{HH}$

7.3 Hz, H$_9$), 0.85 (3H, t, $^3J_{HH}$ 7.3 Hz, H$_{12}$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 173.9 ($\underline{C}$OOH), 173.8 (C$_1$), 153.0 (C$_{15}$), 136.0 (2C, CH$_{\text{Ar-TBDPS}}$), 135.9 (2C, CH$_{\text{Ar-TBDPS}}$), 134.2 (C$_{\text{qAr-TBDPS}}$), 132.7 (C$_{\text{qAr-TBDPS}}$), 129.9 (CH$_{\text{Ar-TBDPS}}$), 129.6 (CH$_{\text{Ar-TBDPS}}$), 127.7 (2C, CH$_{\text{Ar-TBDPS}}$), 127.6 (2C, CH$_{\text{Ar-TBDPS}}$), 82.2 (C$_7$), 78.3 (C$_6$), 76.3 (C$_3$), 75.8 (C$_5$), 61.7 (C$_{14}$), 46.0 (C$_2$), 42.7 (C$_{13}$), 34.6 (C$_4$), 30.7 (C$_{10}$), 26.7 (C($\underline{C}$H$_3$)$_{3\text{TBDPS}}$), 22.3 (C$_8$), 20.1 (C$_{11}$), 19.3 ((CH$_3$)$_3\underline{C}_{\text{TBDPS}}$), 14.0 (C$_{12}$), 10.6 (C$_9$) ppm; MS (ESI$^-$) (*m*/*z*) 596.3 [M − H]$^-$; HRMS (ESI$^+$) for $\mathrm{C_{32}H_{43}NO_8Si}$ [M + Na]$^+$ calcd. 620.2650, found. 620.2651.

*Data for **43** (Isolated in a Mixture with **44**).* ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.81−7.59 (4H, m, H$_{\text{Ar-TBDPS}}$), 7.54−7.33 (6H, m, H$_{\text{Ar-TBDPS}}$), 5.20 (1H, ddd, $^3J_{HH}$ 11.6 Hz, $^3J_{HH}$ 6.7 Hz, $^3J_{HH}$ 3.5 Hz, H$_3$), 4.40 (2H, m, H$_{15}$), 4.36−4.29 (1H, m, H$_2$), 4.06−3.89 (1H, m, H$_{14}$), 3.89−3.81 (1H, m, H$_{14'}$), 3.74 (1H, d, $^3J_{HH}$ 3.2 Hz, H$_5$), 2.81 (1H, t, $^3J_{HH}$ 6.3 Hz, H$_8$), 2.20 (1H, t, $^2J_{HH}$, $^3J_{HH}$ 12.9 Hz, H$_4$), 1.90−1.72 (3H, m, H$_{4'}$, H$_9$, H$_{11}$), 1.70−1.40 (2H, m, H$_{9'}$, H$_{11'}$), 1.38−1.21 (2H, m, H$_{12}$), 1.09 (9H, s, C(C$\underline{H}_3$)$_{3\text{-TBDPS}}$), 0.96 (3H, t, $^3J_{HH}$ 7.6 Hz, H$_{10}$), 0.91 (3H, t, $^3J_{HH}$ 7.3 Hz, H$_{13}$), ^{13}C NMR (100 MHz, CDCl$_3$) δ 173.1 (**C**$_1$), 167.5 (C$_7$), 136.1 (2C, CH$_{\text{Ar-TBDPS}}$), 135.8 (2C, CH$_{\text{Ar-TBDPS}}$), 133.4 (C$_{\text{qAr-TBDPS}}$), 132.1 (C$_{\text{qAr-TBDPS}}$), 130.0 (CH$_{\text{Ar-TBDPS}}$), 129.9 (CH$_{\text{Ar-TBDPS}}$), 127.8 (2C, CH$_{\text{Ar-TBDPS}}$), 127.7 (2C, CH$_{\text{Ar-TBDPS}}$), 77.2 (C$_3$), 71.6 (C$_5$), 64.6 (**C**$_8$), 62.3 (C$_6$), 61.8 (C$_{15}$), 45.8 (C$_2$), 42.7 (C$_{14}$), 33.5 (C$_4$), 30.2 (C$_{11}$), 26.8 (C($\underline{C}$H$_3$)$_{3\text{ester}}$), 20.3 (C$_{11}$), 19.9 (C$_8$), 19.3 (C($\underline{C}$H$_3$)$_{3\text{TBDPS}}$), 14.0 (C$_{13}$), 10.1 (C$_{10}$) ppm; MS (ESI$^+$) (*m*/*z*) 602.3 [M + Na]$^+$, 643.3 [M + Na + MeCN]$^+$, 1181.7 [2M + Na]$^+$; HRMS (ESI$^+$) for $\mathrm{C_{32}H_{41}NO_7Si}$ [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 hour at the same temperature. The reaction was then quenched with H$_2$O (3 mL) before extracting with Et$_2$O (3 × 3 mL). The combined organic extracts were then washed with brine (2 mL), dried over NaSO$_4$, and filtered, and the solvent was evaporated under reduced pressure. Purification by column chromatography (petroleum ether/EtOAc 60/40 to 40/60) afforded **45** as a colorless 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 (400 MHz, CDCl$_3$) δ 7.75−7.65 (4H, m, H$_{\text{Ar-TBDPS}}$), 7.49−7.36 (4H, m, H$_{\text{Ar-TBDPS}}$), 5.92−5.85 (1H, m, N$\underline{H}$), 5.88 (4H, t, $^3J_{HH}$ 7.6 Hz, H$_3$), 3.97 (1H, t, $^3J_{HH}$ 7.1 Hz, H$_5$), 3.65 (1H, t, $^3J_{HH}$ 5.1 Hz, H$_{15}$), 3.35 (1H, ddd, $^2J_{HH}$ 14.2 Hz, $^3J_{HH}$ 10.1 Hz, $^3J_{HH}$ 4.6 Hz, H$_{14}$), 3.30 (3 H, ddd, $^2J_{HH}$ 14.2 Hz, $^3J_{HH}$ 10.1 Hz, $^3J_{HH}$ 4.5 Hz, H$_{14'}$), 3.14 (1H, t, $^3J_{HH}$ 6.3 Hz, H$_7$), 2.50 (1H, dt, $^2J_{HH}$ 14.1 Hz, $^3J_{HH}$ 7.1 Hz, H$_4$), 2.45 (1H, dt, $^2J_{HH}$ 14.1 Hz, $^3J_{HH}$ 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(C$\underline{H}_3$)$_{3\text{ester}}$), 1.44−1.35 (1H, m, H$_{8'}$), 1.29−1.14 (2H, m, H$_{12}$), 1.09 (9H, s, C(C$\underline{H}_3$)$_{3\text{TBDPS}}$), 1.02 (3H, t, $^3J_{HH}$ 7.6 Hz, H$_9$), 0.76 (3H, t, $^3J_{HH}$ 7.3 Hz, H$_{13}$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 171.2 (C$_1$), 167.7 (C$_{10}$), 139.2 (C$_2$), 136.0 (CH$_{\text{Ar-TBDPS}}$), 135.9 (CH$_{\text{Ar-TBDPS}}$), 133.8 (C$_{\text{qAr-TBDPS}}$), 132.4 (C$_{\text{qAr-TBDPS}}$), 130.1 (CH$_{\text{Ar-TBDPS}}$), 129.9 (CH$_{\text{Ar-TBDPS}}$), 129.1 (C$_3$), 127.8 (CH$_{\text{Ar-TBDPS}}$), 127.7 (CH$_{\text{Ar-TBDPS}}$), 82.9 ((CH$_3$)$_3\underline{C}_{\text{ester}}$), 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($\underline{C}H_3$)$_{3\text{ester}}$), 26.9 (C($\underline{C}H_3$)$_{3\text{TBDPS}}$), 22.0 (C$_{12}$), 21.7 (C$_8$), 19.5 ((CH$_3$)$_3\underline{C}_{\text{TBDPS}}$), 13.9 (C$_9$), 10.1 (C$_{13}$) ppm; MS (ESI$^+$) (*m*/*z*): 554.4 [M − *t*Bu + 2H]$^+$, 610.5 [M + H]$^+$, 632.5 [M + Na]$^+$; HRMS (ESI$^+$) for $\mathrm{C_{35}H_{51}NO_6Si}$ [M + Na]$^+$ calcd. 632.3378, found. 632.3372.

*Synthesis of Thioester **50**.* See ref 10. Data for byproducts **52** (obtained using nonoptimized conditions, traces of impurity observed): IR (neat) 3369 (w), 2955 (s), 2876 (m), 1747 (m), 1712 (s), 1677 (s), 1138 (s) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm 7.39−7.17 (5H, m, H$_{\text{Ar}}$), 6.68 (1H, d, $^3J_{HH}$ 8.6 Hz, N$\underline{H}$), 4.61−4.48 (1H, m, H$_{14}$), 4.28 (1H, dd, $^2J_{HH}$ 11.1 Hz, $^2J_{HH}$ 3.5 Hz, H$_{15}$), 4.11 (1H, dd, $^2J_{HH}$ 11.1 Hz, $^3J_{HH}$ 4.0 Hz, H$_{15'}$), 3.86−3.95 (1H, m, H$_3$), 3.53 (1H, dd, $^3J_{HH}$ 9.4 Hz, $^3J_{HH}$ 2.8 Hz, H$_5$) 3.02−2.82 (5H, m, C$\underline{H}_2$Bn, H$_7$, H$_{17}$), 2.35−2.26 (1H, m, H$_2$), 2.19 (1H, ddd, $^2J_{HH}$ 14.8 Hz, $^3J_{HH}$ 9.2 Hz, $^3J_{HH}$ 2.8 Hz, H$_4$), 1.91−1.31 (1H, m, H$_{11}$) 1.75−1.65 (1H, m, H$_{4'}$), 1.65−1.50 (1H, m, H$_8$), 1.53 (9H, s, C(C$\underline{H}_3$)$_3$), 1.42−1.17 (4H, m, H$_{8'}$, H$_{11'}$, H$_{12}$), 1.38 (3H, t, $^3J_{HH}$ 7.3 Hz, H$_9$ or H$_{13}$ or H$_{18}$), 1.08−0.97 (21H, m, C$\underline{H}_{3\text{TES}}$, C$\underline{H}_{3'\text{TES}}$, H$_9$ or H$_{13}$ or H$_{18}$), 0.93 (3 H, t, $^3J_{HH}$ 7.1 Hz, H$_9$ or H$_{13}$ or H$_{18}$), 0.80−0.61 (12H, m, C$\underline{H}_{2\text{TES}}$, C$\underline{H}_{2'\text{TES}}$) ppm; ^{13}C NMR (100 MHz, CDCl$_3$) δ ppm 172.3 (C$_1$), 170.9 (C$_{16}$ or C$_{10}$), 166.4 (C$_{16}$ or C$_{10}$), 137.3 (C$_{\text{qAr}}$), 129.2 (2C, CH$_{\text{Ar}}$), 128.5 (2C, CH$_{\text{Ar}}$), 126.6 (CH$_{\text{Ar}}$), 82.4 ($\underline{C}$(CH$_3$)$_3$), 74.2 (C$_5$), 71.3 (C$_3$), 67.20 (C$_{15}$), 67.17 (C$_6$), 61.4 (C$_7$), 52.1 (C$_2$), 48.8 (C$_{14}$), 40.4 (C$_4$), 37.4 ($\underline{C}$H$_2$Bn), 29.7 (C$_8$ or C$_{11}$ or C$_{12}$), 28.1 (C($\underline{C}$H$_3$)$_3$), 25.4 (C$_{17}$), 21.9 (C$_8$ or C$_{11}$ or C$_{12}$), 21.2 (C$_8$ or C$_{11}$ or C$_{12}$), 14.9 (C$_9$ or C$_{13}$ or C$_{18}$), 14.2 (C$_9$ or C$_{13}$ or C$_{18}$), 10.1 (C$_9$ or C$_{13}$ or C$_{18}$), 7.0 ($\underline{C}$H$_{3\text{TES}}$), 6.9 ($\underline{C}$H$_{3'\text{TES}}$), 5.3 ($\underline{C}$H$_{2\text{TES}}$), 5.1 ($\underline{C}$H$_{2'\text{TES}}$) ppm; MS (ESI$^+$) (*m*/*z*) 818.4 [M + Na]$^+$; HRMS (ESI$^+$) for $\mathrm{C_{41}H_{73}NO_8SSi_2}$ [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 Et$_3$SiH (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 a further 18 h, before filtering through Celite, washing with DCM (15 mL), and concentrating under reduced pressure. Purification via column chromatography (pentane/Et$_2$O 98:2 to 95:5) afforded compound **51** as a colorless 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 Et$_2$O (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 hour. The reaction mixture was allowed to warm to rt slowly and was quenched with H$_2$O (20 mL). The mixture was extracted with ether (2 × 20 mL). The combined organic phases were washed with brine (20 mL), dried over MgSO$_4$, and concentrated in vacuo. Purification via column chromatography (hexane/Et$_2$O 90:10) afforded compound **56** as a white solid (1.33 g, 43%).

*Data for **56**.* IR (neat) 3032, 2954, 2866, 1685, 1591 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 10.59 (1H, s, H$_{12}$), 7.54−7.29 (11H, m, H$_{\text{Ar}}$, H$_3$, H$_6$), 6.80 (1H, d, $^3J_{HH}$ 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, $^3J_{HH}$ 7.2 Hz, H$_7$), 1.90 (1H, tspt, $^3J_{HH}$ 7.2 Hz, $^3J_{HH}$ 6.6 Hz, H$_8$), 0.86 (6H, d, $^3J_{HH}$ 6.6 Hz, H$_9$, H$_{9'}$) ppm; ^{13}C NMR (100 MHz, CDCl$_3$) δ 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$_{\text{qAr}}$), 136.3 (C$_{\text{qAr}}$), 128.7 (2C, CH$_{\text{Ar}}$), 128.51 (C$_2$), 128.48 (2C, CH$_{\text{Ar}}$), 128.2 (2C, CH$_{\text{Ar}}$), 128.1 (2C, CH$_{\text{Ar}}$), 127.2 (2C, CH$_{\text{Ar}}$), 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 $\mathrm{C_{25}H_{26}O_3}$ [M + Na]$^+$ calcd. 397.1774, found. 397.1771.

*Reduction of Aldehyde **56** and TBS-Protection To Give **57**.* To a solution of aldehyde **56** (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 (2 × 25 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 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 an additional 15 min. The mixture was extracted with Et$_2$O (3 × 25 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_2O 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}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53−7.30 (10H, m, H_{Ar}), 7.05 (1H, d, $^3J_{HH}$ 8.4 Hz, H_3), 6.70 (1H, d, $^3J_{HH}$ 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, $^3J_{HH}$ 7.2 Hz, H_7), 1.93 (1H, tspt, $^3J_{HH}$ 7.2 Hz, $^3J_{HH}$ 6.6 Hz H_8), 0.89 (6H, d, $^3J_{HH}$ 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_{qAr}), 137.3 (C_{qAr}), 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_6), 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 $C_{31}H_{42}O_3Si$ $[M + Na]^+$ 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_2O (30 mL) and H_2O (30 mL). The aqueous layer was re-extracted with ether (30 mL), and the combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. Purification via column chromatography (hexane/Et_2O 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}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60−7.53 (2H, m with the presence of $^3J_{HH}$ 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, $^3J_{HH}$ 7.2 Hz, H_7), 1.94 (1H, tspt, $^3J_{HH}$ 7.2 Hz, $^3J_{HH}$ 6.6 Hz, H_8), 0.90 (6H, d, $^3J_{HH}$ 6.7 Hz, H_9, $H_{9'}$), 0.84 (9H, s, H_{15}), −0.01 (6H, s, H_{13}, $H_{13'}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6 (C_1 or C_5), 153.8 (C_1 or C_5), 137.6 (C_{qAr}), 137.3 (C_{qAr}), 134.3 (C_3), 133.1 (C_4 or C_6), 130.0 (C_4 or C_6), 128.5 (2C, CH_{Ar}), 128.3 (2C, CH_{Ar}), 127.9 (CH_{Ar}), 127.8 (CH_{Ar}), 127.7 (2C, CH_{Ar}), 127.1, (2C, CH_{Ar}), 112.5 (C_2), 76.8 (C_{10} or C_{11}), 76.1 (C_{10} or C_{11}), 55.8 (C_{12}), 39.0 (C_7), 29.3 (C_8), 25.9 (C_{15}), 22.5 (C_9 and $C_{9'}$), 18.1 (C_{14}), −5.4 (C_{13} and $C_{13'}$) ppm; MS (ESI$^+$) (m/z) 593 $[M(^{81}Br) + Na]^+$, 591 $[M(^{79}Br) + Na]^+$; HRMS (ESI$^+$) $C_{31}H_{41}{}^{79}BrO_3Si$ $[M + Na]^+$ calcd. 591.1901, found. 591.1882.

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 H_2O (10 mL). The mixture was then allowed to warm up to rt before extracting with Et_2O (3 × 20 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated under reduced pressure. Purification via column chromatography (pentane/Et_2O 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 characterization purposes (major isomer eluted first). The configuration at C1 was not determined.

Data for ***58a*** *(Major Isomer)*. $[\alpha]_D$ +18.6 (c 1.26, $CHCl_3$, 22 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 7.52−7.29 (11H, m, H_{Ar}), 5.22−5.17 (2H, m, H_1, $C\underline{H}HPh$), 5.15−5.09 (2H, m, $C\underline{H}_2Ph$), 5.00−4.93 (1H, m, $CH\underline{H}Ph$), 4.83−4.72 (2H, m, H_{17}), 4.07−3.99 (1H, m, H_3), 3.43 (1H, d, $^3J_{HH}$ 1.3 Hz, $O\underline{H}$-1), 3.32 (1 H, dd, $^3J_{HH}$ 7.0 Hz, $^3J_{HH}$ 5.1 Hz, H_5), 2.71 (1H, t, $^3J_{HH}$ 6.4 Hz, H_7), 2.55 (1H, dd, $^3J_{HH}$ 13.3 Hz, $^3J_{HH}$ 7.4 Hz, H_{14}), 2.39 (1 H, dd, $^3J_{HH}$ 13.4 Hz, $^3J_{HH}$ 7.1 Hz, $H_{14'}$), 2.23 (1 H, dt, $^2J_{HH}$ 14.7 Hz, $^3J_{HH}$ 7.4 Hz, H_4), 2.09−1.95 (2H, m, $H_{4'}$, H_{15}), 1.83−1.75 (1H, m, H_2), 1.63−1.40 (2H, m, H_8, H_{11}), 1.48 (9H, s, $C(C\underline{H}_3)_{3\ ester}$), 1.39−1.16 (4H, m, $H_{8'}$, $H_{11'}$, H_{12}, $H_{12'}$), 1.00−0.85 (27H, m, H_9, H_{16}, $H_{16'}$, $C\underline{H}_{3TES}$), 0.80 (9H, s, $C(C\underline{H}_3)_{3TBS}$), 0.73 (3H, t, $^3J_{HH}$ 6.6 Hz, H_{13}), 0.69−0.55 (12H, m, $C\underline{H}_{2TES}$), −0.03 (3H, s, $C\underline{H}_{3TBS}$), −0.06 (3H, s, $C\underline{H}_{3'TBS}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4 (C_{10}), 156.4 ($\underline{C}OBn$), 154.1 ($\underline{C}OBn$), 138.1 (C_{qAr}), 137.7 (C_{qAr}), 132.6 (C_{qAr}), 130.6 (C_{qAr}), 129.0 (CH_{Ar}), 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 ($(CH_3)_3\underline{C}_{ester}$), 77.3 ($\underline{C}H_2Ph$ (DEPT 135)), 76.6 ($\underline{C}H_2Ph$), 75.9 (C_3), 74.9 (C_5), 71.4 (C_1), 67.0 (C_6), 61.1 (C_7), 55.4 (C_{17}), 47.3 (C_2), 41.3 (C_4), 39.3 (C_{14}), 29.5 (C_{15}), 28.0 ($C(\underline{C}H_3)_{3\ ester}$), 25.8 ($C(\underline{C}H_3)_{3TBS}$), 24.7 ($C_{11}$), 23.0 ($C_{12}$), 22.6 ($C_{16}$ or $C_{16'}$), 22.4 (C_{16} or $C_{16'}$), 21.9 (C_8), 18.0 ($(CH_3)_3\underline{C}_{TBS}$), 14.6 ($C_{13}$), 10.1 ($C_9$), 6.9 ($\underline{C}H_{3TES}$, $\underline{C}H_3{}'_{TES}$), 5.36 ($\underline{C}H_{2TES}$), 4.88 ($\underline{C}H_2{}'_{TES}$), −5.5 ($\underline{C}H_{3TBS}$), −5.7 ($\underline{C}H_3{}'_{TBS}$) 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.), 1749 (m,br.), 1471 (w), 1356 (m), 1245 (m), 1095 (s) cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50−7.28 (11 H, m, H_{Ar}), 5.19−5.12 (2H, m, H_1, $C\underline{H}HPh$), 5.11 (1H, d, $^3J_{HH}$ 4.5 Hz, $CH\underline{H}Ph$), 5.08 (1H, d, $^3J_{HH}$ 4.3 Hz, $C\underline{H}HPh$), 5.00−4.94 (1H, m, $CH\underline{H}Ph$), 4.92−4.89 (1H, m, $O\underline{H}$-1), 4.81 (1H, d, $^3J_{HH}$ 9.6 Hz, H_{17}), 4.75 (1 H, d, $^3J_{HH}$ 9.7 Hz, $H_{17'}$), 4.10 (1H, app. d, J 9 Hz, H_3 or H_5), 3.52 (1H, dd, $^3J_{HH}$ 9.4 Hz, $^3J_{HH}$ 1.5 Hz, H_5 or H_3), 2.80 (1H, t, $^3J_{HH}$ 6.3 Hz, H_7), 2.59 (1H, dd, $^2J_{HH}$ 13.5 Hz, $^3J_{HH}$ 7.0 Hz, H_{14}), 2.44−2.31 (2H, m, H_4, $H_{14'}$), 2.09−1.91 (3H, m, H_2, $H_{4'}$, H_{15}), 1.66−1.57 (1H, m, H_8), 1.53−1.45 (1H, m, $H_{8'}$), 1.36 (9H, s, $C(C\underline{H}_3)_{3\ ester}$), 1.22−1.10 (1H, m, H_{11} or H_{12}), 1.08−0.93 (24H, m, $H_{9,}$, $H_{11'}$, $H_{12'}$, $C\underline{H}_{3TES}$, H_{12} or H_{11}), 0.90 (3H, d, $^3J_{HH}$ 6.5 Hz, H_{16} or $H_{16'}$), 0.89 (3H, d, $^3J_{HH}$ 6.6 Hz, H_{16} or $H_{16'}$), 0.79 (9H, s, $C(C\underline{H}_3)_{3TBS}$), 0.77−0.60 (15H, m, H_{13}, $C\underline{H}_{2TES}$), −0.075 (3H, s, $C\underline{H}_{3TBS}$), −0.079 (3H, s, $C\underline{H}_{3TBS}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ166.3 (C_{10}), 156.7 ($\underline{C}OBn$), 155.1 ($\underline{C}OBn$), 138.2 (C_{qAr}), 138.0 (C_{qAr}), 132.3 (C_{qAr}), 131.2 (C_{qAr}), 130.0 (CH_{Ar}), 128.34 (2C, CH_{Ar}), 128.28 (2C, CH_{Ar}), 127.5 (CH_{Ar}), 127.4 (CH_{Ar}), 127.3 (C_{qAr}), 127.2 (2C, CH_{Ar}), 126.9 (2C, CH_{Ar}), 82.1 ($(CH_3)_3\underline{C}_{ester}$), 77.7 ($\underline{C}H_2Ph$), 76.5 ($\underline{C}H_2Ph$), 74.5 ($C_3$ or C_5), 73.6 (C_3 or C_5), 70.1 (br. s, C_1), 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_{15}), 27.9 ($C(\underline{C}H_3)_{3ester}$), 25.8 ($C(\underline{C}H_3)_{3TBS}$), 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 ($(CH_3)_3\underline{C}_{TBS}$), 14.1 ($C_{13}$), 10.2 ($C_9$), 6.9 ($\underline{C}H_{3\ TES}$, $\underline{C}H_{3'TES}$), 5.4 ($\underline{C}H_{2TES}$), 5.1 ($\underline{C}H_{2TES}$),-5.5 ($\underline{C}H_{3TBS}$),-5.6 ($\underline{C}H_{3'TBS}$) ppm; MS (ESI$^+$) (m/z) 1071.66 $[M + Na]^+$.

Reduction/Deprotection Leading to Hemiacetal ***61a****, and Deprotected Ester* ***62a***. To a solution of **60a** (107 mg, 0.10 mmol, *dr* 67:33, 1 equiv) in toluene (3.2 mL) at −78 °C was added DIBAL-H (1 M 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_2O (3 mL) was added, and the resulting mixture was stirred for a further 1 h at 0 °C. The mixture was filtered through a pad of Celite and 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_2SO_4 and concentrated under reduced pressure. Purification via column chromatography (pentane/Et_2O 95:5 to 9:1), followed by preparative HPLC (hexane/Et_2O 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 (1 M 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 colorless 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 colorless oil (10.9 mg, 15% over 2 steps, *dr* 85:15).

Data for ***61a***. $[\alpha]_D$ +31.8 (c 0.23, $CHCl_3$, 21 °C); IR (neat) 3408 (m, br.), 2955 (s, br.), 2353 (m, br.), 1458 (s), 1212 (m), 1098 (s), 1019 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53−7.35 (10H, m, H_{Ar}), 7.32 (1H, s, H_{Ar}), 5.11 (1H, d, $^{3}J_{HH}$ 5.8 Hz, H_1), 5.05 (1H, d, $^{2}J_{HH}$ 10.9 Hz, $C\underline{H}HPh$), 5.00−4.92 (3H, m, $C\underline{H}HPh$, $C\underline{H}_2Ph$), 4.84 (1H, s, H_7), 4.73 (2H, app. d, $^{3}J_{HH}$ 4.9 Hz, H_{17}), 4.02 (1H, td, $^{3}J_{HH}$ 11.3 Hz, $^{3}J_{HH}$ 5.1 Hz, H_3 or H_5), 3.85 (1 H, d, $^{3}J_{HH}$ 11.4 Hz, H_5 or H_3), 3.35−3.28 (1H, m, $O\underline{H}$-7), 3.24 (1H, dd, $^{3}J_{HH}$ 7.2 Hz, $^{3}J_{HH}$ 5.8 Hz, H_8), 2.60 (1H, dd, $^{2}J_{HH}$ 13.2 Hz, $^{3}J_{HH}$ 7.1 Hz, H_{14}), 2.52 (1 H, dd, $^{2}J_{HH}$ 13.3 Hz, $^{3}J_{HH}$ 7.3 Hz, $H_{14'}$), 2.29 (1 H, t, $^{3}J_{HH}$ 5.5 Hz, $O\underline{H}$-17), 2.25−2.18 (1H, m, $O\underline{H}$-1), 2.06−1.94 (1H, m, H_{15}), 1.76−1.67 (1H, m, H_4), 1.67−1.48 (6H, m, H_2, $H_{4'}$, H_9, $H_{9'}$, H_{11}, $H_{11'}$), 1.37−1.19 (2H, m, H_{12}), 1.06 (3H, t, $^{3}J_{HH}$ 7.5 Hz, H_{10}), 0.92 (3H, d, $^{3}J_{HH}$ 6.8 Hz, H_{16} or $H_{16'}$), 0.91 (3H, d, $^{3}J_{HH}$ 6.8 Hz, H_{16} or $H_{16'}$), 0.82 (3H, t, $^{3}J_{HH}$ 7.3 Hz, H_{13}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1 ($\underline{C}OBn$), 152.8 ($\underline{C}OBn$), 137.2 (C_{qAr}), 136.6 (C_{qAr}), 133.0 (C_{qAr}), 131.9 (C_{qAr}), 129.1 (CH_{Ar}), 128.7 (4C, CH_{Ar}), 128.6 (CH_{Ar}), 128.4 (2C, CH_{Ar}), 128.2 (CH_{Ar}), 127.7 (2C, CH_{Ar}), 127.4 (C_{qAr}), 94.3 (C_7), 77.7 ($\underline{C}H_2Bn$), 76.5 ($\underline{C}H_2Bn$), 71.1 (C_1), 69.8 (C_3 or C_5), 63.0 (C_5or C_3), 61.8 (C_6), 59.6 (C_8), 56.3 (C_{17}), 49.0 (C_2), 39.4 (C_{14}), 37.3 (C_4), 29.3 (C_{15}), 26.6 (C_{11}), 23.3 (C_{12}), 22.6 (C_{16} or $C_{16'}$), 22.4 (C_{16} or $C_{16'}$), 20.6 (C_9), 14.5 (C_{13}), 10.6 (C_{10}); MS (ESI^{+}) (*m*/*z*) 657 $[M + Na]^+$; HRMS (ESI^{+}) for $C_{38}H_{50}O_8$ $[M + Na]^+$ calcd. 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}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53−7.33 (20H, m, H_{Ar}, *major and minor*), 7.32 (1H, s, H_{Ar}, *minor*), 7.26 (1H, s, H_{Ar}, *major*), 5.11−5.08 (1H, m, H_1, *minor*), 5.04 (2H, d, $^{2}J_{HH}$ 11.1 Hz, $C\underline{H}HPh$, *major and minor*), 5.00−4.92 (6H, m, $C\underline{H}_2Ph$, $CH\underline{H}Ph$, *major and minor*), 4.75 (2H, app. d, $^{3}J_{HH}$ 5.9 Hz, H_{17}, *major*), 4.41 (1H, ddd, $^{3}J_{HH}$ 9.1 Hz, $^{3}J_{HH}$ 6.5 Hz, $^{3}J_{HH}$ 3.0 Hz, H_3 or H_5, *major*), 4.31−4.20 (2H, m, H_3 or H_5, *major and minor*), 4.17−4.09 (1H, m, H_3 or H_5, *minor*), 3.73−3.65 (1H, m, $O\underline{H}$-3 or $O\underline{H}$-5, *major*), 3.27 (1H, t, $^{3}J_{HH}$ 6.4 Hz, H_7, *major and minor*), 3.14−3.08 (1H, m, OH, *minor*), 3.04−2.97 (1H, d, $^{3}J_{HH}$ 8.8 Hz, $O\underline{H}$-5 or $O\underline{H}$-3, *major*), 2.86 (1H, br. d, $^{3}J_{HH}$ 9.5 Hz, OH, *minor*), 2.66−2.42 (3H, m, H_{14}, $H_{14'}$,$O\underline{H}$-17, *major*), 2.06−1.89 (3H, m, H_2, H_4, H_{15}, *major*), 1.69−1.51 (3H, m, $H_{4'}$, H_8, $H_{8'}$, $O\underline{H}$-1, *major*), 1.48 (9H, s, $(C\underline{H}_3)_3C$, *major*), 1.44 (9H, s, $(C\underline{H}_3)_3C$, *minor*), 1.32−1.10 (2H, m, H_{12}), 1.09−0.98 (2H, m, H_{11}), 1.06 (3H, t, $^{3}J_{HH}$ 7.7 Hz, H_9, *major*), 0.908 (3H, d, $^{3}J_{HH}$ 6.3 Hz, H_{16} or $H_{16'}$, *major*), 0.904 (3H, d, $^{3}J_{HH}$ 6.2 Hz, H_{16} or $H_{16'}$, *major*), 0.73 (3 H, t, $^{3}J_{HH}$ 7.1 Hz, H_9, *major*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8 (C_{10}), 156.4 ($\underline{C}OBn$), 153.3 ($\underline{C}OBn$), 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 ($(CH_3)_3\underline{C}$), 77.6 ($\underline{C}H_2Bn$), 76.4 ($\underline{C}H_2Bn$), 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_{15}), 29.1 (C_{11}), 28.0 ($C(\underline{C}H_3)_3$), 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 NaHCO3 (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/Et2O 5:5) to give 8 mg of impure keto aldehyde **64**. A mixture of mono-oxidized product and starting material **61a** (9.1 mg, ca. 2:1 respectively) was also isolated. The mixture of starting material **61a** and mono-oxidized 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/Et2O 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 colorless oil.

Data for ***64***. IR (neat) cm^{-1} 3432 (br., m), 2957 (m, br.), 1690 (s), 1556 (m), 1556 (m), 1369 (m), 1094 (s, br.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.33 (1H, s, H_{17}), 7.52−7.33 (11H, m, H_{Ar}), 5.07 (1H, d, $^{2}J_{HH}$ 10.3 Hz, $C\underline{H}HPh$), 5.04 (1H, d, $^{2}J_{HH}$ 10.1 Hz, $CH\underline{H}Ph$), 4.98 (1H, d, $^{2}J_{HH}$ 11.5 Hz, $C\underline{H}HPh$), 4.95 (1H, d, $^{2}J_{HH}$ 11.3 Hz, $CH\underline{H}Ph$), 4.66 (1H, d, $^{3}J_{HH}$ 2.3 Hz, H_7), 4.39 (1H, ddd, $^{3}J_{HH}$ 11.7 Hz, $^{3}J_{HH}$ 4.8 Hz, $^{3}J_{HH}$ 1.3 Hz, H_3), 4.11 (1H, td, $^{3}J_{HH}$ 11.6 Hz, $^{3}J_{HH}$ 4.9 Hz, H_5), 3.36 (1H, dt, $^{3}J_{HH}$ 8.7 Hz, $^{3}J_{HH}$ 4.3 Hz, H_2), 3.22 (1H, t, $^{3}J_{HH}$ 6.5 Hz, H_8), 2.49 (2H, d, $^{3}J_{HH}$ 7.2 Hz, H_{14}), 2.47 (1H, d, $^{3}J_{HH}$ 2.8 Hz, $O\underline{H}$-7), 2.01−1.85 (3H, m, H_4, H_{11}, H_{15}), 1.59−1.45 (4H, m, $H_{4'}$, H_9, $H_{9'}$, $H_{11'}$), 1.44−1.29 (1H, m, H_{12}), 1.29−1.15 (1H, m, $H_{12'}$), 1.03 (3H, t, $^{3}J_{HH}$ 7.5 Hz, H_{10}), 0.92−0.85 (9H, m, H_{13}, H_{16}, $H_{16'}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.6 (C_{17}), 189.1 (C_1), 161.3 ($\underline{C}OBn$), 156.7 ($\underline{C}OBn$), 136.1 (C_{qAr}), 135.81 (C_{qAr}), 135.77 (CH_{Ar}), 132.7 (C_{qAr}), 132.4 (C_{qAr}), 128.9 (2C, CH_{Ar}), 128.68 (CH_{Ar}), 128.65 (2C, CH_{Ar}), 128.60 (2C, CH_{Ar}), 128.5 (CH_{Ar}), 128.2 (2C, CH_{Ar}), 124.3 (C_{qAr}), 94.3 (C_7), 80.2 ($\underline{C}H_2Bn$), 78.2 ($\underline{C}H_2Bn$), 67.5 (C_3), 62.8 (C_5), 61.5 (C_6), 59.5 (C_8), 54.9 (C_2), 38.7 (C_{14}), 36.8 (C_4), 29.1 (C_{15}), 28.1 (C_{11}), 22.5 (C_{16} or $C_{16'}$), 22.3 (C_{16} or $C_{16'}$), 20.9 (C_8), 20.5 (C_{12}), 14.3 (C_{13}), 10.5 (C_{10}) ppm; MS (ESI^{+}) (*m*/*z*) 653 $[M + Na]^+$; HRMS (ESI^{+}) for $C_{38}H_{46}O_8$ $[M + Na]^+$ 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 H_2. Stirring under an atmosphere of H_2 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 **1a** as a pale yellow residue (7.2 mg, 80%). Data for **1a** correspond to those previsouly 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/H_2O (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 $NaHCO_3$ (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 Na_2SO_4, and filtered, and the solvent was evaporated under reduced pressure. The crude was purified by column chromatography (petroleum ether/Et_2O 80:20) to give **67** as a colorless 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***. ^{1}H NMR (400 MHz, CD_3CN) δ 7.57−7.32 (11H, m, H_{Ar}, H_3), 4.99 (2H, s, $C\underline{H}_2Ph$), 4.95 (2H, s, $C\underline{H}_2Ph$), 4.67 (2H, d, $^{3}J_{HH}$ 4.9 Hz, H_{13}), 3.08 (1H, t, $^{3}J_{HH}$ 5.1 Hz, $O\underline{H}$), 2.96 (2H, q, $^{3}J_{HH}$ 7.3 Hz, H_{11}), 2.54 (2H, d, $^{3}J_{HH}$ 7.2 Hz, H_7), 2.01−1.85 (1H, m, H_8), 1.08 (3H, t, $^{3}J_{HH}$ 7.3 Hz, H_{12}), 0.88 (6H, d, $^{3}J_{HH}$ 6.8 Hz, H_9, $H_{9'}$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.5 (C_{10}), 161.1 ($\underline{C}OBn$), 157.0 ($\underline{C}OBn$), 139.0 (C_{qAr}), 138.6 (C_{qAr}), 132.8 (C_2), 132.5 (C_3), 131.7 (C_6), 130.6 (C_4), 130.0 ($\underline{C}H_{Ar}$), 129.9 ($\underline{C}H_{Ar}$), 129.7 ($\underline{C}H_{Ar}$), 129.6 ($\underline{C}H_{Ar}$), 129.6 ($\underline{C}H_{Ar}$), 129.4 ($\underline{C}H_{Ar}$), 79.7 ($\underline{C}H_2Bn$), 78.1 ($\underline{C}H_2Bn$), 55.7 (C_{13}), 40.2 (C_7), 36.9 (C_{11}), 30.4 (C_8), 23.1 (C_9 and $C_{9'}$), 9.1 (C_{12}) 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) were sequentially added $NaHCO_3$ (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 Na_2SO_3 (3 mL) and water (5 mL). The mixture was then extracted with portions of DCM (3 × 10 mL). The combined extracts were washed with $NaHCO_3$ (3 × 7.5 mL), dried over Na_2SO_4, and filtered, and the solvent was evaporated under reduced pressure. The crude residue was then purified by column chromatography (petroleum ether/Et_2O 80:20) to yield **69** as a colorless oil (64 mg, 92%).

Data for ***69***. IR (neat) 3031, 2955, 2869, 1680, 1588 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51−7.32 (15H, m, H_{Ar}), 7.28 (1H, s, H_3, overlapped with the solvent peak), 5.04 (2H, s, $C\underline{H}_2Ph$), 5.02 (2H, s, $C\underline{H}_2Ph$), 4.68 (2H, s, $C\underline{H}_2Ph$), 4.56 (2H, s, $C\underline{H}_2Ph$), 3.00 (2H, q, $^{3}J_{HH}$ 7.4 Hz, H_{11}), 2.54 (2H, d, $^{3}J_{HH}$ 7.1 Hz, H_7), 1.99 (1H, tspt, $^{3}J_{HH}$ 7.1 Hz, $^{3}J_{HH}$ 6.6 Hz, H_8), 1.15 (3H, t, $^{3}J_{HH}$ 7.1 Hz, H_{12}), 0.92 (6H, d, $^{3}J_{HH}$ 6.6 Hz, H_9, $H_{9'}$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.8 (C_{10}),

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160.6 ($\underline{C}$OBn), 156.4 ($\underline{C}$OBn), 137.9 (C_{qAr}), 137.5 (C_{qAr}), 137.0 (C_{qAr}), 131.8 (C_3), 131.5 (C_4), 130.2 (C_2), 128.7 ($\underline{C}H_{Ar}$), 128.7 ($\underline{C}H_{Ar}$), 128.5 ($\underline{C}H_{Ar}$), 128.4 ($\underline{C}H_{Ar}$), 128.0 ($\underline{C}H_{Ar}$), 127.9 ($\underline{C}H_{Ar}$), 127.7 ($\underline{C}H_{Ar}$), 127.6 ($\underline{C}H_{Ar}$), 127.3 ($\underline{C}H_{Ar}$), 126.2 (C_6), 78.8 ($\underline{C}H_2Bn$), 77.0 ($\underline{C}H_2Bn$), 73.3 ($\underline{C}H_2Bn$), 62.7 (C_{13}), 39.1 (C_7), 35.9 (C_{11}), 29.2 (C_8), 22.5 (C_9 and $C_{9'}$), 8.5 (C_{12}) ppm; MS (ESI$^+$) (*m/z*) 545 [M + Na]$^+$; HRMS (ESI$^+$) for $C_{35}H_{38}O_4$ [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 N_2, followed by acetic acid dropwise (15 μL). The reaction was then purged with H_2 by bubbling through the suspension, adding THF periodically to combat evaporation. After 2.5 h under H_2, the mixture was filtered through Celite and washed with THF (3 × 3 mL). The solvent was then evaporated and the crude was purified by column chromatography (petroleum ether/Et_2O 80:20) to yield the triol **70** as a colorless oil (36 mg, 78%).

Data for ***70***. IR (neat) 3403, 3213, 2964, 2914, 1606 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 13.02 (1H, s, O$\underline{H}$), 9.00 (1H, s, O$\underline{H}$), 7.40 (1H, s, H_3), 5.09 (1H, d, $^3J_{HH}$ 5.1 Hz, H_{13}), 2.95 (1H, q, $^3J_{HH}$ 7.1 Hz, H_{11}), 2.43 (2H, d, $^3J_{HH}$ 7.1 Hz, H_7), 2.33 (1H, t, $^3J_{HH}$ 5.3 Hz, $O\underline{H}_{13}$), 1.92 (1H, tspt, $^3J_{HH}$ 7.1 Hz, $^3J_{HH}$ 6.6 Hz, H_8), 1.23 (3H, t, $^3J_{HH}$ 7.3 Hz, H_{12}), 0.93 (6H, d, $^3J_{HH}$ 6.6 Hz, H_9, $H_{9'}$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.7 (C_{10}), 162.1 ($\underline{C}$OH), 159.7 ($\underline{C}$OH), 131.4 (C_3), 120.6 (C_2), 111.9 (C_6), 110.4 (C_4), 58.8 (C_{13}), 38.8 (C_{11}), 31.1 (C_7), 28.5 (C_8), 22.4 (C_9 and $C_{9'}$), 8.7 (C_{12}) ppm; MS (ESI$^+$) (*m/z*) 316. [M + Na + MeCN]$^+$, 527. [2M + Na]$^+$; HRMS (ESI$^-$) for $C_{14}H_{20}O_4$ [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 N_2, followed by acetic acid dropwise (50 μL). The reaction was then purged with H_2 by bubbling through the suspension, adding THF periodically to combat evaporation. After 20 h under H_2, 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 (400 MHz, $CDCl_3$) δ 12.97 (1H, s, O$\underline{H}$), 7.36 (1H, s, H_3), 5.35 (1H, br. s., O$\underline{H}$), 2.97 (2H, q, $^3J_{HH}$ 7.2 Hz, H_{11}), 2.44 (2H, d, $^3J_{HH}$ 7.1 Hz, H_7), 2.14 (3H, s, H_{13}), 1.89 ($CH_2C\underline{H}Me_2$, tspt, $^3J_{HH}$ 7.1 Hz, $^3J_{HH}$ 6.8 Hz, H_8), 1.24 (3H, t, $^3J_{HH}$ 7.2 Hz, H_{12}), 0.94 (6H, d, $^3J_{HH}$ 6.8 Hz, H_9, $H_{9'}$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.7 (C_{10}), 161.1 ($\underline{C}$OH), 158.4 ($\underline{C}$OH), 129.5 (C_3), 118.3 (C_2), 112.7 (C_6), 110.3 (C_4), 39.2 (C_7), 31.2 (C_{11}), 28.7 (C_8), 22.4 (C_9 and $C_{9'}$), 8.7 (C_{13}), 7.5 (C_{12}) ppm; MS (ESI$^-$) (*m/z*) 235 [M − H]$^-$, HRMS (ESI$^+$) for $C_{14}H_{20}O_3$ [M + H]$^+$ calcd. 237.1485, found. 237.1490.

■ ASSOCIATED CONTENT

Supporting Information

This material is available free of charge via the Internet at http://pubs.acs.org/. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00489.

> Characterization data for known compounds, copies of ^1H and ^{13}C spectra of all novel compounds, *dr* determinations, copies of chiral HPLC chromatograms and crystallographic data for compounds ***syn*-9**$_{Tol}$, (±)-***syn*-10**$_{Ph}$, and **17a** (PDF)
>
> Crystallographic data for compounds ***syn*-9**$_{Tol}$, (±)-***syn*-10**$_{Ph}$, and **18a** (CIF)

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Notes

The authors declare no competing financial interest.

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