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Total Synthesis

Stereocontrol by Quaternary Centres: A Stereoselective Synthesis of (−)-Luminacin D

Nathan Bartlett,[a] Leona Gross,[a] Florent Péron,[a] Daniel J. Asby,[a] Matthew D. Selby,[b] Ali Tavassoli,[a] and Bruno Linclau*[a]

Abstract: Very high diastereoselectivity can be achieved by 1,3-chelation-controlled allylation of aldehydes that possess a non-chelating α-ether substituent, even if the α-position is a quaternary centre and/or a spiro-epoxide. This reaction was used as a key step in an enantioselective synthesis of the angiogenesis inhibitor luminacin D.

Natural products continue to be a robust source of novel therapeutics, with approximately 50% of currently approved anticancer drugs being natural products or their derivatives.[1] The luminacin family of natural products, discovered from the fermentation broth of the soil bacterium *Streptomyces* sp.,[2] contains several members that have shown promising anticancer activity in multiple assays and cell lines. Two members of this family, luminacin D (**1a**) and luminacin C2 (**1b**, also known as UCS15A), have been shown to be potent inhibitors of angiogenesis in several in vitro assays.[3] Luminacin D was also shown to inhibit the proliferation of several cancer cell lines.[3]

Additional studies with luminacin C2 have shown it to be a protein–protein interaction inhibitor that targets Src signal transduction by inhibiting the SH3 domain-mediated interactions of Src kinase with its targets, thus preventing the Src-specific tyrosine phosphorylation of numerous proteins.[4] Src kinases play a key role in the signalling and regulation of multiple processes associated with cancer, such as cell migration, cell adhesion, extracellular matrix sensing, cell cycle timing, as well as several poorly understood events necessary for angiogenesis.

Luminacin C2 was further demonstrated to inhibit the invasion and metastasis of model breast cancer cell lines in vitro, by inhibition of the protein–protein interaction of the Src-homology domain of cortactin with AMAP1.[5] The recent report that two structurally related compounds, named migracin A and B (**1c**), inhibit the migration of a breast cancer cell line,[6] provides further evidence for the anticancer potential of this molecule, or its derivatives.

[a] *N. Bartlett, L. Gross, F. Péron, Dr. D. J. Asby, Dr. A. Tavassoli, Dr. B. Linclau*
Department of Chemistry, University of Southampton
Highfield, Southampton SO17 1BJ (UK)
E-mail: bruno.linclau@soton.ac.uk

[b] *M. D. Selby*
UCB, 216 Bath Road, Slough, Berkshire, SL1 WE (UK)

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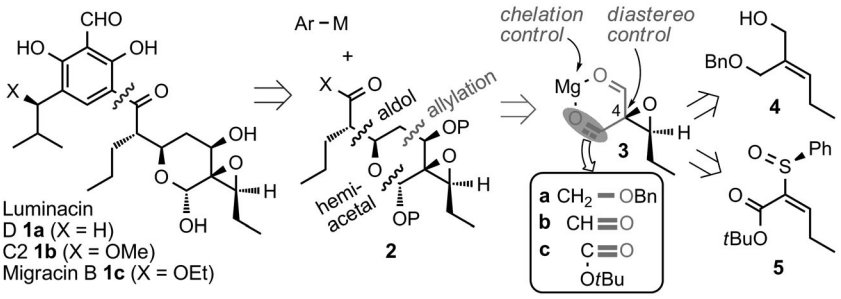
There is comparatively little information about the mode of action or biological function of luminacin D. Given that it is the most potent member of this family in several of the originally reported assays,[3] there is significant potential and need for an approach that enables the synthesis of sufficient quantities of this molecule to enable further research into its cellular mode of action.

There are a few syntheses of the luminacins reported,[7] however, each with shortcomings in terms of length and/or unselective reaction steps. A particular concern is the epoxide introduction, with three total syntheses featuring a late stage-epoxidation step with very low, or undesired selectivity.[7b–d,8] Because of this, we sought to develop a synthetic approach in which an enantiopure epoxide intermediate is assembled first, to then utilise its stereochemistry for diastereoselective completion of the aliphatic portion, from which the luminacins and the migracins can be synthesised.

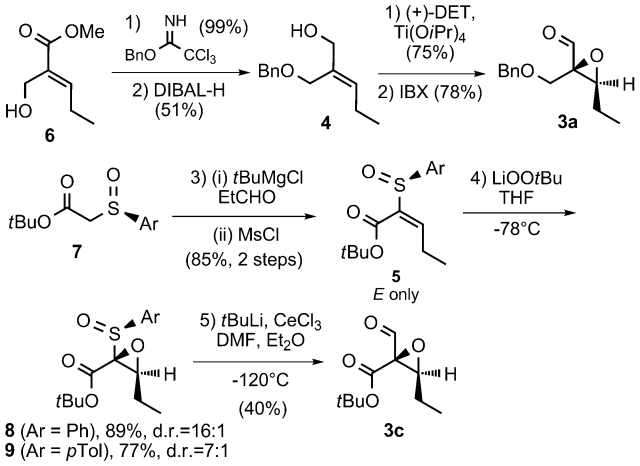
Herein we report a successful total synthesis of (−)-luminacin D using this strategy, and report on the excellent diastereocontrol possible by allylation of aldehydes having α-oxygenated centres, including quaternary centres, under 1,3-chelation conditions. We also unambiguously show that this type of aldehyde addition is consistent with the Cornforth–Evans (CE) model of stereoinduction.

Hence, conventional disconnection leads to the aliphatic fragment **2** (Scheme 1). Its construction was envisaged by spontaneous hemiacetal ring closure, *syn*-aldol reaction, and by the key step, diastereoselective allylation controlled by 1,2-induction of the quaternary epoxide centre of the enantiopure intermediate **3**. This chelation-controlled allylation step was inspired by previous work from our group showing excellent levels of diastereocontrol exerted by *all-C* quaternary stereocentres for allylstannation of 2,2-disubstituted malonaldehydes.[9] However, a 1,3-dialdehyde group (c.f. **3b**) is not desirable in the present case, as it contains four diastereotopic aldehyde faces, and our efforts were directed to investigating **3a** and **3c** as substrates for the allylation reaction.[10] The synthesis of the enantiopure epoxides **3a**,**c** was envisioned from substrates **4** and **5**.

Starting from **6**, synthesised in three steps from methyl acrylate,[7c,11] benzylation and reduction gave **4** as a substrate for a Sharpless epoxidation, which was followed by alcohol oxidation to give **3a** (Scheme 2). The 3-oxopropionate substrate **3c** was synthesised from enantiopure **7**, which was obtained in one step from the corresponding menthyl sulfinyl ester. Two-step Knoevenagel condensation led to **5** as the *E* isomer



Scheme 1. Retrosynthetic analysis, with a 1,3-chelation-mediated allylation as key step.

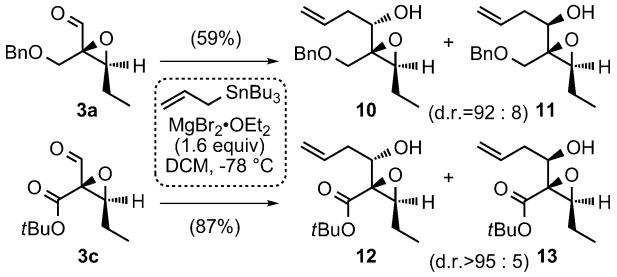


Scheme 2. Synthesis of the allylation substrates.

only, which was then subjected to Fernandez de la Pradilla's vinyl sulfoxide epoxidation methodology.[12] Although replication of their conditions[12b] led to a low yield and selectivity, lowering the temperature and concentration of the reaction gave good diastereocontrol. Interestingly, the phenyl sulfoxide containing **8** was obtained in a 16:1 ratio of (inseparable) diastereomers,[13] but the corresponding *p*-tolyl sulfoxide containing **9** was obtained in a lower ratio (7:1). The relative stereochemistry of **8** was determined by X-ray crystallography after hydrolysis of the ester group.[14] Finally, lithiation of the sulfoxide and treatment with DMF gave **3c**, albeit in a moderate yield. As this operation removes the enantiopure sulfoxide group, **3c** was then obtained in a 7:1 enantiomeric ratio.

The key allylation reactions are shown in Scheme 3. Although treatment of **3** with 3 equiv of $MgBr_2{\cdot}OEt_2$ at $-40\,^{\circ}C$[9] led to epoxide opening to form a bromohydrin (data not shown), reducing the number of equivalents to 1.6, and the temperature to $-78\,^{\circ}C$, fully suppressed this side reaction. Thus, allylation of **3a** led to a mixture of diastereomers **10** and **11** in a good yield and ratio, but the better results were obtained with **3c**, giving isomer **12** virtually exclusively in excellent yield. Interestingly, treatment with allyl magnesium bromide gave a low selectivity (d.r. 7:3),[14] and the use of $BF_3{\cdot}OEt_2$ gave decomposition products. The relative stereochemistry of **10**–**13** was proved by X-ray crystallography of a common derivative.[14]

The stereochemical outcome was rationalised as shown in Figure 1. Chelation, involving the aldehyde and benzyloxy groups,[15] gives rise to two interconverting half-chair structures **I** and **II**. Nucleophilic attack is expected to proceed via a chair-like transition state, as indicated.



Scheme 3. Diastereoselective allylations of α-epoxyaldehydes.

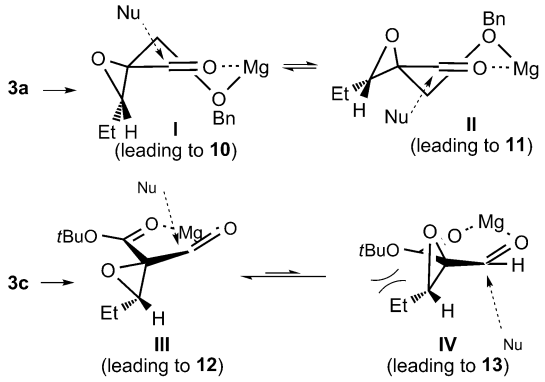


Figure 1. Proposed transition states for reaction of **3**, with **I**/**III** corresponding to a Cornforth–Evans-type, and **II**/**IV** to a polar Felkin–Anh-type model.

Stereocontrol is then further determined by the C–C and C–O substitution at the quaternary centre. With opposite orientations of the epoxide C–O and carbonyl dipoles, the transition state following attack to **I** is akin to a Cornforth–Evans (CE)-type stabilisation, whereas that following attack to **II**, with the C–O bond perpendicular to the plane of the carbonyl group, is comparable to a polar Felkin–Anh (PFA)-type.[16,17] From a steric point of view, both substituents, when in the pseudo-axial position, are expected to hinder nucleophilic attack from that side. The exact model for stereoinduction by non-chelating C–O substituents has been subject to debate,[16] but the experiments here show that the reaction via **I**, leading to **10**, represents the lowest energy transition state and indicating a CE-

type stabilisation is operating. Molecular modelling showed that half-chair **I** is more stable than **II** by 11 kJ mol^{-1}.[14] We believe that the epoxide group is not involved in the $MgBr_2$·OEt_2 mediated chelation, as this would be expected to result in poor diastereoselectivity.[18]

Similar considerations can be made for the reaction of **3c**, with chelation between the two carbonyl groups giving two interconverting "open book" structures[9,10a,e] **III** and **IV**. Apart from the different steric environments between a half-chair and open book conformation, the stereoselectivity compared to **3a** is thought to be enhanced due to the absence of ^{1,2}A strain in **III**, compared to **IV**.[19] This is corroborated by modelling, which showed that **III** is much more stable than **IV**, by 43 kJ mol^{-1}.[14]

To complete the total synthesis, inversion of the alcohol configuration is required (Scheme 4). This is achieved by a Mitsunobu/deprotection process, in which the use of chloroacetic acid[20] gave superior results. Protection as silyl ether, followed by ozonolysis with a phosphine-mediated reduction sequence led to the required aldehyde **14**. It was found that residual phosphorous impurities could be efficiently removed by treatment with Merrifield resin and NaI.[21]

The β-triethylsilyloxy group in **14** is expected to impart the desired aldehyde facial selectivity required for the introduction of the next stereocentre.[17] Indeed, treatment of **14** with the boron enolate derived from **15a** led to a product having the desired relative stereochemistry as the major isomer, but in a moderate 4:1 ratio.[14] The diastereomeric ratio was improved dramatically by employing a matched double diastereo-differentiation process featuring enantiopure oxazolidinone **15b**. Pleasingly, enolate facial induction imposed by the chiral auxiliary is stereodominant, which allowed the removal of the diastereomeric aldol product that was formed by reaction of the minor enantiomer of **14**, after silyl protection of the alcohol groups. Hence, **16** was obtained as an enantiopure diastereomer.

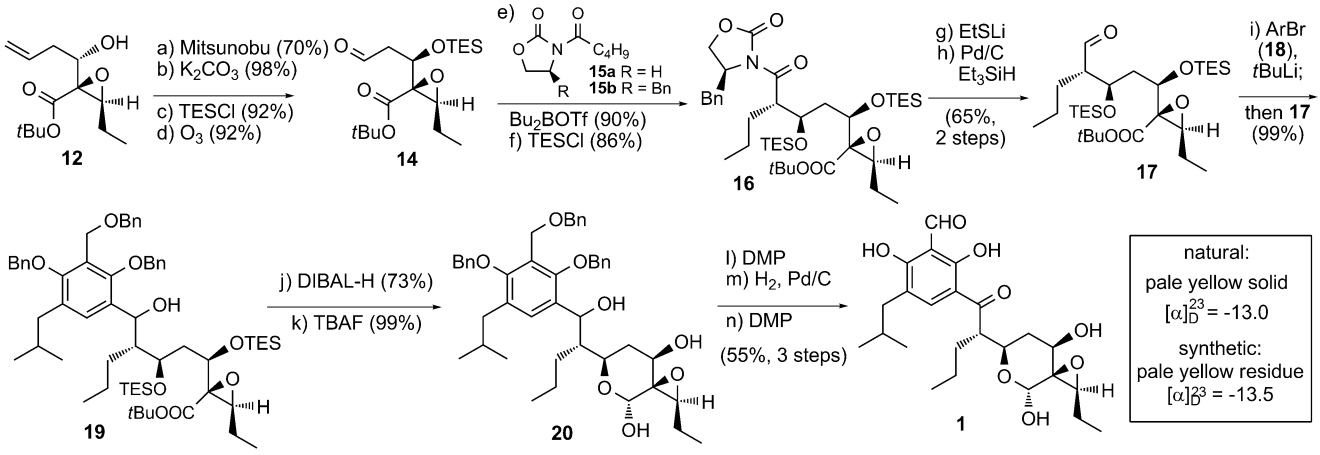
Removal of the auxiliary was achieved by a fully chemoselective ethyl thiolate mediated displacement. Only at higher thiolate concentrations was epoxide opening observed. The resulting thioester was then reduced to give the aldehyde **17**, which was arylated using the aryl bromide **18**[14] in excellent yield.

At this stage the *tert*-butyl ester was reduced to the corresponding aldehyde group, which after desilylation led to formation of the hemiacetal ring **20**. After considerable experimentation, it was found that high-yielding debenzylation at the primary benzylic position was only possible after prior oxidation of the secondary benzylic alcohol. This was achieved in a chemoselective manner using the Dess–Martin periodinane. Hydrogenolysis was then followed by a further oxidation to give luminacin D (**1**). All spectral data and the optical rotation fully corresponded with the data provided by Wakabayashi.[2,14]

We next assessed the effect of **1** on the proliferation of a model breast cancer cell line (MCF-7). Our sample of luminacin D caused a dose-dependent reduction in the proliferation of MCF-7 cells, with an IC_{50} of 55(±4) μM,[14] in-line with reported values for other epithelial cell lines.[3,5]

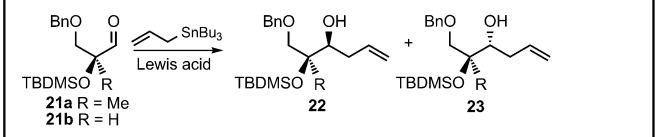
The high stereoinduction provided by the quaternary epoxide centre, in a 1,3-chelation context, clearly is of wider significance for stereoselective synthesis. We further investigated the generality of this process by synthesising a simpler model compound **21a**, in which the quaternary epoxy centre is replaced by an acyclic tertiary (non-chelating)[22] silyl ether (Table 1).

As expected, allylation under chelation conditions proceeded with excellent diastereoselectivity (entry 1), in contrast to allylation under BF_3·OEt_2 activation, which does not involve chelation (entry 2). Treatment of **21a** with allylmagnesium bromide gave low selectivity (entry 3). The selectivity is rationalised by reaction of the half-chair **Va**, via a chair-like CE-type transition state (Figure 2). Somewhat surprisingly, the stereoinduction provided by the larger OTBDMS group is higher compared to the epoxide group. Chelation involving the OTBDMS group, which would lead to a much less selective allylation, is ruled out given the high diastereoselectivity obtained. Interestingly, allylstannation of the corresponding 2-methylated analogue only gives a 2.6:1 ratio of products,[15c] with the major



Scheme 4. Completion of the luminacin D synthesis. a) PPh_3, DIAD, $ClCH_2COOH$, THF; b) MeOH; c) imidazole, DCM; d) PPh_3; Merrifield resin, NaI; e) DIPEA, DCM, −78 °C; f) imidazole, DCM; g) THF; h) DCM; i) THF; j) toluene, −78 °C; k) THF; l) $NaHCO_3$, DCM; m) THF/AcOH.

Table 1. Investigation of stereoinduction by α-quaternary centres.



Entry	R	Lewis acid	Yield [%][a]	Ratio **22**/**23**[b]
1	Me	**$MgBr_2$·OEt_2**	87	**>95:5**
2	Me	BF_3·OEt_2	57	22:78
3	Me	none[c]	87	40:60
4	H	**$MgBr_2$·OEt_2**	53	**>95:5**
5	H	BF_3·OEt_2	81	25:75[24]
6	H	none[c]	81	50:50[24]

[a] Isolated yield. [b] Determined by ^{1}H NMR spectroscopy before chromatography. [c] Allyl magnesium bromide was used.

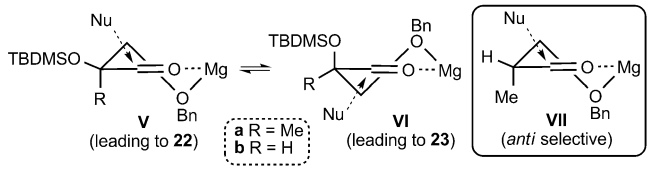


Figure 2. Proposed transition states for formation of **22** and **23**, and comparison with 3-benzyloxy-2-methylpropionaldehyde.

product isomer arising via transition state **VII**[23] as shown. Hence, somewhat counter intuitively, the presence of the α-OTBDMS group serves to increase the selectivity, which is a further indication of the operating CE-type stabilisation. Castle et al. recently demonstrated that analogous ketones (instead of aldehydes) react similarly with excellent diastereoselectivity.[24] The ^{1,2}A strain involving the keto group will further benefit diastereoselectivity.

We also investigated the behaviour of glyceraldehyde **21b** (entries 4–6), for which we found, to our surprise, only a single precedent as substrate under comparable conditions.[26,27] $MgBr_2$·OEt_2 mediated allylstannation was again very selective, to give *syn*-diastereomer **22b**. With no α-methyl group, stereoinduction can only be explained by a CE (**Vb**) versus PFA (**VIb**) competition. The relative configuration of the major isomer **22b** unambiguously shows that for additions to aldehyde **21b** under 1,3-chelation, the stereocontrol instilled by a non-chelating α-OTBDMS group follows a Cornforth–Evans-type model, and also that it leads to a different stereochemical outcome compared to attack to **VII**.

The CE and PFA models can only be distinguished by product outcome for carbonyl additions in which a conformational restraint is imposed on the orientation of the α-stereocentre of the electrophile.[16a] This distinction has been demonstrated by Evans and Marco, who exploited destabilising *syn*-pentane interactions in an aldol Zimmermann–Traxler transition state.[16,28] The examples shown above represent the first cases in which this conformational restriction is imposed by 1,3-chelation and which does not involve a cyclic transition state that includes the nucleophile.

In conclusion, we report that 1,3-chelation-controlled allylations of aldehydes containing a non-chelating α-ether substituent proceed with excellent diastereoselectivity, even when the α position is a quaternary centre or a spiro-epoxide. The relative stereochemistry of the major reaction product unambiguously points towards a contributing CE-type stabilisation of the transition state. ^{1,2}A strain was also shown to have a beneficial effect on the diastereoselectivity. The allylation reaction was exploited as a key step in a successful synthesis of (−)-luminacin D. Other notable features in that synthesis included an epoxide introduction in the first stage of the synthesis, and the high diastereoselectivity achieved in constructing the densely functionalised aliphatic fragment. Furthermore, we have validated the anticancer activity of the synthesised sample. Further investigations to widen the scope of chelation-controlled additions on aldehydes **21**, as well as a large scale synthesis of the aliphatic fragment to provide additional quantities of luminacin D and to achieve the synthesis of migracin A and migracin B for biological evaluation, are underway.

Acknowledgements

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Keywords: allylation · chelation · enantioselectivity · luminacin D · stereoinduction

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