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Total Synthesis of Luminacin D

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Abstract

A highly convergent synthesis of the angiogenesis inhibitor luminacin D has been achieved in 13 linear steps (19 steps total, 5.3% overall yield) utilizing a samarium(II) iodide-mediated mixed tandem aldol/Evans–Tishchenko reaction to construct the carbohydrate precursor. The modular synthetic design will allow derivatization at key positions necessary for biochemical mode of action studies.

A growing class of anticancer pharmaceuticals target angiogenesis, the process of new vascularization by which growing tumors establish a blood supply.¹ Despite an emerging understanding of the complex and highly regulated processes leading to angiogenesis, numerous small molecules currently under investigation have poorly understood mechanisms of action.² The luminacins (Figure 1), isolated recently by Wakabayashi and co-workers from the actinomycete *Streptomyces* sp., represent a potent class of antiangiogenic agents that elicit their biological response via an unconfirmed intracellular target.^{3,4} Herein, we report efficient synthetic access to luminacin D by means amenable to the future derivatization necessary for the identification of its cellular binding protein(s).

Interested in identifying any novel intracellular effectors that elicit an antiangiogenic response, we planned a versatile synthetic approach that could be readily extended to access luminacin-like biochemical probes and chemical analogues.⁵ Ultimately, a strategy involving construction of the C1'–C2' bond by nucleophilic addition of carbohydrate precursor **5** to aldehyde **4** evolved. We found that introduction of the C2'–C11' bond as an unsaturated precursor eliminated problematic retro-aldol-type fragmentation of advanced intermediates saturated at C2'–C11' and delayed introduction of the C2' stereocenter.⁶ Our strategy called for late-stage introduction of the sensitive spiro-epoxypyranose functionality and allowed for installation of the alkyl residues at C2', C8', and C5 by means amenable to future derivatization.

The requisite aryl electrophile (**4**) was prepared efficiently from known triol **6** (Scheme 1).⁷ While exposure of **6** to standard bromination conditions led invariably to over-halogenated species, iodination at the more activated position proceeded cleanly to **7**. Selective benzylation of the phenolic hydroxyls and silylation of the benzylic alcohol afforded **8** (82% yield, two

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Supporting Information Available: Experimental and spectral data pertaining to all new compounds (**3–11**, **13–16**, **18–21**). This material is available free of charge via the Internet at <http://pubs.acs.org>.

steps). Stille cross-coupling with (tributyl)-*isobutenyl*stannane in the presence of catalytic palladium-(II) furnished **9**. Finally, two-step adjustment of the ester oxidation state gave **4**.

Construction of the carbohydrate precursor began with known vinyl iodide **10**⁸, which was elaborated to α -bromo ketone **11** via the protection, acylation, α -bromination sequence illustrated in Scheme 2. Formation of the corresponding samarium enolate by treatment of **11** with 2 equiv of samarium iodide in THF followed by sequential addition of (*E*)-2-bromo-2-pentenal⁹ and acetaldehyde furnished, after basic workup, diol **13** as a single diastereomeric product in excellent yield. Analogy to previous work suggests that the high degree of stereo-induction arises from an organized eight-membered ring chelate (**12**).¹⁰ Protection of **13** as the corresponding acetonide furnished **5**.¹¹

Tandem aldol-Evans–Tishchenko-type additions catalyzed by divalent and/or trivalent samarium species have been previously studied,¹² and variants catalyzed by other metals are also known.¹³ However, the smooth condensation of two different aldehydes via sequential addition greatly enhances the scope of this samarium-mediated transformation.

Metal–halogen exchange of vinyl bromide **5** with *t*-butyllithium at $-78\text{ }^{\circ}\text{C}$ in diethyl ether followed by rapid addition of a chilled solution of **4** in pentane gave a mixture of diastereomeric alcohols that were simultaneously oxidized by Dess–Martin periodinane. Subsequent bis-desilylation cleanly afforded **14** (Scheme 3). Initial plans called for the bis-allylic oxidation of **14** and subsequent acetal removal to afford compounds similar to **17**. We anticipated that epoxidation of **17** would be axially directed by the resident hydroxyl.¹⁴ Unfortunately, attempted cyclization of the requisite bis-aldehyde proved to be frustrating, with apparent scrambling of the C6'–C8' olefin geometry and dehydration always predominating. Fortunately, installation of the epoxide prior to cyclization effectively eliminated these problems.

Although highly diastereoselective epoxidations of primary allylic alcohols have been observed,¹⁵ a model for the observed diastereoselectivity has not been forthcoming. A careful screening of a variety of epoxidation conditions in the present case revealed that VO(acac)₂/TBHP afforded **15** in the best combined regio- and diastereoselectivity (50% isolated yield). The surprising ease with which the resulting diastereomers could be separated and the good efficiency with which **14** could be accessed (nine steps, 33% overall yield) allowed progress to continue toward luminacin D.

Bis-allylic oxidation of **15** with Dess–Martin periodinane and subsequent treatment with a warm solution of acetic acid in THF/H₂O gave the fully functionalized luminacin D spiro-epoxypyranose (**18**) in good yield (Scheme 4). Global reduction of **18** proceeded through **19** under 1 atm of H₂ in the presence of 5% Pd/C to give luminacin D as an epimeric mixture at C2' favoring the natural configuration (ca. 1.5: 1). Luminacin D (**3**) and its C2' epimer (**20**) are separable by preparative thin-layer chromatography.

With a variety of synthetic intermediates in hand, we investigated their antiproliferative profiles. Luminacin D dose dependently inhibited bovine aortic endothelial (BAE) cell proliferation as determined by measuring the incorporation of [³H]-thymidine into cellular DNA. Our results revealed that luminacin D possessed an IC₅₀ = $4.5 \pm 0.7\text{ }\mu\text{M}$, while its immediate synthetic precursors (**18** and **19**) seemed equally potent (Table 1).

An efficient and versatile total synthesis of luminacin D has been achieved (13 linear steps, 5.3% overall yield). The antiproliferative profiles of several synthetic intermediates provide evidence that the C2' alkyl chain and the free phenols may tolerate modification without a detrimental impact on the overall potency of the derivatives. Current synthetic efforts are aimed

at generating biotinylated affinity reagents at these positions. Studies directed toward a molecular mode of action for this class of natural products remain our principle aim.

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Figure 1.

Scheme 1.

Scheme 2.

Scheme 3.

Scheme 4.

Table 1

compound	IC ₅₀
(±)-luminacin D	4.5 ± 0.7 μM
19	4.9 ± 0.6 μM
18	3.4 ± 0.9 μM

Proliferating BAE cells were incubated with vehicle or drug at 37.5 °C for 20 h; [³H]-thymidine was added and the incubation continued for an additional 4 h. Relative [³H]-thymidine incorporation into newly synthesized DNA was quantitated.