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Total Synthesis of Luminacin D

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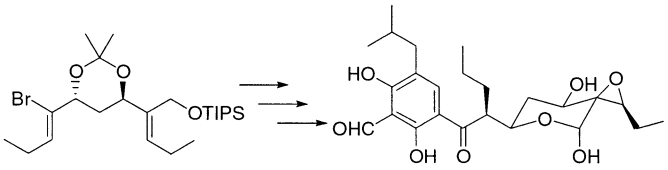
ABSTRACT



Luminacin D

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

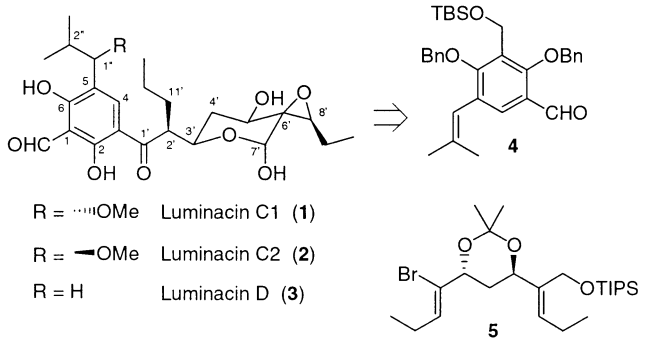


Figure 1.

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(1) (a) Kerbel, R. S. *Carcinogenesis*, **2000**, *21*, 505−515. (b) Oehler, MK.; Bicknell, R. *Br. J. Cancer* **2000**, *82*, 749−752.
(2) Deplanque, G.; Harris, A. L. *Eur. J. Cancer* **2000**, *36*, 1713−1724.
(3) (a) Naruse, N.; Kageyama-Kawase, R.; Funahashi, Y.; Wakabayashi, T. *J. Antibiot.* **2000**, *53*, 579−590. (b) Wakabayashi, T.; Kageyama-Kawase, R.; Naruse, N.; Funahashi, Y.; Yoshimatsu, K. *J. Antibiot.* **2000**, *53*, 591−596. (c) Hata-Sugi, N.; Kawase-Kageyama, K.; Wakabayashi, T. *Biol. Pharm. Bull.* **2002**, *25*(4), 446−451.

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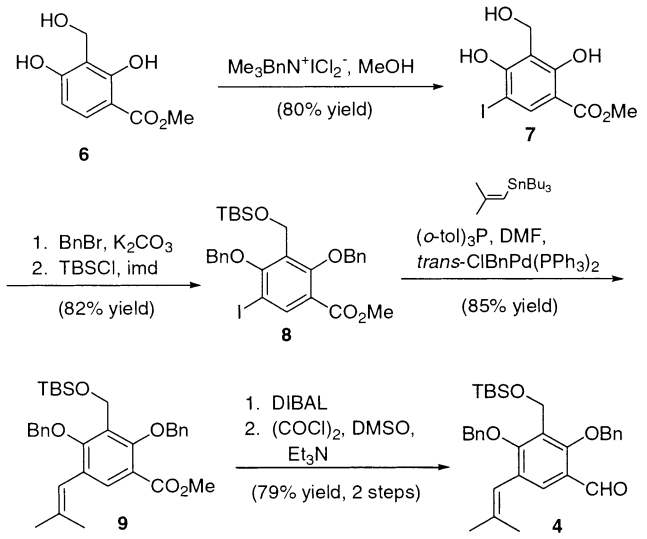
C2′−C11′ bond as an unsaturated precursor eliminated problematic retro-aldol-type fragmentation of advanced intermediates saturated at C2′−C11′ and delayed introduction of the C2′ stereocenter.[6] Our strategy called for late-stage introduction of the sensitive spiro-epoxypyranose functionality and allowed 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

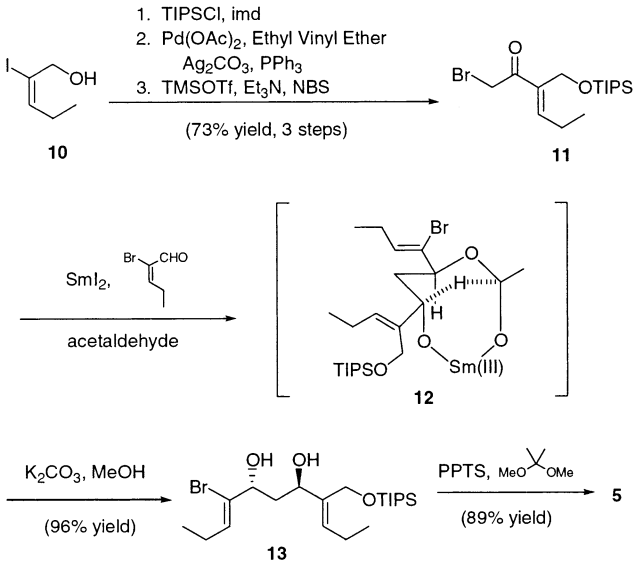
Scheme 1



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 steps). Stille cross-coupling with (tributyl)-*iso*butenylstannane 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

Scheme 2



of (*E*)-2-bromo-2-pentenal[9] 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 °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**

(4) Recently, luminacin C2 was isolated in a screen for Src kinase inhibitors. In vitro experiments suggest that it elicits some of its biological effects via disruption of SH3-mediated association of any number of intracellular proteins with Src. See: (a) Sharma, S.; Oneyama, C.; Yamashita, Y.; Nakano, H.; Sugawara, K.; Hamada, M.; Kosaka, N.; Tamaoki, T. *Oncogene* **2001**, *20*, 2068−2079. (b) Oneyama, C.; Nakano, H.; Sharma, S. *Oncogene* **2002**, *21*, 2037−2050.

(5) Tatsuta and co-workers have recently reported synthetic access to luminacin C1 (**1**) and C2 (**2**). Beginning from L-glucal, their strategy involves 36 linear steps (43 steps total) and has served to establish both the relative and absolute stereochemistry for this class of natural products: Tatsuta, K.; Nakano, S.; Narazaki, F.; Nakamura, Y. *Tetrahedron Lett.* **2001**, *42*, 7625−7628.

(6) The relative configuration of this position remained ambiguous prior to the work of Tatsuta (ref 5).

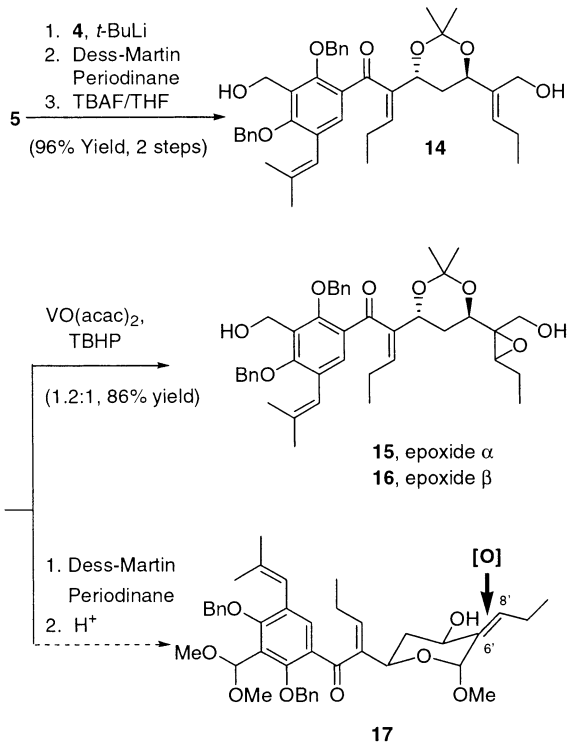
(7) Saimoto, H.; Yoshida, K.; Murakomi, T.; Marimoto, M.; Sashiwa, H.; Shigemosa, Y. *J. Org. Chem*. **1996**, *61*, 6768−6769

(8) Rossi, R.; Carpita, A.; Cossi, P. *Synth. Comm.* **1993**, *23*(2), 143−152.

(9) Lütjens, H.; Knochel, P. *Tetrahedron Lett*. **1994**, *5*(7), 1161−1162.

(10) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447−6449.

Scheme 3



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/H_2O gave the fully functionalized luminacin D spiro-epoxypyranose (**18**) in good yield (Scheme 4). Global

Scheme 4

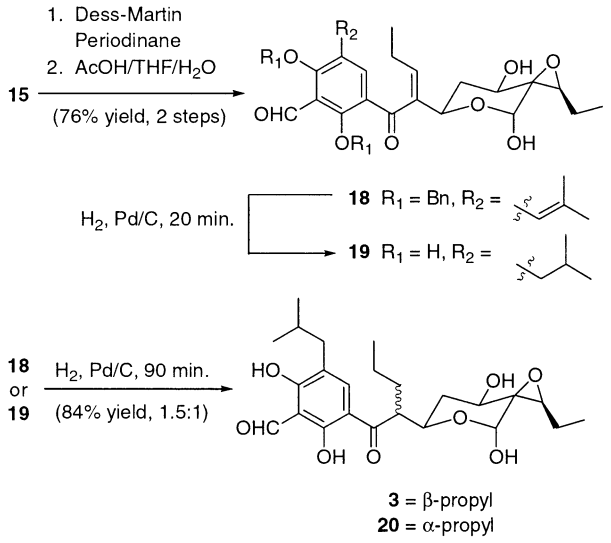


Table 1.[a]

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

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

reduction of **18** proceeded through **19** under 1 atm of H_2 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 [^{3}H]-thymidine into cellular DNA. Our results revealed that luminacin D possessed an $IC_{50} = 4.5 \pm 0.7$ μM, 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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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.

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(11) ^{13}C NMR for **5** is consistent with a twist-chair conformation characteristic of an anti-acetonide; see: Rychnovsky, S. D.; Rogers, B. N.; Richardson, T. I. *Acc. Chem. Res.* **1998**, *31*, 9−17.

(12) (a) Lu, L.; Chang, H.; Fang, J. *J. Org. Chem.* **1999**, *64*, 843−853. (b) Hsu, J.; Fang, J. *J. Org. Chem.* **2001**, *66*, 8573−8584.

(13) For a recent example, see: Mascarehnah, C. M.; Miller, S. P.; White, P. S.; Morken, J. P. *Angew. Chem., Int. Ed.* **2001**, *40*(3), 601−603.

(14) (a) Vedejs, E.; Dent, W. *J. Am. Chem. Soc.* **1989**, *111*, 6861−6862. (b) Barton, D.; Bath, S.; Billington, D.; Gero, S.; Quiclet-Sire, B.; Samadi, M. *J. Chem. Soc., Perkin Trans. 1.* **1995**, 1551−1558.

(15) Hoveyda, A.; Evans, D.; Fu, G. *Chem. Rev.* **1993**, *93*, 1307−1370. (In the present case, application of *m*CPBA favors **16** by 11:1, while Ti(*i*PrO)$_4$ favors **15** by 2:1.)