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SYNTHESIS AND IN VITRO CANCER CELL GROWTH INHIBITORY ACTIVITY OF MONOCYCLIC MODEL COMPOUNDS CONTAINING SPONGISTATIN TRIENE SIDE-CHAINS

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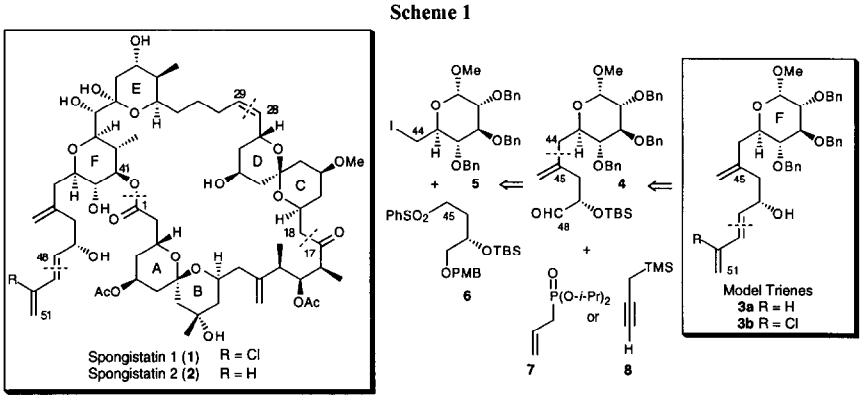
Abstract: Two monosaccharides embodying triene side-chains of the spongistatins display significant in vitro activity against human cancer cell lines.

The spongipyrans, a family of marine natural products with unique bisspiroketal architecture, are extraordinarily potent antitumor agents. The earliest example, spongistatin 4, was isolated in 1982 by Pettit and coworkers.[1a] In 1993, the Pettit,[1] Fusetani[2] and Kitagawa groups[3] independently described spongistatins 1-9, cinachyrolide A, and the altohyrtins A-C, respectively. Spongistatins 1 and 2 (**1** & **2**, Scheme 1), proved to be extremely potent against several highly chemo-resistant tumor types, with GI_{50}s of 1.48 and 8.51 x 10^{-10} M,[1c] respectively. Further studies demonstrated that **1** inhibits the glutamate-induced polymerization of tubulin (IC_{50} 3.6 μM). This Letter details the synthesis and preliminary biological evaluation of simple model compounds containing two of the three triene side-chains of the spongipyrans.

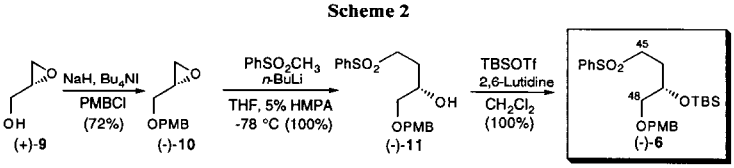
Scheme 1



In our unified approach to the spongistatins,[4] the labile C(48-51) conjugated diene moiety of the side-chain will be introduced at the end of the synthesis. We therefore carried out model studies designed to test this segment of the proposed route. Our initial targets were trienes **3a** and **3b** (Scheme 1), in which a D-glucosyl moiety mimics the F-ring pyran. We envisioned that **3a**, which embodies the unsubstituted diene of spongistatin 2 (**2**), would be generated by Horner-Emmons olefination of the C(48) aldehyde **4** with diisopropyl allylphosphonate (**7**). The chlorinated diene in **3b**, the model for spongistatin 1 (**1**), was expected to arise from the same aldehyde upon treatment with propargyltrimethylsilane (**8**) and $TiCl_4$, according to the method of Pornet.[5] Precursor **4** in turn would be prepared via coupling of known building blocks, iodide **5**[6] with sulfone **6**,[7] followed by Julia methylenation.[8] We have not yet modeled the analogous bromo diene found in altohyrtin B.

Sulfone (-)-**6** was obtained in three steps from commercially available (*R*)-(+)-glycidol [(+)-**9**; Scheme 2]. Protection as the *p*-methoxybenzyl (PMB) ether (NaH, Bu_4NI, PMBCl; 72% yield) and quantitative epoxide opening with the lithio derivative of methyl phenyl sulfone furnished (-)-**11**;[9] the absolute configuration was confirmed by Mosher analysis.[10] Silylation (TBSOTf, 2,6-lut,

Scheme 2



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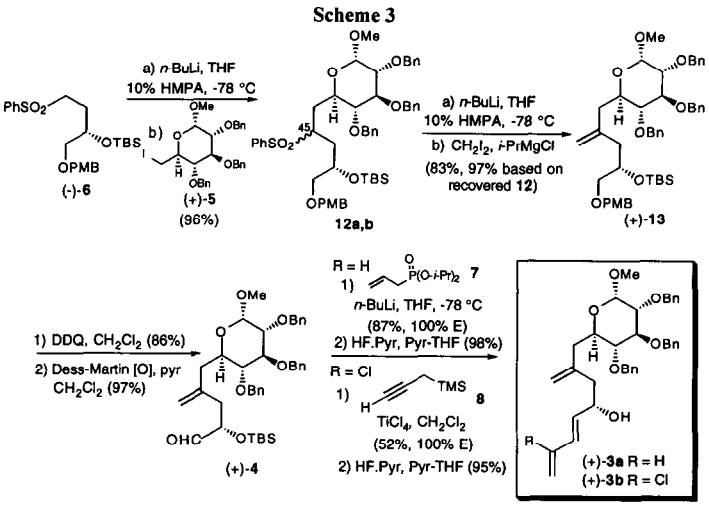
CH_2Cl_2; 100%) completed the synthesis of (-)-**6**.

Coupling of model iodide (+)-**5**, available in five steps from methyl α-D-glucopyranoside,[6] with sulfone (-)-**6** provided **12a,b**[9] in 96% yield as an inconsequential mixture of C(45) epimers (Scheme 3). Introduction of the methylene moiety via the Julia protocol[8] then furnished (+)-**13**[9] (83%). The requisite aldehyde (+)-**4**[9] was generated by removal of the PMB ether with DDQ and Dess-Martin oxidation[11] of the resultant alcohol (83% yield, two steps). Olefination of (+)-**4** with **7** and desilylation furnished exclusively the desired E triene (+)-**3a**[9] (85% yield, two steps). Reaction of (+)-**4** with **8** and $TiCl_4$[5] followed by desilylation likewise afforded the desired E chloro analog (+)-**3b**[9] as a single isomer (49% yield, two steps).

Scheme 3



Preliminary screening has revealed that triene (+)-**3a** is active against six human cancer cell lines, and triene (+)-**3b** against five (Table 1). Surprisingly, the dechloro model compound **3a** displayed greater potency than **3b** in all assays. A variety of other spongistatin analogs are currently under investigation.

Table 1. Cancer cell growth inhibitory activity of model trienes **3a** and **3b** in vitro (GI_{50} values in μg/mL).

	Pancreas-a BXPC-3	Neuroblast SK-N-SH	Thyroid ca SW 1736	Lung-NSC NCI-H460	Pharynx-sq FADU	Prostate DU-145
3a	0.25	0.31	0.70	0.26	0.27	0.32
3b	3.2	2.2	5.8	6.6	5.0	> 10

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