Total Synthesis and Biological Activity of the Proposed Structure of Phaeosphaeride A

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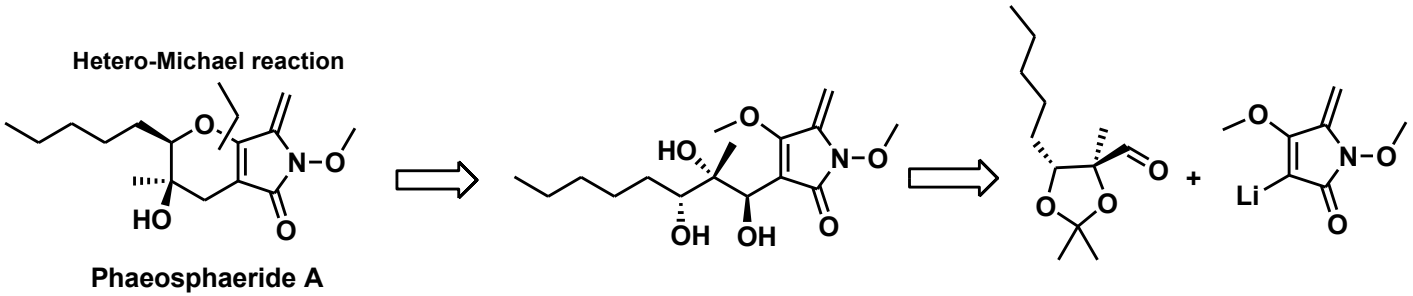


Feng Zhang

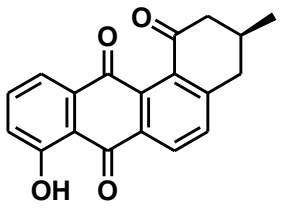
Wipf Group Current Literature

November 3, 2012

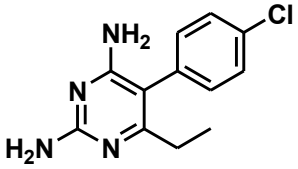
Introduction

- STAT3 is a member of the signal transducer and activator of transcription (STAT) family of transcription factors that relate signals from extracellular signaling protein receptors on the plasma membrane directly to the nucleus.
- STAT3 has been shown to be constitutively activated in cancers of the head and neck, breast, brain, prostate, lung, leukemia, multiple myeloma, lymphoma, pancreas, and others.
- Blocking STAT3 signaling in tumor cells by a dominant negative form of STAT3, antisense approaches, or siRNAs has been shown to induce apoptosis, inhibit cell proliferation, suppress angiogenesis, and stimulate immune responses.
- Therefore, small molecule inhibitors of STAT3 signaling are of great therapeutic potential.

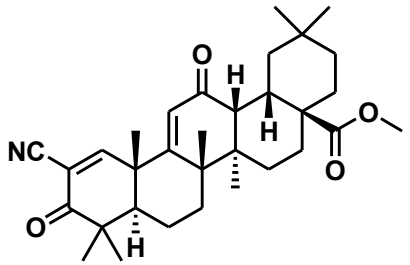
Some known STAT3 inhibitors



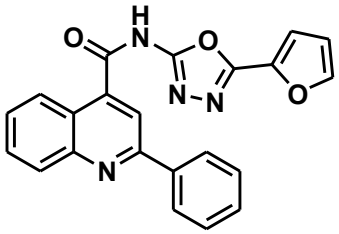
STA21



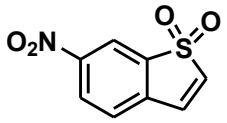
Pyrimethamine



RTA 402



STX-0119



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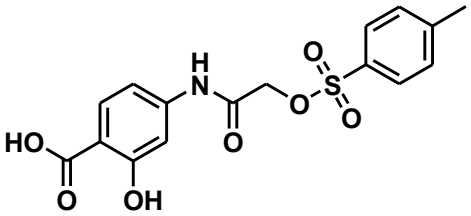
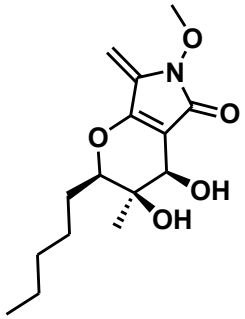


S3I-201

J. Med. Chem. 2012, 55, 6645−6668
Chem. Biol. 2006, 13, 1235−1242
ACS Med. Chem. Lett. 2010, 1, 371–375
Kidney International. 2010, 78, 257–268

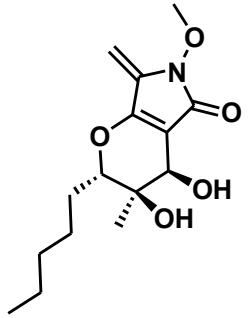
2006, Clardy and co-workers isolated phaeosphaeride A and its stereoisomer, phaeosphaeride B, from the endophytic fungus FA39 (*Phaeosphaeria avenaria*)



Phaeosphaeride A

selectly inhibit STAT3/DNA binding with an IC_{50} of 0.61 mM

inhibiting STAT3-dependent U266 multiple myeloma cells growth with an IC_{50} of 6.7 μM

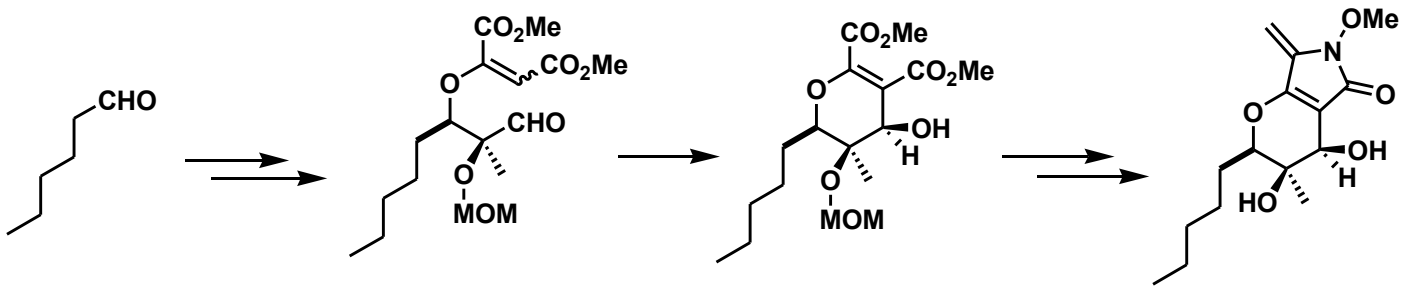


Phaeosphaeride B

inactive against STA3

Maloney, K. N.; Clardy*, J. Org. Lett.* 2006, 8, 4067−4070.

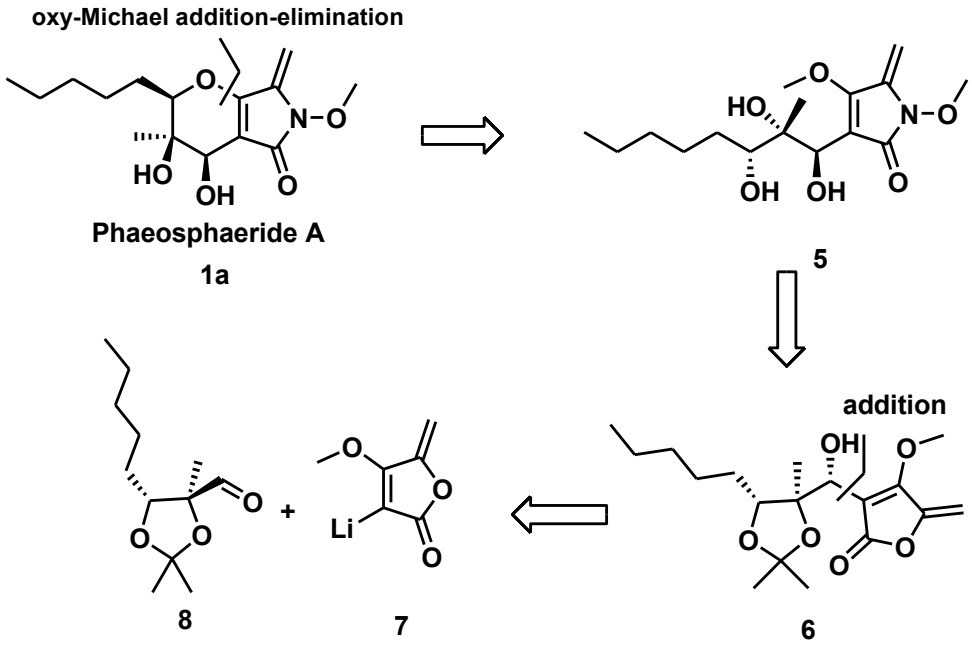
First Total Synthesis



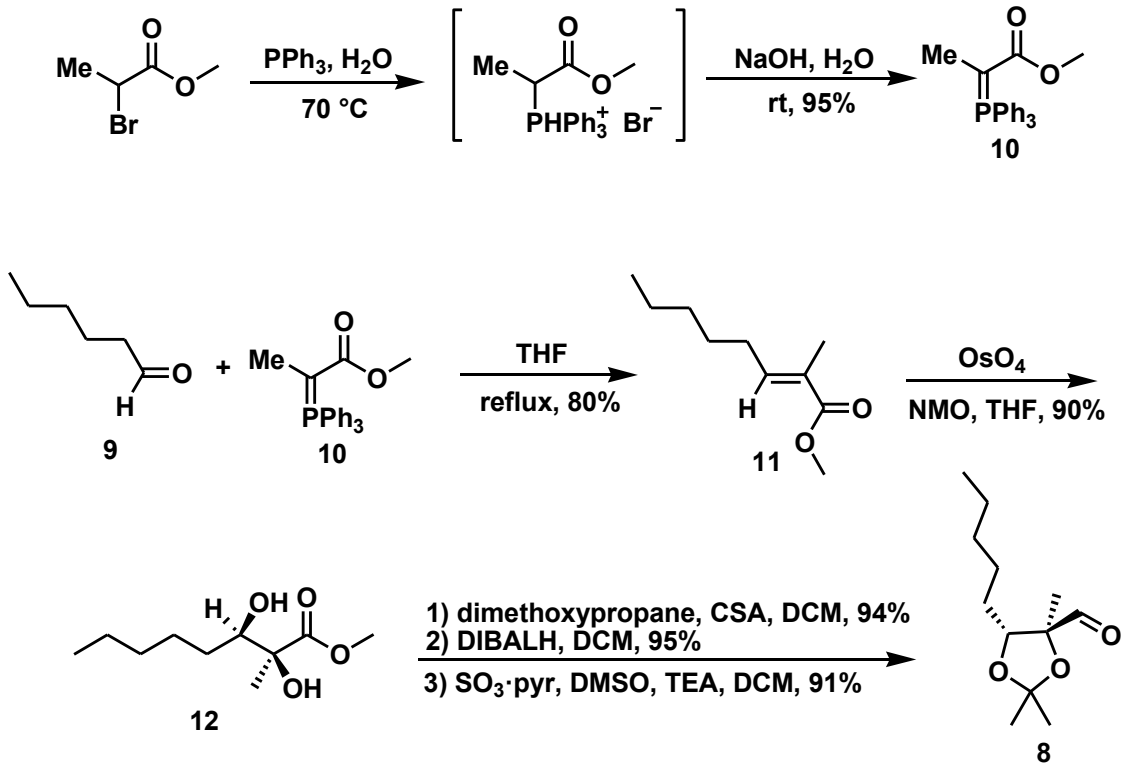
- Six-membered-ring formation by means of an intramolecular vinyl-anion aldol reaction
- The spectral data of synthetic compound did not match with the data reported for the natural phaeosphaeride A

Kobayashi, K.; Tamura, O. *Org. Biomol. Chem*. 2011, 9, 5825−5832.

Retrosynthetic Analysis of Phaeosphaeride A (1a)

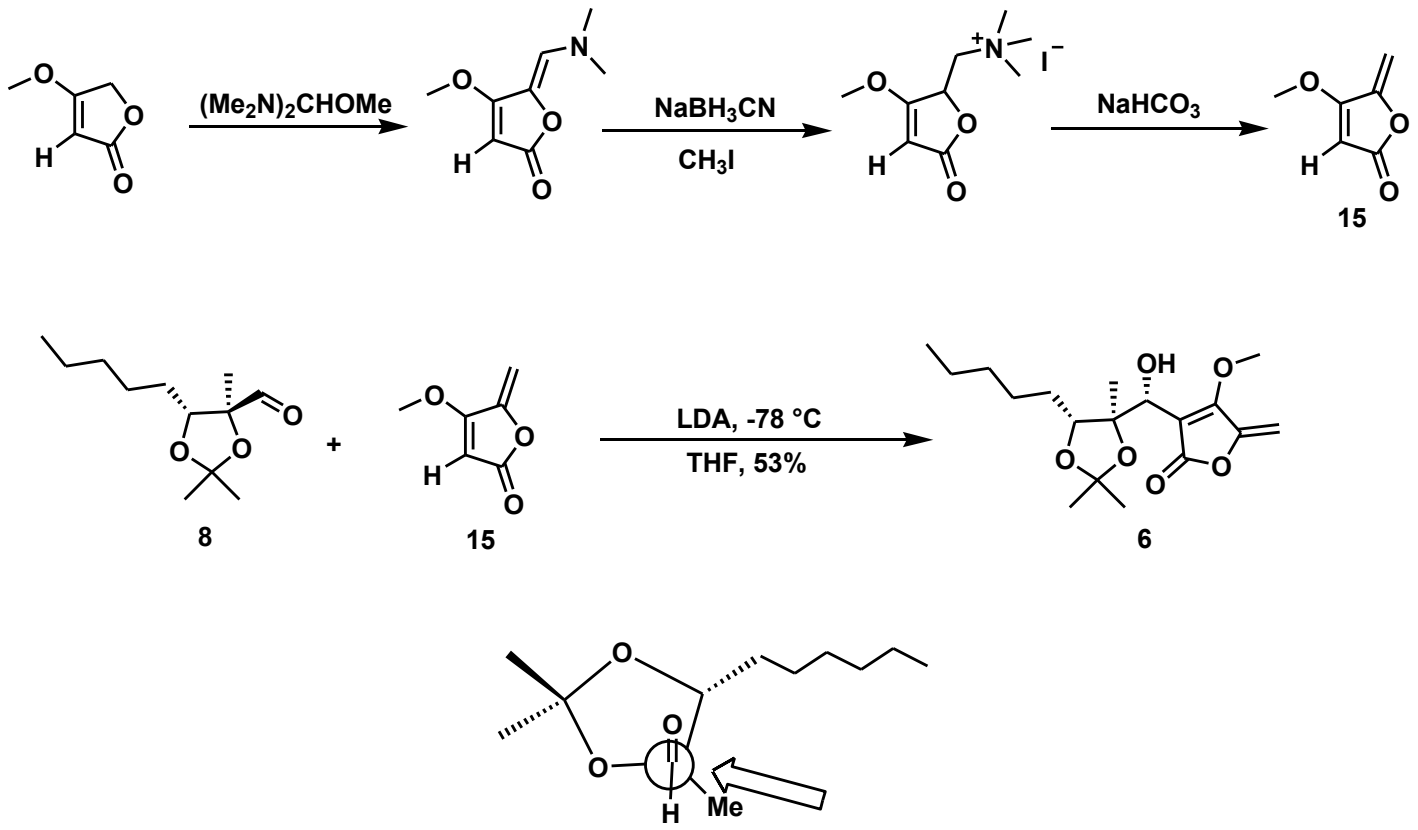


Synthesis of Aldehyde 8



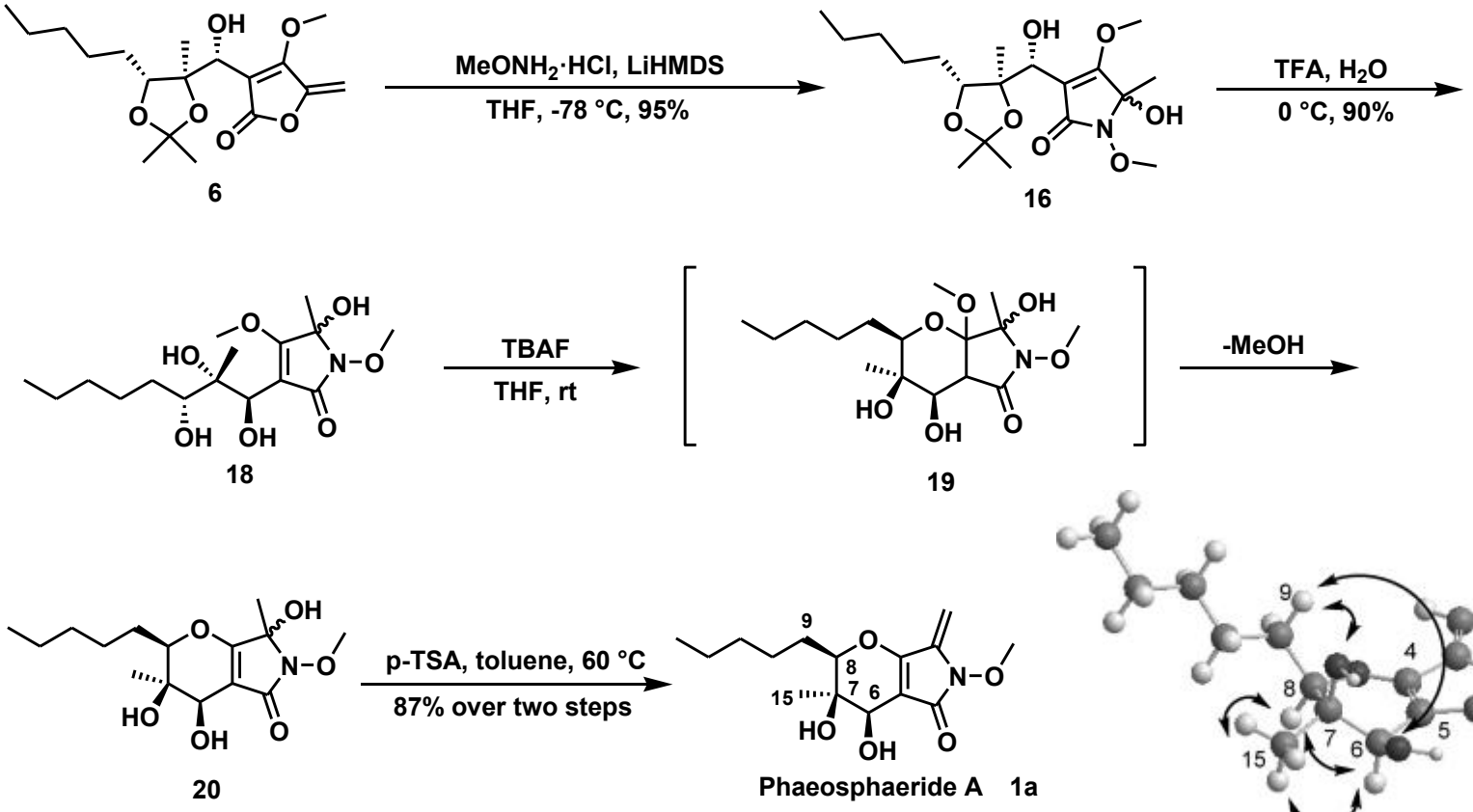
Handa, M.; Roush, W. R. *J. Org. Chem*. 2008, 73, 1031−1035.

Synthesis of Tetronate 6

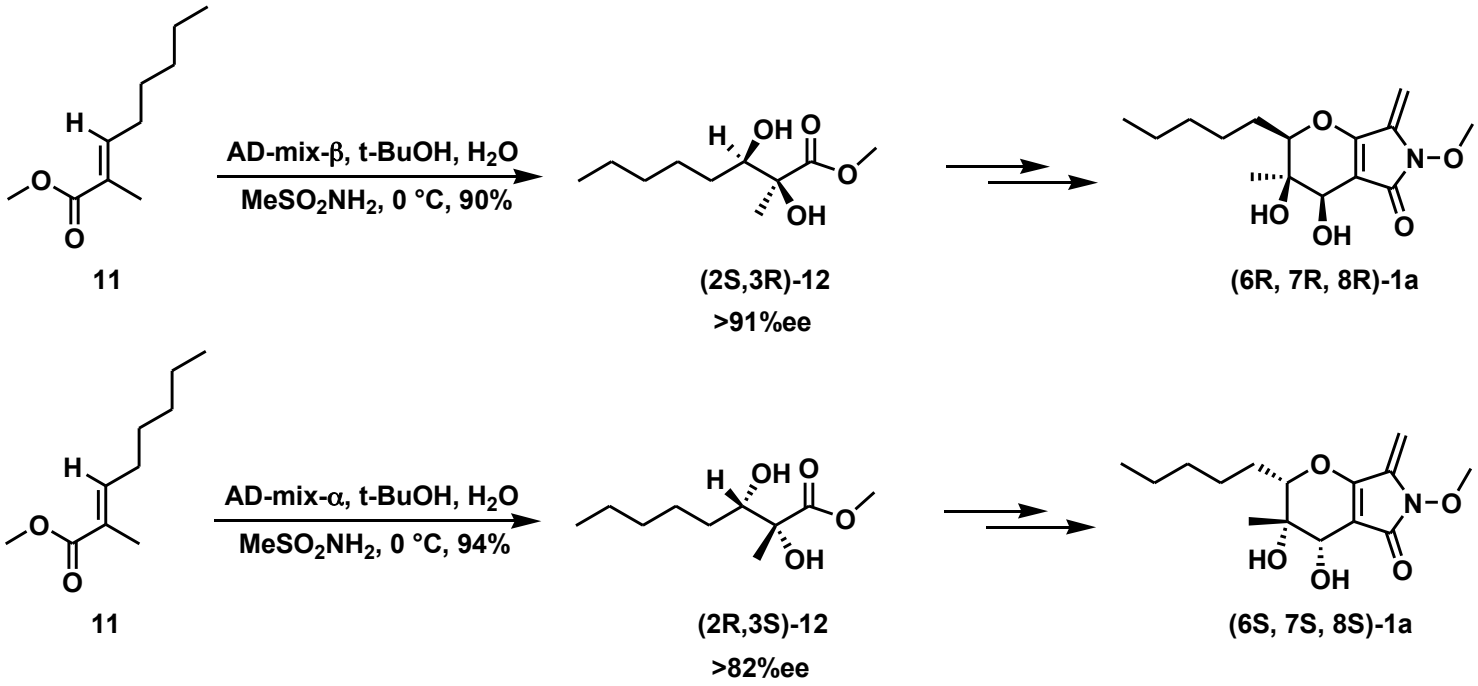


Takeda, K.; Yano, S.; Sato, M.; Yoshii, E. *J. Org. Chem*. 1987, 52, 4135–4137.
Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett*. 1968, 18, 2199–2204.

Completion of the synthesis of 1a

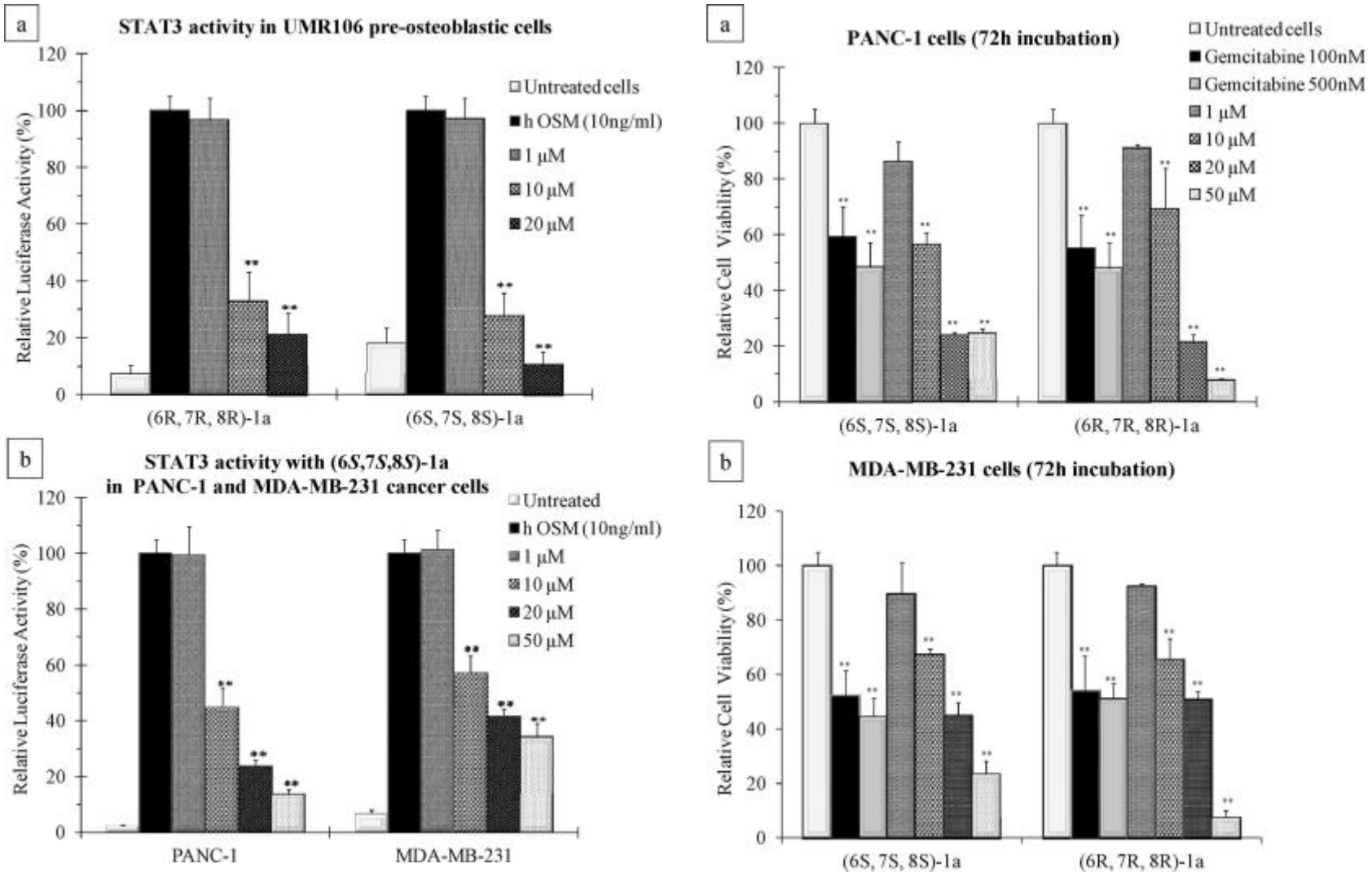


Synthesis of (6R, 7R, 8R)-1a and (6S, 7S, 8S)-1a



Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev*. 1994, 94, 2483–2547.

Biological Evaluation of (6R,7R,8R)-1a and (6S,7S,8S)-1a



Conclusions

- Synthesized the originally proposed structure of phaeosphaeride A **1a** in a highly diastereoselective manner from readily available starting materials.

- NOESY and further crystal structure of (6R, 7R, 8R)-1a confirmed our NMR structural and stereochemical assignments.

- (6R, 7R, 8R)-1a and (6S, 7S, 8S)-1a decrease the growth of pancreatic (PANC-1) and human breast (MDA-MB-231) cancer cells in the low micromolar range.