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A Divergent Synthesis of Spongistatin

Since the dawn of organic chemistry, natural products have long been coveted for their remarkable complexity as well as unmatched bio-activities. Spongistatin is one such natural product possessing activity against human melanoma with a GI50 value of just 25 pM. In addition to medicinal potential, spongistatin is an intriguing synthetic puzzle, containing a multitude of intricate stereocenters as well as two spiroketal subunits that join the A,B and C,D ring systems forming the spiroketal moiety's of the molecule. Spongistatin's two spiroketals exist as two stereoisomers, the axial-axial (A,B) and the axial-equatorial (C,D). The axial-axial spiroketal is favored due to stabilization via the double anomeric effect, whereupon the ring system is stabilized by lengthening of the C-O bond by $n \rightarrow \sigma^*$ donation. However due to poor orbital overlap the axial-equatorial stereoisomer does not benefit from double stabilization. The Cook group has developed a divergent synthesis of highly substituted spiroketals via an ortholactone allylsilane fragment coupling reaction which proceeds through a Sakurai type mechanism. To make this more applicable to spongistatin we aim to develop methodology around less rigid frameworks (scheme 1). We have so far focused on the synthesis of cyclic ortholactones from the C4 unsubstituted dihydropyran, via an oxidative catalytic nucleopalladation reaction. Regretfully the cyclic nature of the molecule provides an increase in stability that prevents the operation of the previously developed spiroketalization conditions (scheme 1). To combat this, recent work has focused on generation of methoxy or ethoxy substituted ortholactones, in order to generate the C4 unsubstituted spiroketals (scheme 2).