Synthesis of QTP Antibiotics and Preparation of BCP Stannanes with application to the Stille Coupling Reaction

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Background Information

This summer the Barbachyn lab worked on two projects simultaneously. The first was the synthesis of novel Quinoline Pyrimidinetrione (QTP) which is a class of promising antibiotics. During his work of Pharmacia he worked on the synthesis of PNU-286607. During his examination of this compound, he found that if a methyl group was on the benzylic position (the position the arrow is pointing to) instead of hydrogen the compound completely lost activity! This led Professor Barbachyn to think that this benzylic position was very sensitive. So, what we attempted to do this summer was to add a variety of substituents to that benzylic position as well as varying R₁, R₂, and R₃.

Our second project was the investigation of the bicyclo[1,1,1]pentyl (BCP) Stannanes and their applications in palladium-catalyzed cross coupling reactions. The BCP subunit is a very fascinating structure because of its unique shape and electronics. It is because of those things that the BCP subunit (the ring system) has been incorporated into drug candidates as an aryl substitution. This substitution gave the drug candidate improved permeability and increased bioavailability. Ideally, this project (in several years) would explore substituting the BCP subunit into possible drug candidates.

Research Methods

QTP: We explored two main routes for the addition of substituents on the benzylic position. The first was an oxidation of an unmodified QTP substituent and the second had an α-hydrozymethyl incorporated into the starting material so after the final cyclization and –OMe or an –OAc would be in the benzylic position. Before attempting the benzylic oxidations we first synthesize the QTP compounds with R₁=NO₂, F or H, R₂= F or H, R₃=F. This synthesis is a two-step process. After obtaining the cyclized QTP compound we attempted to oxidize the benzylic position using a variety of conditions. We also attempted a benzylic bromination using NBS. We also attempted the integration of α-hydroxyacetophenones by chaning the aldehyde (CHO) to a ketone with CH₂OR₄ instead of the H.

BCP: This summer we explored palladium catalyzed cross-coupling reactions with the BCP subunit. Using the Stille reaction we attempted to couple the tin-BCP with several different aryl halides as well as an acid chloride.
We also examined which palladium catalyst (Pd(PPh₃)₄, Pd(PPh₃)₂Cl₂, or Pd(dppf)Cl₂) would give us the best yields.

**Results**

QTP: When we tried to make the QTP from the aldehyde starting material the first step worked well with high yield for most the variation on the benzene rings we tried, but when we had the ketone starting material this first step went poorly and only gave us modest yields. This was as far as the α-hydrozynamethyl incorporations progressed this summer. The second step with the aldehyde as the starting material to form the advanced intermediate prior to the oxidations only gave modest yields often with incomplete conversion of the desired thermodynamic product. Regardless, we pushed two of these compounds (R₁ = NO₂ or H) on to attempt benzylic oxidations. We encountered several problems – including the recovery of starting material, complex mixtures, solubility issues, but we did see evidence of new products that have desirable features. Unfortunately, until we can resolve some of these issues this process is not synthetically useful at the moment. The benzylic bromination looks promising by NMR, but requires MS confirmation and additional work to make to work-up more user friendly.

BCP: Overall the Stille reactions were successful yielding fair results without much optimization. We found that the Pd(PPh₃)₂Cl₂ catalyst consistently gave us the best yields. We hope to perform many more of these Stille reactions with other aryl halogens and acid chlorides. We also hope to synthesize BCP trifluoroborate and silanes for subsequent summers.

**Personal Benefits**

This summer has been such a blessing to me. I have gained valuable experience learning how to run different types of reactions, including air and moister sensitive reactions, learning how to purify samples by liquid chromatography, practicing how to communicate my project to others both in and out of my field, as well as fostering personal qualities that are required for research such as an inquisitive nature, patience, and determination. This summer was also extremely valuable to me because this experience has helped shaped what I would like to do with my biochemistry degree. I learned a lot from Professor Barbachyn about the nature of industry and the pros and cons of working for a big pharmaceutical company. His advice, stories and suggestions has given me a lot to think about in terms of what I want from my job. Overall this summer has taught me soo much about the field I love and about myself.