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Synthesis of Natural Products and Analogues by Directed C-H Activation and Unified Synthesis of Cicutoxin and Virol A *via* Electrocyclic Cyclobutene Ring Opening

Abstract

In general, the work in this thesis is centered on the synthesis of biologically active natural products or structural analogues thereof.

Chapter 1 describes the preparation of several structurally diverse molecules by the utilization of C–H activation methodologies, which are briefly introduced in section 1.1. In section 1.2, the total synthesis of the anti-malarial alkaloid Quinine is presented. The C–H arylation of 3-aminoquinuclidine not only allowed the concise synthesis of the natural product itself but also the preparation of two C-3 arylanalogues.

One of these analogues was shown *in vivo* to have increased antimalarial activity when compared to the natural product itself. In section 1.3, an oxidative approach for the cleavage of the 8-aminoquinoline directing group is presented. Fragmentation of the quinoline moiety by ozonolysis was found to proceed readily, converting the stable amide bond into a labile imide intermediate. The method was found useful for the cleavage of particularly hindered substrates and was further demonstrated in the preparation of aryl-analogues of Dehydroabietic Acid. Section 1.4 describes the functionalization of ring B in the abundant feedstock Oleanolic Acid. By sequential C–H oxidation using a hydroxygroup at C-23 as a natural handle, the C–H oxidation at C-6 in this pentacyclic triterpenoid was achieved. The approach allowed the first synthesis of the polyhydroxylated natural products Uncargenin C and Protobassic Acid.

In chapter 2, the total synthesis of the polyacetylenic toxins Virol A and Cicutoxin is described. Both natural products were previously prepared by extensive use of cross coupling reactions. As described herein, the rapid construction of the common unsaturated motif has been realized by a cuprate addition/4π electrocyclic ring opening reaction. Further modification allowed the preparation of both natural products in a unified manner.