STRATEGIES TOWARDS THE TOTAL SYNTHESIS OF PICROTOXININ

Reported by Shawn Schowe April 8th, 2024.

INTRODUCTION

It can be said that evolution has shaped life's molecules to be incredibly diverse. Natural products (NP)s commonly possesses high three dimensionality, dense functionality, and structural rigidity. Unfortunately, many of today's drugs have gone in the opposite direction by treating highly chiral organisms with flat and racemic drugs, due to the difficulty of chemical synthesis of complex molecules on process scale. Despite these fall backs NP total synthesis has enriched modern knowledge of chemistry and biology.[1]

PICROTOXININ

Belonging to the picrotaxane NP family, picrotoxinin was first to be isolated from the berries of the *Menispermum cocculus* in 1811.[2] In 1951, when technology for structure elucidation was available, Conroy was able to unlock the complex structure of this NP via degradative spectroscopic analysis which was later confirmed via X-ray crystallography.[3] The structure consists of a highly oxidized *cis*-hydrindane core bearing eight contiguous stereo-centers, one quaternary center, and two γ-lactones (Fig. 1). Picrotoxinin has been shown to be the most biologically active of the picrotaxane family. It has strong antagonistic noncompetitive activity against $GABA_A$ receptor which is responsible for binding γ-aminobutyric acid (GABA), this can lead to respiratory irritation, vomiting, convulsions, and death. Given that many drugs (i.e. benzodiazepines, ethanol, barbiturates, etc.) work by binding to this receptor, there is interest in exploring the mechanism of picrotoxinin's potency for pharmacological purposes.[4,5]

SYNTHETIC STRATEGIES TOWARDS PICROTOXININ

Reports for the total synthesis of picrotoxinin span 4 decades and one commonality among each of these syntheses is the similarity in the starting materials, (-)-carvone or carvone like structures are appealing because of their low cost and similarity to the core of picrotoxinin (Fig. 1). Corey and Pearce were the first to report the 17-step total synthesis of picrotoxinin in 1979.[2] They sought to use the chiral feedstock, (-)-carvone to establish the central core of the *cis*-hydrindane, with the most impressive step being the one-pot cyclization of both of both γ-lactones. Later, Yamada and coworkers followed up this synthesis by starting with an achiral cyclohexenone for the initial elaboration of the *cis*-hydrindane core.[6] A key step in this strategy was the novel bridge head oxidation via formation of an enolate followed by oxidation of the α-carbon. In 1989 Yoshikoshi

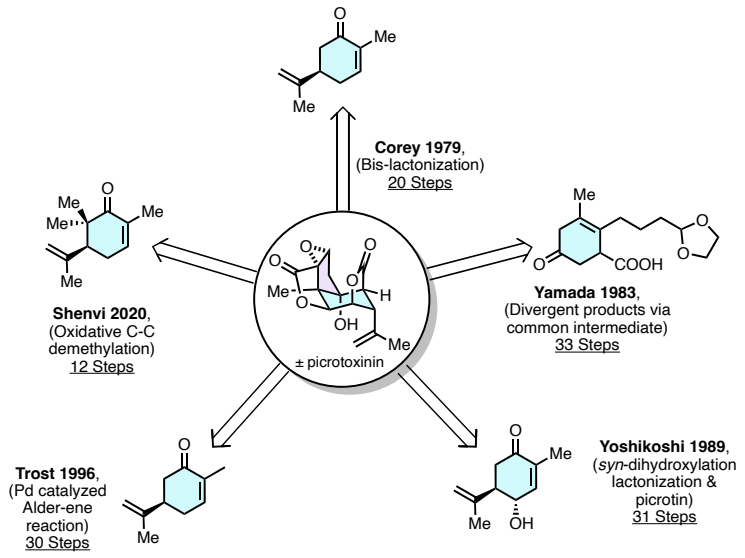

Figure 1. Synthetic strategies toward picrotoxinin. Shown in parentheses are the key steps in the synthesis.

and coworkers put forth an interesting 31 step sequence involving starting from a carvone analog.[7] They wanted to retain an internal cyclic olefin with the hopes of using a *syn*- dihydroxylation to provide a handle for the closure of the lactones. In the coming years, Trost provided an interesting perspective in the synthesis. He proposed utilization of a common intermediate with the ability to access picrotoxinin and NPs in the picrotaxane family. He was able to rapidly access this core via a palladium catalyzed Alder-ene reaction. From this intermediate he was able to obtain two different picrotaxanes. Finally, a modern approach by Shenvi and coworkers has been the most efficient synthesis of this NP thus far.[9] One of the key steps in their synthetic approach was an oxidative C-C demethylation to form the fused lactone. Shenvi invokes that this transformation had not yet been used previously in the context of total synthesis.

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