Introduction

There are lots of things that can kill you in northern Australia. On land, there is the death adder, the tiger snake and the redback spider; in the water, you’d be well advised to give wide berth to the salt water crocodile, the stonefish, the great white shark, and of course, the duck-billed platypus.

The duck-billed platypus?

Consider this: in 1991, a man fishing a river in northern Queensland, Australia happened across a platypus sitting on a log. Thinking it was injured, he picked it up. For his trouble, he spent the next six days in a nearby hospital, suffering from two puncture wounds in his right hand that resulted in "immediate, sustained, and devastating" pain, against which the usual analgesic drugs were almost completely useless. His hand "remained painful, swollen and with little movement for three weeks. Significant functional impairment . . . persisted for three months".

Meanwhile, on the other side of the planet, deep in the rain forests that straddle the border between eastern Peru and Brazil, a young man of the Matses tribe prepares himself to receive the 'hunting magic'. He holds the end of a short wooden stick in a fire for a few minutes, then removes it and presses the red-hot end into the skin of his chest, holding it there for long enough for the skin to be burned. Then he scrapes the burned skin away, and rubs into the wound a paste made from saliva mixed with secretions taken from the skin of a giant leaf frog.

An American journalist named Peter Gorman, who reports having had the frog-skin paste administered in the same manner during a visit to a Matses village, describes what happens next:

"Instantly my body began to heat up. In seconds I was burning from the inside . . . I began to sweat. My blood began to race. My heart pounded. I became acutely aware of every vein and artery in my body and could feel them opening to allow for the fantastic pulse of my blood. My stomach cramped and I vomited violently. I lost control of my bodily functions . . . (and) fell to the ground. Then, unexpectedly, I found myself growling and moving about on all fours. I felt as though animals were passing through me, trying to express themselves through my body."
After the immediate violent effects pass, the Matses hunter is carried by his friends to a hammock to recover. After sleeping for a day, he awakens to find himself with what his people call the 'hunting magic': a state of heightened awareness, possessed of tremendous energy and an abnormally keen sense of vision, hearing and smell. In the words of Mr. Gorman, "everything about me felt larger than life, and my body felt immensely strong... [I was] beginning to feel quite godlike".

There is a connection between the killer platypus in Australia and the 'hunting magic' in the Amazon, and it has to do with the structure and reactivity of what organic chemists refer to as the \(\alpha\)-carbon: the carbon atom positioned adjacent to a carbonyl or imine group in an organic molecule:

![\(\alpha\)-carbon on a ketone and the \(\alpha\)-carbon of an alanine amino acid residue in a protein]

It is this chemistry that we are going to be studying for the next two chapters. But first, let's go back to that river in northern Australia and the fisherman who apparently didn't pay enough attention in his high school wildlife biology class.

The platypus, along with a few species of shrews and moles, is an example of a very rare phenomenon in nature: a venomous mammal. The male platypus possesses a pair of sharp spurs on each of his hind legs near the ankle. These spurs are hollow, and connected by a duct to a venom-producing gland in the thigh. The consensus among scientists who study the platypus is that males use their venomous barbs mainly when fighting each other over territory during mating season. Because healthy animals are often found with multiple scars from spur wounds, a platypus who gets spurred during a fight with a rival will not always die, but the experience is unpleasant enough that he will start looking for real estate a healthy distance down the river.

It is not easy to milk the venom from an angry, thrashing platypus, but there are scientists out there who have done it. It turns out that, like snake and spider venom, the venom from a platypus spur consists of a mixture of neuroactive peptides (peptides are very short proteins - less than 50 amino acids long). Recently, a team of biochemists from the Universities of Sydney, Queensland, and Adelaide reported that they were able to isolate from platypus venom two forms of a 39-amino acid peptide. Further analysis using NMR and mass spectrometry revealed that the two forms of the peptide differed in structure only at a single amino acid: the leucine at the #2 position. In one form, the leucine had the L configuration (or S if using the R/S system), just like the amino acids in virtually all other peptides and proteins found in nature. In the other form, this leucine had the unusual D, or R configuration.

![Peptide with L-Leu at position 2 and peptide with D-Leu at position 2]

Peptides or proteins incorporating D-amino acids are not unheard of in nature, but this was the first time that one had been found in a mammal. Interestingly, the venom from certain marine cone snails and spiders - and, yes, the skin of the giant leaf frog in the Amazon rain forest - also contain neuroactive peptides with D-amino acids.
What is the advantage - to a platypus, cone snail, spider, or frog - of making a venomous peptide with D stereochemistry on one or more of its amino acids? It all has to do with generating diversity of shape and function. These are neuroactive peptides: each one interacts in a very specific way with a specific neural protein, thus exerting a specific neurological effect on the person or animal exposed to the venom. The different spatial arrangement of atoms about the $\alpha$-carbon of D- and L-amino acids will cause a peptide with a D-leucine at position #2, for example, to fold into a different shape than its counterpart with an L-leucine at the same position. Thus, the two peptides may bind differently to one or more proteins in the nervous system, and ultimately may exert different neurological effects - such as intense pain in the case of playpus venom, or the 'hunting magic' effect in the case of the peptide from frog skin. The ability to incorporate D-amino acids greatly expands the potential structural and functional diversity of these short peptides.

The two stereoisomeric platypus venom peptides are encoded by the same gene. The peptides are initially synthesized using all L-amino acids, and then the leucine at position #2 undergoes a 'post-translational modification': in other words, a specific enzyme binds the all-L peptide after it has been synthesized on the ribosome and changes the leucine residue to the D configuration.

It is this reaction - a stereoisomerization reaction that takes place at the a-carbon of an amino acid - that brings us to the central topic of this chapter and the next: chemistry at the $\alpha$-carbon. The key concept to recall from what we have learned about acidity and basicity in organic chemistry, and to keep in mind throughout this discussion, is that $\alpha$-protons (in other words, protons on a-carbons) are weakly acidic. Loss of an $\alpha$-proton forms an enolate - a species in which a negative formal charge is delocalized between a carbon and an oxygen. The 'enolate' term will be very important in the next two chapters, because most of the reactions we see will go through an enolate intermediate.

\[ \text{an enolate} \]

In this chapter, we will first see several examples of isomerization reactions, in which an enzyme acts at the $\alpha$-carbon of a substrate to catalyze the interconversion of two constitutional isomers or stereoisomers. Then, we will be introduced to a reaction type known as the 'aldol addition' and its reverse counterpart, the 'retro-aldol' cleavage reaction. Up to now, we have seen plenty of reactions where bonds were formed and broken between carbon and oxygen, nitrogen, or sulfur. Here, for the first time, we will see how enzymes can catalyze the formation or cleavage - again, at the a position - of carbon-carbon bonds: in other words, we will learn how an $\alpha$-carbon can be either a nucleophile or a leaving group in an enzymatic reaction. This has clear importance for an understanding of metabolism in living things: the molecules of life, after all, are built upon a framework of carbon-carbon bonds, and metabolism is the process by which living cells build up and break down complex biomolecules.

It all starts with the $\alpha$-carbon - and as both the Australian fisherman and the Amazonian hunter could attest,
what happens at the $\alpha$-carbon can have some rather dramatic consequences.