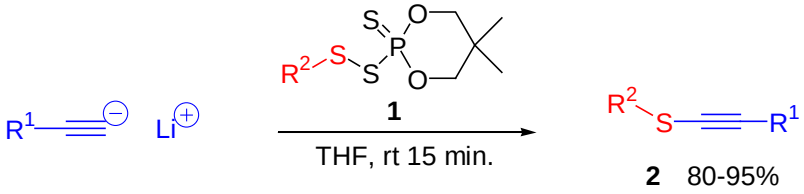
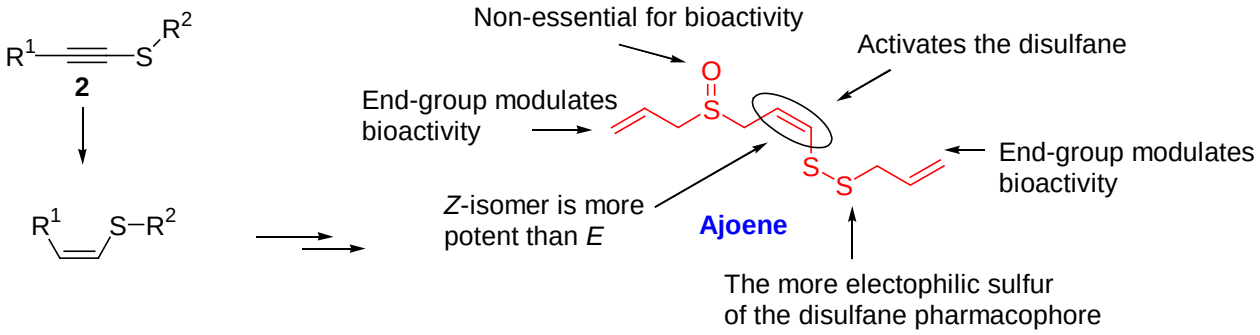
„If it does not work – it is Physics. If it is green and wiggles – it is Biology. If it goes bang and stinks it is Chemistry!" Indeed, there are several organosulfur compounds with terrible reek. The odor of skunk, onion and garlic are the most famous examples. However, properties of organosulfur compounds are much more versatile. There are many of the sweetest compounds (e.g., saccharin) where sulfur is included in the structure. Two of the 20 common amino acids are organosulfur compounds (cysteine and cystine). The antibiotics (e.g. penicillin) and sulfa drugs (sulfonamides) both contain sulfur. While sulfur-containing antibiotics saved many lives, sulfur mustard was a deadly chemical warfare agent. Nature abounds with organosulfur compounds and it means that sulfur is essential for life. A two thiol groups (–SH) of L-cysteine can be oxidized to corresponding disulfane (disulfide) –S–S– and reduction of disulfane to thiols is also possible. This simple reversible transformation is responsible for stabilization of protein structure and allows to keep optimal red/ox equilibrium inside the cell. The properties of disulfanes R–S–S–R can be modulated by the nature of R groups. When unsaturated carbon is attached at least at one sulfur atom, then compound is activated for thiol-disulfane exchange reaction, what improves biological activity (see the structure of Ajoene below). The presence of unsaturated carbon at disulfane functional group is likely to account for its range of biological activities via acting as a sulfenylating agent towards protein thiol (SH) groups.

We have previously demonstrated the preparation of functionalized unsymmetrical molecules, such as dialkyl disulfanes, alkyl aryl disulfanes, diaryl disulfanes, 'bioresistant' disulfanes, and unsymmetrical disulfanes of L-cysteine and L-cystine derivatives based on the phosphorodithioic acid derivatives **1**. The excellent results encouraged us to develop strategy to the preparation of unsymmetrical alkynyl sulfanes **2**.



Among the different classes of alkynes, those directly substituted by a sulfur atom are especially interesting for two reasons: (1) the electron-rich sulfur atom makes the triple bond more reactive, allowing new chemical transformations and (2) they constitute value-added building blocks, as heteroatoms are essential for the physical and biological properties of small molecules. In short, they bring together the new properties conferred by sulfur atoms with the exceptionally rich chemistry of alkynes. Nevertheless, the synthetic potential of sulfur-substituted alkynes has long remained underdeveloped due to the absence of convenient methods to access these often sensitive compounds. The coupling of sulfur with acetylides is indeed not favorable, as both fragments are inherently nucleophilic and an Umpolung (as derivatives **1**) of the reactivity is required.



The aim of the project is focused on the development of alkynyl sulfanes synthesis and their application for the first total synthesis of Ajoene. The successful results will open the studies of anti-thrombotic, antimicrobial, anti-obesity, antifungal, and anti-cancer activities of Ajoene and its derivatives.