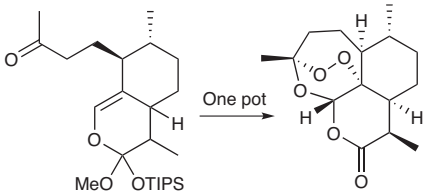
SYNTHESIS

When less yields more

J. Am. Chem. Soc. **134**, 13577–13579 (2012)

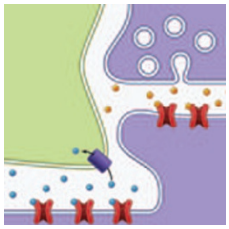


Artemisinin is a critical compound in the treatment of malaria. At the moment, commercial availability of this molecule relies on extraction from natural sources, but the high cost of its isolation limits global usage. Several synthetic routes to access this compound have been reported, and engineered microbes are able to make the artemisinin precursor artemisinic acid, but Zhu and Cook wondered whether a fully synthetic approach using inexpensive precursors might provide a scalable route to the terpene-based natural product. To investigate, the authors devised a five-pot strategy beginning with cyclohexenone that avoids protecting groups and uses cascade or one-pot reactions to quickly build molecular complexity. Clever application of a [4+2] reaction to form the second ring allowed the authors to focus on controlling the reaction pathway but not fret over the stereochemical outcome, as the relevant stereocenters were set in subsequent steps. The introduction of crotyl bromide set the stage for the final step (shown) in which both the seven-membered ring and the peroxide bridge would be formed; testing of a variety of oxidative rearrangement strategies identified singlet oxygen (formed via decomposition of H_2O_2) as the necessary reagent. This sequence, conducted at the gram scale, provides new ideas for managing malaria. *CG*

RECEPTORS

Location is everything

Cell **150**, 633–646 (2012)



CELL PRESS

NMDARs are glutamate receptors involved in various neuronal processes such as learning and memory and are implicated in neurological and psychiatric diseases such as neurodegeneration and schizophrenia. NMDARs are located at both synaptic and extrasynaptic regions of neurons in neuronal cell membranes, and this segregation is thought to mediate the different processes in which NMDARs are implicated, with synaptic receptors involved in synaptic plasticity (related to learning and memory) and extrasynaptic receptors contributing to neuronal synchronization and neurodegenerative processes. NMDAR activation requires a coagonist, several of which have been identified, yet the nature of coagonist control over NMDAR-mediated functions is unclear. To understand the relative contributions of two coagonists, glycine and D-serine, and to identify the yet-unknown coagonist that gates extrasynaptic NMDARs, Papouin *et al.* examined the electrophysiological behavior of hippocampal slices. Using enzymes to selectively degrade either glycine or D-serine, the authors confirmed that synaptic NMDARs use D-serine as a coagonist and identified glycine as the extrasynaptic coagonist. The authors also found differences in the relative amounts of different receptor heterodimer subtypes, whose binding affinities for D-serine and glycine differ, at the two sites. These and further experiments probing synaptic plasticity and excitotoxicity indicate that the location of NMDARs is relevant for their specific involvement in these processes. *MB*

LIPIDS

PI4P takes charge

Science **337**, 727–730 (2012)

Phosphatidylinositol 4-phosphate (PI4P) residing in the membrane of the Golgi apparatus has several ascribed functions, whereas the PI4P found in the plasma membrane (PM) was thought to serve only as a substrate for the kinase PIP5K to generate $PI(4,5)P_2$, which has numerous roles at the PM, including regulation of cell signaling and membrane traffic. To test for a potential PM role of PI4P, Hammond *et al.* enzymatically depleted the PM of either PI4P or $PI(4,5)P_2$. They found that the majority of PM PI4P is not required to maintain steady-state concentrations of $PI(4,5)P_2$ and is dispensable for maintaining the functionally relevant pool of $PI(4,5)P_2$, which must be continuously resynthesized. Instead, the authors found that PI4P contributes to the pool of polyanionic lipids that contribute to the inner PM leaflet's negative charge. In fact, both PI4P and $PI(4,5)P_2$ are required for binding of nonspecific electrostatic PM-binding proteins. Finally, PI4P contributes to and can substitute for $PI(4,5)P_2$ in regulation of TRPV1 channel activation, yet it had no effect on TRPM8 channels, which are specifically dependent on $PI(4,5)P_2$. These results suggest that PI4P fulfills some of the roles of $PI(4,5)P_2$ so that the latter lipid is available to regulate its large repertoire of effectors while the electrostatic properties of the PM are maintained. *MB*

CHAPERONES

Steps to SOD1

Proc. Natl. Acad. Sci. USA **109**, 13555–13560 (2012)

Superoxide dismutase 1 (SOD1), which catalyzes the conversion of superoxide anion to molecular oxygen and hydrogen peroxide, undergoes several maturation events to become an active homodimeric enzyme. Because immature forms of SOD1 have been linked to neurodegenerative disease in humans, Banci *et al.* set out to understand the mechanisms underlying maturation, particularly events involving the copper chaperone for SOD1 (CCS). Using ESI-MS, the authors showed that, *in vitro*, full-length CCS loaded with Cu yields mature dimeric SOD1, bound to both Zn and Cu and with appropriate disulfide bonds from the monomeric Zn-loaded form of SOD1. All of the CCS domains are required for complete maturation, with domain 1 (D1) required for Cu transfer, D2 required for the SOD1-CCS interaction and D3 required for disulfide bond formation. CCS showed reduced ability to transfer Cu to disulfide-oxidized SOD1, indicating that maturation is a stepwise process in which Cu loading precedes disulfide bond formation. NMR of wild-type CCS and CCS bearing mutations in the Cys-X-Cys motif of the D3 domain showed that in mutants with singly or doubly mutated cysteine residues, copper transfer occurred but disulfide formation did not, consistent with the process suggested by ESI-MS. Taken together, these data support a stepwise model of SOD1 maturation, involving Zn acquisition, CCS-SOD1 heterodimer formation, Cu transfer from CCS to SOD1, disulfide bond transfer from CCS to SOD1 and dimerization of SOD1. *AD*