Production of chemicals and biofuels through microbial fermentation is an economical and sustainable alternative for traditional chemical synthesis. Here we present the construction of a Saccharomyces cerevisiae platform strain for high-level production of very-long-chain fatty acid (VLCFA)-derived chemicals. Through rewiring the native fatty acid elongation system and implementing a heterologous Mycobacteria FAS I system, we establish an increased biosynthesis of VLCFAs in S. cerevisiae. VLCFAs can be selectively modified towards the fatty alcohol docosanol (C22H46O) by expressing a specific fatty acid reductase. Expression of this enzyme is shown to impair cell growth due to consumption of VLCFA-CoAs. We therefore implement a dynamic control strategy for separating cell growth from docosanol production. We successfully establish high-level and selective docosanol production of 83.5 mg l⁻¹ in yeast. This approach will provide a universal strategy towards the production of similar high value chemicals in a more scalable, stable and sustainable manner.

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