The Microscale Laboratory

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Keeping Your Students Awake: Facile Microscale Synthesis of Modafinil, a Modern Anti-Narcoleptic Drug

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Undergraduate organic laboratories are invaluable for teaching essential techniques and concepts to aspiring chemists. Keeping the class alert and awake during laboratory sessions poses a different challenge altogether. A successful approach is to have students generate compounds having "real-world relevance" to inspire them and expedite their learning *(1)*. This article outlines an uncomplicated organic synthesis experiment that showcases a prevalent modern anti-narcoleptic drug *(2)*. Limited practical skills are required yet students profit greatly from the mechanistic, stereochemical, and spectroscopic concepts discussed. Additionally, a central nervous system (CNS) stimulant with significant appeal and societal impact is synthesized. *Laboratory instructors should note that modafinil is listed on Schedule IV of the Controlled Substances Act in the United States (3). As such, any potential adopter of this experiment must verify with appropriate authorities that preparation of modafinil is permitted under local regulations.*

Modafinil, 2-(diphenylmethylsulfinyl)acetamide (Figure 1), is a psychostimulant approved in 1998 by the United States Food and Drug Administration for treatment of narcolepsy *(4)*. Narcolepsy is a debilitating neurological disorder characterized by chronic sleepiness and a marked disorganization of sleep and awake patterns *(5)*. Six people per ten thousand (0.06%) in Western Europe and North America are affected in this manner *(6)*.

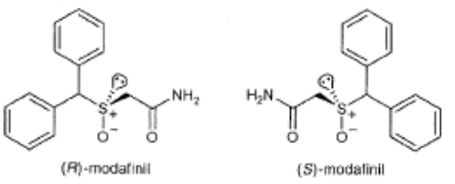


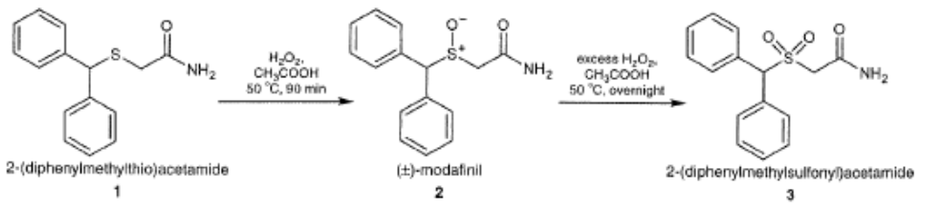
Figure 1. Enantiomers of (±)-modafinil.

Modafinil affords significant advantages over traditional anti-narcoleptic drugs such as amphetamine and methylphenidate as it rarely promotes abusive tendencies *(7)* and exhibits reduced peripheral and central side-effects *(8)*. The compound exerts its biological activity via a mechanism different from other CNS stimulants *(9)* although its precise mode of action is still being vigorously researched.

Modafinil contains a chiral sulfoxide moiety but is prescribed as a racemate and marketed in the United States by Cephalon under the name Provigil *(10)*. The tetrahedral sulfur atom acts as a chirality center (being surrounded by two dissimilar carbon atoms, an oxygen atom and an electron lone pair; Figure 1). Unlike most analogous trisubstituted amines that undergo umbrella-like inversion at the nitrogen atom, sulfoxides are configurationally stable *(11)*.

Racemic modafinil is easily prepared from 2-(diphenylmethylthio)acetamide 1 by peracid oxidation (Scheme I) *(12)*. While almost all undergraduates appreciate that carbon is regularly a chirality center due to its tetravalent nature, fewer recognize that heteroatoms including nitrogen, phosphorus, and sulfur can also act as chirality centers. Moreover very few organic textbooks, articles, or laboratory experiments address the concept of sulfur as a chirality center *(11, 13)*.

In 2003 (±)-modafinil was thrust into mainstream media when United States athlete Kelli White tested positive for the stimulant at the World Track and Field Championships *(14)*. The following year the World Anti-Doping Agency added (±)-modafinil to the list of banned substances based on its ability to increase athletic alertness *(15)*. As many of our students are (ab)users of a common anti-narcoleptic (caffeine), we felt preparation of (±)-modafinil would spark increased laboratory enthusiasm.



Scheme I. Synthesis of (±)-modafinil by sulfide oxidation.