Diastereoselective Synthesis of (±)-Ambrox by Titanium(III)-Catalyzed Radical Tandem Cyclization

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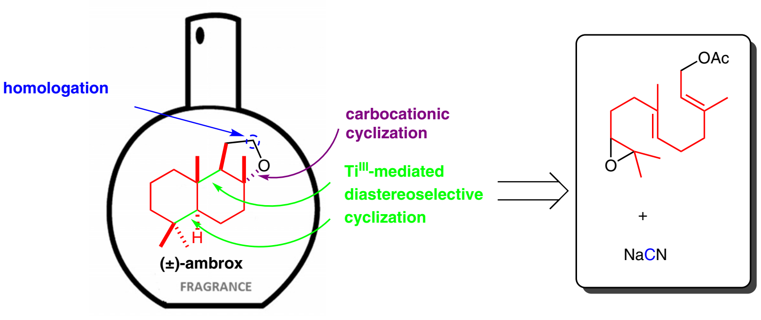
Dedicated to Prof. Emilio Diaz Ojeda



Received: 06.07.2015
Accepted after revision: 23.10.2015

DOI: 10.1055/s-0035-1560594; Art ID: st-2015-b0508-l

Abstract A synthesis of (±)-ambrox, a compound with delicious ambergris-type scent, is presented. The key step is a highly diastereoselective titanocene(III)-catalyzed radical tandem cyclization of a farnesol derivative.

Key words ambrox, natural products, titanocene, radical chemistry, diastereoselective synthesis

Ambrox (**1**) is one of the natural components of ambergris (Figure 1) and, additionally, one of the commercially most important products for providing ambergris-type odor in fine perfumery.[1] Ambergris is a solid, waxy substance produced by photooxidation of ambrein, a substance accumulated in the gut of sperm whales (*Physeter macrocephalus L.*), which has been used in the past as a valuable constituent of fine fragrances due to its exceptional fixative and scent properties.[2] Nevertheless, ambergris itself is no longer used almost anywhere, because natural sources do not meet the increasing demand for perfume ingredients with ambergris-type odor. As a consequence, synthetic ambrox constitutes the most important commercial substitute with the desirable ambergris-type scent. Ambrox (**1**) is considered to be one of the most expensive fragrance ingredients, with a market price well above \$500/kg for the enantiomerically pure product and an annual worldwide production of several tens of tons.[3]

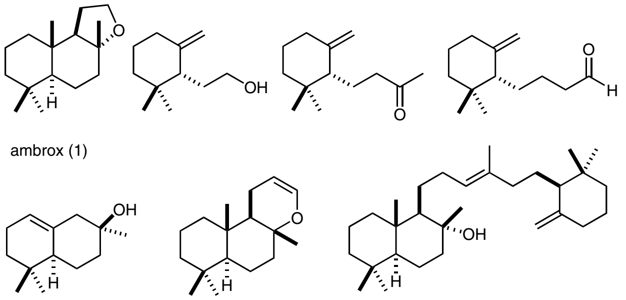


Figure 1 Naturally occurring terpene derivatives isolated from ambergris

Since the first synthesis of this compound was described more than sixty years ago,[4] a considerable number of different synthetic procedures have been reported. These procedures include both semisynthetic methods via oxidative degradation of naturally occurring products, such as sclareol, manool, ambrein, and communic acids,[5] and biomimetic cyclizations of precursors, such as homofarnesic acid, (*E*)-β-farnesene, homofarnesol, farnesylacetic acid and analogues.[6] Nevertheless, many of these procedures are expensive and laborious and/or provide yields that are nor-