

From Ambergris to Cetalox Laevo^a

Tradition, innovation and creation

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Who would have imagined just a few decades ago that perfumers today would have at their disposal an amber product of entirely synthetic origin with a purity that corresponds to more than 99 percent of (-) Ambrox [5]? This achievement has a long and captivating history of scientific discoveries and creative ingenuities, all linked to the enchanting perfume of amber.

Tradition

The manner in which ambergris is formed by the sperm whale^b and then subsequently discovered on far away beaches, transported by ocean currents, contributes much to the mystery and magic of this perfumery substance. This legendary ingredient of the perfumer's palette comes from a pathological animal reaction, which cannot be produced by breeding or cultivation. The prolonged stay in the sea and the combined action of oxygen and solar radiation contribute to ambergris' unique odor. Its complex and subtle character shows facets of amber, incense, exotic wood, earth, camphoraceous,

tobacco, musk, and the smell of the ocean. In most cases, the amber note is immediately appealing to the untrained nose and its scent, despite being very characteristic, is difficult to describe; warm, animal, exciting and mysterious.

Long before it played a key part in perfumery, ambergris was valued for other properties. In the times of *The Thousand and One Nights*, its curative effects on heartaches were widely recognized; it was also burnt like incense for enjoyment of its pleasant scent. Moreover, some East-Asian dishes were spiced with it, whereas the Chinese believed it to be one of the most effective aphrodisiacs.

The first traces of ambergris' use in perfumery go back to the 9th Century BC. Arabs recognized its fixative effects on the evaporation of other oils. In the 14th Century AD, ambergris became one of the most valued perfumery ingredients, along with civet and musk. It was used as a tincture that needed to mature over many months, sometimes even years, before revealing its full fragrance. The most appreciated tinctures were made up of the gray and most valuable part of the ambergris, which has consequently given its name to the precious substance. The white part has no odor; the black part is not highly valued, whereas the brown part is used in some perfumery products.

Innovation

In the 1930s, Firmenich initiated a vast research program on the composition of ambergris. The study of its main component, a triterpene called ambreine [3], complemented research performed by L. Ruzicka, a long-term collaborator based in Zurich. Max Stoll and his Geneva-based team also counted among the pioneers in this research. E. Lederer's

^aCetalox, Grisambrol, Ambrinol, Fixateur 404 and Ambrox DL are registered trade names of Firmenich. In this article, the authors use the following nomenclature: Ambrox, which indicates the product Firmenich commercialized under this name (composed of 90 percent (-) Ambrox); (-) Ambrox, which indicates the enantiomer L, or Laevo, of the molecule called CAS Naphto (2,1-b) furan, dodecahydro — 3a, 6, 6, 9a — tetramethyl, and which presents an optical activity; (+) Ambrox, which indicates the enantiomer D, or Dextro, of the molecule called CAS Naphto (2,1-b) furan, dodecahydro — 3a, 6, 6, 9a — tetramethyl, and which presents an optical activity; (±) Ambrox, which indicates a mixture of equal parts of (-) Ambrox and (+) Ambrox (no optical activity); and racemic, which qualifies the (±) Ambrox.

^bAmbergris, a waxy substance, is produced by the digestive tracts of the sperm whale, perhaps to protect it from the sharp beaks of a major dietary staple — the giant squid.

group joined the team in 1947,⁶ after the results on the structural form of ambreine were presented. Though ambreine counts for just 25-45 percent of the non-volatile components of ambergris, and is odorless, it was regarded as the probable main source of the volatile components of ambergris.^{1,2} These volatiles originating from chemical degradation processes contain some of the key elements of its fragrance.

At the end of the 1940s, Stoll turned away from the research on the original animal substance and initiated research on amber products derived from sclareol [1], which is found in clary sage (*Salvia sclarea*). This alcohol was known to have a light amber odor. Stoll and his collaborators undertook a systematic sclareol degradation to obtain all oxidation products with an odor. Among these products, an unsaturated alcohol and an oxide were selected. The oxide indeed had an amber odor and could be prepared fairly easily. This observation encouraged the researchers to continue their investigations. The

⁶As Lederer's work was almost at the same stage of development as Ruzicka's, the idea of collaboration became obvious.

discovery of Ambrox was just around the corner. Sclareolide [2], derived from sclareol, was the chosen raw material. In fact, this lactone could also be obtained through ambreine oxidation: both molecules already shared a similar bicyclic structure (P-1), as described by Lederer.⁴ The link was taking shape. Stoll suggested a synthesis by the reduction of sclareolide with LiAlH_4 , followed by an acid cyclization of the resulting diol [4] (P-2) to obtain the oxide [5] named Ambrox.⁵ These findings marked a turning point in the commercial production of tricyclic amber products of vegetal origin. The Ambrox molecule, however, was only isolated from the volatile part of the ambergris tincture some 30 years later, thus confirming its natural origin as one of the key odorous components of this precious substance.⁶

Until the 1950s, the so-called amber notes were usually specialties based on labdanum, either in a processed form to give a perfume base or in a blend with vanilla and/or other balsamic notes. Amber 205 (1923) and Ambrarome Synarome (1926) were specialties used in fine perfumery in addition to ambergris, which contributed to the success of many classic perfumes.

Shortly after Stoll's discovery, Firmenich launched two specialties: Fixateur 404 (1952), based on approximately 10 percent of Ambrox, and Gris ambrol (1954), which included both Ambrox and α -ambrolin. This ambergris component gave its name to a third

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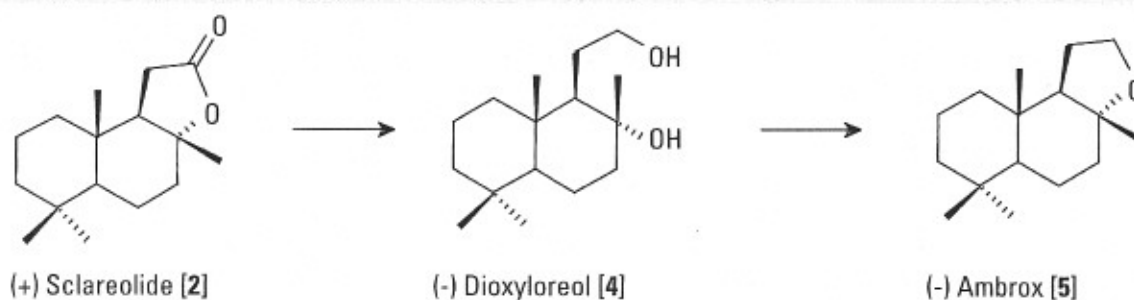
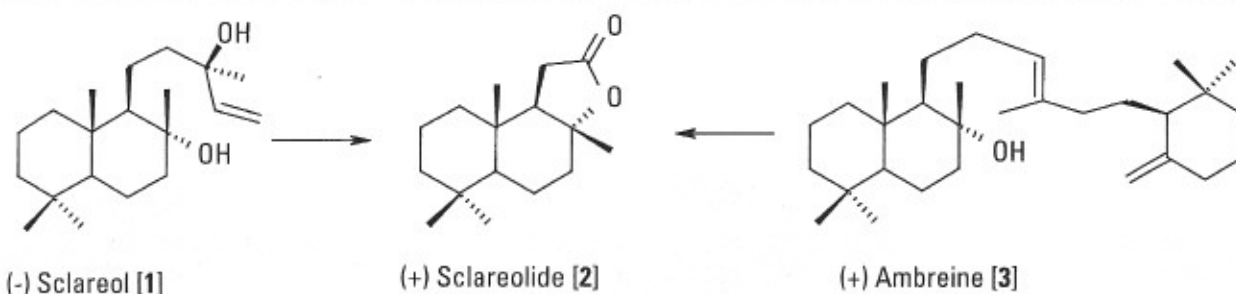
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product created in 1954 — Ambrinol — a mixture of α -, β - and γ -isomers. These products were considered to be important alternatives to the original animal substance, which was rare and expensive. Fixateur 404 particularly influenced perfumery of the 1950s and the 1960s, as it became a dominant amber note in fine perfumery, together with Kephalis (Roure, 1965). Fixateur 404 was used in very small quantities because of its power and distinctive character. However, in the mid 1970s, some perfumers realized that the use of Ambrox was not necessarily solely restricted to fine perfumery, and that it showed excellent performance in shampoos, soaps and detergents. Its smell, diffusion, stability, substantivity and tenacity made it an ingredient with outstanding "SHAPE."^{d,7,8}

Ambrox was not commercialized as such until the end of the 1970s, concurrent with the emergence of the first competitive material Ambroxan (Henkel). The manufacturing of such a product by a soap and detergent company confirmed the importance of its use in functional perfumery. The emergence of Ambrox-type products in turn induced an increased demand in sclareolide from clary sage. At that time, there was only one producer worldwide and so, as clary sage is sensitive to climatic conditions, as with

^dSHAPE is the perfumer's assessment of the odor, cost, technical performance and effectiveness in creation of a perfumery raw material.

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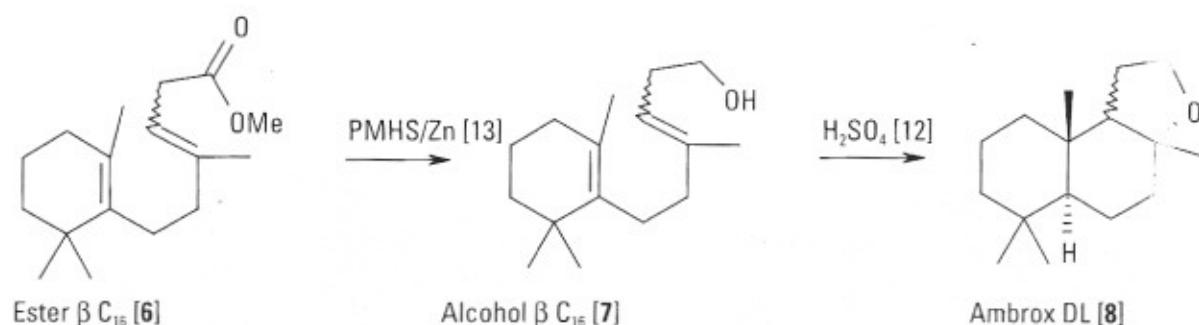
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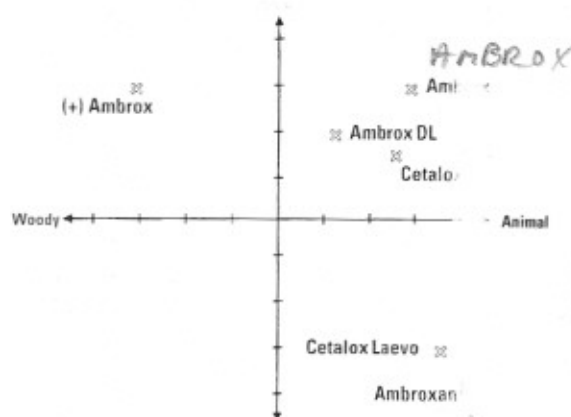
all plants, supplies of sclareolide could not be guaranteed. These combined factors led to a severe shortage in 1988. The experience of fluctuating natural raw material supplies confirmed the need for the development of an entirely synthetic production processes.

In 1955, eager to take part in the amber adventure, George Büchi joined the teams of Ruzicka, Stoll and Lederer and in the early 1980s he proposed a first synthesis of (\pm) Ambrox from β -ionone.⁹ This racemic product was different from the 90 percent of (-) Ambrox product derived from clary sage. Other research groups started to be active in the same field, and at this time experiments were carried out with β -ionone, suggesting syntheses based specifically on the cyclization of homofarnesic acid.^{10,11} The reproduction of the amber odor from petrochemical derivatives had started, announcing the arrival of an alternative to the animal and vegetal derived substances.

The knowledge and know-how accumulated over many years of investigation eventually enabled an economically viable production of (\pm) Ambrox by the cyclization of β C₁₆ alcohol [7] into Ambrox DL [8] (F-3).¹² This new material containing more than 50 percent of (\pm) Ambrox was launched in 1988 not as a substitute to Ambrox but as an alternative amber ingredient.

Subsequent years were devoted to the improvement of the Ambrox DL synthesis to obtain a purer racemic quality and eventually the optically active product. In 1993, after 10 years of investigations of the synthetic production of the Ambrox molecule, with the involvement of numerous research, development and production teams, the first objective was finally reached, with the launch of Cetalox. The

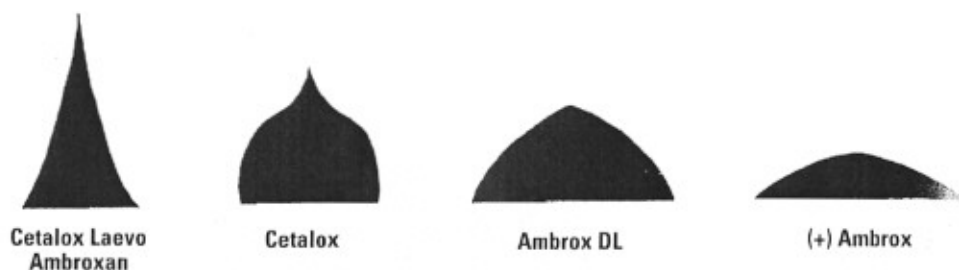
Olfactive chart of Cetalox Laevo, Cetalox, Ambrox DL, Ambrox, Ambroxan products and (+) Ambrox isomer



synthesis of this racemic product of more than 96 percent purity was a milestone in both organic chemistry and process technology. The long process, which required meticulous development and optimization of the reaction conditions, benefited greatly from catalytic chemistry in order to achieve the desired quality. The next step? To move on and reach an optically pure quality of an entirely synthetic Cetalox — and so today, with Cetalox Laevo, the range has been extended.

Creation

Perfumery interest in the amber materials containing more than 99 percent of (-) Ambrox derived from clary sage led to the marketing of Ambrofix (Givaudan) and Sclaxoxan (Charabot), in addition to Ambroxan (now KAO), to mention a few. How is it that materials having the same chemical structure can have different odor nuances? The choice of production ingredients like solvents can slightly modify the odor of amber products. Perhaps the conditioning of the product — whether a



Summary of the isomeric composition of Cetalox Laevo, Cetalox, Ambrox DL, Ambrox and Ambroxan-type products

T-1

	Composition	Origin
Cetalox Laevo	> 99 percent (-) Ambrox	Synthetic
Cetalox	> 96 percent (\pm) Ambrox	Synthetic
Ambrox DL	> 50 percent (\pm) Ambrox and < 50 percent diastereoisomers	Synthetic
Ambrox	~ 90 percent (-) Ambrox	Natural
Ambroxan-type products	> = 99 percent (-) Ambrox	Natural

crystals or as pellets — can also make a difference.

In regards to the composition of the various materials, the (\pm) Ambrox isomer ratio is particularly important for the odor: (-) Ambrox is described as more ambery and as much as two to three times more powerful than (+) Ambrox, which is considered more woody.¹⁴ However, although this variation exists in the odor, it should not be forgotten that according to one's genetic inheritance, people smell one or the other enantiomers differently.

Ambrox, the historical reference, contains approximately 90 percent (-) Ambrox and various ambrols. The latter brings elegance and olibanum nuance to this fine amber, round, powerful and diffusive note. Ambroxan is probably one of the most powerful amber notes. It is very diffusive, dry and animal, with an earthy patchouli and dusty character. Cetalox Laevo is a powerful animal amber note; similar to Ambroxan, it is diffusive, somewhat dusty, with a vetiver orris effect. Cetalox covers a broader olfactive spectrum than the products mentioned above. It's an amber, woody note; warm, full and rich with animal, patchouli and aromatic characters. Although at first it seems less diffusive than Ambrox or Ambroxan, Cetalox develops into a comparatively fuller and more complex note after a few hours.

With at least 50 percent of racemic Ambrox and other diastereoisomers, Ambrox DL is probably the most distinctly dissociated product in this group. The woody character is more pronounced thanks in particular to the presence of a diastereoisomer described as woody; cedarwood. Its warm rich note is woody, cedar, vetiver, complex with a hint of labdanum. T-1, F-4 and F-5 summarize these characteristics and olfactive evaluations.⁶

When studying the characteristics of these various materials, one notes that Cetalox Laevo and Ambroxan are very effective in small quantities thanks to their power and diffusion. However, beyond a certain proportion, the dry animal character prevails, destroys the harmony of the composition, and can give an aggressive, dirty effect. Cetalox, on the other hand, can be used in considerably larger quantities, and although the amber note is clearly effective, the elegance and harmony of the perfume are preserved. The series of accords in T-2 clearly illustrate this phenomenon. In **A**, the amber note harmonizes with the powder notes of the accord, whereas in **B**, the accord is unbalanced by the too-high concentration of Ambroxan. In **C** and **D**, Cetalox lifts the full bodied and powdery character, despite the high concentration, giving the accord an elegant softness characterized by a rich amber note. Being able to use Cetalox in greater quantities increases the substantivity of the creations while preserving their original olfactive directions — an important asset for products applied to the skin, hair and clothes.

⁶The olfactive evaluations of the products as described here, including their various isomers, are based on internal perfumery assessments.

	A	B	C	D
Coumarin 20 percent DIPG	1.0	1.0	1.0	1.0
Raspberry ketone 10 percent DIPG	1.0	1.0	1.0	1.0
Habanolide 50 percent DIPG	1.0	1.0	1.0	1.0
Ambroxan 5 percent DIPG	0.2	0.5	-	-
Cetalox 5 percent DIPG	-	-	2.0	3.0

The outcome of the Ambrox story is certainly not a mystery; the synthetic reproduction of a natural odor is a direction that is well entrenched in the fragrance industry. The goal, of course, is to equal, or even qualitatively improve upon, nature without depending on it, thus allowing mankind to offer essential perfumery products with an ever-improved cost/performance ratio.

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