doi:10.2533/chimia.2021.1082 Chimia 75 (2021) 1082–1084

A Perspective on Chemistry and Society

A Column on the Occasion of the 75th Anniversary of CHIMIA

Givaudan

Fragrance Molecules Need Chemical Biology

Agnes Bombrun* and Jeremy Compton*

*Correspondence: Dr. A. Bombrun, E-mail: agnes.bombrun@givaudan.com
Fragrances S&T, Givaudan Schweiz AG, Kemptpark 50, CH-8310 Kemptthal, Switzerland

Since 2014, ***Dr. Agnes Bombrun*** has been in charge of the Ingredients Research in the Fragrance & Beauty division of Givaudan, based in Kemptthal, Switzerland. Her main responsibilities are to drive dynamically a rich and competitive pipeline of sustainable innovation for the perfumers, which consists of delivering the best fragrance molecules and processes by green chemistry and biotechnology. Agnes started out her career in the pharmaceutical industry. By training she is a chemical engineer (Lyon, France) and an organic chemist with a PhD (Emory University, Atlanta). Agnes was Director of Medicinal Chemistry for Merck Serono and also worked for GSK and Affymax.

With over 30 years' experience in the Fragrance and Flavours industry, ***Jeremy Compton*** has had a diverse global career with significant management positions in commercial, development and research functions across the businesses. Passionate about the positive impact fragrance can have on consumer's lives and how research into new materials, formulations, methods and forms of delivery can make this true. In addition to the UK he has lived and worked in Brazil, Indonesia, France, the United States and Singapore and is now based in Kemptthal, Switzerland where he has been running Fragrance Science and Technology since 2016.

Controversial Origin and Use of Fragrance Molecules

In the fragrance industry, perfumers use a plethora of odorant molecules to create perfumes. Historically the first family of odorant molecules was the Naturals. Extraction and distillation of raw materials coming from plants (flowers, roots, leaves, …) or animals (deer, civet cat, beaver …) gave access to the first used odorant molecules. At the end of the nineteenth century and at the beginning of the twentieth century, perfumers were given the opportunity of multiplying their options by adding synthetic molecules to their creations. A first example is the industrial synthesis of coumarin, which was developed in 1868. Coumarin is present in tonka beans and found up to 50% in Fougère Royale (1884). Another famous illustration is probably Chanel 5 (1921) with the first use of synthetic aldehydes. Since 1980s calone has been used for new olfactive marine notes (New West 1988, Eau D'Issey 1992), and ethyl maltol in the gourmand family (Angel 1992).

Such synthetic molecules, which became available, could be used directly or turned into a more valuable molecule using simple and efficient chemical transformations, inspired by Nature. Interestingly these synthetic molecules were not made for perfumery in the first instance but at the end of the nineteenth century, the exploitation of petroleum gave a unique opportunity to provide feedstocks for liquid fuels, solvents, waxes and the production of many common materials of the modern world. Many synthetic molecules, feedstocks, intermediates or commodities became available on the market for multiple usage, up to an amazing dependence as of today. Approximatively 92%[1] of organic chemical products are produced from petroleum, that is fossil, or mineral oil, and gas. In addition, these same resources are generally used to provide the large quantities of process heat and power needed by the industry. And therefore, reducing greenhouse gas (GHG) emissions and finding alternative renewable sources of feedstocks have been clear targets in the fragrances houses like in many other industry sectors.

Ambition

The industry of perfumery may not be the most impactful but taking into account the urgency and the complexity of the challenge, at Givaudan, in 2019 we launched the FiveCarbon Path™, a new ambition that will drive Givaudan's fragrance molecule developments while delivering on our environmental commitments (Fig. 1). For scientists, the ambition formalises the use of the latest and emerging scientific disciplines to meet the future demands of our industry and consumers' expectations around the world. Odorant molecules may contain heteroatoms but the most predominant atom is Carbon. Consequently, the vital role that carbon atoms play in our industry is at the centre of our FiveCarbon Path™ ambition. Every fragrance that perfumers create is a complex mixture of ingredients, including naturals, which are all based on carbon elements, often as the core backbone. Our new vision concretely implements our approach to innovating responsibly, which considers the potential impact of our processes and products on the environment, by designing ingredients following our unique FiveCarbon Path™. It focuses on:

1. Increasing the use of renewable Carbon,
2. Increasing Carbon efficiency in synthesis,
3. Maximizing biodegradable Carbon,
4. Increasing the 'odour per Carbon ratio' with high impact material and
5. Using upcycled Carbon from side streams.

Such an approach allows us to focus on the different aspects of the challenge and importantly, gives opportunities to deliver various solutions immediately and consolidate the future with innovation. The 12 green chemistry principles are also used and now embrace the whole life cycle of a molecule in perfumery, from the feedstock to its final use or re-use in Fragrances.

There is a necessity to substitute fossil carbon with renewable alternatives – and the three main sources are: biomass, CO_2, and recycling. The 'Renewable Carbon Initiative' (RCI) initiated by the nova-Institute is supporting the transition from fossil to renewable carbon for all organic chemicals and materials (Fig. 2). Givaudan has recently joined the board of RCI, and one year after inauguration, the initiative has already more than 30 member companies. The industry working on chemicals and derived materials is dependent on carbon and with the increasing population the need for many daily products made out of carbon will increase and decarbonisation is not an option. New

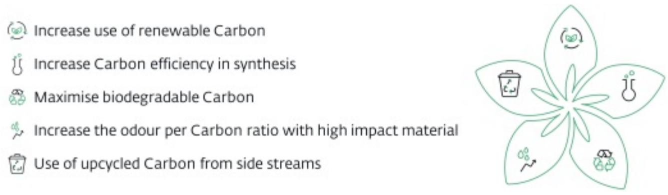

Fig 1. The FiveCarbon Path™.

innovations are on the rise that allow us to tackle the challenge from various angles while having one common goal to reduce the use of virgin petrochemicals and transition to the use of renewable feedstock, to become more circular. Using biomass from wood, CO_2 from fossil power plants and recycled carbon from plastic waste is already a reality and there are many more opportunities. While there are still many hurdles to overcome to achieve a circular carbon management including a supportive policy framework – the journey to become more renewable in perfumery and to play a leading role in this industry is part of our purpose.[2]

Fig. 2. The vision of RCI. It addresses the main cause of anthropogenic climate change by facilitating the transition from fossil C to renewable C for all organic chemicals and materials. Members of the RCI are pioneers who support the urgently needed acceleration and increase of volume of this transformation.

Applications

Being eco minded, the FiveCarbon™ Path is embedded in all research programs. Nevertheless, given that the access and production of iconic molecules, which are biodegradable and powerful, are key assets for the creations of the perfumers, it is of the utmost importance that scientists implement the correct changes to increase the chance of success. Such ambitions are molecule- and process-dependent. Chemistry and biotechnology (fermentation and biocatalysis) have never been so fusional. This can be illustrated by a first example of one of the most used ambery molecules, Ambrofix™ (Fig. 3). Traditionally the feedstock is the diterpene sclareol, currently isolated from clary sage (*Salvia sclarea*), which is then modified and cyclized by classical chemistry steps into Ambrofix™. The availability of a new feedstock farnesene, a diesel and jet fuel precursor produced through fermentation opened new pathways to precursors and derivatives made by green chemistry, for a final biotransformation using a Squalene Hopene Cyclase enzyme. The new biotechnology process of Ambrofix™ is implemented and requires 100 times less land to produce 1 kg of Ambrofix™ compared to the old route based on clary sage. Years of optimization and extensive tests proved that the two processes are giving the same quality with no olfactive impact on the final fragrance. The second example, Ebelia™ (Fig. 4) illustrates the move to a new renewable feedstock, namely furfural, used to make a key intermediate for a fresh fruity cassis note. Ebelia™ can replace cassis molecules traditionally made from intermediates of the petrochemical industry. But the access of such new feedstocks remains limited. The challenge of exploiting biomass, waste gas and recycled feedstock continues to be a challenge.

Furthermore, new molecules combine both higher performance and improved sustainability. This is possible and measured by increasing the ‘odor per Carbon ratio’ with high impact material.

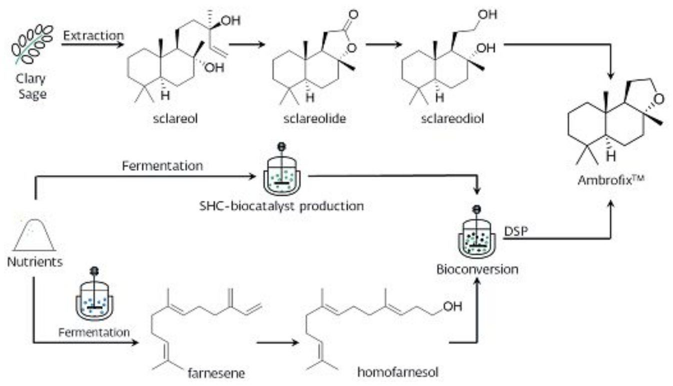

Fig. 3. Synthesis of Ambrofix™. Traditional route ex clary sage and the most recent biotech route to Ambrofix™.

Nympheal™ delivers 13 times more odor per carbon than Lilial. The odor per carbon is measured by a proprietary formula taking into account the number of Carbon of the molecule and the odor threshold, the lowest concentration of a component that can be perceived by the human nose. Ultimately this leads to compacted fragrances, a clear trend in fragrance design and key part of the sustainability journey

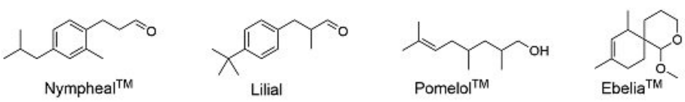

Fig. 4. Chemical structure of fragrance molecules.

Additional Challenges and Solutions

More examples of switching chemistry steps by biotransformations and alternatives feedstocks are coming. The speed and opportunities should increase as many industries as well as the fragrance industry have embarked on this journey for more sustainability. There is a strong need for affordable alternatives. In the beginning of the twenty-first century, establishing new processes based on biomass is shown to face considerable technical and economical obstacles to reaching a scale that can contribute valuable emissions reductions.

At Givaudan, human safety is also part of our purpose. Through our Safe by Design™ initiative, we are leading industry efforts to replace animal testing, while at the same time speeding up the testing process. Scientific innovation centred around early testing of molecules without animals have a wide range of benefits: For consumers by ensuring safety for use on human skin, for customers by bringing products faster to market, and for the environment by creating eco-friendly ingredients. These new approaches are based around an understanding of how biochemical processes can help us to develop and understanding of chemical impact on humans. In 2016 Nympheal™ (Fig. 4) was introduced to replace Lilial, in the white floral olfactive space. Nympheal™ prevents a critical metabolism observed in Lilial.[3] Nympheal™ was launched successfully as a safe replacer.[4] This shows the essential need for a combined approach of chemistry and biochemistry. Recently, a platform for PBT screening without animal testing was established (PeBiToSens™) which is key in the Givaudan Safe by Design™ approach to develop safer and environmentally friendly fragrance ingredients. The determination of persistence (P), bioaccumulation (B) and toxicity (T) plays a central role in the environmental assessment of fragrance chemicals. While P assessment is a standard microbial degradation test, the determination of B (*i.e.* bio concentration in fish) and T (fish acute toxicity) classically involves vertebrate testing. At Givaudan we use the OECD standardised *in vitro* assays based on fish liver cells[5] or liver S9 fractions[6] to determine biotransformation rates. Biotransformation increases excretion from the body and reduces bioaccumulation. The impact on the viability of a gill cell line from rainbow trout as a recently adopted OECD test is used as a surrogate for acute fish toxicity. The environmental profile of the recently launched Pomelol™,[7] a green citrus floral note, was assessed completely without vertebrate testing using the PeBiToSens™[8] platform. Our own laboratories were involved in the validation studies for both these two non-animal test methods ultimately leading to OECD acceptance. By this we helped to make this approach available to the whole chemical industry globally.

Growth with Purpose

The necessity to accelerate innovation in the fragrance industry to support the growing demand in multiple applications while improving sustainability is key. Chemical biology in various optimised combinations is also an essential asset to design, develop, test and understand new solutions. Givaudan chemists, biotechnologists and process experts together are engaged in revolutionary innovation to support our perfumers to create for happier and healthier lives with love for nature.

Received: October 31, 2021

[1] S. J. Bennett, 'Implications of Climate Change for the Petrochemical Industry: Mitigation Measures and Feedstock Transitions', in 'Handbook of Climate Change Mitigation', Eds: W.-Y. Chen, J. Seiner, T. Suzuki, M. Lackner, **2012**, pp 319-357.
[2] F. Kähler, M. Carus, O. Porc, C. vom Berg, 'Turning off the Tap for Fossil Carbon: Future prospects for a global chemical and derived material sector based on renewable carbon', www.renewable-carbon.eu/publications, April **2021**.
[3] H. Laue, R. P. Badertscher, L. Hostettler, Y. Weiner-Sekiya, T. Haupt, A. Nordone, G. M. Adamson, A. Natsch, *Arch. Toxicol*. **2020**, *94*, 4115, https://doi.org/10.1007/s00204-020-02918-9.
[4] H. Laue, S. Kern, R. P. Badertscher, G. Ellis, A. Natsch, *Tox. Sci.* **2017**, *160*, 244, https://doi.org/10.1093/toxsci/kfx178.
[5] OECD, Test No. 319, OECD Guidelines for the Testing of Chemicals. s.l. : OECD Publishing, **2018**, https://doi.org/10.1787/2074577x.
[6] OECD, Test No. 319B, OECD Guidelines for the Testing of Chemicals. s.l. : OECD Publishing, **2018**, https://doi.org/10.1787/2074577x.
[7] OECD, Test No. 249, OECD Guidelines for the Testing of Chemicals. s.l. : OECD Publishing, **2021**, https://doi.org/10.1787/c66d5190-en
[8] H. Laue, L. Hostettler, G. Sanders, G. Kreutzer, A. Natsch, *CHIMIA* **2020**, *74*, 168, https://doi.org/10.2533/chimia.2020.168.