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NEWSLETTER



# EUROCAROTEN

EUROPEAN NETWORK TO ADVANCE CAROTENOID RESEARCH  
AND APPLICATIONS IN AGRO-FOOD AND HEALTH

## CHEMICAL SYNTHESIS OF CAROTENOIDS AND THEIR DERIVATIVES

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### Introduction

Carotenoids are natural pigments that are very abundant in nature, however the low content of carotenoids in plants make their isolation in mass amounts tedious and expensive. That is why there is a growing need for these pigments by the food industry, which could be covered with total synthesis. In fact, nowadays at least some carotenoids ( $\beta$ -carotene, astaxanthin, 8'-apo- $\beta$ -carotenal, ethyl 8'-apo- $\beta$ -carotenoate, canthaxanthin, citranaxanthin) can be produced industrially in ton amounts. Total synthesis can be important in the case of minor carotenoids, where nature does not provide enough for chemical and especially biological investigations. In the production of carotenoids biotechnology is taking an ever growing part nowadays aiming to lower costs and to find solvent-free and environmental-friendly methodologies.

Partial synthesis starting from natural and – if possible – abundant carotenoids constitutes an important part of the current research. The partial syntheses are usually product oriented and utilize reaction types that are easy to accomplish with carotenoids such as esterification. In addition, some new techniques such as click-reaction has recently been implemented in carotenoid synthesis. It must be noted that unfortunately nowadays there is little activity and know-how on the chemical synthesis of and with carotenoids, although carotenoid derivatives

can possess enhanced biological properties or can be important in the clarification of structure-activity relationships or even metabolism. In this newsletter some examples are given of the old and new methods of carotenoid synthesis resulting in pigments with often remarkable structures and properties.

In this specific area of research the must-reads are the reviews of Partali and Sliwka<sup>1-3</sup> and Ito<sup>4</sup>, and in connection with ester synthesis a book chapter of Nagy and Agócs<sup>5</sup> is recommended.

### Total synthesis of carotenoids

Although carotenoids are widespread in nature their isolation in bulk amounts can be achieved economically only for some carotenoids, such as lutein. Biotechnology as an alternative for total synthesis and as a more environment-friendly method has been showing more potential in the production of certain carotenoids, but in most cases chemical synthesis is still more economical.

Another important territory for total synthesis and for biotechnology is the production of rare or minor carotenoids. In these cases for structure elucidation or for biological tests at least mg or gram amounts of

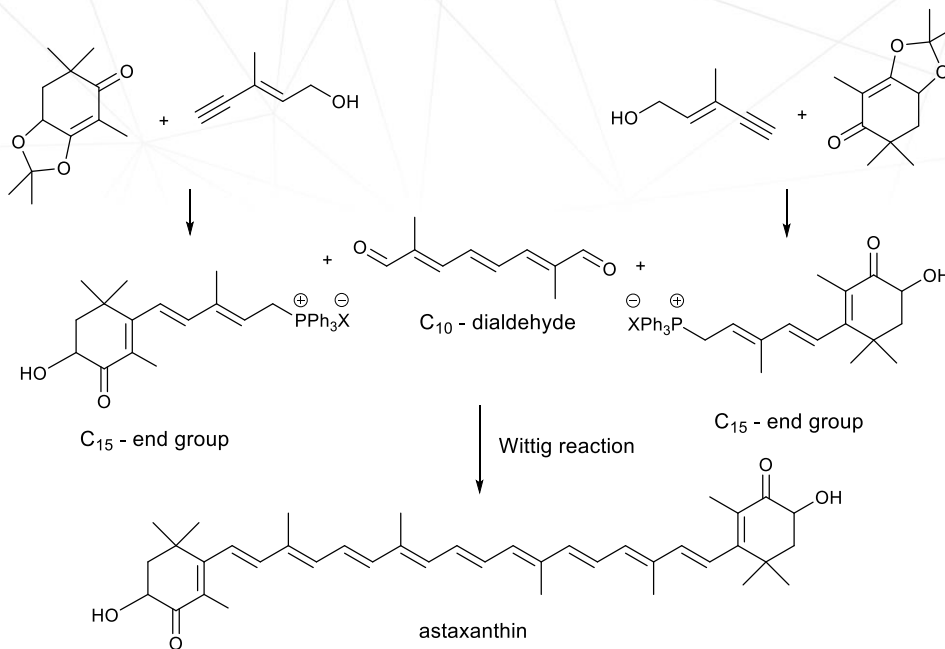


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# CHEMICAL SYNTHESIS OF CAROTENOIDS AND THEIR DERIVATIVES



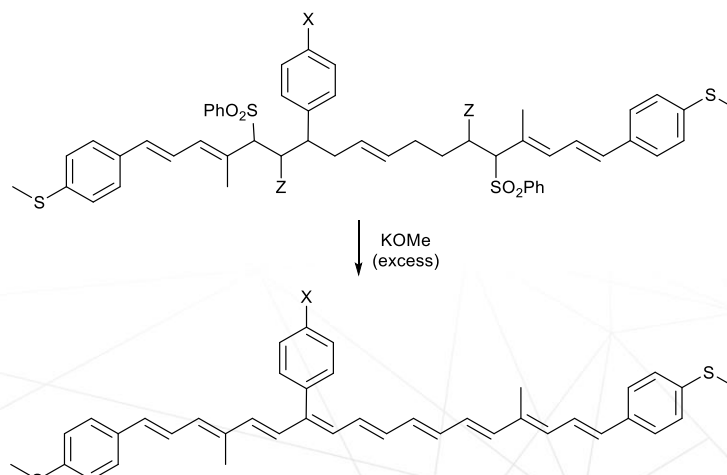
**Figure 1.** Classical block synthesis with Wittig-reaction<sup>6,7</sup>.

carotenoid should be synthesized effectively.

In **Figure 1**, a general scheme is shown for total synthesis that is applied industrially. In addition, it shows how the functionalized end-groups are C-C coupled to the central polyene chain. Coupling can be achieved by the well-known Wittig-reaction (e.g. astaxanthin or  $\beta$ -carotene)<sup>6,7</sup>, or Julia sulphone coupling (e.g. zeaxanthin)<sup>8,9</sup>.

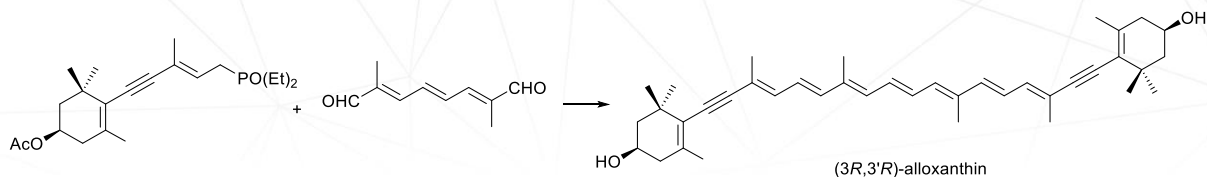
The sulphone can be used for the synthesis of new types of stabilized carotenoid compounds containing sulphur (**Figure 2**)<sup>10</sup>. The target thio-carotenoids can serve as nanosized molecular wires.

Another method for block synthesis goes with phosphonates and aldehydes, it was recently used for the synthesis of minor acid-labile alkyne carotenoids (**Figure 3**)<sup>11</sup>.



**Figure 2.** Sulphones for the total synthesis of carotenoid derivatives<sup>10</sup>.

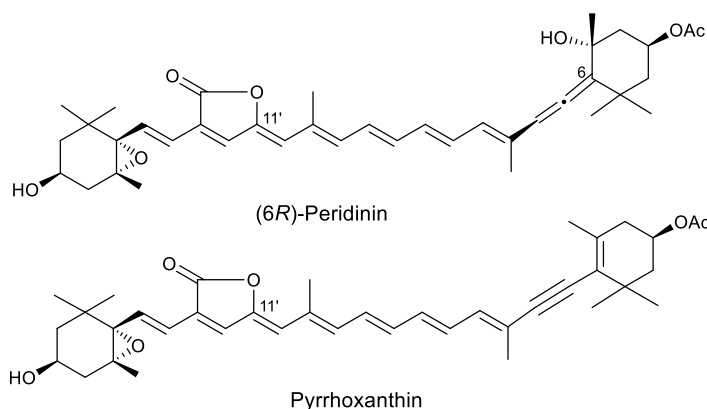
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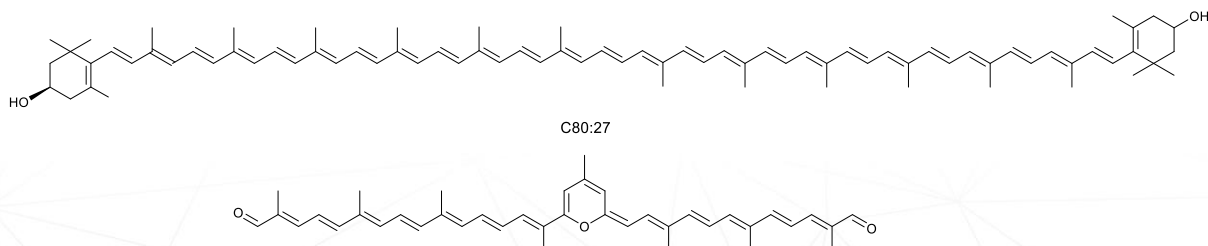
**Figure 3.** Synthesis of alkyne carotenoids with phosphonates<sup>11</sup>.

Ito *et al.* synthesized a lot of minor carotenoids with exotic structures such as peridinin and pyrroxanthin (**Figure 4**), which really show the potency of total synthesis<sup>4</sup>. These, and the work of other groups on total synthesis was summarized in a concise review<sup>4</sup>.

By using similar methodology long polyene chains can be synthesized and even the theoretical absorption maxima can be calculated for very long conjugated chains<sup>12,13</sup> or dialdehydes containing pyran rings can be synthesized with a high absorption wavelength (**Figure 5**)<sup>14</sup>. These compounds have already blue colour, which can be of importance in food industry.



**Figure 4.** Complex minor carotenoids made by total synthesis<sup>4</sup>.



**Figure 5.** How the UV absorption maximum of the polyene chain can be increased<sup>14</sup>.

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## Partial synthesis of carotenoid derivatives

A great deal of semi-synthetic carotenoid derivatives has been synthesized recently that are hydrophilic or even water-soluble to enhance availability or to increase biological effect<sup>15</sup>. To this group belong the various carotenoid sulphate esters synthesized by Liaaen-Jensen *et al.*<sup>16</sup> in the 80s and the sugar esters synthesized by Pfander *et al.* back in the seventies<sup>17</sup>. More recently salts of succinate, phosphate and lysinate esters were synthesized from hydroxy carotenoids (**Figure 6**). The astaxanthin dilysinate salt has a very good water solubility, on the other hand astaxanthin disuccinate has been marketed already as an anti-inflammatory agent (Cardax)<sup>18, 19</sup>.

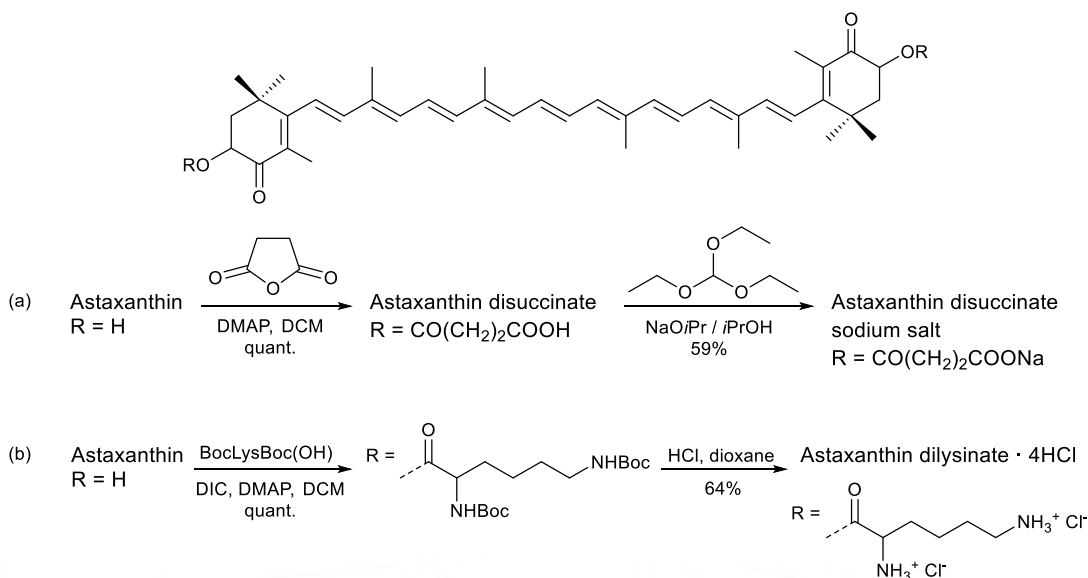
Foss *et al.* synthesized and thoroughly studied remarkable carotenoid derivatized phospholipids (**Figure 7**). A mixture of bromoethyl dichlorophosphate and triethylamine reacted with the previously described

monoglycerides of 8'-apo- $\beta$ -carotenoic acid. In these phospholipids the fatty acid is substituted by a carotenoic acid<sup>20</sup>.

Polyethylene glycols (PEG) can be used to increase water-solubility and decrease logP values for hydrophobic drug molecules (**Figure 8**). For carotenoids several mono- and bifunctional hydroxy carotenoids were esterified with PEGs to increase bioavailability. PEG conjugates can be produced via click-reaction, as well<sup>21</sup>.

Tetraethylene glycol was used as spacer in the synthesis of first generation propeller-like carotenoid dendrimers (**Figure 9**)<sup>22</sup>.

Polymers containing bioactive compounds are of great interest for in vivo delivery usage since they provide local release of the active ingredient and reduce systemic effects. Astaxanthin polyesters were synthesized and the astaxanthin in the formed polymers preserved its anti-inflammatory and antimicrobial effects against clinically associated pathogens (**Figure 10**)<sup>23</sup>.



**Figure 6.** Esterification of astaxanthin by a diacid and an amino acid<sup>18,19</sup>.

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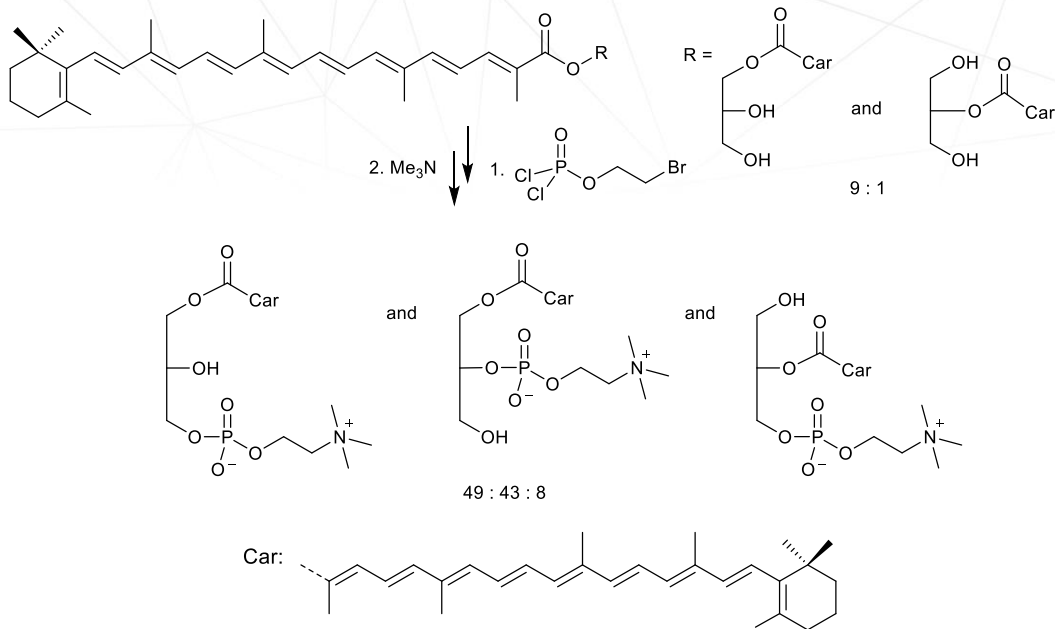


Figure 7. Phospholipids containing carotenoids<sup>20</sup>.

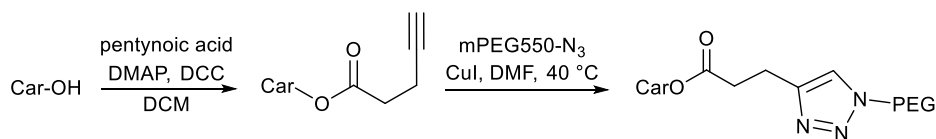


Figure 8. Hydrophilic carotenoids by polyethylene glycol conjugation<sup>21</sup>.

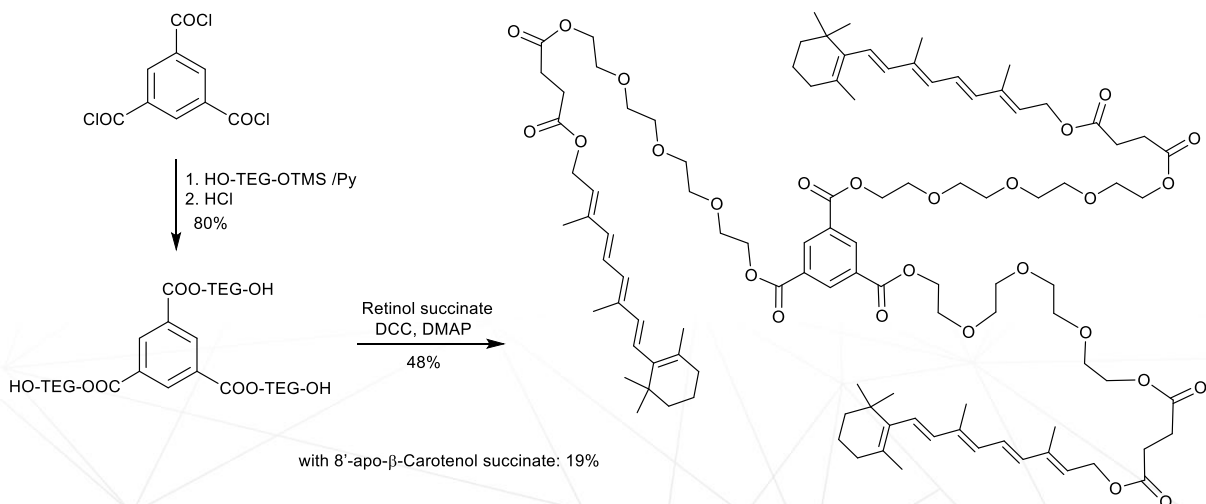
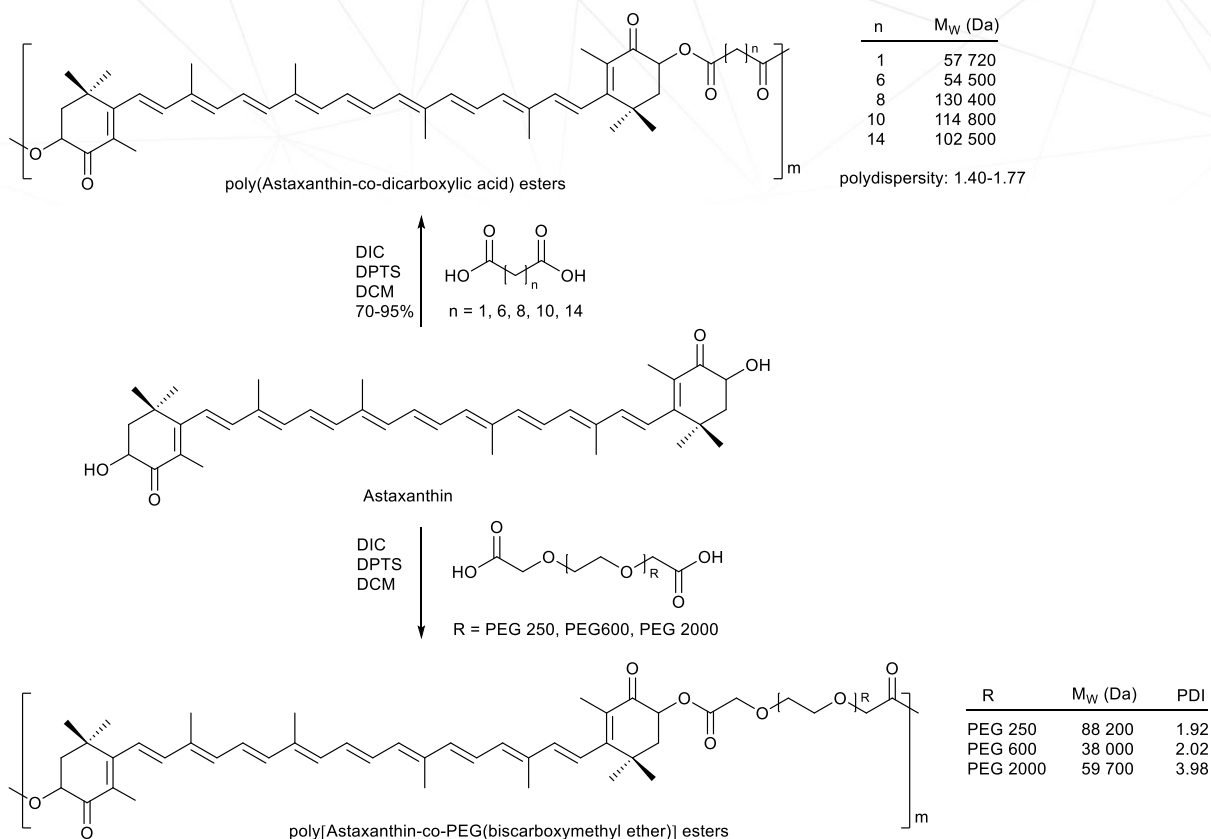


Figure 9. A flexible propeller made of three retinol moieties<sup>22</sup>.

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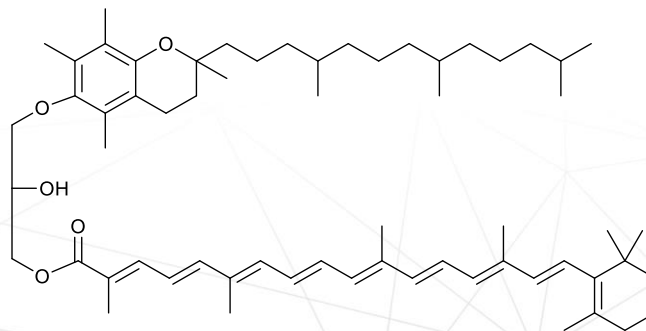


**Figure 10.** Astaxanthin polyesters with diacids and polyethylene glycol diacids<sup>23</sup>.

## Carotenoid-bioactive molecule conjugates

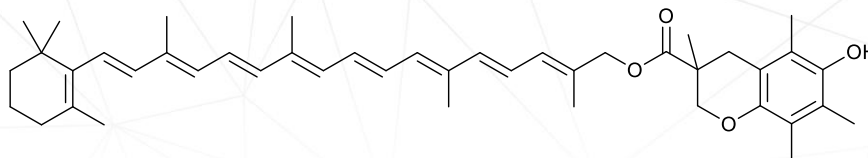
In the past two decades more and more bifunctional drugs have been developed, usually via the conjugation of a known drug molecule with another bioactive

molecule. In an optimum case the activity of both parts of the conjugate remain unchanged or even enhanced through synergism. In these compound the carotenoid can serve as the antioxidant part, of course, but also can facilitate membrane incorporation of the conjugate. There are already examples for such compounds containing carotenoids shown in **Figures 11-17**.

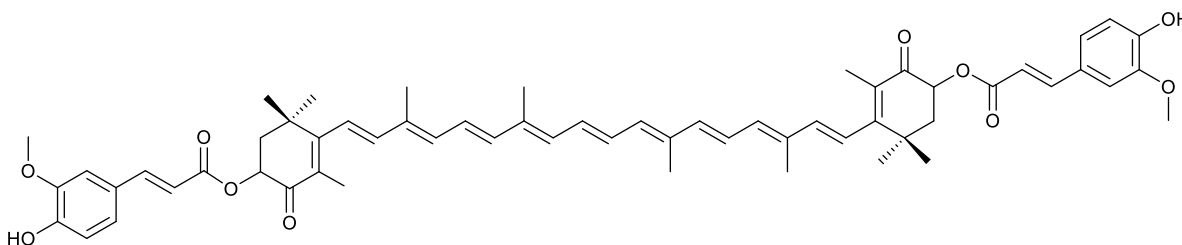


**Figure 11.** A mixed lipid from vitamin E and 8'-apo-β-carotenoid<sup>24</sup>.

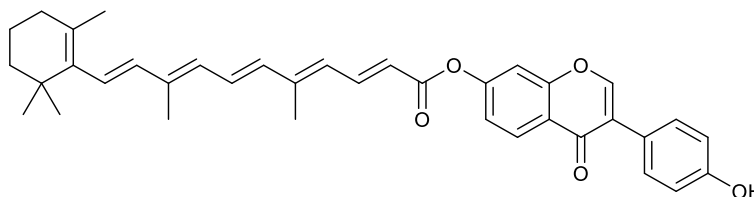
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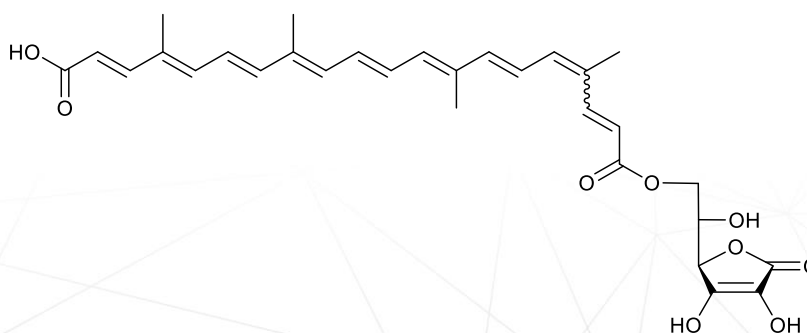
**Figure 12.** Two different antioxidants in one molecule: Trolox and carotenoid<sup>25</sup>.



**Figure 13.** Combination of astaxanthin and ferulic acid: the resulting compound was found to be a better singlet oxygen scavenger than free astaxanthin, as well as a better radical scavenger than free ferulic acid. Regarding cell membranes, this compound may ensure optimal protection against oxidative stress<sup>26</sup>.

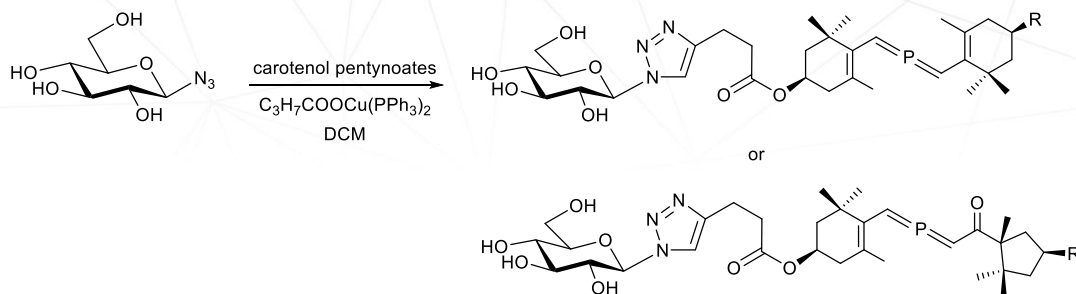


**Figure 14.** Two different antioxidants in one molecule: a flavonoid (daidzein) esterified by a carotenoid acid<sup>27</sup>.

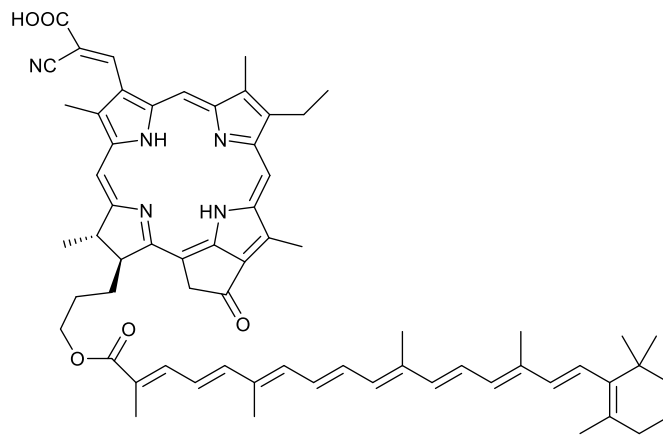


**Figure 15.** A hydrophylic and a hydrophobic antioxidant in one molecule: the ascorbic acid ester of bixin was synthesised using immobilised *C. antarctica* lipase<sup>28</sup>.

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**Figure 16.** Click-reaction of unprotected sugar azides delivers hydrophylic carotenoid-sugar bolaamphiphiles in one-step and with acceptable yields<sup>29</sup>.



**Figure 17.** In an attempt to mimic nature's light harvesting method 8'-apo- $\beta$ -carotenoic acid was coupled to a chlorin derivative. The obtained ester was built into a titania-based solar cell, which showed enhanced performance compared to the cell without the carotenoid. The carotenoid moiety is responsible for the transference of both electron and energy to the chlorin part<sup>30</sup>.

## Concluding remarks

As it was demonstrated in this brief summary, despite carotenoids being sensitive and hard to handle, if enough work and know-how is invested in finding the right conditions and reagents quite a lot of chemistry can be done with them. Although there has been some development in total synthesis of carotenoids, in that area biotechnology is gaining much more ground than 20 years ago.<sup>31</sup> That is also why most papers concentrate on partial synthesis or conjugation, with potentially bioactive substances in mind.

## REFERENCES

1. Sliwka HRP, Partali V, in *Carotenoids: Nutrition, Analysis and Technology*, ed. A. B. Kaczor AB, John M, Wiley & Sons, 2016, pp. 261-289.
2. Sliwka HR, Partali V, *Molecules*, 2012a, **17**, 2877-2928.
3. Sliwka HRP, Partali V, *Acta Biochimica Polonica*, 2012b, **59**, 17-20.
4. Ito M, Yamano Y, Tode C, Wada A, *Arch Biochem Biophys*, 2009, **483**, 224-228.



# CHEMICAL SYNTHESIS OF CAROTENOIDS AND THEIR DERIVATIVES

5. Nagy VD, Agócs A, in *Carotenoid Esters in Foods*, ed. Mercadante AZ, RSC Publishing, 2019, pp. 68-110.
6. Widmer E, Zell R, Broger EA, Cramer Y, Wagner HP, Dinkel J, Schlageter M, Lukac T, *Helv Chim Acta*, 1981, **64**, 2436-2446.
7. Widmer E, Soukup M, Zell R, Broger E, Wagner HP, Imfeld M, *Helv Chim Acta*, 1990, **73**, 861-867.
8. Soukup M, Widmer E, Lukac T, *Helv Chim Acta*, 1990, **73**, 868-873.
9. Bernhard K, Mayer H, *Pure Appl Chem*, 1991, **63**, 35-44.
10. Kim SB, Kim H, Lim B, Meang J, Bae SH, Choi E, Oh JT, Hong I, Jung SY, Yeo JE, Koo S, *Pure Appl Chem*, 2011, **83**, 613-620.
11. Vaz B, Fontan N, Castineira M, Alvarez R, de Lera AR, *Org Biomol Chem*, 2015, **13**, 3024-3031.
12. Zeeshan M, Sliwka HR, Partali V, Martinez A, *Org Lett*, 2012, **14**, 5496-5498.
13. Martinez A, Zeeshan M, Zaidi A, Sliwka HR, Naqvi KR, Partali V, *Comput Theor Chem*, 2018, **1125**, 133-141.
14. Opstad CL, Sliwka HR, Partali V, *Eur J Org Chem*, 2010, 435-439.
15. Hada M, Nagy V, Deli J, Agocs A, *Molecules*, 2012, **17**, 5003-5012.
16. Hertzberg S, Liaaen-Jensen S, *Acta Chem Scand B*, 1985, **39**, 629-638.
17. Pfander H, *Pure Appl Chem*, 1979, **51**, 565-580.
18. Frey DA, Kataisto EW, Ekmanis JL, O'Malley O, Lockwood SF, *Org Process Res Dev*, 2004, **8**, 796-801.
19. Jackson HL, Cardounel AJ, Zweier JL, Lockwood SF, *Bioorg Med Chem Lett*, 2004, **14**, 3985-3991.
20. Foss BJ, Nalum Naess S, Sliwka HR, Partali V, *Angew Chem Int Edit*, 2003, **42**, 5237-5240.
21. Hada M, Nagy V, Takatsy A, Deli J, Hait J, Agocs A, *Tetrahedron Lett*, 2012, **53**, 2480-2482.
22. Hada M, Petrovics D, Nagy V, Boddi K, Deli J, Agocs A, *Tetrahedron Lett*, 2011, **52**, 3195-3197.
23. Weintraub S, Shpigel T, Harris LG, Schuster R, Lewis EC, Lewitus DY, *Polym Chem-Uk*, 2017, **8**, 4182-4189.
24. Larsen E, Abendroth J, Partali V, Schulz B, Sliwka HR, Quartey EGK, *Chem-Eur J*, 1998, **4**, 113-117.
25. Karagiannidou E, Storseth TR, Sliwka HR, Partali V, Malterud KE, Tsimidou M, *Eur J Lipid Sci Tech*, 2003, **105**, 419-426.
26. Papa TBR, Pinho VD, do Nascimento ESP, Santos WG, Burtoloso ACB, Skibsted LH, Cardoso DR, *Free Radical Res*, 2015, **49**, 102-111.
27. Hu F, Bu YZ, Liang R, Duan RM, Wang S, Han RM, Wang P, Ai XC, Zhang JP, Skibsted LH, *Free Radical Res*, 2013, **47**, 413-421.
28. Humeau C, Rovel B, Girardin M, *Biotechnol Lett*, 2000, **22**, 165-168.
29. Agocs A, Bokor E, Takatsy A, Lorand T, Deli J, Somsak L, Nagy V, *Tetrahedron*, 2017, **73**, 519-526.
30. Wang XF, Koyama Y, Wada Y, Sasaki S, Tamiaki H, *Chem Phys Lett*, 2007, **439**, 115-120.
31. Rodriguez-Concepcion M, Avalos J, Bonet ML, Boronat A, Gomez-Gomez L, Hornero-Mendez D, Limon MC, Melendez-Martinez AJ, Olmedilla-Alonso B, Palou A, Ribot J, Rodrigo MJ, Zacarias L, Zhu CF, *Prog Lipid Res*, 2018, **70**, 62-93.

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