SynOpen

Strategies for Total Synthesis of Fucoxanthin from a Commercial Perspective

Sayan Dutta Gupta, Cheol-Ho Pan.

Affiliations below.

Abstract:
Fucoxanthin, the light-harvesting pigment of various algae has shown promising biological activity in pre-clinical and clinical models. It has also received marketing approval as a nutraceutical and cosmetic ingredient in the USA and other countries. The commercial synthesis of this natural ingredient assumes significance because of various drawbacks (low yield, patent infringement, longer duration of cultivation, etc.) associated with its extraction and isolation procedures. This review is intended to provide an appraisal of the total synthesis of fucoxanthin reported to date along with a detailed explanation of the commercially viable one. Finally, we briefly discuss the future of research for the total synthesis of fucoxanthin.

Corresponding Author:
Dr. Sayan Dutta Gupta, Dr. Sayan's Drug Discovery Solutions, Drug discovery, 10/5 MLM Garden Lane, post-Konnagar, 712235 Konnagar, India, sayan@dsdrugdiscoverysolutions.com

Affiliations:
Sayan Dutta Gupta, Dr. Sayan's Drug Discovery Solutions, Drug discovery, Konnagar, India
Cheol-Ho Pan, KIST Gangneung Institute of Natural Products, Natural product Research institute, Gangneung, Korea (the Republic of)

Thieme

Strategies for Total Synthesis of Fucoxanthin from a Commercial Perspective

Sayan Dutta Gupta[1*], Cheol-Ho Pan[2,3*]

[1] Dr. Sayan's Drug Discovery Solutions (DSDDS), Konnagar, WestBengal-712235, India.
[2] KIST Gangneung Institute of Natural Products, Gangneung 25451, Republic of Korea.
[3] Microalgae Ask Us Co., Ltd., Gangneung 25441, Republic of Korea.

*Corresponding Author
Sayan Dutta Gupta
Email: sayan@dsdrugdiscoverysolutions.com
Phone: +91-9393744933
**Cheol-Ho-Pan**
Email: panc@kist.re.kr
Phone: +82-010-22079702

ABSTRACT

Fucoxanthin, the light-harvesting pigment of various algae has shown promising biological activity in pre-clinical and clinical models. It has also received marketing approval as a nutraceutical and cosmetic ingredient in the USA and other countries. The commercial synthesis of this natural ingredient assumes significance because of various drawbacks (low yield, patent infringement, longer duration of cultivation, etc.) associated with its extraction and isolation procedures. This review is intended to provide an appraisal of the total synthesis of fucoxanthin reported to date along with a detailed explanation of the commercially viable one. Finally, we briefly discuss the future of research for the total synthesis of fucoxanthin.
Keywords: Fucoxanthin, Total Synthesis, Commercialization

GRAPHICAL ABSTRACT
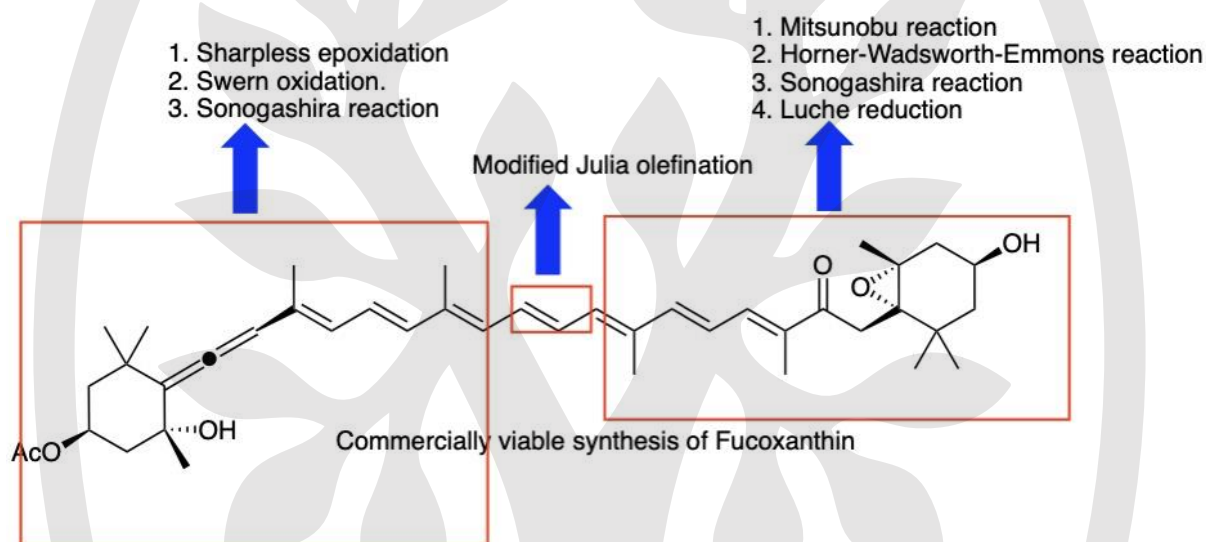
1. INTRODUCTION

Fucoxanthin is the most abundant xanthophyll carotenoid which plays a pivotal role in photosynthesis and photoprotection in various types of algae. It has demonstrated anticancer, anti-oxidant, anti-obesity, anti-diabetic and anti-inflammatory activity which received FDA approval as a nutritional supplement [1,2]. Furthermore, it has shown promising results in phase-II clinical trials to treat metabolic syndrome (MetS) [3]. Besides its primary use as a medicinal agent, it holds a prominent space in cosmetics formulations such as anti-aging, skin brightening and sunscreen. The market for fucoxanthin is valued at 31 million US dollars in 2024 and is projected to grow with a compound annual growth rate (CAGR) of 3.9% from 2024-2032, ultimately reaching 41 million USD [4].

The chemical synthesis of fucoxanthin assumes significance commercially because the yield from natural sources has not crossed 7%. Additionally, there are patent infringement issues with producing fucoxanthin from high-yielding species. Moreover, there are several other bottlenecks in the fucoxanthin extraction process like limited evaluation of scale-up cultivation and extraction, a few unclear steps in its biosynthetic pathway and conflict between biomass and fucoxanthin accumulation under high light conditions [5,6].

The present review summarizes the various total synthesis methodologies available for fucoxanthin. Furthermore, we provide an in-depth analysis of the methodology that exhibits promising potential for commercial success, elucidating its intricacies in detail.

2. Types of Synthetic Strategies

There are two synthetic procedures reported for producing fucoxanthin to date. The major hindrance in its chemical synthesis is the extremely alkali labile β, γ epoxy keto moiety due to which the stereochemical control of both the epoxidation and polyene chain formation were not achieved by the first synthetic procedure reported comprising 30 synthetic steps. Additionally, the synthetic method yielded 8 % [7,8] of fucoxanthin in the final step. The most promising method described so far is by Takayuki Kajikawa et al. in 2012 [9], wherein the stereochemical control of both the epoxidation and polyene chain formation is achieved successfully with a modest yield of 40 % in the final step of synthesis. The primary distinction between this method and the first one lies in forming the epoxide ring as an intermediate rather than in the final step of synthesis (**Figure 1**).

3

BEST SYNTHETIC METHOD
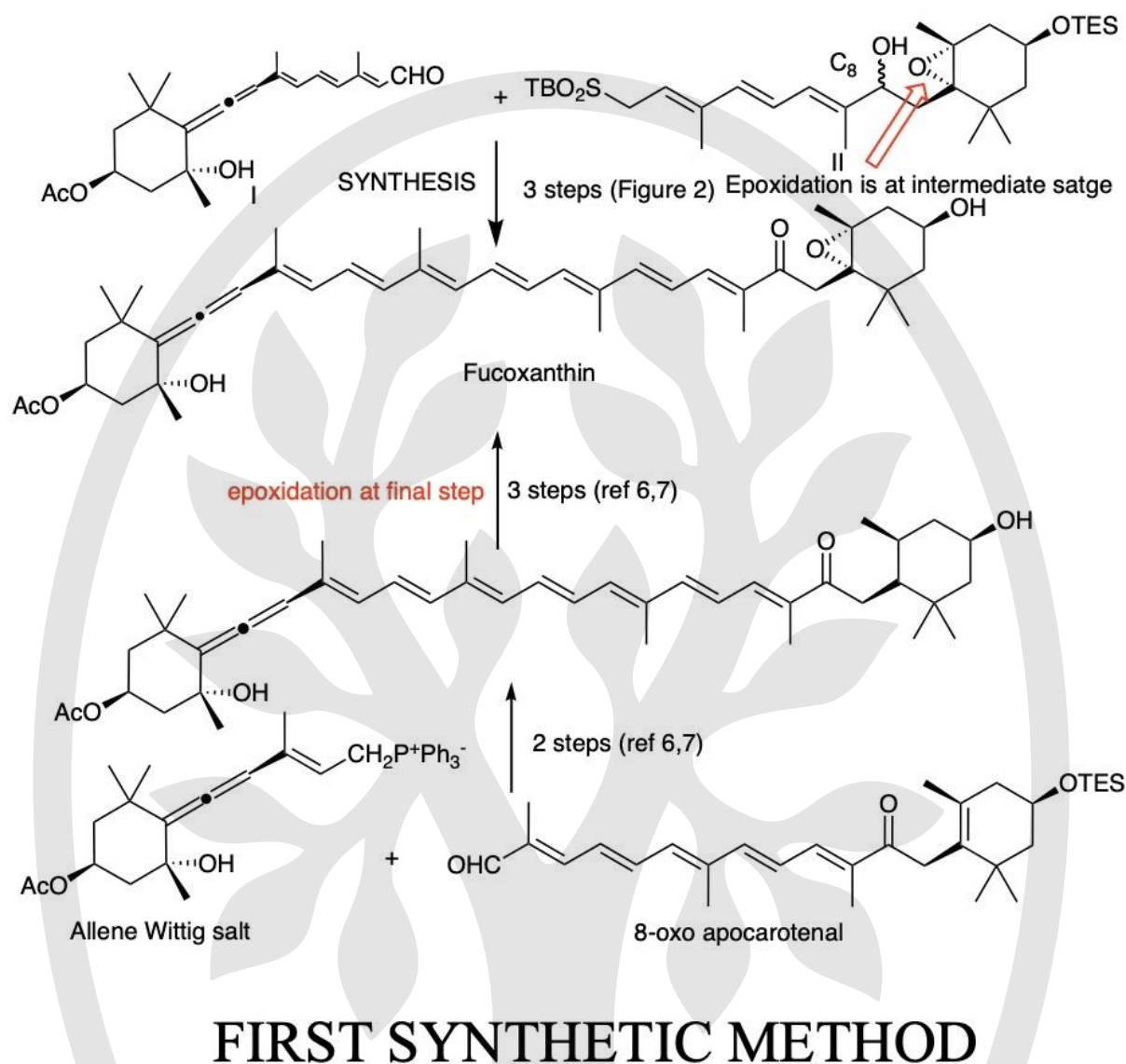
FIRST SYNTHETIC METHOD

Figure 1. Comparison of the reported synthetic methodologies of fucoxanthin.

3. Promising synthetic method (Takayuki Kajikawa's total synthesis)

The most successful synthetic method for fucoxanthin involves the fusion of an allenic segment (**I**) and a hydroxy sulfone fragment (**II**) by the modified Julia olefination method to obtain an isomeric mixture of **28**. The ratio of the isomers was not possible to estimate because of the mixture with C8-epimer (of hydroxy sulfone part) on HPLC analysis. Hence, the mixture of isomers (**28**) was used in the next oxidation step by DMP, wherein the C8 hydroxy group is converted into a ketone one (**29**). This is followed by deprotection of the TES group to obtain cis/trans fucoxanthin isomers. Thereafter, the all-*trans* isomer (**30**) was obtained by keeping the mixture in benzene under fluorescent light in an argon atmosphere for 3 days [9] (**Figure 2**).
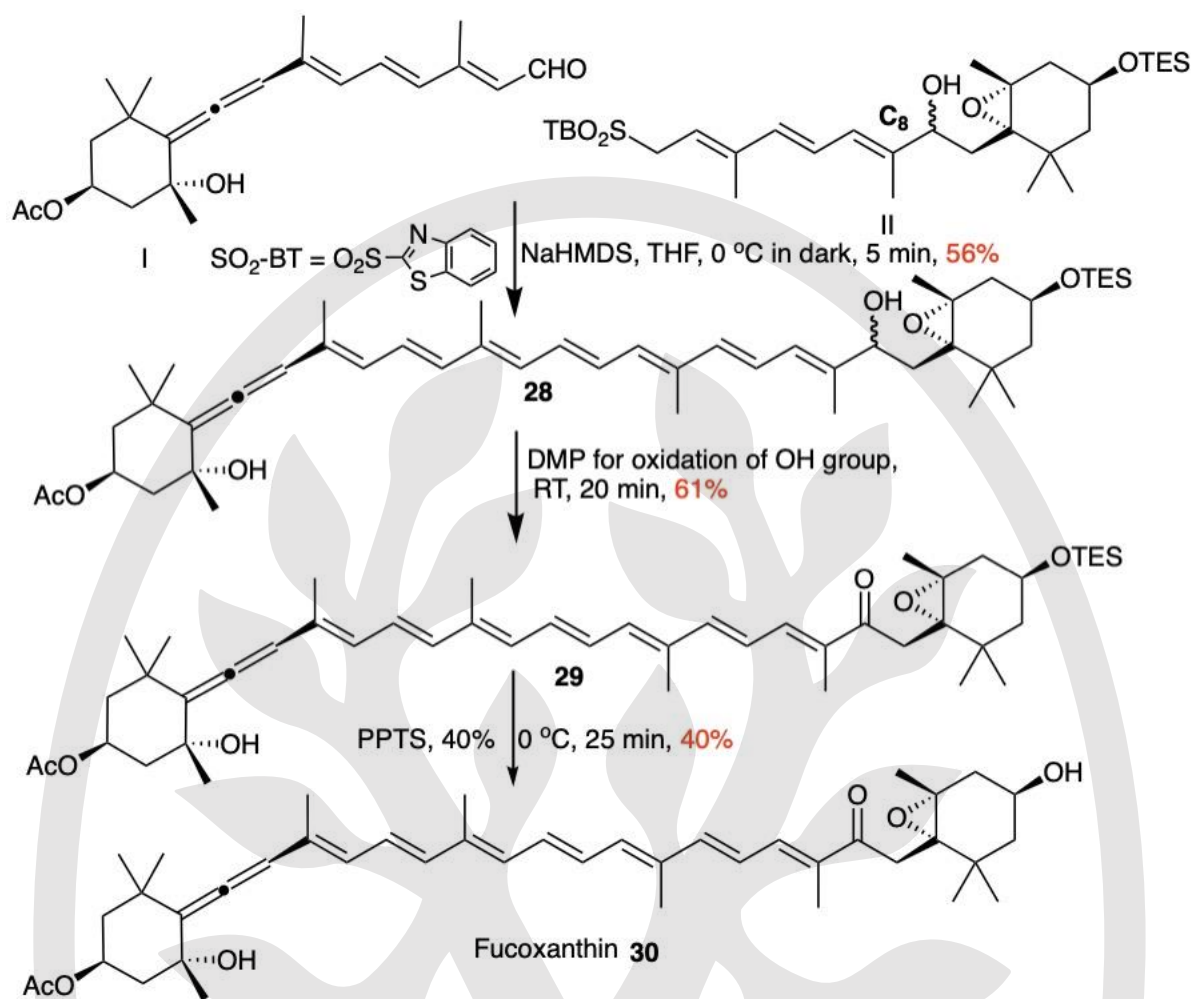
Figure 2: Synthesis of Fucoxanthin. NaHMDS = sodium bis(trimethylsilyl)amide. DMP = Dess-Martin periodinane, PPTS = pyridinium *p*-toluenesulfonate.

3.1. Synthesis of allenic segment I

The allenic segment, **I** was synthesized starting from 4-hydroxy-2,2,6-trimethylcyclohexane-1-one. First, the hydroxy group is protected with TBS, followed by OTf conversion of the ketone group to afford the formation of the methyl ester under a carbon monoxide atmosphere using tetrakis (triphenylphosphine) palladium catalyst [10,11]. The ester is reduced to alcohol with the help of lithium aluminum hydride and for undergoing Sharpless epoxidation using t-butyl hydroperoxide. The diastereomeric mixture (**5**) was subjected to Swern oxidation using oxalyl chloride to obtain the required 5S,6R aldehyde, **6** [11]. This stereocontrolled epoxide formation in good yield is a crucial part of this synthetic procedure. The epoxide was converted into the corresponding acetylene derivative, **7** by utilizing chloromethyl triphenylphosphonium chloride and *n*-BuLi. The intermediate crude vinyl chloride formed is subjected to elimination using potassium ter-butoxide to obtain **7** [11]. The Pd and Cu catalyzed Sonogashira reaction between acetylene **7** and trienyl iodide proceeded smoothly to furnish the desired coupling product **8**, with the complete retention of the stereochemistry, in 81% yield [12]. The reduction of **8** with DIBAL for the construction of the allenic moiety **9** afforded the C20-allenic triol which was oxidized to the corresponding aldehyde **10** with manganese dioxide [9]. The scheme for synthesizing the allenic segment **I** is depicted in **Figure 3**. This crude aldehyde was used in the next acetylation step without further purification to obtain **10 (allenic segment I)**.
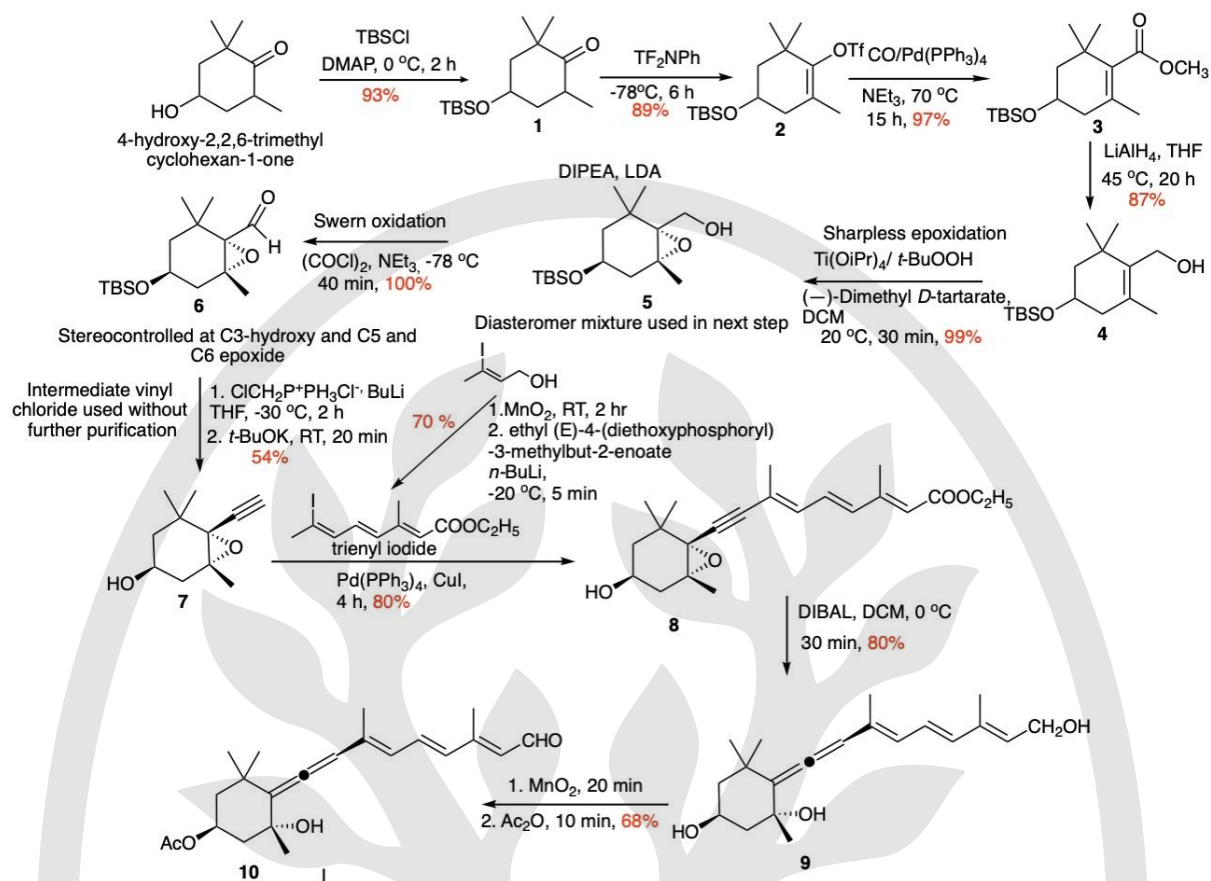
Figure 3: Synthesis of allenic segment for preparing fucoxanthin. TBSCl = Tertiary butyl dimethylsilyl chloride. DMAP = 4-Dimethylaminopyridine. TF$_2$NPh = N-phenylbis (trifluoro methane sulfonamide). DIPEA = *N*,*N*-Diisopropylethylamine, LDA = Lithium Diisopropylamide. Pd(PPh$_3$)$_4$ = Tetrakis(triphenylphosphine)palladium(0). ClCH$_2$P$^+$PH$_3$Cl$^-$ = chloromethyltriphenylphosphonium chloride. Bu-Li = Butyl lithium. DIBAL = Diisobytyl aluminium hydride.

3.2. Synthesis of hydroxy sulfone segment (II)

The synthesis of hydroxy sulfone segment started from 3-epi actinol. First, the alcohol group is TES-protected for the introduction of the aldehyde group at C-5 (**13**) via the formation of an acetylene derivative (**12**) [8,13]. The carbon chain of the aldehyde **13** was extended with the introduction of C8 hydroxyl group by treating **13** with vinyl iodide and *t*-BuLi to produce the desired alcohol (**14**) in high yield. Acetylation of the resulting alcohol (**15**) and then chemoselective removal of the TES group led to the R-homoallylic alcohol **16**. Thereafter, the reaction of organoaluminum peroxide prepared in situ from TBHP and (t-BuO)$_3$Al with **17** exhibited complete stereocontrol and formed the desired compound **17** in 74% yield as a single diastereomer. The inversion of the resulting secondary hydroxyl group under the Mitsunobu reaction conditions using 4-nitrobenzoic acid afforded the diester **18** in 70 % yield in a completely stereocontrolled manner. This was followed by TBAF treatment for deprotecting the terminal OH group to obtain **19**. Thereafter, the alcohol group was oxidized with manganese dioxide and the crude aldehyde was used in the next step of Horner Emmons reaction to obtain E isomer of triene ester **20** in excellent yield. Selective hydrolysis of the p-nitrobenzoyl group (to obtain **21**) and then TES protection of the resulting alcohol afforded the triene ester **22** in excellent yield (Figures **4** and **5**). The ester group of **22** was transformed into

the sulfide **23** by DIBAL reduction followed by the Mitsunobu reaction with 2-mercapto benzothiazole. The C8 of compound **23** was oxidized to the keto group with Dess-Martin periodinane to obtain **24** in 70 % yield. The oxidation of the sulfide to sulfone **25** was carried out by aluminium heptamolybdate and 30% aqueous hydrogen peroxide. Reprotection of the C3 hydroxyl group with TES followed by the Luche reduction afforded the desired hydroxyl sulfone **27** [9] **(Figure 5).**
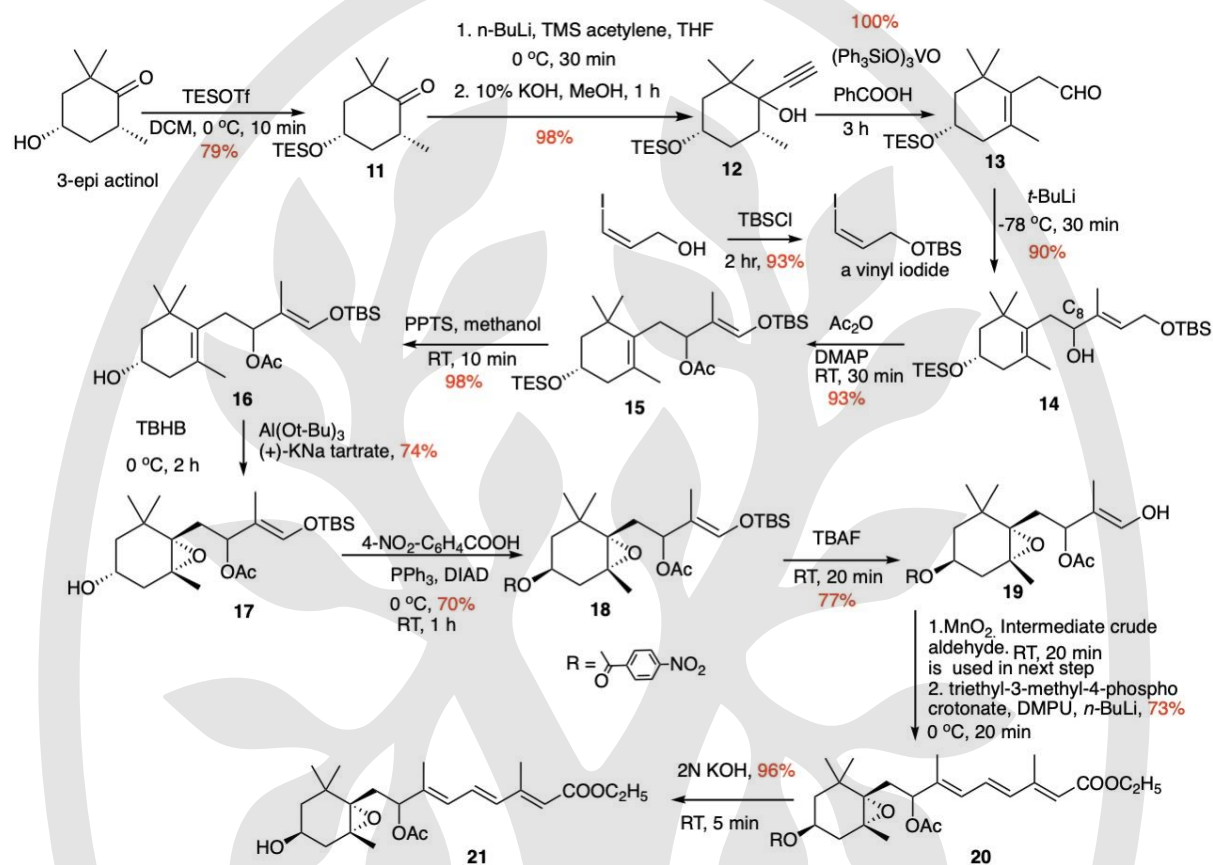

Figure 4. Synthesis of hydroxy sulfone segment for preparing fucoxanthin. Part-I. TES triflate = Triethylsilyl trifluoromethanesulfonate. TMS-acetylene = Trimetyl silyl acetylene. $(Ph_3SiO)_3VO$ = Tris(triphenylsiloxy)vanadium oxide. TBS = tertiary butyl dimethyl silyl group. DMAP = 4-Dimethylaminopyridine. PPTS = Pyridinium paratoluene sulfonate. TBHB = Tertiarybutyl hydroperoxide. PPh$_3$ =. Trimethyl phosphine. DIAD = Diisopropyl azodicarboxylate. TBAF = Tetra *n*-butyl ammonium fluoride. DMPU = N,N′-Dimethylpropylene urea.
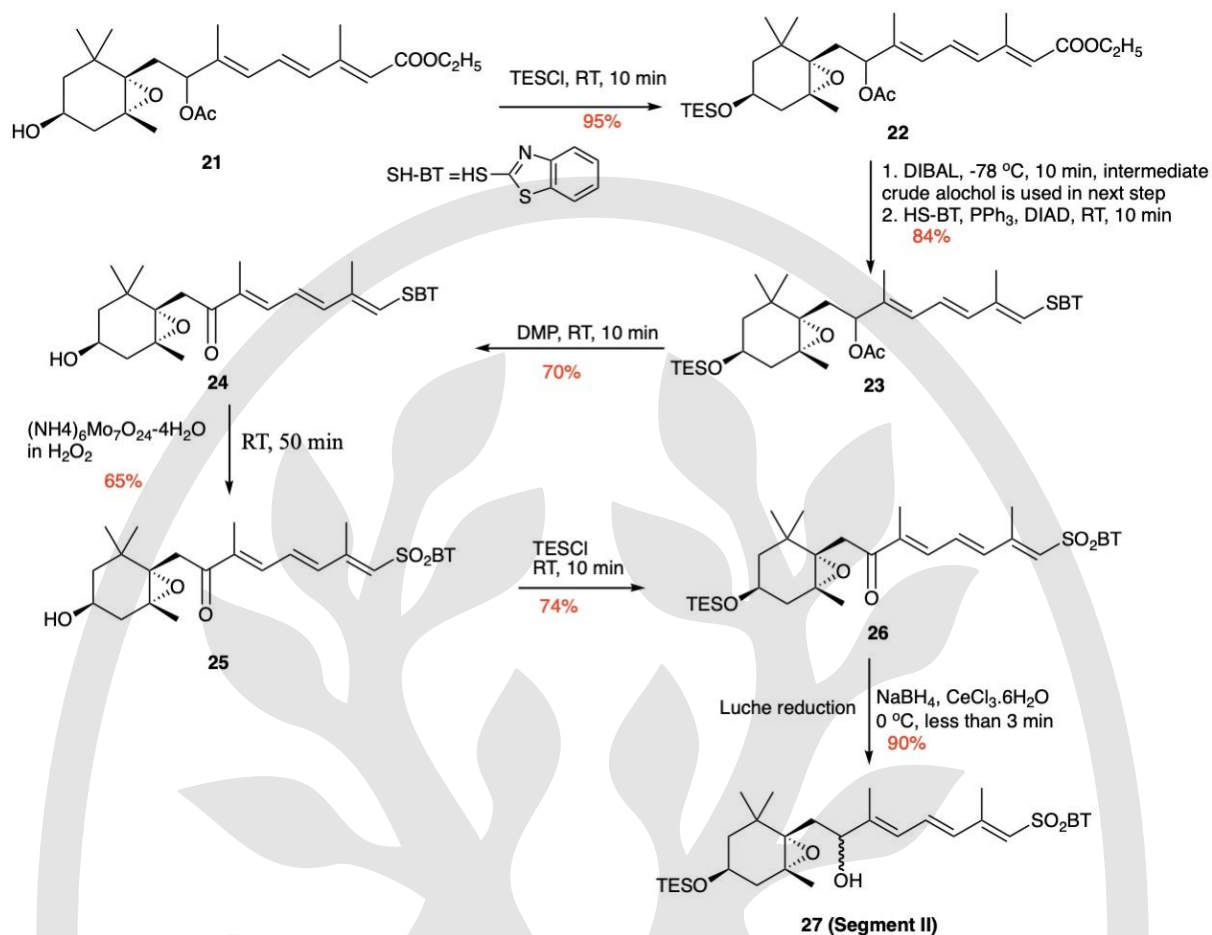
Figure 5. Synthesis of hydroxy sulfone segment for preparing fucoxanthin. Part-II. TESCl = Chlorotriethylsilane. HSBT = 2-mercapto benzothiazole. DIBAL = Diisobytyl aluminium hydride. DIAD = Diisopropyl azodicarboxylate. DMP = Dess-Martin periodinane. CeCl$_3$ = cerium chloride. NaBH$_4$ = Sodium borohydride.

4. FUTURE PERSPECTIVE

There are immense opportunities in the total synthesis of fucoxanthin because only two methods have been reported to date. One of them has the potential for commercialization and is discussed in detail in this review. However, researchers need to find novel ways to improve the total synthesis of fucoxanthin. One such example is the procedure reported by Satoshi Okumura and co-workers for the synthesis of C37 and C32 fucoxanthin [14]. The method employs the fusion of the allenic sulfone segment and aldehydic epoxy fragment by Julia olefination method. It is the reverse of the promising method described in this review, wherein allenic aldehyde segment is fused with an epoxy sulfone fragment (**Figure 6**). The yield for all the steps is between 50-100% with the final step yield of 64%. The tedious step for the introduction of C-8 carbonyl group is reduced by two steps and overall there are 29 steps for getting the final product. It is 10 years since the modified synthetic procedure for C37 fucoxanthin was reported and it is yet to be reported for C42 fucoxanthin (marketed as fucoxanthin). Therefore, we are a little skeptical about this procedure. Nevertheless, this synthetic methodology provided another approach for obtaining fucoxanthin. Additionally, it generated ideas for exploring structure-activity relationship studies of fucoxanthin derivatives.
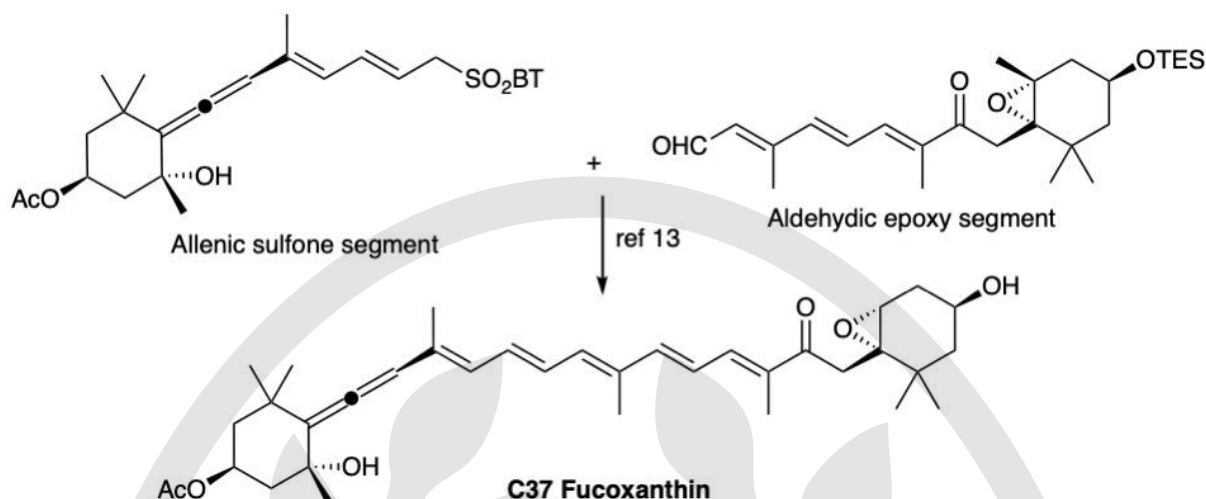
Figure 6. Synthesis of C37 fucoxanthin derivatives.

CONCLUSIONS

The most promising synthesis of fucoxanthin reported to date comprises 32 steps, including the preparation of two intermediates. The advantage of this method is that the yield for synthetic steps can be rated as moderate (50%) to excellent (99%). The final step in fucoxanthin production demonstrates a 5 times improvement in yield (40%) compared to the previous method. Furthermore, to the best of our knowledge, this method does not pose any patent infringement issues. Hence, this synthetic method has the potential for commercial manufacturing of fucoxanthin. The 32 synthetic steps give ample scope for process patents in the future, which can act as a good revenue source for companies engaged in commercial manufacturing of fucoxanthin. An initial assessment of the synthesis costs indicates that it is economically feasible to substitute traditional extraction methods, which are still not widely favored commercially. The primary drawback lies in the multitude of synthetic steps required, posing a potential challenge during scale-up operations. Nonetheless, we are confident that advancements in technology will enable us to gradually surmount these challenges.

ACKNOWLEDGEMENTS

REFERENCES

(1)   Sayuti, N. H.; Muhammad Nawawi, K. N.; Goon, J. A.; Mokhtar, N. M.; Makpol, S.; Tan, J. K. *Nutrients* **2023**, *15*.

(2)   Winarto, J.; Song, D. G.; Pan, C. H. Int. *J. Mol. Sci.* **2023**, *24*, 1.

(3)   López-Ramos, A.; González-Ortiz, M.; Martínez-Abundis, E.; Pérez-Rubio, K. G. J. *Med. Food* **2023**, *26*, 521.

(4)   Fucoxanthin Market Is Set to Fly High in Upcoming Years with Developing CAGR

9

of 3.9% till 2032 | 86+ Report Pages https://www.linkedin.com/pulse/fucoxanthin-market-set-fly-high-upcoming-years-developing-omxoe/ (accessed May 5, 2024).

(5) Wang, S.; Wu, S.; Yang, G.; Pan, K.; Wang, L.; Hu, Z. *Biotechnol. Adv.* **2021**, *53*, 107865.

(6) Kim, S. M.; Jung, Y.-J.; Kwon, O.-N.; Cha, K. H.; Um, B.-H.; Chung, D.; Pan, C.-H. *Appl. Biochem. Biotechnol.* **2012**, *166*, 1843.

(7) YAMANO, Y.; ITO, M. Chem. Pharm. Bull. (Tokyo). **1994**, *42*, 410.

(8) Yamano, Y.; Tode, C.; Ito, M. *J. Chem. Soc. Perkin Trans.* 1 **1995**, *5*, 1895.

(9) Kajikawa, T.; Okumura, S.; Iwashita, T.; Kosumi, D.; Hashimoto, H.; Katsumura, S. *Org. Lett.* **2012**, *14*, 808.

(10) Yamano, Y.; Ito, M. J. Chem. Soc. Perkin Trans. 1 **1993**, 1599.

(11) Furuichi, N.; Hara, H.; Osaki, T.; Mori, H.; Katsumura, S. *Angew. Chemie Int. Ed.* **2002**, *41*, 1023.

(12) Murakami, Y.; Nakano, M.; Shimofusa, T.; Furuichi, N.; Katsumura, S. *Org. Biomol. Chem.* **2005**, *3*, 1372.

(13) Tode, C.; Yamano, Y.; Ito, M. *J. Chem. Soc. Perkin Trans.* 1 **2001**, 3338.

(14) Okumura, S.; Kajikawa, T.; Yano, K.; Sakaguchi, K.; Kosumi, D.; Hashimoto, H.; Katsumura, S. *Tetrahedron Lett.* **2014**, *55*, 407.

Biography

	Dr. Sayan Dutta Gupta received a Ph.D. degree in pharmaceutical chemistry from J.N.T.U., Hyderabad, India. He was awarded the prestigious Brain Pool Fellowship (formerly known as the Korea Research Fellowship) for carrying out anticancer research at KIST, Gangneung Institute of Natural Products. He is an accomplished drug discovery scientist with 18 years of experience in academia and industry. He established Dr. Sayan's Drug Discovery Solutions (DSDDS, https://dsdrugdiscoverysolutions.com/) in January 2024 after identifying gaps and opportunities in the drug discovery domain.
	Dr. Cheol-Ho Pan received a Ph.D. degree in agricultural chemistry from Seoul National University in 2001. He is the Principal research scientist at Natural Product Informatics Research Center, KIST Gangneung Institute of Natural Products, South Korea. Additionally, he is CEO of Microalgae Ask US Co., Ltd. (http://maus2020.com/), a company involved in microalgae culture and extract manufacturing R & D service. He has about 30 years of research experience with more than 15 years in microalgae research. He has published 65 papers and 14 patents to his credit.